CCCLII.—*The Formation and Stability of the* 2-o-*Thiophenyl*-4 : 5-*dihydroglyoxalines.*

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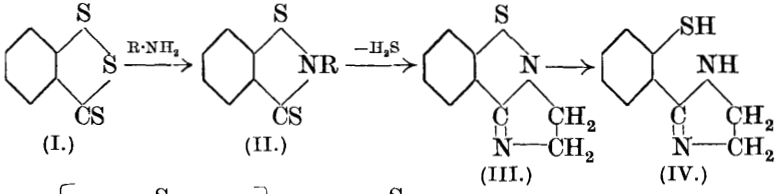
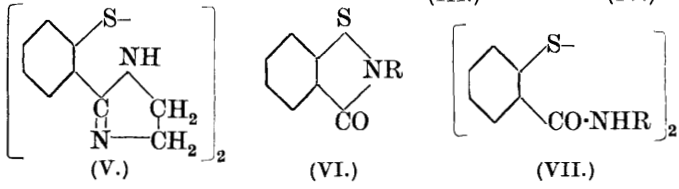
In a previous communication (this vol., p. 1582) it was shown that 2-thio-1 : 2-dihydrobenz*iso*thiazoles (II) are formed from primary amines and 2 : 3-dithiosulphindene (I) : these substances are stable in comparison with the oxygen analogues (VI), which are readily reduced to the disulphides (VII).

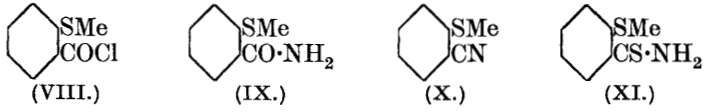
Continuing the study of the formation and stability of these and analogous systems, we have investigated the action of ethylenediamine on 2 : 3-dithiosulphindene, with the result that 2-o-*thiolphenyl*-4 : 5-*dihydroglyoxaline* (IV) has been obtained. This material is evidently formed by intramolecular condensation of the primary

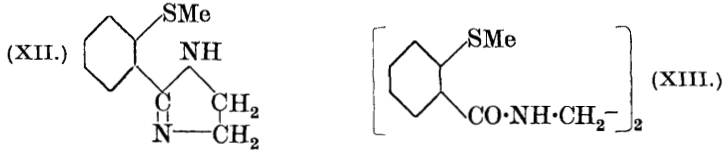
product (II; R = $CH_2 \cdot CH_2 \cdot NH_2$) and reduction of the resulting tricyclic compound (III) by the hydrogen sulphide eliminated:





The solubility of the substance (IV) in acids and alkalis and the formation of a picrate and a silver salt agree with the structure assigned to the compound. Further proof of its constitution has been furnished by the synthesis of the S-*methyl* ether (XII) which is obtained by its methylation.



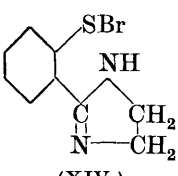


The *amide* (IX), obtained from 2-methylthiolbenzoic acid through the acid chloride (VIII), was converted into the nitrile (X), from which the *thioamide* (XI) was prepared by treatment with hydrogen sulphide according to Kindler's method (*Annalen*, 1923, **431**, 202). The thioamide condensed with ethylenediamine (compare Forssel, *Ber.*, 1892, **25**, 2132) to give a product identical with the *S*-methyl derivative (XII), obtained by direct methylation of the dihydroglyoxaline (IV). The yield of the thioamide in this synthesis was unsatisfactory and it may be noticed that amide (IX) with phosphorus pentasulphide gave the nitrile (X). A more convenient synthesis of the *S*-methyl derivative was attained by direct condensation of the nitrile (X) with ethylenediamine in presence of hydrogen sulphide. Small yields of the *S*-methyl derivative were also

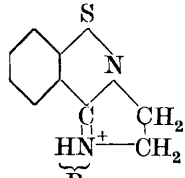
obtained from the *ethylene-diamide* (XIII) by treatment with hydrogen chloride (compare *Ber.*, 1888, **21**, 2334; J., 1926, 804).

