1,5-Dihydro-1,2,3,4-thia(S^{IV})triazoles from Quaternary Salts of *NN*-Disubstituted Thioamides and Sodium Azide

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Quaternary salts [*e.g.* (I)] of disubstituted thioamides react with aqueous sodium azide at room temperature giving high yields of products which are probably 1,5,5-trisubstituted 1,5-dihydro-1,2,3,4-thia(S^{IV})triazoles [*e.g.* (III)]. These are decomposed by dilute acids with loss of nitrogen giving amidines [*e.g.* (VII)] and thiosulphinic *S*-esters [*e.g.* (VIII)]. When the thiatriazole (III) is heated in solution in toluene or cyclohexene, the dithioacetal of benzaldehyde or cyclohex-2-enone (respectively) is formed.

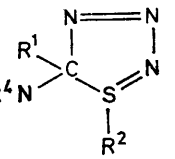
NN-DISUBSTITUTED thioamides, readily prepared by the Willgerodt–Kindler reaction or by treatment of the amide with phosphorus pentasulphide, give high yields of *S*-alkyl quaternary salts with simple alkyl halides.[1,2] These salts are useful synthetic intermediates since they react additively with many nucleophiles, often in aqueous solution at room temperature and usually with elimination of the alkylthio- or disubstituted amino-group.[1,3] Alternatively, with bases, hydrogen halide may be eliminated giving keten *SN*-acetals, which are themselves useful intermediates.[2]

We now report that the quaternary salts react with sodium azide in aqueous solution at room temperature, the reaction usually being complete in 2 h and giving high yields of essentially pure products. Thus the salt

[1] D. A. Peak and F. Stansfield, *J. Chem. Soc.*, 1952, 4067.
[2] R. Gompper and W. Elser, *Org. Synth.*, 1968, **48**, 97.
[3] T. Mukaiyama, T. Yamaguchi, and H. Nohira, *Bull. Chem. Soc. Japan*, 1965, **38**, 2107; T. Yamaguchi, Y. Shimizu, and T. Suzuki, *Chem. and Ind.*, 1972, 380.

(I), obtained from *N*-thiobenzoylmorpholine and iodomethane, gives a 91% yield of a colourless crystalline product which can be recrystallised rapidly from methanol and gives analytical figures agreeing well with the azide structure (II). Its molecular weight, determined osmometrically in toluene solution, also agrees with this structure, which, however, must be discounted since (*a*) the compound shows no azide i.r. absorption and (*b*) it shows intense u.v. absorption at 314 and 255 nm in ethanol or cyclohexane.

1,5-Dihydro-1,2,3,4-thia(S^{IV})triazoles

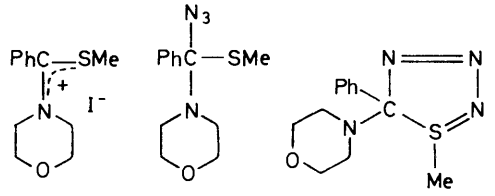


R^1	R^2	R^3	R^4	Yield %	Decomp. p. (°C)	Formula	Analysis (%) [a] C	H	N	$\lambda_{max.}$/ nm (EtOH)	ε [b]	$\nu_{max.}$/cm^{-1} (Nujol)
Ph	Me	O		93 [c]	103	$C_{12}H_{16}N_4OS$	54·55 (54·55)	6·1 (6·1)	21·1 (21·2)	255 314	12,500 11,400	1540vs, 1440, 1280, 1050
$PhCH_2$	Me	O		92 [c]	100	$C_{13}H_{18}N_4OS$	56·2 (56·1)	6·7 (6·5)	20·1 (20·1)	257 314	11,700 12,400	1540vs, 1440, 1260, 930
Ph	Et	O		89 [c]	80	$C_{13}H_{18}N_4OS$	55·45 (56·1)	6·2 (6·5)	20·5 (20·1)	254 314	10,800 9400	1550vs, 1280, 1050, 920
Ph	CH_2:CH·CH_2	O		69 [d]	93	$C_{14}H_{18}N_4OS$	58·0 (57·9)	6·2 (6·2)	19·6 (19·3)	255 313	12,600 10,700	1540vs, 1430, 1260, 1040
Ph	Me	Me	Me	58 [c]	80	$C_{10}H_{14}N_4S$	54·15 (54·05)	6·4 (6·3)	25·3 (25·2)	250 312	8100 8700	1540vs, 1400, 1060, 930
Me	Me	Me	Me	61 [d]	83	$C_5H_{12}N_4S$	37·4 (37·5)	7·5 (7·5)	35·0 (35·0)	253 310	8950 9200	1580vs, 1400, 1260, 1030

