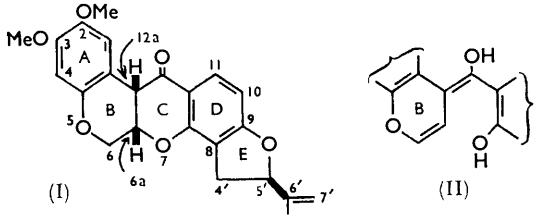
## 555. *Some Chemistry of the* B/C-*Ring System of Rotenoids.*

By L. Crombie, P. J. Godin, D. A. Whiting, and K. S. Siddalingaiah.

A scheme is drawn up to account for the behaviour of rotenone and rotenoids in basic media. Its validity is checked by isolation of various key substances. The chemical behaviour of the latter are studied and lend colour to the proposals. Certain chemical differences between the rotenone and the toxicarol series are explained by the influence of phenolic ionisation on the relative stability of two intermediates. Aspects of the chemistry of the B/C system are simultaneously examined.

This paper deals with certain aspects of the chemistry of the B/C ring system of rotenone (I) and its natural relatives, particularly the reactions in basic media. Such conditions cause racemisation of centres 6a and 12a, and Cahn and his colleagues [1] believed that an intermediate (IIa) * was implicated. Jennen,[2] extending views of Butenandt *et al.*,[3] preferred an intermediate (V). We consider Jennen's treatment of racemisation in the presence of weak bases to be essentially correct, but, with modifications, Cahn's intermediate is required to give a more complete picture of the effect of stronger bases on rotenone. In our view the annexed equilibria (III—X) are set up when the 6a proton is removed by a suitable base.



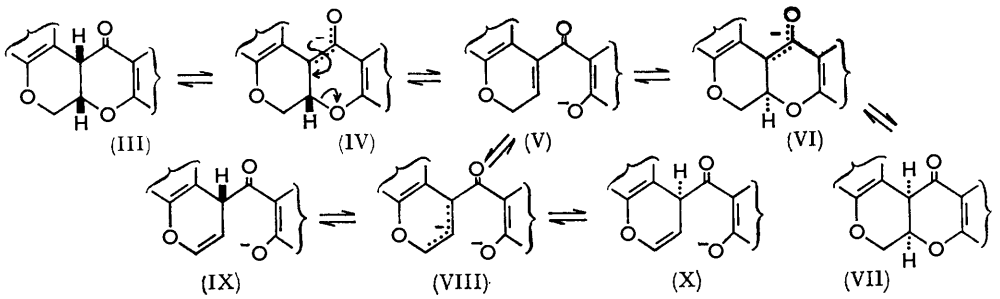

(I) (II)

Although the 6′,7′-olefinic linkage in rotenone is readily shifted by acid treatment *via* carbonium ion intermediates to give the benzofuran isorotenone (IIIc) (centres 6a and 12a being in this case unaffected), in basic medium the configuration at 5′ is unaffected.[1] The ion (IVa) initially formed by action of a base can re-accept a proton giving back unchanged rotenone (IIIa) or rotenone with a *trans*-B/C fusion; the latter is thermodynamically disfavoured and has not yet been isolated. By electronic shifts as shown, ion (IVa) equilibrates with the intermediate ion (Va) which can re-cyclise to give (IIIa) or (VIIa). The equilibrium mixture of diastereoisomers (III—VIIa) is " mutarotenone;" in the case of isorotenone the product is the racemate (III—VIIc).[1] This equilibration is brought

* The lower case letter following the Roman numeral indicates that the complete structural series to which it belongs is as follows: a, 5′β-rotenone; b, 6′,7′-dihydro-5′β-rotenone; c, isorotenone; d, deguelin (R = H) or toxicarol (R = OH); e, 4′,5′-dihydrodeguelin (R = H) or 4′,5′-dihydrotoxicarol (R = OH); f, 6a,12a-dihydro-6*H*-rotoxen-12-one; g, dihydrorotenonic acid; h, rotenonic acid. The omitted pieces of the structures are given in full on p. 2846.

[1] Cahn, Phipers, and Boam, *J.*, 1938, 513.
[2] Jennen, *Bull. Soc. chim. belges*, 1952, **61**, 536.
[3] (*a*) Butenandt and McCartney, *Annalen*, 1932, **494**, 17; (*b*) Butenandt and Hilgetag, *ibid.*, 1933, **506**, 158.

about by mild bases such as sodium acetate in ethanol, and the racemisation rate measures the formation of the ion (Vc). But in stronger bases the species (Vc) becomes involved in prototropic equilibration with the two diastereoisomers (IXa; 12aβ,5′β) and (Xa; 12aα,5′β) *via* the ion (VIII). Later in the paper the isolation of the pure key substances




(Va), (IXa), and (Xa) (protonated) is reported and their behaviour is examined; but, first, some points relating to mutarotenone will be cleared up.

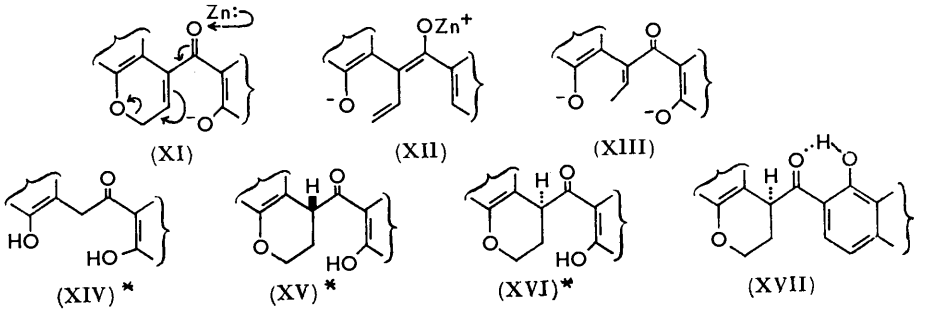
Cahn and his colleagues view mutarotenone as a " quasi-racemic compound " but there is no evidence that it is other than a mixture of two diastereoisomers of rather similar properties. Its special status seems to have arisen from the unsuitability of benzene and ether–benzene as solvents for fractional crystallisation of the mixture. About 50% of natural rotenone can be separated from mutarotenone by using its ability to form a carbon tetrachloride solvate, but preparations of the 6aα,12aα,5′β-component (epirotenone) have hitherto been amorphous.[1] In agreement with a very recent report,[4] we have obtained epirotenone (VIIa) crystalline as the half-methanol solvate and possessing a much higher rotation than earlier samples. A recent claim has been made [5] that if mutarotenone is melted for five minutes at 190° and is then crystallised from ethanol an almost quantitative yield of natural rotenone results. This would necessitate almost complete conversion of the 6aα,12aα,5′β- into 6aβ,12aβ,5′β-material and would be very difficult to explain. The claim seems incorrect as the optical activity of mutarotenone is virtually unaffected by heat; also, destruction of the optical activity at the 5′-centre by acid isomerisation to the isorotenone series gives products from both heated and unheated mutarotenone which have similar slight rotations. It is crystallisation from ethanol (or chloroform–methanol) which effects separation of natural rotenone from epirotenone.

The formation of rotenol (XV—XVIa) and derritol (XIVa) [6,7] when rotenone is treated with zinc and alkali is readily explained as involving the ion (Va). Rotenol arises from 1,4-reduction of the latter, whilst formation of derritol is rationalised as attack as in (XIa) to give (XIIa) which by prototropic shift gives (XIIIa). Reaction is completed by retroaldol condensation. As formulated, rotenol must be a mixture of two diastereoisomers but, although this substance has been mentioned on a number of occasions in the literature (m. p. 120°), its homogeneity has never been questioned. By careful crystallisation it has been possible to resolve the mixture, one diastereoisomer having m. p. 141—143°, $[\alpha]_D^{21}$ −245°, the other m. p. 90°, $[\alpha]_D^{21}$ +33°. These are not epimerised at position 6a by 1 hour's boiling with 5% ethanolic sulphuric acid but dilute alkali rapidly racemises them to an equilibrium mixture and, from this, " ordinary " 12aα,12aβ-rotenol is readily isolated. Connexion of the stereochemical formulæ (XVa) or (XVIa) with each diastereoisomer is not at present possible. (+)-Rotenol has a positive Cotton effect, and

[4] Takahashi, Fukami, and Nakajima, *Bull. Agric. Chem. Soc. Japan*, 1960, **24**, 123.
[5] Miyano and Matsui, *Chem. Ber.*, 1958, **91**, 2044.
[6] Butenandt, *Annalen*, 1928, **464**, 253.
[7] LaForge and Smith, *J. Amer. Chem. Soc.*, 1929, **51**, 2574.

