Potentially tautomeric pyridazino(4, 5-*b*)indolones

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Except where stated, the work in this thesis is original and has not been submitted for any previous degree at this or other university.

A. GÜVEN

1992

Dedicated to my wife, my son, and my mother

ACKNOWLEDGEMENTS

I would like to thank Dr. R. Alan Jones for his guidance and kindness during the course of this work.

I would also like to thank to all staff of the School of Chemical Sciences.

I am also grateful to my wife, Kıymet, for her support over the three years that this study has taken.

ABSTRACT

This thesis is in five chapters. Chapter I reviews the tautomerism, classification of tautomerism, heteroaromatic tautomerism and the methods available for the investigations of heteroaromatic tautomerism.

Chapter II describes the synthesis of the 3, 4–dihydro–4–oxo–5*H*–pyridazino [4, 5–*b*]indoles . Their tautomerism have been studied qualitatively by comparison of the electronic spectra of the tautomeric system with those of ' fixed structure model ' compounds. Measurements of the basicities of the model compounds provided a quantitative evaluation of the tautomeric equilibrium constant (K_T).

Chapter III, the preparation of 1, 2–dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*]indoles, and the synthesis of the corresponding 'fixed structure model' compounds for the tautomerism studies are described. The tautomeric behaviour (oxo-hydroxy) of the 1, 2 –dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*]indoles was investigated, qualitatively and quantitatively by a comparison of IR, UV, and NMR spectral data and by the determination of the pKa values of the ' fixed structure model' compounds.

In chapter IV, the preparation of 1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino [4, 5–*b*]indoles, and the synthesis of the corresponding 'fixed structure model' compounds for the tautomerism studies are described . The tautomeric behaviour (oxo-oxo, oxo–hydroxy, hydroxy–hydroxy) of the 1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H* –pyridazino[4, 5–*b*]indoles was investigated, qualitatively and quantitatively by a comparison of IR, UV, and NMR spectral data and the determination of the pKa values of ' fixed structure model' compounds.

In chapter V, the synthesis of 4–chloro–, 1–chloro–, and 1, 4–dichloro–5*H* –pyridazino[4, 5–*b*]indoles from the corresponding 5*H*– pyridazino[4, 5–*b*]indoles is described, together with a study of nucleophilic displacement reactions of these compounds with nucleophiles.

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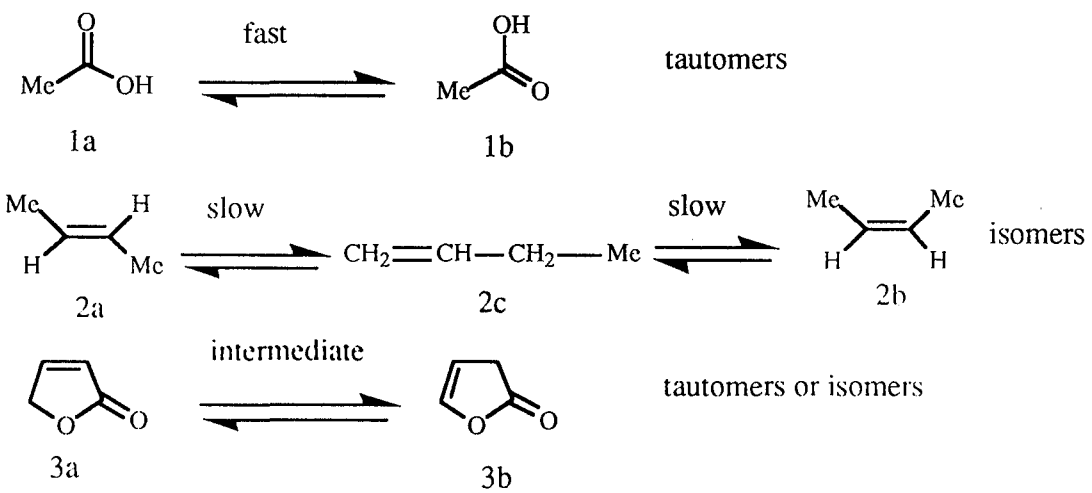
Chapter V Chloro–5*H*–pyridazino[4, 5–*b*]indoles

Chapter I
Tautomerism

1. 0 Tautomerism

1.1 Introduction

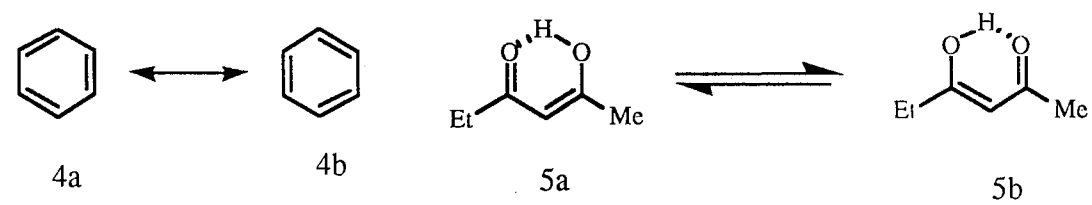
Tautomerism is defined as a phenomenon in which two or more molecular structures exist in dynamic equilibrium with each other, i.e. , the energy barrier between them is small. [1a] There is no hard and fast dividing line between tautomerism and isomerism, but in general, tautomers readily interconvert whereas isomers interconvert much less easily. For example, the two forms of a carboxylic acid (1) are definitely in tautomeric equilibrium whereas, 1-butene (2c) and the 2-butenes (2a) and (2b) are considered as isomers since they are easily separable (Scheme I. 1).



Scheme I. 1

However, there are some borderline cases, for example, because the two butyrolactones (3) can be isolated but are readily interconvertible, they can be considered both as tautomers and as isomers.

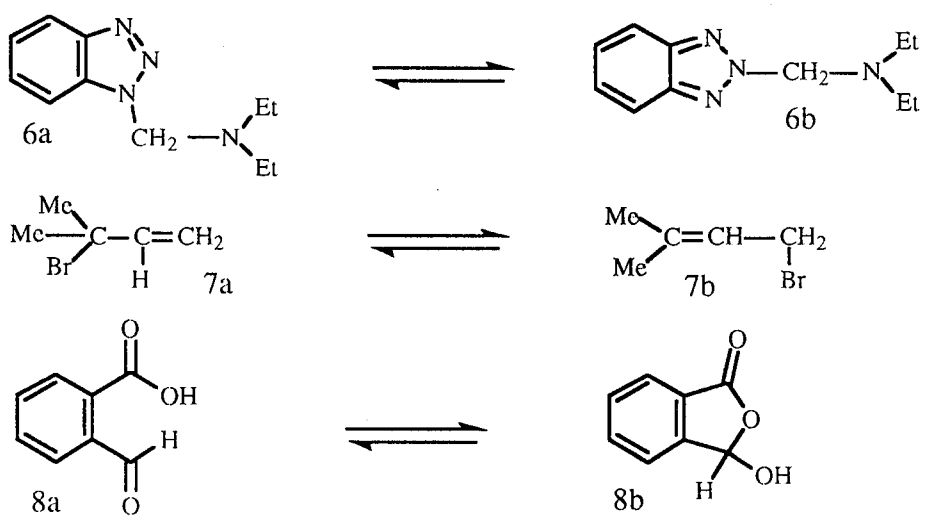
On the other hand, the distinction between tautomerism and mesomerism is usually much better defined. Two tautomers are individual compounds separated by an energy barrier. By contrast, a single compound exhibiting mesomerism exists at an energy minimum between two or more canonical forms (4) which contribute to the actual structure. However, even here some cases near the dividing line do exist. For example, the enol of hexan–2, 4–dione (5) is hydrogen-bonded and there is only small energy gap between it and the other hydrogen-bonded tautomer (Scheme I. 2).



Scheme I. 2

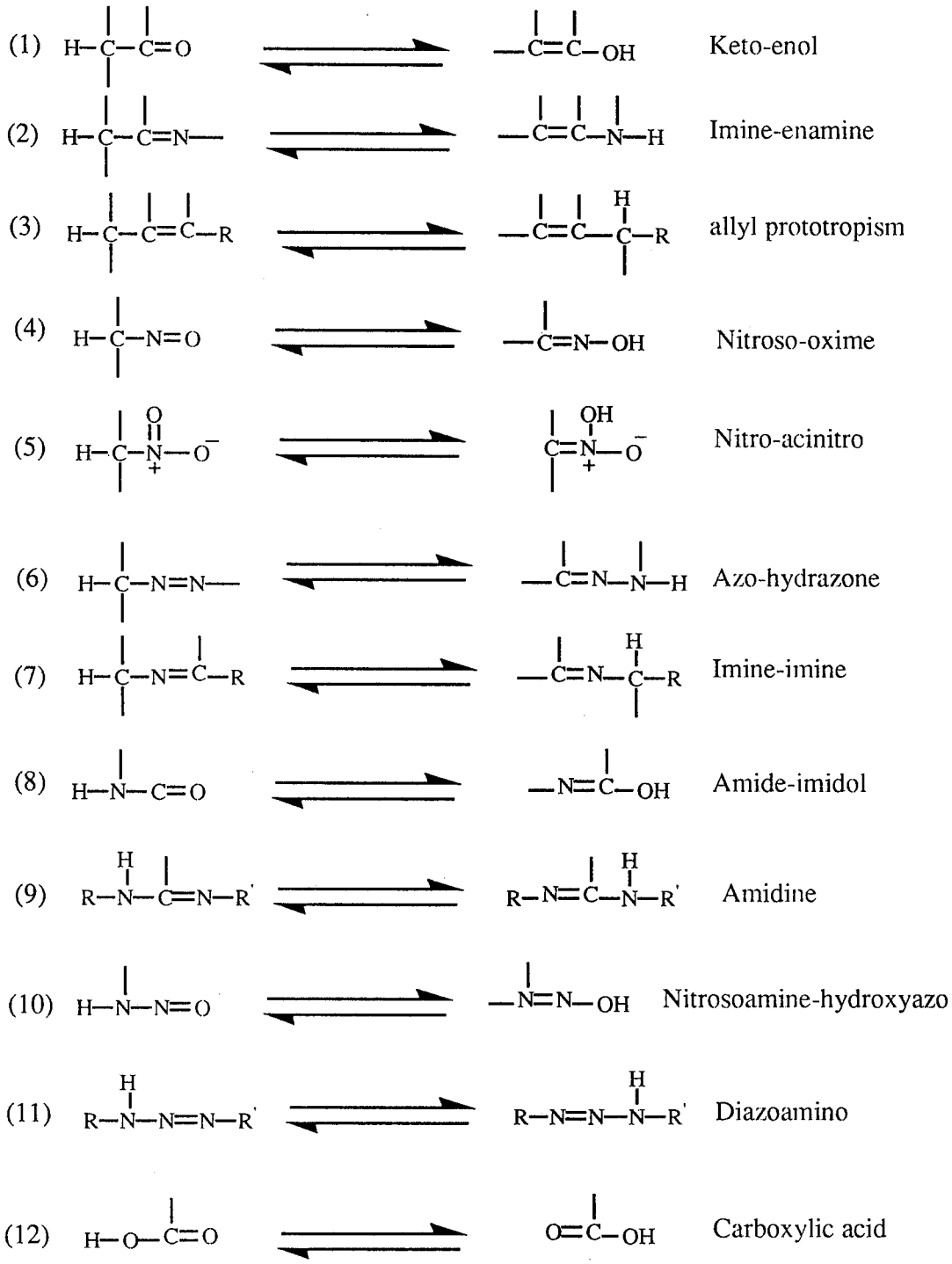
Cases are known of symmetrical hydrogen bonds and therefore the concept of tautomerism and mesomerism can also be considered to merge in rare cases.

The specific formation of two or more tautomeric structures, which differ only in the position of a hydrogen atom with the concominant redistribution of the valance bonds is frequently described as prototropy. Some types of tautomerism (prototropism) are presented at table I. 1. However, several other types of tautomerism exist (Scheme I. 3) : for example, certain substituted benzotriazoles (6) are tautomeric between 1-substituted (6a) and the 2-substituted (6b) benzotriazole forms, [2] anionotropy (7) involving the allyl cation is well-known, and ring-chain tautomerism (8). [1a]



Scheme I. 3

Table I.1 Types of tautomerism (prototropism)

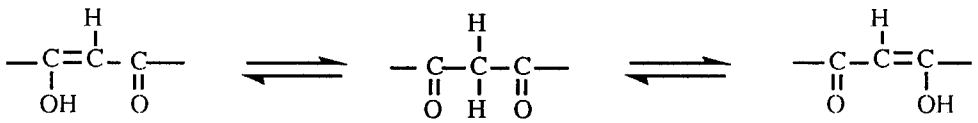


Keto-enol tautomerism :

Keto-enol tautomerism results when a carbonyl compound possesses a α–hydrogen and is in equilibrium with its enol form. In simple cases, the keto-enol equilibrium lies well over to the keto form. The observation can be readily understood by comparing the bond energies of the two systems. The approximate sum of the bond energies in the keto

form (E_{C-C} + $E_{C=O}$ + E_{C-H}) is 1505 kJmol^{-1}, whilst for the enol form the total bond energies ($E_{C=C}$ + E_{C-O} + E_{O-H}) is 1442 kJ mol^{-1}. The keto form is therefore more stable by about kJ 63 mol^{-1} (Table I. 2). Consequently, for simple carbonyl compounds, the keto forms are in equilibrium with small amounts of their respective enols. Steric and electronic factors can, however, influence the position of the equilibrium. Thus, the enol forms of aldehydes are frequently more favoured than they are for the analogous ketones, but carboxylic esters can be considered to be non–enolic in character, although it has been reported [3] that both forms (keto-enol) of acetic acid can be isolated and each can be kept at room temperature for several days.

The presence of a second electron-withdrawing group at the α–carbon atom generally promotes the stability of the enol form relative to the keto structure. This is particularly noticeable with 1, 3–dicarbonyl compounds where the diketo structure (9) is in equilibrium with the enol forms (10) and (11) (Scheme I. 4).



10 9 11

Scheme I. 4

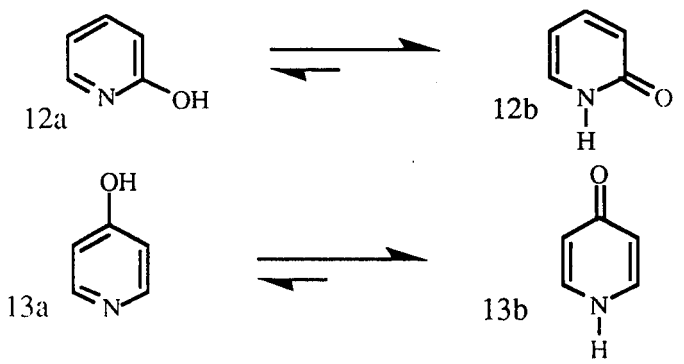
The increased stability of the enol forms is possibly a result of the electronic effects of the two electron-withdrawing substituents upon the acidity of the methylene protons and also the structural effect of forming two enols of comparable energy. Additionally, the formation of the intramolecular H–bonded (5a and 5b, Scheme I. 2) and the conjugative effect help to stabilise the enol form.

The extent of enolization is greatly affected by solvent, concentration and temperature. Thus, acetoacetic ester has an enol content of 0.4 % in water and 19.8 % in toluene. [4] In this case, water reduces the enol form by hydrogen-bonding with the carbonyl group.

Table I. 2 Comparison of Bond energies of Keto-Enol form

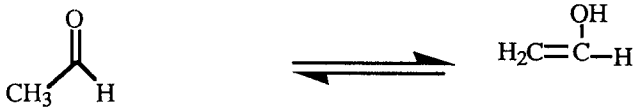
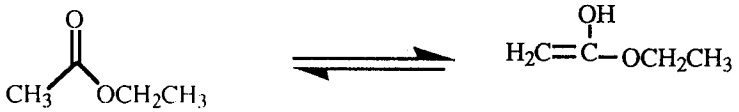
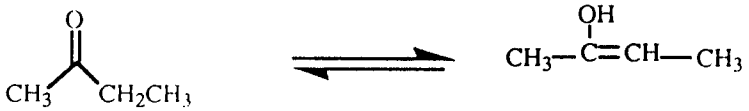
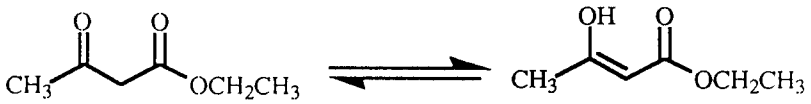
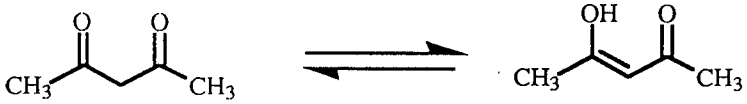
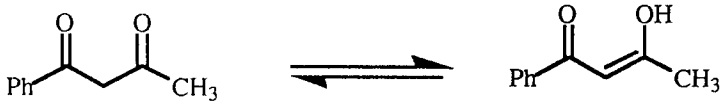
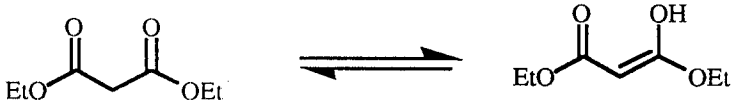
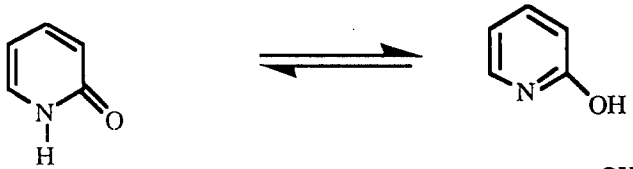
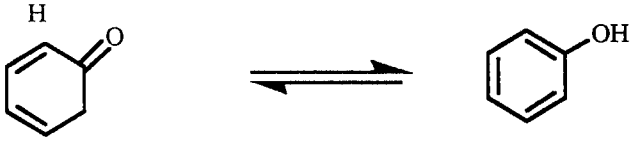
Bond	kJ / mol at 25 °C	Value	calculated from
Keto form			
C–H	401–414	416	CH_4
C–C	347–355	331	C_2H_6
C=O	723–757	435	HCHO
Enol form			
C=C	610–631	591	C_2H_4
C–O	355–380	321	CH_3OH
O–H	460–464	462	H_2O

Phenol-dienone tautomerism is a special case of keto-enol tautomerism. Phenol exists entirely in the enol form, because the alternative keto structure would sacrifice the stability associated with the six π-electron aromatic system. In polycyclic phenols, however, it has been possible in a number of cases to obtain the keto form, [9] and the keto form predominates for heterocyclic compounds such as (12) and (13) [7] (Scheme I. 5).



Scheme I. 5

Table I. 3 The Enol content of some carbonyl compounds [5–8]

Compound	Enol content
	1.5×10^{-4}
	less than 0.1 ppm
	no enol found
	1.2×10^{-1}
	8.0 %
	76.4 %
	89.2 %
	7.7×10^{-3}
	2.5×10^{-1}
	4.8×10^{-3}
	4.1×10^{-6}
	10^{6}
	1.2×10^{-3}
	4×10^{13}

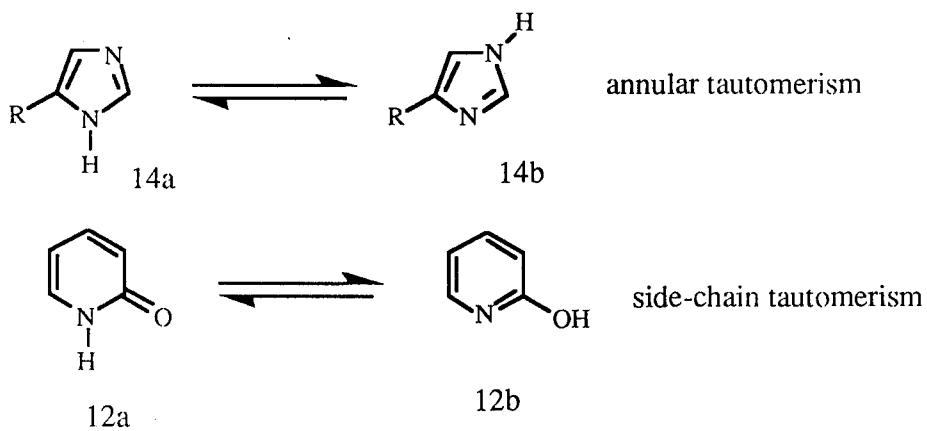
1. 2 The Tautomerism of Heterocycles

1. 2a Principal Types of Tautomerism

The principal types of tautomerism can be classified according to the nature and the position of the atoms between which the protons move. The most common type involves the movement of a proton between a cyclic nitrogen atom and a substituent atom directly connected to the ring. The comprehensive classifications of the possible types are shown in scheme I. 8–I.15.

1. 2b Classification of The Prototropic Tautomerism of Heteroaromatic Compounds

In heterocyclic chemistry, we distinguish between annular (14) and side chain (12) tautomerism. In the former, the mobile hydrogen atom is exchanges between the ring atom, whereas in the latter, the exchange takes places between a ring and a side-chain atoms (Scheme I. 7).



Scheme I. 7

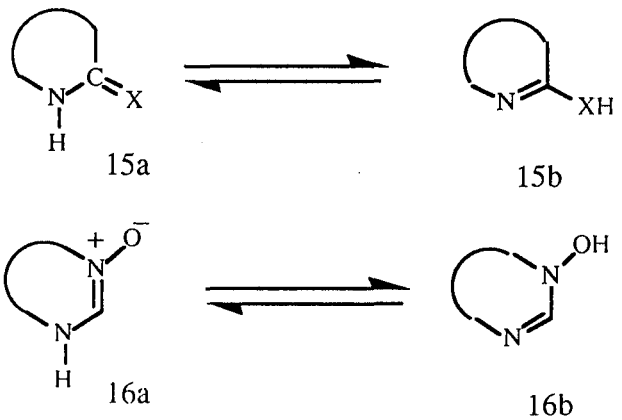
The important potentially tautomeric substituents for side-chain tautomerism are listed in table I. 4.

Table I. 4 Potentially Tautomeric Substituents

—OH, hydroxy	⇌	=O, oxo
—SH, thiol	⇌	=S, thione
—NH_2 , amino	⇌	=NH, imino
—CH_3 , methyl	⇌	=CH_2, methylene
—NHX	⇌	=NX
—CHXY	⇌	=CXY

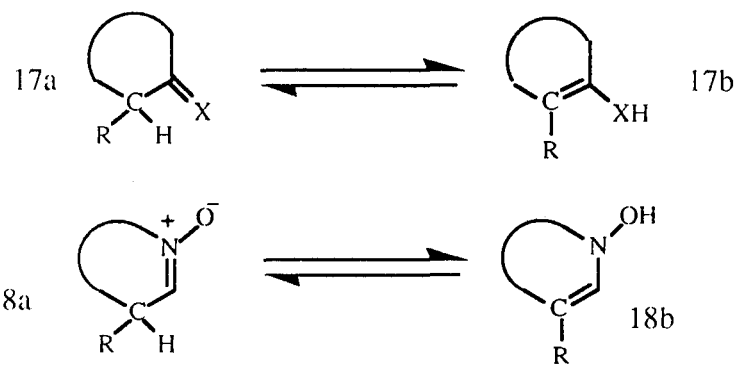
The following examples are typical of ring-side-chain tautomerism (1) to (3), annular tautomerism (4) to (6) and ring-chain tautomerism (7) to (8).

(1) Annular nitrogen and an atom adjacent to the ring (15a ⇌ 15b) and (16a ⇌ 16b) (Scheme I. 8).



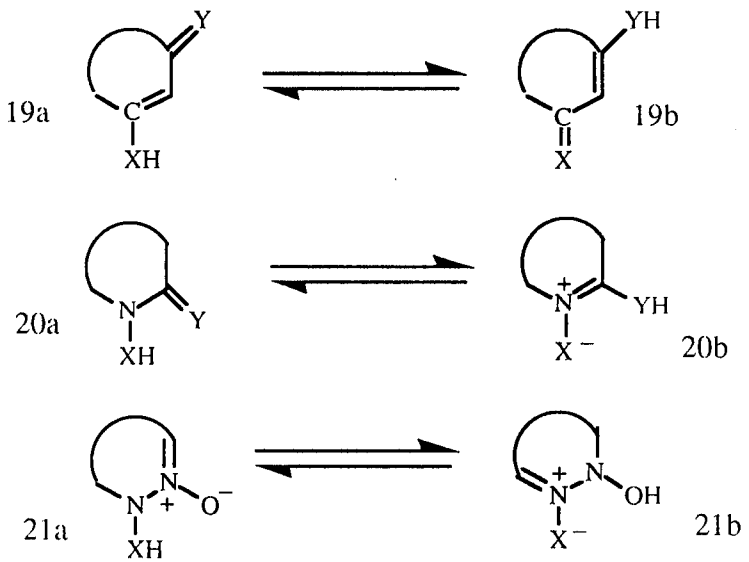
Scheme I. 8

(2) Annular carbon and an atom adjacent to the ring (17a ⇌ 17b) and (18a ⇌ 18b) (Scheme I. 9).



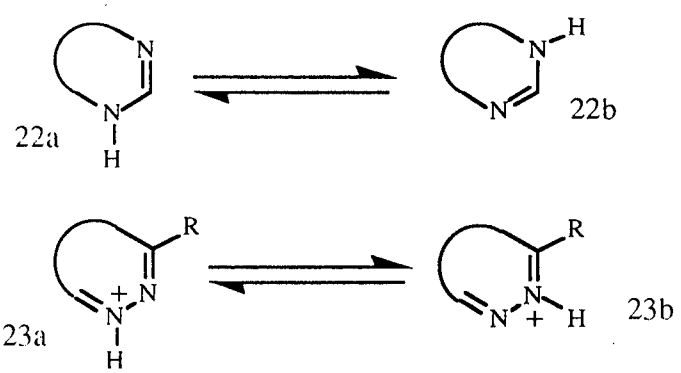
Scheme I. 9

(3) Two atoms adjacent to the ring (19a ⇌ 19b), (20a ⇌ 20b), or (21a ⇌ 21b) (Scheme I. 10)



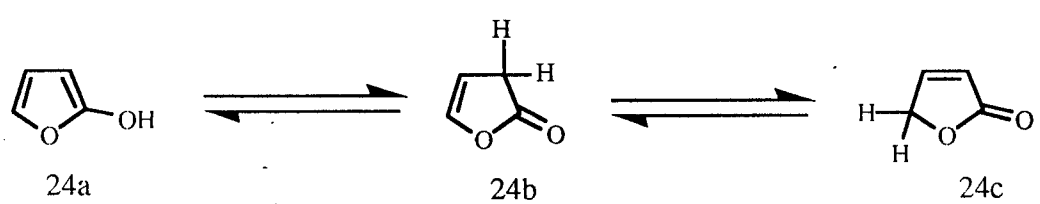
Scheme I. 10

(4) Two annular nitrogen atom : neutral molecules (22a ⇌ 22b) and conjugated acids (23a ⇌ 23b) (Scheme I. 11).



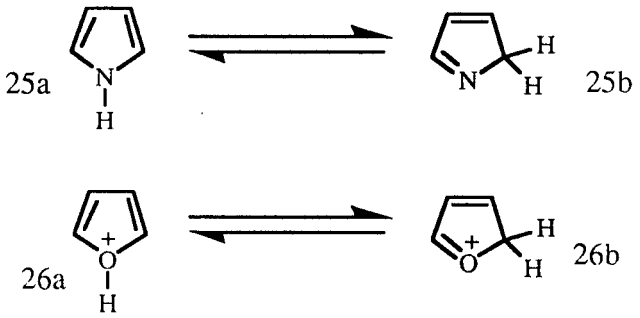
Scheme I. 11

(5) Two annular carbon atoms (24a ⇌ 24b ⇌ 24c) (Scheme I. 12).



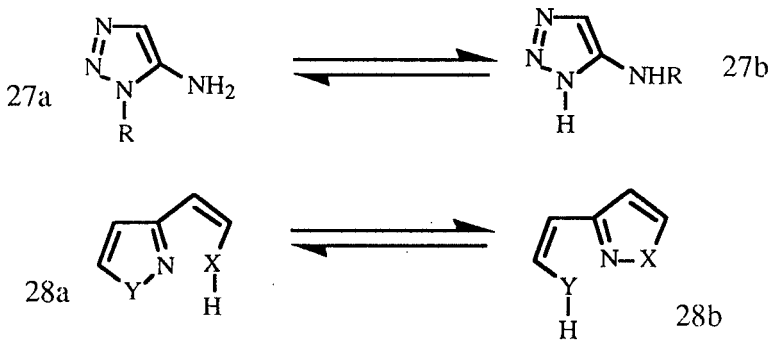
Scheme I.12

(6) Annular carbon and nitrogen atom : neutral molecules (25a ⇌ 25b), and conjugated acids (26a ⇌ 26b) (Scheme I. 13).



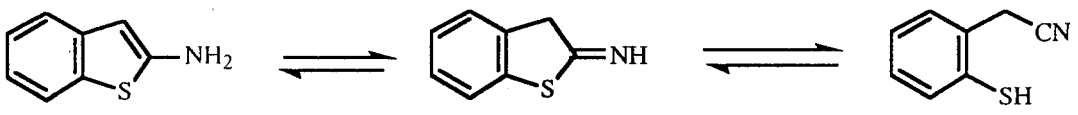
Scheme I. 13

(7) Dimroth (27a ⇌ 27b) and other rearrangement (28a ⇌ 28b) (Scheme I. 14).



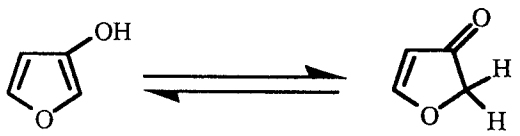
Scheme I. 14

(8) Ring-chain tautomerism (29a ⇌ 29b ⇌ 29c) (Scheme I. 15).



Scheme I. 15

Types 1 and 2 are the most important. An essential difference between them is that in type 1 both tautomers can be aromatic [e. g. , 2-pyridone (12a) and 2-hydroxypyridine (12b) both satisfy the criteria for aromaticity [12] and have large resonance energies], whereas, in type 2 at least one tautomer, that corresponding to 17a (Scheme I. 9), is nonaromatic [e. g. . 3–hydroxyfuran (30a) is aromatic, but 3-furanone (30b) is not] (Scheme I. 16).



30a 30b

Scheme I. 16

In general, tautomerism of type 1 is important for six-membered heterocycles containing at least one annular nitrogen atom, such as pyridines and azines, where type 2 is important for five membered heterocycles with one annular heteroatom, e. g. , pyrroles, furans, and thiophens. Tautomerism of both types 1 and 2 is important for five-membered rings containing two or more annular heteroatoms.

1. 2c The importance of Tautomerism in Chemistry

Reactivity and reaction mechanisms in heterocyclic chemistry can only be properly rationalised if the tautomeric structures of the compounds are known. [1, 12]

31a' 31a 31b 31b'

Scheme I. 17

In the amino form of 2-aminopyridine (31a), electrophiles should attack the ring nitrogen atom, whereas in the tautomeric iminoform (31b), electrophiles should attack exocyclic nitrogen (Scheme I. 17).

An example of the importance of these effects is shown in scheme I.18, where the reactivity of 2–amino pyridine is considered. [11]

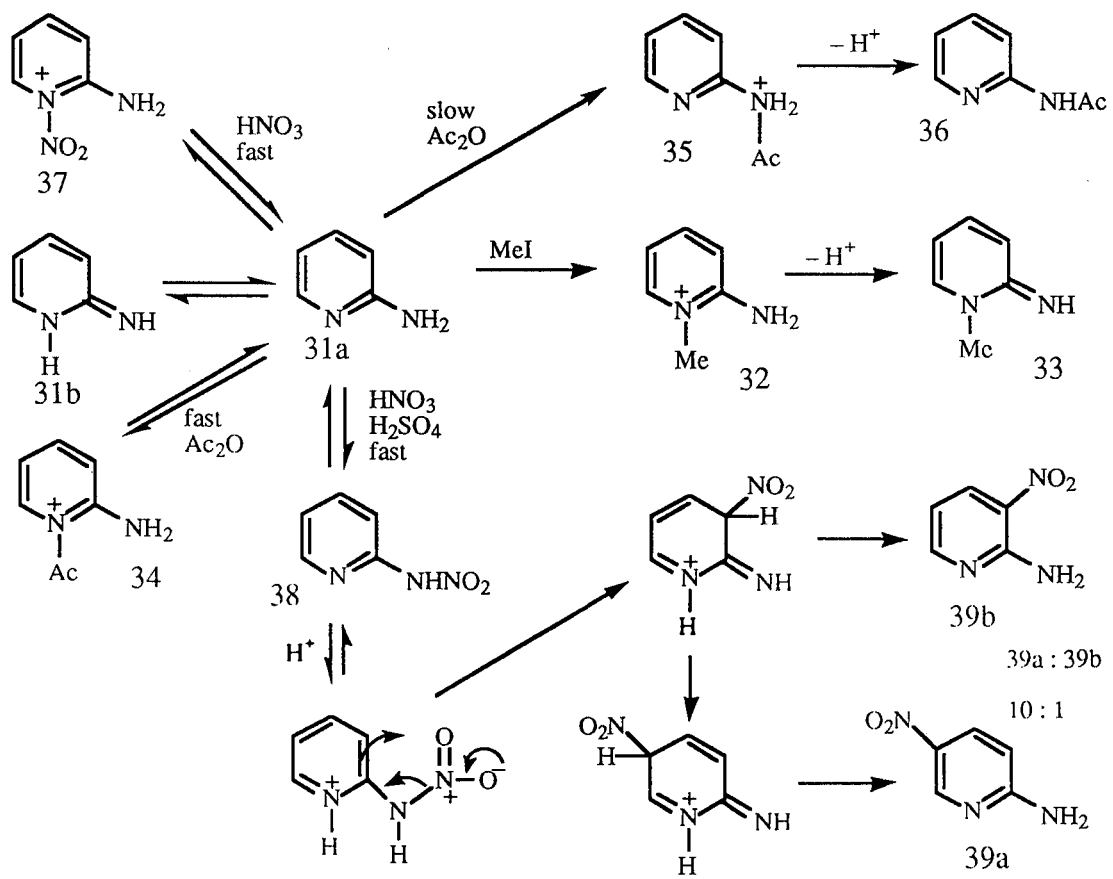
2–Amino pyridine exists predominantly in the amino form. On the reaction with electrophiles, it can yield products of reaction either at the cyclic nitrogen, the acyclic nitrogen, or a ring carbon atom. Thus, methyl iodide gives the product of the reaction of the cyclic nitrogen, whereas acetic anhydride yields the product of reaction at the exocyclic nitrogen, and yet again nitric acid mixed with sulphuric acid yields the 5–nitro compound. However, all these reagents first react at the cyclic nitrogen atom as would be expected from the mesomeric contribution of the zwitterionic structure to the 2–amino form (Scheme I. 18). In the case of methyl iodide, the reaction is irreversible and this determines the product. With acetic anhydride, the initial reaction is fast on the annular nitrogen atom but reversible, and a slower irreversible reaction takes place at the acyclic nitrogen atom. In the case of nitric acid (nitronium cation), reaction at both nitrogen atoms are reversible and, in time the least kinetically preferred, but thermodynamically most

stable 2–amino–5–nitropyridine (39a) and 2–amino–3–nitropyridine (39b) are formed *via* a rearrangement of the 2–nitroaminopyridine (38) (Scheme I. 18). [1b]

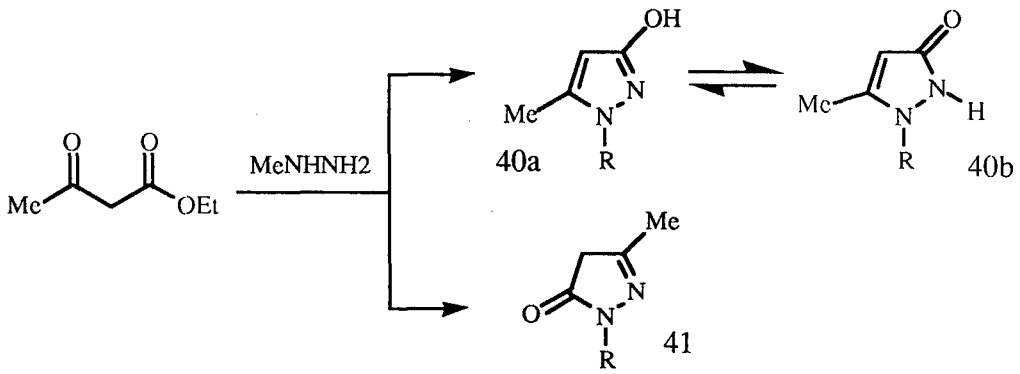
Clearly, any attempted rationalisation of the reactivity of 2–aminopyridine in terms of the imino form would be most misleading. An early example of the consequences of the neglecting tautomerism was the confusion between pyridinethiols and pyridinethiones. These were referred to as pyridinethiols "to follow Chemical Abstracts" and the acidity, alkylation and mechanism of oxidation of a nonexistent thiol groups were described. [1a]

There are numerous examples in the older literature where wrong conclusions have been drawn by correct reasoning on incorrect structures. Sometimes correct conclusions have even been drawn by incorrect reasoning on incorrect structures.

Reasoned prediction of the predominant tautomeric forms of alternative reaction products can sometimes be used to distinguish between two isomeric compounds. For example, the action of substituted hydrazines on ethyl acetoacetate can lead either to a pyrazol–3–one (40) or to a pyrazol–5–one (41) ; from the known tautomerism of these compounds, the presence of a carbonyl band in solution is a good indication of pyrazol–5–one (41) structure, and the lack of such a band points to a pyrazol–3–one (40) (Scheme I. 19).

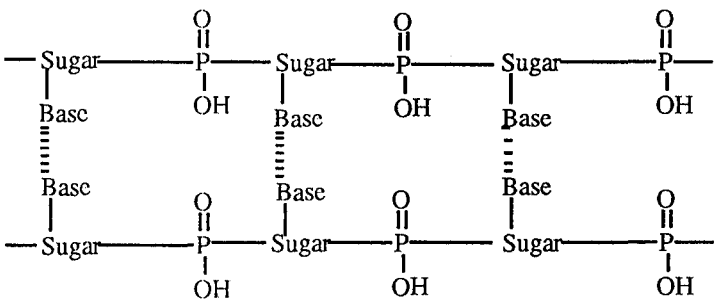


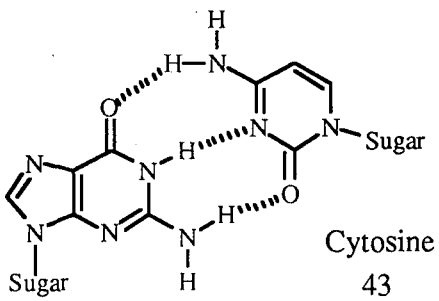
Scheme I. 18

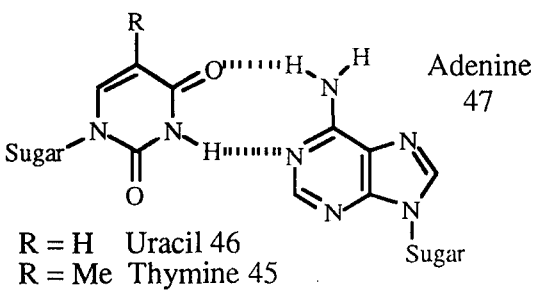


Scheme I. 19

A correct understanding of tautomeric equilibria has been also shown to be very important in the biochemistry of all living cells containing nucleic acids. [1, 12] Nucleic acids (42) consist of a long sugar-phosphate chain in which each sugar molecule carries a heterocyclic base. Two nucleic acid molecules are paired in a double helix, the heterocyclic bases of one molecule hydrogen bonding with those of the other. Cytosine (43) is always bonded with guanine (44), and thymine (45) or uracil (46) always forms hydrogen bonds with adenine (47), the tautomeric form the bases determining the type of hydrogen bonding (Scheme I. 20)



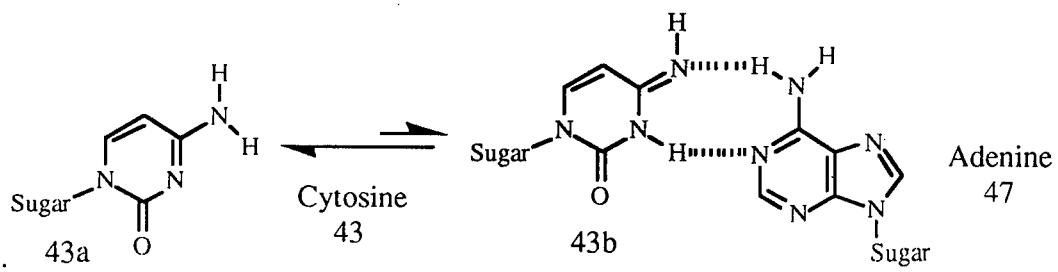




Scheme I. 20

Moreover, tautomerism is of the highest biological importance because it usually determines the frequency of mutations. [1] In its minor tautomeric form, uracil can act as a mimic for cytosine (43) in the base pairing and, conversely, cytosine in its imino-form

(43b) can act as a mimic for uracil and pairs with adenine (47) thereby leading to a mutation (Scheme I.21)

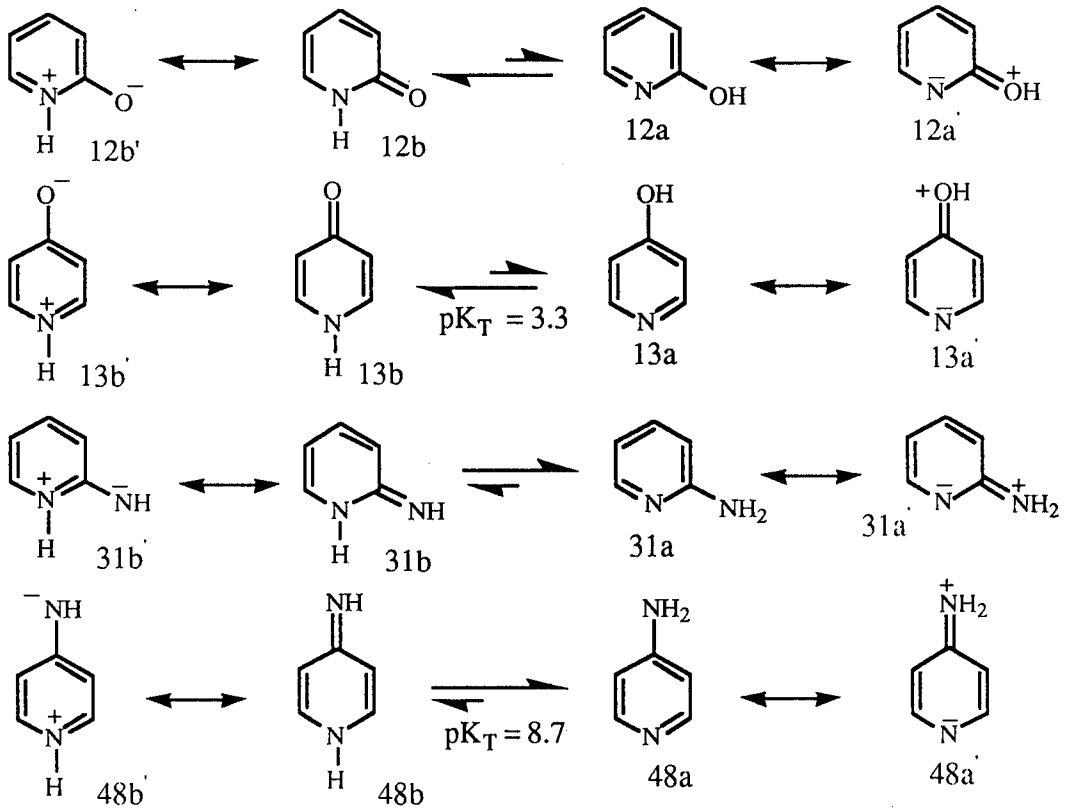


Scheme I. 21

1. 2d Tautomerism of " Hydroxypyridine " and " Aminopyridine"

Pyridine with potentially tautomeric hydroxyl groups α/or γ to the nitrogen atom (12 and 13) exist mainly as the pyridones (12b) and (13b) (Scheme I. 5, Scheme I. 22), whereas analogous aminopyridines (31) and (48) exist mainly as such in the amino forms (31a) and (48a), and not in the imino forms (31b) and (48b), The individual tautomeric forms are stabilised by contribution from charge separated forms, as shown by structure (12a'), (12b'), (13a'), and (13b') for the hydroxy pyridine–pyridone system, and by (31a'), (31b'), (48a'), and (48b') for the aminopyridine-imino pyridine system.

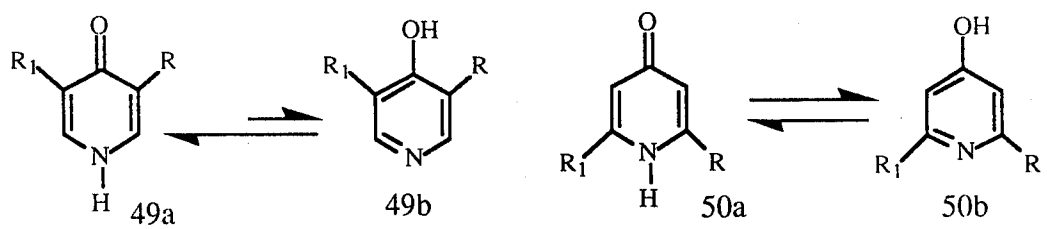
In the case of 48a $\rightleftharpoons$ 48b system, there is ca 50 kJ mol^{-1} difference between the aromatic stabilisation energy of (48a) and (48b), which is responsible for the predominance of amino form (48a). [13, 14]



Scheme I. 22

The contribution from the charge separated forms (31a'), (31b'), (48a'), and (48b') are of moderate importance. However, in the tautomerism between 4–hydroxypyridine (13a) and 4–pyridone (13b), the charge separated forms (13a') in which positive charge resides on the oxygen atom and negative charge is on the nitrogen is of much less importance than the charge separated form (13b'). For this reason, the position of equilibrium (13a $\rightleftharpoons$ 13b) favours the 4–pyridone (13b).

The introduction of substituents, depending on both their nature and position, can either drastically affect the position of tautomeric equilibria, or have little influence. Thus, the effect of chlorine substitution on the tautomerism of 4–hydroxypyridines (49) and (50) is shown in the scheme I. 23. [1] Clearly, substitution of chlorine in the 3- or in both the 3– and 5–position have little effect, but for substitution at the 2– and 6–position, one chlorine makes the two forms almost of equal energy whereas double substitution causes the hydroxypyridine form to be strongly favoured.

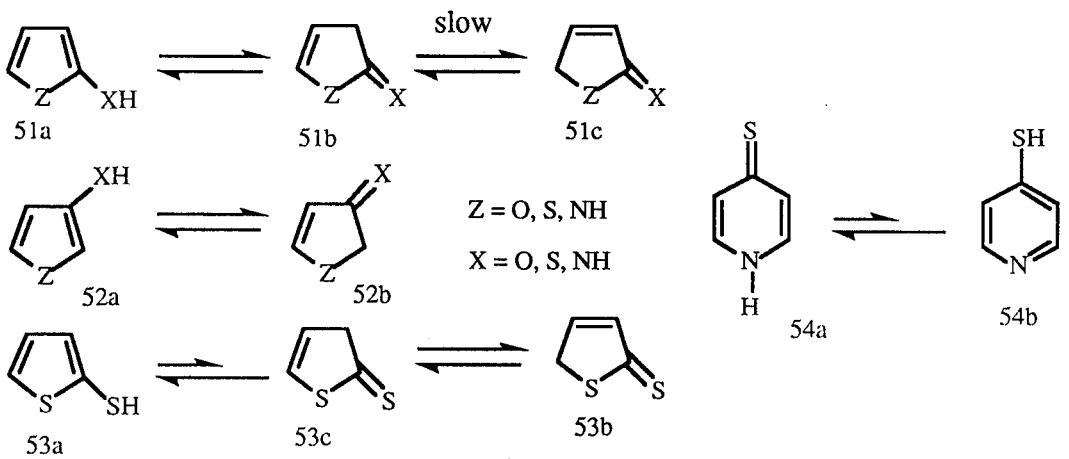


Scheme I. 23

For (49a) ⇌ (49b) system, if R = R_1 = H, or Cl 4-pyridone(49a) form is always favoured by a factor of ca 10^3, as the chlorine atoms have little influence on the acidities of the annular NH group. In contrast, for (50a) ⇌ (50b), if R = R^1 = H the oxo-form (50a) is favoured by a factor of ca 10^8, R = Cl, R_1 = H the ratio (50a) : (50b) is ca 1:1, and, when R = R_1 = Cl the enol form(50b) is favoured by a factor of ca 10^8. The α-chlorine atoms increase the acidity of the annular NH of 50a thereby shifting the equilibrium towards the hydroxy form.

1. 2e Tautomerism of Five-Membered Rings

The tautomeric possibilities for five-membered rings with one heteroatom as shown in scheme I. 24, are different from those found for the pyridines as only one of tautomers is aromatic. [1]



Scheme I. 24

Then, in these compounds, for X = O, non-aromatic forms (51b), (51c), and (52b) are usually preferred. For X = S or NH, the aromatic forms (51a) and (52a) are favoured, but usually only very slightly. Also, tautomerism between two non-aromatic forms is always slow and individual tautomers can be isolated. It is of interest that the mercapto compound (53) in these five-membered rings, in which thiol (53a) dominates in aqueous solution, resembles the N–analogs, rather than the O–analogs as is found with the six-membered ring compounds (54) in which the thione form (54a) exists predominantly in aqueous solution.

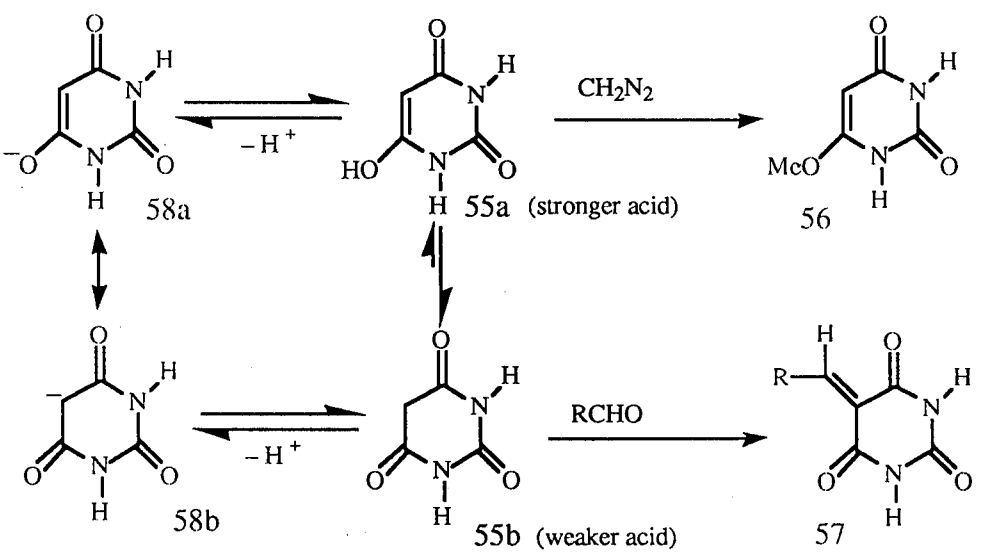
2. 0 Methods of Investigation of Heteroaromatic Tautomerism

2. 1 Chemical Methods

Tautomerism can be studied by various chemical and physical techniques. In principle, it is possible to obtain significant results from chemical evidence, but in practice this is very difficult, and physical methods are much more useful. It should be emphasised that there have been many incorrect conclusions drawn from chemical evidence.

The chemical methods can be subdivided into two interrelated groups : (a) those which depend on the reactivity of a particular structural feature, e. g. , a carbon-carbon double bond or an enolic hydroxyl group, that is present in only one of the tautomeric forms ; those which involve relating the structures of reaction products to the structures of the starting material. Methods of the first type have been used for both qualitative and quantitative investigation. An important limitation is that the rates of interconversion of the tautomeric forms must be small as compared with those of the test reaction(s). The method is further complicated since the test reactions are sometimes complex and it is difficult to be certain that only one tautomer is reacting.

For example, one set of authors [1a] argued for the hydroxyl structure (55a) for barbituric acid on the basis that it was a strong acid and it gave the methoxy derivative with diazomethane. Another set of authors [1a] argued that the trioxo form (55b) was correcton the basis of the condensation reaction of barbituric acid with aldehydes. All of this reasoning is completely incorrect. The correct relationship between acidity and tautomerism is shown in scheme I. 25. [1a]



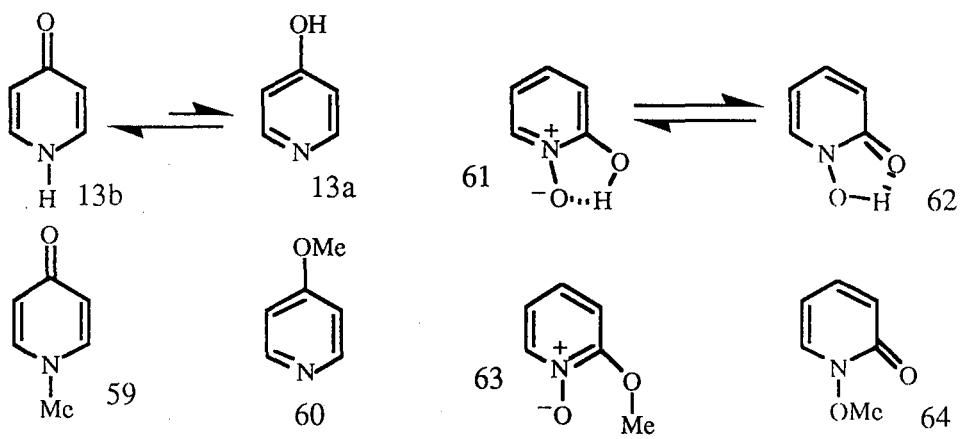
Scheme I. 25

If a pair of tautomers is in equilibrium with the same mesomeric anion, then the weaker acid of the two tautomers will always predominate, and indeed the tautomeric equilibrium constants will be equal to the quotient of the two dissociation constants. It is

well-known that diazomethane reacts with active hydrogen compounds by proton abstraction to give the the methyldiazonium cation which then reacts with the anion. Similarly, the reaction with aldehydes is an aldol condensation which also goes through the anion. In each case, the anion is a mesomeric anion ((58) derived from both the OH and the CH forms, and the explanation for its reactivity with the methyldiazonium cation and in the aldol reaction can be rationalised by the " soft–hard " reagent rule.

2. 2 Physical Methods [1, 11, 12]

Physical methods used to determine tautomeric equilibria can be divided into two groups : spectroscopic and non-spectroscopic methods. Application of the methods to an analysis of tautomeric equilibria can be divided into two main types : those that utilise " fixed derivatives " (59) and (60) and those that do not. The concept of " fixed derivatives " is shown in scheme I. 26 [1a] The methyl or other alkyl derivatives are non-tautomeric compounds of fixed structure and they act as models for the individual tautomers (13a) and (13b), When using fixed derivatives, the properties of the tautomeric compounds (13) are compared with the properties of the two model compounds (59) and (60), (or more, if necessary). Caution must be applied to the procedures involving the fixed structure model compounds, however, as even the replacement of the mobile proton by a methyl group can significantly change the characteristics of the system, as. For example, by the removal of the hydrogen bonding interactions or the introduction of a steric effect. Such is the case in the two O–methyl derivatives (63) and (64), corresponding to the tautomeric system (61 ⇌ 62) (Scheme I. 26).



Scheme I. 26

Non-spectroscopic methods include dipole moment and basicity measurements, and X–ray diffraction. Spectroscopic methods include nuclear magnetic spectroscopy, electronic spectroscopy, infrared and Raman spectroscopy, ultraviolet-visible spectroscopy, X–ray photoelectron spectroscopy (ESCA), mass spectroscopy, and ion cyclotron resonance spectroscopy. [1a] All of the available methods have advantages and

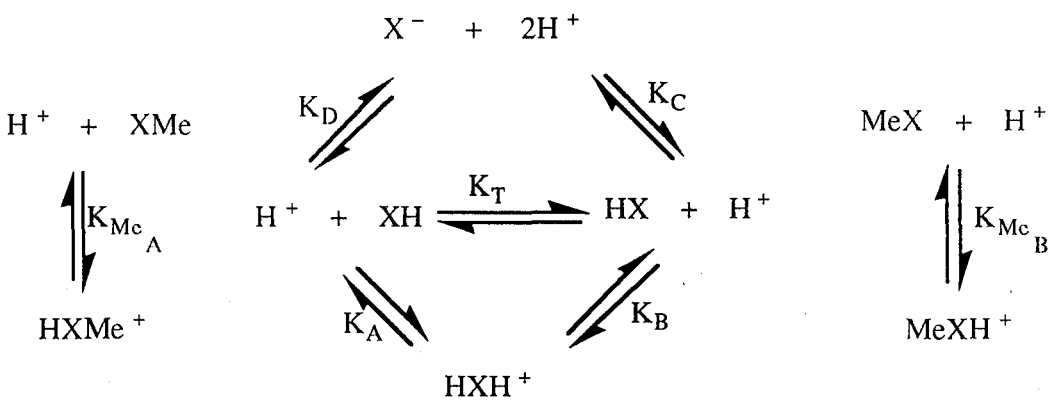
disadvantages. Some of the methods give rise to quantitative data relating to the equilibrium constants, whilst others provide only qualitative information.

Table I. 5 Physical Methods [11]

Methods	Model compound needed		
Qualitative (A)		**Quantitative (B)**	**Phase**
Non-spectroscopic			
Basicity measurement	yes	B	solution
Dipole moment	yes	B	solution
Hammett equation	yes	B	solution
X–ray diffraction	no	–	solid
Polarography		–	solution
Spectroscopic method			
NMR spectroscopy	yes	A	solution
Infrared and Raman spectroscopy	yes	A	solid, liquid, vapour
UV and Visible spectroscopy	yes	A, B	solution, vapour
Mass spectroscopy	no	A	vapour
Equilibrium constant (theoretical)	no	B	

2. 2a Basicity Measurements

The determination of pKa values is the most generally useful method for the investigation of tautomerism. This method was first employed for a study of potentially tautomeric heterocyclic compounds by Tucker and Irvin [15] and also by Angyal and Angyal [16] and the procedure has been described in detail by Albert. [17]



Scheme I. 27

There are two empirical dissociation constants K_1 and K_2 for the conjugate acid (HXH^+) of a tautomeric compound. Constants K_1 and K_2 are, in effect, a summation of

the true dissociation constants K_A, K_B, K_C, and K_D of the individual tautomeric forms and the tautomeric constant, K_T; these constants are related by the following equations

$$K_1 = K_A + K_B \quad (2.1)$$

$$\frac{1}{K_2} = \frac{1}{K_C} + \frac{1}{K_D} \quad (2.2)$$

$$K_T = \frac{K_A}{K_B} = \frac{K_C}{K_D} = \frac{[XH]}{[HX]} = \frac{K_1}{K_B} - 1 = \frac{K_A}{K_1 - K_A} \quad (2.3)$$

As K_A and K_B can not be measured experimentally for the tautomeric system. It is assumed that replacement of a tautomerizable hydrogen by an alkyl group usually methyl has no effect, or only a very small effect, on the ionisation constant ; we define a proportionality constant f between equilibrium constants for the individual tautomers and those of the corresponding methyl derivative,

$$K_A = f_A \cdot K_{MeA} \quad (2.4)$$

$$K_B = f_B \cdot K_{MeB} \quad (2.5)$$

$$K_T = \left(\frac{f_A}{f_B}\right) \frac{K_{MeA}}{K_{MeB}} \quad (2.6)$$

As f_A and f_B are unknown, Eq. (2. 6) can not be used as such, and it is necessary to make one of two alternative simplifying assumption :

i. First assumption : $f_A = f_B = 1$ and equations (2. 4 – 2. 6) can then be written as,

$$K_T = \frac{K_{MeA}}{K_{MeB}} \quad (2.7)$$

$$K_A = K_{MeA}$$

$$K_B = K_{MeB} \quad (2.8)$$

$$K_1 = K_{MeA} + K_{MeB}$$

$$K_T = \frac{K_1}{K_{MeB}} - 1 \quad (2.9)$$

$$K_T = \frac{K_{MeA}}{K_1 - K_{MeA}} \quad (2.10)$$

if it is assumed that, $f_A = f_B = f$, in this case K_T is given by eq. (2. 11)

$$K_T = \frac{K_{MeA}}{K_{MeB}} \quad (2.11)$$

$$f = \frac{K_1}{K_{Me_A} + K_{Me_B}} \qquad (2.\ 12)$$

Using the equation (2. 12), it is possible to test the validity of the first assumption. However, frequently only one fixed structure model compound is employed for the calculation of K_T using equation (2. 10) and if f_A and f_B are not equal, both assumptions are invalid. In practice, it has been shown that value of K_1 is never equal to the sum of the K_{Me_A} and K_{Me_B} , and determination of K_T values using equation (2. 10) can give meaningless results, such as $K_T < 0$ and $K_1 < K_{Me_A}$.

Application of above method to the structural analysis of compounds having more than two tautomeric forms where more than one monocationic structure can be formed from each of the tautomeric forms is more complicated. However, measurement of the second protonation constant of parent tautomers, where a common dication is formed from the two monocations may provide a possible solution to the problem. There are, however, considerable difficulties in the measurement and interpretation of pKa values at very high acidities required for diprotonation.

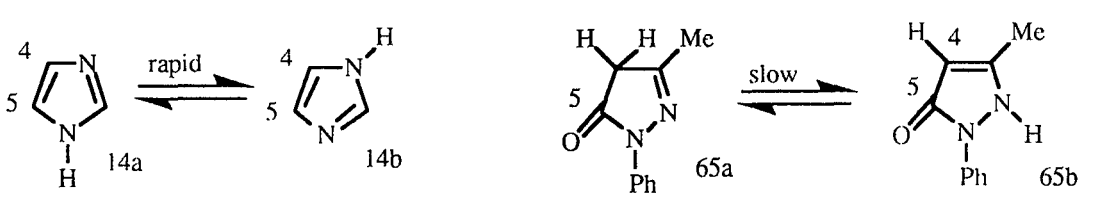
Spinner and Yeoh [18] consider that both equation (2. 3) and (2. 10) give K_T values which are distorted because the base-weakening effect of O–methylation is greater than of N–methylation. They proposed that equation (2. 13) provides a better estimate of the equilibrium constant.

$$\log\left(1 + \frac{1}{K_T}\right) = pK_{OMe} - pK_1 + C \qquad (2.\ 13)$$

Finally, it should be emphasised that despite all the imperfection of the method basicity measurements provide one of the most accurate methods for quantitative study of tautomerism.

2. 2b Nuclear Magnetic Resonance Spectroscopy

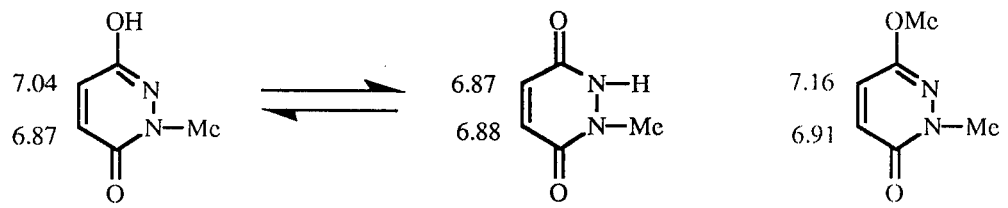
The use of NMR spectroscopy is of particular importance, but can also be misleading if incautiously used. [19] Individual tautomers can only be observed by NMR spectroscopy when the rate of interconversion is slow on the NMR time scale. As an approximate generalisation, it can be stated that, in solution, equilibria not involving C–H bond cleavage (i. e. , where the proton moves between oxygen, nitrogen or sulphur atoms) are fast on the NMR time scale at room temperature, whereas those equilibria which involve a proton moving to or from a carbon atom are normally slow (Scheme I. 28).



Scheme I. 28

In 14a $\rightleftharpoons$ 14b the CH atoms at the 4– and 5– positions show singlet in ^{1}H-NMR and ^{13}C-NMR in solution, even at low temperature, whereas for 65a $\rightleftharpoons$ 65b there are distinct ^{1}H-NMR and ^{13}C-NMR signals for the 4–position $\underline{CH}_2$ and $\underline{CH}$ groups in the two isomers.

The work of Diehl, [20, 21] as extended by Smith, [21] on the effect of substituents on aromatic systems, shows that replacement of methoxyl by hydroxyl shifts an *ortho*–proton 0.011± 0.04 ppm and a *meta*-proton 0.07± 0.04 ppm to higher field. Hence, the aromatic protons for structure (66a) are predicted to occur at δ 7.05 and 6.84 in excellent agreement with experiment values δ 7.04 and 6.87 respectively. The predicted values δ 6.88 and 6.87 for the alternative form (66b) are not in agreement. Thus, the shift in *ortho*-proton and a *meta*-proton signal by the replacement of methoxyl by hydroxyl allows us to distinguish the potentially tautomeric structure forms, such as 66a $\rightleftharpoons$ 66b.



66a 66b 67

Scheme I. 29

2. 2c Ultraviolet and Visible Spectroscopy

Electronic spectroscopy is one of the most widely used methods to study tautomeric equilibria. Comparison of the ultraviolet spectrum of a potentially tautomeric compound with the spectra of both alkylated forms indicates which tautomer predominates. This method is not applicable if the spectra of the potentially tautomeric compound and both alkylated derivatives are very similar. A further limitation is that often only qualitative conclusions can be drawn because no contribution from the spectrum of the minor constituent can be found in the spectrum of the tautomeric compound.

The tautomeric equilibrium constant K_T determination can be determined using equation (2. 15) and taking as the property P the extinction coefficient ε or the absorbance A. To apply this equation,certain conditions must be fulfilled : Beer's law must be valid for the tautomers as well as for the model compounds and the spectra arising from different tautomers must be sufficiently different to avoid a large error in the intensity measurements from overlapping.

Most ultraviolet studies are carried out in solution, but it is possible to measure UV spectra in the vapour phase or in the solid state. [11] The great sensitivity of the method allows measurements to be carried out with dilute solution, which is useful for sparingly soluble compounds.

2. 2d Infrared Spectroscopy

2. 2d Infrared Spectroscopy

Infrared spectroscopy is the only technique which enables a study of the sample in all its physical states : vapour phase, solution, liquid, solid. The vibrational frequencies of some functional groups are frequently very distinctive. Certain absorption bands, for example, those arising from the C–H, OH, C=O, N-H, OR remain within fairly narrow range of frequency but, due to their interaction with other vibrational modes, the exact position of the absorption band can provide important structural information.

It is sometimes difficult or even impossible to determine by IR spectroscopy the tautomeric structure of certain strongly hydrogen-bonded compounds: pyrazol–5-one is a typical case. [11] Also, if the compound crystallizes in two forms, it is difficult to determine by IR spectroscopy whether two tautomers are concerned or a single form exhibiting polymorphism.

Infrared spectroscopy does not deal with single crystals, as is the case is X–ray diffraction, so the technique detects mixtures of tautomers in the solid state.

Most tautomerism studies by infrared spectroscopy are qualitative or at most semiquantitative. However, the measurement of band intensities, either as extinction coefficients ε_A, or as integrated areas A, allows determination of the tautomeric equilibrium constant by applying equation (2. 14)

$$K_T = \frac{\varepsilon_X - \varepsilon_{MeB}}{\varepsilon_{MeA} - \varepsilon_X} \qquad (2.\ 14)$$

2. 2e Mass Spectroscopy

The idea of studying tautomerism in the vapour phase by mass spectrometry is a relatively recent technique. A major disadvantage arises in distinguishing between prototropic equilibria occurring before and after ionisation. If prototropy occurs after ionisation, there will be no simple quantitative relation between the tautomer existing in the vapour phase and the molecule ion involved in the fragmentation process.

Two methods are available to investigate the tautomerism by using mass spectroscopy.

(1) The determination of the ratio of the intensities of daughter ions associated with the fragmentation of the two tautomeric forms as a function of temperature,

(2) a comparison of ion fragmentation of the potentially tautomeric compound with fixed structure derivatives.

3. 0 References

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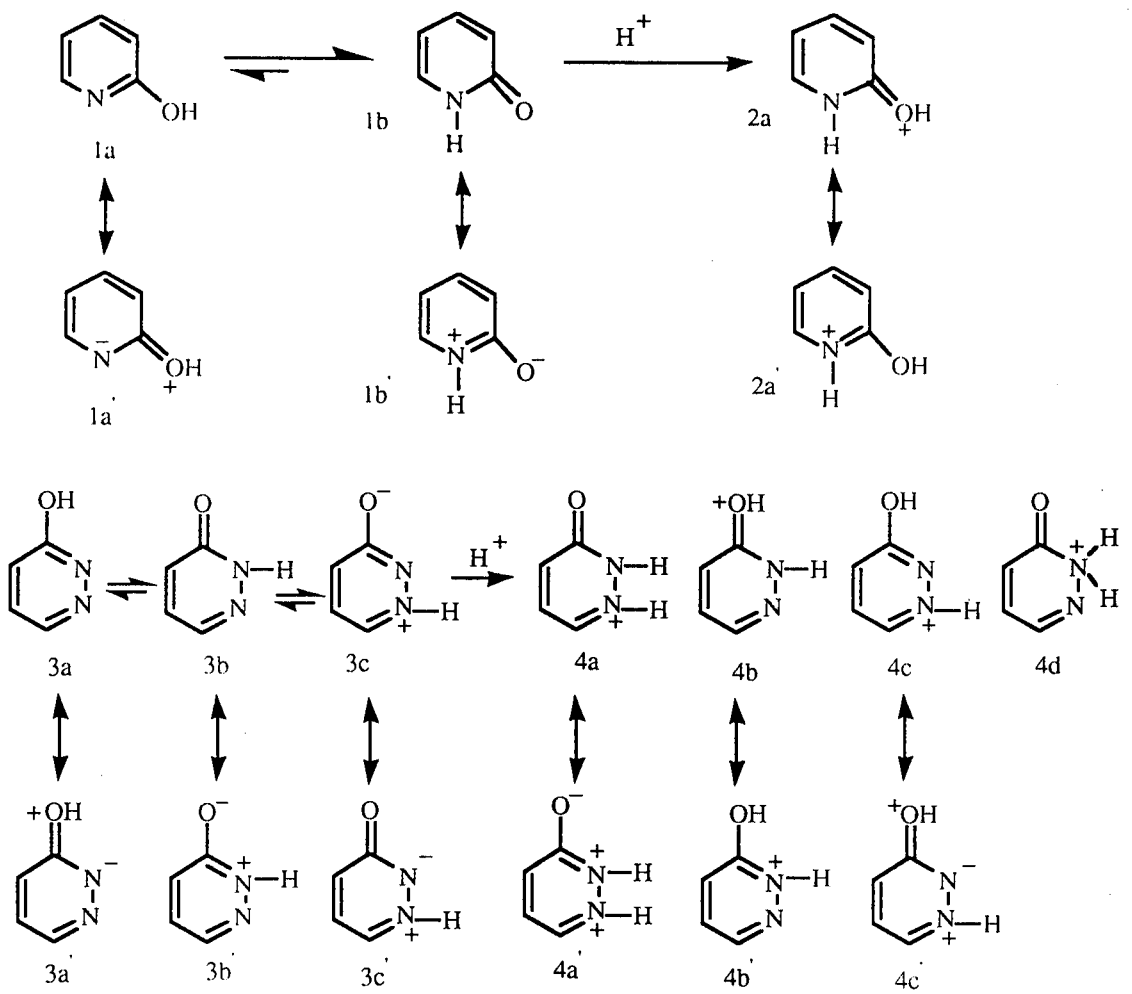
Chapter II

Tautomerism of 3, 4–Dihydro–4–oxo–5*H*–pyridazino(4, 5– *b*)indoles

1. O Tautomerism of Pyridazinones and Fused Pyridazinones

1. 1 Introduction

Simple heterocyclic systems bearing one potentially tautomeric substituent as, for example, the pyridone-hydroxypyridine system (1) were discussed in section I. 1. 1d. In this chapter and the subsequent two chapters we are concerned with a diazine system bearing one or two potentially tautomeric substituents, in particular, the pyridazinones –hydroxypyridazine (3). [1]



Scheme II. 1

Compared with the pyridone-hydroxypyridine system (1a ⇌ 1b), the presence of more than one heteroatom in the ring and of more than one potentially tautomeric substituent increases the number of possible tautomeric structures (Scheme II. 1). One important feature of the potentially tautomeric hydroxypyridines (1) and pyridazines (3) is the possibility of resonance stabilisation of the tautomeric system by zwitterionic structures (1a, 1b, 3a, 3b' and 3c'). However, although in the case of (1b ⇌ 1b') and

(3b ⇌ 3b'), the zwitterionic canonical structures are the thermodynamically more stable canonical forms, this is not so with (1a ⇌ 1a') and (3a ⇌ 3a'), where the charged canonical forms are of much less importance as the positive charge resides on the more electronegative oxygen atom.

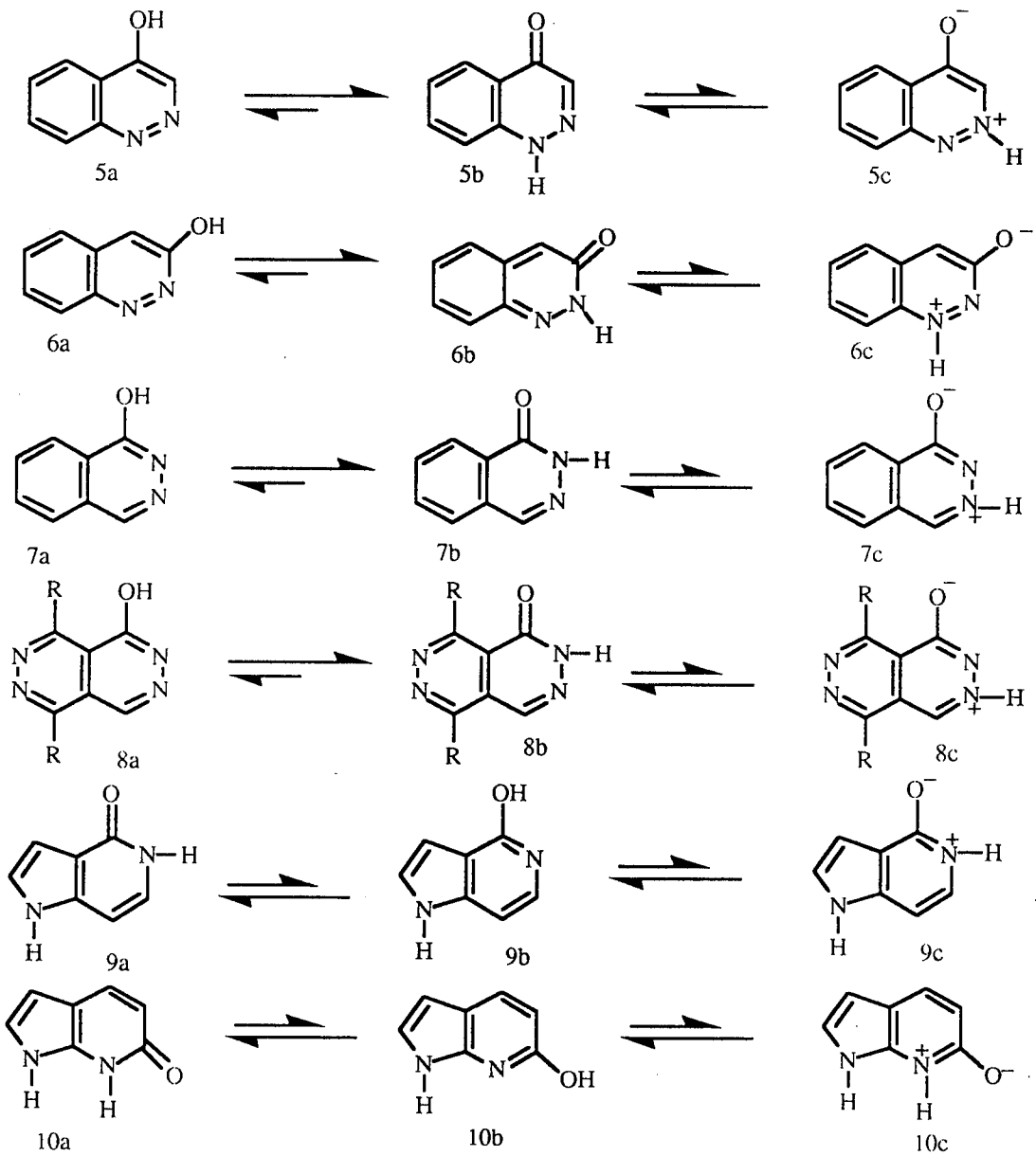
It is well-known that the protonation of 2–pyridone (1) occurs on the oxygen atom [2] such that the aromatic character of the system is preserved (2a ⇌ 2a'). However, for the corresponding pyridazine derivatives (3) there are four possible sites of protonation to give the cations (4a), (4b), (4c), and (4d). Structure (4c) may be eliminated on the grounds of the loss of aromatic character of the system compared with the free base. In the case of the protonated system (4a ⇌ 4a') the positive charges reside on adjacent nitrogen atoms and would not be expected to stabilise the system.

On the basis of ultraviolet spectral data it has been proposed [3] that protonation of pyridazinones occurs on the exocyclic oxygen atom (4b) in a manner analogous to that of the protonation of 2–pyridone (1) to give the cation (4b).

A knowledge of the site of protonation of the potentially tautomeric system and of the model fixed structure system is obviously important in the measurement of the tautomeric equilibrium constant. However, Barlin [4] has reported that 3–hydroxy pyridazine (3) behaves abnormally and appears to have two overlapping pKa values suggesting simultaneous protonation of two different sites. Such behaviour has also been reported [5] to exist with any kind of conjugated system for which there are two protonation sites.

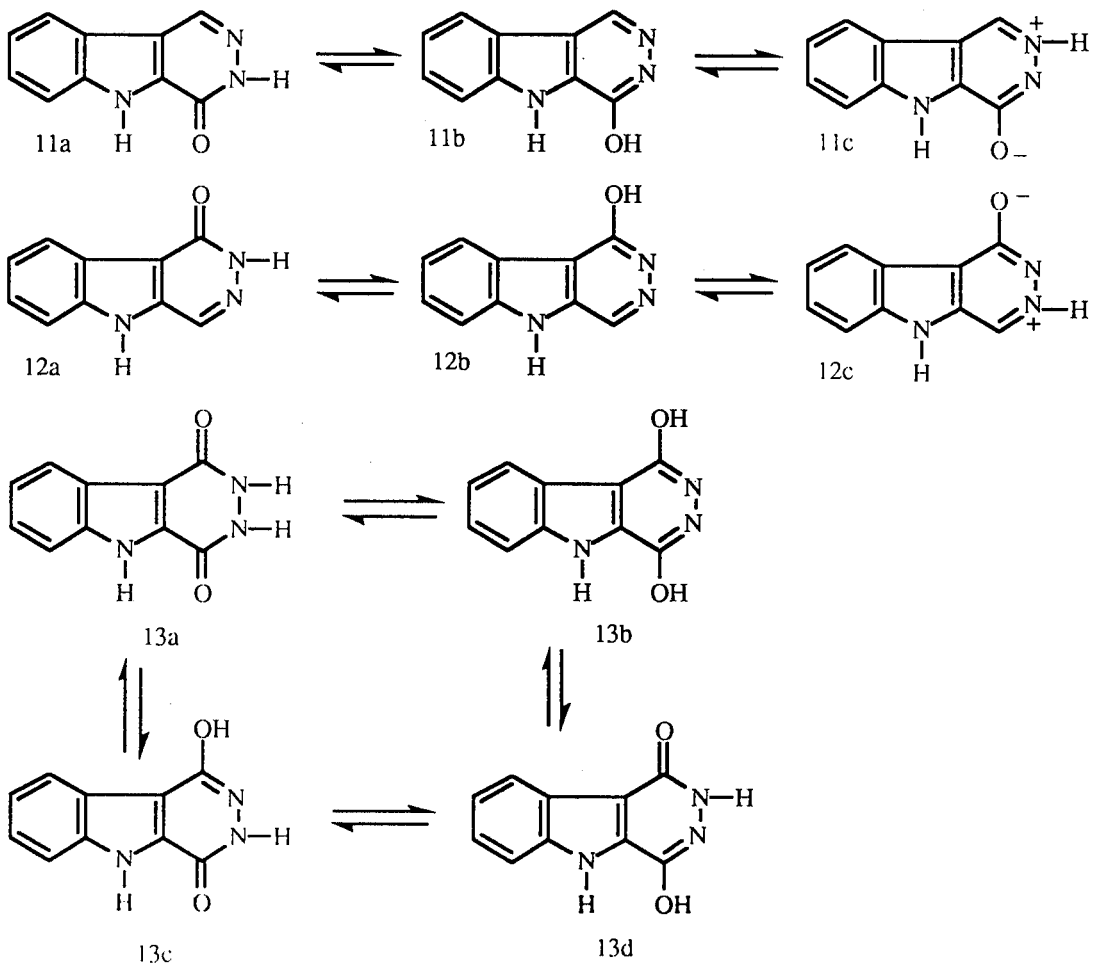
The tautomerism of the benzo and the other fused derivatives of the monohydroxy pyridazines follows the same pattern as the mono cyclic system. Thus, 4–oxocinnoline (5b) and 3–oxocinnoline (6b) exist as such and not the hydroxy cinnolines (5a) and (6a) or betaine structures (5c) and (6c). Similarly, phthalazine–1(2*H*)–one (7b) [6] is the preferred structures of the tautomeric system (7).

Heteroaromatic bicyclic systems with a heteroatom in both rings also exhibit similar tautomeric equilibrium positions with the oxo-form predominating, e. g. . (8b) [7] (9a), [8] and (10a) [8] (Scheme II. 2).



Scheme II. 2

In this study, we have chosen to establish the preferred tautomeric forms of the so-called 3, 4–dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indole (11), of the 1, 2–dihydro –1–oxo–5*H*–pyridazino[4, 5–*b*]indole (12), and of 1, 4–dioxo–1, 2, 3, 4–tetrahydro –5*H*–pyridazino[4, 5–*b*] indole (13). Tautomerism of 4–oxo system is described in this chapter and the 1–oxo and 1, 4–dioxo systems will be discussed in chapter III and chapter IV, respectively.



Scheme II. 3

2. 0 Pyridazinoindoles. – Synthesis

2. 1 Introduction

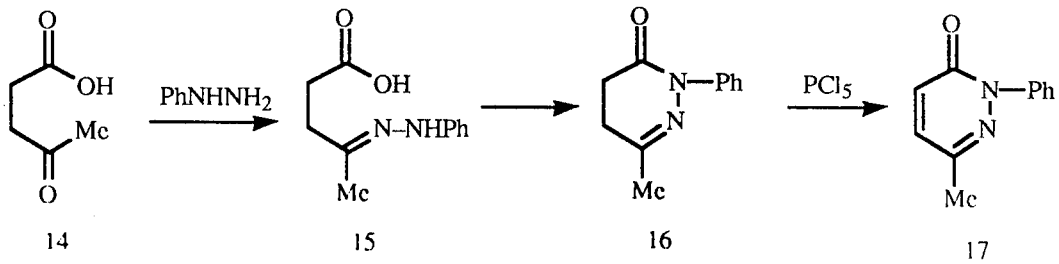
The methods for the preparation of pyridazines and pyridazinones can be grouped into three main categories [9]:

(a) ring closure of acyclic compounds,

(b) alteration of other heterocyclic ring systems, and

(c) substitution and displacement on pyridazine and its derivatives.

