318. *Experiments on the Synthesis of Rotenone and its Derivatives. Part XIV. The Structure of Toxicarol.*

By Stephen W. George and Alexander Robertson.

By the stepwise degradation of the methyl ether of dehydrodihydrotoxicarolic acid, derric acid and 5-hydroxy-7-methoxy-2 : 2-dimethylchroman have been isolated. From this result in conjunction with the established structure of dihydrotoxicarolic acid, structures for dehydrodihydro-, dehydro-, and dihydro-toxicarol, toxicarol, and dihydrodeoxytoxicarol have been deduced.

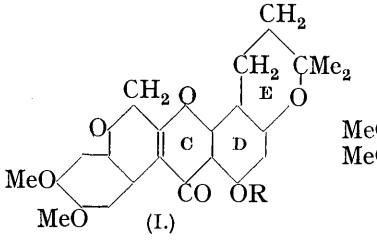
The syntheses of the reference compounds, 5-hydroxy-7-methoxy- and 7-hydroxy-5-methoxy-2 : 2-dimethylchroman, by way of the corresponding chromanones are described.

In connexion with preliminary attempts on the synthesis of dehydrodihydrotoxicarol the preparation of *allo*dihydrotoxicarolic acid and of 5 : 7-dihydroxychromeno-(3′ : 4′ : 2 : 3)-chromone is described.

From experiments on the methylation of dehydrodihydrotoxicarol and the degradation of the resulting *methyl ether* described in the present communication, evidence has been obtained enabling us to make a decision between the alternative formulæ which have been deduced for toxicarol, dihydro-, dehydro- and dehydrodihydro-toxicarol severally from the established structure of dihydrotoxicarolic acid (Part V, J., 1935, 681; Part XII, this vol., p. 279). Dehydrodihydrotoxicarol and not toxicarol or dihydrotoxicarol was chosen as the starting point of the investigation because with the latter compounds, not only is there a possibility of complications arising from the enolisation of the carbonyl group during the methylation process (toxicarol and dihydrotoxicarol yield *O*-diacetyl derivatives), but in the presence of alkaline reagents the stability of the chromanochromanone system is uncertain. Moreover, with toxicarol the instability of the 2 : 2-dimethyl-

Δ^3-chromen residue in the presence of hot aqueous-alcoholic sodium or potassium hydroxide (cf. Part V, *loc. cit.*) is an additional complication.

Although attempts to methylate dehydrodihydrotoxicarol by prolonged treatment with methyl iodide and potassium carbonate in boiling acetone were unsuccessful, the replacement of the iodide by methyl sulphate resulted in a satisfactory yield of the methyl ether; the same product was obtained when the alkylation was effected with methyl iodide and silver oxide in warm anisole. The properties, including the negative ferric reaction, of this substance clearly show that it is an ether and not a *C*-methyl derivative. On hydrolysis with aqueous-alcoholic sodium hydroxide it gave rise to *O-methyldihydrotoxicarolic acid* which, on the basis of the structure of dihydrotoxicarolic acid (II, R = H), can have either formula (II, R = Me) or (V), depending on whether the parent chromenochromone has the angular (I, R = Me) or the linear structure (IV, R = Me) with reference to rings C, D, and E.



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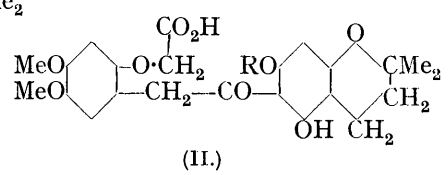

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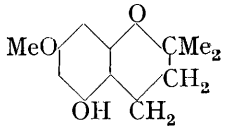

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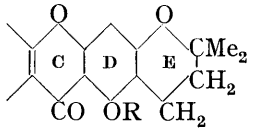
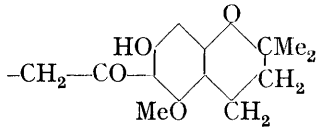
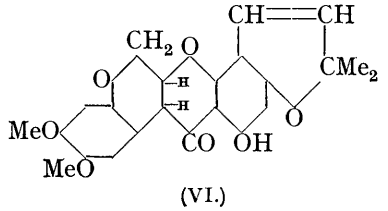




(V.)

