447. *The Biosynthesis of Phenols. Part III.* Oxidative Coupling leading to Geodoxin and Related Compounds.*

By C. H. HASSALL and J. R. LEWIS.

Geodoxin and related compounds may be synthesised from the corresponding *o*-carboxydiphenyl ethers by intramolecular coupling reactions involving lead dioxide and ammonium ceric sulphate as oxidising agents.

IT has been shown that related strains of *Aspergillus terreus* Thom produce the compounds geodin [1] (IIb), geodoxin [2] (IVb), and asterric acid [3] (IIIa). Further, there is evidence indicating that sulochrin (I), a compound isolated from the culture fluid of the fungus *Oospora sulphurea-ochracea*,[4] is related to the *A. terreus* metabolites: not only is it converted into asterric acid by simple stages [3] that could occur *in vivo* but also there is, in the mycelium of *O. sulphurea-ochracea*, a compound known as Nishikawa's substance A, $C_{17}H_{16}O_8$, that has properties (m. p. 214°; diacetyl derivative, m. p. 147°) identical with those of asterric acid.[5] Although direct comparison has not been possible there seems little doubt that substance A is asterric acid.

Comparison of the structures of sulochrin and the *A. terreus* metabolites suggests that a geodoxin analogue may be synthesised from sulochrin by the annexed sequence. This scheme assumes that the chlorine atoms in geodin and geodoxin are introduced in secondary reactions as has been indicated in the case of griseofulvin.[6]

The two steps involved in the conversion of sulochrin into asterric acid have been achieved *in vitro*.[3] It seemed possible that the last stage, the conversion of geodin hydrate (IIIb) into geodoxin was realised *in vivo* by direct oxidative coupling.

To test this route to geodoxin, the simpler acid ether (V) was oxidised under various conditions. Treatment with potassium ferricyanide, which is effective in the oxidative coupling leading to geodin,[7] produced no neutral product in alkaline, acid, or neutral media. However, the use of ammonium ceric sulphate and an active form of lead dioxide [8] yielded the spiran (VI) in 12% and 35% yield respectively. Complementary proof of this

---

* Part II, *J.*, 1960, 4838.

[1] Calam, Clutterbuck, Oxford, and Raistrick, *Biochem. J.*, 1939, **33**, 579.

[2] Hassall and McMorris, *J.*, 1959, 2831.

[3] Curtis, Hassall, Jones, and Williams, *J.*, 1960, 4838.

[4] Nishikawa, *Acta Phytochim., Japan*, 1939, **11**, 167.

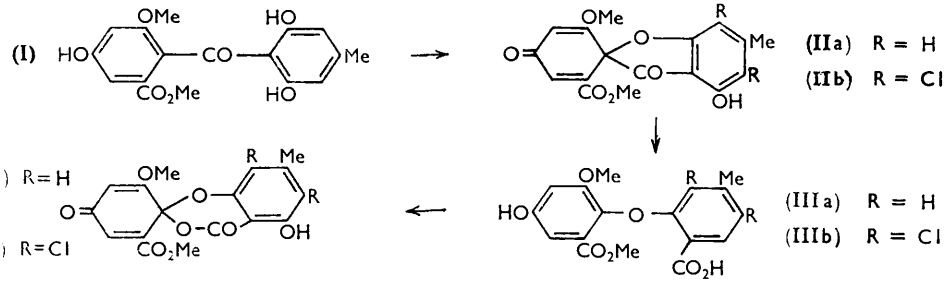
[5] Nishikawa, *Bull. Agric. Chem. Soc. Japan*, 1937, **13**, 1; 1942, **18**, 13.

[6] Macmillan, *J.*, 1954, 2585.

