U. D. C. 541.623 : 535.34.083

Study of Tautomerism by Nuclear Magnetic Resonance Spectroscopy

A.I.Kol'tsov and G.M.Kheifets

The present review describes the contribution of NMR to the study of prototropic tautomerism of various types, with the exception of keto-enol tautomerism, which was dealt with in an earlier review[1]. The bibliography contains 221 references.

CONTENTS

I.	Imine-enamine tautomerism	452
II.	Amide-imidol tautomerism	453
III.	Ketoamine-enolimine tautomerism	454
IV.	Azo-hydrazone tautomerism	457
V.	Amine-imine tautomerism	459
VI.	Nitroso-oxime tautomerism	460
VII.	Nitrone-hydroxylamine tautomerism	461
VIII.	Complex tautomerism of heterocyclic compounds	461
IX.	Ring-chain tautomerism	464
X.	Protonation of molecules with two or more proton-accepting centres	464

I. IMINE-ENAMINE TAUTOMERISM

As with keto-enol tautomerism, the tautomeric change takes place slowly, and it is possible to observe separately the PMR spectra of the two forms:



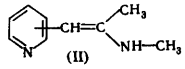
(A) (B)

Ahlbrecht and coworkers[2] obtained the imine (IA) by condensing α-phenylpropionaldehyde with methylamine. Equilibrium with the enamine form (IB) is gradually established. The quantity of the enamine form increases with decrease in temperature and with increase in the polarity of the medium. The same picture is observed for non-chelate enol forms[1]. At 50° the equilibrium mixture contains 72% of the imine (IA) in chloroform and 32% in DMSO†. The amine tautomer (IB) consists of a mixture of the *cis*- and *trans*-isomers. *cis*-*trans*-Isomerisation takes place in the tautomeric change.



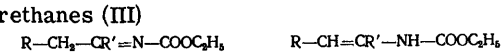
(IA) (IB)

The same authors[3] subsequently studied the influence of substituents on the imine-enamine equilibrium. For example, it was shown that the concentration of the enamine form (II) depends markedly on the position at which the acyclic residue is attached to the pyridine ring (100% enamine in the α- and γ-positions, and 61% in the β-position in DMSO). This result is apparently related to the deficit of electrons in the α- and γ-positions of the heterocyclic ring.



(II)

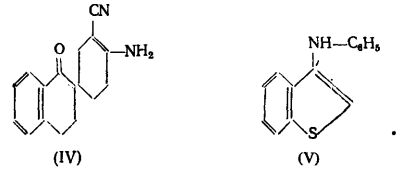
Colvin and coworkers[4] observed the tautomerism of the iminourethanes (III)



(IIIA) (IIIB)

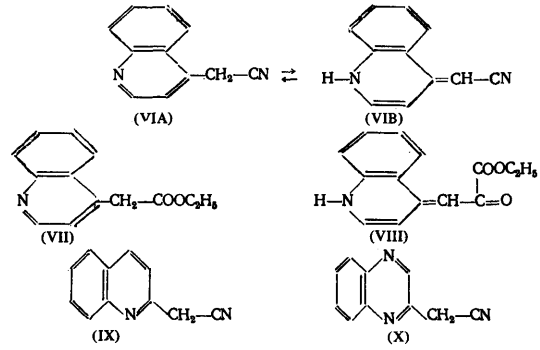
and detected forms (IIIA) and (IIIB) in comparable amounts. The broadened PMR signals of the amino-group lay in the range 3–4 p.p.m. ‡

Compound (IV) exists entirely in the enamine form[5]:



(IV) (V)

The amine form of the 3-phenylamino thianaphthene (V) predominates in neutral solvents[6]. In DMSO, 25% of 4-quinolylacetonitrile is present as the enamine form (VIB), whereas for the ester (VII) the enamine form is not observed, and for the pyruvate (VIII) the enamine form is the chief form[7]. This is apparently due to the stabilisation of the enamine as a result of conjugation between the nitrogen atom of the ring and the functional group of the side chain, which compensates the dearomatization of the heterocyclic ring. The enamine forms of 2-quinolylacetonitrile (IX) and 2-quinoxalylacetonitrile (X) are not detected[7].

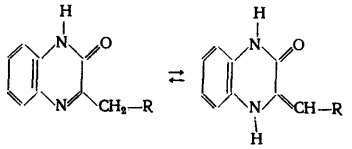


(VIA) (VIB) (VII) (VIII) (IX) (X)

†Dimethyl sulphoxide.

‡In this review the chemical shifts are given in the τ scale.

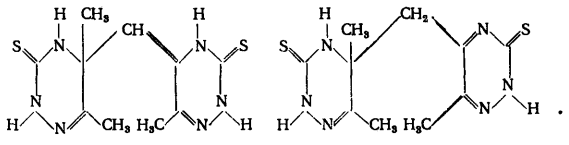
For the oxo-derivatives (XI), in which the aromaticity of the heterocyclic ring is destroyed, however, the enamine form (XIB) predominates in various solvents [7,8]:



(XIA) (XIB)

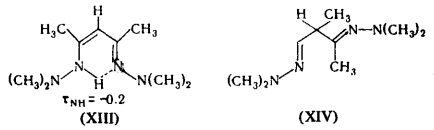
(100% for R = C_6H_5 and 70% for R = CN). The concentration of form (XIB, R = CN) decreases with increase in temperature [8].

For the dimers (XII) in DMSO, the A ⇌ B equilibrium is observed [9]:



(XIIA) (XIIB)

The tautomerism of bis-dialkylhydrazones can be regarded as imine-enamine tautomerism [10]. Acetylacetone bis-dialkylhydrazone exists entirely in the hydrazone-hydrazine form (XIII), whereas the corresponding α-methylacetylacetone derivative exists as 100% dihydrazone (XIV); this is attributed to the instability of the planar chelate structure, resulting from the spatial interaction of the methyl groups:



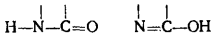
(XIII) (XIV)

For compounds of type (XIII), intra-chelate tautomerism takes place. The rapid migration of the proton between the nitrogen atoms and the consequent effective equivalence of the C–CH_3 groups is indicated by their single PMR signal in the spectrum of compound (XIII). [10]

The imine-enamine tautomerism of *o*-ethylvalerolactam [11] and *N*-isopropylideneisopropylamine [12] has been confirmed by deuteration of the protons on the carbon atoms.

II. AMIDE-IMIDOL TAUTOMERISM

The width and CS§ of the PMR signal of the mobile protons are not reliable criteria for choosing between the amide (A) and imidol (B) forms. The CS of the nitrogen and oxygen (^{17}O) nuclei and the SSCC¶ between these nuclei and the protons are more informative. The more readily available data on the CS of the stable protons of the molecule and, where possible, on the SSCC between these protons and the mobile protons are more frequently used, however.



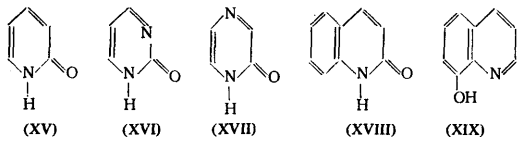
(A) (B)

§Chemical shifts.

¶Spin-spin coupling constants (*J*).

The absence of the imidol form (B) in simple amides† was confirmed by the PMR spectra. In all secondary amides studied, SSC between the α-protons of the substituent and the amide protons (J = 5 Hz) is observed [14,15]. The ^{15}N–H SSCC in formamide is close to 90 Hz. [16] The existence of the imidol form in the amides and hydrazides of phosphorylated carboxylic acids has been reported [17]. The imidol form is more probable for heterocyclic compounds, where it may be stabilised as a result of the formation of a heteroaromatic system. The results of NMR studies of a number of heteroaromatic compounds for which rapid tautomerism of only the amide-imidol type is possible are examined below.

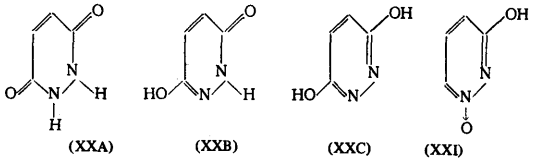
The 2-oxo-derivatives of pyridine (XV), [18] pyrimidine (XVI), [19] pyrazine (XVII), [20] and quinoline (XVIII) [21] exist in the amide form (A). For compound (XV) in non-polar media, ^{15}N–H SSC (90 Hz) is observed at low temperatures. The low values of τ_{NH} (–3.6) are attributed to the formation of dimers with strong InterMHB‡:



(XV) (XVI) (XVII) (XVIII) (XIX)

The amide structure of compounds (XVI) and (XVII) was demonstrated by comparing the CS of the stable protons of the tautomeric and fixed (O- and N-methylated) compounds. These CS were found to be sensitive to the breakdown of the aromaticity of the heterocyclic ring on production of form (A). For compound (XVIII), the ^{14}N CS was measured (235 p.p.m. relative to NO_3^-). This value is typical for amides and differs sharply from the value for 8-quinolinol (XIX) (90 p.p.m.) with sp^2-hybridisation of the nitrogen atom.

Of the three tautomeric forms of 3,6-dioxopyridazine (XX), the symmetrical form (XXA) was first proposed as the predominant form, since the spectrum shows a common signal for the protons in positions 4 and 5§. [21] These protons may also become effectively equivalent, however, if there is rapid exchange between two equivalent forms (XXB). Later, evidence in support of the oxo-hydroxy-structure (XXB) was obtained from the PMR spectra of model compounds [23,24], in agreement with the infrared and ultraviolet spectra [25-27].



(XXA) (XXB) (XXC) (XXI)

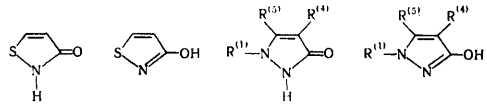
According to the PMR data, and in agreement with the infrared and ultraviolet spectra, 3-hydroxypyridazine-*N*-oxide and its methyl derivatives exist chiefly in the imidol form (XXI). [28]

†Form (B) was erroneously assumed to be present in benzoyl-α-aminoethylbenzene on the basis of optical rotatory dispersion data [13].

‡Intermolecular hydrogen bonding.

§The infrared and ultraviolet spectra indicate that the symmetric dioxo-form (XXC) is unlikely.

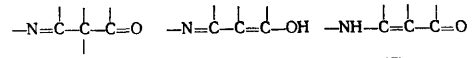
Of the two rapidly interconvertible tautomeric forms of 3-hydroxyisothiazole (XXII), the form (XXIIIB) predominates in $CDCl_3$ (100%) and also in DMSO and methanol (~75%).[29]



(XXIIA) (XXIIB) (XXIIIA) (XXIIIB)

Tautomerism of the amide-imidol type is observed in *N*-substituted pyrazol-3-ones (XXIII, $R^{(1)} = CH_3$, C_6H_5; $R^{(4)}$, $R^{(5)} = H$, CH_3).[30,31] The PMR, infrared, and ultraviolet spectra indicate that in pyridine, these compounds exist chiefly in the hydroxy-form (XXIIIB), whereas in aqueous-alcoholic solutions, appreciable quantities of the oxo-form (XXIIIA) are observed[30,31].

III. KETOAMINE-ENOLIMINE TAUTOMERISM

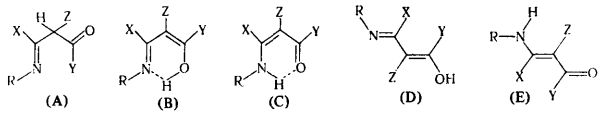


(A) (B) (C)

Like the amide form of the simple amides, the keto-amine form (C) of the vinylogous amides examined below is the most stable. The change to the enolimine form (B) generally takes place if this is accompanied by a significant gain in the energy of conjugation of the molecule as a whole (for example the formation of an aromatic ring). The keto-imine form (A) usually exists in sterically hindered systems.

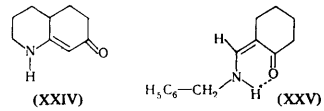
1. Schiff's Bases–Derivatives of β-Dicarbonyl Compounds

The possible tautomeric forms of the Schiff's bases (SB) (A–E) examined here are analogous to the tautomeric forms of the corresponding β-dicarbonyl compounds[1]. The SB usually exist in the stable ketoamine chelate form (C) and in some instances in the non-chelate form E¶ (Table 1).



(A) (B) (C) (D) (E)

The suggestion, based on the ultraviolet spectra[34], that the enol-imine tautomers (B) and (D) exist is refuted by PMR data[32,35]†. The PMR spectra show low-field signals due to the chelate protons ($\tau_{NH} < 1.4$), which are split in the spectra of the compounds containing ^{15}N, with SSCC 88–95 Hz. Moreover, SSC with the protons of the amino-group leads to splitting of the signals of the substituents R = Alk and X = H with SSCC 4.5–8.0 Hz and 12–14 Hz respectively. The keto-amine form also predominates in compounds (XXIV) and (XXV).[39,40]



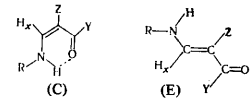
(XXIV) (XXV)

¶The presence of traces of the keto-imine form (A) in some compounds is indicated by deuterium exchange of the α-protons (Z = H) in D_2O.[36,37]

†The enol-imine structure has been assigned to the product of the monocondensation of 4,5-diaminopyrimidine with acetylacetone[38].

