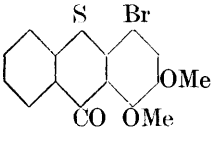
LXX.—*Derivatives of* 1 : 2-*Dihydroxythioxanthone.*

By Alfred A. Levi and Samuel Smiles.

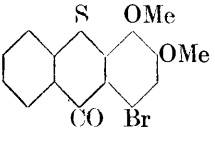
Previous communications (J., 1929, 863, 1322) dealt with the basic character of methoxythioxanthones; it was shown that salts derived from 1-methoxythioxanthones have a peculiar character and enhanced stability and reasons were adduced for assigning to the kations of these a chelate structure (III) containing hydrogen. Four dimethoxy-derivatives were included in the material studied, but of these the 1 : 2-derivative was isolated only in small amount

from the condensation of 2-thiolbenzoic acid with veratrole and was probably obtained in a somewhat impure condition. Further experiments have now been made with derivatives of 1 : 2-dimethoxythioxanthone and the study of 1-methoxy-derivatives has been extended.

4-Bromoveratrole and 2-thiolbenzoic acid in sulphuric acid yield a *bromodimethoxythioxanthone* to which structure (I) or (II) must be assigned. The sulphonyl chloride obtained from 4-bromoveratrole and chlorosulphonic acid evidently has the structure (IV), since after reduction and suitable treatment of the sulphonic group it yielded the *amide* of veratrole-4-sulphonic acid or *diveratryl* 4-*disulphide*. The thiol derived from this 4-bromoveratrole-5-sulphonyl



(I.)



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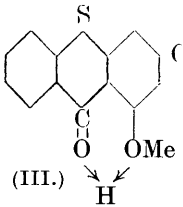
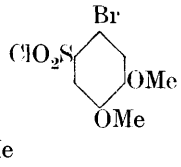
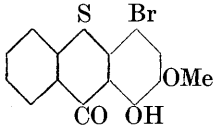


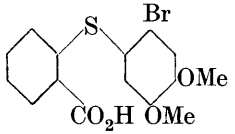
(III.)



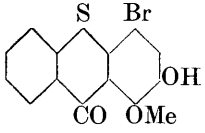
(IV.)

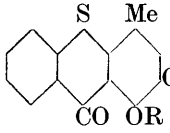
chloride (IV), heated with sodium 2-bromobenzoate in presence of copper, gave the *acid* (V), which was easily converted by dehydration into a bromodimethoxythioxanthone (I), and this was identical with the product in question obtained from bromoveratrole and 2-thiolbenzoic acid. 4-Bromoguaiacol and 5-bromoguaiacol, after condensation with 2-thiolbenzoic acid, gave the *monomethyl* ethers of 4-bromo-1 : 2-dihydroxythioxanthone. The former gave the ether to which the structure (VI) must be ascribed, since it furnished a stable *acetoborate* and could be obtained by suitable demethylation of the dimethyl ether (I). 5-Bromoguaiacol yielded the isomeric monomethyl ether (VII); this did not give a diacetoborate and was easily methylated to give (I). Creosol by a similar method was converted into a *hydroxymethoxy-thioxanthone* to which

(VI.)




(V.)

(VII.)




(VIII.)

the structure (VIII; R = H) is ascribed, since it yielded a stable *diacetoborate* and resembled (VI) in its resistance to methylation by

the usual methods and in its insolubility in aqueous alkali hydroxide. Methylation by the method of Baker and Robinson (J., 1928, 3115) gave 1 : 2-*dimethoxy*-4-*methylthioxanthone* (VIII; R = Me). Finally, 4-*bromo*-1 : 2-*dihydroxythioxanthone* was obtained by demethylation of (VII).

The study of the basic strength of these six derivatives has entirely confirmed the conclusions previously attained from other material. Derivatives containing the 1-hydroxy-group gave no evidence of basic character either with dry hydrogen chloride or with the aqueous reagent.

