

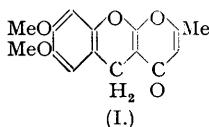
335. *The Chemistry of Fungi. Part VIII. The Oxidation of Methylene Groups in Compounds Analogous to O-Dimethylcitromycin.*

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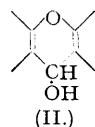
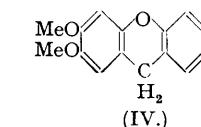
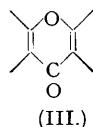
The behaviour of diphenylmethane, fluorene, deoxybenzoin, and a number of xanthenes on oxidation with ozone and with lead tetra-acetate has been compared with that of *O*-dimethylcitromycin. The rapid oxidation of the xanthenes and of anthrone is closely parallel to that of *O*-dimethylcitromycin.

IN the course of experiments on the degradation of citromycetin and its derivatives (Part III, this vol., p. 848) it was discovered that *O*-dimethylcitromycin (I) was oxidised with ozone directly without the intervention of an intermediate ozonide, giving rise to *O*-dimethylcitromycinol (II) and *O*-dimethylcitromycinone (III), the latter of which is also formed when chromic oxide is used as the oxidising agent. Since this action of ozone in converting a reactive methylene group into a carbonyl group appeared to be entirely novel and because the evidence advanced for the structure of citromycetin and its derivatives depends largely on the results obtained from the hydrolytic fission of *O*-dimethylcitromycinone, it seemed desirable to examine, at least in a qualitative manner, the behaviour of compounds having structures analogous to that proposed for the citromycetin series towards ozone under conditions similar to those employed for the production of *O*-dimethylcitromycinone. Since synthetical compounds of the *O*-dimethylcitromycin type (I) are not readily available, we selected several xanthenes of type (IV) which are closely related to the latter and in which the methylene group is well known

to be reactive towards oxidising agents, *e.g.* chromic oxide. At the same time we examined the behaviour of compounds, *e.g.* diphenylmethane, fluorene, and anthrone, in which the methylene group is not part of a heterocyclic oxygen system. The results have been summarised in the table below wherein the products obtained when the same compounds were oxidised with lead tetra-acetate are also given. The latter reagent has already been shown to effect substitution of a hydrogen atom in reactive methylene groups, *e.g.* in diphenylmethane (Dimroth and Schweizer, *Ber.*, 1923, **56**, 1375), in cyclohexene and indene (Criegee, *ibid.*, 1930, **481**, 263), and in cyclopentene (Dane and Elder, *Annalen*, 1939, **539**, 207).



Compound.

Oxidation products obtained with :
(a) Ozone.Oxidation products obtained with :
(b) Lead tetra-acetate.

1. Diphenylmethane	Benzophenone and glyoxal	Diphenylcarbinol acetate (<i>loc. cit.</i>)
2. Fluorene	Fluorenone	Fluorenone
3. Anthrone	Anthraquinone	—
4. Deoxybenzoin	Benzoic acid and glyoxal	Benzoic acetate
5. Xanthen	Xanthhydryl and xanthon	Xanthhydryl and xanthon
6. 1-Methyl-7-isopropylxanthen	The xanthhydryl	The xanthhydryl
7. 1 : 7-Dimethoxyxanthen	The xanthon	The xanthhydryl and the xanthon
8. 2 : 3-Dimethoxyxanthen	The xanthon	The xanthhydryl and the xanthon
9. <i>O</i> -Dimethylcitromycin	<i>O</i> -Dimethylcitromycin-ol and -one	<i>O</i> -Dimethylcitromycinol
10. <i>O</i> -Dimethylcitromycinol	<i>O</i> -Dimethylcitromycinone	—
11. Xanthhydryl	Xanthon	—

The oxidising action of ozone on diphenylmethane, fluorene, and deoxybenzoin is slow, requiring several hours' treatment before appreciable amounts of oxidation products are formed, and under these conditions the intermediate oxidation level (that of carbinol) has not been detected. With this group of compounds the oxidation with lead tetra-acetate requires to be carried out at an elevated temperature for comparatively long periods. On the other hand, anthrone, xanthen, and the substituted xanthenes behave in a manner closely analogous to *O*-dimethylcitromycin and are rapidly oxidised with ozone or with lead tetra-acetate. With the former agent the conversion of the active methylene group into carbinol and/or carbonyl takes place in about 15—20 minutes under conditions comparable with those employed in the case of diphenylmethane, fluorene, and deoxybenzoin. We have also established independently that *O*-dimethylcitromycinol and xanthhydryl are converted into *O*-dimethylcitromycinone and xanthon, respectively, by means of ozone. The isolation of the xanthhydrols and not the xanthhydryl acetates by the oxidation of the xanthenes with lead tetra-acetate is clearly due to the tendency of the acetates, which are in all probability the initial reaction products, to pass into the isomeric xanthylum salts and these are readily hydrolysed with water, an explanation which probably also applies in the case of *O*-dimethylcitromycinol. In this connection it is noteworthy that the oxidation of *O*-dimethylcitromycin with lead tetra-acetate affords an excellent method for the preparation of *O*-dimethylcitromycinol in quantity.