Fission of *O*-methyldihydrotoxicarolic acid by means of hot concentrated potassium hydroxide furnished derric acid and the liquid *5-hydroxy-7-methoxy-2 : 2-dimethylchroman* (III), which was conveniently characterised by formation of the distinctive yellow *p-nitrobenzoate*, identical with a specimen obtained from the synthetical chroman methyl ether. The production of the ether (III) in this manner clearly proves that *O*-methyldihydrotoxicarolic acid must have the structure (II, R = Me), a result which is possible only if *O*-methyldehydrodihydrotoxicarol has formula (I, R = Me). Hence dehydrodihydrotoxicarol is represented by the expression (I, R = H). In this connexion it may be noted that the relative positions of the carbonyl and hydroxyl groups in dihydrotoxicarolic acid have been deduced from the properties of dehydrodihydrotoxicarol (Part V, *loc. cit.*; cf. Clark, *J. Amer. Chem. Soc.*, 1932, **54**, 2537), but the formation of the 5-hydroxy-7-



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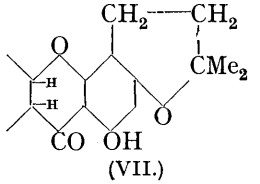

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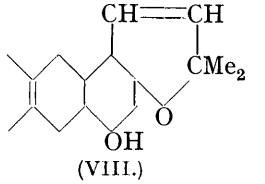

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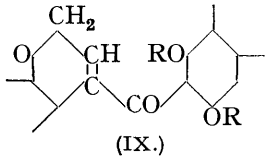

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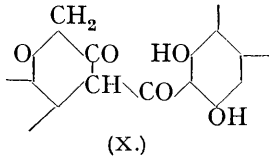
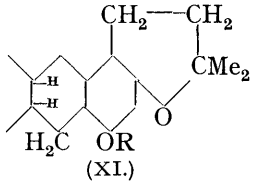


(X.)



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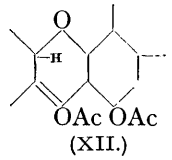


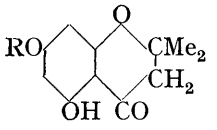
(XII.)

methoxy-2 : 2-dimethylchroman (III) by degradation of *O*-methyldehydrodihydrotoxicarol now affords independent proof that this acid has the structure (II, R = H) and not the

alternative (XVI, R = H). The latter structure would imply that dehydrodihydrotoxicarol has formula (XVII), the methyl ether of which on degradation would give rise finally to (XV) and not to (III).

In the formation of dehydro-compounds of the toxicarol series, *i.e.*, a change from the chromanochromanone to the chromenochromone type, according to standard procedures there is no reason to suppose that the former system undergoes scission with the production of intermediate types, *e.g.*, (IX, R = H) and (X), capable of undergoing cyclisation in two ways and thus resulting in the formation of products having the structure type (I) and (IV), a mechanism by which angular dehydro-derivatives, type (I), could arise from the parent chromanochromanones (toxicarol and dihydrotoxicarol) having the linear structure with respect to rings C, D, and E. This view finds ample support in the behaviour of dehydrotoxicarol on hydrogenation. With a platinum catalyst this compound gives dihydrotoxicarol, identical with that obtained directly from toxicarol (Clark, *J. Amer. Chem. Soc.*, **1931**, **53**, 2264), whilst with a palladium–charcoal catalyst there is formed dehydrodihydrotoxicarol (see p. 1540) which can be subsequently converted into dihydrotoxicarol by means of a platinum catalyst. Consequently, it is clear that toxicarol, dihydrotoxicarol, and dehydrotoxicarol possess the same angular structure with respect to rings C, D, and E as is present in dehydrodihydrotoxicarol (I, R = H) and therefore may be represented by formulæ (VI), (VII), and (VIII) respectively. Thus the angular structure of toxicarol and its derivatives is the same as that obtaining in rotenone, deguelin, and tephrosin, and by analogy it seems probable that sumatrol may be similarly constituted (cf. this vol., p. 497). The possibility that toxicarol and its dihydro-derivative normally exist in the isomeric form, type (IX, R = H), analogous to a chalkone derived from a flavanone, is excluded because on hydrogenation a substance having this structure would be expected to give rise to an analogue of dihydrorotenol (Butendandt, *Annalen*, **1928**, **464**, 253) by saturation of the ethylenic linkage. Further, although on acetylation toxicarol gives rise to an *O*-diacetyl derivative due to the enolisation of the carbonyl group, direct evidence for which has now been secured by the formation of an *oxime*, this diacetate is represented by formula type (XII) and not by (IX, R = Ac), a structure which, moreover, appears to be excluded by its behaviour on catalytic reduction. Under specific conditions (Clark, *J. Amer. Chem. Soc.*, **1931**, **53**, 2264; cf. Part VIII, J., **1936**, 212) *O*-diacetyltoxicarol is converted into a mixture of *O*-diacetyldihydrotoxicarol, type (XII), and *O*-acetyldihydrodeoxytoxicarol. The latter substance cannot be further hydrogenated, or acetylated to a diacetyl derivative, and on deacetylation yields dihydrodeoxytoxicarol which is devoid of a carbonyl group and does not give a ferric reaction. On account of their properties and relationship to toxicarol, it appears reasonably certain that dihydrodeoxytoxicarol and its acetate are represented by formula (XI, R = H) and (XI, R = Ac) respectively.

