# SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

## Part XXXI. A Synthesis of 7-Hydroxy-chromeno-(3′: 4′: 2: 3)-chromone

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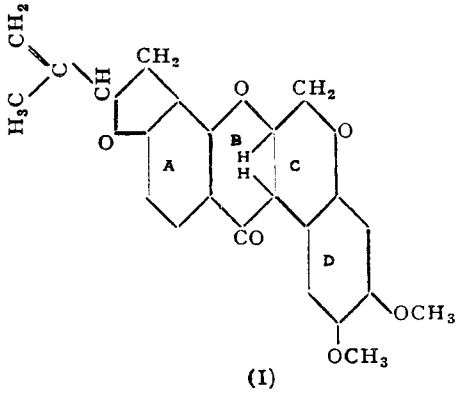
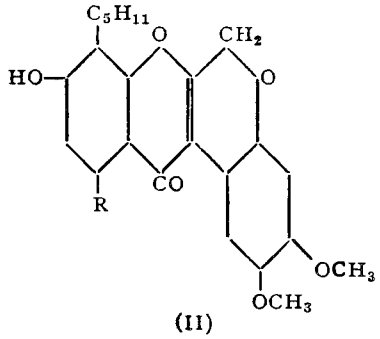
ONE of the most important natural insecticides of plant origin is rotenone (I). A number of related compounds also occur in nature and all these contain a chromanone unit (rings A and B) and a chroman unit (rings C and D). These are therefore known as chromano-chromanones.

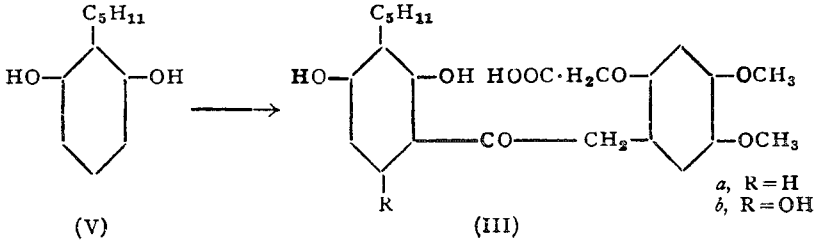
The structure of rotenone has been based mainly on a number of degradation studies. The most important synthetic support for this structure is the synthesis of dehydro-tetrahydro-rotenone (II *a*) by Robertson.[1] It had been found earlier[2] that when this compound is heated with alcoholic alkali in presence of zinc dust, it gives rise to tetrahydro-derrisic acid (III *a*) which could be reconverted into (II *a*) by heating with sodium acetate and acetic anhydride.[3] This conversion was considered by Robertson to take place through the hypothetical stages (IV *a*) and (IV *b*). He prepared (III *a*) starting with tetrahydro-tubanol (V).



(I)

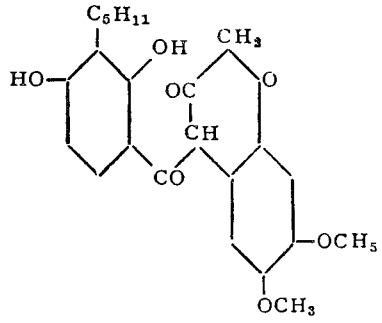


(II)

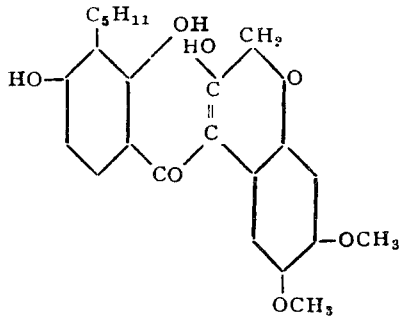


(V) (III)

*a*, R = H
*b*, R = OH

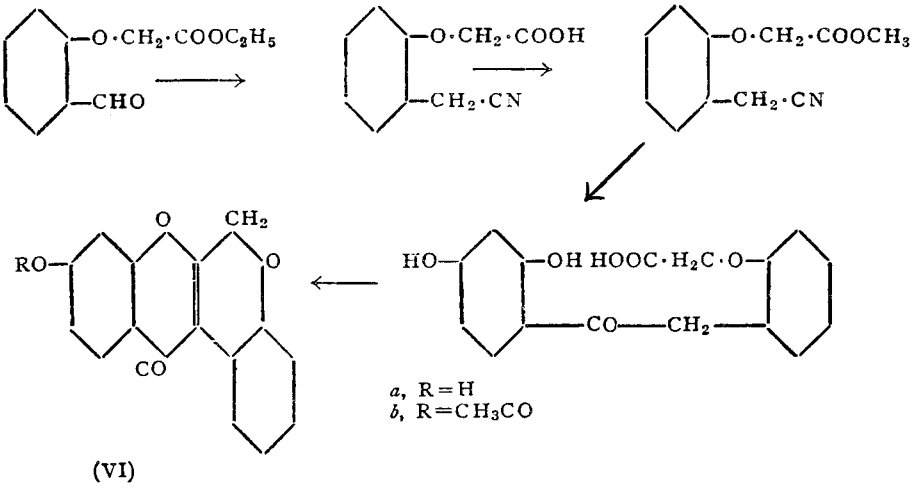


(IV *a*)



