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Structures of Some 2-Aminobenzothiazole Derivatives & Their Sites of Protonation*

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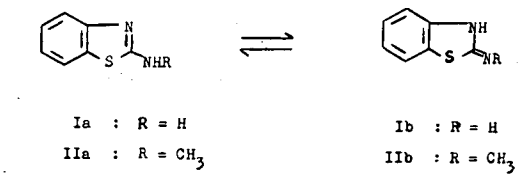
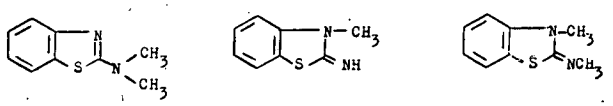
Extensive physical data, viz. dissociation constants and UV, IR and NMR data have been gathered on 2-amino- (I) and 2-methylamino- (II) benzothiazoles, 2-dimethylaminobenzothiazole (III) and 2-imino- (IV) and 2-methylimino- (V) 3-methylbenzthiazolines, to arrive at the structures of I and II, since these are capable of existing in tautomeric forms Ia, Ib and IIa, IIb; compounds III, IV and V have been studied as the frozen models of the amino and imino forms respectively. The dissociation constants of the compounds I-V in methanol and methyl cellosolve indicate preponderance of Ia and IIa. This is further supported by UV and IR data; no conclusion could be drawn from NMR data. The site of protonation in compounds I-III is N_a (nuclear nitrogen) whereas in IV and V it is at N_b (extra-annular nitrogen), as revealed by UV data and NMR data in trifluoroacetic acid.

HETEROAROMATIC compounds containing the unit $-N=C(-NH_2)-$ are capable of existing in two tautomeric forms. 2-Aminobenzothiazole (I) can thus be represented by either the 'amino' structure Ia, the 'imino' structure Ib or an equilibrium mixture thereof. Polarographic studies by Sturm and Hans[1] and spectral (UV and IR) and pK_a measurements by Costa[2] have led them to conclude that 2-aminobenzothiazole was better represented as Ia. These authors recognized the possibility of the equilibrium Ia⇌Ib, far in favour of Ia, but did not try to locate it. 2-Methylaminobenzothiazole (II) is capable of similar tautomerism and we would like to record new and extensive physical data that we have gathered on (II) and relevant models that allow us to conclude that it exists predominantly as IIa, to get a rough idea of the equilibrium constants for the tautomerism Ia⇌Ib and IIa⇌IIb and to locate the site of protonation of these bases. For these studies, 2-dimethylaminobenzothiazole (III) was chosen as the 'frozen' model of the 'amino' form, while 2-imino-3-methylbenzothiazoline (IV) and 2-methylimino-3-methylbenzothiazoline (V), both being likewise incapable of tautomerism, served as models for the 'imino' structure.

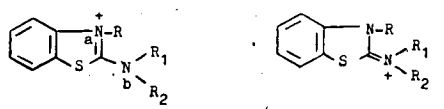


Ia : R = H
IIa : R = CH_3

Ib : R = H
IIb : R = CH_3



III IV V



VIa VIb

Results and Discussion

Dissociation constants — The pK_a values of compounds I-V in 50% aqueous methanol and in 80% methyl cellosolve (MCS) at 25°C are given in Table 1. For the tautomerism in 2-aminopyridine, Angyal and Angyal[3] have derived the expression

$$K_{taut.} = [amino]/[imino] = K_a\ (amino)/K_a\ (imino) \quad ...(1)$$

which can be substituted by the equation

$$K_{taut.} = K_a/K_a\ (nuclear\ methylimino) \quad ...(2)$$

where the numerator is the experimentally determined constant of the heterocylic amine and the denominator, the observed value for the nuclear N-methyldihydroimino derivative [(IV) in the present case]. Using Eq. 2, it can be seen that in 80% MCS, the amino form Ia predominates over the imine Ib by $1{\cdot}95\times10^3$; likewise IIa is preferred to IIb by a factor of $3{\cdot}16\times10^3$. In 50% MeOH, $K_{taut.}$ for 2-aminobenzothiazole (I) is derived as $1{\cdot}66\times10^3$, the corresponding value for II being $1{\cdot}74\times10^3$. Using the relation, $\Delta G = -RT \ln K_{taut.}$, the free energy difference between Ia and Ib or IIa and IIb in dilute methanol solutions can be computed to be about −4·4 kcal/mole. This can be considered to be approximately indicative of the loss of aromatic energy in the change from the amino to the imino form. As expected, this loss is less than what has been arrived at for 2-aminopyridine (7·3 kcal/mole) and 2-aminothiazole (6 kcal/mole)[3].