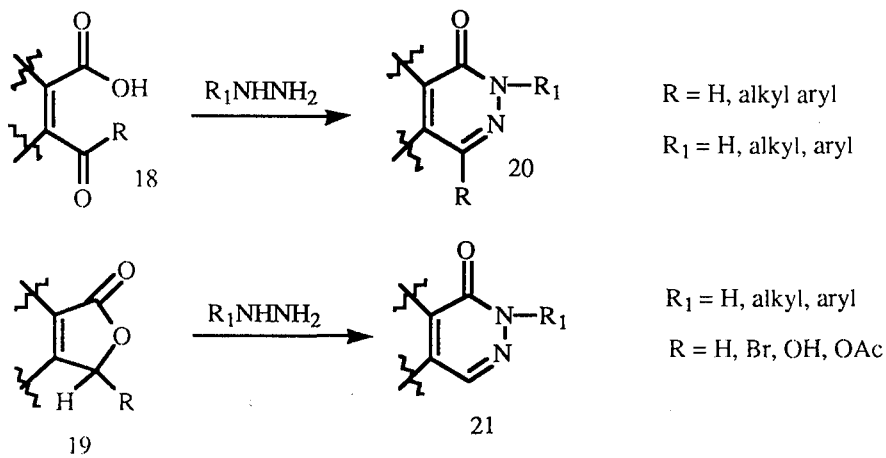
Method (a) generally involves the condensation of hydrazine or its derivatives with carbonyl compounds (carboxylic acids or esters, and their derivatives such as anhydrides and ketones). For example, the first reported pyridazinone [9] was prepared by the cyclisation of levulinic acid (14) with phenylhydrazine followed by oxidation to 3–methyl –6(1*H*)pyridazinone (17) (Scheme II. 4).



14 15 16 17

Scheme II. 4

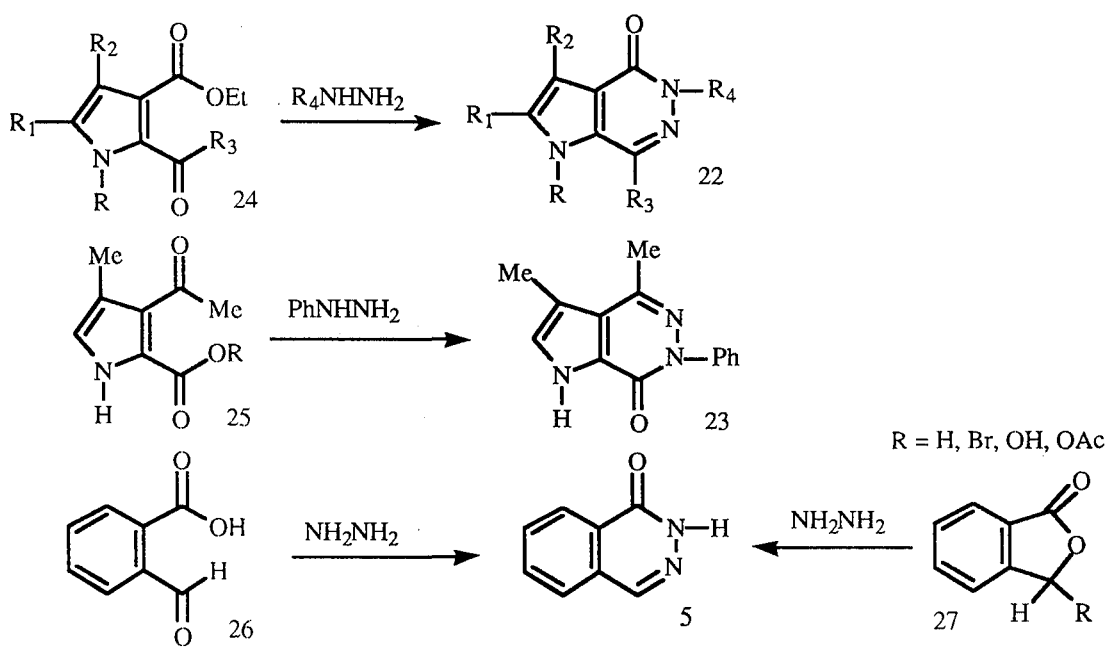
Fused pyridazine–1–ones [10] have been also been prepared generally by cyclisation of aldehydic or keto-acids (18) or their lactone isomers (19) with hydrazine and its derivatives.



18 19 20 21

Scheme II. 5

For example, pyrrolo[2, 3–*d*]pyridazine–4–one (22) and –7–one (23), and 1–(2*H*)–phthalazinone (5) have been synthesised by method (a) (Scheme II. 6). [10]

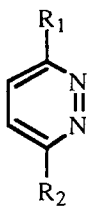


24 22 25 23 26 5 27

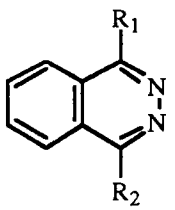
Scheme II. 6

2. 2 Synthesis of Pyridazinoindoles

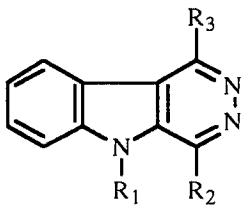
Pyridazinoindoles (30–33) formed from the fusion of the π–excessive indole ring and the π–deficient pyridazine ring, are of interest not only for their fundamental chemistry but also because of their structural relationship to the biologically important pyridazine (28) its derivatives, phthalazine (29) and its derivatives.



28

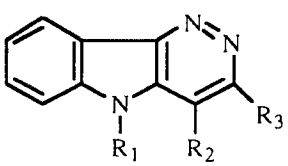


29



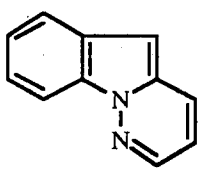
pyridazino[4, 5–*b*]indole

30



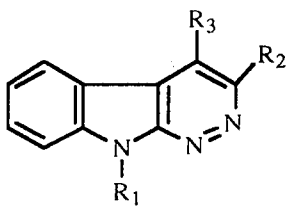
pyridazino[4, 3–*b*]indole

31



pyridazino[2, 3–*a*]indole

32



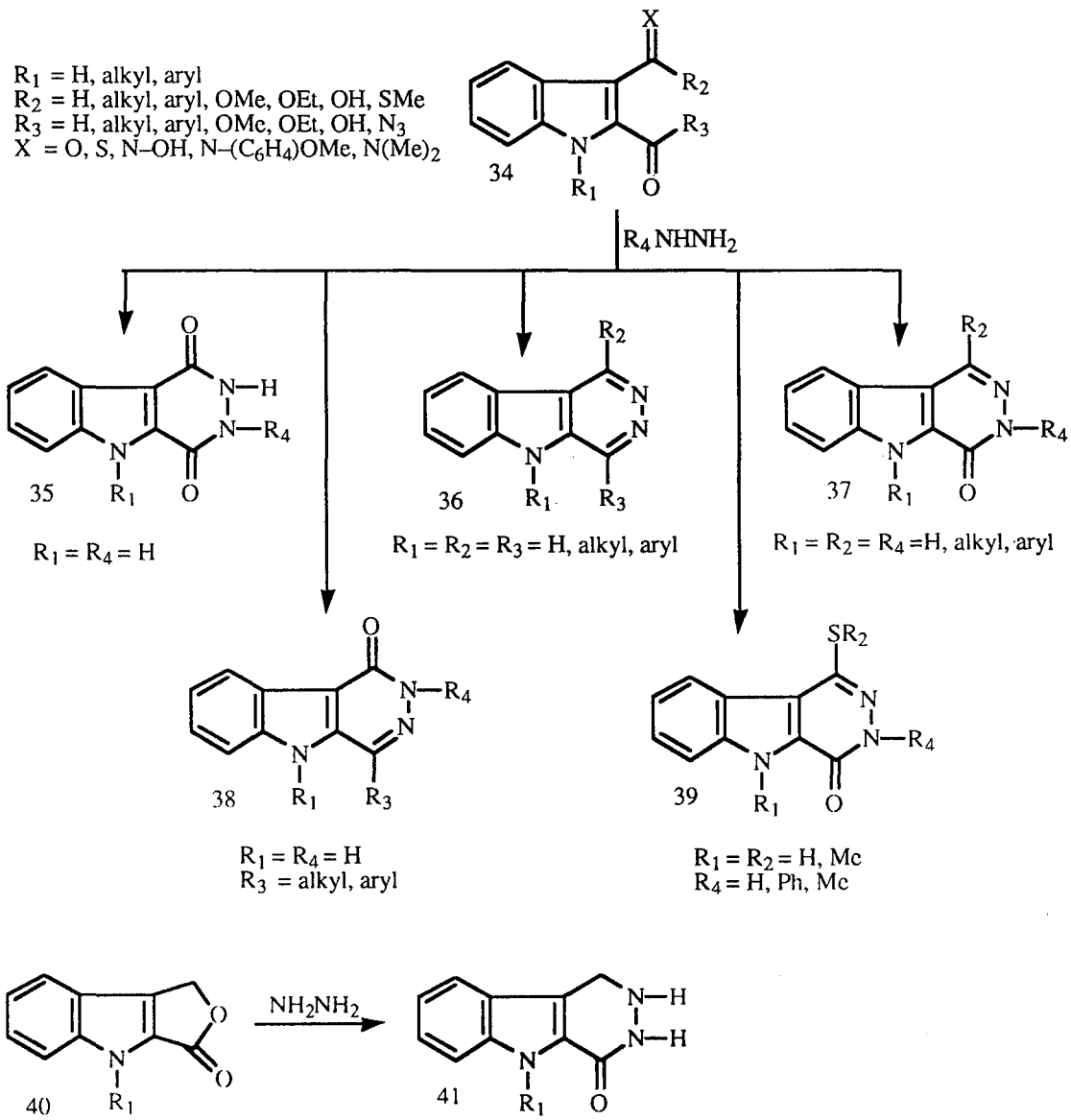
pyridazino[3, 4–*b*]indole

33

Scheme II. 7

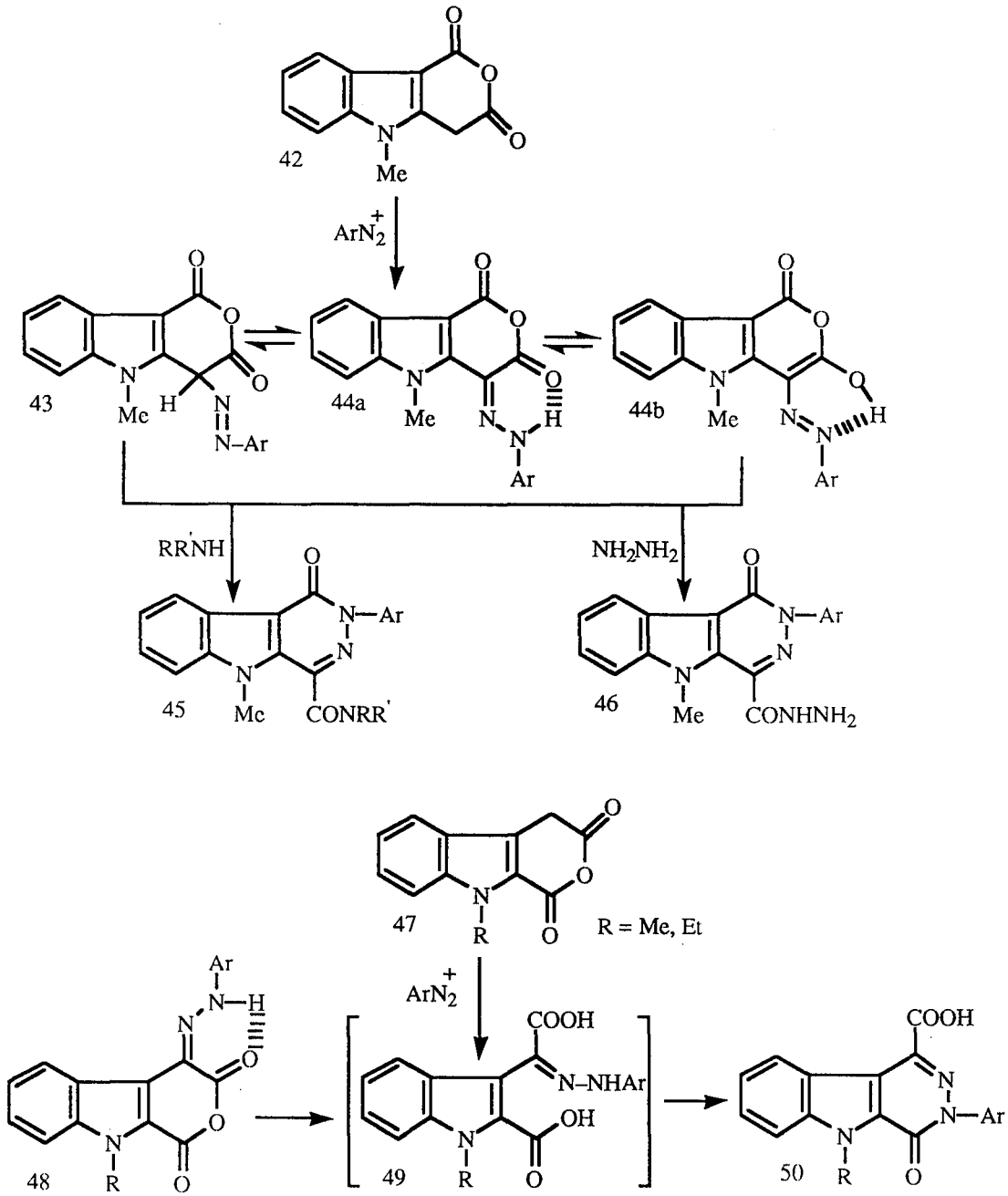
Several methods are available for the preparation of pyridazino[4, 5–*b*]indoles :

(a) Condensation of suitable indole derivatives with hydrazine and its derivatives [12–37] (Scheme II. 8).



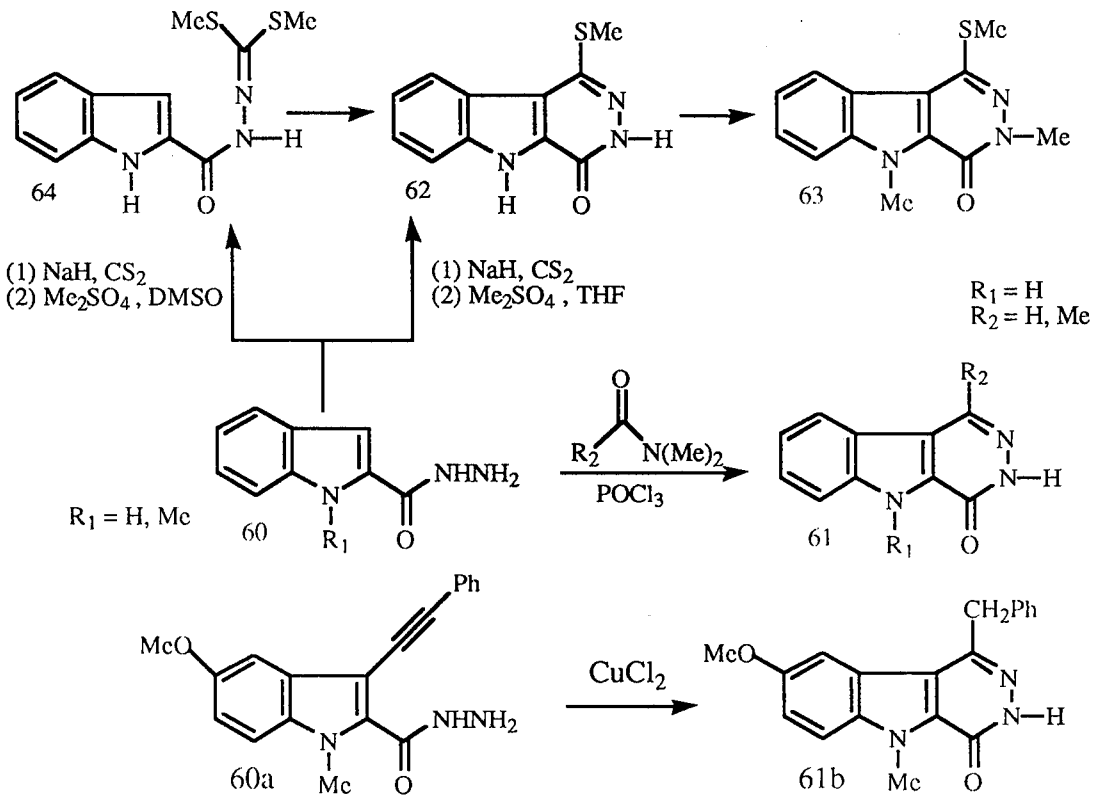
Scheme II. 8

(b) From 1–allylindole–2– or–3–carboxy–2– or– 3–acetic acid anhydrides (42) and (47) with diazonium salts [38] (Scheme II. 9).



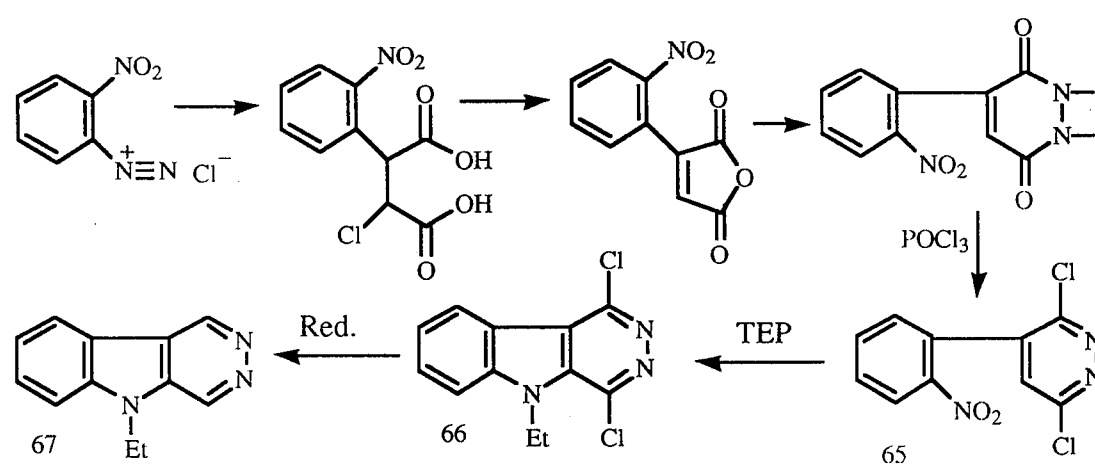
Scheme II. 9

(c) From the cyclisation of 2–indolecarbohydrazides (60) with N, N–dimethylamides, [46] carbon disulfide, and intramolecular cyclisation of indolecarbohydrazide [47] (Scheme II. 10).



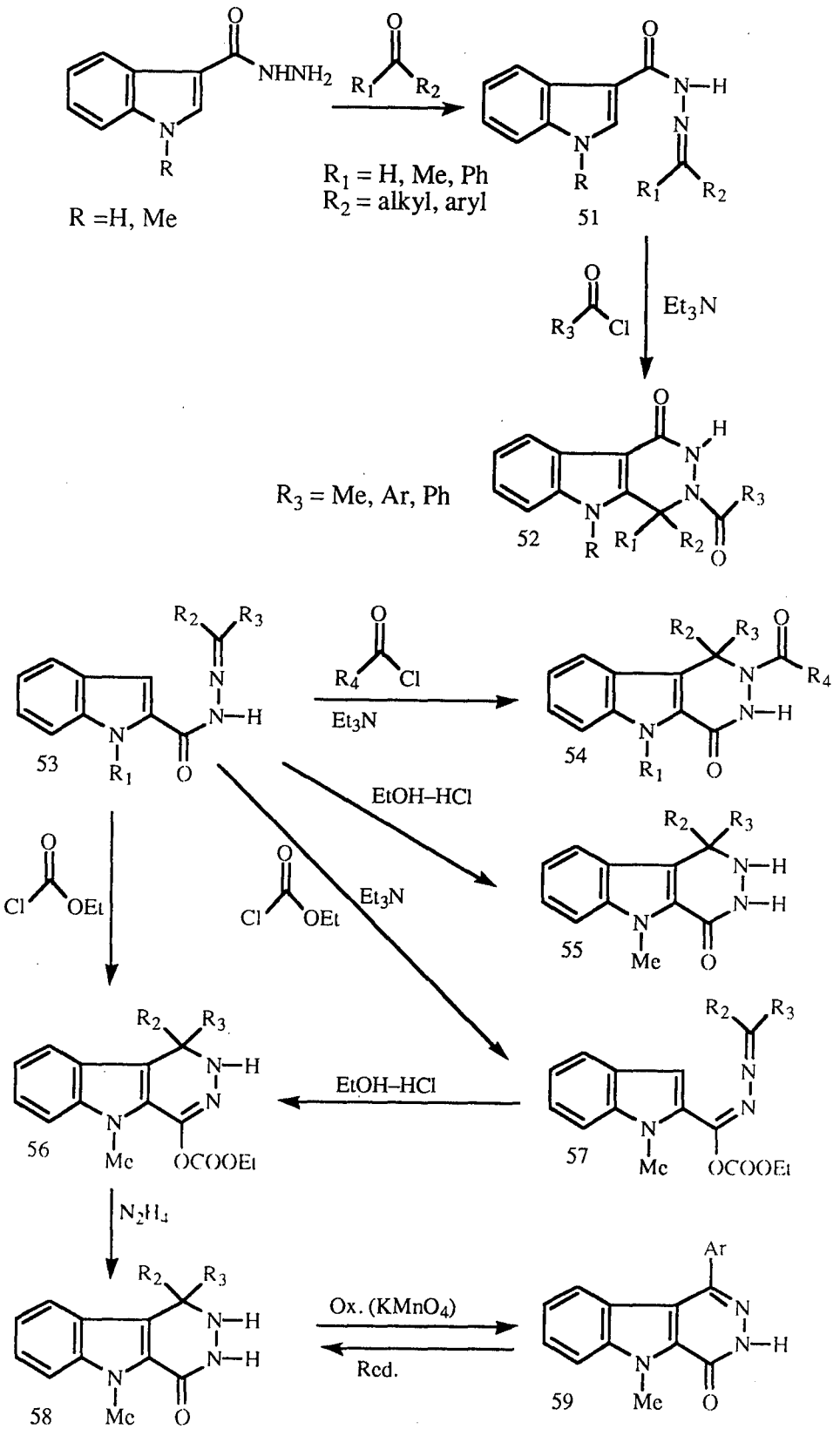
Scheme II. 10

(e) From the intramolecular cyclisation of 3, 6–dichloro–4–(2–nitrophenyl)pyridazine (65) in triethyl phosphite (TEP) [24] (Scheme II. 11).



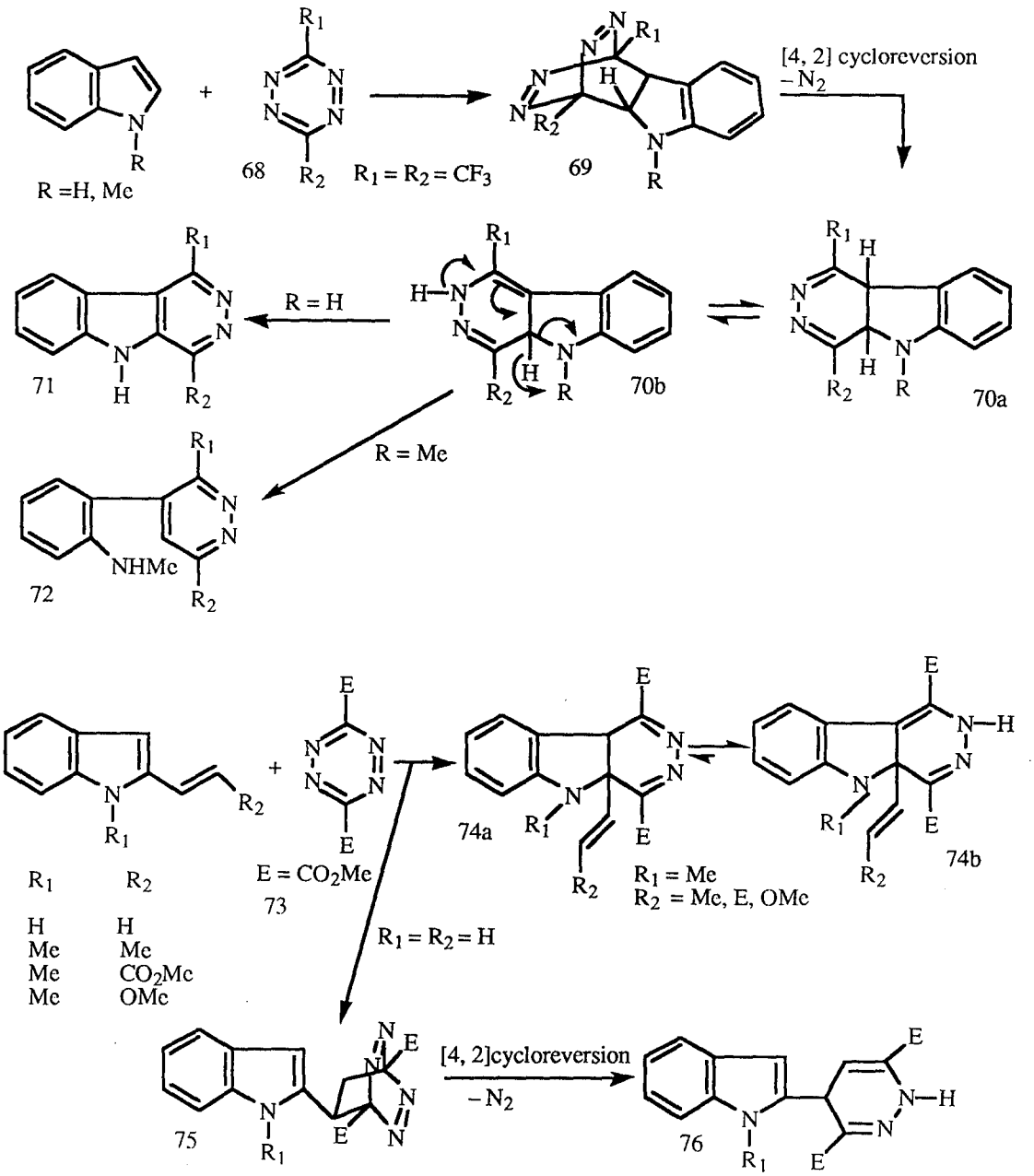
Scheme II. 11

(d) From the cyclisation of 2– and 3–indolecarbohydrazone (51) and (53), [33, 40–44] (Scheme II. 12).


NHNH2
R1 R2
R1 = H, Me, Ph
R2 = alkyl, aryl
R =H, Me
51
Et3N
R3 = Me, Ar, Ph
52
53
R4 Cl
Et3N
54
EtOH–HCl
55
Et3N
56
EtOH–HCl
57
N2H4
Ox. (KMnO4)
Red.
58
59

Scheme II. 12

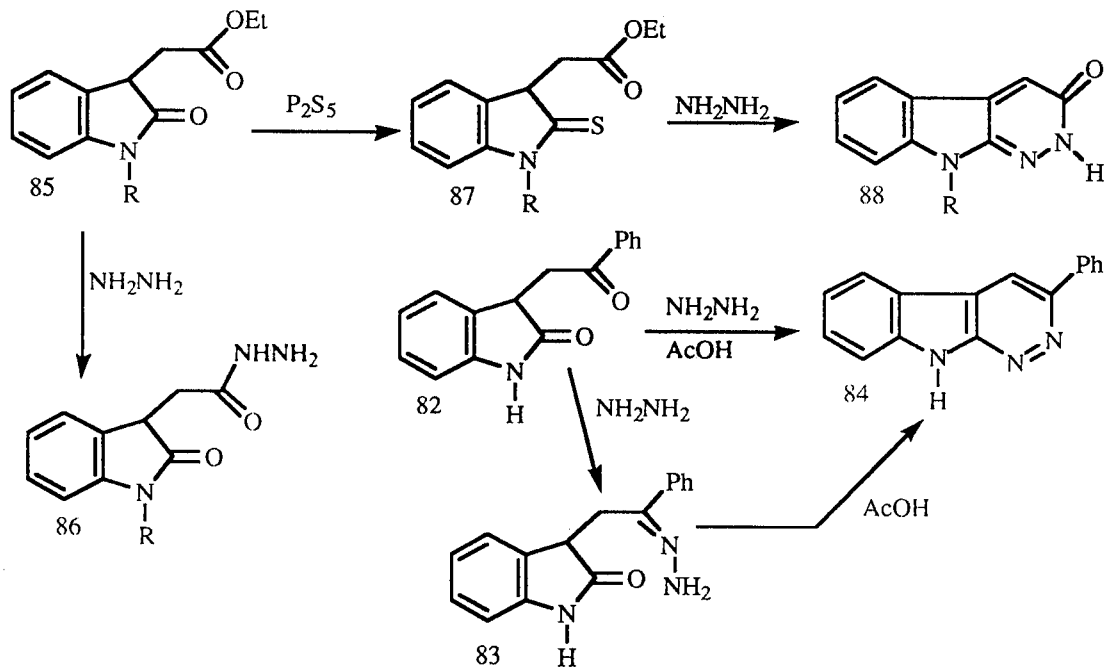
(f) From the cycloaddition reaction of 1, 2, 4, 5–tetrazines (68), (73) with indoles [48–52] (Scheme II. 13).



Scheme II. 13

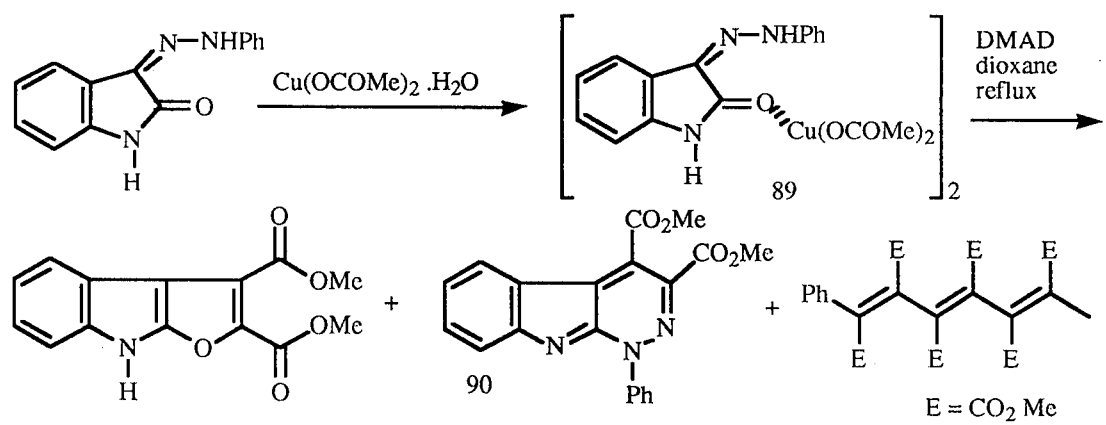
The following procedures are available for the preparation of pyridazino[3, 4–*b*] indoles : [53–55]

(a) From the condensation of indole derivatives with hydrazine and its derivatives (Scheme II. 14).



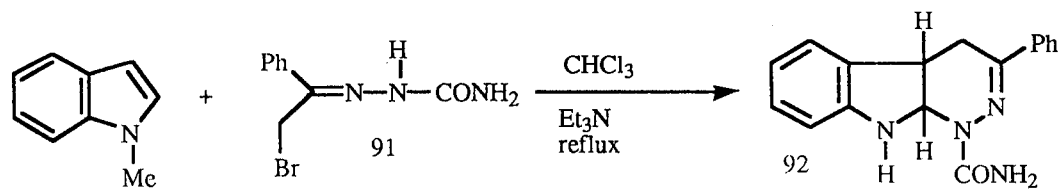
Scheme II. 14

(b) From the reaction of the copper(II) acetate complex of isatin–3–arylhydrazones (89) with dimethyl acetylenedicarboxylate (DMAD) [56] (Scheme II. 15).



Scheme II. 15

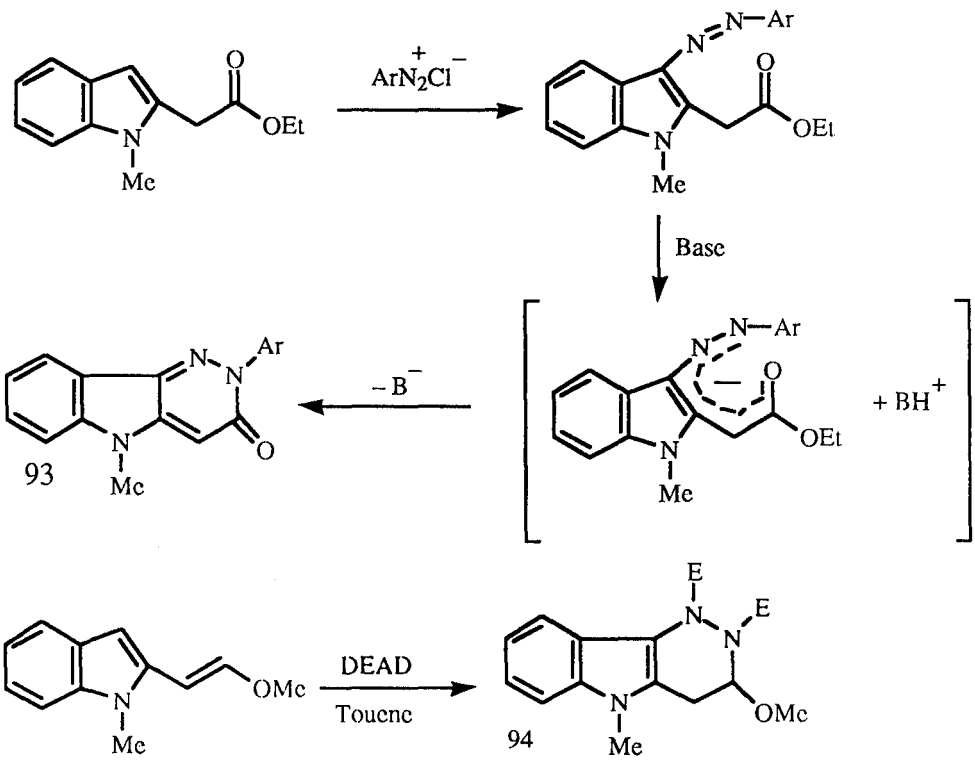
(c) From the reaction of semicarbazone of ω-bromoacetophenone (91) with indoles. [57–58]

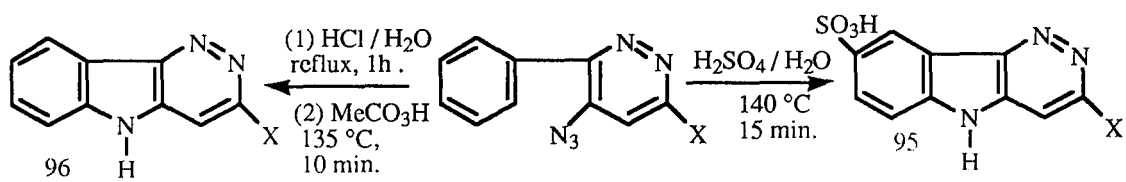


Scheme II. 16

The preparation of (4, 3-*b*)indoles :

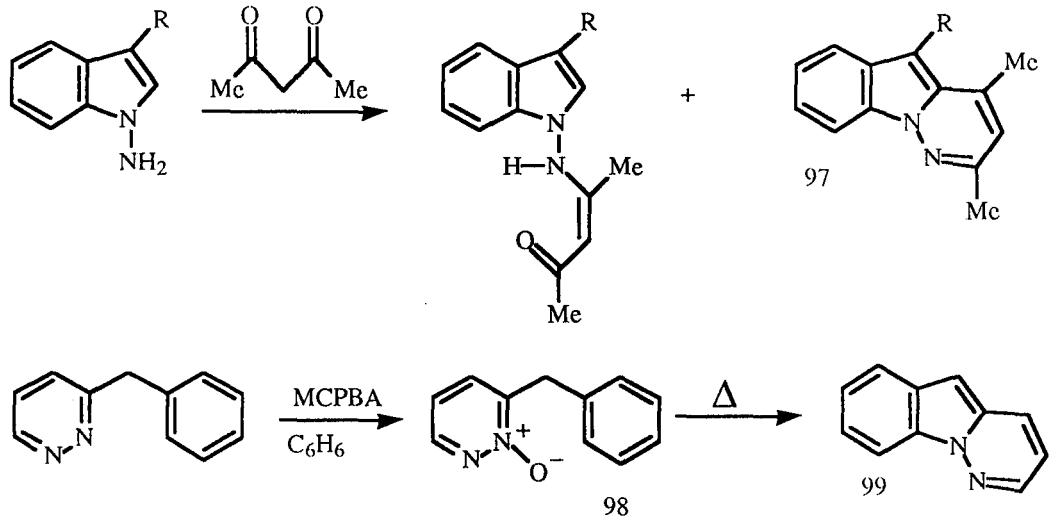
There are few papers in the literature [59–61] which describe the synthesis of pyridazino[4, 3-*b*]indoles (93–96) (Scheme II. 17).





Scheme II. 17

Pyridazino[2, 3–*a*]indoles (97) and (99) can be prepared by the procedures [62–65] shown in scheme II. 18.



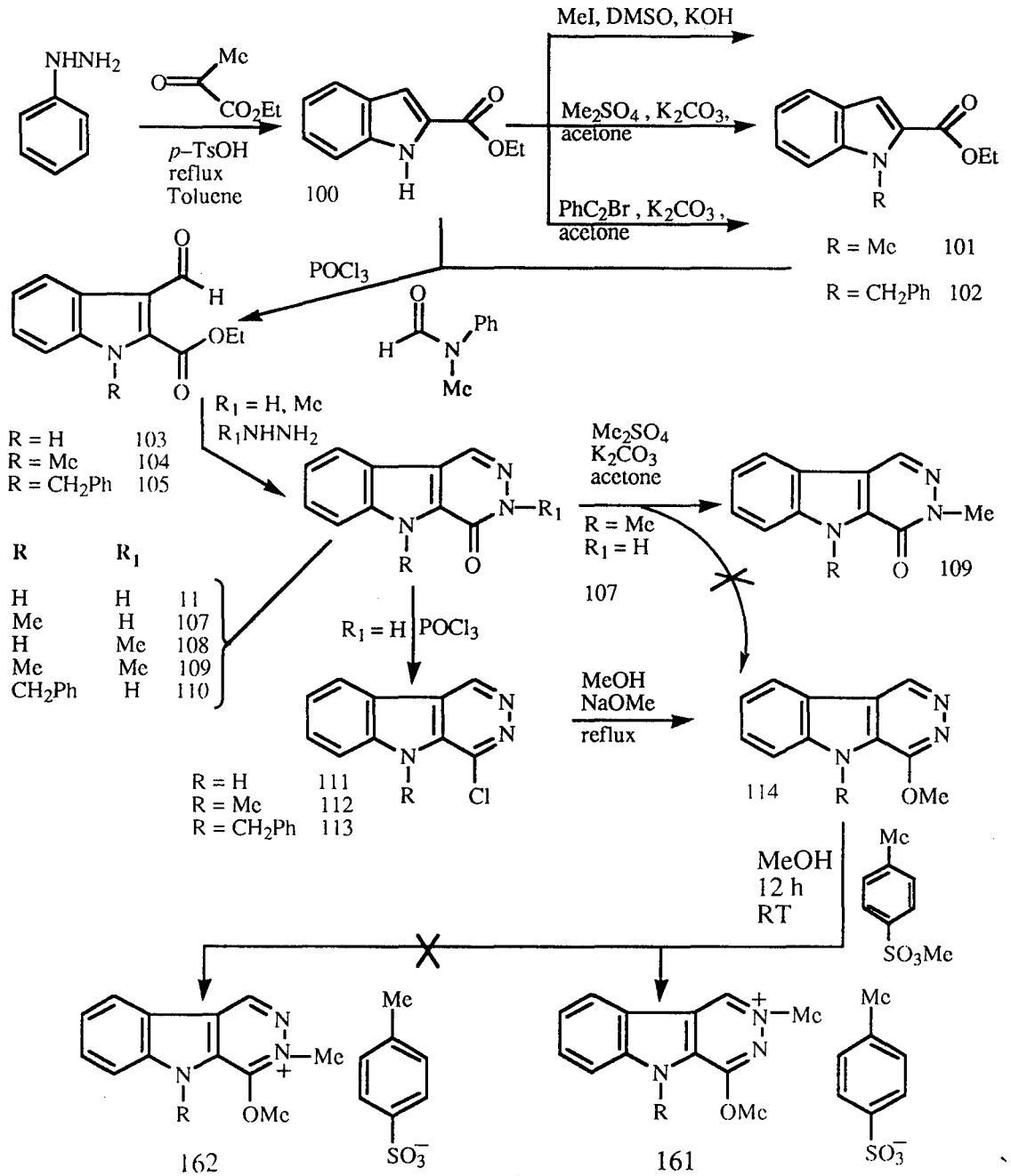
Scheme II. 18

2. 3 Synthesis of 3, 4–dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indoles.

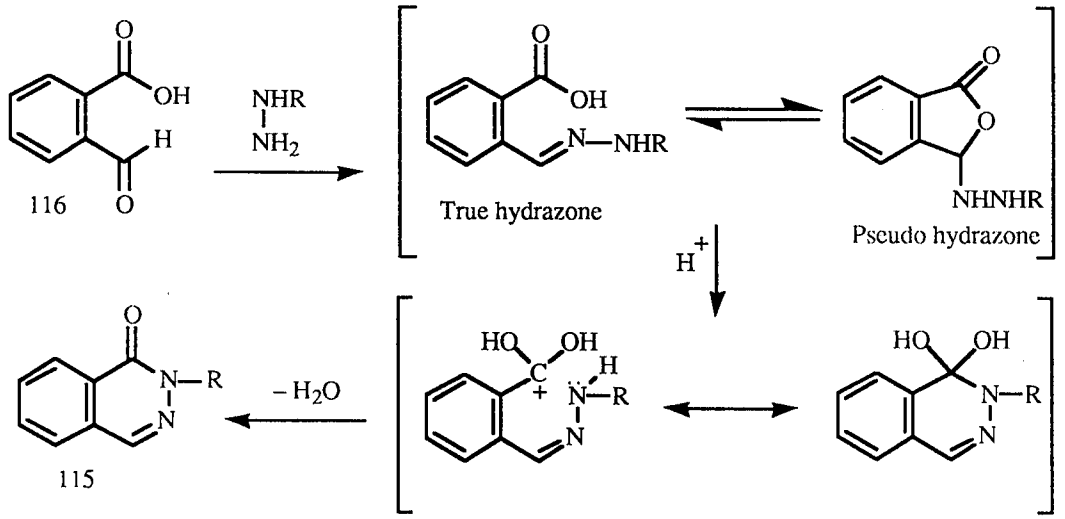
In order to achieve our objective to establish the position of the tautomeric equilibrium, we need to synthesise the cyclic compounds from hydrazine (and its derivatives), and 3–formylindole–2–carboxylic acid (and its derivatives) [15–18, 26–28] to compare then physical properties of the potential tautomeric systems with those of fixed form model 4–oxo–5*H*–pyridazino[4, 5–*b*]indoles and corresponding 4–alkoxy pyridazino[4, 5–*b*] indoles.

Ethyl indole–2–carboxylate (100) was prepared according to the method described by Murakami [66]. Methylation and benzylation of compound (100) were carried out by either the method used by Vega *et al* [67] or as described by Heaney and Ley [68]. The better yield was obtained with the former method compared with the latter. Formylation of indole–2-carboxylates (100), (101), and (102) was carried out according to the Vilsmeir formylation procedure as described in the literature [69] to give corresponding 3–formyl indole–2–carboxylates (103), (104), and (105) in good yields.

Condensation of the 3–formylindole–2–carboxylates (103), (104), and (105) with hydrazine and methyl hydrazine in 2–ethoxyethanol or glycerol produced the corresponding 3, 4–dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indoles (11, 107–110). Compound (109) was also synthesised by methylation of compound (107) in acetone (Scheme II. 19). 2, 5–Dimethyl–4–methoxy–5*H*–pyridazino[4, 5–*b*]indolium toluene –*p*–sulphonate (161) was prepared from 4–methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*] indole (114) and methyl toluene–*p*–sulphonate in good yield. The preparation of compounds (111–114) will be discussed in detail in chapter V.


NHNH2
Me
CO2Et
p-TsOH
reflux
Toluene
100
MeI, DMSO, KOH
Me2SO4 , K2CO3,
acetone
PhC2Br , K2CO3 ,
acetone
R = Me 101
R = CH2Ph 102
POCl3
R = H 103
R = Me 104
R = CH2Ph 105
R1 = H, Me
R1NHNH2
R R1
H H 11
Me H 107
H Me 108
Me Me 109
CH2Ph H 110
Me2SO4
K2CO3
acetone
R = Me
R1 = H
107
109
R1 = H POCl3
R = H 111
R = Me 112
R = CH2Ph 113
MeOH
NaOMe
reflux
114
MeOH
12 h
RT
SO3Me
162
161

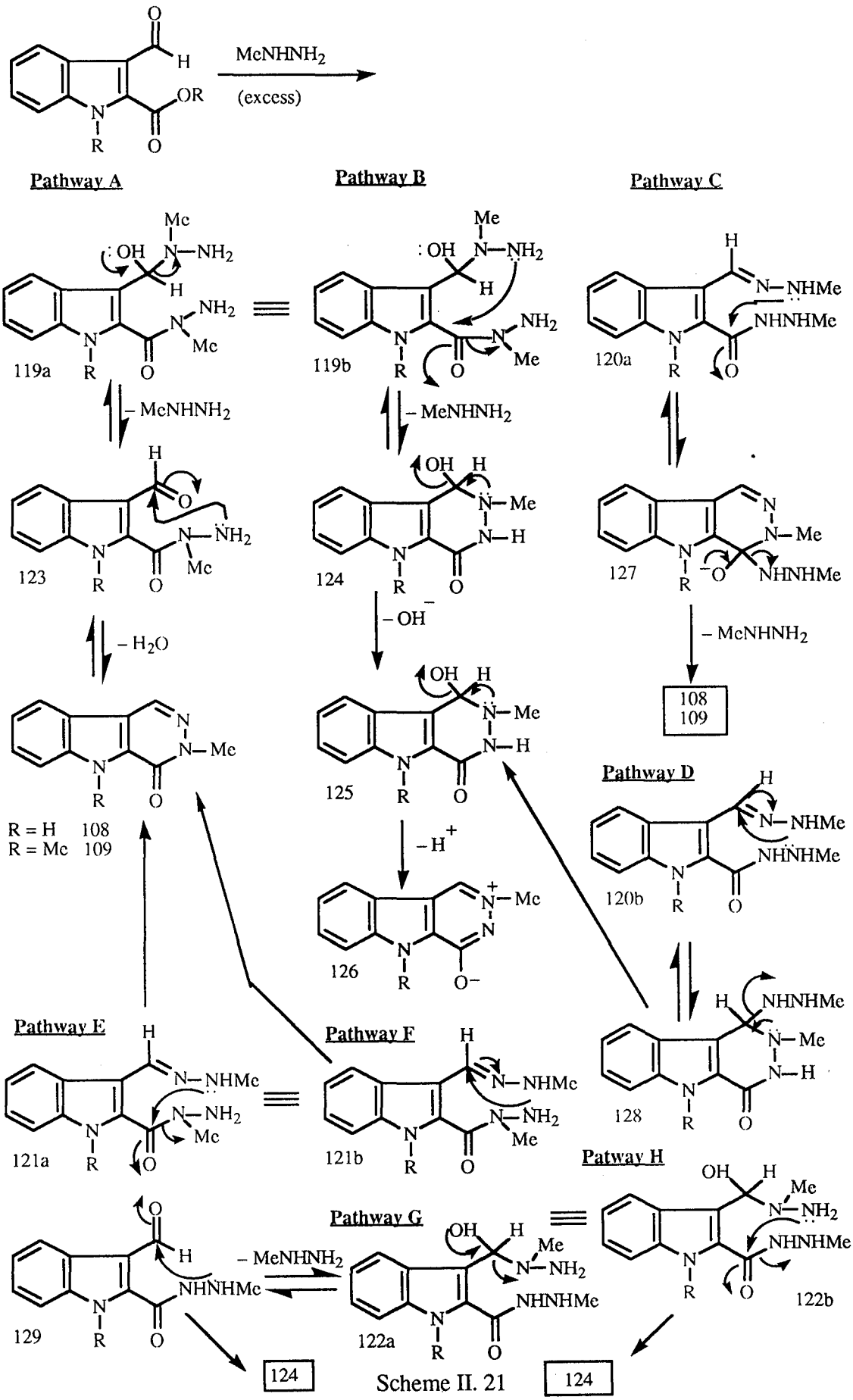
Scheme II. 19



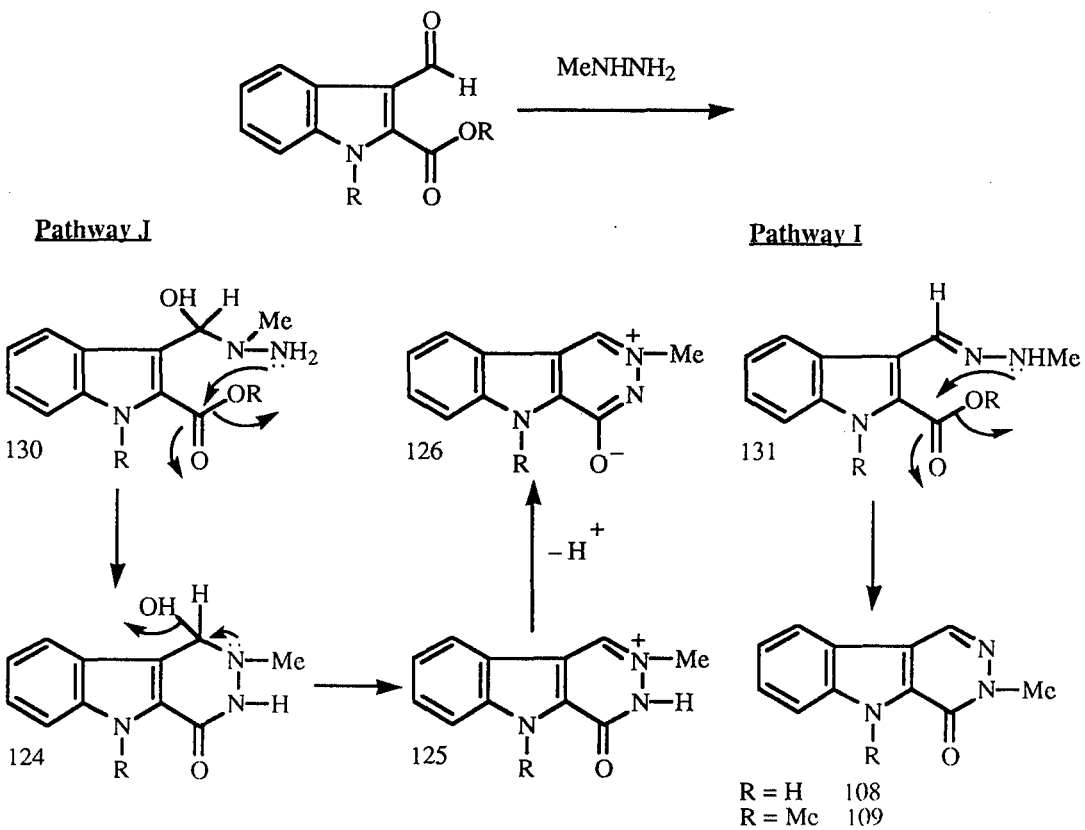
Scheme II. 20

There is no evidence reported in the literature for the mechanism of the reaction of aldehydo– or –keto acid esters of heteroaromatic compounds with hydrazine and its derivatives. A proposed mechanism accounting for the cyclisation of phthaldehydic acid (116) with substituted hydrazines into a 2–substituted phthalazinone (115), has been suggested (Scheme II. 20). [10]

We can also propose a possible mechanism which is based upon our experimental observations. As the aldehyde is more reactive than the ethoxycarbonyl group towards the nucleophilic attack, the acid-catalysed condensation reaction will take place quickly on the formyl carbonyl-carbon atom to give the monohydrazone (131). It has been reported [70] that the cyclisation takes place usually under forcing conditions such as in refluxing acetic acid or when an excess of hydrazine is used. In the latter case, the second carbonyl group may react with hydrazine to give hydrazide (119–121) followed by a nucleophilic attack by β–nitrogen of hydrazide on the more nucleophilic carbon atom of hydrazone (Scheme II. 21). If this mechanism is correct, then the zwitterion (126) would be formed from the reaction with methyl hydrazine *via* (128), (122a), (122b), (119b), and (130) (Scheme II. 21). However, the products (108) and (109) were isolated from the condensation of indoles (103) and (104) with methyl hydrazine. This compound (109) was also prepared from (107) by methylation (Scheme II. 19). The infrared spectra showed strong bands, characteristic of a carbonyl group at 1640–1645 cm^{-1}, 20. and the NMR spectra were fully consistent with those expected for structures (108) and (109) and showed no signals characteristic of the $\underline{CH} = N^+ - R$ group. We can therefore eliminate pathway B, pathway D, pathway G, pathway H, and pathway J in terms of our experimental observations. We propose now that the condensation reaction of 3–formylindole–2–carboxylates with hydrazine takes places *via* pathways A, C, E, F, I.

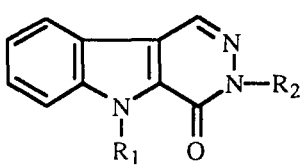

MeNHNH2
(excess)
Pathway A
Pathway B
Pathway C
119a
119b
120a
123
124
127
125
126
108
109
R = H 108
R = Me 109
Pathway D
120b
Pathway E
Pathway F
121a
121b
128
Patway H
Pathway G
129
122a
122b
124
124

Scheme II. 21



Scheme II. 21. 2

Table II. 1 Reaction Products of Ethyl 3–formylindole–2–carboxylate and its Derivatives with Hydrazine and Methyl Hydrazine.



R_1	R_2	Compound	Yield (%)	m. p. (° C)	Reaction
H	H	11	88	326–7	a
H	Me	108	45	298	b
Me	H	107	95	282–3	a
Me	Me	109	38	211	b
Me	Me	109	89	211	c
CH_2Ph	H	110	79	237	a

a. hydrazine hydrate + 2–ethoxyethanol, reflux
b. methylhydrazine + glycerol, reflux
c. from methylation of compound (107) with dimethyl sulphate in acetone.

3. 0 5H–Pyridazino(4, 5–*b*)indoles. – Chemical Reactivity

3. 1 Introduction

The pyridazine ring system is a 1, 2–diaza analogue of benzene. It is a planar molecule for which two Kekulé structures (132a) and (132b) can be drawn, although a greater contribution is made by canonical structure (132a). [71–73] Perturbation of the π–electrons of the ring by the two heteroatom reduces the electron density on the carbon atom of the ring and the system has all of the characteristics of a π–deficient heteroaromatic compound.

132a 132b 133a 133b

Pyridine (133) has a pKa value of 5. 23. [9] When a second nitrogen atom is introduced in place of CH group into the pyridine nucleus, there is a reduction in the basic strength similar to the introduction of a nitro group to pyridine. This drop in pKa value is due to the greater reluctance of the divalent nitrogen to accept a positive charge. Furthermore, the second nitrogen is electron-attracting and thus base-weakening.

The addition of a substituent on the pyridazine nucleus generally has an effect similar to that of the same substituent on benzene. The position of the substituent is also important.

Since the adjacent nitrogen atoms in pyridazine greatly increase the π–deficiency on the carbon atoms, the pyridazine nucleus is resistant to attack by electrophilic reagents. The presence of an electron–releasing group, such as an amino or hydroxyl group, can counteract this effect and allow electrophilic substitution to take place.

The fusion of the indole, which has π–electron excessive pyrrole ring, with the π–electron deficient pyridazine ring would be expected to produce a system which possesses the chemical reactivities of both rings but somewhat modified as a result of mesomeric interaction (134a ⟷ 134b ⟷ 134c) (Figure II. 1).

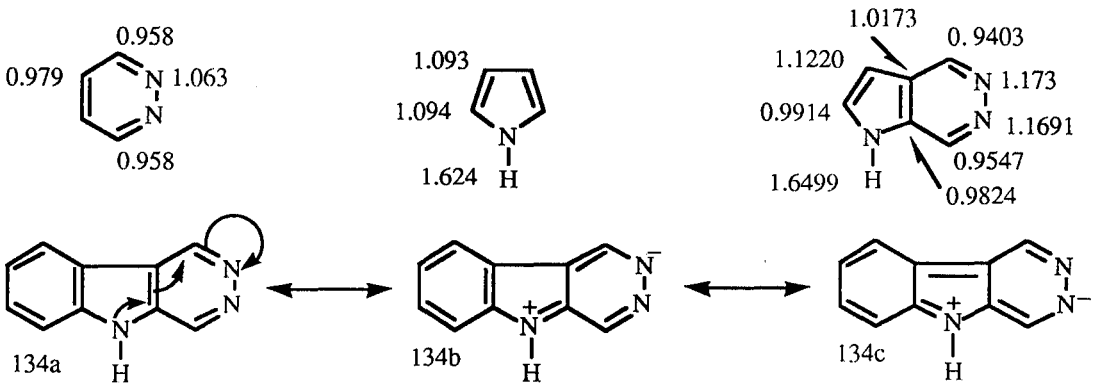
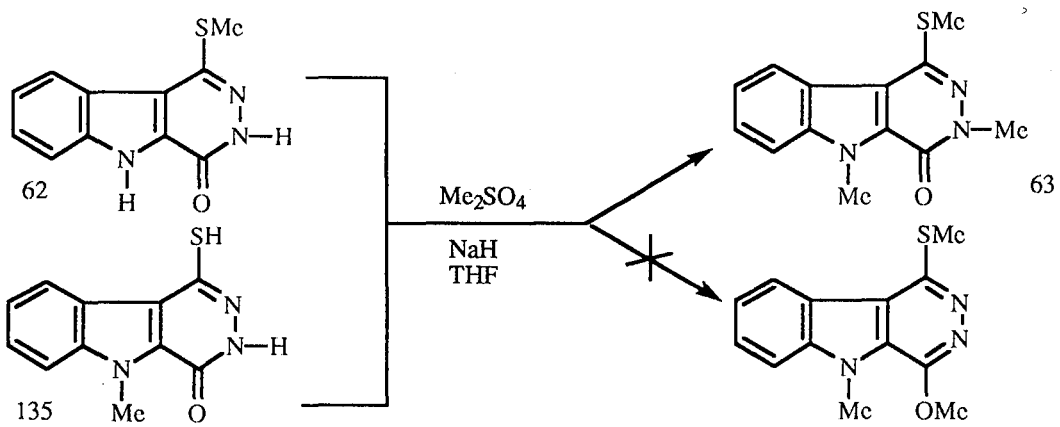


Figure II. 1 Total π–Electron Density of Pyrrolo[2, 3–*d*]pyridazine Compared to the Pyrrole and Pyridazine Rings. [10]

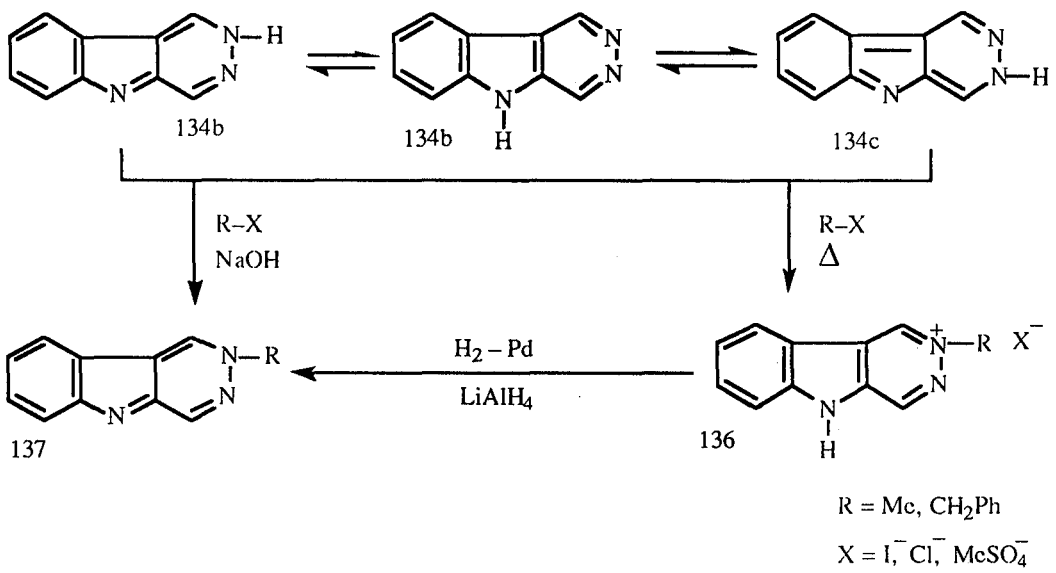
3. 2 Reaction of 4–Oxo–5H–pyridazino[4, 5–*b*]indoles

Methylation of 3, 4–dihydro–1–methylthio–4–oxo–5*H*–pyridazino[4, 5–*b*]indole (62) and 3, 4–dihydro–1–mercapto–5–methyl–4–oxo–5*H*–pyridazino[4, 5–*b*]indole (135) with dimethyl sulphate in THF afforded only 3, 4–dihydro–3, 5–dimethyl –1–methylthio–4–oxo–5*H*–pyridazino[4, 5–*b*]indole (63) [47] (Scheme II. 22).



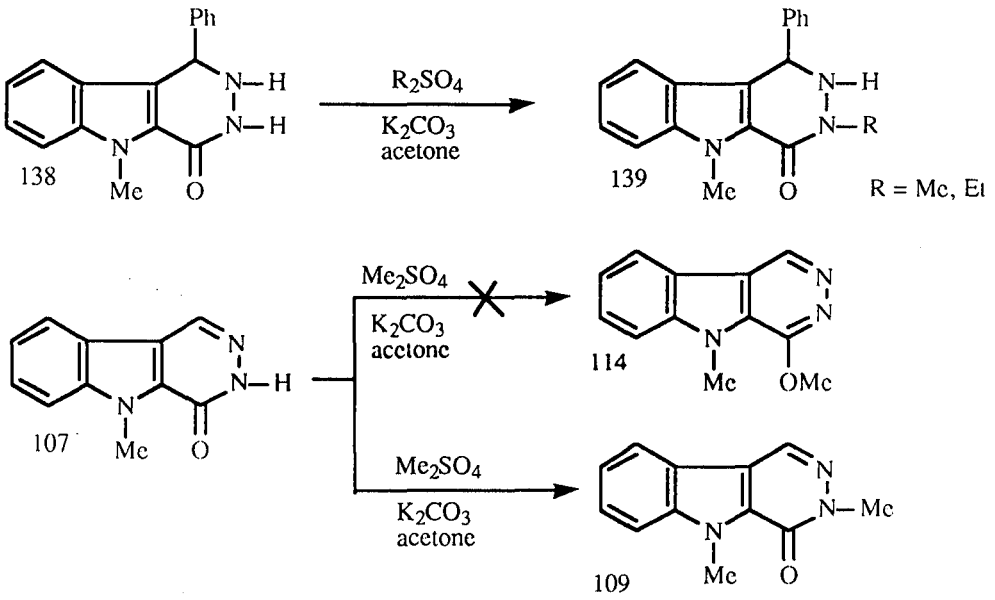
Scheme II. 22

Ovchinnikova *et al* [27] alkylated 5*H*–pyridazino[4, 5–*b*]indole (134) using methyl iodide, dimethyl sulphate, and benzyl chloride as alkylating agents in THF. When base is used, the alkylation provides 2–alkyl–2*H*–pyridazino[4, 5–*b*]indoles (137), whereas in the absence of base, the quaternary salts of the 5*H*–pyridazino[4, 5–*b*]indoles are obtained, which then could be converted into (137) by reduction (Scheme II. 23).



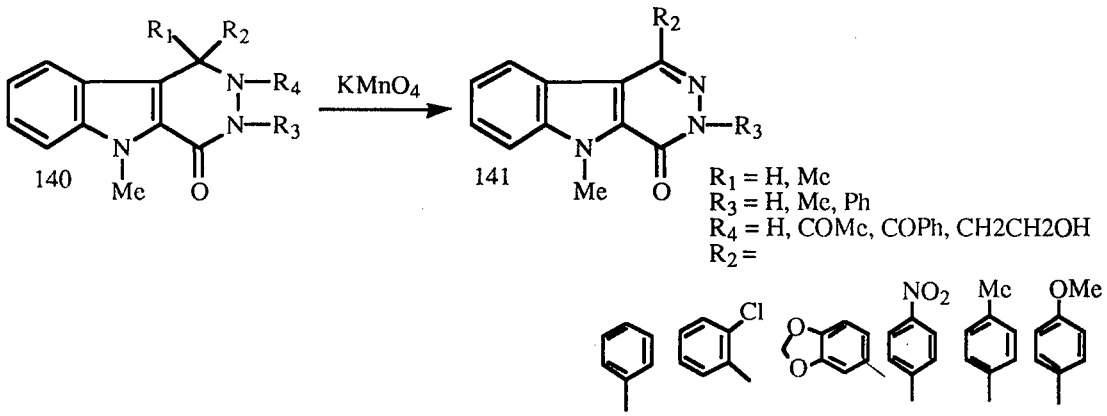
Scheme II. 23

Alkylation of some 4–oxo–5*H*–pyridazino[4, 5–*b*]indoles (138) and (107) was also carried out by Vega and *et al* [17] with dialkyl sulphates in acetone to give corresponding 3–alkyl–4–oxo–5*H*–pyridazino[4, 5–*b*]indoles (139) and (109) (Scheme II. 24).



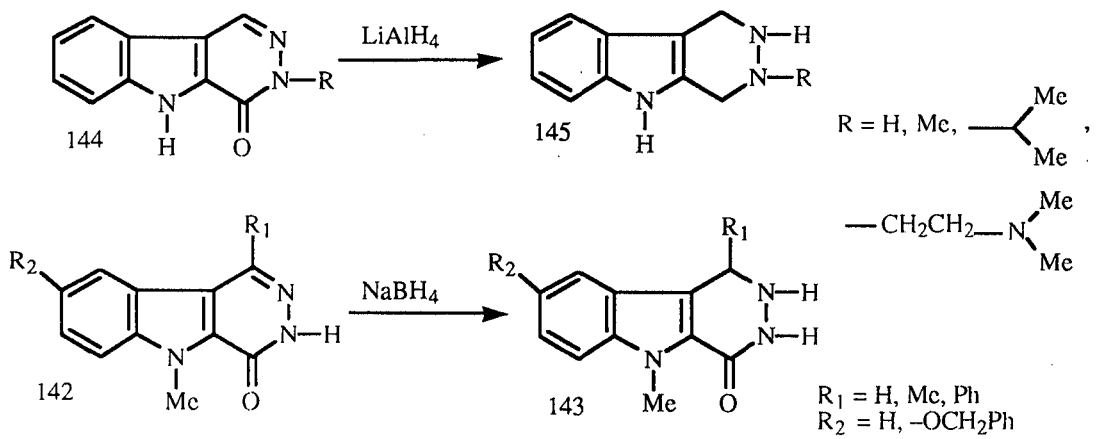
Scheme II. 24

Oxidation of 1, 2, 3, 4–tetrahydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indoles (140) with potassium permanganate yields 3, 4–dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indoles (141) [41, 43, 44b] (Scheme II. 25).



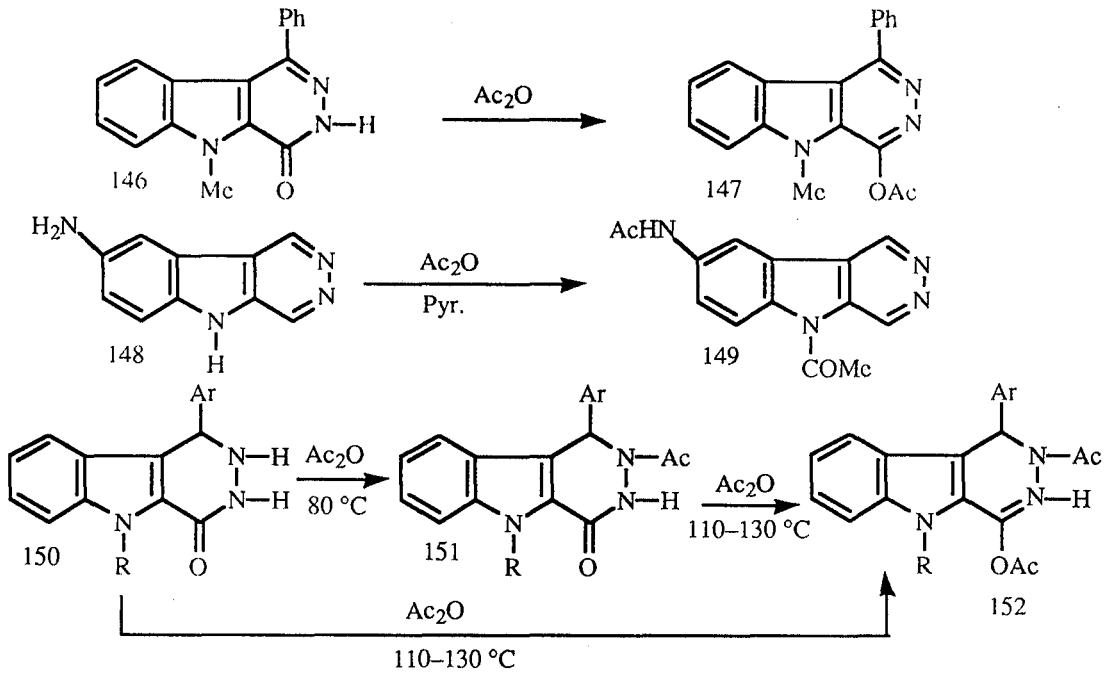
Scheme II. 25

Reduction of 3, 4–dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indoles (142) with sodium borohydride provides 1, 2, 3, 4–tetrahydro–4–oxo–5*H*–pyridazino[4, 5–*b*] indoles (143) [17, 33, 44c] whereas, when lithium aluminiumhydride is used the reduction of 3, 4–dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indoles (144) yields 1, 2, 3, 4–tetrahydro –5*H*–pyridazino[4, 5–*b*]indoles (145) [18] (Scheme II. 26).



Scheme II. 26

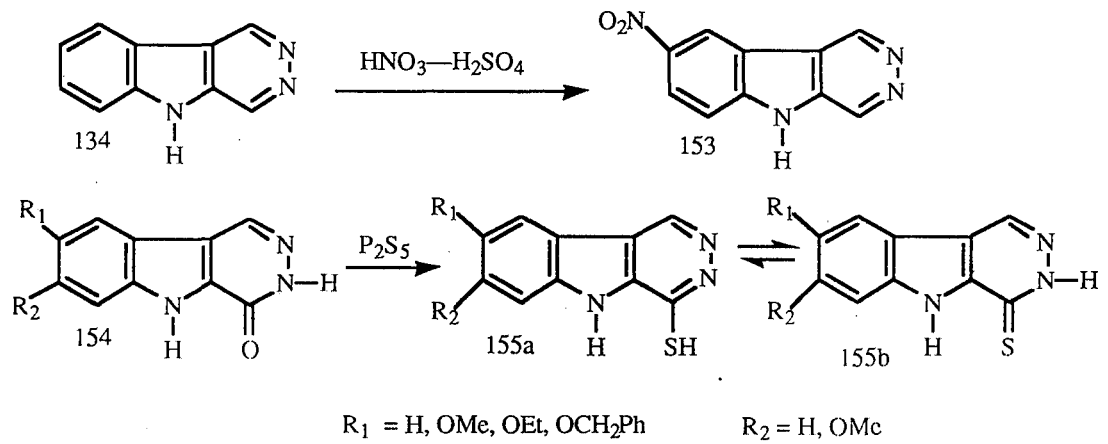
Several 5*H*–pyridazino[4, 5–*b*]indoles (146), (148), and (150) were acylated with acetic anhydride to give the corresponding acylated 5*H*–pyridazino[4, 5–*b*]indoles (147), (149), (151), and (152) (Scheme II. 27). [17, 26, 74]



Scheme II. 27

Nitration of of 5*H*–pyridazino[4, 5–*b*]indole (134) with a mixture of nitric acid (HNO_3) and sulphuric acid (H_2SO_4) gives 8–nitro–5*H*–pyridazino[4, 5–*b*]indole (153) (Scheme II. 28).

The reaction of 5*H*–pyridazino[4, 5–*b*]indoles (154) with phosphorus pentasulfide (P_2S_5) yields the corresponding sulphur derivatives of 5*H*–pyridazino[4, 5–*b*]indoles (155) (Scheme II. 28). [15, 16, 19, 20, 22]



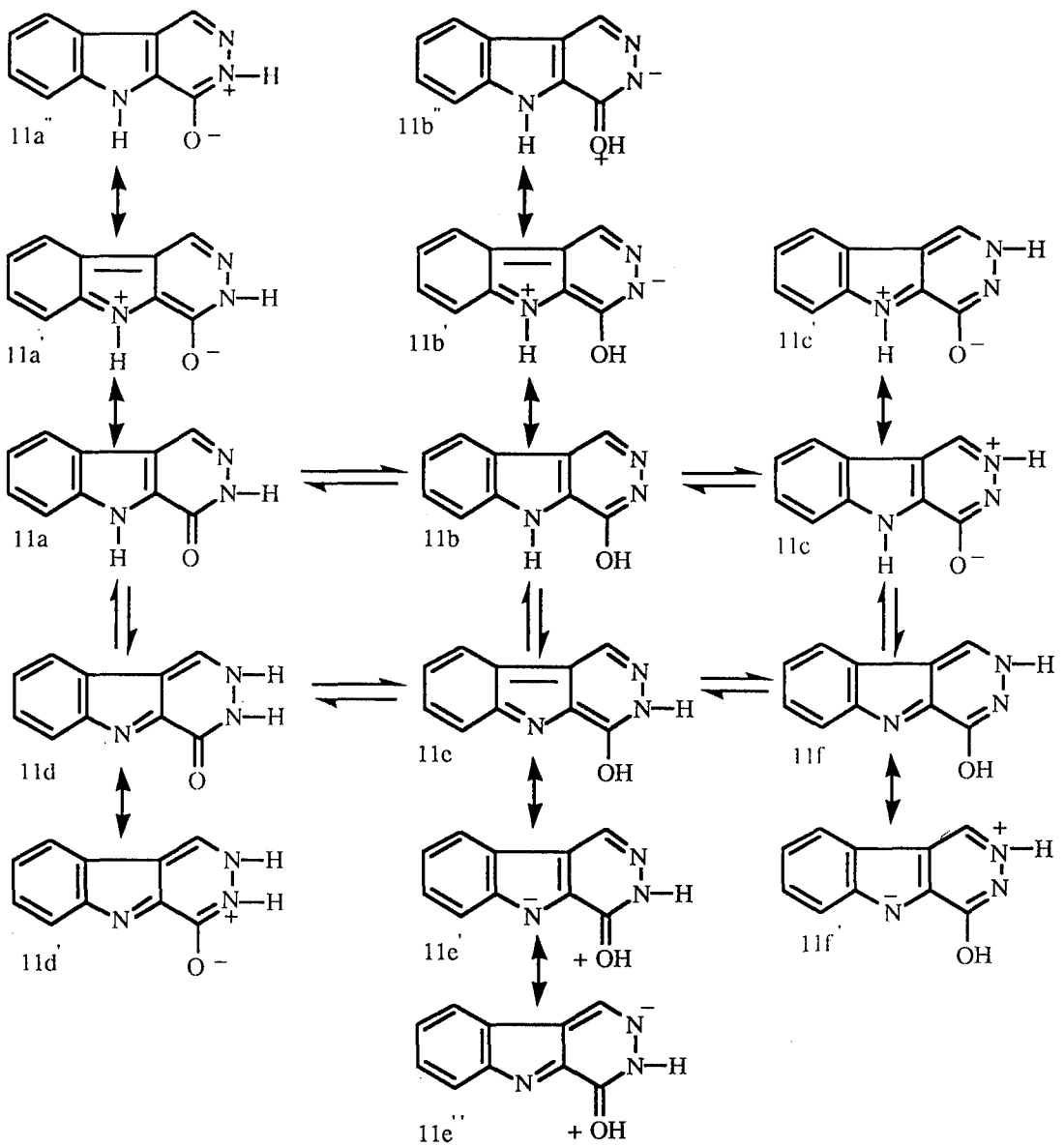
Scheme II. 28

4. 0 3, 4–Dihydro–4–oxo–5*H*–pyridazino(4, 5–*b*)indoles.—Physical Properties

Several tautomeric structures can be drawn, for the 3, 4–dihydro–4–oxo –5*H*–pyridazino[4, 5–*b*]indoles, as shown in scheme II. 29, in which two types of tautomerism are possible. In one case the functional group is involved (11a $\rightleftharpoons$ 11b)

and, in the second case, the annular nitrogen atom on the five-membered ring also becomes involved (11d ⇌ 11e ⇌ 11f). Most of the latter tautomeric structures can be easily excluded from our discussion by comparison of the physical properties of the corresponding parent compound with the model compounds. For example, the absence of a long wavelength band at 400—460 nm characteristic of 2*H*–pyridazino[4, 5–*b*]indole [27] in the ultraviolet spectra of compounds reveals that the tautomerism of the type (11d ⇌ 11e ⇌ 11f) is very unlikely.

The majority of our measurements reveal that the annelation of the pyridazinone ring with indole ring shifts the tautomeric equilibria towards the oxo-structure (11a) (Scheme II. 29).



Scheme II. 29

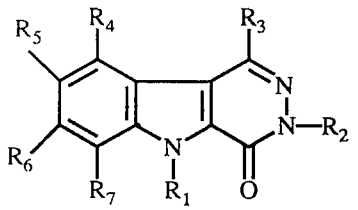
4. 1 NMR Spectroscopic Measurements

^{1}H-NMR chemical shifts of the alkyl group and ring protons of 5 *H*–pyridazino [4, 5–*b*]indoles are presented in table II. 2.

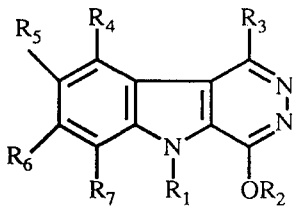
The spectra of 3, 4–dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indoles (11) and (107) show a signal at 12. 84 ppm for (11) and at 12.80 ppm for (107), which are characteristic of NH . We can not suggest in terms of only this data that 3, 4–dihydro–4–oxo–5*H* –pyridazino[4, 5–*b*]indoles exist predominantly in oxo--structure (11a) (Scheme II. 29) because there might be fast proton exchange between NH and OH , but ^{1}H-NMR spectra of the 3, 4–dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indoles (11), (107), (110), and their N(3)–methylated derivatives (108) and (109) show close similarities and significantly different from the spectrum of the O–methylated derivative (114) in the chemical shift of the C(1)–H signal (Table II. 2). Thus, we can postulate that 3, 4–dihydro–4–oxo–5*H* –pyridazino[4, 5–*b*]indoles exist predominantly in the oxo-structure (11a) and not in the hydroxy–structure (11b) (Scheme II. 29).

Introduction of a methyl group on the nitrogen atom of indole ring shifts the C(1)–H proton 0.16–0.36 ppm to high field. The presence of a methyl group on the nitrogen atom of the pyridazine ring N–(3) shifts the C(1)–H protons 0.08-0.28 ppm to higher field (Table II. 2).

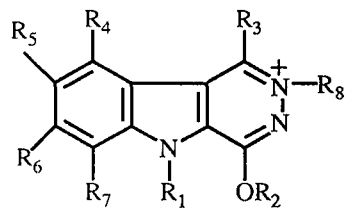
Table II. 2 ^{1}H-NMR Spectra [a] 3, 4–Dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indoles (A) and 4–Methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (B).



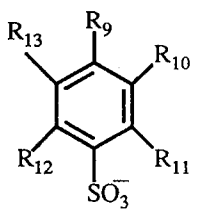
A



B



C



$R_3 = R_4 = R_5 = R_6 = R_7 = R_{10} = R_{11} = R_{12} = R_{13} = H$

R_1	R_2	Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7
A									
H	H	11[c]	12.96 (s)	12.84 (s)	8.84 (s)	8.08–8.36 (dd)	7.20	--------	7.90 (m)
H	Me	108 [c]	12.80 (s)	3.84 (s)	8.76 (s)	8.02–8.24 (dd)	7.20	--------	7.80 (m)
Me	H	107 [c]	4.32 (s)	12.80 (s)	8.68 (s)	8.04–8.28 (dd)	7.20	--------	7.74 (m)
Me	Me	109 [b]	4.35 (s)	3.95 (s)	8.40 (s)	7.85–8.08 (dd)	7.20	--------	7.60 (m)
Bn	H	110 [b]	6.12 (s)	—	8.64 (s)	8.04–8.24 (dd)	7.20	--------	7.80 (m)
B									
Me	Me	114 [b]	4.09 (s)	4.18 (s)	9.35 (s)	7.90–8.10 (dd)	7.20	-------	7.60 (m)
C									
Me	Me	161[d]	4.34 (s)	4.34 (s)	10.64(s)	8.35–8.60 (dd)	7.00	------	8.00 (m)
			R_8 = 4.56 (s)		R_9 = 3.32 (s)	R_{10} — R_{13}	6.90	------	8.00 (m)

a. Chemical shifts are recorded in ppm down from TMS.
b. Spectra recorded in $CDCl_3$.
c. Spectra recorded in DMSO–d_6.