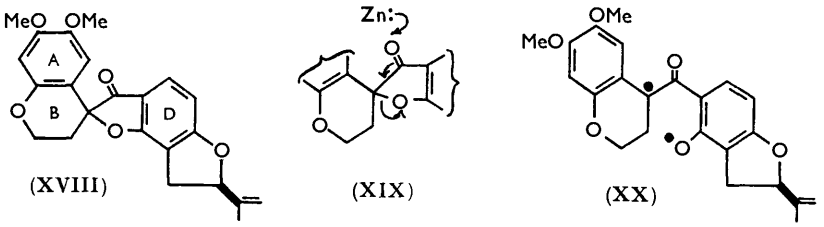
(—)-rotenol a negative one,† but the two curves are not enantiomorphic because of the superimposed constant plain curve due to the 5′-centre.

The first claim to have isolated the 6a,12a-dehydrorotenol (Va, protonated) was made by Haller and LaForge [8] who obtained a white crystalline product, m. p. 124°, when rotenol was treated with alkaline ferricyanide. Later [9] the claim was withdrawn and ring C (cf. XVIII) was thought to be five- or seven-membered. In our hands this reaction gives a powdery mixture of two diastereoisomers (5′β) from which one, corresponding with




* *o*-Phenolic ketones of this type are powerfully chelated, as shown by the position of their hydroxyl (emerging as a skirt from both sides of the C–H stretching complex) and ketone bands in the infrared spectra, thus (XVI) should conventionally be represented as (XVII), but this elaboration is here omitted.

the above, can be crystallised. Its structure is now dealt with. The 12-keto-grouping is intact for it can be reduced with borohydride and the resulting benzylic alcohol can be oxidised back to the original ketone with manganese dioxide. The ketone is not enolisable and its stretching vibration (1704 cm.$^{-1}$) supports a five-membered environment (rotenone 1674 cm.$^{-1}$). No hydroxyl group is present. This suggests that the spiro-structure (XVIII) is correct. Isorotenone is similarly converted into a spiro-compound analogous to (XVIII) ($\nu_{max.}$ 1709 cm.$^{-1}$; cf. isorotenone 1680 cm.$^{-1}$) but, being a racemate, this is at once obtained crystalline (cf. the structure of isorotenolone C,[10] which has $\nu_{max.}$ 1706 cm.$^{-1}$). Proposal (XVIII) is confirmed since the substance,[8] and its analogue from isorotenone, give rotenol and isorotenol respectively, without formation of derritol and isoderritol, when treated with zinc and alkali. This is clear from the representation (XIX). The spiro-compound (XVIII) and its relative are presumably formed in one-electron



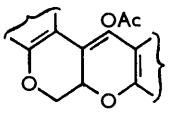

transfer reactions *via* a mono- or a di-radical (XX).[11] Treatment of isorotenol with lead tetra-acetate also gives some of the spiro-compound (iso-series, as XVIII). Refluxing of rotenol with alkaline manganese dioxide in dioxan gives both the spiro-compound (XVIII) (by a radical reaction) and 6a,12a-dehydrorotenone. Presumably, to account

† We thank Professor W. Klyne for this information.

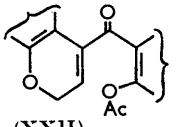
[8] Haller and LaForge, *J. Amer. Chem. Soc.*, 1931, **53**, 2271.
[9] Haller, *J. Amer. Chem. Soc.*, 1932, **54**, 2126.
[10] Crombie and Godin, preceding paper.
[11] Scott, *Proc. Chem. Soc.*, 1958, 195, and references cited there.

for the latter, 6a,12a-dehydrorotenol (Va; protonated) is formed which cyclises to mutarotenone and is then dehydrogenated (see below).

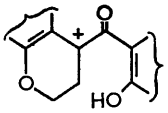
Jennen's work [2] is of particular interest in connection with the isolation of 6a,12a-dehydro-compound (Va; protonated). He reported that, if rotenone in benzene is treated with sodium or with solid sodium hydroxide, a solution of a sodium compound is formed which, if poured into acetylating mixture, gives a yellow acetate, m. p. 134°.



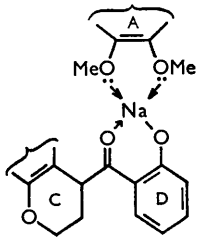
(XXI)



(XXII)



(XXIII)



(XXIV)

Degradative studies were not reported but because the ultraviolet spectrum of this substance differed from that of the enol acetate (XXIa) of rotenone, the new acetate was formulated as (XXIIa), *i.e.*, the trapped form of the intermediate in the racemisation of rotenone; the parent phenol (cf. Va) could not be isolated pure. More extensive investigation now supports Jennen's view and it has proved possible to isolate the pure, yellow, crystalline intermediate (Va; protonated), m. p. 96°, which is chelated (cf. XVII) and can be acetylated to give the acetate (XXIIa). In order that racemates rather than diastereoisomeric pairs should be formed during some chemical transformations, the acetate (XXIIc) from isorotenone has also been made. Jennen's preparation of the sodium compound is of interest. In a solvent of low dielectric constant the sodium compound will exist as an ion pair, inhibiting recyclisation, and either the ion pair of (V), (IV), or (VI) might accumulate. Jennen suggested that his benzene solution contained a polymeric system (XXIV) based on 4-co-ordinated sodium and this would explain why a derivative of (V) is preferred to one of (IV) or (VI) from which the co-ordination complex cannot be formed.

The acetate (XXIIa) showed acetyl (1761 cm.$^{-1}$) and conjugated ketone (1652 cm.$^{-1}$) bands in the infrared spectrum and absorbed 2 mol. of hydrogen catalytically to give an acetate which when hydrolysed gave the known 6',7'-dihydrorotenol (XV—XVIb). This establishes the skeleton and makes the 6a,12a-position of the double bond likely. This position was confirmed by acetylating rotenol and dehydrogenating the product with manganese dioxide in refluxing acetone, which gave the acetate (XXIIa) by rational synthesis. The structure and the place of compounds of the 6a,12a-dehydrorotenol type in rotenoid chemistry is illustrated by the following results.

When treated with the weak base sodium acetate in ethanol 6a,12a-dehydrorotenol (Va, protonated; 5'β) is readily converted into mutarotenone. The acetate (XXIIa) of this dehydro-compound and the corresponding isorotenone derivative (XXIIc) give mutarotenone and (±)-isorotenone, respectively, when refluxed with aqueous pyridine. When refluxed with acid, however, 6a,12a-dehydrorotenol and its acetate give the diastereoisomeric pair of spiro-compounds (XVIII) from which one was isolated crystalline: similarly 6a,12a-isodehydrorotenol acetate (XXIIc) gave the racemic spiro-compound (cf. XVIII). The course of this acid-catalysed cyclisation must be different from that involved in the other preparations of the spiro-compounds and is explained as requiring formation of the tertiary carbonium ion (XXIII) stabilised by the ether-substituted ring A despite the adjacent carbonyl group. It has been necessary to postulate this type of intermediate for the acid-catalysed conversion of *trans*-B/C 12a-methoxy-rotenoids into the *cis*-B/C 12a-methoxyrotenoids [12] and the formation of a spiro-compound in the peltogynol series [13] may be related to it. Hydrolysis of 6a,12a-dehydrorotenol acetate (XXIIa)

[12] Büchi, Crombie, Godin, Kaltenbronn, Siddalingaiah, and Whiting, *J.*, 2843.
[13] Chan, Forsyth, and Hassall, *J.*, 1958, 3174.

with sodium hydroxide gives mutarotenone, but this rapidly undergoes secondary reactions under the strongly alkaline conditions. From the product, a substance m. p. 128—129°, isomeric with rotenone, was isolated in small yield.

If the views developed above are correct, the same substance ought to be obtained merely by treating rotenone with sodium hydroxide solution. This was so. Further, the substance was a mixture of separable diastereoisomers having nearly identical infrared solution spectra. One diastereoisomer had m. p. 150—151°, $[\alpha]_D^{20}$ +203°, the other m. p. 122—123°, $[\alpha]_D^{20}$ −235°, and they represent the 12aβ,5′β (IXa) and the 12aα,5′β-form (Xa) of 6,6a-dehydrorotenol, the two possible diastereoisomers of Cahn's proposed intermediate (keto-form) in the racemisation of rotenone.* Their origin clearly lies in prototropic shifting of the double bond of the true intermediate (Va). (−)-Isorotenone similarly gives a racemic 6,6a-dehydroisorotenol (IX—Xc) which, when boiled with potassium carbonate in wet acetone, yields (±)-isorotenone. As direct intermediates in the racemisation of rotenoids the 6,6a-dehydrorotenols are not acceptable, for when either diastereoisomer was boiled with saturated ethanolic sodium acetate much remained unchanged (though becoming racemised at position 12a). The structure of the two 6,6a-dehydrorotenols is shown by the following facts. Treatment with pyridine and acetic anhydride gives an acetyl derivative (with epimerisation at position 12a) which can be catalytically hydrogenated to 6′,7′-dihydrorotenol acetate and hydrolysed to 6′,7′-dihydrorotenol (XV—XVIb), thus establishing the skeleton. The chelated hydroxyl group is shown by the ferric chloride reaction and infrared data [1651 cm.$^{-1}$ (chelated ketone)]. In view of the skeletal evidence and the existence of an asymmetric centre other than 5′, the double bond in ring B must be at 6,6a. Catalytic hydrogenation of the diastereoisomer of m. p. 150—151° gives 6′,7′-dihydrorotenol having $[\alpha]_D^{20}$ −196°, whilst the diastereoisomer of m. p. 122—123° gives 6′,7′-dihydrorotenol of $[\alpha]_D^{19}$ −86°. Hydrogenation of the rotenol diastereoisomer, m. p. 141—143° (above), gives 6′,7′-dihydrorotenol, $[\alpha]_D^{22}$ −214°. This shows that the latter is configuratively the same as the 6′,7′-dihydrorotenol of m. p 150—151°, though the absolute configuration at position 12a is not known. Some racemisation at position 12a occurs during hydrogenation of compounds (IX) and (X) (nearly complete for one diastereoisomer), and effective double-bond migration from position 6,6a to 6a,12a on the catalyst may be implicated.

