151. *Experiments on the Synthesis of Rotenone and its Derivatives. Part V. The Constitution of* apo*Toxicarol.*

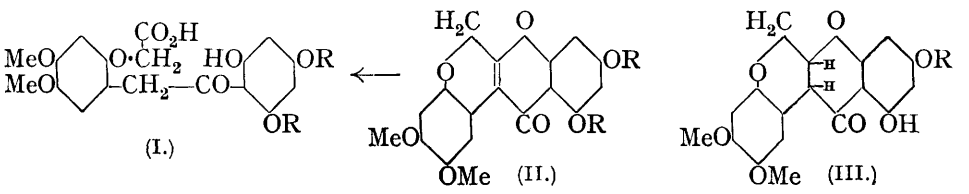
By Reginald G. Heyes and Alexander Robertson.

From the work of Clark (*J. Amer. Chem. Soc.*, 1930, **52**, 2461; 1931, **53**, 2264; 1932, **54**, 1600, 2537) and of Butenandt and Hilgetag (*Annalen*, 1932, **495**, 172; 1933, **506**, 162) it is reasonably certain, as has been suggested by these authors, that toxicarol, $C_{23}H_{22}O_7$, possesses a chromanochromanone nucleus of the rotenone type which can be oxidised to

the dehydro-form (chromenochromone). Further, it can be degraded to derric acid and to dehydronetoric acid and hence the chromano-residue is identical with that present in the rotenone molecule. Unlike rotenone, however, toxicarol on hydrolytic fission with warm 5% alkali solution sheds the elements C_5H_6, yielding *apo*toxicarol, $C_{18}H_{16}O_7$, which is considered by Clark (*loc. cit.*) to retain the chromanochromanone nucleus and by the standard procedure can be converted into dehydro*apo*toxicarol, $C_{18}H_{14}O_7$. It must be remembered, however, that the partial formulæ which have been suggested for toxicarol, *apo*-, and dehydro*apo*-toxicarol (*loc. cit.*) rest entirely on analogy with the behaviour of rotenone, deguelin, and tephrosin; moreover, the nature of the phenol present in the chromanone residue of toxicarol has not been determined.

By analogy with the naturally occurring members of the flavone, flavanone and *iso*-flavone series it seemed to us likely that toxicarol contained a phloroglucinol residue in place of the resorcinol nucleus present in rotenone, deguelin, and tephrosin. Accordingly, on approaching the problem of the constitution of toxicarol and its main degradation products from the synthetical side, we assumed that dehydro*apo*toxicarol had formula (II, R = H) and, therefore, in the first place attempted its synthesis by the general method developed in Parts III and IV (J., 1933, 489, 1163).

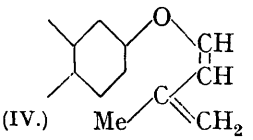
The condensation of methyl 4 : 5-dimethoxyphenoxyacetate-2-acetonitrile with phloroglucinol gave rise to the *keto-acid* (I, R = H) in comparatively good yield, but attempts to effect cyclisation of this compound in the usual manner were unsuccessful. Similarly, using phloroglucinol dimethyl ether, we obtained the *keto-acid* (I, R = Me), but likewise this compound apparently cannot be readily converted into (II, R = Me). The orientation of (I, R = Me) depends on its ferric chloride reaction, a test which has been found to be diagnostic for ketones of this type derived from phloroglucinol dimethyl ether (Robertson and collaborators, J., 1930, 21; 1931, 1245, 1704).