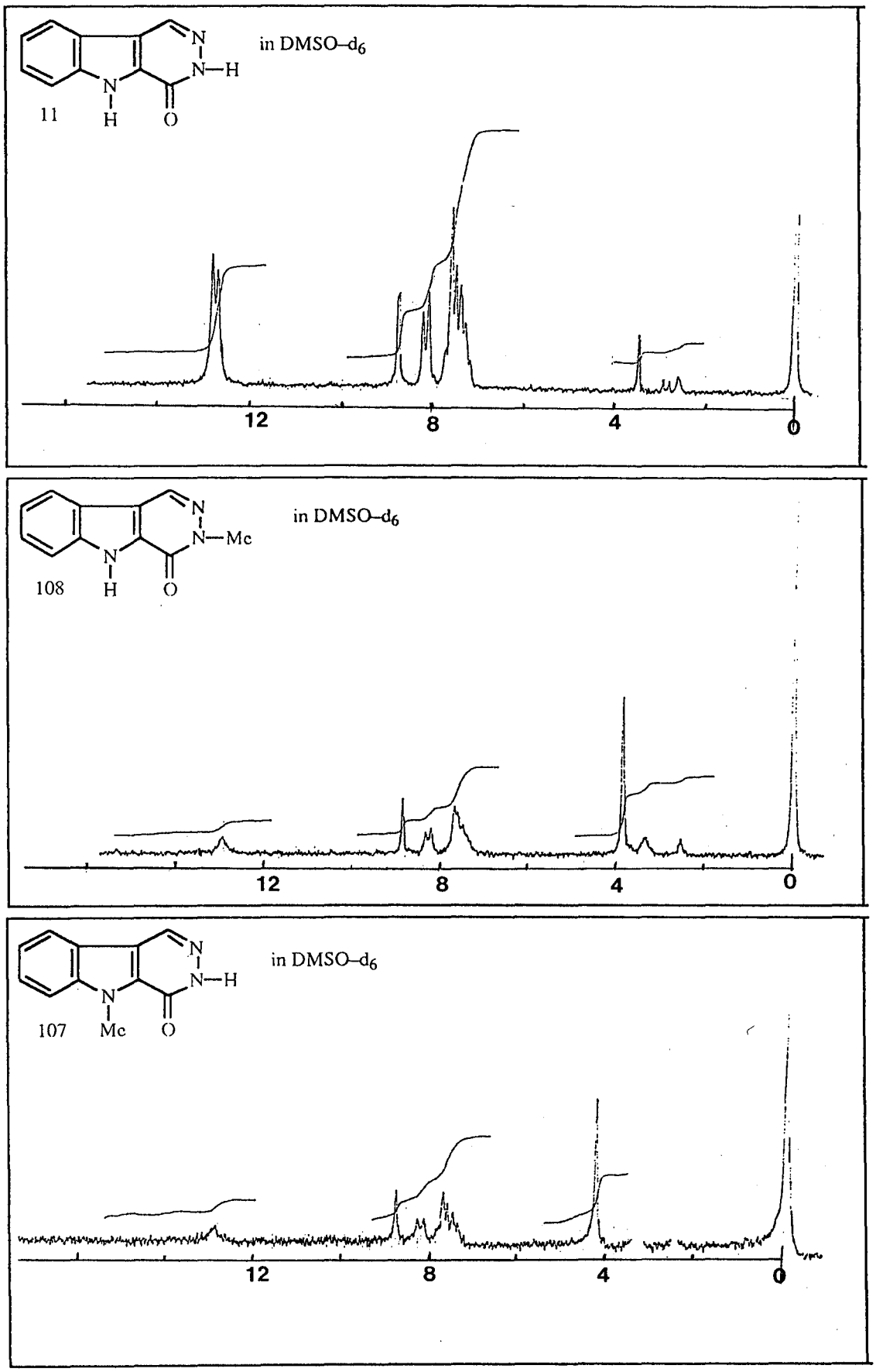


Figure II. 2.1 ^{1}H-NMR Spectra of 3, 4–Dihydro–4–oxo–5*H*–pyridazino[4. 5–*b*] indoles

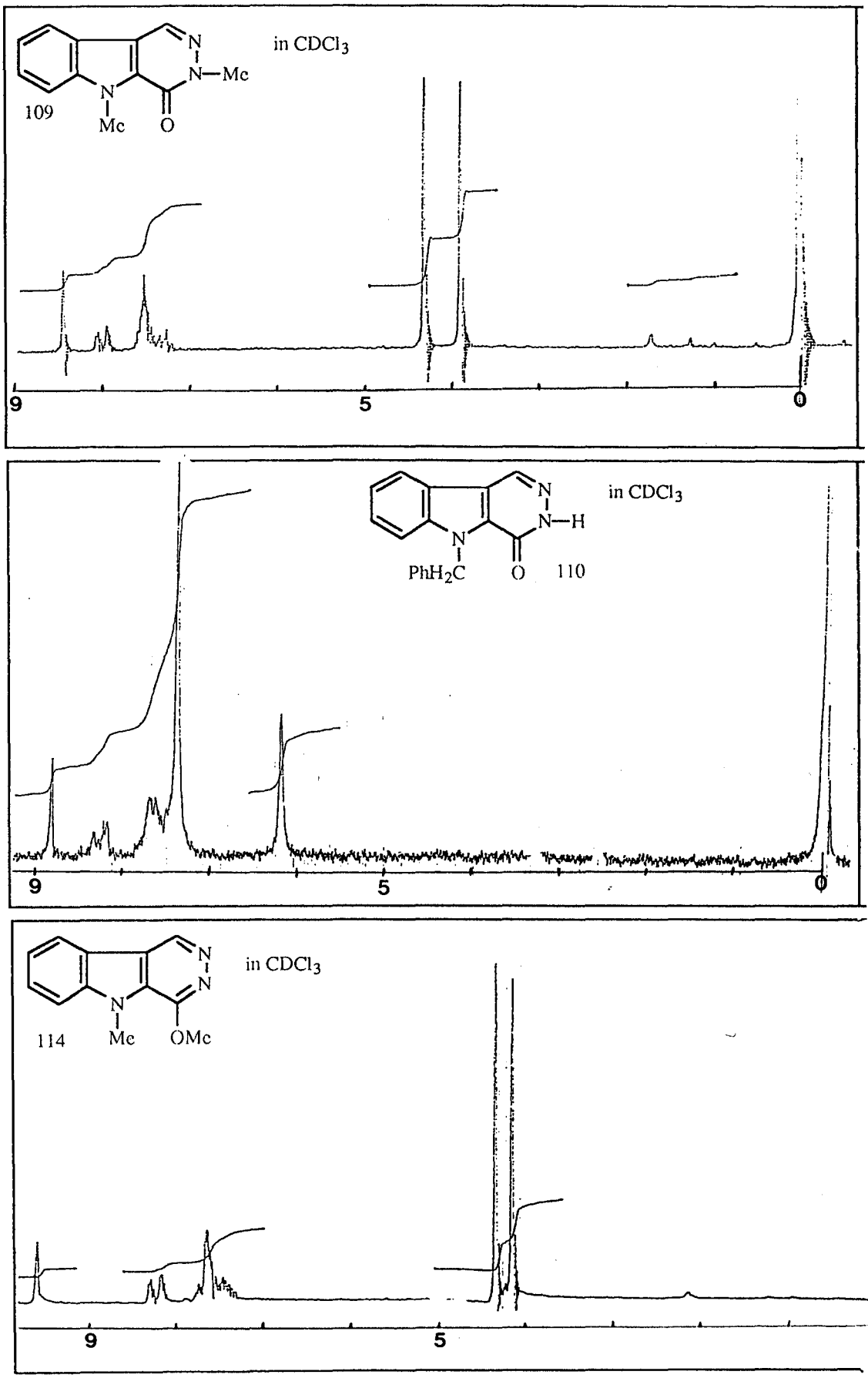


Figure II. 2. 2 ^{1}H-NMR Spectra of 3, 4–Dihydro–5*H*–pyridazino[4. 5–*b*]indoles

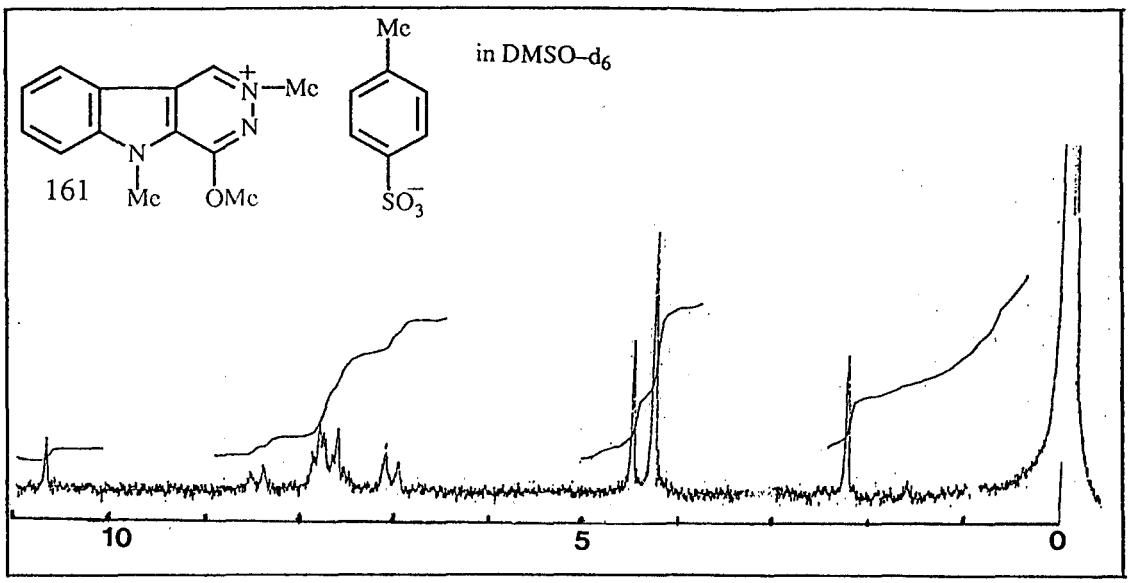


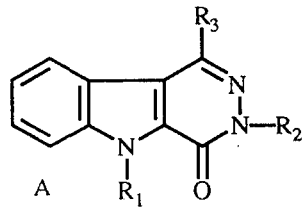
Figure II. 2. 3 ^{1}H-NMR Spectrum of 5*H*–pyridazino[4, 5–*b*]indolium salt

4. 2 Infrared Spectroscopic Measurements

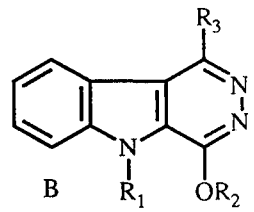
Selected infrared spectral data for 3, 4–dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*] indoles and 4–methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole, measured in the solid state, are presented in table II. 3. The spectra show a complex pattern of absorption between 3000–3350 cm^{-1} with a maximum at about 3100–3250 cm^{-1} for NH derivatives of 5*H*–pyridazino[4, 5–*b*]indoles (11), (107), (108), and (110). The absorption bands are absent in the spectra of the N(3)–methyl derivative (109) and 4–methoxy–5–methyl–5*H* –pyridazino[4, 5–*b*]indole (114). The "amide" group of all those compounds produces $\nu_{C=O}$ in (11), (107), (108), (109), and (110), which usually overlap with C=C and C=N ring stretching bands and vary in intensity from compound to compound in the range 1610–1630 cm^{-1} . The ring stretching bands are stronger in (108), (109), and (114), compared with those of (107) and (110).

The absence of any broad band between 1600–1500 cm^{-1}, which is characteristic of N^+–H and O^- groups of the betaine structure, allow the conclusion that none of 3, 4–dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indoles (11) and (107), and (110) exist in the betaine structures (Scheme II. 29). From the data obtained from infrared spectroscopy we can now suggest that 3, 4–dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indoles exist predominantly in the oxo–structures (11a), not in the hydroxy- structure (11b) and in the betaine structure (11c) (Scheme II. 29)

Table II. 3 Infrared Stretching Frequencies of 3, 4–Dihydro–4–oxo–5*H*–pyridazino [4, 5–*b*]indoles (A) and 4–Methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*] indole (B).



A



B

R1	R_2	Compound	NH or OH (cm^{-1})	C=O (cm^{-1})	C=N, C=C (cm^{-1})
A					
H	H	11 [a]	3140 (m, broad)	1660 (s)	—
H	Me	108 [a]	3130 (w, broad)	1640 (s)	1620 (s)
Me	H	107 [a]	3160 (w, broad)	1680 (s)	1620 (s)
Me	Me	109 [a]	—	1645 (s)	1620 (s)
CH_2Ph	H	110 [a]	3120(w), 3160 (w), 3240 (w)	1660 (s)	1610 (s)
B					
Me	Me	114 [a]	—	—	1610 (s), 1630 (s)

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4. 3 Ultraviolet Spectral Measurements

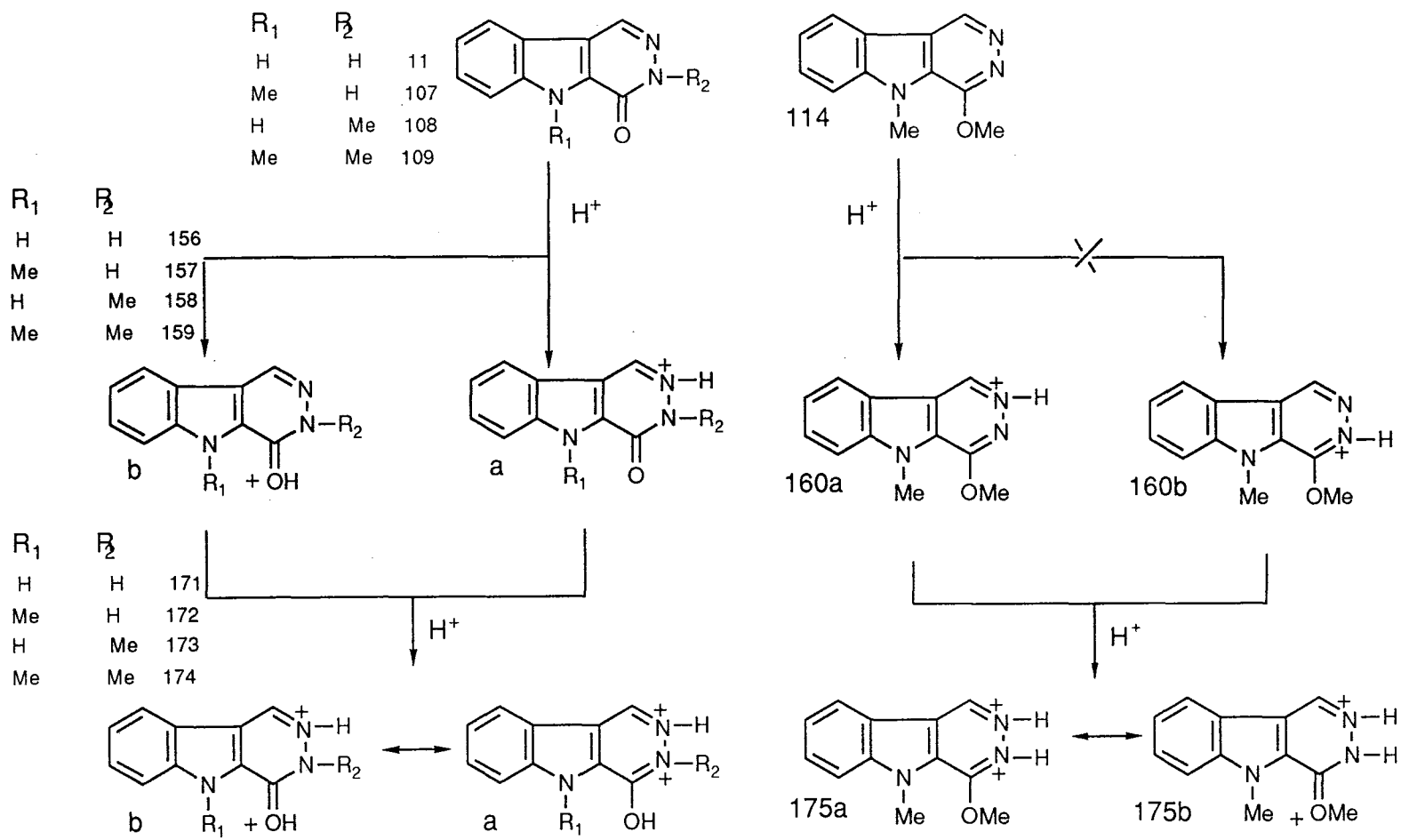
Ultraviolet spectral measurement of 3, 4–dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*] indoles (11), (107), (108), (109), and 4–methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*] indole (114) are recorded in the table II. 4. All compounds show three groups of band in neutral buffer solution ; a low intensity long wavelength bands; a low at 270–340 nm ($\pi \longrightarrow \pi^*$), a medium intensity ($\pi \longrightarrow \pi^*$) band at 240–270 nm, and a high intensity band ($\pi \longrightarrow \pi^*$) at 200–240 nm (Figure II.3, Table II. 5). In acidic media, they also exhibit three groups of bands ; a low intensity long wavelength band at 285–370 nm ($\pi \longrightarrow \pi^*$), high intensity ($\pi \longrightarrow \pi^*$) absorption at 240–280 nm, and a medium intensity ($\pi \longrightarrow \pi^*$) band at 200–240 nm (Figure II. 3).

Upon protonation, all the low intensity bands undergo a bathochromic effect (red shift) 10–28 nm, which is accompanied by a hyperchromic effect except in compound (11) (Table II. 5). The bathochromic effect for compounds (108) and (109) is greater than those of for (11), (107), and (114). The hyperchromic effect observed for all medium intensity bands is accompanied by a bathochromic effect 6–9 nm in (108), (109), and (114). The high intensity bands produce a hypsochromic effect (blue shift) 8–16 nm with a hypochromic effect.

The spectra of neutral and acidic species of 3, 4–dihydro–4–oxo–5*H*–pyridazino [4, 5–*b*]indoles (11), (107), (108), and(109) exhibit very close similarity and differ from the UV spectrum of the O–methylated derivative (114). This observation suggests that 3, 4–dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indole and its derivatives exist in the oxo-structure (11a) not in the hydroxy-structure (11b) in water.

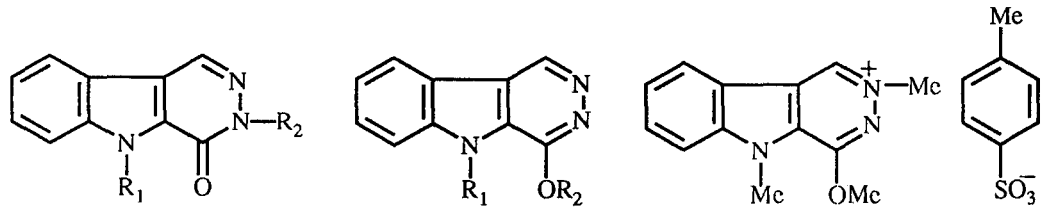
Monoprotonation of 4–methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (114) may take place on either N(2) or N(3) atom. As we mentioned earlier, methylation of 4–methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (114) gives only N(2)–methylated product (161) because of steric hindrance (see also Chapter V). Therefore, we could not manage to prepare model compound (162) to investigate the protonation site of compound (114) fully. But the similarity of log ε values of protonated 4–methoxy–5–methyl–5*H* –pyridazino[4, 5–*b*]indole (160 a') and 2, 5–dimethyl–4–methoxy–5*H*–pyridazino [4, 5–*b*]indolium toluene–*p*–sulphonate (161) shows that protonation of 4–methoxy –5–methyl–5*H*–pyridazino[4, 5–*b*]indole (114) occurs on N(2) atom.

The UV spectra of dicationic species of all 5*H*–pyridazino[4, 5–*b*]indoles (11), (107), (108), (109), and (114) are very similar to each other. In other words, diprotonation of 5*H*–pyridazino[4, 5–*b*]indoles produces a common cation (171–175) (Scheme II. 30, Scheme II. 33, Scheme II. 34, Table II.4, Figure II. 4 .


R1 R2
H H 11
Me H 107
H Me 108
Me Me 109
H+
114
Me
OMe
R1 R2
H H 156
Me H 157
H Me 158
Me Me 159
b
+ OH
a
160a
160b
R1 R2
H H 171
Me H 172
H Me 173
Me Me 174
175a
175b
OH

Scheme II. 30

Table II. 4 Ultraviolet Spectra of 5*H*–pyridazino[4, 5–*b*]indoles



R_1	R_2	Comp.	λ(nm) log ε	λ(nm) log ε	λ(nm) log ε	λ(nm) log ε	λ(nm) log ε	λ(nm) log ε	λ(nm)log ε
Free base									
		A							
H	H	11[a]	226 (4.56)	240 (4.41)	257 (4.29)	265 (4.23)	285 (3.92)	307 (3.83)	320 (3.75)
Me	H	107[a]	230 (4.56)	244 (4.40)	260 (4.34)	268 (4.29)	292 (3.88)	318 (3.88)	332 (3.83)
H	Me	108[a]	227 (4.58)	244 (4.50)	258 (4.31)	264 (4.18)	288 (3.89)	308 (3.84)	322 (3.76)
Me	Me	109[a]	230 (4.55)	248 (4.56)	260 (4.35)	268 (4.24)	299 (3.86)	320 (3.90)	332 (3.83)
		B							
Me	Me	114[b]	207 (4.44)	227 (4.56)	251 (4.78)	254 (4.47)	276 (3.92)	318 (3.65)	328 (3.59)
Monocations									H_0
		11 → 156		215 (4.36)		234 (4.25)	259 (4.52)	307 (3.83)	– 2.78
		107 → 157	206 (4.37)		221 (4.34)	236 (4.26)	262 (4.57)	318(3.95)	"
		108 → 158		210 (4.32)	221 (4.37)	232 (4.21)	258 (4.46)	325 (3.94)	"
		109 → 159		214 (4.39)	222 (4.36)		263 (4.48)	334 (4.04)	"
		114 → 160	203 (4.52)	212 (4.47)		235 (4.30)	262 (4.64)	312 (3.98)	– 2.76
		C							
		161	206 (4.56)	217 (4.57)		238 (4.26)	265 (4.59)	317 (3.99)	+ 7
Dications									
		11 → 171		202 (4.56)	246 (4.36)	278 (4.47)	351 (3.91)		98% H_2SO_4
		107 → 172		206 (4.59)	252 (3.94)	279 (4.33)	361 (3.96)		"
		108 → 173		205 (4.50)	249 (3.94)	279 (4.22)	357 (3.96)		"
		109 → 174		209 (4.37)	254 (4.26)	281 (4.27)	359 (3.80)		"
		114 → 175		204 (4.53)	250 (4.45)	278 (4.50)	355 (3.94)		"

a. in pH 7
b. in pH 9.12

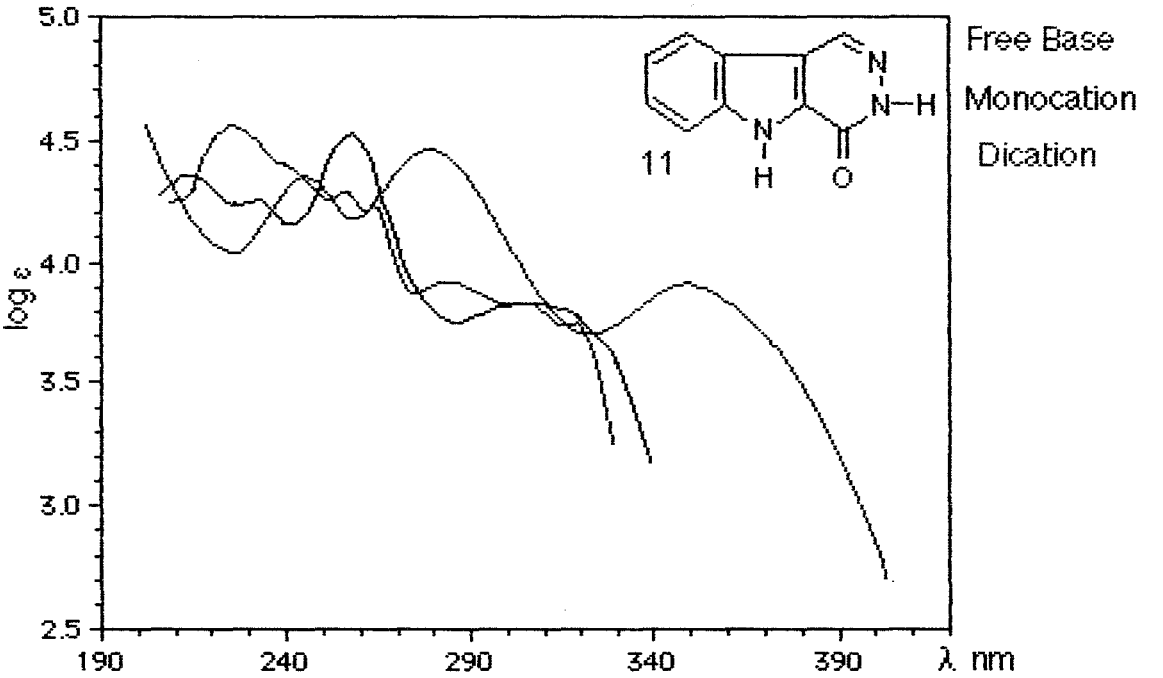


Figure II. 3. 1 Ultraviolet Spectra of 3, 4-Dihydro-4-oxo-5*H*-pyridazino[4,5- *b*] indole in different media.

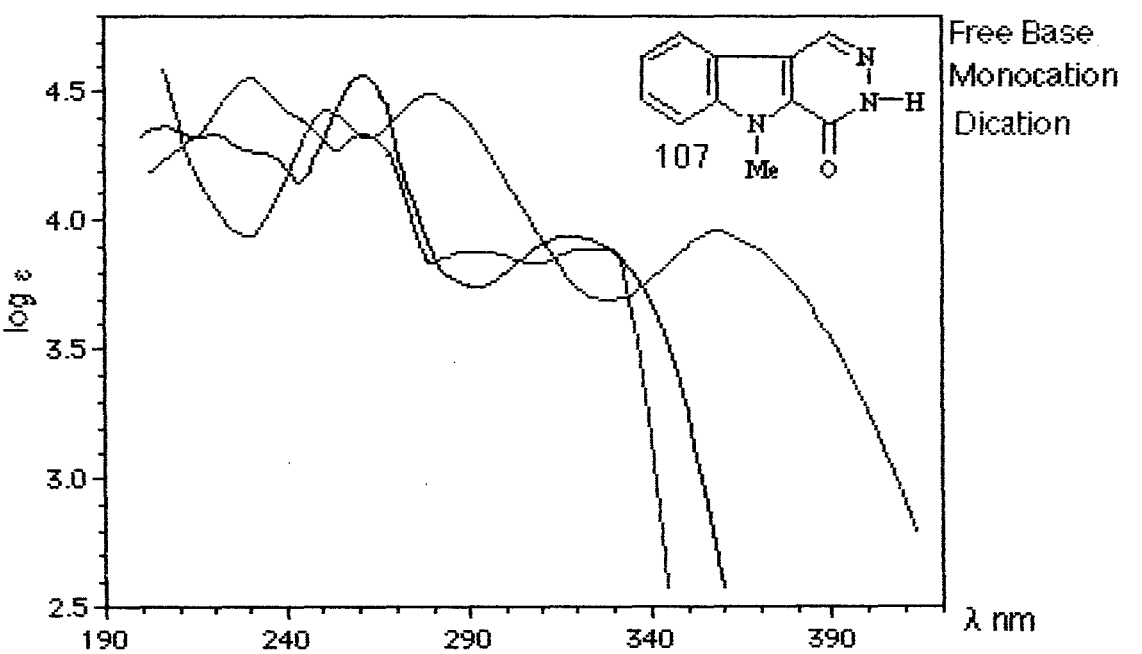


Figure II. 3. 2 Ultraviolet Spectra of 3, 4-Dihydro-5-methyl-4-oxo-5*H*-pyridazino [4,5- *b*]indole in different media.

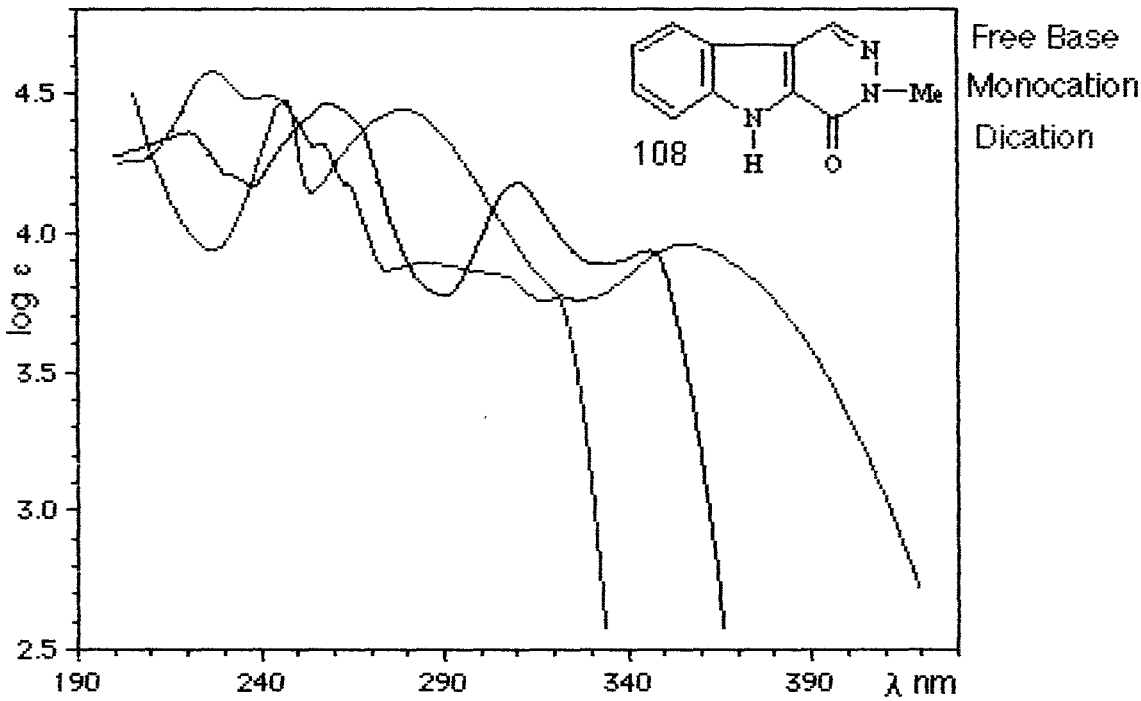


Figure II. 3. 3 Ultraviolet Spectra of 3, 4-Dihydro-3-methyl-4-oxo-5*H*-pyridazino [4,5- *b*]indole in different media.

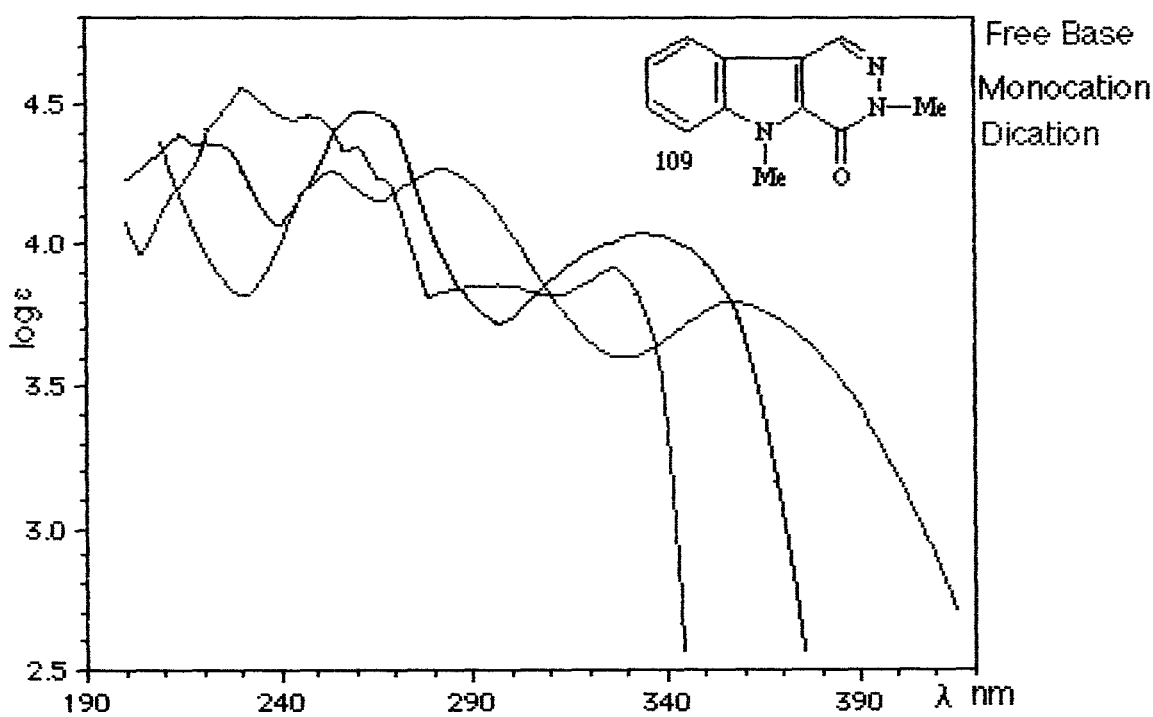


Figure II. 3. 4 Ultraviolet Spectra of 3, 4-Dihydro-3, 5-dimethyl-4-oxo-5*H* -pyridazino [4,5- *b*]indole in different media.

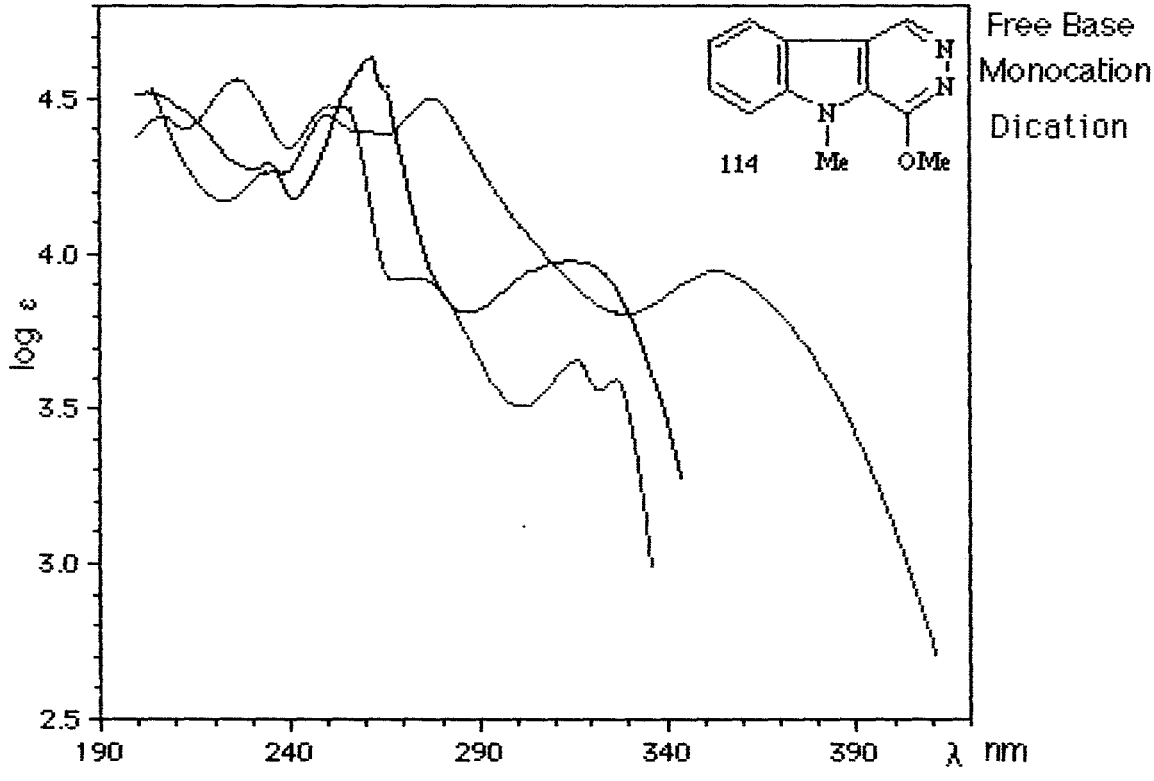


Figure II. 3. 5 Ultraviolet Spectra of 4-Methoxy-5-methyl-5*H*-pyridazino [4,5- *b*]indole in different media.

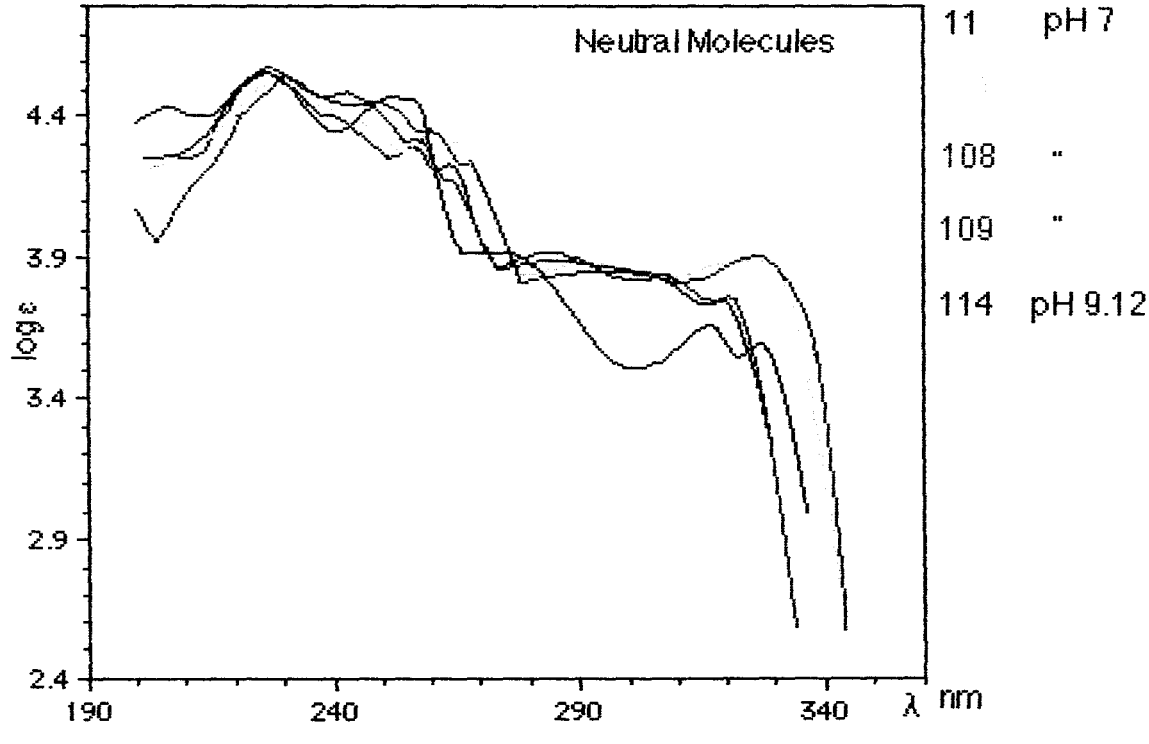


Figure II. 4. 1 Ultraviolet Spectra of Neutral Molecules of : 3, 4-Dihydro-4-oxo-5*H* -pyridazino[4,5- *b*]indoles and 4-Methoxy-5-methyl-5*H*-pyridazino [4,5- *b*]indole.

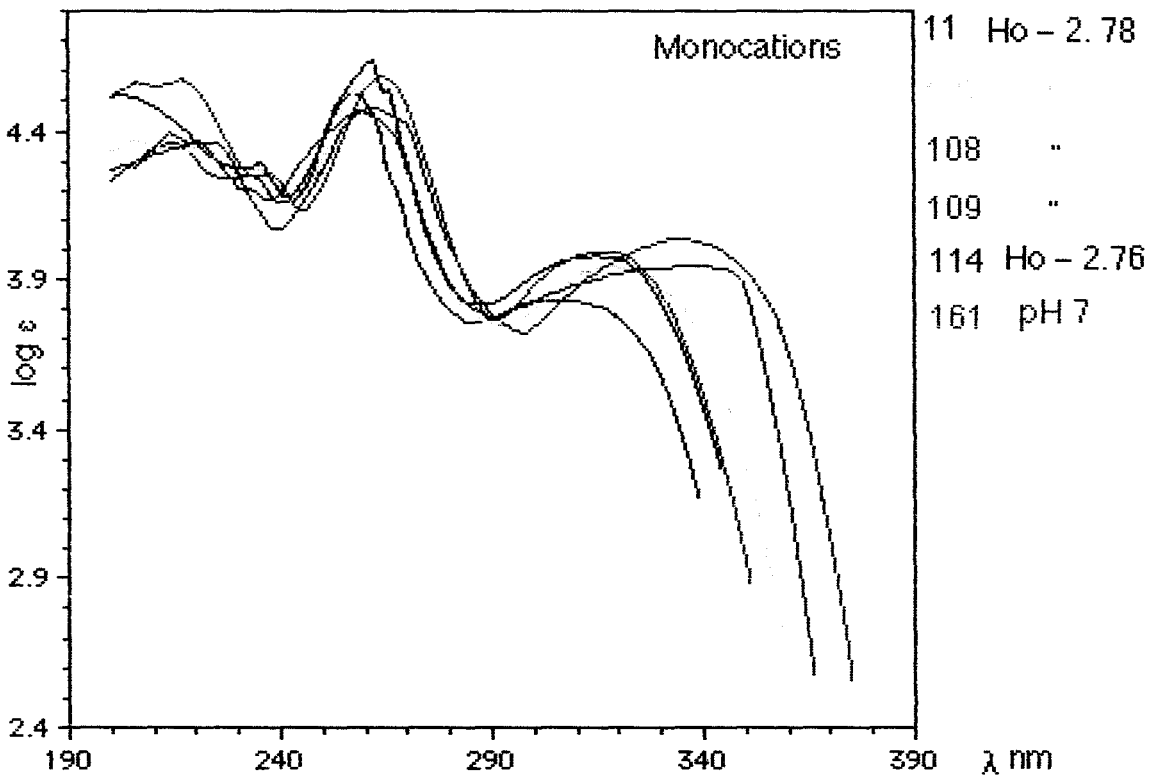


Figure II. 4. 2 Ultraviolet Spectra of Monocationic Species of 3, 4-dihydro-4-oxo-5*H*-pyridazino[4, 5- *b*]indoles, 4-Methoxy-5-methyl-5*H*-pyridazino [4, 5- *b*]indole, and Pyridazino Indolium Salt.

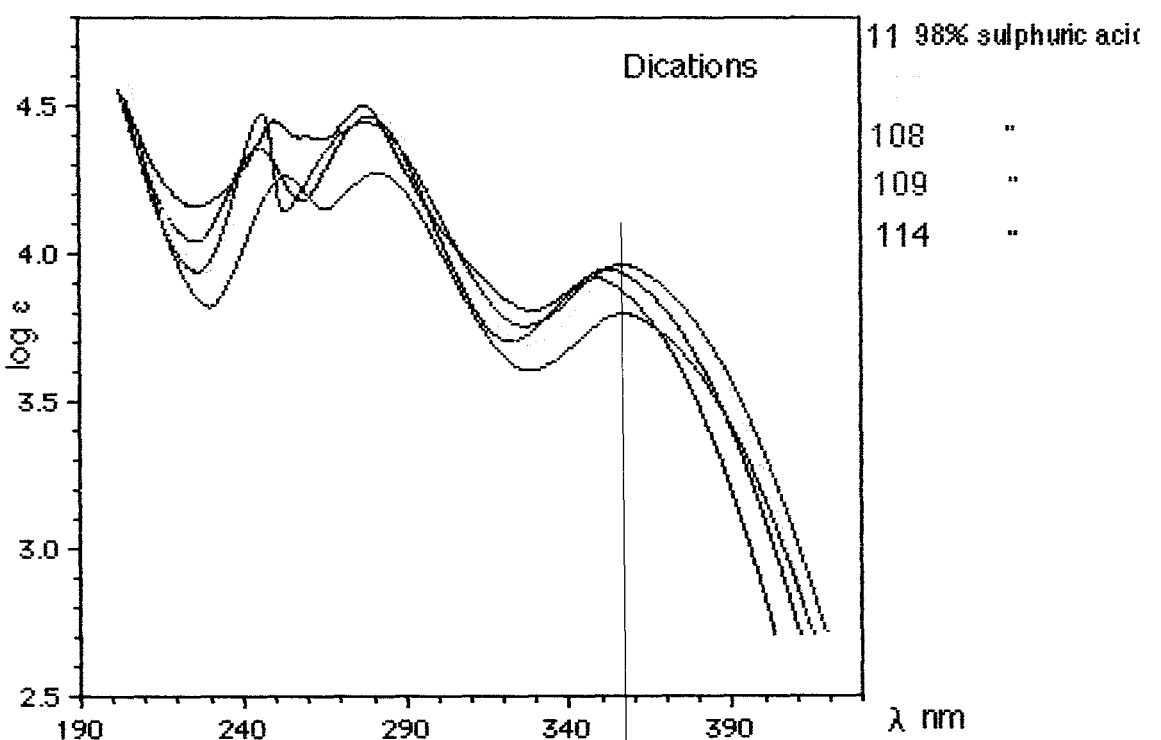
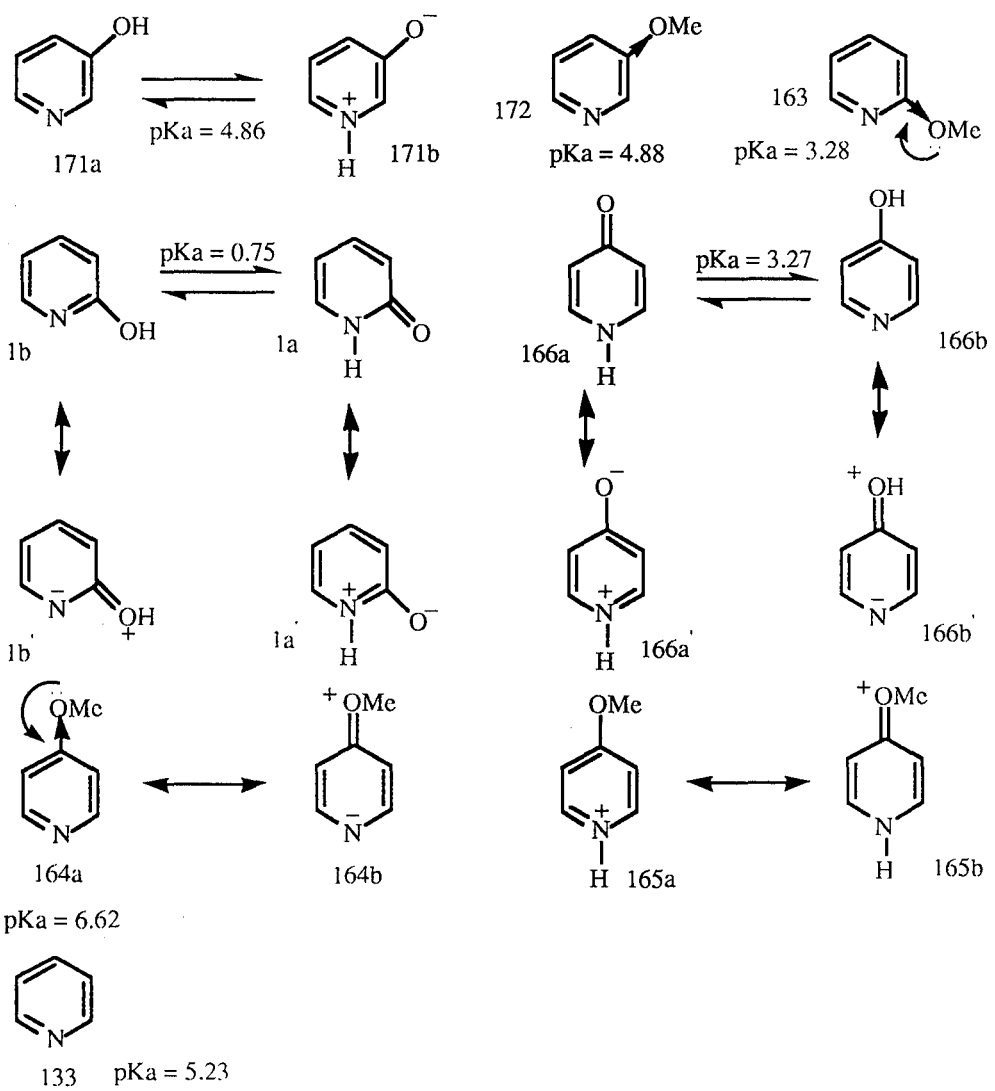


Figure II. 4. 3 Ultraviolet Spectra of Dicationic Species of 5*H*-Pyridazino[4, 5- *b*] indoles

4. 4 Basicity Measurements

The ionisation constants of 3, 4–dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indoles (11), (107), (108), (109), and 4–methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (114) are recorded in the table II. 5.

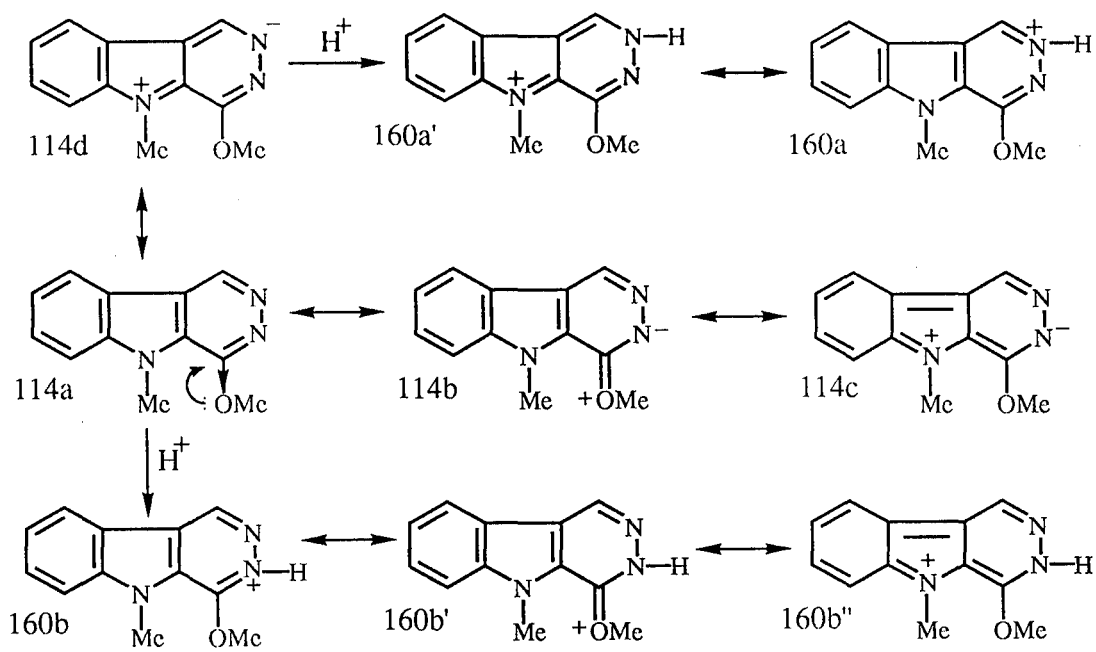
The electronic effect of methoxy and hydroxy groups upon the basicities of the nitrogen hetero aromatic system has been discussed in detail by Albert and Phillips. [75] The pKa value are subject to simultaneous base-weakening electron-withdrawing inductive effect and the mesomeric base-strengthening electron-donating effect of hydroxyl, or methoxy groups and will, therefore, depend upon when the substituents α–, β– or γ– to the ring nitrogen atoms. The nitrogen atom of 3–methoxy– and 3-hydroxypyridine, for example, are subject to an I-effect and hence are slightly weaker bases (pKa = 4.88 and 4.86 respectively) than pyridine (pKa = 5.23).



Scheme II. 31

The nitrogen atom of 2– and 4–methoxypyridines (163) and (164), (pKa = 3.28 and 6.62) are subject to the mesomeric effect, such that the resonance (164a ↔ 164b) results in the formation of the unfavourable charged form (164b) (Scheme II. 31). In the case of protonated form (165a ↔ 165b), the resonance is of more importance than it is for the base (164). Consequently, it would reduce in the case of the 2–isomer (163), or overcome in the case of the 4–isomer (164) the base-weakening I-effect. The weak basicities of 2–and–4–pyridone (1) and (166) (pKa = 0.75 and 3.27) can be rationalised in terms of the importance of strong resonance effect between neutral (1a) and (166a) and charged separated forms (1a') and (166a') of the more stabilised oxo–structures (1a) and (166a).

The pKa of 3.25 for 4–methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (114) indicates that the inductive effect is modified by a mesomeric effect (114a ↔ 114b ↔ 114c ↔ 114d) but the charge forms (114b), (114c) and (114d) (Scheme II. 32) are of less importance in the resonance stabilisation whereas, the cation (160b ↔ 160b' ↔ 160b") and (160a↔ 160a') has higher degree of resonance stabilisation. It is suggested that cations (160a) and (160a') are much more likely compared to cations (160b), (160b') and (160b") in terms of UV spectra of compound (114) and (161) (Table II. 4).



Scheme II. 32

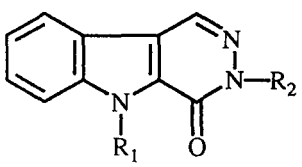
The obtained pKa values of 5*H*–pyridazino[4, 5–*b*]indoles are consistent with the pKa values of 1(2*H*)–phthalazinone and 3(2*H*)–pyridazinones (Table II. 5 and Table II. 6). The indole ring increases the basicities of 3(2*H*)–pyridazinones (7) and (169) and 3–methoxypyridazine (168) by 0.73–1.55 pKa unit, due to the electron-releasing effect of indole ring towards the pyridazine ring.

Examination of pKa values of " methylated fixed model compounds indicates that

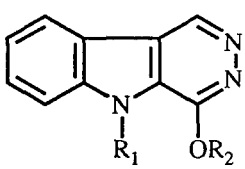
the introduction of a methyl group on the nitrogen atom of the pyridazine ring (108) and (109) results in decrease in the pKa values (ΔpKa = 0.73–1.45) due to an increase in the resonance within the amide system resulting from the electron-donating effect of methyl group. On the other hand, the presence of a methyl group on the indole ring (107) and (109) increases the basicities of (11) by 0.04–0.76 pKa unit.

There is big similarity in the pKa values of these compounds but a significant difference was observed in the pKa value for monoprotonation of (11), (107), (108) and (109) compared with that for 4–methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (114) indicating tautomeric system (11) exists predominantly as the oxo-structure (11a) not in the hydroxyform (11b) (Scheme II. 29).

Table II. 5 pKa Values of 3, 4–Dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indoles (A), and 4–Methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (B).



A



B

Monoprotonation

R_1	R_2	Compound	pKa [a]	Solution
		A		
H	H	11 → 156	−0.29 ± 0.02	b
Me	H	107 → 157	−0.25 ± 0.02	b
H	Me	108 → 158	−1.74 ± 0.02	b
Me	Me	109 → 159	−0.98 ± 0.03	b
		B		
Me	Me	114 → 160	3.25 ± 0.04	c

Diprotonation

		A		
Me	Me	159 → 174	−2.76 ± 0.001	d
		B		
Me	Me	160 → 175	−1.92 ± 0.002	d

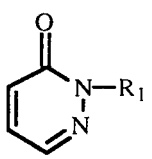
a. The pKa values were determined by the use of the spectroscopic method described by Albert and Serjeant. [76]

b. Determined in buffer solutions and in sulphuric acid solutions ($-2.78 \leqq H_0 \leq 7$) [78]

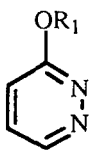
c. Determined in buffer solutions ($0.62 \leq pH \leq 9.12$).

d. Determined in concentrated sulphuric acid solutions.

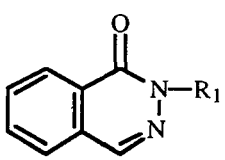
Table II. 6 pKa Values of 1(2*H*)–Phthalazinone and 3(2*H*)–Pyridazinones



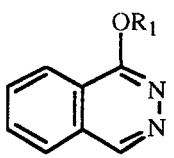
$R_1 = H$ 3
$R_1 = Me$ 167



$R_1 = Me$ 168



$R_1 = H$ 7
$R_1 = Me$ 169



$R_1 = Me$ 170

Compound	pKa
3	– 1.80 [a]
167	– 2.10 [b]
168	2.52 [a]
7	– 2.00 [a]
169	– 4.30 [b]
170	3.77 [b]

a. reference 75 b. reference 77

4. 5 Tautomeric Equilibrium Constants

The preceding discussion establishes qualitatively that the 3, 4–dihydro–4–oxo–5*H* –pyridazino[4, 5–*b*]indoles exist predominantly in the oxo-structure. However, the data used have been limited, because the model compound for the zwitterionic structure (11c) was not available. Thus, we have not been able to obtain quantitative or qualitative evidence for the existence or otherwise of the minor tautomeric forms in the equilibrium system.

The tautomeric pair (11a ↔ 11b) may be interconverted *via* their protonated tautomeric forms of (156a), (156b), (156c), (156d), (171a) and (171b) (Scheme II. 33). The equilibrium between the tautomers described in terms of pK_T may be expressed on the difference between the acidities of conjugate acids of tautomeric bases

$K_T = [B] / [A]$

$K_A = [C] / [A]$	$[A] = [C] / K_A$
$K_B = [D] / [B]$	$[B] = [D] / K_B$
$K_C = [E] / [C]$	$[C] = [E] / K_C$
$K_D = [E] / [D]$	$[D] = [E] / K_D$

$$K_T = \frac{\frac{[D]}{K_B}}{\frac{[C]}{K_A}} = \frac{[D]}{K_B} \cdot \frac{K_A}{[C]}$$

$$K_T = \frac{\frac{\cancel{[E]}}{K_D}}{K_B} \cdot \frac{K_A}{\frac{\cancel{[E]}}{K_C}}$$

$$K_T = \frac{K_A \cdot K_C}{K_D \cdot K_B}$$

$$pK_T = [\,(pK_A + pK_C) - (pK_D + pK_B)\,]$$

$$pK_T = [\,(pKa(A) + pKa(C)) - (pKa(D) + pKa(B))\,]$$

$$pK_T = [\,(pKa_1(A) + pKa_2(A)) - (pKa_2(B) + pKa_1(B))\,]$$

The validity of the relationship requires that protonation of the tautomeric forms must give cation having a common electronic structure. That this is the case for 5*H*–pyridazino[4, 5–*b*] indoles is confirmed by the similarity in the electronic spectra of diprotonated forms of the potentially tautomeric compounds and the fixed forms (Scheme II. 30, Scheme II. 33, Scheme II. 34).

Since the basicities of (11a) and (11b) can not be determined individually as the tautomers interconvert quickly, the value $K_{A'}$, $K_{B'}$, $K_{C'}$ and $K_{D'}$ were obtained from the corresponding " fixed tautomeric " model compounds (109) and (114) (Scheme II. 34). Thus, a quantitative measure can be obtained for the equilibrium.

$$K'_T = \frac{K_{A'} \cdot K_{C'}}{K_{D'} \cdot K_{B'}}$$

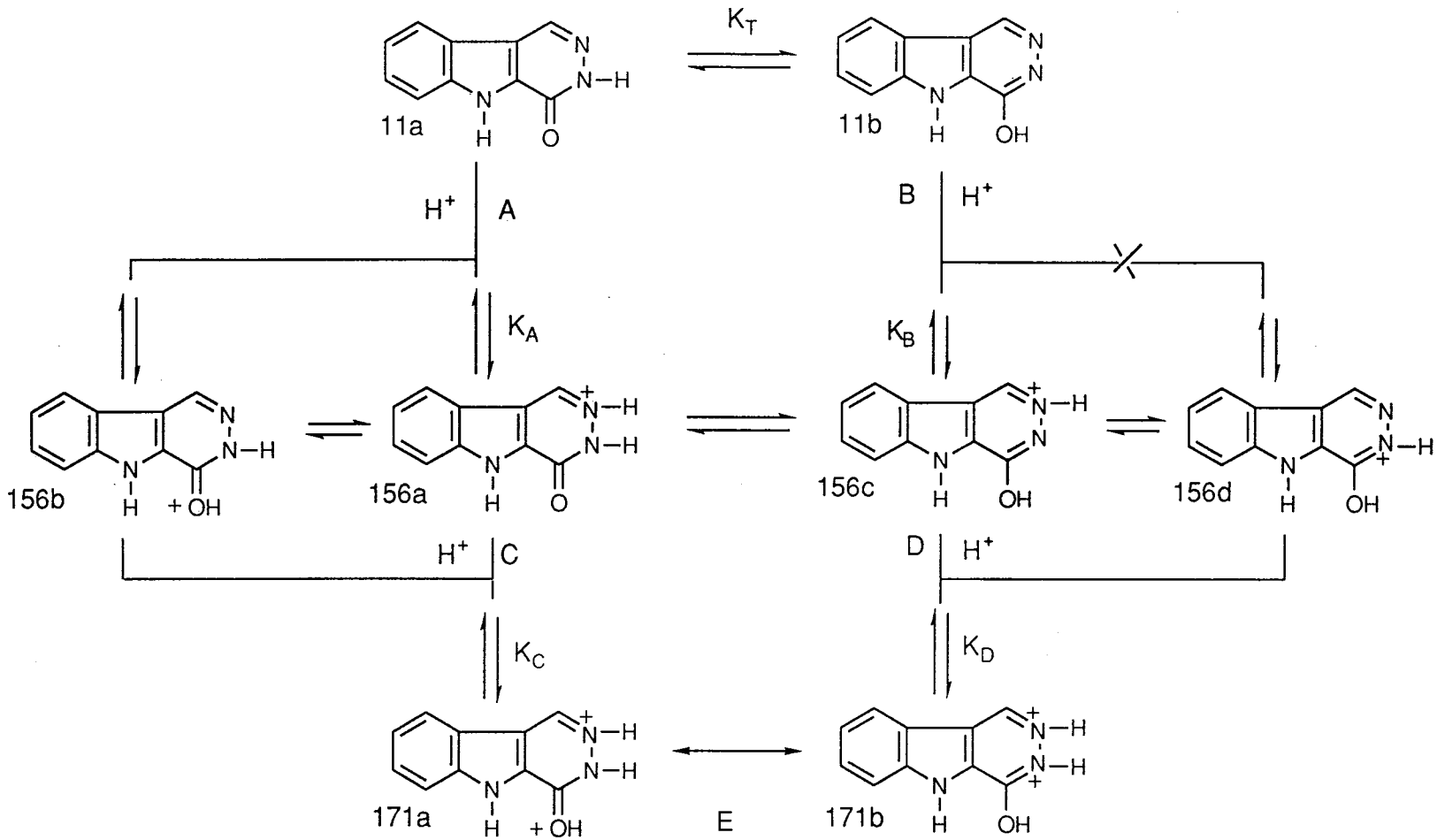
$$pK'_T = [\,pK_{A'} + pK_{C'}\,] - [\,pK_{D'} + pK_{B'}]$$

$$pK'_T = [\,pKa_1(109) + pKa_2(109)] - [\,pKa_2(114) + pKa_1(114)\,]$$

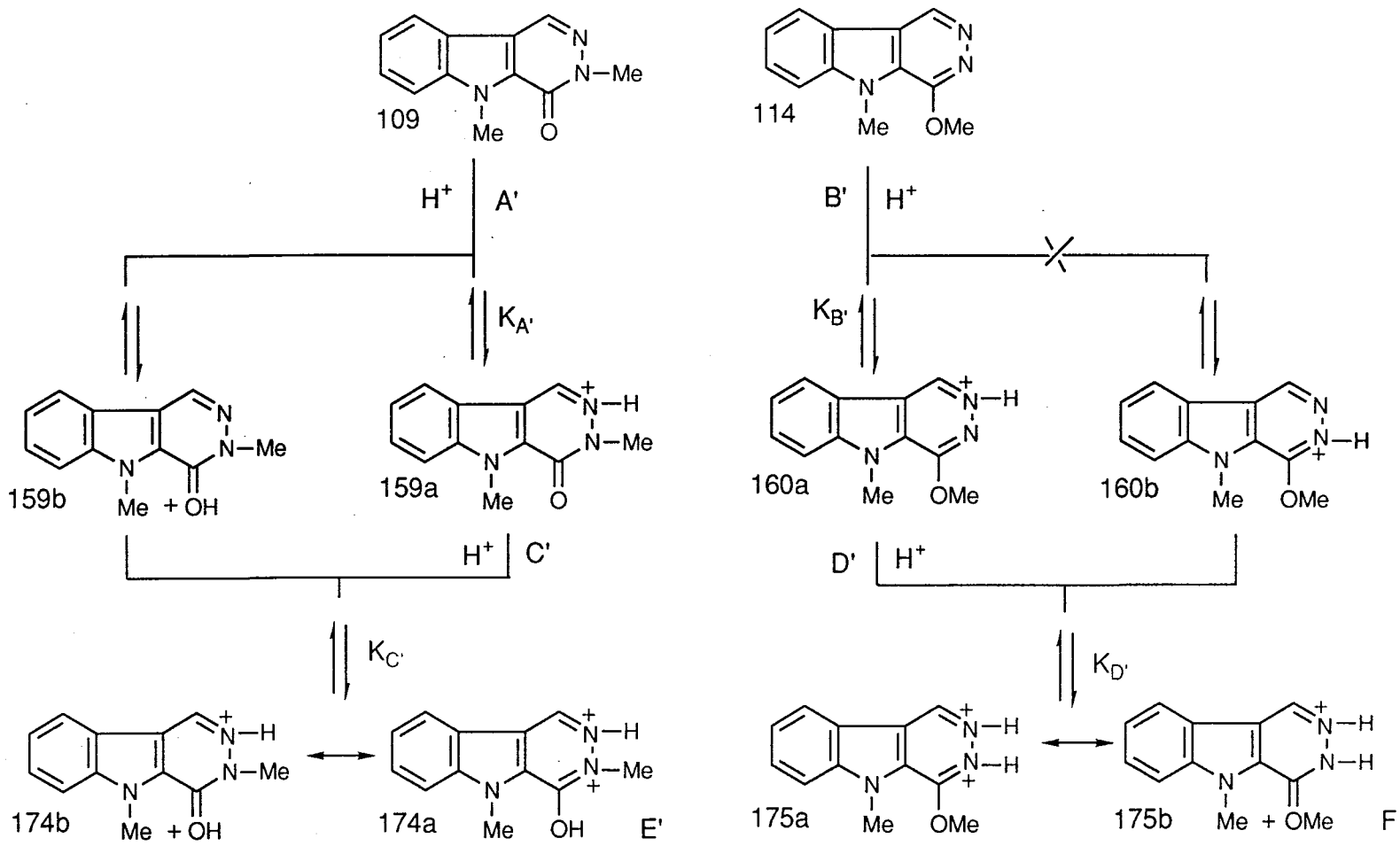
$$pK'_T = [(-0.98) + (-2.76)\,] - [\,(-1.92) + (3.25)\,]$$

$$pK'_T = -5.07$$

This value establishes that the oxo-structure (11a) is favoured to the extent of ca 117, 500 : 1 compared with the hydroxy structure (11b) (Scheme II. 30, Scheme II. 33 and Scheme II. 34).



Scheme II. 33


109
114
H+
A'
B'
H+
KA'
KB'
159b
159a
160a
160b
Me + OH
H+
C'
D'
H+
KC'
KD'
174b
174a
175a
175b
Me + OH
E'
F

Scheme II. 34

5. 0 Experimental

Electronic spectra were measured for ca 10^{-5} M buffered aqueous solutions and sulphuric acid solutions at the pH or H_0 values indicated. Basicities were determined spectrophotometrically using SP8–UV–VIS spectrometer. Infrared spectra were recorded for mulls in nujol or in bromoform using a Perkin -Elmer 295 infrared spectrometer between 4000 and 600 cm^{-1}, and nuclear magnetic resonance spectra were measured in the solvents indicated at 60 MHz using a Jeol spectrometer and all values expressed in parts per million (δ) downfield from tetramethylsilane (TMS) ($\delta = 0$). Melting points were taken using a Reichart microscope hot stage type melting point apparatus, all the values given are uncorrected.

Determination of Ionisation Constants of 5*H*–pyridazino(4, 5–*b*)indoles.

The pKa (monocation and dication formation) values of 5*H*–pyridazino[4, 5–*b*] indoles were determined by the spectrometric procedures described by Albert and Serjeant. [76]

The method depends upon the direct determination of the ratio of molecular species (neutral molecule) to protonated species in a series of non-absorbing buffer solutions or solutions of known H_0. The analytical wavelength was chosen where there was the greatest difference in the intensity of absorption between the neutral and cationic species. Measurement of the intensity of this wavelength at various pH (H_0) values, intermediate between those producing the neutral and cationic species gave the ratio of neutral to cationic species present at each pH (H_0).

In calculating the ratio of the two species present at any pH, it is assumed that Beer's law is obeyed for both species. Thus, the observed optical density, d, at the analytical wavelength will be equal to the sum of the optical densities of the ionised species, d_i , and the molecular species, d_m ,

$$d = d_i + d_m$$

Where d = extinction coefficient x pathlength x concentration

The concentration of the protonated species in the mixture is F_iC, where F_i is the proportion of the cationic species and, hence, its contribution to the observed optical density is ;

$$\varepsilon_i . F_i . C . l$$

Similarly, the contribution of the molecular species to the observed optical density of the mixture is $\varepsilon_m . F_m . C . l$, where F_m is the fraction present in the molecular form. The term ε_i and ε_m are the molecular extinction coefficients of the pure cationic and neutral species, respectively which are related directly to the optical densities. Utilising this data, equation (1) can be used to determine the pKa of the compound.

$$pKa = pH \text{ (or } H_0) + \log \frac{d - d_m}{d_i - d} \qquad (1)$$

The analytical operation involves four steps :

1. The preparation of a stock solution and suitable dilution of it to the appropriate pH or H_0. A 25 ml stock solution of the compound under analysis was prepared in ethanol to facilitate dissolution at a concentration such that when 1 ml is diluted to 50 ml of water of known pH (or H_0). It will give a final concentration of ca 1×10^{-5} — 9×10^{-5} M.
2. A search for the pure spectra of the two species involved in the equilibrium.
3. The choice of an analytical wavelength suitable for the intensity measurements.
4. A search for an approximate value of the pKa value and calculation of pKa; using equation (1).

Ethyl indole–2–carboxylate [66] :

Phenylhydrazine (43.26 g, 0.4 mol.) and ethyl pyruvate (46.48 g, 0.4 mol.) in toluene (1000 ml) were refluxed for 1.5 h in the presence of a trace amount of *p*–toluenesulphonic acid in a round bottomed flask equipped with Dean–Stark apparatus to remove water. The solution prepared above was added to a cooled solution of dehydrated *p*–toluene sulphonic acid in toluene (1000 ml), which had been prepared from *p*–toluenesulphonic acid monohydrate ($TsOH.H_2O$) (114.13 g, 0.6 mol.) by using Dean-Stark apparatus, and the mixture was refluxed for 1.5 h. After the reaction was complete, the reaction mixture was washed, successively with aqueous hydrochloric acid solution (5 %, 500 ml), aqueous sodium hydroxide solution (5 %, 500 ml) and saturated aqueous sodium chloride solution. The remaining acidic and basic aqueous phases were extracted once more with toluene (150 ml). The organic phases were combined and washed well with water (500 ml) and dried ($MgSO_4$). Solvent was evaporated under reduced pressure to give pale yellow solid, which was recrystallised from ethanol to give ethyl indole-2-carboxylate (71.5g, 95 %), as white crystals, m.p. 123–124 °C, [lit. [66], m.p. 121–124 °C]. ^{1}H-NMR($CDCl_3$) : δ 1.42 (t, 3H) ; 4.40 (q, 2H) ; 7.05–7.90 (m, 5H). IR ($CHBr_3$) : $\nu_{max.}$ 3240 and 3310 (b, NH), 1690 (s, C=O) cm^{-1}. $[M^+]$ = 189 a.m.u.

Ethyl 1–methylindole–2–carboxylate :

Method A [68]:

Dimethyl sulphoxide (DMSO) (90 ml) was added to powdered potassium hydroxide (9.63 g, 0.17 mol.) and the mixture was stirred for 15 min. Ethyl indole–2–carboxylate (8.13g, 0.043 mol.) was then added and the mixture was stirred at room temperature for 45 min. Methyl iodide (12.21 g, 0.087 mol.) was added and the mixture was cooled briefly and stirred for a further 45 min. before water (100 ml) was added with stirring. The mixture was left for 30 min. and then extracted with diethyl ether (3 x 50 ml) and washed with water (3x 50 ml). The combined ether extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure to give ethyl 1–methylindole–2–carboxylate (6.45 g, 74 %), as white crystals, m.p. 61.5-62 °C [lit. [67] m.p. 60-61°C]. ^{1}H-NMR ($CDCl_3$) : δ 7.56 –7.80 (dd, 1H, H_4) ; 7.00–7.48 (m, 4H, $H_{3,\ 5-7}$) ; 4.20–4.60 (q, 2H, OCH_2-) ; 4.04 (s, 3H, NCH_3) ; 1.28-1.60 (t, 3H, C-CH_3). IR (nujol) : $\nu_{max.}$ 1670 (C=O) cm^{-1}. $[M^+]$ = 203 a.m.u.

Method B [67]:

A mixture of ethyl indole–2–carboxylate (5 g, 0.026 mol), anhydrous potassium carbonate (100 g, 0.72 mole, dimethyl sulphate (10.94 g, 0.09 mol.) and acetone (170 ml) were refluxed for 8 h with mechanical stirring while protecting the mixture with anhydrous calcium chloride. The addition of an excess of ammonium hydroxide solution (10 %) to the cooled reaction mixture neutralised any remaining reagent. Then, most of the acetone was removed under reduced pressure and water was added to the residual material to dissolve the potassium carbonate. The aqueous mixture was extracted with

dichloromethane, the organic solution was dried (MgSO4) and the solvent removed under reduced pressure. The residual solid was recrystallised from ethanol to give ethyl 1–methylindole–2–carboxylate (5 g, 95 %), m.p. 61.5–62 °C.

Ethyl 3–formylindole–2–carboxylate [69] :

N-Methylformanilide (11.80 g, 0.09 mol) and phosphorus oxychloride (13.40 g, 0.09 mol), protected from atmospheric moisture, were stirred at room temperature for 15 min. To the mixture was added 1, 2–dichloroethane (60 ml), followed by ethyl indole–2 –carboxylate (15 g, 0.08 mol). After refluxing the mixture 1 h, it was poured into a solution of sodium acetate (60 g) in ice-water (120 g), whereupon the product separated. The crude product was collected by filtration and washed with water (100 ml) and diethyl ether (100 ml), and recrystallised from ethanol to give ethyl 3–formylindole–2 –carboxylate (15 g, 87 %), as pale yellow crystals, m.p. 190–192 °C [lit. [15], m.p. 191.5 –192 °C ; lit. [69], m.p. 190.5–192 °C]. ^{1}H-NMR (DMSO-d_6) : δ 12.80 (b, 1H, NH) ; 10.70 (s, 1H, CHO) ; 8.00-8.50 (dd, 1H, H_4) ; 7.10-7.80 (m, 3H, H_{5-7}) ; 4.50 (s, 2H, OCH_2-) ; 1.45 (t, 3H, CH_3). IR : $\nu_{max.}$ 3130 (s, NH), 1750 (s, C=O), 1680 (s, CHO) cm^{-1}. $[M^+]$ = 217 a.m.u.

Ethyl 1–methyl–3–formylindole–2–carboxylate :

N–Methylformanilide (10.97 g, 0.081 mol) and phosphorus oxychloride (12.46 g, 0.081 mol), protected from atmospheric moisture, was stirred at room temperature for 15 min. To the mixture was added 1, 2–dichloroethane (60 ml), followed by ethyl 1–methylindole –2–carboxylate (15 g , 0.074 mol). After refluxing the mixture for 1h, it was poured into a solution of sodium acetate (60 g) in ice-water (120 g). The mixture was extracted with diethyl ether (3 x 100 ml) and the combined ether solutions were washed well with water (3 x 200 ml), and dried ($MgSO_4$). Removal of the solvent gave an oily product. Crystallisation of the crude product from ethanol afforded ethyl 1–methyl–3–formyl indole–2–carboxylate (13.2 g, 77 %), as pale yellow crystals, m.p. 110 °C [lit. [17] m.p. 112–113 °C]. ^{1}H-NMR ($CDCl_3$) : δ 11.65 (s, 1H, CHO) ; 7.20–7.60 (m, 4H, arom.) ; 4.50 (q, 2H, C-CH_2-O) : 3.80 (s, 3H, CH_3N) ; 1.40 (t, 3H, CH_3C). IR (nujol) : $\nu_{max.}$ 1710 (C=O ester), 1660 (C=O, CHO) cm^{-1}. $[M^+]$ = 231 a.m.u.

3, 4–Dihydro–4–oxo–5*H*–pyridazino(4, 5–*b*)indole [15] :

Ethyl 3–formylindole–2–carboxylate (12 g, 0.055 mol) in 2–ethoxyethanol (100 ml) was added to a refluxing solution of hydrazine hydrate ($N_2H_4.H_2O$) (5.9 g, 0.118 mol) in 2–ethoxyethanol (20 ml) dropwise over 1 h and refluxed for a further 4 h. On cooling the solution, white needles separated, which were collected by filtration. Recrystallisation of the product from DMF-water gave 3, 4–dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indole (9 g, 88 %), as white needles, m.p. 326–327 °C [lit.[15] m.p. 326.5–327 °C].

^{1}H-NMR (DMSO-d_6) : δ 12.96(s, 1H, $N_5\underline{H}$); 12.84 (s, 1H, $N_3\underline{H}$) ; 8.84 (s, $1H_1$) ; 8.08–8.36 (dd, 1H, H_9) ; 7.20-7.90 (m, 3H, H_{6-8}). IR (nujol) : $\nu_{max.}$ 3140 (br. m, NH, OH), 1660 (C=O) cm^{-1}. $[M^+]$ = 185 a.m.u.

3, 4-Dihydro-5-methyl-4-oxo-5*H*-pyridazino[4, 5-*b*]indole [28] :

Ethyl 3–formyl-1–methyl– indole–2–carboxylate (10 g, 0.043 mol) in 2–ethoxyethanol (100 ml) was added to a refluxing solution of hydrazine hydrate ($N_2H_4.H_2O$) (4.68 g, 0.09 mol) in 2–ethoxyethanol (20 ml) dropwise over 1 h and then refluxed for a further 4 h. On cooling the solution, white needles separated,which were collected by filtration. Recrystallisation of the crude product from 2–ethoxyethanol afforded 3, 4–dihydro–5 –methyl–4–oxo–5*H*–pyridazino[4, 5–*b*] indole (8.2 g, 95 %) as white needles, m.p. 282–283 °C. [lit. [28] m.p. 282.5–283 °C]. ^{1}H-NMR (DMSO-d_6) : δ 12.80 (br, s, 1H, NH), 8.68 (s, 1H, H_1) ; 8.04-8.28 (dd, 1H, H_9) ; 7.20–7.74 (m, 3H, H_{6-8}) ; 4.32(s, 3H, NCH_3) . IR (nujol) : $\nu_{max.}$ 3160 (br, w), 3230 (br, w) (NH), 1680 (C=O), 1620 (C=N) cm^{-1}. $[M^+]$ = 199 a.m.u.

3, 4-Dihydro-3-methyl-4-oxo-5*H*-pyridazino[4, 5-*b*]indole [18] :

Ethyl 3–formylindole–2– carboxylate (1 g, 4.61 mmol) and methylhydrazine (6.5 g, 0.14 mol) were refluxed in glycerol (20 ml) for 15 min. The solution became yellow, then colourless crystals separated,which were collected after cooling and dilution of the mixture with water (100 ml). Recrystallisation of the crude product from 2–ethoxyethanol afforded 3, 4–dihydro–3–methyl–4–oxo–5*H*–pyridazino[4, 5–*b*]indole (0.41 g, 45 %) as white needles, m.p. 298 °C [lit. [18] m.p. 298–300 °C, lit. [27] m.p. 282–283 °C]. ^{1}H-NMR (DMSO-d_6) : δ 3.84 (s, 3H, NCH_3) ; 8.76 (s, 1H, H_1), 8.02–8.24 (dd, 1H, H_9), 12.80 (br. s, 1H, NH). IR (nujol) : $\nu_{max.}$ 3130 (br. w, NH), 1640 (C=O), 1620 (C=N, C=C) cm^{-1}. (Found : C, 66.3 ; H, 4.4 ; N, 21.0 ; Calc. for $C_{11}H_9N_3O$ C, 66.3 ; H, 4.5 ; N, 21.1). $[M^+]$ =199 a.m.u.

3, 4-Dihydro-3, 5-dimethyl-4-oxo-5*H*-pyridazino[4, 5-*b*]indole :

Method A :

Ethyl 3–formyl–1–methylindole–2–carboxylate (1.5 g, 6.48 mmol) and methylhydrazine (2.12 g, 0.046 mol) were refluxed in glycerol (25 ml) for 15 min. After the reaction was complete,the reaction mixture was cooled and, water (150 ml) was added to the mixture. The precipitate was collected by filtration and dried. Recrystallisation of the crude product from 2–ethoxyethanol afforded 3, 4–dihydro–3, 5–dimethyl–4–oxo–5*H*–pyridazino [4, 5–*b*]indole (0.52 g, 38 %), as white needles, m.p. 211 °C [lit.[17] m.p. 214–215 °C]. ^{1}H-NMR ($CDCl_3$) : δ 8.40 (s, 1H, –CH=N) ; 7.85–8.08 (dd, 1H, H_9) ; 7.20–7.60 (m, 3H, H_{6-8}) ; 4.35 (s, 3H, CH_3N) ; 3.95 (s, 3H, CH_3NCO).

IR (nujol) : $\nu_{max.}$ 1645 (C=O), 1620 (C=N, 1620) cm^{-1}. $[M^+]$ = 213 a.m.u.

Method B [17] :

A mixture of 3, 4–dihydro–5–methyl–4–oxo–5*H*–pyridazino[4, 5–*b*]indole (4 g, 0.02 mol), anhydrous potassium carbonate (27.6 g, 0.2 mol), and dimethyl sulphate (7.59 g, 0.06 mol) were refluxed in acetone (200 ml) with stirring for 8 h. Addition of an excess of ammonium hydroxide solution (10 %) to the cold reaction mixture neutralised any remaining reagent. Then, the solvent was evaporated under reduced pressure and water (250 ml) was added to the residue to dissolve potassium carbonate. The precipitate was filtered, washed well with water, and dried. Recrystallisation of the residue from 2–ethoxyethanol afforded pure 3, 4–dihydro–3, 5–dimethyl–4–oxo–5*H*–pyridazino [4, 5–*b*]indole (3.8 g, 89 %), as white needles, m.p. 211 °C, which was identical with that obtained from method A.

Ethyl 1–benzylindole–2–carboxylate :

Dimethyl sulphoxide (65 ml) was added to powdered potassium hydroxide (7.11 g, 0.13 mol) and the mixture was stirred for 15 min. Ethyl indole–2–carboxylate (6 g, 0.032 mol) was then added and the mixture was stirred at room temperature for 45 min. Benzyl bromide (10.85 g, 0.06 mol) was added and the mixture was cooled briefly and stirred for a further 2 h before water (75 ml) was added with stirring. The mixture was left for 30 min. and then extracted with diethyl ether (3 x 100 ml) and washed with water (3 x 100 ml). The combined ether extracts were dried ($MgSO_4$). The solvent was removed under reduced pressure to give ethyl 1–benzylindole–2–carboxylate (5 g, 56 %), as a yellowish solid, m.p. 54–55 °C [lit. [79] m.p. 58–60 °C]. ^{1}H-NMR ($CDCl_3$) : δ 7.60–7.80 (dd, 1H, H_4) ; 6.80–7.52 (m, 4H, $H_{3,\ 5-7}$) ; 5.80 (s, 1H, CH_2Ph) ; 4.12–4.60 (q, 2H, OCH_2-) ; 1.20–1.45 (t, 3H, -C-CH_3). IR (nujol) : $\nu_{max.}$ 1715 (C=O) cm^{-1}.

Ethyl 1–benzyl–3–formylindole–2–carboxylate :

N–Methylformanilide (2.14 g, 0.016 mol) and phosphorus oxychloride (2.42 g, 0.016 mol), protected from atmospheric moisture, was stirred at room temperature for 15 min. To the mixture was added 1, 2–dichloroethane (20 ml), followed by ethyl 1–benzylindole –2–carboxylate (4 g, 0.014 mol). After refluxing the mixture for 1h, it was poured into a solution of sodium acetate (20 g) in ice-water (40 g). The mixture was extracted with diethyl ether (3 x 50 ml) and washed well with water, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give a solid which was recrystallised from ethanol to give ethyl *1–benzyl–3–formylindole–2–carboxylate* (3 g, 55 %), as yellowish crystals, m.p. 79–80 °C. (Found : C, 74.2 ; H, 5.5 ; N, 4.4 ; $C_{19}H_{17}NO_3$ requires C, 74.3 ; H, 5.6 ; N, 4.6). ^{1}H-NMR ($CDCl_3$) : δ 10.64 (s, 1H, CHO) ; 8.40–8.70 (dd, 1H, H_4) ; 7.00–7.40 (m, 3H, H_{5-7}) ; 5.80 (s, 1H, CH_2Ph) ; 4.26-4.62 (q, 2H, OCH_2-) ; 1.24–1.48 (t, 3H, -C-CH_3). $[M^+]$ = 307 a.m.u. IR (nujol) : $\nu_{max.}$ 1710 (C=O, ester), 1640 (C=O, CHO) cm^{-1}.

5–Benzyl–3, 4–dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indole :

Ethyl 1–benzyl–3–formylindole–2–carboxylate (1 g, 3.25 mmol) in 2–ethoxyethanol (100 ml) was added to a refluxing solution of hydrazine hydrate (N_2H_4 H_2O) (1.63 g, 32.5 mmol) in 2–ethoxyethanol (20 ml) dropwise over 1 h and refluxed for a further 6 h. After cooling the reaction mixture, white crystals separated, which were collected and washed ethanol (50 ml). Recrystallisation of the compound from 2–ethoxyethanol afforded *5–benzyl–3, 4–dihydro–4–oxo–5H–pyridazino[4, 5– b]indole* (0.7 g, 79 %), as white needles, m.p. 237 °C. (Found : C, 73.9 ; H, 4.8 ; N, 15.0 ; $C_{17}H_{13}N_3O$ requires C, 74.2 ; H, 4.8 ; N, 15.3). ^{1}H-NMR ($CDCl_3$) : δ 8.64 (s, 1H, H_1) ; 8.04–8.24 (dd, 1H, H_9) ; 7.20–7.80 (m, 8H, H_{6-8} C-Ph) ; 6.12 (s, 2H, -CH_2-) ; IR (nujol) : $\nu_{max.}$ 3120, 3160, 3240(br. , NH, OH), 1660 (C=O), 1610 (C=N, C=C) cm $^{-1}$. [M^+] = 275 a.m.u.

