534. *Antituberculous Sulphur Compounds. Part IV.* Some Dimercaptopropyl Esters and Related Dithiouronium Bromides.*

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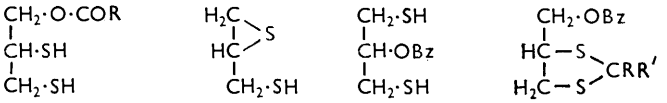
Reaction of 2,3-dimercaptopropan-1-ol with acid chlorides has given a series of dimercaptopropyl esters possessing antituberculosis activity. In attempts to prepare water-soluble analogues the reaction of dibromopropyl esters with thiourea was examined. Several 2,3-dibromopropyl esters rearranged to 2-acyloxytrimethylene-*SS'*-di(thiouronium bromides), which were also obtained from esters of 1,3-dibromopropan-2-ol.

In our examination of derivatives of 2,3-dimercaptopropanol the *O*-acetate (I; R = Me) was found to possess considerable antituberculosis activity. This compound is known to give 3-mercaptopropylene sulphide (II) (which is highly active) when warmed with sodium hydrogen carbonate solution,[1] so it is conceivable that a similar cyclisation occurred under physiological conditions. This led us to prepare a series of dimercaptopropyl esters (I).

The acetate, propionate, and butyrate have been prepared previously in moderate yield by heating 2,3-dimercaptopropanol with the appropriate anhydrides under acidic conditions,[2] but the process involves a tedious fractionation and appears not to be generally applicable. Fifteen new esters have now been prepared very simply and in satisfactory yield by treating 2,3-dimercaptopropanol with equimolecular proportions of an aliphatic or aromatic acid chloride in boiling benzene. In most cases iodometric thiol determinations showed that acylation had occurred almost exclusively on the hydroxyl rather than on a thiol group. Similar treatment of 1,3-dimercaptopropan-2-ol with benzoyl chloride in boiling benzene gave the benzoate (III), although this may have been contaminated with a little *S*-benzoyl derivative since the content of thiol sulphur was less than that of total sulphur.



(I) (II) (III) (IV)

Acylation of the thiol groups in 2,3-dimercaptopropyl benzoate (I; R = Ph) with the appropriate acid chlorides in the presence of pyridine gave 2,3-diacetylthiopropyl and 2,3-dipalmitoylthiopropyl benzoate. The *SS*-dinicotinoyl derivative was prepared under slightly different conditions.

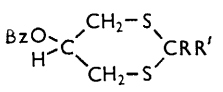
2,3-Dimercaptopropyl benzoate with acetone or benzaldehyde gave isopropylidene (IV; R = R' = Me) and benzylidene (IV; R = Ph; R' = H) derivatives respectively, the same products being obtained by the action of benzoyl chloride and pyridine on 2,3-isopropylidenedithio- and 2,3-benzylidenedithio-propan-1-ol. Either synthesis of 2,3-benzylidenedithiopropyl benzoate (IV; R = Ph, R' = H) apparently gave a mixture of *cis*- and *trans*-isomers,[3] from which one pure component was isolated by repeated crystallisation. 2,3-Dimercaptopropyl benzoate was regenerated from its benzylidene derivative in rather poor yield by treatment with mercuric chloride,[4] the use of sodium in liquid ammonia [5] being precluded by the sensitivity of the dimercapto-ester to bases. The crystalline isopropylidene derivative (V; R = R' = Me), prepared from the benzoate (III), was identical with a specimen obtained from 1,3-isopropylidenedithiopropan-2-ol

* Part III, preceding paper.

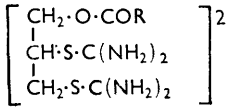
[1] Miles and Owen, *J.*, 1952, 815.
[2] Pavlic, Lazier, and Signaigo, *J. Org. Chem.*, 1949, **14**, 59.
[3] Cf. Roberts and Cheng, *J. Org. Chem.*, 1958, **23**, 983.
[4] Hach, *Chem. Listy*, 1953, **47**, 227.
[5] Stocken, *J.*, 1947, 592.

and benzoyl chloride in pyridine. The benzylidene derivative (V; R = Ph, R′ = H) was probably a mixture of *cis*- and *trans*-isomers.