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TABLE 1 — DISSOCIATION CONSTANTS OF BENZOTHIAZOLE DERIVATIVES

Compound	pK_a	
	50% MeOH	80% MCS
I	4·13	3·37
II	4·11	3·16
III	3·96	3·21
IV	7·35	6·66
V	6·84	5·76

TABLE 2 — UV SPECTRAL DATA OF BENZOTHIAZOLE DERIVATIVES

Compound	λ_{max}, mμ (log ε)	λ_{min}, mμ (log ε)
I	224 (4·50), 265 (4·13), 295 (inflex.) (3·51)	242 (3·77)
II	225 (4·51), 268 (4·13), 298 (inflex.) (3·46)	244 (3·65)
III	226 (4·49), 276 (4·21), 298 (inflex.) (3·64)	244 (3·66)
IV	223 (4·53), 264 (4·08), 290 (3·84), 300 (3·83)	244 (3·81), 285 (3·81), 292 (3·82)
V	222 (4·55), 264 (4·01), 304 (3·77)	248 (3·79), 284 (3·54)

TABLE 3 — IR SPECTRAL DATA (cm^{-1}) OF BENZOTHIAZOLE DERIVATIVES

Compound	νNH	νC=N, νC=C, δNH
I	3400 (m), 3270 (w)	1650 (s), 1630 (m), 1585 (w), 1545 (m), 1525 (s)
II	3220 (m)	1605 (m), 1570 (m), 1555 (m), 1520 (w)
III	—	1600 (s), 1560 (s), 1550 (s)
IV	3250 (s)	1610 (m), 1600 (s), 1575 (s)
V	—	1650 (s), 1585 (m)

s, strong; m, medium; and w, weak intensities.

TABLE 4 — NMR SPECTRAL DATA OF BENZOTHIAZOLE DERIVATIVES

Compound	Solvent $CDCl_3$			δCH_3 in benzene (ppm)
	Aromatic region	δCH_3 (ppm)	δNH (ppm)	
I	6·90-7·50	—	5·90	—
II	6·87-7·67	3·02	~7·75	2·55
III	6·83-7·70	2·92	—	2·63
IV	6·63-7·33	3·37	7·42	2·93
V	6·55-7·33	3·22, 3·05	—	3·12 3·00

UV spectra — Spectra of the bases I-V were measured in 95% EtOH, using a Beckman DB spectrophotometer. From data presented in Table 2, the preponderance of tautomer Ia and IIa for 2-amino- and 2-methylaminobenzothiazoles respectively as the free bases can be inferred. The imino compound IV was characterized by two minima at 285 and 292 mμ and maxima at 290 and 300 mμ, while V showed a well-defined minimum at 284 mμ and maximum at 304 mμ. These were conspicuously absent in compounds I, II and III.

The UV spectra of all these derivatives in 2*N* hydrochloric acid were nearly identical. They exhibited maxima at 215-216, 258±2, 281±1 and 288±2 mμ and minima at 236±4, 274±2 and 285±1 mμ. This suggests that the chromophore is the resonance hybrid VIa⟷VIb, and implies that I, II and III protonate on the nuclear nitrogen (N_a), while IV and V do so on the extra-annular nitrogen (N_b). These were confirmed by NMR spectral studies.

IR spectra — Spectra of compounds I to V were run as nujol mulls, on a Perkin-Elmer 337 grating infrared spectrophotometer. Frequencies of the bands in the region 3200-3500 cm^{-1} (NH stretching) and 1500-1700 cm^{-1} (C=N, C=C, NH bending) are recorded in Table 3. It was not found possible to draw firm conclusions on the structures of I and II in the solid state. Recently, the technique of partial conversion of NH to ND has been utilized to distinguish between -NH-C=NH and -N=C-NH_2 groups[4]. Extension of this to 2-aminobenzothiazole in the solid state did not give a clear-cut result. A dichloroethane solution of I showed bands at 3380 and 3480 cm^{-1} before treatment with D_2O; after treatment of I with D_2O, the spectrum showed these bands with reduced intensity, but a new one was also seen at 3440 cm^{-1}. This can be interpreted to mean that in solution at least a good part of I exists as Ia.

