Preparation of Thiazoles and Benzothiazoles as Possible Anthelmintics.

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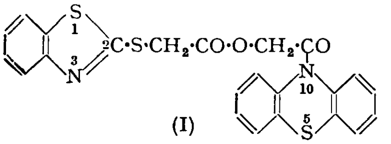
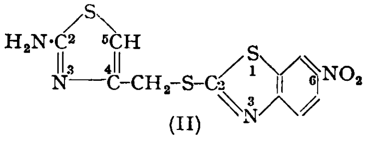
Derivatives of mercaptobenzothiazoles, benzothiazoles, and thiazoles have been prepared, most containing phenothiazine residues. Some of the compounds were very active against liver fluke (*Fasciola hepatica*) *in vitro.*

2-Mercaptobenzothiazole has been found to be lethal towards liver fluke (*Fasciola hepatica*) and to be strongly depressant against the roundworm *Ascaris lumbricoides*, both *in vitro*. On account of this and the structural relation to the anthelmintics 2 : 3-dihydro-3-oxobenzo-1 : 4-thiazine, rhodanine (Mackie and Raeburn, *Brit. J. Pharmacol.*, 1952, **7**, 219; Mackie and Misra, *J.*, 1954, 3919), and phenothiazine, further thiazole derivatives have been prepared.

Compounds were prepared by condensing mercaptobenzothiazoles with 10-chloroacetylphenothiazine or its ω-pyridinium derivative. The *S*-benzylthiuronium and piperazinium salts of (benzothiazolylthio)-acetic and -propionic acid, and the 10-phenothiazinylcarbonylmethyl ester (I) of the former acid were obtained. A sulphone was prepared by condensing 2-methyl-6-benzothiazolesulphonyl chloride with phenothiazine in pyridine. Also derivatives of 2-aminothiazole, such as (II), were prepared. Ziegler (*J. Amer. Chem. Soc.*, 1941, **63**, 2946; 1944, **66**, 744) found that *p*-acetamidobenzenesulphonyl chloride did not react with 2-amino-4-(α-ethoxycarbonylalkyl)thiazoles and concluded that 4-carboxy- or 4-ethoxycarbonyl groups exerted an inhibitory effect on the 2-amino-group of the thiazole in this respect; the compound (II) did not react with toluene-*p*-sulphonyl chloride in pyridine and an analogous reason can be suggested. Although the ease of removal of a 2-halogen atom in benzothiazole was influenced by a nitro-group in the 6-position, to which electrophilic substitution is usually directed (Colonna, *Pubbl. Inst. Chim. Univ. Bologna*, 1943, No. 2—7, 3 ; *Chem. Abs.*, 1947, **41**, 754), 2-chloro-6-nitrobenzothiazole (Katz, *J. Amer. Chem. Soc.*, 1951, **73**, 4007) did not condense with phenothiazine (cf. Gilman and Shirley, *ibid.*, 1944, **66**, 825, 888; Cauquil and Cassadevall, *Compt. rend.*, 1947, **225**, 578).


(I)


(II)

Details of the biological testing will be reported elsewhere, but we may mention the high activity towards liver fluke *in vitro* of some of the compounds, especially 2-mercapto-6-nitrobenzothiazole, which is paralysant at 1 : 80,000.

Experimental

(10-*Acetyl*-2-*phenothiazinylthio*)*benzothiazole*.—A saturated ethanolic solution of 10-chloroacetylphenothiazine, m. p. 118—119° (5·5 g.) (Ekstrand, *Acta Chem. Scand.*, 1949, **3**, 302, gives m. p. 115—116·5°), was shaken with a mixture of a saturated ethanolic solution of mercaptobenzothiazole (3·5 g.) and aqueous sodium acetate (3·5 g. in 5 c.c.). Reaction set in immediately on warming on the water-bath; after 1 hour's refluxing the *product* which separated was recrystallised from benzene as buff prisms (7 g.), m. p. 168—169° (Found : C, 62·9; H, 3·8. $C_{21}H_{14}ON_2S_3$ requires C, 62·1; H, 3·5%).

