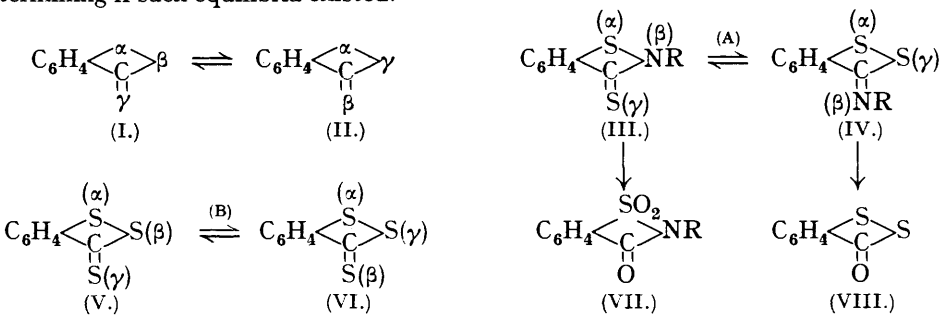
239. *The Possibility of Dynamic Isomerism in Certain Heterocyclic Compounds.*

By E. W. McClelland and C. E. Salkeld.

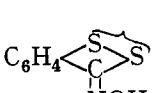
A heterocyclic compound of the type (I) might behave as (I) in equilibrium with (II). 2-Thio-1 : 2-dihydrobenz*iso*thiazoles (III) (McClelland, Warren, and Jackson, J., 1929, 1582) conform to this type, as does 2 : 3-dithiosulphindene (V ⇌ VI), from which they are obtained by the action of primary amines. Regarded in this way, these compounds should be formulated as the equilibria (A) and (B). This investigation was directed to determining if such equilibria existed.



The structure (III) assigned to these thio*iso*thiazoles was based on their oxidation to saccharins (VII). It is now found that they (III; R = Me or Ph) are hydrolysed to 2-dithiobenzoyl (VIII) and 2 : 2′-dithiobenzoic acid, the latter being a disruption of the former. The formation of saccharins by oxidation and of 2-dithiobenzoyl by hydrolysis is in accord with the suggested equilibrium (A).

In contrast to the thio*iso*thiazoles (III or IV; R = alkyl or aryl) the oxime derived from 2 : 3-dithiosulphindene and the corresponding *O*-methyl ether do not react with hydrogen sulphide to give 2 : 3-dithiosulphindene (V), nor are they oxidised to saccharins but instead give sulphones (IX; and IX with OMe for OH) without elimination of sulphur. These results suggest that the oxime type is differently constituted from the thio*iso*-thiazoles previously investigated. The failure to obtain a saccharin from the oxime and its methyl ether appears to exclude the structures (III; R = OH or OMe) and it is concluded that these compounds have the structure (IV; R = OH or OMe), no evidence of an equilibrium (A) having been obtained. Since the oxime does not give 2 : 3-dithiosulphindene with hydrogen sulphide, the reactivity of the thio*iso*thiazoles with hydrogen sulphide may be indicative of their labile nature. The compounds [III or IV; R = NHPh, NH·CO_2Et, or NH·CO·O·C_5H_{11}(*iso*)] also do not give 2 : 3-dithiosulphindene with hydrogen sulphide, indicating that they are similarly constituted to the oxime type (IV) and are not an equilibrium of two forms. The compounds (III or IV; R = NH_2 or CH_2·CH_2·OH) react with hydrogen sulphide to give 2 : 3-dithiosulphindene and therefore may be an equilibrium of two forms (III ⇌ IV).

It is therefore suggested that those compounds (III or IV; R = alkyl or aryl) which on treatment with hydrogen sulphide regenerate 2 : 3-dithiosulphindene, are hydrolysed to 2-dithiobenzoyl, and on oxidation give *N*-substituted saccharins are an equilibrium of the two forms (III ⇌ IV), whereas those (IV; R = OH or OMe) which do not react with hydrogen sulphide, are hydrolysed to 2-dithiobenzoyl, and on oxidation give sulphones without elimination of sulphur have the structure (IV).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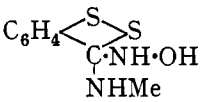
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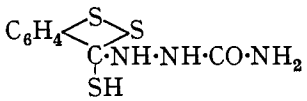
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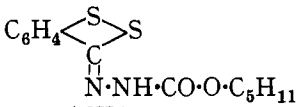

(XII.)