(IV *b*)

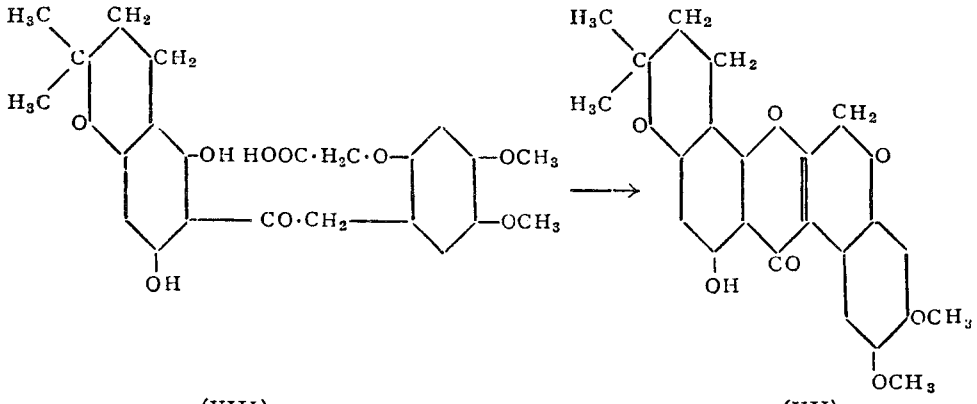
The above synthesis represented the first method of preparation of chromeno-chromones. Following it, simpler chromeno-chromones were also synthesised by Robertson.[4] The simplest of these, 7-acetoxy-chromeno-(3′ : 4′ : 2 : 3)-chromone (VI *b*) was obtained starting from salicyl aldehyde and passing through the steps indicated below.



*a*, R = H
*b*, R = $CH_3CO$

(VI)

Although this method is of wide applicability, it cannot be used for the unambiguous synthesis of 8-alkyl-5: 7-dihydroxy-chromeno-(3: 4′: 2: 3)-chromones of dehydro-tetrahydro-sumatrol type. The trihydroxy acid (III *b*) can give rise to two products, *viz.*, the 6-alkyl and 8-alkyl chromeno-chromones. Kenny, Robertson and George[5] stated that only an 8-alkyl derivative is formed in such a case and they reported the conversion of tetra-hydro-sumatrolic acid (III *b*) into dehydro-tetrahydro-sumatrol (II *b*). Similarly dehydro-dihydro-toxicarol (VII) and not the isomeric compound is said to be formed by treating dihydro-toxicarolic acid (VIII) with sodium acetate and acetic anhydride.[6]



(VIII) (VII)

In the above conversions, both the chromene and chromone units are simultaneously formed. Attempts have been made by Richards, Robertson and Ward[7] to build up first a chromene unit and then a chromone unit, evidently with a view to more firmly establish the presence of such structures in rotenone and its analogues, but these experiments have not been successful.

Although the presence of chromanone and chroman units in rotenone and related compounds is indicated by the degradation reactions, no degradation products containing either the chromanone or chroman unit intact have so far been obtained. As already mentioned, the conversion of acids of tetrahydro-derrisic type (III *a*) into chromeno-chromones postulates some intermediates which have not been isolated. It seemed therefore necessary to evolve a new route for the synthesis of chromeno-chromones in which these ring systems are formed step by step by unambiguous methods. The ambiguities that exist in the original synthesis of 5: 7-dihydroxy-8-alkyl chromeno-chromones have already been pointed out and hence the new procedure should be free from this defect. Such a synthetic route has now been successfully explored.

For this purpose, a method based on the possible biogenetic evolution of the chromano-chromanone ring system would appear to have the best chance of success. No suggestion seems to have been so far made on its biogenesis. The occurrence of the following compounds suggests the stages of a reasonable scheme.

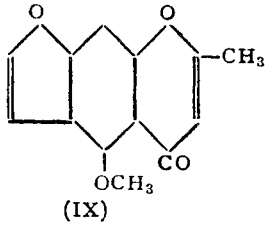
(1) Padmakastein, a simple representative of isoflavanones, was recently discovered by Narasimhachari and Seshadri.[8] It gives the Durham test characteristic of rotenone and related compounds.

