214. *Applications of Proton Resonance Spectroscopy to Structural Problems. Part XVI.* The Structure of Dialkanesulphonyl Derivatives of 2-Aminothiazole.*

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The dialkanesulphonyl derivatives of 2-aminothiazole have one alkanesulphonyl group attached to each nitrogen atom, as shown by infrared and nuclear magnetic resonance spectroscopy, and chemical evidence.

2-Aminothiazole could form disulphonyl derivatives derived from the imino-form (I) or from the amino-form (II). Mixed diarylsulphonyl derivatives (R and R′ = aryl; R ≠ R′) have been assigned structure (I), but in some cases structure (II) has also been proposed (for references and discussion see ref. 1). The synthesis of two isomeric disulphonylated α-amino-*N*-heterocyclic derivatives does not of itself prove the structure. Two such isomers could both be of type (I), or one of them could be of type (II).

Nucleophilic attack on a disulphonyl derivative is somewhat more informative: thus alkaline hydrolysis of compound (III*a*) yields both 2-methanesulphonylaminopyridine and 2-ethanesulphonylaminopyridine, although the latter predominates.[2] We now find that

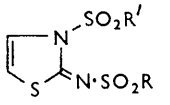
* Part XV, Katritzky and Reavil, in the press.

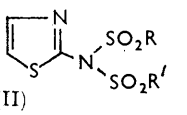
[1] Dorn, Hilgetag, and Rieche, *Angew. Chem.*, 1961, **73**, 567.

[2] Dorn and Hilgetag, *Chem. Ber.*, in the press.

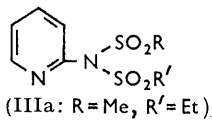
alkaline hydrolysis of the isomeric methanesulphonyl–ethanesulphonyl derivatives (I*a*) and (I*b*) yields, respectively, the methanesulphonyl derivative (IV) and the ethanesulphonyl derivative (V). This indicates that the isomeric methanesulphonyl–ethanesulphonyl compounds both have structures of type (I) because the yields of the monosulphonyl derivatives (IV) and (V) were almost quantitative and in neither case did the hydrolysis yield any of the other isomer. However, this evidence depends on the assumption that a disulphonyl derivative of 2-aminothiazole of type (II) would on hydrolytic fission behave analogously to the pyridine analogue (III*a*), *i.e.*, that it would yield both (IV) and (V). Further, this method of hydrolytic fission is not applicable to disulphonyl derivatives with two identical sulphonyl groups.

(I*a*: R = Me, R′ = Et)
(I*b*: R = Et, R′ = Me)
(I*c*: R = R′ = Me)
(I*d*: R = R′ = Et)

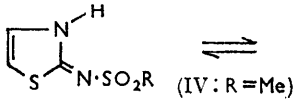




(II)

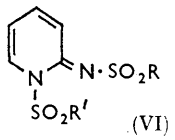


(IIIa: R = Me, R′ = Et)

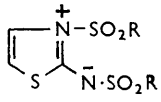


(IV: R = Me)

(V: R = Et)



(VI)



(VII)

The isomeric disulphonyl derivatives (I*a*; I*b*) were prepared in aqueous alkali: under these conditions 2-aminothiazole and 2-aminopyridine yield diarenesulphonyl derivatives of type (I) and (VI). Diarenesulphonyl derivatives of 2-aminopyridine of type (III) can be obtained in anhydrous media containing trimethylamine, or by the rearrangement of the isomers corresponding to type (I) in boiling chlorobenzene or at room temperature with anhydrous trimethylamine.[3] Reaction of 2-aminothiazole, or of the monosulphonyl derivative (V), with methanesulphonyl chloride in the presence of anhydrous trimethylamine yields respectively the disulphonyl derivatives (I*c*) and (I*b*). The disulphonyl derivative (I*c*) is not isomerised in boiling chlorobenzene. The completely different behaviour of compounds (I*a*) and (I*b*) on hydrolysis, despite their similarity in melting points, indicates that at least one of them has a structure of type (I). The similarity of their ultraviolet spectra (Table 1) indicates that they both may have this structure.

TABLE 1.

Ultraviolet spectra (methanol).

	λ_{max} (mμ)	ε	λ_{min} (mμ)	ε
I*a*	226	2,730	211	1290
	280	10,610	245	1480
I*b*	226	2,500	210	1180
	279	10,710	244	1400

The infrared spectra of the isomeric diarenesulphonyl derivatives of 2-aminopyridine of types (III) and (VI) followed three rules,[1] which allow structure determination of diarenesulphonyl derivatives of α-amino-*N*-heterocyclic compounds from the frequency of the SO_2-stretching bands. The proton magnetic resonance spectra of diarenesulphonylaminopyridine are also characteristic of their structure.[4] We have now applied these physical methods to the thiazole derivatives. The infrared spectra (Table 2) of the mixed disulphonyl derivatives (I*a*—*d*) all show frequencies characteristic for structures of type (I) (for a summary of the infrared spectra of heterocyclic compounds see ref. 5).