The oxime (IV; R = OH) was obtained by the action of hydroxylamine on 2 : 3-dithiosulphindene. While the work was in progress Mannessier-Mameli (*Gazzetta*, 1932, **62**, 1067) also obtained this oxime and assigned to it the same structure. The oxime on hydrolysis gave 2-dithiobenzoyl, whereas the sulphone (IX) obtained by oxidation gave 2 : 2′-dithiobenzoic acid. The thio*iso*thiazole (III or IV; R = Me) also reacted with hydroxylamine to give the oxime; hydrogen sulphide was evolved during the reaction, but no other product was isolated.

The formation of the oxime from this source can be accounted for by assuming addition of hydroxylamine at the methylimino-group of the ketimine form (IV), followed by elimination of methylamine from the addition compound (X) as in the amidines (*loc. cit.*). The evolution of hydrogen sulphide indicates reaction of the thio*iso*thiazole in the *iso*thiazole form (III) with hydroxylamine.

The *methyl ether* of the oxime (IV; R = OH), obtained by methylation or by the interaction of *O*-methylhydroxylamine and 2 : 3-dithiosulphindene, exhibited similar properties. It was hydrolysed to 2-dithiobenzoyl and oxidised to a *sulphone* (IX with OMe for OH). An identical sulphone was obtained by methylation of (IX); hydrolysis of these sulphones (IX; IX with OMe for OH) gave 2 : 2′-dithiobenzoic acid.

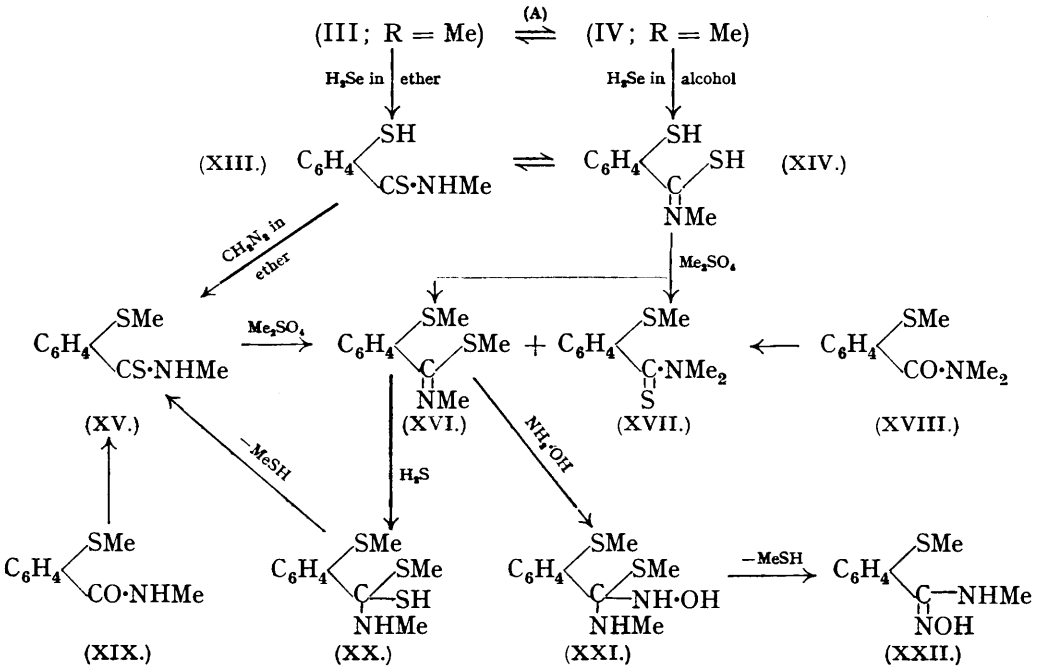
The *compounds* (III or IV; R = CH_2·CH_2·OH, NH_2, or NHPh) were obtained by condensation of 2 : 3-dithiosulphindene with β-aminoethanol, hydrazine, and phenylhydrazine respectively. They reacted vigorously with hydrogen peroxide, but crystalline oxidation products could not be isolated. They gave 2-dithiobenzoyl and 2 : 2′-dithiobenzoic acid on hydrolysis.