(2) Though the synthetic work described in the earlier parts of this series[9, 10] relating to isogenistein and 8-methyl isogenistein do not support

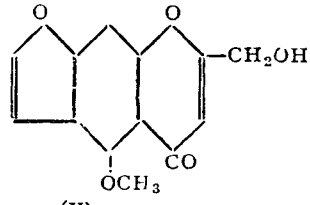
the constitutions given to certain components of soya beans, the isolation of *o*-hydroxy phenyl acetic acid as one of the products of their degradation would indicate that 2′-hydroxy isoflavone structures are present in them. There is no doubt that pterocarpin and homopterocarpin[12] are 2′-hydroxy isoflavan derivatives in which this hydroxyl group is engaged in ether formation.

(3) Although no 2-methyl isoflavone is known so far to occur in nature, the simpler chromones contain a number of representatives having a methyl group in the 2-position. Four such occur in *Eugenia caryophyllata*.[13] Further examples are provided by kellin, visnagin (IX) and chellol (X) isolated from *Ammi visnaga*.[14] Among these, chellol has a hydroxymethyl group in place of the methyl group. Consequently, the postulation of 2-methyl isoflavanones as intermediates in the evolution of rotenone and related compounds has some basis.

(4) There is particular interest in the occurrence of visnagin (IX) and chellol (X) in the same plant *Ammi visnaga*. These two compounds are closely related and visnagin may be considered to arise from chellol by reduction or conversely, chellol can result by oxidation of visnagin.



(IX)



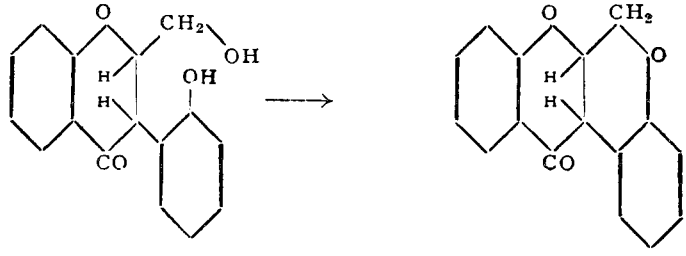
(X)

Such examples of C-methyl and C-carbinol derivatives occurring together are found elsewhere also. Among the anthraquinones, physcion and teloschistin are found to occur together in the lichen *Teloschistes flavicans*.[15] A similar pair is chrysophanol and aloe-emodin, isolated from *Cascara sagrada*.[16]

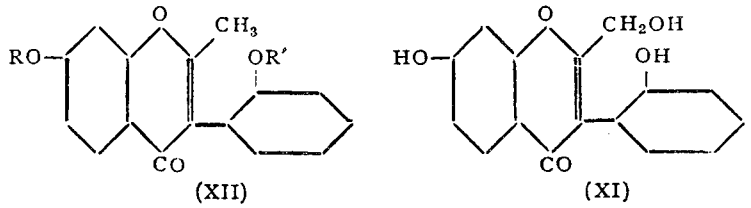
In some Indian strains of the lichen *Parmelia tinctorum*, the depside atranorin is found to occur along with the depsidone, nor-stictic acid[17] or salazinic acid.[18] These three compounds are closely related and represent different stages of oxidation. The second and third have a methyl and a carbinol group respectively in the corresponding positions. As indicated earlier,[19] it is quite possible that the carbinol group represents an earlier stage and the methyl group arises as the result of reduction.

Taking all the abovementioned points into consideration, it is reasonable to conclude that the chroman ring of chromano-chromanones arises by

the elimination of water involving the 2′-hydroxyl group and the carbinol present in the 2-position of an isoflavanone system as indicated below.



As the first step in the adoption of the above biogenetic scheme in the laboratory, the synthesis of the chromeno-chromone (VI *a*) has now been attempted. The main stage is the preparation of a 2′-hydroxy isoflavone with a carbinol group in the 2-position (XI). For this purpose, the related 2-methyl isoflavone (XII *a*) is prepared as the necessary intermediate.