[3] Dorn and Hilgetag, *Chem. Ber.*, 1964, **97**, 695.
[4] Bedford, Dorn, Hilgetag, and Katritzky, *Rec. Trav. Chim.*, 1964, **83**, 189.
[5] Katritzky and Ambler, "Physical Methods in Heterocyclic Chemistry," Acedemic Press, London, 1963, vol. II, p. 161.

TABLE 2.

Infrared spectra of 2-iminothiazoline derivatives (cm.$^{-1}$).

	2-Subst.	$CH_3 \cdot SO_2$	$C_2H_5 \cdot SO_2$	$CH_3 \cdot SO_2$	$CH_3 \cdot SO_2$	$C_2H_5 \cdot SO_2$	$C_2H_5 \cdot SO_2$
	3-Subst.	H	H	$CH_3 \cdot SO_2$	$C_2H_5 \cdot SO_2$	$CH_3 \cdot SO_2$	$C_2H_5 \cdot SO_2$
1.	ν Ring	1417m	1427m	1408m	1428w 1418w	1405w	1409m
2.	ν SO_2 asym.*			1367vs	1371s	1391vs	1360s
3.	ν Ring	1334m	1334m	1328m	1327s	1335m	1321m
4.	?			1317m	1318s	1312m	
5.	ν SO_2 asym.	1300vs	1308s 1277vs	1300vs	1307vs 1285s	1305s 1283vs	1300s, 1292s, 1279s
6.	?			1260w	1259w	1259w	1262sh
7.	ν Ring	1230sh	1242m		1232w	1242w	1238m
8.	νSO_2 sym.*			1184vs	1175s	1198s	1175s
9.	ν SO_2 sym.	1146vs 1110vs	1132vs 1116vs	1145vs 1132vs	1142vs 1136vs	1144s 1126vs	1134vs
10.	$\Delta\nu$	154, 190	166, 161	155, 168	165, 149	161, 159	166, 145
11.	$\Delta\nu$ *			183	196	193	185

Spectra were obtained as KBr discs (*ca.* 4 mg./g.) on a Jena IR 10 spectrophotometer.
w, m, s, vs indicate relative intensities: weak, medium, strong, very strong. sh indicates shoulder.
* Indicates high frequency νSO_2 bands assigned to the RSO_2 group attached to cyclic nitrogen.
$\Delta\nu$ is the difference νSO_2 (asym.) — νSO_2 (sym.).
$\Delta\nu$* is the corresponding difference for the high-frequency bands.

1200—1450 *cm.*$^{-1}$ *Region.*—The asymmetric O=S=O vibrations of monosulphonylated amines occur at 1351—1261 cm.$^{-1}$.[1] Absorption at 1308—1277 cm.$^{-1}$ (s—vs), often a doublet or triplet, is here so assigned (Table 2, row 5). The differences ($\Delta\nu$) of the frequency of the asymmetrical and the symmetrical SO_2-vibrations for the present compounds are 145—190 cm.$^{-1}$ (Table 2, row 10). The corresponding differences for 15 compounds of type CH_3SO_2R'' and $C_2H_5SO_2R''$ [6-8] are 145—190 cm.$^{-1}$. The infrared spectra of the disulphonyl derivatives show a second band (s—vs) outside the normal region for the asymmetrical O=S=O stretch. This is assigned to the asymmetric SO_2 band of the sulphonyl residue on the ring nitrogen atom, which has been shifted to higher frequencies.

Additional bands are also expected and found. (*a*) 1428—1405 cm.$^{-1}$ (w—m) (Table 2, row 1): many substituted thiazoles absorb at 1445—1385 cm.$^{-1}$,[9] corresponding to a thiazole ring vibration at 1385 cm.$^{-1}$ (vs) (film).[10] (*b*) 1335—1321 cm.$^{-1}$ (m—s) and 1242—1230 cm.$^{-1}$ (w—m) (Table 2, rows 3 and 7): numerous substituted thiazoles show ring vibrations,[5] at 1345—1290 and 1250—1195 cm.$^{-1}$ (m—s). Thiazole itself absorbs at 1320 and 1247 cm.$^{-1}$. (*c*) Three of the disulphonyl derivatives of 2-aminothiazole absorb at 1315 cm.$^{-1}$ (m—s) and all show a weak band near 1260 cm.$^{-1}$ (Table 2, rows 4 and 6). The origin of these bands is not clear.