2, 5–Dimethyl–4–methoxy–5*H*–pyridazino[4, 5–*b*]indolium toluene–*p*–sulphonate :

4–Methoxy–5–methyl–5*H*– pyridazino[4, 5–*b*]indole (51 mg, 0.239 mmol) and methyl toluene–*p*–sulphonate (44.5 mg, 0.239 mmol) were kept at room temperature in methanol (5 ml) for 12 h. Diethyl ether (20 ml) was added to the mixture. The precipitate was collected and dried. Crystallisation of the solid from ethanol-diethyl ether gave pure *2, 5–dimethyl–4–methoxy–5H–pyridazino[4, 5– b]indolium toluene-p–sulphonate* (90 mg, 95%), as white solid, m.p. 239 °C. (Found : C, 59.87 ; H, 5.14 ; N, 10. 31 ; S, 8.22 ; $C_{20}H_{21}N_3O_4S$ requires C, 60.14; H, 5.30; N, 10.52 ; S, 8.03. ^{1}H-NMR (DMSO-d_6) : δ 10.64 (s, 1H, H_1); 8.40–8.60 (dd, 1H, H_9); 7.00–8.00 (m, 7H, aromatic); 4.56 (s, 3H, CH_3) ; 4.33 (s, 6H, $2CH_3$); 2.32 (s, 3H, Me-Ph-SO_3).

The synthesis of **4–methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole** is described in detail in chapter V.

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CHAPTER III

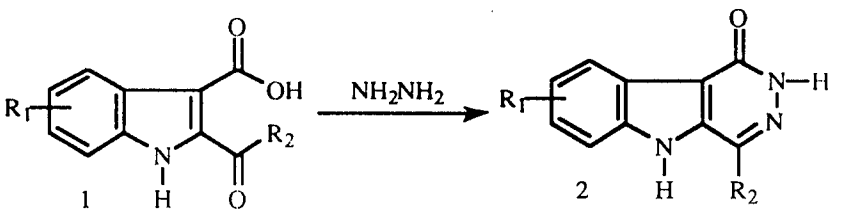
Tautomerism of 1, 2–Dihydro–1–oxo–5*H*–pyridazino(4, 5–*b*)indoles

1. 0 1-Oxo-5*H*-pyridazino(4, 5-*b*)indoles. - Synthesis

1.1 Introduction

There are relatively few papers reported in the literature [1, 2, 3, 30] on the synthesis of 1-oxo-5*H*-pyridazino[4, 5-*b*]indoles.

Zhungietu and Zorin [1] used the condensation of suitable 2-acylindole-3-carboxylic acids and derivatives (1) with hydrazine to prepare 1, 2-dihydro-1-oxo-5*H*-pyridazino [4, 5-*b*]indoles (2). (Scheme III. 1).

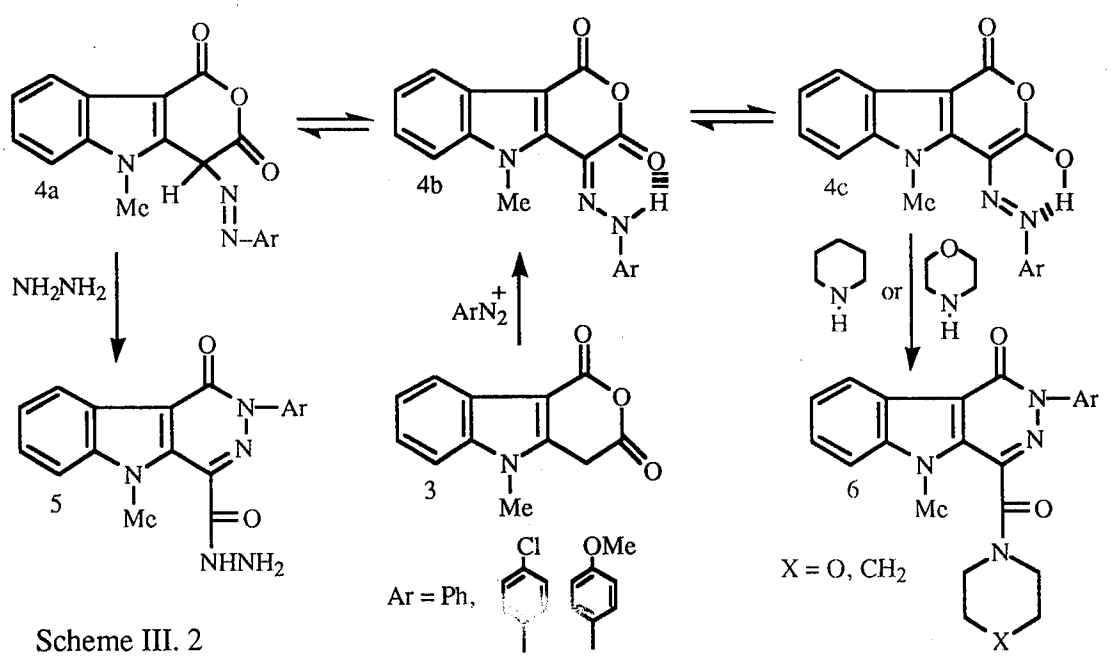


R_1 = H, 8-Br, 6-Me, 8-OMe
8-Me, 8-Cl

R_2 = Me, Ph, C_6H_4Cl-*p*, C_6H_4Br-*p*

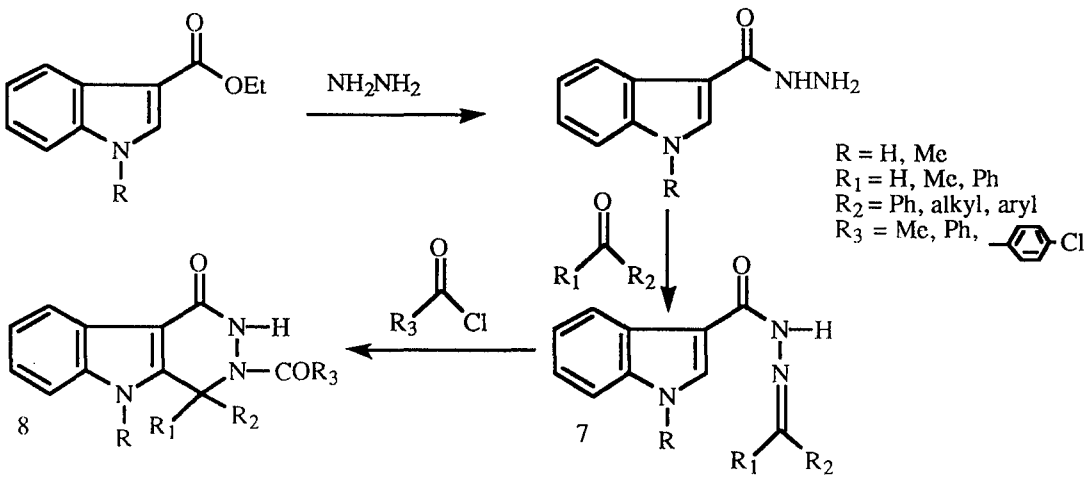
Scheme III. 1

A second preparation of 1, 2-dihydro-1-oxo-5*H*-pyridazino[4, 5-*b*]indoles was carried out by Vega, Palop, *et al* [2] starting with 2-(3-carboxy-1-methylindole)acetic acid anhydride (3), which was reacted with diazonium salts to give α-hydrazino-cyclic anhydrides (4). Subsequent reaction with hydrazine, morpholine, or piperidine in boiling xylene gave the 1, 2-dihydro-1-oxo-5*H*-pyridazino[4, 5-*b*] indoles (5) and (6) (Scheme III. 2).



Scheme III. 2

A third method for the preparation of 1–oxo–5*H*–pyridazino[4, 5–*b*]indoles involves cyclisation of suitable 3–indolecarbohydrazones (7) with acyl halides [3, 30] (Scheme III. 3).

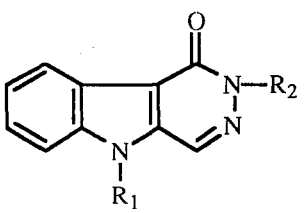


Scheme III. 3

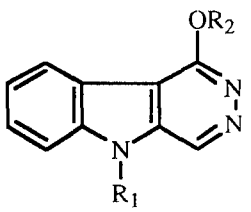
The activities of compounds (8) have been studied by Vega *et al* on spontaneously hypertensive rats in connection with their antihypertensive properties and the effects on the cardiac rhythm. Ten of the studied compounds showed significant antihypertensive activities.

1. 2 Synthesis of 1, 2–Dihydro–1–oxo–5*H*–pyridazino(4, 5–*b*)indoles

In order to establish the position of tautomeric equilibrium of 1, 2–dihydro–1–oxo –5*H*–pyridazino[4, 5–*b*]indole (9), we need to prepare relevant compounds (9) and (10) to compare their physical properties with those of fixed form model compounds (11–14).



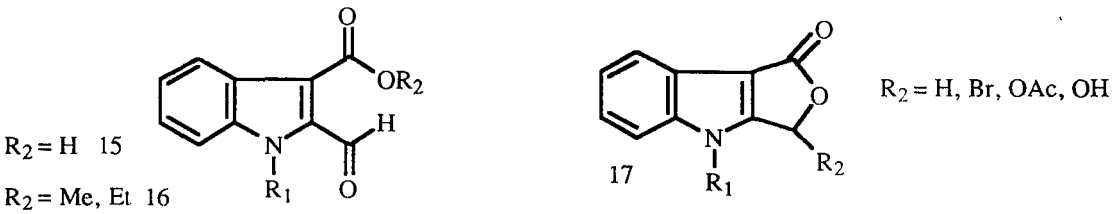
R_1	R_2	
H	H	9
Me	H	10
H	Me	11
Me	Me	12



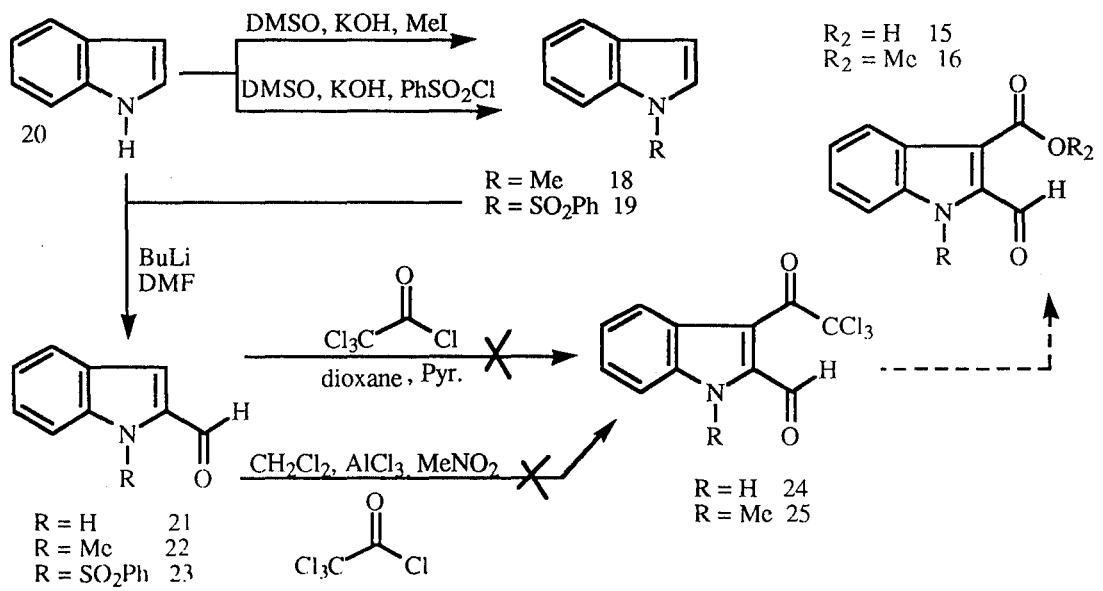
R_1	R_2	
H	Me	13
Me	Me	14

Although some of 1, 2–dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*]indoles are available using literature procedures, the parent 1, 2–dihydro–1–oxo–5*H*–pyridazino [4, 5–*b*]indole (9), its O–methyl derivatives (13) and (14) and N–methyl derivatives (10), (11), and (12) are novel compounds.

We chose the standard method used by Zhungietu *et al*, [1] to prepare 1–oxo –5*H*–pyridazino[4, 5–*b*]indoles (9–14) from 2–formylindole–3–carboxylic acid (15), its ester (16) or its lactone derivatives (17). The starting compounds (15–17) were also previously unknown compounds.

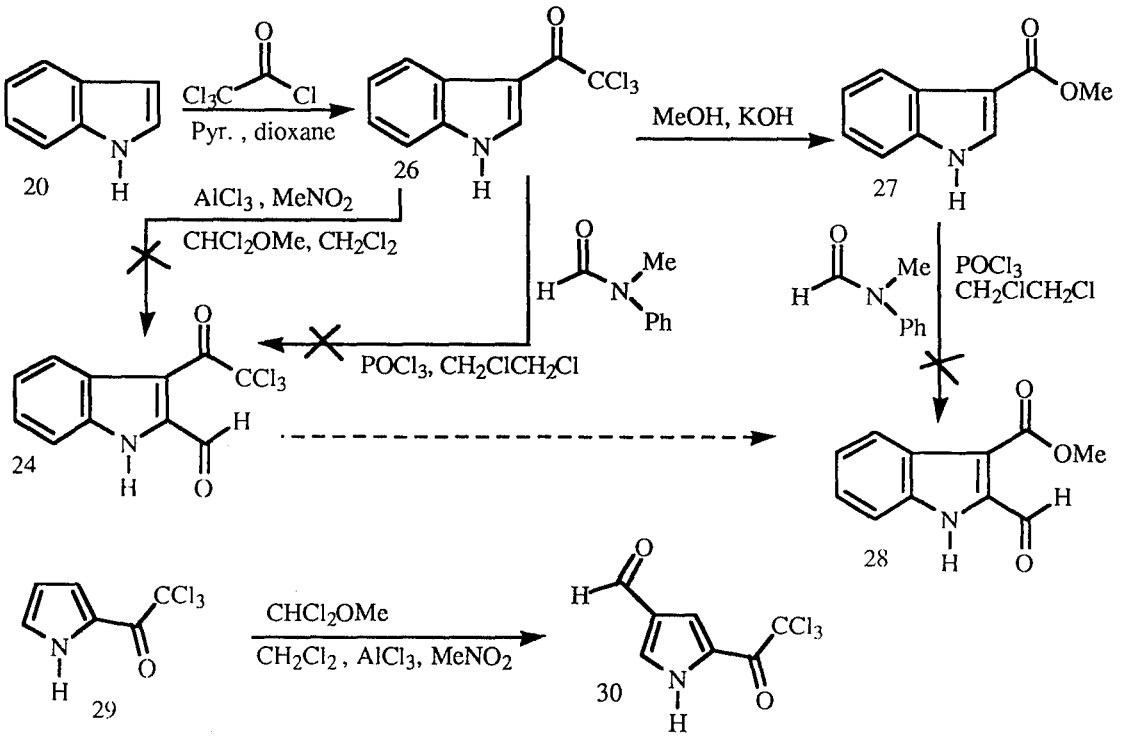


We tried to prepare the esters (15) and (16) from the 2–formyl–3–trichloroacetyl indoles (24) and (25). 1–Methylindole (18) and 1–benzenesulphonylindole (19) were prepared according to the procedure described by Heaney and Ley [4] and converted into the 2–formylindoles (21), [5] (22), [6] (23) [7] by standard procedures. However, acylation of (21) and (22) with trichloroacetyl chloride using two different procedures [8, 9] failed to give the desired 2–formyl–3–trichloroacetylindoles (24) and (25) (Scheme III. 4).



Scheme III. 4

In an alternative route to compounds (15) and (16) the required 3–trichloroacetyl indole (26) was prepared as described by the literature procedure, which was easily converted into the ester (27). Formylation of 3–trichloroacetylindole (26) by using two different procedures [9, 10] failed to give 2–formyl–3–trichloroacetylindole (24). Similarly, formylation of methyl indole–3–carboxylate (27) according to the Vilsmeir formylation procedure also failed to give methyl 2–formylindole–3– carboxylate (28) (Scheme III. 5). These observations contrast with the formylation of 2–trichloroacetylpyrrole (29) which has been carried out successfully by Garrido and Buldain [9] to give 4–formyl–2–trichloro acetylpyrrole (30) (Scheme III. 5).



Scheme III. 5

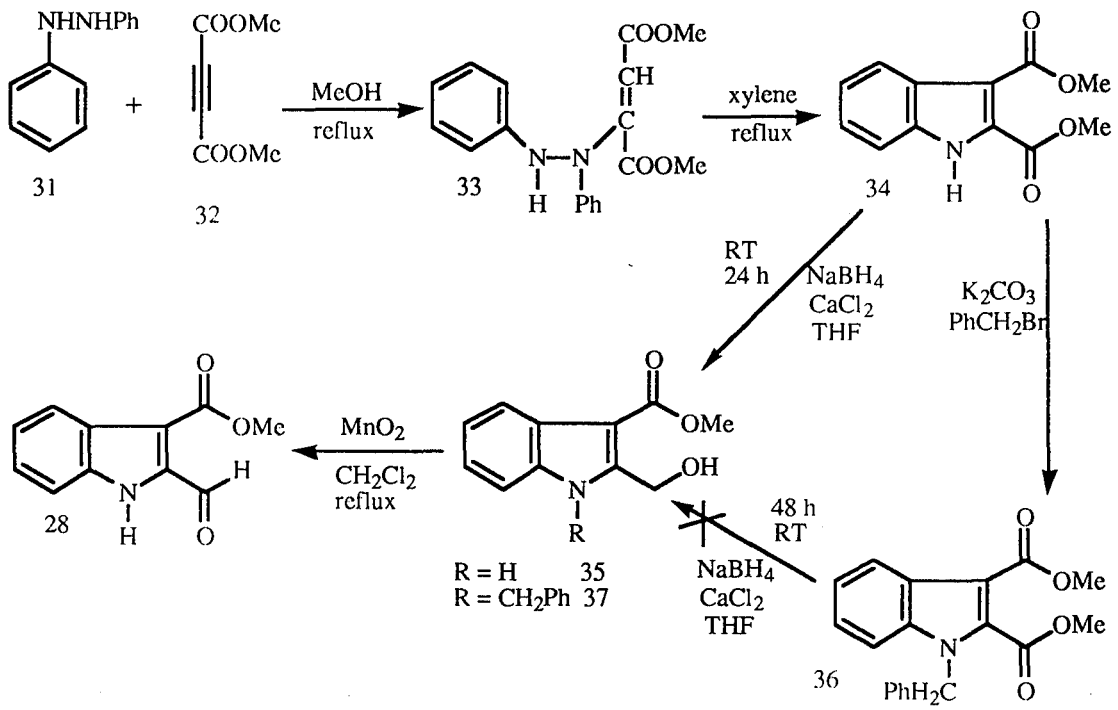
A search of the literature led us to a procedure for the preparation of 2–hydroxy methylindole– 3–carboxylate (35) from dimethyl indole–2, 3–dicarboxylate (34) (Scheme III. 6). [11]

Dimethyl indole–2, 3–dicarboxylate (34), prepared according to the procedure described in the literatures,[12, 13] was reduced with sodium borohydride in the presence of calcium chloride in THF at room temperature to yield methyl 2–hydroxymethylindole –3–carboxylate (35) in quantitative yield. Subsequent oxidation with freshly prepared manganese dioxide in dichloromethane [14] gave methyl 2–formylindole–3–carboxylate (28) in good yield (Scheme III. 6).

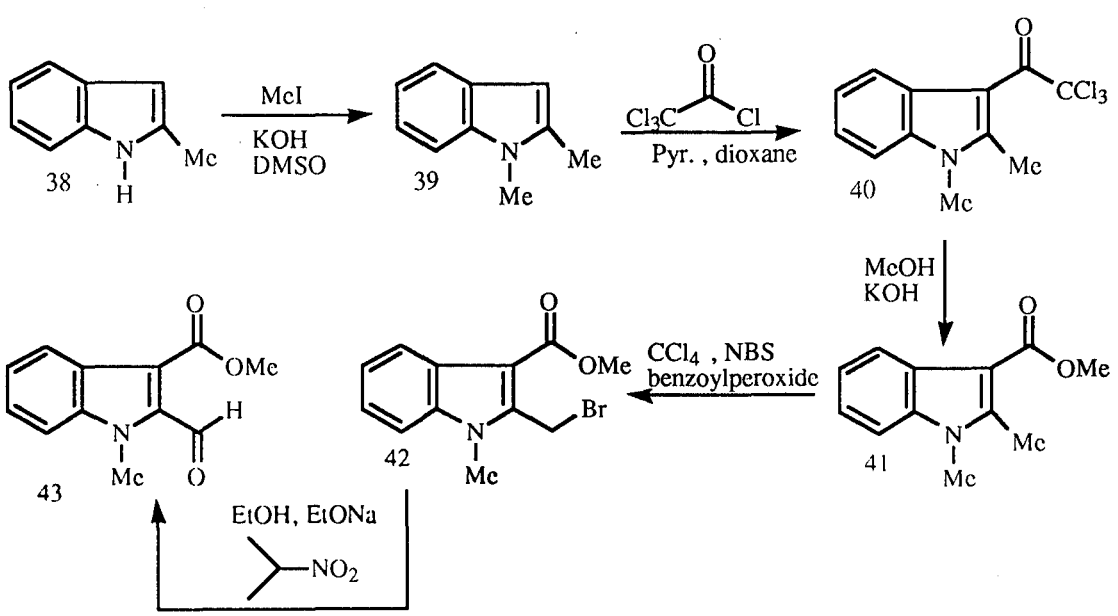
The same reduction conditions were applied to dimethyl 1–benzylindole–2, 3 –dicarboxylate (36) (for preparation, see section IV) to prepare methyl 1–benzyl–2 –hydroxymethylindole–3–carboxylate (37), but the reduction did not give the expected product (37) in spite of the longer reaction time, and we recovered only the starting material (36) (Scheme III. 6).

Methyl 2–formyl–1–methylindole–3–carboxylate (43) was synthesised from commercially available 2–methylindole (38) (Scheme III. 7). Methylation of 2–methylindole (38) was carried out according to the literature to give 1, 2–dimethyl indole, [4] which was acylated with trichloroacetyl chloride in dioxane [8] to give 1, 2–dimethyl–3–trichloroacetylindole (40) in good yield. Base-catalysed reaction with methanol gave methyl 1, 2–dimethylindole–3–carboxylate (41) in quantitative yield. Reaction of (41) with NBS (N–bromosuccinimide) in CCl_4 in the presence of a trace amount of benzoylperoxide provided methyl 2–bromomethyl–1–methylindole–3 –carboxylate (42) (81 % yield), [23] which was converted into methyl 2–formyl–1–methyl

amount of benzoylperoxide provided methyl 2–bromomethyl–1–methylindole–3 –carboxylate (42) (81 % yield), [23] which was converted into methyl 2–formyl–1–methyl indole–3–carboxylate (28) by procedures used by Beck and Lynch [18] and Hass and Bender [19] (Scheme III. 7).



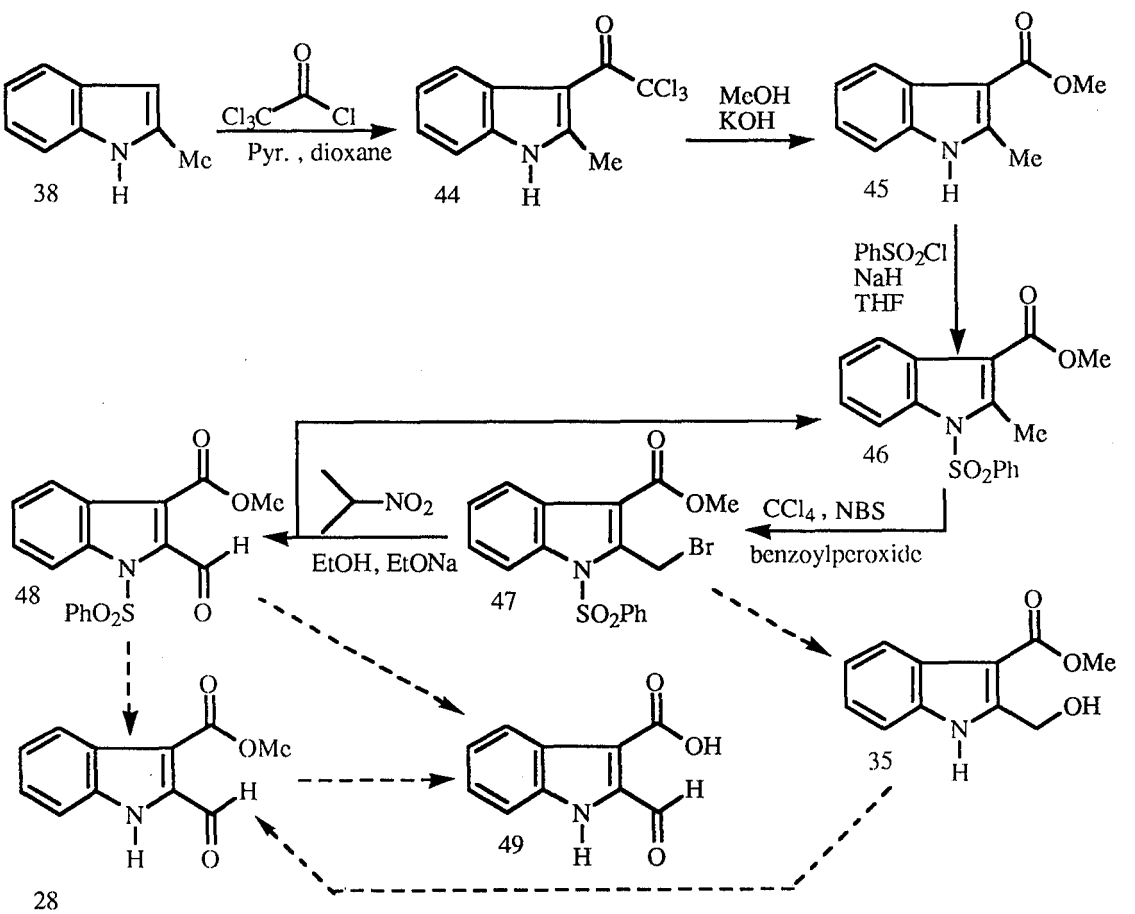
Scheme III. 6



Scheme III. 7

Methyl 2–formylindole–3–carboxylate (28) (Scheme III. 6) can be synthesised by an analogous method. Commercially available 2–methylindole (38) was acylated with trichloroacetyl chloride in the presence of pyridine in dioxane [8] to give 2–methyl–3 –trichloroacetylindole (44) [16, 17] in good yield. 2–Methyl–3–trichloroacetylindole (44) was then converted into methyl 2–methylindole–3–carboxylate (45) in quantitative yield according to the procedure as described in the literature. [21] Methyl 2–methylindole–3 –carboxylate (45) was N-protected using benzenesulphonyl chloride in THF [24] to give methyl 1–benzenesulphonyl–2–methylindole–3–carboxylate (46), which was then converted into methyl 1–benzenesulphonyl–2–bromomethyl indole–3–carboxylate (47) with NBS in the presence of benzoylperoxide in CCl_4. Oxidation of methyl 1–benzene sulphonyl–2–bromomethylindole–3– carboxylate (47) with 2–nitropropane, sodium ethoxide in ethanol according to the procedure described in the literature [18] gave two compounds 1–benzenesulphonyl–2–methylindole–3-carboxylate (46) and methyl 1–benzenesulphonyl–2–formylindole–3–carboxylate (48), although they could not be separated by column chromatography, which were identified by ^{1}H-NMR. Compound (47) should be a good starting material for the preparation of compounds (35), (48), (28), and (49).

Due to the lack of time these procedures were not investigated further.

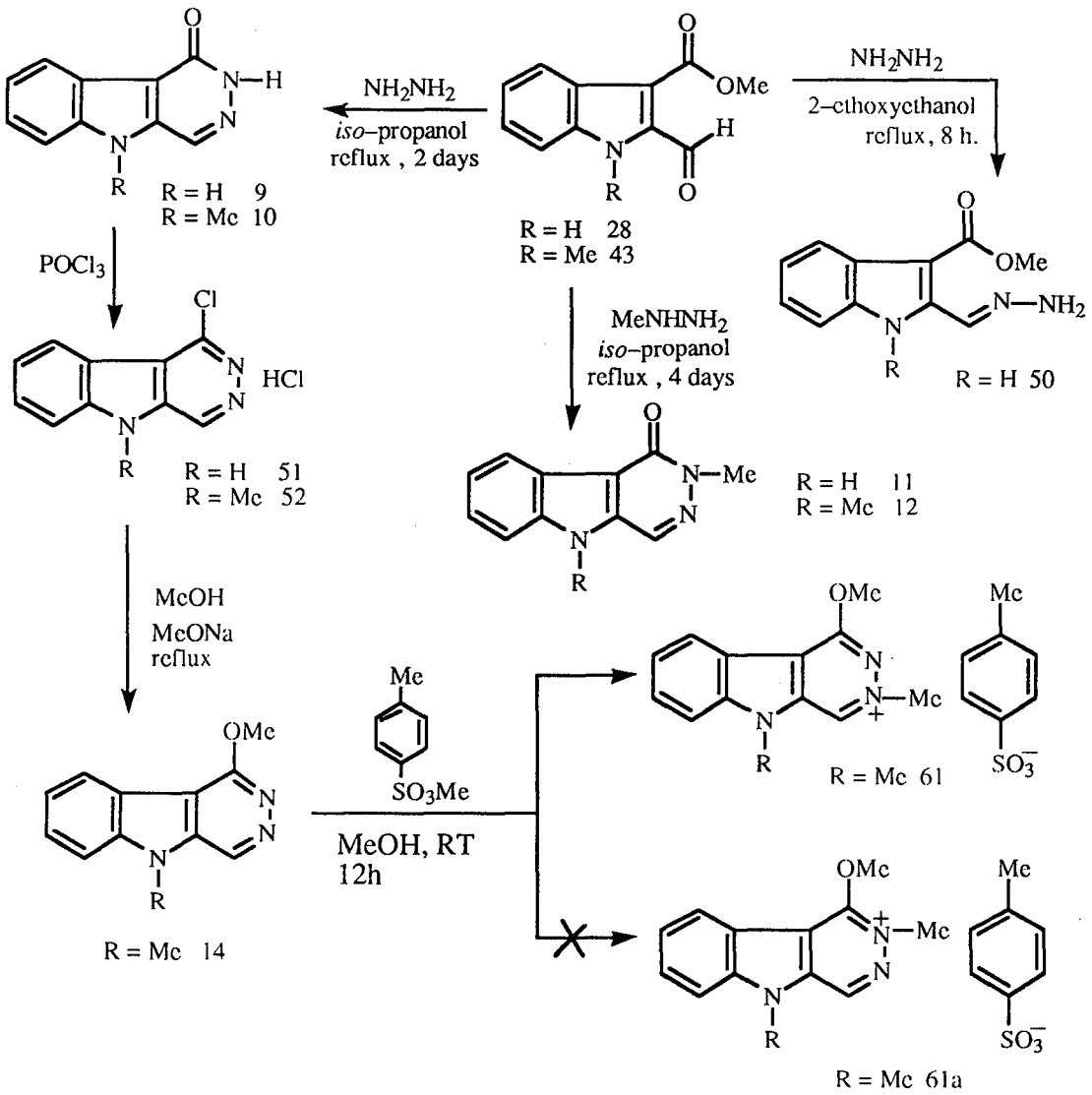


Scheme III. 8

The reaction of methyl 2–formylindole–3–carboxylate (28) with hydrazine hydrate gave methyl 2–formylindole–3–carboxylate hydrazone (50), instead of the expected 1, 2–dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*]indole (9). The structure (50) was confirmed by infrared spectroscopy, ^{1}H-NMR spectroscopy, mass spectroscopy, and elemental analysis. 1, 2–dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*]indole (9) and 1, 2–dihydro–5–methyl–1–oxo–5*H*–pyridazino[4, 5–*b*]indole (10) were prepared from the reaction of methyl 2–formylindole–3–carboxylate (28) and methyl 2–formyl–1 –methylindole–3–carboxylate (43) with hydrazine hydrate 1, 2–dihydro–3–methyl–1–oxo –5*H*–pyridazino[4, 5–*b*]indole (11) and 1, 2– dihydro–2, 5–dimethyl–1–oxo–5*H* –pyridazino[4, 5–*b*]indole (12) were also prepared in an analogous manner from the reaction of methyl 2–formyl indole–3– carboxylate (28) and methyl 2–formyl–1–methyl indole–3 –carboxylate (43) with methyl hydrazine.

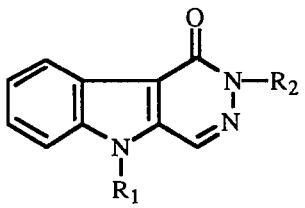
Compounds (9) and (10) when reacted with phosphorus oxychloride, gave 1–chloro–5*H*–pyridazino[4, 5–*b*]indole hydrochloride (51) and 1–chloro–5–methyl–5*H* –pyridazino[4, 5–*b*]indole hydrochloride (52). The latter was converted into 1–methoxy –5–methyl–5*H*–pyridazino[4, 5–*b*] indole (14) with sodium methoxide in refluxing methanol. 3, 5–Dimethyl–1–methoxy–5*H*–pyridazino[4, 5–*b*]indolium toluene –*p*–sulphonate (61) was prepared from the reaction of 1–methoxy–5–methyl–5*H* –pyridazino[4, 5–*b*]indole (14) and methyl toluene–*p*–sulphonate in methanol in good yield. Compounds (14), (51), and (52) will be discussed in detail in section V.

There is no reported mechanism for the reaction of 2–formylindole–3–carboxylic acid or its ester with hydrazine and its derivatives. We base a possible mechanism for the reaction of 3–formyl –2–carboxylate with hydrazine and its derivatives upon our experimental observations in section II.


NH2NH2
iso–propanol
reflux , 2 days
NH2NH2
2–ethoxyethanol
reflux, 8 h.
R = H 9
R = Me 10
R = H 28
R = Me 43
R = H 50
POCl3
MeNHNH2
iso–propanol
reflux , 4 days
HCl
R = H 51
R = Me 52
R = H 11
R = Me 12
MeOH
MeONa
reflux
SO3Me
MeOH, RT
12h
R = Me 14
R = Me 61
R = Me 61a

Scheme III. 9

Table III. 1 Reaction Products of Methyl 2–formylindole–3–carboxylate and Methyl 2–formyl–1–methylindole–3–carboxylate with Hydrazine and Methylhydrazine.



R_1	R_2	Compound	Yield (%)	M. P. (°C)	Reaction
H	H	9	76	> 320	a
Me	H	10	93	325	a
H	Me	11	43	312–3	b
Me	Me	12	66	173–4	b

a. Hydrazine hydrate ($NH_2NH_2\ H_2O$) + *iso*-propanol + reflux, 2 days.
b. Methylhydrazine ($MeNHNH_2$) + *iso*-propanol + reflux, 4 days.

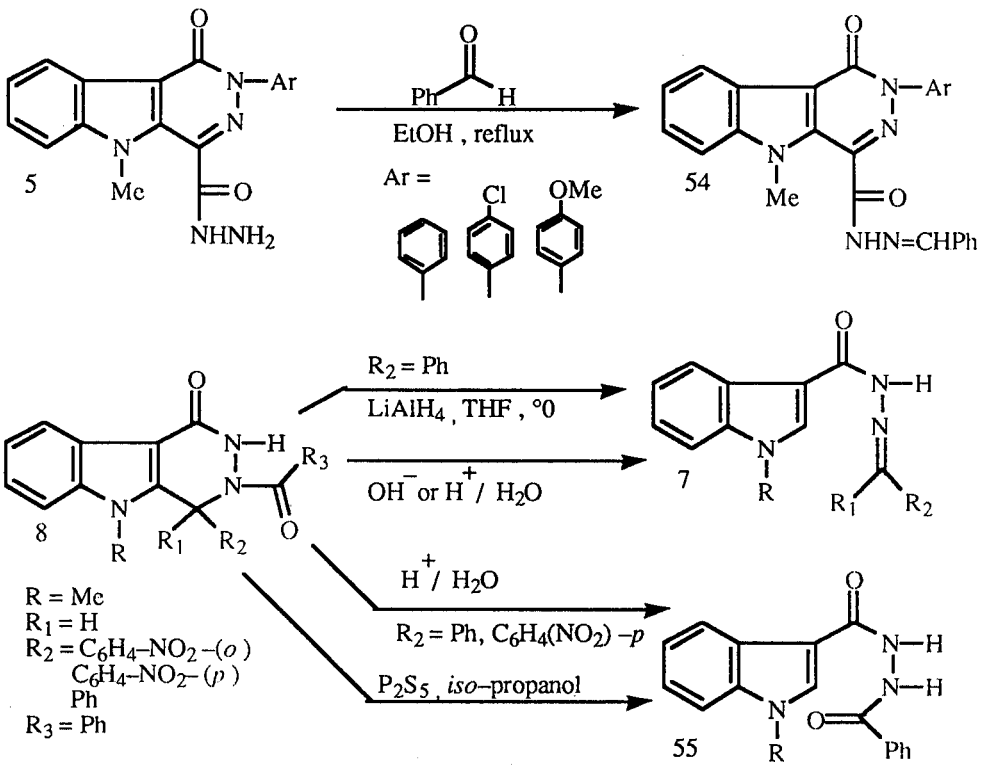
2. 0 1–Oxo–5*H*–pyridazino[4, 5–*b*]indole. – Chemical Reactivity

As we mentioned earlier in this chapter , there are few papers reported in the literature on 1–oxo–5*H*–pyridazino[4, 5–*b*]indoles. [1–3, 30] Hence, little is known about their chemical reactivity.

The reaction of 1–oxo–5*H*–pyridazino[4, 5–*b*]indoles with phosphorus oxychloride will be discussed in detail in section V.

The condensation reaction of 2–aryl–4–carbohydrazido–5–methyl–1–oxo–1, 2 –dihydro–5*H*–pyridazino[4, 5–*b*]indoles (5) with benzaldehydes provides the corresponding 2–aryl–4–(N^2–benzylidenecarbohydrazido)-5–methyl–1–oxo–1, 2–dihydro –5*H*–pyridazino[4, 5–*b*]indoles (54) (Scheme III. 10)

The ring opening reaction of 1–oxo–5*H*–pyridazino[4, 5–*b*]indoles (8) has been described by Vega and *et al* [30] by using different methods (Scheme III. 10).

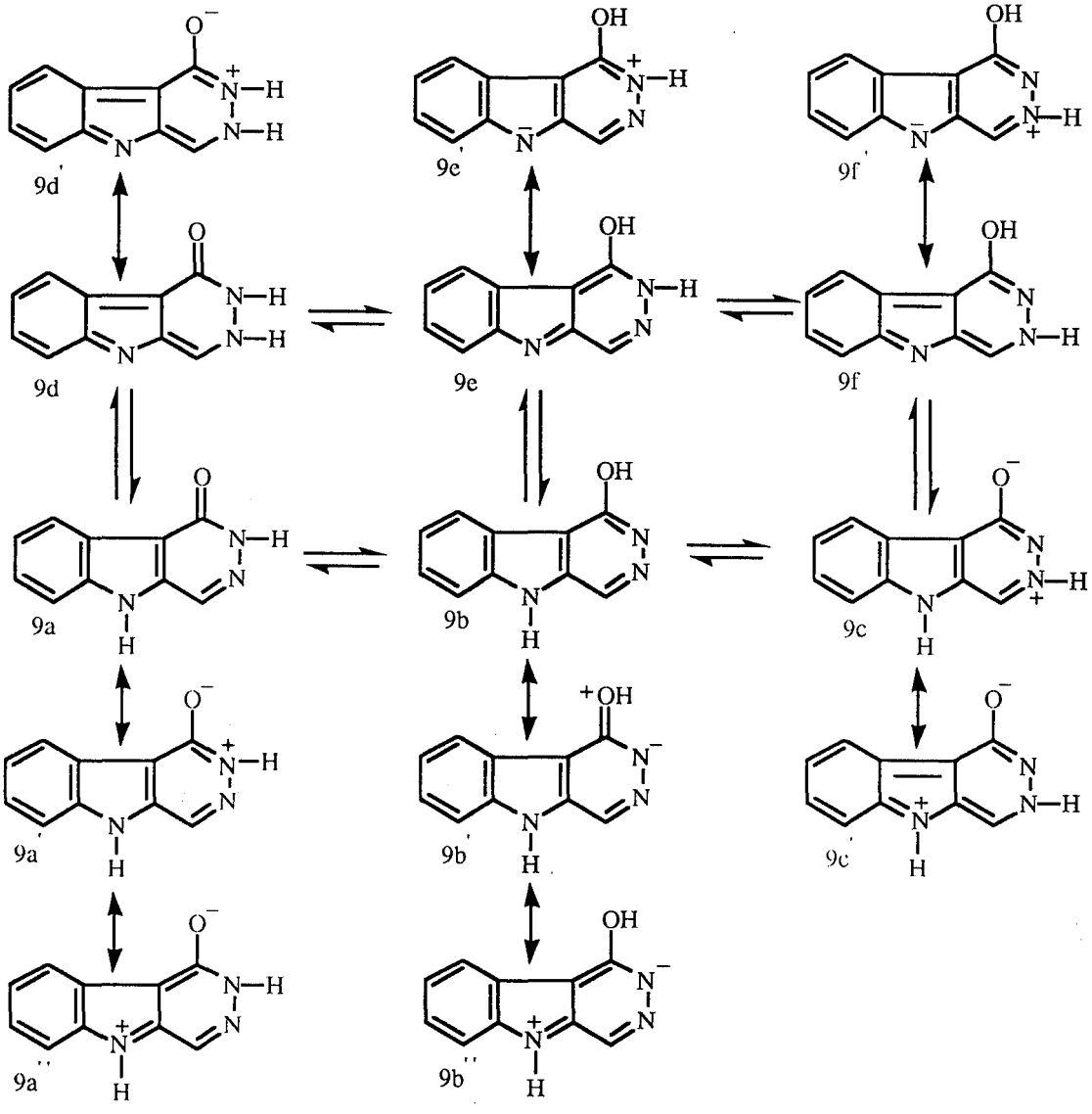


Scheme III. 10

3. 0 1, 2-Dihydro-1-oxo-5*H*-pyridazino[4, 5-*b*]indoles. - Physical Properties.

Several tautomeric structures are possible for the 1, 2-dihydro-1-oxo-5*H* -pyridazino[4, 5-*b*]indoles (Scheme III. 11). Two types of tautomerism are possible. In one case, it involves the functional group (9a ⟷ 9b) and in the second case, the annular atom (9d ⟷ 9e ⟷ 9f). Most of the tautomeric structures can be easily excluded from our discussion by the comparison of physical properties of the corresponding parent compound (9) with its model compounds (12) and (14). For example, the absence of a long wavelength band over 400 nm characteristic 2*H* -and 3*H* -pyridazino[4, 5-*b*]indoles [25] indicates that the annular tautomerism is very unlikely in the system (9d ⟷ 9e ⟷ 9f).

The majority of our measurements show that the tautomeric equilibria of 1, 2-dihydro-1-oxo-5*H*-pyridazino[4, 5-*b*]indoles favours in the oxo-form (9a) (Scheme III.11).



Scheme III. 11

3. 1 NMR Spectroscopic Measurements

^{1}H-NMR Spectroscopy

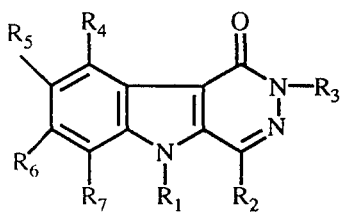
The ^{1}H-NMR chemical shifts of the alkyl group and ring protons of 1, 2–dihydro–1 –oxo–5*H*–pyridazino[4, 5–*b*]indoles (9–12) and 1–methoxy–5–methyl–5*H*–pyridazino [4, 5–*b*]indole (14) are presented in the table III. 2.

The spectra of 1, 2–dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*]indoles (9) and (10) exhibit a signal in (9) at 12.24 and in (10) at 12.7 ppm, which is characteristic of the NH groups (Table III. 2). Due to the possibility of fast proton exchange between NH and OH in the system, we can not confirm that 1, 2–dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*] indoles exist predominantly in the oxo-structure (9a) from these data. ^{1}H-NMR spectra of 1, 2–dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*] indoles (9) and ((10), and their

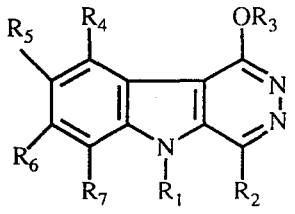
N(2)–methylated derivatives (11) and (12) resemble to each other, but show significant differences from the spectrum of O–methylated derivative (14) in the chemical shift of C(4) protons. Thus, these ^{1}H-NMR spectral data allow us to suggest that the predominant tautomeric structure is oxo-form (9a) of 1, 2–dihydro–1–oxo–5*H*–pyridazino [4, 5–*b*] indoles and not hydroxy-structure (9b) (Scheme III. 11).

Introduction of a methyl group on the nitrogen atom of pyridazine ring N(2) atom shifts the C(4) proton 0.52 ppm to high field, whereas a methyl group on the nitrogen atom of the indole ring N(5) shifts the C(4) proton 0.32 ppm to high field (Table III. 2).

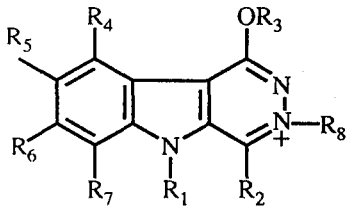
Table III. 2 ^{1}H-NMR Spectra[a] of 1, 2–Dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*] indoles and 1–Methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indoles.



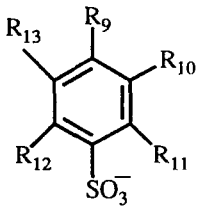
A



B



C



$R_2 = R_4 = R_5 = R_6 = R_7 = R_{10} = R_{11} = R_{12} = R_{13} = H$

R_1	R_3	Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7
A									
H	H	9 [b]	12.64 (br. s)	8.40 (s)	12.24 (br. s)	8.06–8.28 (dd)	7.20---------- 7.80 (m)		
Me	H	10 [b]	4.00 (s)	8.60 (s)	12.72 (br. s)	8.08–8.34 (dd)	7.25 ---------- 7.80 (m)		
H	Me	11 [b]	no peak	8.40 (s)	3.80 (s)	8.12–8.32 (dd)	7.20 ---------- 7.80)m)		
Me	Me	12 [c]	3.92 (s)	8.08 (s)	3.84 (s)	8.24–8.56 (dd)	7.10 ---------- 7.60 (m)		
B									
Me	Me	14 [c]	3.86 (s)	9.10 (s)	4.35 (s)	8.00–8.30 (dd)	7.16 ---------- 7.80 (m)		
C									
Me	Me	61	4.14 (s)	10.30 (s)	4.30 (s)	8.10–8.30 (dd)	6.90 ---------- 8.00 (m)		
			R_8 4.54 (s)	R_9 2.24 (s)		R_{10} — R_{13}	6.90 ---------- 8.00 (m)		

a. Chemical shifts are recorded in ppm down from TMS.

b. Spectra recorded in DMSO–d_6

c. Spectra recorded in $CDCl_3$.

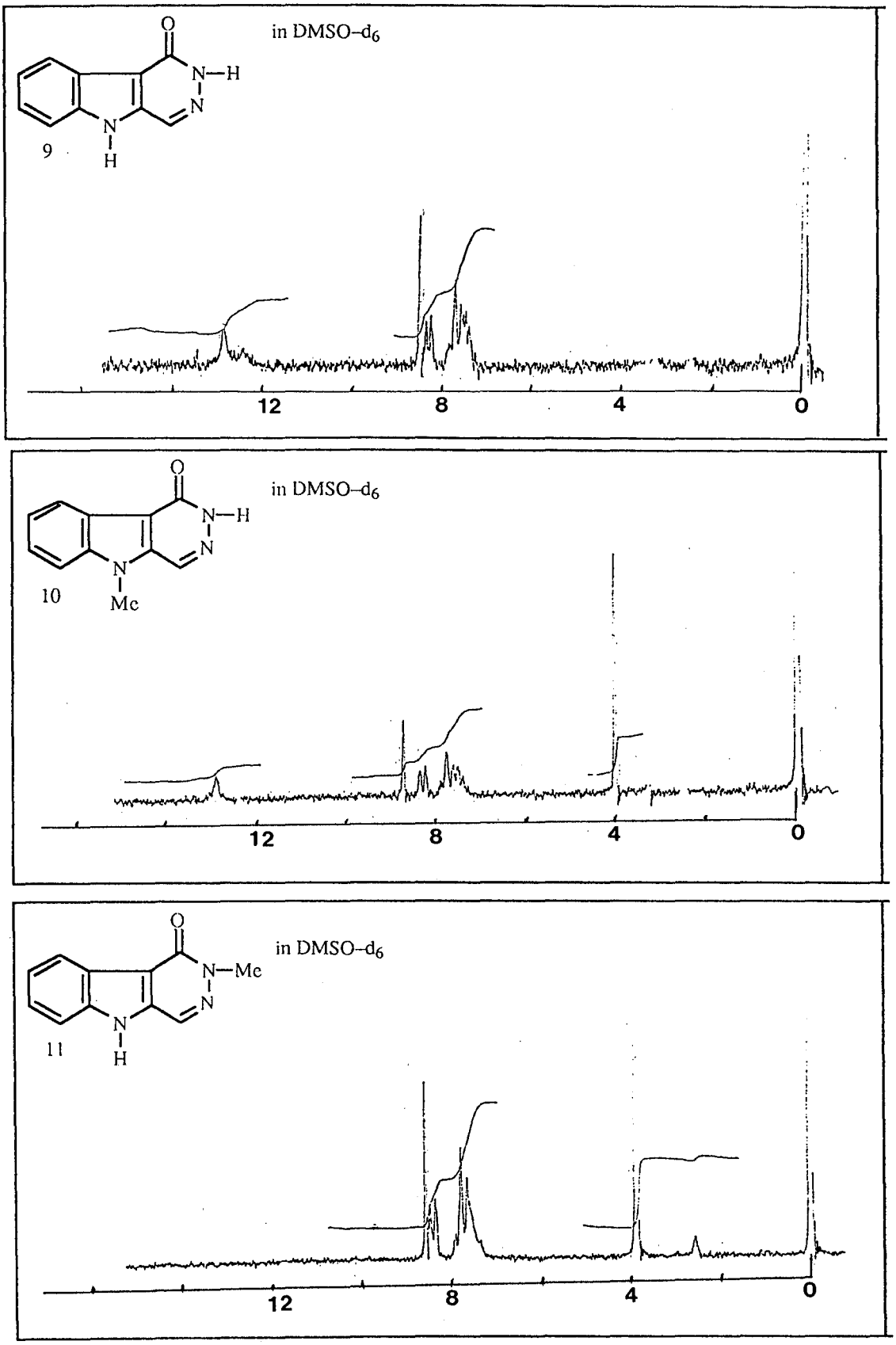


Figure III. 1. 1 ^{1}H-NMR Spectra of 1, 2–Dihydro–1–oxo–5*H*–pyridazino[4. 5–*b*] indoles

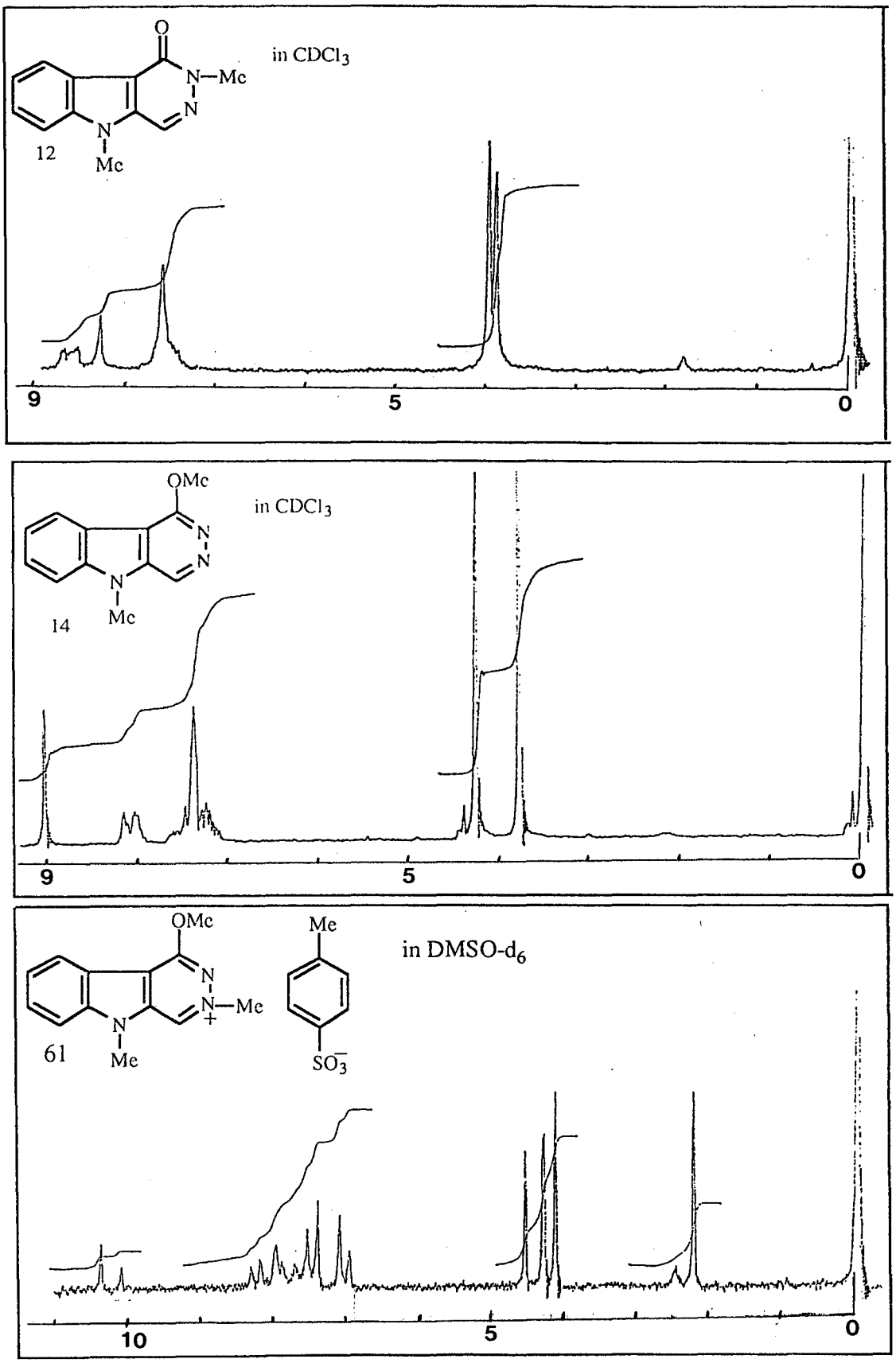


Figure III. 1. 2 ^{1}H-NMR Spectra of 1, 2–Dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*] indoles and 1–Methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole.

3. 2 Infrared Spectroscopic Measurements

The infrared spectra of 1, 2–dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*]indoles (9), (10), (11), (12), and 1–methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (14), measured in the solid state, are presented in the table III. 3.

Spectra of 1, 2–dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*]indole (9) and 1, 2–dihydro–2–methyl–1–oxo–5*H*–pyridazino[4, 5–*b*]indole (11) show absorption bands between 3100–3300 cm^{-1} with a maximum at about 3200 cm^{-1}. The corresponding absorption bands are absent in the spectra of 1, 2–dihydro–5–methyl–1–oxo–5*H* –pyridazino[4, 5–*b*]indole (10), 1, 2–dihydro–2, 5–dimethyl–1–oxo– 5*H*–pyridazino [4, 5–*b*]indole (12), and 1–methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (14).

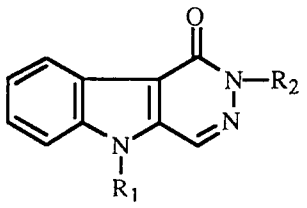
The amide group of compounds (9), (10), and (12) gives a strong $\nu_{C=O}$ absorption in the range of 1630–1655 cm^{-1}. In the case of compound (10) $\nu_{C=O}$ absorption band is broad and of medium intensity in the range of 1640 cm^{-1}. Absorption for the amide groups of these compounds usually overlaps the C=C, C=N ring stretching bands.

The ring stretching bands in the range 1530–1630 cm^{-1} usually show weak bands compared with the carbonyl bands. The infrared spectra of 1–methoxy–5–methyl–5*H* –pyridazino[4, 5–*b*]indole (14) show characteristic strong bands at 1570–1580 cm^{-1} and medium bands at 1620 cm^{-1}, respectively due to the C=C and C=N ring stretching vibrations.

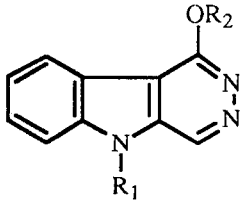
The absence of any broad band between 1800–3000 cm^{-1} or broad strong bands between 1500 -1600 cm^{-1}, which are characteristic of NH^{+} and O^{-} groups of the betaine structure (9c), allow the conclusion that 1, 2–dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*] indoles do not exist in the zwitterionic-structure form (9c) (Scheme III. 11)

All data obtained from infrared spectra indicate that 1, 2–dihydro–1–oxo–5*H* –pyridazino[4, 5–*b*]indoles exist predominantly in the oxo-structure (9a) not in the hydroxy-structure (9b) or in the zwitterionic structure (9c) (Scheme III. 11).

Table III. 3 Infrared Stretching Frequencies of 1, 2–Dihydro–1–oxo–5*H*–pyridazino [4, 5–*b*]indoles (A) and 1–Methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*] indole (B).



A



B

R_1	R_2	Compound	NH or OH (cm^{-1})	C=O (cm^{-1})	C=C or C=N (cm^{-1})
A					
H	H	9 [a]	3200 (m, s)	1650 (s)	1575 (w), 1625 (w)
Me	H	10 [a]	–	1640 (m, broad)	–
H	Me	11 [a]	3100–3300 (m, broad)	1630 (s, broad)	1550 (w)
Me	Me	12 [a]	–	1655 (s)	1560 (w), 1620(m)
B					
Me	Me	14 [a]	–	–	1570 (s), 1580 (s), 1620 (m).

a. Nujol mull

3. 3 Ultraviolet Spectral Measurements

The ultraviolet spectra of 1, 2–dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*]indoles (9–12) and 1–methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (14) are recorded in the table III. 4.

In a neutral buffer, all compounds show two groups of bands : a low intensity long wavelength ($\pi \rightarrow \pi^*$) band at 260–350 nm and high intensity ($\pi \rightarrow \pi^*$) band at 200–270 nm. In acidic media (i. e. , monocations of those compounds), the system exhibit three group of bands ; a low intensity long wavelength ($n \rightarrow \pi^*$) band at 270–400 nm, high intensity ($\pi \rightarrow \pi^*$) band at 230–280 nm, and medium intensity ($\pi \rightarrow \pi^*$) band at 200–230 nm. (Figure III. 2, Figure III. 3.)

Upon protonation, all of low intensity bands undergo a bathochromic effect (red shift) 10–30 nm, which is accompanied by a hyperchromic effect. The bathochromic effect observed for (14) is greater than those for (9), (10), (11), and (12). All high intensity bands also undergo a bathochromic effect, but with a hypochromic effect.

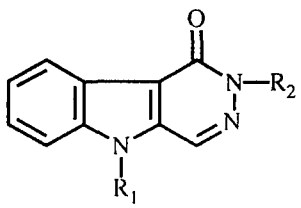
The spectra of neutral and acidic species of 1, 2–dihydro–1–oxo–5*H*–pyridazino [4, 5–*b*] indoles (9–12) show very close similarity but, some difference from the UV spectra of the O-methylated derivative (14). This observation suggests that 1, 2–dihydro –1–oxo–5*H*–pyridazino[4, 5–*b*]indoles exist predominantly in the oxo-structure (9a), and not in the hydroxy-structure (9b) in water (Scheme III. 11).

the hydroxy-structure (9b) in water (Scheme III. 11).

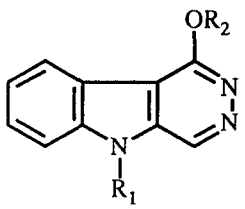
Monoprotonation of 1–methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (14) may take place on either N(2) or N(3) atom. Methylation of 1–methoxy–5–methyl–5*H* –pyridazino[4, 5–*b*]indole gives only N(3)-methylated compound (61) (see also Chapter IV), which is model compound of protonated 1–methoxy–5–methyl–5*H*–pyridazino [4, 5–*b*]indole (14). Similarities of log ε values of compound (14) and compound (61) indicates that protonation of 1–methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole occurs on N(3) atom.

The diprotonation of all 5*H*–pyridazino[4, 5–*b*]indoles give almost identical UV spectra (Figure III. 3, Table III. 4).

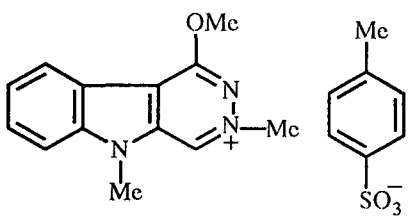
Table III. 4 Ultraviolet Spectra of 1, 2–Dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*] indoles.



A

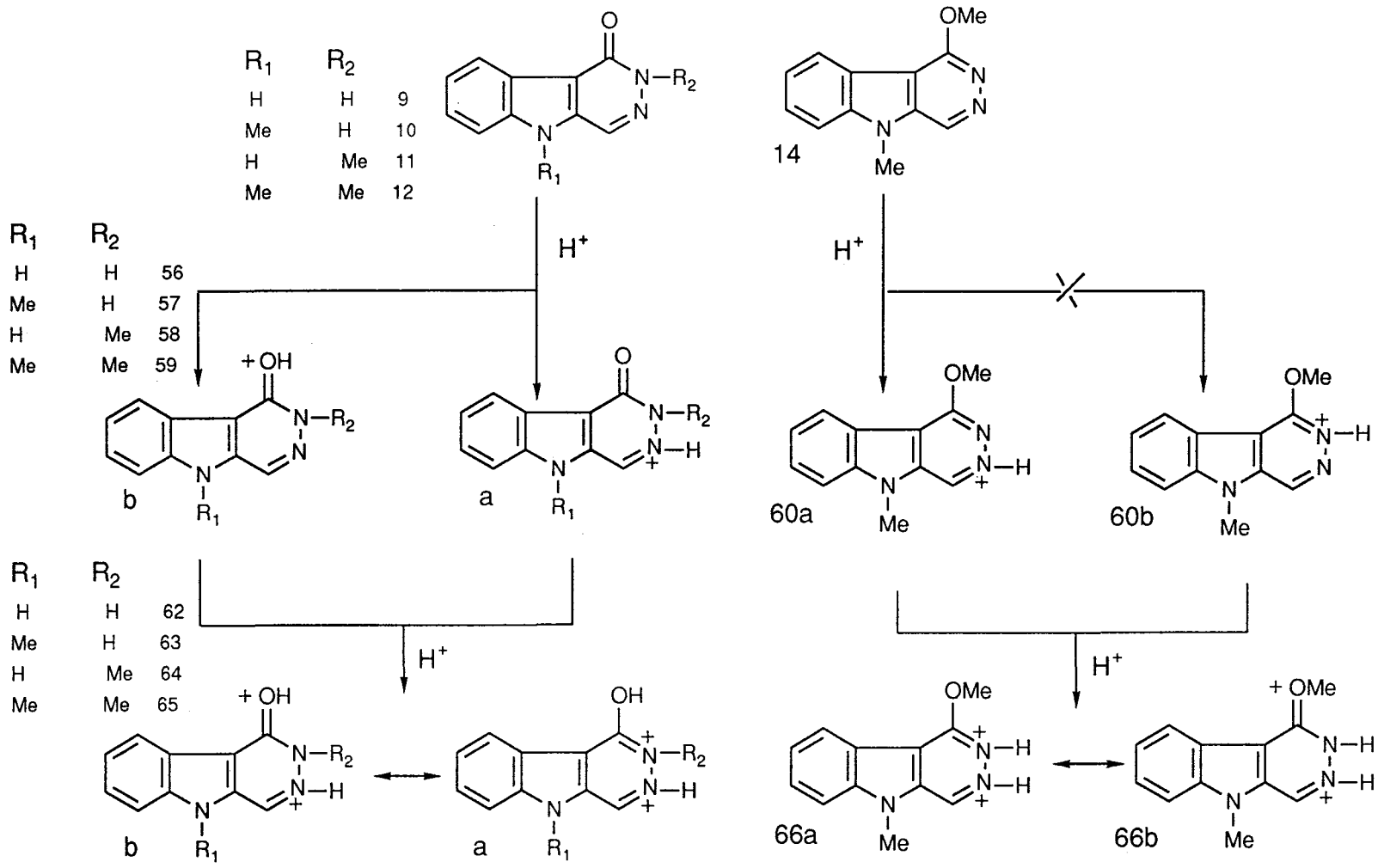


B



C

R_1	R_2	Compound	λ(nm) log ε	λ(nm) log ε	λ(nm) log ε	λ(nm) log ε	pH
Free-base							
A							
H	H	9	203 (4.40)	234 (4.58)	306 (4.12)		7
Me	H	10	203 (4.40)	244 (4.60)	310 (3.99)		"
H	Me	11	203 (4.51)	238 (4.65)	310 (4.10)		"
Me	Me	12	204 (4.49)	242 (4.64)	316 (4.07)		"
B							
Me	Me	14		236 (4.89)	288 (4.09)	322 (3.91)	9.12
Monocation							H_0
A							
9 → 56			221 (4.40)	250 (4.53)	314 (3.98)		– 2.78
10 → 57			225 (4.27)	253 (4.46)	320 (3.87)		"
11 → 58			228 (4.44)	246 (4.51)	318 (4.00)		"
12 → 59			228 (4.36)	250 (4.49)	320 (3.91)		"
B							
14 → 60			225 (4.23)	248 (4.62)	320 (4.18)	352 (3.79)	– 0.50
C							
61		202 (4.67)	222 (4.56)	248 (4.59)	322 (4.25)	354 (3.82)	+ 7
Dications							
56 → 62			226 (4.15)	274 (3.85)	360 (4.13)	98% sulphuric acid	
57 → 63			226 (4.14)	274 (4.34)	366 (4.38)	"	
58 → 64			226 (4.29)	273 (4.39)	361 (4.22)	"	
59 → 65			220 (4.19)	269 (4.28)	358 (4.06)	"	
60 → 66			226 (4.28)	272 (4.40)	365 (4.17)	"	



Scheme III. 12

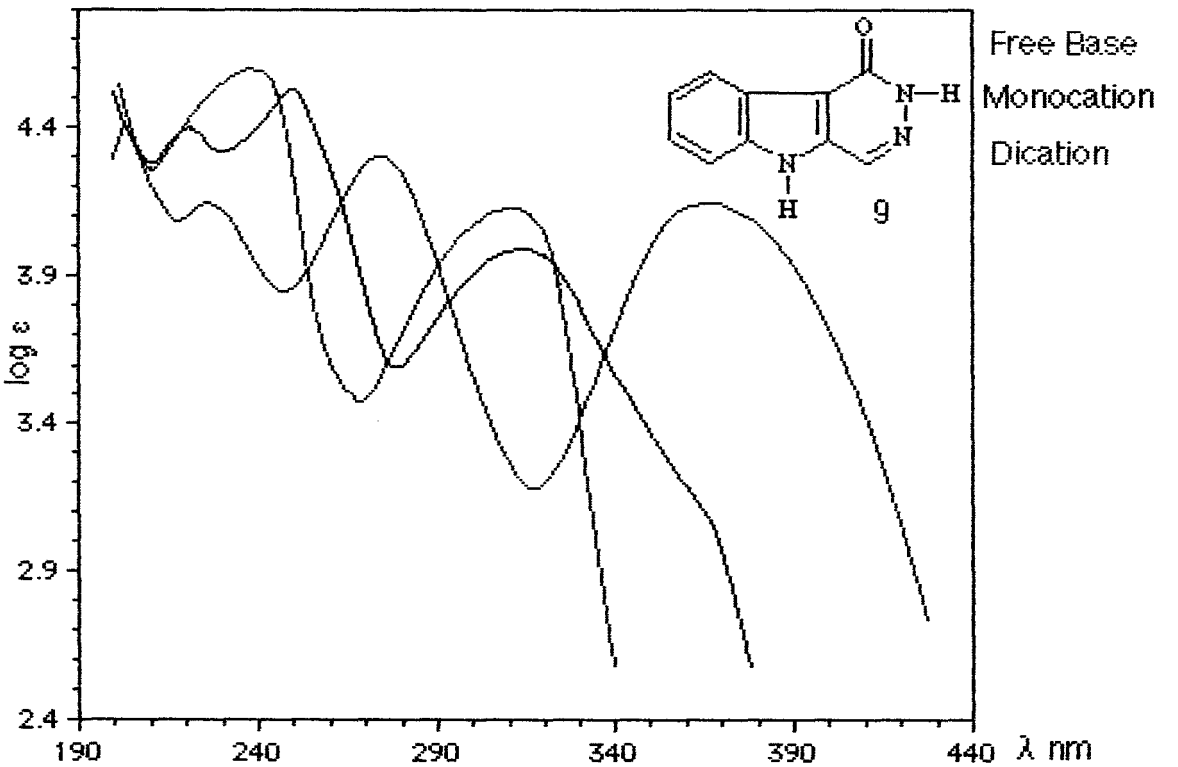


Figure III. 2. 1 Ultraviolet Spectra of 1,2-Dihydro-1-oxo-5*H*-pyridazino[4,5-*b*] indole in different media.

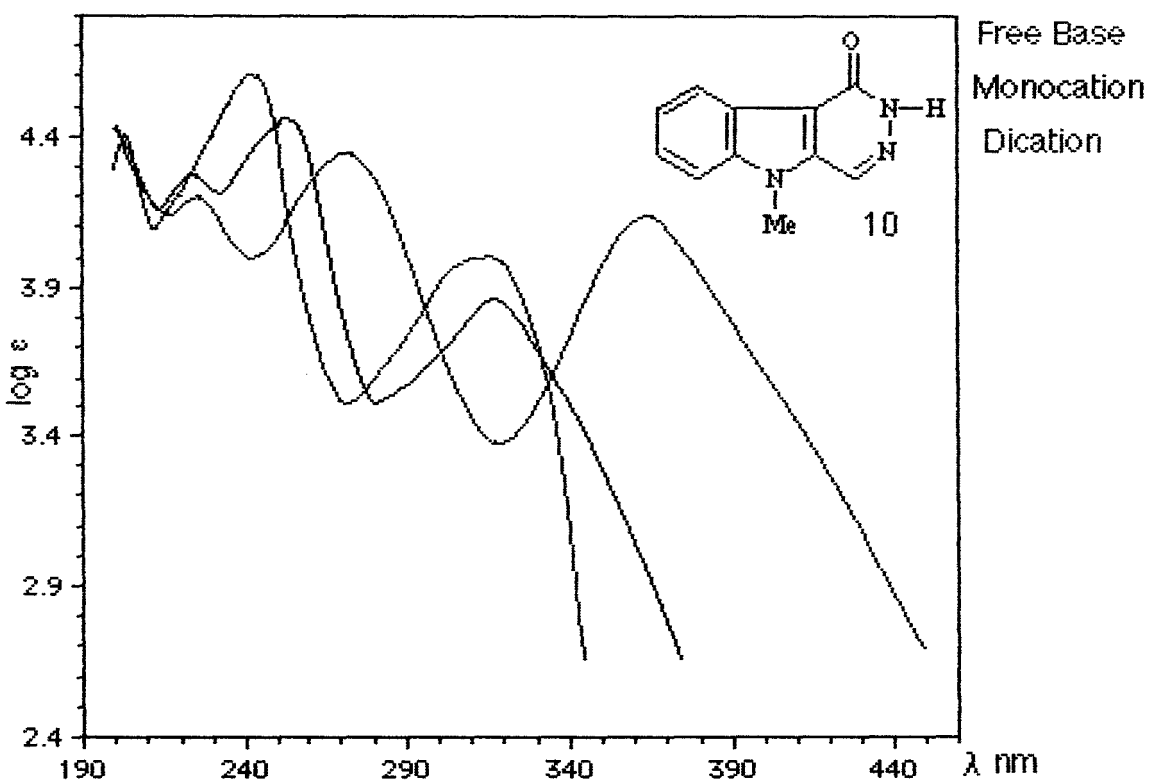


Figure III. 2. 2 Ultraviolet Spectra of 1,2-Dihydro-5-methyl-1-oxo-5*H*-pyridazino [4,5-*b*]indole in different media.

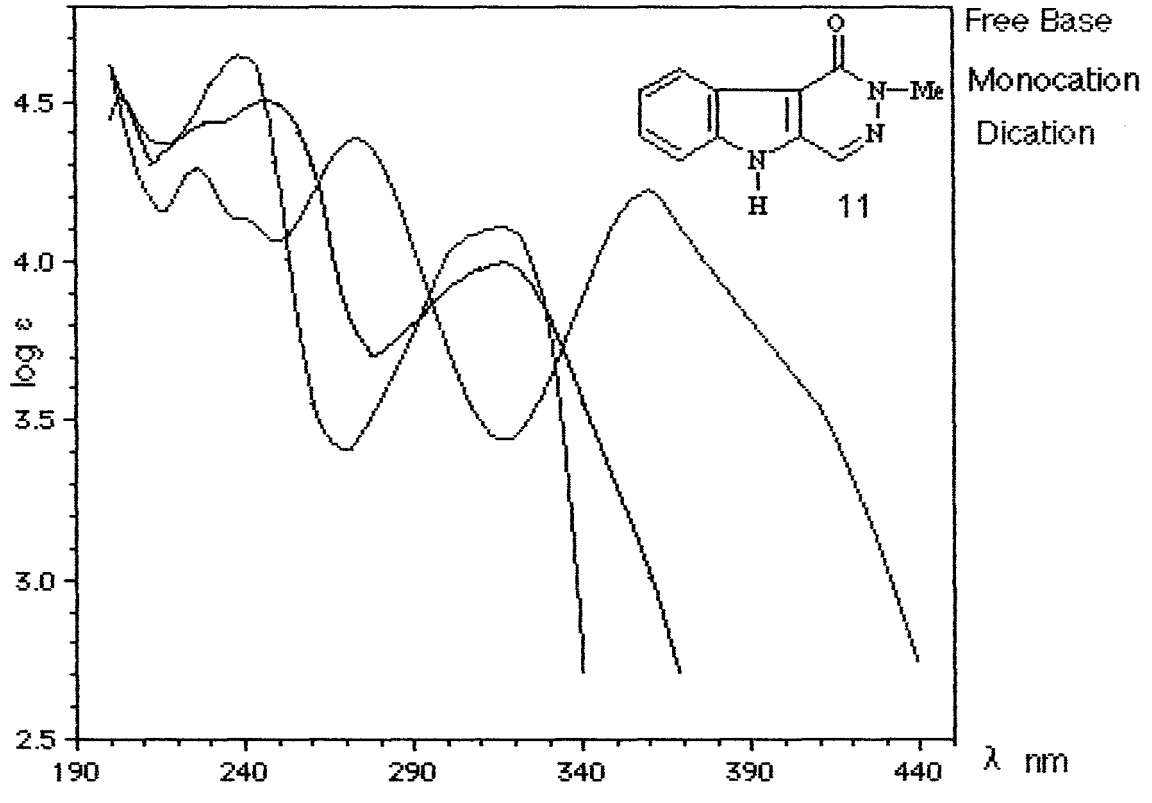


Figure III. 2. 3 Ultraviolet Spectra of 1,2-Dihydro-2-methyl-1-oxo-5*H*-pyridazino [4,5-*b*]indole in different media.

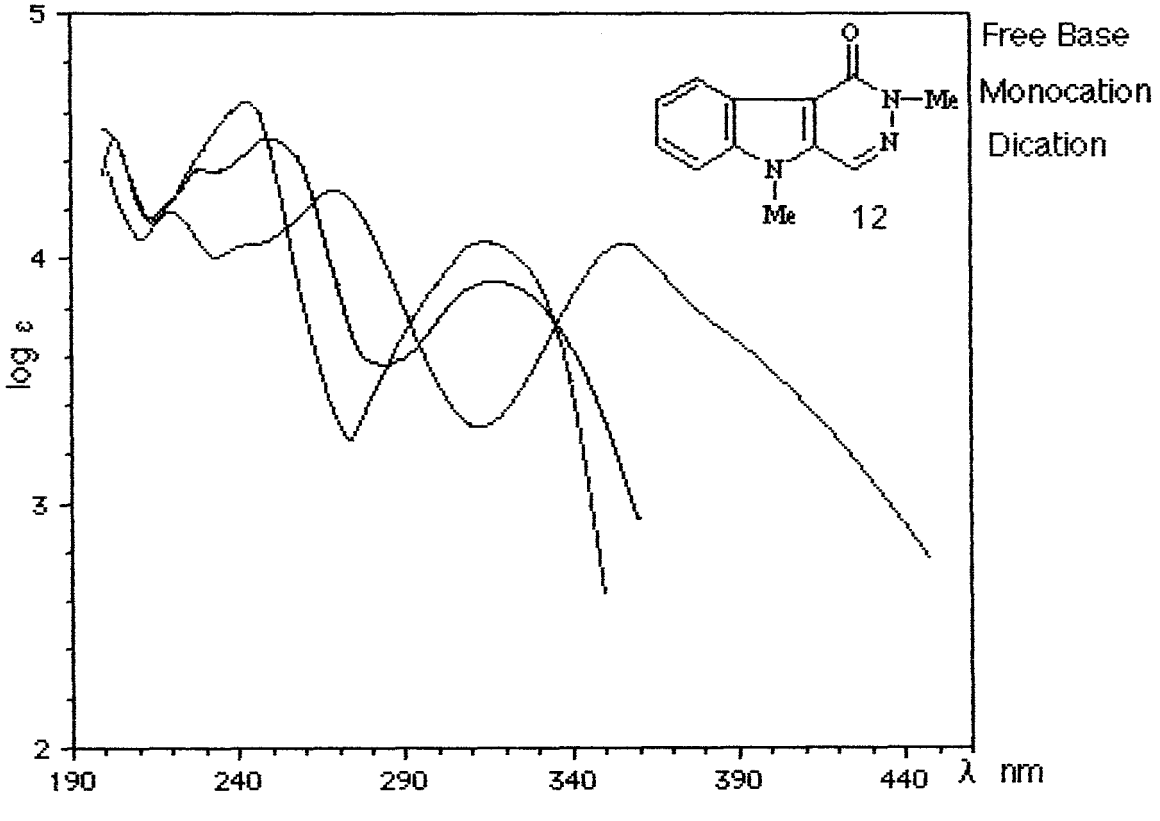


Figure III. 2. 4 Ultraviolet Spectra of 1,2-Dihydro-2,5-dimethyl-1-oxo-5*H*-pyridazino[4,5-*b*]indole in different media.

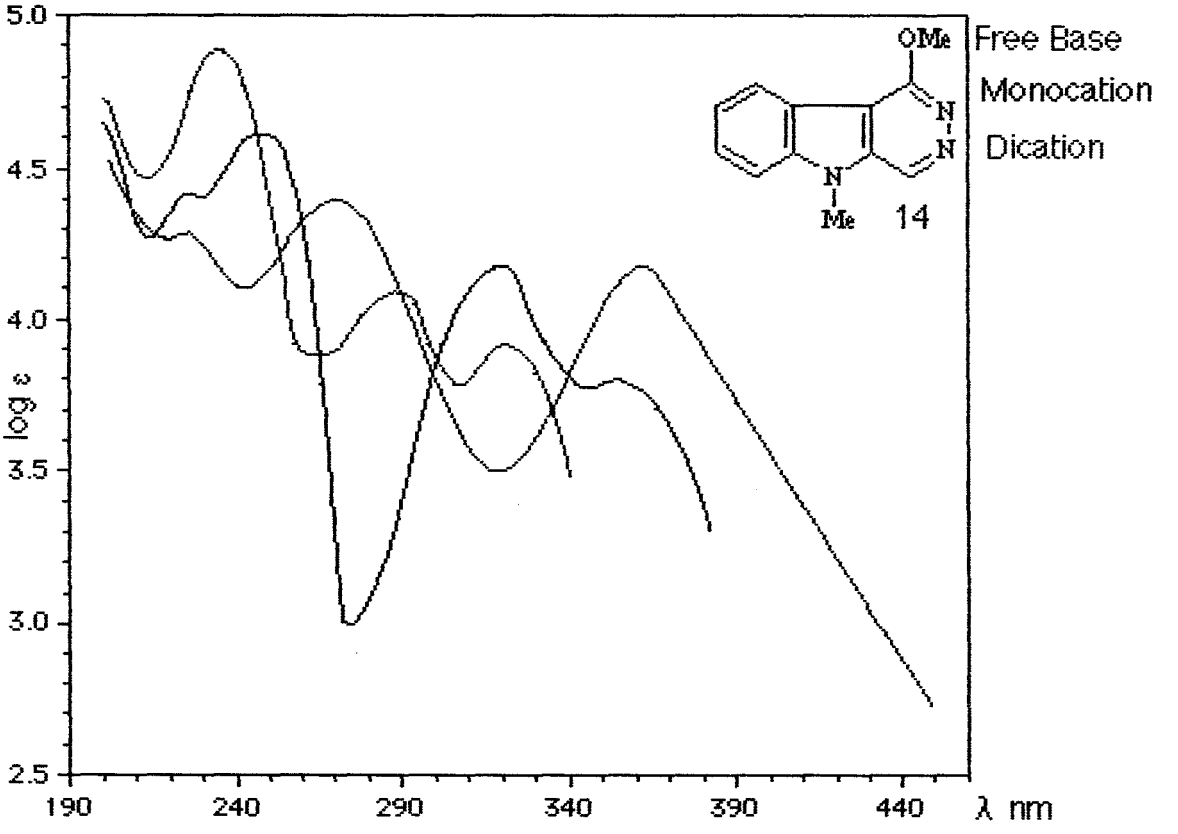


Figure III. 2. 5 Ultraviolet Spectra of 1-Methoxy-5*H*-pyridazino[4,5- *b*]indole in different media.

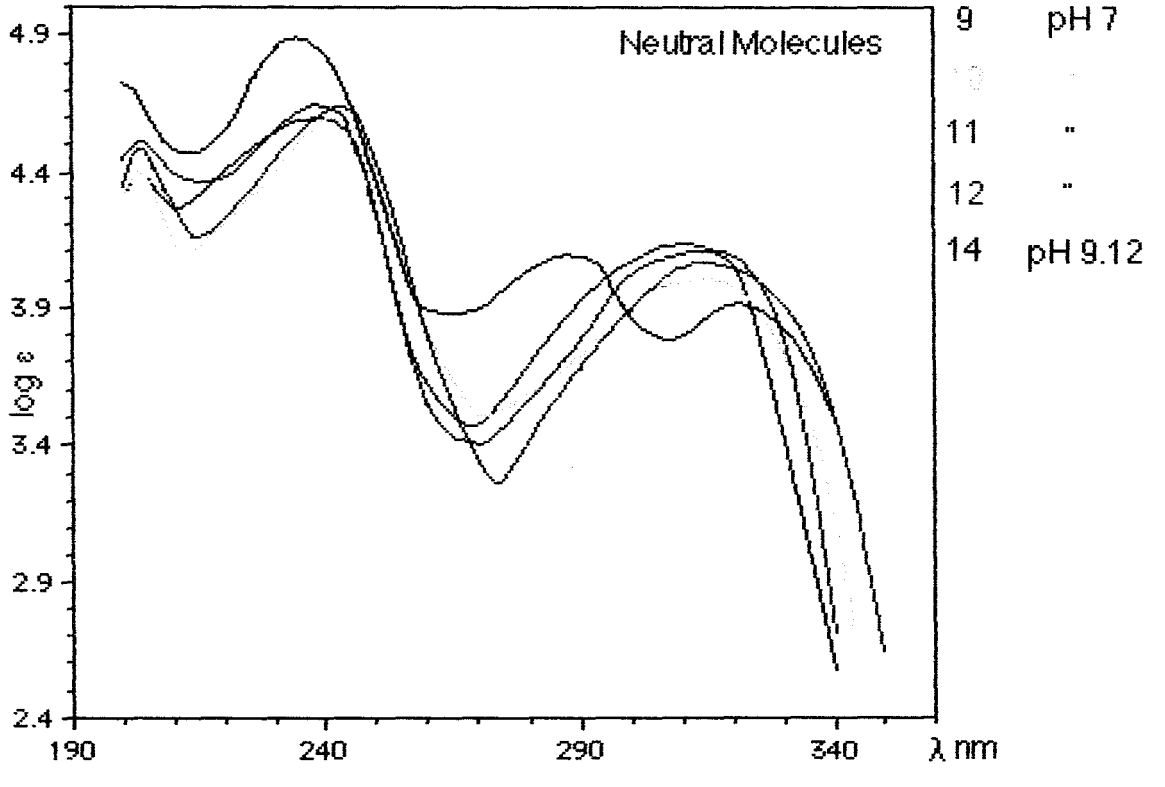


Figure III. 3. 1 Ultraviolet Spectra of Neutral Molecules of : 1, 2-Dihydro-1-oxo-5*H* -pyridazino[4, 5- *b*]indoles (9-12) and 1-Methoxy-5-methyl-5*H* -pyridazino[4, 5- *b*]indole (14).