Semicarbazide reacted with 2 : 3-dithiosulphindene; hydrogen sulphide was not evolved and the product, which was soluble in alkali, appeared to be the *addition compound* (XI). Attempts to obtain a semicarbazone from this by elimination of hydrogen sulphide were unsuccessful; when the material was heated in xylene, ammonia was evolved. The iso*amyl carboxylate* (XII) corresponding to the semicarbazone was obtained, however, by boiling with *iso*amyl alcohol (compare this vol., p. 1050). The formation of the addition compound suggests that the first stage in the reaction of a base with 2 : 3-dithiosulphindene is addition to the thioketonic link. The isolation of the primary product in the reaction with semicarbazide is attributed to its insolubility. Neither the addition compound nor the *iso*amyl carboxylate derived from it was affected by hydrogen sulphide; both gave 2-dithiobenzoyl and 2 : 2′-dithiobenzoic acid on hydrolysis.

Since the thio*iso*thiazoles react with hydrogen sulphide to give 2 : 3-dithiosulphindene, it seemed of interest to investigate the action of hydrogen selenide to determine whether a selenium analogue of 2 : 3-dithiosulphindene, if formed, would have the selenium in the (β) or the (γ) position (V). Hydrogen selenide reacted readily with the thio*iso*thiazole (III or IV; R = Me), but, unlike hydrogen sulphide, acted as a reducing agent and did not form a selenium analogue of 2 : 3-dithiosulphindene. The product of this reduction in alcohol was an unstable thiol, for which the formula (XIV ⇌ XIII) is suggested, since on methylation with methyl sulphate in alkali it gave the thioamide (XVI) as the main product and a small amount of the *N*-dimethylthioamide (XVII). The formation of the thioamide (XIV) is in accord with reduction of the *iso*thiazole in the ketimine form (IV). Its formation by reduction of the *iso*thiazole form (III) and subsequent enolisation of (XIII) cannot

be excluded. On the other hand, reduction of the *iso*thiazole in ether and methylation of the product with diazomethane in ether gave the thioamide (XV). This is in agreement with reduction of the thiazole in the *iso*thiazole form (III), although here also its formation from the ketimine form (IV) through ketonisation of (XIV) cannot be excluded. These results, whilst in accord with the suggested equilibrium (A), are inconclusive.

The structures of these thioamides were confirmed by the following syntheses. 2-*Methylthiobenzomethylamide* (XIX), from 2-methylthiobenzoyl chloride and methylamine, was converted into the corresponding *thioamide* (XV) by Kindler's method (*Annalen*,



1923, **431**, 209). Methylation of the thioamide gave the required *product* (XVI); at the same time a small amount of the N-*dimethylthioamide* (XVII) was formed. The *N*-dimethylthioamide (XVII) was synthesised from 2-methylthiobenzoyl chloride and dimethylamine, the *amide* (XVIII) thus obtained being converted into the requisite thioamide (XVII). The thioamide (XVI) is partially demethylated to the thioamide (XV) by hydrogen sulphide. This is attributed to addition of hydrogen sulphide at the methylimino-group with formation of the unstable intermediate (XX) and subsequent elimination of methylthiol. The thioamide (XVI) also reacted with hydroxylamine to give the *amidoxime* (XXII), presumably by elimination of methylthiol from the intermediate addition compound (XXI). These reactions are in contrast to those of the similarly constituted amidines (compare Bernthsen, *Annalen*, 1878, **192**, 29; *Ber.*, 1877, **10**, 1238), where hydrogen sulphide and hydroxylamine effect replacement of the methylimino-group by sulphur and the oximino-group respectively.

In conclusion it appears that the reactions of the thio*iso*thiazoles can be adequately accounted for by assuming a dynamic equilibrium of the type postulated and negative evidence has not been forthcoming. Mechanisms for the reactions described can be devised on the basis of ring fission and closure, but the simpler interpretation of an equilibrium of two isomeric forms is not necessarily thereby excluded.

Experimental.

The compounds (III or IV, R = Me, $CH_2 \cdot CH_2 \cdot OH$, Ph, NH_2, or NHPh; IV, R = OH or OMe; IX; IX with OMe for OH; XI; XII) were hydrolysed by heating with concentrated

hydrochloric acid in a sealed tube at 130—160° for 2 hours. The product was diluted with water, and the solid collected. 2-Dithiobenzoyl was isolated from the solid by steam distillation; 2 : 2′-dithiobenzoic acid remained in the residue. These products were both obtained from the above compounds with the exception of (IX and IX with OMe for OH), which gave only 2 : 2′-dithiobenzoic acid.

