553. *The Absolute Configuration of Rotenone.*

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

The absolute configuration of natural rotenone is determined at centres 6a and 5′ by exhaustive ozonolysis and oxidation. The 5′-centre was extracted from the rotenone degradation product (−)-dihydrotubaic acid as (+)-3-hydroxy-4-methylpentanoic acid. Synthesis and resolution gave the (−)-form of the latter, and this was degraded to (−)-2-methylpentan-3-ol, which can be related to L-glyceraldehyde by correlations in the literature. The 5′-centre of rotenone has the (*R*)-configuration. Ozonolysis of the enol acetate of dihydrorotenone, which has the same configuration as rotenone at positions 6a and 5′, gave (−)-D-glyceric acid containing the 6a-centre, whose configuration is therefore (*S*).

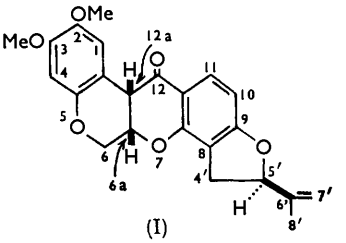
Conformation in the rotenone molecule, which has the stable form of B/C fusion, is considered. Closely related 12a-hydroxy-derivatives are shown to be more stable with a *cis*- than with a *trans*-fusion. Reduction of rotenone and compounds known to have the same B/C fusion as rotenone, [(±)-isorotenone, (−)- and (±)-dihydrodeguelin] gives crystalline 12-hydroxy-compounds which show intramolecular hydrogen bonding. This is adequately explained only when $O_{(5)}$ is the acceptor, a situation possible only with a *cis*-fusion. Other evidence supports the assignment and it is in agreement with study of the hydrogenation of rotenoid derivatives. It follows that the configuration of rotenone at 12a is (*S*), and the complete configuration is (6a*S*, 12a*S*, 5′*R*), as shown in formula (I).

Structural investigations of the insecticidal compound rotenone, which occurs in members of the Leguminosæ, culminated in the proposal (I, without stereochemical designation).[1] The stereochemical problem could be solved by three determinations of absolute configuration, two determinations of absolute and one of relative configuration, or one determination of absolute and two of relative configuration. We have chosen the second course. First, the absolute configuration is determined at 5′, and then again at 6a since it would be difficult to relate these centres to each other. Finally, the mode of

[1] (*a*) LaForge and Haller, *J. Amer. Chem. Soc.*, 1932, **54**, 810; (*b*) Butenandt and McCartney, *Annalen*, 1932, **494**, 17; (*c*) Takei, Miyajima, and Ono, *Ber.*, 1932, **65**, 1041; (*d*) Robertson, *J.*, 1932, 1380.

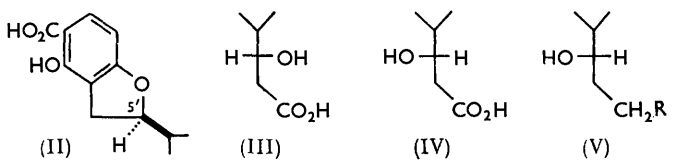
fusion of the B/C ring system is decided: this relates 6a to 12a. The result is shown in formula (I): rotenone has the (6a*S*,12a*S*,5′*R*) configuration.*

Rotenone is cleaved by alkali to give tubaic acid which is readily hydrogenated to dihydrotubaic acid [2] (II), retaining the rotenone configuration at position 5′. On



(I)

exhaustive ozonolysis,[3] followed by oxidation with hydrogen peroxide, dihydrotubaic acid gave (+)-3-hydroxy-4-methylpentanoic acid (III) characterised as its *p*-bromophenacyl ester. Since further degradation is required to derive a compound which has already been correlated with glyceraldehyde, supplies of the enantiomorphic acid (IV) were obtained by synthesis and resolution. A Reformatski reaction between isobutyraldehyde and benzyl bromoacetate, followed by hydrogenolysis of the benzyl grouping, gave the (±)-acid which was resolved *via* the quinine salt to give the (−)-acid (IV). The latter was reduced by lithium aluminium hydride to the (−)-diol (V; R = OH), which was converted into the monotoluene-*p*-sulphonate (V; R = $MeC_6H_4{\cdot}SO_2{\cdot}O$) and reduced



(II) (III) (IV) (V)

further with lithium aluminium hydride to (−)-2-methylpentan-3-ol (V; R = H), characterised as the (−)-3,5-dinitrobenzoate. The infrared spectra of the alcohol (V; R = H) and its 3,5-dinitrobenzoate in solution were identical with those of the racemic compounds prepared from (±)-3-hydroxy-4-methylpentanoic acid.

(−)-2-Methylpentan-3-ol has previously been correlated with L-glyceraldehyde, the isopropyl ultimately replacing the aldehyde group of the latter, and the ethyl group replacing the $\cdot CH_2OH$. The major steps in the correlation are (−)-2-methylpentan-3-ol $\xrightarrow{\text{ref. 4}}$ (+)-α-hydroxybutyric acid $\xrightarrow{\text{ref. 5}}$ (+)-β-hydroxybutyric acid $\xrightarrow{\text{ref. 6}}$ (+)-lactic acid $\xrightarrow{\text{ref. 7}}$ (+)-glyceric acid $\xrightarrow{\text{ref. 8}}$ L-(−)-glyceraldehyde: details of the intermediate transformations are contained in the references above the arrows. (+)-3-Hydroxy-4-methylpentanoic acid from (−)-dihydrotubaic acid is thus related to D-glyceraldehyde and hence rotenone has the (*R*)-configuration [9] at position 5′.

* See Büchi, Kaltenbronn, Crombie, Godin, and Whiting, *Proc. Chem. Soc.*, 1960, 274, for a preliminary communication.

[2] Takei and Koide, *Ber.*, 1929, **62**, 3030.

[3] Schmid and Ebnöther, *Helv. Chim. Acta*, 1951, **34**, 1041; Hardegger, Gempeler, and Züst, *ibid.*, 1957, **40**, 1819, and earlier papers cited there.

[4] Levene and Marker, *J. Biol. Chem.*, 1933, **101**, 413.

[5] Levene and Haller, *J. Biol. Chem.*, 1927, **74**, 343.

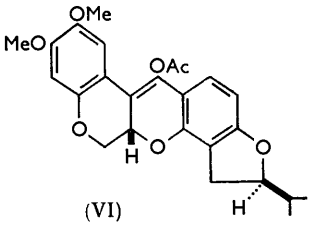
[6] Levene and Haller, *J. Biol. Chem.*, 1925, **65**, 49; 1926, **67**, 329.

[7] Freudenberg, *Ber.*, 1914, **47**, 2027.

[8] Wohl and Schellenberg, *Ber.*, 1922, **55**, 1404.

[9] (*a*) Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81; (*b*) Feldman, *J. Org. Chem.*, 1959, **24**, 1556.

The absolute configuration at position 6a was determined as follows. Treatment of rotenone with acetic anhydride and sodium acetate yields a mixture of enol acetates epimeric at position 6a. Only one has been isolated crystalline and this has the natural configuration at $C_{(6a)}$ because acid-hydrolysis, which does not racemise the latter centre, yields only natural rotenone:[10] this has been confirmed. Also, enol acetylation of rotenone under acid conditions (isopropenyl acetate) gives the same crystalline acetate. The enol acetate was hydrogenated to acetyl 6′,7′-dihydrorotenone[11] (VI) which can also



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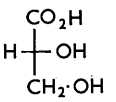


(VII)

be made direct from 6′,7′-dihydrorotenone by the isopropenyl acetate–acid technique: like acetylrotenone[10,12] it exists in dimorphic forms. Exhaustive ozonolysis of acetyl-6′,7′-dihydrorotenone gave a mixture of acids which were purified by ion-exchange chromatography. Paper chromatography[13] of the product indicated a mixture of glyceric and 3-hydroxy-4-methylpentanoic acid which was converted into the mixed *p*-bromophenacyl esters. The derivative insoluble in hot hexane was recrystallised from benzene–hexane, and had m. p. 109—111°, $[\alpha]_D^{25}$ −1·49°. Its m. p. was undepressed by varying proportions of *p*-bromophenacyl (−)-glycerate, m. p. 109—111°, $[\alpha]_D^{25}$ −1·9°, made from authentic (−)-glyceric acid[14] (VII) which has been related to D-glyceraldehyde. The hexane-soluble fraction gave the *p*-bromophenacyl ester of (+)-3-hydroxy-4-methylpentanoic acid (above). Rotenone therefore has the (*S*)-configuration at position 6a. The hydrogen atom at 6a is used as a reference point below and its orientation is designated β.