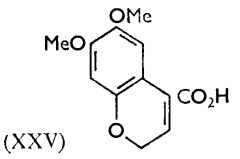
Other information which is readily accommodated by acceptance of the ion (V) as being formed in alkaline solutions of rotenoids is the isolation of dehydronetoric (toxicaric) acid (XXV) on oxidation of rotenone or toxicarol by alkaline peroxide.[3a,14,15] Further, rotenoids give a different series of compounds when oximated with hydroxylamine hydrochloride in the presence of sodium hydroxide from those obtained by oximation with the same reagent in the presence of sodium acetate.[6] The latter are considered to be normal oximes (XXVI), and the former isoxazolines (iso-oximes)[3,6,16] (XXVII) which would arise from attack on the ion (V) as in (XXIX). Spectral information supports the constitution of these derivatives. Rotenoid oximes (XXVI) have " free " hydroxyl bands near 3592 cm.$^{-1}$ (cf. α-tetralone oxime, 3595 cm.$^{-1}$), whilst the iso-oximes have strongly chelated hydroxyl groups: there are two chelated bands near 3170 and 3080 cm.$^{-1}$ ($CaF_2$, $CCl_4$, $<\sim$0·005M). The presence of the two bands suggests that the two tautomers (XXVII) and (XXVIII) may be present.

Cahn and his colleagues have carried out comparative studies of the reactions of rotenone and toxicarol.[1] The work on toxicarol provides an interesting complement to

* On hearing of this, Professor S. H. Harper recently recalled work (unpublished) he had done in 1942 on the alkaline treatment of rotenone. His original notes show that he isolated the pure diastereoisomer, m. p. 151°, but an adequate formulation could not be arrived at. All his observations agree with the structure above and we thank him for this information.

[14] Butenandt and Hilgetag, *Annalen*, 1932, **495**, 172.
[15] Clark, *J. Amer. Chem. Soc.*, 1932, **54**, 2537.
[16] LaForge and Haller, *J. Amer. Chem. Soc.*, 1932, **54**, 810.

that described above, and rationalisation is now attempted. (±)-α-Toxicarol (XXX) is readily equilibrated with (±)-β-toxicarol (XXXII) when treated with potassium carbonate in wet acetone, and the structure of both compounds is securely founded.[1,17] This provides good evidence for the existence of a 6a,7-opened intermediate which we consider to be (XXXI)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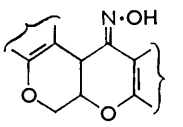
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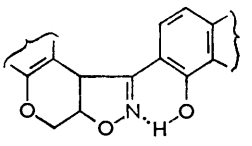
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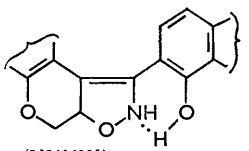
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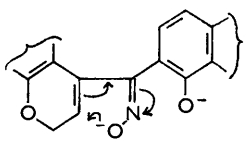
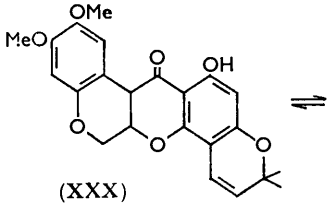

(XXIX)

or the monoprotonated form, and new terms have to be added to the scheme of alkaline behaviour on p. 2877. When a benzene solution of natural (—)-α-toxicarol * is treated with a little methanolic potassium hydroxide, there is an immediate shift in rotation from —66° to +276°; thereafter there is a steady fall towards zero (the behaviour of sumatrol is related).[1,18] If, immediately after addition of alkali, the solution is acidified, unracemised (—)-α-toxicarol is recovered.[1] These phenomena are said [1] to be due to enolisation of the ketone prefatory to 6a,7-cleavage to give the species (II). In our view the immediate positive surge in the rotation is due to ionisation of the 11-phenolic hydroxyl; racemisation then proceeds *via* the di-ion (XXXI). The immediate shift of the main ultraviolet maximum of toxi-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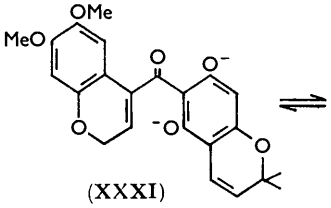
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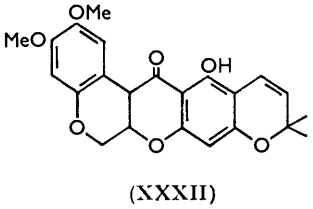

(XXXII)

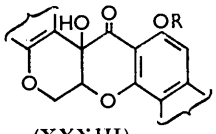
carol from 272·5 mμ in ethanol to 280 mμ in M/20-aqueous-alcoholic sodium hydroxide has also been put down to enolisation,[1] but it is due to phenolic ionisation. Thus the spectrum of (±)-12a-hydroxytoxicarol (XXXIII; R = H), although the compound cannot enolise, suffers a shift of $\lambda_{max.}$ from 273 to 283 mμ under similar conditions. On the other hand, (±)-12a-hydroxytoxicarol 11-acetate (XXXIII; R = Ac) has $\lambda_{max.}$ 270 mμ in neutral ethanol and in alkaline ethanol if the peak is measured at once (gradually the maximum shifts to 280 mμ as the acetate is hydrolysed). Recognition of this simple ionisation process helps us to understand further experimental facts.

Rotenone is methylated by methyl sulphate in boiling acetone containing water if potassium carbonate or potassium hydroxide is present: the product is the 6a-racemised acid-labile enol ether (XXXIVa).[19] However, when (±)-α- or (±)-β-toxicarol is similarly treated the product, in good yield, is the acid-stable ether (XXXVd). Potassium carbonate, when added to (—)-α-toxicarol in aqueous acetone, causes the characteristic

* The prefix (—) refers to benzene solution; the sign changes in certain other solvents.

[17] George and Robertson, *J.*, 1937, 1535.
[18] Harper, *J.*, 1939, 812.
[19] Cahn, Phipers, and Boam, *J.*, 1938, 734.

strong positive surge of rotation followed by a slow decline to zero and is obviously basic enough largely to ionise the $C_{(11)}$-phenol group. Removal of the 12a-proton from ionised α-toxicarol leads to the enolate (XXXVI) but the juxtaposition of the two negative charges must greatly destabilise this relative to the derivative (XXXVII). Consequently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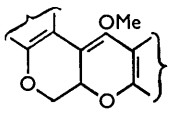
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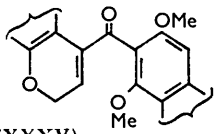
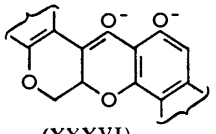
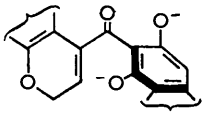
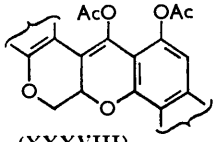

(XXXV)


(XXXVI)

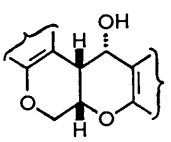

(XXXVII)

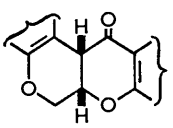

(XXXVIII)

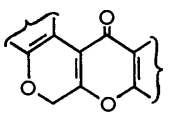
the relative stabilities and equilibrium concentrations of species (IV) and (V) are likely to be very different in the cases of rotenone and toxicarol, attack on the open form (XXXVII) being much more likely in the latter case. In the open form, the aromatic ring D can rotate to relieve unfavourable interaction between the carbonyl dipole and the phenoxide ion.