1110—1200 *cm.*$^{-1}$ *Region.*—The symmetrical O=S=O stretch of monosulphonylated amines occurs at 1170—1117 cm.$^{-1}$ (S);[1] the present compounds absorb at 1146—1110 cm.$^{-1}$ (vs). [Many 2-substituted thiazoles absorb at 1160—1130 cm.$^{-1}$,[5] but this band is hidden here by the strong, SO_2 symmetrical stretch]. The disulphonylated derivatives show a second band at 1198—1175 cm.$^{-1}$ (s—vs) (Table 2, row 8) which is the symmetric analogue of the high-frequency shifted asymmetric SO_2 band. The difference ($\Delta\nu$*) between the high-frequency asymmetrical and symmetrical SO_2 bands is 183—196 cm.$^{-1}$. The assignment of these high-frequency asymmetric and symmetric SO_2 bands is supported by the agreement between $\Delta\nu$ and $\Delta\nu$*.[11]

The infrared rules for disulphonylated amines [1] support structures of type (I). The spectra expected for dialkanesulphonyl derivatives of type (III) are appreciably different.

[6] Katritzky and Jones, *J.*, 1960, 4497.
[7] Gramstad and Haszeldine, *J.*, 1956, 173.
[8] Baxter, Cymerman-Craig, and Willis, *J.*, 1955, 669.
[9] Mijovic and Walker, *J.*, 1961, 3381.
[10] Taurins, Fenyes, and Jones, *Canad. J. Chem.*, 1957, **35**, 423.
[11] Bellamy and Williams, *J.*, 1957, 863.

TABLE 3.

Nuclear magnetic resonance spectra of dialkanesulphonyl derivatives of 2-aminothiazole (I).

Alkyl group in (I)		Ring protons			2-RSO_2N=				3-RSO_2–			
					R = Et			R = Me	R = Et			R = Me
R	R′	4-H τ	5-H τ	*J* 4/5 (c./sec.)	τCH_2	τCH_3	*J* (c./sec.)	τ	τCH_2	τCH_3	*J* (c./sec.)	τ
Me	Me	2·61	3·32	5·2	—	—	—	6·81	—	—	—	6·37
Et	Me	2·60	3·32	5·2	6·72	8·59	7·4	—	—	—	—	6·36
Me	Et	2·62	3·35	5·2	—	—	—	6·82	6·12	8·60	7·3	—
Et	Et	2·61	3·33	5·2	6·71	8·60	7·5	—	6·12	8·60	7·5	—

Proton Resonance Spectra.—0·5M-Solutions of the disulphonyl derivatives in the deuterohydrate of dichlorotetrafluoroacetone as solvent were measured at 40 Mc./sec. (Table 3). The spectra all showed a pair of doublets due to the 4- and 5-position hydrogen atoms, the invariance of the shifts of these peaks suggesting that all the derivatives are of the same structural type. Methyl and ethyl groups showed the expected singlet or triplet–quadruplet patterns; an unsymmetrical structure for the dimethanesulphonyl (I*c*), and diethanesulphonyl (I*d*) derivatives follows from the occurrence of methyl (or ethyl) groups in two different environments. The results for the mixed derivatives fall clearly into line.

The chemical shift of the methyl or methylene groups attached to sulphonyl occurs at significantly lower fields for the sulphonyl groups attached to the 3-position cyclic nitrogen than for those attached to the 2-position exocyclic nitrogen. This in the main reflects the importance of canonical form (VII), although it may be partly due to a ring current effect.

EXPERIMENTAL

Melting points were determined on a micro Kofler hot-stage apparatus.

2-*Methanesulphonamidothiazole* (IV).—Methanesulphonyl chloride (0·15 mole) was added dropwise with agitation during 30 min. at 0° to 1-aminothiazole (0·15 mole) in dry pyridine (26 c.c.). After being stirred for 5 hr. and kept for 24 hr. at 20°, the thick semi-crystalline mass was added to ice (45 g.). The resulting solid crystallised (charcoal) from water to yield the 2-*methanesulphonamide derivative* (17·7 g., 66%) as plates, m. p. 225—226° (Found: C, 26·8; H, 3·3; N, 15·6. $C_4H_6N_2O_2S_2$ requires C, 26·9; H, 3·4; N, 15·7%).