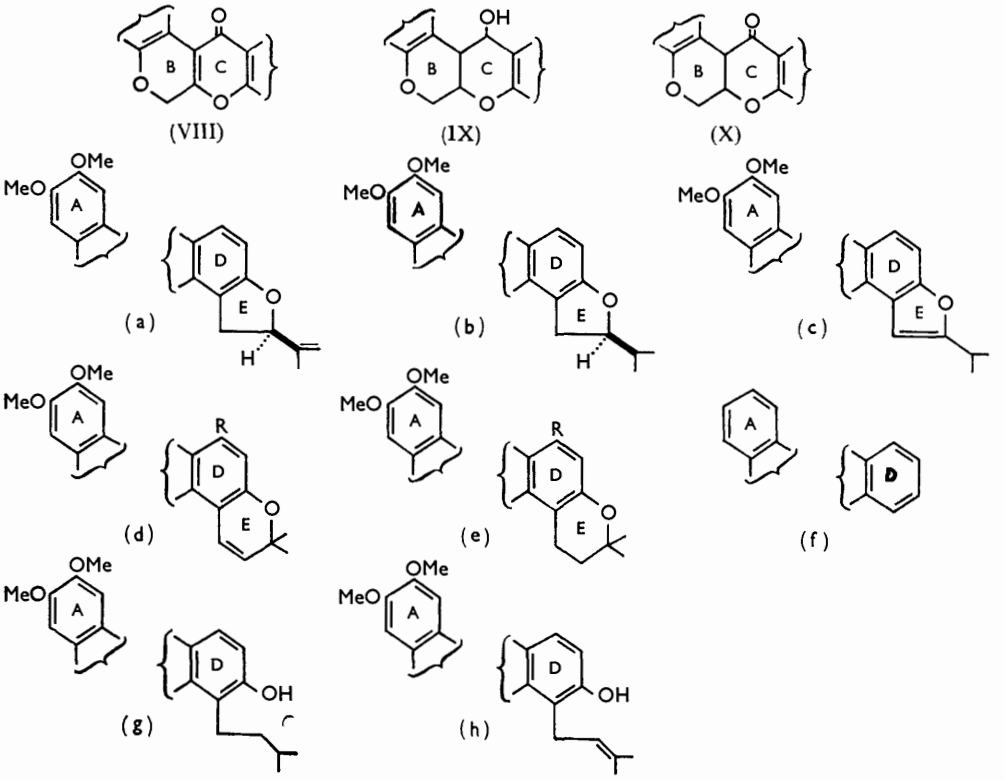
Cahn and his colleagues[10] have established that natural rotenone has the stable form of B/C fusion: they thought this might be *trans*, but reserved judgment. It was later suggested[15] that if rotenone had a *cis*-fusion a spatial relationship with DDT and methoxychlor could be developed to accommodate their common biological activity. The theory is highly speculative and no convincing chemical evidence was forthcoming. More recently, Miyano and Matsui[16] claim to have determined that rotenone has the *trans*-fusion. 6a,12a-Dehydrorotenone (VIIIa) was treated with sodium borohydride to give an amorphous alcohol (IXa) which, on Oppenauer oxidation, yielded a mixture of two diastereoisomers ("mutarotenone"),[10] one of which was natural rotenone. Such a sequence should lead to a product with the thermodynamically stable fusion and this work only confirms the earlier view.[10] Their claim to have decided from molecular models that the *trans*-B/C fusion is more stable than the *cis*- seems to us to be unacceptable.

Models for rotenone can be set up as follows. Aromatic ring D and atoms 7, 12, and 12a are coplanar or nearly so: resonance energy will be maximal if the 12-keto-group, and hence $C_{(12a)}$, is coplanar with ring D. Aromatic ring A, and atoms 5 and 12a, are coplanar, Atom 12a is common to the two approximately planar, but not coplanar, systems. Strain is taken up by deviation of atoms 6 and 6a from coplanarity with either system, *i.e.*, ring B can be a quasi-boat or quasi-chair. The two limiting conformations of the flexible

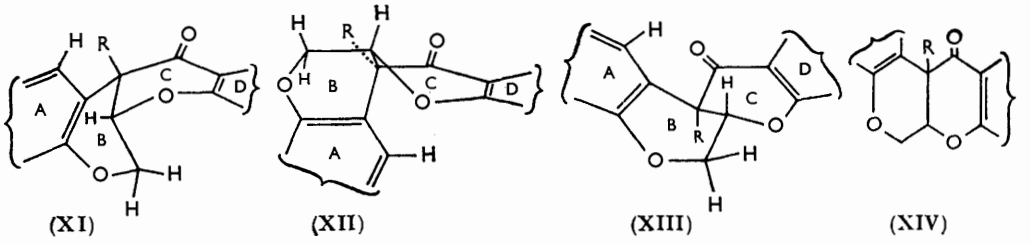
[10] Cahn, Phipers, and Boam, *J.*, 1938, 513.
[11] Smith and LaForge, *J. Amer. Chem. Soc.*, 1932, **54**, 2996.
[12] Cahn and Boam, *J. Soc. Chem. Ind.*, 1935, **54**, 42T.
[13] Palmer, *Science*, 1956, **123**, 415; *Connecticut Agr. Exp. Station Bull.*, 1955, No. 589.
[14] Anderson, *Amer. Chem. J.*, 1909, **42**, 401.
[15] Hummer and Kenaga, *Science*, 1951, **113**, 653.
[16] Miyano and Matsui, *Chem. Ber.*, 1958, **91**, 2044.

cis-fusion (XI and XII; R = H) and the one rigid *trans*-fusion (XIII; R = H) are represented in the formulæ annexed with ring B as a quasi-chair.

Natural rotenone, (—)-isorotenone [(Xc), configuratively the same at $C_{(6a)}$ and $C_{(12a)}$ as the former [10]] and other 12a-unsubstituted relatives are known only with the B/C fusion in its stable form. The difficulty attending isolation of the other fusion concerns enolisation at 12a. But in the case of the 12a-hydroxy-derivatives both fusions are known and have been



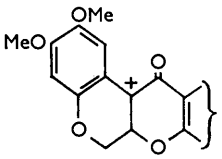
assigned by methods independent of assumptions about the configuration of rotenone itself.[17] Thus (±)-isorotenolone A is the *cis*-fused racemate (XIVc; R = OH), and (±)-isorotenolone B the corresponding *trans*-fused form. These give corresponding methyl



ethers when treated with methyl iodide and silver oxide. When the methyl ether of (±)-isorotenolone A is refluxed with methanolic sulphuric acid, except for the formation of 6a,12a-dehydro-compound (VIIIc), it is recovered unchanged. But similar treatment of the methyl ether of (±)-isorotenolone B converts it into the derivative of A (and dehydro-compound). The corresponding rotenolone methyl ethers (XIVa; R = OMe) behave

[17] Crombie and Godin, following paper; *Proc. Chem. Soc.*, 1960, 276.

analogously and the interconversion probably involves the carbonium ion (XV—XVII) which, despite its unfavourable placing α- to the ketone, is stabilised by resonance: the situation is not without precedent.[18] The partial positive charge at $C_{(12)}$ is also diminished by resonance involving the *o*- and *p*-oxygenated ring D. When acetylated by refluxing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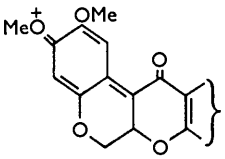
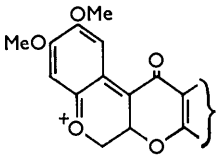
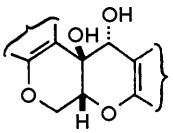
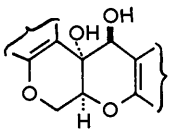

(XVI)


(XVII)

acetic acid–acetic anhydride containing sodium acetate, (±)-isorotenolone A and B each give 6a,12a-dehydroisorotenone and the same acetate (XIVc; R = OAc). The diol produced when the latter is reduced with lithium aluminium hydride is the same as that obtained when (±)-isorotenolone A is reduced and differs from either of the diols obtained when (±)-isorotenolone B is similarly treated. This diol is the racemate[17] (XVIIIc–XIXc), and the acetate is of the *cis*-series. It again follows that the thermodynamically stable product, produced under equilibrating conditions, has the *cis*-B/C junction. Examin-


(XVIII)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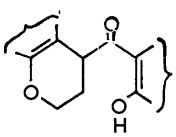
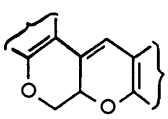
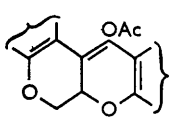
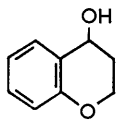

(XX)

ation of models (XI—XIII) for non-bonded interactions which might destabilise one fusion relative to the other suggests a likely cause is interaction between the 1-hydrogen and the 12-ketonic oxygen atom. In the rigid *trans*-fusion the distance between atomic centres is ~2·05 Å (ring B a quasi-chair; ~1·95 Å if a quasi-boat; measurements with Barton-type models). Interaction is relieved in the *cis*-fusion.

Direct evidence in favour of the *cis*-B/C fusion in rotenone itself was obtained as follows. Reduction of (±)-isorotenone (Xc) with potassium borohydride gave a crystalline hydroxy-compound (IXc) in more than 80% yield. The latter was also obtained by hydrogenating (±)-isorotenone in ethyl acetate over Adams platinum at 100°/60 atm. [some isorotenol (XXc) being formed], or by treating 6a,12a-dehydroisorotenone with borohydride. The hydroxy-compound (IXc) is readily dehydrated by phosphorus oxychloride in pyridine,


(XXI)


(XXII)

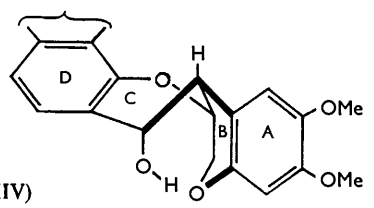

(XXIII)

dilute mineral acid, or chromatography on acid alumina, giving the stilbene-like compound (XXIc), and comparison of the ultraviolet absorption of the latter with that of isorotenone enol acetate (XXIIc) confirms the presence of such a chromophore.[17] Similar crystalline alcohols were also obtained from (±)- and (−)-4′,5′-dihydrodeguelin [β-dihydrorotenones, (Xe; R = H): these have the same B/C fusions as natural rotenone],[19-22] but the alcohol

[18] House and Reif, *J. Amer. Chem. Soc.*, 1955, **77**, 6525.
[19] Haller and LaForge, *J. Amer. Chem. Soc.*, 1934, **56**, 2415.
[20] Haller, *J. Amer. Chem. Soc.*, 1931, **53**, 733.
[21] Clark, *J. Amer. Chem. Soc.*, 1931, **53**, 2369.
[22] (*a*) Haller and LaForge, *J. Amer. Chem. Soc.*, 1931, **53**, 3426; (*b*) LaForge, Haller, and Smith, *Chem. Rev.*, 1933, **12**, 181.