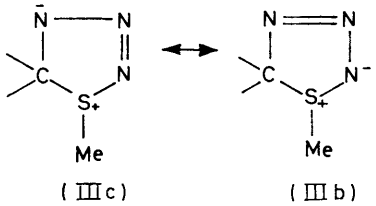
[a] Found values; required values in parentheses. [b] Intensities decrease rapidly. [c] Crystallised from methanol. [d] Crystallised from light petroleum (b.p. 40—60°).

Several analogous compounds with similar properties (see Table) have been prepared from the corresponding quaternary salts. They decompose with vigorous nitrogen evolution between 80 and 105°, but can be kept in the dry state for several days at room temperature or for several months at 0° with only slight decomposition. They are insoluble in water, but readily soluble in organic solvents.

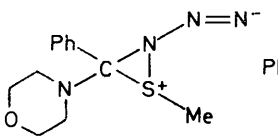
Since replacement of the phenyl group by methyl or benzyl has no appreciable effect on the u.v. absorption, the aromatic double bonds cannot be involved in extended conjugation, and the only structures which can be proposed are the 1,5-dihydro-1,2,3,4-thia(S^{IV})triazole structure (III) and, much less probably, the three-membered ring structure (IV), both of which have dipolar forms which would account for the long-wavelength u.v. absorption. Furthermore, these compounds all absorb strongly in the 1540—1580 cm^{-1} range, as do also the well-known 5-substituted 1,2,3,4-thia(S^{II})triazoles,[4] and it has been suggested that this absorption is that of the thiatriazole ring as a whole. A final choice between the two cyclic structures must await the results of *X*-ray crystallographic analysis.



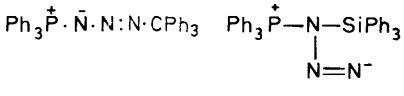
(I) (II) (IIIa)



(IIIc) (IIIb)



(IV)



(V) (VI)

Open-chain analogues of the structures (III) and (IV) exist in the iminophosphorane series [(V) [5,6] and (VI),[7] respectively].

[4] K. A. Jensen, A. Holm, and C. Th. Pedersen, *Acta Chem. Scand.*, 1964, **18**, 566.
[5] E. Bergmann and H. A. Wolff, *Ber.*, 1930, **63**, 1176.
[6] J. E. Leffler, U. Honsberg, Y. Tsuno, and I. Forsblad, *J. Org. Chem.*, 1961, **26**, 4810.
[7] J. S. Thayer and R. West, *Inorg. Chem.*, 1964, **3**, 406.