The *disulphide* (V) was isolated as a subsidiary product of the reaction between ethylenediamine and 2 : 3-dithiosulphindene, but the tricyclic compound (III) could not be detected.

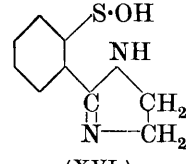
Cyclic compounds of the type (VI) have been obtained from the disulphides (VII) by treatment with bromine (Reissert, *Ber.*, 1928, **61**, 1308). The possibility of synthesising the tricyclic compound (III) from the disulphide (V) by a similar method was therefore investigated. Attempts to oxidise the thiol (IV) to the disulphide (V) by means of ferric chloride were unsuccessful owing to the formation of metallic complexes: but reaction of the thiol (IV) with the calculated amount of bromine gave the hydrobromide of the required disulphide.



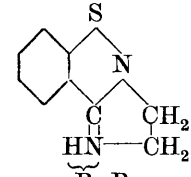
(XIV.)



(XV.)



(XVI.)



(XVII.)

Reaction of the disulphide base (V) with one molecular proportion of bromine yielded a material, presumably the sulphur bromide (XIV). This substance in warm acetic acid gave the tricyclic *hydrobromide* (XV), which was also obtained when the disulphide hydrobromide was treated with bromine. In contrast to the preparation from the base, hydrogen bromide was liberated in accordance with the structure assigned to the tricyclic salt. Attempts to obtain the tricyclic base (III) were unsuccessful: when the hydrobromide was treated with alkali, the disulphide (V) was obtained instead of the cyclic compound. The production of the former may be explained by decomposition of the unstable sulphenic acid (XVI) formed by hydrolytic fission and is confirmed by the observation that the yield of disulphide from this source is less than that from the hydrobromide of the disulphide (compare Zincke and Farr, *Annalen*, 1912, **391**, 58). The tricyclic hydrobromide (XV), in contrast to the latter, yields the hydriodide by treatment with aqueous potassium iodide.

Reaction of the thiolphenyldihydroglyoxaline (IV) or the corresponding disulphide (V) with excess of bromine gave a *perbromide* (XVII) of the tricyclic hydrobromide. The character assigned to this compound is supported by the facts that on treatment with water it yields the tricyclic hydrobromide and is re-formed by the

action of bromine on the latter. The possibility of the whole or part of the labile bromine being linked to sulphur is not excluded, but the structure (XVII) appears on the available evidence to be the most probable.

An analogous series of perhalides has been obtained from the methylthiolphenyldihydroglyoxaline (XII). For instance, treatment of the hydriodide with iodine gave a *periodide*, $C_{10}H_{12}N_2S,HI,I_2$, from which the hydriodide was regenerated by the action of sulphur dioxide, and direct treatment of the base with bromine gave a hydrobromide or a *perbromide*, $C_{10}H_{12}N_2S,HBr,Br_2$, according to the conditions. This reaction is analogous to the formation of the hydrobromide and perbromide of 2 : 4 : 5-tri*cyclo*hexyl-4 : 5-dihydroglyoxaline (*Helv. Chim. Acta*, 1928, **11**, 944).

The failure to isolate the tricyclic compound either in the primary condensation of ethylenediamine and 2 : 3-dithiosulphindene or by basifying its hydrobromide leads to the conclusion that the S–N link is unstable and is analogous in this respect to that in the 2-keto-1 : 2-dihydrobenz*iso*thiazoles (VI). Replacement of the carbonyl oxygen by nitrogen, unlike replacement by sulphur (compare this vol., *loc. cit.*), does not appear to stabilise the S–N link.

The instability of the tricyclic base is also evident in the behaviour of its salts. The hydrobromide liberates iodine from potassium iodide in acid solution, presumably owing to reduction at the S–N link, and is reduced by hydrogen sulphide to the hydrobromide of the mercaptan (IV); and iodine is set free when a concentrated aqueous solution of the hydriodide is boiled. The relative stability of the salts of the tricyclic compound as compared with the base may be attributed to the enhanced positive character of the sulphur (compare this vol., *loc. cit.*), consequent on the tendency of the positive polar nitrogen to withdraw electrons from the former (XV).