(IXa) from natural rotenone could be crystallised only as its methanol solvate. In the infrared spectrum these unsolvated alcohols showed a free (or lightly bonded) hydroxyl and a bonded hydroxyl group (the latter giving the stronger band). Figures are: (±)-(IXc), 3613, 3566 cm.$^{-1}$, Δ 47 *, Δ_s 63 *; (−)-(IXe; R = H), 3611, 3564 cm.$^{-1}$, Δ 47, Δ_s 65 (all LiF–CCl_4, c <0·005M). The solvated alcohol from rotenone has the same two bands at 3612 and 3561 cm.$^{-1}$, Δ 51, Δ_s 68, together with a third at 3641 cm.$^{-1}$ (primary hydroxyl of methanol).

Without prior assumption about the relative configurations at centres 6a, 12a, or 12, molecular models were examined to trace the acceptor seat of the hydrogen bond. Acceptors in rings C, D, or E do not offer a suitable explanation, particularly since chroman-4-ol † (XXIII) has only a single band at 3615 cm.$^{-1}$ (cf. 1-hydroxytetralin 3614 cm.$^{-1}$). There are two significant possibilities. Either the hydrogen bond is formed to aryl ring A or to $O_{(5)}$. If a *trans*-B/C fusion is postulated, bonding of the former but not the latter type is possible when the 12-hydroxyl group is β (*i.e.*, 6aβ,12aα,12β) ‡; if it is α-, neither type is feasible. With the 12-hydroxyl β, it is less well orientated towards, and more distant from, the aromatic π-electrons than in a 2-arylethanol. In comparably substituted examples of the latter a stronger bond (larger Δ and Δ_s) would be expected. Data for arylethanols are: 2-phenylethanol,[24] 3631, 3604 cm.$^{-1}$, Δ 27, Δ_s 38; 2-*m*-methoxyphenylethanol,[24] 3631, 3605 cm.$^{-1}$, Δ 26, Δ_s 37; 2-*p*-methoxyphenylethanol,[24] 3633, 3602 cm.$^{-1}$, Δ 31, Δ_s 40; 2-(3,4-dimethoxyphenyl)ethanol 3632, 3594 cm.$^{-1}$, Δ 38 Δ_s 48 (cf. 3,4-dimethoxyphenylmethanol 3612 cm.$^{-1}$). This explanation is not, therefore, supported. A *cis*-B/C fusion with a β-oriented hydroxyl (6aβ,12aβ,12β) also gives no satisfactory explanation. But when the hydroxyl is α- in this series (6aβ, 12aβ, 12α), particularly when ring B is a quasi-boat,



(XXIV)

close approach of the 12-hydroxyl to $O_{(5)}$ is possible, as in (XXIV). Conformational equilibrium will result in the presence of a free and a bonded band. Such ether bonding provides a suitable explanation for the fairly large Δ and Δ_s values and, in confirmation, 2-(3,4,6-trimethoxyphenyl)ethanol has three bands in the hydroxyl region—at 3633, 3602, and 3547 cm.$^{-1}$, Δ 31 and 86, Δ_s 40 and 95. The second band is ascribed to aryl bonding and the third to bonding to the oxygen of the 6-methoxyl group, a situation resembling that in (XXIV) but freer from geometrical restriction.§

The hydroxy-compounds of the type (IX), in the three series mentioned (a, c, and e; R = H), thus have the 12-hydroxyl group *trans* to the 12a-hydrogen atom, in agreement with the ready dehydration, and the *cis*-B/C fusion must also be present in rotenone and

* Δ = Difference between first and second hydroxyl absorption. Δ_s = Difference between second hydroxyl absorption and a standard primary (3642 cm.$^{-1}$) or secondary (3629 cm.$^{-1}$) value as appropriate.[23]

† We thank Professor O. Dann for this specimen.

‡ In the racemates, of course, 6aα, 12aβ, and 12α also; discussion is in terms of (−)-rotenone or (−)-4′,5′-dihydrodeguelin.

§ A recent report,[25] based on examination of 32 compounds having the crinane nucleus, states that the stretching frequencies for secondary hydroxyl groups bonded to the π-electrons of a double bond or an aromatic ring (substituted by methylenedioxy) occur between 3602 and 3581 cm.$^{-1}$. Hydroxyl groups bonded to adjacent ether or hydroxyl groups absorb between 3582 and 3526 cm.$^{-1}$ (weak bonds in other series give, of course, higher $\nu_{max.}$ values).

[23] Cole and Jefferies, *J.*, 1956, 4391.

[24] Schleyer, Wintner, Trifan, and Bacskai, *Tetrahedron Letters*, 1959, No. 14, 1.

[25] Fales and Wildman, Abs. Amer. Chem. Soc. 138th Meeting, Sept. 11–16, 1960, p. 19P.

those compounds related to it. Hence natural rotenone is (6a*S*,12a*S*,5′*R*.)* † The formation of compound (XXIV) by attack of borohydride ion on the corresponding 12-ketone (XI—XII), or by catalytic hydrogenation, is as expected because approach of the reagent to the ketone or the ketone to the catalyst would involve the less hindered β-face. This is noticeable when the rotenolones and isorotenolones are reduced. The *trans*-B/C compounds (B series; XIIIa or c; R = OH) give two diols, since either face is open to attack, but it has been possible to isolate only one diol from parallel reductions among the *cis*-B/C compounds [17] (A series; XI—XIIa or c; R = OH). It is of incidental interest that *cis*-B/C forms in the rotenolones and isorotenolones and their derivatives are, in contrast to the *trans*-forms, frequently solvated. Various solvates are well known in the natural rotenoids.[27] Solvate formation may be associated with provision by the bent *cis*-skeleton, in contrast to the rigid and fairly planar *trans*-structure, of suitable lattice spaces (cf. *cis*-A/B steroids).[28] (−)-Isorotenone, with the same 6aβ,12aβ-configuration as rotenone, has a positive Cotton effect in methanol, max. 390 mμ, [α] +180°, and the curve for (+)-isorotenone is enantiomeric in detail.‡ Such information is difficult to interpret at the present time on the basis of the octant rule,[29] but a positive Cotton effect seems not inconsistent if the B/C system in rotenone is *cis*-fused.

The remainder of this paper considers the hydrogenation of unsaturated derivatives of rotenone, a process which has bearing on the stereochemistry discussed above. If 6′,7′-dihydrorotenone (Xb) has a *cis*-B/C fusion as claimed above, it should be accessible by catalytic hydrogenation, with *cis*-addition, of the 6a,12a-dehydro-compounds (VIIIa) or (VIIIb). But as proof of a *cis*-B/C fusion in rotenone such an experiment is open to objection. Thus, the addition of hydrogen might be 1,4 rather than 1,2, or the initially produced unstable fusion might stereomutate to the more stable one under the reaction conditions. There is also experimental difficulty inasmuch as the tetra-substituted pyrone double bond in the approximately planar A/B/C/D system is difficult to hydrogenate and other reactions such as 1′,5′- or 6a,7-ether cleavage, or reduction and hydrogenolysis at position 12, can occur, often critically dependent on the conditions used. In the present work, 6a,12a-dehydrorotenone (VIIIa) gave, on hydrogenation over platinum in ethyl acetate at 25°/10 atm., besides 6′,7′-dihydro-6a,12a-dehydrorotenone (VIIIb), the 1′,5′-seco-compound (VIIIg). On the other hand, hydrogenation of 6′,7′-dihydro-6a,12a-dehydrorotenone over platinum at 70°/60 atm. in the same solvent gave the 6a,7-*seco*-compound, dihydrorotenol (XXb). Nonetheless, the matter has been examined because, apart from intrinsic interest, the results must fit into a consistent and explicable pattern if our stereochemical views are accepted.

Recent writers have overlooked that the first successful 6a,12a-reduction of a rotenoid was Clark's conversion [30] of 6a,12a-dehydrotoxicarol (VIIId; R = OH) into (±)-4′,5′-dihydrotoxicarol (Xe; R = OH), identical with that made by hydrogenating (±)-toxicarol (Xd; R = OH). We have confirmed this (platinum catalyst in acetic acid at 70° and atmospheric pressure) and find that if an active catalyst is used the temperature can be lowered to 20°. Similarly, the synthetic 6a,12a-dehydro-compound [31] (VIIIf) yields

* Dr. W. D. Ollis has kindly informed us that in collaboration with Professor Djerassi it has been found that the natural rotenoids toxicarol, elliptone, pachyrrhizone, and munduserone, as well as sumatrol 11-acetate, have the same positive Cotton effect as natural rotenone.[26] It therefore seems that they also are (6a*S*,12a*S*)-compounds.