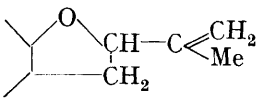
As there did not seem to be an immediate prospect of effecting the synthesis of (II, R = H), we turned our attention to a study of the hydrolytic fission of dehydro*apo*toxicarol. Under the usual conditions whereby members of the dehydrorotenone series and even dehydrodihydrotoxicarol itself are converted into acids of the derrisic acid type (I), dehydro-*apo*toxicarol is decomposed completely, but ultimately, by short treatment with warm 2% aqueous sodium hydroxide, we were able to convert the compound into the keto-acid (I, R = H), identical with the synthetic material. This result makes it clear that dehydro-*apo*toxicarol has the structure (II, R = H), in agreement with the fact that it forms a *diacetate*, and hence *apo*toxicarol may be represented by formula (III, R = H). Further, with methyl sulphate, *apo*toxicarol gives only a monomethyl ether (compare Clark, *loc. cit.*) and, since it is well known that in compounds of the type (III, R = H) a chelate system obtains and the hydroxyl in the *o*-position to the carbonyl group is difficult to methylate, this ether has the orientation (III, R = Me), which is supported by the fact that the compound gives a ferric chloride reaction.

By analogy with the other members of this series it is reasonably certain that the residue C_5 lost in the formation of *apo*toxicarol from toxicarol with the simultaneous generation of a new hydroxyl group has the isoprene skeleton. As has already been remarked by Clark (*loc. cit.*), methylation and acetylation experiments with *apo*toxicarol, toxicarol, and dehydro*apo*toxicarol, as well as the ferric chloride reaction of toxicarol, make it clear that the free phenolic hydroxyl group in toxicarol is in the *o*-position to the carbonyl group, *i.e.*, position 5 in *apo*toxicarol, thus accounting for the insolubility in dilute aqueous sodium hydroxide. Hence the C_5 residue in toxicarol is linked at the 7-hydroxyl group of

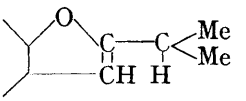
*apo*toxicarol. Since toxicarol contains only one ethylenic linkage, this residue, C_5H_8,* is not present as an ether of the type (IV) but forms part of a ring system (types V, VI, VII, or VIII).



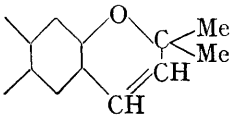
(IV.)



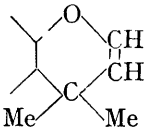
(V.)



(VI.)



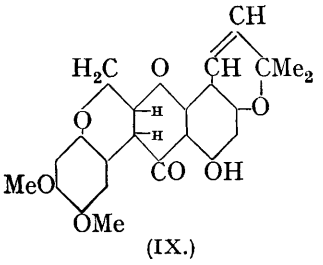
(VII.)



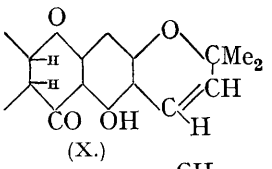
(VIII.)

The presence of a dihydrofuran residue of the tubaic acid type (V) as in rotenone is excluded because, unlike rotenone, toxicarol or dihydrotoxicarol cannot be reduced to give phenols of the rotenonic acid type by opening of the dihydrofuran ring and because toxicarol does not isomerise in the presence of mineral acid to give an *iso*toxicarol. A structure of the type (V), as well as the furan type (VI), is also excluded by the fact that the hydrolytic fission of toxicarol is accompanied, as we have now shown, by the formation of acetone. The benzofuran usneol, containing a phloroglucinol nucleus, is stable to alkali under similar conditions (Curd and Robertson, J., 1933, 714, 1173), and in any case fission of a furano-compound of the type (VI) would be expected to give *iso*butyric acid and not acetone.

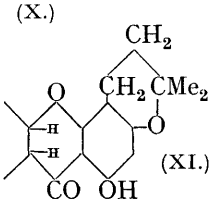
On the other hand, the formation of acetone can be readily explained on the basis of ring systems of the *gem*-substituted chromen types (VII) and (VIII). By analogy with deguelin (J., 1932, 1380), which on treatment with hot alkali has now been found to give rise to acetone, it would seem not unlikely that toxicarol embodies the 2 : 2-dimethyl-Δ^3-chromen residue (VII) and that the production of acetone by hydrolytic fission of both deguelin and toxicarol follows the lines suggested by Heilbron and his co-workers (J., 1927, 2007) for the decomposition of 2 : 2-diphenyl-Δ^3-chromens.