(XII) (XI)

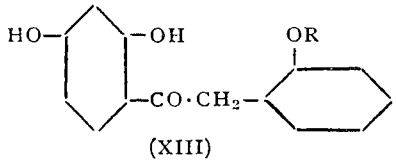
*a*, R = R′ = H
*b*, R = R′ = $CH_3CO$
*c*, R = H, R′ = $CH_3$
*d*, R = R′ = $CH_3$
*e*, R = $CH_3$, R′ = H

It is well known that a methyl group situated in the 2-position of chromones and isoflavones is highly reactive and yield 2-styryl derivatives on condensation with aromatic aldehydes.[20, 21] In a recent publication[22] was described the successful substitution of a hydrogen atom of the 2-methyl group of isoflavones with a bromine atom using N-bromo succinimide as reagent. This reaction has now been applied to the case of the diacetoxy methyl isoflavone (XII *b*) and the product subsequently converted into 7-hydroxy-chromeno-(3′ : 4′ : 2 : 3)-chromone (VI *a*).

The required isoflavone (XII *a*) could presumably be obtained from 2 : 4 : 2′-trihydroxy phenyl benzyl ketone (XIII *a*) and therefore the preparation of this ketone was attempted by the Hoesch condensation of *o*-hydroxy phenyl acetonitrile[4] with resorcinol. The ketimine hydrochloride was formed in a good yield. On hydrolysis with water, a product melting at 146–48° and having a negative ferric reaction in alcoholic solution was

obtained. However it gave a deep pink colour with ferric chloride in aqueous solution and it was identified as *o*-hydroxy phenyl acetic acid. No trace of the ketone could be detected. Complete fission seems to be taking place during hydrolysis. Similar results have been obtained by using C-methyl phloroglucinol in place of resorcinol in the above Hoesch condensation and it appears that 2′-hydroxy phenyl benzyl ketone cannot be prepared by the Hoesch reactions.

The required 2-methyl-7 : 2′-diacetoxy isoflavone (XII *b*) has been prepared by an alternative route. Condensation of *o*-methoxy phenyl acetonitrile[9] with resorcinol gives 2 : 4-dihydroxy-2′-methoxy phenyl benzyl ketone (XIII *b*). On heating with acetic anhydride and sodium acetate, the dihydroxy ketone (XIII *b*) yields 2-methyl-7-acetoxy-2′-methoxy isoflavone, which on hydrolysis gives rise to the 7-hydroxy compound (XII *c*). By demethylation with aluminium chloride in benzene solution, it is converted into 2-methyl-7 : 2′-dihydroxy isoflavone (XII *a*). This does not give any colour with alcoholic ferric chloride. Acetylation of the product yields the required diacetate (XII *b*).

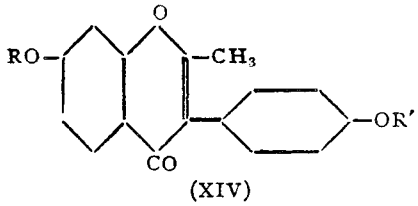



(XIII)

*a*, R=H
*b*, R=$CH_3$

On heating 2-methyl-7 : 2′-diacetoxy isoflavone with one mole of N-bromo succinimide in carbon tetrachloride solution in presence of benzoyl peroxide, succinimide slowly crystallises out. The mother-liquors yield 2-bromomethyl-7 : 2′-diacetoxy isoflavone. When this compound is heated with alcoholic hydrochloric acid for 2 hours, hydrolysis of the acetyl groups takes place and simultaneously the bromine atom is replaced by the hydroxyl group, giving rise to (XI). Attempts at closing the chromone ring by heating (XI) with acetic anhydride were not successful. However, it is found that when an acetone solution of this compound is heated with anhydrous potassium carbonate, one mole of water is removed and 7-hydroxy-chromeno-(3′ : 4′ : 2 : 3)-chromone (VI *a*) is obtained. This product, on acetylation, yields the acetate (VI *b*) melting at 182–83°. Robertson,[4] who obtained it by a different route discussed earlier, reported the melting point to be 178°. Hence these two substances may be considered to be identical. The present method therefore constitutes an unambiguous synthesis of a chromeno-chromone and confirms the validity of the earlier synthesis.[4]

