532. *Antituberculous Sulphur Compounds. Part II.* Some Cyclic Sulphides Derived from Dimercaptoalkanols.*

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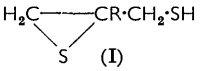
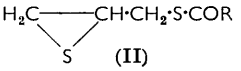
A number of dimercaptoalkanols have been converted, through their triacyl derivatives, into acylthioalkylene sulphides. Cyclic sulphides have also been prepared by treating dimercaptoalkanols with hydrochloric acid followed, where necessary, by a weak base. The latter cyclisation procedure may, however, result in the formation of either three- or five-membered rings, depending on the relative positions of the functional groups.

The discovery of appreciable antituberculosis activity in 2,3-dimercaptopropanol (BAL) led us to examine some of its simple derivatives. The *O*-acetate,[1] di-*S*-acetate,[2] and triacetate [3,4] were found to possess considerable antituberculosis activity both *in vitro* and *in vivo*. The action of bases on these derivatives gives 3-mercaptopropylene sulphide (I; R = H) or its *S*-acetyl derivative (II; R = Me),[2,4] both of which have now been shown to be powerful antituberculosis agents *in vivo*. We therefore prepared analogous cyclic derivatives of other acylated dimercaptoalkanols.

The tripropionate and tributyrate of 2,3-dimercaptopropanol were readily prepared by using the appropriate anhydride in the presence of sodium propionate and sodium butyrate respectively. However, application of Miles and Owen's cyclisation procedure,[2] in which the ester is distilled with sodium hydrogen carbonate solution at about 60°/150 mm., to these compounds was not as satisfactory as with the triacetate. The tripropionate slowly gave 3-propionylthiopropylene sulphide (II; R = Et), but much starting material distilled unchanged, and the tributyrate gave no more than a trace of 3-butyrylthiopropylene sulphide (II; R = Pr^n). In view of these results study of the cyclisation of triacyl derivatives of other dimercaptoalkanols was restricted to the acetates.



(I)



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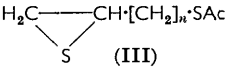


(III)

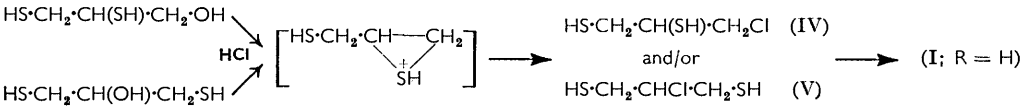
All the dimercaptoalkanols described in Part I gave good yields of triacetates when heated with acetic anhydride and anhydrous sodium acetate. Distillation of the appropriate triacetates with sodium hydrogen carbonate solution in the usual way gave satisfactory yields of four new acetylthioethylethylene sulphides (*i.e.*, III; $n = 2$, and the three isomeric monomethyl derivatives of II; R = Me) and of two homologues (III; $n = 3$ and 4). The presence of the ethylene sulphide ring in each product was confirmed by the isolation of trimethylsulphonium iodide upon treatment with an excess of methyl iodide at room temperature for some days.[2,5] Under these cyclisation conditions, therefore, ethylene sulphides are apparently formed in preference to alternative structures containing larger rings. Although the triacetates of the two dithioglycerols differ markedly in their tendency to undergo cyclisation to 3-acetylthiopropylene sulphide,[6] (2-acetylthioethyl)ethylene sulphide (III; $n = 2$) was obtained with equal facility from either 2,4-di(acetylthio)butyl or 3-acetylthio-1-acetylthiomethylpropyl acetate. No acylthio-episulphide could be isolated when the usual cyclisation procedure was applied to 2,11-di(acetylthio)undecyl acetate, methyl α-acetoxy-β-acetylthio-α-acetylthiomethylpropionate,

* Part I, preceding paper.

[1] Pavlic, Lazier, and Signaigo, *J. Org. Chem.*, 1949, **14**, 59.
[2] Miles and Owen, *J.*, 1952, 817.
[3] Evans, Fraser, and Owen, *J.*, 1949, 248.
[4] Harding and Owen, *J.*, 1954, 1528.
[5] Culvenor, Davies, and Heath, *J.*, 1949, 282.
[6] Cf. Fitt and Owen, *J.*, 1957, 2240.