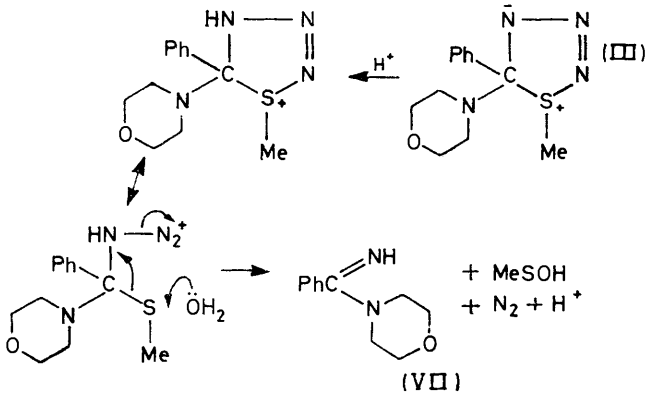
Evidence for the cyclic structures proposed is given by the reaction of these compounds with dilute acids. For example with 2N-hydrochloric acid at room temperature, compound (III) decomposes with vigorous nitrogen evolution and the amidine (VII), isolated as its *N*-bromo-derivative, is formed in high yield together with *S*-methyl methanethiosulphinate (VIII), identical with a sample prepared by peroxyacid oxidation of dimethyl disulphide. Alkyl esters of thiosulphinic acids are known [8] to arise from alkanesulphenic acids, which may here be generated as shown.

Thiosulphinic esters have useful pharmacological properties,[9] especially allicin [10] from garlic, and the preparation of the latter from the readily obtained *S*-allyl compound (see Table) is being investigated.

When a solution of the dihydrothia(S^{IV})triazole (III) in toluene is slowly heated to the b.p., a clean reaction with controlled evolution of nitrogen occurs, and the amidine (VII) is formed in high yield. The neutral fraction of the product evidently contains benzaldehyde dimethyl dithioacetal (IX), since with Brady's reagent it gives benzaldehyde 2,4-dinitrophenylhydrazone.

In an attempt to trap any nitrene intermediate, the thia(S^{IV})triazole (III) was heated in cyclohexene solution, but, when nitrogen evolution ceased, the products were the same amidine and the dithioacetal (X) of cyclohex-2-enone, again recognised by formation of the dinitrophenylhydrazone.

The mechanism of these reactions is not clear, but may involve formation of the amidine by transfer of a benzylic or allylic proton from the solvent with loss of

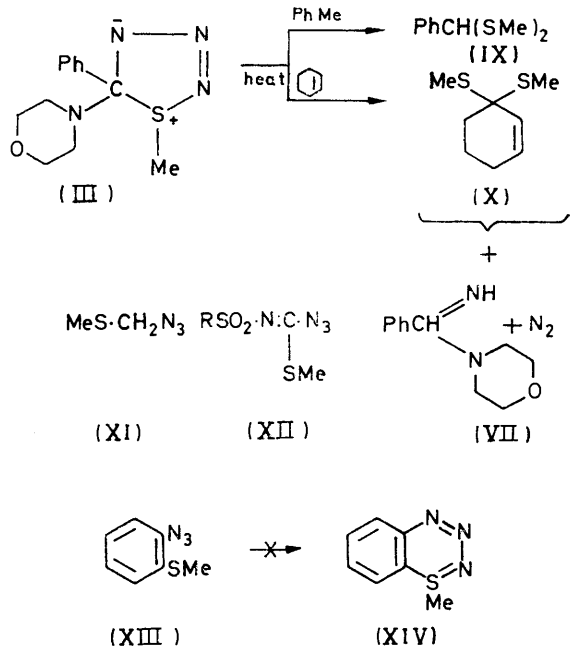


$$2\,MeSOH \longrightarrow MeSO{\cdot}SMe + H_2O$$

(VIII)

nitrogen and initial formation of a sulphide, which then disproportionates by a radical reaction. Analogous disproportionation of ethylthioacetonitrile in the presence of peroxide has been observed.[11]

In view of these results it is interesting that simple α-azido-thioethers, *e.g.* (XI), show the spectroscopic and chemical properties of azides [12] rather than of dihydrothia(S^{IV})triazoles, as do also the compounds (XII).[13] In



an attempt to obtain the dihydrothia(S^{IV})triazine (XIV), 2-methylthiophenyl azide (XIII) was prepared, but this showed only the i.r. and u.v. absorption characteristics of an azide. No reaction appeared to occur with pentamethylthiouronium iodide and sodium azide, nor with the quaternary methiodide from dimethylthioformamide under these conditions.

