The Prototropic Tautomerism of Heteroaromatic Compounds[1,2,3]

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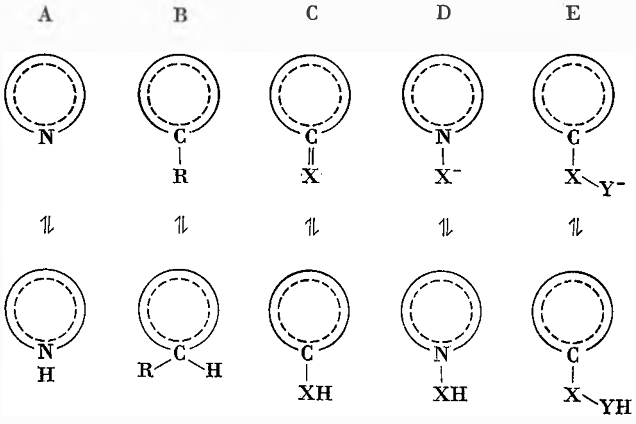
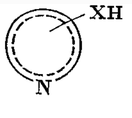
Summary

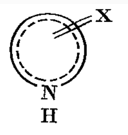
A survey is made of the present knowledge of heteroaromatic tautomerism, covering its definition and scope, experimental and theoretical significance, methods of study, the available results and the conclusions and generalisations which can now be drawn.

The prototropic tautomerism of heteroaromatic compounds comprises all those cases where a mobile hydrogen atom can move (as a proton) from one site to another in a heteroaromatic molecule. The most common type (cf. 1 ⇌ 2) involves the movement of a proton between a cyclic nitrogen atom and a substituent atom directly connected to the ring. A comprehensive classification of the possible types is shown in Scheme I. The top row of formulae in Scheme I shows the various sites available: (A) a cyclic sp^2-hybridised nitrogen, (B) an sp^2-hybridised ring carbon; (C) an sp^2-hybridised atom directly attached to a ring carbon atom; (D) an atom directly attached to a ring nitrogen; and (E) a side chain atom not directly attached to the ring. The lower row of formulae in Scheme I shows the corresponding potential sites from which a proton can be removed. Any heteroaromatic molecule which contains at least one site of the type shown in the upper together with one of those shown in the lower row of formulae in Scheme I is capable of prototropy.

Scheme I




(1)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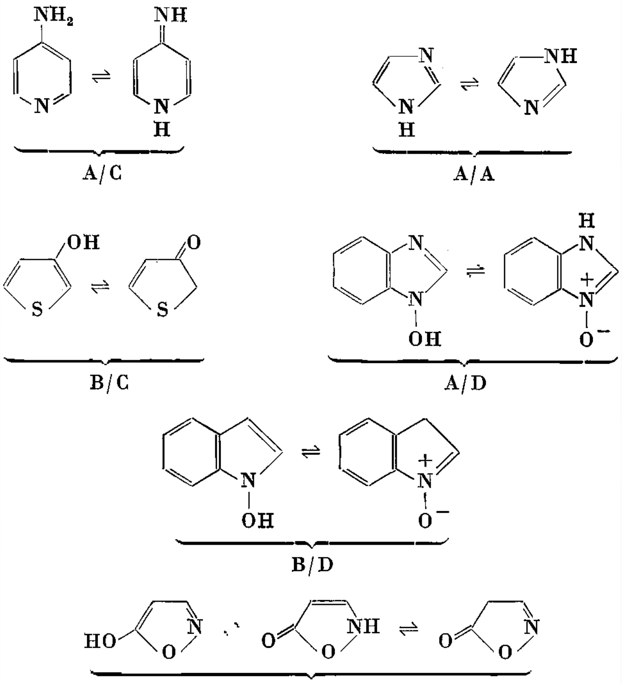
Scheme II



(Captial letters refer to types in Scheme I)

The prototropic tautomerism of heteroaromatic compounds can be classified according to the sites: a few examples are given in Scheme II. The number of possible classes is very large[2] and the present article is concerned mainly with the tautomerism of substituents, i.e. types A/C, and A/B/C in Scheme II. The most important substituents which can become involved in tautomerism are shown in Table 1.

Table 1. Tautomeric Substituents

—OH, Hydroxy	⇌	:O, oxo
—SH, Thiol	⇌	:S, thione
—NH_2, Amino[a]	⇌	:NH, imino
—CH_3, Methyl[b]	⇌	:CH_2, methylene

[a] NHR substituted amino can have properties considerably modified.
[b] CHRR′ can be similarly modified.

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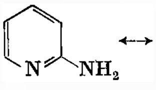
[1] Based on lectures given on March 7th 1969 at the Basler Chemische Gesellschaft and on May 13th 1969 at the Dutch National Symposium on Heterocyclic Chemistry, Lunteren.

[2] A full account of this subject up to 1962 is given by A. R. Katritzky and J. M. Lagowski, *Adv. Heterocyclic Chem. 1* (1963) 311 and 339, *2* (1963) 1 and 27.

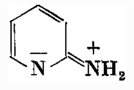
[3] See also shorter accounts (a) A. R. Katritzky, *Quaderni de La Ricerca Scientifica 53* (1968) 36; (b) A. R. Katritzky, *Chem. & Ind. 1965*, 331.

I. The Importance of Heteroatomic Tautomerism

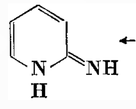
Having defined the subject it is necessary to consider the reasons why its study is of significance. All chemists are aware of the tremendous increase in factual knowledge which has been made recently in all branches of chemistry; in this general advance heterocyclic chemistry has certainly not been left behind. It is no longer possible to try and commit to memory all the methods of synthesis and all the reactions of even a fairly small class of heterocyclic compounds. It is now quite essential to place the old facts and the new ones together in a proper systematic scheme and to use the logic behind the scheme to remember them. Several recent textbooks have in fact taken this approach.[4] It is quite fundamental to a rational organisation of the reactions of heterocyclic (or any other group of) compounds that they should be depicted in the reaction mechanism scheme in the correct tautomeric form. For this, it is necessary to know the position of equilibrium between the two or more tautomers that may be present or, more precisely, to know the energy difference between the alternative forms. In addition to tautomeric forms, it is naturally important to consider, in any study of reactivity, the concentrations of the various ionic species which exist, and thus pK_a values are also highly significant. One example of the importance of tautomeric structure in the interpretation of reaction mechanisms will be given. 2-Aminopyridine can exist as such (**3**) or in the imino form (**5**); both of these tautomeric forms are mesomeric, thus **3** has contributions from the charge-separated structure **4**, and the imino form **5** from the charge-separated structure **6**. A cursory glance at the structures indicates that the amino compound should be attacked by electrophiles at the ring nitrogen atom, whereas the imino compound should be attacked by electrophiles at the exocyclic nitrogen atom. For a correct interpretation of the chemistry of 2-aminopyridine, it is thus clearly necessary to realise which of the two forms in entering into the reaction.



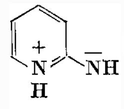
(**3**)



(**4**)



(**5**)

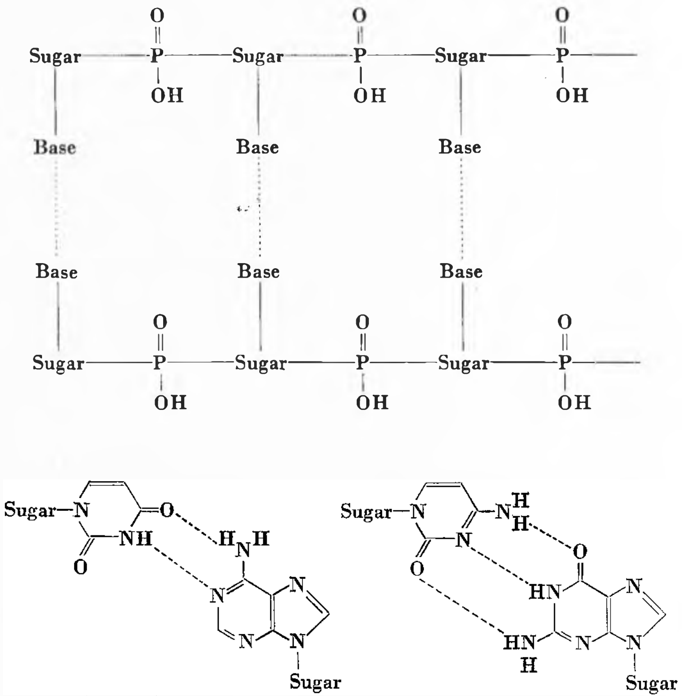


(**6**)