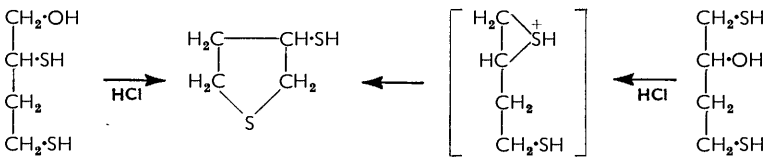
or 2,3-diacetylthio-1-acetylthiomethylpropyl acetate, probably owing to the low solubility of these compounds.

Both the previous synthesis [2] from 2,3-dimercaptopropyl acetate and the alternative thermal dehydration of 2,3-dimercaptopropanol [7] give rather poor yields of 3-mercaptopropylene sulphide (I; R = H) together with much polymer. In view of the antituberculosis activity of the sulphide we tried to develop an improved and general synthesis. Better yields of 3-mercaptopropylene sulphide have now been obtained by a process similar to that of Coltof [8] for simple ethylene sulphides. Treatment of 2,3-dimercaptopropanol with concentrated hydrochloric acid at room temperature for two days gave a chloro-dithiol, which in the presence of a base such as sodium hydrogen carbonate or calcium carbonate lost the elements of hydrogen chloride to give the episulphide: strong bases caused extensive polymerisation. Since Davies and Savige [9] obtained the same mercaptopropyl chloride from 2-mercaptopropan-1-ol and 1-mercaptopropan-2-ol, rearrangement through a cyclic sulphonium ion could have occurred at the first stage. Consequently our intermediate may have been compound (IV) or (V) or a mixture of the two, and we failed to prove its structure. 3-Mercaptopropylene sulphide was similarly prepared from 1,3-dimercaptopropan-2-ol, but this alcohol was less reactive than its isomer towards hydrochloric acid and even when the mixture was heated the yield of chloro-dithiol, again unidentified, was comparatively low. The marked inferiority of 1,3-dimercaptopropan-2-ol to 2,3-dimercaptopropan-1-ol as a source of 3-mercaptopropylene sulphide parallels the previously noted difference in the tendency of the derived triacetates to undergo cyclisation to 3-acetylthiopropylene sulphide in the presence of alkali.



A dimercaptobutyl chloride of uncertain structure was readily obtained from 1,3-dimercapto-2-methylpropan-2-ol by means of cold concentrated hydrochloric acid: it gave the sulphide (I; R = Me) on treatment with sodium hydrogen carbonate. Both 2,3-dimercaptobutan-1-ol and 3,4-dimercaptobutan-2-ol were similarly converted into mercapto-episulphides, but in these cases the structures of the end-products as well as those of the intermediates are equivocal. All the mercapto-episulphides gave trimethylsulphonium iodide when kept with an excess of methyl iodide, confirming the presence of the ethylene sulphide ring. The two thiols (I; R = H and Me) were characterised as crystalline phenylurethanes.

The action of cold concentrated hydrochloric acid on 2,4-dimercaptobutan-1-ol (VI) differed from its action on the dimercaptoalkanols considered hitherto in that the product was, not a chloro-dithiol, but 3-mercaptothiophan (VII), characterised as the phenylurethane. Rather surprisingly, this product was also obtained from 1,4-dimercapto-

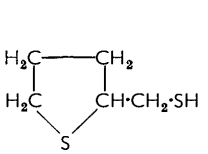


butan-2-ol (IX) under similar conditions, presumably *via* the cyclic sulphonium ion (VIII). The preferential formation, by acid, of the five-membered ring contrasts with the conversion

[7] Signaigo, U.S.P. 2,436,233.
[8] Coltof, B.P. 508,932; U.S.P. 2,183,860.
[9] Davies and Savige, *J.*, 1950, 317.

of the derived triacetates into the three-membered ring structure (III; $n = 2$) by the action of sodium hydrogen carbonate. With an excess of methyl iodide 3-mercaptothiophan gave a crystalline methiodide, which with cold sodium hydrogen carbonate solution afforded a thiol-free product tentatively formulated as 3-methylthiothiophan.

