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The Structure of Dimeric 2-Aminothiazole

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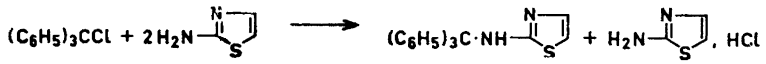
2-Aminothiazole reacts with its hydrochloride to give a dimeric form of 2-aminothiazole. The structure of this compound has been studied by means of proton magnetic resonance and is proposed to be 2-amino-5-(2-imino-4-thiazolidinyl)-thiazole (III). A possible reaction mechanism for the formation of the dimer is suggested.

Some twenty years ago, Dahlbom and Ekstrand [1] prepared 2-triphenylmethylaminothiazole by treating triphenylmethylchloride with excess 2-aminothiazole in benzene, according to the equation:



The trityl derivative was obtained in good yield but the by-product isolated was not the expected 2-aminothiazole hydrochloride but a compound having the empirical formula $C_6H_8N_4S_2 \cdot HCl$ and melting at 223–224°. On treatment with alkali, this hydrochloride gave an amine of the composition $C_6H_8N_4S_2$, m.p. 192–193°. Apparently, the 2-aminothiazole hydrochloride initially formed had reacted with 2-aminothiazole to give a dimeric compound. The correctness of this assumption was verified by heating equivalent amounts of 2-aminothiazole and 2-aminothiazole hydrochloride, either in benzene or in the absence of solvent, on a water bath; the hydrochloride of the dimeric 2-aminothiazole was formed in good yield. No attempts were made at this juncture to elucidate the structure of this dimeric compound, which formed a dipicrate and reacted with acetic anhydride to form a triacetyl derivative.

In 1956 the same compound was encountered by Beyer and Berg [2] when they attempted to prepare bis-(2-thiazolyl)-amine by melting equivalent amounts of 2-aminothiazole and its hydrochloride.

In connection with work on the NMR-spectra of thiazoles, the structures of the dimers of 2(3H)-thiazolone and of 4-methyl-2(3H)-thiazolone were elucidated.[3] We therefore found it worth while to include the dimer of 2-aminothiazole in our investigations. The NMR-spectra of 2-aminothiazole and its dimer were studied in dimethyl sulphoxide (DMSO) and in trifluoroacetic acid (TFA) solution, in which solvents the dimer is sufficiently soluble.

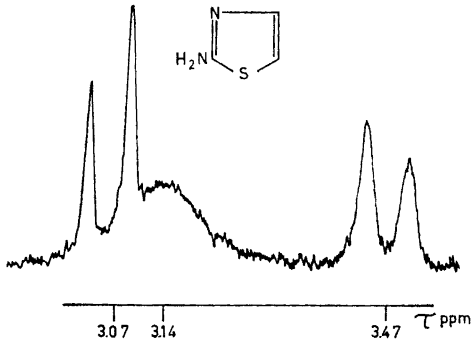
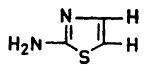


Fig. 1. NMR-Spectrum of 2-aminothiazole (I) in dimethyl sulphoxide.

The NMR-spectrum of 2-aminothiazole (Fig. 1, Table 1) indicates that this compound exists in DMSO in the amino-form (I). The 4- and 5-hydrogen resonances occur as doublets with a coupling of 3.7 c/s, which is of the same magnitude as in non-tautomerizable thiazoles,[4] while in 2(3H)-thiazolone J_{45} is 5.3 c/s.[3] The NH_2 resonance falls as a somewhat broadened band in the aromatic region (3.14 τ), as is also the case with the amino resonance of 2-aminopyrimidine.[5]

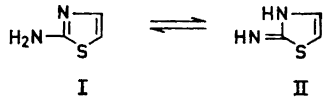
For the tautomeric imino-form (II) two NH resonances are expected, if rapid prototropy is excluded, and even if this is not the case, the NH resonance of the imino form should occur at much lower field. In 2(3H)-thiazolone, the NH resonance occurs at -1.14 τ.[3] Furthermore, a stable imino-form would give couplings between the ring NH and the other hydrogens, as is the case in 2(3H)-thiazolone.[3] From investigations of the dissociation constants of 2-

Table 1. Chemical shift data and coupling constants.