Most of the 2,3-dimercaptopropyl esters described above had considerable antituberculosis activity in mice, but were somewhat undesirable from the clinical standpoint because of their oily nature and insolubility in water. We therefore turned to the water-soluble solid which Meinhard [6] formulated as 3-benzoyloxypropylene-*SS*′-di(thiouronium bromide) (VI; R = Ph). Unfortunately, the structure of Meinhard's compound is open to doubt because the alleged 2,3-dibromopropyl benzoate used in its preparation had been obtained by a method later shown [7] to yield a mixture of the benzoates of 2,3-dibromopropan-1-ol and 1,3-dibromopropan-2-ol. There, is, moreover, a possibility of structural rearrangement during nucleophilic displacement of halogen from certain 2-acyloxyalkyl halides.[8]



(V)



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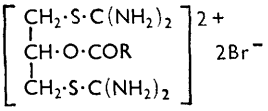
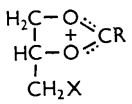
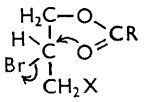


(VII)

Meinhard reported that when the dibromo-ester was heated with thiourea in acetone the dithiouronium salt began to separate within three hours, but when we repeated the reaction with authentic 2,3-dibromopropyl benzoate no solid had appeared after 48 hours' refluxing and more than half of the thiourea was then recovered. In a similar reaction with the isomeric benzoate (of 1,3-dibromopropan-2-ol), a crystalline product, presumably 2-benzoyloxytrimethylene-*SS*′-di(thiouronium bromide) (VII; R = Ph), began to separate after 3 hr.; the yield reached a maximum (36%)in 24 hr. The greater reactivity of the diprimary bromide is paralleled by the behaviour of 1,3- and 1,2-dibromopropane.[9] In view of these results Meinhard's experiment would be expected to have given the 1,3-dithiouronium salt (VII; R = Ph) and not, as he supposed, the isomer (VI; R = Ph). Since, however, our product (VII; R = Ph) had m. p. 258° (decomp.), the nature of Meinhard's material, which had m. p. 138—141°, remains obscure.



(VIII)



(IX) X = Br or $[SC(NH_2)_2]^+$

(X)

Better yields of the dithiouronium salt (VII; R = Ph) were obtained by carrying out the reaction of thiourea with the benzoate of 1,3-dibromopropan-2-ol in boiling ethyl methyl ketone, acetic acid, or freshly purified dioxan instead of acetone. However, reaction with the isomeric 2,3-dibromopropyl benzoate in boiling acetic acid or dioxan involved rearrangement and gave the same dithiouronium salt (VII; R = Ph). This has a possible parallel in the thermal rearrangement of certain esters of dibromopropanols.[7,10] Somewhat above 100° both 2,3-dibromopropyl benzoate and the isomeric benzoate undergo partial rearrangement to a mixture of the two. In the presence of thiourea, however, one might expect the equilibrium to be displaced by preferential removal of the more reactive 1,3-dibromide as dithiouronium salt (VII; R = Ph), which would thus become the major end-product from either isomer. There is, however, probably no clear distinction between rearrangement before and during reaction with thiourea: a resonating cation (VIII) could be supposed to arise either by dissociation of

[6] Meinhard, *Monatsh.*, 1950, **81**, 1050.
[7] Nayler, *J.*, 1959, 189.
[8] Fairbourne, *J.*, 1930, 369.
[9] Levy and Campbell, *J.*, 1939, 1442.
[10] Edwards and Hodges, *J.*, 1953, 3427.

the ion-pair proposed as an intermediate in the thermal rearrangement [7] or directly from a bromo-ester by anchimerically assisted ionisation as in (IX), and this could give either dithiouronium salt (VI or VII) on combination with thiourea. Participation of a dioxolanium ion (VIII) in the displacement of halogen from 2-acyloxyalkyl halides, first specifically suggested by Winstein and Buckles,[11] is essentially a re-formulation in terms of electronic theory of Fairbourne's explanation for rearrangements of this type.[8]