The *trans*-isomers (E, Z = H) of the keto-amine tautomer, detected for a number of amino-derivatives of β-aldoketones (Table 1) and acetoacetic ester[41], are characterised by high values of τ_{NH} (> 3.3) and the SSCC between the vinyl protons ($J_{HC=CH}$ = 12–13.5 Hz). For the *cis*-forms (C, Z = H) $J_{HC=CH}$ = 7–8 Hz, and the α-protons are less shielded in view of the proximity of the carbonyl oxygen atom[32] (Table 1). The SSCC with the amine protons are the same for the *cis*- and *trans*-isomers.

Table 1. *cis*-*trans* Isomerism of Schiff's base derivatives of β-ketoaldehydes[32]:



(C) (E)

Compounds			Medium	Concn., M	Concn. of tautomers, %		τ_{NH}		τ_Z		J_{H_X-Z}, Hz	
R	Z	Y			C	E	C	E	C	E	C	E
H	H	CH_3	—[a]	—			0.9	3.3	4.97	4.58	7.5	12,8
			$CDCl_3$	2,0	90	10	0.3	3.3	4.95	4.61	7.9	13,2
H	CH_3	CH_3	$CDCl_3$		25	75	b	4.8	8.18	8.33		
CH_3	H	CH_3	—[a]	—	0	100	—	b	—	4.87	—	13.3
			$CDCl_3$	1.9	64	36	0.3	b	5.01	4.84	7.3	13.1
			$CDCl_3$	1.0	75	25	0.4	b	5.02	4.81	7.4	13.3
CH_3	CH_3	CH_3	$CDCl_3$	1.6	43	57	0.4	4.9	8.20	8.35	—	—
$CH_2C_6H_5$	H	CH_3	a	—	90	10	0.1	—	5.03	4.72	7.4	11.8
			$CDCl_3$		100	0	0.1	—	4.97	—	7.5	—
CH_3	H	C_6H_5	$CDCl_3$		100	0	—0.2	—	4.32	—	7.4	—
C_2H_5	H	C_6H_5	$CDCl_3$		100	0	—0.3	—	4.31	—	7.6	—
C_6H_5	H	CH_3[c]	CCl_4		100	0	—2.77	—				

[a] Pure liquids.
[b] Very broad signals.
[c] Ref. 33.

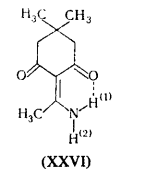
The concentration of the *trans*-isomer increases when the α-hydrogen atom (Z) is replaced by a methyl group and decreases when the methyl groups on the nitrogen atom and the carbonyl group (R and Y) are replaced by phenyl or benzyl groups (Table 1). These effects are related to the steric interactions of the substituents in the isomers (C) and (E).[32] Dilution in inert solvents decreases the proportion of the *trans*-isomer as a consequence of the rupture of the IntraMHB, which stabilises form (E).[32]

trans-Isomers were not detected in the SB derivatives of acyclic β-diketones[36,42].

The chelate amine protons of the SB are more shielded than the protons in the chelates of the corresponding β-dicarbonyl compounds, but the nature of the dependence of τ_{NH} and τ_{OH} on the substituents X and Y is the same[32,36,41,42]. τ_{NH} decreases by almost 3 p.p.m. on going from R = H to R = C_6H_5 (Table 1). Low values of τ_{NH}, indicating strong IntraMHB‡, are characteristic of the SB derivatives of the 2-acyldimedones (XXVI)[41] and (XXVII).[33] As in the β-keto-esters, the replacement of the COOAlk group in the SB by the CSSAlk group leads to a sharp decrease (by ~4 p.p.m.) in the shielding of the chelate proton of compound (XXVIII).[43] The medium and

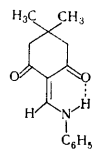
‡Intramolecular hydrogen bonding.

the temperature have little influence on τ_{NH} and the SSCC for the SB, indicating fairly strong IntraMHB and the stability of the keto-amine form (C).



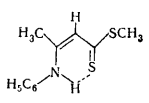
(XXVI)

$\tau_{NH}^{(1)} = -2,10$, $\tau_{NH}^{(2)} = +2,60$ (CDCl$_3$)



(XXVII)

$\tau_{NH} = -6,45$ (CCl$_4$)

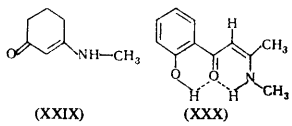


(XXVIII)

$\tau_{NH} = -4,88$ (CCl$_4$)

A significant decrease in τ_{NH} for the chelate forms (C) is observed with increase in the electron-accepting properties of the substituent R.[36]

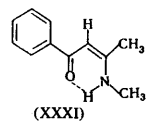
In the non-chelate keto-amine forms (acyclic *trans*-isomers and compounds of the type (XXIX)), an increase in τ_{NH} is observed with increase in temperature and on dilution in inert solvents. The SSCC with the amine protons remain unchanged[42].



(XXIX)

(XXX)

$\tau_{NH} = -0,80$ (CDCl$_3$)

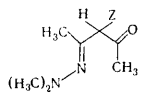


(XXXI)

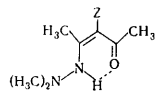
$\tau_{NH} = -1,31$ (CDCl$_3$)

As in the β-dicarbonyl compounds, the IntraMHB in the corresponding SB with a carbonyl group involved in other hydrogen bonding (XXX)[45] is slightly weaker than ordinary IntraMHB (XXXI).[42]

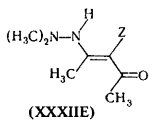
Domnin and Yakimovich[10] demonstrated the presence of three tautomeric forms in the products of the monocondensation of β-diketones with dimethylhydrazine (XXXII, Z = Alk). The concentration of the chelate form (C) decreases with increase in the polarity of the medium and the size of the substituent Z. For compound (XXXII, Z = H), only the chelate keto-hydrazine form (C) was detected. The corresponding derivatives of 2-acetyl-2-benzoylcyclohexanones also exist in a chelate form of type (C) (τ_{NH} = –0.5).



(XXXIIA)



(XXXIIC)



(XXXIIE)

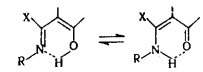
2. Schiff's Bases—Derivatives of *o*-Acylphenols and *o*-Acylnaphthols

In these compounds, which form condensed systems of chelate and aromatic rings, conjugation has a significant influence on the imine-amine equilibrium B ⇌ C (Table 2). The existence of the amine form, which predominates in all SB previously described, is possible in this instance only when the aromatic character of the rings is destroyed; this requires the expenditure of large quantities of energy (tens of kcal mole^{-1}).[46] Nevertheless, the existence of considerable quantities of the amine form in many instances has been demonstrated by means of the NMR spectra§ (see Table 2).

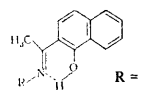
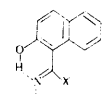
§The amine form of compounds of this type was previously detected by ultraviolet spectroscopy[47].

Measurement of the ^{15}N–H SSCC made it possible to determine fairly accurately the constant for the amine-imine equilibrium at various temperatures, and other thermodynamic constants (Table 2).

Table 2. Concentrations and differences in the enthalpies of the tautomers of aromatic Schiff's bases, and the CS and SSCC of the chelate protons (concentration 0.2 M):



(B) (C)

Compound	Medium	T, °C	τ,	SSCC, Hz			Concn. of tautomers, %		$-\Delta H$, kcal mole^{-1}	References
				^{15}N–H	HN–CH	NH–R	B	C		
										
X=H, R-iso-C_3H_7[a]	CCl_4	20	–2.73	—	0	0	100	0		45
X=H, R=$CH_2C_6H_5$	$CDCl_3$	30	–2.70	—	0	0	100	0		46
X=H, R=C_6H_5	$CDCl_3$	30	–3.22	0	0	—	100	0		48
	$CDCl_3$	–50	–3.61	0	0	—	100	0		
	C_2H_5OH	0	–5.02	13.1		—	85.5	14.5		
X=CH_3, R=CH_3	$CDCl_3$	20	–6.50	17	—		81	19	1.5	49
	$CDCl_3$	–50		32.4	—		64	36		
	CH_3OH	–50		68.2	—		24.2	75.8		
X=CH_3, R=C_6H_5	$CDCl_3$	30	–4.59	0	—	—	100	0		48,49
	$CDCl_3$	–40	–5.01	0	—	—	100	0		
 R = CH_3										
	$CDCl_3$	50	–5.92	76.9	—	4.6	14.6	85.4	2.3	42,44
	$CDCl_3$	15	–5.79	80.3	—	4.8	10.8	89.2		
R=$CH_2C_6H_5$	$CDCl_3$	30	–6.14	—	—	4.8				46,50
R=C_6H_5	$CDCl_3$	30	–6.99	27.5	—	—	69.4	30.6	1.1[b]	48
	$CDCl_3$	–30	–7.41	36.5	—	—	59.4	40.6		
										
X=H, R=CH_3	$CDCl_3$	30	–4.29	64.5			28.3	71.7	2.7	42,46
	$CDCl_3$	0	–4.20	72.3	9.8	4.6	19.7	80.3		
	$CDCl_3$	–45	–4.02	81.4	11.2	5.1	9.6	90.4		
	pyridine	31	–4.78	58.2			35.3	64.7	1.8	
X=H, R=t-C_4H_9	$CDCl_3$	30	–4.70	—	10.5	—	20	80		36
X=H, R=$CH_2C_6H_5$	$CDCl_3$	30	–4.80	—	6.4	3.0	50	50		36
	CCl_4	30	–4.70	—	5.9					46
X=H, R=C_6H_5	$CDCl_3$	30	–5.44	33.0		—	63.3	36.7	1.5	48
	$CDCl_3$	15	–5.51	36.1	5.2	—	59.9	40.1		
	$CDCl_3$	–40	–5.69	49.4	6.9	—	44.1	54.9		
	CCl_4	30	–4.95	12.3		—	86.3	13.7	0.4	
X=CH_3, R=CH_3	$CDCl_3$	30	–3.80	—	—	0	100	0		50
X=CH_3, R=$CH_2C_6H_5$	$CDCl_3$	30	–6.30	—	—	0	100	0		

[a]Concentration 0.02 M.
[b]0.1 in CH_3CN.

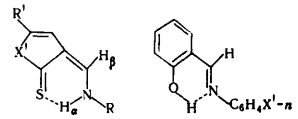
According to the results in Table 2, the concentration of the amine form (C) in α-naphthol derivatives is much greater than that in the analogous derivatives of β-naphthol and phenol. The replacement of an alkyl substituent on the nitrogen atom in α-naphthol derivatives by an aryl substituent leads to a decrease in the percentage of the amine

form. The percentage of the amine form is greater in the SB derivatives of 1-formyl-2-naphthol than in the 1-acetyl-2-naphthol derivatives.

With increase in the polarity of the medium in the order CCl_4, $CHCl_3$, and CH_3OH, the concentration of the keto-amine form increases considerably. Decrease in temperature has the same effect.

The introduction of different substituents into the benzene ring of the SB derivative of 2-hydroxyl-1-naphthaldehyde and aniline has little influence on the concentration of the intrachelate tautomers. In almost all compounds of this type, the SSCC for the chelate and aldehyde protons have values of 3–5 Hz (25–40% of the amine form) [36].

The SB derivatives of 2-thiol-3-formylfurans and 2-thiol-3-formylthiophens (XXXIII) (X′ = O, S; R, R′ = H, Alk, Ar) exist chiefly in the chelate amine form in different solvents. This is indicated by the SSCC values:



(XXXIII) (XXXIV)

$^{15}N-H_\alpha$ = 86 Hz, $H_\alpha-H_\beta$ = 13–15 Hz, and τ_{NH} has values between −2 and −5. [51]

For derivatives of salicylaldehyde (XXXIV), which exist entirely in the enol-imine form, the dependence of τ_{OH} on the substituent X′ (−3.45, −3.25, and −2.58 Ψ for X′ = OCH_3, H, and NO_2 [30]) is the opposite of that observed for τ_{NH} in aliphatic keto-amines. In the naphthol derivatives, the CS of the chelate proton is determined not only by the shielding action of the substituent R, but also by the concentration of intrachelate tautomers (XXX) (Table 2).