The n.m.r. spectra of the compounds (III) *etc.*, are in agreement with their formulation. When the *S*-methyl group is present it gives a singlet at τ 7·1—7·2 (*cf.* Me_2S, τ 7·9). In the spectrum of 5-dimethylamino-1,5-dimethyl-1,5-dihydrothia(S^{IV})triazole the two *N*-methyl groups have the same chemical shift, whereas they occur as two separate singlets in the spectrum of the 5-dimethylamino-1-methyl-5-phenyl homologue, showing that the phenyl but not the methyl group hinders free rotation around the C–NMe_2 bond.

The mass spectrum of compound (III) at 70 eV shows no molecular ion peak, probably owing to the ready loss of nitrogen; an abundant ion at $M - 28$ is present.

EXPERIMENTAL

I.r., u.v., and n.m.r. spectra were recorded with Unicam SP 1200, Unicam SP 800, and Varian T 60 instruments, respectively.

NN-Disubstituted Thioamides.—Dimethylthioacetamide

[8] F. Ostermayer and D. S. Tarbell, *J. Amer. Chem. Soc.*, 1960, **82**, 3754.

[9] La Verne D. Small, J. H. Bailey, and C. J. Cavallito, *J. Amer. Chem. Soc.*, 1947, **69**, 1710; U.S.P. 2,508,745/1950.

[10] C. J. Cavallito, J. S. Buck, and C. M. Suter, *J. Amer. Chem. Soc.*, 1944, **66**, 1952; A. S. Weisberger and J. Pensky, *Cancer Res.*, 1958, **18**, 1301.

[11] R. T. Brown, unpublished information.

[12] H. Bohme and D. Morf, *Chem. Ber.*, 1957, **90**, 446.

[13] R. Neidlein and W. Haussmann, *Tetrahedron Letters*, 1966, 5401.

was prepared by the reaction of dimethylacetamide with phosphorus pentasulphide in boiling carbon disulphide. The other thioamides were made by the Willgerodt–Kindler reaction. For the preparation of dimethylthiobenzamide this was conveniently modified as follows to avoid using a sealed tube.

Benzaldehyde (10·6 g, 0·1 mol) was shaken with aqueous dimethylamine (25—30% w/v; 54 ml, 0·3 mol) for 12 h at room temperature with occasional cooling. The upper layer was separated, dried (Na_2SO_4), and heated on a steam-bath under reflux with sulphur (4·8 g, 0·15 g atom), dimethylformamide (5 ml), and toluene-*p*-sulphonic acid (0·2 g). Evolution of dimethylamine was complete in 5 min. The mixture was heated for 30 min more, water (70 ml) was added, and the flask was stoppered and shaken with ice-cooling. The precipitated oil solidified as yellow granules which were filtered off, washed, dried, and crystallised from light petroleum (b.p. 80—100°; 375 ml) forming yellow plates (12·1 g) of dimethylthiobenzamide sufficiently pure for quaternisation; τ (CCl_4) 2·80 (5H, s, aromatic), 6·59 (3H, s, NMe) and 6·99 (3H, s, NMe).

Quaternary Salts of Thioamides.—These were prepared by treatment of the thioamide with the alkyl halide in boiling acetone.[1]

1,5-*Dihydro*-1,2,3,4-*thia*(S^{IV})*triazoles.*— 4-[α-(Methylthio)-benzylidene]morpholinium iodide (I)[1] (15·7 g, 0·045 mol) was added to a solution of sodium azide (23·4 g, 0·36 mol) in water (224 ml). After shaking, a clear solution resulted from which crystals rapidly separated. The mixture was kept at room temperature for 1·5 h, then in ice for 0·5 h, and the product was filtered off, washed with water, and dried, forming cream-white hair crystals (11·1 g, 93%) which, after rapid recrystallisation from methanol (decomposition may have occurred if heating was prolonged) gave 1,5-*dihydro*-1-*methyl*-5-*morpholino*-5-*phenyl*-1,2,3,4-*thia*(S^{IV})*triazole* (III) as large needles which decomposed with vigorous nitrogen evolution at 103°, *M* (osmometric in toluene) 261 ($C_{12}H_{16}N_4OS$ requires 264); see Table for analysis and u.v. and i.r. spectra; τ ($CDCl_3$) 2·6 (5H, m, aromatic), 6·3 (8H, m, morpholino), and 7·17 (3H, s, SMe).