Several 2-acyloxytrimethylene-*SS'*-di(thiouronium bromides) (VII) were prepared from thiourea and substituted benzoates of 1,3-dibromopropan-2-ol in boiling acetic acid or ethyl methyl ketone, but the isomeric salts (VI) could not be prepared. Upon reaction with thiourea, 2,3-dibromopropyl *p*-toluate, *p*-anisate, and *p*-chlorobenzoate behaved in much the same way as the benzoate, giving little or no product in low-boiling solvents such as acetone, whilst yielding the rearranged bromides at higher temperatures. No pure thiouronium salts could be prepared from the 2,3-dibromopropyl esters of stronger aromatic acids, such as *p*-nitro-, 3,5-dinitro-, and 2,4-dichloro-benzoic acid, which would be expected to be relatively resistant to thermal isomerisation.

The reaction of thiourea with the acetates and phenylacetates of the dibromopropanols was also investigated. Neither of the phenylacetates has been described hitherto, but the pure 1,3-dibromo-ester has now been prepared as a low-melting solid and the crude 2,3-dibromo-ester as an oil. Reaction of the acetates and phenylacetates with thiourea in boiling acetic acid led to contamination of the products with ammonium salts. The pure 2-acetoxy-bromide (VII; R = Me) was obtained from the acetate of 1,3-dibromopropan-2-ol in boiling ethyl methyl ketone, or more slowly from 2,3-dibromopropyl acetate. The phenylacetoxy-compound (VII; R = CH_2Ph) was likewise prepared from the 1,3-dibromide in ethyl methyl ketone. Attempts to prepare the bromides (VI; R = Me or CH_2Ph) failed.

During attempts to bring about reaction of thiourea with the acetate or phenylacetate of 1,3-dibromopropan-2-ol in boiling acetone a sparingly soluble crystalline solid, $C_{11}H_{20}N_4S_2$, was isolated. It presumably had structure (X), analogous to " triacetone diurea " which is formed from acetone and urea in the presence of hydrogen chloride [12] (in the present experiments condensation with the solvent may have been induced by a trace of hydrogen bromide derived from the dibromo-esters).

Several of the thiouronium salts were tested for antituberculosis activity in mice, but none was active.

Experimental

Reaction of 2,3-Dimercaptopropanol with Carboxylic Acid Chlorides.—The acid chloride (0·1 mole) was added to 2,3-dimercaptopropanol (0·1 mole) in dry benzene (100 ml.), and the solution was refluxed until evolution of hydrogen chloride ceased. The cooled mixture was stirred with an aqueous suspension of calcium carbonate, then the benzene layer was separated, washed, dried, and evaporated *in vacuo*. The residue was normally distilled under reduced pressure, but the solid 2,3-dimercaptopropyl *p*-(toluene-*p*-sulphonamido)benzoate was recrystallised from benzene–light petroleum. Details of individual 2,3-*dimercaptopropyl esters*, all of which are new, are tabulated.

2-*Mercapto*-1-*mercaptomethylethyl Benzoate*.—Benzoyl chloride (28 g.) was added to 1,3-dimercaptopropan-2-ol (24·8 g.) in dry benzene (140 ml.) and the solution was refluxed for 8 hr., then distilled under reduced pressure. A colourless liquid (15·8 g.), b. p. 126—136°/0·4 mm., was collected and redistilled, to give the *benzoate*, b. p. 126°/0·2 mm. (Found: C, 52·3; H, 5·0; total S, 28·6; thiol S, 25·3. $C_{10}H_{12}OS_2$ requires C, 52·6; H, 5·3; total S, 28·1; thiol S, 28·1%).

2,3-*Diacetylthiopropyl Benzoate*.—Acetyl chloride (15·6 g.) was added slowly to a stirred solution of 2,3-dimercaptopropyl benzoate (22·8 g.) and pyridine (15·8 g.) in dry benzene (500 ml.). The mixture was refluxed for 1 hr., cooled, and poured into water. Distillation of the dried benzene layer gave 2,3-*diacetylthiopropyl benzoate* (21 g.), b. p. 164°/0·15 mm., n_D^{20} 1·5640 (Found: C, 53·5; H, 5·0; S, 20·8. $C_{14}H_{16}O_4S_2$ requires C, 53·8; H, 5·2; S, 20·5%).