3. α-Azaheterocyclic Ketones, Esters, and Pyruvates

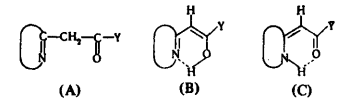
For these compounds, three tautomeric forms are possible (Table 3). The chelate forms (B) and (C), stabilised by IntraMHB, are similar to those for the SB considered above. The existence of form (C) is possible only with breakdown of the aromaticity of the heterocyclic ring. The marked tendency for the keto-amine form (C) to be produced is realised more readily in these compounds than in the SB-derivatives of phenol and naphthol, since the breakdown of the aromaticity of the heterocyclic ring takes place more readily [59].

For the esters (Y = OAlk), form (B) is not observed, and the A ⇌ C equilibrium is displaced considerably towards (A) for pyridine, quinoline, and quinoxaline, and towards (C) for cyclic amides and esters, when the aromaticity of the heterocyclic ring is decreased (see Table 3).

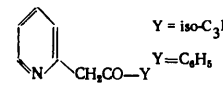
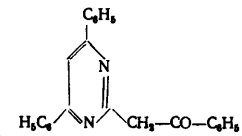
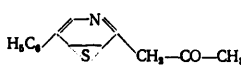
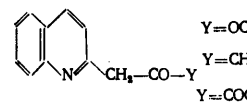
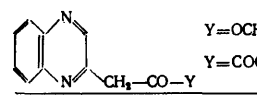
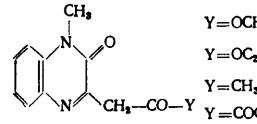
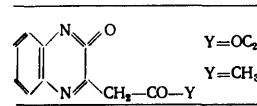
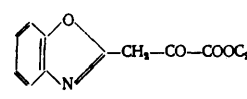
In the ketones (Y = Alk, Ar) and more particularly the pyruvates (Y = COOAlk), the concentration of the keto-imine form (A) is much smaller than for the corresponding esters, and the B ⇌ C equilibrium is determined by the nature of the heterocyclic ring.

For pyridine [52,53], the phenol form (B) is produced, and form (C) is not observed, since $^{15}N-H$ SSC is not observed. With increase in temperature, form (B) for a number of compounds is converted into form (A). [52,53] For the ketones and pyruvates derived from quinoline, quinoxaline, 2-oxo-1,2-dehydroquinoxaline, and other compounds, Mondelli and Merlini [7] detected form (C), in a number of instances in equilibrium with form (A). Form (B) was regarded as unlikely, because of the absence of the marked SSC of the vinyl and methyl protons (Y = CH_3), characteristic of form (B) with $J \simeq 1$ Hz. This conclusion was confirmed by the ultraviolet and infrared spectra [52,53].

Table 3. Tautomeric composition and shielding of the acidic proton for a series of α-azaheterocyclic ketones, esters, and pyruvates.



(A) (B) (C)

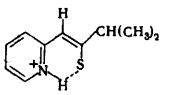
Compound	Medium	Concn. of tautomers, % (A)	(B)	(C)	$\tau_{NH(OH)}$	References
 Y = iso-C_3H_7	CS_2	10	90	0	−4.0	52,53
Y = C_6H_5	CS_2	15	85	0		52,53
	$CDCl_3$	33	67	0	−4.5	54
	CCl_4	70	30	0		55
	DMSO	88	12	0		
 Y = OC_2H_5	$CDCl_3$	100[a]	0	0	—	7
Y = CH_3	$CDCl_3$	25	0	75	−5.0	7
	DMSO	35	0	65	−4.8	7
Y = $COOC_2H_5$	$CDCl_3$	0	0	100[a,b]	−5.7	7
 Y = OCH_3	$CDCl_3$	100[a]	0	0	—	7
Y = $COOC_2H_5$	$CDCl_3$	0	0	100[a]	−3.8	7
 Y = OCH_3	$CDCl_3$	30	0	70		56
Y = OC_2H_5	$CDCl_3$	0	0	100	−1,20	7,56
Y = CH_3	$CDCl_3$	0	0	100[a]	−3,30	7
Y = $COOC_2H_5$	$CDCl_3$	0	0	100[a]	−4,0	7
 Y = OC_2H_5	$CDCl_3$	0	0	100[a]	−0.7	7,57
Y = CH_3	$CDCl_3$	0	0	100[a]	−2,4	7,8,56
	DMSO	0	100	—	−0,37	58

[a] Same concentration in DMSO.
[b] The analogous *para*-derivative likewise does not contain form A.

The preference for a given chelate form (B or C) is apparently determined by the energy of dearomatization of the heterocyclic ring.

The marked downfield shift of the chelate proton and the fact that it depends little on concentration [7] indicate strong IntraMHB. The CS increases in the order: esters,

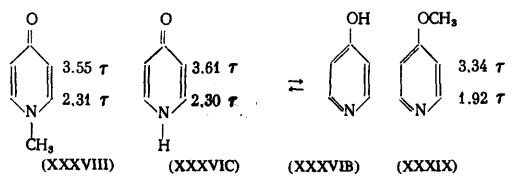
ketones, pyruvates (Table 2). The same picture is observed for the β-dicarbonyl compounds[1]. A noteworthy feature is the very strong downfield shift for 2-picolinyl isopropyl thioketone (τ = −8.60) compared with its oxygen analogue (τ = −4.0). This is attributed[60] to the participation of the bipolar form (XXXV) in the tautomeric equilibrium.



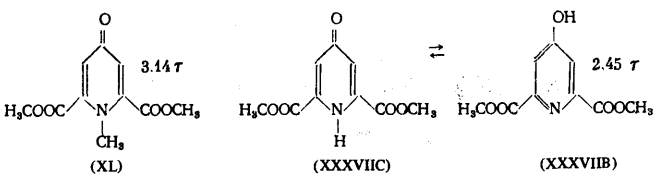
(XXXV)

4. Derivatives of 4-Hydroxypyridine

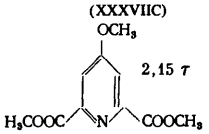
4-Hydroxypyridine (XXXVI) and its 3,5-disubstituted derivatives exist in the keto-amine form (pyridones-4) (XXXVIC),[61] whereas for various 2,6-disubstituted 4-hydroxypyridines, in particular compound (XXXVII), the enolimine hydroxy-form (XXXVIIB) predominates. These data were obtained by comparing the CS of the stable protons¶ of the tautomeric and model compounds (XXXVIII–XLI).[62,63] The pyridone-4 (XXXVI) is characterised by a low value for τ_{NH} (−3.92 in $CDCl_3$).[64]



(XXXVIII) (XXXVIC) (XXXVIB) (XXXIX)

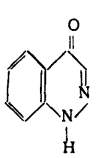


(XL) (XXXVIIC) (XXXVIIB)



(XLI)

4-Cinnolone (XLII) and its derivatives exist in the oxo-form[65,66].



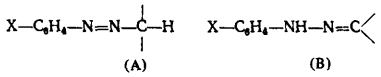
(XLII)

¶In water for 4-hydroxypyridine and in $CDCl_3$ for its 2,6-disubstituted derivatives.

IV. AZO-HYDRAZONE TAUTOMERISM

1. Arylhydrazones and Similar Compounds

For the phenylhydrazones of aldehydes and ketones, two tautomeric forms are possible:



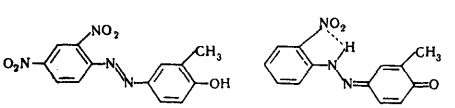
(A) (B)

The PMR spectra of freshly prepared solutions of phenylhydrazones in various solvents, and also of semicarbazones and thiosemicarbazones, contain lines due to only the hydrazone form (B).[67-69] With the passage of time, solutions of some phenylhydrazones become yellow, and the PMR spectra, instead of the signals of the –NH– (τ_{NH} = 2–3) and =CH– groups, show the signals of the protons on saturated carbon atoms, characteristic of the azo-form (A).[67] In inert media, the transformation B → A proceeds to completion in several minutes or tens of minutes, whereas in polar media the transformation is not complete even after several hours. InterMHB with the solvent molecules apparently stabilises form (B). In a number of instances the PMR spectra reveal *cis-trans*-isomerism of tautomer (B).[67,68]

2. Azophenols and Heterocyclic Azo-compounds

In contrast to the situation for the hydrazones examined above, the tautomerism of azophenols and similar compounds involves the transfer of protons between nitrogen and oxygen atoms. The PMR CS of the –NH– and –OH groups in general are not characteristic, so that information on the tautomeric composition is usually obtained from the CS of the stable protons of the ring, and also from the ^{14}N and ^{17}O CS. The *ortho*-protons of the aromatic ring of the azo-form (Ar–N=N–) absorb in lower fields (1.9–2.2 τ) than the corresponding protons of the hydrazone form (Ar–NH–N=) ($\tau > 2.5$). Moreover, the breakdown of the aromaticity on going from the phenolic to the quinone ring structure produces an upfield shift of the signals of the corresponding protons[70].

The PMR spectra of 4-hydroxy-3-methyl-2,4-dinitroazobenzene in $CDCl_3$ showed the signals of both the azophenol (XLIIIA) and quinone-hydrazone (XLIIIB) tautomers. Instead of the singlet signal of the methyl group[7,68] of form (XLIIIA), the spectrum of form (XLIIIB) shows two doublets (7.79 and 7.88 τ; $J_{HC=C-CH_3}$ = 1.4 Hz), which apparently belong to two stereo-isomers.

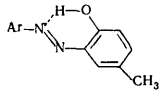


(XLIIIA) (XLIIIB)

The low value of τ_{NH} (−2.33) indicates IntraMHB for compound (XLIIIB).[70] Polar solvents bring about a marked displacement of the equilibrium towards the azo-form. In dimethylacetamide, the signals of form (XLIIIB) were not detected.

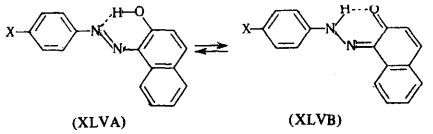
Derivatives of 2-hydroxy-5-methylazobenzene (XLIV), where Ar = nitro- and methoxy-derivatives of benzene, exist completely in the azo-form. The *ortho*-protons of

the substituent Ar absorb in the range 1.9–2.4 τ, and the values of τ_{OH} lie between −2.5 and −3.5 τ.[70,71]



(XLIV)

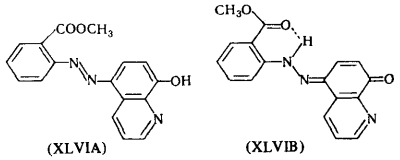
Derivatives of 1-phenylazo-2-naphthol (XLV) give an NMR spectrum which is averaged as a result of rapid intrachelate tautomeric transformations:



(XLVA) (XLVB)

Berrie and coworkers[72] compared the CS of ^{14}N in the α-position relative to the benzene ring (XLV, X = H) (111 τ) with that for compounds which are models of form (A) (−129 τ) and form (B) (175 τ) and found that $CDCl_3$ contains 21% of form (A). The concentration of form (XLV) is decreased to 3% for X = CN, and increased to 48% for X = OCH_3. This tendency was confirmed by the PMR data[70] and also by the infrared and ultraviolet spectra[70]. The *meta*-substituents have a weaker influence on the tautomeric equilibrium[72]. The percentage of the azo-form is greatest in inert media (62% for compound (XLV, X = H) in hexane) and smallest in aqueous-alcohol solution[72]. The values of τ for the chelate protons of compound (XLV) are extremely low: between −5.6 and −6.1.[71,72]

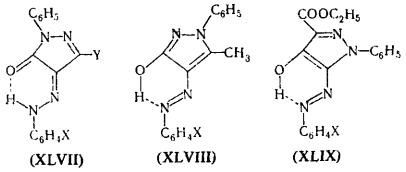
2-Phenylazo-1-naphthol exists in the hydrazone and azo-forms, and the PMR data[70] and the ^{17}O CS[73] indicate that the former predominates in $CDCl_3$. On the other hand, for 2-phenylazo-3-naphthol the equilibrium is displaced towards the azo-form[70]. The azo-form has also been assumed for 4-phenylazo-1-naphthol[70], for which, in contrast to the other phenylazonaphthols, IntraMHB is impossible. The same paper gives PMR data supporting the hydrazone structure for 1-phenylazo-2-anthrol. The spectrum of 5-*o*-carbomethoxyphenylazo-8-quinolinol in $CDCl_3$ shows the individual signals of the azophenol form (XLVIA) and the quinone hydrazone form (XLVIB) (33% and 67%). The spectra of the tautomers differ primarily in the values for the mobile protons (τ_{OH} = 4.6; τ_{NH} = −2.7).



(XLVIA) (XLVIB)

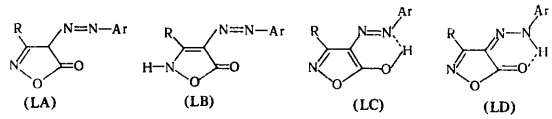
Moreover, the protons in position 4 of the quinoline ring are more shielded in form (XLVIB), in which the aromaticity is destroyed[70].