The authentic 5-hydroxy-7-methoxy-2 : 2-dimethylchroman (III) required for the present work was prepared by the partial methylation of the chromanone (XIII, R = H) and subsequent reduction of the resulting *methyl ether* (XIII, R = Me) by Clemmensen's method. Although the chroman (III) has been isolated as a viscous liquid which has not so far solidified, it was conveniently characterised by formation of the well-crystallised *p*-nitrobenzoate.



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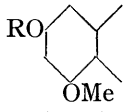

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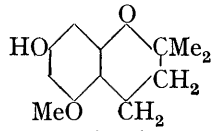


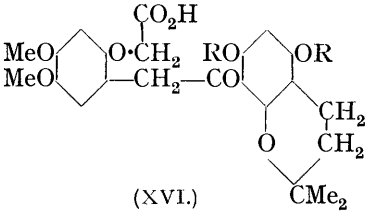
(XV.)

The orientation of (XIII, R = Me), and consequently that of (III), follows from the fact that, owing to chelation of the carbonyl and hydroxyl groups at the 4- and the 5-position, compounds of the type (XIII, R = H) are preferentially alkylated at the *p*-position to the carbonyl group. In agreement with the structure (XIII, R = Me), the ether is sparingly soluble in dilute aqueous sodium hydroxide and gives a strong ferric reaction.

In order to obtain confirmatory evidence of the orientation of (III) the isomeric *ether*

(XV) was synthesised. Benzylation of 5 : 7-dihydroxy-2 : 2-dimethylchromanone gave rise to the *benzyl ether* (XIII, R = CH_2Ph), the properties of which are similar to those of the corresponding methyl ether (XIII, R = Me) and therefore determine its orientation. Methylation of (XIII, R = CH_2Ph) gave rise to (XIV, R = CH_2Ph), which on debenzylation by reductive fission with hydrogen and a palladium–charcoal catalyst furnished 7-*hydroxy*-5-*methoxy*-2 : 2-*dimethylchromanone* (XIV, R = H). On reduction according to the method of Clemmensen, this compound yielded the *chroman* (XV), and, since the structure of the latter ether has been independently confirmed in these laboratories (private communication from Dr. T. S. Subramaniam) that of the isomeride (III) is conclusively established.

In the course of attempts to synthesise dehydrodihydrotoxicarol by application of the standard chromenochromone synthesis (Part III, J., 1933, 489), methyl 2-cyanomethyl-4 : 5-dimethoxyphenoxyacetate was condensed with 5 : 7-dihydroxy-2 : 2-dimethylchroman according to the method of Hoesch, but on hydrolysis of the resulting viscous oil the only crystalline product obtained was an acid which, since it is isomeric and not identical with dihydrotoxicarolic acid, must have the structure (XVI, R = H). The orientation ascribed to this compound, which we have named allo*dihydrotoxicarolic acid*, is in agreement with the fact that application of the Gattermann reaction to 5 : 7-dihydroxy-2 : 2-dimethylchroman yields only the 8-formyl derivative (this vol., p. 286).



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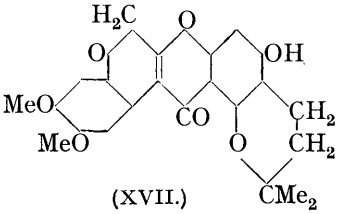

(XVII.)

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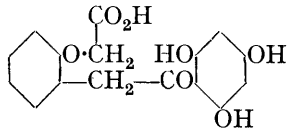

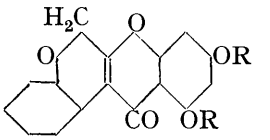

(XIX.)

By cyclisation of the acid (XVI, R = H) with boiling acetic anhydride containing sodium acetate, it was hoped to obtain the acetate of *allo*dehydrodihydrotoxicarol (XVII), but the only product which we were able to isolate from the reaction mixture appears to be a *hydrate* of *O*-diacetyl*allo*dihydrotoxicarolic acid (XVI, R = Ac), which on deacetylation with warm alcoholic hydrochloric acid regenerated the parent acid.