The results described in this communication serve to reinforce the arguments already adduced in support of the structure (1) for *O*-dimethylcitromycin (Part III, *loc. cit.*).

EXPERIMENTAL.

1-Methyl-4-isopropylxanthon.—2-(5'-Methyl-2'-isopropylphenoxy)benzoic acid, m. p. 102°, was prepared by the method of Lespagnol *et al.* (*Bull. Soc. chim.*, 1939, **6**, 1625) who gave m. p. 98°. On being heated under reflux with acetyl chloride (30 ml.) containing concentrated sulphuric acid (15 drops) for 10 minutes (method of Gottesmann, *Ber.*, 1933, **66**, 1168) (3 g.) this gave 1-methyl-4-isopropylxanthon (2.6 g.) which crystallised from aqueous alcohol forming colourless needles, m. p. 91° (Found : C, 81.0; H, 6.4. Calc. for C₁₇H₁₆O₂ : C, 81.0; H, 6.4%) (compare Lespagnol *et al.*, *loc. cit.*, who give m. p. 85°). Reduction of this xanthon (1 g.), suspended in 95% alcohol, with sodium amalgam (from 0.4 g. of sodium and 2 g. of mercury) according to Hollemann's method (*Org. Synth.*, Coll. Vol. I, p. 554) in the course of about 15 minutes, followed by dilution of the reaction mixture with water and isolation of the product with ether, gave 1-methyl-4-isopropylxanthhydryl which formed colourless needles (0.8 g.), m. p. 94°, from aqueous methanol (Found : C, 79.9; H, 7.2. Calc. for C₁₇H₁₈O₂ : C, 80.3; H, 7.1%) (compare Lespagnol, *et al.*, *loc. cit.*, who give m. p. 85°). This compound formed an orange solution of the xanthylum salt in 2*N*-hydrochloric acid. Prepared by Adriani's procedure (*Rec. Trav. chim.*, 1915, **35**, 180) the *N*-phenyl-*N'*-(1-methyl-4-isopropylxanthylum)urea separated from dioxan in slender

colourless needles, m. p. 221° (decomp.) (Found : C, 77.2; H, 6.7; N, 7.2. $C_{24}H_{24}O_2N_2$ requires C 77.4; H, 6.5; N, 7.5%).

Reduction of 1-methyl-4-isopropylxanthone (2.0 g.) with sodium (8 g., added in portions) and boiling alcohol (100 ml.) according to Kostanecki's method (*Ber.*, 1908, **41**, 1325) and precipitation of the product with water gave 1-methyl-4-isopropylxanthen (1.6 g.), which formed colourless prisms, m. p. 40—41°, from methanol (Found : C, 85.1; H, 7.4. $C_{17}H_{18}O$ requires C, 85.7; H, 7.6%). A current of ozone and oxygen was passed into a solution of this compound (0.5 g.) in chloroform (40 ml.) during 20 minutes, and a solution of the residual brown oil, left on evaporation of the solvent in a vacuum, in a little methanol was treated with phenylurea in acetic acid, giving rise to colourless needles of the phenylurea derivative (0.2 g.), m. p. 220—221°, after purification, identical with an authentic specimen (Found : N, 7.9%). The oxidation product did not appear to contain appreciable amounts of 1-methyl-4-isopropylxanthone.

When a mixture (agitated) of 1-methyl-4-isopropylxanthen (0.4 g.), acetic acid (6 ml.), and lead tetra-acetate (1.6 g.) was kept at room temperature for 1 hour a test portion did not give a precipitate with phenylurea, but 4 hours later when the mixture was diluted with water (50 ml.) and extracted with ether evaporation of the washed and dried extract left an oil which, on treatment with phenylurea in acetic acid, gave the phenylurea derivative as slender needles (0.2 g.), m. p. 220—222° (decomp.), after recrystallisation from dioxan (Found : N, 7.6%). After the separation of this compound, evaporation of the filtrate gave an intractable product from which 1-methyl-4-isopropylxanthone could not be isolated.