2,3-Dimercaptopropyl benzoate (11·4 g.) and palmitoyl chloride (30·2 g.) similarly gave

[11] Winstein and Buckles, *J. Amer. Chem. Soc.*, 1942, **64**, 2780.
[12] Weinschenk, *Ber.*, 1901, **34**, 2185.

2,3-*dipalmitoylpropyl benzoate* (36 g.), prisms (from acetone), m. p. 40° (Found: C, 71·1; H, 10·2; S, 9·2. $C_{42}H_{72}O_4S_2$ requires C, 71·5; H, 10·3; S, 9·1%).

2,3-*Dinicotinoylthiopropyl Benzoate.*—A solution of nicotinoyl chloride (14·2 g.) in dry ether (10 ml.) was added dropwise with stirring to 2,3-dimercaptopropyl benzoate (11·4 g.) in the same solvent (90 ml.). Next morning the yellow (presumed) hydrochloride (20·1 g.) was filtered off and stirred with ether and an aqueous suspension of calcium carbonate. The basic ester passed into the ether layer, which was separated, washed, and dried. Removal of the solvent *in vacuo* left a crude solid (7·64 g.; m. p. 104—109°) which, after several crystallisations from ethanol–light petroleum, gave pure 2,3-*dinicotinoylthiopropyl benzoate*, m. p. 119—120° (Found:

2,3-*Dimercaptopropyl esters* (I).

No.	R	Reflux (hr.)	Yield (%)	B. p./mm.	n_D^{20}
1	$[CH_2]_{11}$·Me	2	55	166°/0·0001	—
2	$CH<(CH_2)_5$	1	78	108—109°/0·05	1·5248
3	CH_2Cl *	2	27	86°/0·12	1·5432
4	$[CH_2]_2$·CO_2Et	16	45	132°/0·01	1·5074
5	$[CH_2]_2$·SMe	4	54	118—119°/0·02	1·5449
6	CH_2·SEt	4	38	109—111°/0·07	1·5488
7	CH_2·S·CH_2Ph	5	30	148°/0·0001	1·5945
8	CH_2Ph	2	28	136°/0·4	1·5699
9	Ph	8	59	120°/0·1	1·5855
10	C_6H_4·OMe-*p*	22	40	138°/5 × 10^{-5}	1·5892
11	C_6H_4Cl-*o*	18	47	130°/1 × 10^{-5}	1·5956
12	C_6H_4Cl-*p*	16	41	123°/1 × 10^{-5}	1·5989
13	$C_6H_3Cl_2$(2,4-)	16	50	138°/5 × 10^{-5}	1·6086
14	$C_{10}H_7$-α	2	25	155°/3 × 10^{-5}	1·4866
15	C_6H_4·NHTs †	16	50	M. p. 134°	—

	Found (%)					Required (%)			
No.	C	H	Total S	Thiol S	Formula	C	H	Total S	Thiol S
1	62·8	10·6	17·1	16·9	$C_{19}H_{38}O_2S_2$	62·9	10·6	17·7	17·7
2	51·0	7·7	27·4	28·7	$C_{10}H_{18}O_2S_2$	51·2	7·7	27·4	27·4
3	29·2	5·0	31·8	—	$C_5H_9O_2S_2Cl$	29·9	4·5	32·0	—
4	42·9	6·1	25·8	—	$C_9H_{16}O_4S_2$	42·8	6·4	25·4	—
5	37·3	5·8	41·0	27·9	$C_7H_{14}O_2S_3$	37·1	6·2	42·5	28·3
6	37·1	6·2	42·2	29·0	$C_7H_{14}O_2S_3$	37·1	6·2	42·5	28·3
7	50·7	5·7	—	21·3	$C_{12}H_{16}O_2S_3$	50·0	5·6	—	22·2
8	54·6	5·8	25·5	26·6	$C_{11}H_{14}O_2S_2$	54·5	5·8	26·5	26·5
9	52·2	5·1	28·6	—	$C_{10}H_{12}O_2S_2$	52·6	5·3	28·1	—
10	50·8	5·6	24·5	24·0	$C_{11}H_{14}O_3S_2$	51·1	5·5	24·8	24·8
11	45·7	4·3	—	25·0	$C_{10}H_{11}O_2S_2Cl$	45·7	4·2	—	24·4
12	45·9	4·3	24·3	24·3	$C_{10}H_{11}O_2S_2Cl$	45·7	4·2	24·4	24·4
13	40·5	3·4	21·8	—	$C_{10}H_{10}O_2S_2Cl_2$	40·4	3·4	21·6	—
14	60·8	5·6	—	23·0	$C_{14}H_{14}O_2S_2$	60·4	5·1	—	23·0
15	51·0	4·8	23·4	—	$C_{17}H_{19}O_4NS_3$	51·4	4·8	24·2	—

