461. *Cytotoxic Compounds. Part III.*[1] *Some Derivatives of* p-(NN-*Di*-2-*chloroethyl- and of* p-(NN-*Di*-2-*bromoethyl-amino*)*thiophenol.*

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Thiolcarbonates, thiolcarbamates, and thiolesters, derived from the above " nitrogen mustards," have been prepared. Some mercurial compounds are also described.

Syntheses of *p*-(*NN*-di-2-chloroethylamino)thiophenol (I) and its dibromo-analogue (II) were described in Part I.[2] In view of the biological results obtained [3] on some of the urethanes described in Part II,[1] it was desirable to prepare analogues (thiolcarbonates and thiolcarbamates) based on the thiols (I) and (II).

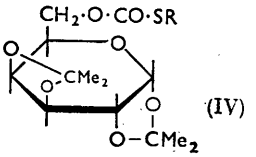
The thiolcarbonates (III; Y = Et and Pr^{i}) and (IV) were readily obtained by reaction of the thiol (I), as potassium salt or in pyridine, with the appropriate chloroformate. The bromo-analogue of the ester (III; Y = Pr^{i}) was made similarly from the bromo-thiol (II), and also from the chloro-ester (III; Y = Pr^{i}) by reaction with lithium bromide; the latter method was used to obtain the bromo-analogue of (III; Y = cholesteryl) and of the galactose derivative (IV). Conditions could not be established for the selective removal of the isopropylidene groups in the sugar derivative (IV).

An alternative route to thiolcarbonates of type (III) would be reaction of an alcohol with *p*-(*NN*-di-2-chloroethylamino)phenyl chlorothiolformate (V); the latter reagent

[1] Part II, Benn, Creighton, Owen, and White, preceding paper.
[2] Benn, Owen, and Creighton, *J.*, 1958, 2800.
[3] Danielli, *Ann. Reports British Empire Cancer Campaign*, 1956, **34**, 398; 1957, **35**, 410; 1958, **36**, 527; 1959, **37**, 575.

would also be useful in other types of reactions. Although the pure compound could not be isolated, it was prepared as a crude oil by interaction of the thiol (I) and carbonyl chloride in ether. Treatment of a solution of the oil in benzene with propan-2-ol gave the thiolcarbonate (III; Y = Pr^{i}) identical with that obtained by the other route, whilst reaction with 2,4-dinitrophenol (a metabolic poison) gave the corresponding 2,4-dinitrophenyl ester, a compound which on enzymic fission would yield *two* toxic components.

R = *p*-$(CH_2Cl\cdot CH_2)_2N\cdot C_6H_4\cdot$ R′ = *p*-$(CH_2Br\cdot CH_2)_2N\cdot C_6H_4\cdot$



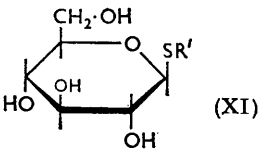
R·SH (I) R′·SH (II) R·S·CO_2Y (III) (IV)

R·S·COCl (V)

R·S·CO·NH·C_6H_4·CO_2Y(*p*) (VI; Y = Me) (VII; Y = H)

R·S·CO·NH·CH_2·CO_2Y (VIII; Y = Me) (IX; Y = H)

R·S·CO·NH·C_6H_4·NEt_2(*p*) (X)



(XI)

R·S·Hg·C_6H_4·NEt_2(*p*) (XII) R·Hg·S·C_6H_4·NEt_2(*p*) (XIII) R·HgCl (XIV) R·Hg·R (XV)

The desirability of conferring water-solubility on a nitrogen mustard was stressed in the preceding paper, and some of the reagents described there have also been useful in the present connection. Methyl *p*-isocyanatobenzoate reacted with the thiol (I) to give the thiolcarbamate (VI), also obtained from the chlorothiolformate (V) and methyl *p*-aminobenzoate, and by treatment with boiling 1 : 1 hydrochloric–acetic acid it was possible to effect preferential hydrolysis of the methyl ester group to give the acid (VII). Similarly, methyl isocyanatoacetate was used to obtain the ester (VIII) and thence the acid (IX), the bromo-analogue of which was likewise prepared from the bromo-thiol (II) and also by halide-exchange from (IX). The advantage of methyl esters in these syntheses was shown by the fact that the ethyl ester corresponding to (VIII) was much more resistant to hydrolysis, and the free acid (IX) could not be obtained from it, more extensive fission occurring under the more drastic conditions required. The basic thiolcarbamate (X) was prepared by reaction of *p*-*NN*-diethylaminophenyl isocyanate with the thiol (I).