EXPERIMENTAL.

2-o-*Thiolphenyl*-4 : 5-*dihydroglyoxaline* (IV).—A solution of 2 : 3-dithiosulphindene (20 g.) in alcohol (400 c.c.) and ethylenediamine (10 c.c.) was boiled for 8 hours and evaporated to dryness, the residue extracted with sulphuric acid (2*N*), and the extract made alkaline with ammonium carbonate (2*N*). The precipitate (15 g.) crystallised from alcohol in yellow plates, m. p. 244° (decomp.; softening at 210°) (Found: C, 60·7; H, 5·9; N, 15·3; S, 18·6; *M*, 177. $C_9H_{10}N_2S$ requires C, 60·6; H, 5·7; N, 15·7; S, 18·0%; *M*, 178).

2-o-*Thiolphenyl*-4 : 5-*dihydroglyoxaline* is sparingly soluble in cold water, chloroform and benzene and readily soluble in sodium hydroxide (2*N*) and hydrochloric acid (2*N*). It gives a green

coloration, fading to brown, with ferric chloride, a white precipitate with mercuric chloride, and forms a silver salt. The picrate, obtained as yellow needles from alcoholic picric acid, becomes red at 165—170° and melts at 242° (decomp.).

2-*Methylthiolbenzoyl Chloride* (VIII).—2-Methylthiolbenzoic acid (*Annalen*, 1907, **351**, 401) (13·5 g.) was heated on the water-bath with an excess of thionyl chloride (26 g.) until the evolution of hydrogen chloride ceased (10 minutes). The thionyl chloride was removed under reduced pressure and the residual yellow oil, which crystallised on cooling, was purified from ether and dried in a vacuum. The acid chloride thus obtained as colourless needles, m. p. 75—76°, was used in the subsequent experiments.

2-*Methylthiolbenzamide* (IX).—2-Methylthiolbenzoyl chloride (10·5 g.) in ether was added to an excess of aqueous ammonia (*d* 0·880). The *product* crystallised from water (charcoal) in colourless needles (8·4 g.), m. p. 149—150° (Found : C, 56·8; H, 5·3. C_8H_9ONS requires C, 57·4; H, 5·4%).

Di-2-*methylthioldibenzoylethylenediamine* (XIII).—Ethylenediamine (4 g.) in ether was slowly added to an ethereal solution of 2-methylthiolbenzoyl chloride (10 g.) and the resulting solid was washed with water, crystallised from dilute acetic acid and finally from alcohol, giving colourless needles (9·5 g.), m. p. 191—192° (Found : C, 59·7; H, 5·8. $C_{18}H_{20}O_2N_2S_2$ requires C, 60·0; H, 5·6%).

2-*Methylthiolbenzonitrile* (X).—2-Methylthiolbenzamide (7 g.) was refluxed in xylene (200 c.c.) with phosphoric oxide (10 g.) for 5 hours. The solution was decanted and the xylene removed in steam. The residual material, crystallised from ligroin–ether, had m. p. 36° (Found : C, 63·9; H, 5·1. Calc. for C_8H_7NS : C, 64·4; H, 4·7%) (compare *Ber.*, 1915, **48**, 1247).

The nitrile was also obtained when phosphorus pentasulphide was substituted for phosphoric oxide in the above preparation.

2-*Methylthiolbenzothioamide* (XI). — 2-Methylthiolbenzonitrile (5 g.), dissolved in alcohol (100 c.c.) containing sodium ethoxide (1 g.), was saturated with hydrogen sulphide at —15°. The solution was heated under pressure at 90—100° for 4 hours and filtered when cold. The filtrate was evaporated under reduced pressure at 20°, and the residual oil extracted with ether. The material obtained on evaporation of the ethereal extract was fractionally crystallised from ethyl alcohol, the lower-melting fractions, consisting of unchanged nitrile, being rejected; finally, the *thioamide*, m. p. 128—131°, was obtained in yellow needles in poor yield (Found : S, 34·6. $C_8H_9NS_2$ requires S, 35·0%).