A cyclic sulphide was also formed when 2,5-dimercaptopentan-1-ol was treated with cold concentrated hydrochloric acid. The product, characterised as the phenylurethane, is probably 2-mercaptomethylthiophan (X), in view of the apparent ease of formation of the thiophan ring. The six-membered ring of the alternative structure (XI) is not formed readily under such conditions: thus 1,6-dimercaptohexan-2-ol, which could theoretically give compound (XII) or (XIII), or a chloro-dithiol, reacted only sluggishly with cold concentrated hydrochloric acid and no pure product was isolated.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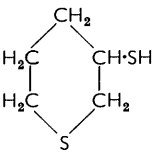
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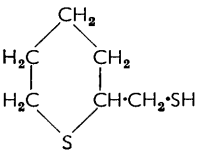
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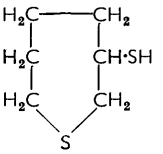
(XIII)

The deactivating effect of a carboxyl substituent was illustrated by the recovery of α-hydroxy-β-mercapto-α-mercaptomethylpropionic acid after a week in concentrated hydrochloric acid. No pure products were isolated from the action of hydrochloric acid on 2,11-dimercaptoundecan-1-ol or on 3-hydroxy-2-mercaptopropyl 2-mercaptopropyl sulphide.

The new compounds described in this paper were tested against experimental human type tuberculosis (H37Rv) in mice. Several of the chloro-thiols, the mercaptoalkylene sulphides, the acylthioalkylene sulphides, and the triacyl derivatives of dimercaptoalkanols showed antituberculosis activity, to be reported by Mr. D. M. Brown and his colleagues.

Experimental

Triacyl Derivatives of Dimercaptoalkanols.—A mixture of the dimercaptoalkanol (0·1 mole), the acid anhydride (0·65 mole), and the anhydrous sodium salt of the corresponding acid (0·2 mole) was refluxed for 8 hr., cooled, and diluted with ether. The sodium salt was removed with water, and the ether solution was dried and distilled. Details for individual *triacyl derivatives*, all of which were colourless or pale yellow liquids, are given in Table 1.

Reaction of Triacyl Derivatives with Sodium Hydrogen Carbonate Solution.—(*a*) A mixture of 2,3-dipropionylthiopropyl propionate (17·5 g.), sodium hydrogen carbonate (20 g.), and water (200 ml.) was distilled slowly under nitrogen at about 60°/150 mm., more water being added as required. After 22 hr. the condensate no longer contained oily drops, and distillation was stopped. The distillate was extracted with light petroleum, and the extracts were washed, dried, and distilled to give 3-*propionylthiopropylene sulphide* (3·7 g.) (see Table 2) and unchanged tripropionate (8 g.), b. p. 120—127°/0·01 mm.

(*b*) 2,3-Dibutyrylthiopropyl butyrate (20 g.) was distilled with sodium hydrogen carbonate solution at about 70°/200 mm. for 20 hr. After being worked up as in (*a*), the distillate gave only a trace of 3-*butyrylthiopropylene sulphide* (see Table 2), but mainly unchanged tributyrate (17 g.). The tributyrate also distilled substantially unchanged when the experiment was conducted at atmospheric pressure. Distillation at 70°/200 mm. in the presence of ethylene glycol (added to increase the solubility of the tributyrate) gave some 6% of 3-butyrylthiopropylene sulphide, but the main product was non-volatile polymer.

(*c*) Each of the triacetates (Nos. 3—9 in Table 1) was distilled with sodium hydrogen carbonate solution at about 70°/200 mm. as previously described. It was usually necessary to collect about 1 l. of distillate during about 7 hr. The distillate was extracted with light petroleum or chloroform, and the extracts were washed, dried, and distilled. All the *acylthioalkylene sulphides* (see Table 2) were colourless or pale yellow mobile liquids: no unchanged triacetate was found.