2-*Mercapto*-6-*nitrobenzothiazole*.—To concentrated sulphuric acid (145 c.c.) was added gradually mercaptobenzothiazole (33 g.), followed by potassium nitrate (22 g.) portionwise, at <10° with stirring. After 1 hr. the product was poured into water, a mixture of the 6-nitro-derivative and 6 : 6′-dinitrodibenzothiazole disulphide separating. This dissolved when refluxed with aqueous sodium sulphide for 20 min., and the solution was filtered and acidified with dilute acetic acid; the 6-nitro-derivative was precipitated and recrystallised from glacial acetic acid in yellow needles (30 g.), m. p. 255—256°. Teppema and Sebrell (*J. Amer. Chem. Soc.*, 1927, **49**, 1779) gave m. p. 255—256°, and Drozdov and Stavroskaya (*J. Gen. Chem. U.S.S.R.*, 1937, **7**, 2313) m. p. 226°.

Similarly, 2-(10-*acetylphenothiazinylthio*)-6-*nitrobenzothiazole* was prepared from 2-mercapto-6-nitrobenzothiazole (2 g.) as pale yellow plates (from benzene) (2 g.), m. p. 222—224° (Found: C, 56·5; H, 3·0. $C_{21}H_{13}O_3N_3S_3$ requires C, 55·9; H, 2·9%).

N-(10-*Phenothiazinylcarbonylmethyl*)*pyridinium Salts*.—Dry pyridine (5 g.) was added to a boiling absolute ethanolic solution (35 c.c.) of 10-chloroacetylphenothiazine (11 g.) and the mixture refluxed for 8 hr. The separated pyridinium chloride was filtered off hot and purified by refluxing with absolute ethanol; it formed colourless prisms (10 g.), m. p. 252—253°. Dahlbom (Swed. P. 136,720/1952) gives m. p. 252—253°.

This pyridinium compound (3 g.) in water (15 c.c.) was added gradually to aqueous-ethanolic sodium mercaptobenzothiazole (pH 6—7; from 1 g. of the mercapto-compound) at 0—5°. The product was chilled in ice (1 hr.), then filtered off, washed with water, and recrystallised from acetone–light petroleum (b. p. 40—60°), forming yellow, shining prisms of the *salt* (2 g.), m. p. 96—98° (vigorous decomp. at 100°), of the pyridinium and thiol derivatives (Found: C, 64·1; H, 4·4. $C_{26}H_{19}ON_3S_3$ requires C, 64·3; H, 3·9%).

The *salt* from 2-mercapto-6-nitrobenzothiazole (1·5 g.) and the pyridinium compound (2·7 g.) was obtained similarly. It was purified by dissolving it in cold acetone, adding ethyl acetate to turbidity, and storage in ice overnight. (The compound decomposed in hot acetone.) It was obtained as yellow prisms (1·2 g.), m. p. 132—134° (decomp.), becoming red at 120° (Found: C, 58·1; H, 3·8. $C_{26}H_{18}O_3N_4S_3$ requires C, 58·9; H, 3·4%). The impure sample decomposed readily at 100°.

10-*Phenothiazinylcarbonylmethyl* (2-*Benzothiazolylthio*)*acetate*.—2-Mercaptobenzothiazolyl-acetic acid (Kucherov, *J. Gen. Chem. U.S.S.R.*, 1949, **19**, 752) gave the S-*benzylthiuronium* salt as colourless prismatic needles, m. p. 167—168°, from aqueous ethanol (Found: C, 52·5; H, 4·1. $C_{17}H_{17}O_2N_3S_3$ requires C, 52·1; H, 4·3%), and the *piperazinium* salt in colourless shining plates, m. p. 184°, from ethanol (Found: C, 48·2; H, 4·2. $C_{22}H_{24}O_4N_4S_4,H_2O$ requires C, 47·7; H, 4·7%).

A boiling saturated ethanolic solution of 10-iodoacetylphenothiazine (5 g.) (Dahlbom and Ekstrand, *Acta Chem. Scand.*, 1949, **3**, 302) was refluxed with a saturated ethanolic sodium hydroxide solution of the acid (3 g.; pH 6—7) on the water-bath for 2 hr., and the crystalline precipitate was recrystallised from benzene as colourless, shining prisms (3·5 g.) of the required *ester* (I), m. p. 148—150° (Found: C, 59·7; H, 3·3. $C_{23}H_{16}O_3N_2S_3$ requires C, 59·5; H, 3·4%).