The acetyl, propionyl, and benzoyl derivatives of the bromo-thiol (II), which were required for comparison with the corresponding chloro-compounds derived from (I), were prepared from the latter derivatives by exchange reactions with lithium bromide, a method which usually gave better results than direct acylation of the thiol (II). In the same way the tetra-*O*-acetyl-β-D-glucoside of (II) was obtained from that of (I); solvolytic deacetylation then furnished the glucothioside (XI).

Reaction of the thiol (I) with *p*-*NN*-diethylaminophenylmercuric chloride gave the mercurial (XII). The isomer (XIII) was prepared by condensation of *p*-(*NN*-diethylamino)thiophenol with *p*-(*NN*-di-2-chloroethylamino)phenylmercuric chloride (XIV). The latter reagent, prepared *via* the corresponding mercuric acetate by mercuration of *NN*-di-2′-chloroethylaniline, reacted similarly with thiophenol but behaved differently towards aliphatic thiols; with 2-mercaptoethanol, for instance, the products were the diarylmercury (XV) and di-(2-hydroxyethylthio)mercury, whilst with propane-2-thiol

it gave what appeared to be a mixture of isopropylthiomercuric chloride and di-isopropylthiomercury.

For reasons mentioned before,[1] several non-mustard analogues were prepared in the course of this work, mostly by application of the methods discussed above.

Ross's method [4] was again used to determine the extent of hydrolysis of some of the mustards after 30 min. in boiling 50% aqueous acetone (see Table).

Rates of hydrolysis.

R = *p*-(*NN*-Di-2-chloroethylamino)phenyl. R′ = *p*-(*NN*-Di-2-bromoethylamino)phenyl.

Compound	mmole in acetone (25 c.c.) + water (25 c.c.)	Hydrol. (%) in 30 min. at 66°	Compound	mmole in acetone (25 c.c.) + water (25 c.c.)	Hydrol. (%) in 30 min. at 66°
R·S·CO_2Pr^i	0·3	5	R′·SAc	0·5	26
(IV)	0·5	3	R′·S·COEt	0·5	24
(IV; R′ analogue)	0·3	23	R′·S·COPh	0·3	26
R·S·CO·NH·CH_2·CO_2H	0·3	7	R′·S·(tetra-*O*-acetyl-glucosyl)	0·3	29
R′·S·CO·NH·CH_2·CO_2H	0·4	40			

Experimental

Microanalyses were by Miss J. Cuckney and the staff of the Organic Microanalytical Laboratories.

p-(NN-*Di*-2-*chloroethylamino*)*phenyl Chlorothiolformate* (V).—A solution of *p*-(*NN*-di-2-chloroethylamino)thiophenol [2] (10·0 g.) and pyridine (3·2 g.) in dry ether (250 c.c.) was slowly added (1 hr.) to a stirred solution of carbonyl chloride (10 g.) in ether (250 c.c.) through which carbonyl chloride was continuously passed. The precipitate was filtered off, and the filtrate was concentrated under reduced pressure to an oil (10 g.). This crude chlorothiolformate was characterised by reaction in benzene with aniline to give *p*-(*NN*-di-2-chloroethylamino)-phenyl *N*-phenylthiolcarbamate,[2] m. p. and mixed m. p. 143°.

S-p-(NN-*Di*-2-*chloroethylamino*)*phenyl* O-*Isopropyl Thiolcarbonate* (III; Y = Pr^i).—(i) Isopropyl chloroformate (2·44 g.) in chloroform (10 c.c.) was added to a mixture of *p*-(*NN*-di-2-chloroethylamino)thiophenol (5·0 g.) in chloroform (25 c.c.) and potassium hydroxide (1·2 g.) in ethanol (5 c.c.). The mixture was stirred for 6 hr., and then filtered and concentrated. Recrystallisation of the residue from methanol gave the *thiolcarbonate* (4·5 g., 66%), m. p. 84°, raised to 87° on further recrystallisation (Found: C, 50·7; H, 5·6; N, 4·4. $C_{14}H_{19}Cl_2NO_2S$ requires C, 50·0; H, 5·7; N, 4·2%).

(ii) A saturated solution of sodium isopropoxide in propan-2-ol was added dropwise to a stirred solution of *p*-(*NN*-di-2-chloroethylamino)phenyl chlorothiolformate (4·5 g.) in benzene (100 c.c.) until a test portion, shaken with water, gave an alkaline reaction. The mixture was filtered, and the filtrate was washed with water, dried, and evaporated to a residue which on recrystallisation from methanol gave the thiolcarbonate (4·0 g.), m. p. 79—81°, raised on recrystallisation to 84°.