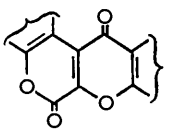
Acetylation of rotenone by refluxing sodium acetate–acetic anhydride gives the enol acetate (XXIa) with racemisation at position 6a; although formation of the ion (V) must be invoked to account for racemisation, the major acetylation attack is on ions (IV) and (VI). If (—)-α-toxicarol [or (—)-dihydro-α-toxicarol, for which better experimental evidence is available [19]] is treated for a short time with the reagent, the optically active 11-phenol monoacetate can be isolated, but on long treatment the racemised diacetate (XXXVIII) is obtained. Sodium acetate in acetic anhydride must be a much weaker base than potassium carbonate in wet acetone and the stationary concentration of phenoxide ion will be very low [ethanolic sodium acetate causes no positive rotatory surge when added to (—)-α-toxicarol]. The phenol can be acetylated with little racemisation. Longer treatment causes racemisation of this acetate *via* the open form (V) but the stationary concentration of the latter need only be low and ordinary enol-acetylation, as in the case of rotenone, takes precedence. The diacetate of the open form of toxicarol [corresponding to (XXXV)] can be made by treating toxicarol with sodium hydroxide in benzene and pouring the mixture into acetylating mixture.[2]

A characteristic reaction of rotenoids is their 6a,12a-dehydrogenation, usually carried out by treatment with iodine and potassium acetate in ethanol, which causes α-iodination and dehydrohalogenation.[20] A driving force is gain of pyrone resonance energy and perhaps relief of angle strain. We find active manganese dioxide to be an excellent


(XXXIX)


(XL)


(XLI)


(XLII)

reagent for such dehydrogenations, and other levels of oxidation of the B/C system can be effected. Starting with hydroxy-compound (XXXIX) it is possible to oxidise to the rotenone level (XL), though it is difficult to prevent some over-oxidation to (XLI). The conversion (XL ⟶ XLI) is very smooth and proceeds in higher yield than by earlier

[20] LaForge, Haller, and Smith, *Chem. Rev.*, 1933, **12**, 181.

methods. In some 11-hydroxy-rotenoids (α- and β-toxicarol) oxidation proceeds still further to the rotenonone level (XLII). The conversion (XL) ⟶ (XLI) is a surface reaction and the *cis*-arrangement of the two hydrogens on the manganese dioxide may be helpful. Earlier preparations of compounds of the rotenonone type (XLII) have given poor yields, but we find that the conversion of 6a,12a-dehydro-compounds (XLI) can be satisfactorily carried out by oxidation with lead tetra-acetate. 6a,12a-Dehydro-rotenoids are useful intermediates in the degradation of rotenoids as they are hydrolysed by base to compounds of the derrisic acid type which can be degraded further.

## Experimental

For general experimental procedures see p. 2852. Rotations are for benzene solutions unless otherwise stated.

6aβ,12aβ,5′β- *and* 6aα,12aα,5′β-*Rotenone Mixture* (*Mutarotenone*).—Natural rotenone (25 g.), anhydrous sodium acetate (125 g.), and ethanol (500 ml.) were heated under reflux for 4 hr. The mixture was poured into water and kept at 0° for 12 hr. Crystalline mutarotenone (24·9 g.), m. p. 138—142°, $[\alpha]_D^{25}$ −99·7° (*c* 2), was filtered off. A specimen of the latter (1 g.) was refluxed with sodium acetate (5 g.) in ethanol (25 ml.) for 3 hr. more: isolation gave mutarotenone (0·96 g.), $[\alpha]_D^{25}$ −101° (*c* 1·4).

Mutarotenone (420 mg.; $[\alpha]_D^{25}$ −99·7°) was kept at 60° for 1 hr. with concentrated sulphuric acid (4 ml.) and acetic acid (3 ml.), then poured into water. Isorotenone, $[\alpha]_D^{21}$ −9·7° (*c* 1·65), was obtained. A second and a third isomerisation gave $[\alpha]_D^{25}$ −3·0° (*c* 2·64 in $CHCl_3$) and $[\alpha]_D^{25}$ −1·1° (*c* 1·29 in $C_6H_6$).

The same mutarotenone (5·03 g.) was crystallised from ethanol as follows: first crystallisation (2·01 g.), $[\alpha]_D^{21}$ −208 (*c* 1·9); third crystallisation (1·10 g.), m. p. 164·5—166°, $[\alpha]_D^{21}$ −218° (*c* 1·2) {natural rotenone has m. p. 165—166°, $[\alpha]_D^{20}$ −228° (*c* 2·22)}. By crystallisation from benzene–ether, material of m. p. 147°, $[\alpha]_D^{23}$ −144° (*c* 2·24), was obtained but no stationary value of rotation and m. p. is reached by crystallisation from benzene–ether, ethanol, methanol–chloroform, or carbon tetrachloride until pure (−)-rotenone is isolated (lit.,[1] for mutarotenone, m. p. 145—146°, $[\alpha]_D$ −80° to −86°).

Mutarotenone, $[\alpha]_D^{25}$ −99·7°, was heated in a " Pyrex " tube at 20° above its m. p. for 20 min.[5] and then had $[\alpha]_D^{22}$ −104° (*c* 2·3). When isomerised with concentrated sulphuric and acetic acid the heated product (424 mg.) gave isorotenone (410 mg.), $[\alpha]_D^{22}$ −9·85° (*c* 2·3). Parallel crystallisation (once) of unheated and heated mutarotenone (1 g.) from ethanol gave rotenone (0·4 g.), $[\alpha]_D^{21}$ −208° (*c* 1·9), and (0·3 g.), $[\alpha]_D^{21}$ −187° (*c* 0·5), respectively.

6aα,12aα-5′β-*Rotenone* (" d-*Epirotenone* ").—Mutarotenone (100 g.) was crystallised from carbon tetrachloride, and the mother-liquors were evaporated and crystallised from benzene–ether (2 weeks). After filtration, the filtrate was evaporated, dissolved in ether, and kept for several weeks. The product was again filtered and the filtrate on evaporation gave 6aα,12aα,5′β-rotenone concentrate, a glass, $[\alpha]_D^{18}$ +25·6° (*c* 0·74). Cahn, Phipers, and Boam [1] report $[\alpha]_D$ +30° for their specimen but recently Nakajima and his colleagues [4] have reported m. p. 89—91°, $[\alpha]_D$ +72·5°, for the methanol solvate of *d*-epirotenone. A crystal of this material was kindly supplied by Professor Nakajima but had decomposed (softened 90°, m. p. 144°) and failed to cause crystallisation of the glass from methanol.

The glass, $[\alpha]_D^{18}$ +25·6°, was kept in ether for some weeks at 20° and the mixture was filtered. The filtrate was evaporated, dissolved in methanol, kept for some days, and then filtered. This methanol crystallisation and rejection of the crystalline material was repeated twice more. Finally the filtrate was treated with charcoal and kept at 0°, to give 6aα,12aα,5′β-rotenone (VIIa), m. p. 86—89°, $[\alpha]_D^{21}$ +56° (*c* 2), as the methanol solvate; further crystallisation from methanol gave material of m. p. 90°, $[\alpha]_D^{18}$ +75·6° (*c* 0·6) (Found: C, 68·85; H, 5·9. Calc. for $C_{23}H_{22}O_6,\frac{1}{2}CH_3{\cdot}OH$: C, 68·8; H, 5·9%). The infrared solution spectrum was closely similar to that of natural rotenone.

*Diastereoisomers of Rotenol* (XVa and XVIa).—Rotenone (40 g.), zinc dust (80 g.), and ethanol (1·2 l.) were heated to the b. p. and 10% aqueous potassium hydroxide (400 ml.) was added; the mixture was stirred and refluxed for 3½ hr. and then filtered. The filtrate was acidified with 2N-hydrochloric acid and extracted with ether. The ethereal extracts were extracted with 2N-potassium hydroxide and evaporated, to give the " neutral " fraction. The

basic extract contained derritol and in some cases was worked up for this. In one such experiment the acidic fraction was dissolved in a minimum of hot methanol and cooled to 0°, to give derritol, m. p. 160—161°, $[\alpha]_D^{20\cdot5}$ −74° (*c* 2·1 in $CHCl_3$) {lit.,[7] m. p. 164°, $[\alpha]_D^{20}$ −66·2° (*c* 3·4 in $CHCl_3$}. Four further crops of derritol were isolated but the fifth crop was crude rotenol, m. p. 112—114°, $[\alpha]_D^{21}$ −116° (*c* 2·4) (correct infrared spectrum). Rotenol is not insoluble in alkali but is extracted only slowly from ethereal solution by aqueous base.