Solvent	Concentration weight %	τ_{H_2N}	τ_4	τ_5	J_{45}
DMSO	7.9	3.14	3.07	3.47	3.70
TFA	10.9	≈ -1.42	2.86	3.24	4.65

aminothiazole and some suitable derivatives, the proportion of amino to imino form in aqueous solution has been estimated to be 20 000:1.[6]



I II

The doublet at the higher field 3.47 τ is assigned to the 5-hydrogen, as it is known from other aromatic amines [5,7] that the amino group, due to its electron-donating +M effect, shifts the "*para*"-hydrogen about 1 ppm towards higher field and, furthermore, the 5-hydrogen resonance of thiazole itself occurs at the highest field.[4]

In TFA solution, the J_{45} coupling increases to 4.65 c/s and the amino resonance coincides with that of the solvent (about $-1.42\,\tau$). As trifluoroacetic acid is a strong acid, it is most probable that the spectrum observed in this solvent is that of the protonated form of 2-aminothiazole.

The spectrum of the dimer (Fig. 2, Table 2) is in many respects similar to that of the corresponding dimer of 2(3H)-thiazolone,[3] and suggests the corre-

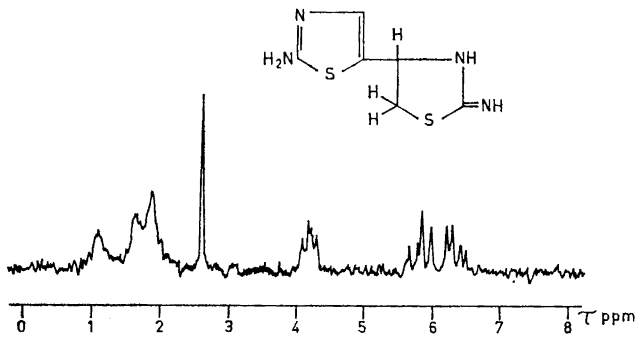
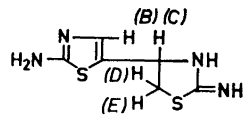
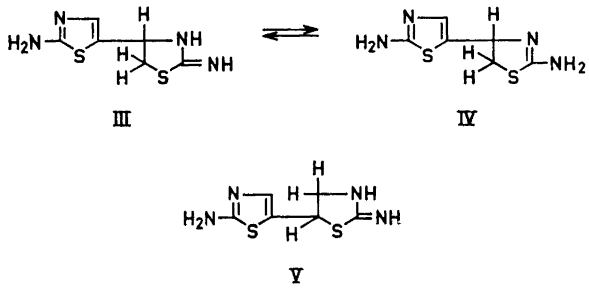


Fig. 2. NMR-Spectrum of dimer of 2-aminothiazole (III) in trifluoroacetic acid.

Table 2. Chemical shift data and coupling constants for dimer of 2-aminothiazole.



Solvent	Concentration weight %	τ_B	τ_C	τ_D	τ_E	J_{BC}	J_{CD}	J_{CE}	J_{DE}
DMSO	8.0	3.26	4.83	6.47	6.93	0.90	7.30	7.30	10.70
TFA	8.0	2.62	4.26	5.88	6.38		7.70	5.10	12.10



III IV

V

sponding structure III or the tautomeric form IV. The sharp resonance at 2.62 τ in TFA, corresponding to one hydrogen, has similar shift as the 4-hydrogen in 2-aminothiazole and is ascribed to hydrogen B of III. The bands at 4.26 τ, 5.88 τ and 6.38 τ constitute an ABX spectrum (Fig. 3) characteristic for a

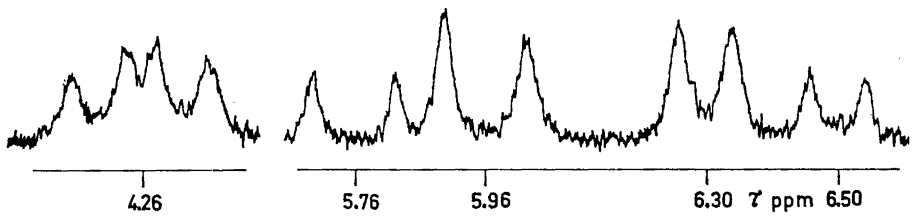


Fig. 3. NMR-Spectrum of the CH—CH_2 part of dimer of 2-aminothiazole in trifluoroacetic acid

