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I.—*Stereoisomerism of Disulphoxides and Related Substances. Part V. The Dioxides of 3:5-Dimethylthiolbenzoic Acid.*

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IN Part III (J., 1928, 3189) a number of pairs of diastereoisomeric disulphoxides of the type A·SO·B·SO·A were described. Of the two isomerides in such cases, one should be an internally compensated substance, the other externally compensated and potentially optically active. Confirmation of this view was not possible in the examples referred to, owing to the absence of any group in the molecule which would allow of a resolution into the optically active antipodes. The isolation of a suitable pair of disulphoxides is now described, one of which is shown to be separable into enantiomorphous forms.

The substance first studied proved to be unsuitable, for although *s-diphenylthiolethane-mm'-dicarboxylic acid*, $C_2H_4(S·C_6H_4·CO_2H)_2$, when oxidised in the form of its *dimethyl ester*, yielded a pair of *dioxides*, of m. p. 195° and 126—129° respectively, the hydrolysis of the ester dioxides was accompanied by a disruption of the molecule so that the isomeric free acids were not isolated. This reaction, which has not yet been investigated in detail, is reminiscent of the scission of 1:4-disulphones by alkalis (Stuffer, *Ber.*, 1890, **23**, 1408, 3226).

Attention was then directed to 3:5-*dimethylthiolbenzoic acid*, which was synthesised as follows.

Carboxybenzene-3:5-disulphonyl chloride, the method of preparation of which was improved, was reduced in the usual manner, and the resulting 3:5-*dithiolbenzoic acid* isolated in the form of its disulphide, 3:5-*disulphidobenzoic acid*. Methylation of the regenerated dithiol yielded the required dimethylthiolbenzoic acid. The product of oxidation of this acid by hydrogen peroxide was separated by fractional crystallisation into the α -*dioxide*, m. p. 251° (decomp.), and the β -*dioxide*, m. p. 209° (decomp.), which were present in approximately equal proportion.

Considerable difficulty was found in effecting a resolution of either of these isomerides into optically active forms, perhaps on account of the weakness of the acid caused by the presence in the molecule of two sulphoxyl groups of definitely basic properties. The salts of these acids with strychnine, cinchonine, quinine, *l*-menthylamine and the active phenylethylamines could not be obtained crystalline, but those with brucine were suitable for study. The brucine salt of the α -dioxide was recrystallised unchanged, whereas that of the β -isomeride showed a continuous increase of rotatory power when it was fractionally crystallised from chloroform. Owing to lack of material, the process had to be interrupted after seven crystallisations when it was still evidently incomplete. The acid recovered from the salt of highest rotation was 1-3 : 5-dimethylthiolbenzoic acid dioxide of m. p. 200—202° (decomp.) and had $[\alpha]_D -99.6^\circ$ for a 1.89% aqueous solution.

From the mother-liquors of the separation an acid was recovered having a positive rotation $[\alpha]_D +9.1^\circ$ in 2% aqueous solution. When this was fractionally crystallised, the mother-liquors furnished a dextrorotatory acid having $[\alpha]_D +22.7^\circ$ in 2.64% aqueous solution. The purification could not be carried further with the amount of acid available.

Although the optically active acids were thus not isolated in a state of optical purity, the results afford confirmation of the stereochemical relationship of the pairs of disulphoxides under discussion : the α -dioxide of dimethylthiolbenzoic acid has the *meso*-configuration, the β -dioxide being potentially active.

EXPERIMENTAL.

s-Diphenylthiolethane-*mm'*-dicarboxylic Acid.—*m*-Dithiobenzoic acid (92 g.) was reduced by heating with glucose (92 g.) and sodium hydroxide (48 g. in 100 c.c. of water) in alcohol (300 c.c.) under reflux and addition of a further equal amount of alkali during $\frac{1}{2}$ hour, followed by ethylene dibromide (65 g.). The solution was cooled and acidified, and the *diphenylthiolethane-*mm'*-dicarboxylic acid* collected, washed, and dried (yield, 86 g.). It separated from boiling acetic acid as a white micro-crystalline powder, m. p. 265° (decomp.), insoluble in most solvents (Found : C, 57.1; H, 4.45. $C_{16}H_{14}O_4S_2$ requires C, 57.5; H, 4.2%).

Oxidation of the sodium salt with hydrogen peroxide in aqueous solution yielded a product so sparingly soluble that a pure substance could not be isolated.