The 1-methoxy-derivatives yielded soluble red salts of differing stability and by using the method of hydrolysis previously described (Roberts and Smiles, *loc. cit.*) to determine the approximate relative basic strengths it was found that 1 : 2-dimethoxy-4-methylthioxanthone gave the most stable salts of the series, their stability being of the same order as that of 1-methoxy-4-methyl- and 1 : 4-dimethoxy-thioxanthone salts. The salts formed by the 4-bromo-derivatives of 1 : 2-dimethoxy- and 2-hydroxy-1-methoxy-thioxanthones were closely similar to one another in stability, but were considerably less stable than the salts of 1 : 2-dimethoxy-4-methylthioxanthone. The last-named substance was the only one of the series yielding a salt of definite composition, B,2HCl, with dry hydrogen chloride. Further evidence confirming the chelate structure assigned to the kations of the salts formed by these 1-methoxy-derivatives may be adduced from the relative stabilities of the diacetoborates of the 1-hydroxythioxanthones, which are known to contain a similar chelate structure. The relative stabilities of these substances in benzene solutions of comparable molar strength were studied by decomposition with alcohol under standard conditions. The characteristic colour of the diacetoborate was discharged as decomposition proceeded, and the completion of the process was determined by comparison with solutions of the 1-hydroxythioxanthones of the same molar strength. In column 2 of the appended table the 1-hydroxythioxanthones are arranged in order of increasing stability of their diacetoborates as observed by this method. The stabilities of the diacetoborates formed by the two last-named are similar to one another but considerably greater than those of the 4-bromo-derivatives. The similar behaviour of the salts of 1-methoxythioxanthones is evident from column 1, which contains these substances arranged in increasing order of stability.

Salts.	Diacetoborates.
4-Bromo-1 : 2-dimethoxy- } 4-Bromo-2-hydroxy-1-methoxy- }	4-Bromo-1-hydroxy-2-acetoxy- } 4-Bromo-1-hydroxy-2-methoxy- }
1 : 2-Dimethoxy-4-methyl- } 1-Methoxy-4-methyl- }	1-Hydroxy-4-methyl- } 1-Hydroxy-2-methoxy-4-methyl- }

When the negative character of the carbonyl oxygen concerned in these chelate rings is lessened by conversion of the thio- into the sulphone group (McClelland, J., 1929, 1590; Cohen and Smiles, J., 1930, 408), the stabilities of the salts and of the corresponding diacetoborates are remarkably diminished. For instance, none of the 1-methoxy-sulphones examined showed basic character and the diacetoborate of 1-hydroxy-2-methoxy-4-methylthioxanthone dioxide was the only one of this series sufficiently stable to be isolated in a pure condition.

In conclusion, attention is directed to the results of demethylation. In examining the combination of the 4-bromo-derivatives (*e.g.*, I and VII) with dry hydrogen chloride it was found that partial demethylation took place at 15—20°. Further experiments have shown that in the hot aqueous reagent demethylation may be effected with all 1-methoxy-derivatives; moreover, the process is selective in presence of other methoxyl groups. The materials examined (column 1) and the products obtained (column 2) were as follows :

1-Methoxy-4-methyl-	1-Hydroxy-4-methyl-
1 : 4-Dimethoxy-	1-Hydroxy-4-methoxy-
4-Bromo-1 : 2-dimethoxy-	4-Bromo-1-hydroxy-2-methoxy-
4-Bromo-2-hydroxy-1-methoxy-	4-Bromo-1 : 2-dihydroxy-
1 : 2-Dimethoxy-4-methyl-	1-Hydroxy-2-methoxy-4-methyl-

It is evident without further comment that this selective attack of the 1-methoxyl is adequately explained by the structure assigned (III) to the kation of the salts. This interpretation suggests that the 1-hydroxy-compounds formed contain a similar chelate structure, which is also indicated by the insolubility of all the 1-hydroxythioxanthones examined in aqueous sodium hydroxide.

EXPERIMENTAL.

Derivatives of Veratrole.—*4-Bromoveratrole-5-sulphonyl chloride* (IV). 4-Bromoveratrole (20 g.) was slowly added to well-cooled chlorosulphonic acid (40 c.c.); the solution was then poured over ice, the mixture being thoroughly stirred during the decomposition. The semi-solid mass of the sulphonyl chloride solidified after being washed with cold water; it was not further purified but was analysed in the form of the *amide*, which separated from acetic acid in needles, m. p. 236° (Found : C, 32·4; H, 3·6; Br, 27·2; S, 10·8. $C_8H_{10}O_4NBrS$ requires C, 32·2; H, 3·4; Br, 27·0; S, 10·8%). The substance was further identified by conversion into the disulphide and the sulphinic acid as subsequently described.