3-Substituted 1-phenyl-4-arylazopyrazol-5-ones (XLVII, Y = CH_3 or C_6H_5) in $CDCl_3$ exist in the hydrazone form, irrespective of the nature of the substituent X[70,71,74]. The spectra of the compounds with the ^{15}N isotope in the α-position relative to the benzene ring show doublet signals in weak fields (τ_{NH} lies between −3 and 3.5 τ; J_{NH} = 96 Hz). In DMSO and pyridine, compound (XLVII, Y = CH_3) apparently exists as a mixture of the hydrazone and azo-forms[74]. For the azo-derivatives of pyrazol-3-ones (XLVIII) and pyrazol-4-ones (XLIX), however, the azo-form predominates, with higher values of τ_{OH} (0–1.6) (XLVII). For compounds (XLVII–XLIX) it was impossible to detect the oxo-form, in which the mobile proton is joined to the nitrogen or carbon atoms of the ring. These results agree with the infrared spectra[71].



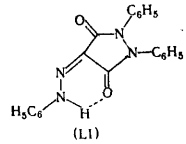
(XLVII) (XLVIII) (XLIX)

For 4-arylazoisooxazol-5-ones (L) in $CDCl_3$, the hydroxy-azo-form (C) and the hydrazone form (D) are not observed, and of the two remaining forms, form (B) predominates:



(LA) (LB) (LC) (LD)

irrespective of the substituents R (H, CH_3, C_6H_5, *p*-$NO_2C_6H_4$) and Ar (C_6H_5, CH_3O–C_6H_4).[75]



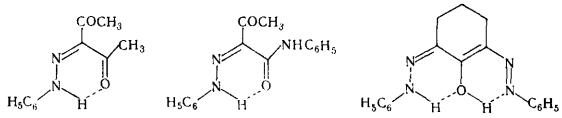
(LI)

τ_{NH} = −3,4

Of the three possible forms of 4-phenylazo-1,2-diphenyl-3,5-dioxopyrazolidine, the chelate hydrazone form (LI) is realised in various solvents[76].

3. Azoketones, Formazans, and Osazones

Phenylazo-derivatives of acetylacetone and acetoacetanilide exist in the chelate hydrazone forms (LII) and (LIII) respectively[70].



(LII) (LIII) (LIV)

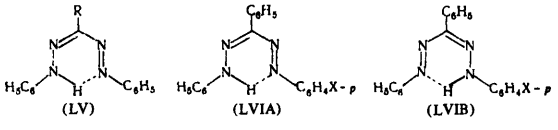
τ_{NH} = −4,00 τ_{NH} = −4,63; −1,47

Cyclohexanone-2,1,3-dihydrazone can exist in two forms: a red form, to which the chelate enol phenylhydrazone-phenylazo-structure (LIV) was assigned, and a yellow ketohydrazone form[77]. The hydrazone form, which exists as the hydrate, is converted into the red azo-form on dehydration. Two analogous forms were also found for other hydrazones of 1,2,3-tricarbonyl compounds.

The existence of tautomerism in formazans was clearly demonstrated by Mester and coworkers[78]. The PMR spectrum of the formazan of *D*-galactose penta-acetate (LV, R = monosaccharide residue) with one ^{15}N α-atom (relative to C_6H_5) (Fig. 1) shows an NH signal, split to form a doublet (J_{NH} = 46.5 Hz), expected for rapid intrachelate† migration of the proton between equivalent positions. When both α-nitrogen atoms are ^{15}N isotopes, the NH signal is split to form a triplet with component ratio 1 : 2 : 1 and J_{NH} = 46.5 Hz, since in the migration

†τ_{NH} depends little on temperature and the medium.

process the proton interacts (alternately) with two ^{15}N atoms.



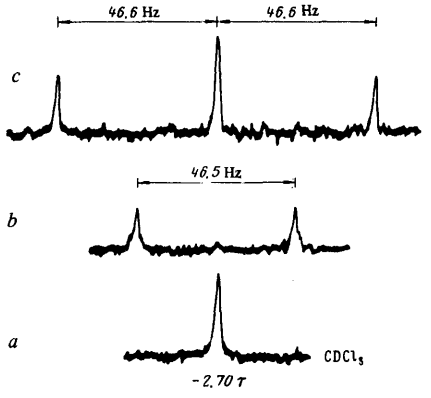
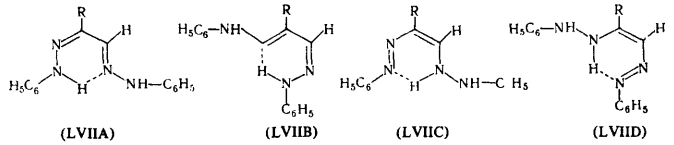


Figure 1. *a*) Low-field part of the PMR spectrum of the formazan of *D*-galactose penta-acetate in dioxan (60 MHz); *b*) the same with one ^{15}N atom; *c*) the same with two ^{15}N atoms [78].

Qualitatively similar PMR spectra should also be observed for a mesomeric structure with symmetrically arranged mobile protons, but this possibility was excluded on the basis of theory [79] and the infrared spectra [80]. In the nonsymmetrical formazans (LVI) the position of the tautomeric equilibrium depends markedly on the nature of the substituent X. When X = OCH_3, the magnitude of the splitting of the (NH...N=) PMR signal is 86.5 Hz, which corresponds to 4% of form A and 86% of form B. For compound (LVI, X = NO_2), form (A) predominates (100%), since splitting is not observed. In the symmetrical structure (LVI, X = H), the splitting is equal to 45 Hz, which is half J_{NH} = 90 Hz. In compounds (LVI), τ_{NH} varies between −4.6 and −5.7 (in $CDCl_3$). [81]

The PMR spectra of the osazones of monosaccharides in dioxan (LVII, R = monosaccharide residue) with two ^{15}N atoms in the α-positions relative to C_6H_5 show two signals due to mobile protons: the chelate proton (τ_{NH} = −2.20) and the non-chelate proton (τ_{NH} = 0.79). Both signals are split to form doublets (J_{NH} = 94.5 Hz and 93 Hz). [82] Thus both protons are joined directly to ^{15}N atoms; this agrees with the previously proposed [83] bis-phenylhydrazone

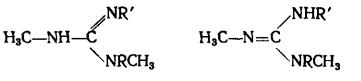


structure (LVII, A or B) and excludes the azo-form (LVII, C and D). The tautomerism of 1,2,3-tris-phenylhydrazone derivatives of propane, cyclopentane, and cyclohexane have been studied [77].

V. AMINE-IMINE TAUTOMERISM

In the amine-imine tautomeric transformation, the mobile proton moves from one nitrogen atom to another. The corresponding PMR signals are not always observed separately and usually are not characteristic. In such instances, the CS of the stable protons of tautomeric and model compounds are compared.

The splitting of the PMR signals of the methyl groups as a result of SSC with the protons on the nitrogen atoms (J = 5 Hz) made it possible to determine the structure of the predominant tautomer (A) of guanidine derivatives (LVIII, R = H, R′ = Cl, and R = Cl, R′ = H). [84]



Of the two possible tautomeric forms of the amidoximes (LIX, R = C_6H_5, $COOC_2H_5$, $CH_2C_6H_5$, or $C(NH_2)$=NOH), the amino-oxime-form (A) is realised in various solvents [57,85].

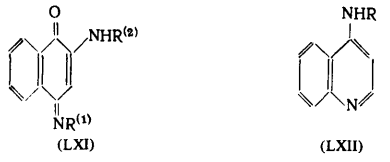


The spectra show the signals of the amine and oxime groups (τ_{NH_2} = 4–5.5; τ_{OH} = 0–1), with intensity ratio 2:1. The PMR of the broad lines was used to determine the tautomeric form of cyanoguanidine (LX) in the crystalline state. Kotera and coworkers [86] compared with experimental value of the second moment of the PMR line with the calculated values for the two possible forms, and concluded that cyanoguanidine has the diamino-structure (LXA).

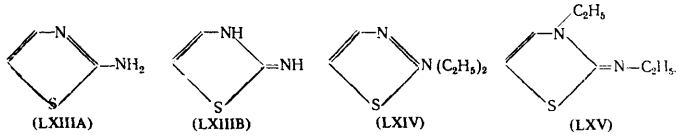


The NMR spectrum of 2-amino-1,4-naphthoquinonimine (LXI) showed that at room temperature an equilibrium between the *o*- and *p*-quinonimines is established [87].

4-Aminoquinolines exist in the amino-form (LXII) in various solvents [88,99].

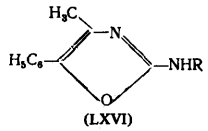


In $CDCl_3$, the CS of the vinyl protons of the potentially tautomeric 2-aminothiazole (LXIII) and the model compound (LXIV) almost coincide (2.86 and 3.52 τ) and differ sharply from the corresponding values for compound (LXV) (3.45 and 4.20 τ). This provides evidence in support of the amino-form (LXIIIA). [90]



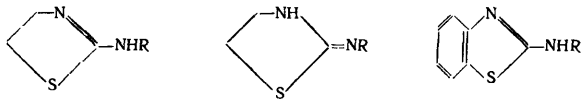
The same result was obtained for 4-phenyl-2-aminothiazole derivatives [91].

In the same way it was found [92] that 2-amino-5-phenyl-4-methyl-2-oxazolines (LXVI, R = H, CH_3, or C_6H_5) exist in the amino-form. It was pointed out [90,92] that the ultraviolet spectra do not give clear-cut information on the structure of these compounds.



(LXVI)

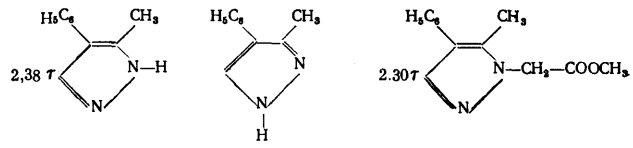
Sheinker and coworkers [93,94] showed that derivatives of 2-aminothiazoline (LXVII) exist in $CDCl_3$ in the amino-form (LXVIIA) if R = H, $CH_2C_6H_5$, or $COCH_3$, and in the imino-form (LXVIIB) if R = COC_6H_5, $COOCH_3$, or $COCCl_3$. In the derivatives with structure (A), the methylene protons in position 4 absorb in the range 6.0–6.1 τ, whereas in the tautomeric and fixed compounds with structure (B) they absorb in the range 6.3–6.5 τ. This effect is due to the deshielding influence of the neighbouring unsaturated nitrogen atom.



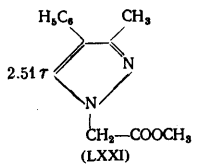
(LXVIIA) (LXVIIB) (LXVIII)

The amino-structure was also assigned to 2-aminobenzothiazoles (LXVIII) on the basis of the CS of the exocyclic nitrogen (310–320 τ). [95]

Comparison of the CS of the vinyl protons of 3-methyl-4-phenylpyrazole (LXIX) and its non-tautomeric derivatives (LXX) and (LXXI) leads to the conclusion that the form (LXIXA) predominates [96].

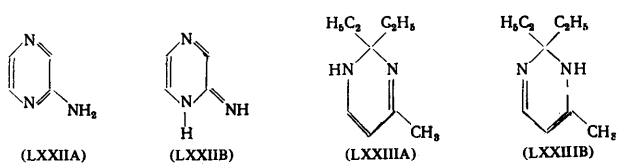


(LXIXA) (LXIXB) (LXX)



(LXXI)

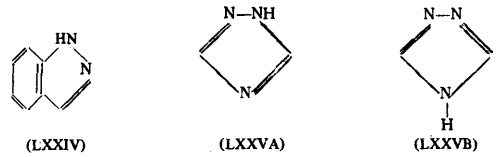
Aminopyrazine in various solvents exists in the amino-form (LXXIIA). This is indicated by the change in the CS and SSCC of the stable protons on breakdown of the aromaticity characteristic of the imino-form (LXXIIB). [20] 1,2-Dihydropyrimidine (LXXIII) in DMSO exists as a mixture of forms A and B in the ratio 2 : 1. [97]



(LXXIIA) (LXXIIB) (LXXIIIA) (LXXIIIB)

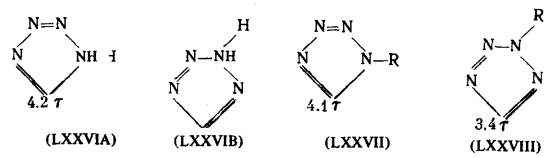
For indazole and its derivatives, the structure (LXXIV) shows best agreement with the PMR spectra [98].

The two signals of the vinyl protons in the spectrum of non-substituted 1,2,4-triazole in hexamethylphosphoramide at −34° indicate that under these conditions the unsymmetrical (1-H)-form (LXXVA) predominates [99].