The " neutral " fraction crystallised from methanol to give " ordinary " rotenol (13 g.), m. p. 114·5—116·5°, $[\alpha]_D^{19}$ −120° (*c* 1·81), (m. p. 120° on recrystallisation) {lit.,[6,7,21,22] m. p. 115—120°, 119°, 120° $[\alpha]_D^{20}$ −77·3° (*c* 3·98 in $CHCl_3$)}. The material was crystallised six times from methanol, to give (−)-5′β-*rotenol*, m. p. 141—143°, $[\alpha]_D^{21}$ −245° (*c* 2·52) (Found: C, 69·7; H, 6·2; O, 24·15. $C_{23}H_{24}O_6$ requires C, 69·7; H, 6·1; O, 24·2%). The mother-liquors were repeatedly crystallised from methanol and finally gave (+)-5′β-*rotenol*, m. p. 90°, $[\alpha]_D^{20}$ +33° (*c* 0·7) (Found: C, 69·45; H, 6·0%). The chloroform solution spectra of (+)-, (−)-, and " ordinary " rotenol were virtually identical, but as mulls they could be differentiated.

*Racemisation of* (+)- *and* (−)-5′β-*Rotenol.*—(+)-5′β-Rotenol (10·97 mg.) in acetone (0·6 ml.) was treated with 0·02% ethanolic potassium hydroxide (0·6 ml.). Polarimetric rotations were followed, $[\alpha]_D^{20}$ becoming constant at −64·5°. (−)-5′β-Rotenol (11·37 mg.) was treated similarly, giving final $[\alpha]_D^{20}$ −64·5°.

(+)-Rotenol (20 mg.) and anhydrous sodium acetate (50 mg.) in ethanol (2 ml.) were refluxed for 4 hr. Water was added and, on cooling to 0°, " ordinary " rotenol (19 mg.), m. p. and mixed m. p. 114—117°, $[\alpha]_D^{19}$ −104° (*c* 1·82), was obtained.

(−)-Rotenol (500 mg.), treated with sodium acetate (3 g.) in ethanol as above, gave " ordinary " rotenol (460 mg.), m. p. and mixed m. p. 118—119°, $[\alpha]_D^{21}$ −110·5° (*c* 2).

(−)-Rotenol (250 mg.) was refluxed for 1 hr. with 5% ethanolic sulphuric acid (50 ml.). On cooling and filtration an almost theoretical yield of unchanged (−)-rotenol, m. p. and mixed m. p. 142—143°, $[\alpha]_D^{22}$ −238° (*c* 1·75), was recovered.

(−)-6′,7′-*Dihydro*-5′β-*rotenol.*—(−)-5′β-Rotenol (105 mg.) in ethyl acetate (15 ml.) was hydrogenated over palladium–barium sulphate (80 mg.), to give (−)-6′,7′-dihydro-5′β-rotenol (90 mg.), m. p. 137—138°, $[\alpha]_D^{22}$ −214° (*c* 1·74) (see below).

5′β-*Diastereoisomers of the Spiro-compound* (XVIII).—(*a*) Warm potassium ferricyanide (900 mg.) in water (10 ml.) was added to rotenol (500 mg.) in 5% ethanolic potassium hydroxide. The mixture was shaken overnight, poured into water, and continuously extracted with ether. Evaporation of the ether left a gum which was chromatographed from benzene on alumina (N5) and then dissolved in methanol and poured into water, to give a powder, m. p. 75—80°, containing the two 5′β-diastereoisomers (Found: C, 69·8; H, 5·6. Calc. for $C_{23}H_{22}O_6$: C, 70·05; H, 5·6%), $\nu_{max.}$ 1704 (C=O), 1623, 1603, 1502 (aryl), and 913 (isopropenyl) cm.$^{-1}$. There was no hydroxylic absorption and no coloration with ferric chloride. Crystallisation from ethanol gave one diastereoisomer, m. p. 119—121°, $[\alpha]_D^{20}$ −88° (*c* 0·64) (lit.,[8] m. p. 124°).

(*b*) Rotenol (314 mg.) was heated under reflux with alkaline active manganese dioxide (3 g.) in dioxan (15 ml.) for 3 hr. Filtration and addition of a little water to the filtrate gave 6a,12a-dehydrorotenone (60 mg.), m. p. and mixed m. p. 219—222° (infrared confirmation). The filtrate was further diluted with water and extracted with chloroform. Evaporation of the extract gave the spiro-compound (XVIII) (95 mg.), amorphous, identified by its infrared spectrum (mull). Shaking at 20° with the above reagent gave mainly unchanged rotenol.

*Racemic Spiro-compound* (XVIII, *but of the Isorotenone Series*).—(*a*) Isorotenol (2 g.) was treated with potassium ferricyanide (3·6 g.) in alkali as above. The mixture was acidified and chromatographed from benzene on alumina (N1) to give, after crystallisation from methanol, the *spiro-racemate* of the isorotenone series (320 mg.) as plates, m. p. 126° (Found: C, 69·7; H, 5·85. $C_{23}H_{22}O_6$ requires C, 70·05; H, 5·6%), $\lambda_{max.}$ 240 (4·72), 246i (4·65), 264i (4·02), 281 (4·06), 290 (4·02), and 335 (3·74) mμ, $\nu_{max.}$ 1709 (C=O), 1634, 1597 and 1504 cm.$^{-1}$ (aryl).

(*b*) Isorotenol (1 g.) was treated with lead tetra-acetate (5 g.) in glacial acetic acid (25 ml.) for 2 hr. The solution was poured into water, and the whole crude product was chromatographed from benzene on alumina (N1). The infrared spectrum (chloroform) of the main product showed that spiro-compound had been formed directly ($\nu_{max.}$ 1709 cm.$^{-1}$ and general character of the spectrum) but acetoxy-substituted material was also present [$\nu_{max.}$ 1750 cm.$^{-1}$ (Ac)]. The product was shaken for 5 days with 10% methanolic potassium hydroxide (10 ml.) then

[21] Takei, Miyajima, and Ono, *Ber.*, 1932, **65**, 279.
[22] Haller and LaForge, *J. Amer. Chem. Soc.*, 1931, **53**, 3426.

heated to the b. p. and poured into dilute hydrochloric acid. The precipitate was filtered off, chromatographed as above, and crystallised from methanol to give the spiro-racemate, plates, m. p. and mixed m. p. with the above sample 125°. Identity was confirmed by the infrared spectrum (mull). Apart from direct formation, the spiro-compound may also originate by hydrolysis of 12a-acetoxyisorotenol and subsequent cyclisation. From a structural point of view both routes have the same import.

*Reduction of Spiro-compound* (XVIII) *and Oxidation of the Reduction Product.*—The spiro-compound (500 mg.) in ethanol (30 ml.) was treated at 60° for 1 hr. with potassium borohydride (250 mg.) and potassium hydroxide (100 mg.) in water (10 ml.). After 5 hr. at 20° the solution was poured into water, and the amorphous solid was isolated (400 mg.). It showed hydroxyl but no carbonyl absorption in the infrared spectrum (mull). The alcohol (400 mg.) was shaken for 12 hr. with active manganese dioxide (2 g.) in acetone (10 ml.). The whole was filtered and the manganese dioxide was washed with chloroform. Evaporation of the filtrate and washings gave a powder identical with the starting spiro-ketone (mull infrared spectrum).

*Treatment of the Racemic Spiro-compound* [*as* (XVIII), *but of the Isorotenone Series*] *with Zinc and Alkali.*—The spiro-compound (250 mg.), zinc dust (1 g.), 95% ethanol (10 ml.), and 40% aqueous potassium hydroxide (2·5 ml.) were refluxed for 2 hr. The mixture was filtered, acidified, and extracted with ether. These extracts were treated to afford acidic and neutral fractions. When crystallised from methanol the neutral gum (195 mg.) gave isorotenol (115 mg ), m. p. and mixed m. p. 129—130°; identity was confirmed by infrared spectra (mull and solution). The acid fraction gave only impure isorotenol (10 mg.), identified spectroscopically.

Authentic isorotenol, m. p. 131°, was made by isomerisation of rotenol with sulphuric acid in glacial acetic acid (lit.,[8] m. p. 131°).

6a,12a-*Dehydrorotenol* (Va) *and its Acetate* (XXIIa).—Rotenone (5 g.) in dry benzene (100 ml.) was added to sodium wire (3 g.) under benzene (300 ml.). The mixture was then refluxed under dry nitrogen for 4 hr. and the pale yellow solution was decanted, washed with 4N-hydrochloric acid and then with chalk suspension, and dried ($MgSO_4$). Evaporation gave a gum which, when dissolved in ethanol and kept at 0° for 60 hr., gave 6a,12a-*dehydrorotenol* (3·8 g.) as yellow needles, m. p. 94—96° (from methanol), $[\alpha]_D^{17}$ −75° (*c* 1·8) (Found: C, 70·1; H, 5·7. $C_{23}H_{22}O_6$ requires C, 70·05; H, 5·6%), $\lambda_{max.}$ 305 (4·31), 315i (4·29) mμ, $\nu_{max.}$ 1646 (chelated unsaturated ketone), 1616, 1590i, and 1497 (aryl) cm.$^{-1}$. The compound gave a red ferric reaction. Jennen, using a different technique, obtained impure material, m. p. 76—78°. 6a,12a-Dehydrorotenol (150 mg.) was kept at 20° for 12 hr. with acetic anhydride (3 ml.) and pyridine (2 ml.). Working up gave the acetate (125 mg.), m. p. 138° alone or mixed with the specimen recorded below (infrared confirmation).