Elimination of bromine from this sulphonyl chloride was effected as follows. (a) A solution of the purified potassium salt (5 g.) obtained by hydrolysis of the sulphonyl chloride, in aqueous potassium hydroxide (100 c.c., 2%), was treated with hydrogen in presence of

palladium on a calcium carbonate support (Busch and Stove, *Ber.*, 1916, **49**, 106). The clear liquid, which contained bromine ions, was neutralised and evaporated and the dried residue was converted into the sulphonyl chloride and thence into the amide. This, after purification, had m. p. 137° and was identical with a sample of veratrole-4-sulphonamide (Hindmarsh, Knight, and Robinson, J., 1917, **111**, 953). (b) The sulphonyl chloride was submitted to vigorous reduction with tin and hot hydrochloric acid. The thiol, which was removed from the reacting mixture by a current of steam, yielded *diveratryl 4-disulphide* on oxidation. This separated from benzene and light petroleum in needles, m. p. 94° (Found : C, 56·4; H, 5·3. $C_{16}H_{18}O_4S_2$ requires C, 56·8; H, 5·3%), which were identical with a sample of the disulphide prepared by usual methods from veratrole-4-sulphonyl chloride.

4-Bromoveratrole-5-sulphinic acid. Since reduction of the sulphonyl chloride by the usual method removed nuclear halogen, the required disulphide was obtained from the sulphinic acid. The crude bromoveratrolesulphonyl chloride was shaken with a warm concentrated solution of sodium sulphite (5 mols.) until it dissolved, sodium carbonate being added at intervals to maintain alkalinity. The required *sulphinic acid* was liberated from the clear and cooled solution by addition of 60% sulphuric acid. It separated from benzene in prisms, m. p. 122° (Found : C, 34·0; H, 3·2. $C_8H_9O_2BrS$ requires C, 34·1; H, 3·2%).

Di-4-bromoveratryl 5-disulphide. A hot solution of the sulphinic acid (140 g.) in alcohol (500 c.c.) was treated with concentrated hydriodic acid (10 c.c., *d* 1·9), sulphur dioxide being led into the solution at intervals to remove iodine as it appeared. The required *disulphide*, which separated during the process and was collected from the cold mixture, crystallised from alcohol in fibrous needles, m. p. 118—119° [Found : C, 38·5; H, 3·2; Br, 31·8; S, 12·8. $(C_8H_8O_2Br)_2S_2$ requires C, 38·7; H, 3·2; Br, 32·2; S, 12·9%].

Derivatives of Thioxanthone.—4-Hydroxy-1-methylthioxanthone. A cooled mixture of sulphuric acid (100 c.c.) and 2-thiolbenzoic acid (5 g.), to which *p*-cresol (10 g.) had been gradually added, was stirred (½ hr.) and then poured over ice. The insoluble product was purified by conversion into the sparingly soluble potassium salt; the required material after sublimation in a vacuum was obtained in yellow needles, m. p. 245° (Found : C, 68·9; H, 4·2. $C_{14}H_{10}O_2S$ requires C, 69·4; H, 4·1%). Methylation in aqueous alkali yielded 4-methoxy-1-methylthioxanthone (Roberts and Smiles, *loc. cit.*). The substance did not yield a diacetoborate.

1-Hydroxy-4-methylthioxanthone. (a) When a solution of 1-methoxy-4-methylthioxanthone in concentrated hydrochloric acid was

boiled (½ hr.), the colour gradually faded and the required product separated in almost theoretical yield. Purified from light petroleum, it formed deep yellow needles, m. p. 160°; these were insoluble in aqueous alkali hydroxide (Found: C, 69·1; H, 4·4. $C_{14}H_{10}O_2S$ requires C, 69·4; H, 4·1%). The red *diacetoborate* was purified from acetic anhydride and formed needles, m. p. 236°; these were decomposed by hot water, liberating the thioxanthone [Found: $C_{14}H_{10}O_2S$, 65·7. $C_{14}H_9O_2S{\cdot}B(O{\cdot}CO{\cdot}CH_3)_2$ requires $C_{14}H_{10}O_2S$, 65·4%].

(b) The same material was obtained by diazotising 1-amino-4-methylthioxanthone (Ullmann and von Glenck, *Ber.*, 1916, **49**, 2491) with amyl nitrite in acetic acid. The red product which separated after decomposition of the diazo-compound in presence of sulphuric acid was extracted with hot alcohol. The solution deposited the required material, which was purified and identified in the usual manner.