There are of course numerous examples in the older literature where wrong conclusions have been drawn by correct reasoning on incorrect structures and sometimes correct conclusions have been drawn by incorrect reasoning on incorrect structures! We must realise that the classical chemists were often confused by the lack of accurate data on tautomeric equilibria, and we must credit them for their progress in spite of the lack of modern theory. However, it is unfortunately true that many incorrect inferences are still being drawn today. One of the reasons for this is the unfortunate tendency of some otherwise highly intelligent and reasonable chemists to represent tautomeric heterocyclic compounds by other than the predominantly existing tautomer. As will become clear during the course of this survey, the information presently available now enables us to predict with a good chance of success the predominant tautomeric structure for nearly all the heterocyclic compounds that we are likely to encounter. Surely *this* is the structure by which they should be named and, more importantly, depicted in reaction schemes. It is perhaps not essential to trained heterocyclic chemists that they use the correct structure, as they should be able to avoid most of the pitfalls with which such a practice is associated; however, it seems very difficult to expect Biochemists and Biologists to have any understanding of the subject at all if we do not write down what we mean.

A good example of the potential dangers involved is given by the case of the nucleic acids. It is well known that these compounds consist of sugar phosphate chains, that various heterocyclic bases are linked to the sugar molecules, and that hydrogen bonding between base pairs links together two such chains in a double helix. It is clearly important that, e.g., uracil exists in the dioxo form and that adenine exists in the amino form, in order for the double helix to have the correct hydrogen bonding, as shown in Scheme III. Considerable confusion

Scheme III



Uracil Adenine

Cytosine Guanine

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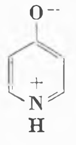
[4] Cf., e.g., A. R. Katritzky and J. M. Lagowski, *The Principles of Heterocyclic Chemistry*, Methuen, London/New York 1967; also available in translation as *Principles de la Chimie des Composés Hétérocycliques*, Gauthier-Villars, Paris 1968; *Chemie der Heterocyclen*, Springer, Heidelberg 1968, and in other languages.

was initially engendered because uracil was frequently written in the hydroxy form by chemists: a graphic account has been given[5] of the difficulties encountered in sorting this out.

There is a further possible importance of tautomerism with respect to the nucleic acids. It is well known that the transfer of genetic information occurs by the nucleic acid double helix becoming unwound and each of the sugar phosphate chains building onto it a new complimentary chain: thus, every uracil molecule takes up a new adenine molecule, *etc.* Occasionally a "mistake" occurs and this is seen as a mutation in the replicated nucleic acid. The mechanism of such "mistakes" is not yet clearly understood, but there is at least a strong possibility that they could occur by the uracil reacting in the tautomeric hydroxy form of which a very small amount is present at equilibrium.[6] Uracil in the monohydroxy form has a structure which prevents it from pairing with adenine, but it now resembles cytosine and can thus pair satisfactorily with guanine. A genetic "mistake" or mutation could arise in this manner.

The question of the description of the tautomeric forms is an important one. Some authors have described the tautomerism between 4-hydroxypyridine and 4-pyridone as between the "aromatic" and the "non-aromatic" form. In the writer's opinion, this is most misleading as 4-pyridone must be considered an aromatic compound on all the major criteria of aromaticity. In particular, all the ring atoms have a *p*-orbital suitably aligned for cyclic conjugation and the HÜCKEL rule is obeyed. Although there has been considerable controversy[7,8] regarding the magnitude of the ring current in the 4-pyridone, all measurements agree in showing some aromaticity. Other authors accept the aromaticity of pyridones but argue that e.g. 4-pyridone should be depicted as the zwitterionic structure **7**. Of course, this canonical form is an important contributor to the resonance hybrid of 4-pyridone but it would be quite inconsistent to depict 4-pyridone solely as **7**. We would all write acetamide down in the uncharged form **8** rather than **9**. It is both conventional and convenient to write uncharged forms for mesomeric species rather than charged ones. Again, we normally write benzene with three double bonds, in full knowledge that the "double" and "single" bonds in such a formulation all have the same length.



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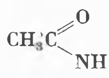
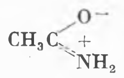


$CH_3C(=O)NH_2$

(8)

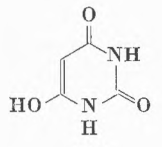


$CH_3C(O^-)=\overset{+}{N}H_2$

(9)

II. Methods of Investigation of Hetero-aromatic Tautomerism

Available methods may be divided into two classes: chemical and physical. There are many examples of incorrect conclusions being reached regarding the tautomeric structure of a heteroaromatic compound from the incautious application of chemical methods. A classical case is barbituric acid: of the many tautomeric structures that can be drawn from this compound, two were widely disputed and considerable spurious chemical evidence was originally offered in support of both hydroxy-structure **10** and trioxo-structure **11**. Thus, the hydrostructure **10** was favoured over the trioxo form **11**: (a) because of the strongly acidic character of barbituric acid, and (b) because diazomethane reacts with barbituric acid to yield the methoxy derivative **13**.



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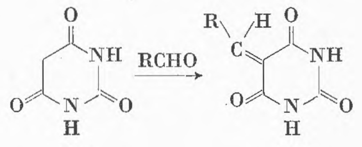
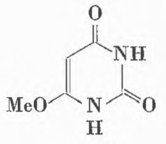


(11) (12)



(13)

It is easily seen that both these lines of reasoning are incorrect. If the hydroxy form **10** did predominate, then it would have to be a *weaker* acid than the tautomer **11**; from elementary thermodynamic considerations, it can be shown that $pK_a\ (\mathbf{10}) - pK_a\ (\mathbf{11}) = \log K_T$. Further, although it used to be believed that diazomethane reacted with active hydrogen compounds to insert a methyl group precisely in the place of the hydrogen atom GOMPPER[9] has shown that such reactions do not involve any so called *direct* replacement of hydrogen by methyl. The correct mechanism involves first the formation of the anion and the methyldiazonium cation, these intermediate products then react together to give the methylated derivative. The position taken up by the entering methyl group depends on the structure of the anion, particularly on the relative electro-negativities of the various electrophilic centers.

The old protagonists for the trioxo form **11** were on equally weak ground with their contention that the reaction of barbituric acid with aldehydes to give compounds of structure **12** indicated the presence in barbituric acid of a methylene group. This last reaction is a type of aldol condensation, the mechanism of which involves either the hydroxy form or, more likely, the

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[5] J. D. WATSON, *The Double Helix; a personal account of the discovery of the structure of* DNA, Werderfeld, London 1968.

[6] J. D. WATSON and F. H. C. CRICK, *Cold Spring Harbour Symposium Quant. Biol. 18* (1953) 123.

[7] J. A. ELVIDGE and L. M. JACKMAN, *J. Chem. Soc. 1961*, 859.

[8] R. J. ABRAHAM and W. A. THOMAS, *J. Chem. Soc. (B) 1966*, 127.

[9] R. GOMPPER, *Adv. Heterocyclic Chem. 2* (1963) 245.

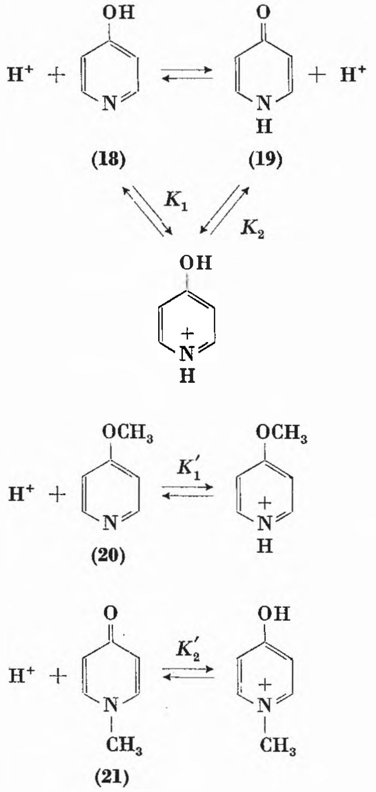
mesomeric anion in which the charge is spread between the carbon and oxygen atoms.