2-o-*Methylthiolphenyl*-4 : 5-*dihydroglyoxaline* (XII).—(a) *By direct methylation*. A solution of 2-*o*-thiolphenyl-4 : 5-dihydroglyoxaline

(2 g.) in methyl alcohol (50 c.c.) and methyl iodide (3 c.c.) was heated on the water-bath till colourless (10 minutes). Water (25 c.c.) was then added and the alcohol and excess of methyl iodide were distilled off. The *hydriodide* (2·9 g.) of the required material crystallised on cooling: after purification from water, it was obtained in large colourless plates, m. p. 208° (Found: I, 39·3. $C_{10}H_{12}N_2S,HI$ requires I, 39·7%). The *base*, obtained on addition of alkali to an aqueous solution of the hydriodide, crystallised from aqueous alcohol in colourless leaflets, m. p. 100° (Found: C, 62·0; H, 6·5; *M*, 202. $C_{10}H_{12}N_2S$ requires C, 62·4; H, 6·3%; *M*, 192).

2-*o*-Methylthiolphenyl-4 : 5-dihydroglyoxaline is readily soluble in hot water, giving a strongly basic solution. It forms a picrate, which crystallises from acetic acid in yellow needles, m. p. 207°, and an oily nitroso-compound.

(b) *From 2-methylthiolbenzothioamide.* The crude thioamide was heated with an excess of ethylenediamine and a few drops of water until the evolution of hydrogen sulphide ceased. The excess of ethylenediamine was evaporated, and a solution of the residue in alcohol was boiled with charcoal and filtered. From the oily material which separated on cooling, a picrate, m. p. 206—207°, was isolated. A solution of the picrate in alkali was extracted with ether, and the ethereal extract shaken with hydriodic acid: the crystalline hydriodide which separated had m. p. 207—209°, alone or mixed with the hydriodide obtained in the preceding experiment, and yielded an identical base.

The following synthesis obviated the isolation of the thioamide: A solution of 2-methylthiolbenzonitrile (1 g.) in ethyl alcohol (50 c.c.) and ethylenediamine (1·5 c.c.) was saturated with hydrogen sulphide at −15°. The mixture was heated under pressure for 4 hours at 110°. The viscous liquid obtained by concentration of the solution was extracted with hot hydrochloric acid, and the cold extract was mixed with an aqueous solution of potassium iodide; the required material was then precipitated as hydriodide (1 g.), from which the base, identical with that obtained by direct methylation, was isolated in the usual way.

(c) *From di-2-methylthioldibenzoylethylenediamine.* Dry hydrogen chloride was passed into the molten diamide at 260—270° for 1 hour. The product was boiled with water and the solution was filtered from the tarry material, treated with charcoal, acidified, filtered, made alkaline, and extracted with ether; from the ethereal solution a picrate, m. p. 206°, was obtained which yielded the hydriodide of the methyl derivative.

2 : 2′-oo′-*Dithiodiphenyl*-4 : 5-*dihydroglyoxaline* (V).—A solution of bromine (0·96 g.) (1 mol.) in glacial acetic acid (8 c.c.) was gradually

added with stirring to 2-*o*-thiolphenyl-4 : 5-dihydroglyoxaline (2 g.) (2 mols.), dissolved in glacial acetic acid (8 c.c.). The precipitate (2·6 g.) was crystallised from glacial acetic acid and finally from alcohol. The *dihydrobromide* of the required substance was thus obtained in colourless needles, m. p. 283° (Found : Br, 30·7; S, 12·3. $C_{18}H_{18}N_4S_2,2HBr$ requires Br, 31·0; S, 12·4%). Silver bromide is not precipitated on addition of silver nitrate to an aqueous solution of this hydrobromide except in presence of nitric acid. The same phenomenon was observed with the halide salts of other 2-*o*-thiophenyl-4 : 5-dihydroglyoxalines. The hydrobromide (1·9 g.) on treatment with alkali yielded the disulphide *base* (1·0 g.), which separated from alcohol in yellow rhombic crystals, m. p. 198° (Found : C, 61·1; H, 5·5; N, 15·5; S, 18·4. $C_{18}H_{18}N_4S_2$ requires C, 61·0; H, 5·1; N, 15·8; S, 18·1%). The picrate has m. p. 247—248° (decomp.).