The effect of hydrogen sulphide on certain of the following compounds was determined by saturating their alcoholic solutions with hydrogen sulphide and keeping them at room temperature for 2 days. The product was precipitated by water. By this treatment the compounds (III or IV, R = CH_2·CH_2·OH or NH_2) gave 2 : 3-dithiosulphindene, but the compounds (IV, R = OH, OMe, NH·CO_2Et, or NHPh; XI; XII) did not.

Oxime from 2:3-*Dithiosulphindene* (IV; R=OH).—2 : 3-Dithiosulphindene (5 g.), fused sodium acetate (10 g.), and hydroxylamine hydrochloride (10 g.) were refluxed in alcohol (200 c.c.) for 10 minutes. The oxime precipitated by water crystallised from alcohol in yellow needles, m. p. 208°; yield, 90% (Found: C, 45·7; H, 2·3; N, 7·7; *M*, 188. Calc. for $C_7H_5ONS_2$: C, 45·9; H, 2·7; N, 7·6%; *M*, 183). The oxime was also obtained when a solution of 2-thio-1-methyl-1 : 2-dihydrobenz*iso*thiazole (III or IV; R = Me) (2 g.) in alcohol (100 c.c.) was refluxed for 2½ hours with hydroxylamine hydrochloride (2·5 g.) and anhydrous sodium acetate (3 g.). The product was poured into water, and the oxime (0·3 g.) precipitated; the mother-liquor contained an oily product.

The *sulphone* (IX), obtained by heating the above oxime (1 g.) in acetic acid with hydrogen peroxide (2·5 c.c. of 30%) for 10 minutes at 100°, crystallised from alcohol as a white microcrystalline powder, m. p. 177° (Found: C, 39·1; H, 2·5; S, 29·2. $C_7H_5O_3NS_2$ requires C, 39·1; H, 2·3; S, 29·8%). More prolonged oxidation gave the same product. Methylation of the sulphone was effected as follows: The sulphone (1 g.) in alcohol (5 c.c.) was ground to a paste with potassium carbonate (3 g.) and methyl sulphate (0·9 g.) and set aside for 30 minutes. The solid was collected, washed with water, and extracted with ether. The ethereal solution was dried over sodium sulphate and evaporated. The residue crystallised from alcohol and was identical with the sulphone (IX; OH = OMe) described below.

The Methyl Ether of the Oxime (IV; R = OMe).—A solution of the afore-mentioned oxime (5 g.) in sodium hydroxide (10 g.) and water (100 c.c.) was shaken with methyl sulphate (10 g.) for 2 hours. The product was collected, distilled in steam, and purified from methyl alcohol, from which it was obtained in yellow needles, m. p. 55° (Found: C, 48·5; H, 3·8. $C_8H_7ONS_2$ requires C, 48·7; H, 3·6%). The O-*methyl ether* was also obtained when 2 : 3-dithiosulphindene (1 g.), *O*-methylhydroxylamine (1·7 g.), anhydrous sodium acetate (1·8 g.), and alcohol (40 c.c.) were refluxed for 2½ hours and the product, precipitated by water, purified as above. The corresponding *sulphone* (IX; OH = OMe), obtained by oxidation as in the previous experiment, crystallised from aqueous alcohol in white plates, m. p. 135° (Found: C, 41·5; H, 3·0. $C_8H_7O_3NS_2$ requires C, 41·9; H, 3·1%).

Condensation of β-*Aminoethanol with* 2 : 3-*Dithiosulphindene*.—A solution of 2 : 3-dithiosulphindene (5 g.) in ethyl alcohol (300 c.c.) and β-aminoethanol (5 g.) was refluxed for 3 hours. The solution was evaporated to about 30 c.c., and concentrated hydrochloric acid (50 c.c.) added. The solution was diluted with water and filtered, and the filtrate neutralised with sodium carbonate. The precipitated material crystallised from methyl alcohol in yellow needles, m. p. 107°; yield, 60% (Found: C, 51·1; H, 4·6. $C_9H_9ONS_2$ requires C, 51·2; H, 4·3%). The *substance* formed an *acetyl* derivative, which crystallised from methyl alcohol in yellow plates, m. p. 64·5° [Found: C, 52·0; H, 4·6 (Schoeller). $C_{11}H_{11}O_2NS_2$ requires C, 52·1; H, 4·4%].