1 : 7-Dimethoxy-xanthhydrol and -xanthen.—Prepared from 1 : 7-dimethoxyxanthone (Graebe and Ebrard, *Ber.*, 1882, **15**, 1677) (1 g.) by the Hollemann procedure (*loc. cit.*) 1 : 7-dimethoxyxanthhydrol formed colourless prisms (0.6 g.), m. p. 84°, from methanol (Found : C, 70.0; H, 5.6. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.4%) (cf. Zerner and von Loti, *Monatsh.*, 1913, **34**, 993, who gave m. p. 74—76°). This compound gave a violet solution with 2N-hydrochloric acid, and with phenylurea in acetic acid formed N-phenyl-N'-(1 : 7-dimethoxyxanthyl)urea which separated from dioxan in colourless slender needles, m. p. 232° (decomp.) (Found : C, 70.0; H, 5.8; N, 7.8. $C_{22}H_{20}O_4N_2$ requires C, 70.2; H, 5.4; N, 7.4%).

Reduction of 1 : 7-dimethoxyxanthone (1 g.) by the sodium and alcohol method yielded 1 : 7-dimethoxyxanthen (0.6 g.) which crystallised from methanol in colourless needles, m. p. 79° (Found : C, 74.2; H, 5.9. $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.8%). Oxidation of this compound (0.2 g.) in chloroform (25 ml.) with ozone and oxygen during 20 minutes gave a dark solution from which the solvent was removed and the resinous product extracted with light petroleum (b. p. 40—60°). On recrystallisation from methanol the extracted material gave 1 : 7-dimethoxyxanthone (0.1 g.) in colourless needles, m. p. and mixed m. p. 147—149°. The phenylurea derivative of 1 : 7-dimethoxyxanthhydrol was formed when a mixture of the xanthen (0.2 g.), acetic acid (3 ml.), and lead tetra-acetate (0.8 g.) was kept at room temperature for 2 hours and a test sample (0.5 ml.) treated with phenylurea. On isolation the product (0.05 g.) had m. p. 228—230° (decomp.) undepressed on admixture with an authentic specimen (Found : N, 7.5%). The remainder of the reaction mixture was then kept for 24 hours and diluted with water (50 ml.), giving only 1 : 7-dimethoxyxanthone, which formed colourless needles (0.1 g.), m. p. and mixed m. p. 149°, from methanol. When the reaction was carried out at 40—50° 1 : 7-dimethoxyxanthhydrol could not be detected.

2 : 3-Dimethoxyxanthone (IV).—3 : 4-Dimethoxydiphenyl ether has been prepared by Asahina and Tanase (*Proc. Imp. Acad. Tokyo*, 1940, **16**, 297; *Chem. Abs.*, 1940, **34**, 7096) who prepared the xanthone from it by means of carboxyl chloride and aluminium chloride, but the details were not available to us and the following procedure was employed to synthesise this xanthone. The interaction of 4-bromoveratrole (7 g.) and sodium phenoxide (from 9.4 g. of phenol) in the presence of copper bronze (0.1 g.) according to the method of Ullmann and Stein (*Ber.*, 1906, **39**, 623) gave 3 : 4-dimethoxydiphenyl ether as a colourless oil (6.8 g.), b. p. 195—205°/20 mm., which solidified on being kept, and then separated from methanol in diamond-shaped plates, m. p. 50° (Found : C, 72.8; H, 6.2. Calc. for $C_{14}H_{14}O_2$: C, 73.0; H, 6.1%). A stream of hydrogen chloride was led into a stirred mixture of this ether (10 g.), benzene (40 ml.), and zinc cyanide (20 g.) at 0° for 3 hours, and aluminium chloride (16 g.) was then introduced, followed by the passage of hydrogen chloride for a further 2 hours. 3 Days later the reaction mixture was treated with ice (100 g.) and concentrated hydrochloric acid (50 ml.), and then boiled for $\frac{1}{2}$ hour. On isolation with ether, the aldehyde was obtained as a viscous amber oil (6.6 g.) which gave a semicarbazone, forming colourless squat prisms, m. p. 210—211°, from methanol (Found : C, 61.3; H, 5.8; N, 13.3. $C_{16}H_{17}O_4N_3$ requires C, 61.0; H, 5.4; N, 13.3%). The crude aldehyde (4 g.), dissolved in acetone (100 ml.), was oxidised with powdered potassium permanganate (10 g.) added in the course of 2 hours. Next day the filtered mixture was cleared with sulphur dioxide, the acetone was distilled off, and the residue was extracted with ether. Isolated from the extracts by means of aqueous sodium hydrogen carbonate and by extraction of the precipitate of manganese dioxide with the same reagent, 2-(3' : 4'-dimethoxyphenoxy)benzoic acid (3.5 g.) was purified by repeated crystallisation from aqueous methanol with considerable loss and then from acetone-light petroleum (b. p. 40—60°), forming clusters of tiny colourless needles, m. p. 174—175° (Found : C, 65.0; H, 5.4. $C_{15}H_{14}O_5$ requires, C, 65.7; H, 5.1%). Cyclisation of the crude acid (3 g.) with boiling acetyl chloride containing sulphuric acid (15 drops) in the course of 10 minutes gave 2 : 3-dimethoxyxanthone, which formed colourless needles (2.1 g.), m. p. 164°, from methanol (Found : C, 70.4; H, 5.0. Calc. for $C_{15}H_{12}O_4$: C, 70.3; H, 4.7%). From the liquors left from the purification of the xanthone a small amount of a second acid, probably 4-(3' : 4'-dimethoxyphenoxy)benzoic acid, was obtained. This compound would arise from small amounts of the corresponding aldehyde present in the crude Gattermann product employed for the oxidation.