S-p-(NN-*Di*-2-*bromoethylamino*)*phenyl* O-*Isopropyl Thiolcarbonate*.—(i) Potassium hydroxide (1·6 g.) in ethanol (5 c.c.) was added to *p*-(*NN*-di-2-bromoethylamino)thiophenol [2] (1·0 g.) in chloroform (25 c.c.) at −80° under nitrogen, and a solution of isopropyl chloroformate (0·5 g.) in chloroform (3 c.c.) was added. The mixture was shaken and allowed to warm to room temperature during 3 hr., and was then filtered and evaporated to a solid residue. Recrystallisation from methanol gave the *thiolcarbonate* (0·4 g.), m. p. 103° (Found: C, 39·9; H, 4·7; N, 3·4. $C_{14}H_{19}Br_2NO_2S$ requires C, 39·5; H, 4·5; N, 3·3%).

(ii) A solution of *S*-*p*-(*NN*-di-2-chloroethylamino)phenyl *O*-isopropyl thiolcarbonate (1·45 g.) in isobutyl methyl ketone (20 c.c.), containing lithium bromide (4 g.), was refluxed for 4 hr., then cooled, diluted with chloroform (50 c.c.), washed with water, dried, and concentrated. Recrystallisation of the product from methanol gave the thiolcarbonate (1·0 g.), m. p. 102°.

S-p-(NN-*Di*-2-*chloroethylamino*)*phenyl* O-*Ethyl Thiolcarbonate* (III; Y = Et).—Prepared from the potassium salt of *p*-(*NN*-di-2-chloroethylamino)thiophenol and ethyl chloroformate,

[4] Ross, *J.*, 1949, 183.

as described for the isopropyl ester, the *thiolcarbonate* (yield 73%), after recrystallisation from methanol, had m. p. 73° (Found: C, 48·7; H, 5·6; N, 4·2. $C_{13}H_{17}Cl_2NO_2S$ requires C, 48·45; H, 5·3; N, 4·35%).

S-p-(NN-*Di*-2-*chloroethylamino*)*phenyl* O-(1,2:3,4-*Di*-O-*isopropylidene*-D-*galactose*) 6-*Thiolcarbonate* (IV).—Potassium hydroxide (2·0 g.) in ethanol (50 c.c.), and 1,2:3,4-di-*O*-isopropylidene-D-galactose 6-chloroformate [5] (9·5 g.) were successively added to a solution of *p*-(*NN*-di-2-chloroethylamino)thiophenol (8·9 g.) in chloroform (100 c.c.) under nitrogen. The mixture was stirred for 20 hr., then washed with water, dried, and concentrated to an oil which was taken up in a little hot ethanol and kept at *ca.* 5° overnight. The resulting solid (15·0 g.), m. p. 99—100°, was recrystallised from ethanol to give the *thiolcarbonate* as large rhombs (14·2 g., 74%), m. p. 104—105°, $[\alpha]_D^{23}$ −47° (*c* 5 in $CHCl_3$) (Found: C, 51·8; H, 6·2; Cl, 13·3. $C_{23}H_{31}Cl_2NO_7S$ requires C, 51·5; H, 5·8; Cl, 13·2%), $\lambda_{max.}$ 2730 Å (ε 27,300).

S-p-(NN-*Di*-2-*bromoethylamino*)*phenyl* O-(1,2:3,4-*Di*-O-*isopropylidene*-D-*galactose*) 6-*Thiolcarbonate*.—The preceding thiolcarbonate (4·0 g.), lithium bromide (8·0 g.), and isobutyl methyl ketone (60 c.c.) were heated together at 100° for 6 hr. to give the *dibromo-analogue*, pale yellow rhombs (3·9 g., 84%), m. p. 107—108° [from chloroform–light petroleum (b. p. 40—60°)], $[\alpha]_D^{23}$ −40° (*c* 5 in $CHCl_3$) (Found: O, 17·8; Br, 25·6. $C_{23}H_{31}Br_2NO_7S$ requires O, 17·9; Br, 25·6%), $\lambda_{max.}$ 2750 Å (ε 30,000).

O-*Cholesteryl* S-p-(NN-*Di*-2-*bromoethylamino*)*phenyl Thiolcarbonate*.—Cholesteryl chloroformate [6] (6·0 g.) in chloroform (20 c.c.) was added to a stirred mixture of *p*-(*NN*-di-2-chloroethylamino)thiophenol (3·3 g.) in chloroform (40 c.c.) and potassium hydroxide (0·75 g.) in ethanol (20 c.c.) under nitrogen. The mixture was stirred for 24 hr. and worked up to give an oil, which was treated with lithium bromide (12 g.) in boiling isobutyl methyl ketone (40 c.c.) for 6 hr. The product crystallised when set aside at 0° with ethanol–light petroleum (b. p. 100—120°), and after five recrystallisations from light petroleum (b. p. 60—80°) it gave the *thiolcarbonate* as fibrous needles (2·0 g.), m. p. 115°, $[\alpha]_D^{23}$ −30° (*c* 3 in $CHCl_3$) (Found: Br, 21·2. $C_{38}H_{57}Br_2NO_2S$ requires Br, 21·3%), $\lambda_{max.}$ 2760 Å (ε 29,000).