(c) A small quantity of this 1-hydroxythioxanthone is formed in the condensation of *p*-tolyl carbonate with 2-thiolbenzoic acid. After hydrolysis of the crude product the required substance was separated from the 4-hydroxy-1-methyl derivative by its insolubility in aqueous sodium hydroxide. After sublimation in a vacuum it had m.p. 160° and was identified in the usual manner.

4-*Bromo*-1 : 2-*dimethoxythioxanthone* (I). (a) 4-Bromoveratrole (20 g.) was slowly added to a cooled and stirred mixture of 2-thiolbenzoic acid (14 g.) and sulphuric acid (300 c.c.). After ¼ hour, the product was isolated as usual and treated with aqueous alkali to remove acids present (yield, 40%). The required *substance* separated from acetic acid in yellow needles, m. p. 159°, which gave a bright red solution with cold concentrated hydrochloric acid (Found: C, 51·3; H, 3·1. $C_{15}H_{11}O_3BrS$ requires C, 51·2; H, 3·1%). Attempts to isolate a hydrochloride by treatment with the dry reagent failed owing to partial demethylation during the process.

(b) 4-Bromo-5-thiolveratrole (20 g.) (prepared from the corresponding disulphide by reduction with glucose in presence of alkali and not completely purified), amyl alcohol (70 c.c.), 2-bromobenzoic acid (20 g.), and potassium carbonate were boiled together (14 hours). After the alcohol had been removed by a current of steam, the residue was triturated with warm aqueous alkali. The solution when acidified yielded the impure 2-*bromo*-4 : 5-*dimethoxy*-2′-*carboxydiphenyl sulphide* (V). This separated from hot alcohol (charcoal) in needles, m. p. 211—212° (Found: C, 48·7; H, 3·7. $C_{15}H_{13}O_4BrS$ requires C, 48·7; H, 3·5%). The crimson solution of this substance in sulphuric acid was kept at 15° (2 hours). The product, isolated by addition of the solution to ice and purified from light petroleum or by sublimation, had m. p. 160° and was identified

in the usual manner with the product obtained from (a) and by its behaviour on hydrolysis with hydrochloric acid.

4-*Bromo*-2-*hydroxy*-1-*methoxythioxanthone* (VII). 5-Bromoguaiacol (20 g.) was gradually added to a cooled and stirred mixture of 2-thiolbenzoic acid (15 g.) in sulphuric acid (300 c.c.). The product, isolated as usual, was completely soluble in aqueous alkali hydroxide; carbonic acid liberated the required *thioxanthone* (25% yield) from this solution. It was purified from acetic acid and formed yellow needles, m. p. 208° (Found : C, 49·4; H, 2·8. $C_{14}H_9O_3BrS$ requires C, 49·8; H, 2·6%). The substance was readily methylated by methyl sulphate in aqueous alkali, yielding the 1 : 2-dimethoxy-derivative (I). It did not yield a diacetoborate.

4-*Bromo*-1 : 2-*dihydroxythioxanthone* was precipitated in almost theoretical yield when a solution of (VII) in concentrated hydrochloric acid was boiled. It separated from benzene in orange needles, m. p. 212° (Found : C, 48·2; H, 2·4. $C_{13}H_7O_3BrS$ requires C, 48·2; H, 2·1%), and yielded a red crystalline diacetoborate of the acetyl derivative. The purple sodium salt was sparingly soluble in water; other metallic derivatives such as those of iron and chromium were insoluble and highly coloured.

4-*Bromo*-1-*hydroxy*-2-*methoxythioxanthone* (VI) was (a) obtained by hydrolysis of (I) with boiling hydrochloric acid and when purified from acetic acid formed orange needles, m. p. 191°, which were insoluble in aqueous alkali hydroxide (Found : C, 49·5; H, 2·9; Br, 23·2; S, 9·4. $C_{14}H_9O_3BrS$ requires C, 49·8; H, 2·6; Br, 23·7; S, 9·5%). The red crystalline *diacetoborate* was obtained in the usual manner; it was hydrolysed by hot water [Found : $C_{14}H_9O_3BrS$, 72·3. $C_{14}H_8O_3BrS{\cdot}B(O{\cdot}CO{\cdot}CH_3)_2$ requires $C_{14}H_9O_3BrS$, 72·4%].