* Decomp. on storage. † Ts = *p*-C_6H_4Me·SO_2.

C, 60·5; H, 4·4; N, 6·6; S, 14·8. $C_{22}H_{18}O_4N_2S_2$ requires C, 60·2; H, 4·1; N, 6·4; S, 14·6%).

2,3-*Isopropylidenedithiopropyl Benzoate.*—(*a*) Benzoyl chloride (14 g.) was added dropwise to a stirred mixture of 2,3-isopropylidenedithiopropan-1-ol [5] (16·4 g.) and pyridine (40 ml.) at 15°, with cooling; the mixture was warmed at 30° for 30 min., then poured on ice. The *benzoate* was collected, dried, and crystallised from light petroleum (60 ml., b. p. 60—80°) as prisms (22 g.), m. p. 81—83° (Found: C, 57·7; H, 5·8; S, 24·0. $C_{13}H_{16}O_2S_2$ requires C, 58·2; H, 6·0; S, 23·9%).

(*b*) (With R. Ward) 2,3-Dimercaptopropyl benzoate (3 g.) in acetone (50 ml.) was treated with concentrated hydrochloric acid (4 drops) and refluxed for 16 hr. Evaporation *in vacuo* left a solid (2·5 g.) which, after several crystallisations from light petroleum, had m. p. 82—83° alone or mixed with the product of method (*a*).

2,3-*Benzylidenedithiopropyl Benzoate.*—(*a*) Concentrated hydrochloric acid (3 drops) was added to 2,3-dimercaptopropyl benzoate (9·7 g.) and benzaldehyde (4·6 ml.) in benzene (20 ml.). The mixture was set aside for 20 hr., then evaporated *in vacuo*. Trituration of the residual oil with methanol gave a white powder (8·0 g.), m. p. 55—63°. After three crystallisations from methanol and two from 1 : 2 benzene–light petroleum the product (3·4 g.) still melted over a

wide range (70—82°) and was probably a mixture of the geometrical isomers of 2,3-benzylidenethiopropyl benzoate (Found: C, 64·7; H, 5·3; S, 20·2. Calc. for $C_{17}H_{16}O_2S_2$: C, 64·5; H, 5·1; S, 20·3%). Three further crystallisations from 1 : 1 benzene–light petroleum followed by three from methanol gave needles (1·08 g.) of constant m. p. 95—96°, presumably consisting of one pure *isomer* (Found: C, 64·7; H, 5·4; S, 20·1%).

(*b*) The mixed isomers [5,13] of 2,3-benzylidenedithiopropanol (42·4 g.) were dissolved in pyridine (120 ml.) and stirred at 0° whilst benzoyl chloride (20 ml.) was added during 10 min. The mixture was stirred for 3 hr. at 0°, set aside for 18 hr. at room temperature, then poured into ice-water. After acidification with hydrochloric acid, the oil was extracted with chloroform, washed, and dried. The solvent was removed *in vacuo* and the residual oil triturated with methanol to give the mixed isomeric benzoates (34·4 g.), m. p. 59—66°, not depressed on admixture with crude material of similar m. p. prepared by method (*a*). Seven crystallisations from benzene–light petroleum, followed by three from methanol, gave the pure isomer as needles of constant m. p. (and mixed m. p.) 95—96°.