S-p-(NN-*Di*-2-*chloroethylamino*)*phenyl* O-2,4-*Dinitrophenyl Thiolcarbonate*.—2,4-Dinitrophenol (1·8 g.) in chloroform (50 c.c.) was added to a solution of crude *p*-(*NN*-di-2-chloroethylamino)phenyl chlorothiolformate (3·1 g.) and pyridine (0·8 c.c.) in chloroform (44 c.c.), and the mixture was shaken for 1 hr., then washed with water, dried, and concentrated. Recrystallisation of the residue from acetone–ethanol–light petroleum (b. p. 60—80°) gave a bright yellow powder of the *thiolcarbonate* (2·1 g.), m. p. 117° (Found: C, 44·5; H, 3·6; N, 9·0. $C_{17}H_{15}Cl_2N_3O_6S$ requires C, 44·35; H, 3·3; N, 9·6%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(p-*Methoxycarbonylphenyl*)*thiolcarbamate* (VI).—(i) Methyl *p*-aminobenzoate (1·0 g.) in dry benzene (60 c.c.) containing pyridine (0·5 c.c.) was added to a stirred solution of *p*-(*NN*-di-2-chloroethylamino)phenyl chlorothiolformate (2·0 g.) in benzene (50 c.c.); the mixture was stirred at 50° for 90 min., and then cooled, washed with water, dried, and evaporated to an oil, which crystallised when triturated with light petroleum (b. p. 40—60°). Recrystallisation from methanol gave cubes of the *thiolcarbamate* (2·0 g., 70%), m. p. 143° (Found: C, 53·35; H, 4·8; Cl, 16·25; S, 8·3. $C_{19}H_{20}Cl_2N_2O_3S$ requires C, 53·4; H, 4·7; Cl, 16·5; S, 7·5%).

(ii) *p*-(*NN*-Di-2-chloroethylamino)thiophenol (5·0 g.) and methyl *p*-isocyanatobenzoate [7] (3·5 g.) were heated together for 4 hr. at 100° in a sealed tube. Recrystallisation of the product from methanol gave the ester (6·6 g., 77%), m. p. and mixed m. p. 138—140°.

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(p-*Carboxyphenyl*)*thiolcarbamate* (VII).—The methyl ester (2·5 g.) was refluxed in 1 : 1 acetic acid–concentrated hydrochloric acid (125 c.c.) for 40 min. and then cooled to 0°. Ice-water (30 c.c.) was added and the precipitate was filtered off and recrystallised from benzene to give the *acid* (1·8 g., 73%), m. p. 175° (Found: N, 7·2; Cl, 17·3. $C_{18}H_{18}Cl_2N_2O_3S$ requires N, 6·8; Cl, 17·2%).

p-(NN-*Di*-2-*bromoethylamino*)*phenyl* N-(p-*Methoxycarbonylphenyl*)*thiolcarbamate*.—Reaction of *p*-(*NN*-di-2-bromoethylamino)thiophenol (3·05 g.) with methyl *p*-isocyanatobenzoate (1·6 g.) and pyridine (0·1 c.c.) at 100° for 4 hr. gave the *thiolcarbamate* (3·5 g., 76%), m. p. 156°, raised to 161° on further recrystallisation (Found: C, 44·85; H, 4·0; Br, 30·9. $C_{19}H_{20}Br_2N_2O_3S$ requires C, 44·2; H, 3·9; Br, 31·0%).

[5] Haworth, Porter, and Waine, *Rec. Trav. chim.*, 1938, **57**, 541.
[6] Wieland, Honold, and Pascual-Vila, *Z. physiol. Chem.*, 1923, **130**, 326.
[7] Siefken, *Annalen*, 1949, **562**, 75.