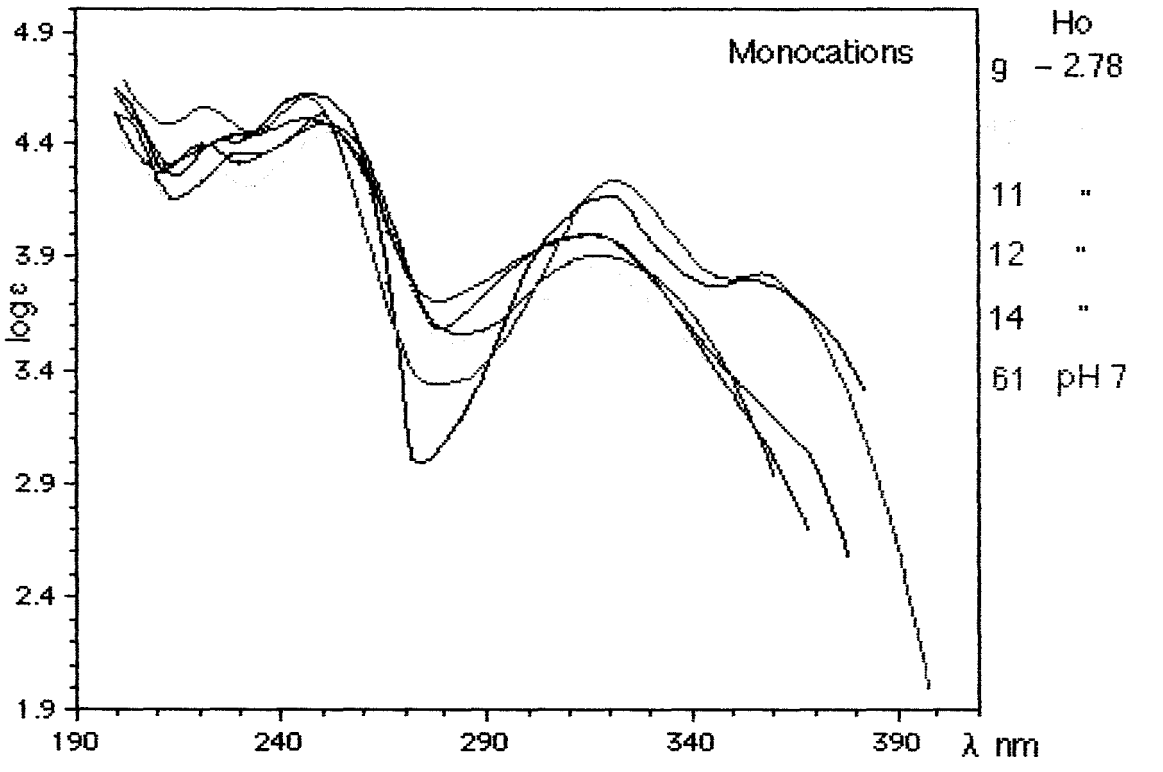


Figure III. 3. 2 Ultraviolet Spectra of Monocationic Species of : 1, 2-Dihydro-1-oxo -5*H*-pyridazino[4, 5- *b*]indoles and 1-methoxy-5-methyl-5*H* -pyridazino[4, 5- *b*] indole.

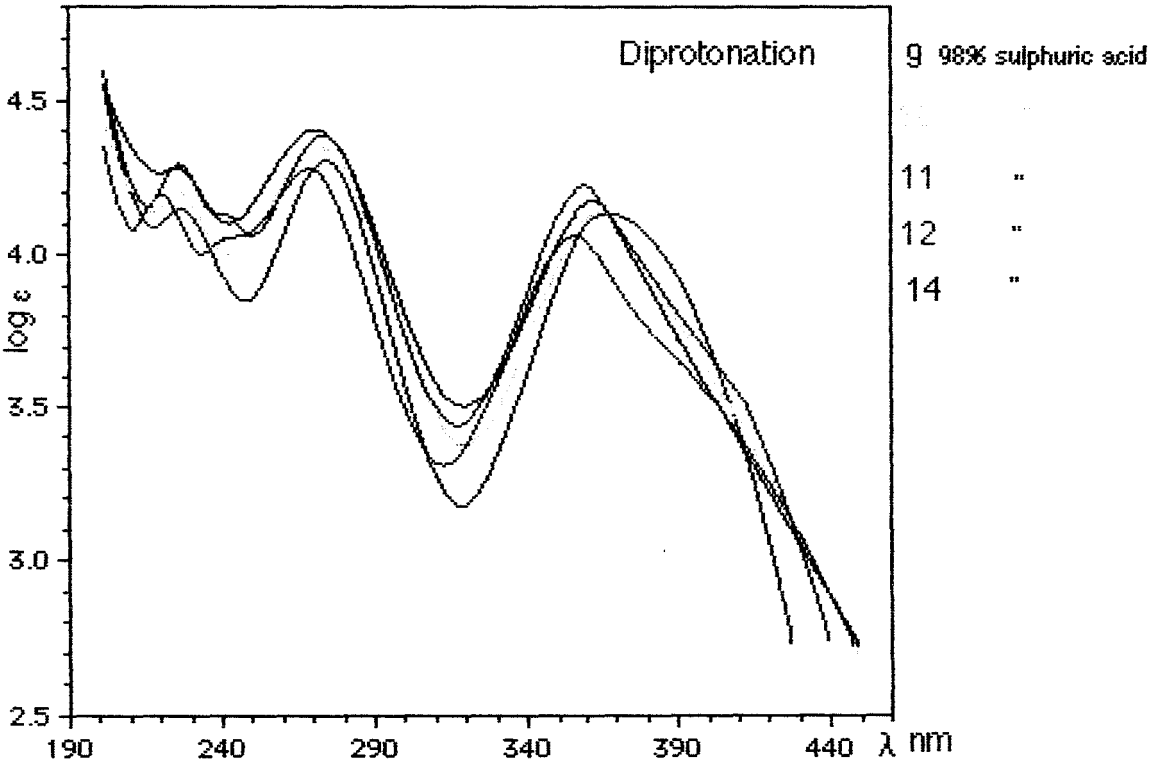


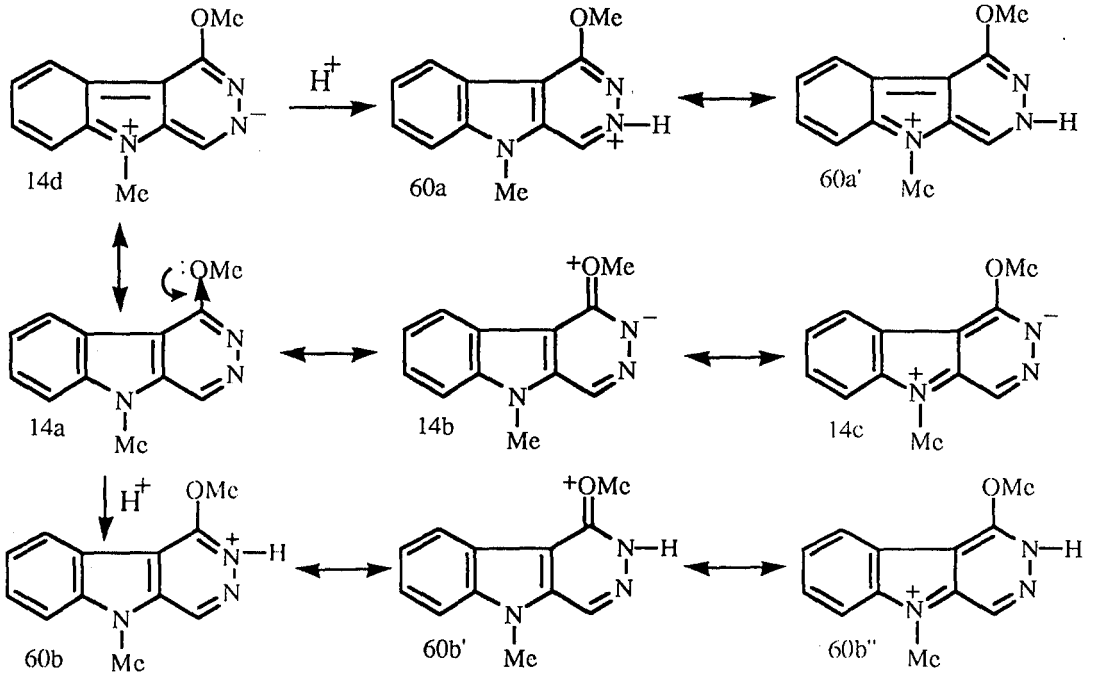
Figure III. 3. 3 Ultraviolet Spectra of Dicationic Species of 5*H*-Pyridazino[4,5- *b*] indoles

3. 4 Basicity Measurements

The ionisation constants of 1, 2–dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*]indoles (9–12) and 1–methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (14) are recorded in the table III. 5

The electronic effect of methoxy and hydroxy groups upon the basicities of the nitrogen heteroaromatic system has been discussed in the section II. 4. 4. All pKa values of compounds (9–12) and (14) are consistent with those of corresponding 3(2*H*)–pyridazinones and 1(2*H*)–phthalazinones (see Table III. 5 and Table II. 6). The electron-donating group indole increases the basicity of 3(2*H*)–pyridazinone ring by 0.67–1.04 pKa unit. A methyl group on the nitrogen atom of indole ring (10) and (12) also increases the basicity of 5*H*–pyridazino[4, 5–*b*]indole ring by 0.15–0.37 pKa unit. In contrast, the presence of a methyl group on the nitrogen atom of pyridazine ring (11) and (12) decreases the basicity of pyridazino[4, 5–*b*]indole by 0.27–0.49 pKa unit.

The pKa of 3.27 for 1–methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (14) indicates that the inductive effect is modified by a mesomeric effect (14a ↔14b ↔14c ↔ 14d) but the charged forms (14b), (14c) and (14d) are of less importance in the stabilisation, whereas the cation (60b ↔ 60b' ↔ 60b") and (60a ↔ 60a') has higher degree of resonance stabilisation. Cations (60a), (60a'), (60b), and (60b") are much more likely compared to cation (60b') (Scheme III. 13). But in the view of UV data obtained from 3, 5–dimethyl–1–methoxy–5*H*–pyridazino[4, 5–*b*]indolium salt (61) cations (60a) and (60a') seems to be more likely compared to (60b) and (60b"). Compound (61) of course is a model compound of (60a) and (60a').



Scheme III. 13

There is a close similarity in the pKa values of 1, 2–dihydro–1–oxo–5*H*–pyridazino [4, 5–*b*]indoles (9), (10), (11), and (12), but they are significantly different from the pKa value for 4–methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (14), indicating that 1, 2–dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*]indoles (9), (10), and (11) exist predominantly in the oxo-structure (9a) and not in the hydroxy-structure (9b) (Scheme III. 11).

3. 5 Tautomeric Equilibrium Constants

The preceding discussion establishes qualitatively that 1, 2–dihydro–1–oxo–5*H* – pyridazino[4, 5–*b*]indoles exist in the oxo-form predominantly (Scheme III. 11). However, the model compounds for zwitterionic-structure (9c) were not available. Thus, we have not been able to obtain quantitative or qualitative evidence for the existence or otherwise of minor tautomeric forms in the equilibrium.

Applying the approach described in the section II. 4. 5, the equilibrium constant (K_T) for the tautomeric equilibrium (9a $\rightleftharpoons$ 9b) can be calculated using the pKa values for the protonation of the " fixed tautomeric " model compounds.

The tautomeric form (9a $\rightleftharpoons$ 9b) may be interconverted *via* their protonated tautomeric forms (56a $\rightleftharpoons$ 56b $\rightleftharpoons$ 56c $\rightleftharpoons$ 56d) and (62a $\leftrightarrow$ 62b) (scheme III. 14). Since the model compounds (12) and (14) produce a common cations (65) and (66) (Table III. 5 and Scheme III. 15) for the diprotonation, the pKa values of (12) and (14) gave a quantitative measure of pK_T.

The equilibrium between the tautomers described in terms of pK_T may be expressed on the difference between the acidities of conjugate acids of tautomeric bases.

$K_T = [B] / [A]$

$K_A = [C] / [A]$ $\qquad$ $[A] = [C] / K_A$

$K_B = [D] / [B]$ $\qquad$ $[B] = [D] / K_B$

$K_C = [E] / [C]$ $\qquad$ $[C] = [E] / K_C$

$K_D = [E] / [D]$ $\qquad$ $[D] = [E] / K_D$

$$K_T = \frac{\frac{[D]}{K_B}}{\frac{[C]}{K_A}} = \frac{[D]}{K_B} \cdot \frac{K_A}{[C]}$$

$$K_T = \frac{\frac{\cancel{[E]}}{K_D}}{K_B} \cdot \frac{K_A}{\frac{\cancel{[E]}}{K_C}}$$

$$K_T = \frac{K_A \cdot K_C}{K_D \cdot K_B}$$

$$pK_T = [\ (\ pK_A + pK_C) - (\ pK_D + pK_B\ )\ ]$$

$$pK_T = [\ (\ pKa(A) + pKa(C)\ ) - (\ pKa(D) + pKa(B)\ )\ ]$$

$$pK_T = [\ (\ pKa_1(A) + pKa_2(A)\ ) - (\ pKa_2(B) + pKa_1(B)\ )\ ]$$

The validity of the relationship requires that protonation of the tautomeric forms must give a cation having a common electronic structure. That this is the case for 5*H*–pyridazino[4, 5–*b*] indoles is confirmed by the similarity in the electronic spectra of diprotonated forms of the potentially tautomeric compounds and the fixed forms (Scheme III. 12, Scheme III. 14, Scheme III. 5 and Figure III. 3).

Since the basicities of (9a) and (9b) can not be determined individually as the tautomers interconvert quickly, the value $K_{A'}$, $K_{B'}$, $K_{C'}$ and $K_{D'}$ were obtained from the corresponding " fixed tautomeric " model compounds (12) and (14) (Scheme III. 15). Thus, a quantitative measure can be obtained for the equilibrium.

$$K'_T = \frac{K_{A'}\ K_{C'}}{K_{D'}\ K_{B'}}$$

$$pK'_T = [\ pK_{A'} + pK_{C'}\ ] - [\ pK_{D'} + pK_{B'}]$$

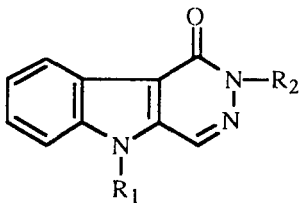
$$pK'_T = [\ pKa_1(12) + pKa_2(12)] - [\ pKa_2(14) + pKa_1(14)\ ]$$

$$pK'_T = [(\ -1.25) + (-3.68)\ ] - [\ -0.98) + (3.27)\ ]$$

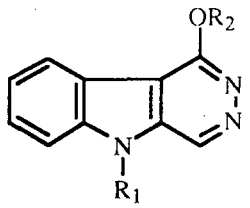
$$pK'_T = -\ 7.22$$

It was established that for 1, 2–dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*]indole the oxo-form (9a) is favoured to the extent of ca 16, 600, 000 : 1 compared with the hydroxy-form (9b) (Scheme III. 14).

Table III. 5 pKa Values of 1, 2–Dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*]indoles (A) and 1–Methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (B).



A



B

Monoprotonation

R_1	R_2	Compound	pKa [a]	Solution
	A			
H	H	9 → 56	– 1.13 ± 0.03	b
Me	H	10 → 57	– 0.76 ± 0.03	b
H	Me	11 → 58	– 1.40 ± 0.03	b
Me	Me	12 → 59	– 1.25 ± 0.02	b
	B			
Me	Me	14 → 60	3.27 ± 0.09	c

Diprotonation

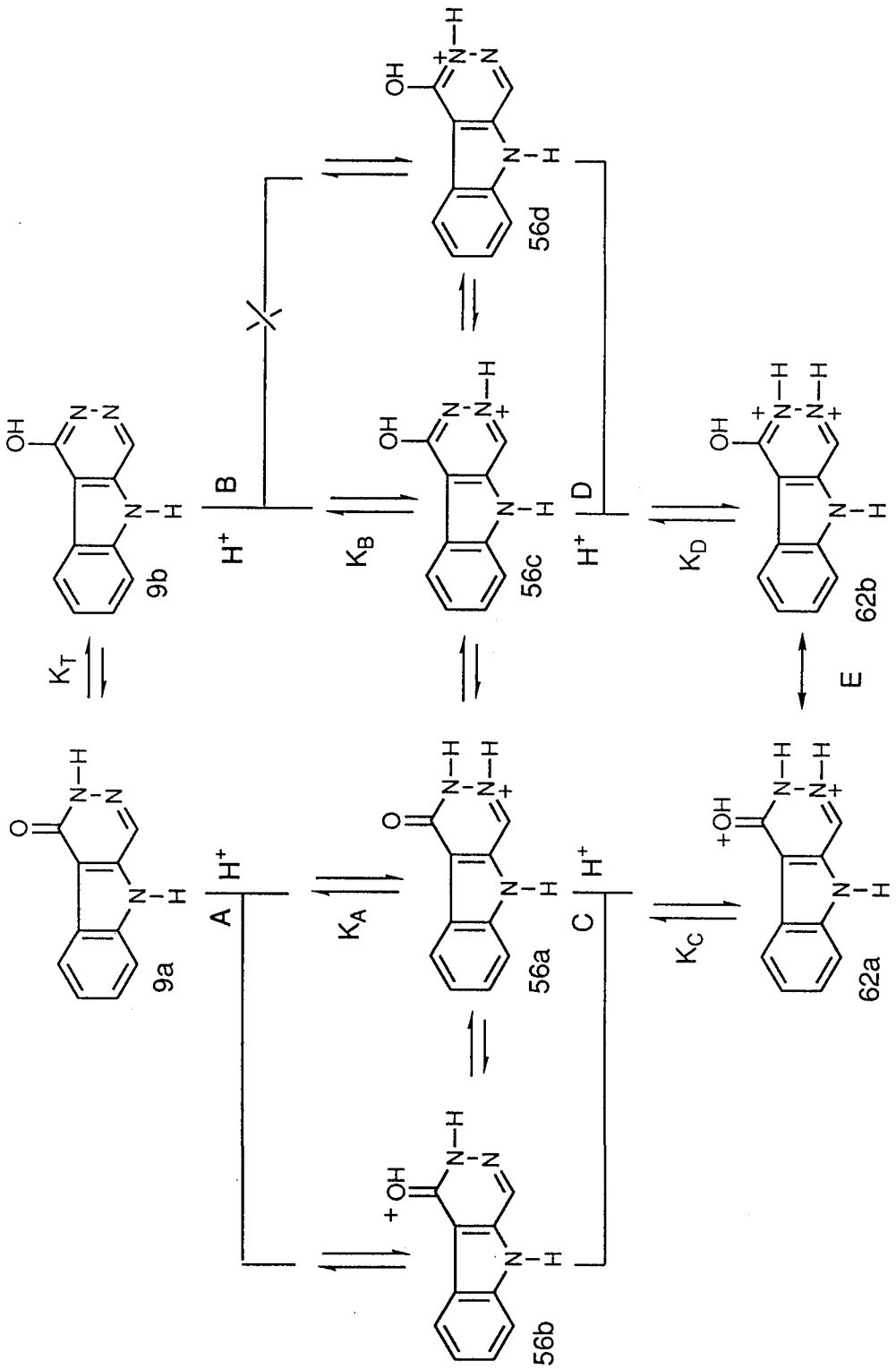
	A			
Me	Me	59 → 65	–3.68 ± 0.005	d
	B			
Me	Me	60 → 66	–0.98 ± 0.001	d

a. The pKa values were determined by the use of the spectroscopic method described by Albert and Serjeant. [28]

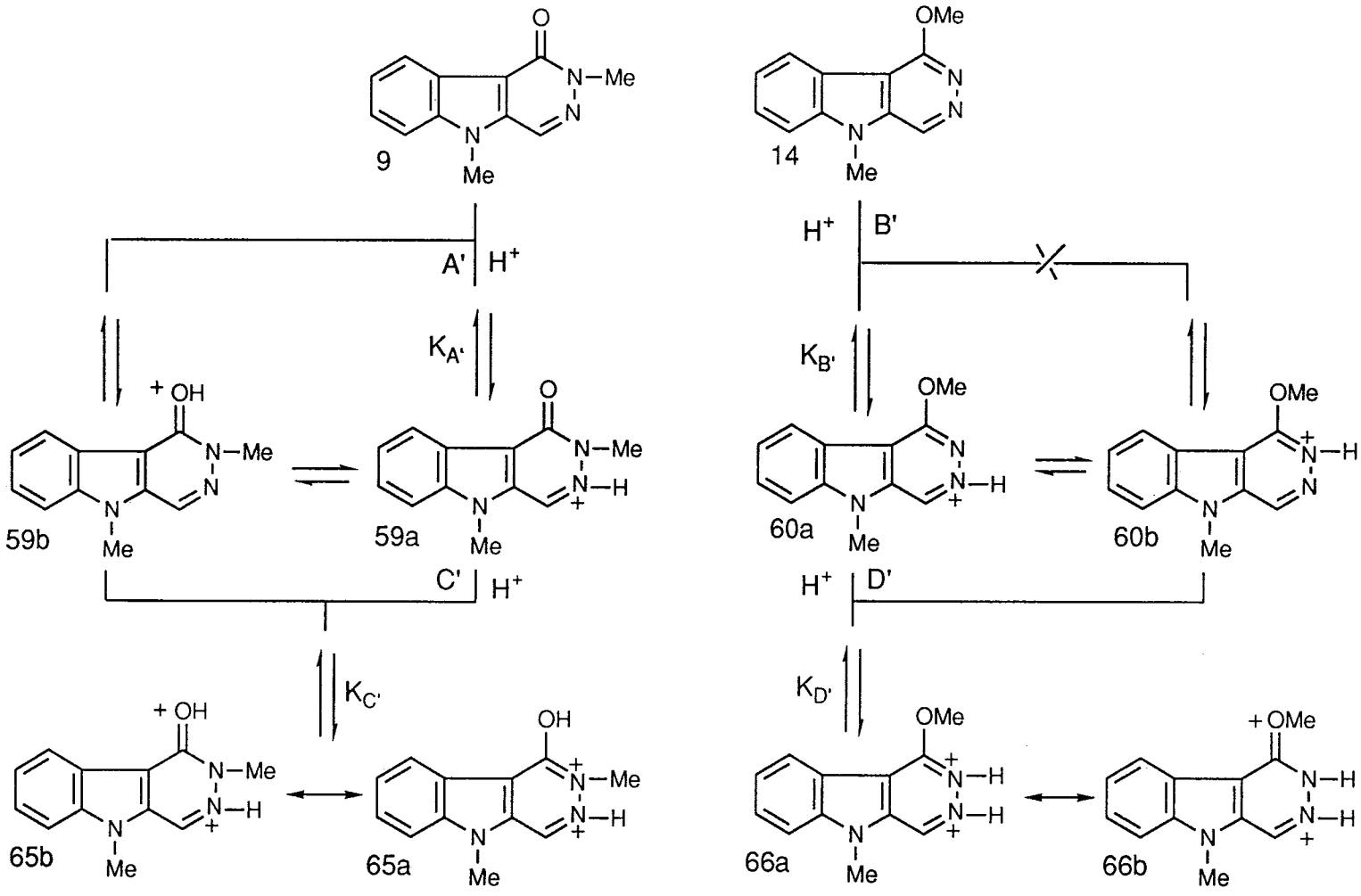
b. Determined in buffer solutions and in sulphuric acid solutions ($-2.78 \leq$ pH or $H_0 \leq 7$). [29]

c. Determined in buffer solutions and in sulphuric acid solutions ($-0.50 \leq$ pH or $H_0 \leq 9.12$). [29]

d. Determined in concentrated sulphuric acid solutions.



Scheme III. 14



Scheme III. 15

4. 0 Experimental

1–Methylindole :

Dimethyl sulphoxide (360 ml) was added to potassium hydroxide (38.52 g, 0.69 mol) and the mixture was stirred for 15 min. Indole (20 g, 0.17 mol) was then added and the mixture was stirred for 45 min. Methyl iodide (49.25 g, 0.35 mol) was added and the mixture was cooled briefly and stirred for a further 45 min. before water (200 ml) was added. The mixture was extracted with diethyl ether (3x100 ml) and the combined extracts were washed with water (3 x 100 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give 1–methyl indole (21 g, 94 %), as an oil, b.p. 95 °C at 8 mm Hg [lit. [31] b.p. 95 °C 8 mm Hg]. ^{1}H-NMR ($CDCl_3$) : δ 7.40–7.72 (dd, 1H, H_4) ; 7–7.20 (m, 3H, H_{5-7}) ; 6.72–6.80 (d, 2H, H_2) ; 6.32–6.40 (d, 2H, H_3) ; 3.40 (s, 3H, NCH_3). IR (liq.) : $\nu_{max.}$ 3060, 1515, 1465, 1320, 1240 cm^{-1}.

1–Benzenesulphonylindole :

Crushed potassium hydroxide (22.45 g, 0.4 mol) in dry dimethyl sulphoxide (DMSO) was stirred for 15 min. Indole (11.70 g , 0.10 mol) was then added portionwise and the solution was stirred for further 1 h. Benzenesulphonyl chloride (35.4 g, 0.20 mol) was added by syringe and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (200 ml), and then extracted with diethyl ether (3 x 100 ml) The extracts were washed with water (2 x 150 ml), dried ($MgSO_4$), and solvent was removed under reduced pressure to give a solid, which was recrystallised from diethyl ether–hexane furnishing 1–benzenesulphonylindole (19 g, 74 %), as a yellow solid, m.p. 77.6–78.6 °C [lit. [7] m.p. 76–76.5 °C, lit. [32] m.p. 77.5–79 °C]. ^{1}H-NMR ($CDCl_3$) : δ 6.64 (d, 1H, H_2) ; 7.20–8.20 (m, 10 H). IR (nujol) : $\nu_{max.}$ 1445, 1370, 1260, 1200, 1170, 1090 cm^{-1}. $[M^+]$ = 257 a.m.u.

2–Formylindole [5] :

Indole (10 g, 0.085 mol) in dry tetrahydrofuran (THF) (150 ml) was cooled to – 70 °C and *n* –butyllithium (1.6 M in hexane ; 54.7 ml, 0.088 mol) was slowly added dropwise. The solution was kept at – 70 °C for 30 min. and then added to an excess of carbon dioxide. The solution was allowed to rise to room temperature.The solvent was evaporated under reduced pressure to remove excess carbon dioxide to give lithium indole–1–carboxylate. THF (150 ml) was added to the reaction mixture and the solution was cooled to –70 °C. t–Butyllithium (1.6 M in *n* –pentane ; 1.6 ml) was carefully added to avoid increasing the solution temperature. The solution was kept at –70 °C for 1 h and then the mixture was added to dimethylformamide (DMF) (12.4 g, 0.17 mol) in THF (10 ml) at –70 °C for 2 h. Water (1 ml) was added to the mixture slowly at – 70 °C. The reaction mixture was allowed reach to room temperature and then poured into aqueous ammonium chloride solution. The aqueous phase was poured into aqueous sulphuric acid solution (100 ml, 5 %) at 0 °C. The precipitate was collected by filtration and dried. Recrystallisation of the

product from ethanol afforded 2–formylindole (3.5 g, 27.5 %), m.p. 141–142 °C [lit.[5] m.p. 135–138 °C], as a brown solid. ^{1}H-NMR ($CDCl_3$) : δ 6.90–8.00 (m, 6H, $H_{1-2,\ 4-7}$) ; 9.90 (s, 1H, CHO). IR (nujol) : $\nu_{max.}$ 1680 (C=O) cm^{-1} . [M^+] = 145 a m.u. (Found : C, 74.3 ; H, 4.8 ; N, 9.6 ; calc. for C_9H_7NO C,74.5 ; H, 4.9 ; N, 9.7 %).

2–Formyl–1–methylindole [6] :

n –Butyllithium (1.55 M in hexane ; 45.6 ml, 0.089 mol) was added dropwise to stirred solution of 1–methylindole (10 g, 0.075 mol) in dry diethyl ether (200 ml) under nitrogen. The mixture was refluxed for 6 h. After cooling of the reaction mixture to room temperature, DMF (dimethyl formamide) (5.55 g, 0.076 mol) was added to the mixture. The reaction mixture was refluxed for 2 h and then stirred at 20 °C for 12 h. Water (100 ml) was added and the mixture was extracted with diethyl ether (3x50 ml). The combined ether extracts were washed with water (100 ml) and dried ($MgSO_4$), and the solvent was removed to give a solid which was recrystallised from ethanol to give 2–Formyl–1 –methylindole (7 g, 58 %), as a yellow solid, m.p. 83–84 °C [lit. [6] m.p. 83–85 °C]. ^{1}H-NMR ($CDCl_3$) : δ 4.02 (s, 3H, NCH_3) ; 7.13–7.72 (m, 5H, $H_{3,\ 4-7}$) ; 9.82 (s, 1H, CHO). IR (nujol) : $\nu_{max.}$ 1680 (C=O) cm^{-1}. [M^+] = 159 a.m.u.

1–Benzenesulphonyl–2–formylindole :

n –Butyllithium (1.6 M in hexane ; 62 ml, 0.1 mol) was cautiously added to diisopropyl amine (10.9 g, 0.112 mol) in dry THF (200 ml) at 0 °C under nitrogen. The solution was cooled to –78 °C and 1–benzenesulphonylindole (25.7 g, 0.1 mol) in dry THF (240 ml) was added rapidly and the mixture was stirred at this temperature for 2h . The mixture was allowed to warm to 5 °C over 1 h . and then recooled to – 78 °C. Dry DMF (dimethylformamide) (7.3 g, 0.1 mol) in THF (40 ml) was added rapidly *via* a syringe and the reaction mixture was stirred at room temperature overnight. The solution was then poured into hydrochloric acid (400 ml, 1 %) and the organic layer was then separated. The aqueous phase was extracted with dichloro methane (3 x 150 ml). The extracts were combined with the organic phase above and the solvent was removed after drying the organic phase ($MgSO_4$) under reduced pressure to give an oil, which was triturated using petroleum ether-diethyl ether affording 1–benzenesulphonyl–2–formylindole (15 g, 52 %), as a yellow solid, m.p. 110–112 °C [lit. [7] m.p.111–111.5 °C]. ^{1}H-NMR ($CDCl_3$) : δ 7.12–7.68 (m, 7H) ; 7.76–8.08 (m, 3H) ; 10.40 (s, 1H, CHO). IR (Bromoform) : $\nu_{max.}$ 1670 (s, C=O) cm^{-1}. [M^+] = 285 a.m.u.

Methyl indole–3–carboxylate :

3–Trichloroacetylindole (5 g, 0.019 mol) in methanol (100 ml) containing potassium hydroxide solution (a few drops, 60 %) was refluxed for 15 min. and then the reaction mixture was cooled and diluted with water (50 ml). The precipitate was collected by filtration and dried. Recrystallisation of the crude product from methanol–water afforded

methyl indole–3–carboxylate (3 g, 90 %) , as white needles, m.p.150–151 °C [lit. [33] m.p. 151–152 °C]. IR (nujol) : $\nu_{max.}$ 3200 (br. , NH), 1670 (C=O) cm^{-1}. $[M^+]$ = 175 a.m.u.

3–Trichloroacetylindole :

Trichloroacetyl chloride (10 g, 0.055 mol), followed by indole (5.85 g, 0.05 mol), was added to pyridine (4.35 g, 0.055 mol) in dioxane (60 ml) with stirring. The resulting mixture was stirred for 1h at room temperature and then poured into water (200 ml). The precipitate was collected by filtration, dried, and recrystallised from ethanol to give 3–trichloroacetylindole (9 g, 69 %), m.p. 235–236 °C [lit. [8] m.p. 235–237 °C]. ^{1}H-NMR ($CDCl_3$) : δ 8.60–8.65 (d, 1H, H_2) ; 7.20–8.40 (m, 5H, H_{4-7}). IR (nujol) : $\nu_{max.}$ 3200 (br. , NH), 1635 (C=O) cm^{-1}. $[M^+]$ = 262.8 a.m.u.

The attempted preparation of methyl 2–formylindole–3–carboxylate :

N–Methylformanilide (1.69 g, 0.0125 mol) and phosphorus oxychloride (1.92g, 0.0125 mol), protected from atmospheric moisture, were stirred at room temperature for 15 min. To the mixture was added 1, 2–dichloro- ethane (20 ml), followed by methyl indole–3–carboxylate (2 g, 0.0114 mol). After refluxing the reaction mixture for 1 h. The mixture was poured into a solution of sodium acetate (7.5 g) and ice-water (15 g), whereupon the product separated. The crude product was collected by filtration, washed well with water, and dried. Recrystallisation of the product from methanol-water gave a white solid, melting point, TLC, NMR, and IR of which are identical with starting material (1.45 g, 73 %).

The attempted preparation of 2–formyl–3–trichloroacetylindole :

N–Methylformanilide (4.055 g, 0.03 mol) and phosphorus oxychloride (4.6 g, 0.03 mol), protected from atmospheric moisture, were stirred at room temperature for 15 min. To the mixture was added 1, 2–dichloroethane (40 ml) followed by 3–trichloroacetylindole (4 g, 0.015 mol) . After refluxing the mixture for 1 h, the reaction mixture was poured into a solution of sodium acetate (7.5 g) in ice-water (15 g), whereupon a product separated. The crude product was collected by filtration, washed well with water, and dried. Recrystallisation of the crude product from ethanol gave starting material (3.5 g, 88 %).

The attempted preparation of 2–formyl–3–trichloroacetylindole :

A solution of 1, 1–dichloro– dimethylether ($CHCl_2OCH_3$) (2.1 g, 0.018 mol) in dichloromethane (30 ml) was added at – 20 °C to a mixture of 3–trichloroacetylindole (4 g, 0.015 mol) and aluminium chloride (4.87 g, 0.036 mol) in nitromethane (30 ml) and dichloromethane (30 ml). The mixture was stirred for 18 h at – 20 °C and then poured into ice-water. The organic phase was separated, and the aqueous phase was extracted with diethyl ether (3 x 50 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated to dryness. The residue was crystallised from ethanol to give yellowish starting material (3.2 g, 80 %).

The attempted preparation of 2–formyl–3–trichloroacetylindole :
Trichloroacetyl chloride (1.37 g, 7.58 mmol), followed by 2–formylindole (1 g, 6.89 mmol), was added to pyridine (0.6 g, 7.58 mmol) in dioxane (20 ml) with stirring. The resulting mixture was stirred for 2 h at room temperature. The mixture was then poured into water (50 ml). The precipitate was collected, washed with water (100 ml), and dried. Recrystallisation of the crude product from ethanol gave only starting material (0.75 g, 75 %).

The attempted preparation of 2–formyl–1–methyl–3–trichloroacetylindole :
A solution of trichloroacetyl chloride (1.43 g, 7.85 mmol) in dichloromethane (5 ml) was added at – 20 °C to a mixture of 2–formyl–1–methylindole (1 g, 6.28 mmol) and aluminium chloride (1.05 g, 7.85 mmol) in nitromethane (10 ml) and dichloromethane (5 ml). The mixture was stirred for 18 h at –20 °C and poured into ice-water. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 x 50 ml). The combined extracts were dried ($MgSO_4$) and the solvent evaporated to dryness. The residue was crystallised from ethanol to give yellow starting material (0.78 g, 78 %).

The attempted preparation of 2–formyl–1–methyl–3–trichloroacetylindole :
Trichloroacetyl chloride (1.43 g, 7.85 mmol), followed by 2–formyl–1–methylindole (1 g, 6.28 mmol), was added to pyridine (0.62 g, 7.85 mmol) in dioxane (20 ml) with stirring. The resulting mixture was stirred for 2 h at room temperature. The mixture was poured into water (50 ml) . The precipitate was collected and dried. Recrystallisation of the crude product from ethanol gave only starting material (0.83 g, 83 %)..

Dimethyl 2–(1, 2–diphenylhydrazino)butendioate :
To a solution of 1, 2–diphenylhydrazine (29.11 g, 0.158 mol) in methanol (75 ml) was added dimethyl acetylenedicarboxylate (24.75 g, 0.174 mol) with stirring over 15 min. The reaction mixture was refluxed for 30 min. and then left overnight. The crystals, which were very hard, were collected by filtration, and washed with cold methanol (100 ml). Recrystallisation of the product from methanol gave dimethyl 2–(1, 2–diphenylhydrazino) –butendioate (44 g, 85 %), as white needles, m.p. 138 °C, [lit.[12, 13] m.p. 137–138 °C]. ^{1}H-NMR (DMSO–d_6) : δ 9.06 (s, 1H, NH) ; 6.74–7.80 (m, 10H) ; 5.00 (s, 1H, C=CH) ; 4.08 (s, 3H, OCH_3) ; 3.92 (s, 3H, OCH_3). IR (nujol) : $\nu_{max.}$ 3280 (NH), 1670 and 1740 (C=O) cm^{-1}. $[M^+]$ = 326 a.m.u.

Dimethyl indole–2, 3–dicarboxylate :
A solution of dimethyl 2–(1, 2–diphenylhydrazino) butendioate (30.8 g, 0.094 mol) in xylene (150 ml) was refluxed for 2 h. The reaction mixture was kept at 0 °C for 3–4 h. The crystals were collected and dried. Recrystallisation of the product from aqueous methanol (70 %) gave dimethyl indole–2, 3–dicarboxylate (15 g, 68 %), as white needles, m.p. 113 °C [lit. [12, 13] m.p. 114 °C]. ^{1}H-NMR ($CDCl_3$) : δ 8.00–8.24 (dd, 1H, H_4) ; 7.24–7.66 (m,

cm^{-1}. $[M^+]$ = 233 a.m.u.

Methyl 2–hydroxymethylindole–3–carboxylate :

Dimethyl indole–2, 3–dicarboxylate (9.8 g, 0.042 mol), sodium borohydride ($NaBH_4$) (3.4 g, 0.09 mol) and water-free calcium chloride ($CaCl_2$) (5.04 g, 0.045 mol) in dry tetrahydrofuran (THF) (600 ml) were stirred for 24 h at room temperature. Then, water (10 ml) and diethyl ether (200 ml) were added to the mixture. The mixture was left until gas evolution ceased and then filtered. The filtrate was dried ($MgSO_4$) and evaporated to give a residue which was crystallised from ethanol-water to give methyl 2–hydroxy methylindole–3–carboxylate (8.1 g, 94 %), as white solid, m.p. 151–153 °C [lit. [11] m.p. 152–153 °C]. ^{1}H-NMR ($CDCl_3$) : δ 7.2–8.8 (m, 4H, H_{4-7}) ; 6.1 (s,1H, OH) ; 5.64 (s, 2H, CH_2O) ; 3.90 (s, 3H, OCH_3). IR (nujol) : $\nu_{max.}$ 3300–3400 (NH and OH), 1665 (C=O) cm^{-1}. $[M^+]$ = 205 a.m.u.

Methyl 2–formylindole–3–carboxylate :

Freshly prepared activated manganese dioxide (33.89 g, 0.39 mol) was added to a stirred solution of methyl 2–hydroxymethylindole–3–carboxylate (8 g, 0.039 mol) in dry dichloromethane (400 ml) and the reaction mixture was refluxed for 2 h after the addition of the manganese dioxide. The hot reaction mixture was filtered through celite and the spent reagent was washed well with dichloromethane. Evaporation of the solvent gave a yellow solid, which was recrystallised from ethanol to give pure *methyl 2–formylindole –3–carboxylate* (6.9 g, 87 %), as a yellow solid, m.p. 165–166 °C. ^{1}H-NMR ($CDCl_3$) : δ 10.60 (s, 1H, CHO) ; 8.12–8.36 (dd, 1H, H_4) ; 7.20–7.50 (m, 3H, H_{5-7}) ; 4.00 (s, 3H, OCH_3). IR (nujol) : $\nu_{max.}$ 3300 (NH), 1680 (C=O ester), 1650 (C=O ald.). $[M^+]$ = 203 a.m.u (Found : C, 64.8 ; H, 4.5 ; N, 6.7 ; $C_{11}H_9NO_3$ requires C, 65.0 ; H, 4.5 ; N, 6.9 %).

1, 2–Dimethylindole :

Dimethyl sulphoxide (DMSO) (150 ml) was added to crushed potassium hydroxide (17 g, 0.3 mol). The mixture was stirred for 15 min., 2–methylindole (10 g, 0.08 mol) was added, and the mixture was stirred for 45 min. To the reaction mixture was added methyliodide (21.64 g, 0.152 mol) and the mixture was cooled briefly and stirred for a further 45 min. before water (150 ml) was added. The mixture was extracted with diethyl ether (3 x 100 ml) and the extracts were washed with water (3 x 50 ml) . The combined ether phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give a residue, which was crystallised from petroleum ether (40–60 °C) furnishing 1, 2 –dimethylindole (9.3 g, 85 %), as yellow needles, m.p. 55–56 °C [lit. [31] m.p. 52–53 °C, lit. [34] m.p. 54–55 °C]. ^{1}H-NMR ($CDCl_3$) : δ 7.24–7.60 (dd, 1H, H_4) ; 6.88–7.25 (m, 3H, H_{5-7}) ; 6.20 (s, 1H, H_3) ; 3.52 (s, 3H, NCH_3) ; 2.32 (s, 3H, C–CH_3). $[M^+]$ = 145 a.m.u.

1, 2–Dimethyl–3–trichloroacetylindole :

Trichloroacetyl chloride (41.32 g, 0.23 mol), followed by 1, 2–dimethylindole (30 g, 0.21

1, 2-Dimethyl-3-trichloroacetylindole :

Trichloroacetyl chloride (41.32 g, 0.23 mol), followed by 1, 2-dimethylindole (30 g, 0.21 mol), was added to pyridine (19.12 g, 0.23 mol) in dioxane (240 ml) with stirring. The resulting mixture was stirred for 1 h at room temperature and then poured into water (400 ml). The precipitate was collected and dried. Recrystallisation of the product from ethanol gave *1, 2-dimethyl-3-trichloro acetylindole* (59.5 g, 85 %), as white needles, m.p. 156 –158 °C. ^{1}H-NMR ($CDCl_3$) : δ 8.00–8.40 (dd, 1H, H_4) ; 7.10–7.40 (m, 3H, H_{5-7}) ; 3.68 (s, 3H, NCH_3) ; 2.72 (s, 3H, C–CH_3). IR (nujol) : $\nu_{max.}$ 1640 (C=O) cm^{-1}. $[M^+]$ = 290.8 a.m.u. (Found : C, 49.7 ; H, 3.3 ; N, 4.8 ; Cl, 36.3 ; $C_{12}H_{10}Cl_3NO$ requires C, 49.6 ; H, 3.5 ; N, 4.8 ; Cl, 36.6 %).

Methyl 1, 2-dimethylindole-3-carboxylate :

1, 2–Dimethyl–3–trichloroacetylindole (5 g, 0.017 mol) in methanol (100 ml) containing aqueous potassium hydroxide(60 %, a few drops) was refluxed for 10 min. The mixture was cooled and diluted with water (50 ml).The precipitate was collected and dried. Recrystallisation of the product from methanol-water gave pure methyl 1, 2–dimethyl indole–3–carboxylate (3.35 g, 96 %), as white needles, m.p. 144–5 °C, [lit. [16, 17, 34] m.p. 142–143 °C]. ^{1}H-NMR ($CDCl_3$) : δ 7.90–8.20 (dd, 1H, H_4) ; 7.00–7.40 (m, 3H, H_{5-7}) ; 3.96 (s, 3H, NCH_3) ; 3.60 (s, 3H, OCH_3) ; 2.86 (s, 3H, CCH_3). IR (nujol) : $\nu_{max.}$ 1665 (C=O) cm^{-1}. $[M^+]$ = 203 a.m.u.

Methyl 2-bromomethyl-1-methylindole-3-carboxylate :

A mixture of methyl 1, 2–dimethyl indole–3–carboxylate (10 g, 0.05 mol) and N–bromo succinimide (NBS) (8.76 g, 0.05 mol) in dry carbon tetrachloride (350 ml) containing benzoyl peroxide (20 mg) were refluxed for 4 h. The hot solution was filtered and evaporated to give a solid, which was recrystallised from carbon tetrachloride to give pure *methyl 2-bromomethyl-1-methyl indole-3-carboxylate* (11.2 g, 81 %), as white needles, m.p. 123–124 °C. ^{1}H-NMR ($CDCl_3$) : δ 8.00–8.30 (dd, 1H, H_4) ; 7.18–7.44 (m, 3H, H_{5-7}) ; 5.20 (s, 2H, CH_2Br) ; 4.00 (s, 3H, OCH_3) ; 3.80 (s, 3H, NCH_3). IR (nujol) : ν_{max} 168 (C=O) cm^{-1}. $[M^+]$ = 281.8 a.m.u. (Found : C, 51.4 ; H, 4.3 ; N, 4.9 ; Br, 27.8 ; $C_{12}H_{12}BrNO_2$ requires C, 51.1 ; H, 4.3 ; N, 5.0 ; Br, 28.0 %).

Methyl 2-formyl-1-methylindole-3-carboxylate :

To the solution of sodium ethoxide (3.38 g, 0.05 mol) in ethanol (60 ml) was added 2–nitropropane (5.75 g, 0.065 mol) and mixture was stirred for 30 min. and methyl 2–bromomethyl–1–methylindole –3–carboxylate (14 g, 0.05 mol) was then added. The resulting mixture was refluxed for 2 h with stirring. After cooling of the mixture, the precipitate was collected, and washed with water (200 ml), and dried. Recrystallisation of the crude product from *iso*–propanol gave pure *methyl 2-formyl -1-methylindole-3 -carboxylate* (8.9 g, 82 %), as yellowish needles, m.p. 126–8 °C. ^{1}H-NMR ($CDCl_3$) : δ

10.80 (s, 1H, CHO) ; 8.12–8.40 (dd, 1H, H_4) ; 7.20–7.60 (m, 3H, H_{5-7}) ; 4.15 (s, 3H, OCH_3) ; 4.00 (s, 3H, NCH_3). IR (nujol) : $\nu_{max.}$ 1680 (C=O ester), 1650 (C=O ald.) cm^{-1}. $[M^+]$ = 217 a.m.u. (Found : C, 66.2 ; H, 5.1 ; N, 6.4 ; $C_{12}H_{11}NO_3$ requires C, 66.4 ; H, 5.1 ; N, 6.5 %).

2–Methyl–3–trichloroacetylindole :

Trichloroacetyl chloride (18.68 g, 0.103 mol), followed by 2–methylindole (12.25 g, 0.09 mol), was added to pyridine (8.64 g, 0.103 mol) in dioxane (100 ml) with stirring. The resulting mixture was stirred for 1 h at room temperature and then poured into water (300 ml). The precipitate was collected and dried. Recrystallisation of the compound from ethanol afforded 2–methyl–3–trichloro acetylindole (20 g, 78 %), as white needles, m.p. 171–172 °C [lit. [21] m.p. 167 °C]. ^{1}H-NMR ($CDCl_3$) : δ 8.13– 8.40 (dd, 1H, H_4) ; 7.13–7.45 (m, 3H, H_{5-7}) ; 2.80 (s, 3H, CH_3). IR (nujol) : $\nu_{max.}$ 3300 (NH), 1620 (C=O) cm^{-1}. $[M^+]$ = 276.9 a.m.u.

Methyl 2–methylindole–3–carboxylate :

2–Methyl–3–trichloroacetylindole (11 g, 0.04 mol) in methanol (200 ml) containing aqueous potassium hydroxide (60 %, a few drops) was refluxed for 15 min. The reaction mixture was cooled and diluted with water (100 ml). The precipitate was collected, washed well with water, and dried. Recrystallisation of the product from methanol-water gave methyl 2–methylindole–3–carboxylate (7.17 g, 95 %), as white needles, m.p. 171 –172 °C [lit. [22] m.p. 165 °C]. ^{1}H-NMR ($CDCl_3$) : δ 8.00–8.26 (dd, 1H, H_4) ; 7.06–7.40 (m, 3H, H_{5-7}) ; 3.94 (s, 3H, OCH_3) ; 2.74 (s, 3H, C–CH_3). IR (nujol) : $\nu_{max.}$ 3285 (NH), 1660 (C=O) cm^{-1}. $[M^+]$ = 189 a.m.u. (Found : C, 69.9 ; H, 5.9 ; N, 7.4 ; calc. for $C_{11}H_{11}NO_2$ C, 69.8 ; H, 5.9 ; N, 7.4 %).

Methyl 1–benzenesulphonyl–2–methylindole–3–carboxylate :

To a solution of methyl 2– methyl indole–3–carboxylate (24 g, 0.13 mol) in dry (THF) tetrahydrofuran (300 ml) was added sodium hydride (3.96 g, 0.165 mol) portionwise with stirring. The solution was refluxed for 30 min. before benzenesulphonyl chloride (24.64 g, 0.14 mol) was added dropwise. The resulting mixture was refluxed for 1h further, cooled and the solvent was evaporated to dryness under reduced pressure. Water (100 ml) was added and the precipitate was collected and dried. Recrystallisation of the product from ethanol gave *methyl 1–benzenesulphonyl–2–methyl indole–3– carboxylate* (40.15 g, 97 %), as brown solid, m.p. 91–92 °C. ^{1}H-NMR ($CDCl_3$) : δ 7.20 –8.40 (m, 9H, arom.) ; 3.92 (s, 3H, OCH_3) ; 3.00 (s, 3H, C – CH_3). IR (nujol) : $\nu_{max.}$ 1660 (C=O) cm^{-1}. $[M^+]$ = 328.9 a.m.u. (Found : C, 62.2 ; H, 4.5 ; N, 4.2 ; S, 9.4 ; $C_{17}H_{15}NO_4S$ requires C, 62.0 ; H, 4.6 ; N, 4.3 ; S, 9.7 %).

Methyl 1–benzenesulphonyl–2–bromomethylindole–3–carboxylate :

Methyl 1–benzene sulphonyl–2–methylindole–3–carboxylate (36 g, 0.11 mol) and N–bromo succinimide (19.45 g, 0.11 mol) in dry carbon tetrachloride (400 ml) containing benzoylperoxide (20 mg) was refluxed for 5 h. The succinimide was filtered off and the solvent was evaporated to give a residue. Recrystallisation of the product from DMF-ethanol gave *methyl 1–benzene sulphonyl–2–bromomethylindole–3– carboxylate* (35.2 g, 79 %), as colourless needles, m.p. 122–124 °C. ^{1}H-NMR ($CDCl_3$) : δ 7.20–8.30 (m, 9H, arom.) ; 5.56 (s, 2H, CH_2Br) ; 4.00 (s, 3H, OCH_3). IR (nujol) : ν_{max} 1650 (C=O) cm^{-1}. $[M^+]$ = 408.8 a.m.u. (Found : C, 50.5 ; H, 3.4 ; N, 3.5 ; S, 8.0 ; $C_{17}H_{14}BrNO_4S$ requires C, 50.0 ; H, 3.5 ; N, 3.4 ; S, 7.9).

Methyl 1–benzenesulphonyl–2–formylindole–3–carboxylate :

To the solution of sodium ethoxide (5.03 g, 0.096 mol) in ethanol was added 2–nitropropane (8.51 g, 0.096 mol) with stirring. The mixture was then stirred for 30 min. and methyl 1–benzene sulphonyl–2–bromomethyl indole–3– carboxylate (30 g, 0.073 mol) was added for 2 h with stirring. After cooling of the reaction mixture, the precipitate was collected, washed well with water, and dried. Recrystallisation of the compound from ethanol gave a mixture of methyl 1–benzene sulphonyl–2–formylindole–3– carboxylate and methyl 1–benzenesulphonyl– 2–methylindole–3–carboxylate (9.4 g , 37%), as a light brown solid, m.p. 95–97 °C, which could not be separated by column chromatography.

Attempted preparation of the 1, 2–dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*] indole :

To a boiling solution of methyl 2–formylindole–3–carboxylate (0.5 g, 2.46 mmol) in 2–ethoxyethanol (50 ml) was added hydrazine hydrate (0,6 g, 12 mmol) dropwise over 1 h and the resulting mixture was then refluxed for 7 h. On cooling of the reaction mixture, greenish crystals formed and were collected and dried. Recrystallisation from ethanol gave *methyl 2–formylindole–3–carboxylate hydrazone* (0.38 g, 84 %), as greenish needles, m.p. 175–6 °C, instead of 1, 2–dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*]indole. ^{1}H-NMR ($CDCl_3$) : δ 8.48 (s, 1H, HC=N–NH_2) ; 7.80–8.20 (dd, 1H, H_4) ; 7.08–8.90 (m, 3H, H_{5-7}) ; 3.92 (s, 3H, OCH_3). IR (nujol) : $\nu_{max.}$ 3420 (s, NH), 3200– 3300 (br. , NH), 1665 (C=O), 1620 (C=N) cm^{-1}. $[M^+]$ = 217 a.m.u. (Found : C, 60.9 ; H, 5.1 ; N, 19.2 ; calc. for $C_{11}H_{11}N_3O_2$ C, 60.8 ; H, 5.1 ; N, 19.3 %).

1, 2–Dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*]indole :

To a boiling solution of methyl 2–formyl indole–3–carboxylate (1 g, 4.92 mmol) in *iso*-propanol (100 ml) was added hydrazine hydrate (1.3 g, 0.026 mol) dropwise over 1 h and the resulting mixture was refluxed for 48 h. On cooling the reaction mixture, white needles separated, which were washed with ethanol (100 ml), and dried. Recrystallisation from DMF-water gave pure *1, 2– dihydro–1–oxo–5H–pyridazino[4, 5– b]indole* (0.69 g, 76 %), as white crystals, m.p. > 320 °C. ^{1}H-NMR (DMSO–d_6) : δ 12.64 (br. s,1H,

$N_5\underline{H}$), 12.24 (br. s, 1H, $N_2\underline{H}$), 8.40(s, 1H, H_4) ; 8.06–8.28 (dd, 1H, H_9) ; 7.20– 7.80 (m, 3H, H_{6-8}). IR (nujol) : $\nu_{max.}$ 3200 (NH, OH), 1650 (C=O), 1625, 1575 (C=N, C=C) cm^{-1}. $[M^+]$ = 185 a.m.u. (Found : C, 64.8 ; H, 3.6 ; N, 22.6 ; $C_{10}H_7N_3O$ requires C, 64.9 ; H, 3.8 ; N, 22.7 %).

1, 2-Dihydro-2-methyl-1-oxo-5*H*-pyridazino(4, 5-*b*)indole :

To a boiling solution of methyl 2–formyl indole–3–carboxylate (0.6 g, 2.95 mmol) in *iso*-propanol (100 ml) was added methylhydrazine (0.68 g, 0.015 mol) dropwise over 1 h and the resulting mixture was refluxed for 4 days. On cooling the reaction mixture, white crystals separated, which were collected, washed with ethanol (100 ml), and dried. Recrystallisation of the crude product from 2–ethoxyethanol gave *1, 2– dihydro–2 –methyl–1–oxo–5H–pyridazino[4, 5– b]indole* (0.25 g, 43 %), as white needles, m.p. 312–313 °C. ^{1}H-NMR (DMSO–d_6) : δ 8.40 (s, 1H, H_4) ; 8.12–8.32 (dd, 1H, H_9) ; 7.20 –780 (m, 3H, H_{6-8}) ; 3.80 (s, 3H, NCH_3). IR (nujol) : $\nu_{max.}$ 3100–3300 (br. , NH, OH), 1630 (C=O), 1550 (C=C, C=N) cm^{-1}. $[M^+]$ = 199 a.m.u. (Found : C, 66.3 ; H, 4.3 ; N, 21.4 ; $C_{11}H_9N_3O$ requires C, 66.3 ; H, 4.6 ; N, 21.1 %).

1, 2-Dihydro-5-methyl-1-oxo-5*H*-pyridazino(4, 5-*b*) indole :

To a boiling solution of methyl 2–formyl–1–methylindole–3–carboxylate (8 g, 0.037 mol) in *iso*-propanol (150 ml) was added hydrazine hydrate (10 g, 0.2 mol) dropwise over 1 h and the resulting mixture was refluxed for 48 h. On cooling the reaction mixture, white crystals separated, which were collected, washed with ethanol (100 ml), and dried. Recrystallisation of the crude product from 2–ethoxyethanol gave *1, 2– dihydro–5 –methyl–1–oxo–5H–pyridazino[4, 5– b]indole* (6.8 g, 93%), as white needles, m.p. 325 °C. ^{1}H-NMR (DMSO–d_6) : δ 12.72 (br. s, 1H, $N_2\underline{H}$),8.60 (s, 1H, H_4) ; 8.08–8.34 (dd, 1H, H_9) ; 7.25–7.80 (m, 3H, H_{6-8}) ; 4.00 (s, 3H, NCH_3). IR (nujol) : $\nu_{max.}$ 1640 (C=O) cm^{-1}. $[M^+]$ = 199 a.m.u. (Found : C, 66.0 ; H, 4.6 ; N, 21.1 ; $C_{11}H_9N_3O$ requires C, 66.3 ; H, 4.6 ; N, 21.1 %).

1, 2-Dihydro-2, 5-dimethyl-1-oxo-5*H*-pyridazino(4, 5-*b*)indole :

To a boiling solution of methyl 2–formyl–1–methylindole–3–carboxylate (1 g, 4.60 mmol) in *iso*-propanol (100 ml) was added methylhydrazine (1 g, 0.02 mol) dropwise over 1 h . The resulting mixture was refluxed for 4 days. On cooling the reaction mixture, white needles separated which were collected, washed with ethanol (25 ml), and dried. Recrystallisation of the crude product from 2–ethoxy ethanol gave *1, 2–dihydro–2, 5 – dimethyl–1–oxo–5H–pyridazino[4, 5– b]indole* (0.65 g, 66 %), as white needles, m.p. 173–174 °C. ^{1}H-NMR ($CDCl_3$) : δ 8.24–8.56 (dd, 1H, H_9) ; 8.08 (s, 1H, H_4) ; 7.10–7.60 (m, 3H, H_{6-8}) ; 3.92 (s, 3H, N_5–CH_3) ; 3.84 (s, 3H, N_2–CH_3). IR (nujol) : $\nu_{max.}$ 1655 (C=O), 1620, 1560 (C=N, C=C) cm^{-1}. $[M^+]$ = 213 a.m.u. (Found : C, 67.4 ; H, 5.2 ; N, 19.6 ; $C_{12}H_{11}N_3O$ requires C, 67.6 ; H, 5.2 ; N, 19.7 %).

Dimethyl 1–benzylindole–2, 3–dicarboxylate (6 g, 0.0186 mol), sodium borohydride ($NaBH_4$) (1.55 g, 0.041 mol), and water-free calcium chloride (2.27 g, 0.0205 mol) in dry tetrahydrofuran (THF) were stirred for 48 h at room temperature. To the reaction mixture was added water (5 ml) and diethyl ether (200 ml). The mixture was left until the gas evolution ceased and then filtered. The filtrate was dried ($MgSO_4$) and evaporated to afford a residue, which was crystallised from ethanol-water to give white crystalline starting material.

3, 5–Dimethyl–1–methoxy–5*H*–pyridazino(4, 5–*b*)indolium toluene–*p*–sulphonate :

1–Methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (22 mg, 0.095 mmol) and methyl toluene–*p*–sulphonate (19.5 mg, 0.095 mmol) were kept at room temperature in methanol (5 ml) for 12 h. Diethyl ether (20 ml) was added to the mixture. The precipitate was collected and dried. Crystallisation of the solid from ethanol-diethyl ether gave *3, 5–Dimethyl–1–methoxy–5H–pyridazino[4, 5 – b]indolium toluene–p–sulphonate* (35 mg, 92 %), as a white solid, m.p. 160 °C (dec.). (Found C, 59.30; H, 5.29 ; N, 10.20 ; S, 8.27 requires C, 60.14 ; H, 5.30 ; N, 10.52 ; S, 8.03). ^{1}H-NMR (DMSO-d_6) : δ 10.30 (s, ^{1}H, H_4); 6.90–8.30 (m, 8H, aromatic); 5.54 (s, 3H, CH_3); 4.30 (s, 3H, CH_3); 4.14 (s, 3H, CH_3); 2.24 (s, 3H, Me-Ph-SO_3).

The synthesis of **1–Methoxy–5*H*–pyridazino(4, 5–*b*)indole** is described in detail in chapter V.

5. 0 References

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Chapter IV

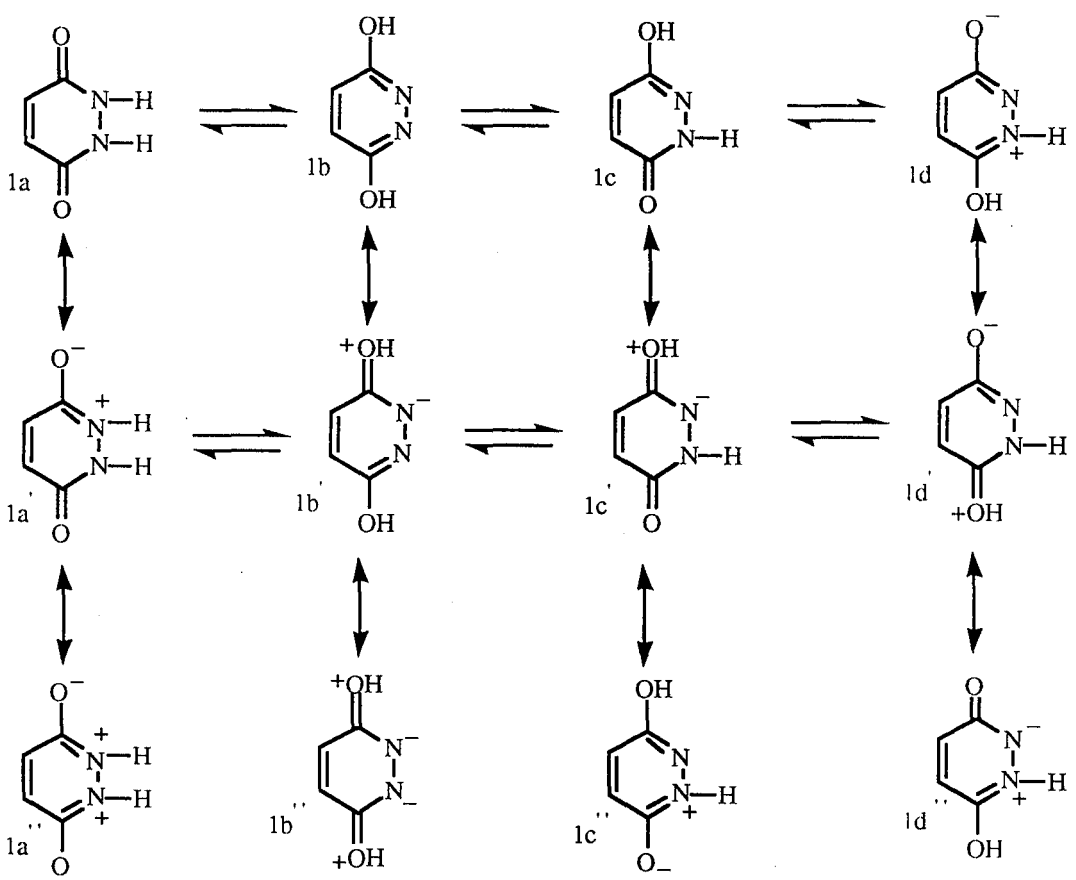
Tautomerismof 1, 4–Dioxo–1, 2, 3, 4–tetrahydro–5H–pyridazino(4, 5–b)indole

1. 0 Tautomerism of Pyridazinedione and Fused Pyridazinediones

1. 0 Introduction

Simple heterocyclic systems bearing one potentially tautomeric centre as, for example, the pyridone-hydroxypyridine system were discussed in the section I. 1. 2d. In this chapter we are concerned with diazine system bearing two potentially tautomeric centres, in particular, dihydroxy systems. [1]

Compared with the pyridone-hydroxypyridine system, the presence of more than one hetero atom in the ring and of more than one potentially tautomeric substituent increases the number of possible tautomeric structures. Thus, for maleic hydrazide, four tautomeric forms are possible (Scheme IV. 1). There is an additional hydroxy–oxo tautomeric form (1c) for the system having potentially tautomeric substituents, compared with the simpler 3(2*H*)–pyridazinone (see Section II. 1. 1).



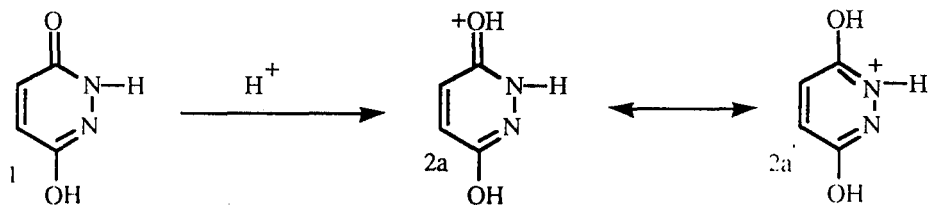
Scheme IV. 1

One of the important features of the potentially tautomeric hydroxypyridines and hydroxy pyridazines is the possibility of resonance stabilisation of the tautomeric system by the zwitterionic structures (1a', 1a", 1b', 1b", 1c', 1c", and 1d', 1d"). However, although in the case of (1c ⟷ 1c') and (1a ⟷ 1a') the zwitterionic canonical structures are thermodynamically more stable canonical forms, this is not the case with

(1b ⟷ 1b') where the charged canonical form is much less importance as the positive charge resides on the more electronegative oxygen atom. Similarly, the zwitterionic structure (1d') is thermodynamically less stable than the zwitterionic structure (1d) for the same reason.

The tautomerism of maleic hydrazide (1) has previously been investigated by several techniques in the solid state and in a variety of solvents. [2] The proton resonance spectrum of maleic hydrazide (1) has been interpreted to the favour of the dioxo–form (1a) [2d, 3] whereas much of other evidence indicates that mono-oxo-mono-hydroxy structure (1c) is predominant. [2c] The hydroxy-form (1c) is stabilised by the contribution from the charge separated form (1c") and of lesser importance (1c') in which the positive charge resides on the oxygen atom and negative charge on the nitrogen atom.

Protonation of maleic hydrazide (1) has been reported [4] to occur on the exocyclic oxygen atom to give the cation (2) (Scheme IV. 2).



Scheme IV. 2

A knowledge of the site of protonation of the potentially tautomeric system and of the model fixed structure system is obviously important in the measurement of the tautomeric equilibrium constants.

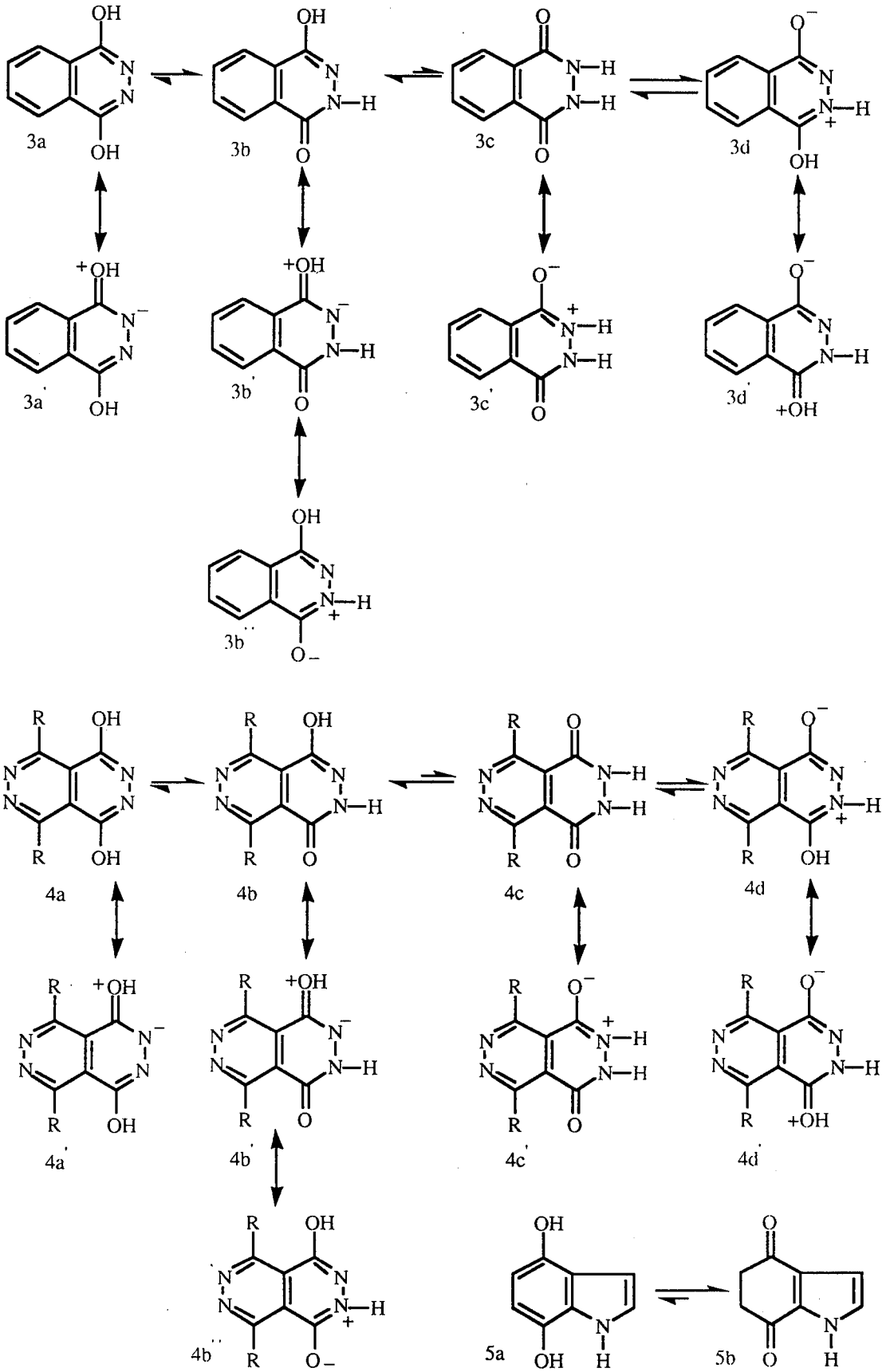
However, Barlin [2b, 5] has reported that maleic hydrazide (1) its N, N'–dimethyl derivatives behave abnormally and appear to have two overlapping pKa values suggesting protonation at two different sites. Thus, the spectroscopic data at various H_0 values for maleic hydrazide gave a pKa value which falls with increasing acidity. Examination of the data utilising a computer programme indicated the data to be consistent with two overlapping pKa values, [2b] a phenomenon which seemed intrinsically unlikely. [5] Barlin [5] has reexamined this anomalous behaviour by ^{1}H-NMR spectroscopy which again indicates that protonation of maleic hydrazide is not simple. Such a behaviour has also been reported [6] to exist with other kinds of conjugated system for which there are two protonation sites. This is particularly the case for potentially tautomeric systems where it is possible for the position of the tautomeric equilibrium to shift depending upon the pH of the solution.

The tautomerism of the benzo derivatives of dihydroxy–pyridazines has also been found to follow the same pattern as the monocyclic system. Thus, 1–hydroxyphthalazine –4–one (3b) (Scheme IV. 3) is the preferred structure of the tautomeric system (3). [1]

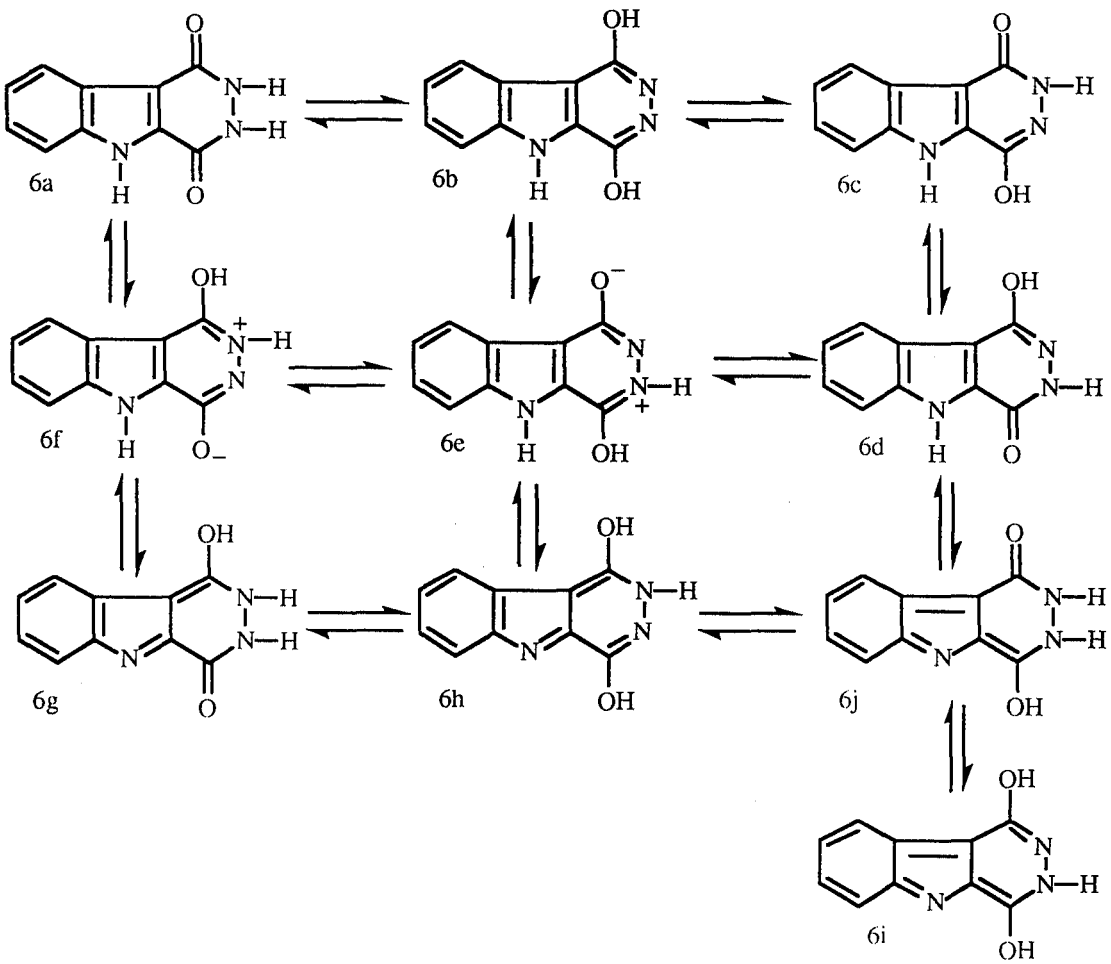
Heteroaromatic bicyclic systems with heteroatoms in both rings also exhibit similarly a tautomeric equilibrium position with the mono-hydroxy-mono-oxo forms

predominating, e. g. , (4b) [7] (Scheme IV.3). In contrast with usually preferred hydroxy-tautomeric form of most phenols (Section I. 1. 1), it has been reported that in the 4, 7–dihydroxyindole⇌4, 7–dioxo–4, 5, 6, 7–tetrahydroindole tautomeric equilibrium (5a⇌5b) the oxo-form is more stable. [8]

In view of these apparently analogous observations, it is of interest to examine the position of the tautomeric equilibria of 1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino [4, 5–*b*]indole (Scheme IV. 4). In this study we will establish the preferred tautomeric forms of the so-called 1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino[4, 5–*b*] indole (6), which could have a dioxo-structure (6a), dihydroxy-structure (6b), mono-hydroxy-mono-oxo structures(6c) and (6d), zwitterionic structures (6e) and (6f), and annular tautomerism (6g), (6h), (6j), and (6i) (Scheme IV. 3).



Scheme IV. 3

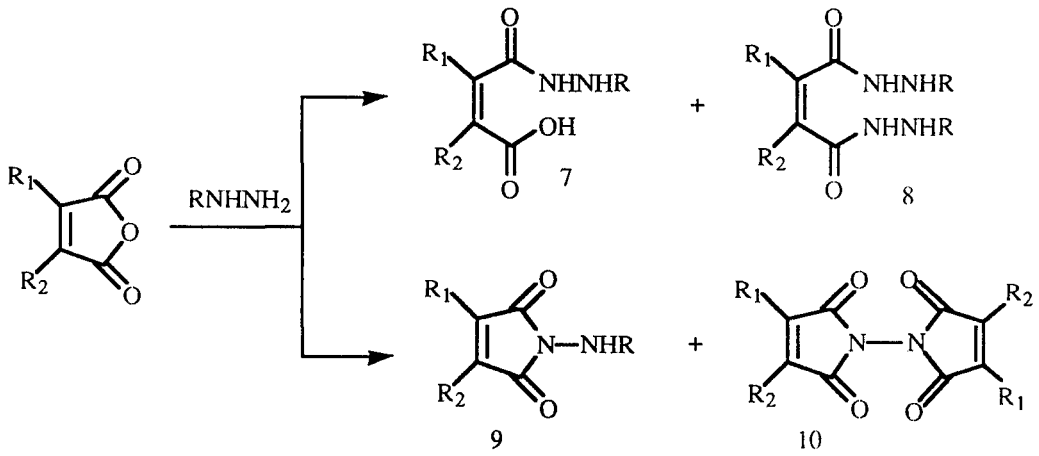


Scheme IV. 4

2. 0 1, 4-Dioxo-1, 2, 3, 4-tetrahydro-5*H*-pyridazino(4, 5-*b*)indole. - Synthesis

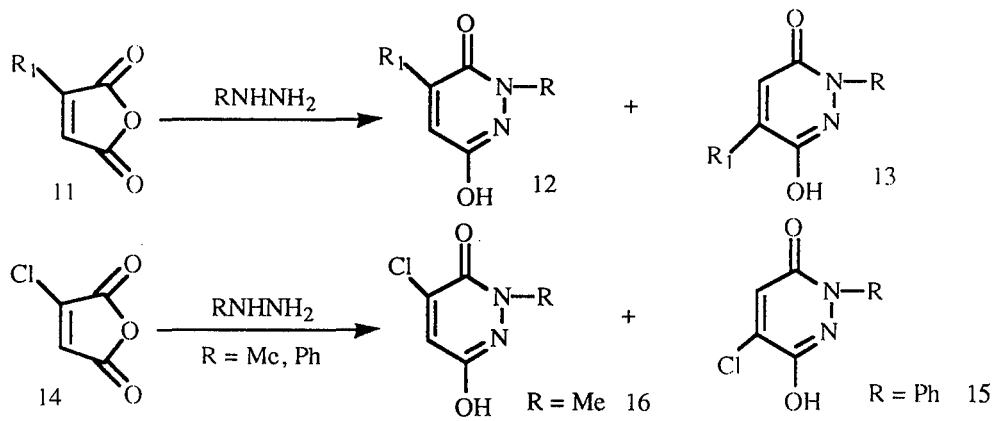
2. 1 Introduction

A common and versatile method for the preparation of pyridazinedieones consists of the cyclisation of maleic acid derivatives with hydrazines. [24] The reaction is applicable to nearly all derivatives of maleic anhydride and generally gives high yields when proper conditions are employed. However, it is subject to numerous side reaction and can lead to difficult mixtures if precautions are not observed. These by products are generally mono–(7) and dihydrazides (8), N–aminomaleimides (9), and N, N'–bisimides (10), but they usually rearrange and are cyclised to the desired products by a proper choice of solvents, reaction temperature, and rate of addition of reactants (Scheme IV. 5). [9, 24]



Scheme IV. 5

The reaction between a mono substituted maleic anhydride (11) and a mono substituted hydrazine can produce two isomers (12) and (13) (Scheme IV. 6). In most cases the isomers are formed in approximately equal amounts, and reaction conditions appear to have little effect upon their distribution. [24] Structural differences and steric effects seems to be the controlling factors, although no generally applicable rules can be stated. For example, chloromaleic anhydride (14) gives predominantly the 5–chloro isomer (15) with phenylhydrazine, but the 4–chloro isomer (16) predominates with methylhydrazine (Scheme IV. 6). [24]



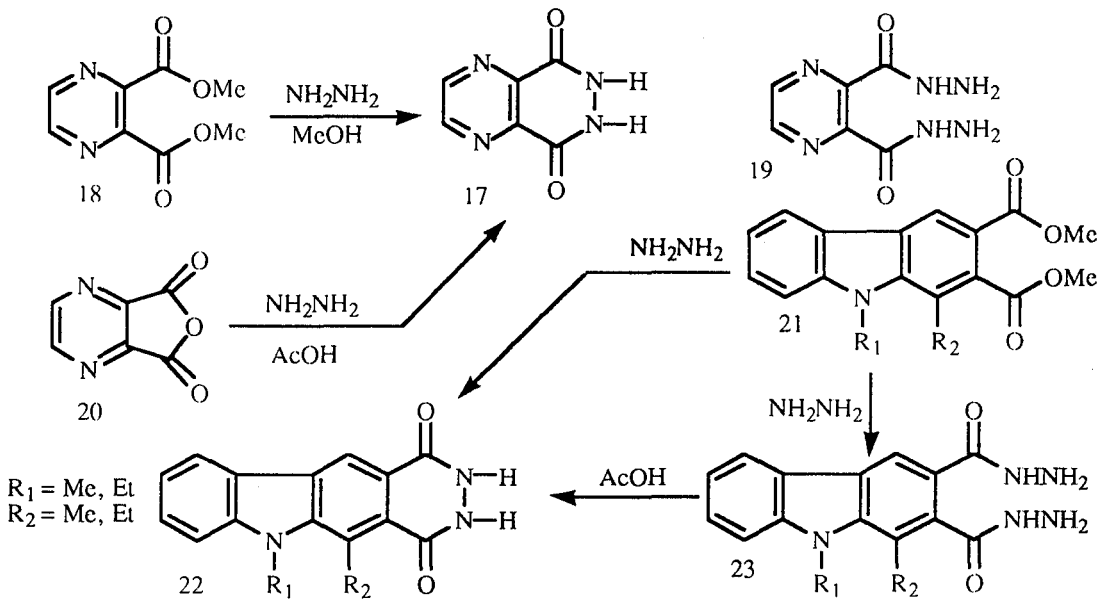
Scheme IV. 6

The cyclisation of aromatic *ortho*–dicarboxylic esters or cyclic anhydrides with hydrazine and its derivatives is a convenient procedure for the synthesis of condensed pyridazinediones.