2,3-*Dimercaptopropyl Benzoate from the Benzylidene Derivative*.—Crude 2,3-benzylidenedithiopropyl benzoate (from 42·4 g. of 2,3-benzylidenedithiopropanol) was suspended in ethanol (400 ml.) and stirred with cadmium carbonate (40 g.). The mixture was kept at 60—70° whilst mercuric chloride (64 g.) in ethanol (400 ml.) was added during 2 hr., then stirred for 4 hr. more at the same temperature. The cooled suspension was filtered and the cream-coloured mercaptide was washed with boiling water (1 l.). It was then stirred vigorously with methanol at 0° whilst hydrogen sulphide was passed in for 4 hr. Mercuric sulphide was removed and the colourless filtrate and methanol washings were evaporated under reduced pressure in nitrogen. The residual oil was dissolved in ether, washed with sodium hydrogen carbonate solution and water, dried, and distilled, to give 2,3-dimercaptopropyl benzoate (5·44 g.), b. p. 111—121°/0·02 mm. A redistilled specimen had b. p. 115—117°/0·04 mm. (Found: C, 52·4; H, 5·4; S, 27·9. Calc. for $C_{10}H_{12}O_2S_2$: C, 52·6; H, 5·3; S, 28·1%).

5-*Benzoyloxy*-2,2-*dimethyl*-1,3-*dithian*.—(*a*) 2-Mercapto-1-mercaptomethylethyl benzoate (5 g.) in acetone (50 ml.) was treated with concentrated hydrochloric acid (0·4 ml.) and refluxed for 16 hr. The mixture was evaporated *in vacuo* and the residue was crystallised from ethanol, to give the *isopropylidene derivative* (1·2 g.), m. p. 85—87° (Found: C, 58·1; H, 6·0; S, 23·6. $C_{13}H_{16}O_2S_2$ requires C, 58·2; H, 6·0; S, 23·9%). On admixture with the isomeric 2,3-isopropylidenedithiopropyl benzoate (m. p. 81—83°) the m. p. was 64—65°.

(*b*) Benzoyl chloride (3·2 g.) was added dropwise to a stirred solution of 1,3-isopropylidenedithiopropan-2-ol [14] (3·7 g.) in pyridine (25 ml.) at 0°. After being stirred for 1 hr. the mixture was concentrated *in vacuo* and poured into water. The product was extracted with ether and the extracts were washed with cold dilute hydrochloric acid and then with water. Evaporation of the dried ether solution left a solid (5·6 g.), m. p. 73—76°, which on recrystallisation from ethanol had m. p. and mixed m. p. 85—87°.

5-*Benzoyloxy*-2-*phenyl*-1,3-*dithian*.—Concentrated hydrochloric acid (1 drop) was added to 2-mercapto-1-mercaptomethylethyl benzoate (0·58 g.) and benzaldehyde (0·3 ml.) in benzene (6 ml.). After 20 hr. the solvent was removed *in vacuo* and the residue was triturated with light petroleum to give a white powder (0·83 g.), m. p. 95—99°. Three recrystallisations from benzene–light petroleum raised the m. p. to 111—113°, but a constant value was not attained and the material was probably a mixture of the geometrical isomers of the dithian (Found: C, 64·1; H, 5·2; S, 19·9. Calc. for $C_{17}H_{16}O_2S_2$: C, 64·5; H, 5·1; S, 20·3%).

2-*Benzoyloxytrimethylene*-SS′-*di*(*thiouronium Bromide*).—(*a*) A solution of 2-bromo-1-bromomethylethyl benzoate [7] (3·22 g.) and thiourea (1·52 g.) in dry acetone (40 ml.) was refluxed with stirring for 24 hr. The suspension was cooled and a first crop (0·70 g.) of white powder, m. p. 258° (decomp.), was collected. Two further crops of less pure material were obtained by concentrating the filtrate, bringing the yield of *dithiouronium salt* to 1·69 g. (36%). Recrystallisation from methanol gave colourless prisms, m. p. 258° (decomp.) (Found: C, 30·3; H, 3·9; N, 12·3; S, 13·4. $C_{12}H_{18}O_2N_4S_2Br$ requires C, 30·4; H, 3·8; N, 11·8; S, 13·5%). Better results were obtained when the acetone solvent was replaced by ethyl methyl ketone (58% yield), acetic acid (69% yield), or freshly purified dioxan (53% yield), the mixture being refluxed for 24 hr. in each case.