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(*Methoxycarbonylmethyl*)*thiolcarbamate* (VIII).—*p*-(*NN*-Di-2-chloroethylamino)thiophenol (5·0 g.) and methyl isocyanatoacetate [1] (2·35 g.) were heated together at 100° for 3 hr. in a sealed tube. Recrystallisation of the product from carbon tetrachloride–light petroleum (b. p. 40—60°) gave the *thiolcarbamate* (5·9 g., 82%), m. p. 79—80° (Found: C, 46·3; H, 5·0. $C_{14}H_{18}Cl_2N_2O_3S$ requires C, 46·0; H, 5·0%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(*Ethoxycarbonylmethyl*)*thiolcarbamate*.—Prepared in a similar way from *p*-(*NN*-di-2-chloroethylamino)thiophenol (1·0 g.) and ethyl isocyanatoacetate [7] (0·5 g.) the *thiolcarbamate* (1·3 g., 65%), after recrystallisation from ethanol–light petroleum (b. p. 40—60°), had m. p. 82° (Found: C, 47·8; H, 5·2. $C_{15}H_{20}Cl_2N_2O_3S$ requires C, 47·5; H, 5·3%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(*Carboxymethyl*)*thiolcarbamate* (IX).—*p*-(*NN*-Di-2-chloroethylamino)phenyl *N*-(methoxycarbonylmethyl)thiolcarbamate (5·7 g.) was refluxed for 4 min. with 1 : 1 acetic acid–concentrated hydrochloric acid (30 c.c.) and then cooled to 0°. Ice-water (80 c.c.) was added, followed by saturated sodium hydrogen carbonate solution to bring the pH to *ca.* 3. The precipitate, after recrystallisation from benzene–light petroleum (b. p. 40—60°) gave the *acid* as plates (4·5 g., 81%), m. p. 105—106° (Found: C, 44·9; H, 4·7; Cl, 20·1. $C_{13}H_{16}Cl_2N_2O_3S$ requires C, 44·45; H, 4·6; Cl, 20·2%).

The ethyl ester, refluxed in 1 : 1 acetic acid–concentrated hydrochloric acid for varying periods, gave either unchanged ester or non-crystallisable oils.

p-(NN-*Di*-2-*bromoethylamino*)*phenyl* N-(*Methoxycarbonylmethyl*)*thiolcarbamate*.—*p*-(*NN*-Di-2-bromoethylamino)thiophenol (1·5 g.) and methyl isocyanatoacetate (0·6 g.) were heated together at 100° for 3 hr. The product was extracted with boiling 1 : 1 chloroform–carbon tetrachloride (25 c.c.), and the solution, decanted from residual oil, was diluted with light petroleum (b. p. 40—60°) to incipient precipitation. Storage overnight at 0° gave a solid which was several times recrystallised from carbon tetrachloride–light petroleum (b. p. 40—60°) to give the *thiolcarbamate* (0·7 g.), m. p. 80—81° (Found: C, 37·3; H, 4·2. $C_{14}H_{18}Br_2N_2O_3S$ requires C, 37·0; H, 4·0%).

p-(NN-*Di*-2-*bromoethylamino*)*phenyl* N-(*Carboxymethyl*)*thiolcarbamate*.—(i) The above methyl ester (0·6 g.) was refluxed with 1 : 1 acetic acid–concentrated hydrochloric acid (16 c.c.) for 2½ min., then cooled and partly neutralised with 2N-sodium hydroxide (50 c.c.). Extraction with chloroform gave a solid, which on recrystallisation from benzene gave plates (0·35 g., 60%) of the *acid* (containing one mol. of benzene of crystallisation), m. p. 120° (Found: C, 43·75; H, 4·5; Br, 31·0. $C_{13}H_{16}Br_2N_2O_3S,C_6H_6$ requires C, 44·0; H, 4·3; Br, 30·8%).

(ii) A solution of lithium bromide (15 g.) and *p*-(*NN*-di-2-chloroethylamino)phenyl *N*-(carboxymethyl)thiolcarbamate (3·1 g.) in isobutyl methyl ketone (160 c.c.) was heated at 120° overnight. The product, isolated as described for similar reactions above, gave the acid (solvated) (2·75 g., 60%), m. p. 124°.

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(p-NN-*Diethylaminophenyl*)*thiolcarbamate* (X).—*p*-*NN*-Diethylaminophenyl isocyanate [1] (3·75 g.) and *p*-(*NN*-di-2-chloroethylamino)thiophenol (5·0 g.), heated together at 100° for 3 hr. in a sealed tube, gave the *thiolcarbamate* (6·4 g., 74%) as solvated needles (from carbon tetrachloride), m. p. 140° (Found: C, 54·0; H, 5·35; Cl, 20·6. $C_{21}H_{27}Cl_2N_3OS,\frac{1}{5}CCl_4$ requires C, 54·0; H, 5·8; Cl, 20·6%). Recrystallisation from benzene–light petroleum (b. p. 40—60°), although less satisfactory, gave the thiolcarbamate, m. p. 140—141°, free from solvent (Found: C, 57·6; H, 5·8; Cl, 15·65. $C_{21}H_{27}Cl_2N_3OS$ requires C, 57·3; H, 6·2; Cl, 16·1%).

p-(NN-*Di*-2-*bromoethylamino*)*phenyl Thiolacetate*.—(i) Reaction of *p*-(*NN*-di-2-chloroethylamino)phenyl thiolacetate [2] (5·0 g.) with lithium bromide (7 g.) in boiling isobutyl methyl ketone (30 c.c.) for 3 hr. gave the *dibromo-compound* (4·5 g., 69%), needles [from light petroleum (b. p. 60—80°)], m. p. 70° (Found: C, 37·7; H, 4·2; Br, 41·8. $C_{12}H_{15}Br_2NOS$ requires C, 37·8; H, 4·0; Br, 41·7%), $\lambda_{max.}$ 2740 Å (ε 26,300).