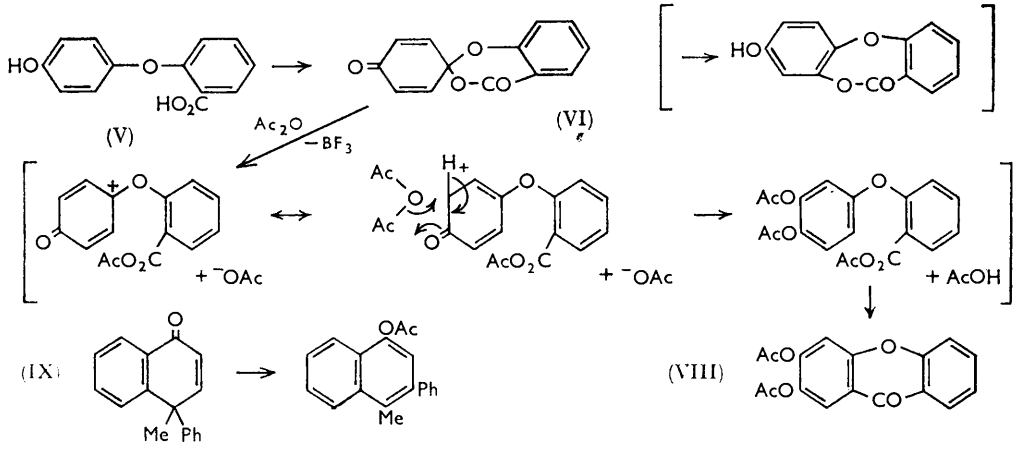
[7] Scott, *Proc. Chem. Soc.*, 1958, 195.

[8] Kuhn and Hammer, *Chem. Ber.*, 1950, **83**, 413.

structure came from spectroscopic data and from the fact that hydrogenolysis, with uptake of one mol. of hydrogen, regenerated the acid. A curve obtained by subtracting the ultraviolet absorption curve of salicylic acid from that of the spiran (VI) had $\lambda_{max.}$ 245 mμ (ε 6400). This is consistent with the cross-conjugated dienone system,[2] as is an infrared band near 1670 cm.$^{-1}$ that has been found also in the spectra of geodin,[9] geodoxin,[2] and picrolichenic acid.[10] The partial synthesis of geodoxin has been achieved in 88% yield by oxidation of the substituted diphenyl ether (IIIb) with lead dioxide. Dechlorogeodoxin (IVa) has been prepared in a similar manner from asterric acid.



There is interest in examining the behaviour of the model spiro-lactone (VI) in the presence of acid as a rearrangement similar to that of the hemiquinone [11] (IX) might lead to a product (VII) analogous to a depsidone. This work is still in progress but one clearly defined case that throws light on the properties of this system deserves mention now. Treatment of the compound (VI) with boron trifluoride in acetic anhydride led to the formation of 2,3-diacetoxyxanthone which was identified by comparison with the xanthone synthesised from 2-carboxy-3′,4′-dimethoxydiphenyl ether. The reaction with boron trifluoride in acetic anhydride may be interpreted as resulting from attack of the electrophilic " acetylium ion " on the lactone bridge of the spiran. This is followed by redistribution of charge, attachment of the acetate residue to position 3′, and condensation to give xanthone (VIII). There is, then, no indication that under these conditions the 2′-position tends to acquire positive character to favour a shift of the carboxy-group from the 1′- to the 2′-position, leading to the compound (VII).



---

[9] Barton and Scott, *J.*, 1958, 1767.

[10] Wachtmeister, *Acta Chem. Scand.*, 1958, **12**, 147.

[11] Arnold and Buckley, *J. Amer. Chem. Soc.*, 1949, **71**, 1781.

EXPERIMENTAL

M. p.s were determined by means of a Kofler block. Ultraviolet spectra were measured for ethanol solutions on a Unicam spectrophotometer. Infrared spectra were measured by Dr. H. E. Hallam and Mr. D. Jones for potassium bromide discs on a Grubb–Parsons double-beam spectrometer.

2-Carboxy-4′-hydroxydiphenyl Ether (V).—2-Carboxy-4′-methoxydiphenyl ether (3 g.; m. p. 146—147°; methyl ester, m. p. 60—62°, b. p. 127°/0·2 mm.), which was prepared by Ungnade and Rubin's method,[12] was demethylated by refluxing glacial acetic acid (30 ml.) containing hydrogen bromide (48% w/w; 10 ml.) for 2 hr. The hydroxy-acid recrystallised from benzene as plates, m. p. 158—159° (2 g.).

1,2,3,4-*Tetrahydro*-4-*oxo*-1,3-*dioxanaphthalenespirocyclohexa*-2′,5′-*dien*-4′-*one* (VI).—(a) *By use of ammonium ceric sulphate.* A solution of ammonium ceric sulphate (2·75 g.) in water (50 ml.) was added, dropwise, with vigorous stirring during 1 hr. to a mixture of carbon tetrachloride (50 ml.) and 2-carboxy-4′-hydroxydiphenyl ether (V) (1 g.) in water (250 ml.) containing sodium carbonate (2 g.). After being stirred for a further hour, the solution was acidified and extracted with ether. The extract was washed with water and saturated sodium hydrogen carbonate solution, dried, and evaporated to leave the neutral *compound* (VI) (120 mg., 12%) which, crystallised from benzene–light petroleum (b. p. 60—80°), had m. p. 164—166° (Found: C, 68·2; H, 3·8; O, 28·1. $C_{13}H_8O_4$ requires C, 68·4; H, 3·5; O, 28·1%), $\lambda_{max.}$ 240, 298 mμ (ε 8450, 1920). The subtraction curve compound (V) — salicylic acid gave $\lambda_{max.}$ 245 mμ (ε 6400). The infrared spectrum showed maxima at 1745 (lactone) and 1675 cm.$^{-1}$ (conjugated CO).