Incidentally, methylation experiments have been carried out with 2-methyl-7: 2′-dihydroxy isoflavone (XII *a*). On heating with excess of methyl iodide and potassium carbonate in acetone solution, this compound gives rise to a product soluble in dilute sodium hydroxide. It is different from 2-methyl-7: 2′-dimethoxy isoflavone (XII *d*) prepared by methylation of 2-methyl-7-hydroxy-2′-methoxy isoflavone (XII *c*). Its composition and properties show that it is a monomethyl ether but it is not identical with the 2′-monomethyl ether (XII *c*) and therefore it should be 2-methyl-7-methoxy-2′-hydroxy isoflavone (XII *e*). Confirmation is provided by the acetate of this compound being also different from 2-methyl-7-acetoxy-2′-methoxy isoflavone. Under the same conditions of methylation, 2-methyl-7: 4′-dihydroxy isoflavone (XIV *a*) yields predominantly the dimethyl ether (XIV *b*) along with a small quantity of the 7-methyl ether (XIV *c*) an authentic sample of which is obtained conveniently by the partial demethylation[23] of (XIV *b*). There is thus clear indication that the 2′-hydroxy group is somewhat resistant to methylation. The absence of any ferric reaction in the case of 2-methyl-7: 2′-dihydroxy isoflavone (XII *a*) shows that there is no chelate bond between the carbonyl group and the 2′-hydroxyl group and therefore the resistance of the 2′-hydroxyl group to methylation should be due to other factors, probably steric. In the above methylation, besides the alkali-soluble monomethyl ether (XII *e*), a small amount of alkali insoluble dimethyl ether (XII *d*) is also formed and this shows that the resistance to methylation is not very strong.




(XIV)

*a*, R = R′ = H
*b*, R = R′ = $CH_3$
*c*, R = $CH_3$, R′ = H

## EXPERIMENTAL

*Hoesch condensation using o-hydroxy phenyl acetonitrile*

To a solution of *o*-hydroxy phenyl acetonitrile (8 g.) and dry resorcinol (8 g.) in dry ether (250 c.c.) was added fused zinc chloride (2 g.). The mixture was cooled to 0° and dry hydrogen chloride passed through it for 4 hours. After 16 hours, the ketimine hydrochloride was separated from the ether layer, washed with dry ether twice and then heated with water (150 c.c.) for

2 hours. On cooling to 0°, a small amount of dark solid separated. This was filtered off and the filtrate concentrated to 25 c.c. on a steam-bath and cooled. Colourless crystals separated. When recrystallised from water, the product was obtained as colourless rectangular prisms melting at 146–48°. A mixed melting point with an authentic sample of *o*-hydroxy phenyl acetic acid was not depressed. Yield, 5·5 g. It was soluble in aqueous sodium bicarbonate and gave a deep pink colour with ferric chloride in aqueous solution.

2 : 4-*Dihydroxy-2'-methoxy phenyl benzyl ketone* (*XIII* b)

Resorcinol (12 g.) and *o*-methoxy phenyl acetonitrile[9] (13 g.) were dissolved in dry ether (150 c.c.) and zinc chloride (2 g.) was added. Dry hydrogen chloride was passed for 5 hours through the mixture, cooled in an ice-bath. It was left overnight in the ice-chest. The ether layer was decanted off from the heavy dark red oily ketimine hydrochloride which was then washed with dry ether and heated with water (150 c.c.) for 2 hours in a water-bath. The sticky solid that came out on leaving overnight in the refrigerator was separated by decanting off the aqueous layer. It was then macerated with cold alcohol (10 c.c.) when a colourless solid separated. It was filtered and washed with a small amount of ice-cold alcohol. When crystallised from the same solvent, 2 : 4-dihydroxy-2'-methoxy phenyl benzyl ketone was obtained as colourless square plates and prisms melting at 159–60°. Yield, 6·3 g. It gave a reddish pink colour with alcoholic ferric chloride. It dissolved in dilute sodium carbonate to give a colourless solution (Found: C, 70·1; H, 5·5; $C_5H_{14}O_4$ requires C, 69·8; H, 5·4%).

2-*Methyl-7-acetoxy-2'-methoxy isoflavone*

The above ketone (4 g.) was heated with fused sodium acetate (8 g.) and acetic anhydride (50 c.c.) for 12 hours at 170–80° and the solution poured on crushed ice. After 4 hours, most of the acetic acid was carefully neutralised with dilute sodium hydroxide. On leaving overnight, a sticky solid separated. The aqueous layer was decanted off and residue crystallised from alcohol twice. 2-Methyl-7-acetoxy-2'-methoxy isoflavone separated as long colourless rectangular rods and prisms melting at 113–15°. Yield, 2·3 g. It was easily soluble in hot alcohol (Found: C, 70·4; H, 5·3; $C_{19}H_{16}O_5$ requires C, 70·4; H, 4·9%).

2-*Methyl-7-hydroxy-2'-methoxy isoflavone* (*XII* c)

The above acetate (2·1 g.) was dissolved in alcohol (100 c.c.) and treated with concentrated sulphuric acid (4·5 c.c.). The solution was refluxed for 2 hours. On cooling the hydroxy compound crystallised out. Yield,

1·65 g. When recrystallised from alcohol twice, it was obtained in the form of very thick colourless rectangular prisms melting at 225–27°. It did not give any colour with alcoholic ferric chloride and was soluble in dilute sodium carbonate (Found: C, 72·1; H, 5·0; $C_{17}H_{14}O_4$ requires C, 72·4; H, 5·0%).