2 : 3-Dimethoxy-xanthhydrol and -xanthen.—Reduction of the foregoing xanthone (0.4 g.) with sodium amalgam furnished 2 : 3-dimethoxyxanthhydrol (0.3 g.), which crystallised from methanol in colourless prisms, m. p. 92° (Found : C, 69.9; H, 5.6. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.4%). This compound, which gave a deep yellow solution with 2N-hydrochloric acid and did not appear to form a phenylurea derivative readily, was characterised by being converted into 2 : 3-dimethoxyxanthylum ferrichloride

which formed yellow needles, m. p. 204° (decomp.), from acetic acid (Found : C, 41.3; H, 3.1; Fe, 12.7. $C_{15}H_{13}O_3, FeCl_4$ requires C, 41.0; H, 3.0; Fe, 12.7%).

Reduction of 2 : 3-dimethoxyxanthone (1 g.) with sodium and alcohol gave rise to 2 : 3-dimethoxyxanthen (0.8 g.), forming colourless prisms, m. p. 88°, from light petroleum (b. p. 40—60°) (Found : C, 74.5; H, 6.1. $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.8%). On treatment with ozone and oxygen in chloroform (30 ml.) during 20 minutes this xanthen (0.2 g.) was converted into 2 : 3-dimethoxyxanthone (0.1 g.), m. p. and mixed m. p. 160°, after purification, but the presence of 2 : 3-dimethoxyxanthrydrol could not be detected in the reaction mixture.

When a solution of 2 : 3-dimethoxyxanthen (0.2 g.) in acetic acid (3 ml.) containing lead tetra-acetate (0.8 g.) had been kept for 1 hour a test portion (0.5 ml.) was diluted with water and extracted with ether. Evaporation of the combined extracts, which had been washed with aqueous sodium hydrogen carbonate, left a residue giving a deep yellow solution in 2*N*-hydrochloric acid characteristic of 2 : 3-dimethoxyxanthrydrol. On being kept for 24 hours the main portion of the original reaction mixture then contained only 2 : 3-dimethoxyxanthone, which formed colourless needles (0.15 g.), m. p. 160—162°, undepressed on admixture with an authentic specimen, from methanol.

The following compounds were also oxidised with ozone and with lead tetra-acetate.

(a) *Diphenylmethane*. A stream of ozone and oxygen was passed into a solution of this compound (2 g.) in chloroform (75 ml.) at 0° for 4 hours, and the product left on evaporation of the solvent in a vacuum was dissolved in methanol (30 ml.). Half of this solution, with an excess of alcoholic 2 : 4-dinitrophenylhydrazine sulphate, gave a mixed product (0.6 g.), which after having been extracted with warm acetic acid consisted mainly of glyoxal bis-2 : 4-dinitrophenylhydrazone (0.1 g.), forming scarlet needles, m. p. and mixed m. p. 320° (decomp.), from dioxan (Found : N, 25.8. Calc. for $C_{14}H_{10}O_8N_8$: N, 26.8%). On being cooled the acetic acid extracts gave benzophenone dinitrophenylhydrazone, m. p. and mixed m. p. 236°, after purification from dioxan (Found : N, 15.2. Calc. for $C_{19}H_{14}O_4N_4$: N, 15.5%). Examination of the second portion of the methanolic solution, which contained 0.5 g. of diphenylmethane, failed to reveal the presence of diphenylcarbinol.