The acid (48 g.), dissolved in alkali (17.2 g. of potassium hydroxide in 30 c.c. of water), was added to methyl sulphate (37.6 g.) on the steam-bath. The *dimethyl* ester obtained, after crystallising thrice

from methyl alcohol, formed prisms, m. p. 73° , soluble in all the ordinary solvents (Found : C, 59.7; H, 5.0. $C_{18}H_{18}O_4S_2$ requires C, 59.7; H, 5.0%).

Isomeric Dioxides of Dimethyl Diphenylthiolethanedicarboxylate.—The ester (25 g.) in glacial acetic acid (500 c.c.) was oxidised with hydrogen peroxide (18.4 g. of 25.9% H_2O_2). After 48 hours the solution was evaporated, and the residue fractionally crystallised from 50% acetic acid. The less soluble α -dioxide was readily obtained pure (yield, 10 g.) and the m. p., 195° (decomp.), was unchanged by further crystallisation (Found : C, 54.2; H, 4.9. $C_{18}H_{18}O_6S_2$ requires C, 54.8; H, 4.6%).

This substance, reduced with zinc dust and hydrochloric acid in acetic acid, yielded the parent disulphide, m. p. 73° , as proved by direct comparison and the m. p. of a mixture.

From the mother-liquors of the above crystallisation a much more soluble β -dioxide was isolated; after being recrystallised several times from methyl alcohol, it melted at 126 – 129° (decomp.). Like the α -isomeride it yielded the parent disulphide by reduction; there can be little doubt that it is a disulphoxide, but by an oversight the specimen was hydrolysed without having been analysed.

Hydrolysis of these dioxides by alcoholic potassium hydroxide caused some profound disruption of the molecule, the crude acid obtained having an equivalent of 113 (in place of the expected 185).

Disulphonation of Benzoic Acid.—By the following modification of Barth and Senhofer's method (*Annalen*, 1871, **159**, 217) the use of a sealed tube was avoided and the product isolated as sulphonyl chloride. Benzoic acid (120 g.) was heated in an open flask with fuming sulphuric acid (240 c.c. of 40% SO_3) and phosphoric oxide (180 g.) at 200° for 1 hour and at 250° for 2 hours. The mixture was cooled, chlorosulphonic acid (600 c.c.) added, and the temperature raised to and kept at 150 – 180° for 1 hour so that the chlorosulphonic acid boiled without escaping. The liquid when cool was run slowly into ice-water, and the crude disulphonyl chloride filtered off, washed, and dried (average yield in four preparations, 102 g.).

The carboxybenzene-3 : 5-disulphonyl chloride crystallised from benzene in stout needles, m. p. 193° (Found : Cl, 22.0. Calc. : Cl, 22.3%). Hopfgartner (*Monatsh.*, 1893, **14**, 690) gives m. p. 183° .

Preparation of 3 : 5-Dimethylthiolbenzoic Acid.—Carboxybenzene-disulphonyl chloride (120 g.), dissolved in glacial acetic acid (1800 c.c.) in a 10-litre flask, was reduced by the addition of concentrated hydrochloric acid (280 c.c.) and then, in small portions and with vigorous mechanical stirring, zinc dust (72 g.). When all had dissolved, like amounts of acid and zinc dust were added in a

similar manner. The mixture was allowed to become hot during the process (2—3 hours). The solution was warmed on the steam-bath, and ferric chloride (240 g.) added. Precipitation of the disulphide was hastened by dilution with water and the product was collected, washed, and dried at 100° (average yield, 66 g.). 3 : 5-Disulphidobenzoic acid was thus obtained as a white powder, m. p. 195—200° (decomp.), so sparingly soluble in all available solvents that it could not be crystallised. It has no doubt a much higher molecular weight than that indicated by the formula (Found : S, 33.7. $C_7H_4O_2S_2$ requires S, 34.8%).

Reduction of this disulphidobenzoic acid (46 g.) was effected by heating with glucose (53 g.) and alcohol (250 c.c.) during the gradual addition of sodium hydroxide (50 g. in 100 c.c. of water). The mixture was then cooled, and methyl sulphate (63 g.) carefully added. After several hours the alcohol was removed in steam and the product precipitated by acidification was collected, washed, and dried at 100° (yield, 38 g.). 3 : 5-Dimethylthiolbenzoic acid crystallises from ethyl acetate in square or hexagonal-shaped plates, m. p. 153° (Found : S, 29.9; equiv., by titration, 214. $C_9H_{10}O_2S_2$ requires S, 29.9%; equiv., 214). The sodium salt is very readily soluble in water, but crystallises well from ethyl acetate in clusters of radiating needles, m. p. 283° (decomp.) (Found : Na, 9.5. $C_9H_9O_2S_2Na$ requires Na, 9.7%).