Hydrazone from 2 : 3-*Dithiosulphindene*.—A solution of 2 : 3-dithiosulphindene (5 g.) in ethyl alcohol (400 c.c.) containing hydrazine hydrochloride (11·4 g.) and anhydrous sodium acetate (9·1 g.) was refluxed for 2 hours. The solution was poured into water, filtered, and basified. The solid *product* crystallised from methyl alcohol in orange plates, m. p. 125° (Found: C, 46·0; H, 3·4. $C_7H_6N_2S_2$ requires C, 46·1; H, 3·3%).

Ethyl chloroformate (0·6 g.) was added to a solution of the above hydrazone (1 g.) in ether (10 c.c.) containing a few drops of pyridine. The *product* obtained after removal of the ether crystallised from methyl alcohol (charcoal) in orange plates, m. p. 96° (Found: C, 47·4; H, 4·5; *M*, 266. $C_{10}H_{10}O_2N_2S_2$ requires C, 47·2; H, 4·0%; *M*, 254).

Phenylhydrazone from 2 : 3-*Dithiosulphindene*.—2 : 3-Dithiosulphindene (1 g.) and phenylhydrazine (5 c.c.) were heated together at 100° for 10 minutes. The *solid* obtained by stirring the product with hydrochloric acid (2*N*) crystallised from alcohol in brown needles, m. p. 106° (Found: C, 60·4; H, 3·9. $C_{13}H_{10}N_2S_2$ requires C, 60·4; H, 3·9%).

Reaction of 2 : 3-*Dithiosulphindene with Semicarbazide*.—A solution of 2 : 3-dithiosulphindene

(10 g.) in ethyl alcohol (300 c.c.) was refluxed for 12 hours with anhydrous sodium acetate (13·3 g.) and semicarbazide hydrochloride (18·3 g.). The solid which had separated was collected (a further quantity was obtained by concentration of the alcoholic mother-liquor), washed with water, and extracted with sodium hydroxide (2*N*). Acidification of the extract gave a yellow material (5 g.). Attempts to purify the *compound* (XI) by crystallisation from alcohol resulted in less pure material melting over a greater range than that obtained by precipitation from alkaline solution; a specimen obtained by the latter process had m. p. 205—212° (Found: C, 37·1; H, 3·3. $C_8H_9ON_3S_3$ requires C, 37·0; H, 3·5%).

The compound (1 g.) was refluxed with *iso*amyl alcohol (50 c.c.) for 6 hours. Concentration of the solution gave isoamyl 1-*keto*-2 : 3-*dithioindenehydrazone*-β-*carboxylate* (XII), which crystallised from alcohol in yellow needles, m. p. 105° (Found: C, 52·5; H, 5·5; S, 22·0; N, 9·8. $C_{13}H_{16}O_2N_2S_2$ requires C, 52·7; H, 5·4; S, 21·6; N, 9·5%).

Syntheses of Thioamides.—2-*Methylthiobenzomethylamide* (XIX). An ethereal solution of 2-methylthiobenzoyl chloride (J., 1929, 2625) (from 17 g. of the acid) was added to ice-cooled aqueous methylamine (30 g. of 33%). The precipitated material crystallised from water in white plates, m. p. 140°; yield, 82% (Found: C, 59·8; H, 6·1. $C_9H_{11}ONS$ requires C, 59·6; H, 6·1%).

2-*Methylthiobenzomethylthioamide* (XV).—The foregoing amide (16 g.) in xylene (250 c.c.) was shaken in the cold with finely ground phosphorus pentasulphide (9 g.) and potassium sulphide (9 g.); the mixture was refluxed for 2½ hours and filtered hot. The residue was refluxed for a further 3 hours with xylene (100 c.c.) and filtered hot. The two filtrates were combined, the xylene removed in steam, and the residual oil extracted with ether. The dried ethereal solution was evaporated to small bulk, and the *thioamide* precipitated by addition of light petroleum (b. p. 40—60°), from which it crystallised in white needles, m. p. 71°; yield, 57% [Found: C, 54·8; H, 5·9; S, 32·3 (Schoeller). $C_9H_{11}NS_2$ requires C, 54·8; H, 5·6; S, 32·5%].