(b) *By use of lead dioxide.* A mixture of 2-carboxy-4′-hydroxydiphenyl ether (V) (500 mg.), chloroform (10 ml.), ether (5 ml.), and the freshly prepared, active form of lead dioxide (10 g.) was shaken for 16 hr. The solution was filtered; the lead dioxide was washed with ether, and the combined filtrate and washings were extracted with sodium hydrogen carbonate solution to remove unchanged acid. The dried ether extract was evaporated to give a solid, m. p. 164—166° (175 mg., 35%), identical with material obtained in the previous experiment. Acidification of the sodium hydrogen carbonate solution, followed by extraction and working up in the usual way, gave unchanged starting material (20 mg.).

Attempts to prepare the spirolactone (VI) from 2-carboxy-4′-hydroxydiphenyl ether by electrolysis or alkaline potassium ferricyanide or ferric chloride in chloroform, were not successful.

Hydrogenolysis of the Spiro-lactone (VI).—The spiro-lactone (36 mg.) in ethanol (25 ml.) was shaken with 5% palladium–charcoal (0·5 g.) in the presence of hydrogen. Hydrogen (4·1 ml.; 1 mol. = 3·8 ml.) was taken up. Evaporation of the filtered solution gave a solid which was dissolved in ether and washed with sodium hydrogen carbonate solution. Acidification of this solution and extraction with ether led to a solid (23 mg.), m. p. and mixed m. p. with 2-carboxy-4′-hydroxydiphenyl ether, 157—158°. The infrared spectra were identical.

Reaction of the Spiro-lactone (VI) *with Acetic Anhydride and Boron Trifluoride.*—The spiro-lactone (50 mg.), acetic anhydride (10 ml.), and boron trifluoride–ether complex (0·2 ml.) were left together for 30 min., then poured into water. An ether extract of the mixture was washed with sodium hydrogen carbonate solution, dried, and evaporated to give a solid (41 mg.). Crystallisation from methanol–acetone gave needles, m. p. 189—191°, which gave no colour with ferric chloride in aqueous methanol; on admixture with 1,2-diacetoxyxanthone [13] (m. p. 198°; lit., 190°) it had m. p. 165—180°. The identity of this compound as 2,3-diacetoxyxanthone, for which Liebermann and Lindenbaum [14] gave m. p. 186°, was confirmed by hydrolysis with 10% methanolic potassium hydroxide at room temperature, overnight, to 2,3-dihydroxyxanthone which was purified by sublimation at 240°/0·9 mm. to give needles, m. p. 291—194° (Liebermann and Lindenbaum [14] gave m. p. 294°). Treatment of this product (75 mg.) in refluxing acetone (100 ml.) with anhydrous potassium carbonate (5 g.) and dimethyl sulphate (10 ml.) for 12 hr. gave needles, m. p. 163—164° (Found: C, 70·2; H, 4·5; O, 24·7. Calc. for $C_{17}H_{12}O_6$: C, 70·3; H, 4·7; O, 25·0%). The m. p. was undepressed on admixture with authentic 2,3-dimethoxyxanthone, synthesised by the procedure detailed below, and the infrared spectra of the two samples were identical.

---

[12] Ungnade and Rubin, *J. Org. Chem.*, 1951, **16**, 1311.

[13] Davies, Lamb, and Suschitzky, *J.*, 1958, 1790.

[14] Liebermann and Lindenbaum, *Ber.*, 1904, **37**, 2735.