It is not the purpose of this article to heap scorn on the chemists of twenty years or more ago who advanced such evidence in good faith. They knew no better. Unfortunately, such evidence is still, on occasion, advanced today in the literature.

It should be emphasized that it is possible to apply chemical methods to the study of heterocyclic tautomerism. Suppose tautomeric form **14** reacts with a reagent to give **15**, while tautomeric form **16** reacts with the same reagent to give **17**. The ratio of the products **15** and **17** will depend on the tautomeric ratio K_T and the ratio of the individual rate constants k_y and k_z. Unless k_y/k_z is known or can be estimated nothing definite can be deduced as regards K_T from the product ratio. At present, the physical methods are certainly much easier to apply and more reliable and the rest of this lecture will be devoted to infomation obtained using them. However, in some cases it is difficult to apply physical methods and it may well be that in certain cases chemical methods will make a comeback. A promising example involves the study of the kinetics of hydrogen-deuterium exchange.[10]

$$\underset{(15)}{\mathrm{Y}} \xleftarrow{k_y} \underset{(14)}{\mathrm{HX}} \overset{K_T}{\rightleftharpoons} \underset{(16)}{\mathrm{XH}} \xrightarrow{k_z} \underset{(17)}{\mathrm{Z}}$$

Scheme IV



Physical methods for the study of tautomerism often depend on the concept of "fixed derivatives". By a fixed derivative is meant a model compound in which the tautomerism has been frozen, usually by substitution of a methyl group for the labile hydrogen atom. Thus, for 4-hydroxypyridone **18** and 4-pyridone **19** the corresponding fixed derivatives are 4-methoxypyridine **20** and 1-methylpyridone **21**. The basis of many physical methods is to compare some property of the potentially tautomeric compounds with the same property of each of the two (or more) fixed forms. An example of this is shown in Figure 1, where the ultraviolet spectrum of 4-pyridthione is compared with the spectra of its two alternative methyl derivatives. Two things are quite clear from Figure 1: first, that 4-pyridthione exists mainly in the thione form and not as a mercapto compound; second, that there are nevertheless small but significant differences between the ultraviolet spectrum of 4-pyridthione and its 1-methyl derivative. Differences of this magnitude are normally found in ultraviolet spectra as a result of the substitution of a hydrogen by an alkyl group. The conclusion then is that 4-pyridthione exists mainly as such, but one cannot be sure if the tautomeric equilibrium is such that 1%, 0.1%, or some smaller proportion, exists in the mercapto form.

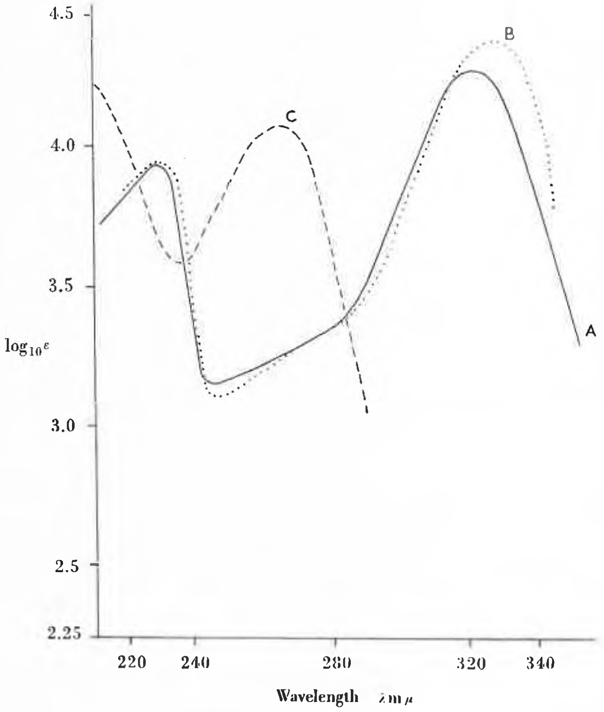


Figure 1. Ultraviolet spectra of (A) 4-pyridthione, (B) 1-methyl-4-pyridthione, and (C) 4-methylthiopyridine

Similar considerations apply quite generally to the deductions which can be drawn from the comparison of the relevant properties of the fixed derivatives with the ultraviolet and also with the infrared or nuclear magnetic

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[10] U. Bressel, A. R. Katritzky and J. Lea, *J. Chem. Soc. (B)*, in press.

resonance spectrum, or the dipole moment, of the tautomeric compound. All these methods are important and allow conclusions as to the predominant tautomeric form. However, a quantitative estimate of the equilibrium constant can only be made from such methods provided that K_T occurs in the range of *ca.* 0.05 to 20, i.e., provided a considerable proportion exists in both the tautomeric forms in question.

To obtain a quantitative estimate of the equilibrium constant of a tautomeric compound existing largely in one form, the basicity method is usually the most useful. This method can be illustrated by the tautomeric equilibrium of 4-pyridone (**19**) with 4-hydroxypyridine (**18**), (Scheme IV). The tautomeric equilibrium constant K_T is related to the two individual basicity constants K_1 and K_2 by the relation that $K_T = K_2/K_1$. The basicities of (**19**) and (**18**) cannot of course by determined individually as the tautomers interconvert very quickly, however, values K_1' and K_2' can be obtained from the corresponding fixed derivatives (**20**) and (**21**). A good estimate for K can thus be obtained using the equation $K_T = K_2'/K_1'$, which is usually applied in the form $pK_T = pK_2' - pK_1'$.

The most commonly used physical methods are given in Table 2. Several can be used without fixed derivatives; infrared and NMR spectroscopy are particularly important in this respect. The use of magnetic resonance spectra in the determination of the tautomeric structure of a compound has become so common that the important distinction between "fast" and "slow" equilibria must be emphasized. Under normal conditions, a tautomeric equilibrium which involves the fission of an OH, NH, or SH bond, and the formation of a new bond of one of these types, is a rapid process on the NMR time scale. The NMR spectrum that is observed for such a system will therefore be a time average weighed according to the proportions of the two tautomeric forms which are present. Such a time-averaged spectrum is clearly more difficult to interpret than the spectrum observed for the alternative situation of a "slow" tautomeric equilibrium. Equilibria which involve the formation or the fission of at least one CH bond are normally slow on the NMR scale. In these cases, the observed spectrum consists of the superposition of two individual spectra, one due to each tautomer. Although the above generalisations are usually valid, in special cases "slow" or "fast" equilibria can be found in other situations.

Table 2. Physical Methods for the Investigation of Tautomerism

	[a]	[b]
Ultraviolet spectra		*
Infrared spectra	*	*
Nuclear Magnetic Resonance	*	*
Basicity Measurements		*
X-Ray crystallography	*	
Dipole Moments		*
Polarography		*
Molecular orbital Calculations	*	
Hammett equation		*
Molar refractivity	*	

[a] This column refers to the use of the method without fixed derivatives.

[b] This column refers to the use of fixed derivatives.

III. The Tautomerism of Pyridines

Some of the available results on the tautomerism of pyridines are given in Table 3. It is of fundamental importance that 4-hydroxypyridine exists mainly as 4-pyridone whereas 4-aminopyridine exists mainly as such, and not in the imino form (cf. structures **22** to **25**). The reason for this difference can be understood on simple valence bond considerations. The individual tautomers are mesomeric and are stabilised by contributions from charge separated forms as shown in structures **26** to **29** for the 4-aminopyridine system and in structures **30** to **33** for 4-pyridone. In the case of 4-aminopyridine, the contributions from the charge separated forms (**26**, **29**) are of moderate and about equal importance; although the imino form **28** has some aromatic character, that of the amino form **27** is considerably greater and is responsible for its predominance. However, in the tautomerism between 4-hydroxypyridine and 4-pyridone, the charge-separated form (**30**), in which positive charge resides on oxygen and negative on nitrogen, is of much less importance than the other charge-separated form (**34**), and for this reason the equilibrium (**31** $\rightleftharpoons$ **32**) swings over in favour of 4-pyridone. Molecular orbital calculations give similar results.

Table 3. The Tautomerism of Substituted Pyridines[a]

Substituent	log K_T[b]	Reference
4-OH	-3.3	[c]
3-OH	-0.1	[d]
4-NH_2	$+3.3$	[e]
4-NHAc	$+6$	[f]
4-$NHSO_2Me$	-1.5	[g]
4-CH_3	$> +6$	[h]
4-CH_2COPh	$+2.6$	[i]
4-CH_2SO_2Ph	$+7.6$	[j]
4-SH	-4.6	[k, l]
3-SH	-2.2	[l]

[a] Values apply to aqueous solutions.