† /6/-Rotenone on the (*R*/*S*)-symbolism, /7/-rotenone on the α/β-system, according to Feldman's notation.[9b]

‡ We thank Professor K. Wiesner and Dr. F. Bickelhaupt, University of New Brunswick, for these measurements.

[26] Djerassi, Ollis, and Russell, *J.*, 1961, 1448.
[27] Jones, *J. Amer. Chem. Soc.*, 1931, **53**, 2738.
[28] L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, 1959, p. 58.
[29] Moffit, Woodward, Djerassi, and Klyne, unpublished work; C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill, New York, 1960.
[30] Clark, *J. Amer. Chem. Soc.*, 1931, **53**, 2264.
[31] LaForge, *J. Amer. Chem. Soc.*, 1933, **55**, 3040.

a ketone (Xf), the structure of which is confirmed by dehydrogenation back to (VIIIf). The ketone (Xf) is the parent of the rotenoid series and has the stable fusion since it can also be made by reducing (VIIIf) with borohydride * to give (XIXf), followed by chromic acid oxidation and is not epimerised by base. Hydrogenation of (—)-6′,7′-dihydro-6a,12a-dehydro-5′(*R*)-rotenone (VIIIb) is more complicated experimentally, since a mixture of two diastereoisomers with the same B/C fusion (6′,7′-dihydrorotenone and 6′,7′-dihydroepirotenone according to Cahn's usage,[9] or 6aβ,12aβ,5′β and 6aα,12aα,5′β) is produced. The former is readily isolated, identical with authentic material, but polarimetric results on the stereomutation of the whole product indicate that considerably more 6′,7′-dihydroepirotenone than 6′,7′-dihydrorotenone is formed. Thus, in all three hydrogenations the stable fusion is being produced from a reaction which, barring the contingencies mentioned, might be expected to give a *cis*-product. Since the 5′-isopropyl group of 6′,7′-dihydrorotenone is β-oriented (see above), the production of more *cis*-B/C material of the epi-series (6aα,12aα) than the " natural " series (6aβ,12aβ) is reasonably explained as due to hindrance by the (*R*)-5′ substituent to approach of this side to the catalyst surface. The A/B/C/D/E system of 6′,7′-dihydro-6a,12a-dehydrorotenone is approximately planar. Dann and Volz [34] have, in this connexion, recently found that hydrogenation of 6a,12a-dehydrorotenone in dimethylformamide over a palladium catalyst at 40°/250 atm. gives diastereoisomers of (IXb) which, when oxidised, produce considerably more 6′,7′-dihydroepirotenone than 6′,7′-dihydrorotenone. This agrees with our results.

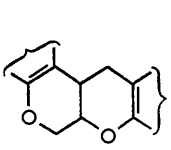
On the other hand, two recent papers [35,36] by Takahashi and his colleagues conflict with our results and, interpretatively, with each other. Thus, catalytic hydrogenation of (—)-6′,7′-dihydro-6a,12a-dehydro-5′(*R*)-rotenone, under conditions similar to those we have used, is said to lead to two diastereoisomers of dihydrorotenone belonging to the unstable or " allo " ring-junction series.[9] As the claim that rotenone is *trans* [16] is accepted, these are said to be *cis*-B/C forms. From the data given [36] we feel that these may be *cis*-forms, but mixtures of dihydrorotenone and dihydroepirotenone of the stable series and not new compounds of the " allo " series. These authors have also reported the catalytic hydrogenation of the 6a,12a-dehydro-compound (VIIIf), and their product,[35] from its m. p., is the same racemate as we obtained. Rightly, we think, they consider it a *cis*-compound, but we have shown above that it also has the stable fusion, so their views on the hydrogenation of (—)-6′,7′-dihydro-6a,12a-dehydrorotenone do not seem in accord with their own findings. Reduction of the dehydro-ketone (VIIIf) with borohydride gives an alcohol (IXf) (m. p. 180°; acetate, m. p. 163°) which is clearly different from one (m. p. 239°; acetate, m. p. 147°) isolated [37] from the mixture of products obtained when the 6a,12a-dehydro-ketone (VIIIf) is reduced over palladium at 40°/200 atm. Both, on oxidation, give the same ketone (Xf). Our alcohol of m. p. 180° is expected to be the racemate with a *cis*-B/C fusion and a *trans*-12a-H,12-OH relationship. Since the alcohol of m. p. 239° is not easily dehydrated, or easily oxidised with chromic acid, it seems reasonable that it should have a *cis*-12a-H,12-OH relationship. With a *cis*-B/C fusion the 12aα-hydrogen might be somewhat hindered to chromic acid oxidation, though because of the reaction conditions it does not necessarily follow that the parent alcohol must have the same fusion as the derived

* Presumably the unsaturated ketone is reduced 1,4 and the boron derivative decomposes under the reaction conditions to give the ketone (Xf) which is then further reduced.[16] There seems some evidence that zinc dust and alkali can cause 1,4-reduction in similar systems, since treatment of 6a,12a-dehydrorotenone can give derritol besides derrisic acid, and 6a,12a-dehydroelliptone behaves similarly.[32] This would be rational if 1,4-reduction were competing with hydrolysis of 6a,12a-dehydrorotenone, since the rotenone diastereoisomers would then undergo further degradation to derritol.[33]

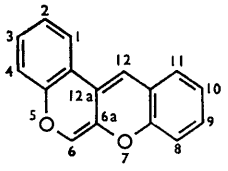
[32] Harper, *J.*, 1942, 587.
[33] Crombie, Godin, Whiting, and Siddalingaiah, *J.*, 1961, 2876.
[34] Dann and Volz, *Annalen*, 1960, **631**, 102.
[35] Fukami, Takahashi, Konishi, and Nakajima, *Bull. Agric. Chem. Soc. Japan*, 1960, **24**, 119.
[36] Takahashi, Fukami, and Nakajima, *Bull. Agric. Chem. Soc. Japan*, 1960, **24**, 123.
[37] Dann and Volz, *Annalen*, 1960, **631**, 111.

ketone. These hydrogenation experiments are thus consistent with the proposed B/C fusion.

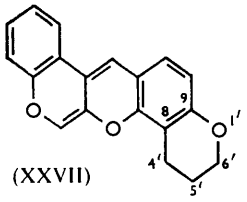
Other hydrogenation work has interest in connection with the stereochemical results obtained above. Hydrogenolysis of either (±)-4′,5′-dihydrodeguelin [(±)-β-dihydrorotenone] (Xe; R = H),* or its borohydride reduction product (IXe; R = H) gives the (±)-deoxy-compound (XXVe; R = H) which must retain the same *cis*-B/C fusion as rotenone. It has been found that catalytic hydrogenation of the (±)-12,12a-olefin (XXIe; R = H), made by dehydrating the alcohol (IXe; R = H), gives the same *cis*-B/C compound (XXVe; R = H). Experiments with (−)-4′,5′-dihydrodeguelin and with rotenone give a similar result except that in the dehydration to produce the 12,12a-olefin there is some racemisation at 6a. Thus, the hydrogenation of this olefin in the (−)-4′,5′-dihydrodeguelin series leads to *cis*-B/C compound (XXVe; R = H) which is separable into the (±)-form (above) and the (−)-form identical with the product obtained by hydrogenolysis of the (−)-ketone (Xe; R = H) or (−)-alcohol (IXe; R = H). Similarly, catalytic hydrogenolysis of rotenone, its borohydride reduction product (IXa), and rotenone enol acetate (XXIIa) all give the same compound (XXVb), $[\alpha]_D$ −148·5° to −150·5°, but dehydration of (−)-alcohol (IXa) and then hydrogenation gave (XXVb), $[\alpha]_D$ −128·2°, though identical in respect of m. p. and infrared, and ultraviolet spectra with specimens having the full optical activity. Partial racemisation during the dehydration occurs, but there may also be further racemisation during hydrogenation. Therefore, in the three examples taken, catalytic hydrogenation has occurred by attack of hydrogen on the β-face of the 12,12a-olefinic compounds (XXI) and not the α, which would give a *trans*-B/C product. Examination of molecular models indicates that in the structures (XXIe; R = H), (XXIb), and (XXIIb), $C_{(12a)}$ is perhaps less accessible to the catalyst surface from the α- than from the β-side, but the apparently high stereospecificity of attack is rather surprising. There are probably other factors also involved. If the transition state tends to resemble the final product, addition to the β-face gives a *cis*-B/C-species in which the two aromatic rings are twisted away from the catalyst and the final species would be rapidly desorbed.



(XXV)



(XXVI)



(XXVII)

Nomenclature.—Rotenoid literature abounds with trivial names for degradation products; where well established, these are used here for brevity, but confusion can arise. Thus rotenol ordinarily refers to the phenol (XXa):[38] it has been applied to a different compound,[39] and recently has been used for still a third.[16] "Ring Index" naming is cumbrous and confusing in that the essential A/B/C/D ring systems may take on different numbering, depending on the nature of ring E. A simple solution would be to give each rotenoid a trivial name and to number as in formula (I). After consultation with the

* (−)-4′,5′-Dihydrodeguelin is made by cyclising the phenolic ketone (Xh) in an acid medium. The latter ketone, which results from hydrogenation of rotenone under controlled conditions, was considered to be a product of 1,4-reduction,[19–22] but it has also been formulated [10] as a 1,2-ether cleavage product, *i.e.*, as the isopropenyl analogue of (Xh). Both structures could lead to the tertiary carbonium ion required for cyclisation. Structure (Xh) is correct, for the nuclear magnetic resonance spectrum shows two "unsaturated" methyl groups, *i.e.*, Me attached to C:C (τ 8·36 and 8·27). We thank Dr. J. W. Lown for this information

[38] Butenandt, *Annalen*, 1928, **464**, 253; cf. Haller and LaForge, *J. Amer. Chem. Soc.*, 1930, **52**, 4505; Takei, Miyajima, and Ono, *Ber.*, 1931, **64**, 1000.