TABLE 1. *Triacyl derivatives of dimercaptoalkanols.*

No.	Derivatives of	Acyl group	B. p./mm.	n_D^{20}	Yield (%)	Formula	Found (%) C	Found (%) H	Found (%) S	Required (%) C	Required (%) H	Required (%) S
1	2,3-Dimercaptopropan-1-ol	COEt	132—136°/0·1	1·5038	79	$C_{12}H_{20}O_4S_2$	—	—	22·1	—	—	21·9
2	2,3-Dimercaptopropan-1-ol	$COPr^n$	156—160°/0·15	1·4940	84	$C_{15}H_{26}O_4S_2$	—	—	19·2	—	—	19·2
3	2,3-Dimercaptobutan-1-ol	Ac	107°/0·04	1·5123	77	$C_{10}H_{16}O_4S_2$	44·8	5·9	24·2	45·4	6·1	24·3
4	2,4-Dimercaptobutan-1-ol	Ac	117—119°/0·1	1·5122	71	$C_{10}H_{16}O_4S_2$	45·5	5·9	23·6	45·4	6·1	24·3
5	1,4-Dimercaptobutan-2-ol	Ac	119—120°/0·1	1·5095	77	$C_{10}H_{16}O_4S_2$	45·3	6·5	24·5	45·4	6·1	24·3
6	3,4-Dimercaptobutan-2-ol	Ac	106°/0·2	1·5085	80	$C_{10}H_{16}O_4S_2$	45·2	5·8	—	45·4	6·1	—
7	1,3-Dimercapto-2-methylpropan-2-ol	Ac	115—116°/0·1	1·5118	86	$C_{10}H_{16}O_4S_2$	45·7	6·1	24·4	45·4	6·1	24·3
8	2,5-Dimercaptopentan-1-ol	Ac	134—136°/0·03	1·5107	74	$C_{11}H_{18}O_4S_2$	47·5	6·7	23·3	47·5	6·5	23·0
9	1,6-Dimercaptohexan-2-ol	Ac	122—124°/0·03	1·5044	92	$C_{12}H_{20}O_4S_2$	49·5	7·1	—	49·3	6·9	—
10	2,11-Dimercaptoundecan-1-ol	Ac	156—170°/0·0006	1·4943	77	$C_{17}H_{30}O_4S_2$	56·4	8·3	17·4	56·3	8·3	17·7

TABLE 2. *Acylthioalkylene sulphides.*

Compound	Prepared from No.*	B. p./mm.	Yield (%)	n_D^{20}	Formula	Found (%) C	Found (%) H	Found (%) S	Required (%) C	Required (%) H	Required (%) S
3-Propionylthiopropylene sulphide	1	45—47°/0·01	38	—	$C_6H_{10}OS_2$	44·4	6·0	39·6	44·4	6·2	39·5
3-Butyrylthiopropylene sulphide	2	67°/0·25	1	—	$C_7H_{12}OS_2$	48·2	6·7	—	47·7	6·9	—
(1-Acetylthioethyl)ethylene sulphide	3	64—66°/0·1	69	1·5401	$C_6H_{10}OS_2$	44·2	6·5	39·0	44·4	6·2	39·5
(2-Acetylthioethyl)ethylene sulphide †	4, 5	66°/0·05	65, 62	1·5504	$C_6H_{10}OS_2$	44·2	6·3	—	44·4	6·2	—
1-Acetylthiomethyl-2-methylethylene sulphide	6	42°/0·08	59	—	$C_6H_{10}OS_2$	44·4	6·0	39·8	44·4	6·2	39·5
1-Acetylthiomethyl-1-methylethylene sulphide	7	41°/0·15	53	1·5397	$C_6H_{10}OS_2$	44·5	6·0	39·6	44·4	6·2	39·5
(3-Acetylthiopropyl)ethylene sulphide	8	78—80°/0·15	46	1·5428	$C_7H_{12}OS_2$	48·1	6·9	36·6	47·7	6·9	36·4
(4-Acetylthiobutyl)ethylene sulphide	9	78°/0·05	56	1·5382	$C_8H_{14}OS_2$	50·9	7·6	34·1	50·5	7·4	33·7

* The numbers refer to Table 1.

† Specimens of this compound prepared from the two different triacyl compounds (Nos. 4 and 5) had n_D^{26} 1·5477 and n_D^{22} 1·5498 respectively.

Action of Hydrochloric Acid on Dimercaptoalkanols.—(*a*) Addition of 2,3-dimercaptopropan-1-ol (100 g.) to concentrated hydrochloric acid (200 ml.) gave a clear solution, which after 5 min. began to deposit an oil. The mixture was stirred vigorously for 48 hr., then diluted with water and extracted with ether. The extracts were washed and dried, and the ether was removed, finally under reduced pressure, to leave the crude chloro-dithiol (104 g.) as an almost colourless foul-smelling liquid. A distilled specimen had b. p. 30—31°/0·1 mm. (Found: C, 25·1; H, 5·0; S, 45·7. Calc. for $C_3H_7S_2Cl$: C, 25·3; H, 5·0; S, 44·9%).