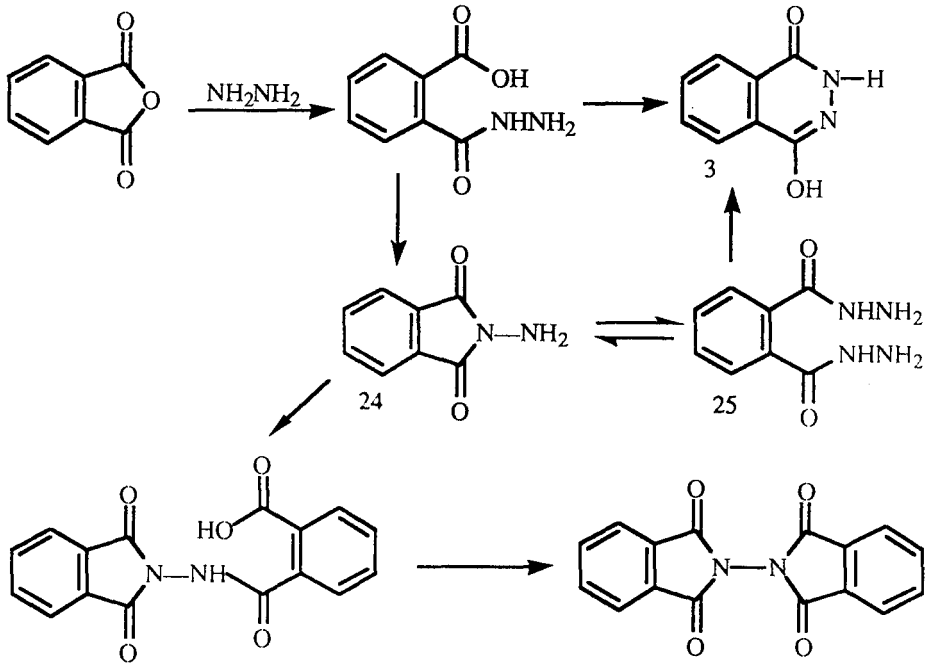
It is clear from inconsistencies in the literature that the cyclisation reaction of this type gives a number of unexpected products. The cyclic hydrazide (17) was first synthesised by Jones [11] by heating the diester (18) with hydrazine in methanol. Yale and coworkers, [12] however, claimed that the product was the dihydrazide (19). Hemmerich [13]

prepared (17) from (20) and hydrazine in acetic acid (Scheme IV. 7).

Similar cyclisation reaction of hydrazine with carbazole–2, 3–dimethyl dicarboxylate (21) gives the corresponding 1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H* –pyridazino[4, 5–*b*]indoles (22) depending upon the reaction conditions (Scheme IV. 7).[14] Multiple reaction pathways are involved in a cyclisation of this type and, for the synthesis of phthalhydrazide (3), Drew and Hatt [15, 16] have proposed the sequence shown in scheme IV. 8. The rearrangement of N–amino phthalimide (24) in the presence of hydrazine to form the cyclic hydrazide (3) is considered to occur by consecutive addition and loss of hydrazine with the hydrazide (25) functioning as an intermediate. Other substituents being the same, the presence of two hydrazide groups in *ortho*–positions is thus considered to favour the formation of the six membered ring (3), but , if one of the hydrazide groups is replaced by CO_2H, $CONH_2$, CONHNHPh, the five membered ring (24) is formed in preference to (3).



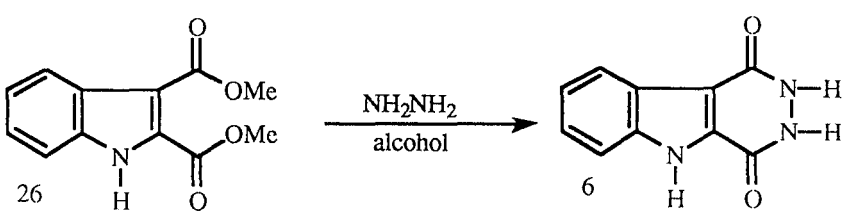
Scheme IV. 7



Scheme IV. 8

2. 2 1, 4-Dioxo-1, 2, 3, 4-tetrahydro-5*H*-pyridazino(4, 5-*b*)indoles. - Synthesis

The parent 1, 4-dioxo-1, 2, 3, 4-tetrahydro-5*H*-pyridazino[4, 5-*b*]indole (6) is the only compound which has been described in the literature. [17, 18] This compound (6) was synthesised by Huntress [17] and Vega and *et al* [18] from the condensation of dimethyl indole-2, 3-dicarboxylate (26) with hydrazine using a similar procedure (Scheme IV. 9).



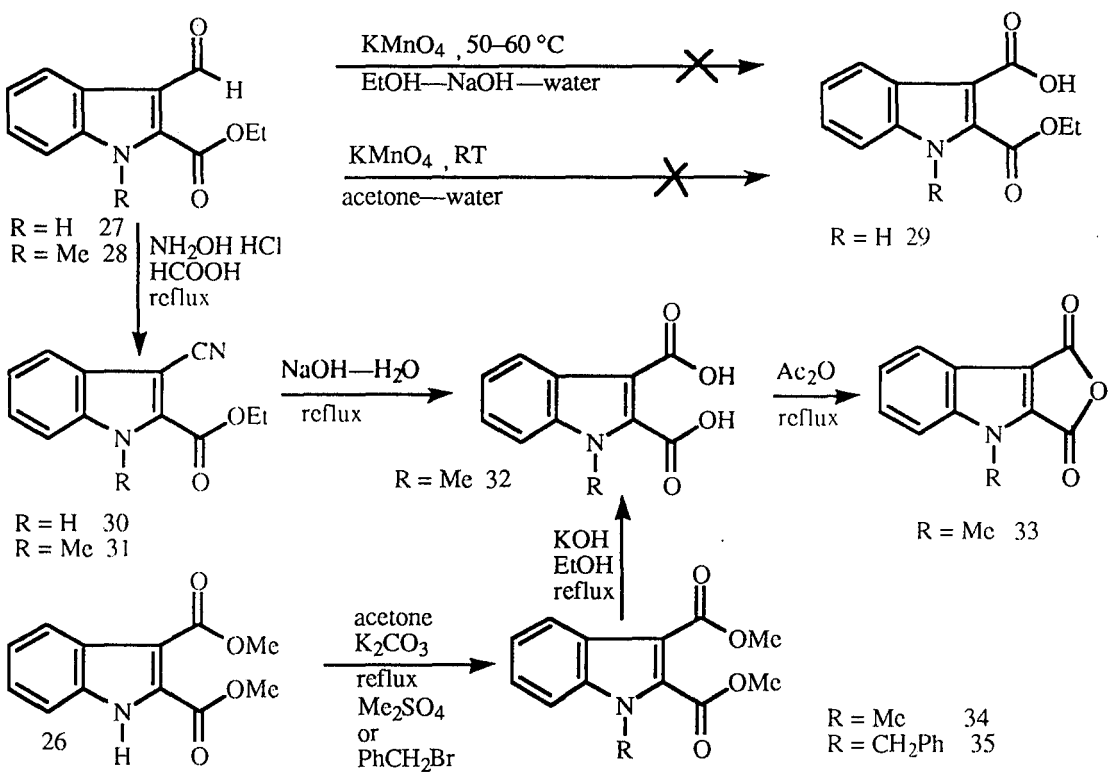
Scheme IV. 9

2. 3 Synthesis of 1, 4-Dioxo-1, 2, 3, 4-tetrahydro-5*H*-pyridazino(4, 5-*b*) indoles

To establish the position of tautomeric equilibrium of 1, 4-dioxo-1, 2, 3, 4 -tetrahydro-5*H*-pyridazino[4, 5-*b*]indole (6) (Scheme IV. 4), we need to prepare relevant cyclic compounds from hydrazine, its derivatives, and indole 2, 3-dicarboxylic acid, its ester or anhydride to compare their physical properties with those of fixed form models.

The preparation of dimethyl indole–2, 3–dicarboxylate (26) was discussed in detail in the section III. 1. 2 and our attempts to synthesize indole–2, 3–dicarboxylic acid and related compounds from the readily available compounds have already been described in chapter II. Oxidation of ethyl 3–formylindole–2–carboxylate (27) (see also Section II. 2. 3) with potassium permanganate under two different conditions failed to give the desired product (29) recovering only the starting material (27) (Scheme IV. 10). Therefore, we converted (27) and (28) into ethyl 3–cyanoindole–2–carboxylates (30) and (31) using the procedure described in the literature. [19] Compound (31) was later hydrolysed according to the procedure in the literature [20] to give 1–methylindole–2, 3 –dicarboxylic acid (32), which is identical with that obtained from the hydrolysis of dimethyl 1–methylindole–2, 3 –dicarboxylate (34), prepared from the methylation of dimethyl indole–2, 3 –dicarboxylate (26). [21] The N–benzyl derivative of dimethyl indole–2, 3–dicarboxylate (35) was also prepared in same way from the reaction of dimethyl indole–2, 3 –dicarboxylate (26) with benzylbromide, potassium carbonate in boiling acetone.

When methyl indole–2, 3–dicarboxylic acid (32) was refluxed in acetic anhydride it provided methyl indole–2, 3–dicarboxylic acid anhydride (33) (Scheme IV. 10).

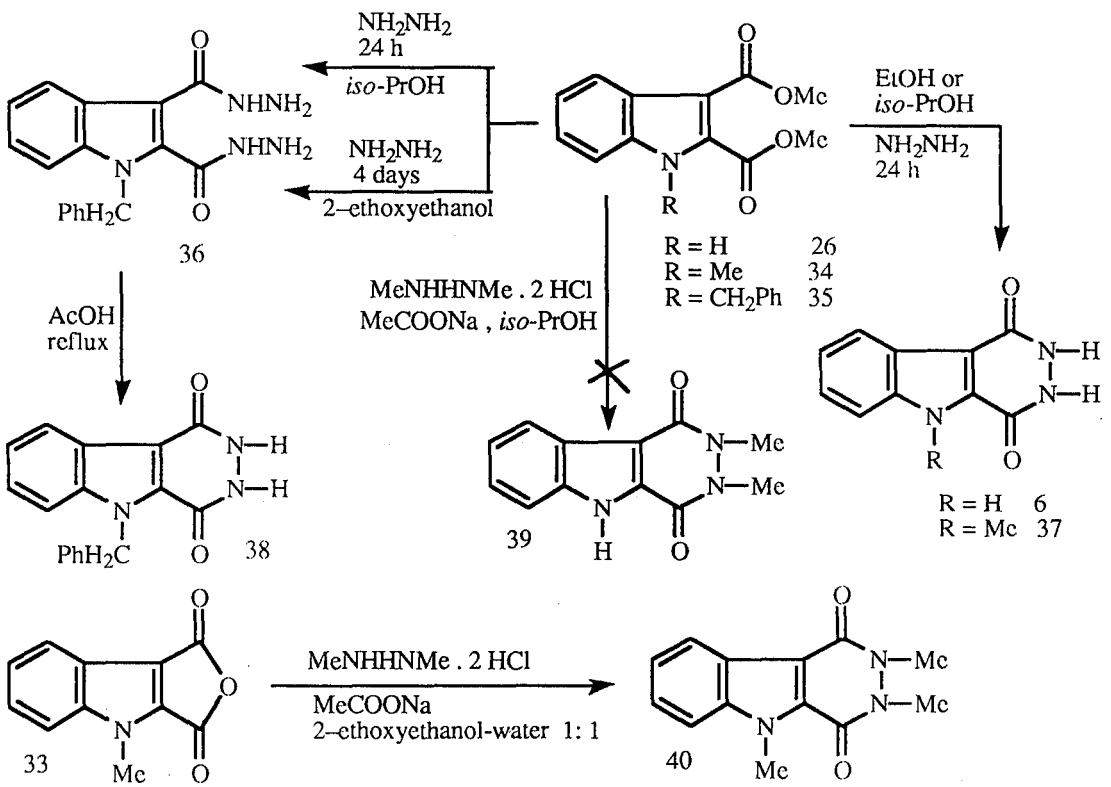


Scheme IV. 10

1, 4–Dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino[4, 5–*b*]indole (6) was prepared according to the procedure as described in the literature [18] (Scheme IV. 11). Following a similar procedure we prepared 1, 4–dioxo–5–methyl–1, 2, 3, 4–tetrahydro–5*H* –pyridazino[4, 5–*b*]indole (37). Dimethyl 1–benzylindole–2, 3–dicarboxylate (35) was refluxed with hydrazine in *iso*–propanol to give only 1–benzylindole–2, 3–dihydrazide

(36), instead of the required tricyclic compound (38).When 2–ethoxyethanol was used as solvent and reaction time prolonged to 4 days, we still obtained compound (36), which was then refluxed in acetic acid for 24 h to give the desired 5–benzyl–1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino[4, 5–*b*]indole (38) in quantitative yield.

Attempts to prepare 1, 4–dioxo–2, 3–dimethyl–1, 2, 3, 4–tetrahydro–5*H* –pyridazino[4, 5–*b*]indole (39) from dimethyl indole–2, 3–dicarboxylate (26) and 1, 2–dimethylhydrazine dihydrochloride in *iso*–propanol in the presence of sodium acetate failed to give the expected product (39). The reaction of 1–methylindole–2, 3–dicarboxylic anhydride (33) with 1, 2–dimethyl hydrazine dihydrochloride in 2–ethoxy ethanol-water mixture (1 : 1) in the presence of sodium acetate afforded 1, 4– dioxo –1, 2, 3, 4–tetrahydro–2, 3, 5–trimethyl–5*H*–pyridazino[4, 5–*b*] indole (40) in 50 % yield (Scheme IV. 11).



Scheme IV. 11

The reaction of dimethyl indole–2, 3–dicarboxylate (34) with methylhydrazine in *iso*–propanol could give the two isomers (42) and (44) (Scheme IV. 12). However, we obtained only the N(3)–methyl derivative (44) and we did not detect any N(2)–methyl derivative (42) .

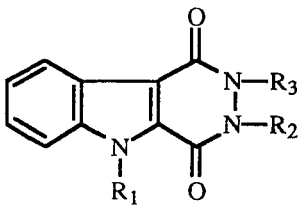
Compounds (42) and (44) were also synthesised by using different approach to confirm the structures of (41) and (42) obtained from first preparation (Scheme IV. 12). First, we prepared 3, 5– dimethyl–1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino [4, 5–*b*]indole (44) from 1–methoxy– 5–methyl–5*H*–pyridazino[4, 5–*b*]indole (50) (for preparation see Section V.), by the reaction with methyl iodide to form the

3, 5–dimethyl–1–methoxy–5*H*–pyridazino[4, 5–*b*]indolium salt (51). The salt was not isolated but used directly for next step. Oxidation of compound (51) with potassium ferricyanide in dioxane in the presence of potassium hydroxide provided 3, 4–dihydro –3, 5–dimethyl–1–methoxy–4–oxo–5*H*–pyridazino[4, 5–*b*]indole (45) *via* the probable intermediate (52). Compound (45) was hydrolysed with hydrochloric acid-methanol mixture to give 3, 5–dimethyl–1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino[4, 5–*b*] indole (44) in 71 % yield.

2, 5–Dimethyl–1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino[4, 5–*b*]indole (42) was also prepared using same procedure. The reaction of 4–methoxy–5–methyl –5*H* –pyridazino[4, 5–*b*] indole (47) (for preparation see Section V.) with methyl iodide in methanol gave 2, 5–dimethyl 4–methoxy–5*H*–pyridazino[4, 5–*b*]indolium salt (48), which was not isolated but was oxidised directly with potassium ferricyanide in dioxane in the presence of potassium hydroxide to give 1, 2–dihydro–2, 5–dimethyl–4–methoxy –1–oxo–5*H*–pyridazino[4, 5–*b*]indole (46) in 51 % yield, probably *via* (49). Compound (46) was then hydrolysed with a hydrochloric acid-methanol mixture to give 2, 5–dimethyl–1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino[4, 5–*b*]indole (42) in 64% yield (Scheme IV. 12). Although we could not get good elemental analysis for compound (42), the structure of the compound (42) was confirmed by ^{1}H-NMR spectroscopy, IR spectroscopy, and mass spectroscopy.

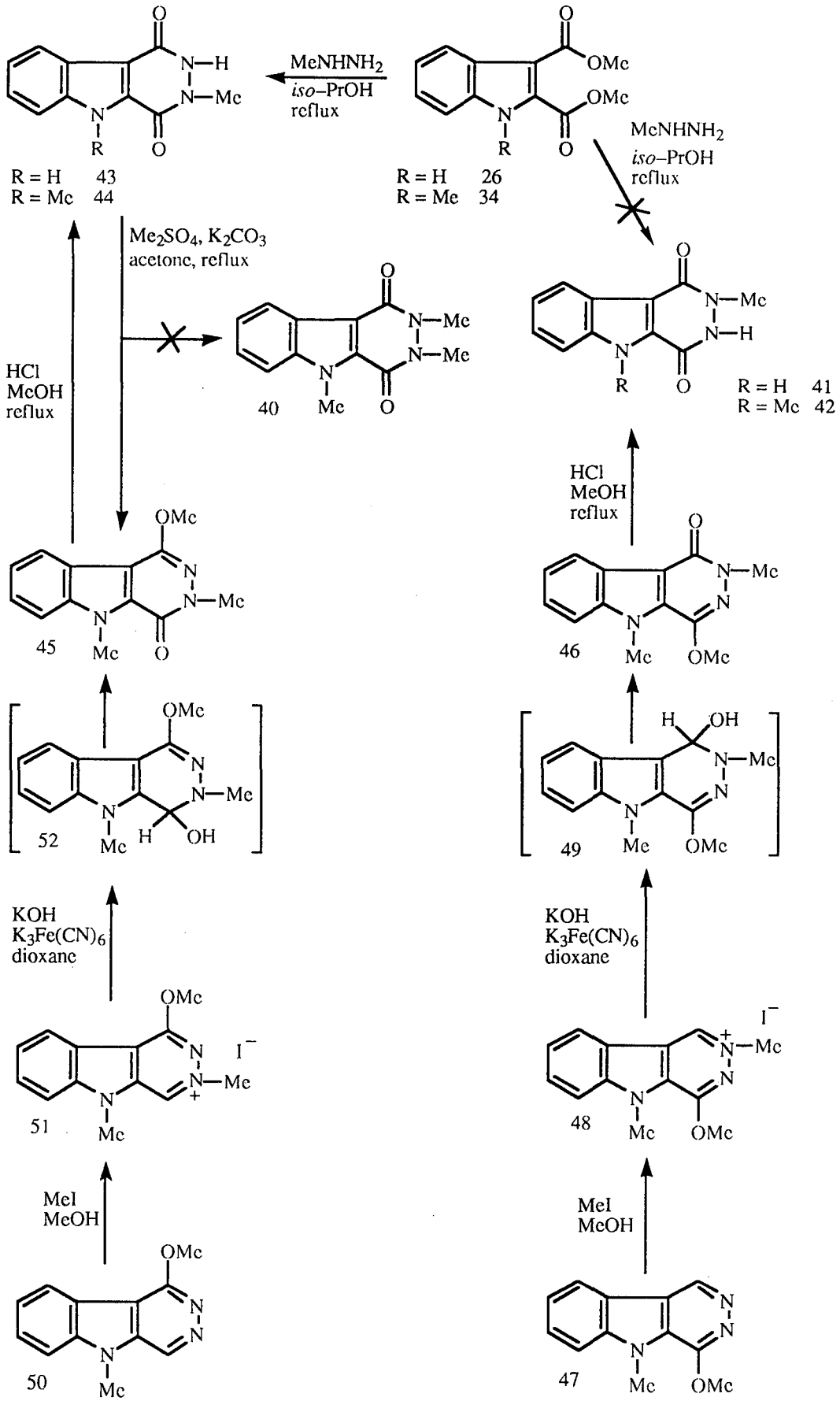
Methylation of 3, 5–dimethyl–1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino [4, 5–*b*] indole (44) with dimethyl sulphate in acetone provided only 3, 4–dihydro–3, 5 –dimethyl–1–methoxy–4–oxo–5*H*–pyridazino[4, 5–*b*]indole (45), which is fully consistent of with that obtained from compound (50) (Scheme IV. 12).

Table IV. 1 Reaction of indole–2, 3–dicarboxylates and methyl indole–2, 3 –dicarboxylic anhydride with hydrazine and its derivatives



R_1	R_2	R_3	Compound	Yield (%)	M. P. °C	Reaction
H	H	H	6	70	> 330	a
Me	H	H	37	81	> 325	b
CH_2Ph	H	H	38	99	322	c
H	Me	Me	39	no reaction		d
Me	Me	Me	40	50	222	e
Me	Me	H	44	54	305	f

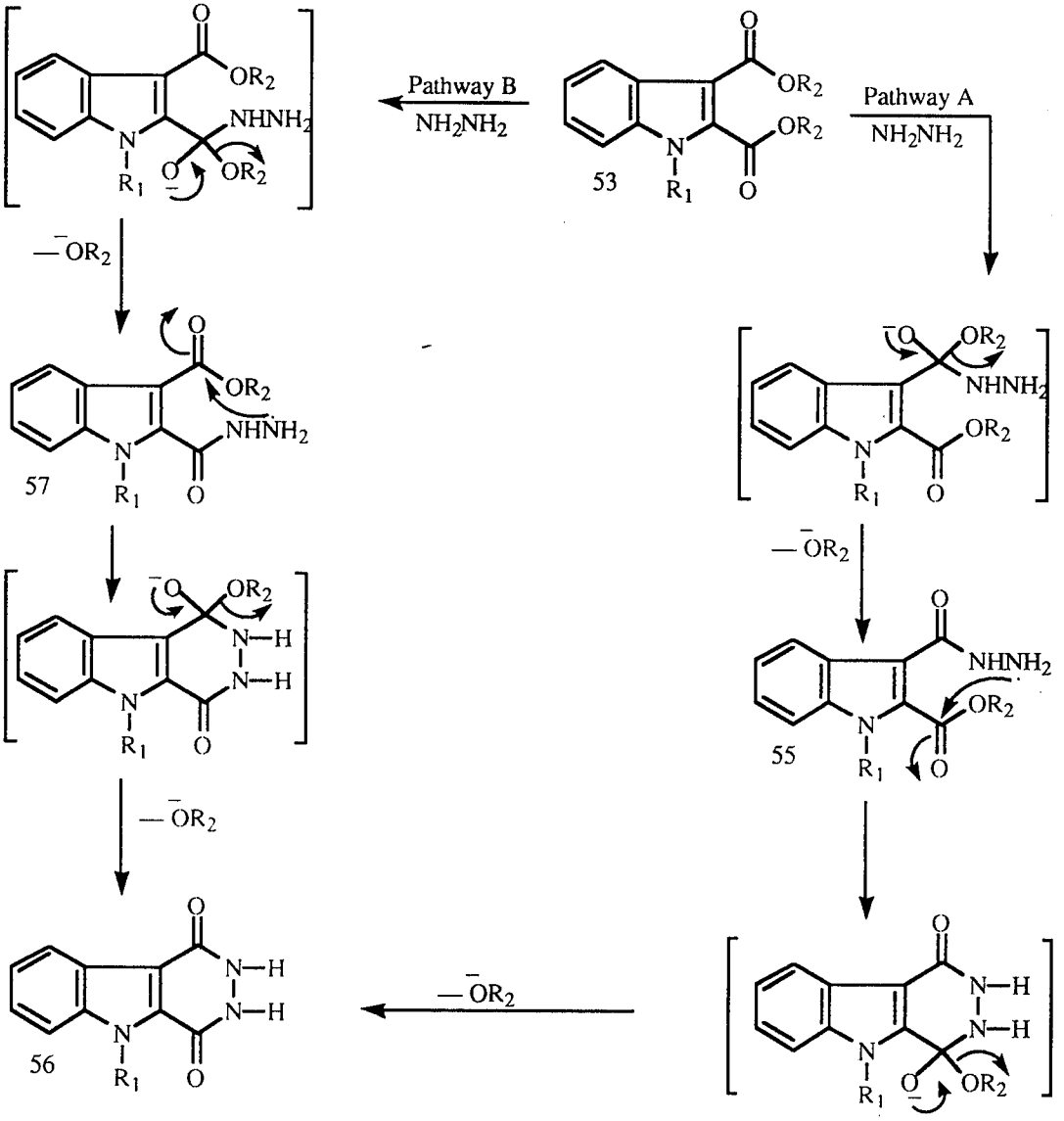
a. (26), Hydrazine hydrate ($NH_2NH_2\ H_2O$), in EtOH, reflux, 10 h.
b. (34), Hydrazine hydrate ($NH_2NH_2\ H_2O$), in *iso*–Propanol, c. HCl, reflux 24 h.
c. From the cyclisation of (35) in acetic acid.
d. (26), MeNHHNMe . 2HCl, in *iso*–Propanol, sodium acetate, reflux 7 days.
e. (33), MeNHHNMe . 2HCl, in 2–ethoxyethanol : water (1 : 1), sodium acetate, reflux 24 h.
f. (34), $MeNHNH_2$, in *iso*–Propanol, reflux 4 days.


MeNHNH2
iso-PrOH
reflux
R = H 43
R = Me 44
R = H 26
R = Me 34
Me2SO4, K2CO3
acetone, reflux
HCl
MeOH
reflux
40
R = H 41
R = Me 42
45
46
52
49
KOH
K3Fe(CN)6
dioxane
51
48
MeI
MeOH
50
47

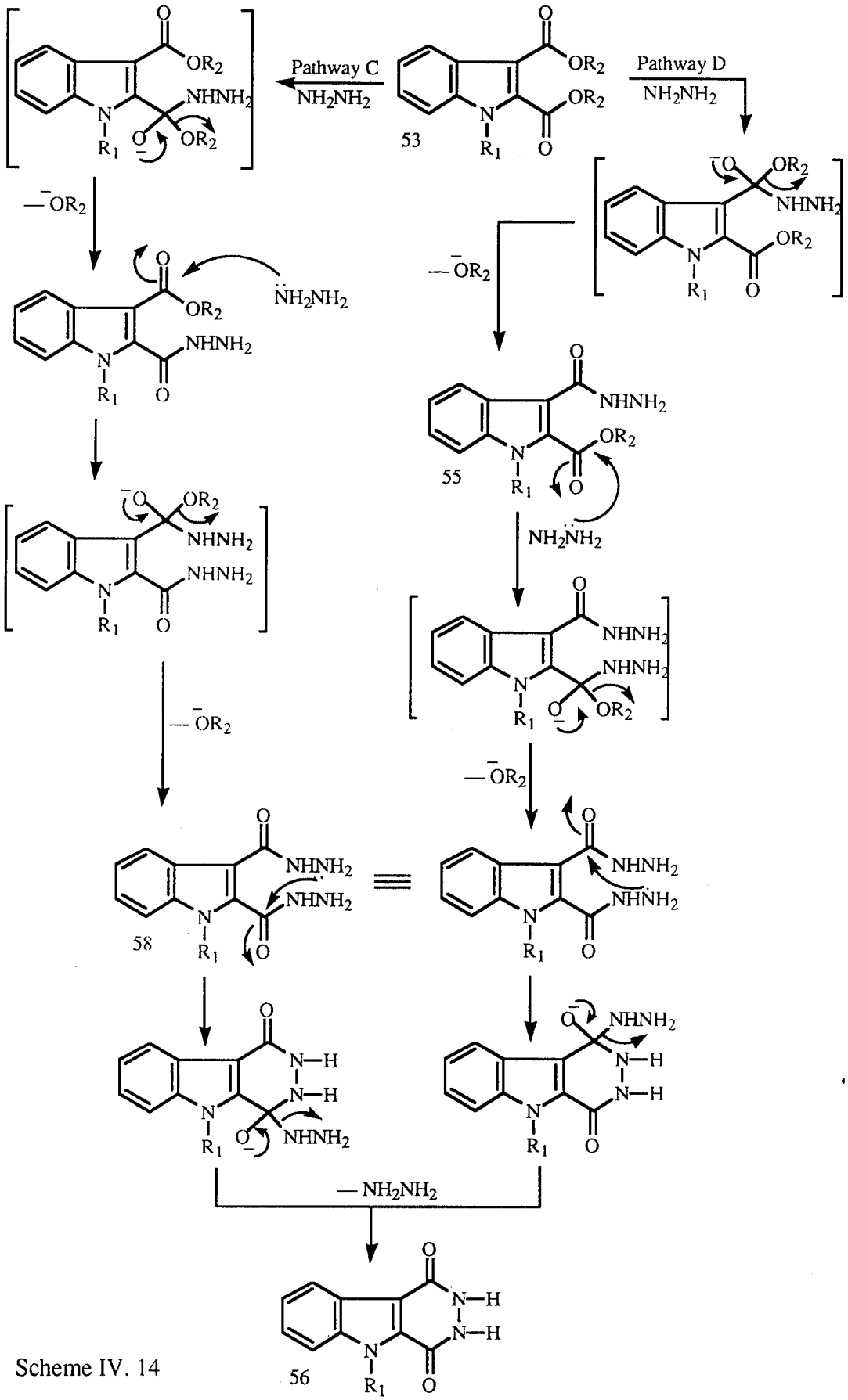
Scheme IV. 12

The mechanism for the formation of 1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H* –pyridazino[4, 5–*b*] indoles from the reaction of indole–2, 3–dicarboxylates with hydrazine or its derivatives has not been investigated. However, it probably involves a nucleophilic attack by the hydrazine on one or both carbonyl groups. In the reaction of indole–2, 3–dicarboxylates with hydrazine, the cyclisation can follow four different pathways (Scheme IV. 13 and Scheme IV. 14). When an excess of hydrazine is used, pathway C and pathway D are more likely. In terms of lower reactivity of carbonyl group at 3–position compared with that at 2–position, pathway A can be eliminated. In the case of methylhydrazine, the sequence could be more complex.

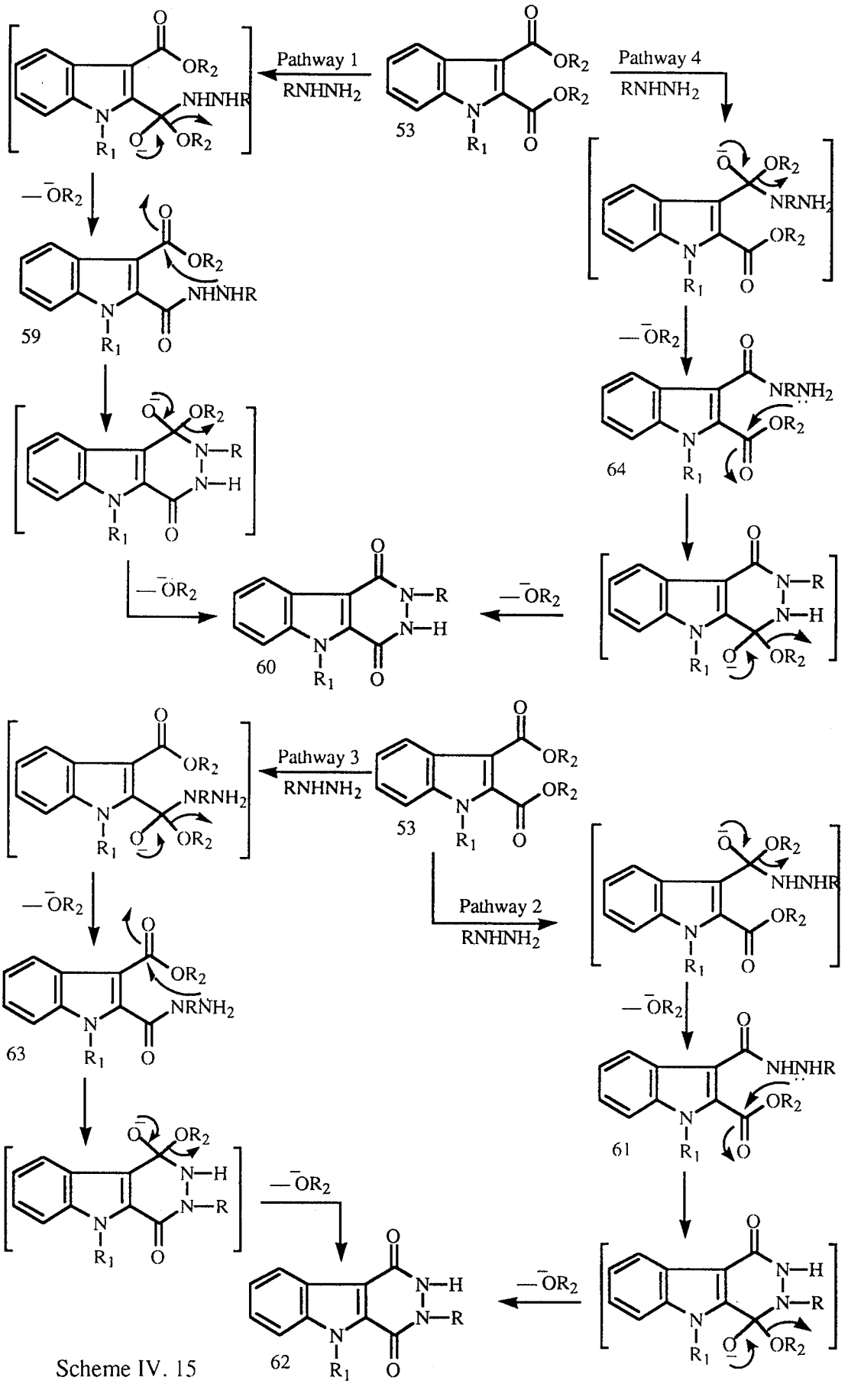
The possible pathways of the cyclisation of indole–2, 3–dicarboxylates with alkyl hydrazine is depicted in scheme IV. 15 and scheme IV. 16. Most of the pathways can be excluded in terms of experimental or other reasons. For example, pathway 1 is impossible due to our observations in which we isolated only N(3)–methyl derivatives (44) from the reaction of corresponding indole–2, 3 –dicarboxylate with methylhydrazine (Scheme IV. 12). Pathway 2 can also be eliminated due to the lower reactivity of carbonyl group at 3–position over that at 2–position. Pathways 3, 4, and 6 are unlikely due to steric effects and the lower reactivity of carbonyl group at 3–position. Therefore, now we suggest that cyclisation reaction of indole–2, 3–dicarboxylates with methylhydrazine takes place *via* pathway (5b) (Scheme IV. 16).


Pathway B
NH_2NH_2
Pathway A
NH_2NH_2
53
57
55
56
$-\bar{O}R_2$
$-\bar{O}R_2$
$-\bar{O}R_2$
$-\bar{O}R_2$

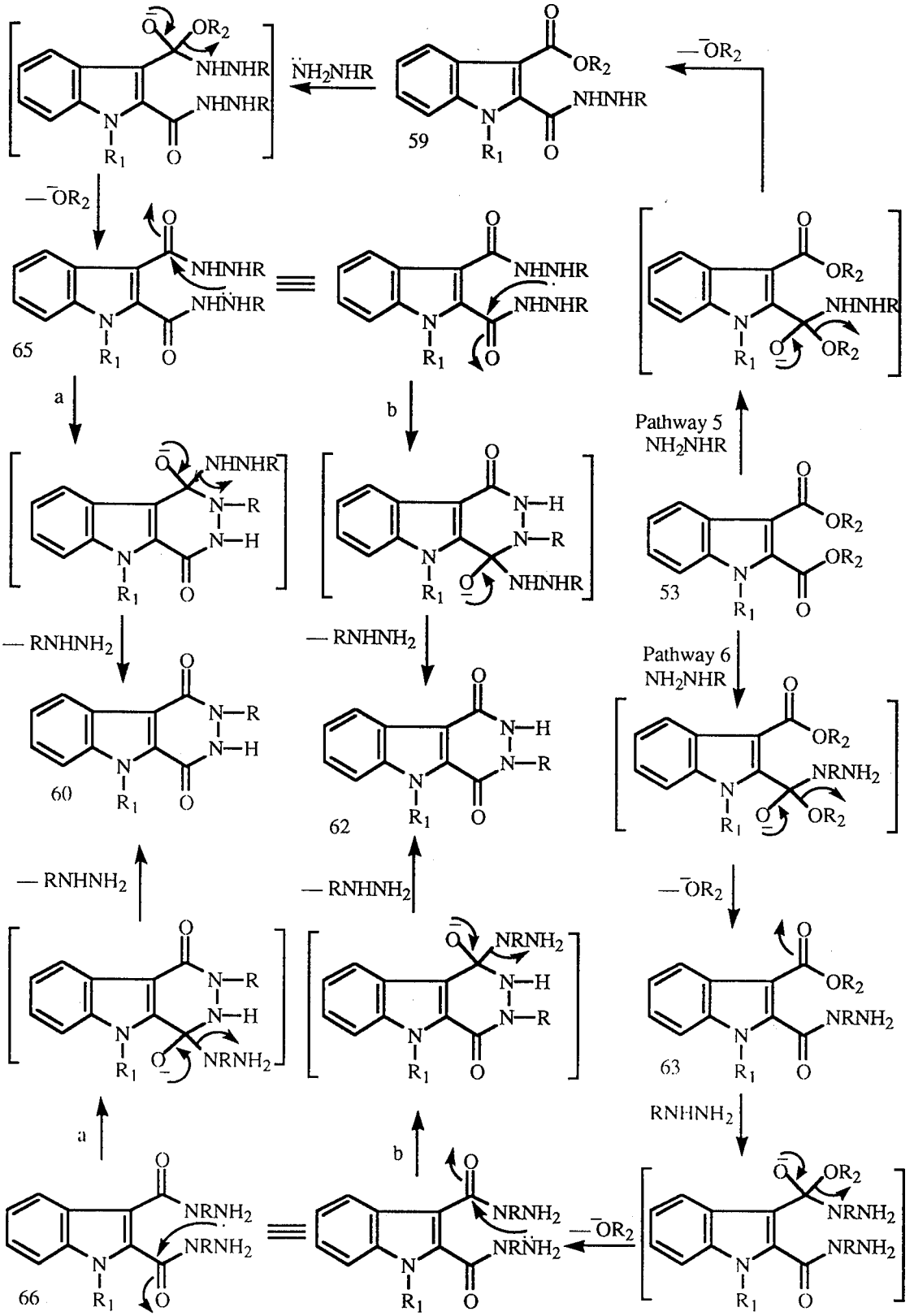
Scheme IV. 13


Pathway C
NH_2NH_2
Pathway D
NH_2NH_2
53
55
58
56
$-\bar{O}R_2$
NH_2NH_2
$-NH_2NH_2$

Scheme IV. 14


Pathway 1
RNHNH2
Pathway 4
RNHNH2
Pathway 3
RNHNH2
Pathway 2
RNHNH2
53
59
64
60
63
61
62

Scheme IV. 15


59
65
53
60
62
63
66
Pathway 5
NH2NHR
Pathway 6
NH2NHR
a
b
— RNHNH2
RNHNH2
—OR2

Scheme IV. 16

3. 0 1, 4–Dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino(4, 5–*b*)indoles. – Physical properties

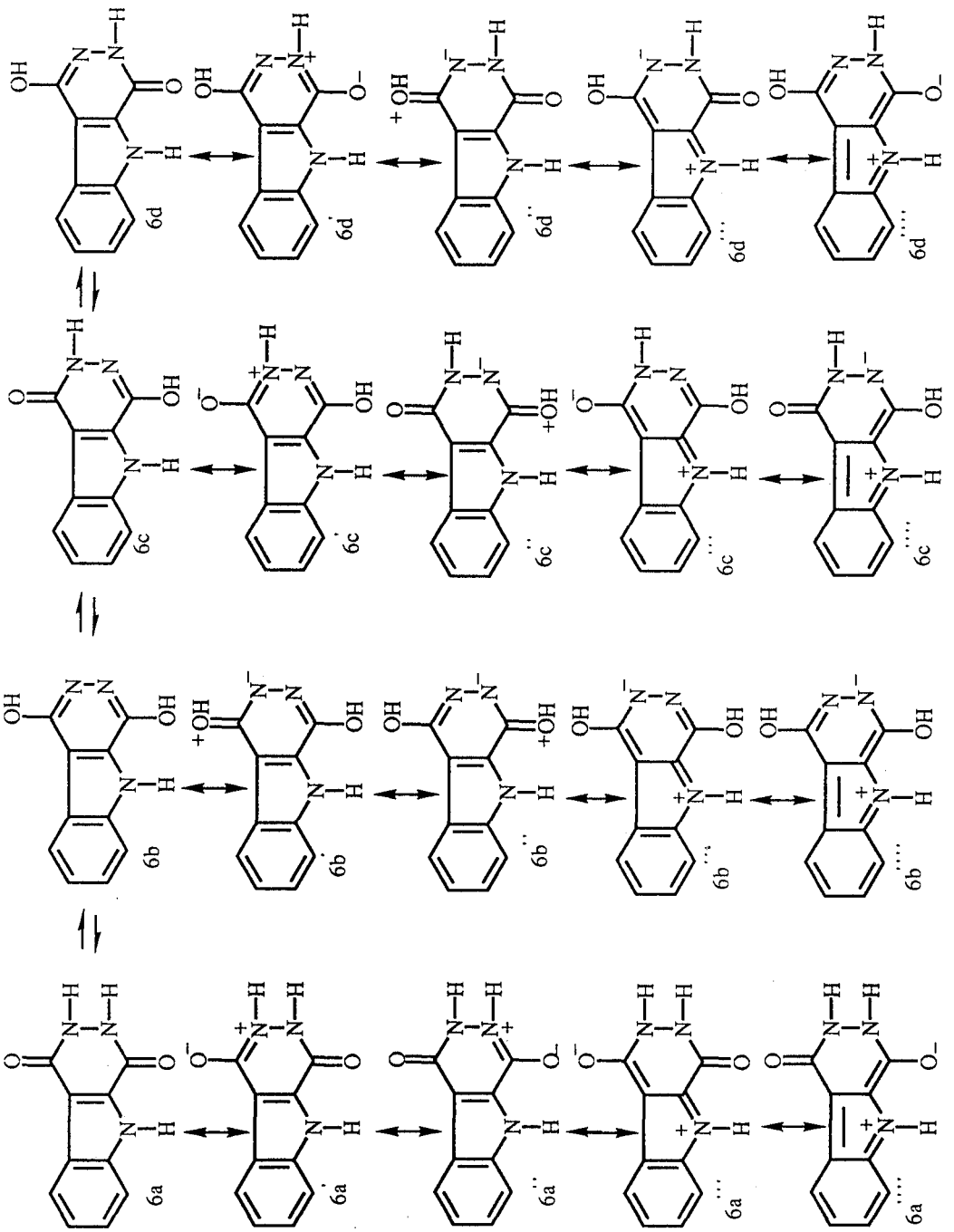
Several tautomeric structures can be drawn for the 1, 4–dioxo–1, 2, 3, 4 –tetrahydro–5*H*–pyridazino[4, 5–*b*]indoles, as shown in scheme IV. 17. Two types of tautomerism are possible; in one case it involves the functional group (6a $\rightleftharpoons$ 6b $\rightleftharpoons$ 6c $\rightleftharpoons$ 6d) and in the second case, the annular tautomerism (6g $\rightleftharpoons$ 6h $\rightleftharpoons$ 6j $\rightleftharpoons$ 6i). Most of the tautomeric structures can be easily excluded from our discussion by comparison of the physical properties of the parent compound (6) with its model compounds (37), (39–45). For example, the absence of a long wavelength band over 400 nm characteristic of 2*H* and 3*H*–pyridazino[4, 5–*b*]indoles [21b] indicates that the annular tautomerism is very unlikely in the system (6g $\rightleftharpoons$ 6h $\rightleftharpoons$ 6j $\rightleftharpoons$ 6i). In addition, zwitterionic structures (6e) and (6f) can be eliminated in terms of the data obtained from infrared spectra in which there is no characteristic signal of O^- / NH^+ group.

3. 1 ^{1}H-NMR Spectroscopic Measurements

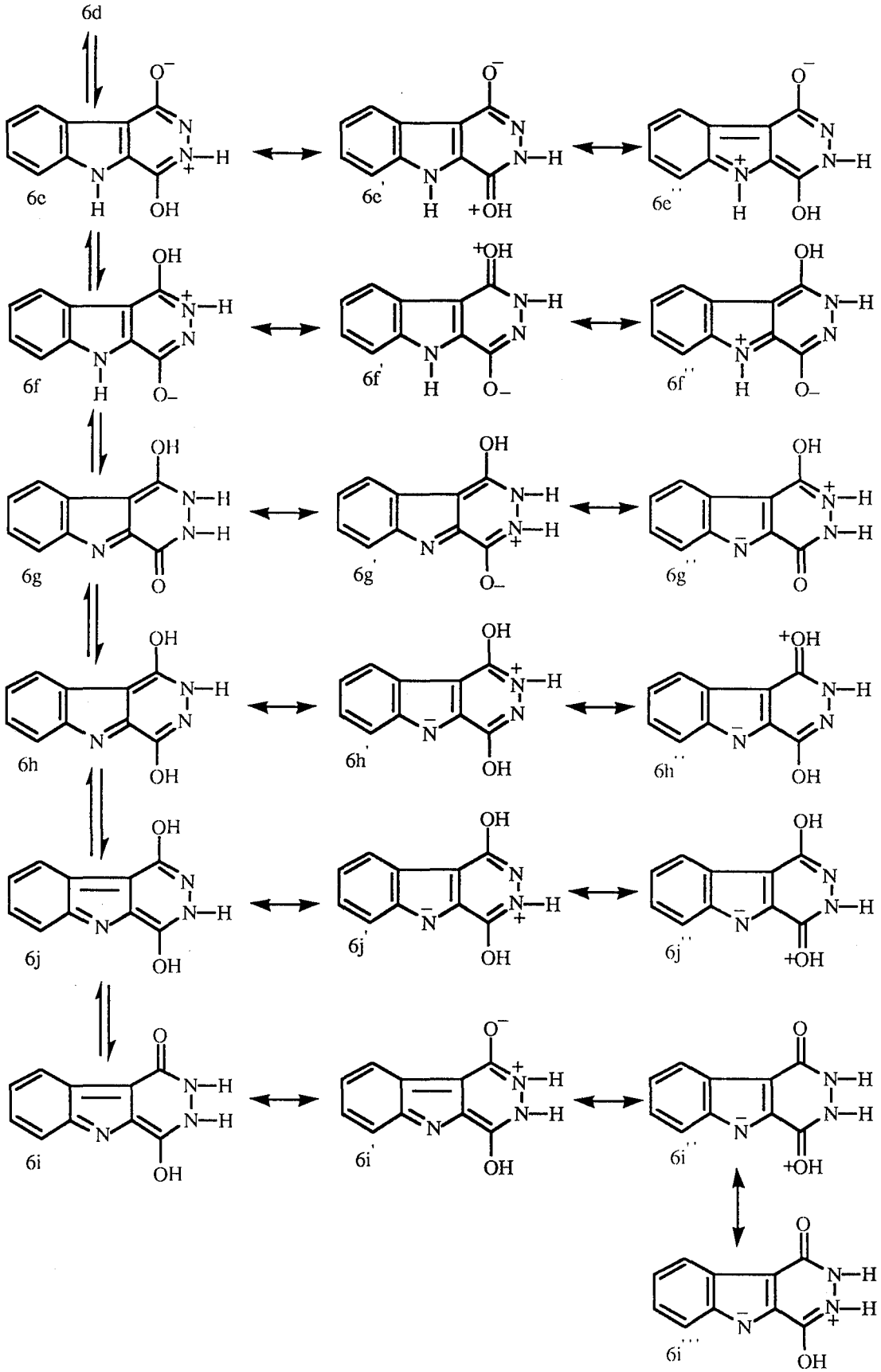
The ^{1}H-NMR chemical shifts of alkyl and ring protons of 1, 4–dioxo–1, 2, 3, 4 –tetrahydro–5*H*–pyridazino[4, 5–*b*]indole and its derivatives are presented in table IV. 2.

Although the spectra of 1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino[4, 5–*b*] indoles (6) and (37) have characteristic of N(2)–H and N(3)–H signals at 12.56, 11.40, and 11.60, it is difficult to suggest that 1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino [4, 5–*b*]indoles (6) and (37) exist in dioxo–form (6a) (Scheme IV. 17), since there could be fast proton exchange between OH and NH .

The data obtained from ^{1}H-NMR spectroscopy does not allow us to distinguish the predominant tautomers in the system.

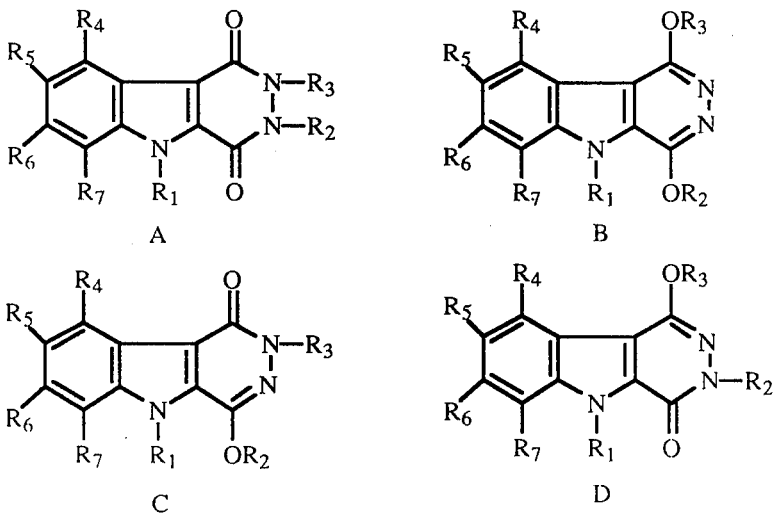


Scheme IV. 17



Scheme IV. 17 (continued)

Table IV. 2 ^{1}H-NMR Spectra [a] of 1, 4–Dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino [4, 5–*b*]indole and its derivatives



$R_4 = R_5 = R_6 = R_7 = H$

R_1	R_2	R_3	Compound	R_1	R_2	R_3	R_4	R_5 R_6 R_7
A								
H	H	H	6 [b]	12.56(s)	11.40(br. , s)	11.40(br. , s)	8.08–8.30(dd)	7.30–7.90(m)
Me	H	H	37 [b]	4.20(s)	11.60(br. , s)	11.60(br. , s)	8.10–8.35(dd)	7.20–7.90(m)
Me	Me	H	44 [b]	4.36(s)	3.92(s)	no peak	8.12–8.36(dd)	7.40–7.80(m)
Me	H	Me	42 [b]	4.38(s)	no peak	4.10(s)	8.30–8.60(dd)	7.60–7.90(m)
Me	Me	Me	40[c]	4.20(s)	3.70(s)	3.70(s)	8.20–8.48(dd)	7.20–7.60(m)
Bn	H	H	38 [b]	6.00(s)	no peak	no peak	8.00–8.30(m)	7.20–7.60(m)
B								
Me	Me	Me	67 [c, e]	4.15(s)	4.30(s)	4.25(s)	8.12–8.36(m)	7.20–7.60(m)
C								
Me	Me	Me	46 [c]	4.00(s)	4.00(s)	3.80(s)	8.12–8.60(m)	7.20–7.60(m)
D								
Me	Me	Me	45 [c]	4.00(s)	3.76(s)	4.24(s)	7.90–8.16(m)	7.20–7.60(m)

a. Chemical shifts are recorded in ppm down from TMS.
b. Spectra recorded in DMSO–d_6 .
c. Spectra recorded in $CDCl_3$.
d. For preparation see section V.

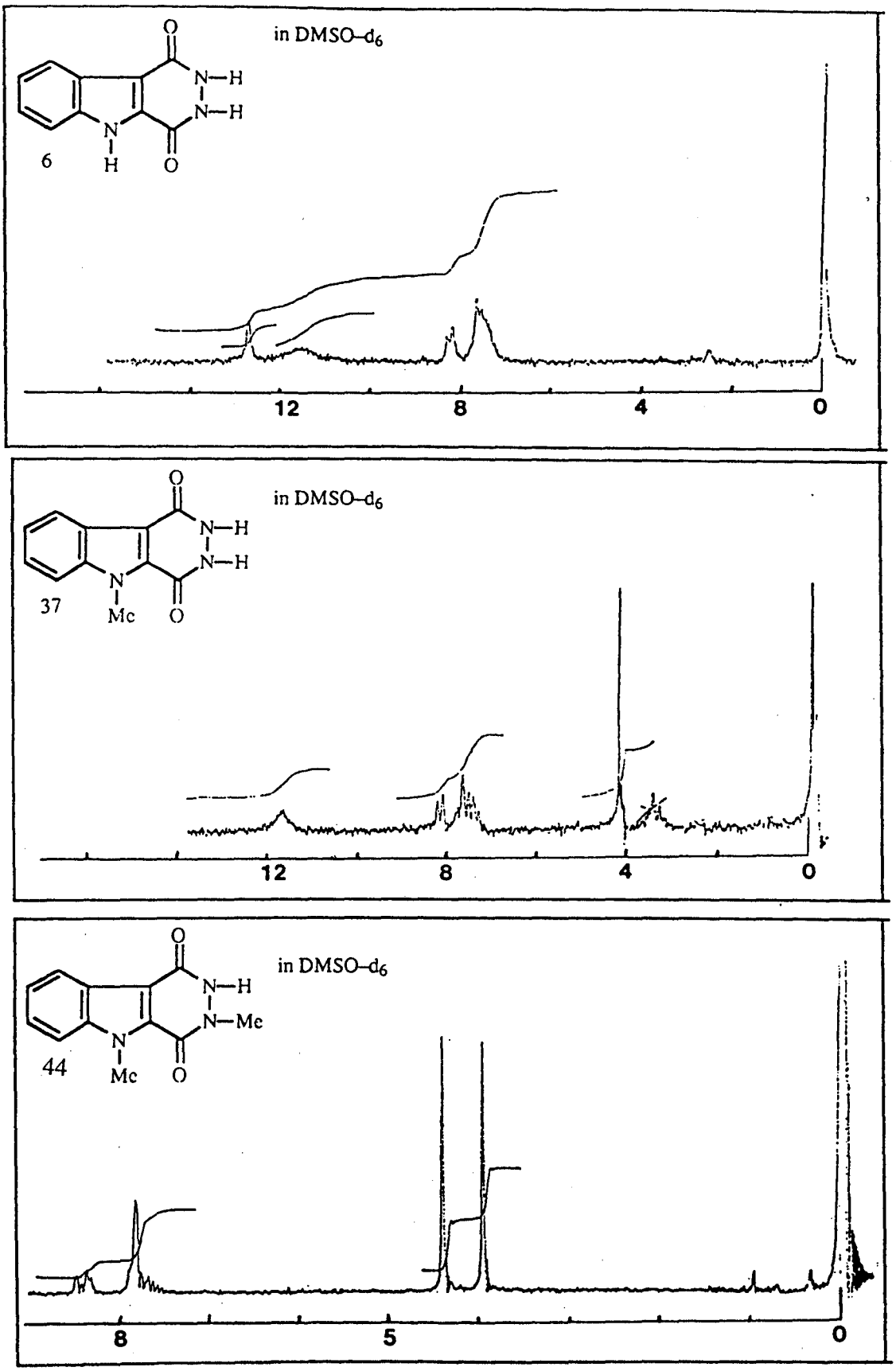


Figure IV. 1. 1 ^{1}H-NMR Spectra of 1. 4–Dioxo–1, 2, 3, 4–tetrahydro–5*H* –pyridazino[4, 5–*b*]indoles.

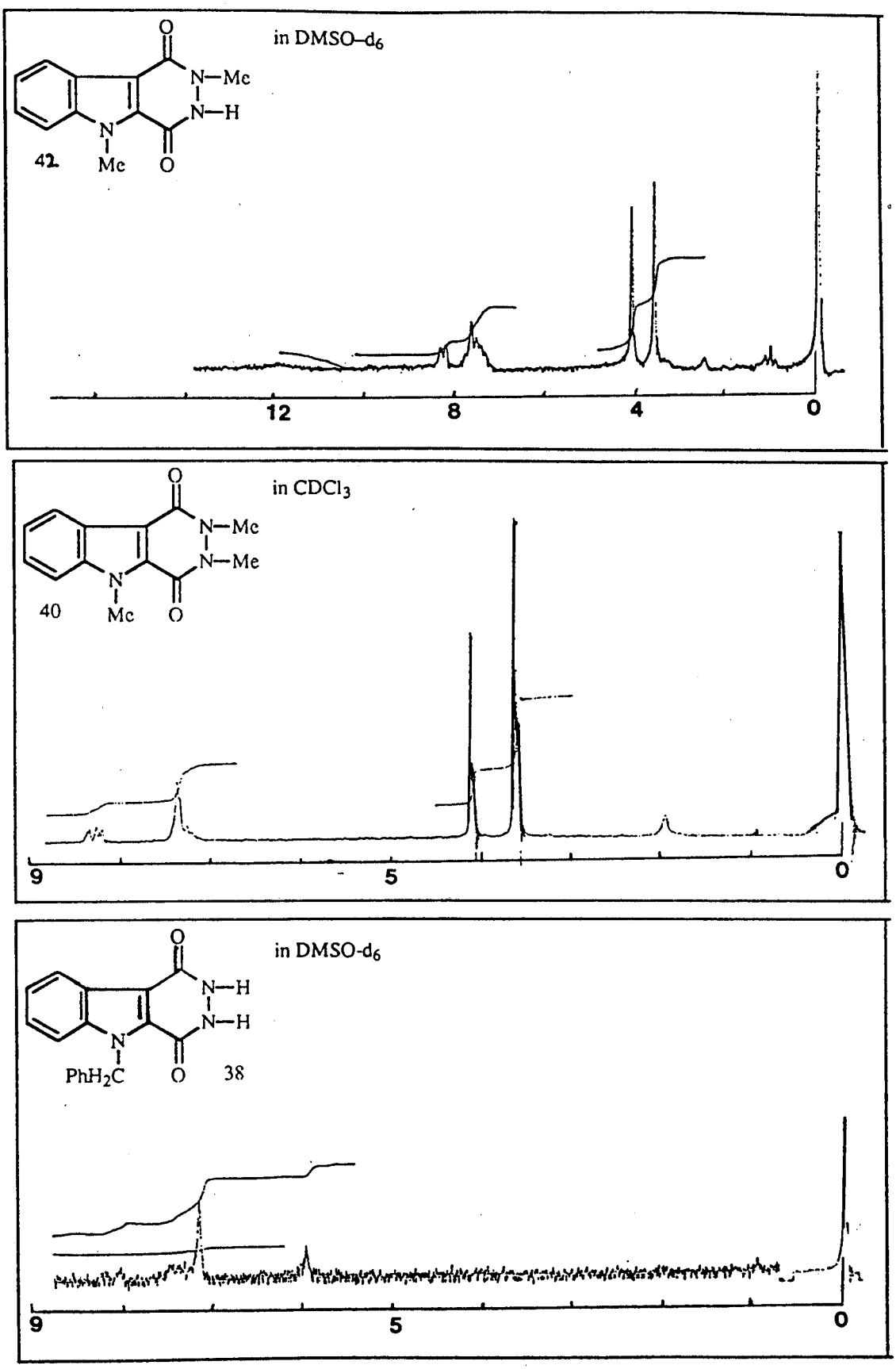


Figure IV. 1. 2 ^{1}H-NMR Spectra of 1, 4–Dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino [4, 5–*b*]indoles.

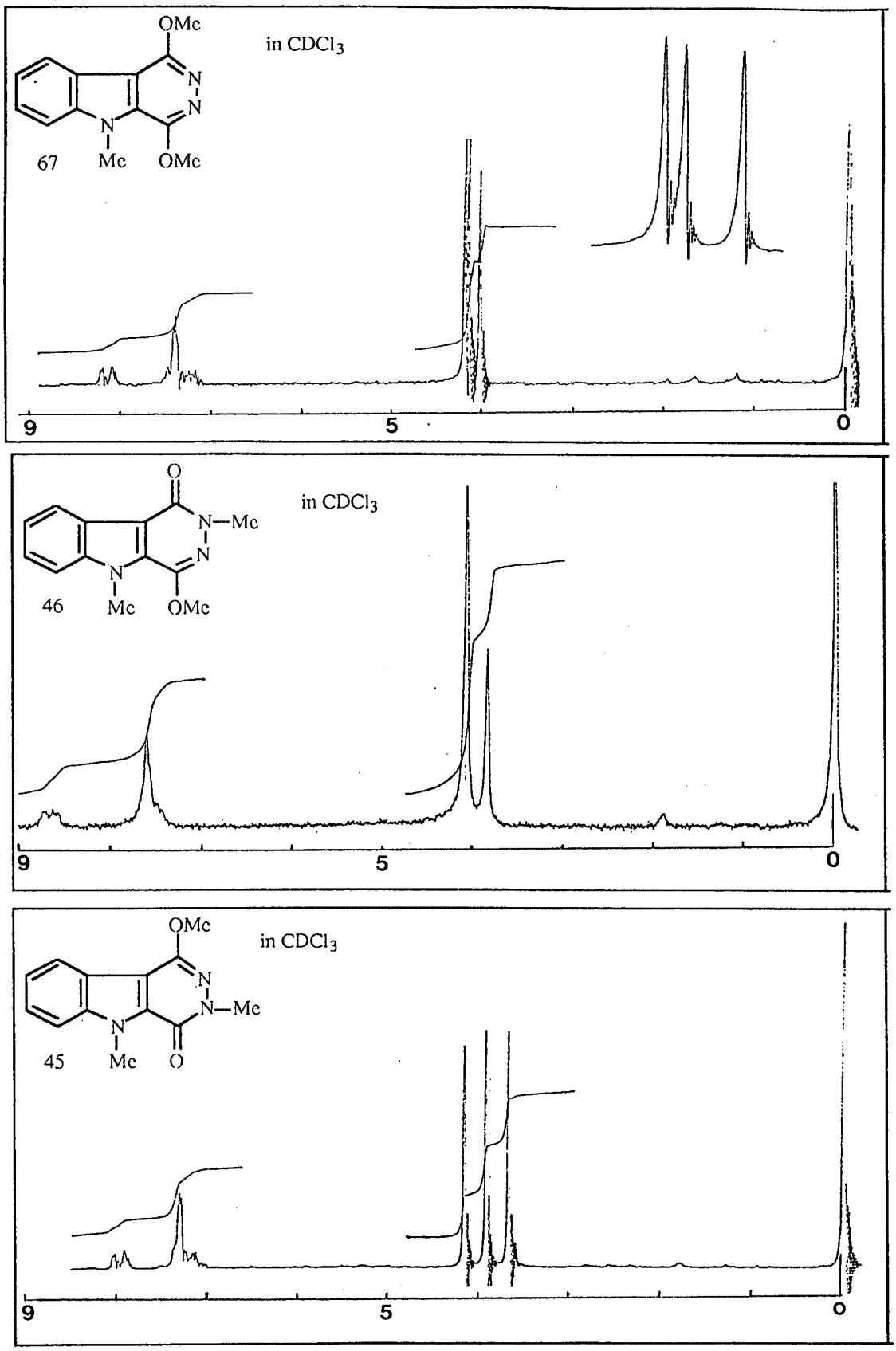


Figure IV. 1. 3 ^{1}H-NMR Spectra of 5*H*–pyridazino[4, 5–*b*]indoles.

3. 2 Infrared Spectroscopic Measurements

The infrared spectra of 1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino[4, 5–*b*] indole and its derivatives measured in the solid state are presented in table IV. 3.

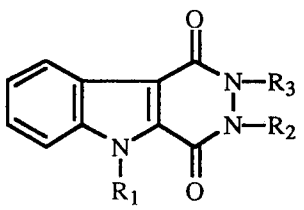
The infrared spectra of 1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino[4, 5–*b*] indoles (6) and (37) show a complicated pattern of absorption bands between 2700–3300 cm^{-1} with maxima at about 3400 cm^{-1}. There are also several strong bands between 1550–1670 cm^{-1}, with maxima corresponding $\nu_{C=O}$ stretching bands at 1635, 1645, and 1655 cm^{-1}. The broad bands observed between 2500–3500 cm^{-1} can be assigned to a strong intermolecular H–bonded system, as well as to OH, NH, and N^{+}–H stretchings vibrations. However, these observation are absent in the spectra of the 2, 3, 5–trimethylated derivative (40) and even in the spectrum of 3, 5–dimethylated derivative (44), whereas, the spectrum of 2, 5–dimethylated derivative (42) shows slightly broadened bands between 3100–3500 cm^{-1}, which could result from H–bonding, from the presence of the hydroxy-oxo-forms (6c) and (6d), or minor betaine-structures (6e) and (6f) (Scheme IV. 17).

In the spectrum of (6) and (37), the presence of two strong carbonyl bands at 1645 and 1655 cm^{-1} eliminates the possibility of dihydroxy–structure (6b).

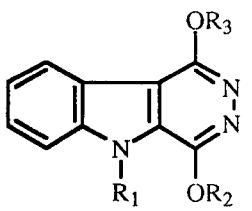
A definite conclusion differentiating between the dioxo (6a) and the oxo-hydroxy-structures (6c) and (6d) can be achieved by comparison with the spectra of the fixed form model compounds (40), (67), (46), and (45). For these systems, the multiple carbonyl bans are absent in the mono alkoxyl derivatives (45) and (46), compared with the parent compound (6) for which there are two bands at 1635 and 1645 cm^{-1}. In addition, 3, 5–dimethylated derivative (44) and 2, 5–dimethylated derivative (42) also show two overlapping carbonyl bands at 1630 and 1640 cm^{-1}. The 2, 3, 5–trimethylated derivative (40) has two carbonyl bands at 1640 and 1660 cm^{-1}.

The data from the infrared spectra of parent 1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H* –pyridazino[4, 5–*b*]indole (6) and other fixed model compounds do not give an evidence fully indicating that 1, 4–dioxo–1, 2, 3, 4– tetrahydro–5*H*–pyridazino[4, 5–*b*]indoles (6) and (37) exist predominantly in the dioxo–form (6a). We also do not have sufficient evidence to eliminate completely the other tautomeric structures (Scheme IV. 17).

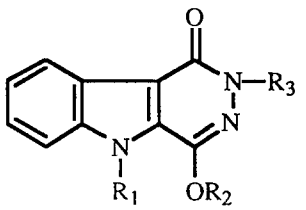
Table IV. 3 Infrared Stretching Frequencies of 1, 4–Dioxo–1, 2, 3, 4–tetrahydro –5*H*–pyridazino[4, 5–*b*]indole and its derivatives.



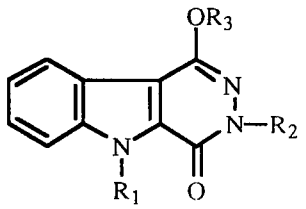
A



B



C



D

R_1	R_2	R_3	Compound	NH or OH (cm^{-1})	C=O (cm^{-1})	C=N, C=C (cm^{-1})
			A			
H	H	H	6 [a]	3050–3300(m, broad)	1635(w), 1645(s)	1625(s), 1590(w)
Me	H	H	37 [b]	2700–3300(m, broad)	1655(s)	1625(w)
Me	Me	H	44 [a]	–	1630(w), 1640(s)	1585(w), 1615(m)
Me	H	Me	42 [a]	3100–3500(m, broad)	1630(w), 1640(s)	1615(s)
Me	Me	Me	40 [a]	–	1640(s), 1660(m)	1610(w)
Bn	H	H	38 [b]	2500–3300(s, broad)	1670(s)	1625(s, broad)
			B			
Me	Me	Me	67 [a, c]	–	–	1570(m), 1620(w)
			C			
Me	Me	Me	46 [a]	–	1640(s)	1600w), 1620(m)
			D			
Me	Me	Me	45 [a]	–	1645(s0	1580(s)

a. Nujol mull
b. Bromoform
c. For preparation see section V.

3. 3 Ultraviolet Spectral Measurements

The ultraviolet spectra of 1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino[4, 5–*b*] indole and its derivatives are recorded in table IV. 4.

All compounds, when measured in neutral buffer solutions show two groups of bands ; a low intensity long wavelength ($\pi \rightarrow \pi^*$) band at 260–365 nm and high intensity

($\pi \rightarrow \pi^*$) bands at 200–260 nm. The cations of the compounds also show two group of bands ; low intensity long wavelength ($\pi \rightarrow \pi^*$) bans at 270–415 nm and medium intensity ($\pi \rightarrow \pi^*$) bands at 200–270 nm. (Scheme IV. 18, Figure IV. 2, figure IV. 3).

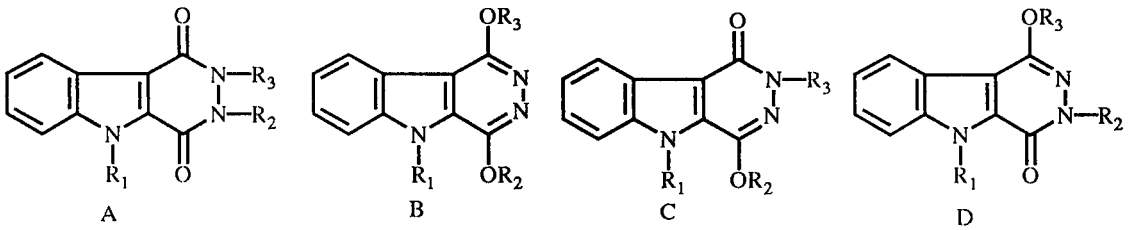
Upon protonation, the all low intensity bands undergo a bathochromic effect (red shift) of 10–50 nm, which is accompanied by a hyperchromic effect. The high intensity bands also produce a bathochromic effect, which is generally accompanied by a hypochromic effect.

Logε values of compounds (6), (37), (40), (42), (44), (45), and (46) in neutral and acidic solutions (monoprotonations) resemble each other but they are different from those of 1, 4–dimethoxy–5*H*–pyridazino[4, 5–*b*]indole (67) (Table IV. 5).

UV spectra of these compounds (6, 37, 40, 42, 44, 45, 46) in 98% sulphuric acid are very similar to each other (Figure IV. 3. 3).

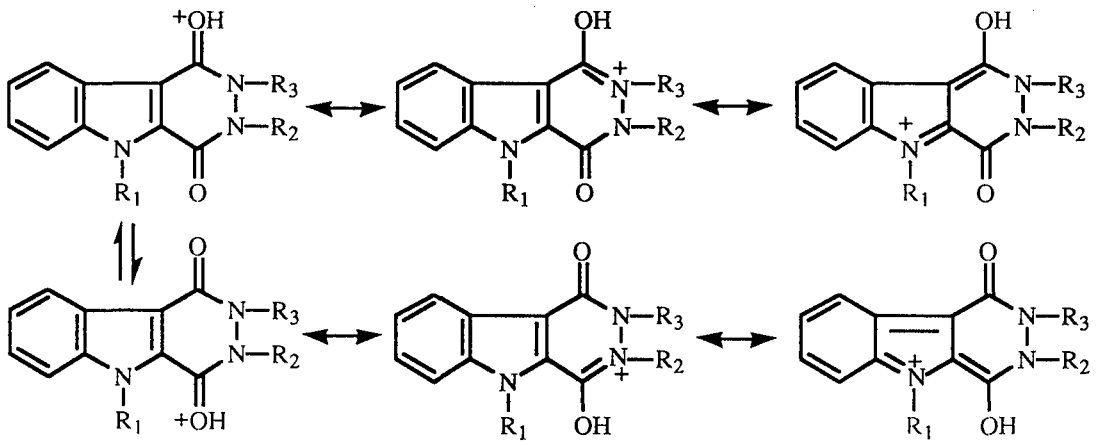
After the examination of all data, we suggest that 1, 4–dioxo–1, 2, 3, 4–tetrahydro –5*H*–pyridazino[4, 5–*b*]indoles (6) and (37) do exist in the dioxo-structure (6a) in equilibrium with in the oxo-hydroxy–structures (6c) and (6d), but not with the dihydroxy–structure (6b) (Scheme IV. 17).

Table IV. 4 Ultraviolet Spectra of 1, 4–Dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino [4, 5–*b*]indole and its Derivatives

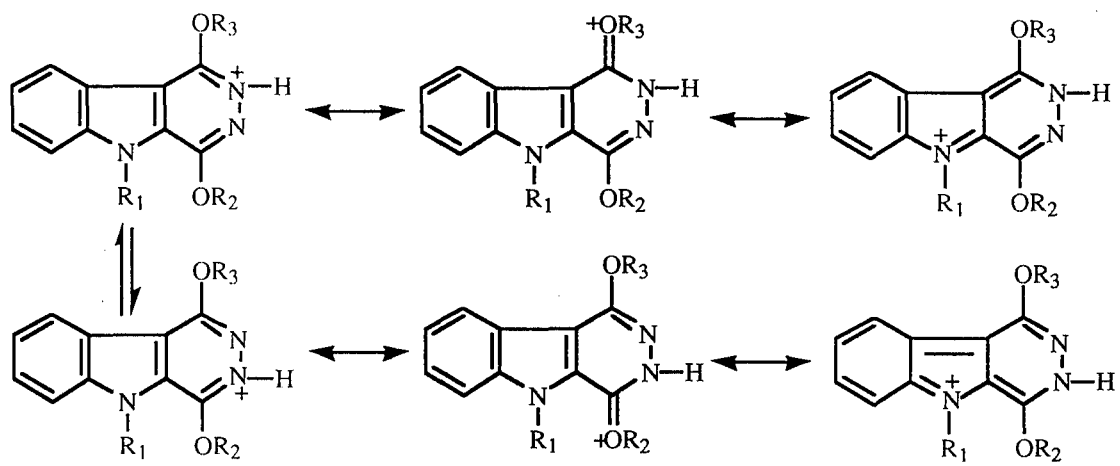


R_1	R_2	R_3	compound	λ(nm)log ε	λ(nm)log ε	λ(nm)log ε	λ(nm)log ε	λ(nm)log ε	λ(nm)log ε	pH
Free base										
A										
H	H	H	6	208 (4.54)	224 (4.70)	300 (3.92)				7
Me	H	H	37	209 (4.44)	233 (4.65)	305 (3.90)				7
Me	Me	H	44	205 (4.36)	231 (4.69)	315 (3.89)				7
Me	Me	Me	40	226 (4.54)	238 (4.59)	315 (4.12)				7
B										
Me	Me	Me	67	204 (3.54)	231 (3.93)	284 (2.96)	310 (2.96)	324 (2.96)		9.12
C										
Me	Me	Me	46	204 (4.43)	235 (4.73)	300 (4.03)	308 (4.09)	322 (4.03)		7
D										
Me	Me	Me	45	230 (4.69)	236 (4.67)	244 (4.59)	292 (3.96)	317 (3.97)	331 (3.88)	7
Monocations										Ho
6 → 68					214 (4.39)	238 (4.45)	312 (3.95)			−4.80
37 → 69						245 (4.55)	311 (3.98)			−4.80
44 → 70				206 (4.57)	214 (4.51)	244 (4.65)	314 (4.23)			−4.52
40 → 72				208 (4.58)	218 (4.49)	247 (4.68)	320 (4.29)			−4.80
67 → 73				204 (3.71)	237 (3.69)	248 (3.73)	301 (3.11)			+0.97
46 → 74				205 (4.49)	222 (4.43)	252 (4.60)	306 (4.01)			−4.80
45 → 75				207 (4.51)	219 (4.46)	242 (4.63)	312 (4.17)			−4.80
Dications										
68 → 79					233 (4.66)	266 (4.38)	342 (4.12)			98 % H_2SO_4
69 → 80				202 (4.52)	238 (4.37)	266 (4.34)	344 (4.11)			"
70 → 81				204 (4.53)	240 (4.40)	266 (4.36)	346 (4.08)			"
72 → 82				206 (4.47)	246 (4.43)	265 (4.33)	352 (4.07)			"
73 → 83				202 (4.51)	239 (4.39)	268 (4.42)	343 (4.09)			"
74 → 84				205 (4.32)	241 (4.46)	271 (4.26)	345 (3.99)			"
75 → 85				201 (4.55)	240 (4.43)	267 (4.42)	345 (4.16)			"

Monocations

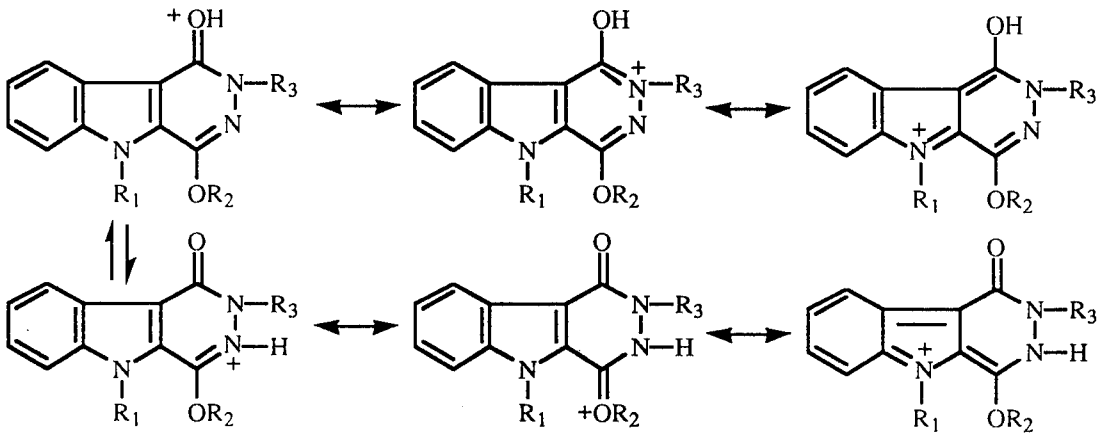


R_1	R_2	R_3	Compound
H	H	H	6 → 68
Me	H	H	37 → 69
Me	Me	H	44 → 70
Me	Me	Me	40 → 72

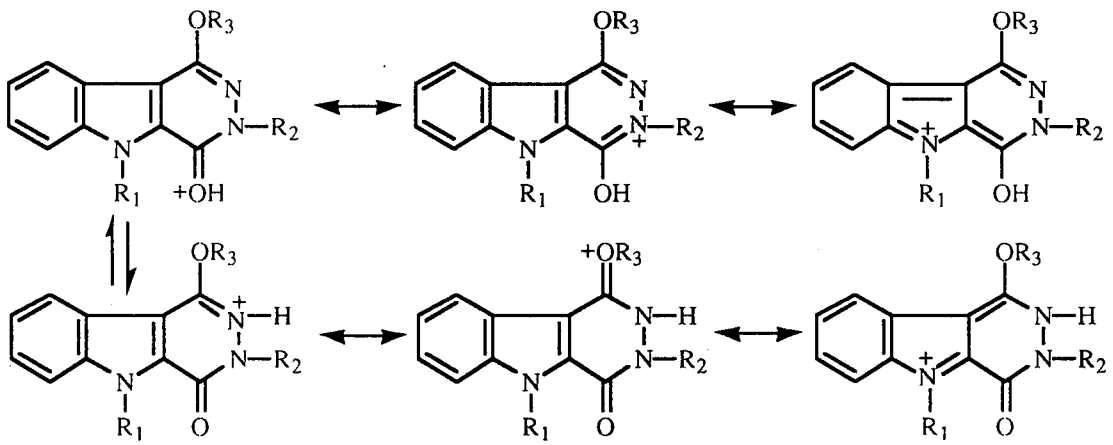


$R_1 = R_2 = R_3 = Me$ 67 → 73

Scheme IV. 18. 1



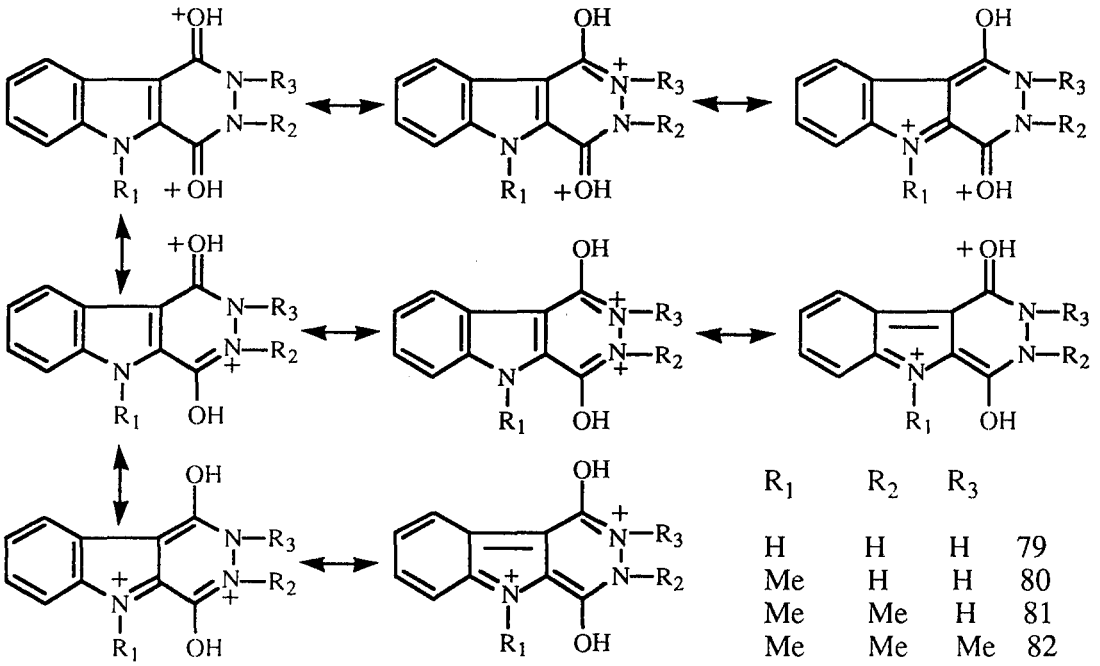
$R_1 = R_2 = R_3 = Me$ 46 → 74



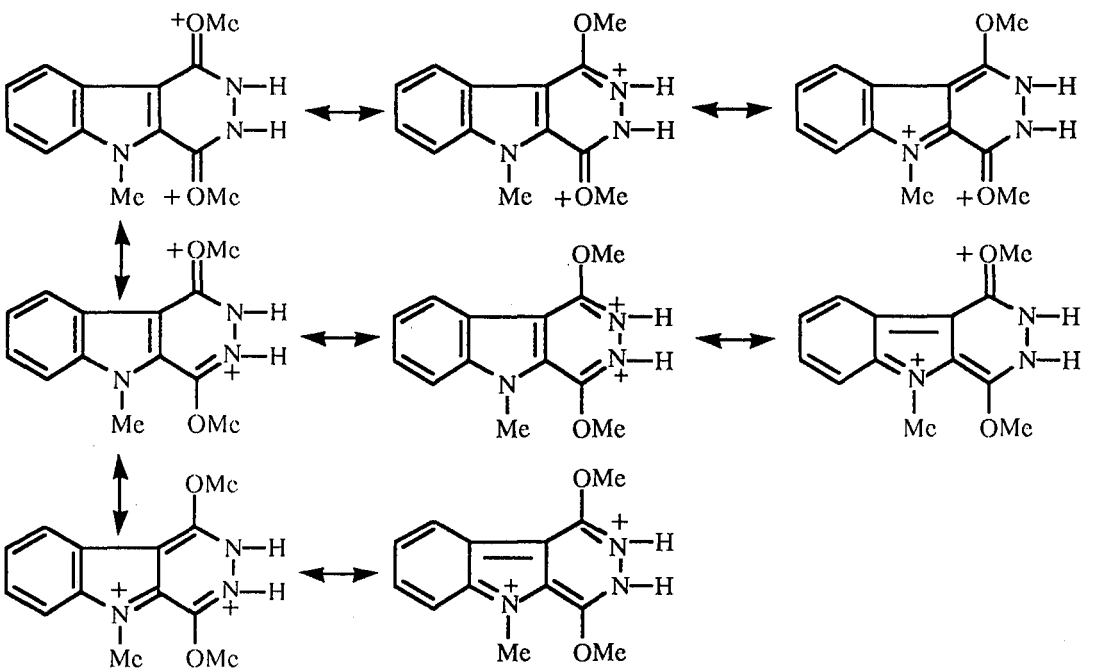
$R_1 = R_2 = R_3 = Me$ 45 → 75

Scheme IV. 18. 2

Dications



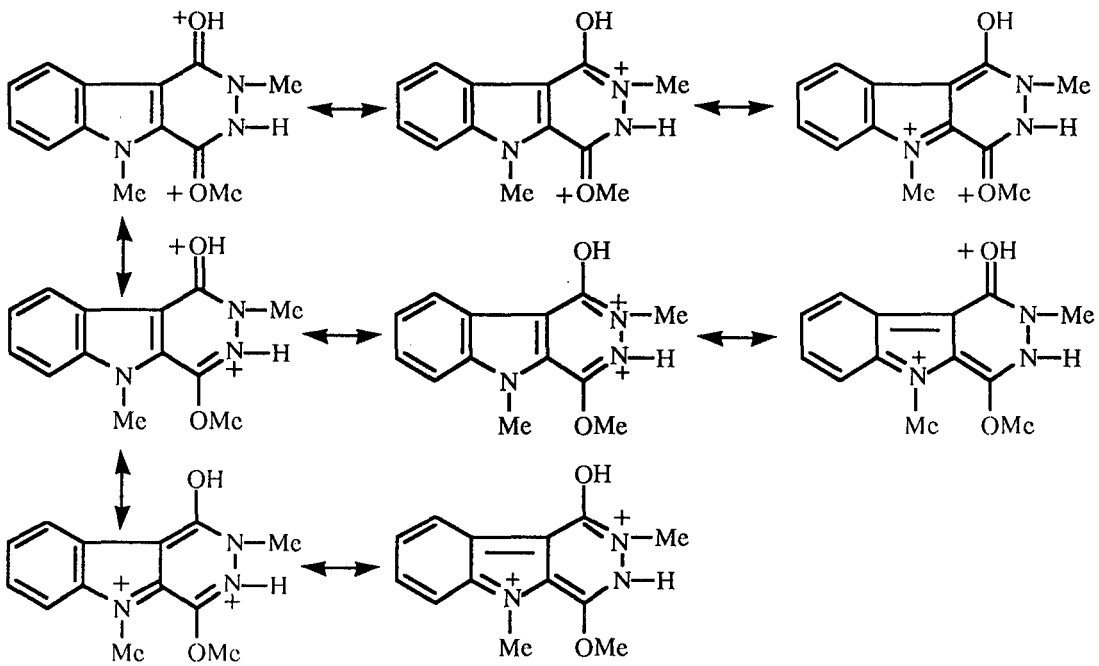
R_1	R_2	R_3	
H	H	H	79
Me	H	H	80
Me	Me	H	81
Me	Me	Me	82



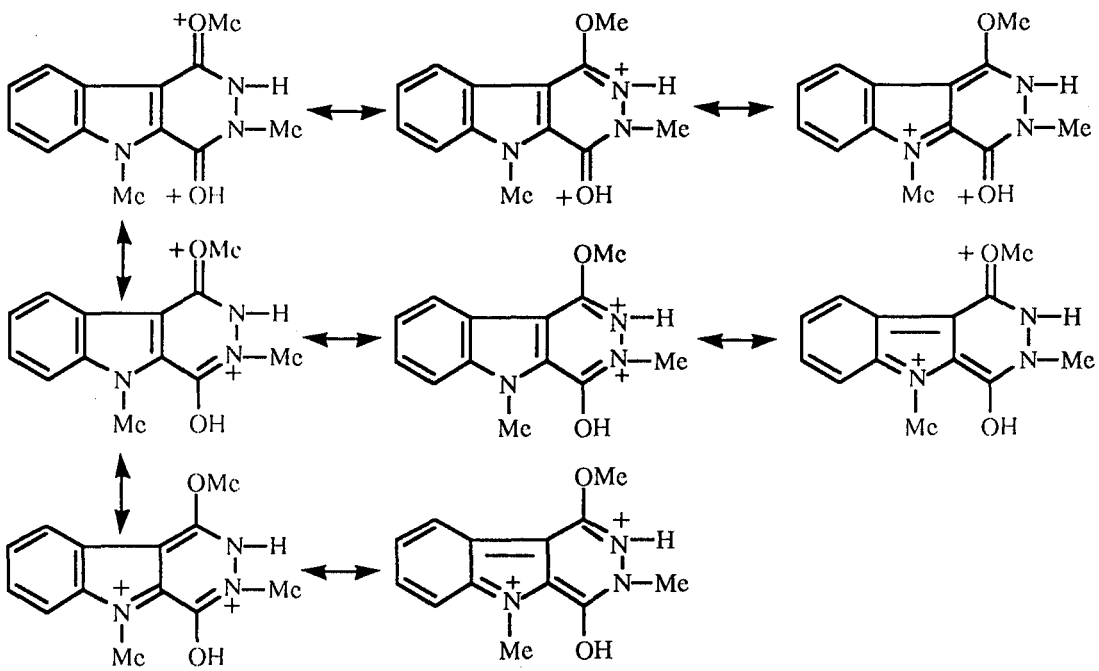
83

Scheme IV. 18. 3

Dications



84



85

Scheme IV. 18. 4

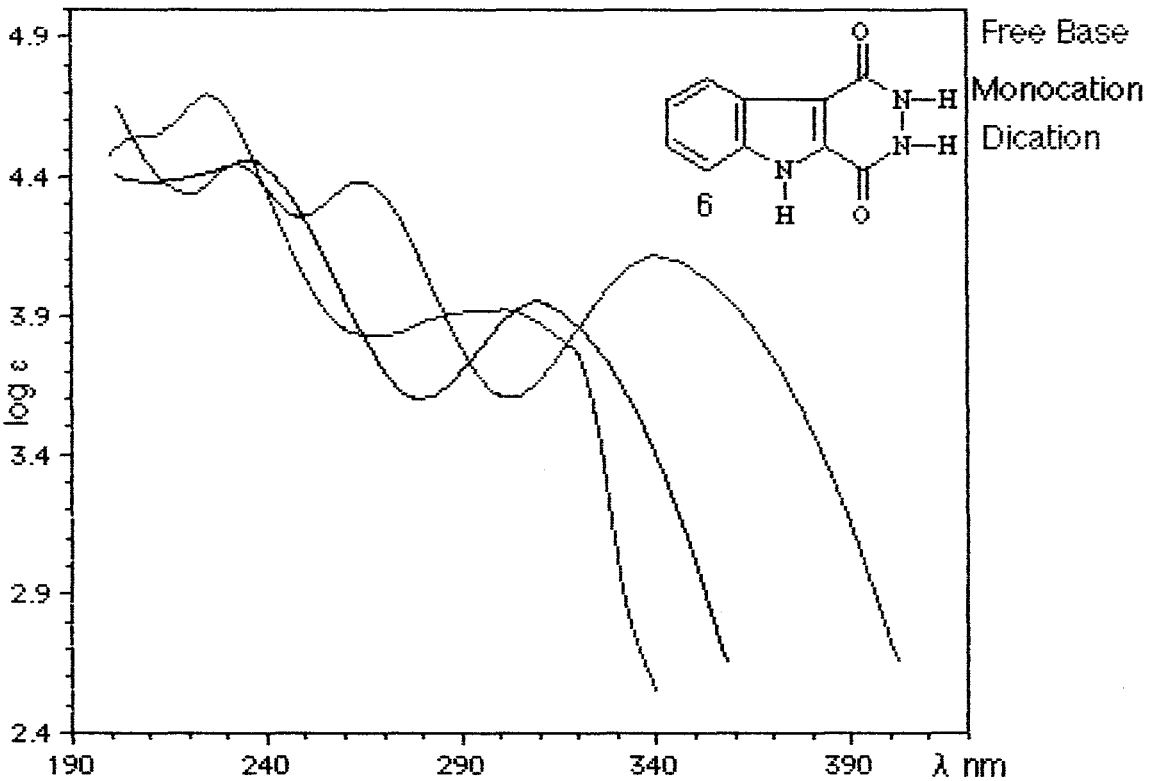


Figure IV. 2. 1 Ultraviolet Spectra of 1,4-Dioxo-1,2,3,4-tetrahydro-5*H*-pyridazino [4,5-*b*]indole in different media.