NMR spectra — Approximately 30% (wt/vol.) solutions of compounds I-V in $CDCl_3$ were used. Spectra were run on a Varian A-60 spectrometer, using TMS as internal standard. Probe temperature was about 40°C. Chemical shift data are recorded in Table 4. The signals of the aromatic protons in all these derivatives were too complex to be analysed. But it was seen that relative to their location in III, the 'frozen' 'amino' form, the aromatic proton signals of the iminobenzothiazolines IV and V were shifted upfield by about 0·3 ppm. This may be considered to be the consequence of decreased total aromaticity in IV and V. The recorded chemical shifts of the aromatic protons in I and II suggest that these exist in the 'amino' form. A similar, but more clear-cut phenomenon has been encountered for aminothiazoles and iminothiazolines[5]. The position of the methyl signals in II, III, IV and V was of no help in adding weight to the conclusion derived from the aromatic region. Comparison of NMR spectra run in benzene with those in $CDCl_3$ or CCl_4 often help to delineate special features of organic molecules, which have sites of unsaturation and consequently experience special interactions with aromatic solvents[6,7]. The methyl signals in compounds II-V did undergo significant shifts to higher fields in benzene (Table 4). The near identity of the positions of these peaks in II and III, in comparison with those of the methyl groups in IV and V, again indicated the existence of II as IIa. However, in the absence of a clear knowledge of the origin of these upfield shifts in benzene, this point cannot be stretched too far.

The methyl signal in the spectrum of 2-methylaminobenzothiazole (II) was found to be a singlet.

This can be rationalized either on the basis of the imine structure IIb or of a fast exchange of the NH proton in IIa under the conditions of measurement (probe temperature 40°C). Evidence that the later situation obtained, was gathered from low temperature measurements on the $CDCl_3$ solutions of II. As the temperature was decreased to 0 and −10°C, the methyl signal broadened; maximum broadening was observed at −20°C, whereas at −30°C, the signal was seen as a doublet, of nearly equal heights, with a coupling constant of about 5 *cps*. At −30°C then, the intermolecular exchange of the amine proton was slow enough to permit observation of its coupling with the methyl protons. Rae[8] has shown that observation of NH-CH coupling is possible at normal temperatures, only if the pK_a is smaller than 3·5. For somewhat stronger bases, the use of pyridine as solvent helps to suppress the proton exchange enough to allow NH-CH coupling. However, this was not realized in the case of II (methyl singlet at 3·13 ppm in pyridine).

NMR spectroscopy has proved to be a powerful tool for observation of the site of protonation of organic bases, including very weak ones like indole[9]. The spectrum of 2-dimethylaminobenzothiazole (III) in trifluoroacetic acid (TFA) showed a singlet at 3·50 ppm for the two methyl groups, signifying that if protonation had occurred, it was on N_a. This proton was not easily located and we like to ascribe to it a broad hump centred around 11·40 ppm, overlapping with the TFA peak at 12·13 ppm. It appears likely that the proton on the benzothiazole was exchanging with TFA at an intermediate rate. The spectrum of 2-methylaminobenzothiazole (II) in this solvent showed a doublet for the methyl group at 3·35 ppm ($J = 4$ *cps*), four aromatic protons and one NH proton as a broad hump at 8·33 ppm. These data indicated that protonation was probably taking place on N_a, and that the exchange rate of the hydrogen on N_b was suppressed to allow observation of coupling with the methyl group. The NMR spectrum of 2-aminobenzothiazole (I) in TFA was again indicative of nuclear protonation. As in the case of III, the signal due to the proton donated to I or II by TFA was probably present as a low hump partially overlapping with the signal of the acid. In contrast to II, the NMR spectrum of the more basic isomer, 2-imino-3-methyl-benzothiazoline (IV) in TFA showed in the region 7·3 to 8·4 ppm, in addition to four aromatic protons, signals due to two more, presumably those attached to a nitrogen. The methyl signal was a singlet at 3·95 ppm, showing that N_b and not N_a had protonated. The TFA spectrum of 2-methylimino-3-methylbenzothiazoline (V) again showed the introduction of one acidic proton (broad hump at 8·05 ppm) and two methyl signals, a singlet at 3·87 ppm and a doublet at 3·37 ppm ($J = 4·5$ *cps*). Comparison with the data presented for IV leads to the interpretation that in V, N_b had accepted the additional proton, and that in the resonance hybrid VIa⟷VIb for the salts of IV and V, VIa probably played a dominant role.

Experimental Procedure

2-Methylimino-3-methylbenzothiazoline (V) was prepared by bromine oxidation of N,N′-dimethyl-N-phenylthiourea and crystallized from *n*-hexane; m.p. 66-67° (Found: C, 60·32; H, 5·59; N, 16·08. $C_9H_{10}N_2S$ requires C, 60·66; H, 5·66; N, 15·72%). Commercial 2-aminobenzothiazole (I) was purified by crystallization. Compounds II, III and IV were prepared by literature procedures.

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Note added in proof

After this manuscript was accepted for publication, the authors have come across a reference by A. Mathias, *Molec. Phys.*, **12** (1967), 381; wherein ^{14}N decoupling has been used to show that I and II exist in the amino forms Ia and IIa respectively.

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