Rotenone (3 g.) was added to sodium hydroxide pellets (45 g.) and stirred under dry benzene (300 ml.) at 60° in a nitrogen atmosphere. The mixture was heated for 7 hr. (becoming blood-red) and then decanted into acetic anhydride (400 ml.) containing fused, powdered sodium acetate (45 g.). After refluxing for 5 hr. in nitrogen the mixture was poured on ice, and the benzene layer isolated and evaporated to a gum which crystallised from methanol (charcoal), to give 6a,12a-dehydrorotenol acetate (2·37 g.), m. p. 138—139° (Found: C, 68·5; H, 5·8. Calc. for $C_{25}H_{24}O_7$: C, 68·80; H, 5·55%), $[\alpha]_D^{22}$ −84·5° (*c* 1·76), $\lambda_{max.}$ 284 (4·19) mμ, $\nu_{max.}$ 1761 (Ac), 1652 (unsatd. ketone), 1613, and 1506 (aryl) cm.$^{-1}$. Chromatography from benzene on alumina raised the m. p. to 139—140°. Jennen [2] gives m. p. 134°, $[\alpha]_D$ −74°, $\lambda_{max.}$ 284 mμ (4·19). An identical product was obtained by using sodium wire (1 g.) in place of sodium hydroxide.

6a,12a-*Dehydroisorotenol.*—Isorotenone (3 g.) was treated with sodium hydroxide (45 g.) in benzene as above, and the resulting solution was acetylated as above. Working up gave 6a,12a-*dehydroisorotenol acetate* (500 mg.), m. p. 161·5—162·5° (Found: C, 68·75; H, 5·65%), $\lambda_{max.}$ 244 (4·55), 280 (4·09) and 314 (3·81) mμ, $\nu_{max.}$ (mull) 1761 (Ac), 1650 (unsatd. ketone), 1616, 1587, 1572, and 1513 (aryl) cm.$^{-1}$. In an experiment with isorotenone (12 g.) and sodium wire (3 g.) the yield was 4 g.

6a,12a-*Dehydrorotenol Acetate by Dehydrogenation of Rotenol Acetate.*—Rotenol (250 mg.) was treated with pyridine (1·5 ml.) and acetic anhydride (2 ml.) for 12 hr. Working up and chromatography gave rotenol acetate (two diastereoisomers) as an amorphous solid (Found: C, 68·65; H, 5·85. Calc. for $C_{25}H_{26}O_7$: C, 68·5; H, 5·95%), $[\alpha]_D^{20}$ −103° (*c* 1·48), $\lambda_{max.}$ (in ethanol or ethanolic 0·01N-potassium hydroxide) 290 (4·24) mμ, $\nu_{max.}$ 1762 (Ac), 1687 (C=O) cm.$^{-1}$. Earlier failure to obtain this material crystalline has been reported.[16]

Rotenol acetate (350 mg.) was heated under reflux for 2·5 hr. with active manganese dioxide in acetone (25 ml.). Working up and crystallisation from methanol gave dehydrorotenol acetate (XXIIa) (50 mg.), m. p. and mixed m. p. 138°. An infrared spectrum (mull) confirmed the identity.

*Hydrogenation of* 6a,12a-*Dehydrorotenol Acetate.*—The acetate (225 mg.) was hydrogenated in ethyl acetate (15 ml.) over 5% palladium–barium sulphate (2 mols. of $H_2$ absorbed). Working up gave amorphous 6′,7′-dihydrorotenol acetate (200 mg.). Rotenol acetate (240 mg.), similarly hydrogenated, absorbed 1 mol. of hydrogen, giving the amorphous *6′,7′-dihydrorotenol acetate* (220 mg.) with infrared mull spectrum closely similar to that of the first specimen (Found: C, 68·25; H, 6·5. $C_{25}H_{28}O_7$ requires C, 68·15; H, 6·4%), $\lambda_{max.}$ 282 (3·92) and 330 (3·85) mμ $\nu_{max.}$ 1761 (Ac), 1658 (C=O) cm.$^{-1}$.

6′,7′-Dihydrorotenol acetate (first specimen) was refluxed for 20 min. with 5% ethanolic sulphuric acid (25 ml.). Working up gave a gum (140 mg.) which crystallised from methanol to give 6′,7′-dihydrorotenol (60 mg.), m. p. and mixed m. p. 130—131°. Gum, crystals, and authentic material had identical infrared spectra in chloroform.

In another experiment, 6a,12a-dehydrorotenol acetate (500 mg.) was hydrogenated over 5% palladised charcoal (500 mg.) in ethyl acetate (20 ml.). Working up gave a gum which crystallised to give *6′,7′-dihydro-1′,5′-secorotenol acetate* (XV—XVIg) (26 mg.), m. p. 162—163° (Found: C, 68·15; H, 6·95. $C_{25}H_{30}O_7$ requires C, 67·85; H, 6·83%), $\nu_{max.}$ (mull) 1744 (OAc), 1680 (C=O) cm.$^{-1}$.

*Acid-treatment of* 6a,12a-*Dehydrorotenol, its Acetate, and* 6a,12a-*Isodehydrorotenol Acetate.*—6a,12a-Dehydrorotenol (300 mg.) was refluxed with 10% methanolic sulphuric acid (25 ml.) for 40 min. The blue solution was poured into water and extracted with ether. The extracts were washed with sodium hydrogen carbonate solution and water. Drying, evaporation, and chromatography from benzene on alumina (K3) gave the powdery mixture of 5′β-diastereoisomers of the spiro-compound (XVIIIa); identity with the specimen above was confirmed by the infrared (mull) spectrum, and crystallisation to give the diastereoisomer, m. p. and mixed m. p. 119—121°. 6a,12a-Dehydrorotenol acetate under similar conditions gave the same diastereoisomeric mixture (infrared) and the diastereoisomer, m. p. and mixed m. p. 119—121°.

6a,12a-Isodehydrorotenol acetate (700 mg.) similarly gave, after 60 minutes' refluxing, the racemic spiro-compound of the isorotenone series (cf. XVIII) (260 mg.), m. p. and mixed m. p. 126° (correct infrared spectrum).

*Treatment of* 6a,12a-*Dehydrorotenol with Sodium Acetate.*—The dehydro-compound (150 mg.) was refluxed for 2½ hr. with ethanol (8 ml.) saturated with sodium acetate, and then poured into water. The solid was filtered off, washed with a little methanol, and dried (150 mg.; m. p. 98—110°); the infrared spectrum (mull) was almost identical with that of mutarotenone.

*Treatment of* 6a,12a-*Dehydrorotenol Acetate and* 6a,12a-*Dehydroisorotenol Acetate with Aqueous Pyridine.*—(*a*) 6a,12a-Dehydroisorotenol acetate (300 mg.) was refluxed with pyridine (9 ml.) and water (2 ml.) for 30 min. The mixture was cooled, poured into dilute hydrochloric acid, and extracted with ether. The extract was washed, dried, and evaporated, and the residue crystallised from methanol, to give (±)-isorotenone, m. p. 166—169° (140 mg.) (correct infrared mull spectrum).

(*b*) 6a,12a-Dehydrorotenol acetate (300 mg.) was similarly refluxed for 90 min. Working up gave a glass (220 mg.) which on chromatography (alumina K1) from benzene gave 6a,12a-racemised rotenone (35 mg.), m. p. 110°. The infrared solution spectra of the glass and crystals were closely similar to that of rotenone.

*Hydrolysis of* 6a,12a-*Dehydrorotenol Acetate with Alcoholic Potassium Hydroxide.*—The acetate (500 mg.) was heated under reflux for 20 min. with N-alcoholic potassium hydroxide (15 ml.), and the red solution was acidified with dilute acetic acid and extracted with ether. The ethereal extract was washed, dried, and evaporated to a foamy resin that was chromatographed from benzene on alumina. The Durham test on the gummy product was positive but storage in methanol afforded the pale yellow 6,6a-dehydrorotenol (mixture of 5′β,12a-diastereoisomers) (20 mg.; Durham test negative), m. p. 128—129° (Found: C, 70·15; H, 5·75. Calc. for $C_{23}H_{22}O_6$: C, 70·05; H, 5·6%), $[\alpha]_D^{23·5}$ −96° (*c* 1·09), $\lambda_{max.}$ 242 (4·11) and 297 (4·34) mμ, $\nu_{max.}$ (mull) 1650i, 1640, 1620i, 1608, 1595 cm.$^{-1}$. The substance gave a red ferric reaction. A second experiment gave the diastereoisomers, m. p. 120—121°, which had identical infrared characteristics (chloroform) with the mixture above.

