## 337. *Sumatrol. Part II. The Synthesis of Dehydrotetrahydrosumatrol.*

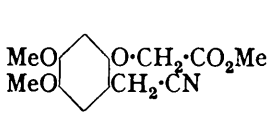
By Thomas S. Kenny, Alexander Robertson, and (in part) Stephen W. George.

Condensation of the nitrile (I) with the phenol (II) by Hoesch's method and hydrolysis of the product gave rise to the acid (III, R = H) along with a phenolic by-product. On cyclisation with hot acetic anhydride and sodium acetate this acid (III, R = H) gave the diacetate of dehydrotetrahydrosumatrol and on deacetylation the latter furnished dehydrotetrahydrosumatrol, for which two formulæ (IV, R = H) and type (V) are possible. In agreement with the angular orientation for sumatrol (VI) it appears probable that the compound has structure (IV).

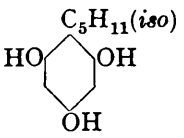
From the results of dehydrogenation and hydrolysis experiments it was concluded in Part I (J., 1937, 497) that sumatrol was a 5-hydroxydimethoxychromanochromanone and since, like rotenone, sumatrol gave rise to dihydro- and tetrahydro-derivatives, which

could be oxidised to the corresponding dehydro-products, it was suggested that the compound contained an *iso*propylenedihydrofurano-system. As a further step in the study of the constitution of this substance it seemed essential that the structure of tetrahydrosumatrol or of its dehydro-derivative should be conclusively established and, though the analytical procedure employed in the case of toxicarol (J., 1935, 681; 1937, 1535) could have been applied, it was decided, in view of the small reserves of tetrahydro- and dehydrotetrahydro-sumatrol available, to attempt the synthesis of the latter compound.

Reduction of phlor*iso*valerophenone by Clemmensen's method gave iso*amylphloroglucinol* (II), which on condensation with methyl 2-cyanomethyl-4 : 5-dimethoxyphenoxyacetate (I) by the method of Hoesch and subsequent hydrolysis of the crude ketimine in the usual manner, followed by hydrolysis of the resulting ester (III, R = Me) with alkali, yielded *tetrahydrosumatrolic acid* (III, R = H), which in most of our experiments was accompanied by a phenolic by-product. Cyclisation of the acid (III, R = H) with boiling acetic anhydride and sodium acetate furnished a small yield of the diacetate of dehydrotetrahydrosumatrol, which on deacetylation with warm aqueous alcoholic hydrochloric acid gave rise to dehydrotetrahydrosumatrol in almost quantitative yield, identical in every way with a specimen prepared from sumatrol.



(I.)



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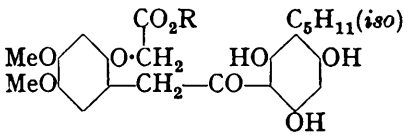
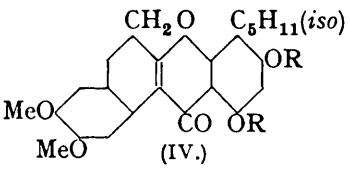
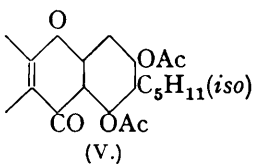


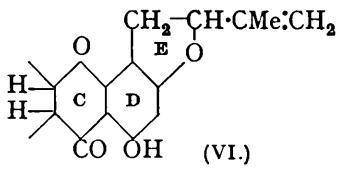
(III.)



(IV.)



(V.)



(VI.)

Though on cyclisation tetrahydrosumatrolic acid yielded only acidic material (crude diacetate of the acid) along with *O*-diacetyldehydrotetrahydrosumatrol, it is clear that this acid could give rise to two cyclisation products represented by formula (IV, R = Ac) and (V), which correspond to the angular and the linear structure respectively with reference to rings C, D, and E of sumatrol (Part I, *loc. cit.*). By analogy with toxicarol we prefer the angular structure which has been tentatively suggested for sumatrol (J., 1937, 1537) and accordingly consider that dehydrotetrahydrosumatrol is represented by the expression (IV, R = H). In support of this view it may be noted that, whereas dihydrotoxicarolic acid on cyclisation might be expected to give rise to two products, only one, the diacetate of dehydrodihydrotoxicarol, having the angular structure, appears to be formed (compare J., 1935, 1535). The structure now established for dehydrotetrahydrosumatrol implies that the formula suggested in Part I (*loc. cit.*) for tetrahydrosumatrol should have the *iso*amyl residue in the 8- and not the 6-position and further by analogy with the formation of tetrahydrorotenone from rotenone it now seems reasonably certain that sumatrol contains the *iso*propylenedihydrofuran (VI) system present in rotenone.