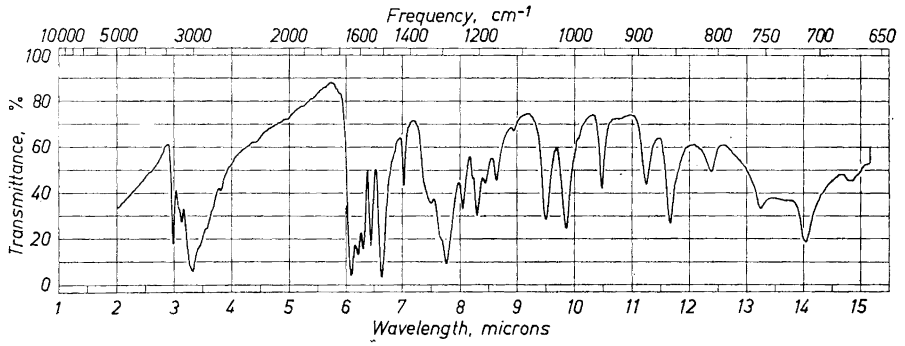


Fig. 4. IR-Spectrum of dimer of 2-aminothiazole (III) in KBr.

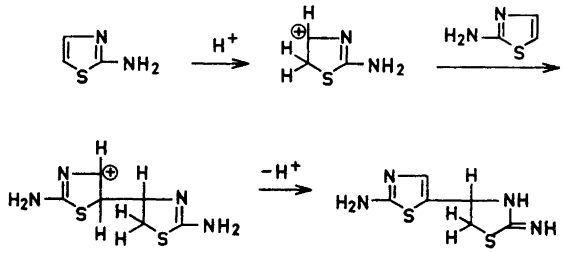
CH—CH_2 grouping, and have coupling constants very similar to those observed for the dimer of 2(3H)-thiazolone.[3] Thus the band at 4.26 τ shows splittings of 5.10 c/s and 7.70 c/s and is ascribed to hydrogen C, which couples to the two nonequivalent hydrogens of the CH_2 group. The splitting due to coupling between the geminal hydrogens is 12.1 c/s.

It is interesting to note that in DMSO solution the magnitude of the two vicinal couplings in the CH—CH_2 group are equal (7.30 c/s) while the geminal

coupling has decreased to 10.70 c/s. This could be due to solvent dependance of the conformation of the thiazolidine ring, but it seems more probable that protonation is responsible for this effect.

A long-range coupling of 0.90 c/s is observed between hydrogen B and hydrogen C, which also occurs in the case of the 2(3H)-thiazolone dimer.[3] The thiazole hydrogen resonance (B) at 3.26 τ occurs thus as a doublet and the hydrogen C resonance as a 1:2:1 triplet (7.30 c/s), where each line shows an additional splitting of 0.9 c/s.

It is not possible on the basis of the NMR-spectrum of the dimer alone to distinguish between structure III, where the 4-position of the thiazolidine ring is connected to the 5-position of the thiazole ring and structure V, where both rings are connected *via* the 5-positions. However, it seems probable that the dimer of 2-aminothiazole has a structure analogous to those of the dimers of 2(3H)-thiazolone and 4-methyl-2(3H)-thiazolone, which we have shown to have the two rings connected unsymmetrically.[3] The probable mechanism of the dimerisation also supports structure III. The first step in this reaction is presumably an addition of a proton to the 5-position of the thiazole nucleus, as it is well known that this position is easily attacked by electrophilic reagents.[8] The carbonium ion thus formed then attacks the 5-position of the second molecule of 2-aminothiazole:

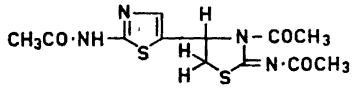


In this connection, it is interesting to note that 2-aminothiazole hydrochloride does not give a dimer on heating. This may be due to the fact that the +M-effect of the amino group, which is responsible for the high electron density in the 5-position, is annulled on protonisation of the amino group.