The crude chloro-dithiol (104 g.) was stirred vigorously for 2 hr. with sodium hydrogen carbonate (70 g.) in water (600 ml.), carbon dioxide being evolved. 3-Mercaptopropylene sulphide was then extracted into ether, washed, dried, and distilled; it had b. p. 61—65°/20 mm., n_D^{20} 1·5813 (yield, 49 g., 57%) (Miles and Owen [2] give b. p. 66—67°/20 mm., n_D^{18} 1·5810) (Found: C, 34·0; H, 5·4. Calc. for $C_3H_6S_2$: C, 33·9; H, 5·7%). With phenyl isocyanate at room temperature it slowly gave the phenylurethane, m. p. 100° (from cyclohexane) (Miles and Owen [2] give m. p. 102°) (Found: C, 53·3; H, 4·8; N, 6·5. Calc. for $C_{10}H_{11}ONS_2$: C, 53·3; H, 4·9; N, 6·2%).

(*b*) A solution of 1,3-dimercaptopropan-2-ol (20 g.) in concentrated hydrochloric acid (60 ml.) was heated in a sealed tube at 70—80° for 18 hr., cooled, and diluted with water. The colourless viscous oil which separated was extracted into ether (some insoluble polymer being discarded), washed, dried, and distilled. The chloro-dithiol (5·94 g.) was collected at 33—40°/0·1—0·2 mm. There remained a large residue of viscous oil, but raising the bath-temperature above 80° caused very extensive decomposition. Redistillation of the chloro-dithiol, b. p. 35—36°/0·1 mm., was always accompanied by slight decomposition with loss of hydrogen chloride (Found: C, 25·7; H, 4·8; S, 45·9; Cl, 22·9. Calc. for $C_3H_7S_2Cl$: C, 25·3; H, 4·9; S, 44·9; Cl, 24·9%).

The chloro-dithiol (5·9 g.; once distilled) was shaken overnight with calcium carbonate (7 g.) and water (70 ml.) to give 3-mercaptopropylene sulphide (1·98 g.), b. p. 64—65°/22 mm., n_D^{21} 1·5814, isolated as in (*a*).

(*c*) The initially clear solution of 1,3-dimercapto-2-methylpropan-2-ol (10 g.) in concentrated hydrochloric acid (20 ml.) became turbid after a few minutes. It was shaken for 45 hr., diluted with water, and extracted with ether. Distillation of the washed and dried extracts gave the *chlorodithiol* (?) (5·08 g.), b. p. 44—46°/0·9 mm. Redistillation gave a colourless mobile liquid, b. p. 30—31°/0·1 mm., n_D^{20} 1·5477 (Found: C, 30·6; H, 5·5; S, 40·9. $C_4H_9S_2Cl$ requires C, 30·7; H, 5·8; S, 40·9%).

The reaction was repeated, but instead of distilling the crude chloro-dithiol it was shaken with sodium hydrogen carbonate (8 g.) in water (80 ml.) for 2½ hr. 1-*Mercaptomethyl*-1-*methylethylene sulphide* was isolated by ether-extraction and distilled as a colourless mobile liquid, b. p. 66—67°/17 mm., n_D^{24} 1·5534 (4·71 g., 54%) (Found: C, 39·7; H, 6·5; S, 53·6. $C_4H_8S_2$ requires C, 40·0; H, 6·7; S, 53·3%). When kept with phenyl isocyanate for some days it gave the *phenylurethane*, platelets, m. p. 80—81° (from benzene–light petroleum) (Found: C, 55·1; H, 5·3; N, 6·1; S, 26·7. $C_{11}H_{13}ONS_2$ requires C, 55·2; H, 5·5; N, 5·9; S, 26·8%).

(*d*) A solution of 2,4-dimercaptobutan-1-ol (13·8 g.) in concentrated hydrochloric acid (20 ml.) became turbid after five min. The mixture was shaken for 3 days, then diluted with water and extracted with ether. Distillation of the washed and dried extracts gave 3-mercaptothiophan (4·5 g.), b. p. 27—28°/0·04 mm. (Found: C, 39·7; H, 6·6; S, 53·1. Calc. for $C_4H_8S_2$: C, 40·0; H, 6·7; S, 53·3%). The phenylurethane separated from light petroleum in needles, m. p. 108—109°, alone or mixed with an authentic specimen [2] kindly supplied by Dr. Owen (Found: N, 6·1. Calc. for $C_{11}H_{13}ONS_2$: N, 5·9%).