2-*Ethanesulphonamidothiazide* (V), prepared similarly (13·8 g., 48%), formed as plates (50% ethanol) or needles (water), m. p. 128° (Found: C, 31·1; H, 4·3; N, 14·7. $C_5H_8N_2O_2S_2$ requires C, 31·2; H, 4·2; N, 14·6%).

For the preparation of the disulphonyl derivatives, the hydrogen chloride released was neutralised by (1) N-sodium hydroxide, or (2) sodium carbonate. The second method was preferable as the finely divided disulphonyl derivatives hydrolysed readily at 20°. Another method (3) used trimethylamine, which was released from its hydrochloride, dried through sodium hydroxide and absorbed in anhydrous benzene. The benzene solution was determined by titration with 0·1N-hydrogen chloride (Bromothymol Blue indicator).

3-*Methanesulphonyl*-2-(*methanesulphonylimino*)*thiazoline* (I*c*).—*Method* (1). Methanesulphonyl chloride (12·2 g.) was added to 2-methanesulphonamidothiazole (15·7 g.) in N-sodium hydroxide (106 c.c., 1·2 mol./mol. of IV) with stirring and cooling to 20° during 25 min. After 75 min. stirring, N-sodium hydroxide was added to pH 6 (Taschiro indicator), followed by further ice-cold N-sodium hydroxide (60 c.c.). The washed precipitate yielded the *disulphonyl derivative* (7·2 g., 32%) as needles (from water or n-propanol), m. p. 204·5—206° (Found: C, 23·3; H, 3·4; N, 10·9. $C_5H_8N_2O_4S_3$ requires C, 23·4; H, 3·2; N, 10·9%). The alkaline liquors acidified with hydrochloric acid gave recovered 2-methanesulphonamidothiazole (9·3 g., 59%).

Method (2). Methanesulphonyl chloride (0·2 mole) was added dropwise during 15 min. with stirring at 0° to 2-aminothiazole (0·1 mole) in dry pyridine (35 c.c.). Trimethylamine (0·2 mole) in benzene (50 c.c.) was then added dropwise, and the whole was stirred for 2 hr. at 0°. After standing for 4 days at 20°, the disulphonyl derivative (I*c*) (24·1 g., 94%) was filtered off and

washed; it had m. p. 197—199°, raised to 204·5—206° by recrystallisation from water. The infrared spectrum was identical with that of the product from method (1).

The disulphonyl derivative dissolved in N-sodium hydroxide at 20° with evolution of heat; acidification then gave compound (IV).

3-*Ethanesulphonyl*-2-(*methanesulphonylimino*)*thiazoline* (I*a*).—*Method* (2). Ethanesulphonyl chloride (0·052 mole) was added to 2-methanesulphonamidothiazole (0·05 mole) in N-sodium hydroxide (50 c.c.) with stirring, and cooling at 0°, during 10 min. Stirring was continued for 30 min. at 0°; the mixture gradually warmed to 20°. After 50 min., Taschiro indicator was turned blue-violet, and then 4N-sodium carbonate (13 c.c.) was added during 45 min. (green indicator reaction). The mixture was cooled to 0°, N-sodium hydroxide (5 c.c.) added, and stirred for 30 sec. The precipitated and washed *iminothiazoline* (8·0 g., 59%) formed plates, m. p. 124—125°, raised by recrystallisation from benzene to 125·5° (Found: C, 26·7; H, 4·0; N, 10·5. $C_6H_{10}N_2O_4S_3$ requires C, 26·6; H, 3·7; N, 10·4%). Acidification of the alkaline liquors gave recovered compound (IV) (1·3 g., 15%).

Method (1) yielded compound (I*a*) (37%) and compound (IV) (32%).

2-(*Ethanesulphonylimino*)-3-*methanesulphonyl-thiazoline* (I*b*).—*Methods* (1) *and* (2). These gave the *iminothiazoline* (52 and 59%) as plates, m. p. 132°, from benzene or water (Found: C, 26·8; H, 3·4; N, 10·4. $C_6H_{10}N_2O_4S_3$ requires C, 26·6; H, 3·7; N, 10·4%).

Method (3). Methanesulphonyl chloride (0·04 mole) was added with stirring and cooling to 0° during 10 min. to compound (V) (0·04 mole) in dry pyridine (20 c.c.). This was followed by trimethylamine (0·04 c.c.) in benzene (10 c.c.) during 15 min. After 4 days at 20°, the iminothiazoline (I*b*) was washed and recrystallised from benzene or from water (5·6 g., 52%), m. p. 132°. The infrared spectrum was identical with that of the compound prepared according to method (2).