[b] log K_T = log [pyridinoid form[/ [ring NH form].

[c] A. Albert and J. N. Phillips, *J. Chem. Soc. 1956*, 1294.

[d] S. F. Mason, *J. Chem. Soc. 1957*, 5010.

[e] S. J. Angyal and C. L. Angyal, *J. Chem. Soc. 1952*, 1461.

[f] R. A. Jones and A. R. Katritzky, *J. Chem. Soc. 1959*, 1317.

[g] R. A. Jones and A. R. Katritzky, *J. Chem. Soc. 1961*, 378.

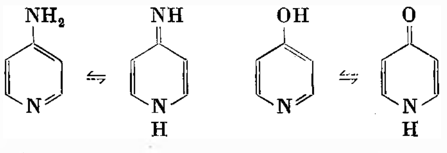
[h] cf. Ref. [2].

[i] A. R. Katritzky, H. Z. Kusharska and J. D. Rowe, *J. Chem. Soc. 1965*, 3090.

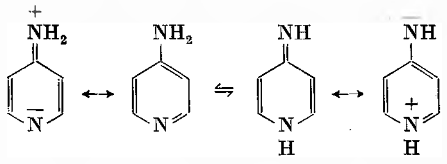
[j] S. Golding, A. R. Katritzky and H. Z. Kucharsak, *J. Chem. Soc. 1965*, 3090.

[k] R. A. Jones and A. R. Katritzky, *J. Chem. Soc. 1958*, 3610.

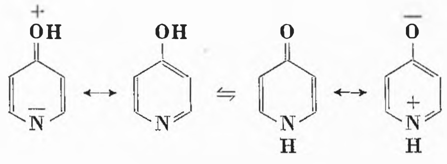
[l] A. Albert and G. B. Barlin, *J. Chem. Soc. 1959*, 2384.



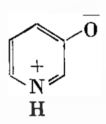
(22) (23) (24) (25)



(26) (27) (28) (29)



(30) (31) (32) (33)



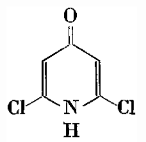
(34)

Similar generalisations apply to the corresponding 2-substituted pyridines. Further, these results are applicable to a host of polycyclic derivatives of pyridine, e.g., quinolines, isoquinolines, acridines, for all of which the generalisations can be made that compounds with amino-groups situated α or γ to the ring nitrogen exist as such but that the derivatives with a potential hydroxy group α and γ to the ring nitrogen atom tend to exist as the oxo tautomer with the labile proton prefering to reside on the nitrogen atom.

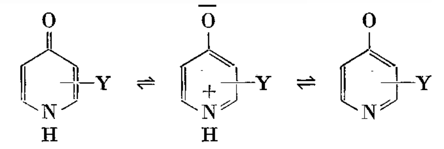
When the substituent group is β to the nitrogen atom the equilibrium swings very much more in favour of the "benzenoid" aromatic form. Thus 3-hydroxypyridine itself exists in aqueous solution in comparable amounts as the true hydroxy derivative and as the zwitterionic structure (**34**). Here it is not possible to write an uncharged canonical form for the zwitterionic structure (**34**).

A) Effects of Substituents

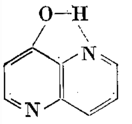
In a great many cases, substitution of the pyridine ring does not fundamentally alter the position of a tautomeric equilibrium and the generalisations just mentioned hold. However, there are two important exceptions to this. The first arises when there are strongly electron withdrawing (by the inductive or resonance effects) substituents *alpha* to the nitrogen atom. Such substituents tend to shift the equilibrium in favour of pyridonoid form. This effect is illustrated by the consequences of chloro substitution on the tautomerism of 4-pyridone.[12] 3,5-Dichloro-4-pyridone, in which the chlorine substituents are both β to the ring nitrogen atom, exists largely in the pyridone form. However, with 2-chloro-4-pyridone, comparable amounts of the 4-hydroxy-2-chloropyridine and 2-chloro-4-pyridone coexist in aqueous solution and 2,6-dichloro-4-pyridone **35** exists in aqueous solution very largely as 2,6-dichloro-4-hydroxy-pyridine. This behaviour may be rationalised by considering the pK_a values of the individual tautomers. Each of the tautomeric forms **36**, **38** of a substituted pyridone is in equilibrium with the same cation **37**. The effect of substitution on both the pK value of the conjugate acid **37** for the loss of the NH proton and the pK_a value for the loss of the OH proton can each be calculated by a Hammett type equation[13] as shown in Scheme V. By this means it is possible to estimate the tautomeric position of any substituted pyridone.[14]



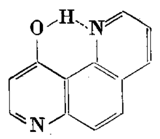
(35)



(36) (37) (38)



(39)



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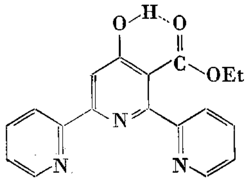
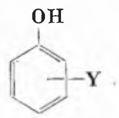


(41)

Scheme V



i

$$pK_T = pK(\mathbf{36}) - pK(\mathbf{38})$$

where $pK(\mathbf{36})$ refers to proton loss from nitrogen and $pK(\mathbf{38})$ refers to proton loss from oxygen in the common conjugate acid **37**.

$$pK(\mathbf{36}) = 8.65 - 5.9\,\sigma_s$$
$$pK(\mathbf{37}) = pK(\mathrm{i}) - 6.7$$
$$pK_T = 2.0 - 5.9\,\sigma_s + pK(\mathrm{i})$$

where σ_s refers to the substituent constants of ref. [13].

---

[12] A. R. Katritzky, J. D. Rowe and S. K. Roy, *J. Chem. Soc. (B) 1967*, 758; for similar work see E. W. Perseleni, L. I. Yakontov, D. M. Krasnokutskaya and U. N. Sheinker, *Dokl. Akad. Nauk. SSSR 177* (1967) 592.

[13] J. Clark and D. D. Perrin, *Quart. Rev. 18* (1964) 295.

[14] A. Gordon, A. R. Katritzky and S. K. Roy, *J. Chem. Soc. (B) 1968*, 556.

Some results are shown in Table 4. The pattern of the effect of substituents on 4-pyridone tautomerism is now clear: whereas 3-substituents tend to affect the pK_a values of the OH and NH forms roughly equally, substituents at the 2-position have a much greater influence on the acidity of a hydrogen in the NH group than in OH-group.

Table 4. Effect of C-Substituents on the Tautomeric Equilibrium of 4-Pyridone with 4-Hydroxypyridine[a]

Substituents	$\log_{10} K_T$ calc.	obs.
3-NH_2	5.0	3.6
3,5-diCl	2.2	2.4
2-Cl	-0.1	-0.3
2,6-diMe	2.1	3.7
2,6-diCO_2Me	-1.4	-1.1

[a] Taken from Ref. [14].

The second important effect of substituents on tautomeric equilibria is the stabilisation of one particular tautomeric form by means of hydrogen bonding. Thus, compound **39** exists partly in the hydroxy form shown,[15] whereas compound **40** exists essentially completely in the hydroxy form,[16] because of the hydrogen bonds of varying strengths that are formed between the hydroxyl groups and the nitrogen atoms, as indicated. Hydrogen bond acceptance by an oxygen atom is less effective in general, but it can occur as, for example, in structure **41**.[17]

B) Tautomeric Substituents other than Hydroxy or Amino

In general, the tautomeric behaviour of potential mercapto compounds resembles that of their hydroxy analogues. Similarly, methyl derivatives resemble their amino analogues for the tautomeric view point. For the same ring-system, ring-position, and substituents, the K_T values are in the following order, SH < OH < NH_2 < CH_3, increasing in favour of the "pyridinoid" form. The position of methyl in this order clearly follows from the considerations of mesomerism discussed above (cf. formula **26** to **33**). It is of some interest that the effect of sulphur in favouring the pyridonoid or betaine form is greater than that of oxygen. The reason for this is connected with the fact that SH groups are more acidic than OH groups under normal conditions in aqueous solution.