(b) *Deoxybenzoin*. The product obtained with ozone as in the case of (a) was found to contain unchanged deoxybenzoin, benzoic acid, and glyoxal (isolated as the 2 : 4-dinitrophenylhydrazone). The addition of red lead (8.5 g.) in the course of 3 hours to a solution of deoxybenzoin (2 g.) in acetic acid (15 ml.) at 100° and subsequent dilution of the cooled reaction mixture with water gave rise to the acetate of benzoin (2 g.), forming prisms, m. p. 82°, from methanol, identified by comparison with an authentic sample.

(c) *Fluorene*. The product obtained with ozone from this compound (2 g.) consisted of unchanged material (0.8 g.) and fluorenone. The latter was isolated as the 2 : 4-dinitrophenylhydrazone (0.8 g.) forming orange-red plates, m. p. 299—300° (decomp.), from dioxan (Found : N, 15.6. Calc. for $C_{19}H_{12}O_4N_4$: N, 15.6%). The oxidation of fluorene with lead tetra-acetate in boiling acetic acid was remarkably slow, and in the course of 4 hours gave only a small amount of fluorenone, isolated as the 2 : 4-dinitrophenylhydrazone (0.1 g.), m. p. 302° (decomp.) after purification from dioxan (Found : N, 15.2%).

(d) *Xanthen*. When a stream of ozone and oxygen was led into a solution of xanthen (1 g.) in chloroform (50 ml.) for $\frac{1}{2}$ hour, and the solvent evaporated in a vacuum, crystallisation of the residue from alcohol gave xanthone (0.4 g.), m. p. and mixed m. p. 174°. Treatment of the alcoholic liquor with phenylurea gave the *N*-phenyl-*N'*-xanthylurea in slender needles (0.5 g.), m. p. 230° (decomp.) (Found : N, 8.5. Calc. for $C_{20}H_{16}O_2N_2$: N, 8.9%).

A mixture of xanthen (0.45 g.), lead tetra-acetate (2.4 g.), and acetic acid was kept at room temperature for 1 hour with occasional shaking, and a test portion of the mixture then gave the *N*-phenyl-*N'*-xanthylurea (0.1 g.), m. p. 230—232° (Found : N, 8.6%). Next day the main portion of the reaction mixture was found to contain only xanthone (0.3 g.), m. p. and mixed m. p. 173°, which was precipitated with water.

(e) *Anthrone*. Treatment of this compound (2 g.) in chloroform (75 ml.) with ozone for $\frac{1}{2}$ hour gave rise to anthraquinone, m. p. 265—270° after purification, which was identified by comparison with an authentic specimen. 10-Hydroxyanthrone was not formed in detectable amount.

O-Dimethylcitromycinol.—Red lead (20 g.) was added in small portions to a solution of *O*-dimethylcitromycin (5.5 g.) in acetic acid (30 ml.) at 30—40° in the course of 1 hour. $\frac{1}{2}$ Hour later, the solution, which gave a negative test for lead tetra-acetate with starch-iodide paper, began to deposit the crystalline alcohol and was poured into water (100 ml.), giving a crystalline precipitate of citromycinol which after having been well washed with water and dried, had m. p. 236—238° (decomp.); yield, 4.8 g. Re-crystallised from a large volume of acetone the compound formed colourless needles, m. p. 242° (decomp.) (Found : C, 62.1; H, 4.8. Calc. for $C_{15}H_{14}O_6$: C, 62.1; H, 4.8%).

When the reaction was carried out at higher temperatures, e.g. 70—100°, considerable decomposition occurred but *O*-dimethylcitromycinone did not appear to be formed.

It may be noted that the decomposition temperature, 242°, given here for *O*-dimethylcitromycinol differs from that recorded in Part III (*loc. cit.*). The variation is entirely due to the slower rate of the melting point determination (slow heating up to 230° and then at rate of approximately 1° per minute).

Ozone and oxygen were passed into a solution of *O*-dimethylcitromycinol (0.15 g.) in chloroform (75 ml.) for 20 minutes, and a part of the resulting *O*-dimethylcitromycinone separated. After evaporation of the solvent, the residual product was extracted with alcohol and the residue crystallised from acetic acid, giving *O*-dimethylcitromycinone (0.05 g.), pale buff needles, m. p. 315—317° (decomp.), identified by comparison with an authentic specimen.