3-*Ethanesulphonyl*-2-(*ethanesulphonylimino*)*thiazoline* (I*d*).—Compound (V) (0·005 mole) gave by method 2, but using N-sodium carbonate, the *diethanesulphonyl derivative* (1·06 g., 75%) as plates, m. p. 124°, raised by recrystallisation from benzene to 127° (Found: C, 29·7; H, 4·4; N, 9·9. $C_7H_{12}N_2O_4S_3$ requires C, 29·6; H, 4·3; N, 9·9%).

Hydrolytic Fission of the Disulphonyl Derivatives (I*a*) *and* (I*b*).—The monosulphonyl derivatives (IV) and (V) are relatively soluble in water at 20°. The hydrolyses yielded the monosulphonyl derivative and the alkanesulphonic acid (method 4), or its barium salt (soluble in water but not in ethanol at 20°) (methods 5 and 6). Methods 5 and 6 could be applied to compound (I*a*) because compound (V) is ethanol-soluble at 20°, unlike compound (IV). Products were dried at 95° to constant weight.

Method (4). Compound (I*a*) (0·02 mole) barium hydroxide octahydrate (0·05 mole), and water (90 c.c.) were boiled 6 hr. N-Sulphuric acid to precipitate all the barium (calculated by titration of the barium hydroxide against methyl red) was then added; the barium sulphate was filtered off hot and washed with boiling water (total 200 c.c.). Successive concentrations (to 25 c.c.) yielded compound (IV) (3·3 g.), m. p. 225—226° (0·155 g.), m. p. 223—224° (0·064 g.), m. p. 222—224° (total, 98·7%). Phenylhydrazine (0·02 mole) in ethanol (5 c.c.), added to the mother-liquor and washings, yielded the phenylhydrazine salt of ethanesulphonic acid (3·85 g., 88%), m. p. 177—179° raised by recrystallisation from water to 183·8—184° (lit.,[12] m. p. 182·8°). The aqueous solution of 0·178 g. of the salt required 8·24 c.c. (calc. 8·17) of 0·1N-sodium hydroxide on titration with phenolphthalein.

Method (5). Compound (I*b*) (0·015 mole), barium hydroxide octahydrate (0·0375 mole), and water (67·5 c.c.) were boiled for 5½ hr. under reflux, and N-sulphuric acid added to the boiling solution such that 0·0075 mole of the barium was not precipitated. The whole was filtered hot and the precipitate washed with boiling water. After concentration of the filtrate (150 to 35 c.c.), compound (V) crystallised in plates (1·175 g.), m. p. 128°. The mother-liquor was evaporated in vacuum and the residue was dried for 2 hr. at 95° [4·205 g.; expected, 2·524 g. of barium methanesulphonate hemihydrate and 1·709 g. of compound (V), *i.e.*, total 4·233 g.]. Extraction with anhydrous ethanol (8 × 8 c.c.) at 20° and evaporation gave the barium salt (2·51 g.) which crystallised from aqueous ethanol and was dried at 95° for 2 hr. [Found: Ba, 40·7. Calc. for $(CH_3SO_3)_2Ba,\frac{1}{2}H_2O$: Ba, 40·8%]. The weight was unaltered after 10 hours' drying at 205°. From an aqueous solution of the barium salt, the barium ion was precipitated with N-sulphuric acid and the calculated quantity of phenylhydrazine was added to the concentrated filtrate. The phenylhydrazine salt of methanesulphonic acid crystallised [m. p.

[12] Latimer and Bost, *J. Amer. Chem. Soc.*, 1937, **59**, 2500.

202—204° (decomp.), lit.,[12] m. p. 193·5—194° (decomp.)] and was washed with ethanol and ether. This salt (0·137 g.), titrated against phenolphthalein, needed (6·80 c.c., calc. 6·71 c.c.) of 0·1N-sodium hydroxide. An ethanolic extract (of 4·205 g.) gave compound (V) (1·695 g.), m. p. 125·5—126·5° (together with the 1·175 g., 99·5%).

Method (6). Compound (I*b*) (2·000 g.) was hydrolysed as in method (5). Carbon dioxide was led into the boiling solution until precipitation was complete. The filtrate was vacuum-evaporated to give compound (V) (1·422 g., 100%) [dissolved by anhydrous ethanol at 20° (m. p. 125—126·5°)] and barium salts (1·344 g.; expected 1·245 g. of barium methanesulphonate hemihydrate, together with barium carbonate). From an aqueous solution of the barium salts, the barium ion was eliminated with N-sulphuric acid, and phenylhydrazine (0·80 g.) added to yield the phenylhydrazine salt of methanesulphonic acid (1·346 g., 89%).

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