In the same way were obtained the following homologues (see Table): 5-*benzyl*-1-*methyl*-5-*morpholino*-, τ 2·67 (5H, s, aromatic), 5·52 (2H, s, $PhCH_2$), 6·35 (8H, s, morpholino), and 7·08 (3H, s, SMe); 1-*ethyl*-5-*morpholino*-5-*phenyl*-, τ 2·7 (5H, m, aromatic), 6·5 (10H, m, CH_2 of Et and morpholino), and 8·61 (3H, t, Me); 1-*allyl*-5-*morpholino*-5-*phenyl*-, τ 2·6 (5H, m, aromatic), 4·0 (1H, m, CH=), 4·8 (2H, m, CH_2=), 6·05 (2H, d, *J* 8 Hz, CH_2S), and 6·25br (8H, s, morpholino); 5-*dimethylamino*-1-*methyl*-5-*phenyl*-, τ 2·3 (5H, m, aromatic), 6·39 (3H, s, NMe), 6·79 (3H, s, NMe), and 7·15 (3H, s, SMe); 5-*dimethylamino*-1,5-*dimethyl*-, τ 6·84 (6H, s, NMe_2), 7·23 (3H, s, SMe), and 7·52 (3H, s, CMe).

Thermal Decomposition of 1,5-*Dihydro*-1-*methyl*-5-*morpholino*-5-*phenyl*-1,2,3,4-*thia*(S^{IV})*triazole* (III).—(*a*) A solution of the thiatriazole (10·0 g) in toluene (200 ml) was heated to its b.p. during 20 min. Much gas evolution occurred. Boiling under reflux was continued for 15 min, the solution becoming pale yellow, and the toluene was then evaporated off *in vacuo*. The remaining oil was dissolved in dichloromethane (100 ml) and extracted with aqueous hydrochloric acid (2N; 4 × 50 ml). The combined extracts were boiled, treated with charcoal, cooled, and filtered, and the filtrate was basified with an excess of concentrated sodium hydroxide solution to precipitate the amidine (VII). An excess of bromine water was added with shaking and ice-cooling and the precipitated 4-(N-*bromobenzimidoyl*)*morpholine* was filtered off, washed, and dried (7·5 g, 74%). Crystallisation from ethanol gave slightly yellow plates, m.p. 140° (decomp.) (Found: C, 48·9; H, 4·8; Br, 29·7. $C_{11}H_{13}BrN_2O$ requires C, 49·05; H, 4·8; Br, 29·7%). The N-*benzoyl derivative* of the amidine formed slightly yellow plates (from ethanol), m.p. 153—154° (Found: C, 73·2; H, 6·2; N, 9·45. $C_{18}H_{18}N_2O_2$ requires C, 73·5; H, 6·1; N, 9·5%).

The dichloromethane solution, after the extraction with acid, was evaporated and the residual oil was distilled (b.p. 88° at 35 mmHg), giving impure benzaldehyde dimethyl dithioacetal (IX) (Found: S, 33·8. Calc. for $C_9H_{12}S_2$: S, 34·8%). With Brady's reagent this gave benzaldehyde 2,4-dinitrophenylhydrazone, m.p. 240° (lit.,[14] 237°), identical with an authentic specimen.

(*b*) A solution of the thiatriazole (1·0 g) in cyclohexene (20 ml) was slowly heated to its b.p., gas being evolved, and after being boiled under reflux for 10 min the pale yellow solution was evaporated and worked up as in (*a*), yielding the same amidine (VII) and a neutral fraction containing the dimethyl thioacetal (X) of cyclohex-2-enone. The latter gave the corresponding 2,4-dinitrophenylhydrazone, m.p. 160—162° (lit.,[15] 168°) (Found: C, 52·0; H, 4·5; N, 20·3. Calc. for $C_{12}H_{12}N_4O_4$: C, 52·2; H, 4·35; N, 20·3%).