In view of the negative results obtained in attempting the cyclisation of the acid (XVI, R = H) and of 4 : 5-dimethoxyphenoxyacetic acid-2-phloracetophenone (Part V, *loc. cit.*), we investigated the cyclisation of the analogous *keto-acid* (XVIII), which was obtained in a satisfactory yield by the condensation of methyl 2-cyanomethylphenoxyacetate and phloroglucinol according to the standard procedure. On being boiled with acetic anhydride and sodium acetate, this compound gave rise to a small yield of the *diacetate* (XIX, R = Ac), which on deacetylation in the usual manner furnished the *chromenochromone* (XIX, R = H), and in consequence of this result we are re-investigating the cyclisation of 4 : 5-dimethoxyphenoxyacetic acid-2-phloracetophenone and related compounds. In connexion with these experiments it is of interest to note that, whereas according to Clark (*loc. cit.*) cyclisation of dihydrotoxicarolic acid (II, R = H) gives only *O*-acetyldehydrodihydrotoxicarol (I, R = Ac), it would normally be expected that this reaction would also yield the isomeride (IV, R = Ac). In our experiments on the conversion of dihydrotoxicarolic acid (II, R = H) into dehydrodihydrotoxicarol (I, R = H), we have found that, in addition to (I, R = Ac), the reaction mixture contains a considerable quantity of acidic material having a negative ferric reaction (presumably the diacetate of dihydrotoxicarolic acid) and a resinous residue from which a small amount of crystalline neutral product was obtained when it was treated with methyl-alcoholic sodium hydroxide. This

substance, which does not appear to be identical with (I, R = H), may possibly be *iso*-dehydrodihydrotoxicarol (IV, R = H), but owing to lack of material we have been unable to make a detailed examination of it.

Experimental.

5-Hydroxy-7-methoxy-2 : 2-dimethylchroman (III).—A mixture of 5 : 7-dihydroxy-2 : 2-dimethylchromanone (Part XII, *loc. cit.*) (2 g.), methyl iodide (0·5 c.c.), potassium carbonate (4 g.), and acetone (100 c.c.) was heated on the steam-bath for 3 hours; after 1½ hours more iodide (0·5 c.c.) and more carbonate (2 g.) were added. On isolation, the product was found to consist of almost pure *5-hydroxy-7-methoxy-2 : 2-dimethylchromanone* (XIII, R = Me), which separated from dilute alcohol in thick needles, m. p. 65—66° [Found : C, 65·0; H, 6·2; OMe, 15·0. $C_{11}H_{11}O_3$(OMe) requires C, 64·9; H, 6·3; OMe, 14·0%]. This compound, which is soluble in warm acetic acid or benzene and sparingly soluble in light petroleum or 2% aqueous sodium hydroxide, gives a bright red coloration with alcoholic ferric chloride. The 2 : 4-*dinitrophenylhydrazone* formed squat, blood-red prisms, m. p. 254°, from hot ethyl acetate (Found : N, 13·8. $C_{18}H_{18}O_7N_4$ requires N, 13·9%).

A mixture of the chromanone methyl ether (2 g.), amalgamated zinc dust (80 g.), alcohol (20 c.c.), concentrated hydrochloric acid (34 c.c.), and water (46 c.c.) was kept at room temperature for 2 days and, after the addition of 12% hydrochloric acid (20 c.c.), was heated on the water-bath for 1 hour and then refluxed for 6 hours (more acid, 20 c.c., was added). On being isolated with ether, the resulting *chroman* was purified by distillation in a vacuum and obtained as a viscous, pale reddish-brown oil (0·9 g.), b. p. 125—128°/0·4 mm., which has not been induced to crystallise [Found : OMe, 14·8. $C_{11}H_{13}O_2$(OMe) requires OMe, 14·9%]. It is soluble in 2% aqueous sodium hydroxide and does not give a ferric reaction. Interaction of this compound (0·5 g.) with *p*-nitrobenzoyl chloride (0·6 g.) in pyridine (5 c.c.) at about 50° for several days gave rise to the p-*nitrobenzoate* (0·8 g.), which was separated from a little *p*-nitrobenzoic acid by means of aqueous sodium bicarbonate and then crystallised from 95% alcohol (charcoal), forming characteristic, squat, yellow prisms, m. p. 122°, which retained their colour after repeated purification (charcoal) (Found : C, 63·8; H, 5·4; N, 4·1. $C_{19}H_{19}O_6N$ requires C, 63·9; H, 5·3; N, 3·9%).