The effect of substitution within the amino-group on the tautomerism of amino derivatives, and of side-chain substitution on the tautomerism of methyl groups, is of interest. For amino-group substitution, conjugation is of little importance, as illustrated by the tautomerism of acyl-amino-pyridines which is very similar to those of the amino analogues. On the other hand, the inductive effect is marked; e.g. α- and γ-methanesulphonamidopyridines exist in comparable amounts in the imino and the amino form in aqueous solution (cf. Table 5). The position is just the opposite as regards substitution at a methyl group. Here the influence of the inductive effect is small and sulphonylmethylpyridines do not differ very much in their tautomeric behaviour from the methylpyridines. By contrast, the influence of resonance effects is large, thus an appreciable proportion of an α- or γ-acetonylpyridine exists in the "pyridonoid" form and α- and γ-dicyanomethylpyridines tend to go over predominantly to the NH form. The explanation (cf. ref.[18]) for this variable behaviour depends on possibilities for conjugation between a substituent on nitrogen and (a) the lone pair on nitrogen or (b) a multiple bond formed by this nitrogen with a carbon atom but not with both (a) and (b) at the same time.

Table 5. Effect of Substitution in NH_2 or CH_3 on Pyridine Tautomeric Equilibria

	Substitution in NH_2-group	CH_3-group
Inductive effect	large: for $NHSO_2Me$ imino form important	small: for CH_2SO_2R little effect of K_T of CH_3
Conjugative effect	small: for NHAc little imino form	large: for CH_2COPh appreciable proportion of :CHCOR

C) Effect of Solvent on Pyridine Tautomeric Equilibria

All the preceding results have refered to aqueous solution. In solvents of lower dielectric constant the tautomeric situation can change considerably, which is particularly noticeable when the equilibrium is fairly delicately balanced in aqueous solution. This is illustrated by 2-chloro-4-pyridone for which Figure 2 shows the ultraviolet spectra in water and in aqueous ethanol solutions of varying composition. The marked changes in the spectrum are due to significant changes in the tautomeric equilibrium; in fact, in absolute ethanol the compound exists essentially completely as 2-chloro-4-hydroxypyridine. This finding can be rationalised on the basis of the results already given. As explained above, the reason for the preference of the oxoform in pyridone-hydroxypyridine equilibria is the contribution to the resonance hybrid of charge-separated canonical forms of type **33**. The stabilisation afforded by such structures will be much less in media of low dielectric constant and this can be sufficient to tilt the balance. Recently, a quantitative relationship has been established[19] be-

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[15] D.N. Bailey, D.M. Hercules and T.D. Eck, *Anal. Chem. 39* (1967) 877.

[16] A.R. Katritzky and J. Lea, unpublished work.

[17] E. Muller, R. Haller and K.W. Merz, *Chem. Ber. 99* (1966) 445.

[18] A.R. Katritzky, H.Z. Kuchasku and J.D. Rowe, *J. Chem. Soc. (B) 1965*, 3094.

[19] A. Gordon and A.R. Katritzky, *Tetrahedron Letters 1968*, 2767.

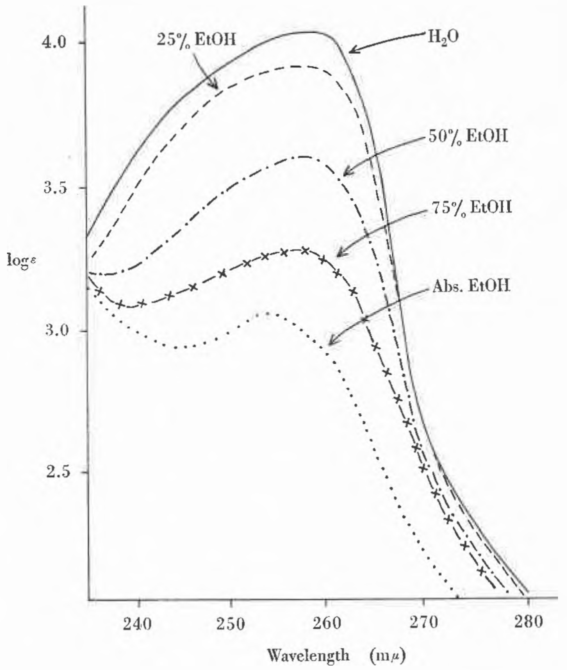


Figure 2. Ultraviolet spectra of 2-chloro-4-pyridone in aqueous ethanol and in water, taken from ref. [12]

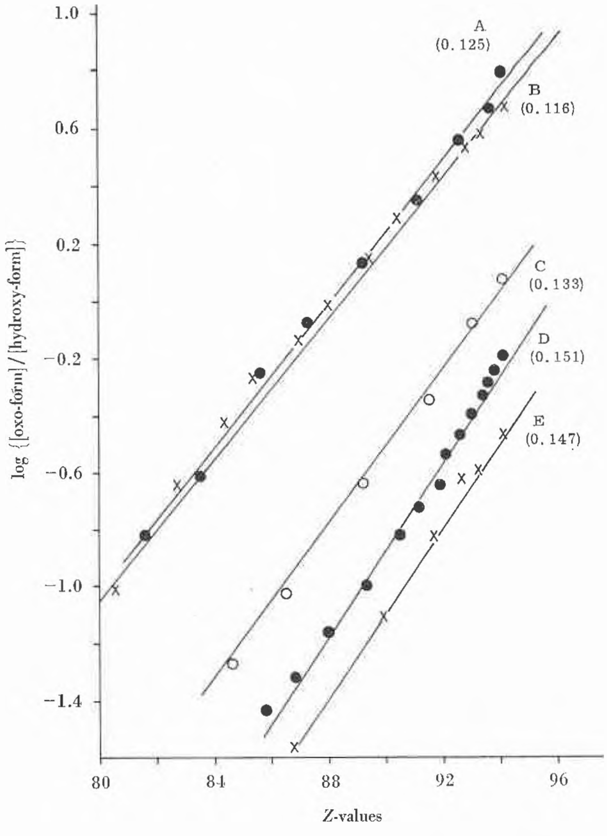
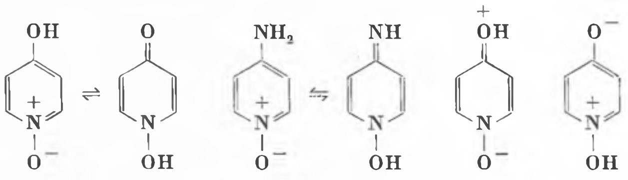


Figure 3. Plots of log [oxo-form]/[hydroxy-form] measured in ethanol water mixtures against Z-values for (A) 6-chloro-2-(solid points); (B) 2,3,5-trichloro-4-(crosses); (C) 2-chloro-4-pyridone; (D) 3-hydroxypyridine; and (E) 2,6-dimethoxycarbonyl-4-pyridone. The lines shown for each compound were fitted by the least squares method; the slopes are given, taken from ref. [19]

tween heteroaromatic tautomeric equilibrium constants and solvent polarity Z-values (see Figure 3).

D) Pyridine 1-Oxides

Pyridine 1-oxides carrying a substituent such as hydroxyl or amino are also potentially tautomeric substances. Thus 4-hydroxypyridine 1-oxide (**42**) is in equilibrium with 1-hydroxy-4-pyridone (**43**), and the corresponding equilibrium for 4-aminopyridine 1-oxide is as indicated (**44** ⇌ **45**). The K_T values for pyridine 1-oxides are displaced from those of the corresponding pyridine by factors of *ca.* 10^3 in favour of the pyridinoid form. Thus, 4-hydroxypyridine 1-oxide exists to about equivalent amounts in forms **42** and **43** whereas the equilibrium for the 4-amino analogue **44** ⇌ **45** favours **44** by the very large value of *ca.* 10^8. The explanation follows quite logically from the considerations of mesomerism already discussed. Thus, the forms **42** and **43** of 4-hydroxypyridine 1-oxide are stabilised respectively by the mesomeric contributors **46** and **47**. Canonical form **46** of 4-hydroxypyridine 1-oxide is relatively more important than canoncical form **31** of 4-hydroxypyridine because the minus charge resides on oxygen rather than on nitrogen. On the other hand canonical form **47** of 1-hydroxy-4-pyridone is relatively less important than form **33** of 4-pyridone because the nitrogen atom on which the positive charge resides has had its electronegativity decreased by the adjacent oxygen atom. Other work on tautomeric pyridine 1-oxides is in line with these findings.[20]



(42) **(43)** **(44)** **(45)** **(46)** **(47)**

E) Summary and Rules for the Tautomerism of Substitued Pyridines

The above discussion may be summarised in the following way. The pyridinoid form is favoured over the form with the hydrogen attached to the ring nitrogen by the following:

(1) Increasingly in the series SH < NH < CH_3.
(2) By the tautomeric substituent being β to the ring nitrogen rather than in the α- or γ-position.
(3) By the presence of electron-withdrawing carbon substituents near to the ring nitrogen atom.
(4) By media of low dielectric constant.
(5) By carbon substituents which can form strong hydrogen bonds to the tautomeric substituent.
(6) In N-oxides compared to the corresponding pyridines.