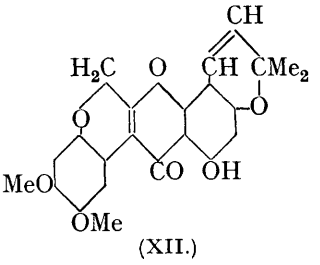
(IX.)



(X.)



(XI.)



(XII.)

We therefore tentatively suggest that toxicarol is represented by formula (IX) or (X), *i.e.*, 5-hydroxydeguelin type (J., 1932, 1384). Further, dihydro- and dehydro-toxicarol are similarly related to the corresponding deguelin derivatives and may be represented by structures typified in formulæ (XI) and (XII) respectively.

The toxicarol used was prepared by the method of Cahn and Boam (*J. Soc. Chem. Ind.*, 1935, **54**, 42T) from " Sumatra-type " resin, for which we are much indebted to Messrs. Cooper, McDougall, and Robertson, Ltd., London.

Experimental.

4 : 5-*Dimethoxyphenoxyacetic Acid*-2-*phloracetophenone* (I, R = H).—A mixture of powdered methyl 4 : 5-dimethoxyphenoxyacetate-2-acetonitrile (J., 1933, 1163) (3·8 g.), anhydrous

* The formation of *apo*toxicarol from toxicarol entails a net loss of the elements C_5H_6 and, therefore, the C_6 skeleton in this ring system must carry 8 H atoms.

phloroglucinol (7 g.), and fused zinc chloride (4 g.) in anhydrous ether (150 c.c.) was slowly saturated with hydrogen chloride with occasional shaking; after 8—9 hours the solid suspension was replaced by a thick, dark brown oil. Six days later the ethereal layer was decanted and the syrupy residue was washed five times with dry ether (100 c.c.) and heated with water (150 c.c.) on the steam-bath for 3 hours. Next day the solid product was collected, well washed, and extracted with aqueous sodium bicarbonate (50 c.c.). Acidification of the extract with hydrochloric acid precipitated the *keto-acid* as a reddish solid, which crystallised from 60% aqueous acetone (charcoal) as a *dihydrate* in colourless diamond-shaped plates, m. p. 215° (decomp.) (Found: loss on drying at 105° in a high vacuum, 8·5. $C_{18}H_{18}O_9,2H_2O$ requires H_2O, 8·7%. Found in anhydrous material: C, 56·9; H, 4·7. $C_{18}H_{18}O_9$ requires C, 57·1; H, 4·8%). The compound is sparingly soluble in benzene or ligroin and readily soluble in methyl or ethyl alcohol. With alcoholic ferric chloride it gives a deep red coloration.

4 : 5-*Dimethoxyphenoxyacetic Acid*-2-(2′ : 4′-O-*dimethyl*)*phloracetophenone* (I, R = Me).—Ether (150 c.c.) containing methyl 4 : 5-dimethoxyphenoxyacetate-2-acetonitrile (2·7 g.), phloroglucinol dimethyl ether (7 g.), and zinc chloride (4 g.) was saturated with hydrogen chloride and kept for 6 days. After being washed with ether, the oily product was heated with water (150 c.c.) on the steam-bath for 3 hours, and 2 days later acidic material was isolated from the crude solid by means of aqueous sodium bicarbonate; on hydrolysis with 5% hydrochloric acid at 100° the residue insoluble in aqueous sodium bicarbonate gave a further quantity of acid. The *keto-acid* was isolated from material, which had been once crystallised from aqueous methyl alcohol, by 26 extractions with boiling benzene and then purified by repeated crystallisation from 60% methyl alcohol (charcoal), from which it separated in colourless elongated plates, m. p. 196—197° (Found, C, 58·9; H, 5·2. $C_{20}H_{22}O_9$ requires C, 59·1; H, 5·4%). This compound is readily soluble in ethyl acetate, chloroform, and alcohol, and gives a wine-red ferric chloride reaction.