[39] Takei, Koide, and Miyajima, *Ber.*, 1930, **63**, 1369.

Editor, however, we have used, where necessary, a longer but more systematic procedure. Rotenoids are named from the parent rotoxen (XXVI). The synthetic compound (VIIIf) becomes 6*H*-rotoxen-12-one † and (Xf) 6a,12a-dihydro-6*H*-rotoxen-12-one.* The compound (XXVII) is 5′,6′-dihydro-4*H*-pyrano(3′,2′-8,9)rotoxen, and natural rotenone with full configurational prefixes is 6aβ,12aβ,4′,5′-tetrahydro-2,3-dimethoxy-5′β-isopropenylfurano(3′,2′:8,9)-6*H*-rotoxen-12-one.* The prefix "seco" is useful in dealing with degradation product in which rings C or E is broken.

Experimental

Unless otherwise indicated the following apply. Ultraviolet spectra were determined for ethanol solutions: log ε in parentheses, follows $\lambda_{max.}$, and i indicates an inflexion. Infrared spectra were determined for chloroform solutions with sodium chloride optics. Molecular weights were determined ebullioscopically in benzene or chlorobenzene. In chromatographic work the letters N, A, or K together with a numeral refer to neutral, acid, and alkaline alumina of the numbered Brockmann grade. Instantaneous m. p.s determined on a Kofler hot-bar are indicated (br.). Evaporation signifies evaporation under diminished pressure, and drying infers the use of anhydrous sodium sulphate.

Rotenone.—Commercial cubé-timbo resin (2 kg.) in carbon tetrachloride (10 l.) was set aside at 0° and the crystals were filtered off and washed with carbon tetrachloride and then methanol. Dissolution in trichloroethylene, filtration, and dilution of the filtrate with methanol caused crystallisation of rotenone (654 g.). Recrystallisation from trichloroethylene and drying at 70° gave rotenone, m. p. 165—166° (or polymorph, m. p. 185—186°), $[\alpha]_D^{20}$ −228° (*c* 2·22 benzene), $\lambda_{max.}$ 217 (4·47), 236 (4·18), 244 (4·11), and 295 (4·23) mμ, $\nu_{max.}$ 1674 (C=O), 1610, 1511 (aryl), and 909 (vinyl) cm.$^{-1}$ {lit.,[40,10] m. p. 163°, 181—183° $[\alpha]_D$ −226° (in benzene)}.

Ozonolysis and Oxidation of (−)-Dihydrotubaic Acid.—Natural rotenone was degraded to tubaic acid, m. p. 128·5—130°, according to Takei and Koide's procedure [2] (lit.,[2] m. p. 129°), and this was hydrogenated in ethyl acetate over 5% palladium–barium sulphate to give (−)-dihydrotubaic acid, m. p. 167—168°, $[\alpha]_D^{25}$ −91° (in $CHCl_3$) {lit.,[2] m. p. 166°, $[\alpha]_D^{20}$ −82°}. (−)-Dihydrotubaic acid (1·05 g.) in chloroform (50 ml.) was ozonised (8 mg. of O_3/min.) at 0° for 3½ hr. The chloroform solution was poured off from a small amount of white crystalline material and evaporated to give an oil which was refluxed for 30 min. with water (25 ml.). The aqueous solution was continuously extracted with ether for 17 hr. and the extract was dried and evaporated to give a brown oil which slowly crystallised. Chromatography of the solid on silica gel from benzene and elution with benzene–ether, gave fractions which appeared from their infrared spectra to be mixtures of the expected hydroxy-keto-acid and the hydroxy-acid (III) ($\nu_{max.}$ 1742 and 1712 cm.$^{-1}$).

The brown oil (270 mg.) in 4% potassium hydroxide (10 ml.) was treated with 30% hydrogen peroxide (4 ml.) in one portion, with cooling. After 1 hr. at 20° the solution was warmed at 50° for 15 min. Water (20 ml.) was added and sulphur dioxide was passed through the solution until it was acidic to Congo Red. Extraction of the product with ether gave an oil (208 mg.) which was chromatographed on silica gel; elution with chloroform–ether (20 : 1) gave (+)-3-hydroxy-4-methylpentanoic acid (154 mg.), a liquid ($\nu_{max.}$ 1712 cm.$^{-1}$), $[\alpha]_D^{25}$ +26·4° ± 0·6° (*c* 2·1 in $CHCl_3$), characterised as the *4-bromophenacyl ester*, m. p. 73·5—74°, $[\alpha]_D^{26}$ +13·6° ± 1° (*c* 0·74 in $CHCl_3$) (Found: C, 51·4; H, 5·35. $C_{14}H_{17}O_4Br$ requires C, 51·1; H, 5·2%).

(±)-3-*Hydroxy*-4-*methylpentanoic Acid.*—Approx. 20 ml. of a mixture of benzyl bromoacetate [41] (58·8 g.), isobutyraldehyde (19·4 g.), benzene (100 ml.), and ether (40 ml.) were added to granulated zinc (16·8 g.) with warming and stirring. When reaction started, the remainder of the mixture was added dropwise during 1 hr., sufficient heat being applied to maintain refluxing. Refluxing was continued for 1 hr. and the product was cooled and extracted with 10% sulphuric acid. The organic layer was washed with saturated sodium hydrogen carbonate solution and then water, dried ($MgSO_4$), and evaporated. Since attempted distillation caused some dehydration the crude benzyl 3-hydroxy-4-methylpentanoate (20 g.) in ethyl acetate

* This use of the suffix "one" accords with *Chemical Abstracts* practice. An alternative name for (VIIIf) is 6,12-dihydro-12-oxorotoxen; and similarly for the analogous ketones, rotenone itself having a hexahydro-prefix (not tetrahydro).

[40] Cahn, *J.*, 1934, 1129.
[41] Clarke, *J.*, 1910, 416.

(125 ml.) was hydrogenolysed over 7% palladium–strontium carbonate. The calculated amount of hydrogen was consumed in 7½ hr. and the solution was filtered through " Celite " and evaporated. The product was chromatographed on silica gel to give (±)-3-hydroxy-4-methylpentanoic acid, characterised as the (±)-4-*bromophenacyl ester*, m. p. 83·5—84° (Found: C, 51·5; H, 5·5%). The infrared spectra of this (±)-acid and its (±)-ester were identical (solutions) with those of the corresponding (+)-compounds (above).

Optical Resolution of (±)-3-*Hydroxy*-4-*methylpentanoic Acid.*—(±)-Acid (5·44 g.) in ethyl acetate (50 ml.) was added to a warm solution of quinine in ethyl acetate (200 ml.). Concentration gave a quinine salt (8·0 g.), m. p. 147·5—151·5°, $[\alpha]_D$ −143·5° ± 0·5° (in EtOH). Recrystallisation from ethyl acetate gave quinine salt (5·7 g.), m. p. 151·5—153°, $[\alpha]_D^{25}$ −145° ± 2° (*c* 1·03 in EtOH). The acid (2·9 g.), $[\alpha]_D^{28}$ −24·7° ± 0·6° (*c* 0·98 in $CHCl_3$), was isolated from this salt by treatment with 10% sulphuric acid and extraction with ether. Its infrared spectrum was identical with that of the specimen of enantiomeric (+)-acid (above). The 4-*bromophenacyl ester* had m. p. 74—75°, $[\alpha]_D^{25}$ −14·4° (*c* 2 in $CHCl_3$), and the same infrared spectrum as the (+)-ester (Found: C, 51·4; H, 5·4%).

(±)- *and* (−)-4-*Methylpentane*-1,3-*diol.*—(±)-3-Hydroxy-4-methylpentanoic acid (1·92 g.) was added dropwise to lithium aluminium hydride (0·76 g.) in ether (25 ml.), and the mixture was refluxed for 2 hr. Water (5 ml.) was added and the ethereal solution was decanted. The residue was thoroughly extracted with ether, and the combined ethereal solutions were dried and evaporated. Distillation at 10 mm. (bath 130°) gave (±)-4-methylpentane-1,3-diol (1·26 g.), characterised as the *di*-α-*naphthylurethane*, m. p. 136—137° (Found: C, 73·6; H, 6·15. $C_{28}H_{28}O_4N_2$ requires C, 73·65; H, 6·2%).

The (−)-acid (2·9 g.), similarly reduced, gave (−)-4-methylpentane-1,3-diol (2·1 g. crude) which when distilled at 13 mm. (bath 130—135°) had n_D^{25} 1·4482 and $[\alpha]_D^{27}$ −6·9° ± 0·2° (*c* 2·84 in $CHCl_3$). Its infrared spectrum was the same as that of the (±)-diol. The *di*-α-*naphthylurethane* of the (−)-diol had m. p. 134·5—136·5° (Found: C, 73·95; H, 6·4%).