Oxidation of Dimethylthiolbenzoic Acid to a Pair of Dioxides.—Hydrogen peroxide (132 g. of 25% strength), diluted with acetic acid (350 c.c.), was gradually added to a solution of dimethylthiolbenzoic acid (104 g.) in acetic acid (2420 c.c.). After 12 hours, the solvent was removed in steam, and the solution evaporated and kept in a vacuum over sodium hydroxide. The crude mixture of dioxides (119 g.) was powdered and extracted with boiling 90% aqueous alcohol (480 c.c.). The residue (39 g.), α -3 : 5-dimethylthiolbenzoic acid dioxide, was recrystallised from 90% alcohol. The substance crystallises from hot water in long prisms, m. p. 251° (decomp.) (Found : S, 26.0; equiv., by titration, 245.6. $C_9H_{10}O_4S_2$ requires S, 26.0%; equiv., 246.2).

The alcoholic extract of the crude dioxides deposited crystals of β -3 : 5-dimethylthiolbenzoic acid dioxide on cooling, which were purified by several crystallisations from ethyl alcohol (yield, 20 g.). The substance crystallises from water in tufts of fine needles, m. p. 209° (decomp.), and is much more soluble in ethyl alcohol and water than the α -isomeride (Found : S, 25.9%; equiv., by titration, 245.3).

Examination of the α - and β -Dioxides as to the Possibility of Resolution into Optically Active Components.— α -3 : 5-Dimethyl-

thiolbenzoic acid dioxide was dissolved with brucine (1 mol.) in hot chloroform, and the *brucine* salt obtained in large plates containing chloroform of crystallisation. The solvent was removed at 100° in a vacuum; the residual powder had m. p. 170—175° (decomp.) (Found: N, 4.5. $C_{32}H_{36}O_8N_2S_2$ requires N, 4.4%). The salt, which was very soluble in chloroform, was recrystallised twice from this solvent.

A solution of the ammonium salt of this acid, recovered from the brucine salt by the action of aqueous ammonia and repeatedly extracted with chloroform to remove all the alkaloid, was found to be optically inactive.

The *brucine* salt of β -3 : 5-dimethylthiolbenzoic acid dioxide was prepared in chloroform solution, from which it crystallised in large plates containing solvent of crystallisation. The solvent was lost gradually in air and completely at 100° in a vacuum. The dried salt had m. p. 130° (Found: N, 4.7%) and was readily soluble in chloroform, but sparingly soluble in other solvents. The optical rotatory power in chloroform was $[\alpha]_D -28.4^\circ$ ($c = 10.3$, $l = 0.5$) and became, after successive crystallisations from this solvent ($c = 10$), -28.4° , -36.5° , -41.5° , -46.4° , -48.7° , -50.0° , -52.0° , -59.7° . At this point the salt had m. p. 184° and was not optically pure, but the quantity of material was not sufficient for further fractionation. The salt (3.5 g.) was decomposed by aqueous ammonia and freed from brucine by repeated extraction of the solution with chloroform. The ammonium salt was converted into the barium salt by means of an excess of barium hydroxide, the ammonia driven off, and carbon dioxide passed in to remove the excess of baryta. The solution was filtered, and the exact equivalent of sulphuric acid (determined on a portion) added. After the barium sulphate had been removed, the solution was evaporated to dryness on the water-bath. The 1-3 : 5-dimethylthiolbenzoic acid dioxide thus obtained (1.4 g.) crystallised from 50% alcohol in minute needles with a straight extinction, m. p. 200—202° (decomp.). It was readily soluble in water or alcohol. Its rotatory power in water was $[\alpha]_D -99.65^\circ$ ($c = 1.887$, $l = 2$, $\alpha = -3.76^\circ$) (Found: S, 26.0. $C_9H_{10}O_4S_2$ requires S, 25.9%).

From the chloroform mother-liquors a brucine salt was recovered which had m. p. 140° (decomp.) and a rotatory power of $[\alpha]_D + 0.59^\circ$ in chloroform ($c = 10$, $l = 0.5$).

The salt was freed from brucine and, by the method described above, an optically impure acid (9 g.) was recovered which had $[\alpha]_D + 9.09^\circ$ in water ($c = 1.980$, $l = 2$). When this was recrystallised from ethyl alcohol, the more active portions were found in the mother-liquor, and by fractional crystallisation an optically impure

d-3 : 5-dimethylthiolbenzoic acid dioxide was obtained, m. p. 190—205° (decomp.), having $[\alpha]_D + 22.7^\circ$ in water ($c = 2.640$, $l = 0.5$) (Found : S, 25.4%).

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