2-*Methylthiobenzo*-NS-*dimethylthioamide* (XVI).—A solution of the foregoing thioamide (5 g.) in alcohol (60 c.c.) and potassium hydroxide (5 g.) was shaken with methyl sulphate (9·5 g.) for 5 minutes and poured into water. The emulsion formed was extracted with ether, and the extract dried and evaporated. The residue was extracted with hydrochloric acid (2*N*), and the extract filtered and neutralised with ammonium carbonate. The oily *product* solidified on stirring and crystallised from light petroleum (b. p. 40—60°) in white plates, m. p. 68·5° (Found: C, 56·7; H, 6·1. $C_{10}H_{13}NS_2$ requires C, 56·8; H, 6·2%). The residue remaining after the extraction with hydrochloric acid crystallised from aqueous alcohol, had m. p. 80—82°, and gave no depression with 2-methylthiobenzodimethylthioamide (XVII). From a solution of 2-methylthiobenzo-*NS*-dimethylthioamide (0·5 g.) in alcohol (15 c.c.) saturated with hydrogen sulphide and kept for 24 hours, 2-methylthiobenzomethylthioamide (XV) was isolated by addition of water and extraction with ether.

2-*Methylthiobenzomethylamidoxime* (XXII).—2-Methylthiobenzo-*NS*-dimethylthioamide (0·95 g.) in alcohol (50 c.c.) was refluxed with hydroxylamine hydrochloride (1 g.) and anhydrous sodium acetate (1 g.) for 1½ hours and kept over-night. The *material* which had separated crystallised from alcohol in white needles, m. p. 194° [Found: C, 55·1; H, 6·0 (Schoeller). $C_9H_{12}ON_2S$ requires C, 55·1; H, 6·2%].

2-*Methylthiobenzodimethylamide* (XVIII).—Dry dimethylamine was passed through a solution of 2-methylthiobenzoyl chloride (from 8 g. of the acid) in carbon tetrachloride until absorption ceased. The solution was filtered, dried over sodium sulphate, and evaporated on the water-bath. The residual liquid was distilled under reduced pressure; b. p. 168—170°/10 mm. yield, 35% (Found: C, 61·3; H, 6·3. $C_{10}H_{13}ONS$ requires C, 61·5; H, 6·7%).

2-*Methylthiobenzodimethylthioamide* (XVII).—A solution of the foregoing amide (2 g.) in benzene (5 c.c.) and phosphorus pentasulphide (1 g.) was refluxed for 2 hours. The solution was decanted from the solid, filtered, and evaporated. The residual oil solidified on addition of a little alcohol. A further quantity of material was obtained by extraction of the solid left after decantation with alcohol, from which it was precipitated by addition of water. The *thioamide* crystallised from aqueous alcohol (50%) in yellow plates, m. p. 83° (Found: C, 56·7; H, 5·8. $C_{10}H_{13}NS_2$ requires C, 56·8; H, 6·2%).

Action of Hydrogen Selenide on 2-*Thio*-1-*methyl*-1 : 2-*dihydrobenz*iso*thiazole* (III or IV; R = Me).—(i) *In alcohol.* A solution of the *iso*thiazole (1 g.) in alcohol (100 c.c.) was saturated with hydrogen selenide, kept for 2 hours, and filtered. The filtrate was mixed with sodium hydroxide (5 g.) in water (50 c.c.) and shaken with methyl sulphate (5 c.c.); water (100 c.c.) was added after 10 minutes, and the resulting emulsion extracted with ether. The dried ethereal solution was evaporated, and the residue extracted with hydrochloric acid (2*N*). The acid extract when

basified gave 2-methylthiobenzo-*NS*-dimethylthioamide (XVI); yield, 60%. A small amount of material left after the hydrochloric acid extraction was 2-methylthiobenzodimethylthioamide (XVII).

(ii) ***In ether.*** A solution of the *iso*thiazole (1 g.) in dry ether (100 c.c.) was saturated with hydrogen selenide and filtered from precipitated selenium. An ethereal solution of diazomethane (0·45 g. approximately) was added to the filtrate; a vigorous evolution of nitrogen occurred. The solution was evaporated to about 20 c.c., and light petroleum (b. p. 40—60°) added. The material precipitated, after crystallisation from light petroleum, had m. p. 70—71° and gave no depression with 2-methylthiobenzomethylthioamide (XV).

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