Our investigation of the phenolic by-product, which has also been obtained by the action of ethereal hydrogen chloride and zinc chloride on *iso*amylphloroglucinol, has not yet been completed.

## Experimental.

*Phlor*isov*alerophenone*.—Karrer and Rosenfeld (*Helv. Chim. Acta*, 1921, **4**, 712) describe the preparation of this compound by Hoesch's method and give m. p. 95° and 176—178° for the hydrate and anhydrous material respectively. On the other hand, Rosenmund and Lohfert (*Ber.*, 1928, **61**, 2607) have obtained this ketone by the Friedel–Crafts procedure with nitrobenzene as a diluent, but give m. p. 145° without recording analytical data. We have prepared the ketone in quantity according to the method of the latter authors and by the follow-

ing improved modification: A mixture of anhydrous phloroglucinol (16 g.; 1·25 mols.) and powdered aluminium chloride (20 g.; 1·5 mols.) was dissolved in nitrobenzene (200 c.c.) in the course of 1 hour, and *iso*valeryl chloride (13 g.; 1 mol., from synthetic *iso*valeric acid) then added to the solution at 0°. Three days later the reaction mixture was treated with ice (200 g.) and dilute hydrochloric acid (200 g.) and extracted six times with ether, the extracts washed with water and then with aqueous sodium bicarbonate, the ether distilled on the steam-bath, the nitrobenzene removed in a current of steam, and the warm residual aqueous liquor decanted from the insoluble resin. On cooling, the aqueous solution (agitate) deposited the ketone in rhombic prisms. Repeated extraction of the resinous material by boiling with the aqueous filtrate from the main crop of crystals or with benzene gave further small quantities of the ketone. On being recrystallised several times from water, this compound formed the hydrate in thick, pale yellow plates (8—10 g.), which gave a deep reddish-brown ferric reaction and were readily dehydrated, yielding anhydrous material, m. p. 145° (Found for a specimen dried in a high vacuum at 105°: C, 63·0; H, 6·7. Calc. for $C_{11}H_{14}O_4$: C, 62·9; H, 6·7%). On being warmed with aqueous or alcoholic solutions of 2 : 4-dinitrophenylhydrazine in the usual manner, the ketone did not yield the hydrazone, but when a solution of the compound (1 g.) in alcohol (10 c.c.) was added to a paste of 2 : 4-dinitrophenylhydrazine (1 g.) and concentrated sulphuric acid (2 c.c.) which had been treated with alcohol (15 c.c.), and the reaction mixture then warmed on the steam-bath, dark red needles of the required *hydrazone* separated; a further quantity was precipitated by the addition of water. Recrystallised from alcohol, this derivative formed dark red needles, m. p. 196° (Found: N, 14·4. $C_{17}H_{18}O_7N_4$ requires N, 14·2%).

Condensation of phloroglucinol (1·5 g.) and *iso*valeronitrile (1·5 g.) with excess of hydrogen chloride and zinc chloride (1·5 g.) in ether (40 c.c.) and hydrolysis of the product with water (20 c.c.) on the steam-bath for ½ hour and then under reflux furnished a product, m. p. 166—168°, which on repeated purification from water had m. p. 182—183°. This material, which gave a reddish-brown ferric reaction in alcohol, appeared to be a mixture and on being heated in a high vacuum at 110—115° gave a sublimate of phlor*iso*valerophenone, m. p. and mixed m. p. 145°, leaving a dark residue (compare Karrer and Rosenfeld, *loc. cit.*).

iso*Amylphloroglucinol.*—A solution of the foregoing ketone (2 g.) in alcohol (20 c.c.) was added to 12% hydrochloric acid (80 c.c.), containing amalgamated zinc dust (50 g.), and after the addition of more acid (20 c.c.) 2 days later the mixture was heated on the steam-bath for 1 hour and then under reflux for 6 hours with the addition of more acid (20 c.c.). The cooled, filtered solution was extracted six times with ether, the combined extracts washed with aqueous sodium bicarbonate, dried, and evaporated, and the dark viscous residue dissolved in warm chloroform. The *phenol*, which separated from the cooled solution, formed colourless needles (1·2 g.), m. p. 126°, from benzene, which gave a faint blue coloration with aqueous ferric chloride and a negative reaction with the alcoholic reagent (Found: C, 67·4; H, 8·2. $C_{11}H_{16}O_3$ requires C, 67·4; H, 8·2%). A similar yield of the phenol was obtained when the reduction was carried out by Martin's procedure (*J. Amer. Chem. Soc.*, 1936, **58**, 1438).