A small quantity of this disulphide was also obtained by fractionation of the crude material in the primary condensation.

Action of Bromine on the 2-Thiophenyl-4 : 5-dihydroglyoxalines. Tricyclic Hydrobromide (XV).—A suspension of the disulphide (V) (2 g.; 1 mol.) in carbon tetrachloride (25 c.c.) was triturated with bromine (1 mol.) in carbon tetrachloride (6 c.c.). The material was collected and boiled with glacial acetic acid (10 c.c.) until a colourless solution was obtained. The tricyclic *hydrobromide* (1·7 g.) crystallised from the cold solution and was purified from alcohol, giving colourless needles, m. p. 259° (Found : Br, 30·9. $C_9H_8N_2S,HBr$ requires Br, 31·1%). A more convenient method is to brominate the disulphide in hot chloroform solution; the tricyclic hydrobromide then crystallises at once. An identical product was obtained when 2 : 2′-*oo*′-dithiodiphenyl-4 : 5-dihydroglyoxaline hydrobromide (1 mol.) was treated with bromine (1 mol.) in glacial acetic acid, and the solution boiled. In contrast to the previous preparation, hydrogen bromide was evolved.

The tricyclic hydrobromide yields a picrate, m. p. 241—242° (decomp.), liberates iodine from potassium iodide in presence of acetic acid, and is reduced by hydrogen sulphide to the hydrobromide of the mercaptan (IV); with aqueous potassium iodide, the hydriodide is precipitated. When a concentrated solution of the latter is boiled, iodine is liberated. The hydrobromide (1·0 g.) on treatment with alkali (1 mol.) gave 2 : 2′-*oo*′-dithiodiphenyl-4 : 5-dihydroglyoxaline (0·35 g.) (V).

Tricyclic Perbromide (XVII).—2-*o*-Thiolphenyl-4 : 5-dihydroglyoxaline (2 g.) in warm glacial acetic acid (10 c.c.) was mixed with a solution of bromine (6 g.) in glacial acetic acid (40 c.c.) : the mixture was boiled until complete solution had taken place, hydrogen

bromide being evolved. The material (4·4 g.) deposited on cooling was washed with ether and crystallised from glacial acetic acid, giving orange plates, m. p. 139—140° (Found: Br, 57·0; labile Br, 36·0; S, 7·8. $C_9H_8N_2S,HBr,Br_2$ requires Br, 57·5; labile Br, 38·3; S, 7·7%). An identical product was obtained by similar treatment of the tricyclic hydrobromide (XV) with excess of bromine and also from the disulphide (V), but without evolution of hydrogen bromide. The perbromide (8·7 g.), when boiled with water (50 c.c.), yielded the tricyclic hydrobromide (3·0 g.).

2-*o*-Methylthiolphenyl-4 : 5-dihydroglyoxaline (XII) on similar treatment with excess of bromine gave a *material* which crystallised from acetic acid in orange plates, m. p. 128—134° (Found: Br, 56·0; labile Br, 36·2. $C_{10}H_{12}N_2S,HBr,Br_2$ requires Br, 55·4; labile Br, 36·9%).

The hydriodide of the base (0·4 g.) in hot alcohol was treated with iodine (0·35 g.); on addition of ligroin, a brown crystalline *material* was obtained, m. p. 114° (Found: I, 66·45; labile I, 43·6. $C_{10}H_{12}N_2S,HI,I_2$ requires I, 66·3; labile I, 44·2%). The hydriodide is regenerated by the action of sulphur dioxide on the periodide.

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