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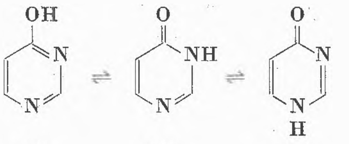
[20] R. A. Jones and A. R. Katritzky, *J. Chem. Soc. 1960*, 2937.

IV. The Tautomerism of Azines

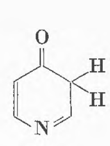
The pattern of tautomerism of six-membered rings containing two heterocyclic nitrogen atoms is very similar to that of the pyridines just considered; therefore, the discussion will concentrate on the three main differences that are found.

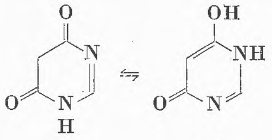
In the first place, the existence of a second cyclic nitrogen atom clearly means that additional NH forms are possible. Thus, 4-hydroxy-pyrimidine (**48**) is in equilibrium with two pyrimidinones **49** and **50**. In general, it is found that the amide forms (as **49**) are more stable than the "vinologous" amide forms (as **50**), by small factors of about 2 to 3, but that hydroxy forms are not highly populated.

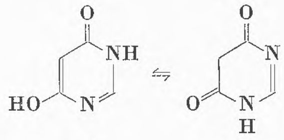

(48) (49) (50)

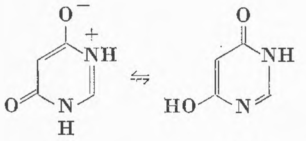
A second difference is the importance in certain azines of non-aromatic forms. Tautomeric pyridines can exist in non-aromatic forms and we should really name 4-pyridone as 1**H**-4-pyridone to indicate that the mobile hydrogen atom is residing on the nitrogen atom and to distinguish it from, e.g., 3**H**-4-pyridone (**51**). However, in pyridine chemistry such non-aromatic tautomeric forms are seldom important (for an exception, see ref. [21]). They occur more frequently in azine tautomerism. Thus barbituric acid has now been shown [22] to exist predominantly in the form (**11**). A non-aromatic tautomer has also been postulated to exist to a significant extent in the tautomerism of malonyl-formamidine. This compound was investigated almost simultaneously by four different groups of workers. In 1964 an Australian [23] group concluded that the tautomeric equilibria could be represented by (**52** ⇌ **53**) but a Russian group [24] suggested (**54** ⇌ **52**). A Japanese group [25] in 1965 supported (**54** ⇌ **52**). However, work carried out in Norwich [26] indicates that the non-aromatic form is not of great importance in this particular case and that (**55** ⇌ **54**) depicts the predominant and the next most important tautomeric forms.

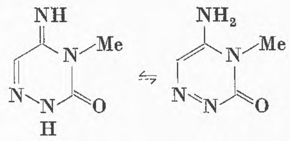
The third important peculiarity of azine tautomerism is that structures with a formal N=N double bond are destablised and tend to be avoided even if this means that an otherwise unexpected tautomeric structure will predominate. Thus, it was found in Prague [27] and confirmed in Norwich, [28] that 3-methyl-6-azacytosine exists predominantly in the imino form (**56**) rather than the expected amino-form **57**. An even more surprising case is found in an analogous ethyl derivative **58** which actually exists to considerable extent in the ethylidine form **59**. [29] The destabilisation of structures containing N=N double bonds is found in other area of heterocyclic chemistry, e.g. in aza analogues of norcaradiene. [30]

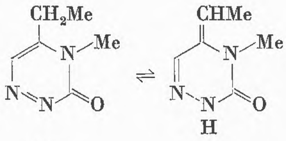

(51)


(52) (53)


(54) (52)


(55) (54)


(56) (57)


(58) (59)

V. Tautomeric Furans, Thiophenes and Pyrroles

So far we have been concerned mainly with tautomerism of type A/C. We have seen that non-aromatic forms are rarely invoked in the tautomerism of pyridine derivatives and not very often in the azine series. However, the typical tautomerism of substituted furans, thiophenes and pyrroles is of type B/C (cf. Schemes I and II). 2-Substituted derivatives (**60**) are in equilibrium with forms **61** and **62** whereas the 3-substituted compounds **63** equilibrate with form **64**. From the available data (summarised in Table 6), the following generalisations can be made: (1) For potential hydroxy derivatives,

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[21] A. R. Katritzky, F. D. Popp and J. D. Rowe, *J. Chem. Soc. (B) 1966*, 562.

[22] J. J. Fox and D. Shugar, *Bull. Soc. Chim. Belges 61* (1952) 44.

[23] D. J. Brown and T. Teitei, *Australian J. Chem. 17* (1964) 567.

[24] G. M. Kheifets and N. V. Khromov-Borisov, *Zhur. Obschei. Khim. 34* (1964) 3134.

[25] Y. Inoue, N. Furutachi and K. Makanishi, *J. Org. Chem. 31* (1966) 175.

[26] A. R. Katritzky, F. D. Popp and A. J. Waring, *J. Chem. Soc. (B) 1966*, 565.

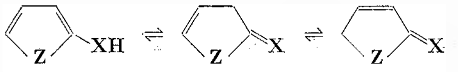
[27] J. Gut, J. Jonas, and J. Pithan, *Coll. Czech. Chem. Comm. 29* (1964) 1394.

[28] N. Bacon, A. J. Boulton, R. T. C. Brownlee, A. R. Katritzky and R. D. Topsom, *J. Chem. Soc. 1965*, 5230.

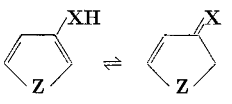
[29] W. E. Taft and R. G. Shepherd, *J. Med. Chem. 10* (1967) 883.

[30] (a) R. G. Annet, R. B. Jahns and K. R. Markham, *Chem. Comm. 7* (1965) 128. (b) G. Maier, *Chem. Ber. 98* (1965) 2438. (c) A. B. Turner, H. W. Heine, J. Irving and J. B. Bush Jr., *J. Amer. Chem. Soc. 87* (1965) 1050.

the non-aromatic forms are usually preferred whereas the mercapto and amino compounds generally exist as such. (However, investigations of these amino and mercapto derivatives is often difficult because of great instability towards oxidation, dimerisation etc.). (2) Tautomerism between two forms, particularly between two non-aromatic forms, involves the breaking of carbon-hydrogen bonds and is correspondingly a slower process. Frequently individual tautomers can be isolated. (However, it should be emphasised that other substituents considerably affect the pattern of tautomerism, particularly when hydrogen bonding becomes possible.)



(60) **(61)** **(62)**



(63) **(64)**

Table 6. Tautomerism of Substituted Pyrroles, Furans and Thiophenes

Ring	Substituted position	Substituent OH	NH_2	SH
Pyrrole	2	$C=O^{a}$	$NH_2{}^{b}$	–
	3	$C=O^{c}$	$NH_2{}^{b}$	–
Furan	2	$C=O^{d}$	$NH_2{}^{e}$	–
	3	$C=O^{f}$	$NH_2{}^{e}$	–
Thiophene	2	$C=O^{g}$	$NH_2{}^{h}$	SH^{i}
	3	$C=O^{j}$	$NH_2{}^{h}$	SH^{i}

[a] H. Plieniaaer and M. Decker, *Liebig's Ann. Chem. 598* (1956) 198.
[b] C. A. Grob and H. Utzinger, *Helv. Chim. Acta 37* (1954) 1256.
[c] A. Treibs and A. Ohorodnik, *Liebig's Ann. Chem. 611* (1958) 149
[d] M. P. Cava, C. L. Wilson and C. J. Williams, *J. Amer. Chem. Soc. 10* (1956) 27.
[e] R. Kuhn and G. Kruger, *Chem. Ber. 89* (1956) 1473.
[f] P. Emmott and R. Livingstone, *J. Chem. Soc. 1958*, 4629; P. Ramart-Lucas and M. van Cowenbergh, *Bull. Soc. Chim. France 1935*, 1381.
[g] S. Gronowitz and R. A. Hoffman, *Ark. Kem. 15* (1960) 499.
[h] R. A. Hoffman and S. Gronowitz, *Ark. Kem. 16* (1961) 563.
[i] S. Gronowitz and R. A. Hoffman, *Ark. Kem. 15* (1960) 499; R. A. Hoffman and S. Gronowitz, *Ark. Kem. 16* (1961) 515 and 563; S. Gronowitz, P. Moses and A. B. Hörnfeldt, *Ark. Kem. 17* (1961) 237.
[j] S. J. Holt, A. E. Kellie, D. G. O. Sullivan and P. W. Sadler, *J. Chem. Soc. 1958*, 1217.