(*e*) A solution of 1,4-dimercaptobutan-2-ol (10 g.) in concentrated hydrochloric acid (20 ml.) became turbid rather slowly. After being shaken for 4 days, the mixture was worked up as in (*d*) to yield 3-mercaptothiophan (3·53 g.), b. p. 30°/0·3 mm. (Found: C, 39·9; H, 6·6%), identified as the phenylurethane, m. p. and mixed m. p. 107—109°.

(*f*) 2,5-Dimercaptopentan-1-ol (5 g.) dissolved in concentrated hydrochloric acid (10 ml.) to give a clear solution, from which an oil began to separate after 5 min. The mixture was shaken for 48 hr. and 2-*mercaptomethylthiophan* (?) was isolated by ether-extraction and distilled to give a liquid (2·61 g.), b. p. 89—90°/12 mm., n_D^{18} 1·5696 (Found: C, 44·4; H, 7·5. $C_5H_{10}S_2$ requires C, 44·7; H, 7·5%). The *phenylurethane*, prepared in boiling benzene, crystallised from benzene–light petroleum in prisms, m. p. 87—89° (Found: N, 5·3; S, 25·4. $C_{12}H_{15}ONS_2$ requires N, 5·5; S, 25·3%).

3-*Acetylthiothiophan.*—A mixture of 3-mercaptothiophan (2·1 g.), acetic anhydride (8 ml.),

and anhydrous sodium acetate (2 g.) was refluxed for 2½ hr., cooled, diluted with water, and extracted with ether. Distillation of the washed and dried extracts gave **3-*acetylthiothiophan*** (2·31 g.), b. p. 58—60°/0·15 mm., n_D^{25} 1·5569 (Found: C, 44·1; H, 6·1; S, 39·2. $C_6H_{10}OS_2$ requires C, 44·4; H, 6·2; S, 39·5%). In common with thiophan itself,[10] this compound exhibited no strong infrared absorption peaks between 9 and 10 μ, whereas the isomeric (2-acetylthioethyl)ethylene sulphide, ethylene sulphide,[11] propylene sulphide, and 3-acetylthiopropylene sulphide all absorb strongly at 9·5—9·6 μ. The spectra of 3-acetylthiothiophan and (2-acetylthioethyl)ethylene sulphide also differ in several other respects, notably in the 7·6—8·3 μ region.

Reaction of Cyclic Sulphides with Methyl Iodide.—(*a*) When 3-mercaptopropylene sulphide, 1-mercaptomethyl-1-methylethylene sulphide, or any of the acylthioalkylene sulphides reported in Table 2 was kept for some days in an excess of methyl iodide at room temperature trimethylsulphonium iodide was formed. It was identified by mixed m. p. after recrystallisation from ethanol. The m. p. of this iodide depends greatly on the rate of heating, but an average value is 197—198° (decomp.).

(*b*) 3-Mercaptothiophan (15 g.) in methyl iodide (50 ml.) was set aside for 2 days. It gave a white solid (27·2 g.), m. p. 92—94° (after washing with acetone and ether). This ***methiodide*** crystallised from methanol in prisms, m. p. 94—95° (Found: C, 23·0; H, 4·8; S, 24·8. $C_5H_{11}S_2I$ requires C, 22·9; H, 4·2; S, 24·5%). A solution in cold water immediately decolorised iodine.

A solution of the methiodide (20 g.) in cold water (300 ml.) was treated with sodium hydrogen carbonate (15 g.) in cold water (200 ml.). An oil began to separate at once and carbon dioxide was evolved freely for several min. After 40 min. the mixture was extracted with ether, and the extracts were washed, dried, and distilled to give **3-*methylthiothiophan*** (?) (8·8 g.), b. p. 89—90°/12 mm., n_D^{17} 1·5481 (Found: C, 44·8; H, 7·8; S, 47·1. $C_5H_{10}S_2$ requires C, 44·7; H, 7·5; S, 47·8%).

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[10] Hartough, "Thiophene and its Derivatives," Interscience Publishers, New York, 1952, p. 108.
[11] Guthrie, Scott, and Waddington, *J. Amer. Chem. Soc.*, 1952, **74**, 2795.