7-Benzyloxy-5-methoxy-2 : 2-dimethylchromanone (XIV, R = CH_2Ph).—Benzylation of 5 : 7-dihydroxy-2 : 2-dimethylchromanone (2 g.) by means of benzyl bromide (1·4 c.c., added in two portions) and excess of potassium carbonate in boiling acetone (100 c.c.) in the course of 3 hours gave rise to *5-hydroxy-7-benzyloxy-2 : 2-dimethylchromanone* (XIII, R = CH_2Ph) (2·2 g.), which separated from alcohol in thick colourless rods, m. p. 134°, giving a reddish-brown coloration with alcoholic ferric chloride (Found : C, 72·5; H, 6·1. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·0%). The 2 : 4-*dinitrophenylhydrazone* formed deep red rods, m. p. 242°, from hot alcohol (Found : N, 11·8. $C_{24}H_{22}O_7N_4$ requires N, 11·7%).

Methylation of the benzyl ether (2 g.) with excess of methyl iodide and potassium carbonate in boiling acetone (100 c.c.) for 6 hours yielded *7-benzyloxy-5-methoxy-2 : 2-dimethylchromanone*, which separated from aqueous alcohol as a *monohydrate* in colourless elongated, slender rods, m. p. 81—82°, insoluble in aqueous sodium hydroxide and having a negative ferric reaction [Found : C, 69·1; H, 6·6; OMe, 9·1. $C_{18}H_{17}O_3$(OMe),H_2O requires C, 69·1; H, 6·7; OMe, 9·4%]. This compound, which is readily soluble in alcohol or ethyl acetate, gave a 2 : 4-*dinitrophenylhydrazone*, forming slender red needles, m. p. 215°, from ethyl acetate (Found : N, 11·3. $C_{25}H_{24}O_7N_4$ requires N, 11·4%). The *anhydrous* chromanone, which was obtained by drying the hydrated variety over phosphoric oxide in a vacuum, separated from light petroleum in hexagonal prisms, m. p. 111° [Found : C, 73·1; H, 6·5; OMe, 10·3. $C_{18}H_{17}O_3$(OMe) requires C, 73·1; H, 6·4; OMe, 9·9%].

7-Hydroxy-5-methoxy-2 : 2-dimethylchromanone (XIV, R = H).—Debenzylation of 7-benzyloxy-5-methoxy-2 : 2-dimethylchromanone (5 g.), dissolved in acetic acid (300 c.c.), was effected with hydrogen (approx. 450 c.c. absorbed) and a palladium–charcoal catalyst (from 2 g. of charcoal and 0·2 g. of palladium chloride) in 2 hours. After the separation of the catalyst, the greater part of the solvent was distilled, the residue was diluted with water and neutralised with sodium bicarbonate, and the *chromanone* (3·0 g.) was isolated with ether. Crystallised from 95% alcohol, it formed colourless, elongated rectangular prisms, m. p. 208—209° (Found : C, 64·7; H, 6·3. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%). The 2 : 4-*dinitrophenylhydrazone* separated from hot ethyl acetate in short, dark red rods, m. p. 275° (decomp.) (Found : N, 14·0. $C_{18}H_{18}O_7N_4$ requires N, 13·9%).

7-Hydroxy-5-methoxy-2 : 2-dimethylchroman (XV).—A mixture of 7-hydroxy-5-methoxy 2 : 2-dimethylchromanone (2 g.), alcohol (20 c.c.), 15% hydrochloric acid (100 c.c.), and amalgamated zinc dust (80 g.) was kept for 2 days, treated with 12% hydrochloric acid (20 c.c.), heated on the steam-bath for 1 hour, and after the addition of more 12% hydrochloric acid (20 c.c.) boiled for 6 hours. On isolation with ether, the *chroman* (1·3 g.) crystallised from light petroleum (b. p. 80—100°) in short rectangular prisms, m. p. 103—104°, readily soluble in aqueous sodium hydroxide and having a negative ferric reaction [Found : C, 69·3; H, 7·8; OMe, 15·0. $C_{11}H_{13}O_2(OMe)$ requires C, 69·2; H, 7·7; OMe, 14·9%]. Interaction of the chroman (0·3 g.) and *p*-nitrobenzoyl chloride (0·4 g.) in pyridine (10 c.c.) at 50—60° for several days gave the p-*nitrobenzoate* (0·4 g.), which formed almost colourless elongated rods, m. p. 143°, from 95% alcohol (Found : N, 4·0. $C_{19}O_{19}O_6N$ requires N, 3·9%).