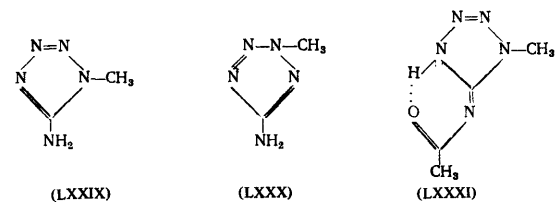
(LXXIV) (LXXVA) (LXXVB)

Benzotriazole exists in the 1-H-form. At room temperature, rapid exchange of protons between positions 1 and 3 is observed, as indicated by the symmetrical spectrum of the aromatic protons [100]. The similarity in the CS of the C–H protons of tetrazole (LXXVI) and its 1-alkyl-derivatives (LXXVII) confirms that in DMPA the tetrazole exists chiefly in the (1-H)-form [101].



(LXXVIA) (LXXVIB) (LXXVII) (LXXVIII)

5-Amino-1-methyl- and 5-amino-2-methyltetrazoles exist in the amino-forms (LXXIX) and (LXXX), but for 5-acetamido-1-methyltetrazole the imino-form (LXXXI), stabilised by IntraMHB, was detected [102].

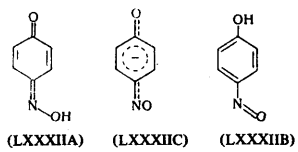


(LXXIX) (LXXX) (LXXXI)

PMR data have demonstrated the equivalence of the four pyrrole rings in various porphyrin derivatives; this is attributed to rapid tautomerism of the amine-imine type [103].

VI. NITROSO-OXIME TAUTOMERISM

Three groups of authors [104–106] have used PMR together with infrared and ultraviolet spectroscopy to study the tautomerism of *p*-nitrosophenols.



(LXXXIIA) (LXXXIIC) (LXXXIIB)

The PMR spectra of 4-nitrosophenol (LXXXII) in DMSO, D_2O acetone, tetrahydrofuran, and other organic solvents indicate that the protons in positions 2 and 6 and 3 and 5 are equivalent. On this basis, Fischer and coworkers [104] concluded that the nitroso-form (B) predominates, with rapid rotation about the C–N bond. Other workers [105,106], however, correctly point to rapid A ⇌ B transformation via the mesomeric anion (C).

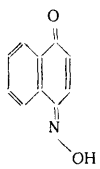
The PMR spectra of form (A), unlike those of form (B), are in fact characterised by different CS for the protons of the ring situated in the *syn*- and *anti*-positions relative

to the oxime group‡. The fact that the CS of the signals of the protons in positions 3 and 5 (and also 2 and 6) coincide, however, does not prove that form (B) predominates, since the same picture will be observed for rapid exchange of (A) with even a small quantity of (B). In the process there is rapid interconversion of equivalent stereo-isomers of form (A).

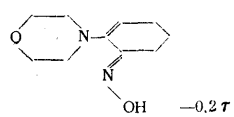
The correct conclusions[105,106] are confirmed by the fact that the values of the CS and SSCC of the nitrosophenol are intermediate between the corresponding values for the model compounds 4-nitrosoanisole and 1,4-benzoquinone-monoxime methyl ether. The addition of a small quantity of HCl or trifluoroacetic acid (TFA) suppresses the ionisation and leads to a sharp decrease in the rate of the tautomeric transformation. This is revealed by a broadening of the PMR signals in these solvents, and in dioxan containing a trace of HCl or TFA it is possible to observe separately the spectra of both tautomers, the concentrations of which correspond to 83–86% of the oxime form and 17–14% of the nitroso-form. An analogous picture is observed in pure dibutyl and dipropyl ethers, in which ionisation is unlikely. These conclusions agree with the ultraviolet spectra in the same solvents.

2-Methyl-, 3-methyl-, 2,6-dimethyl-, and 3,6-dimethyl-derivatives of 4-nitrosophenol, and also 2-chloro-4-nitrosophenol, exist to the extent of more than 95% in the benzoquinonemonoxime form. It has been shown that 3-substituted 1,4-benzoquinonemonoximes exist only in the *anti*-form[106].

Fischer and coworkers[104] compared the PMR spectra of 4-nitroso-1-naphthol and 1,4-naphthoquinonemonoxime methyl ether, and concluded that in DMSO the quinone-oxime form (LXXXIII) predominates.



(LXXXIII)

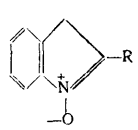


(LXXXIV)

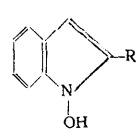
According to PMR data[107], the nitroso-derivative of 1-morpholinecyclohexane in deuterochloroform is present entirely in the form of the oxime (LXXXIV).

VII. NITRONE-HYDROXYLAMINE TAUTOMERISM

Mousseron-Canet and Boca[108,109] showed that the position of the A ⇌ B equilibrium for *N*-hydroxyindoles (LXXXV) depends markedly on the proton-donating properties of the solvent (0% of form A in pyridine and in DMSO, 33% in CCl_4, and 100% in phenol). It was suggested that in neutral solvents and in the absence of a solvent, the tautomers (A) and (B) are combined in associates by InterMHB.



(LXXXVA)

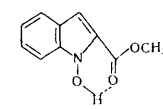


(LXXXVB)

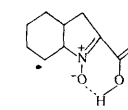
‡Moreover, form (A) should show stronger SSC through the −C=C− bond.

On dilution with proton-donating or proton-accepting solvents, the associates break down and form new InterMHB, which stabilises the corresponding tautomeric form. Since the tautomeric transformation is slow (the proton migrates between the carbon atoms and the heteroatom[1]), the spectra of tautomers (A) and (B) are observed separately. The spectrum of the nitrone (A) contains the signal of the methylene group (6–7 τ) and the spectrum of the enhydroxylamine (B) contains the signals of the *N*-hydroxyl (3.9–4.3 τ) and vinyl protons. It should be noted that the positive charge on the nitrogen atom decreases the value of the CS of the protons of the condensed aromatic ring (by 0.2–0.3 τ) and, more particularly, of the methyl group in position 2 (by 0.8 to 1.1 τ) in the nitrone form, compared with the enhydroxylamine form.

Methyl *N*-hydroxyindolecarboxylate in chloroform is present almost entirely in the hydroxylamine form[110]. The low value of the CS of the hydroxyl proton indicates the chelate structure (LXXXVI).



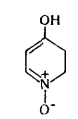
−0,03 τ
(LXXXVI)



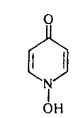
−0,40 τ
(LXXXVII)

On the other hand, with 4-bromo-1-hydroxyindole-2-carboxylic acid the chelate stabilises the nitrone form (LXXXVII).[110]

Nitrone-hydroxylamine tautomerism is observed for 4-hydroxypyridine-*N*-oxide (LXXXVIII). In contrast to the tautomerism of the *N*-hydroxyindoles, however, in this instance the proton migrates rapidly between the oxygen atoms, and the overall PMR spectrum of the two tautomeric forms is observed.



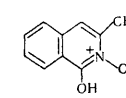
(LXXXVIIIA)



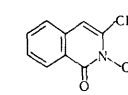
(LXXXVIIIB)

Using models of the tautomeric forms, Katritzky and coworkers[111] found that in aqueous solutions the tautomers (LXXXVIII A and B) are present in the ratio 3 : 2.

On the basis of ultraviolet and PMR spectroscopy, it was concluded[112] that the equilibrium (LXXXIXA ⇌ LXXXIXB) is displaced towards the hydroxylamine form (LXXXIXB).



(LXXXIXA)



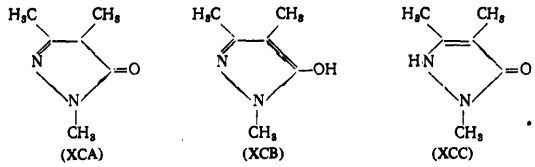
(LXXXIXB)

VIII. COMPLEX TAUTOMERISM OF HETEROCYCLIC COMPOUNDS

This section gives the results of studies of the tautomeric composition of five- and six-membered heterocyclic rings which can exist in more than the two tautomeric forms. Simpler examples were examined above.

1. Five-membered Heterocyclic Rings

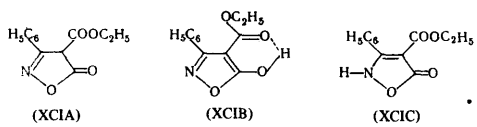
1,3,4-Trimethylpyrazolone-5 (XC), like other 1-substituted pyrazol-5-ones, may exist in three tautomeric forms:



(XCA) (XCB) (XCC)

The PMR spectrum of this compound in chloroform [113], in addition to the intense signals of form (A), shows signals characteristic of forms (B) and (C), or one of them (C(4)–CH_3 8.27; N–CH_3 6.60; NH and (or) OH 1.07 τ). These CS coincide with those for the *N*-methylated derivative, which is a model of form (XCC) and differ from those for the model of form (XCB) (C(4)–CH_3 8.06 τ; N–CH_3 6.46 τ). Thus the pyrazolone (XC) contains form (A) and a smaller quantity of form (C).

3-Phenyl-4-carbethoxyisoxazol-5-one (XCI) can also exist in three tautomeric forms:



(XCIA) (XCIB) (XCIC)

Table 4. Tautomeric composition of derivatives of pyrazol-5-one [30] and isoxazol-5-one [114].

Compound	Chloroform	Methanol	Water	Pyridine
Pyrazol-5-one				
3-Methyl-	A[a]	60%B + 40%C	10%B + 90%C	B
4-Methyl-	A	70%B + 30%C	15%B + 85%C	B
3,4-Dimethyl-	A	35%B + 65%C	C	B
1,3-Dimethyl-	A	25%B + 75%C	C[b]	B
1,4-Dimethyl-	C > A	20%B + 80%C	C	B
1,3,4-Trimethyl-	A > C	C	C	B > C > A
1-Phenyl	A	—	—	—
1-Phenyl-3-methyl	A	C	C[b]	—
1-Phenyl-3,4-dimethyl	50%A + 50%C	C	90%C + 10%A[c]	—
1,3-Diphenyl	A	—	—	—
1-Methyl-3-phenyl	A	—	—	—
Isoxazol-5-one				
3-Methyl-	A[d]	—	—	—
3-Phenyl	A[d]	—	—	—
3-Phenyl-4-methyl	40%A + 60%C	—	—	—
3,4-Tetramethylene-	80%A + 20%C	—	—	—
3-Phenyl-4-carbethoxy-	Bf	—	—	—
3,4-Dimethyl-	70%A[e]	0%A[e]	0%A[e]	30%A[e]

[a] A, B, and C represent the CH-, OH-, and NH-forms respectively (see compounds XC and XCI); [b] 10% A according to ultraviolet spectra [113]; [c] according to Ref. 112; [d] in CCl_4; [e] according to Ref. 115.

The PMR spectrum of its solution in $CHCl_3$ [114] does not contain the signal of a methine proton, and this eliminates the CH-form (A). The mobile proton absorbs in very weak fields (–2.25 τ). This value is much lower than the CS of the group in the NH-form (C) of other isoxazolones (between 0 and +1 τ) [113] and shows good agreement with the chelate structure (B). The tautomeric compositions of other pyrazol-5-ones and isoxazol-5-ones are given in Table 4.

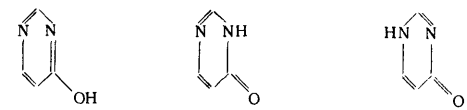
The results in Table 4, obtained by PMR spectroscopy, show that methylation of the nitrogen atom of the pyrazolones increases the concentration of the NH-form (C) at the expense of the CH- and OH-forms (A) and (B). The introduction of an alkyl group in position 4 also displaces the equilibrium considerably towards the NH-form (C) in both pyrazolones and isoxazolones. The CH-form, which predominates in CCl_4 and $CHCl_3$ (particularly in dilute solutions) is almost absent in polar media, in which the NH- and OH-forms are stabilised by InterMHB. The concentration of the OH-form increases with increase in the proton-accepting power of the solvent.

In latter work, the magnetic resonance of the protons [116] and ^{13}C nuclei [117] gave additional information on the tautomerism of 1-phenylpyrazol-5-ones. Electron-donating substituents in position 3 of the ring displace the equilibrium considerably towards the CH-form in various solvents, and electronegative substituents stabilise the OH-form. The influence of substituents and the medium on the keto-enol equilibrium of 2-phenylthiazolin-4-one [118] and 2-phenylthiazolin-5-one [119] has been studied. In the latter instance it was suggested that dilute solutions in polar solvents contain an appreciable quantity of the mesoionic form in addition to the CH- and OH-forms.

Studies of the tautomerism of five-membered heterocyclic compounds by various methods were briefly reviewed in a paper by Elguero and coworkers [30].