The final residue insoluble in benzene appeared to contain a small amount of the isomeric keto-acid.

Hydrolysis of Dehydroapotoxicarol with Alkali.—The preparation of *apo*toxicarol was carried out according to directions of Clark (*loc. cit.*), but it was found that when the hydrolysis was carried out in an atmosphere of nitrogen the crude product was much cleaner.

A mixture of dehydro*apo*toxicarol (0·1 g.), prepared from *apo*toxicarol by Clark's method (*loc. cit.*), acetic anhydride (1 c.c.), and pyridine (0·5 c.c.) was boiled for 2 minutes and then kept for 24 hours. On isolation the *diacetate* formed pale yellow needles from alcohol–acetic acid, m. p. 202° [Found: C, 61·9; H, 4·4; CH_3·CO, 23·7. $C_{18}H_{12}O_7(CO{\cdot}CH_3)_2$ requires C, 62·0; H, 4·2; CH_3·CO, 20·2%].

(A) Dehydro*apo*toxicarol (0·5 g.) was refluxed with alcohol (18 c.c.) containing 50% aqueous potassium hydroxide (3·75 c.c.) and zinc dust (0·75 g.) for 1 hour, and the cooled solution acidified with hydrochloric acid and extracted six times with ether. Removal of the solvent left a residue, from which derric acid was isolated by means of aqueous sodium bicarbonate and identified by comparison with an authentic specimen, m. p. and mixed m. p. 168°; a small amount of a phenolic product was isolated with ether from the sodium bicarbonate solution of the crude derric acid.

(B) A suspension of dehydro*apo*toxicarol (0·5 g.) in 2% aqueous sodium hydroxide (18 c.c.) was heated on the water-bath for 20 minutes, cooled, acidified with hydrochloric acid, and kept at 0° for 16 hours. The resulting 4 : 5-dimethoxyphenoxyacetic acid-2-phloracetophenone was purified by means of aqueous sodium bicarbonate and, on crystallisation from aqueous acetone, formed almost colourless, diamond-shaped prisms of the dihydrate identical in every way with an authentic specimen, m. p. and mixed m. p. 214° (Found in material dried over sulphuric acid: C, 52·2; H, 5·2; H_2O, 8·9. Calc. for $C_{18}H_{18}O_9,2H_2O$: C, 52·2; H, 5·3; H_2O, 8·7%. Found in a specimen dried at 105° in a high vacuum: C, 57·4; H, 5·0%).

Hydrolysis of Toxicarol and Deguelin with Alkali.—(A) A solution of toxicarol (3 g.) in absolute alcohol (56 c.c.) and water (45 c.c.) containing potassium hydroxide (22·5 g.) was heated on the water-bath for 3½ hours, cooled, acidified, and distilled on the steam-bath. Treatment of the distillate with 2 : 4-dinitrophenylhydrazine (Brady's method, J., 1931, 756) gave a precipitate of acetone-2 : 4-dinitrophenylhydrazone (1 g.; about 57% of the theoretical), m. p. 124—125°, which formed yellow needles from alcohol, m. p. 127—128°, identical with an authentic specimen.

Hydrolysis of toxicarol (2·2 g.) under the conditions used for the preparation of *apo*toxicarol gave rise to acetone (0·25 g. of 2 : 4-dinitrophenylhydrazone; about 19—20% of the theoretical; the yield of *apo*toxicarol under the same conditions is approx. 10% of the theoretical).

(B) Deguelin (0·2 g.) was refluxed with boiling 33% alcoholic potassium hydroxide (10 c.c.) for

7·5 hours and the acidified solution distilled. Addition of 2 : 4-dinitrophenylhydrazine to the distillate gave a precipitate (0·02 g.) of acetone-2 : 4-dinitrophenylhydrazone. Under less drastic conditions, *e.g.*, heating with 20% alcoholic potassium hydroxide on the steam-bath for 4 hours, acetone is not formed.

UNIVERSITY OF LIVERPOOL. [*Received, April 8th,* 1935.]