*2-Methyl-7: 2′-dimethoxy isoflavone* (*XII* d)

The above hydroxy isoflavone (0·5 g.) in acetone (50 c.c.) was heated with dimethyl sulphate (0·2 c.c.) and potassium carbonate (2 g.) for 4 hours. The acetone solution was separated from the potassium salts by filtration and then distilled. The residue was treated with water. After keeping overnight, the solid was filtered and crystallised from alcohol. 2-Methyl-7: 2′-dimethoxy isoflavone came out as long colourless rectangular rods melting at 138–39°. Yield, 0·4 g. (Found: C, 72·9; H, 5·4; $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%). It was insoluble in dilute sodium hydroxide and was easily soluble in alcohol, ethyl acetate and acetone.

*2-Methyl-7: 2′-dihydroxy isoflavone* (*XII* a)

2-Methyl-7-hydroxy-2′-methoxy isoflavone (1 g.) was suspended in dry benzene (50 c.c.) and treated with anhydrous aluminium chloride (3 g.) and the mixture refluxed for 2 hours. The dark semi-solid residue left on distillation of the solvent was treated with ice and hydrochloric acid (6 c.c.). After 2 hours, the colourless solid was filtered and purified by dissolution in aqueous sodium carbonate (10%). 2-Methyl-7: 2′-dihydroxy isoflavone crystallised from alcohol as colourless rhombohedral prisms melting at 241–43° (decomp.). Yield, 0·6 g. It did not give any colour with alcoholic ferric chloride (Found: C, 72·0; H, 4·7; $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%).

In later experiments, it was found that this dihydroxy isoflavone could be directly and conveniently obtained from 2-methyl-7-acetoxy-2′-methoxy isoflavone which is easily soluble in benzene unlike 2-methyl-7-hydroxy-2′-methoxy isoflavone. In this case, deacetylation and demethylation take place simultaneously by the treatment described in the above para.

*2-Methyl-7: 2′-diacetoxy isoflavone* (*XII* b)

The above dihydroxy compound (1·6 g.) was heated with acetic anhydride (20 c.c.) and pyridine (3 c.c.) for 2 hours at 150° and the solution poured on crushed ice. The colourless precipitate was filtered after 15 hours and crystallised from alcohol when the diacetate separated as colourless tablets melting at 117–19°. Yield, 1·35 g. It was easily soluble in alcohol (Found: C, 68·4; H, 4·4; $C_{20}H_{16}O_6$ requires C, 68·2; H, 4·6%).

*2-Bromomethyl-7 : 2′-diacetoxy isoflavone*

2-Methyl-7 : 2′-diacetoxy isoflavone (1·15 g.) was dissolved in carbon tetrachloride (40 c.c.). Freshly prepared and dried N-bromo succinimide (0·58 g., 1 mole) and benzoyl peroxide (0·05 g.) were added and the mixture refluxed on a water-bath. The heavy crystals of N-bromo succinimide dissolved slowly and after 15 hours, when all the N-bromo succinimide had dissolved, the clear solution was cooled. Succinimide crystallised out and the crystals floated on the solution. The crystals were filtered off and washed with a small quantity of carbon tetrachloride. These melted at 124–25° and a mixed melting point with an authentic sample of succinimide was not depressed. The filtrate was distilled and the residual oil washed twice with hot water. The residue was then extracted with ether and the ether solution dried over anhydrous sodium sulphate. The residue left on distillation of ether did not solidify on cooling to 0° and could not be obtained as a solid. Qualitative tests proved the presence of bromine in the substance. It was directly hydrolysed as described below.

*Hydrolysis to 2-hydroxymethyl-7 : 2′-dihydroxy isoflavone (XI)*

The above acetate (1·2 g.) was dissolved in alcohol (25 c.c.) and mixed with concentrated hydrochloric acid (25 c.c.). The mixture was refluxed on a water-bath for 2 hours. The solution was cooled, diluted with water (75 c.c.) and left overnight in the refrigerator. The precipitated solid was collected and crystallised from alcohol twice when 2-hydroxymethyl-7 : 2′-dihydroxy isoflavone (XI) separated as very thick colourless tablets melting at 219–22° (decomp.). Yield, 0·5 g. (Found: C, 67·3; H, 4·6; $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·2%). It was sparingly soluble in alcohol. It gave no test for the presence of bromine. The easy hydrolysis of the bromide under the above conditions is significant. The same effect is produced even when the compound is boiled for 5 minutes with a mixture of alcohol (1 part) and conc. hydrochloric acid (1 part).