(ii) Acetylation of *p*-(*NN*-di-2-bromoethylamino)thiophenol with acetic anhydride in pyridine at room temperature gave a poor yield (15%) of the thiolacetate, m. p. 64—66°, undepressed on admixture with the pure ester described above.

p-(NN-*Di*-2-*chloroethylamino*)*phenyl Thiolpropionate*.—Prepared in 82% yield by treatment of *p*-(*NN*-di-2-chloroethylamino)thiophenol with propionic anhydride in pyridine at room temperature, the *ester* crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 60° (Found: Cl, 23·1. $C_{13}H_{17}Cl_2NOS$ requires Cl, 23·2%).

p-(NN-*Di*-2-*bromoethylamino*)*phenyl Thiolpropionate*.—Treatment of the above thiolpropionate with lithium bromide, as described for the thiolacetate, gave needles of the *dibromo-analogue*, m. p. 69° [from light petroleum (b. p. 60—80°)] (Found: Br, 40·5. $C_{13}H_{17}Br_2NOS$ requires Br, 40·45%), $\lambda_{max.}$ 2740 Å (ε 24,900).

p-(NN-*Di*-2-*bromoethylamino*)*phenyl Thiolbenzoate*.—(i) Reaction of *p*-(*NN*-di-2-chloroethylamino)phenyl thiolbenzoate [2] with lithium bromide in boiling isobutyl methyl ketone for 4 hr. gave pale yellow needles (82%) of the *dibromo-analogue*, m. p. 110—111° (from chloroform–ethanol) (Found: C, 46·1; H, 4·0; Br, 36·3. $C_{17}H_{17}Br_2NOS$ requires C, 46·05; H, 3·9; Br, 36·1%), $\lambda_{max.}$ 2390, 2740 Å (ε 14,200, 32,800).

(ii) Benzoylation of *p*-(*NN*-di-2-bromoethylamino)thiophenol with benzoic anhydride in pyridine gave a 60% yield of crude thiolbenzoate, m. p. 103—109°.

p-(NN-*Di*-2-*bromoethylamino*)*phenyl* 2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucothioside*.—Prepared by reaction of the dichloro-analogue [2] (4·0 g.) with lithium bromide (8 g.) in boiling isobutyl methyl ketone (25 c.c.) for 5 hr., the compound crystallised from propan-2-ol in prisms (3·5 g., 76%), m. p. 119—120°, $[\alpha]_D^{23}$ −41° (*c* 2 in $CHCl_3$) (Found: O, 21·2; Br, 23·6. $C_{24}H_{32}Br_2NO_9S$ requires O, 21·5; Br, 23·8%).

p-(NN-*Di*-2-*bromoethylamino*)*phenyl* β-D-*Glucothioside* (XI).—Sodium (4 mg.) was added to the above tetra-acetate (1·0 g.) in dry methanol (30 c.c.), and the solution was set aside overnight, then saturated with carbon dioxide and evaporated to dryness. Crystallisation from ethanol–light petroleum (b. p. 40—60°) gave the *glucothioside dihydrate* as needles (0·45 g., 60%), m. p. 90° (Found: O, 20·8; Br, 30·3. $C_{16}H_{23}Br_2NO_5S,2H_2O$ requires O, 20·8; Br, 29·8%).

[p-(NN-*Di*-2-*chloroethylaminophenyl*)*thio*]-(p-NN-*diethylaminophenyl*)*mercury* (XII).—*p*-(*NN*-Di-2-chloroethylamino)thiophenol (4·0 g.) in acetone (16 c.c.) was mixed with *N*-ethanolic sodium ethoxide (15·4 c.c.), and the solution was added to *p*-*NN*-diethylaminophenylmercuric chloride [3] (6·1 g.) in acetone (110 c.c.). The mixture was diluted to 500 c.c. with light petroleum (b. p. 40—60°) and then filtered. The precipitate was washed with water and recrystallised from acetone to give the *mercurial* (4·4 g., 47%), m. p. 126—127° (Found: C, 40·5; H, 4·6; S, 5·7. $C_{20}H_{26}Cl_2HgN_2S$ requires C, 40·2; H, 4·4; S, 5·4%), $\lambda_{max.}$ 3000 Å (ε 31,400).