[With T. S. SUBRAMANIAM.] *Condensation of Phloroglucinol Monomethyl Ether and ββ-Dimethylacryl Chloride.*—To a solution of the ether (12 g.) in nitrobenzene containing aluminium chloride (14 g.), ββ-dimethylacryl chloride (Part XII, *loc. cit.*) (from 10 g. of the acid) was added during 1 hour, and 7 days later the reaction mixture was treated with ice (300 g.) and hydrochloric acid (40 c.c.) and thoroughly extracted with ether. After being washed with dilute hydrochloric acid and then with aqueous sodium bicarbonate, the combined extracts were evaporated, and the nitrobenzene distilled by means of steam. After the nitrobenzene had been removed, a quantity of solid separated from the subsequent aqueous distillate, and on recrystallisation from dilute alcohol this gave 5-hydroxy-7-methoxy-2 : 2-dimethylchromanone in elongated slender prisms (0·9 g.), m. p. 63—64°, identical with a specimen prepared by methylation of 5 : 7-dihydroxy-2 : 2-dimethylchromanone.

After the separation of 5-hydroxy-7-methoxy-2 : 2-dimethylchromanone, the residual hot aqueous liquors were decanted from the insoluble resinous material, and on being kept for several weeks gradually deposited a small amount of 7-hydroxy-5-methoxy-2 : 2-dimethylchromanone, which formed colourless prisms (0·2 g.), m. p. and mixed m. p. 209—210°, from alcohol.

Toxicarol Oxime.—A mixture of toxicarol (0·5 g.), hydroxylamine hydrochloride (0·5 g.), and pyridine (5 c.c.) was heated on the water-bath for 7—8 hours and then treated with ice-water. Crystallisation of the precipitated product (0·4 g.) from 50% alcohol and then from 95% alcohol gave the *oxime* in colourless irregular plates, m. p. 236—237° (Found : C, 65·0; H, 5·6; N, 3·3. $C_{23}H_{23}O_7N$ requires C, 65·0; H, 5·5; N, 3·3%).

Dehydrodihydrotoxicarol Methyl Ether (I, R = Me).—It has been found that, whereas on hydrogenation with a platinum catalyst dehydrotoxicarol is converted into dihydrotoxicarol (Clark, *J. Amer. Chem. Soc.*, 1931, **53**, 2268), yet when a palladium–charcoal catalyst is employed dehydrodihydrotoxicarol is obtained. Hydrogenation of dehydrotoxicarol (Clark, *loc. cit.*) (1 g.), dissolved in acetic acid (500 c.c.), with a palladium–charcoal catalyst (from 2 g. of charcoal and 0·2 g. of palladium chloride) and hydrogen (approx. 130 c.c. absorbed) at atmospheric pressure was complete in about 35 minutes. The filtered solution was evaporated in a vacuum, and the residual dehydrodihydrotoxicarol crystallised from methyl alcohol–chloroform, forming elongated yellow rods, m. p. 259°, identical with a specimen prepared from dihydrotoxicarol (Clark, *loc. cit.*).

A mixture of dehydrodihydrotoxicarol (1 g.), methyl sulphate (0·5 c.c.), acetone (40 c.c.), and potassium carbonate (3 g.) was heated on the steam-bath for 8 hours (a test sample of the product did not give a ferric reaction). On isolation, the *ether* (0·7 g.) separated from methyl alcohol–chloroform and then from alcohol–chloroform in almost colourless, squat prisms, m. p. 216°, having a negative ferric reaction [Found, in material dried in a high vacuum at 100° : C, 67·8; H, 5·7; OMe, 21·0. $C_{21}H_{15}O_4(OMe)_3$ requires C, 67·9; H, 5·7; OMe, 21·9%].

Methylation of dehydrodihydrotoxicarol (0·5 g.) with excess of silver oxide and of methyl iodide in boiling anisole (20 c.c.) during 5 days afforded the same methyl ether (0·3 g.), m. p. 216°, after purification from chloroform–methyl alcohol.

Dihydrotoxicarolic Acid Monomethyl Ether (II, R = Me).—The foregoing methyl ether (4·2 g.) dissolved in a warm mixture of alcohol (50 c.c.) and 30% aqueous potassium hydroxide (20 c.c.) in the course of 10 minutes, and after the addition of more 30% aqueous potassium hydroxide (20 c.c.) and zinc dust (0·5 g.) the solution was vigorously refluxed for 30 minutes, filtered, and acidified with excess dilute hydrochloric acid. Next day the precipitated *acid* (4 g.) was collected, well washed with water, and crystallised several times from dilute acetone (charcoal), forming clusters of colourless, elongated prisms, m. p. 203° after slight sintering at 198—200° (Found : C, 62·6; H, 6·3. $C_{24}H_{28}O_9$ requires C, 62·6; H, 6·1%). This compound, which readily dissolves in aqueous sodium bicarbonate with the liberation of carbon dioxide,

is moderately soluble in alcohol or acetone and gives a wine-red coloration with alcoholic ferric chloride.