*7-Hydroxy-chromeno-(3′ : 4′ : 2 : 3)-chromone (VI a)*

The above compound (0·3 g.) was dissolved in dry acetone (100 c.c.) and the solution refluxed for 10 hours with anhydrous potassium carbonate (3 g.). Acetone was then distilled off and water was added to the residue, when a clear solution was obtained. It was acidified with hydrochloric acid and the precipitated solid was collected and crystallised twice from alcohol, when it came out as pale yellow needles and rectangular rods melting at 240–42° (decomp.). Yield, 0·17 g. It was easily soluble in alcohol (Found: C, 72·3; H, 4·1; $C_{16}H_{10}O_4$ requires C, 72·2; H, 3·8%).

The acetate (VI *b*) was prepared by acetylation of the above hydroxy compound with acetic anhydride and pyridine. It was crystallised twice from alcohol and then from a mixture of alcohol and acetic acid, when it separated as colourless plates and needles melting at 182–83°. It was sparingly soluble in alcohol and benzene and easily in acetic acid. Robertson[4] who obtained it by a different route gives the m.p. as 178° (Found: C, 69·6; H, 4·2; $C_{18}H_{12}O_5$ requires C, 70·1; H, 3·9%).

2-*Methyl-7-methoxy-2'-hydroxy isoflavone* (*XII* e)

2-Methyl-7: 2'-dihydroxy isoflavone (0·4 g.) was dissolved in dry acetone (150 c.c.) and the solution refluxed with methyl iodide (3 c.c.) and anhydrous potassium carbonate (2 g.) for 3 hours. The potassium salts were filtered off and washed with acetone. The liquid residue left on distilling off acetone was treated with ether (100 c.c.) and aqueous sodium hydroxide (30 c.c. of 10%). The alkaline layer was drawn off and the ether solution extracted with small volumes of aqueous sodium hydroxide two more times. The combined alkaline solution was cooled to 0° and acidified. The colourless precipitate was filtered and crystallised from alcohol. 2-Methyl-7-methoxy-2'-hydroxy isoflavone separated as colourless rectangular plates and prisms melting at 238–40°. It was sparingly soluble in alcohol. It was insoluble in dilute sodium carbonate. Yield, 0·29 g. (Found: C, 72·0; H, 5·4; $C_{17}H_{14}O_4$ requires C, 72·4; H, 5·0%).

The ether solution left after extraction with alkali was washed with water and then distilled. The residue crystallised from alcohol as colourless rectangular rods melting at 138–39°. A mixed melting point with 2-methyl-7: 2'-dimethoxy isoflavone (XII *d*) described earlier was not depressed. Yield, 25 mg.

2-*Methyl-7-methoxy-2'-acetoxy isoflavone*

2-Methyl-7-methoxy-2'-hydroxy isoflavone (0·25 g.) was acetylated with acetic anhydride (4 c.c.) and pyridine (5 drops) at 140° during 2 hours. The acetate crystallised from alcohol as colourless stout rectangular prisms melting at 197–99°. It was very sparingly soluble in alcohol (Found: C, 70·5; H, 5·3; $C_{19}H_{16}O_5$ requires C, 70·4; H, 4·9%).

2-*Methyl-7-hydroxy-4'-methoxy isoflavone*

This compound was prepared earlier by Baker *et al.*[20] by the hydrolysis of its acetate with alcoholic potash. The hydrolysis has now been carried out using alcoholic sulphuric acid.

2-Methyl-7-acetoxy-4'-methoxy isoflavone (2·4 g.) was dissolved in alcohol (200 c.c.), concentrated sulphuric acid (8 c.c.) was added and the

mixture refluxed in a water-bath for 2 hours. Water (200 c.c.) was added and the alcohol removed by distillation. The precipitate was collected and crystallised from alcohol. 2-Methyl-7-hydroxy-4'-methoxy isoflavone was obtained as colourless stout prisms melting at 280–81°. Yield, 2·0 g.

2-*Methyl*-7 : 4'-*dimethoxy isoflavone* (*XIV* b)

2-Methyl-7-hydroxy-4'-methoxy isoflavone was prepared by Baker *et al.*[20] by the hydrolysis of its acetate with alcoholic potash. This hydrolysis has now been carried out more conveniently using alcoholic sulphuric acid, the procedure being the same as already described for the preparation of (XII *c*). For the methylation of this hydroxy compound, methyl sulphate and potassium hydroxide were employed in the past.[20] It is more convenient to use methyl sulphate and potassium carbonate in dry acetone solution. The product (XIV *b*) melts at 170–71°.