For the hydroxyl and the amino compounds, there is thus a certain similarity between the tautomeric behaviour here and that found for the six-membered rings. Throughout organic chemistry, carbonyl groups are more frequently found than C=N imine groups. However, by contrast, for the five-membered ring compounds, the mercapto derivatives now resemble their amino analogues rather than the hydroxy compounds. The thiocarbonyl group is only stable when it is highly polarised, with a large contribution from $C-S^-$. This is easier to achieve in the six-membered rings, where the thiocarbonyl tautomer is conjugated on both sides with the rest of the molecule; in the thiocarbonyl tautomeric forms of pyrroles, thiophenes and furans the contribution from $C-S^-$ is significantly smaller because the thiocarbonyl tautomer is now non-aromatic.

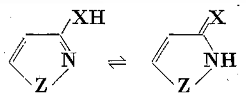
VI. Tautomeric Azoles

The tautomerism of substituted azoles is more complicated than any of the classes of compound thus so far encountered and is frequently of type A/B/C (cf. Scheme II, where the example of 5-hydroxyisoxazole is shown). In addition, pyrazoles and imidazoles, even if they do not contain a potentially tautomeric substituent are capable of tautomerism of type A/A (cf. Scheme II). However, this article concentrates on the tautomerism of *substituted* heterocyclic compounds and the interesting subject of A/A tautomerism cannot be further discussed because of space limitations.

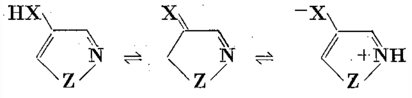
Up to the present, considerable work has been carried out on azoles with two heteroatoms and we shall therefore concentrate on summarising their behaviour to the exclusion of derivatives with three- or four-heteroatoms which are much less well explored. We must consider separately the azoles with the heteroatoms in the adjacent 1,2-positions and in the spaced 1,3-positions.

A) Azoles with Heteroatoms in the 1,2-Positions

3-Substituted isoxazoles, pyrazoles and isothiazoles can exist in two tautomeric forms (**65**, **66**; Z = O,N or S). Available results (Table 7) can be summarised as follows: not only do amino compounds exist as such as expected, but so do the hydroxy compounds under most conditions. The stability of the OH forms of these 3-hydroxy-1,2-azoles is explained by the weakened basicity of the ring nitrogen atom in the 2-position due to the adjacent heteroatom at the 1-position and the oxygen substituent at the 3-position. From the preceding discussion of the effect of chloro-substituents on pyridone tautomerism, it is not unexpected that such a concentration of electron-withdrawing groups near the basic nitrogen atom causes a compound to exist mainly in the OH form.



(65) **(66)**



(67) **(68)** **(69)**

Table 7. Tautomerism of 3-Substituted Azoles with Heteroatoms-1,2

Substituent	Ring	Reference	Phase (s)	Method (s)	Conclusions
OH	1-substituted-pyrazole	a, b	C_6H_{12}, $CHCl_3$, H_2O, Xtal	IR, UV, NMR, *pK*	OH except in H_2O where OH/NH coexist
	isoxazole	c	C_6H_{12}, $CHCl_3$, H_2O, Xtal	IR, UV, NMR, *pK*	mainly OH in all media
	isothiazole	d	MeOH, Xtal	IR, UV	OH
NH_2	1-substituted-pyrazole	e	MeOH, KBr	UV, IR	NH_2
	isoxazole	f	$CHCl_3$, H_2O	IR, NMR	NH_2
	isothiazole	g	CCl_4	IR	NH_2

[a] A. R. Katritzky and F. W. Maine, *Tetrahedron 20* (1964) 319.
[b] See Ref. [32].
[c] A. J. Boulton, A. R. Katritzky, A. Majid Hamid and S. Øksne, *Tetrahedron 20* (1964) 2835.
[d] J. Goerdeler and W. Mittler, *Chem. Ber. 96* (1963) 944; J. Goerdeler and U. Keuser, *Chem. Ber. 97* (1964) 3106.
[e] H. Dorn, G. Hilgetag and A. Zubek, *Chem. Ber. 99* (1966) 183.
[f] A. J. Boulton and A. R. Katritzky, *Tetrahedron 21* (1961) 51.
[g] J. Goerdeler, *Angew. Chem. 74* (1962) 498; J. Goerdeler and W. Mittler, *Chem. Ber. 96* (1963) 944; W. R. Hatchard, *J. Org. Chem. 29* (1964) 660.

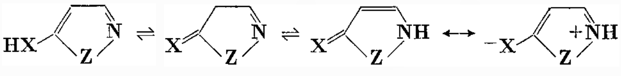
Table 8. Tautomerism of 5-Substituted Azoles with Heteroatoms-1,2

Substituent	Ring	Reference	Phase (s)	Method (s)	Conclusions
OH	1-substituted-pyrazole	a, b	C_6H_{12}, $CHCl_3$, EtOH, H_2O, Xtal	IR, UV, NMR, *pK*	CH in non polar; increasing NH in polar; NH favoured by 4-subst.
	isoxazole	c	C_6H_{12}, $CHCl_3$, EtOH, H_2O, Xtal	IR, UV, NMR, *pK*	
NH_2	1-substituted-pyrazole	d	CCl_4	NMR, IR	NH_2
	isoxazole	e	$CHCl_3$, H_2O	IR, NMR	NH_2
	isothiazole	f	CCl_4	IR	NH_2
SH	isoxazole	g	C_6H_{12}, CCl_4, MeOH, Xtal	IR, UV	SH

[a] See Ref. [31].
[b] See Ref. [32].
[c] A. R. Katritzky, S. Øksne and A. J. Boulton, *Tetrahedron 18* (1962) 770.
[d] H. Dorn and A. Zubek, *Chem. Ber. 101* (1968) 3265.
[e] A. J. Boulton and A. R. Katritzky, *Tetrahedron 12* (1961) 51.
[f] J. Goerdeler, *Angew. Chem. 74* (1962) 498; J. Goerdeler and W. Mittler, *Chem. Ber. 96* (1963) 944; W. R. Hatchard, *J. Org. Chem. 29* (1964) 660.
[g] G. Adembri and R. Nesi, *J. Heterocyclic Chem. 4* (1967) 54.

The 4-substituted analogues can exist in two uncharged tautomeric forms **67** and **68** and in addition, in the zwitterionic form **69**. This type of tautomerism has been very little investigated up until the present, and it is not yet possible to make any sound generalisations.

For 5-substituted isoxazoles, pyrazoles, and isothiazoles, three uncharged tautomeric forms are possible (**70**, **71** and **72**). Considerable work has been carried out in these series and some conclusions are recorded in Table 8. Once again the amino derivatives exist as such. In the case of the hydroxy compounds, the hydroxyl form is of little importance (except, as will be seen later, in special cases where a suitable substituent in the 4-position can form a hydrogen bond with the 5-hydroxyl group). The relative occurance of the 4H-oxo form (**71**) and 2H-oxo tautomer (**72**) depends on the substitution pattern and on the solvent. Tautomer (**72**) is considerably more polar than **71**, with a large contribution from the charge-separated canonical structure **73**. Hence, it is not unexpected that the 2H-oxo tautomer **72** is strongly favoured by polar media. A substituent at the 4-position also tends to favour form **72** over **71** because of conjugation or hyperconjugation of the 4-substituent with the 3,4-double bond. Some detailed results for isoxazolin-5-ones are given in Table 9, and 1-phenylpyrazolin-5-ones show a similar pattern.[31, 33]



(70) **(71)** **(72)** **(73)**

The most complex tautomerism for azoles with heteroatoms in the 1,2-position occurs for pyrazoles which are not substituted on nitrogen. Scheme VI shows the four important tautomeric structures (**74** to **77**) for 3-methylpyrazolin-5-one and **78**, **79** as examples of other possible structures. A detailed investigation of this system[33] dis-

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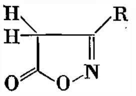
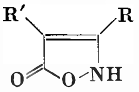
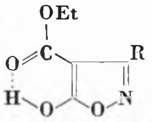
[31] A. R. Katritzky and F. W. Maine, *Tetrahedron 20* (1964) 299.
[32] See also: J. Elguero, R. Jacquier and G. Tarrago, *Bull. Soc. Chim. France 1967*, 3780.
[33] A. R. Katritzky, F. W. Maine and S. Golding, *Tetrahedron 21* (1965) 1693.