(*b*) A solution of 2,3-dibromopropyl benzoate [7] (3·22 g.) and thiourea (1·52 g.) in acetic acid

[13] Miles and Owen, *J.*, 1950, 2938.
[14] Adams *et al.*, *J.*, 1960, 2649.

(40 ml.) was refluxed with stirring for 24 hr., during which the same thiouronium salt (2·45 g., 52%) separated, having m. p. and mixed m. p. 258° (decomp.).

2-p-*Toluyloxytrimethylene*-SS′-*di*(*thiouronium Bromide*).—A solution of 2-bromo-1-bromomethylethyl *p*-toluate [7] (3·36 g.) and thiourea (1·52 g.) in acetic acid (40 ml.) was refluxed with stirring for 24 hr., during which the crystalline product (3·38 g., 69%) separated. Recrystallisation from methanol–ethyl acetate gave needles of the *dithiouronium salt*, m. p. 249° (decomp.) (Found: C, 31·9; H, 4·3; N, 11·8; S, 12·8. $C_{13}H_{20}O_2N_4S_2Br_2$ requires C, 32·0; H, 4·1; N, 11·5; S, 13·1%). The same compound was obtained in 54% yield from 2,3-dibromopropyl *p*-toluate.

2-p-*Anisoyloxytrimethylene*-SS-*di*(*thiouronium Bromide*).—A solution of 2-bromo-1-bromomethylethyl *p*-anisate [7] (3·52 g.) and thiourea (1·52 g.) in dry ethyl methyl ketone (40 ml.) was refluxed with stirring for 24 hr., during which a bulky solid separated (3·18 g., 63%). Recrystallisation from ethanol–ethyl acetate gave rosettes of the *dithiouronium bromide* which melted at 198—200°, but the melt only became clear when decomposition (gas evolution) ensued at 221—223° (Found: C, 30·9; H, 3·8; N, 10·8; S, 12·1. $C_{13}H_{20}O_3N_4S_2Br_2$ requires C, 31·0; H, 4·0; N, 11·1; S, 12·7%). The same compound was obtained when 2-bromo-1-bromomethylethyl (73% yield) or 2,3-dibromopropyl *p*-anisate (61% yield) was heated with thiourea in acetic acid for 24 hr.

2-p-*Chlorobenzoyloxytrimethylene*-SS′-*di*(*thiouronium bromide*) was similarly prepared from the 1,3-dibromo-compound in acetic acid in 55% yield; it had m. p. 242—244° (decomp.) (from methanol–ether) (Found: C, 28·6; H, 3·5; S, 12·7. $C_{12}H_{17}O_2N_4S_2Br_2Cl$ requires C, 28·3; H, 3·4; S, 12·6%). The same compound was similarly obtained in 28% yield from 2,3-dibromopropyl *p*-chlorobenzoate.

2-(2,4-*Dichlorobenzoyloxy*)*trimethylene*-SS′-*di*(*thiouronium bromide*), prepared from 2-bromo-1-bromomethylethyl 2,4-dichlorobenzoate [7] in acetic acid (40 ml.), formed cubes (58%), m. p. 233—234° (decomp.) (from methanol–ether) (Found: C, 26·8; H, 3·3; N, 10·6; S, 11·5. $C_{12}H_{16}O_2N_4S_2Br_2Cl_2$ requires C, 26·5; H, 3·0; N, 10·3; S, 11·8%).

2-p-*Nitrobenzoyloxytrimethylene*-SS′-*di*(*thiouronium bromide*), prepared from 2-bromo-1-bromomethylethyl *p*-nitrobenzoate [7] in dry ethyl methyl ketone (68% yield), recrystallised from methanol–ethyl acetate as needles, m. p. 259—260° (decomp.) (Found: C, 27·2; H, 3·2; S, 12·1. $C_{12}H_{17}O_4N_5S_2Br_2$ requires C, 27·7; H, 3·3; S, 12·3%).