An attempt to prepare the corresponding propionate gave only a resin.

β-(2-*Benzothiazolylthio*)*propionic Acid*.—This acid (Gribbens, U.S.P. 2,416,052/1947) gave a S-*benzylthiuronium* salt, colourless shining plates (from aqueous ethanol), m. p. 147—148° (Found: C, 53·5; H, 4·2. $C_{18}H_{19}O_2N_3S_3$ requires C, 53·3; H, 4·7%), and the *piperazinium* salt, colourless prisms (from ethanol), m. p. 168—169° (Found: C, 51·6; H, 4·9. $C_{24}H_{28}O_4N_4S_4$ requires C, 51·1; H, 5·0%).

2-*Methylbenzothiazole*-6-*sulphonic Acid*.—This acid was obtained by the method of Kiprianov, Ushenko, and Sych (*J. Gen. Chem. U.S.S.R.*, 1945, **15**, 200) in colourless shining plates (from water), m. p. >310° (Found: C, 39·1; H, 3·5. Calc. for $C_8H_7O_3NS_2,H_2O$: C, 38·9, H, 3·6%). Kiprianov *et al.* give m. p. 295°. The S-*benzylthiuronium* salt crystallised from aqueous ethanol as colourless plates, m. p. 149—150° (Found: C, 46·9; H, 4·2. $C_{16}H_{17}O_3N_3S_3,H_2O$ requires C, 46·5; H, 4·6%).

2-*Methyl*-6-*benzothiazolyl* 10-*Phenothiazinyl Sulphone*.—2-Methylbenzothiazole-6-sulphonyl chloride (4·5 g.) (*idem, loc. cit.*) was added to a suspension of phenothiazine (3·5 g.) in pyridine (3 c.c.). On gentle warming a vigorous reaction ensued. The mixture was kept overnight, ethanol (5 c.c.) added, and the separated *sulphone* recrystallised from aqueous acetone (charcoal), forming colourless, prismatic needles (2·5 g.), m. p. 190—191° (Found: C, 58·5; H, 3·7. $C_{20}H_{14}O_2N_2S_3$ requires C, 58·5; H, 3·4%).

β-(2-*Amino*-4-*thiazolylmethylthio*)*propionic Acid*.—2-Amino-4-thiazolylmethylthiuronium hydrochloride (5 g.) (Sprague, Land, and Ziegler, *J. Amer. Chem. Soc.*, 1946, **68**, 2155), β-chloropropionic acid (2·5 g.), and aqueous sodium hydroxide (3·5 g. in 30 c.c.) were refluxed on the water-bath for 2·5 hr. Dilute hydrochloric acid was cautiously added to pH ~4. The precipitate, when recrystallised from water, gave the pure *acid* as light brown needles (2·5 g.), m. p. 177—178° (Found: C, 38·3; H, 4·6. $C_7H_{10}O_2N_2S_2$ requires C, 38·5; H, 4·6%).

2-*Amino*-4-(6-*nitro*-2-*benzothiazolylthio*)*methylthiazole*.—A hot aqueous-ethanolic solution (10 c.c.) of 2-amino-4-chloromethylthiazole hydrochloride (*idem, loc. cit.*) (1·5 g.) was refluxed with an ethanolic sodium hydroxide (1 g.) solution of 2-mercapto-6-nitrobenzothiazole (1·5 g. in 30 c.c.) for 2 hr., and the product which separated was filtered off, washed with ethanol, and recrystallised from dilute acetic acid. The *methylthiazole* was obtained as yellowish-brown, prismatic needles (1·5 g.), m. p. 230—231° (decomp.) (Found : C, 41·2; H, 2·7. $C_{11}H_8O_2N_4S_3$ requires C, 40·7; H, 2·5%). The *picrate* formed yellow needles, m. p. 210—211° (Found : N, 17·7. $C_{17}H_{11}O_9N_7S_3$ requires N, 17·7%), from acetone.

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