(+)- *and* (−)-6,6a-*Dehydro*-5′β-*rotenol*.—Rotenone (20 g.) was refluxed under nitrogen with 2N-potassium hydroxide (500 ml.). The solution became red and after 5 min. was poured into acetic acid (60 ml.) in water (2·5 l.). The mixture was extracted with ether, and the extracts were combined and shaken with charcoal, magnesium carbonate, and magnesium sulphate for 1 hr. After filtration, the solution was evaporated and the yellow gum was dissolved in a minimum of hot methanol. Crystallisation gave a diastereoisomeric mixture of 6,6a-dehydro-5′β-rotenols (6·5 g.), m. p. 105—110°. This was resolved by crystallisations from methanol, to give (+)-6,6a-*dehydro*-5′β-*rotenol*, m. p. 150—151° (Found: C, 70·3; H, 5·8%), $[\alpha]_D^{20}$ +203° (*c* 2), $\lambda_{max.}$ 244 (4·14), and 296 (4·36) mμ, $\nu_{max.}$ 1656i, 1637, 1621i, 1603, and 1555 cm.$^{-1}$, and (−)-6,6a-*dehydro*-5′β-*rotenol*, m. p. 122—123° (Found: C, 69·75; H, 5·5%), $[\alpha]_D^{20}$ −235° (*c* 2). The solution infrared spectrum of the latter was identical with that of the former. The mixture of diastereoisomers (5 g.) could also be obtained by adding 20% ethanolic potassium hydroxide (100 ml.) to rotenone (20 g.) in boiling ethanol (500 ml.), refluxing the mixture for 5 min., acidifying it with concentrated hydrochloric acid, and working it up as before.

*Racemic* 6,6a-*Dehydroisorotenol*.—(−)-Isorotenone (5 g.) was treated as above (second method), to give (±)-6,6a-*dehydroisorotenol* (0·35 g.), colourless needles (from methanol), m. p. 112° (Found: C, 69·65; H, 5·6. $C_{23}H_{22}O_6$ requires C, 70·05; H, 5·6%), $\nu_{max.}$ 1656i, 1629, 1595 cm.$^{-1}$.

*Hydrogenation of* (+)- *and* (−)-6,6a-*Dehydro*-5′β-*rotenol*.—The (+)-compound (100 mg.) in ethyl acetate (15 ml.) was hydrogenated over palladium–barium sulphate (2 mol. absorbed). Working up gave 6′,7′-dihydrorotenol, m. p. 135—136° (Found: C, 69·7; H, 6·75. Calc. for $C_{23}H_{26}O_6$: C, 69·35; H, 6·6%), $[\alpha]_D^{20}$ −196° (*c* 0·9) {whole unpurified product, $[\alpha]_D^{17}$ −187° (*c* 0·5)}. The m. p. was not depressed on admixture with the (−)-6′,7′-dihydro-5′β-rotenol (above), and the infrared spectra were the same. The product (25 mg.) was boiled for 3 hr. in ethanol (2 ml.) saturated with sodium acetate, and gave " ordinary " 6′,7′-dihydrorotenol (diastereoisomers), m. p. and mixed m. p. 129—130°, $[\alpha]_D^{20}$ −95° (*c* 0·9).

Similarly hydrogenated, (−)-6,6a-dehydro-5′β-rotenol gave 6′,7′-dihydrorotenol, m. p. 120—123°, $[\alpha]_D^{19}$ −86° (*c* 0·6); the infrared solution spectrum was the same as that of " ordinary " 6′,7′-dihydrorotenol. Racemisation and purification were completed as above, to give " ordinary " 6′,7′-dihydrorotenol, m. p. and mixed m. p. 130°, $[\alpha]_D^{20}$ −89° (*c* 1·2).

*Acetylation of* 6,6a-*Dehydrorotenol*.—The mixture of 5′β,12a-epimers (300 mg.), pyridine (3 ml.), and acetic anhydride (4 ml.) was kept at 20° for 16 hr. Working up and chromatography from chloroform–benzene (1 : 1) on alumina (K1) gave the *acetate*, m. p. 139° (from methanol) (Found: C, 69·05; H, 5·75. $C_{25}H_{24}O_7$ requires C, 68·8; H, 5·55%), $[\alpha]_D^{18}$ −70·2° (*c* 1·75), $\lambda_{max.}$ 335 (4·22) mμ and plateau-like peak 235—280 (4·05) mμ, $\lambda_{max.}$ (in $CHCl_3$) 1748 (OAc), 1650 (C=O). Acetylation of the (+)-5′β-epimer gave the acetate, m. p. 139—140°, $[\alpha]_D^{18}$ −73° (*c* 1), and that of the (−)-5′β-epimer gave material of m. p. 139—140°, $[\alpha]_D^{18}$ −72·5° (*c* 2·1), showing that racemisation occurs at position 12a. The acetate depressed the m. p. of 6a,12a-dehydro-5′β-rotenol acetate (m. p. 138—139°) to 120°. Hydrogenation of the acetate in ethyl acetate over palladium–barium sulphate gave a powdery product, the infrared spectrum of which (solution) was identical with that of dihydrorotenol acetate (above). The infrared band at 903 cm.$^{-1}$ (vinyl) disappears on hydrogenation.

*Treatment of* (±)-6,6a-*Isodehydrorotenol with Potassium Carbonate*.—(±)-6,6a-Isodehydrorotenol (300 mg.) was refluxed with acetone (10 ml.) containing an excess of potassium carbonate for 8 hr. Working up and chromatography from benzene on alumina (N3) gave (±)-isorotenone (120 mg.), m. p. and mixed m. p. 170°.

*Treatment of* (±)-6,6a-*Dehydrorotenol with Sodium Acetate*.—6,6a-Dehydrorotenol (5′β,12a-epimers, m. p. 121—124°) (300 mg.) was refluxed for 3 hr. with ethanol (30 ml.) saturated with sodium acetate. The product had m. p. 112—117°, and infrared measurement ($CHCl_3$) showed it to be virtually unchanged dehydrorotenol. (+)-6,6a-Dehydro-5′β-rotenol, similarly treated for 10 hr., gave mainly unchanged but 12a-racemised material, m. p. 118° to 144°, $[\alpha]_D^{19}$ −55° (*c* 1·4) (infrared identification); (−)-6,6a-dehydro-5′β-rotenol behaved similarly (10 hours' refluxing), the product having m. p. 118—144°, $[\alpha]_D^{19}$ −62° (*c* 1·9), with infrared characteristics as above.

*Oximes and Iso-oximes of Rotenoids*.—Rotenone α-oxime crystallised from ethanol in needles, m. p. 237°, $\lambda_{max.}$ 235 (4·36), 282 (4·24), 300 (4·06), and 312 (3·90) mμ, $\nu_{max.}$ ($CaF_2$, $CCl_4$; $<\sim$0·005M) 3592 cm.$^{-1}$, $\nu_{max.}$ (NaCl, $CHCl_3$; $\sim$0·04M) 1650i, 1613, 1600i, and 1502 cm.$^{-1}$ with a broad band near 3226 cm.$^{-1}$ (intermolecularly bonded OH). Rotenone β-oxime, needles, m. p. 249°, had

infrared data identical with that above, confirming its polymorphic nature [lit.,[23] α-form, m. p. 237°; β-form, m. p. 249° (stable)]. The β-oxime was unchanged by refluxing 5% ethanolic sodium hydroxide (5 hr.) and had $\nu_{max.}$ (NaCl, $CHCl_3$; ~0·04M) 3591 cm.$^{-1}$. Rotenone iso-oxime crystallised from acetone–ethanol after chromatographic purification, and had m. p. 210—211° (lit.,[6] m. p. 208° or 230°) (Found: C, 67·5; H, 5·8. Calc. for $C_{23}H_{23}NO_6$: C, 67·5; H, 5·6%), $\lambda_{max.}$ 287 (4·17) mμ, $\nu_{max.}$ ($CaF_2$, $CCl_4$; <~0·005M) 3162b and 3081b cm.$^{-1}$, $\nu_{max.}$ (NaCl, $CHCl_3$; ~0·04M) 3175b, 3058b, 1637, 1610, and 1502 cm.$^{-1}$. The compound gave a strong brown-purple ferric reaction.