The positions of the four N-hydrogens present an additional problem. From the NMR spectrum in DMSO it is clear that there is a similar amino group in the dimer as in 2-aminothiazole, as it shows a broad resonance at 3.26 τ. The other two N-hydrogen resonances could not be found, as they probably coincide with that of the solvent and/or occur as very broad resonances at low field. In TFA solution, however, three broad bands are observed (Fig. 2) with approximate relative intensities of 1:1:2 at 1.10 τ, 1.64 τ, and 1.88 τ, well displaced from the solvent resonance at -2.25 τ. This indicates that at least in TFA solution the structure is that represented by formula III.

That the triacetyl derivative of the dimer is derived from the form represented by formula III is patently clear. 2-Aminothiazole gives with acetic anhydride only a monoacetyl derivative, and there is no reason to believe that the 2-aminothiazole moiety of the dimer would react otherwise. It seems reason-

able to assume therefore that the other two acetyl groups are situated on the two nitrogens of the thiazolidine part of the molecule:



EXPERIMENTAL

The NMR-spectra were obtained at 60 Mc/s using a Varian A-60 instrument. The chemical shifts are given in τ-units, using tetramethylsilane as internal standard. The IR-spectrum of III was recorded on a Perkin-Elmer No. 21 instrument equipped with NaCl prism.

Preparation of the dimer of 2-aminothiazole (III)

A. 2-Aminothiazole (5.0 g, 0.05 mole) and 2-aminothiazole hydrochloride (6.8 g, 0.05 mole) were suspended in benzene (75 ml) and the mixture refluxed for 4 h. After cooling to room temperature, the resulting light yellow crystals (10.0 g) were collected. The crude product was dissolved in boiling water (50 ml) and decolourised with carbon. On cooling, white crystals (5.8 g) of m.p. 222–223° (decomp.) were collected. One more recrystallisation from water afforded the pure hydrochloride of the dimer melting at 223–224° (decomp.). (Found: C 30.3; H 3.77; Cl 14.8; N 23.4; S 27.3. $C_6H_8N_4S_2$·HCl requires C 30.4; H 3.83; Cl 15.0; N 23.7; S 27.1).

In order to obtain the free dimeric base the hydrochloride was dissolved in water and the solution made alkaline with concentrated ammonia. The base separated as flakes and was purified by recrystallisation from water. It melted at 192–193° with decomposition. According to analysis, the crystalline base contained two moles of water. (Found: C 30.8; H 5.17; N 23.5; S 27.2; H_2O 15.2. Calc. for $C_6H_8N_4S_2$·2 H_2O: C 30.5; H 5.12; N 23.7; S 27.1; H_2O 15.3). The water could be removed by drying the dihydrate at 105°. (Found: C 36.2; H 4.20; N 28.2; S 32.0. Calc. for $C_6H_8N_4S_2$: C 35.9; H 4.01; N 27.9; S 31.9).

B. 2-Aminothiazole (5.0 g) and 2-aminothiazole hydrochloride (6.8 g) were thoroughly mixed and heated on a steam bath for 3 h. The mixture melted at first but began to solidify shortly after. The crystalline mass was dissolved in a small amount of hot water and decolourised with carbon. After cooling, the hydrochloride of the dimer (8.2 g) was collected, giving a product melting at 221–222° (decomp.). Further recrystallisation raised the m.p. to 223–224° (decomp.).

A *dipicrate* of III was obtained by dissolving the dimer in N sulphuric acid and adding an excess of picric acid. The crude yellow product was recrystallised from 50 % ethanol, giving a pure product melting at 244–245° (decomp.). (Found: C 32.8; H 2.16; N 21.5; S 9.58. Calc. for $C_6H_8N_4S_2$·2 $C_6H_3N_3O_7$: C 32.8; H 2.14; N 21.3; S 9.74).

Triacetyl derivative of III. The dimer III (1 g) was added to acetic anhydride (4 ml), whereupon the mixture became warm and the acetyl derivative began to separate. The product (1.2 g) of m.p. 233–235° was recrystallised from acetic anhydride, giving white crystals melting at 234–236°. (Found: C 44.1; H 4.31; N 17.0; S 19.9. Calc. for $C_{12}H_{14}N_4O_3S_2$: C 44.2; H 4.32; N 17.2; S 19.7).

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