(b) Condensation of 4-bromoguaiacol (20 g.) with 2-thiolbenzoic acid (15 g.) in sulphuric acid (300 c.c.) was effected as usual. The solid product was added to hot aqueous alkali hydroxide (2*N*). The insoluble material consisted chiefly of the required 1-hydroxy-derivative (20% yield); this was purified from acetic acid and by subsequent conversion into the diacetoborate. Hydrolysis of this derivative yielded a material which had m. p. 191° and was identical with the product obtained by hydrolysis of (I).

1-*Hydroxy*-2-*methoxy*-4-*methylthioxanthone* (VIII; R = H) was obtained by condensation of creosol with 2-thiolbenzoic acid under the usual conditions. The product was treated with aqueous alkali; the residue consisted of the desired substance (20% yield). Purified from alcohol, this formed red needles, m. p. 173—174°, which were insoluble in alkali hydroxide or hydrochloric acid (Found : C, 65·9; H, 4·6. $C_{15}H_{12}O_3S$ requires C, 66·1; H, 4·4%). The substance formed a purple *diacetoborate* which was hydrolysed with difficulty

[Found : $C_{15}H_{12}O_3S$, 68·0. $C_{15}H_{11}O_3S{\cdot}B(O{\cdot}CO{\cdot}CH_3)_2$ requires $C_{15}H_{12}O_3S$, 68·0%].

1 : 2-*Dimethoxy*-4-*methylthioxanthone* (VIII; R = Me), obtained in almost theoretical yield from (VIII, R = H) by the method of Baker and Robinson (*loc. cit.*), separated from alcohol in yellow needles, m. p. 125°, which were readily soluble in cold hydrochloric acid (Found : C, 67·1; H, 5·2. $C_{16}H_{14}O_3S$ requires C, 67·1; H, 4·9%). With the boiling reagent, (VIII) was obtained in almost theoretical yield and identified in the usual manner. When the dimethoxy-compound was treated with dry hydrogen chloride (15°; 1 atm.) until constant weight was attained, a deep red *dihydrochloride* was formed (Found : HCl, 20·1. $C_{16}H_{14}O_3S,2HCl$ requires HCl, 20·3%).

4-*Bromo*-1-*hydroxy*-2-*methoxythioxanthone dioxide*. Hydrogen peroxide (2·5 c.c.; 30%) was added to a solution of the thioxanthone (VI) (2 g.) in acetic acid (20 c.c.). The mixture was gradually warmed to 100° and maintained at that temperature until the disappearance of the red colour indicated that oxidation was complete. The required *dioxide* separated from the cooled solution and after purification from acetic acid formed yellow prisms, m. p. 243° (Found : C, 45·2; H, 2·8. $C_{14}H_9O_5BrS$ requires C, 45·5; H, 2·4%). The substance gave an unstable diacetoborate.

1-*Hydroxy*-2-*methoxy*-4-*methylthioxanthone dioxide* was obtained in the same way by oxidation of (VIII; R = H). It separated from acetic acid in yellow needles, m. p. 190° (Found : C, 59·2; H, 3·7. $C_{15}H_{12}O_5S$ requires C, 59·2; H, 3·9%). The red *diacetoborate* had m.p. 222° and was sufficiently stable for isolation [Found : $C_{15}H_{12}O_5S$, 70·9. $C_{15}H_{11}O_5S{\cdot}B(O{\cdot}CO{\cdot}CH_3)_2$ requires $C_{15}H_{12}O_5S$, 70·4%].

1 : 2-*Dimethoxy*-4-*methylthioxanthone dioxide*, prepared in the same manner, formed yellow needles, m. p. 154° (Found : C, 60·5; H, 4·9. $C_{16}H_{14}O_5S$ requires C, 60·3; H, 4·4%).

4-*Bromo*-1 : 2-*dimethoxythioxanthone dioxide* was obtained by the intensive methylation of the potassium salt of the corresponding 1-hydroxy-derivative. It separated from alcohol in yellow needles, m. p. 165° (Found : C, 46·9; H, 3·2. $C_{15}H_{11}O_5BrS$ requires C, 47·0; H, 2·8%). Attempts to obtain this substance by oxidation of (I) with hydrogen peroxide led to the unexpected elimination of halogen as oxyhalogen acid and the formation of a product which from analytical data was evidently 1 : 2-*dimethoxythioxanthone dioxide*. This formed pale yellow plates, m. p. 246°, from acetic acid (Found : C, 59·0; H, 3·6; S, 10·3; *M*, 311, 304. $C_{15}H_{12}O_5S$ requires C, 59·2; H, 3·9; S, 10·5%; *M*, 304).

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