2-*Methyl*-7-*methoxy*-4'-*hydroxy isoflavone* (*XIV* c)

To a solution of the above compound (1 g.) in acetic anhydride (10 c.c.), hydriodic acid (15 c.c., d. 1·7) was added and the mixture heated in an oil-bath at 115–20° for 30 minutes and then cooled and diluted with aqueous sodium bisulphite (80 c.c.). The precipitate was collected and treated with aqueous sodium carbonate (10%). The undissolved residue was filtered and macerated with aqueous sodium hydroxide (5%) repeatedly. Almost the whole of it dissolved. The filtrate on acidification yielded 2-methyl-7-methoxy-4'-hydroxy isoflavone (0·5 g.). It came out as colourless rectangular prisms from alcohol and melted at 242–44° (Found: C, 72·5; H, 5·4; $C_{17}H_{14}O_4$ requires C, 72·4; H, 5·0%).

The acetate crystallised from alcohol as colourless needles and plates melting at 160–62° (Found: C, 69·9; H, 5·3; $C_{19}H_{16}O_5$ requires C, 70·4; H, 5·0%).

2-*Methyl*-7 : 4'-*dihydroxy isoflavone* (*XIV* a)

To a solution of 2-methyl-7-acetoxy-4'-methoxy isoflavone (1·7 g.) in hot benzene (50 c.c.), anhydrous aluminium chloride (6 g.) was added and the mixture refluxed for 2 hours. Benzene was then distilled off and ice and hydrochloric acid (10 c.c.) were added. After 2 hours, the precipitate was collected and purified by dissolution in aqueous sodium carbonate. When crystallised from alcohol, 2-methyl-7 : 4'-dihydroxy isoflavone was obtained as colourless thin rectangular plates melting at 315–18° (decomp.). Yield, 1·1 g. It was easily soluble in hot alcohol. It did not give any colour with ferric chloride in alcoholic solution. (Found: C, 71·8; H, 5·0; $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%).

The diacetate separated from alcohol as colourless thick rectangular prisms melting at 192–93° (Found: C, 68·4; H, 4·8; $C_{20}H_{16}O_6$ requires C, 68·0; H, 4·5%).

*Methylation of 2-methyl-7: 4'-dihydroxy isoflavone*

A solution of the above dihydroxy compound (0·4 g.) in acetone (150 c.c.) was treated with methyl iodide (3 c.c.) and potassium carbonate (3 g.). The mixture was refluxed for 3 hours. The potassium salts were filtered off and washed with acetone. The solvent was distilled off from the filtrate and water was added to the residue. The precipitate was collected and treated with aqueous sodium hydroxide (5%). The insoluble portion was filtered, washed with water and crystallised from alcohol. It separated as flat prisms melting at 170–71°, alone or when mixed with an authentic sample of 2-methyl-7: 4'-dimethoxy isoflavone (XIV *b*). Yield 0·18 g.

The sodium hydroxide solution was acidified and the precipitate collected and crystallised from alcohol. It was obtained as colourless rectangular prisms melting at 242–44°. A mixed melting point with an authentic sample of 2-methyl-7-methoxy-4'-hydroxy isoflavone (XIV *c*) was not depressed. Yield 25 mg.

## SUMMARY

The evolution of the chromano-chromanone unit present in rotenone and related compounds is of much interest. From a consideration of a number of structures occurring in nature, it is suggested that 2-hydroxy-methyl-2'-hydroxy isoflavanone or its equivalent is an intermediate and it undergoes ring closure by dehydration.

Based on this hypothesis, a synthesis of 7-hydroxy-chromeno-(3': 4'; 2: 3)-chromone has now been achieved. 2-Methyl-7: 2'-diacetoxy isoflavone is converted into a 2-bromomethyl compound by treatment with N-bromo succinimide. On hydrolysis and treatment with potassium carbonate in acetone, it yields 7-hydroxy-chromeno-(3': 4': 2: 3)-chromone.

Though attempts to prepare the required diacetoxy isoflavone directly from 2: 4: 2'-trihydroxy phenyl benzyl ketone have not been successful, it could be obtained starting from 2: 4-dihydroxy-2'-methoxy phenyl benzyl ketone and treatment of the intermediate 2-methyl-7-acetoxy-2'-methoxy isoflavone with aluminium chloride in benzene solution, followed by acetylation.

Methylation of 2-methyl-7: 2'-dihydroxy isoflavone with excess of methyl iodide gives rise to the 7-methyl ether, indicating the existence of a considerable difference in the reactivities of the 7 and 2'-hydroxyl groups. The

negative ferric reaction of these 2'-hydroxy compounds shows absence of chelation.

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