(±)- *and* (−)-4-*Methyl*-1-*toluene*-p-*sulphonyloxypentan*-3-*ol.*—Toluene-*p*-sulphonyl chloride (2·03 g.) was added to (±)-4-methylpentane-1,3-diol (1·26 g.) in dry pyridine (15 ml.) with cooling. The mixture was kept at 20° for 11 hr. and then poured into ether (100 ml.) and extracted with 5% hydrochloric acid, 2% aqueous sodium carbonate, and water. The ethereal solution was dried and evaporated to give the crude (±)-toluene-*p*-sulphonate (1·47 g.) having the characteristic bands (1176 and 915 $cm.^{-1}$) of such a derivative. Attempted distillation or chromatography on alumina (N1) caused decomposition.

(−)-4-Methylpentane-1,3-diol (1·39 g.) similarly gave a crude (−)-toluene-*p*-sulphonate (1·8 g.).

(±)- *and* (−)-2-*Methylpentan*-3-*ol.*—The crude (±)-toluene-*p*-sulphonate (1·47 g.) was refluxed with lithium aluminium hydride (228 mg.) in ether (10 ml.) for 4 hr. Water (5 ml.) was added, the ether layer decanted, the residue extracted with ether, and the ethereal solution dried and evaporated. Distillation of the residue at atmospheric pressure gave (±)-2-methylpentan-3-ol (258 mg.) (bath 135—140°), n_D^{25} 1·4173 (lit.,[42] n_D^{20} 1·4175), characterised as the 3,5-*dinitrobenzoate*, m. p. 81—82° (Found: C, 52·95; H, 5·6. $C_{13}H_{16}O_6N_2$ requires C, 52·7; H, 5·45%).

Similarly the crude (−)-toluene-*p*-sulphonate (1·8 g.) gave (−)-2-methylpentan-3-ol (411 mg.), distilling at atmospheric pressure from a bath at 135—145° and having n_D^{25} 1·4184, $[\alpha]_D^{27}$ −8·5° ± 0·25° (*c* 3·31 in EtOH) {lit., $[\alpha]_D$ −9·8° (homogeneous) [4] and for the enantiomorph $[\alpha]_D$ +16·4° (*c* 1·06 in EtOH) [43]}. The 3,5-*dinitrobenzoate* had m. p. 89—92°, $[\alpha]_D^{26}$ +4·9° ± 0·6° (*c* 1·1 in $CHCl_3$) (Found: C, 52·25; H, 5·45%). The infrared spectra of the two (±)-compounds were the same as those of the two (−)-compounds.

Rotenone Enol-acetate (*Acetylrotenone*).—(*a*) Rotenone (60 g.), anhydrous sodium acetate (30 g.), and acetic anhydride (950 ml.) were refluxed for 1 hr. and the mixture was cooled and poured into water (1·6 l.) and stirred for 1 hr. The precipitated sticky solid was washed with water and crystallised from ethanol, to give rotenone enol-acetate, m. p. 160—163° (23 g.), raised by re-crystallisation to m. p. 162—164° (20·8 g.). A similar preparation gave the dimorph, m. p. 136—137° (Found: C, 68·65; H, 5·75. Calc. for $C_{25}H_{24}O_7$: C, 68·8; H, 5·55%), $[\alpha]_D^{22}$ −156° (*c* 2·05 in C_6H_6), $\lambda_{max.}$ 220 (4·40), 255 (4·15), 315 (4·04), 354 (4·54) and 372 (4·46) mμ,

[42] Pukirev, *Trans. Inst. Pure Chem. Reagents* (*U.S.S.R.*), 1939, No. 16, 73; *Chem. Abs.*, 1943, **37**, 4686.

[43] Pickard and Kenyon, *J.*, 1913, **103**, 1923.

inflexions at 246, 263, 302 mμ, $\nu_{max.}$ 1761 (Ac), 1619 and 1502 (aryl) cm.$^{-1}$. Cahn, Phipers, and Boam [10] give m. p. 137° and 159—160°, $[\alpha]_D$ −172·5° (in C_6H_6), $\lambda_{max.}$ 250 (4·24), 354 (4·47), and 373 (4·44) mμ.

(*b*) Rotenone (1 g.), isopropenyl acetate (6 g.) and concentrated sulphuric acid (1 drop) were refluxed together for 15 min. Acetone was then gradually distilled off and finally isopropenyl acetate was removed *in vacuo*. The residue was crystallised from ethanol (charcoal), to give colourless acetylrotenone, m. p. 164—165° (Found: C, 69·0; H, 5·75%), $[\alpha]_D^{22}$ −155·5° (*c* 2 in C_6H_6), $\lambda_{max.}$ 255 (4·16), 355 (4·63), and 370 (4·44) mμ. When an ethanolic solution of the form of m. p. 136—137° was seeded with the form of m. p. 164—165° it crystallised in the higher-melting form: the infrared solution spectra of the two forms were identical.

Dihydrorotenone Enol-acetate.—(*a*) The enol-acetate of rotenone (20·6 g.) was hydrogenated in acetone (300 ml.) over 5% palladium–barium sulphate (2 g.). Filtration, working up, and crystallisation from ethanol gave dihydrorotenone enol-acetate (16·8 g.), m. p. 208·5—210·5°, $[\alpha]_D^{26}$ −161° (*c* 1·4 in C_6H_6) (lit.,[11] m. p. 209—211°).

(*b*) (−)-Dihydrorotenone (1 g.), isopropenyl acetate (6 g.), and concentrated sulphuric acid (3 drops) were boiled together for 2 hr. Working up gave the enol acetate (0·64 g.), colourless needles, in a second form, m. p. 174—175°, $[\alpha]_D^{20}$ −164° (*c* 1·4 in C_6H_6), having the same solution infrared spectrum as the higher-melting form.

Ozonolysis of Dihydrorotenone Enol-acetate.—The acetate (5 g.) in methanol–chloroform (1 : 1; 100 ml.) was ozonised at 0° for 12 hr. (50% excess). The solvent was evaporated and the oily residue refluxed for 30 min. with water (50 ml.). Evaporation of the water at 50° left a brown residue which was dissolved in methanol–chloroform (1 : 1) and again ozonised (1 hr.). Working up as before left a brown solid (4·6 g.) which was chromatographed on ion-exchange resin (Dowex 1X10; acetate form; 100—200 mesh) in a column (1·7 × 14·5 cm.) with N-acetic acid as eluant. Fractions of 25 ml. were collected and examined by paper chromatography to decide in which fractions glyceric acid was present. [The system of Palmer [13] was used: the solvent system was ethyl ether–88% formic acid–water (5 : 2 : 1), and the spray reagent a 0·04% ethanolic solution of Bromophenol Blue.] As a contaminant with high R_F value (0·96—1·00) was present, ion-exchange chromatography was repeated. Evaporation of the appropriate fractions at 50° gave a mixture (160 mg.) of glyceric and 3-hydroxy-4-methylpentanoic acid. The mixture was converted into the 4-bromophenacyl esters and crystallised from ethanol. After drying, the crystals were extracted three times with boiling hexane, and the insoluble portion was crystallised from benzene–hexane; a further recrystallisation gave the (−)-4-*bromophenacyl glycerate* (35·2 mg.), m. p. 109—111°, $[\alpha]_D^{25}$ −1·49° ± 0·2° (*c* 4·36 in acetone). The m. p. was not depressed by the authentic specimen below and the infrared spectra were identical (Found: C, 43·2; H, 3·5. $C_{11}H_{11}BrO_5$ requires C, 43·6; H, 3·65%). Chromatography of the hexane-soluble portion on alumina (N4) gave the (+)-4-bromophenacyl ester, m. p. 73—73·5°, $[\alpha]_D^{25}$ +12·2° ± 0·2° (*c* 2·31 in $CHCl_3$), of (−)-3-hydroxy-4-methylpentanoic acid. The infrared spectrum was identical with that of the specimen described above.

Optical Resolution of (±)-*Glyceric Acid.*—Glyceric acid was resolved according to Anderson's procedure [14] and gave a calcium salt, $[\alpha]_D^{24}$ +14·4° (*c* 2·12 in H_2O), {lit., $[\alpha]_D^{20}$ +14·0° (in H_2O)}. The 4-bromophenacyl ester had m. p. 109—111°, $[\alpha]_D^{25}$ −1·9° ± 0·2° (*c* 5·62 in acetone). (±)-4-*bromophenacyl glycerate* had m. p. 120—122° (Found: C, 43·2; H, 3·55%).

Treatment of (±)-*Isorotenolone A and B Methyl Ethers with Methanolic Acid.*—(±)-Isorotenolone B methyl ether [17] (200 mg.) was refluxed with concentrated hydrochloric acid (0·75 ml.) in methanol (17 ml.) for 15 min. After cooling, 6a,12a-dehydroisorotenone (71 mg.), m. p. and mixed m. p. 194—195° (decomp.), was filtered off. Evaporation gave more dehydroisorotenone (18 mg.), and then isorotenolone A methyl ether (56 mg.) as needles, m. p. and mixed m. p. 152—153° (and infrared mull comparison) after crystallisation from methanol.

(±)-Isorotenolone A methyl ether [17] (100 mg.) under identical conditions gave 6a,12a-dehydroisorotenone (31 mg.) and recovered methyl ether (48 mg.), m. p. and mixed m. p. 152°.

Acetylation of (±)-*Isorotenolone A and B.*—(±)-Isorotenolone A (400 mg.) was refluxed for 15 min. with acetic anhydride (2·5 ml.), glacial acetic acid (1 drop), and anhydrous sodium acetate (2·5 g.). Methanol was added and the mixture poured into water. The precipitate was filtered off, boiled with methanol, and freed from 6a,12a-dehydroisorotenone (160 mg.; m. p. and mixed [33] m. p. 192°) by filtration. Concentration of the filtrate gave (±)-*isorotenolone A acetate* (62 mg.), m. p. 165° (Found: C, 66·6; H, 5·3. $C_{25}H_{24}O_8$ requires C, 66·35; H, 5·35%).