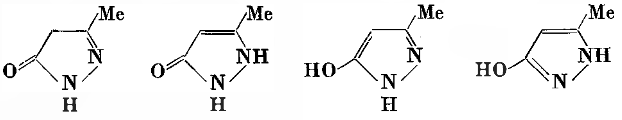
Table 9. Tautomerism of isoxalin-5-ones: summary of predominant forms[a]

	R = Me, *t*-Bu, Ph, *p*-NO_2PH, *p*-MeOPh, CH in cyclohexane, CCl_4,$CHCl_3$ and solid state *ca.* 3 : 1 CH : NH in H_2O
	R′ = Me, Br, Br, Br, Br R = Ph, *t*-Bu, Ph, *p*-NO_2PH, *p*-MeOPh } $(CH_2)_4$ CH in cyclohexane, mainly CH in $CHCl_3$, NH in H_2O, solid state
	R = Me, Ph OH in cyclohexane OH + NH in $CHCl_3$ NH in H_2O and solid state

[a] A.R.Katritzky, S.Øksne and A.J.Boulton, *Tetrahedron 18* (1962) 770.

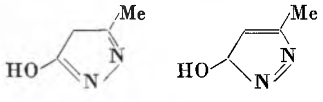
Scheme VI

Four Significant Tautomeric Structures for 3-Methyl-5-pyrazolone



74 75 76 77

Other non-important structures include:



78 79

closed that in aqueous solution (polar medium) the importance of the tautomers is **75** > **77** ≫ **76** or **74** whereas in cyclohexane solution, (non-polar medium) **77** > **74** ≫ **75** or **76**. These conclusions are in good agreement with what is expected from the simpler cases, although it is somewhat surprising that the hydroxy form **77** is so much to the forefront.

B) Azoles with Heteroatoms in the 1- and 3-Positions

The tautomerism of 2-substituted 1,3-azoles (**80** ⇌ **81**) is summarised in Table 10. Whereas amino compounds occur invariably as such, all the potential hydroxy derivatives exist in the oxo form, and in this series the sulphur compounds resemble their oxygen analogues. There is a close analogy between the tautomerism for

Table 10. Tautomerism of 2-Substituted Azoles with Heteroatom-1,3

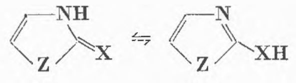
Substituent	Ring	Reference	Phase (s)	Method (s)	Conclusions
OH	1-substituted-imidazole	a	KBr disc	IR	NH
	oxazole	a	MeOH, CCl_4	UV, IR	NH
	thiazole	b	alcohol, CS_2	UV, IR	NH
NH_2	1-substituted-imidazole	c	0.1 N aq. KCl, EtOH/aq KCl	*pK*	NH_2
	oxazole	d	MeOH	UV	NH_2
	thiazole	e,f	EtOH, $CDCl_3$	UV, NMR	NH_2
SH	1-substituted-imidazole	a,g	liquid film, MeOH, EtOH	IR, UV	NH
	oxazole	a	CCl_4, MeOH	IR, UV	NH
	thiazole	g,h	CCl_4, EtOH	IR, UV	NH

[a] R.Gompper and H.Herlinger, *Chem. Ber. 89* (1956) 2816 and 2825.
[b] G.Klein and B.Prijs, *Helv. Chim. Acta 37* (1954) 2057.
[c] B.T.Storey, W.W.Sullivan and C.L.Moyer, *J. Org. Chem. 29* (1964) 3118.
[d] R.Gompper and F.Effenburger, *Chem. Ber. 92* (1959) 1928.
[e] M.Sélim, M.Sélim, O.Tétu, G.Drillien and P.Rumpf. *Bull. Soc. Chim. France 12* (1956) 3527.
[f] L.M.Werbel, *Chem. & Ind. 1966*, 1634.
[g] A.Lawson and H.V.Morley, *J. Chem. Soc. 1956*, 1103.
[h] J.Goerdeler and W.Mittler, *Chem. Ber. 96* (1963) 944; J.Goerdeler and W.Keuser, *Chem. Ber. 97* (1964) 3106.

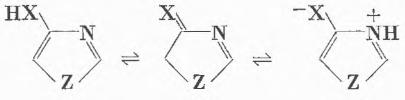
Table 11. Tautomerism of 4- and 5-Substituted Azoles with Heteroatoms-1,3

Substituent	Ring	Reference	Phase (s)	Method (s)	Conclusions
4-OH	oxazole	a	EtOH, Xtal, Me_2SO	UV, IR, NMR	CH
	thiazole	b	Me_2SO, Me_2CO	NMR, IR	OH and CH
5-OH	oxazole	c	Xtal	NMR	CH
5-NH_2	oxazole	d	$CDCl_3$, Xtal	IR, NMR	NH_2

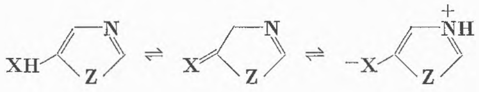
[a] H.Najer, R.Guidicelli, J.Menin and N.Voronine, *Bull. Soc. Chim. France 1967*, 207.
[b] S.Gronowitz, B.Mathiasson, R.Dahlbom, R.Holmberg and K.A.Jensen, *Acta Chem. Scand. 19* (1965) 1215.
[c] F.Weggand and W.Steglich, *Angew. Chem. 73* (1961) 433.
[d] G.Kille and J.-P.Fleury, *Bull. Soc. Chim. France 1967*, 4619.



(80) (81)



(82) (83) (84)



(85) (86) (87)

all these derivatives with the corresponding 2-substituted pyridines.

4-Substituted 1,3-azoles exist in two non-charged tautomeric forms **82** and **83** together with the zwitterionic form **84**. 5-Substituted 1,3-azoles also exist in forms **85** and **86** together with the zwitterionic forms **87**. Some of the limited results are summarised in Table 11: for the potential hydroxy forms, the non-aromatic tautomers of type **83** and **86** clearly can be of importance, but a detailed discussion must await further work.

VII. Summary and Conclusions

In this short article it has not been possible to give more than a brief indication of some of the most important tautomeric situations in heterocyclic chemistry. We have not considered at all heterocyclic rings other than five- and six-membered with one or two hetero-atoms; further, several of the classes of tautomerism shown in Scheme I have either not been mentioned at all or very briefly. There is much additional work to be done and there are several facets of heterocyclic tautomerism that we still do not begin to understand. However, having said all this, it should be emphasised that a great deal *is* understood and with the results already in the literature, we now either know, or can make an intelligent guess at, the predominant tautomeric form for perhaps 99% of the compounds that are likely to be encountered as natural products or in the course of organic synthetic or degradative studies. The relative stabilities of these tautomeric forms are governed by logical rules which are fairly easy to understand. A little effort in this direction will be amply repaid by the increased understanding of the mechanism of heterocyclic reactions which will follow.

It is important that all heterocyclic chemists should depict the structures of potentially tautomeric compounds in their predominant form. This is of enormous help in rationalising their physico-chemical properties and their chemical reactions. Such help is desirable enough for heterocyclic chemists themselves, but even more important for the other scientists who have to deal with heterocycles, particularly the biologists who will become confused and misled unless we do write down what we mean.

I would like to express my thanks to the many chemists who have collaborated in the research on tautomerism carried out by my own group successively in Oxford, Cambridge and Norwich over the period 1954 to 1969, some of whose names are mentioned in the references.