2. Six-membered Heterocyclic Rings

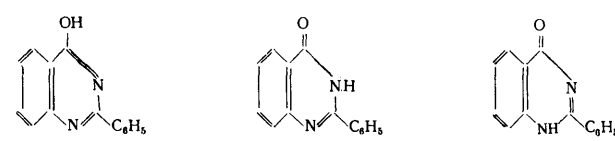
4-Hydroxypyrimidine (XCII) can exist in three tautomeric forms:



(XCIIA) (XCIIB) (XCIIC)

Comparison of the CS and SSCC for 4-hydroxypyrimidine and its methylated derivatives (Table 5), which provide models of the three tautomeric forms, indicates that the predominant form is the quasi-*o*-quinone form (B) in DMSO [120] and in water [121]§. To choose between (B) and (C) it is first of all necessary to compare the CS of the C_5–H signals, which show smaller changes than the others on *N*-methylation [121]. For the SSCC J_{56}, a linear correlation with the bond order is observed (calculation by the MO method for structures A, B, and C [121]). The same method was used to show that a form of type (B) predominates for 4-thiopyrimidine [120].

2-Phenyl-4-hydroxyquinazoline (XCIII) can exist in three analogous tautomeric forms:



(XCIIIA) (XCIIIB) (XCIIIC)

§In agreement with the infrared and Raman spectra [122,123]. According to ultraviolet spectroscopy, tautomers (B) and (C) are present in water in the ratio 2:1. [124]

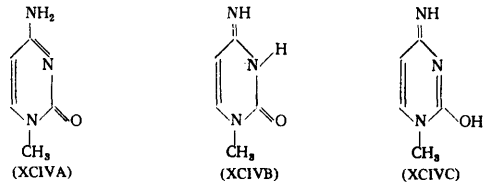
In aromatic dicyclic compounds the signal of the proton in the *peri*-position relative to a carbonyl group lies at lower fields (1.7–1.9 τ) than the other aromatic protons ($\tau > 2.0$), because of the deshielding action of the C=O bond [70,125]. The fact that the PMR spectrum of compound (XCIII) in DMSO contains a low-field doublet signal of the aromatic proton C_5–H (1.87 τ) reduces the problem to the choice between the two oxo-forms (B) and (C). In the *N*-methylated derivatives which are models of forms (B) and (C) the *peri*-proton absorbs at 1.90 τ and 1.77 τ respectively, provinding evidence in support of the amide form (B), in agreement with the infrared and ultraviolet spectra [126].

Table 5. Parameters of the PMR spectra of 4-hydroxypyrimidine and its methylated derivatives [120,121].

Compound	Medium	CSτ,			SSCC, Hz			Model form
		H_2	H_4	H_5	H_2–H_4	H_2–H_5	H_5–H_6	
4-Hydroxypyrimidine	DMSO [a]	1.80	3.63	2.05	1.0	0.5	6.3	—
	D_2O	1.63	3.49	2.02	1.0	1.2	7.15	
3-Methyl-4-pyrimidone	DMSO	1.50	3.58	2.05	0.85	—	6.0	B
	D_2O	1.58	3.45	2.01	0.80	0.6	6.8	
1-Methyl-4-pyrimidone	DMSO	1.70	3.98	2.28	0.5	2.5	7.0	C
	D_2O	1.64	3.67	2.21	0.6	2.5	7.5	
4-Methoxypyrimidine	DMSO	1.27	3.03	1.45	1.1	0.4	5.4	A
	D_2O	1.32	3.05	1.55	1.2	0.8	6.2	

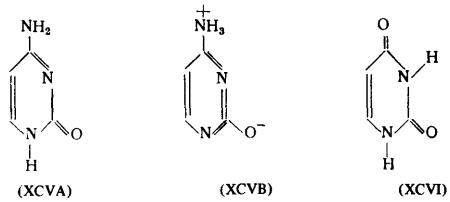
[a]The parameters of the spectra agree with earlier data [19].

The PMR spectrum of 1-methylcytosine (XCIV) with a ^{15}N atom in the amino-group shows splitting (J_{NH} = 90 Hz) of the signal, the intensity of which corresponds to two protons. This provides unambiguous evidence in support of the amino-form (A). [127]



(XCIVA) (XCIVB) (XCIVC)

Analysis of the PMR spectra of cytosine (XCV), for which seven tautomeric forms are possible, confirms the generally accepted form (XCVA) in DMSO and D_2O. [128]



(XCVA) (XCVB) (XCVI)

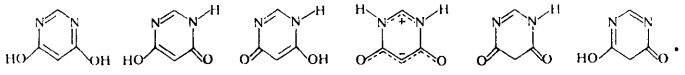
The CS and SSCC (J_{56}) of cytosine and *N*-methylcytosine (XCIV) almost coincide, and the values differ considerably from those predicted for the bipolar form (XCVB), which was erroneously assumed in earlier work [129]. The tautomerism of cytosine nucleosides has been studied [127, 130,131].

PMR spectroscopy has confirmed the diamide structure of uracil (XCVI), for which six tautomeric forms are possible [19,129]. The PMR spectrum of uracil is shown in Fig. 2. The components of the C_6–H doublet (J_{56} = 7.6 Hz) are split as a result of SSC with the amide proton (J_{61} = 5.7 Hz), and the components of the C_5–H doublet are split to form a triplet, as a consequence of SSC with the two amide protons ($J_{51} = J_{53}$ = 1.4 Hz). On heating, the splitting due to the amide protons disappears as a consequence of their rapid intermolecular exchange, leaving only the splitting due to the SSC of the C_5–H and C_6–H protons. The PMR method has also been used to study many potentially tautomeric derivatives of uracil and thiouracil [132,133]. It has been concluded that the diamide form is preferred.



Figure 2. PMR spectrum of uracil in DMSO (40 MHz). [19]

For 4,6-dihydroxypyrimidine (XCVII), which is an isomer of uracil, six tautomeric forms (A–F) are possible:



(XCVIIA) (XCVIIB) (XCVIIC) (XCVIID) (XCIIE) (XCVIIF)

Table 6. Chemical shifts of the PMR of 4,6-dihydroxypyrimidine and its methylated derivatives [134].

Compound	Medium	CSτ,			Model form
		C_5–H	C_4–H	OH or H	
4,6-Dihydroxypyrimidine (XCVII)	DMSO	1.90	4.85$_a$	–1.60[b]	—
	D_2O	1.60	—	—	
N-Methyl derivative (CII)	DMSO	1.76	4.75	–1.30	—
	D_2O	1.46	4.90	—	
O-Methyl derivative (CI)		2.00	2.00	4.56	–2.20	—
		2.07	2.07	4.46	—	
3-Methyl-6-methoxypyrimidone-4- (XCVIII)		1.62	1.62	4.40	—	B
		1.76	1.76	4.42	—	
4,6-Dimethoxypyrimidine (XCIX)	DMSO	1.63	3.85	—	A
Mesomeric betaine (C)	DMSO[c]	—	—	—	D
	D_2O	0.95	4.9	—	

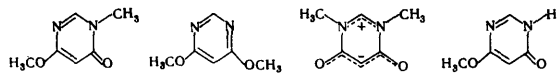
[a]Soluble on heating, C_5–H proton then replaced by deuterium; [b]overall signal of the NH and OH protons; [c]sparingly soluble in DMSO.

Comparison¶ of the CS of 4,6-dihydroxypyrimidine and its *O*- and *N*-methylated derivatives with completely (XCVIII–C) and partly† (CI and CII) fixed structures (Table 6) led to the following conclusion [134]: 1) the mono-*O*-methyl-derivative in aqueous solutions and in DMSO

¶With allowance for the influence on the CS of the C_2–H and C_5–H protons of the neighbouring OCH_3 and N–CH_3 groups.

†For compound (CI) tautomeric forms of types A, B, C, and F are possible, and for compound (CII) forms of types B, C, D, and E are possible.

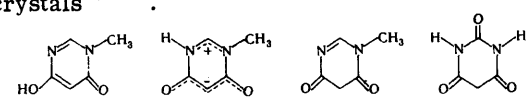
exists in the oxo-hydroxy-form (CI); 2) the mono-*N*-methyl-derivative and 4,6-dihydroxypyrimidine itself exist in DMSO in the oxo-hydroxy-form (CIIB) and (XCVIIB) respectively, whereas in water they exist chiefly in the bipolar ionic form (CIID) and (XCVIID) in equilibrium with a very small quantity of the dioxo-form‡ (CIIE) and (XCVIIE).



(XCVIII) (XCIX) (C) (CI)

The PMR data agree with the results obtained by ultraviolet [135,136] and infrared [137] spectroscopy.

NMR data indicate [134] that barbituric acid in DMSO exists in the trioxo-form (CIII), as in aqueous solutions [139] and crystals [139-141].



(CIIB) (CIID) (CIIE) (CIII)

IX. RING-CHAIN TAUTOMERISM

Ring-chain tautomerism (R-CT) of the electrophilic type (in Jones' terminology [142]) is accompanied in the great majority of examples by the migration of a proton. It can therefore undoubtedly be regarded as a form of prototropic tautomerism§.

In an examination of physical methods used to study R-CT, Jones points out that NMR is becoming one of the most valuable methods used for this purpose [142].

Because of lack of space, we cannot examine the work on R-CT carried out by means of NMR, but the following list, which illustrates Jones' prediction, may to some extent provide a useful supplement to his review.

NMR spectra have been used to study the mutarotation of sugars [144-149], aminosugars [150], and osazones of ascorbic acid [151], and the temperature dependence of the formation of hemiacetals of hydroxyketones [152] and lactones of laevulinic acid [153]. The R-CT of *o*-acylcarboxylic acids [154-159] and the similar transformation of the hemialdehydes of carboxylic acids of the benzene, pyridine, and thiophene series [157,158] have been studied. NMR has been used to study the R-CT of oxazolidines [159,160], various oxadiazines [161-165], thiazolidine- [166] and thiadiazolidine-2-thiones [167], dihydrobenzothiazoles [168], tetrahydropyrimido-4,5-*d*-pyrimidines [169], and the products of the condensation of *o*-hydroxybenzylamine with aldehydes and ketones [170]. R-CT has also been studied in alkaloids which are derivatives of indole [171].

X. DETERMINATION OF THE POINT OF PROTONATION OF UNCHARGED MOLECULES WITH TWO OR MORE PROTON-ACCEPTING CENTRES

Neutral tautomeric forms are the products of the protonation of a mesomeric anion at a given proton-accepting centre. Analogously, the protonation of neutral molecules with two or more proton-accepting centres may lead to the formation of cations with different structures in a state of dynamic equilibrium, which can be regarded as prototropic tautomerism.

The methods examined above are fully applicable to the study of tautomeric equilibrium in these systems by NMR spectroscopy.

Here, as in paragraph IX, we shall restrict ourselves to giving a list (which does not claim to be complete) of papers dealing with NMR studies of the protonation of compounds of various classes: the saturated amides of carboxylic [172-177] and sulphonic [176,178] acids, nitrosoamines [179], phenol and aromatic ethers [180-183], α-diazoketones [184], α,β-unsaturated β-aminocarbonyl compounds [185,189], guanidine [86], nitroguanidine [187], and biguanide [188], 4-dimethylaminoazobenzene [189], pyrroles [190,191] and pyrrolethiazoles [192], thiophenes [193], indoles [194], and indolizines [195,196], imidazoles [197,198] and imidazopyridines [199], pyrazolines [200], various benzazoles [201], 2- [202,203] and 4-pyridones [111,204,205] and their thio-analogues [206], aminopyridines [206], *N*-hydroxypyridine [207], and aminoquinolines [89], 4-phenylpyrimidine [208], and various amino- and hydroxypyrimidines [209], 4,6-dihydroxypyrimidine and its derivatives [134], 1-methylcytosine [127,210], caffeine [211], *s*-triazolo-(1,5*a*)-pyrimidines [212], cinnolines [213], and pteridines [214], nitro- [215,216] and acylazulenes [217] and pseudoazulenes [218], and 3-phenylsydnone [219]. NMR has also been used to study the structures of salts of heterocyclic enamines [220,221].