Hydrolytic Fission of Dihydrotoxicarolic Acid Monomethyl Ether.—When a mixture of the acid (2·4 g.), alcohol (20 c.c.), and 50% aqueous potassium hydroxide (25 c.c.) was heated (oil-bath) in nitrogen to 200—205° during 20 minutes, the alcohol distilled, and at about 160—180° the dipotassium derivative of the acid, which appeared to be sparingly soluble in the concentrated aqueous potassium hydroxide, separated as a light brown layer. The mixture was then maintained at 205° for 15 minutes, cooled, and dissolved in water (150 c.c.), and the solution acidified with a slight excess of hydrochloric acid. After having been neutralised with sodium bicarbonate, the solution was thoroughly extracted with ether (6 × 50 c.c.), and the combined extracts washed, dried, and evaporated. The residual viscous brown residue was digested with three successive portions of boiling light petroleum (b. p. 40—60°) (40 c.c.), leaving a small amount of brown resin, and on being evaporated the combined light petroleum extracts gave a moderately viscous light brown oil, a specimen of which did not crystallise in the presence of a crystal of 7-hydroxy-5-methoxy-2 : 2-dimethylchroman. By means of excess of *p*-nitrobenzoyl chloride and warm pyridine, the main portion of the product was converted into the *p*-nitrobenzoate, which separated from 95% alcohol in characteristic yellow prisms, m. p. 123°, identical in every way with an authentic specimen (Found : C, 63·8; H, 5·1; N, 4·0%).

After the separation of the phenolic fraction, the aqueous liquors were acidified with excess hydrochloric acid and extracted with ether (8 × 50 c.c.). Evaporation of the washed and dried extracts left derric acid (0·7 g.), which separated from ethyl acetate–light petroleum (b. p. 60—80°) and then ether–ligroin in needles, m. p. 168°, undepressed by admixture with a synthetical specimen, m. p. 168° (Part II; J., 1932, 1380).

allo*Dihydrotoxicarolic Acid* (XVI, R = H).—When ether (200 c.c.) containing 5 : 7-dihydroxy-2 : 2-dimethylchroman (Part XII, *loc. cit.*) (5 g.), methyl 2-cyanomethyl-4 : 5-dimethoxyphenoxyacetate (Part IV, J., 1933, 1163) (5 g.), and well-powdered zinc chloride (6 g.) was slowly saturated with hydrogen chloride, the solid was gradually replaced by a viscous red oil. After 6 days more ether (50 c.c.) was added, the solvent decanted, and the oily residue triturated with fresh solvent (4 × 50 c.c.) to remove hydrogen chloride and hydrolysed with water (50 c.c.) on the steam-bath for 2 hours. Next day the semi-solid was collected and boiled with alcohol (60 c.c.) and 15% aqueous sodium hydroxide (40 c.c.), containing zinc dust (1 g.), for 1 hour, and the filtered solution acidified with excess dilute hydrochloric acid. The *acid* (3 g.) thus precipitated was purified by means of aqueous sodium bicarbonate and then by crystallisation from aqueous methyl alcohol (charcoal), forming a *hydrate* in transparent rectangular prisms, m. p. 148°, which gave a purple coloration with alcoholic ferric chloride (Found : C, 59·4; H, 6·3. $C_{23}H_{26}O_9,H_2O$ requires C, 59·5; H, 6·0%. Found, in material dried at 100° in a high vacuum : C, 61·7; H, 5·8. $C_{23}H_{26}O_9$ requires C, 61·9; H, 5·8%). Mixed with dihydrotoxicarolic acid, this compound melted at about 136°.

A mixture of the acid (1 g.), sodium acetate (0·6 g.), and acetic anhydride (14 c.c.) was gently boiled for 15 minutes, and after cooling, the anhydride was decomposed with alcohol (10 c.c.) and water (50 c.c.). Next day the solid (0·6 g.) was collected, well washed, and crystallised from methyl alcohol (charcoal), giving the *monohydrate* of the *O*-diacetyl derivative of the acid in tiny, colourless, rectangular prisms, m. p. 211—212°, soluble in dilute aqueous sodium hydroxide and having a negative ferric reaction (Found, in material dried in a desiccator at room temperature : C, 58·9; H, 5·6. $C_{27}H_{30}O_{11},H_2O$ requires C, 59·1; H, 5·8%). On being dried at 100° in a high vacuum, this compound appeared to undergo slight decomposition [Found : C, 61·0; H, 5·7. Calc. for $C_{27}H_{30}O_{11}$: C, 61·1; H, 5·7%. Calc. for $C_{25}H_{24}O_8$ (*O*-diacetyl*allo*-dihydrotoxicarol) : C, 66·4; H, 5·3%].