p-(NN-*Di*-2-*chloroethylamino*)*phenylmercuric Chloride* (XIV).—A hot solution of mercuric acetate (30 g.) in ethanol (300 c.c.) was added to *NN*-di-2′-chloroethylaniline [2] (20 g.) in ethanol (100 c.c.), and the mixture was set aside for 3 hr. and then cooled to 0°. The solid was collected and recrystallised from acetone, containing a few drops of acetic acid, to give needles of p-(NN-*di*-2-*chloroethylamino*)*phenylmercuric acetate* (32 g., 72%), m. p. 141° (Found: C, 30·4; H, 3·3. $C_{12}H_{15}ClHgNO_2$ requires C, 30·2; H, 3·2%). This acetate (28 g.) was added to a hot solution of lithium chloride (6 g.) in ethanol (500 c.c.). After 2 hr. the mixture was boiled and filtered hot to give, on cooling, needles of p-(NN-*di*-2-*chloroethylamino*)*phenylmercuric chloride* (21 g., 79%), m. p. 154—155°, raised to 156° on further recrystallisation from ethanol (Found: C, 26·7; H, 3·1. $C_{10}H_{12}Cl_3HgN$ requires C, 26·5; H, 2·7%).

[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]-[p-(NN-*diethylaminophenyl*)*thio*]*mercury* (XIII).—N-Ethanolic sodium ethoxide (10·0 c.c.) was added to *p*-(*NN*-diethylamino)thiophenol [2] (2·0 g.) in ethanol (7·0 c.c.), and the solution was poured into a stirred solution of *p*-(*NN*-di-2-chloroethylamino)phenylmercuric chloride (4·5 g.) in acetone (40 c.c.). The mixture, now containing a yellow precipitate, was diluted to 100 c.c. with light petroleum (b. p. 40—60°) and filtered. The solid was washed with water and recrystallised from acetone to give the *mercurial* (3·6 g., 60%), m. p. 66—67° (Found: C, 40·9; H, 4·5; S, 5·2. $C_{20}H_{26}Cl_2HgN_2S$ requires C, 40·2; H, 4·4; S, 5·4%), $\lambda_{max.}$ 2900 Å (ε 37,400).

[p-(NN-*Di*-2-*chloroethylamino*)*phenylthio*](*phenyl*)*mercury*.—A solution of thiophenol (0·2 g.) in N-ethanolic sodium ethoxide (2·0 c.c.) was added to *p*-(*NN*-di-2-chloroethylamino)phenylmercuric chloride (0·9 g.) in warm acetone (10 c.c.). The solution was then diluted with water (50 c.c.), and the precipitate was collected and recrystallised from acetone–methanol to give the *mercurial* (0·9 g.) as fibrous needles, m. p. 99—100° (Found: C, 36·5; H, 3·6; N, 2·7. $C_{16}H_{17}Cl_2HgNS$ requires C, 36·5; H, 3·25; N, 2·7%).

Di-[p-(NN-*di*-2-*chloroethylamino*)*phenyl*]*mercury*.—(i) A solution of *p*-(*NN*-di-2-chloroethylamino)phenylmercuric chloride (0·6 g.) in pyridine (4 c.c.) was refluxed over copper powder (0·8 g.) under nitrogen for 20 min. and then cooled, diluted with ether (20 c.c.), and shaken with 2N-sulphuric acid (15 c.c.). The dried ether layer on evaporation gave a solid which on

[3] Whitmore, Hanson, and Carnahan, *J. Amer. Chem. Soc.*, 1929, **51**, 894.

recrystallisation from aqueous acetone formed needles of the *mercurial* (0·25 g., 60%), m. p. 132° (Found: C, 37·8; H, 4·1; N, 4·7. $C_{20}H_{24}Cl_4HgN_2$ requires C, 37·8; H, 3·8; N, 4·4%).

(ii) A solution of *p*-(*NN*-di-2-chloroethylamino)phenylmercuric chloride (0·90 g.) in acetone (10 c.c.) was added to 2-mercaptoethanol (0·16 g.) in N-ethanolic sodium ethoxide (2·0 c.c.). The mixture was diluted with water to 50 c.c. to precipitate an oil which gradually crystallised. Recrystallisation of a portion from aqueous acetone gave the above diarylmercury, m. p. 132°. Recrystallisation of another portion from acetone–light petroleum (b. p. 40—60°) gave di-(2-hydroxyethylthio)mercury, m. p. 119—121° (lit.,[9] m. p. 123°) (Found: C, 13·4; H, 3·4. Calc. for $C_4H_{10}HgO_2S_2$: C, 13·5; H, 2·8%).