REFERENCES

1. A. I. Kol'tsov and G. M. Kheifets, Uspekhi Khim., 40, 1646 (1971) [Russ. Chem. Rev., No. 9 (1971)].
2. H. Ahlbrecht, J. Blecher, and F. Kröhnke, Tetrahedron Letters, 439 (1964).
3. H. Ahlbrecht and S. Fischer, Tetrahedron, 26, 2837 (1970); 26, 4777 (1970).
4. D. M. Colvin, B. C. Uff, and J. W. Lewis, Tetrahedron Letters, 6079 (1966).
5. S. Baldwin, J. Org. Chem., 26, 3288 (1961).
6. N. P. Buu-Hoi, Bull. Soc. chim. France, 2658 (1965).
7. R. Mondelli and L. Merlini, Tetrahedron, 22, 3253 (1966).
8. H. Sterk and T. Kappe, Monatsch. Chem., 100, 1274 (1969).
9. J. Adams and R. G. Shepherd, Tetrahedron Letters, 2747 (1968).
10. N. A. Domnin and S. I. Yakimovich, Zhur. Org. Khim., 1, 658 (1965).
11. V. G. Granik, B. M. Pyatin, I. V. Persianova, E. M. Peresleni, N. P. Kostyuchenko, R. G. Glushkov, and Yu. N. Sheinker, Zhur. Org. Khim., 6, 1117 (1970).
12. M. Pfau and C. Ribiere, J. Chem. Soc. (D), 66 (1970).
13. V. M. Potapov and A. P. Terent'ev, Zhur. Obshch. Khim., 31, 1720 (1961); 33, 2702 (1963).
14. L. Skulski, G. C. Palmer, and M. Calvin, Roczn. Chem., 68, 789 (1964).
15. L. Skulski, Bull. Acad. polon. Sci. Ser. Sci. chim., 12, 299 (1964).
16. B. Sunners, L. H. Piette, and W. G. Schneider, Canad. J. Chem., 38, 681 (1960).
17. A. I. Razumov, T. V. Zykova, and R. L. Yafarova, Zhur. Obshch. Khim., 39, 346 (1969).
18. R. A. Coburn and G. O. Dudek, J. Phys. Chem., 72, 1177 (1968).
19. S. Gronowitz, B. Norrman, B. Gestblom, B. Mathiasson, and R. A. Hoffman, Arkiv Kemi, 22, 65 (1964).

‡On the basis of a study of the kinetics of C_5–H deuterium exchange.

§R-CT of the non-prototropic type is regarded as a particular case of valency isomerisation [143].

20. R. H. Cox and A. A. Bothner-By, J. Phys. Chem., 72, 1642 (1968).
21. P. Hampson and A. Mathias, Chem. Comm., 371 (1967).
22. R. Gompper and P. Altreuther, Z. anal. Chem., 170, 205 (1959).
23. A. R. Katritzky and A. J. Waring, J. Chem. Soc., 1523 (1964).
24. O. Ohashi, M. Mashima, and M. Kubo, Canad. J. Chem., 42, 970 (1964).
25. Yu. N. Sheinker and Yu. I. Pomerantsev, Zhur. Fiz. Khim., 30, 79 (1956).
26. Yu. N. Sheinker, T. V. Gortinskaya, and T. P. Sycheva, Zhur. Fiz. Khim., 31, 599 (1957); J. Chim. Phys., 55, 217 (1958).
27. D. M. Miller and R. W. White, Canad. J. Chem., 34, 1510 (1956).
28. H. Igeta, T. Tsuchiya, M. Nakajima, and H. Yokogawa, Chem. Pharm. Bull. (Tokyo), 17, 163 (1969); Chem. Abs., 71, 38 884 (1969).
29. A. W. K. Chan, W. D. Crow, and I. Gosney, Tetrahedron, 26, 2497 (1970).
30. J. Elguero, R. Jacquier, and G. Tarrago, Bull. Soc. chim. France, 3780 (1967).
31. D. F. O'Brien and J. W. Gates, J. Org. Chem., 31, 1538 (1966).
32. G. O. Dudek and G. P. Volpp, J. Amer. Chem. Soc., 85, 2697 (1963).
33. S. Forsen and M. Nilsson, Arkiv Kemi, 19, 41 (1963); 20, 41 (1963).
34. L. A. Kozitsina, N. B. Kupletskaya, and Yu. O. Kolesnik, Zhur. Obshch. Khim., 32, 1586 (1962).
35. J. Dabrowski, J. Terpinski, and K. Kamienska-Trela, Roczn. Chem., 39, 709 (1965).
36. N. M. D. Brown and D. C. Nonhebel, Tetrahedron, 24, 5655 (1968).
37. J. Dabrowski and J. Terpinski, Roczniki Chem., 41, 697 (1967).
38. S. Chatterjee, D. H. Trites, and E. J. Modest, Nature, 203, 970 (1968).
39. C. A. Grob and H. J. Wilkens, Helv. Chim. Acta, 50, 725 (1967).
40. H. E. A. Kramer, Tetrahedron Letters, 969 (1963); Ann., 696, 15 (1966).
41. G. O. Dudek and G. P. Volpp, J. Org. Chem., 30, 50 (1965).
42. G. O. Dudek and E. P. Dudek, J. Amer. Chem. Soc., 86, 4283 (1964).
43. M. Saquet and A. Thuillier, Bull. Soc. chim. France, 2841 (1967).
44. G. O. Dudek and E. P. Dudek, Tetrahedron, 23, 3245 (1967).
45. J. J. Charette, Spectrochim. acta, 19, 1275 (1963).
46. G. O. Dudek, J. Amer. Chem. Soc., 85, 694 (1963).
47. L. A. Kazitsina, L. L. Polstyanko, I. B. Kupletskaya, T. N. Ignatovich, and A. P. Terent'ev, Dokl. Akad. Nauk SSSR, 125, 807 (1959); Zhur. Obshch. Khim., 31, 313 (1961).
48. G. O. Dudek and E. P. Dudek, Dokl. Akad. Nauk SSSR, 88, 2407 (1966).
49. G. O. Dudek and E. P. Dudek, Chem. Comm., 464 (1965).
50. G. O. Dudek and R. H. Holm, J. Amer. Chem. Soc., 83, 3914 (1961).
51. V. S. Bogdanov, M. A. Kalik, Ya. L. Danyushevskii, and Ya. L. Gol'dfarb, Izv. Akad. Nauk SSSR, Ser. Khim., 2782 (1967); 675 (1970).
52. G. Klose and E. Uhlemann, Tetrahedron, 22, 1373 (1966).
53. G. Klose and K. Arnold, Mol. Phys., 11, 1 (1966).
54. O. A. Zagulyaeva and V. P. Mamaev, Izv. Sibir. Otd. Akad. Nauk SSSR, Ser. Khim., No. 12, 55 (1967).
55. T. R. Govindachari, S. Rajappa, and K. Nagarajan, Helv. chim. acta, 51, 2102 (1968).
56. D. D. Chapman, J. Chem. Soc. (C), 806 (1966).
57. C. L. Bell, C. N. V. Nambury, and L. Bauer, J. Org. Chem., 29, 2873 (1964).
58. B. Golankiewiez and K. Golankiewiez, Bull. Acad. polon. sci. ser. Sci. chim., 14, 199 (1966).
59. J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry" (Translated into Russian), Vol. 2, Izd. Mir, Moscow, 1968, p. 293.
60. G. Klose, P. Thomas, E. Uhlemann, and J. Maerki, Tetrahedron, 22, 2695 (1966).
61. A. R. Katritzky, Z. Chem., 3, 81 (1963).
62. R. Haller, Tetrahedron Letters, 3175 (1965).
63. A. Gordon, A. R. Katritzky, and S. K. Roy, J. Chem. Soc. (B), 556 (1968).
64. R. A. Coburn and G. O. Dudek, J. Phys. Chem., 72, 3681 (1968).
65. J. M. Bruce, P. Knowles, and L. S. Besford, J. Chem. Soc., 4044 (1964).
66. A. R. Katritzky, E. Lunt, B. Ternai, and G. J. T. Tiddy, J. Chem. Soc. (B), 1243 (1967).
67. R. O. 'Connor, J. Org. Chem., 26, 4375 (1961).
68. G. J. Karabatsos, F. M. Vane, R. A. Taller, and N. Hsi, J. Amer. Chem. Soc., 86, 3351 (1964).
69. J. Buckingham, Quart. Rev., 23, 37 (1969).
70. B. L. Kaul, P. M. Nair, A. V. R. Rao, and K. Venkataraman, Tetrahedron Letters, 3897 (1966).
71. F. A. Snavely and C. H. Yoder, J. Org. Chem., 33, 513 (1968).
72. A. H. Berrie, P. Hampson, S. W. Longworth, and A. Mathias, J. Chem. Soc. (B), 1308 (1968).
73. E. Lippert, D. Samuel, and E. Fischer, Ber. Bunsenges. Phys. Chem., 69, 155 (1965).
74. G. J. Lestina and T. H. Regan, J. Org. Chem., 34, 1685 (1969).
75. G. Cum, G. Lo Vecchio, and M. C. Aversa, Gazz. chim. Ital., 95, 583 (1965).
76. R. Mondelli and L. Merlini, Gazz. chim. Ital., 95, 1371 (1965).
77. A. J. Fatiadi and H. S. Isbell, Carbohyd. Res., 5, 302 (1967).
78. L. Mester, A. Stephen, and J. Parello, Tetrahedron Letters, 4119 (1968).
79. G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond" (Translated into Russian), Izd. Mir, Moscow, 1964.
80. A. Foffani, C. Pecile, and S. Ghersetti, Tetrahedron Letters, 16 (1959).
81. P. B. Fischer, B. L. Kaul, and H. Zollinger, Helv. Chim. Acta, 51, 1449 (1968).
82. L. Mester, G. Vass, A. Stephen, and J. Parello, Tetrahedron Letters, 4053 (1968).
83. O. L. Chapman, Tetrahedron Letters, 2599 (1966).
84. A. Heesing and G. Maleck, Tetrahedron Letters, 3851 (1967).
85. L. Brand, Meded. Vlaam. Chem. Vez., 29, 56 (1967).
86. A. Kotera, T. Morita, S. Aoyagi, Y. Kakiuchi, S. Nagakura, and K. Kume, Nippon Kagaku Zasshi, 82, 298 (1961).
87. F. J. Bullock, J. F. Tweedie, and D. D. McRitchie, J. Chem. Soc. (C), 1799 (1969).
88. J. C. Craig Jnr., and D. E. Pearson, J. Heterocycl. Chem., 5, 631 (1968).