2-(3,5-*Dinitrobenzoyloxy*)*trimethylene*-SS′-*di*(*thiouronium bromide*), prepared from 2-bromo-1-bromomethylethyl 3,5-dinitrobenzoate [7] in dry ethyl methyl ketone (yield, 65%), recrystallised from methanol–ethanol–ethyl acetate as needles, m. p. 222—224° (decomp.) (Found: C, 25·7; H, 3·0; N, 14·5; S, 11·2. $C_{12}H_{16}O_6N_6S_2Br_2$ requires C, 25·5; H, 2·9; N, 14·9; S, 11·4%).

2-*Acetoxytrimethylene*-SS′-*di*(*thiouronium Bromide*).—A solution of 2-bromo-1-bromomethylethyl acetate [10] (2·6 g.) and thiourea (1·52 g.) in dry ethyl methyl ketone (40 ml.) was refluxed with stirring for 24 hr., during which a white plastic mass separated. The mixture was cooled and the product broken up to a hygroscopic powder, which was collected [2·19 g.; m. p. 168—174° (decomp. 185°)]. This was dissolved in boiling ethanol (50 ml.) and filtered from a little insoluble material, and the filtrate was diluted with hot ethyl acetate (50 ml.). The fairly pure *dithiouronium dibromide* (1·24 g., 30%) separated on cooling in needles, m. p. 191—192° (decomp.). After further crystallisation from the same solvents the m. p. was 192—194° decomp.) (Found: C, 20·7; H, 4·0; N, 13·6; S, 15·3. $C_7H_{16}O_2N_4S_2Br_2$ requires C, 20·4; H, 3·9; N, 13·6; S, 15·5%).

(*b*) Reaction of 2,3-dibromopropyl acetate [10] and thiourea was also carried out in ethyl methyl ketone, but the mixture was refluxed for 72 hr. Recrystallisation of the crude product, m. p. 161—166° (decomp.), from ethanol–ethyl acetate gave the dithiouronium dibromide (17% yield), m. p. and mixed m. p. 192—194° (decomp.).

2-*Bromo*-1-*bromomethylethyl Phenylacetate*.—Phenylacetyl chloride (7·7 g.) and 1,3-dibromopropan-2-ol (10·9 g.) were heated on the steam-bath for 5 hr., then cooled and diluted with ether. After being washed with sodium hydrogen carbonate solution and then with water, the ether solution was dried and evaporated. The residual oil crystallised when cooled strongly under methanol, and the white solid (11·3 g.) was collected by rapid filtration and washed with very cold methanol. Further purification was effected by dissolution in methanol (25 ml.) at room temperature, followed by strong cooling, to give colourless plates of 2-*bromo*-1-*bromomethylethyl phenylacetate*, m. p. 18—20° (Found: C, 39·5; H, 3·6. $C_{11}H_{12}O_2Br_2$ requires C, 39·3; H, 3·6%).

This ester (3·36 g.) and thiourea (1·52 g.) in ethyl methyl ketone were refluxed with stirring for 24 hr., during which a white powder separated (2·1 g., 43%). Recrystallisation from methanol–ethanol–ethyl acetate gave rods of *2-phenylacetoxytrimethylene-SS'-di(thiouronium bromide)*, m. p. 213—214° (decomp.) (Found: C, 32·2; H, 4·4; N, 11·4; S, 12·8. $C_{13}H_{20}O_2N_4S_2Br_2$ requires C, 32·0; H, 4·1; N, 11·5; S, 13·1%).

2,2-Di-(N'-isopropylidenethioureido)propane.—(*a*) A solution of 2-bromo-1-bromomethylethyl acetate (2·6 g.) and thiourea (1·52 g.) in dry acetone (40 ml.) was refluxed with stirring for 24 hr., during which white crystals separated (0·82 g.). The product was insoluble in water and most organic solvents, but was purified by dissolution in boiling dimethylformamide followed by addition of hot water. On cooling, the *product* separated in needles, m. p. 259° (decomp.) (Found: C, 48·4; H, 7·4; N, 20·4; S, 23·4. $C_{11}H_{20}N_4S_2$ requires C, 48·5; H, 7·4; N, 20·6; S, 23·5%).

(*b*) The same compound (0·38 g.) was obtained when 2-bromo-1-bromomethylethyl phenylacetate (3·36 g.) was used instead of the acetate.

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