(±)-Isorotenolone B (250 mg.) similarly gave 6a,12a-dehydroisorotenone (120 mg.) and

(±)-isorotenolone A acetate (32 mg.), m. p. and mixed m. p. 165°: the infrared solution spectrum was identical with that of the specimen described above, $\nu_{max.}$ 1742 (OAc), 1689 (C=O), 1618, 1595, and 1504 (aryl) cm.$^{-1}$.

(±)-Isorotenolone A acetate (50 mg.) was refluxed with acetic anhydride (0·5 ml.), glacial acetic acid (1 drop), and sodium acetate (50 mg.) for 30 min. After cooling, methanol was added: when this mixture was kept at 0°, 6a,12a-dehydroisorotenone (40 mg.), m. p. and mixed m. p. 195—196° (decomp.), separated.

Reduction of (±)-Isorotenolone A Acetate with Lithium Aluminium Hydride.—The acetyl compound (1 g.) in dry tetrahydrofuran was added slowly to lithium aluminium hydride (1 g.) in tetrahydrofuran (35 ml.), and the whole was stirred under nitrogen for 5 hr. Ethyl acetate and then ammonium chloride solution were added. The mixture was filtered through kieselguhr, and the filtrate was extracted with chloroform. The extract was dried and evaporated, and the residue (m. p. 208°) was chromatographed from chloroform–benzene (1 : 1) on alumina (N4) and then crystallised from chloroform–light petroleum (b. p. 60—80°), to give the (±)-*iso*-A diol [17] (XVIII—XIXc) (570 mg.), m. p. and mixed m. p. 216° (and infrared comparison). In an identical experiment, except that reflux conditions were used, the yield was 848 mg.

Reduction of (±)-Isorotenone with Potassium Borohydride.—(−)-Isorotenone, prepared [44] from (−)-rotenone by the sulphuric–acetic acid method, had m. p. 176° or 185°, $[\alpha]_D^{23\cdot5}$ −80° (*c* 2 in C_6H_6), $\lambda_{max.}$ 243 (4·69), 248 (4·64), 261 (4·18), 279 (4·05), and 330 (3·65) mμ, $\nu_{max.}$ 1680 (C=O), 1617, 1597, 1513 (aryl bands) cm.$^{-1}$ [lit., m. p. 176° or 184° (two forms)]; in chloroform it is dextrorotatory, $[\alpha]_D^{23}$ +8° (*c* 2).[45] Treatment with potassium carbonate in acetone [10] gave (±)-isorotenone, m. p. 172°, $[\alpha]_D$ 0°: the infrared (solution) and ultraviolet spectra were identical with those above (lit.,[19] m. p. 170—171°). (±)-Isorotenone (5 g.) in tetrahydrofuran (40 ml.) and water (20 ml.) was treated with potassium borohydride at 0° for 7 days. The mixture was refluxed for 3 hr. and then heated with 10% potassium hydrogen carbonate solution (30 ml.) overnight. The product was poured on ice and the *12α-hydroxy-compound* (IXc) (4·12 g.) was filtered off: from chloroform–methanol it formed needles, m. p. 193° (Found: C, 69·55; H, 6·35. $C_{23}H_{24}O_6$ requires C, 69·7; H, 6·1%), $\lambda_{max.}$ 251 (4·38), 258 (4·40), 280i (4·03), 290 (4·11) and 297i (3·95) mμ, $\nu_{max.}$ 1621, 1600, 1587, and 1499 cm.$^{-1}$ (aryl).

Reduction of 6a,12a-*Dehydroisorotenone with Sodium Borohydride.*—The ketone (1 g.) in tetrahydrofuran at 50° was treated with sodium borohydride (0·4 g.) in 90% aqueous ethanol (10 ml.) and kept at 50° for 1 hr. and at 20° for 4 hr. The solution was washed with brine, dried, and evaporated, to give solid (0·9 g.) which, crystallised from methanol, gave the 12-hydroxy-compound (IXc), m. p. and mixed m. p. 192—194°. Chromatography from benzene–chloroform (1 : 1) on alumina (K1) gave unchanged material, but on alumina (A1) a yellow band appeared which on elution gave the 12,12a-dehydro-compound (XXIc), m. p. and mixed m. p. 179°.

High-pressure Hydrogenation of (±)-Isorotenone.—Isorotenone (3 g.) in ethyl acetate (50 ml.) was hydrogenated at 100°/60 atm. over Adams platinum catalyst for 7 days. The mixture was filtered, the filtrate evaporated, and the residue chromatographed from benzene on alumina (N1), to give isorotenol (XXc) (0·33 g.), m. p. and mixed m. p. 131—132° (Found: C, 69·9; H, 6·35. Calc. for $C_{23}H_{24}O_6$: C, 69·7; H, 6·1%). Continued elution gave the 12α-hydroxy-compound (IXc) (1·5 g.), m. p. 195° (from ethanol). Identity with the above specimen was established by mixed m. p. and infrared comparison.

Pressure Hydrogenation of 6a,12a-*Dehydrorotenone.*—6a,12a-Dehydrorotenone (9·5 g.) in ethyl acetate (200 ml.) was hydrogenated over Adams catalyst (2 g.) at 25°/10 atm. for 36 hr. The mixture was warmed and filtered and the filtrate was concentrated. 6a,12a-Dehydro-6′,7′-dihydrorotenone (3·5 g.), m. p. and mixed m. p. 226—227°, separated and was filtered off. The filtrate was evaporated and the residue was dissolved in chloroform (50 ml.) and extracted with 2% aqueous potassium hydroxide. The alkaline extracts were acidified with 4N-hydrochloric acid and extracted with chloroform. Evaporation of the extract and crystallisation from ethanol gave the 1′,5′-*seco*-compound (VIIIg), m. p. 218° (decomp.), $\lambda_{max.}$ (in acid ethanol) 241 (4·40), 276 (4·39), and 304 (4·26) mμ, $\lambda_{max.}$ (in alkaline ethanol) 204i (4·42), 270 (4·46), 282i (4·42), and 316 (4·36) mμ, $\nu_{max.}$ 3236 (intermolecularly bonded OH), 1631 (unsatd. ketone), 1603 and 1499 (aryl) cm.$^{-1}$ [lit.,[46] for (VIIIg) (" dehydrodihydrorotenonic acid "), m. p. 221°].

[44] Wright, *J. Amer. Chem. Soc.*, 1928, **50**, 3358.
[45] Butenandt and Hildebrandt, *Annalen*, 1930, **477**, 245.
[46] LaForge and Smith, *J. Amer. Chem. Soc.*, 1930, **52**, 3603.

Pressure Hydrogenation of 6a,12a-*Dehydro*-6′,7′-*dihydrorotenone*.—The ketone (2 g.) was hydrogenated over Adams catalyst (500 mg.) in ethyl acetate (25 ml.) at 70°/60 atm. for 7 days. The catalyst was filtered off, the filtrate evaporated, and the residue crystallised from ethanol, to give 6′,7′-dihydrorotenol (1·53 g.), needles, m. p. 133° (lit.,[47] 131°) (Found: C, 69·2; H, 6·55. Calc. for $C_{23}H_{26}O_6$: C, 69·35; H, 6·6%), $\nu_{max.}$ 1636 (chelated ketone), 1616, 1499, and 1484 (aryl) cm.$^{-1}$; there was a broad band beneath the C–H stretching vibrations due to the chelated hydroxyl.

Hydrogenation of 6a,12a-*Dehydro*-α-*toxicarol*.—6a,12a-Dehydro-α-toxicarol was prepared according to Cahn *et al.*[10] (who give m. p. 226—227°) and had m. p. 230—231° (Found: C, 67·1; H, 5·0; O, 27·15. Calc. for $C_{23}H_{20}O_7$: C, 67·65; H, 4·95; O, 27·4%), $\nu_{max.}$ 1654 (chelated ketone), 1613, 1578, and 1513 (aryl) cm.$^{-1}$ (the chelated hydroxyl forms a broad band at the base of the C–H vibrations), $\lambda_{max.}$ 237 (4·43), 270 (4·61), 280 (4·61), and 332 (4·17) mμ. The dehydro-compound (1 g.) was hydrogenated in glacial acetic acid over Adams platinum at 75° until 125 ml. of hydrogen (N.T.P.) had been absorbed. The catalyst was filtered off and the product was chromatographed from chloroform on alumina (N). Crystallisation gave (±)-4′,5′-dihydro-α-toxicarol, m. p. 206°, mixed m. p. 208°, $\lambda_{max.}$ 302 (4·36) mμ, $\nu_{max.}$ 1638 (chelated ketone), 1617, 1586, and 1506 (aryl) cm.$^{-1}$. The infrared spectrum was superimposable on that of the (±)-specimen below.