89. J. Renault and J. C. Cartron, Compt. rend., 262 (C), 1161 (1966).
90. L. M. Werbel, Chem. Ind. (London), 1634 (1966).
91. M. Gabrielle, S. Mohamed, and S. Maguerite, Bull. Soc. chim. France, 3270 (1968).
92. J. R. Carson, G. I. Poos, and H. R. Almond, Jnr., J. Org. Chem., 30, 2225 (1965).
93. Yu. N. Sheinker, E. M. Peresleni, A. I. Kol'tsov, N. M. Bazhenov, and M. V. Vol'kenshtein, Dokl. Akad. Nauk SSSR, 148, 878 (1963).
94. E. M. Peresleni, V. I. Sheichenko, and Yu. N. Sheinker, Zhur. Fiz. Khim., 40, 38 (1966) [Russ. J. Phys. Chem., No. 1 (1966)].
95. E. F. Mooney and P. H. Winson, in "Annual Rev. of NMR Spectras", Ed. E. F. Mooney, vol. 2, London–N.-Y., Acad. Press, 1969, p. 125.
96. J. A. Moore and C. L. Habraken, J. Amer. Chem. Soc., 86, 1456 (1964).
97. S. Hoffman and E. Muchle, Ztschr. Chem., 66 (1969).
98. N. P. Buu-Hoi, J.-P. Hoeffinger, and P. Jacquignon, Bull. Soc. chim. France, 2019 (1964).
99. L. T. Creagh and P. Truitt, J. Org. Chem., 33, 2956 (1968).
100. A. N. Nesmeyanov, V. N. Babin, L. A. Fedorov, M. I. Rybinskaya, and E. I. Fedin, Tetrahedron, 25, 4667 (1969).
101. D. W. Moore and A. G. Whittaker, J. Amer. Chem. Soc., 82, 5007 (1960).
102. R. N. Butler, J. Chem. Soc. (B), 680 (1969).
103. E. D. Becker, R. B. Bradley, and C. J. Watson, J. Amer. Chem. Soc., 83, 3743 (1961).
104. A. Fischer, R. M. Golding, and W. C. Tennant, J. Chem. Soc., 6032 (1965).
105. R. K. Norris and S. Sternhell, Aust. J. Chem., 19, 841 (1966).
106. H. Uffmann, Tetrahedron Letters, 4631 (1966); Naturforsch., 226, 491 (1967).
107. H. Metzger, Tetrahedron Letters, 203 (1964).
108. M. Mousseron-Canet and J. P. Boca, Bull. Soc. chim. France, 1296 (1967).
109. M. Mousseron-Canet, J. P. Boca, and V. Tabacik, Spectrochim. Acta, A23, 717 (1967).
110. R. M. Acheson, C. J. Q. Brookes, D. P. Dearnaley, and B. Quest, J. Chem. Soc. (C), 504 (1968).
111. R. A. Y. Jones, A. R. Katritzky, and J. M. Lagowski, Chem. Ind. (London), 870 (1960).
112. E. J. Moriconi and F. J. Creegan, J. Org. Chem., 31, 2090 (1966).
113. A. R. Katritzky and F. W. Maine, Tetrahedron, 20, 299 (1964).
114. A. R. Katritzky, S. Oksne, and A. J. Boulton, Tetrahedron, 18, 777 (1962).
115. A. Maquestiau, Y. van Haverbeke, and F. N. Muller, Bull. Soc. chim. Belges, 79, 343 (1970).
116. G. A. Newman and P. J. S. Pauwels, Tetrahedron, 25, 4605 (1969); 26, 1571 (1970).
117. J. Feeney, G. A. Newman, and P. J. S. Pauwels, J. Chem. Soc. (C), 1842 (1970).
118. S. Gronowitz, B. Mathiasson, R. Dahlbom, B. Holmber, and K. A. Jensen, Acta chem. Scand., 19, 1215 (1965).
119. W. Steglich, G. Hoefle, L. Wilschowitz, and G. C. Barrett, Tetrahedron Letters, 169 (1970).
120. L. Bauer, G. E. Wright, B. A. Mikrut, and C. L. Bell, J. Heterocycl. Chem., 2, 447 (1965).
121. Y. Inoue, N. Furutachi, and K. Nakanishi, J. Org. Chem., 31, 175 (1966).
122. S. F. Mason, J. Chem. Soc., 4874 (1957).
123. A. Albert and E. Spinner, J. Chem. Soc., 1221 (1960).
124. S. F. Mason, J. Chem. Soc., 5010 (1957); D. J. Brown, E. Hoerger, and S. F. Mason, J. Chem. Soc., 211 (1955).
125. S. C. Pakrashi and J. Bhattacharyya, Tetrahedron, 24, 1 (1968); 19, 1011 (1963).
126. Y. Hagiwara, M. Kurihara, and N. Yoda, Tetrahedron, 25, 783 (1969).
127. H. T. Miles, R. B. Bradley, and E. D. Becker, Science, 142, 1569 (1963).
128. A. R. Katritzky and A. J. Waring, J. Chem. Soc., 3046 (1963).
129. J. P. Kokko, J. H. Goldstein, and L. Mandell, J. Amer. Chem. Soc., 83, 2909 (1961).
130. E. D. Becker, H. T. Miles, and R. B. Bradley, J. Amer. Chem. Soc., 87, 5575 (1965).
131. T. L. V. Ulbricht, Tetrahedron Letters, 1027 (1963).
132. J. P. Kokko, L. Mandell, and J. H. Goldstein, J. Amer. Chem. Soc., 84, 1042 (1962).
133. S. Gronowitz and R. A. Hoffman, Arkiv. Kemi, 16, 459 (1960).
134. G. M. Kheifets, N. V. Khromov-Borisov, A. I. Kol'tsov, and M. V. Volkenstein, Tetrahedron, 23, 1197 (1967).
135. G. M. Kheifets, N. V. Khromov-Borisov, and A. I. Kol'tsov, Dokl. Akad. Nauk SSSR, 166, 635 (1966).
136. G. M. Kheifets and N. V. Khromov-Borisov, Zhur. Org. Khim., 2, 1511 (1966).
137. Yu. N. Boyarchuk, M. V. Vol'kenshtein, G. M. Kheifets, and N. V. Khromov-Borisov, in collected papers "Khimiya Geterotsiklicheskikh Soedinenii. I. Azotsoderzhashchie Geterotsikly" (Collected Papers on the Chemistry of Heterocyclic Compounds. I. Nitrogen-containing Heterocyclic Rings", Izd. Zinatne, Riga, 1967, p. 338.
138. M. Eigen, G. Ilgenfritz, and W. Kruse, Chem. Ber., 98, 1623 (1965).
139. S. Ghose, G. A. Jeffrey, B. M. Craven, and J. O. Warwicker, Acta Cryst., 13, 1034 (1960).
140. Yu. N. Sheinker and Yu. I. Pomerantsev, Zhur. Fiz. Khim., 30, 79 (1956).
141. Y. Sato, K. Kotera, T. Takahashi, and T. Meshi, Yakugaku Zasshi, 80, 976 (1960).
142. P. R. Jones, Uspekhi Khim., 35, 1589 (1966) [Russ. Chem. Rev., No. 9 (1966)].
143. G. V. Domareva-Mandel'shtam and I. A. D'yakonov, Uspekhi Khim., 35, 1324 (1966) [Russ. Chem. Rev., No. 7 (1966)].
144. M. Rudrum and D. F. Shaw, J. Chem. Soc., 52 (1965).
145. R. U. Lemieux and J. D. Stevens, Canad. J. Chem., 44, 249 (1966).
146. A. S. Perlin, Canad. J. Chem., 44, 539 (1966).
147. J. D. Stevens and H. G. Fletcher, J. Org. Chem., 33, 1799 (1968).
148. T. E. Acckee et al., Carbohyd. Res., 6, 498 (1968).
149. S. J. Angyal, Angew. Chem., Intern. Ed., 8, 157 (1969).
150. D. Horton, J. S. Jewell, and K. D. Philips, J. Org. Chem., 31, 3843 (1966).
151. J. M. Rao and P. M. Nair, Tetrahedron, 26, 3833 (1970).
152. H. Sterk, Monatsh. Chem., 99, 407 (1968).
153. H. Sterk, Monatsh. Chem., 99, 1770 (1968).
154. R. P. Jones and P. J. Desio, J. Org. Chem., 30, 4293 (1965).
155. J. Finkelstein, T. Williams, V. Toome, and S. Traiman, J. Org. Chem., 32, 3229 (1967).
156. P. M. Pojer, E. Ritchie, and W. C. Taylor, Aust. J. Chem., 21, 1375 (1967).

157. B. Paul and W. Korytnyk, Chem. Ind. (London), 230 (1967).
158. S. Gronowitz, B. Gestblom, and B. Mathiasson, Ark. Kemi., 20, 407 (1963).
159. J. V. Paukstelis and L. L. Lambing, Tetrahedron Letters, 299 (1970).
160. H. E. Smith and N. E. Cooper, J. Org. Chem., 35, 2212 (1970).
161. L. C. Dorman, J. Org. Chem., 32, 255 (1967).
162. B. V. Ioffe and A. A. Potekhin, Tetrahedron Letters, 3505 (1967).
163. A. A. Potekhin and B. V. Ioffe, Dokl. Akad. Nauk SSSR, 179, 1120 (1968).
164. L. B. Volodarskii, Yu. G. Putsykin, and V. I. Mamatyuk, Zhur. Org. Khim., 5, 355 (1969).
165. Yu. G. Putsikin and L. B. Volodarskii, Izv. Akad. Nauk SSSR, Ser. Khim., 86 (1969).
166. R. W. Lamon and W. P. Blum, J. Heterocycl. Chem., 4, 349 (1967).
167. R. H. Mayer and D. Lauerer, Annalen, 731, 142 (1970).
168. F. J. Goetz, J. Heterocycl. Chem., 4, 80 (1967).
169. R. E. Harmon, J. L. Parsons, and S. K. Gupta, J. Org. Chem., 34, 2760 (1969).
170. A. F. McDonagh and H. E. Smith, J. Org. Chem., 33, 1 (1968).
171. H. Fritz and P. Losacker, Annalen, 709, 135 (1967).
172. J. H. Ottenheym, W. van Raayen, J. Smidt, M. P. Groenewege, and T. A. Veerkamp, Rec. Trav. chim., 80, 1211 (1961).
173. D. G. Kowalewski and V. J. Kowalewski, Arkiv. Kemi, 16, 373 (1961).
174. C. A. Bunton, B. N. Figgis, and B. Nayak, Adv. Mol. Spect., 3, 1209 (1962).
175. R. J. Gillespie and T. A. Birchall, Canad. J. Chem., 41, 148 (1963).
176. T. A. Birchall and R. J. Gillespie, Canad. J. Chem., 41, 2642 (1963).
177. V. C. Armstrong and R. B. Moodie, J. Chem. Soc. (B), 275 (1968).
178. F. M. Menger and L. Mandell, J. Amer. Chem. Soc., 89, 4424 (1967).
179. S. J. Kuhn and J. S. McIntyre, Canad. J. Chem., 44, 105 (1966).
180. T. Birchall, A. N. Bourns, R. J. Gilespie, and P. J. Smith, Canad. J. Chem., 42, 1433 (1964).
181. D. M. Brouwer, E. L. Mackor, and C. Maclean, Rec. Trav. chim., 85, 109, 114 (1966).
182. A. J. Kresge and L. E. Hakka, J. Amer. Chem. Soc., 88, 3868 (1966).
183. A. J. Kresge and L. E. Hakka, Z. phys. Chem., 43, 349 (1964).
184. M. Allard, J. Levisalles, and J. M. Sommer, J. Chem. Soc. (D), 1515 (1969).
185. H. E. A. Kramer and R. Gompper, Tetrahedron Letters, 969 (1963).
186. H. E. A. Kramer, Annalen, 696, 15 (1966).
187. E. Price, R. D. Barefoot, A. S. Tompa, and J. U. Lowe, Jnr., J. Phys. Chem., 71, 1608 (1967).
188. K. M. Wellman, D. L. Harris, and P. J. Murphy, Chem. Comm., 568 (1967).
189. I. Gränacher, H. Suhr, A. Zenhaeusern, and H. Zollinger, Helv. Chim. Acta, 44, 313 (1961).
190. Y. Chiang and E. B. Whipple, J. Amer. Chem. Soc., 85, 2763 (1963).
191. Y. Chiang, R. L. Hinman, S. Theodoropulos, and E. B. Whipple, Tetrahedron, 23, 745 (1967).
192. B. B. Molloy, D. H. Reid, and S. McKenzie, J. Chem. Soc., 4368 (1965).
193. H. Hogeveen, Rec. Trav. chim., 85, 1072 (1966).
194. R. L. Hinman and E. B. Whipple, J. Amer. Chem. Soc., 84, 2534 (1962).
195. M. Fraser, S. McKenzie, and D. H. Reid, J. Chem. Soc. (B), 44 (1966).
196. W. L. F. Armarego, J. Chem. Soc. (B), 191 (1966).
197. A. Mannschreck, W. Seitz, and H. A. Staab, Ber. Bunsenges. Phys. Chem., 67, 470 (1963).
198. C. G. Overberger, J. C. Salamone, and S. Yaroslavsky, J. Org. Chem., 30, 3580 (1965).
199. W. W. Paudler and H. L. Blewitt, J. Org. Chem., 31, 1295 (1966).
200. J. L. Aubagnac, Tetrahedron Letters, 3709 (1967).
201. E. Barni, G. Di Modica, and A. Gasco, J. Heterocycl. Chem., 4, 139 (1967).
202. A. R. Katritzky and R. E. Reavill, J. Chem. Soc., 753 (1963).
203. R. H. Cox and A. A. Bothner-By, J. Phys. Chem., 73, 2465 (1969).
204. A. R. Katritzky and R. A. Y. Jones, Proc. Soc. (London), 313 (1960).
205. P. J. Van der Haak and T. J. de Boer, Rec. Trav. chim., 83, 186 (1964).
206. A. R. Katritzky and R. E. Reavill, J. Chem. Soc., 3825 (1965).
207. R. A. Abramovitch and J. B. Davis, J. Chem. Soc. (B), 3827 (1966).
208. V. M. S. Gil, Rev. Port. Quim., 11, 214 (1969).
209. R. Wagner and W. von Philipsborn, Helv. Chim. Acta, 53, 299 (1970).
210. B. W. Roberts, J. B. Lambert, and J. D. Roberts, J. Amer. Chem. Soc., 87, 5409 (1965).
211. H. Stamm, Annalen, 731, 174 (1970).
212. W. W. Paudler and L. S. Helmick, J. Heterocycl. Chem., 5, 691 (1968).
213. D. E. Ames, G. V. Boyd, A. W. Ellis, and A. C. Lovesey, Chem. Ind. (London), 458 (1966); J. Chem. Soc. (B), 748 (1967).
214. A. Dieffenbacher, R. Mondelli, and W. Philipsborn, Helv. Chim. Acta, 49, 1355 (1966); 52, 743 (1969).
215. J. Schulze and F. A. Long, Proc. Chem. Soc., 364 (1962).
216. D. Meuche and E. Heilbronner, Helv. Chim. Acta, 45, 1965 (1962).
217. D. Meuche, D. Dreyer, K. Hafner, and E. Heilbonner, Helv. Chim. Acta, 50, 1178 (1967).
218. G. V. Boyd and A. W. Ellis, J. Chem. Soc. (B), 349 (1966).
219. G. A. Olah, D. P. Kelly, and N. Suciu, J. Amer. Chem. Soc., 92, 3133 (1970).
220. A. G. Cook (Editor), "Enamines", New York–London, Marcel Dekker Inc., 1969.
221. H. Wamhoff, Tetrahedron, 26, 3849 (1970).

Institute of Macromolecular Compounds,
Academy of Sciences of the USSR
Pavlov Medical Institute,
Leningrad