Reaction of the Thia(S^{IV})*triazole* (III) *with Acid.*—(*a*) The thiatriazole (0·40 g) was added to aqueous hydrochloric acid (2N; 16 ml). Vigorous gas evolution occurred and an almost clear solution was formed, which was filtered and basified with an excess of concentrated sodium hydroxide solution; an excess of bromine water was then added. After ice-cooling and shaking, the almost colourless *N*-bromo-amidine was filtered off, washed with water, and dried (0·27 g); it was identical (i.r. spectrum) with that already described.

(*b*) The thiatriazole (0·40 g) was added to saturated ethanolic picric acid (16 ml). The reaction, with vigorous gas evolution, was slightly exothermic. The mixture was cooled to room temperature and the picrate was filtered off, washed with cold ethanol, and dried (0·474 g, 69%); m.p. 203°; i.r. spectrum identical with that of the picrate from the amidine (VII) prepared by thermal reactions.

(*c*) Experiment (*a*) was repeated with 2N-hydrochloric acid saturated with sodium chloride, and the product was extracted with ether. The extract was washed repeatedly with 2N-acid saturated with salt, then dried (Na_2SO_4) and evaporated *in vacuo*. The remaining pale yellow oil, *S*-methyl methanethiosulphinate, liberated iodine from acidified potassium iodide solution. Its n.m.r. spectrum ($CDCl_3$) consisted of two singlets (1 : 1) at τ 7·05 and 7·35, identical with the spectrum of an authentic sample prepared by oxidation of dimethyl disulphide with *m*-chloroperbenzoic acid. The oil had n_D^{25} 1·5482, $\lambda_{max.}$ (EtOH) 243, $\lambda_{min.}$ 225 nm [lit.,[9] n_D^{25} 1·5481, $\lambda_{max.}$ (EtOH) 245—248, $\lambda_{min.}$ 225 nm].

2-*Methylthiophenyl Azide* (XIII).—2-Aminobenzenethiol (12·5 g, 0·1 mol) was dissolved in a solution of sodium hydroxide (12·0 g, 0·3 mol); the solution was filtered and the filtrate cooled in ice and stirred while dimethyl sulphate (12·6 g, 0·1 mol) was added dropwise during 10 min. Stirring was continued with cooling for 10 min, then at room temperature for 16 h, and the 2-methylthioaniline was

[14] N. R. Campbell, *Analyst.*, 1936, **61**, 392.
[15] K. Dimroth and K. Resin, *Ber.*, 1942, **75***B*, 322.

extracted with ether (2 × 75 ml). The extract was dried (Na_2SO_4) and evaporated, and the product distilled; b.p. 142° at 30 mmHg (11·2 g).

The 2-methylthioaniline (1·39 g, 0·01 mol) dissolved in N-hydrochloric acid (30 ml) was cooled in ice while a saturated solution of sodium nitrite was added dropwise with stirring until a blue colour was obtained with starch–iodide paper. To the ice-cooled solution was added dropwise, with stirring, a solution of sodium azide (5·20 g, 0·08 mol) in water (50 ml). After stirring and cooling in ice for 30 min more, the *2-methylthiophenyl azide* was filtered off, washed with water, dried, and crystallised from light petroleum (b.p. 40—60°). It formed yellow crystals, m.p. 52° (Found: C, 50·85; H, 4·3; N, 25·3. $C_7H_7N_3S$ requires C, 50·9; H, 4·25; N, 25·45%), $\lambda_{max.}$ (EtOH) 287 and 301 nm (ε 1900 and 2400), $\nu_{max.}$ (Nujol) 2100 cm^{-1}, τ (CCl_4) 2·8 (4H, m, aromatic) and 7·69 (3H, s, SMe).

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