4 : 5-*Dimethoxyphenoxyacetic Acid*-2-iso*amylphloracetophenone* (*Tetrahydrosumatrolic Acid*) (III, R = H).—A mixture of *iso*amylphloroglucinol (6 g.), methyl 2-cyanomethyl-4 : 5-dimethoxyphenoxyacetate (J., 1933, 1163) (4 g.), powdered zinc chloride (6 g.), and ether (200 c.c.) was saturated with hydrogen chloride. Seven days later more ether (150 c.c.) was added, the solvent was decanted, and, after being washed with ether (4 × 50 c.c.), the residual oil was heated with water (100 c.c.) on the steam-bath for 2 hours. Next day the aqueous liquor was decanted, the viscous product heated with 5% aqueous potassium hydroxide (60 c.c.) and zinc dust (1 g.) on the steam-bath for 1 hour, the resulting filtered solution acidified with hydrochloric acid and the oily precipitate thoroughly extracted with aqueous sodium bicarbonate, leaving an insoluble phenolic by-product. Acidification of this extract with hydrochloric acid gave *tetrahydrosumatrolic acid*, containing resinous impurities. On repeated crystallisation from 20% aqueous acetone the acid formed elongated prisms, m. p. 206°, readily soluble in acetone, alcohol, and chloroform and slightly soluble in benzene [Found: C, 61·6; H, 6·3; OMe, 13·9. $C_{21}H_{22}O_7(OMe)_2$ requires C, 61·6; H, 6·3; OMe, 13·8%]. It gave a purple coloration with alcoholic ferric chloride.

On being crystallised from dilute alcohol, the phenolic by-product, which was insoluble in aqueous sodium bicarbonate, formed colourless needles, m. p. 134°, soluble in acetone, ethyl acetate, and hot benzene and having a negative ferric reaction in alcohol or water (Found: C, 70·4; H, 8·9. Calc. for $C_{22}H_{30}O_5$: C, 70·6; H, 8·0%). Prepared by the acetic anhydride–pyridine method, the acetate separated from aqueous alcohol in colourless needles, m. p. 51°,

insoluble in aqueous sodium hydroxide [Found: C, 66·4; H, 7·9. Calc. for $C_{30}H_{38}O_9$ (tetra-acetate): C, 66·4; H, 7·0%. Calc. for $C_{32}H_{40}O_{10}$ (penta-acetate): C, 65·6; H, 6·9%].

*Dehydrotetrahydrosumatrol* (IV, R = H).—A mixture of the foregoing acid (0·8 g.), sodium acetate (0·45 g.), and acetic anhydride (10 c.c.) containing acetic acid (0·5 c.c.) was refluxed for 15 minutes, and the excess of anhydride decomposed with water (140 c.c.). The resulting brown solid was extracted with aqueous sodium bicarbonate to remove acidic material, and the insoluble residue crystallised from 50% acetone and then methyl alcohol, giving *O*-diacetyl-dehydrotetrahydrosumatrol (IV, R = Ac) in pale straw-coloured, slender needles, m. p. 193—194° with slight sintering at 189°, soluble in chloroform, benzene, or ethyl acetate and having a negative ferric reaction (Found: C, 65·4; H, 5·7. Calc. for $C_{27}H_{28}O_9$: C, 65·3; H, 5·7%). This compound was identical in every way with a specimen of the natural diacetate, which has been found to have m. p. 193—194° after sintering at 187°, and not m. p. 197° as stated in Part I (*loc. cit.*).

A solution of the diacetate (0·05 g.) in alcohol (5 c.c.) and concentrated hydrochloric acid (2 c.c.) was boiled for 10 minutes and on removal of the greater part of the alcohol the residue deposited dehydrotetrahydrosumatrol, which formed clusters of pale yellow, elongated, flat prisms, m. p. 218°, alone or mixed with a natural specimen (Part I, *loc. cit.*) (Found: C, 67·0; H, 6·0. Calc. for $C_{23}H_{24}O_7$: C, 67·0; H, 5·9%). The dark green ferric reaction of the synthetical compound was identical with that of the natural substance.

The authors are indebted to the Government Grants Committee of the Royal Society for a research grant and to the Department of Scientific and Industrial Research for a maintenance grant to one of them (T. S. K.).

UNIVERSITY OF LIVERPOOL. [*Received, August 24th,* 1939.]