(±)-Isorotenone oxime formed needles, m. p. 218° (decomp.) (lit.,[24] m. p. 230°) (Found: C, 67·7; H, 5·6; N, 3·2. Calc. for $C_{23}H_{23}NO_6$: C, 67·5; H, 5·6; N, 3·4%), $\lambda_{max.}$ 242 (4·70), 247 (4·67), 278 (3·93), 310 (3·45), and 322 (3·40) mμ, $\nu_{max.}$ ($CaF_2$, $CCl_4$; <~0·005M) 3593 cm.$^{-1}$, $\nu_{max.}$ (NaCl, $CHCl_3$) ~0·04M) 3610 (free OH), 3257 (intermolecularly bonded OH), 1621, 1587, and 1502 cm.$^{-1}$. (±)-Isorotenone iso-oxime, m. p. 191—192° (lit.,[25] m. p. 192° ) (Found: C, 67·4; H, 5·65%), had $\nu_{max.}$ ($CaF_2$, $CCl_4$; <~0·005M) 3168b and 3088b cm.$^{-1}$, and gave a strong purple-black ferric reaction.

Dihydrorotenone oxime crystallised from chloroform–carbon tetrachloride in needles, m. p. 259°, $\lambda_{max.}$ 235 (4·27), 242i (4·13), 283 (4·18), 302 (3·97), and 315 (3·83) mμ, $\nu_{max.}$ ($CaF_2$, $CCl_4$; <~0·005M) 3592 cm.$^{-1}$, $\nu_{max.}$ (NaCl, $CHCl_3$; ~0·04M) 3597 (free OH) and 3311 (intermolecularly bonded OH), 1626i, 1616, 1597, and 1499 cm.$^{-1}$. The same compound was made by hydrogenating rotenone β-oxime over Adams catalyst in acetone. It was recovered unchanged when treated with concentrated hydrochloric acid for 64 hr.

α-Tetralone oxime formed prisms (from methanol), m. p. 104°, $\nu_{max.}$ ($CaF_2$, $CCl_4$, <~0·005M) 3595 cm.$^{-1}$. Cyclohexanone oxime had m. p. 90°, $\nu_{max.}$ ($CaF_2$, $CCl_4$, <~0·005M) 3602 cm.$^{-1}$.

(±)-12a-*Hydroxytoxicarol and its Acetate.*—(±)-Diacetyltoxicarol [26] (350 mg.) in acetic acid (10 ml.) was treated with 10% sodium dichromate in acetic acid (2 ml.) for 24 hr. at 20° and then poured into water and filtered. The solid, crystallised from aqueous acetic acid, had m. p. 180—182° (110 mg.), raised by crystallisation from methanol to m. p. 185° (lit.,[26] m. p. 184°). In neutral ethanol this (±)-12a-hydroxytoxicarol 11-acetate had $\lambda_{max.}$ 270 (4·50) mμ. In 0·01N-ethanolic potassium hydroxide the value was 270 (4·44) mμ after 1 min., but after 10 min. the peak had shifted to 280 (4·56) mμ.

(±)-12a-Hydroxytoxicarol 11-acetate (50 mg.) was refluxed with 10% ethanolic potassium hydroxide (1 ml.) for 15 min. The product, crystallised from hot aqueous acetic acid, had m. p. 219° (40 mg.), raised by crystallisation from methanol to 224° (lit.,[26] 226—227°). In neutral ethanol (±)-12a-hydroxytoxicarol had $\lambda_{max.}$ 273 (4·47) mμ, and in 0·01N-ethanolic potassium hydroxide 283 (4·59) mμ. In (±)-toxicarol the main band in ethanol was at 274 (4·61) mμ, shifted to 282 (4·56) mμ in 0·01N-ethanolic potassium hydroxide.

*Behaviour of* (−)-α-*Toxicarol in Alkaline Solution.*—The natural ketone [(−) in benzene] had $[\alpha]_D^{15}$ +84·3° (*c* 0·52 in acetone containing 28% of water). (−)-α-Toxicarol (*c* 0·56) in acetone (with 28% of water) containing 1·9% of potassium carbonate had: $[\alpha]_D^{15}$ +208°, +63·6°, +35·2°, 0° (after 5, 90, 210, and 1140 min.). (−)-α-Toxicarol had $[\alpha]_D^{15}$ +110° (*c* 0·24 in ethanol). The following rotations were observed for (−)-α-toxicarol (*c* 0·22) in ethanol containing 1% of sodium acetate: $[\alpha]_D^{15}$ +104°, +99° (after 10 and 420 min.). (−)-α-Toxicarol in ethanol containing 10% of water had $\lambda_{max.}$ 232 (4·19), 272 (4·55), and 295 (4·14) mμ. In the same solvent containing 2% of sodium acetate the values were 232 (4·25), 272 (4·53), and 295 (4·11) mμ (read after 30 min.).

*Oxidation of the Hydroxy-compound* (XXXIXa) *by Manganese Dioxide.*—Rotenone was reduced with lithium aluminium hydride in tetrahydrofuran, and the amorphous product (no C=O absorption, strong OH band; no Durham test) was used. The hydroxy-compound (1 g.) in acetone (50 ml.) was shaken with active manganese dioxide (20 g.) for 3 hr. After filtration and washing of the manganese dioxide with acetone, the acetone solution gave a solid (950 mg.) which crystallised from ethanol, to give 6a,12a-dehydrorotenone (60 mg.), m. p. and mixed m. p. 226—228°, then rotenone (total 446 mg.). Identity was confirmed by mixed m. p.s and the blue Durham reaction.

[23] Harper, *J.*, 1939, 1424.
[24] Takei, *Ber.*, 1928, **61**, 1003.
[25] Takei, Miyajima, and Ono, *Ber.*, 1931, **64**, 1000.
[26] Clark, *J. Amer. Chem. Soc.*, 1934, **56**, 987.

*Dehydrogenation of Natural Rotenone and* (−)-*Isorotenone with Manganese Dioxide.*—(−)-Isorotenone (1 g.) was shaken at 20° with active manganese dioxide (10 g.) and acetone (50 ml.) for 12 hr. Working up as above and crystallisation from chloroform–methanol gave 6a,12a-dehydroisorotenone (784 mg.), m. p. and mixed m. p. 194—195°, $\nu_{max.}$ ($CHCl_3$), 1634 (aryl conj. α-unsatd. ketone), 1613, 1582, and 1502 cm.$^{-1}$. (−)-Isorotenone (10 g.) was refluxed with active manganese dioxide (50 g.) in acetone (250 ml.) and gave 6a,12a-dehydroisorotenone (7·5 g.), m. p. 195—196°.

Rotenone (2 g.) was shaken for 5 days at 20° with active manganese dioxide (10 g.) in acetone. Working up gave 6a,12a-dehydrorotenone (1·34 g.), m. p. and mixed m. p. 223—224° (from chloroform–methanol), $\nu_{max.}$ ($CHCl_3$) 1634 cm.$^{-1}$ (C=O). Rotenone (1 g.), when refluxed with acetone (30 ml.) containing active manganese dioxide (5 g.) for 3 hr., gave 6a,12a-dehydrorotenone (0·68 g.), m. p. and mixed m. p. 224°.

*Oxidation of* α- *and* β-*Toxicarol with Manganese Dioxide.*—(−)-α-Toxicarol (100 mg.) was shaken with active manganese dioxide (1 g.) in acetone for 7 hr. The solid was filtered off and washed with chloroform. The filtrate and washings were diluted with methanol, and the precipitate was collected and crystallised from chloroform and methanol, to give the orange lactone (XLIId; R = OH) (29 mg.), m. p. 290—291° (decomp.) (Found: C, 65·25; H, 4·3. Calc. for $C_{23}H_{18}O_8$: C, 65·4; H, 4·3%), $\nu_{max.}$ (mull) 1742 (lactone) and 1650 (chelated ketone) cm.$^{-1}$ (lit.,[14] m. p. 283—284°). (±)-β-Toxicarol (100 mg.) similarly gave the corresponding compound in the β-series [cf. (XXXII)] (55 mg.), orange needles, m. p. 298—299° (decomp.) (Found: C, 65·45; H, 4·45%), $\nu_{max.}$ (mull) 1748 and 1653 cm.$^{-1}$.

*Oxidation of* 6a,12a-*Dehydrorotenone with Lead Tetra-acetate.*—Dehydrorotenone (1·4 g.) in glacial acetic acid (50 ml.) was shaken with lead tetra-acetate (5 g.) for 7 days. Water (50 ml.) was added and the precipitate was filtered off, washed with methanol, and extracted with boiling chloroform. The chloroform extract was concentrated and methanol was added. The precipitate was collected and, after crystallisation from chloroform–methanol, gave rotenonone (1·05 g.), yellow plates, m. p. and mixed m. p. 295—297° (decomp.) (Found: C, 67·75; H, 4·55. Calc. for $C_{23}H_{18}O_7$: C, 68·0; H, 4·45%), $\lambda_{max.}$ (in $CHCl_3$) 265 (4·40), 298 (4·33), and 345 (3·95) mμ, $\nu_{max.}$ 1730 (lactone), 1645 (unsatd. ketone), 1620, 1596, 1557, and 1502 (aryl) cm.$^{-1}$.

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