Reaction of p-(NN-*Di-2-chloroethylamino*)*phenylmercuric Chloride with Propane-2-thiol.*—Propane-2-thiol (0·75 g.) in benzene (15 c.c.) was added to *p*-(*NN*-di-2-chloroethylamino)-phenylmercuric chloride (0·45 g.) in ethanol (5 c.c.) and benzene (50 c.c.) at 35°, and the mixture was refluxed for 15 min. and then cooled. Recrystallisation of the precipitated solid from ethanol–dioxan gave a product of m. p. *ca.* 220° (decomp.), probably a mixture of isopropylthiomercuric chloride and di-isopropylthiomercury (Found: C, 12·5; H, 2·6; Cl, 7·5. Calc. for C_3H_7ClHgS: C, 11·6; H, 2·3; Cl, 11·4. Calc. for $C_6H_{14}HgS_2$: C, 20·55; H, 4·0; Cl, 0·0%).

OS-*Diphenyl Thiolcarbonate.*—Phenyl chloroformate (3·1 g.) in chloroform (5 c.c.) was added to a mixture of thiophenol (2·2 g.) in chloroform (20 c.c.) and potassium hydroxide (1·1 g.) in ethanol (15 c.c.). The mixture was shaken for 2 hr., filtered, and evaporated to an oil which crystallised from ethanol to give needles of *diphenyl thiolcarbonate* (1·5 g.), m. p. 62° (Found: C, 68·4; H, 4·6. $C_{13}H_{10}O_2S$ requires C, 67·8; H, 4·4%).

O-*Isopropyl* S-*Phenyl Thiolcarbonate.*—Prepared in a similar way from isopropyl chloroformate (7·3 g.) and thiophenol (6·4 g.) this *ester* was an oil, b. p. 78—80°/1 mm., n_D^{20} 1·5436 (Found: C, 60·8; H, 6·2; S, 16·6. $C_{10}H_{12}O_2S$ requires C, 61·2; H, 6·2; S, 17·0%).

S-*Isopropyl* S-*Phenyl Dithiolcarbonate.*—Phenyl chlorothiolformate [10] (1·7 g.) was added to propane-2-thiol (0·75 g.) and pyridine (0·8 g.). The mixture was diluted with benzene (15 c.c.), washed with water, dried, and distilled to give the *dithiolcarbonate*, b. p. 84—85°/0·1 mm., n_D^{18} 1·5920 (Found: C, 56·4; H, 6·1; S, 29·7. $C_{10}H_{12}OS_2$ requires C, 56·6; H, 5·7; S, 30·2%).

Phenyl N-(*Methoxycarbonylmethyl*)*thiolcarbamate*, prepared by reaction of thiophenol and methyl isocyanatoacetate at 100°, crystallised from methanol in flat needles, m. p. 117—118° (Found: C, 53·1; H, 5·1. $C_{10}H_{11}NO_3S$ requires C, 53·3; H, 4·9%).

p-(NN-*Diethylamino*)*phenyl* N-(*Methoxycarbonylmethyl*)*thiolcarbamate*, prepared by reaction of *p*-(*NN*-diethylamino)thiophenol with methyl isocyanatoacetate at 100°, after recrystallisation from carbon tetrachloride–light petroleum (b. p. 40—60°) had m. p. 67° (Found: C, 56·7; H, 6·75; N, 9·65. $C_{14}H_{20}N_2O_3S$ requires C, 56·7; H, 6·8; N, 9·45%).

p-(NN-*Diethylamino*)*phenyl* N-(*Carboxymethyl*)*thiolcarbamate.*—The above methyl ester (5·2 g.) was refluxed with a 1 : 1 mixture of acetic acid and concentrated hydrochloric acid (35 c.c.) for 3 min. and then cooled to 0°, diluted with water (50 c.c.), and partly neutralised with 2N-sodium hydroxide (150 c.c.). Extraction with chloroform gave the acid as an oil. The *piperidine* salt, recrystallised from nitromethane, had m. p. 108° (Found: C, 58·2; H, 7·6; N, 10·9. $C_{18}H_{29}N_3O_3S$ requires C, 58·8; H, 7·95; N, 11·4%).

Phenyl N-(p-NN-*Diethylaminophenyl*)*thiolcarbamate.*—A solution of phenyl chlorothiolformate (3·45 g.) and *NN*-diethyl-*p*-phenylenediamine (from 4·0 g. of hydrochloride) in ether (150 c.c.) was refluxed for 10 min., then cooled, shaken with saturated aqueous sodium hydrogen carbonate (125 c.c.), and extracted with ether to give the *thiolcarbamate* (2·5 g.), m. p. 80—81° [from light petroleum (b. p. 60—80°)] (Found: C, 67·5; H, 6·8. $C_{17}H_{20}N_2OS$ requires C, 67·95; H, 6·7%).

The product (1·5 g.) was boiled with methyl iodide (35 c.c.) for 5 hr. Dilution with ether, and recrystallisation of the precipitate from methanol–ether gave the *methiodide* (1·3 g.), m. p. 187° (Found: C, 48·4; H, 5·3. $C_{18}H_{23}IN_2OS$ requires C, 48·85; H, 5·2%).

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