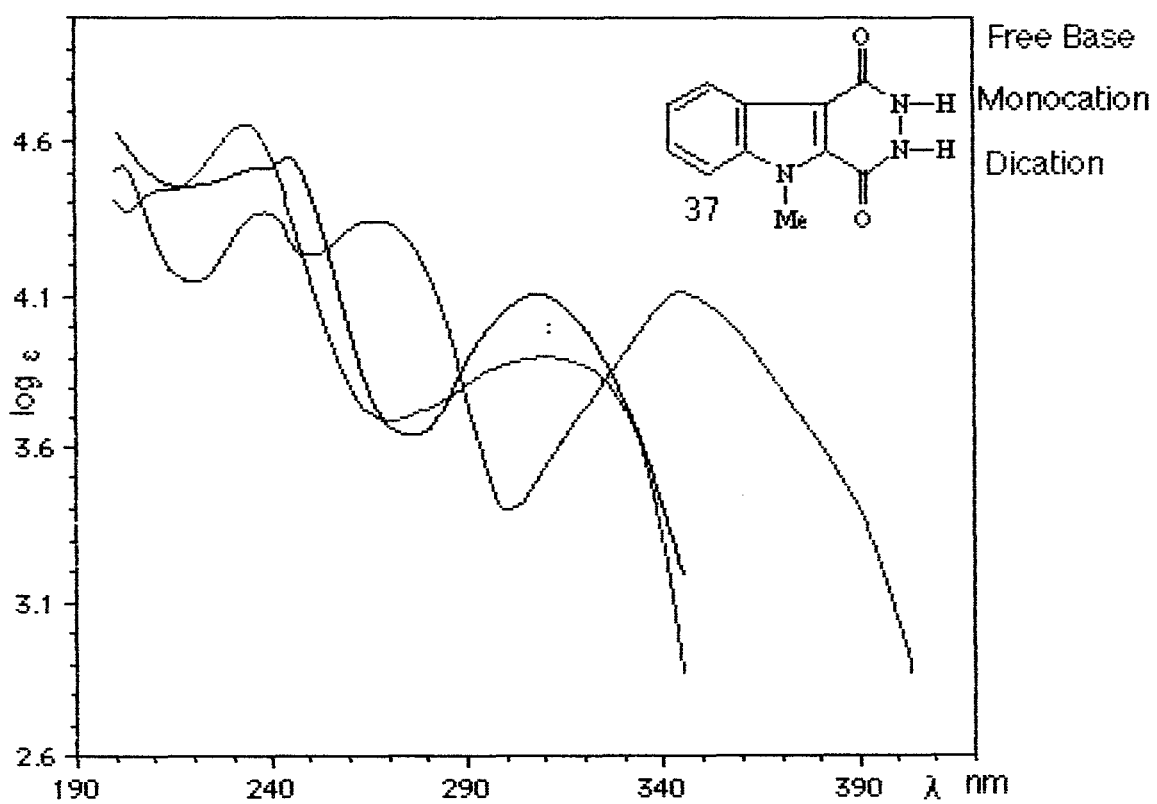


Figure IV. 2. 2 Ultraviolet Spectra of 1,4-Dioxo-5-methyl-1,2,3,4-tetrahydro-5*H*-pyridazino[4,5-*b*]indole in different media.

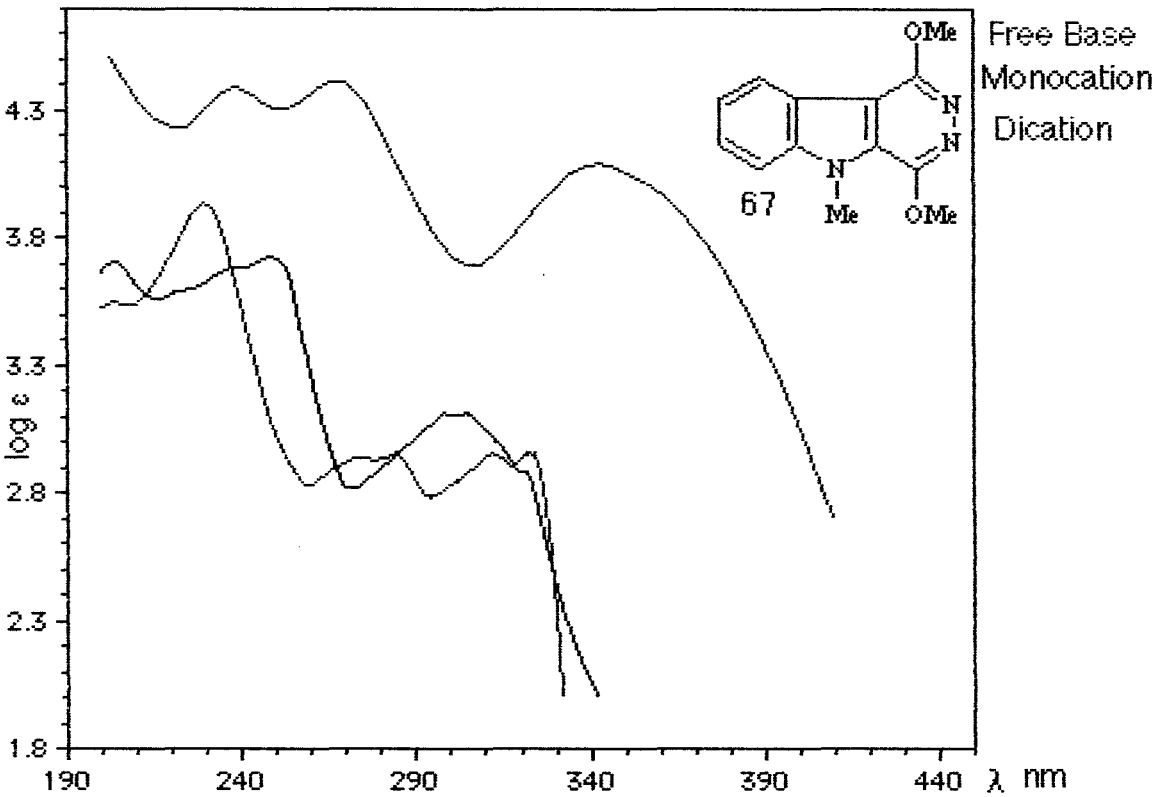


Figure IV. 2. 3 Ultraviolet Spectra of 1,4-Dimethoxy-5-methyl-5*H*-pyridazino [4,5- *b*]indole in different media.

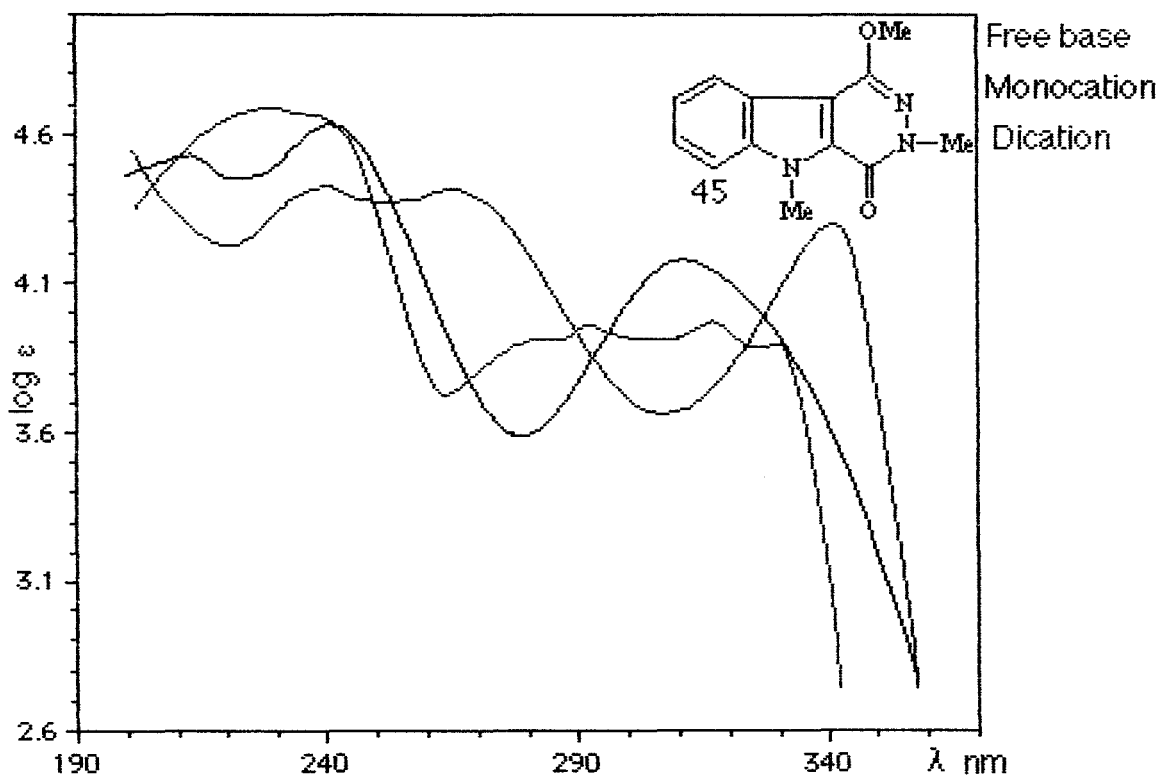


Figure IV. 2. 4 Ultraviolet Spectra of 3,4-Dihydro-3,5-dimethyl-1-methoxy-4-oxo -5*H*-pyridazino[4,5- *b*]indole in different media.

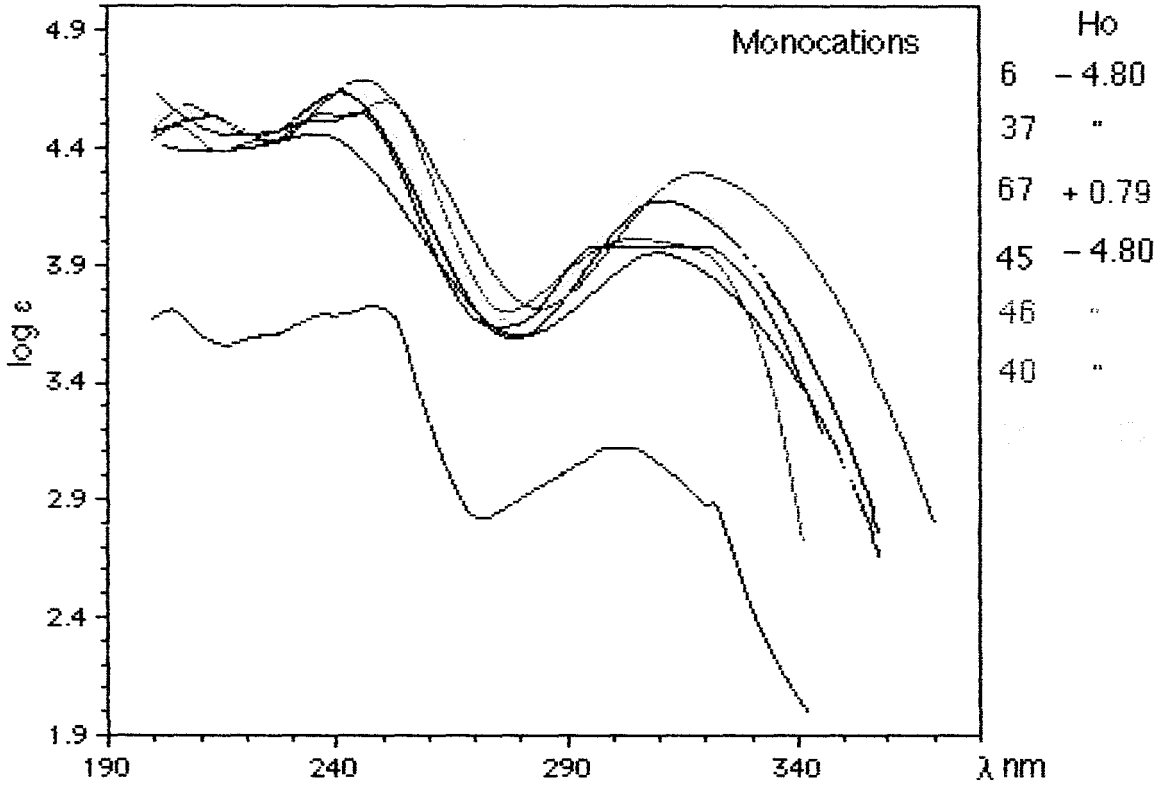


Figure IV. 3. 2 Ultraviolet Spectra of Monocations Species of 5*H*-pyridazino[4,5- *b*] indole.

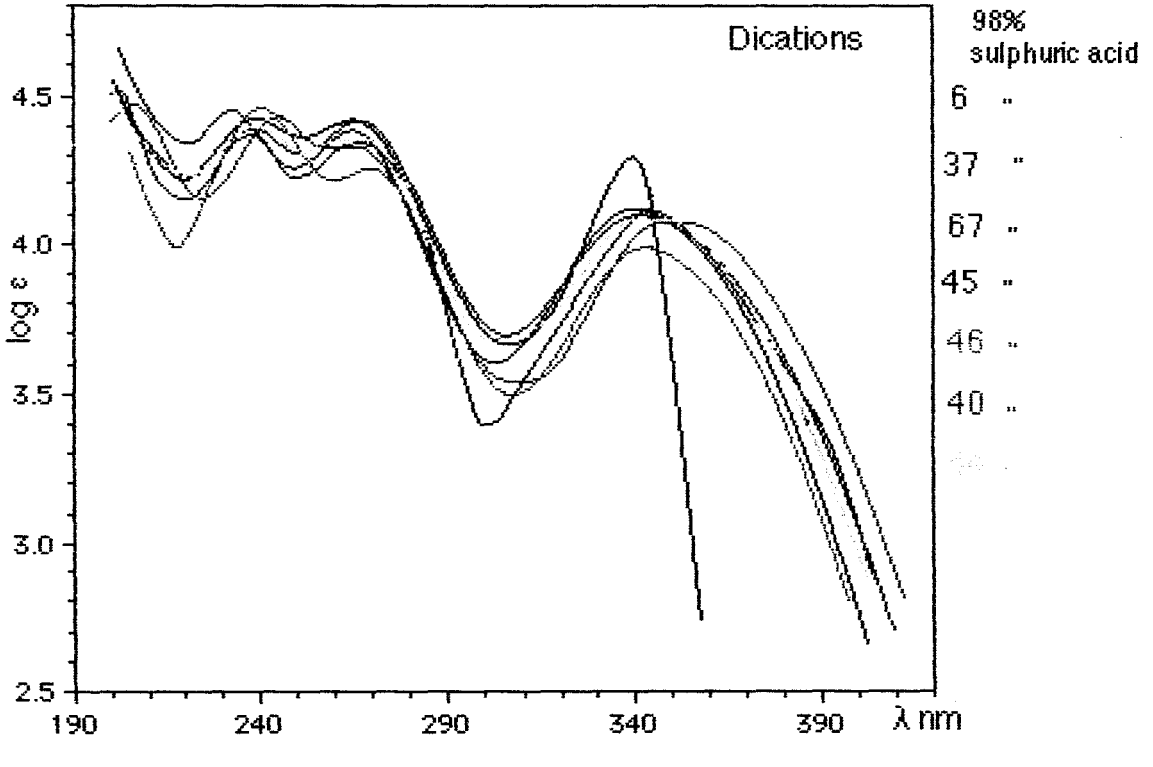


Figure IV. 3. 3 Ultraviolet Spectra of Dications Species of 5*H*-pyridazino[4,5- *b*] indole.

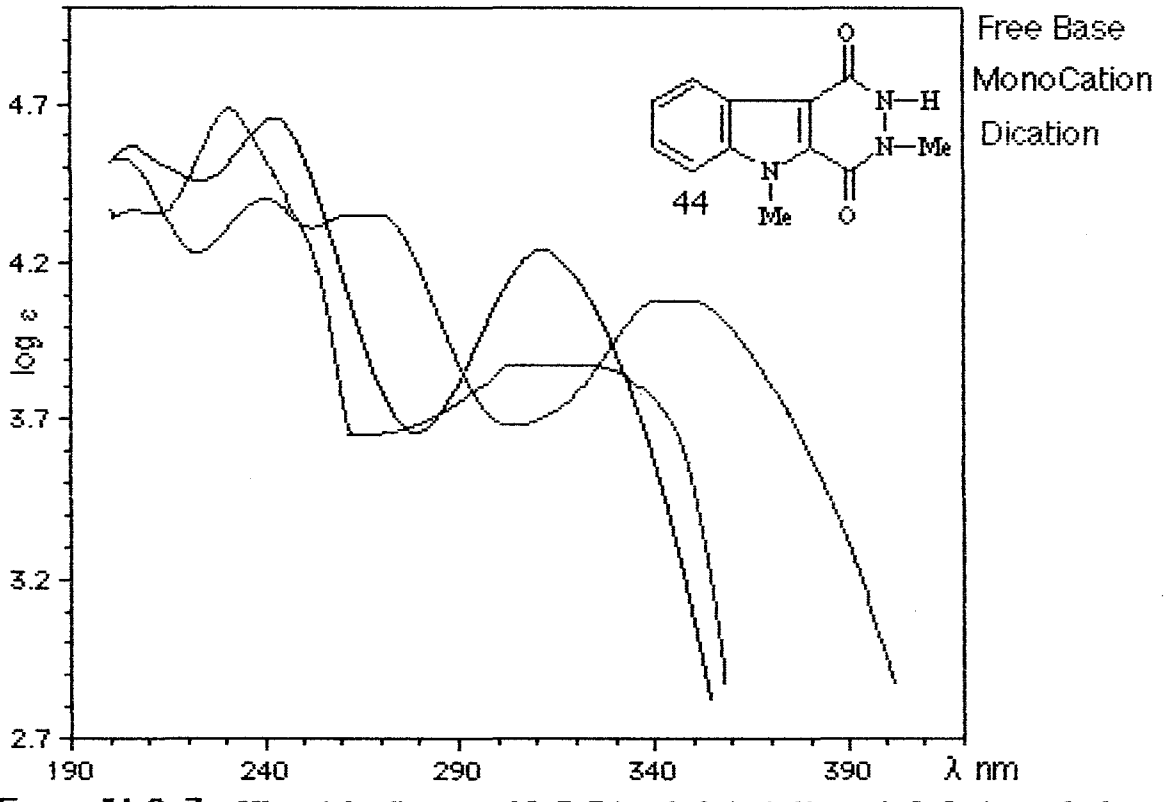


Figure IV. 2. 7 Ultraviolet Spectra of 3,5-Dimethyl-1,4-dioxo-1,2,3,4-tetrahydro -5*H*-pyridazino[4,5- *b*]indole in different media.

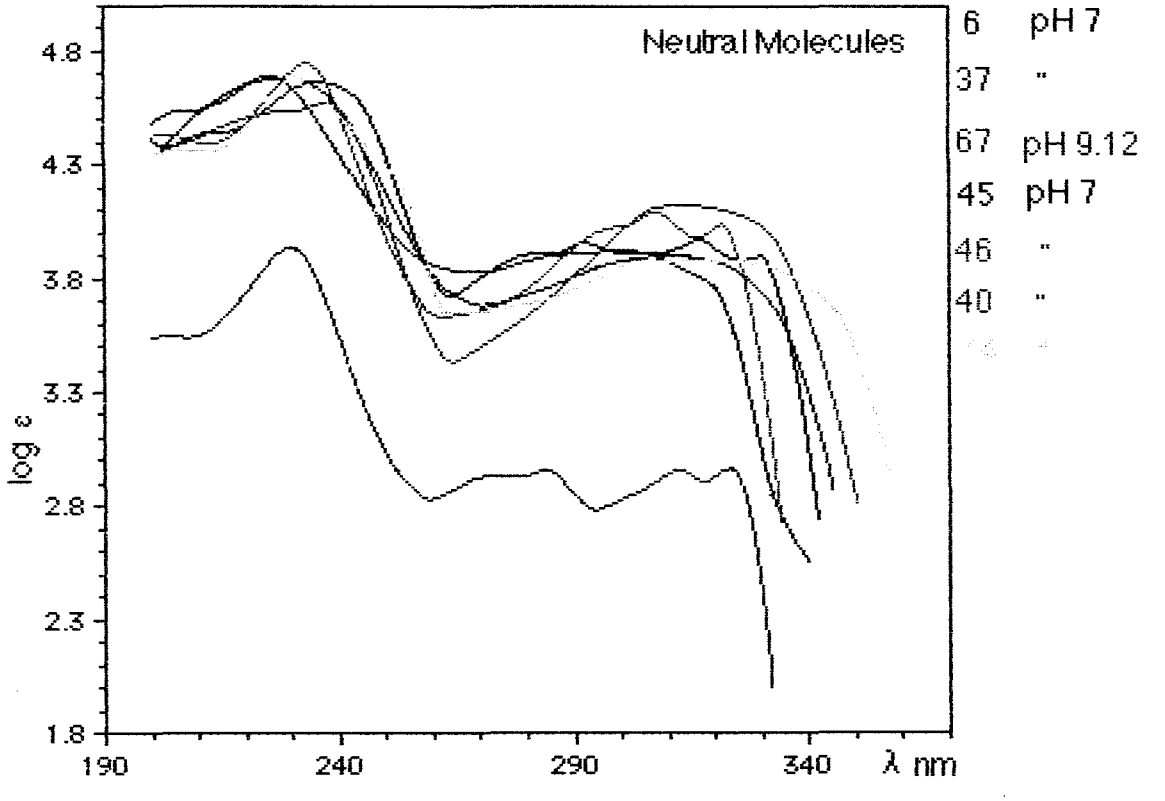


Figure IV. 3. 1 Ultraviolet Spectra of Neutral Species of 5*H*-pyridazino[4,5- *b*] indole.

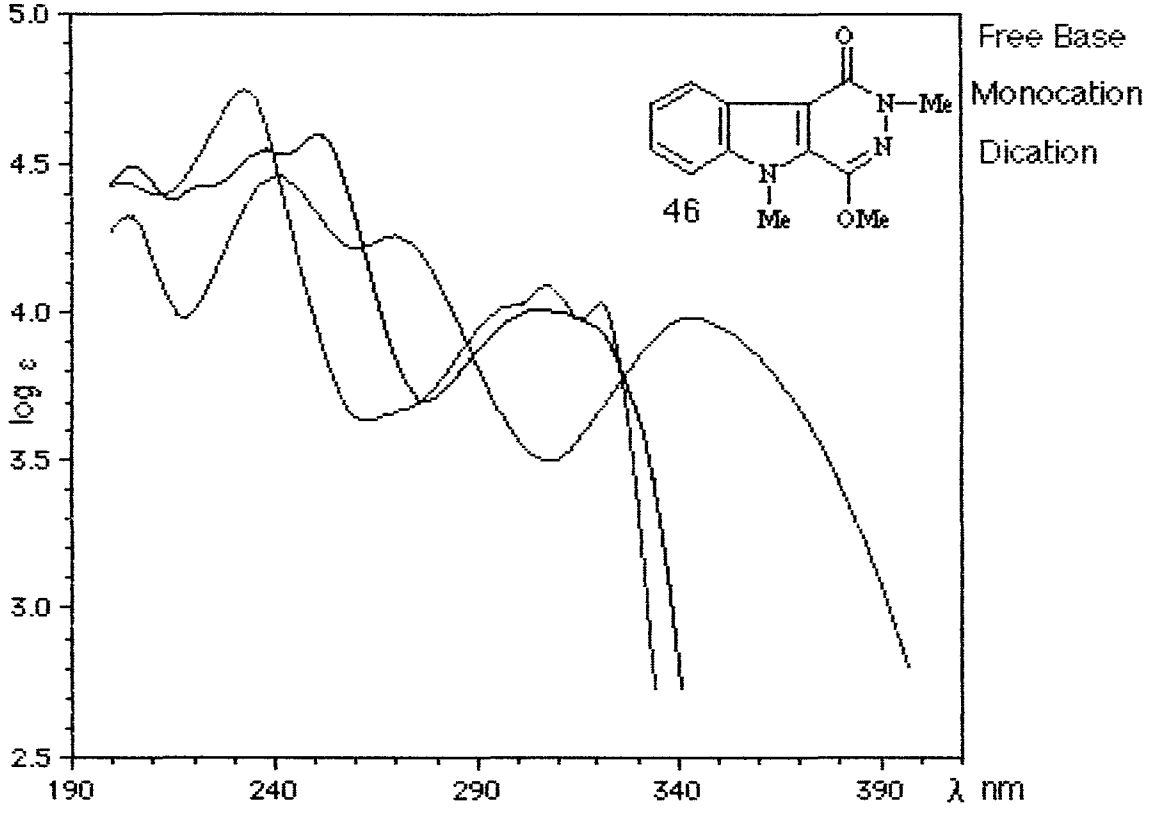


Figure IV. 2. 5 Ultraviolet Spectra of 1,2-Dihydro-2,5-dimethyl-4-methoxy-1-oxo -5*H*-pyridazino[4,5- *b*]indole in different media.

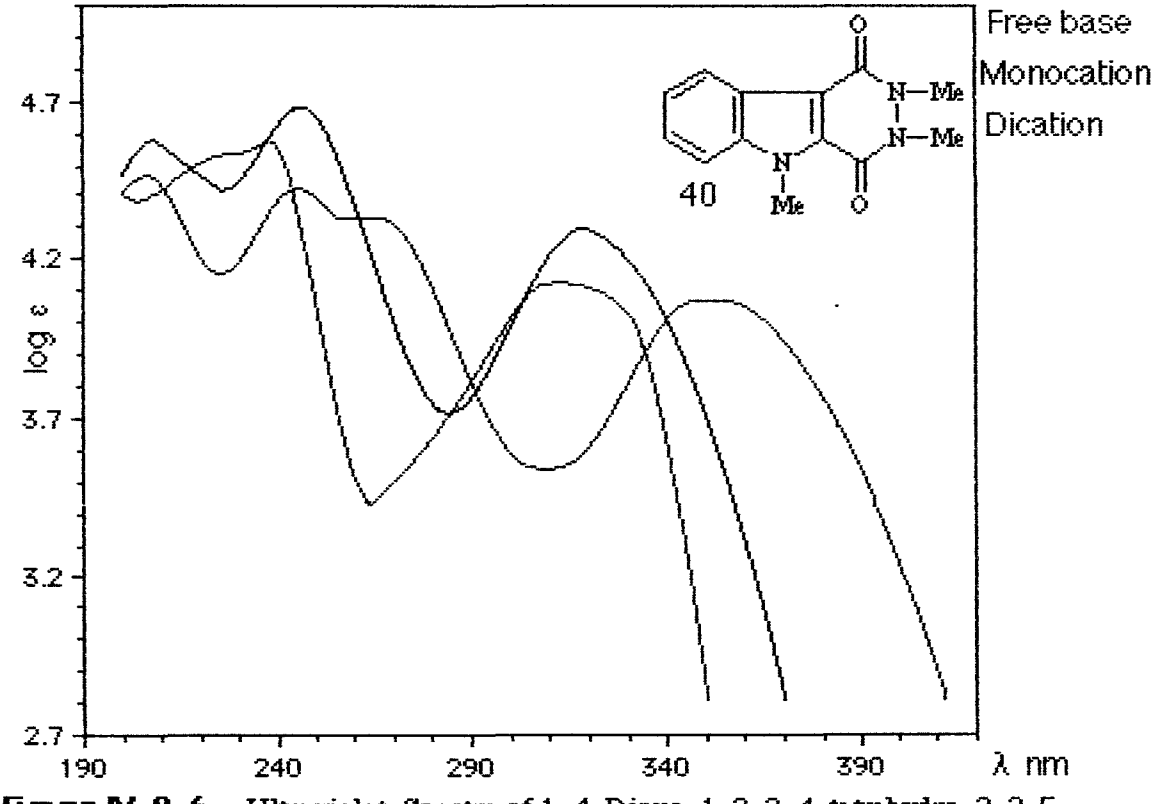
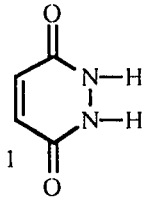


Figure IV. 2. 6 Ultraviolet Spectra of 1,4-Dioxo-1,2,3,4-tetrahydro-2,3,5 -trimethyl-5*H*-pyridazino[4,5- *b*]indole in different media.

3. 4 Basicity Measurements

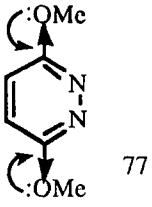
The ionisation constants of 1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino [4, 5–*b*]indole and its derivatives are recorded in the table IV. 5.

The electron-donating indole system increases the basicities of 3, 6–pyridazinedione (1) and dimethoxypyridazine (77) by 2.05 and 0.45 pKa units, respectively (Scheme IV. 19, Table IV. 5).



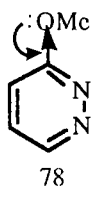
1

pKa = – 0.99 [2b]
" = – 3.28 [2b]
" = – 2.20 [22]
" = – 0.97 [25]



77

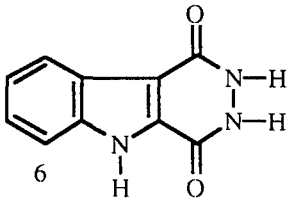
pKa = 1.61 [22]



78

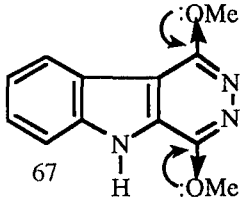
pKa = 2.52 [22]

decreasing basicitiy



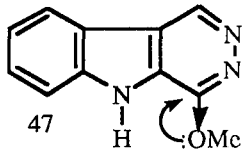
6

pKa = – 0.10 [b]



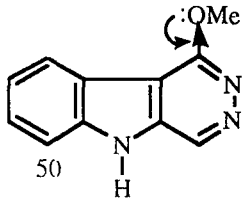
67

pKa = 2.06 [b]



47

pKa = 3.25 [a]



50

pKa = 3.27 [a]

Scheme IV. 19

a. See section II. 4. 4 and section III. 3. 4
b. See table IV. 6

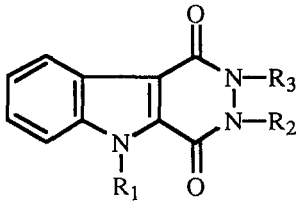
Introduction of a second methoxy group to 3–methoxypyridazine (78) decreases the basicity of (78) (pKa = 2.52) by 0.91 pKa units (77) (pKa = 1.61). This observation indicated that the inductive effect of the second methoxy group is of more importance compared with the mesomeric effect (Scheme IV. 19). We noted similar results in the measurement of the basicities of the corresponding 5*H*–pyridazino[4, 5–*b*]indoles (67), (50), and (47) (Scheme IV. 19). Introduction of a second methoxy group in either 1–methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (50) (pKa = 3.27) or 4–methoxy –5–methyl–5*H*–pyridazino[4, 5–*b*]indole (47) (pKa = 3.25) decreased the basicities of those compounds by ca. 1.20 pKa unit (67) (pKa = 2.06).

Examination of the pKa values of 5*H*–pyridazino[4, 5–*b*]indoles indicates that the presence of a methyl group on the nitrogen atom of pyridazine ring (44) results in a decrease in the pKa values (ΔpKa = 1.67) compared with that of (37). The introduction of a second methyl group on the nitrogen atom of pyridazine ring (40) causes a further

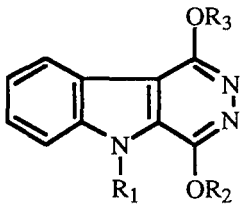
decrease in the pKa values (ΔpKa = 0.64), due to an increase in the resonance within the amide system resulting from electron–donating effect of the methyl group. On the other hand, the presence of a methyl group on the nitrogen atom of indole ring (37) does not affect the basicity of the parent 1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino[4, 5–*b*] indole (6) (Table IV. 5).

The replacement of one of the oxo groups in 1, 4–dioxo–2, 3, 5–trimethyl–5*H* –pyridazino[4, 5–*b*]indole (40) by a methoxy group at the 1–position (45) or the 4–position (46) increases the basicity of compound (40) by 0.95–1.48 pKa unit.

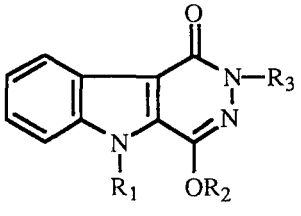
Table IV. 5 pKa [a] Values of 1, 4–Dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino [4, 5–*b*]indole and its derivatives.



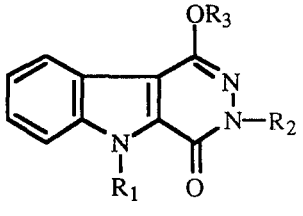
A



B



C



D

Monoprotonation

A			Compound	pKa	solution
	H	H	H	6 → 68	– 0.10 ± 0.03	b
	Me	H	H	37 → 69	– 0.005 ± 0.01	b
	Me	Me	H	44 → 70	– 1.67 ± 0.001	b
	Me	Me	Me	40 → 72	– 2.31 ± 0.02	b
B						
	Me	Me	Me	67 → 73	2.06 ± 0.04	c
C						
	Me	Me	Me	46 → 74	– 1.36 ± 0.01	d
D						
	Me	Me	Me	45 → 75	– 0.83 ± 0.004	b

Diprotonation

72 → 82	– 2.61 ± 0.002	e
73 → 83	– 2.05 ± 0.16	e
74 → 84	– 6.66 ± 0.00	e
75 → 85	– 2.77 ± 0.00	e

a. The pKa values were determined by the use of the spectroscopic method described by Albert and Serjeant. [23]

b. Determined in buffer and sulphuric acid solutions (98 % ≤ H_0 ≤ 7). [26]

c. Determined in buffer solutions (0.79 ≤ pH ≤ 9.12).

d. Determined in buffer and sulphuric acid solutions (– 4.80 ≤ H_0 ≤ 7). [26]

e. Determined in concentrated sulphuric acid solutions.

3. 5 Tautomeric Equilibrium Constants

The preceding discussion establishes qualitatively that the 1, 4–dioxo–1, 2, 3, 4 –tetrahydro–5*H*–pyridazino[4, 5–*b*]indoles (6) and (37) exist predominantly in the dioxo -structure (6a) along with a significant amount of the hydroxy-oxo structures (6c) and (6d), and not in the dihydroxy structure (6b) in the equilibrium. Due to the lack of model compounds for the zwitterionic structures (6e) and (6f), we have not been able to obtain quantitative evidence for the existence of the minor tautomeric form in the equilibrium system (Scheme IV. 17).

Applying the approach described in section II. 4. 5 a calculation of equilibrium constant (K_T) for the tautomeric equilibrium (6a $\rightleftharpoons$ 6b $\rightleftharpoons$ 6c $\rightleftharpoons$ 6d) using the pKa values for the monoprotonation of the " fixed tautomeric form " model compounds is possible.

The tautomeric forms (6a $\rightleftharpoons$ 6b $\rightleftharpoons$ 6c $\rightleftharpoons$ 6d) may be interconverted *via* their protonated form (68a $\rightleftharpoons$ 68b $\leftrightarrow$ 68c $\rightleftharpoons$ 68d) and (68a' $\rightleftharpoons$ 68b' $\rightleftharpoons$ 68c' $\rightleftharpoons$ 68d') (Scheme IV. 20, Scheme IV. 21). Therefore, the basicities of tautomeric structure forms (6a), (6b), (6c), and (6d) can not be determined individually. Hence, the value K'_{T1}, K'_{T2}, and K'_{T3} were obtained from the corresponding " fixed tautomeric " model compounds (40), (67), (45), and (46) (Scheme IV. 22).

The model compounds (40), (67), (45), and (46) did not produce a common monocation due to different protonation sites, but giving monocations (72), (73), (74), and (75) (Scheme IV. 18, Scheme IV. 20, Scheme IV. 21, and Scheme IV. 22). Upon the second protonation of these fixed tautomeric model compounds we obtained a common cation (79) and the pKa values of (40), (67), (45), and (46) gave a quantitative measure

6a $\rightleftharpoons$ 6b

$$pK'_{T1} = [\, pK_{A'} + pK_{C'} \,] - [\, pK_{D'} + pK_{B'} \,]$$

$$pK'_{T1} = [\, pKa_1(40) + pKa_2(40) \,] - [\, pKa_2(67) + pKa_1(67) \,]$$

$$pK'_{T1} = [\, (-2.31) + (-2.61) \,] - [\, (-2.05) + (2.06) \,]$$

$$pK'_{T1} = -4.93$$

6a $\rightleftharpoons$ 6c

$$pK'_{T2} = [\, pK_{A'} + pK_{C'} \,] - [\, pK_{G'} + pK_{F'} \,]$$

$$pK'_{T2} = [\, pKa_1(40) + pKa_2(40) \,] - [\, pKa_2(46) + pKa_1(46) \,]$$

$$pK'_{T2} = [\, (-2.31) + (-2.61) \,] - [\, (-6.66) + (-1.36) \,]$$

$$pK'_{T2} = 3.1$$

6a $\rightleftharpoons$ 6d

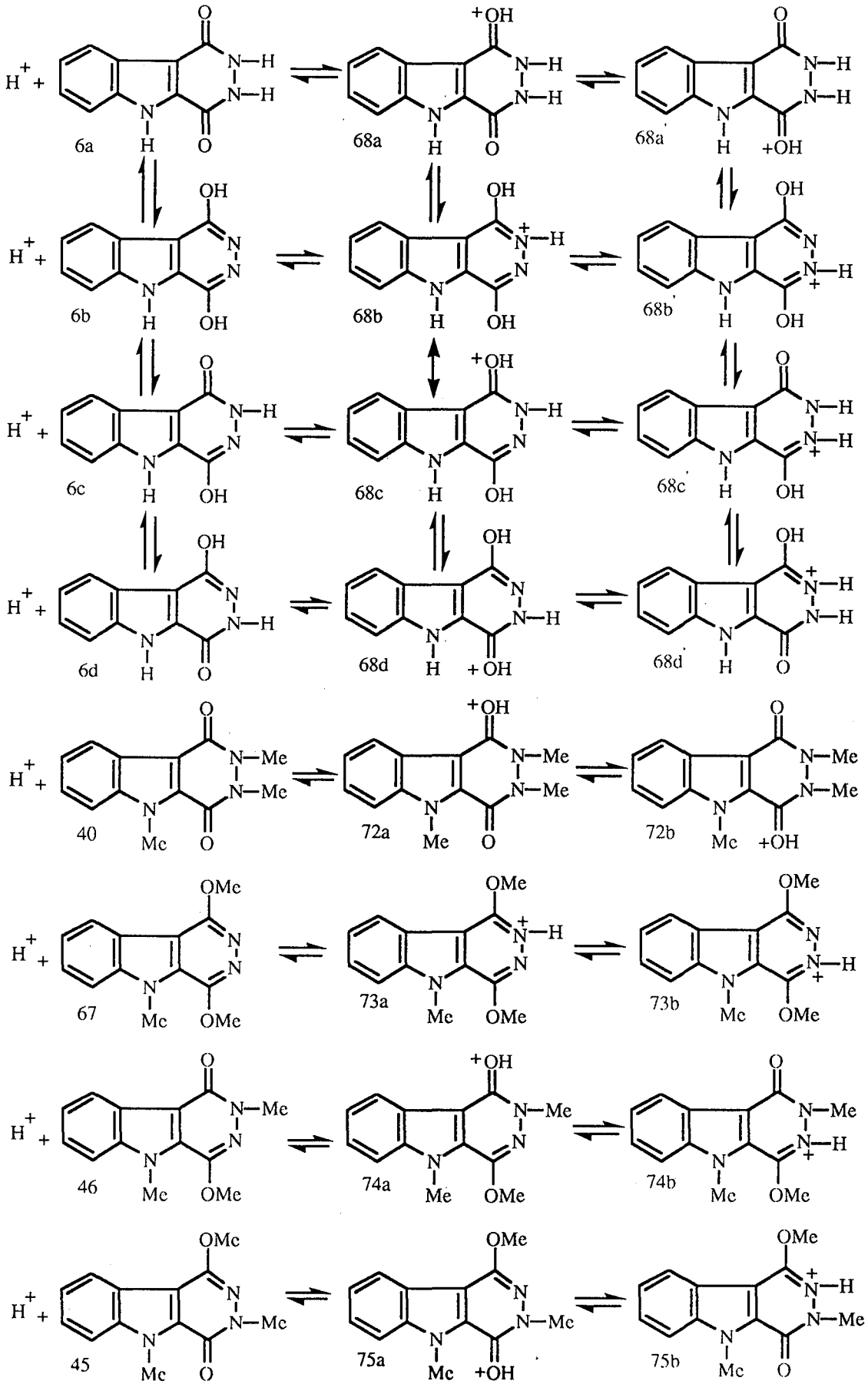
$$pK'_{T3} = [\, pK_{A'} + pK_{C'} \,] - [\, pK_{I'} + pK_{H'} \,]$$

$$pK'_{T3} = [\, pKa_1(40) + pKa_2(40) \,] - [\, pKa_2(45) + pKa_1(45) \,]$$

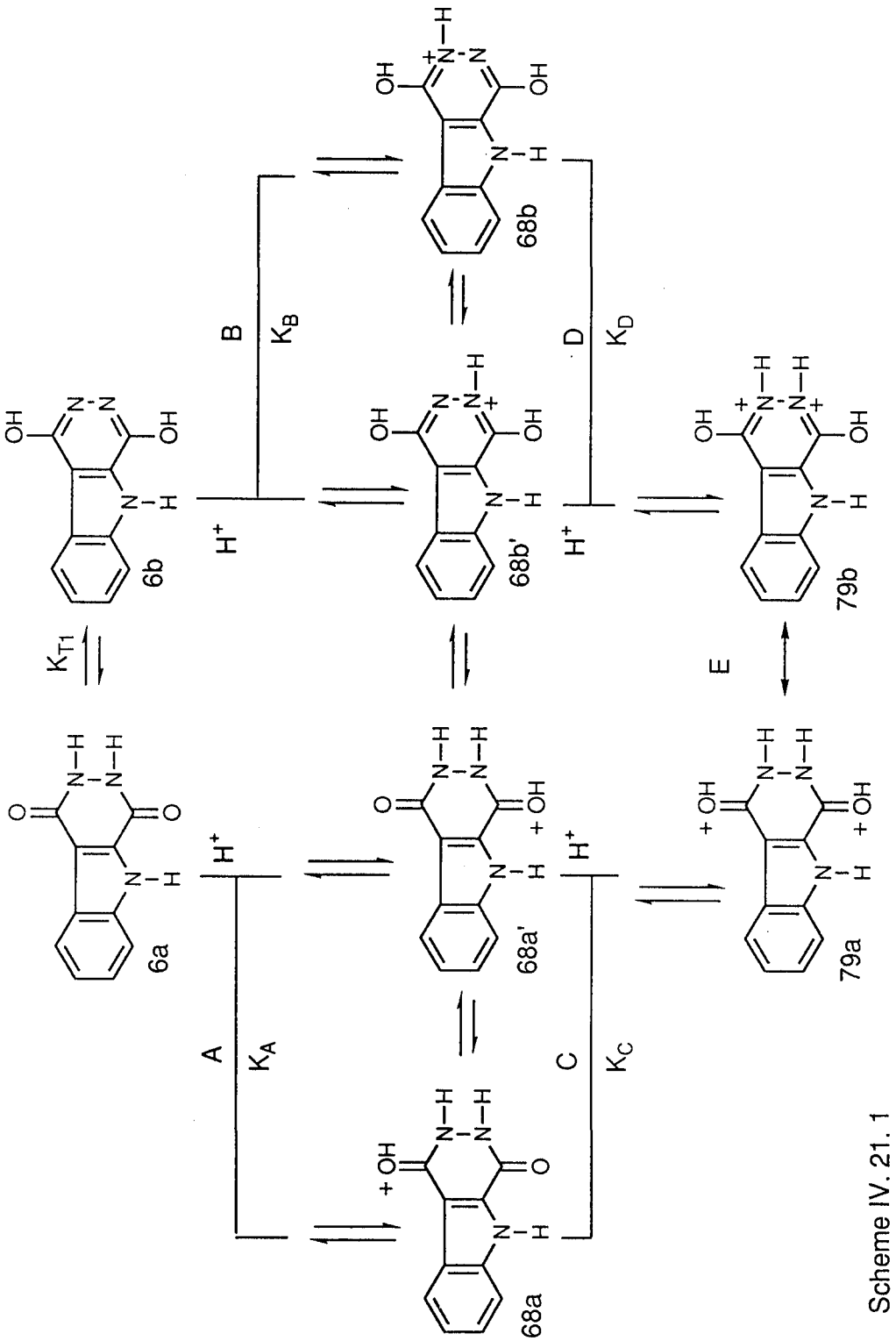
$$pK'_{T3} = [\, (-2.31) + (-2.61) \,] - [\, (-2.77) + (-0.82) \,]$$

$$pK'_{T3} = -1.33$$

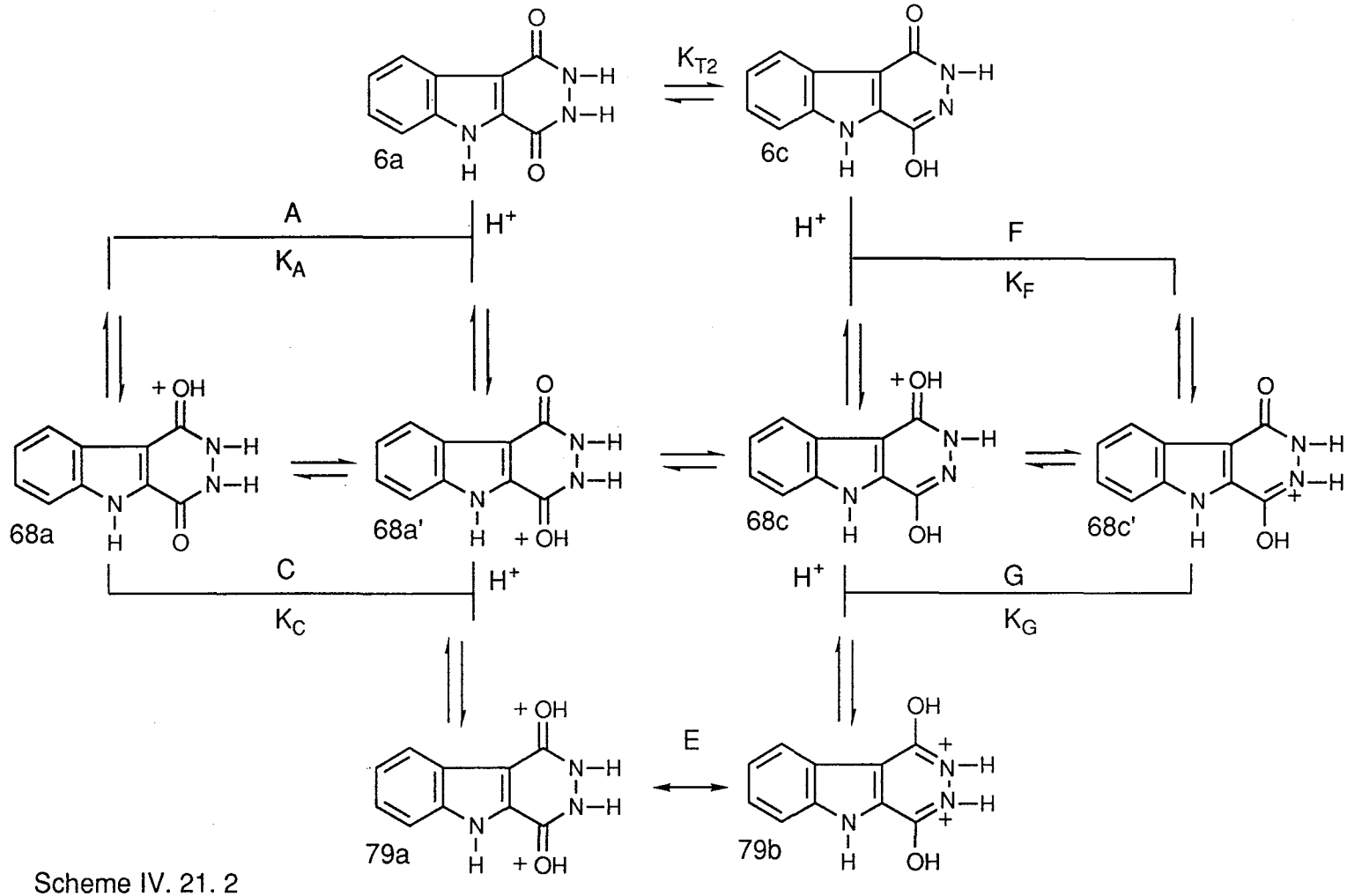
for the equilibria (6a $\rightleftharpoons$ 6b $\rightleftharpoons$ 6c $\rightleftharpoons$ 6d). The other data and pKa values of the model compounds establish that for tautomeric equilibria 1, 4–dioxo–1, 2, 3, 4–tetrahydro –5*H*–pyridazino[4, 5–*b*]indole system, the hydroxy–oxo structure (6c) is the preferred tautomeric form with the ratio of 6a : 6b : 6c : 6d being $10^{4.93}$: 1 : $10^{8.03}$: $10^{3.6}$.


6a
68a
68a
6b
68b
68b
6c
68c
68c
6d
68d
68d
40
72a
72b
67
73a
73b
46
74a
74b
45
75a
75b

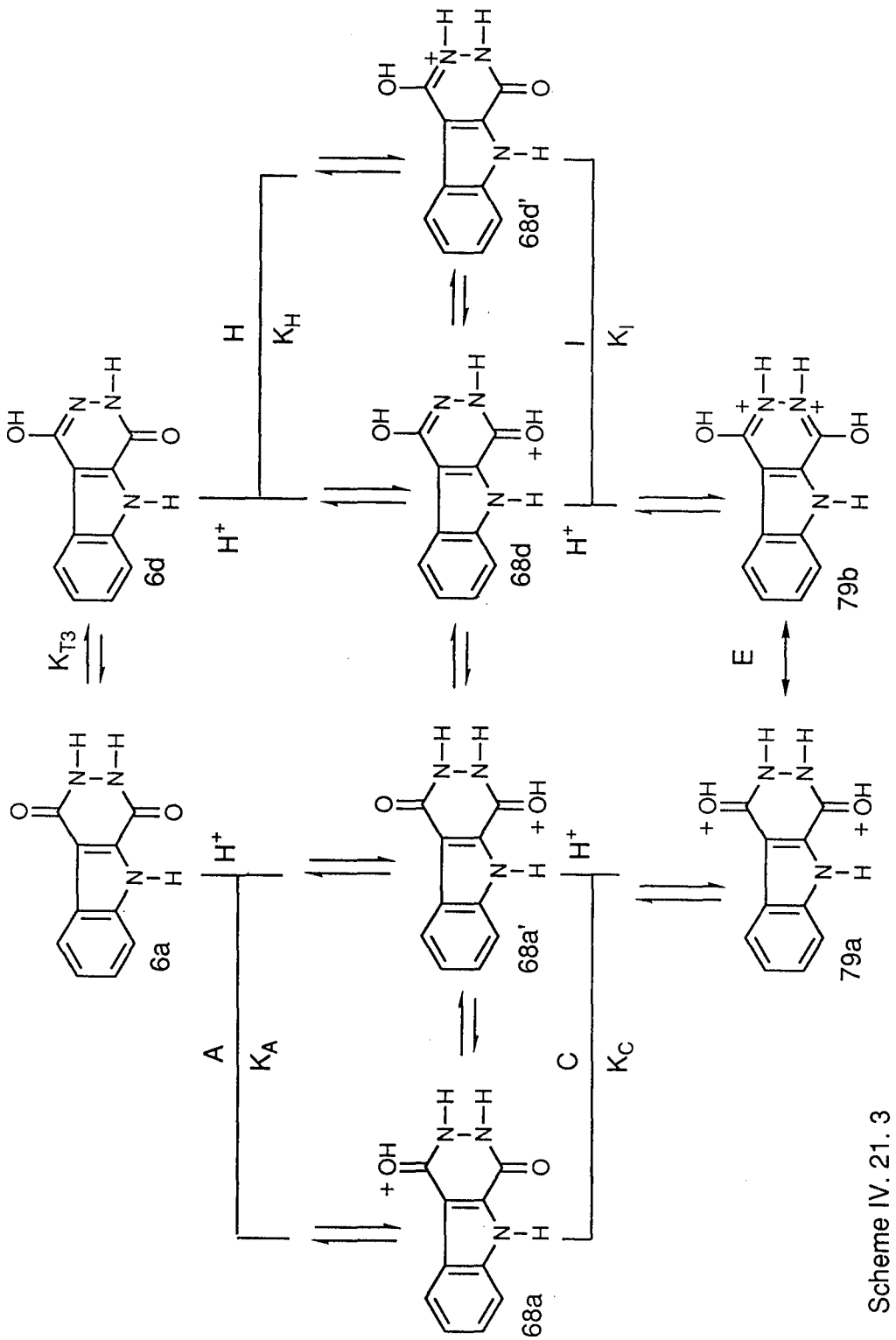
Scheme IV. 20



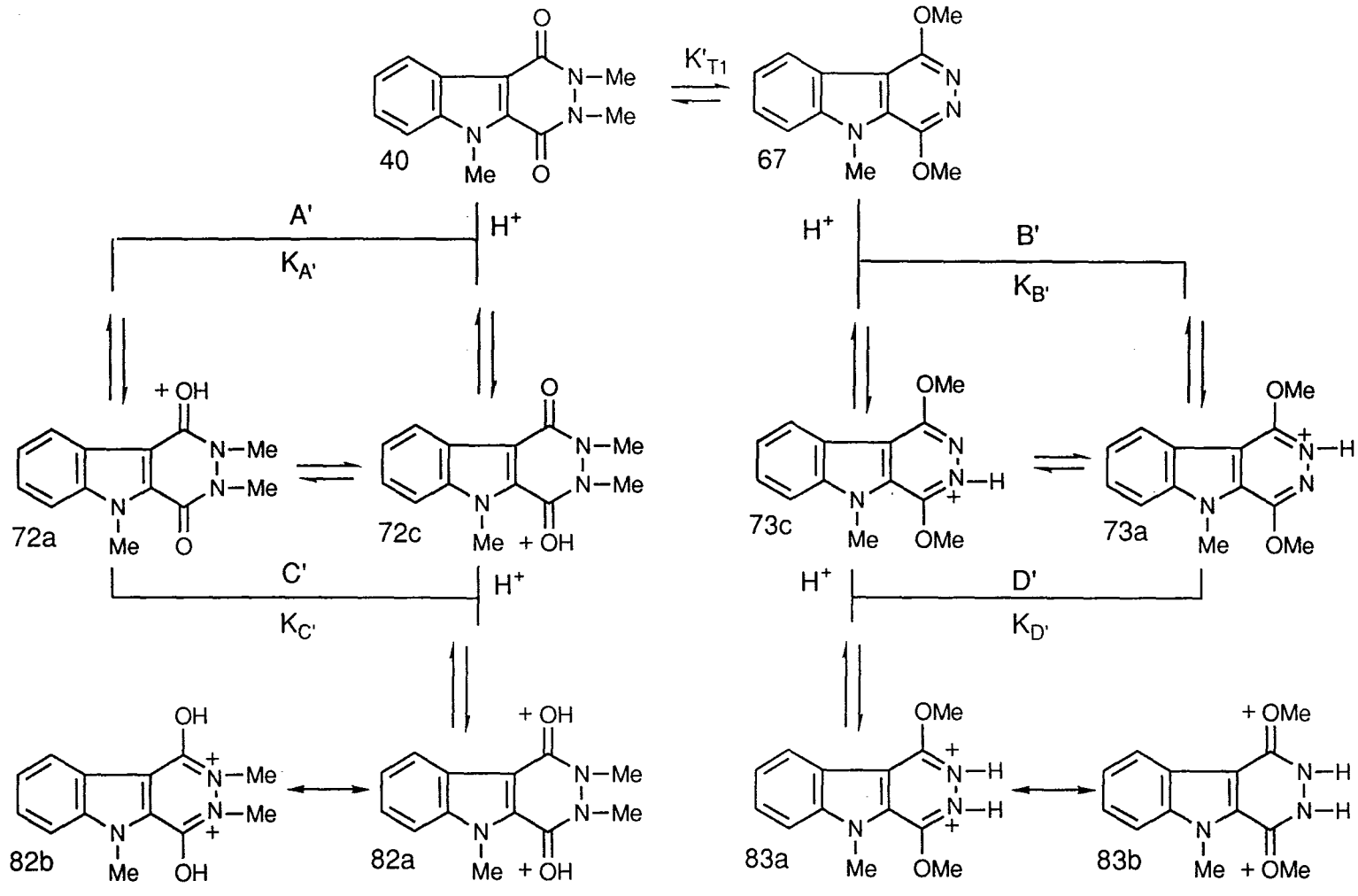
Scheme IV. 21. 1



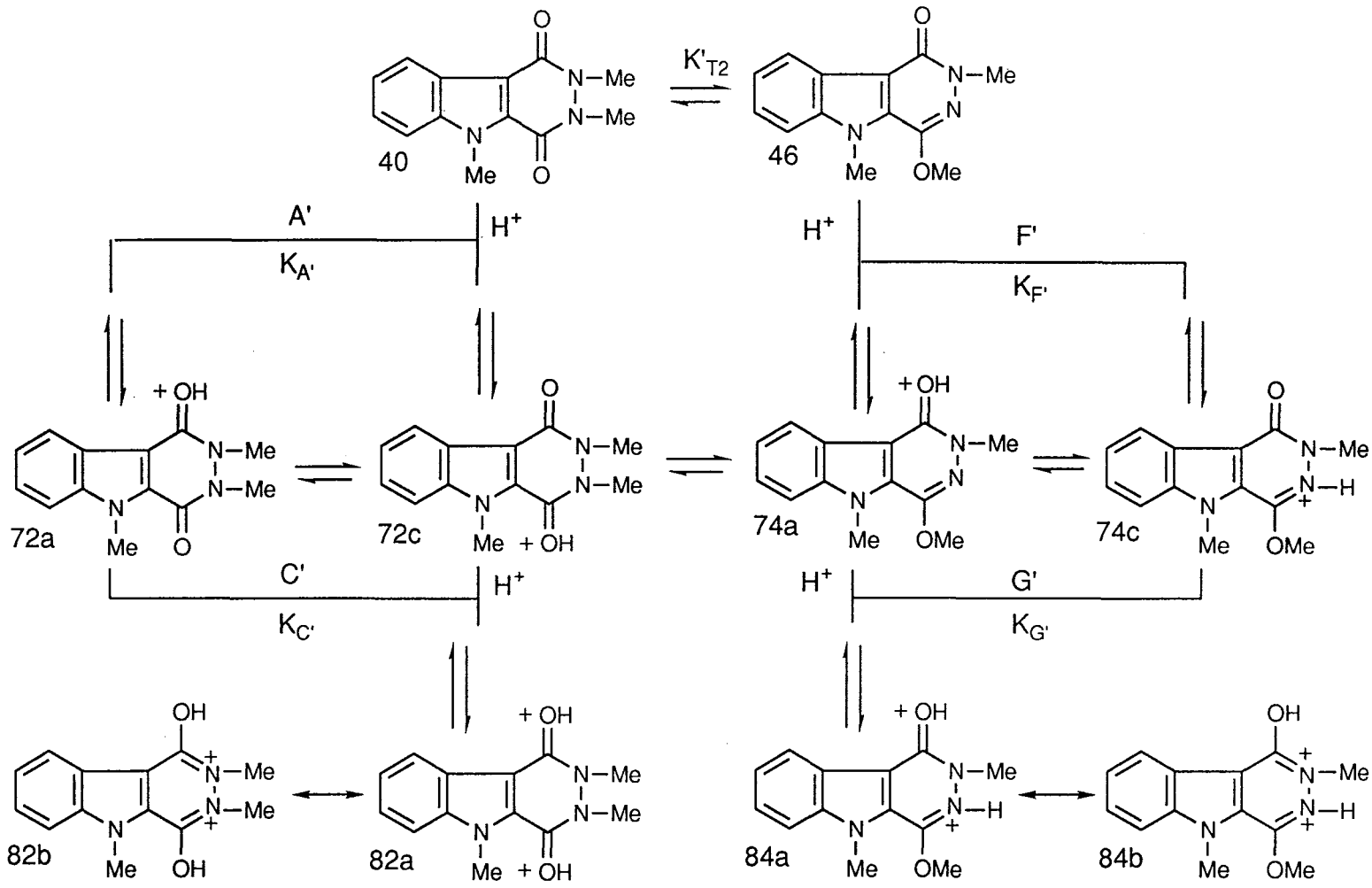
Scheme IV. 21. 2



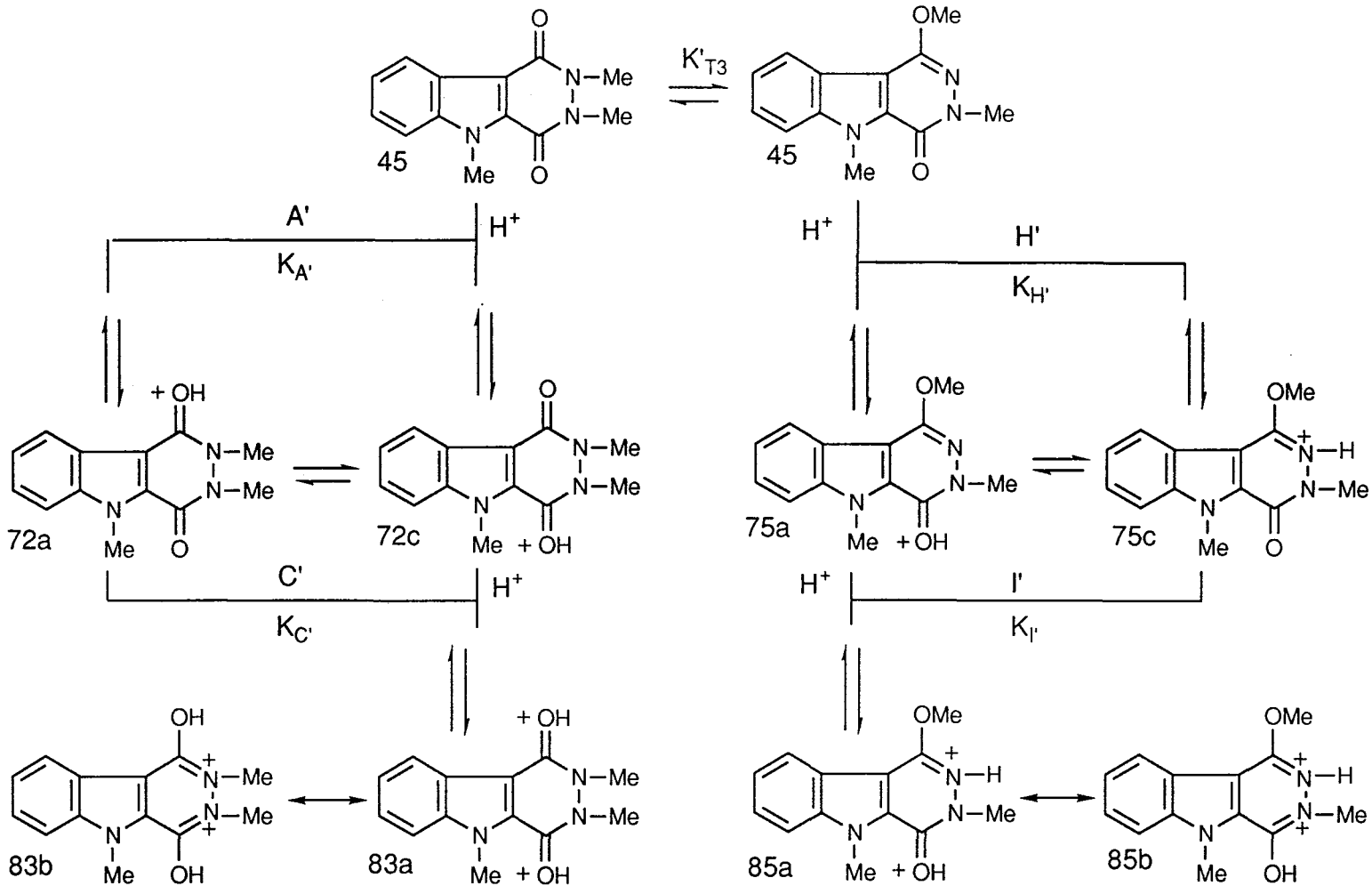
Scheme IV. 21. 3



Scheme IV. 22. 1



Scheme IV. 22. 2



Scheme IV. 22. 3

4. 0 Experimental

Dimethyl 1–methylindole–2, 3–dicarboxylate:

A mixture of dimethyl indole–2, 3–dicarboxylate (2 g, 8.58 g), anhydrous potassium carbonate (32 g, 0.23 mol), dimethyl sulphate (3.53 g, 0.028 mol), and acetone (75 ml) were refluxed for 8 h with stirring while protecting the mixture with a tube of anhydrous calcium chloride. The addition of an excess of ammonium hydroxide solution (10 %) to the cold reaction mixture neutralised any remaining agent. Most of the acetone was removed under reduced pressure and water was added to the residual material to dissolve the potassium carbonate. The aqueous mixture was extracted with dichloromethane (3 x 50 ml) and the organic solution was dried (MgSO4) and evaporated under reduced pressure. The residue was crystallised from diethyl ether–petroleum ether to give dimethyl 1–methyl–indole–2, 3–dicarboxylate (1.8 g, 85 %), as a yellow solid, m.p. 35 °C [lit. [27] m.p. 35 °C, lit. [28] m.p. 158 °C). ^{1}H-NMR ($CDCl_3$) : δ 7.92–8.20 (m, 1H, H_4) ; 7.20–7.40 (m, 3H, H_{5-7}) ; 3.94 (s, 3H, OCH_3) ; 3.86 (s, 3H, OCH_3) ; 3.76 (s, 3H, NCH_3). IR ($CHBr_3$) : $\nu_{max.}$ 1725 (C=O) cm^{-1}. [M^+] = 247 a.m.u. (Found : C, 63.2 ; H, 5.4 ; N, 5.7 ; calc. for $C_{13}H_{13}NO_4$ C, 63.2 ; H, 5.3 ; N, 5.7 %).

Dimethyl 1–benzylindole–2, 3–dicarboxylate :

A mixture of dimethyl indole–2, 3–dicarboxylate (5 g, 0.02 mol), anhydrous potassium carbonate (80 g, 0.58 mol), benzyl bromide (10.98 g, 0.064 mol), and acetone (200 ml) were refluxed for 8 h with stirring while protecting the mixture with a tube of anhydrous calcium chloride. The addition of an excess of ammonium hydroxide solution (10 %) to the cooled reaction mixture neutralised any remaining agent. Most of the acetone was evaporated under reduced pressure and water was added to the residue to dissolve potassium carbonate. The aqueous mixture was extracted with dichloromethane (3 x 100 ml) and the organic phase was dried (MgSO4) and evaporated under reduced pressure. The residue was crystallised from diethyl ether–petroleum ether to give dimethyl 1–benzylindole–2, 3–dicarboxylate (6.5 g , 94 %), as white needles, m.p. 101–102 °C [lit. [29] m.p. 102 °C]. ^{1}H-NMR ($CDCl_3$) : δ 8.00–8.20 (m, 1H, H_4) ; 7.00–7.40 (m, 8H, $H_{5-7\ and\ -Ph}$) ; 5.40 (s, 2H, NCH_2Ph) ; 3.88 (s, 3H, OCH_3) ; 3.84 (s, 3H, OCH3). IR ($CHBr_3$) : $\nu_{max.}$ 1705 (C=O) cm^{-1}. [M^+] = 323 a.m.u.

1–Methylindole–2, 3–dicarboxylic anhydride :

1–Methylindole–2, 3–dicarboxylic acid (3 g, 0.014 mol) was refluxed in acetic anhydride (50 ml) for 2 h. After cooling of the reaction mixture, crystals separated, which were collected, dried, and recrystallised from acetic anhydride to give 1–methylindole–2, 3 –dicarboxylic anhydride (2.6 g, 94.5 %), m.p. 208 °C [lit. [28] m.p. 209 °C]. ^{1}H-NMR ($CDCl_3$) : δ 7.20–8.00 (m, 4H, H_{4-7}) ; 4.00 (s, 3H, NCH_3). IR (nujol) : $\nu_{max.}$ 1755, 1830 cm^{-1}. [M^+] = 201 a.m.u.

The attempted preparation of 2–ethoxycarbonylindole–3–carboxylic acid.

Method A:

Potassium permanganate (2.1 g, 0.014 mol) in a acetone-water mixture (1:1 250 ml) was added with stirring over 3 h to ethyl 3–formylindole–2–carboxylate (1 g, 4.6 mmol) in acetone (150 ml). The resulting mixture was treated with $NaHSO_3$ (75 ml, 10 %) in 1M HCl (w/w), and the clear solution was extracted with dichloromethane (3 x 50 ml). The organic phase was dried (MgSO4), and evaporated under reduced pressure. After crystallisation of the residue, we recovered only starting material, ethyl 3–formylindole –2–carboxylate (1.75 g, 83 %).

Method B :

Ethyl 3–formylindole–2–carboxylate (1g, 4.6 mmol) was dissolved in ethanol (50 ml) and made alkaline with aqueous sodium hydroxide (0.25 N, 5 ml). Potassium permanganate (7.56 g, 0.048 mol) in water (60 ml) was heated to 50–60 °C, and then added to the ethyl 3–formylindole–2 –carboxylate solution with stirring. After 5 min the resulting hot mixture was filtered and the ethanol was evaporated under reduced pressure. The residual product was extracted with diethyl ether (3 x 50 ml) and again extracted with diethyl ether (3 x 50 ml) after acidification with hydrochloric acid. The combined organic phase was dried (MgSO4) and evaporated to dryness. The crude product was crystallised from ethanol to give starting material (0.8g, 80 %).

1–Methylindole–2, 3–dicarboxylic acid :

Method A :

A suspension of ethyl 3–cyano–1–methyl indole–2–carboxylate (10 g, 0.043 mol) in sodium hydroxide solution (10 N, 75 ml) was refluxed under a stream of nitrogen for 7 h. (Evolution of ammonia diminished in the last hour). The resulting mixture was cooled to –5 °C, diluted with crushed-ice (300 g), and acidified to pH 7.5 with hydrochloric acid (12 N) with stirring and continued cooling. The solution was extracted with ethyl acetate (3 x 150 ml) to remove impurities. The organic phase was stirred at 5 °C and acidified to pH 2.0 with hydrochloric acid (2N). The precipitate was collected, and dried, and recrystallised from *iso*–propanol to give 1–methylindole–2, 3–dicarboxylic acid (5 g, 53 %), as white solid, m.p. 208 °C [lit. [28] m.p. 218 °C, lit. [30] m.p. 208–9 °C]. ^{1}H-NMR (DMSO–d_6) : δ 13.05 (s, 2H, COOH) ; 7.27–8.16 (m, 4H, H_{4-7}) ; 3.90 (s, 3H, CH_3–N). IR ($CHBr_3$) : $\nu_{max.}$ 3200–3450 (br, OH), 1700 (C=O) cm^{-1}.

Method B :

Dimethyl 1–methylindole–2, 3–dicarboxylate (2 g, 8.089 mmol) in ethanolic potassium hydroxide solution (0.5 N, 100 ml) was refluxed for 2 h. After cooling, the precipitated potassium salt of 1–methylindole–2, 3–dicarboxylic acid was collected, washed with ethanol (100 ml), and dried. The salt was dissolved in water (20 ml), acidified with diluted hydrochloric acid solution. The white precipitate was collected, dried and recrystallised from *iso*–propanol to give 1–methylindole–2, 3–dicarboxylic acid (1.6 g, 90 %), as a white solid, which was identical with that obtained from method A.

Ethyl 3–cyanoindole–2–carboxylate :

Ethyl 3–formylindole–2–carboxylate (1 g, 4.6 mmol) and hydroxylamine hydrochloride (0,416 g, 5.98 mmol) in formic acid were refluxed for 30 min and then allowed to cool to room temperature. The mixture was diluted with ice-water (100 g), neutralised with sodium hydroxide solution (5 %), and extracted with diethyl ether (3 x 50 ml). The organic phase was dried ($MgSO_4$), was evaporated to dryness and the residue was crystallised from ethanol to give *ethyl 3–cyanoindole–2–carboxylate* (0.9 g, 92 %), as a brown solid, m.p. 165–166 °C. ^{1}H-NMR ($CDCl_3$) : δ 7.20–8.00 (m, 4H, H_{4-7}) ; 4.32 –4.80 (q, 2H, OCH_2–C) ; 1.32–1.72 (t, 3H, O–C–CH_3). IR (nujol) : $\nu_{max.}$ 3290 (NH), 2210 (CN), 1690 (C=O) cm^{-1}. [M^+] = 214 a.m.u. (Found : C, 66.0 ; H, 4.7 ; N, 12.7 ; $C_{12}H_{10}N_2O_2$ requires C, 67.3; H, 4.7 ; N, 13.1 %).

Ethyl 3–cyano–1–methylindole–2–carboxylate :

Ethyl 3–formyl–1–methylindole–2–carboxylate (30 g, 0.1297 mol) and hydroxylamine hydrochloride (11.716 g, 0.1686 mol) in formic acid (100 ml) were refluxed for 30 min and then allowed to cool to room temperature. The mixture was diluted with ice–water (500 g), neutralised with sodium hydroxide solution (5 %), and extracted with diethyl ether (3 x 250 ml). The organic phase was dried (MgSO4), and the solvent was removed under reduced pressure. The residue was crystallised from ethanol to give *ethyl 3–cyano –1– methylindole–2–carboxylate* (28 g, 95 %), as yellow needles, m.p. 128–9 °C. ^{1}H-NMR ($CDCl_3$) : δ 7.60 – 7.92 (m, 1H, H_4) ; 7.20–7.60 (m, 3H, H_{5-7}) ; 4.24–4.72 (q, 2H, O–CH_2–C) ; 4.12 (s, 3H, NCH_3) ; 1.32–1.70 (t, 3H, O–C–CH_3). IR ($CHBr_3$) : $\nu_{max.}$ 2210 (s, CN), 1715 (C=O) cm^{-1}. [M^+] = 228 a.m.u. (Found : C, 68.0 ; H, 5.2 ; N, 12.2 ; $C_{13}H_{12}N_2O_2$ requires C, 68.4 ; H, 5.3 ; N, 12.3 %)

1, 4–Dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino[4, 5–*b*]indole :

Hydrazine hydrate (5 g, 0.1 mol) was added to a solution of dimethyl indole–2, 3 –dicarboxylate (5 g, 0.021 mol) in a minimal amount of boiling ethanol dropwise. The reaction mixture was refluxed for 10 h. After cooling a precipitate formed and was collected. The solid material was dissolved in warm ammonium hydroxide (60 °C, 10 %) and the product was again precipitated by neutralisation with hydrochloric acid (1 N). The precipitated product was successively washed with hydrochloric acid (1 N, 5 x 20 ml), water (5 x 20 ml), and warm ethanol (5 x 20 ml) and then dried. Recrystallisation of the compound from DMF-water gave 1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino [4, 5–*b*] indole, (3 g, 70 %), m.p. >330 ° C [lit. [18] m.p. 330 °C, lit. [17] m.p. 360 °C]. ^{1}H-NMR(DMSO-d_6) : δ 12.56 (s, 1H, NH) ; 11.40 (s, 2H, CONH) ; 8.08–8.30 (m, 1H, H_9) ; 7.30–7.90 (m, 3H, H_{6-8}). IR (nujol) : $\nu_{max.}$ 3050–3300 (br, NH, OH), 1635, 1645 (C=O), 1590, 1635 (C=N, C=C) cm^{-1} . [M^+] = 201 a.m.u. (Found : C, 59.5 ; H, 3.5 ; N, 20.9 ; calc. for $C_{10}H_7N_3O_2$ C, 59.7 ; H, 3.5 ; N, 20.9 %).

1, 4–Dioxo–5–methyl–1, 2, 3, 4–tetrahydro–5*H*–pyridazino(4, 5–*b*)indole :
Hydrazine hydrate (10 g, 0.2 mol) was added to a solution of dimethyl 1–methylindole –2, 3–dicarboxylate (3 g, 0.012 mol) in boiling *iso*–propanol (50 ml) dropwise. Concentrated hydrochloric acid (5 ml) was added and the resulting mixture was refluxed for 24 h. On cooling, a precipitate formed and was collected , washed with water (5 x 20 ml) and ethanol (5 x 20 ml), and dried. Recrystallisation of the compound from DMF afforded pure *1, 4–dioxo–5– methyl–1, 2, 3, 4 –tetrahydro–5H–pyridazino[4, 5– b] indole* (2.1 g, 81.4 %), as a white solid, m.p. > 325 °C. ^{1}H-NMR (DMSO-d_6) : δ 11.60 (s, 2H, CONH), 8.10–8.35 (m, 1H, H_9) ; 7.20–7.80 (m, 3H, H_{6-8}) ; 4.20 (s, 3H, NCH3). IR (nujol) : $\nu_{max.}$ 2700–3300 (br, NH, OH), 1655 (C=O), 1625 (C=N) cm^{-1}. [M^+] = 215 a.m.u. (Found : C, 61.2 ; H, 4.2 ; N, 19.5 ; $C_{11}H_9N_3O_2$ requires C, 61.4 ; H, 4.2 ; N, 19.5 %).