2,3-*Dimethoxyxanthone*.—This compound has been prepared by Asahina and Tanase [15] by the treatment of 3,4-dimethoxydiphenyl ether with carbonyl chloride and aluminium chloride, but the details were not available to us. It has also been prepared by Cavill, Robertson, and Whalley [16] by the action of boiling acetyl chloride containing sulphuric acid on an acid, m. p. 174—175°, which was prepared from 3,4-dimethoxydiphenyl ether by the action of zinc cyanide, hydrogen chloride, and aluminium chloride under the usual conditions of the Hoesch synthesis, followed by oxidation of the resulting aldehyde with potassium permanganate. The acid was assumed to be 2-carboxy-3′,4′-dimethoxydiphenyl ether although the method of synthesis left open the alternatives 2′- and 6′-carboxy-3′,4′-dimethoxydiphenyl ether. We have found it convenient to prepare 2-carboxy-3′,4′-dimethoxydiphenyl ether by heating 4-bromoveratrole (22 g.) with sodium methyl salicylate (30 g.; prepared from methyl salicylate and sodium methoxide followed by removal of methanol in a high vacuum) and copper bronze (0·5 g.) at 260° for 1·5 hr. The crude acid fraction (9·5 g.) was obtained by dilution with water, acidification, extraction with ether, washing of the ether layer with sodium hydrogen carbonate solution, and acidification of this alkaline extract. This crude acid with methanol–sulphuric acid gave an oil; on distillation thereof the major fraction (4·5 g.), b. p. 175—178°/1·5 mm., was 2-*methoxycarbonyl*-3′,4′-*dimethoxydiphenyl ether*, m. p. 68—69° (Found: C, 66·6; H, 5·9; O, 27·8. $C_{16}H_{15}O_5$ requires C, 66·7; H, 5·6; O, 27·8%). Hydrolysis of this methyl ester gave 2-*carboxy*-3′,4′-*dimethoxydiphenyl ether* (4·1 g.) which, crystallised from methanol, had m. p. 149—150° (Found: C, 65·8; H, 5·2; O, 29·0. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·2; O, 29·2%). This compound is evidently different from that, m. p. 174—175°, which was assigned this structure by Cavill *et al.* From the evidence now available their compound must be 6′-carboxy-3′,4′-dimethoxydiphenyl ether.

Cyclisation was accomplished by refluxing 2-carboxy-3′,4′-dimethoxydiphenyl ether (310 mg.) in acetyl chloride (5 ml.) containing concentrated sulphuric acid (5 drops) for 15 min. The mixture was poured on ice and extracted with ether. The ether layer was washed with dilute sodium hydroxide solution, dried, and evaporated to leave a solid (120 mg.) which crystallised from acetone as needles, m. p. 164—165°. Cavill *et al.*[16] record m. p. 164° for 2,3-dimethoxyxanthone.

Partial Synthesis of Geodoxin.—Geodin hydrate [17] (97 mg.) was shaken with ether (20 ml.) and active lead dioxide (1 g.) for 2 hr. The mixture was filtered and the dioxide was washed with fresh ether. Evaporation of the combined filtrate and washings gave geodoxin (86 mg., 88%) which, crystallised from chloroform–pentane, had m. p. and mixed m. p. 211—212°. The infrared spectrum was authentic.

Dechlorogeodoxin (IVa).—A mixture of asterric acid (III*c*) (100 mg.), ether (5 ml.), and lead dioxide (2·5 g.) was shaken for 3 hr. Working up as in the previous experiment gave *dechlorogeodoxin* (70 mg., 71%), which crystallised from benzene–pentane as a pale yellow solid, m. p. 170—173° (Found: C, 58·8; H, 4·2; O, 36·5. $C_{17}H_{14}O_8$ requires C, 59·0; H, 4·1; O, 37·0%), $\lambda_{max.}$ 265, 318 mμ (ε 12,980, 7470). The subtraction curve dechlorogeodoxin − *p*-orsellinic acid gave $\lambda_{max.}$ 270, 328 mμ (ε 11,500, 5800). The infrared spectrum showed bands at 1730 (lactone and CO_2Me) and 1670 cm.$^{-1}$ (conjugated CO).

We are grateful to Imperial Chemical Industries Limited for a grant and a Fellowship (to J. R. L.), and to B.P. Ltd. and Mond Nickel Co. for financial support.

DEPARTMENT OF CHEMISTRY,
UNIVERSITY COLLEGE OF SWANSEA.

[*Received, November 25th*, 1960.]

---

[15] Asahina and Tanase, *Proc. Imp. Acad. Tokyo*, 1940, **16**, 297; *Chem. Abs.*, 1940, **34**, 7096.
[16] Cavill, Robertson, and Whalley, *J.*, 1949, 1567.
[17] Calam, Clutterbuck, Oxford, and Raistrick, *Biochem. J.*, 1947, **41**, 458.