The same diacetate, m. p. and mixed m. p. 211°, was obtained when the *allo*dihydrotoxicarolic acid (1·4 g.) was vigorously refluxed with acetic anhydride (20 c.c.) and sodium acetate (1 g.) for 35 minutes. Deacetylation of this acetate (0·2 g.) by means of boiling alcohol (8 c.c.) containing concentrated hydrochloric acid (2 c.c.) for 15 minutes, and subsequent addition of water (50 c.c.) to the cooled solution, afforded *allo*dihydrotoxicarolic acid, which separated from aqueous methyl alcohol as the hydrate, m. p. 147°, having the characteristic ferric reaction.

[With William Hilton.] *Phenoxyacetic Acid-2-phloracetophenone* (XVIII).—The condensation of methyl 2-cyanomethylphenoxyacetate (Part III, J., 1933, 492) (3 g.) and phloroglucinol (5 g.) in ether (50 c.c.) was effected with zinc chloride (3 g.) and excess of hydrogen chloride in the course of 4 days. After the addition of more solvent (100 c.c.), the ethereal layer was decanted, and the viscous dark brown product washed with ether (4 × 25 c.c.) and heated with water (100 c.c.) on the steam-bath for 1½ hours. Next day, the *keto-acid* was isolated and, after

having been separated from a small amount of a gelatinous solid by means of aqueous sodium bicarbonate (50 c.c.), formed colourless elongated prisms, m. p. 184—185° after sintering at 180°, and containing solvent of crystallisation, from 60% alcohol (Found, in a specimen dried in a high vacuum at 100°: C, 60·4; H, 4·7. $C_{16}H_{14}O_7$ requires C, 60·3; H, 4·4%). With alcoholic ferric chloride this compound gave a wine-red coloration.

5 : 7-*Dihydroxychromeno*-(3′ : 4′ : 2 : 3)-*chromone* (XIX, R = H).—The foregoing acid (1 g.) was boiled with acetic anhydride (14 c.c.) and sodium acetate (0·6 g.) for 15 minutes, the excess anhydride was decomposed with alcohol (10 c.c.) and water (24 c.c.), and next day the light brown *diacetate* (XIX, R = Ac) was collected, washed, and crystallised from ethyl alcohol (charcoal), forming colourless needles (0·2 g.), m. p. 240—241° after slight sintering at about 217°, having a negative ferric reaction (Found: 65·5; H, 4·2. $C_{20}H_{14}O_7$ requires C, 65·6; H, 3·9%).

Deacetylation of this compound (0·3 g.), dissolved in boiling alcohol (10 c.c.), was effected with concentrated hydrochloric acid (2·5 c.c.) in 15 minutes, and the *chromenochromone* precipitated by the addition of saturated brine (50 c.c.). Purified from 60% alcohol, this compound formed colourless needles (0·1 g.), m. p. 256—257°, readily soluble in alcohol or acetone and giving an olive-green coloration with alcoholic ferric chloride (Found: C, 68·2; H, 3·8. $C_{16}H_{10}O_5$ requires C, 68·1; H, 3·6%).

Cyclisation of Dihydrotoxicarolic Acid.—A mixture of the acid (2·7 g.), sodium acetate (1·5 g.), and 95% acetic anhydride (15 c.c.) was vigorously refluxed for 15 minutes, the greater part of the anhydride was removed in a vacuum, and the residue was treated with water (100 c.c.). Two days later the solid was collected, washed, and ground with excess of aqueous sodium bicarbonate. The insoluble residue was well washed with water and dissolved in boiling methyl alcohol. On cooling, the solution quickly deposited the acetate of dehydrodihydrotoxicarol in pale yellow prisms, m. p. 240°, after recrystallisation from acetic acid. Acidification of the aqueous sodium bicarbonate extract gave a precipitate of acidic material, which had only a faint ferric reaction and on deacetylation with *N*-aqueous sodium hydroxide furnished dihydrotoxicarolic acid identical with an authentic specimen.

The dark brown methyl-alcoholic filtrate from the crude acetate was warmed to about 50°, mixed with half its volume of 2*N*-aqueous sodium hydroxide, kept at room temperature for ½ hour, and poured into excess water. To facilitate the isolation of the colloidal product thus precipitated, it was adsorbed on a little charcoal and then extracted from the air-dried charcoal by means of boiling acetic acid. On cooling, the extract deposited a small amount of material which after repeated crystallisation from alcohol–acetic acid formed clusters of tiny yellow prisms, m. p. 238—239° (decomp.), sparingly soluble in alcohol and giving a dark green coloration with alcoholic ferric chloride.

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