Attempted preparation of 1, 4–dioxo–2, 3–dimethyl–1, 2, 3, 4–tetrahydro – 5*H*–pyridazino(4, 5–*b*) indole :
Dimethyl indole–2, 3–dicarboxylate (1 g, 4.29 mmol) and 1, 2–dimethylhydrazine dihydrochloride (2.28 g , 0.017 mol), and sodium acetate (2.8 g, 0.034 mol) were refluxed in *iso*-propanol (50 ml) for 7 days. After the cooling, the precipitate was collected, washed with ethanol (50 ml) and well water, and dried. Recrystallisation of the compound from ethanol gave only starting material (0.9g, 90 %).

1, 4–Dioxo –1, 2, 3, 4–tetrahydro–2, 3, 5–trimethyl–5*H*–pyridazino(4, 5–*b*) indole :
1–Methylindole–2, 3–dicarboxylic anhydride (1 g, 4.97 mmol), 1, 2–dimethylhydrazine dihydrochloride (6.61 g , 0.0497 mol), and sodium acetate (8.15 g , 0.099 mol) were refluxed in 2–ethoxyethanol–water mixture (1:1 50 ml) for 24 h. After cooling, the precipitate was collected, washed well with water, and dried. Recrystallisation of the residue from 2–ethoxy ethanol-ethanol afforded *1, 4–dioxo–1, 2, 3, 4–tetrahydro–2, 3, 5 – trimethyl–5H–pyridazino[4, 5– b]indole* (0.6 g, 50 %), as white needles, m.p. 222 °C. ^{1}H-NMR ($CDCl_3$) : δ 8.20–8.48 (m, 1H, H_9) ; 7.20–7.60 (m, 3H, H_{6-8}) ; 4.20 (s, 3H, N–CH_3 indole) ; 3.70 (s, 6H, O=C–NCH_3). IR (nujol) : $\nu_{max.}$ 1640, 1660 (C=O), 1610 (C=C) cm^{-1}. [M^+] = 243.1 a.m.u. (Found : C, 64.3 ; H, 5.5 : N, 17.3 ; $C_{13}H_{13}N_3O_2$ requires C, 64.2 ; H, 5.4 ; N, 17.3 %).

1, 2–Dihydro–2, 5–dimethyl–4–methoxy–1–oxo–5*H*–pyridazino(4, 5–*b*)indole
4–Methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (0.6 g, 2.81 mmol) and methyl iodide (0.8 g, 5.63 mmol) were refluxed in methanol (50 ml) for 1 h. The residue, resulting from evaporation of solvent, was refluxed for 30 min with a mixture of dioxane (30 ml), water (30 ml), potassium hydroxide (5.84 g, 0.104 mol), and potassium ferricyanide (2.32 g, 2.815 mmol). The cooled mixture was diluted with water (100 ml) and the precipitate was collected, washed with water, and dried. Recrystallisation of the

residue from ethanol gave *1, 2–dihydro–2, 5–dimethyl–4–methoxy–1–oxo– 5H –pyridazino[4, 5– b]indole* (0.35 g, 51 %), as a white solid, m.p. 198 °C. ^{1}H-NMR (DMSO-d_6) : δ 8.30–860 (m, 1H, H_9) ; 7.200–7.60(m, 3H, H_{6-8}) ; 4.00 (s, 6H, N–CH_3 indole, and OCH_3) ; 3.80 (s, 3H, O=C–N– CH_3). IR (nujol) : $\nu_{max.}$ 1640 (C=O), 1600, 1620 (C=N, C=C)) cm^{-1}. [M$^+$] = 243 a.m.u. (Found : C, 64.1 ; H, 5.4 ; N, 17.2 ; $C_{13}H_{13}N_3O_2$ requires C, 64.2 ; H, 5.4 ; N, 17.3 %).

3, 4–Dihydro–3, 5–dimethyl–1–methoxy–4–oxo–5*H*–pyridazino(4, 5–*b*)indole : Method A :

1–Methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (0.4 g, 1.876 mmol) and methyl iodide (0.53 g, 3.75 mmol) were refluxed for 1 h in methanol (50 ml). The residue obtained from evaporation of solvent was refluxed 30 min. with a mixture of dioxane (30 ml), water (30 ml), potassium hydroxide (3.89 g, 0.069 mol), and potassium ferricyanide (1.544 g, 4.69 mmol). The cooled reaction mixture was diluted with water (100 ml) and the precipitate formed was collected, washed well with water, and dried. Recrystallisation of the residue from ethanol gave *3, 4–dihydro–3, 5– dimethyl–1– methoxy–4–oxo–5H –pyridazino[4, 5– b]indole* (0.4 g , 87.7 %), as a white solid, m.p. 189–9 °C, ^{1}H-NMR ($CDCl_3$) : δ 7.90–8.16 (dd, 1H, H_9) ; 720–7.60 (m, 3H, H_{6-8}) ; 4.24 (s, 3H, OCH_3) ; 4.00 (s, 3H, NCH_3 indole) ; 3.76 (s, 3H, O=C–N–CH_3). IR (nujol) : $\nu_{max.}$ 1645 (C=O), 1580 (C=N, C=C) cm^{-1}. [M$^+$] = 243 a.m.u. (Found : C, 64.0 ; H, 5.4 ; N, 17.1 ; $C_{13}H_{13}N_3O_2$ requires C, 64.2 ; H, 5.4 ; N, 17.3 %).

Method B :

A mixture of 2, 5–dimethyl–1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino[4, 5–*b*] indole (0.95 g, 4.14 mmol), anhydrous potassium carbonate (15.58 g , 0.112 mol), and dimethyl sulphate (1.7 g, 0.014 mol) in acetone (50 ml) was refluxed with stirring. The addition of an excess of ammonium hydroxide solution (10 %) to the cooled reaction mixture neutralised any remaining reagent. Most of the acetone was removed under reduced pressure and water was added to the residue to dissolve the potassium carbonate. The aqueous mixture was extracted with dichloromethane (3 x 50 ml) and the organic extracts were dried ($MgSO_4$). The solvent was removed under reduced pressure to dryness and the residue was crystallised from 2–ethoxyethanol to give 3, 4–dihydro–3, 5 –dimethyl–1–methoxy–5*H*–pyridazino[4, 5–*b*]indole, (0.9 g , 89 %). IR , NMR, and mass spectra, m.p. , pKa are identical with that obtained by method A.

3, 5–Dimethyl–1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino(4, 5–*b*)indole Method A :

3, 4–Dihydro–3, 5–dimethyl–1–methoxy–4–oxo–5*H*–pyridazino[4, 5–*b*]indole (0.15 g, 6.17 mmol) in a mixture of concentrated hydrochloric acid (30 ml) and methanol (10 ml) was refluxed for 12 h Solvent was evaporated under reduced pressure. To the residue, water was added, the precipitate was collected, and dried. Recrystallisation of the residue

from DMF-ethanol gave *3, 5– dimethyl–1, 4–dioxo–1, 2, 3, 4–tetrahydro–5H –pyridazino[4, 5– b]indole* (0.1 g , 71 %), as a white solid, m.p. 305 °C (decomp.). ^{1}H-NMR (DMSO-d_6) : δ 8.12–8.36 (m, 1H, H_9) ; 7.40–7.80 (m, 3H, H_{6-8}) ; 4.36 (s, 3H, NCH_3 indole) ; 3.92 (s, 3H, O=C–N–CH_3). IR (nujol) : $\nu_{max.}$ 1630, 1640 (C=O), 1585, 1615 (C=N, C=C) cm^{-1}. [M^+] = 229 a.m.u. (Found : C, 62.9 ; H, 4.7 ; N, 18.3 ; $C_{12}H_{11}N_3O_2$ requires C, 62.9 ; H, 4.8 ; N, 18.3 %).

Method B :

Dimethyl 1–methylindole–2, 3–dicarboxylate (1 g, 4.044 mmol) and methylhydrazine (0.93 g, 0.02 mol) were refluxed in *iso*–propanol for 4 days. Solvent was removed under reduced pressure . Water (100 ml) was added to the residue. The precipitate was filtered, washed well with water and dried. The crystallisation of the crude compound from DMF–EtOH gave only *3, 5–dimethyl–1, 4–dioxo –1, 2, 3, 4–tetrahydro–5H–pyridazino [4, 5– b]indole* (0.5 g, 54%), as a white crystal, which was identical with that obtained method A above.

2, 5–Dimethyl–1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino(4, 5–*b*)indole

1, 2– Dihydro–2, 5–dimethyl–4–methoxy–1–oxo–5*H*–pyridazino[4, 5–*b*]indole (0.15 g, 6.17 mmol) in a mixture of concentrated hydrochloric acid (30 ml) and methanol (10 ml) was refluxed for 24 h. Solvent was removed under reduced pressure. Water was added to the residue and the precipitate was collected, dried. Recrystallisation of the compound from ethanol–water gave *2, 5 –dimethyl–1, 4– dioxo–1, 2, 3, 4–tetrahydro–5H –pyridazino[4, 5– b]indole* (90 mg, 64 %), as a white solid, m.p. 305–7 °C. ^{1}H-NMR (DMSO-d_6) : δ 8.30–8.60 (m, 1H, H_9) ; 7.60–7.90 (m, 3H, H_{6-8}) ; 4.38 (s, 3H, NCH_3 indole) ; 4.10 (s, 3H, O=C–N–CH_3). IR (nujol) : $\nu_{max.}$ 3100–3500 (br. , NH, OH), 1630, 1640 (C=O), 1615 (C=N) cm^{-1}. [M^+] = 229 a.m.u. (Found : C, 61.8 ; H, 5.0 ; N, 17.5 ; $C_{12}H_{11}N_3O_2$ requires C, 62.9 ; H, 4.8 ; N, 18.3).

The Attempted preparation of 5–benzyl–1, 4–dioxo–1, 2, 3, 4–tetrahydro–5*H* –pyridazino(4, 5–*b*) indole :

Hydrazine hydrate (1.86 g, 0.037 mol) was added dropwise to a solution of dimethyl 1–benzylindole–2, 3–dicarboxylate (3 g, 9.278 mmol) in boiling *iso*–propanol (50 ml). The reaction mixture was refluxed 24 h. On cooling, the white crystalline product was collected, washed with water (100 ml) and ethanol (100 ml), and dried. Recrystallisation of the compound from *iso*–propanol gave *1–benzylindole–2, 3–dicarbonylhydrazide* (2.5 g, 92.5 %), as white needles, m.p. 328 °C. ^{1}H-NMR (DMSO–d_6) : δ 8.00–8.30 (m, 1H, H_4) ; 7.10–7.60 (m, 8H, $H_{5-7\ and\ -Ph}$) ; 6.04 (s, 2H, N–$C\underline{H}_2$–Ph). IR ($CHBr_3$) : $\nu_{max.}$ 3120 and 3260 (br, NH), 1625 (C=O) cm^{-1}. [M^+] = 323 a.m.u. (Found : 63.0 ; H, 5.4 ; N, 21.7 ; $C_{17}H_{17}N_5O_2$ requires C, 63.2; H, 5.3 ; N, 21.7 %).

The Attempted preparation of 5-benzyl-1, 4-dioxo-1, 2, 3, 4-tetrahydro-5*H*-pyridazino(4, 5-*b*)indole :

Hydrazine hydrate (10 g, 0.2 mol) was added dropwise to a solution of dimethyl 1–benzylindole–2, 3–dicarboxylate (5 g, 0.016 mol) in boiling 2–ethoxyethanol (50 ml). The reaction mixture was refluxed for 4 days. On cooling, white crystals formed and were collected, washed with water (200 ml) and ethanol (200 ml), and dried. Recrystallisation of the compound from 2–ethoxyethanol gave only *1–benzylindole–2, 3–dicarbonyl hydrazide* (4.5 g, 100%).

Preparation of 5-benzyl-1, 4-dioxo-1, 2, 3, 4-tetrahydro-5*H*-pyridazino (4, 5-*b*) indole :

1–Benzylindole–2, 3–dicarbonylhydrazide (4.5 g, 0.0139 mol) was refluxed in acetic acid (100 ml) for 24 h. After cooling, white crystals formed and was collected, washed water (200 ml) and ethanol(200 ml), and dried. Recrystallisation of the compound from 2–ethoxyethanol gave *5–benzyl–1, 4–dioxo–1, 2, 3, 4–tetrahydro–5H–pyridazino [4, 5–b]indole* (4 g, 99%), as white needles, m.p. 322 °C. ^{1}H-NMR (DMSO–d_6) : δ 8.00–830 (m, 1H, H_9) ; 7.20–7.60 (m, 8H, $H_{6-8 \text{ and } -Ph}$) ; 6.00 (s, 2H, N–CH_{2-Ph}). IR ($CHBr_3$) : $\nu_{max.}$ 2500–3300 (br, NH, OH), 1670 (C=O), 1625 (C=N, C=C) cm^{-1}. $[M^+]$ = 291 a.m.u. (Found : C, 70.0 ; H, 4.4 ; N, 14.4 ; $C_{17}H_{13}N_3O_2$ requires C, 70.1 ; H, 4.5 ; N, 14.4 %).

The synthesis of **1, 4-Dimethoxy-5-methyl-5*H*-pyridazino(4, 5- b)indole** is described in detail in chapter V.

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Chapter V

Chloro-5*H*-pyridazino(4, 5-*b*)indoles

1. 0 Halopyridazines

The ease of preparation and the reactivity of halopyridazines have been the subject of detailed reviews. [1, 2] Not only do these compounds serve as intermediates for a wide variety of syntheses, but many halopyridazines have also shown biological activity. In particular, they have been reported to be herbicides, fungicides, and antituberculosis, antitumor and antimicrobial agents.

Halopyridazines are prepared [1, 2] almost exclusively from the corresponding pyridazinones, using phosphorus oxychloride, phosphorus pentachloride, phosphorus oxybromide, or phosphorus pentabromide. Several other methods involve the nucleophilic replacement of other groups, such as $-NO_2$ and $-N_2^+$ or the oxidation of a hydrazino group with sodium hypochlorite. The reaction of active bromo compounds with pyridazine N–oxides (8) and the reaction of bromine with pyridazines and pyridazinones (12) have also been used successfully in the synthesis of bromopyridazines and dihydropyridazines. A further widely used procedure for the preparation of halopyridazines is through the ring closure of halogen containing precursors with hydrazine or substituted hydrazines (14) $\rightarrow$ (15).

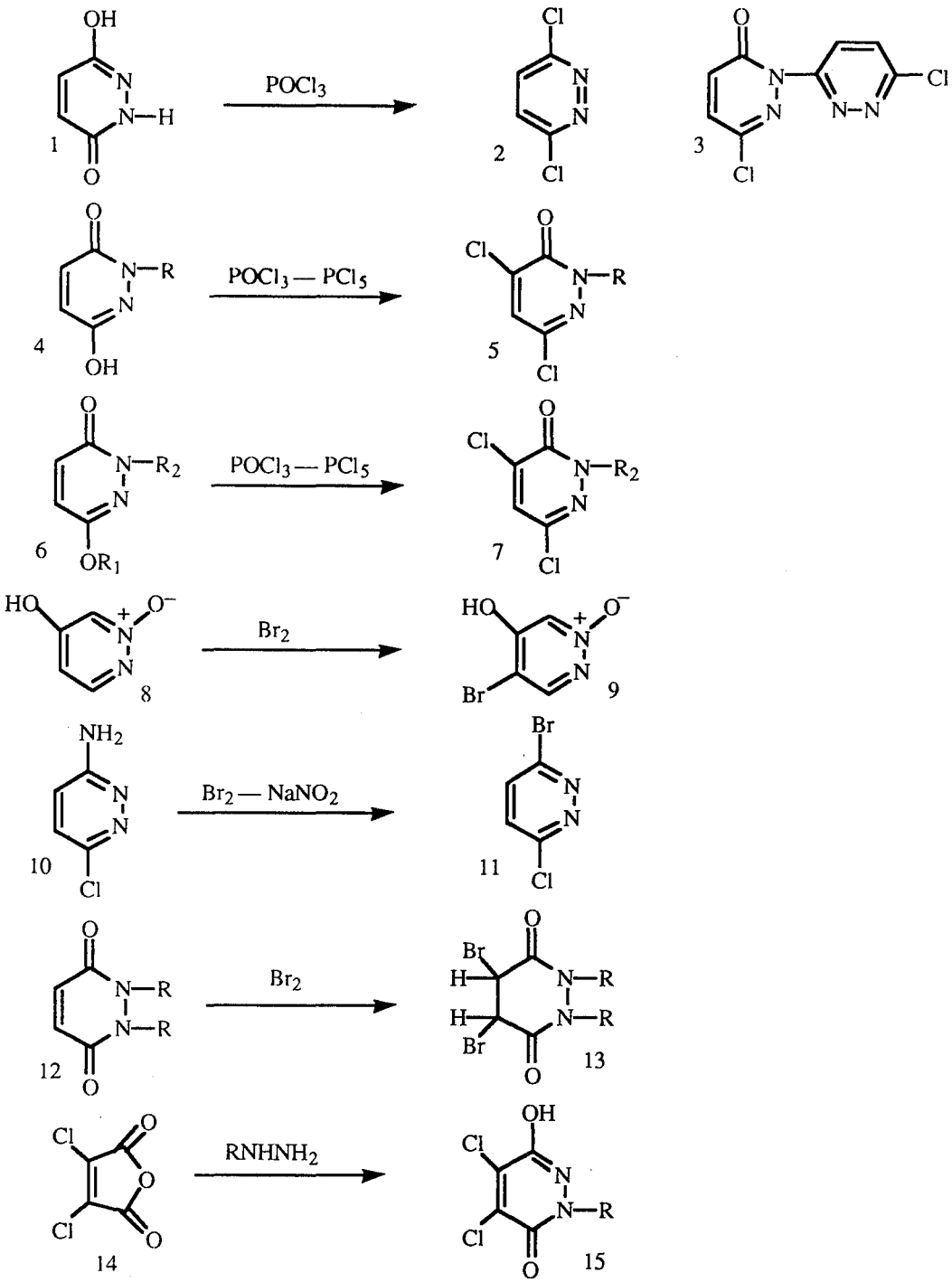
A dimeric side product (3) is often formed in the reaction of pyridazinones with phosphorus oxychloride (1) $\rightarrow$ (2). Feuer and Rubinstein [3] reported that the dimeric products were not produced directly from the reaction of maleic hydrazide and phosphorus oxychloride. In addition to the nucleophilic reaction of the C = O site of the pyridazinones, it has been noted that a combination of phosphorus oxychloride and phosphorus pentachloride result in the substitution of chlorine on the ring, as illustrated in the examples (4) $\rightarrow$ (5) and (6) $\rightarrow$ (7). The replacement of a methoxy group by chlorine has also been observed. [4]

Halogenated pyridazines play an important part in pyridazine chemistry since nucleophilic displacement of the halogen with variety of nucleophiles is possible. However, the reactivity of the halopyridazines towards nucleophilic attack is known to be affected by both the nature and the position of the halogen and other substituents and also the nature of the nucleophile and the reaction conditions.

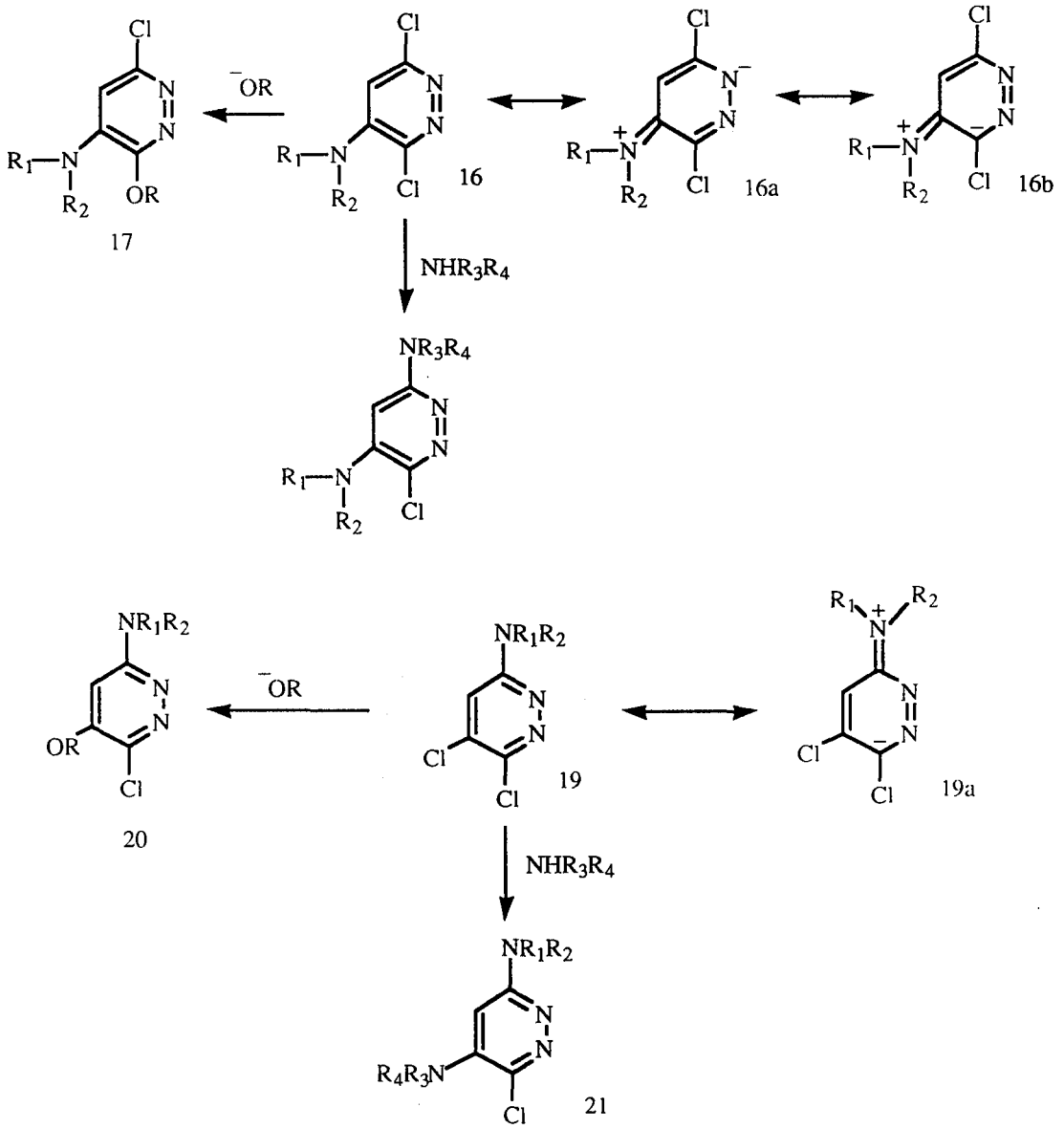
As a result of activation by the additional halogens, 3, 6–dihydropyridazines and related polyhalogenated pyridazines are more reactive. One chlorine of 3, 6–dichloro pyridazine is replaced by nucleophiles more readily than the other. This effect is due to the electron–releasing effect of the incoming group which counteracts the electron deficient character of the pyridazine ring. For example, 3, 6–dichloropyridazine is hydrolysed rapidly with hot aqueous sodium hydroxide solution to give 6–chloro–(2*H*)–pyridazine –3–one, [4, 5] whilst the second chlorine atom remains unaffected even after several hours.

It has been claimed by Fenton [6] that the course of those reactions is governed by steric factors. Nucleophilic substitution by alkoxide ions and by dimethylamine on 4–dialkylamino–3, 6–dichloropyridazines (16) result in the selective displacement of the chlorine atom. Secondary amines replace the chlorine atom of the 6–position, which is

explicable in terms of the deactivation of the 3–position to nucleophilic attack. However, in contrast, alkoxide ions yield 3–alkoxy derivatives, in due to possibly steric control of the reaction . In the case of compound (19) both nucleophiles replace the chlorine atom of the 4–position. This obviously is not a sterically controlled reaction and is best explained in terms of the resonance form (19a) in which the 3–position is deactivated to nucleophilic attack. However, the increase in the double bond character of the N=N bond introduces an unfavourable interaction of the nitrogen lone pairs, which would tend to increase the energy of (19a). Similarly (16b) should be a less important canonical structure, compared with (16a), and the formation of (17) should not too unexpected on electronic grounds (Scheme V. 2).

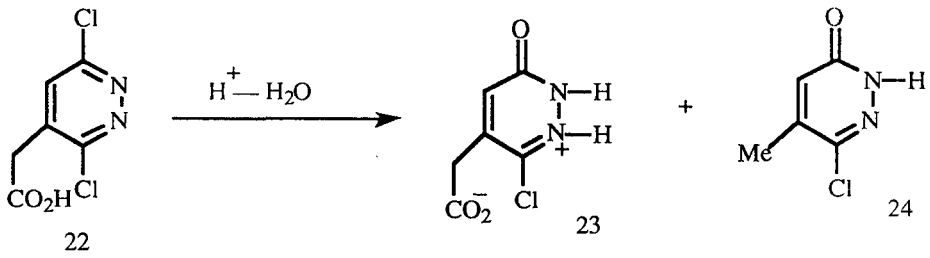

OH
N
N–H
O
1
POCl3
Cl
N
N
Cl
2
O
N
N
N–N
Cl
Cl
3
O
N–R
N
OH
4
POCl3 — PCl5
O
Cl
N–R
N
Cl
5
O
N–R2
N
OR1
6
POCl3 — PCl5
O
Cl
N–R2
N
Cl
7
HO
+
O–
N
N
8
Br2
HO
+
O–
N
N
Br
9
NH2
N
N
Cl
10
Br2 — NaNO2
Br
N
N
Cl
11
O
N–R
N–R
O
12
Br2
O
Br
H
N–R
H
N–R
Br
O
13
Cl
O
O
Cl
O
14
RNHNH2
OH
Cl
N
N–R
Cl
O
15

Scheme V. 1



Scheme V. 2

The reactivity of the monochloro diazines has been studied by Chan and Miller, [7] who reported that the order of reactivity with nucleophiles is 2–chloropyrimidine > 4–chloropyrimidine > 4–chloropyridazine ≈ 3–chloropyridazine ≈ 2–chloropyridazine. All of those compounds are more susceptible to nucleophilic attack than the 3–chloro–1 –methylpyridinium ion. The reactivity of halopyridazines is also increased with an increase in the electronegativity of the annular nitrogen atom in the order N < N^+– O^- < N^+–Me. Thus, for example, the facile hydrolysis of the dichloro–derivative (22), in acidic media, has been considered to occur *via* initial protonation of the ring, which aids nucleophilic attack at both the 3–and 6–position [8] (Scheme V. 3).

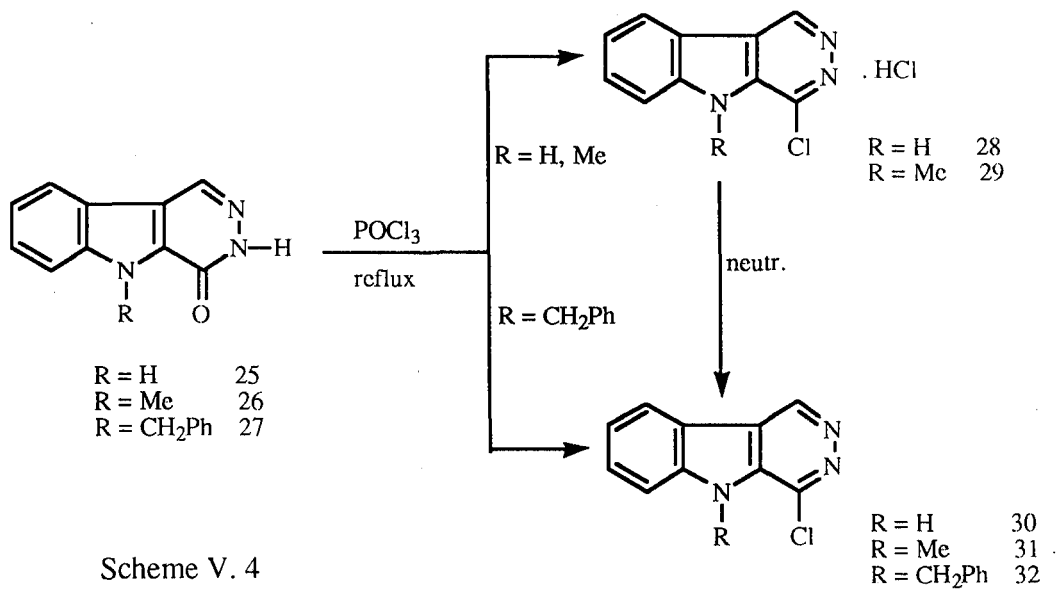


Scheme V. 3

2. 0 1- And, 4-Chloro and 1, 4-Dichloro-5*H*-pyridazino[4, 5-*b*]indoles

2. 1 Synthesis of 4-Chloro-5*H*-pyridazino[4, 5-*b*]indoles

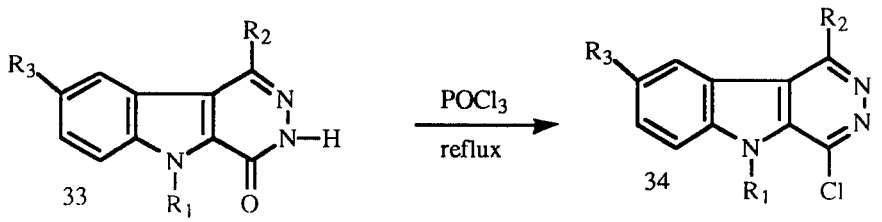
4-Chloro-5*H*-pyridazino[4, 5-*b*]indoles (30), [9, 10, 11] (31), [9, 10, 11] and (32) were prepared from the reaction of the corresponding 3, 4-dihydro-4-oxo-5*H* -pyridazino[4, 5-*b*]indoles (25, (26), and (27) with phosphorus oxychloride (Scheme V. 4 and Chapter II). 4-Chloro-5*H*-pyridazino[4, 5-*b*]indole (30) and its 5-methyl derivative (31) were obtained by hydrolysis of the monohydrochloride salts of the corresponding chloro-5*H*-pyridazino[4, 5-*b*]indoles (28) and (29), whereas, the 5-benzyl derivative (32) was obtained as free base (Scheme V. 4). Although the melting points of 4-chloro-5*H*-pyridazino[4, 5-*b*]indole (30) (> 325 °C) and 4-chloro -5-methyl-5*H*-pyridazino[4, 5-*b*]indole (31) (199-200 °C) are inconsistent with those (273 °C and 181 °C, respectively) reported by Suvarov,[10] the structures of (30) and (31) were confirmed by infrared spectroscopy, nuclear magnetic spectroscopy, mass spectroscopic data, and elemental analysis. The structure of 5-benzyl-4-chloro-5*H* -pyridazino[4, 5-*b*]indole (32) was also confirmed by IR, ^{1}H-NMR, and mass spectroscopic data and elemental analysis in which there is a slight deviation from the theoretical value in carbon analysis.



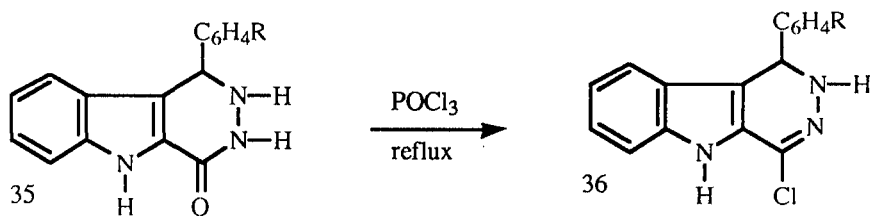
Scheme V. 4

Several 4–chloro–5*H*–pyridazino[4, 5–*b*]indoles (34) and (36) have been reported in the literature [11–16] (Scheme V. 5).

Hiremath [14] has claimed that 6–bromo–3, 4–dihydro–8–methyl–4–oxo–5*H* –pyridazino[4, 5–*b*]indole (37) was unaffected on refluxing with excess of phosphorus oxychloride or phosphorus pentachloride in nitrobenzene and that the corresponding 4–chloro–5*H*–pyridazino[4, 5–*b*] indole (38) was formed. However, on reaction with a equimolar quantity of phosphorus oxychloride and phosphorus pentachloride compound, (39) was isolated (Scheme V. 6).

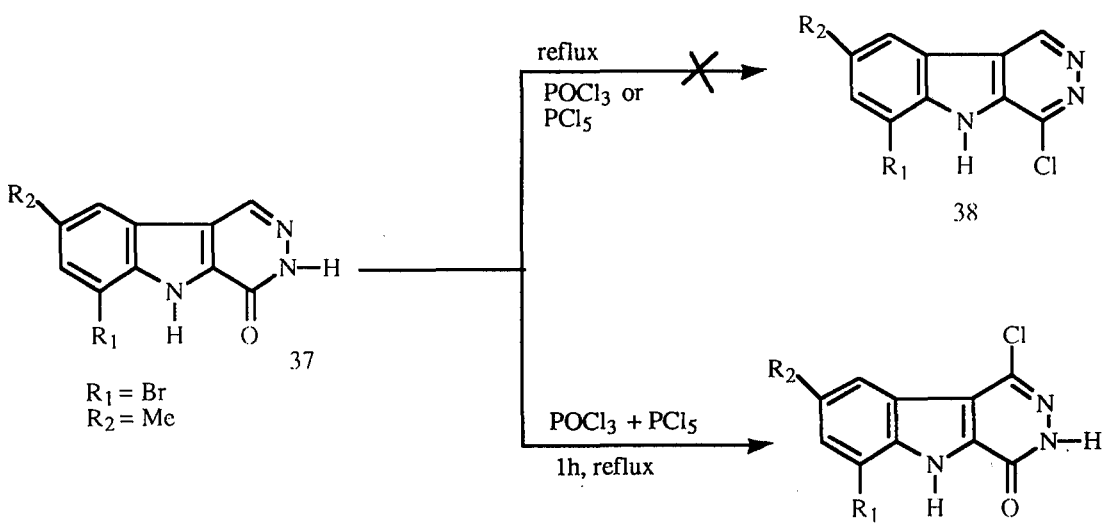


R_1 = H, Me, Et
R_2 = H, C_6H_4R, CH_2Ph
R_3 = H, NO_2 , OCH_2Ph, OMe



R = H, *p*–OMe, *p*–Me, *p*–Cl, *p*–OH, *m*–OMe, *o*–Cl

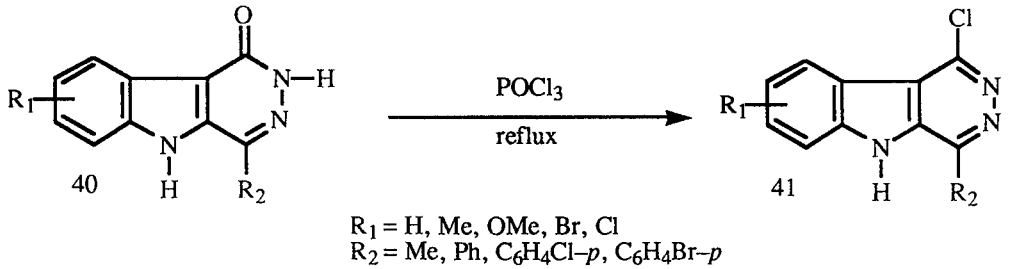
Scheme V. 5



Scheme V. 6

2. 2 Synthesis of 1–Chloro–5*H*–pyridazino[4, 5–*b*]indoles

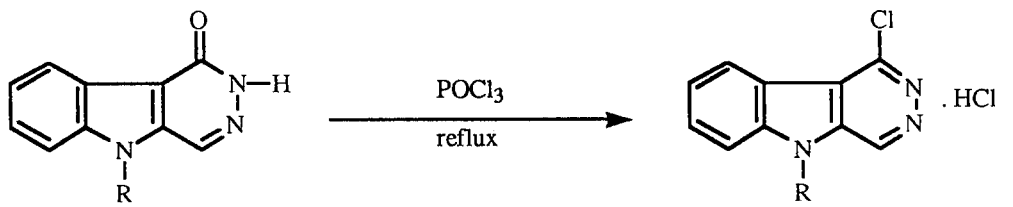
As mentioned earlier in section III. 1. 1 relatively few papers are available on the reactivity of 1, 2–dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*]indoles (40). [17, 19] Thus, there are only a limited number of 1–chloro–5*H*–pyridazino[4, 5–*b*]indoles (41) described in the literature, which were synthesised by Zhungietu [17] (Scheme V. 7).



R_1 = H, Me, OMe, Br, Cl
R_2 = Me, Ph, C_6H_4Cl–*p*, C_6H_4Br–*p*

Scheme V. 7

The parent 1–chloro–5*H*–pyridazino[4, 5–*b*]indole (42) and its 5–methyl derivative (43) were prepared from the corresponding 1, 2–dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*] indoles (44) and (45) (for preparation see Section III. 1. 2) with phosphorus oxychloride. Although we could not obtain satisfactory elemental analysis for compound (42), its structure was confirmed by IR, ^{1}H-NMR, and mass spectroscopy (Scheme V. 8).



R = H 44
R = Me 45

R = H 42
R = Me 43

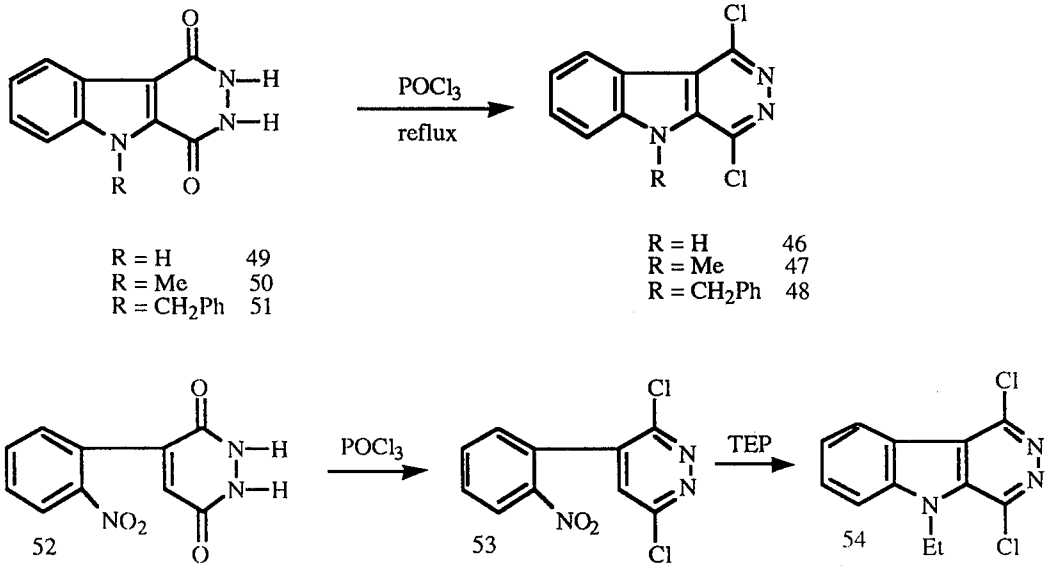
Scheme V. 8

2.3 Synthesis of 1, 4–Dichloro–5*H*–pyridazino[4, 5–*b*]indoles

Only two 1, 4–dichloro–5*H*–pyridazino[4, 5–*b*]indoles (46) and (54) have been described in the literature; both compounds were synthesised by Vega [18] and Kurihara [12] using two different procedures (Scheme V. 9). 1, 4–Dioxo–1, 2, 3, 4–tetrahydro–5*H* –pyridazino[4, 5–*b*]indole (49) was refluxed with phosphorus oxychloride to give the corresponding 1, 4–dichloro–5*H*–pyridazino[4, 5–*b*]indole (46) as the free base. [18] Kurihara [12] synthesised 1, 4–dichloro–5–ethyl–5*H*–pyridazino[4, 5–*b*]indole (54) by the cyclisation of 4–(2–nitrophenyl)–3, 6–dichloropyridazine system (53) with TEP (triethylphosphite) (Scheme V. 9).

1, 4–Dichloro–5*H*–pyridazino[4, 5–*b*]indole (46) was prepared according to the

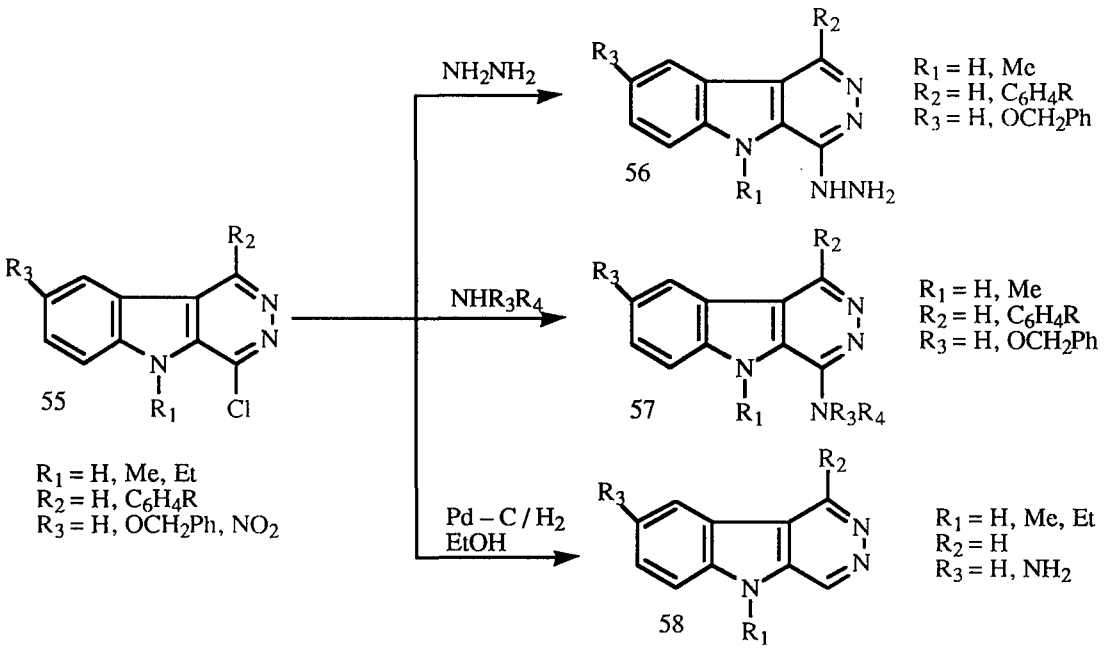
procedure described in the literature. [18] Using the same procedure we also synthesised 5–methyl and 5–benzyl–1, 4–dichloro–5*H*–pyridazino[4, 5–*b*]indoles (47) and (48) (Scheme V.9).



Scheme V. 9

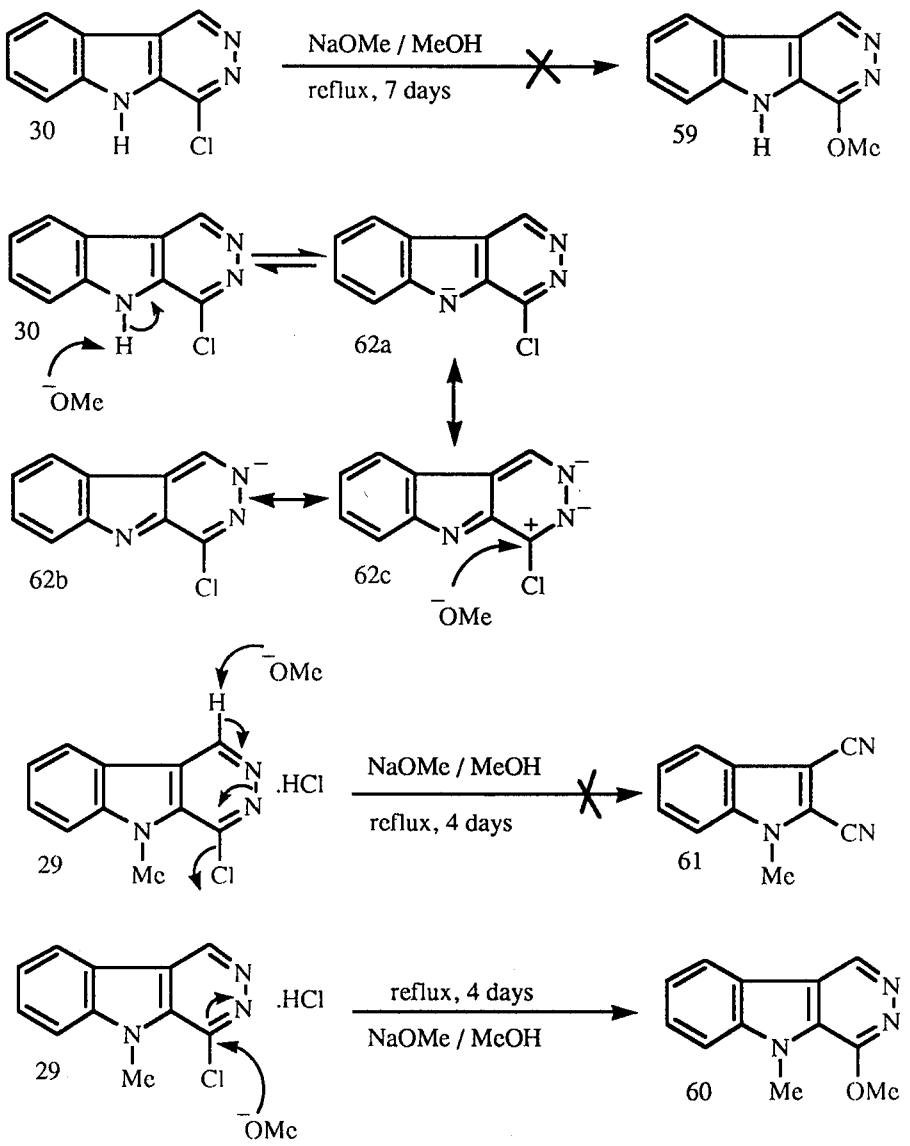
2. 4 Nucleophilic Displacement Reactions and Reduction of 4–Chloro–5*H* –pyridazino(4, 5–*b*)indoles.

The reduction of 4–chloro–5*H*–pyridazino[4, 5–*b*]indoles (55) has been carried out with hydrogen in the presence of Pd–C to give the corresponding 5*H*–pyridazino[4, 5–*b*] indoles (58) [10, 12, 13] (Scheme V. 10) and the reaction of 4–chloro–5*H*–pyridazino [4, 5–*b*]indoles (55) with hydrazine and amines has been reported by Vega [9, 11], Kogan and Vlasova [16] to give corresponding 5*H*–pyridazino[4, 5–*b*]indoles (56), (57), and (58) (Scheme V. 10).



Scheme V. 10

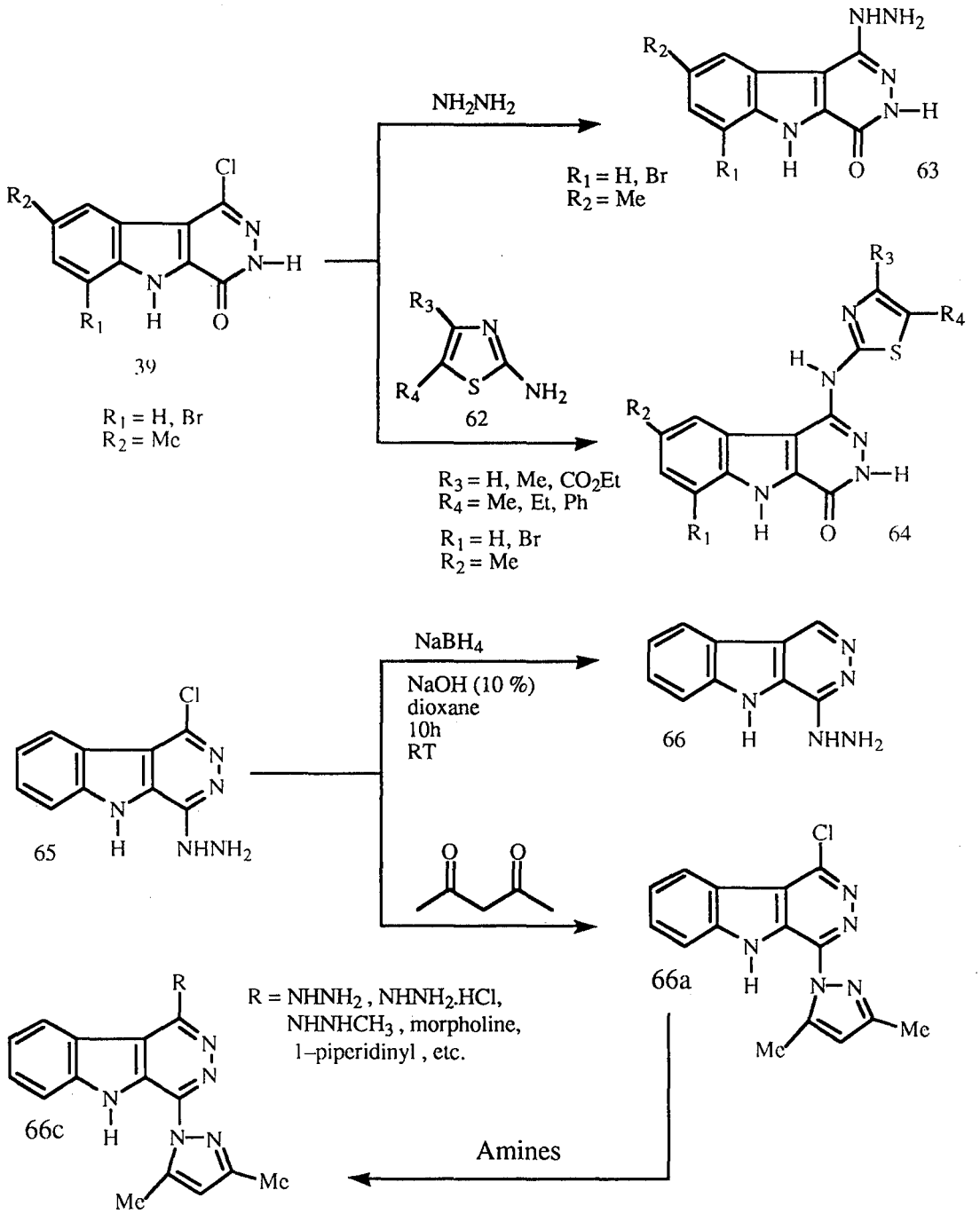
There is no report in the literature of the reaction between 4–chloro–5*H*–pyridazino [4, 5–*b*]indoles and sodium methoxide or sodium ethoxide to give 4–alkoxy–5*H* –pyridazino[4, 5–*b*]indoles. We found that 4–chloro–5*H*–pyridazino[4, 5–*b*]indole (30) failed to give the 4–methoxy–5*H*–pyridazino[4, 5–*b*]indole (59) when refluxed with sodium methoxide in methanol for seven days since the methoxide anion probably generates anion (62) in which two negative charges are adjacent each other (Scheme V. 11). However, when 4–chloro–5–methyl–5*H*–pyridazino[4, 5–*b*]indole monohydro chloride salt (29) was refluxed with sodium methoxide in methanol for 4 days, 4–methoxy –5–methyl–5*H*–pyridazino[4, 5–*b*]indole (60) was obtained in good yield without formation of the side-product (61) (Scheme V. 11).



Scheme V. 11

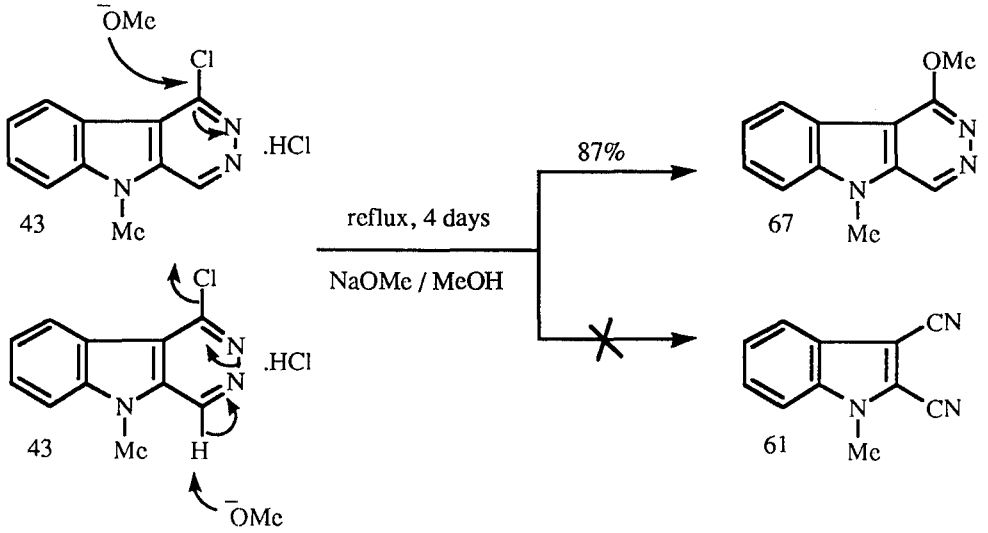
2. 5 Nucleophilic Displacement and Reduction of 1–Chloro–5*H*–pyridazino (4, 5–*b*)indoles

Treatment of 1–chloro–3, 4–dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indole (39) with hydrazine and 2–aminothiazoles (62) has provided the corresponding 1–hydrazino and 1–amino–5*H*–pyridazino[4 , 5–*b*]indoles [14] (63) and (64)(Scheme V. 12) and Vega [18] has reduced 1–chloro–4–hydrazino–5*H*–pyridazino[4, 5–*b*]indole (65) with sodium borohydride to yield 4–hydrazino–5*H*–pyridazino[4, 5–*b*]indole (66) in 51% yield (Scheme V. 12).



Scheme V. 12

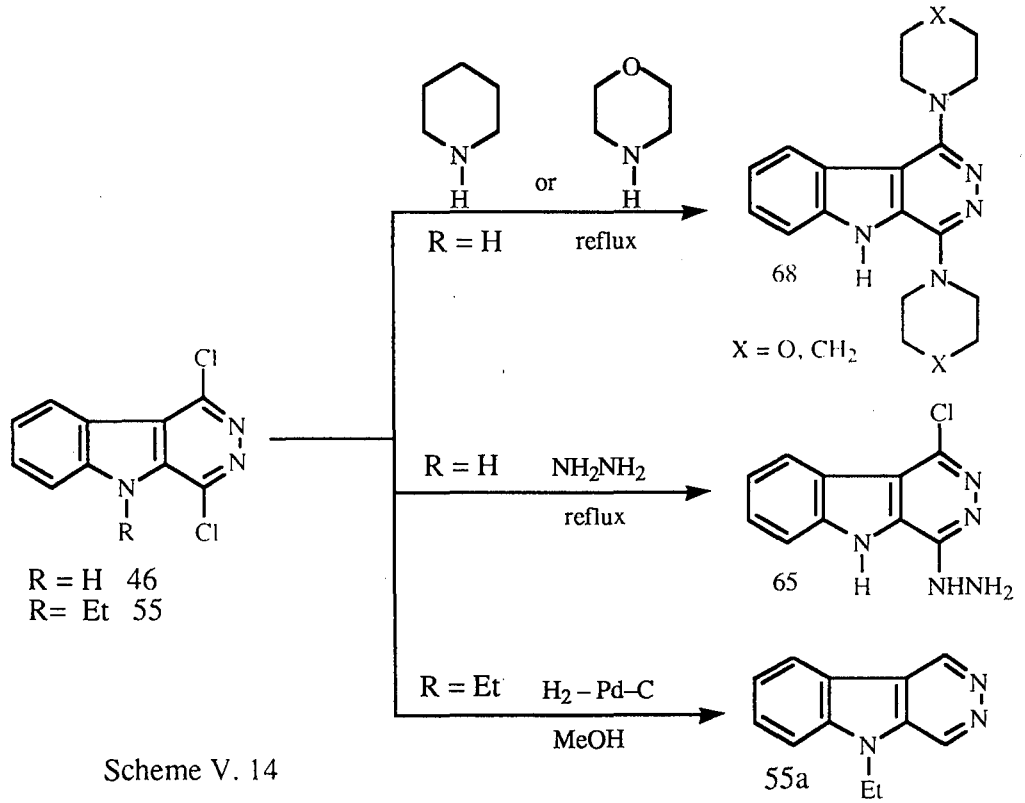
We found that the reaction of 1–chloro–5–methyl–5*H*–pyridazino[4, 5–*b*]indole monohydrochloride salt (43) with sodium methoxide in methanol gave 1–methoxy–5 –methyl–5*H*–pyridazino[4, 5–*b*]indole (67) in 87 % yield. The alternative product (61) was not isolated (Scheme V. 13).



Scheme V. 13

2. 6 Nucleophilic Displacement Reactions and reduction of 1, 4-Dichloro -5*H*-pyridazino(4, 5-*b*)indoles

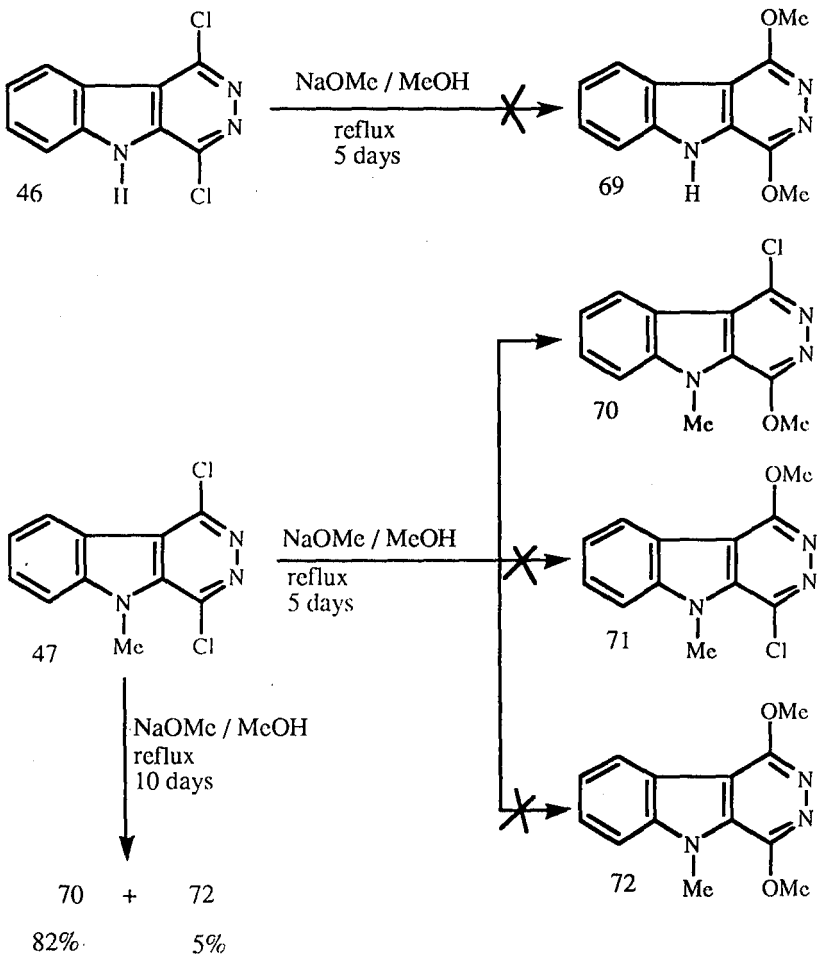
Treatment of 1, 4–dichloro–5*H*–pyridazino[4, 5–*b*]indole (46) with morpholine and piperidine has been reported to give the 1, 4–diamino–derivatives of 5*H*–pyridazino [4, 5–*b*]indole (68) whereas, when hydrazine is used, only 1–chloro–4–hydrazino–5*H* –pyridazino[4, 5–*b*]indole (65) is isolated. [18, 19] Reduction of 1, 4–dichloro–5–ethyl –5*H*–pyridazino[4, 5–*b*]indole (54) with H_2–Pd–C produces 5–ethyl–5*H*–pyridazino [4, 5–*b*]indole (55b) [12] (Scheme V. 14).



Scheme V. 14

We found that when 1, 4–dichloro–5*H*–pyridazino[4, 5–*b*]indole (46) was refluxed with sodium methoxide in methanol for five days, it failed to give the expected 1, 4–dimethoxy–5*H*–pyridazino[4, 5–*b*] indole (69) and only starting material (46) was recovered (Scheme V. 14).

In contrast, 1, 4–dichloro–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (47), when refluxed with sodium methoxide for five days, gave 1–chloro–4–methoxy–5–methyl–5*H* –pyridazino[4, 5–*b*]indole (70). 4–Chloro–1–methoxy–5–methyl–5*H*–pyridazino [4, 5–*b*]indole (71) was not formed due to the lower reactivity of the C(1) atom towards nucleophiles compared with C(2) atom (scheme V.15). Under the same conditions, but an extended reaction time of ten days the reaction gave two compounds (70) (82% yield), and 1, 4–dimethoxy–5*H*–pyridazino[4, 5–*b*]indole (72) in (5% yield) and separated by chromatography (Scheme V. 15).



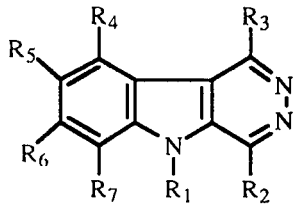
Scheme V. 15

3. 0 Chloro– and Methoxy– 5*H*–pyridazino[4, 5–*b*]indoles– Physical Properties

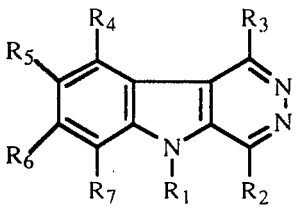
3. 1 ^{1}H-NMR Spectroscopic Measurements

^{1}H-NMR spectra of 1–chloro, 4–chloro, and 1, 4–dichloro–5*H*–pyridazino [4, 5–*b*]indoles and of their methoxy derivatives are presented in the table V. 1.

Table V. 1 ^{1}H-NMR Spectra [d] of Chloro– and Methoxy– 5*H*–pyridazino[4, 5–*b*] indoles



A



B . HCl

R_1	R_2	R_3	Compound	R_1	R_2	R_3	R_4	R_5 R_6 R_7	Solvent
A									
H	Cl	H	30	13.50(s)	—	10.55(s)	8.30–8.70(dd)	7.30 —— 8.10(m)	a
Me	Cl	H	31	4.28(s)	—	9.60(s)	8.00–8.20(dd)	7.20 —— 7.80(m)	b
Bn	Cl	H	32	6.04(s)	—	9.74(s)	8.12–8.32(dd)	6.80 —— 7.80(m)	a
H	Cl	Cl	46	13.50(s)	—	—	8.30–8.45(dd)	7.40 —— 7.85(m)	a
Me	Cl	Cl	47	4.64(s)	—	—	8.50–8.80(dd)	7.80 —— 8.20(m)	c
Bn	Cl	Cl	48	6.38(s)	—	—	8.60–8.90(dd)	7.00 —— 8.20(m)	c
Me	OMe	Cl	70	4.08(s)	4.28(s)	—	8.24–8.50(dd)	7.20 —— 7.80(m)	b
Me	OMe	H	60	4.10(s)	4.32(s)	9.40(s)	7.96–8.20(dd)	7.20 —— 7.60(m)	b
Me	H	OMe	67	3.87(s)	9.10(s)	4.36(s)	8.00–8.30(dd)	7.20 —— 7.80(m)	b
Me	OMe	OMe	72	4.15(s)	4.30(s)	4.25(s)	8.12–8.36(dd)	7.20 —— 7.60(m)	b
B									
H	Cl	H	28	13.50(s)	—	10.55(s)	8.30–8.70(dd)	7.30 —— 8.10(m)	a
Me	Cl	H	29	4.28(s)	—	9.60(s)	8.00–8.20(dd)	7.20 —— 7.80(m)	b
H	H	Cl	42	12.48(s)	9.56(s)	—	8.20–8.50(dd)	7.30 —— 8.10(m)	a
Me	H	Cl	43	4.14(s)	9.94(s)	—	8.35–8.65(dd)	7.70 —— 8.00(m)	a

a. Spectra recorded in DMSO–d_6
b. Spectra recorded in $CDCl_3$
c. Spectra recorded in CF_3COOH
d. Chemical shifts are recorded in ppm down from TMS.

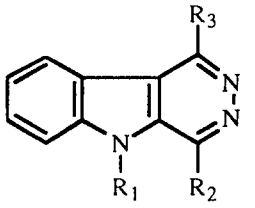
3.2 Infrared Spectroscopic Measurements

Infrared spectra of 1–chloro, 4–chloro, and 1, 4–dichloro–5*H*–pyridazino[4, 5–*b*] indoles and of their methoxy derivatives are presented in the table V. 2

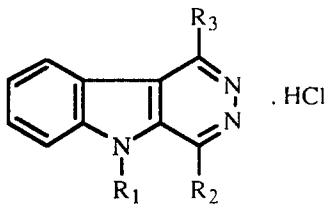
The infrared spectra of chloro– and methoxy–5*H*–pyridazino[4, 5–*b*]indoles show characteristic of C=C, and C=N ring stretching bands between 1570–1650 cm^{-1}. The presence of broad bands in the range 2000–2800 cm^{-1}, which is characteristic of the N^+H

groups, supports the structures of chloro–5*H*–pyridazino[4, 5–*b*]indole monohydro chloride salts (28), (29), (42), and (43) (Table V. 2).

Table V. 2 Infrared Stretching Frequencies of Chloro– and Methoxy–5*H*–pyridazino [4, 5–*b*]indoles.



A



B

R_1	R_2	R_3	Compound	NH (cm^{-1})	C=N, C=C (cm^{-1})
A					
H	Cl	H	30 [a]	3060	1575(s), 1600(s), 1630(s)
Me	Cl	H	31 [a]	—	1590(m), 1620(s)
CH_2Ph	Cl	H	32 [a]	—	1615(w), 1650(w)
H	Cl	Cl	46 [a]	3000–3300(br. , m)	1590(m), 1620(m)
Me	Cl	Cl	47 [b]	—	1580(s), 1615(s)
CH_2Ph	Cl	Cl	48 [b]	—	1590(s), 1615(s)
Me	OMe	Cl	70 [b]	—	1575(s), 1620(m)
Me	OMe	H	60 [a]	—	1610(s), 1630(s)
Me	H	OMe	67 [a]	—	1580(s), 1620(m)
Me	OMe	OMe	72 [a]	—	1570(m), 1620(w)
B					
H	Cl	H	28 [a]	—	1600(s), 1630(s)
Me	Cl	H	29	—	1595(s), 1625(s)
H	H	Cl	42 [a]	3100–3500(br. , w)	1600(w), 1620(s)
Me	H	Cl	43	—	1585(m), 1625(m)

a. Nujol mull
b. Bromoform

4. 0 Experimental

4–Chloro–5*H*–pyridazino[4, 5–*b*]indole [9–11] :

3, 4–Dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indole (2.2 g, 0.012 mol) and phosphorus oxychloride (60 ml) were refluxed for 4 h with stirring. After cooling, the precipitate was collected and washed with diethyl ether (50 ml) and petroleum ether (40–60 °C, 100 ml). Recrystallisation of the product from ethanol gave 4–chloro–5*H*–pyridazino[4, 5–*b*] indole hydrochloride (2.9 g, 100 %), as yellow needles, m.p > 325 °C [lit. [9, 11] m.p. > 325 °C, lit. [10] m. p. 235 °C]. ^{1}H-NMR (DMSO–d_6) : δ 13.50 (sb, 1H, NH) ; 10.55 (s, 1H, H_1) ; 8.30–870 (dd, 1H, H_9) ;7.30–8.10 (m, 3H, H_{6-8}). IR (nujol) : $\nu_{max.}$ 3060 (s, NH), 1575, 1600, 1630 (C=N, C= C) ; 630 (C–Cl) cm^{-1}. [M^+] = 203 a.m.u. (with loss of HCl).

Neutralisation of the 4–chloro–5*H*–pyridazino[4, 5–*b*]indole hydrochloride with saturated sodium bicarbonate solution afforded, 4–chloro–5*H*–pyridazino[4, 5–*b*]indole m.p. > 325 °C [lit. [10] m. p. 272.5–273 °C]. [M^+] = 203 a.m.u. Analytical sample was prepared by crystallisation of the compound from ethanol . (Found : C, 58.8 ; H, 2.9 ; N, 20.4 ; Cl, 17.0 : calc. for $C_{10}H_6ClN_3$ C, 59.0 ; H, 3.0 ; N, 20.6 ; Cl, 17.4 %).

4–Chloro–5–methyl–5*H*–pyridazino[4, 5–*b*]indole [10, 11] :

3, 4–Dihydro–5–methyl–4–oxo–5*H*–pyridazino[4, 5–*b*] indole (0.5 g, 2.5 mmol) and phosphorus oxychloride (20 ml) were refluxed with stirring for 4 h. After the reaction was complete, the mixture was cooled. The precipitate product was collected and washed with diethyl ether (50 ml) and petroleum ether (40–60 °C, 100 ml). Recrystallisation of the crude product from ethanol afforded 4–chloro–5–methyl–5*H*–pyridazino[4, 5–*b*]indole hydrochloride (0.6 g, 94 %), as yellowish needles, m.p. 263 °C [lit. [10] m. p. 262.5–63 °C, lit. [11] m. p. 263 °C]. ^{1}H-NMR ($CDCl_3$) : δ 9.60 (s, 1H, H_1) ; 8.00–8.20 (dd, 1H, H_9) ; 7.20–7.80 (m, 3H, H_{6-8}) ; 4.28 (s, 3H, CH_3N). IR (nujol) : $\nu_{max.}$ 1590, 1620 (C=N, C=C), 630 (C–Cl) cm^{-1}. [M^+] = 217 a.m.u. (with loss of HCl).

Neutralisation of the 4–chloro–5–methyl–5*H*–pyridazino[4, 5–*b*]indole mono hydrochloride with saturated sodium bicarbonate solution afforded free base, 4–chloro–5 –methyl–5*H*–pyridazino[4, 5–*b*]indole. Analytical sample was prepared by crystallising the compound from ethanol. m.p. 199–200 °C (decomps.) [lit. [10] m.p. 180.5 –181 °C (decomps.)]. [M^+] = 217 a.m.u. (Found : C, 60.3 ; H, 3.6 ; N, 19.2 ; Cl, 16.0 ; calc. for $C_{11}H_8ClN_3$ C, 60.7 ; H, 3.7 ; N, 19.3 ; Cl, 16.3 %).

4–Methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole :

4–Chloro–5–methyl–5*H*–pyridazino[4, 5–*b*]indole hydrochloride (1 g, 3.94 mmol) and sodium methoxide (2.13 g, 39.4 mmol) were refluxed in methanol (100 ml) for 4 days. After the reaction was complete, the solvent was removed under reduced pressure. water

(150 ml) was added to the residue and the precipitate which formed was collected and washed well with water to remove excess sodium methoxide, and dried. Recrystallisation of the crude compound from methanol-water gave *4–methoxy –5–methyl–5H–pyridazino [4, 5– b]indole* (0.89 g, 95 %), as white crystals, m.p. 167–8 °C. $[M^+]$ = 213 a.m.u. ^{1}H-NMR ($CDCl_3$) : δ 9.40 (s, 1H, H_1) ; 7.96–8.20 (dd, 1H, H_9) ; 7.20–7.60 (m, 3H, H_{6-8}) ; 4.32 (s, 3H, CH_3O) ; 4.10 (s, 3H, CH_3N). IR (nujol) : $\nu_{max.}$ 1610, 1630 (C=N, C=C) cm^{-1}. (Found : C, 67.6 ; H, 5.0 ; N, 19.6 ; $C_{12}H_{11}N_3O$ requires C, 67.6 ; H, 5.2 ; N, 19.7 %).

Attempted preparation of 4–methoxy–5*H*–pyridazino(4, 5–*b*) indole :

4–Chloro–5*H*–pyridazino[4, 5–*b*]indole (1 g, 4.9 mmol) and sodium methoxide (3 g, 0.056 mol) were refluxed in methanol (100 ml) for seven days. After the reaction was complete, the solvent was removed under reduced pressure, and then water (150 ml) was added to the mixture. The precipitate was collected and washed well with water to remove excess sodium methoxide. Crystallisation of the product from methanol-water gave the starting material (0.82 g, 82 %).

5–benzyl–4–chloro–5*H*–pyridazino(4, 5–*b*)indole:

1–Benzyl–3,4–dihydro–4–oxo–5*H*–pyridazino[4, 5–*b*]indole (0.5 g, 1.8 mol) and phosphorus oxychloride (20 ml) were refluxed with stirring for 4 h. After the reaction was complete, the mixture was cooled. The precipitated product was collected and washed diethyl ether (50 ml) and petroleum ether (40–60 °C, 100 ml). Recrystallisation of the product from ethanol gave *5–benzyl–4–chloro–5H–pyridazino[4, 5– b] indole* (0.5 g, 83 %), m.p. 219–220 °C. ^{1}H-NMR (DMSO–d_6) : δ 9.74 (s, 1H, H_1) ; 8.12–8.32 (dd, 1H, H_9) ; 6.80–7.80 (m, 8H, H_{6-8}, $_{C-Ph}$) ; 6.04 (s, 2H, $-CH_2-$). IR (nujol) : $\nu_{max.}$ 1615,1650 (C=N, C=C) cm^{-1}. $[M^+]$ = 292.9 a.m.u. (Found : C,67.5 ; H, 4.2 ; N, 11.7 ; $C_{17}H_{12}ClN_3$ requires C, 69.5 ; H, 4.1 ; N, 12.1 %).

1–Chloro–5–methyl–5*H*–pyridazino(4, 5–*b*)indole :

1, 2–Dihydro–5–methyl–1–oxo–5*H*–pyridazino[4, 5–*b*] indole (1.5 g, 7.53 mmol) and phosphorus oxychloride (30 ml) were refluxed with stirring for 6 h. The solvent was evaporated and the residue was triturated with diethyl ether. The precipitate was collected, and dried, and recrystallised of the residue from ethanol-water to afford *1–chloro–5 –methyl–5H–pyridazino[4, 5– b]indole* as *monohydrochloride salt* (1.6 g, 97.6 %), as a yellow solid, m.p. 235–7 °C. ^{1}H-NMR (DMSO-d_6) : δ 9.94 (s, 1H, H_4) : 8.35–8.65 (dd, 1H, H_9) ; 7.70–8.00 (m, 3H, H_{6-8}) ; 4.14 (s, 3H, NCH_3). IR (nujol) : $\nu_{max.}$ 1585, 1625 (C=N, C=C) cm^{-1}. $[M^+]$ = 217 a.m.u. (with loss of HCl). (Found : C, 51.9 ; H, 3.5 ; N, 16.4 ; Cl, 27.3 ; $C_{18}H_{18}ClN_3$ HCl requires C, 52.0 ; H, 3.6 ; N, 16.5 ; Cl, 27.9 %).

1–Methoxy–5–methyl–5*H*–pyridazino(4, 5–*b*)indole :

1–Chloro–5–methyl–5*H*–pyridazino[4, 5–*b*]indole hydrochloride (0.75 g, 2.95 mmol) and sodium methoxide (5 g, 0.092 mol) were refluxed in methanol (75 ml) for 4 days . The solvent was removed under reduced pressure. The residue was washed well with water to remove excess sodium methoxide, and dried. Recrystallisation of the crude product from methanol-water afforded pure *1–methoxy–5–methyl–5H–pyridazino [4, 5– b]indole* (0.55 g, 87.4 %), as white needles, m.p. 136–137 °C. ^{1}H-NMR ($CDCl_3$) : δ 9.10 (s, 1H, H_4) ; 8.00–8.30 (dd, 1H, H_9) ; 7.20–7.80 (m, 3H, H_{6-8}) ; 4.36 (s, 3H, OCH_3) ; 3.87 (s, 3H, NCH_3). IR (nujol) : $\nu_{max.}$ 1570, 1580, 1620 (C=N, C=C) cm^{-1}. $[M^+]$ = 213 a.m.u. (Found : 67.4 ; H, 5.4 ; N, 19.5 ; $C_{12}H_{11}N_3O$ requires C, 67.6 ; H, 5.2; N, 19.7 %).

1–Chloro–5*H*–pyridazino(4, 5–*b*)indole :

1, 2–Dihydro–1–oxo–5*H*–pyridazino[4, 5–*b*]indole (1 g, 2.50 mmol) and phosphorus oxychloride (30 ml) were refluxed for 6 h with stirring. The solvent was evaporated under reduced pressure and the residue was triturated with diethyl ether. The crude product was dried and recrystallised from ethanol-water to give *1–chloro–5H–pyridazino[4, 5–b] indole, as monohydrochloride salt* (0.7 g , 50 %), m.p. 300–303 °C.

^{1}H-NMR (DMSO–d_6) : δ 12.48 (br. s, 1H, $N_5\underline{H}$), 9.56 (s, 1H, H_4) ; 8.20–8.50 (dd, 1H, H_9) ; 7.30–8.10 (m, 3H, H_{6-8}). IR (nujol) : $\nu_{max.}$ 3100-3500 (br. w, NH, OH), 1600, 1620 (C=N, C=C). $[M^+]$ = 203 a.m.u. (with loss of HCl). (Found : C, 54.6 ; H, 3.1 ; N, 18.1 ; $C_{10}H_6ClN_3$ HCl requires C, 50.0 ; H, 2.9 ; N, 17.5 %).

The Attempted preparation of 1, 4–dimethoxy–5–methyl–5*H*–pyridazino (4, 5–*b*) indole :

A mixture of 1, 4–dichloro–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (1 g, 3.97 mmol) and sodium methoxide (4 g, 0.074 mol) was refluxed in methanol (100 ml) for 5 days. After cooling, the reaction mixture was filtered and the solid was washed with methanol (100 ml). The combined methanolic solvents were evaporated under reduced pressure and water (100 ml) was added to the residue. The precipitate was collected, washed well with water, and dried. Recrystallisation from methanol-water gave only *1–chloro–4–methoxy –5–methyl–5H–pyridazino[4, 5– b]indole* (0.6 g, 61 %), as white crystals, m.p. 153–4 °C. ^{1}H-NMR ($CDCl_3$) : δ 8.24–8.50 (m, 1H, H_9) ; 7.20–7.80 (m, 3H, H_{6-8}) ; 4.28 (s, 3H, OCH_3) ; 4.08 (s, 3H, NCH_3). IR ($CHBr_3$) : $\nu_{max.}$ 1575, 1620 (C=N, C=C) cm^{-1}. $[M^+]$ = 247 a.m.u. (Found : C, 58.4 ; H, 4.1 ; N, 16.9 ; Cl, 14.3 ; $C_{12}H_{10}ClN_3O$ requires C, 58.2 ; H, 4.1 ; N, 17.0 ; Cl, 14.3 %).

1, 4–Dimethoxy–5–methyl–5*H*–pyridazino(4, 5–*b*)indole :

A mixture of 1, 4–dichloro–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (1 g, 3,97 mmol) and sodium methoxide (4 g, 0.074 mol) in methanol (100 ml) was refluxed for 10 days.

After cooling, the mixture was filtered and the solid was washed with methanol (100 ml). The combined methanolic solutions were evaporated. Water (100 ml) was added to the residue. The precipitate was collected, washed well with water, and dried. The two products were separated by column chromatography (ethyl acetate) to give 1–chloro–4 –methoxy–5–methyl–5*H*–pyridazino[4, 5–*b*]indole (0.8 g, 81.6 %), which is identical with that obtained previously, and *1, 4–dimethoxy–5–methyl–5H–pyridazino [4, 5– b] indole*, which was recrystallised from ethanol-water (50 mg, 5.1 %), as a white needles, m.p. 178–9 °C. ^{1}H-NMR ($CDCl_3$) : δ 8.12–8.36 (m, 1H, H_9) ; 7.20–7.60 (m, 3H, H_{6-8}) ; 4.30 (s, 3H, N=C_4– OCH_3) ; 4.25 (s, 3H, N=C_1– OCH_3) ; 4.15 (s, 3H, N– CH_3). IR (nujol) : $\nu_{max.}$ 1570, 1620 (C=N, C=C) cm^{-1}. [M^+] = 243 a.m.u. (Found : C, 64.1 ; H, 5.4 ; N, 16.9 ; $C_{13}H_{13}N_3O_2$ requires C, 64.2 ; H, 5.4 ; N, 17.3 %).

The Attempted preparation of 1, 4–dimethoxy–5*H*–pyridazino[4, 5–*b*]indole

A mixture of 1, 4–dichloro–5*H*–pyridazino[4, 5–*b*]indole (1 g, 4.2 mmol) and sodium methoxide (5 g, 0.092 mol) was refluxed in methanol (100 ml) for 5 days. After cooling, the reaction mixture was filtered, and the solid was washed with methanol (100 ml). the methanolic solutions were removed under reduced pressure and water (100 ml) was added to the residue. The crude product was washed well with water, and dried. Recrystallisation of the residue from methanol-water gave only starting material (0.8 g, 80 %).

1, 4–Dichloro–5*H*–pyridazino[4, 5–*b*]indole [18] :

1, 4–Dioxo–1, 2, 3, 4–tetrahydro–5*H*–pyridazino[4, 5–*b*]indole (3 g, 0.0149 mol) was suspended in phosphorus oxychloride (60 ml) and the mixture was warmed to 90 °C for 4 h. On cooling, the precipitated product was collected, washed successively with water (5 x 30 ml), ethanol (5 x 50 ml), and diethyl ether (5 x 50 ml), and dried. Recrystallisation of the compound from DMF gave 1, 4–dichloro–5*H*–pyridazino[4, 5–*b*]indole (3 g, 85 %), m.p. 245 °C. [lit. [18] m.p. 250 °C]. ^{1}H-NMR (DMSO–d_6) : 13.50 (br, 1H, NH indole) ; 8.30–8.45 (m, 1H, H_9) ; 7.40–7.85 (m, 3H, H_{6-8}). IR (nujol) : $\nu_{max.}$ 3000–3300 (br, NH), 1590, 1620 (C=N, C=C) cm^{-1}. [M^+] = 237 a.m.u.

1, 4–Dichloro–5–methyl–5*H*–pyridazino[4, 5–*b*]indole :

1, 4–Dioxo–5–methyl–1, 2, 3, 4–tetrahydro–5*H*–pyridazino[4, 5–*b*]indole (2 g, 9.04 mmol) was suspended in phosphorus oxychloride and the mixture was refluxed for 6 h. On cooling, the precipitated product was collected, washed successively with water (5 x 20 ml), ethanol (5 x 50 ml), and diethyl ether (5 x 50 ml), and dried. Recrystallisation of the compound from DMF-ethanol afforded *1, 4–dichloro–5–methyl–5H–pyridazino [4, 5– b]indole* (1.8 g, 79 %), as a white solid, m.p. 224–5 °C. ^{1}H-NMR (CF_3COOH) : 8.50–8.80 (dd, 1H, H_9) ; 7.80–8.20 (m, 3H, H_{6-8}) ; 4.64 (s, 3H, NCH_3). IR ($CHBr_3$) : $\nu_{max.}$ 1580, 1615 (C=N, C=C) cm^{-1}. [M^+] = 252 a.m.u. (Found : C, 52.2 ; H, 2.6 ; N, 16.7 ; Cl, 27.8 ; $C_{11}H_7Cl_2N_3$ requires C, 52.4 ; H, 2.8 ; N, 16.7 ; Cl, 28.1 %).

5–Benzyl–1, 4–dichloro–5*H*–pyridazino[4, 5–*b*]indole :

5–Benzyl–1, 4–dioxo–1, 2, 3, 4– tetrahydro–5*H*–pyridazino[4, 5–*b*]indole (4 g, 0.014 mol) was suspended in phosphorus oxychloride (60 ml) and then the mixture was refluxed 6 h. After cooling, the reaction mixture was poured into ice-water (500 g). The precipitated product was collected, washed well with water, and dried. Recrystallisation of the compound from DMF-ethanol gave *5–benzyl–1, 4– dichloro–5H–pyridazino [4, 5– b]indole* (4.1 g, 91 %), as a white solid, m.p. 186 °C. ^{1}H-NMR (CF_3COOH) : δ 8.60–8.90 (m, 1H, H_9) ; 7.00–8.20 (m, 8H, H_{6-8} and –Ph) ; 6.38 (s, 2H, N–CH_2–). IR ($CHBr_3$) : $\nu_{max.}$ 1590, 615 (C=N, C=C) cm^{-1}. [M^+] = 328.9 a.m.u. (Found : C, 62.3 ; H, 3.3 ; N, 12.8 ; Cl ; 21.6 ; $C_{17}H_{11}Cl_2N_3$ requires C, 62.2 ; H, 3.4 ; N, 12.8 ; Cl ; 21.6 %).

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