(±)-α-Toxicarol was catalytically hydrogenated to give (±)-4′,5′-dihydro-α-toxicarol, m. p. 209—210° (Found: C, 66·55; H, 6·0; O, 27·5. Calc. for $C_{23}H_{24}O_7$: C, 67·0; H, 5·85; O, 27·15%) (lit.,[30] m. p. 205°, clear at 209°), $\lambda_{max.}$ 300 (4·39) and 344 (3·68) mμ. (−)-4′,5′-Dihydro-α-toxicarol, made similarly, had m. p. 184—185° (Found: C, 67·0; H, 6·15%), $[\alpha]_D^{20}$ −36·6° (*c* 2 in C_6H_6) [lit.,[10] m. p. 178—180°, $[\alpha]_D$ −57° (in C_6H_6)], $\nu_{max.}$ 1639 (chelated ketone) cm.$^{-1}$, $\lambda_{max.}$ 298 (4·40) mμ; its infrared spectrum (solution) was identical with that of the (±)-form.

Reduction of 6H-*Rotoxen*-12-*one with Borohydride*.—The ketone (VIIIf) was made by La-Forge's method,[31] except that dropwise addition of ethyl bromoacetate in the final stage considerably raised the yield (42%); it had m. p. 134—135° (lit.,[31] m. p. 135°) (Found: C, 76·85; H, 4·3. Calc. for $C_{16}H_{10}O_3$: C, 76·8; H, 4·05%), $\lambda_{max.}$ 217 (4·45) and 265 (4·38) mμ, and a flat inflexion between 288 and 305 mμ, $\nu_{max.}$ 1639 (unsatd. ketone), 1626, 1609, 1563, and 1494 (aromatic bands) cm.$^{-1}$. [A specimen of rotoxen-6,12-dione, made by use of ethoxalyl chloride in place of bromoacetic acid,[31] had m. p. 242—243° (lit.,[31] 240°) (Found: C, 72·85; H, 3·3. Calc. for $C_{16}H_8O_4$: C, 72·75; H, 3·05%), $\lambda_{max.}$ 234 (4·04), 250 (4·14), 265 (4·28), 279 (4·25), and 353 (3·94) mμ, $\nu_{max.}$ 1743 (lactone), 1658 (C=O), 1621, 1586, 1562, and 1494 (aromatic) cm.$^{-1}$.]

The ketone (VIIIf) (1 g.) in tetrahydrofuran (50 ml.) was warmed to 60° and potassium borohydride (0·4 g.) in 50% aqueous ethanol (10 ml.) was added. The solution was kept at 60—65° for 90 min. and then washed with saturated sodium chloride solution, dried, evaporated, and crystallised, to give the *hydroxy-compound* (IXf), m. p. 179—180°, unchanged by chromatography on alumina (K) (Found: C, 75·7; H, 5·75. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·55%), $\lambda_{max.}$ 275 (3·74) mμ, $\nu_{max.}$ (mull) 3247 (OH) cm.$^{-1}$. The *acetyl derivative* [from the chromanol (IXf) with acetic anhydride and pyridine] had m. p. 163° (Found: C, 73·2; H, 5·35. $C_{18}H_{16}O_4$ requires C, 72·95; H, 5·45%), $\lambda_{max.}$ 277 (3·74) mμ, $\nu_{max.}$ (mull) 1733 (acetate) cm.$^{-1}$. For the stereoisomer Dann and Volz report [37] m. p. 238—239° (acetyl derivative m. p. 147—147·5°).

6a,12a-*Dihydro*-6H-*rotoxen*-12-*one by Oxidation of the Hydroxy-compound* (IXf).—The hydroxy-compound (IXf), m. p. 179—180° (200 mg.), in acetone (5 ml.) was treated with chromium trioxide and kept overnight. The whole was filtered and the filtrate was diluted with water and extracted with ether, to give a solid (150 mg.) which, when crystallised from methanol, gave the ketone (Xf), m. p. 163° (Found: C, 76·5; H, 4·8. Calc. for $C_{16}H_{12}O_3$: C, 76·2; H, 4·8%), $\lambda_{max.}$ 255 (3·96) and 322 (3·47) mμ, $\nu_{max.}$ (mull) 1695 cm.$^{-1}$. The m. p. of the specimen was not depressed on admixture with Dann and Volz's ketone,[37] m. p. 165—166·5°, kindly supplied by Professor O. Dann. Fukami *et al.*[35] give m. p. 162—163° but record $\lambda_{max.}$ 225 (3·95) and 320 (3·48) mμ. The ketone (25 mg.) was unaltered when refluxed for 90 min. with potassium carbonate (10 mg.) in acetone (3 ml.). The ketone (50 mg.) and sodium acetate (150 mg.) were dissolved in ethanol (5 ml.), iodine (100 mg.) in ethanol (5 ml.) was added, and the whole was refluxed for 30 min., and then refluxed for 30 min. more with 20% ethanolic sulphuric acid (5 ml.); working up in the usual way gave the 6a,12a-dehydro-ketone (VIIIf), m. p. and mixed m. p. 133°.

6a,12a-*Dihydro*-6H-*rotoxen*-12-*one by Hydrogenation of* 6H-*Rotoxen*-12-*one*.—The ketone (VIIIf) (400 mg.) was hydrogenated over Adams catalyst (60 mg.) in acetic acid (80 ml.) at 20°

until 1·5 mol. of hydrogen had been absorbed. The catalyst was filtered off, the filtrate diluted with much water, and the precipitate collected with ether. The ethereal solution was washed with chalk suspension, dried, and evaporated, and the residue was crystallised from aqueous ethanol to give the ketone (Xf) (m. p. 130—140°, 250 mg., crude), m. p. and mixed m. p. 163° (50 mg.) after further crystallisation from methanol. The infrared spectrum (mull) was identical with that of the specimen described above. The spectrum of the material of m. p. 130—140° showed it to be the ketone contaminated with the hydroxy-compound (IXf).

Reduction of Rotenone with Lithium Aluminium Hydride.—Rotenone (6·0 g.) in dry tetrahydrofuran (50 ml.) was treated under nitrogen with a slurry of lithium aluminium hydride (1·8 g.) in dry tetrahydrofuran. The mixture was heated under reflux for 15 min., then cooled, and water was added. The product was just acidified and extracted with chloroform. Working up in the usual way gave a foam which gave no blue Durham test, $[\alpha]_D^{20}$ −208° (*c* 2 in C_6H_6), $\nu_{max.}$ 3541 (OH), 1653 vw (C=C), 1619 and 1511 (aryl) cm.$^{-1}$, $\lambda_{max.}$ 220 (4·35) and 286 (3·79) mμ. When kept under methanol for a long period the *hydroxy-compound* (IXa) formed cubic solvated crystals, m. p. 94° with frothing (Found: C, 67·3; H, 6·55. $C_{23}H_{24}O_6,CH_3{\cdot}OH$ requires C, 67·3; H, 6·6%). Except for methanol absorption the infrared solution spectrum was identical with that of the glass above. When the crystals were heated *in vacuo* for 8 hr. at 65° the methanol absorption disappeared, but the glass obtained on cooling crystallised again only from methanol and required seeding. When the hydroxy-compound was shaken with acid alumina in chloroform, dehydration could be observed by following the decline of the infrared hydroxylic absorption.

α-*Tetralol and Chroman-4-ol.*—α-Tetralol was made by treating α-tetralone (5 g.) in water (5 ml.) and tetrahydrofuran (25 ml.) with potassium borohydride (2·5 g.) at 0° for some days. The mixture was refluxed for 1 hr., then refluxed for 3 hr. with 10% potassium carbonate solution and poured on ice. Isolation and working up gave α-tetralol (3·2 g.), b. p. 124°/3 mm., n_D^{23} 1·5650 (lit.,[48] b. p. 132—143°/12 mm., n_D^{17} 1·5671). Chroman-4-ol was a gift from Professor O. Dann and had m. p. 44—45° and originated from Meerwein–Ponndorf reduction of chroman-4-one.[49]

(−)- *and* (±)-4′,5′-*Dihydrodeguelin* ("β-*Dihydrorotenone*").—Rotenone (5 g.) in pyridine (20 ml.) was hydrogenated over palladium–barium sulphate (2 g.) until 1 mol. of hydrogen had been absorbed. After filtration, the solution was diluted with much water, and the precipitate was extracted with ether. The ethereal solution was washed with 2N-alkali, the alkaline extracts were acidified, and the rotenonic acid was collected (0·7 g.); it had m. p. 206—210° (from methanol) (Found: C, 69·95; H, 6·1. Calc. for $C_{23}H_{24}O_6$: C, 69·7; H, 6·1%), $\lambda_{max.}$ 234 (4·18) and 292 (4·22) mμ, $\nu_{max.}$ 3333 (OH), 1669 (C=O), 1597 and 1502 cm.$^{-1}$ (aryl), $\nu_{max.}$ (mull) 1656 (C=O) cm.$^{-1}$ {lit.,[10] m. p. 206—208°, $[\alpha]_D$ +46° (in $CHCl_3$)}. Rotenonic acid (500 mg.) was dissolved in concentrated sulphuric acid (1·5 ml.) and glacial acetic acid (6 ml.), warmed for 15 min., and poured into water. The precipitate was filtered off, dissolved in chloroform, washed with 2N-alkali and water, dried, and recovered, giving (−)-4′,5′-dihydrodeguelin which, crystallised from a small volume of chloroform, had m. p. 155—156° (Found: C, 69·3; H, 6·0%), $[\alpha]_D^{19}$ −95·2° (*c* 3·9 in C_6H_6), $[\alpha]_D^{19}$ −22·6° (*c* 3·7 in $CHCl_3$), $\lambda_{max.}$ 234 (4·19) and 288 (4·28) mμ, $\nu_{max.}$ 1669 (C=O) cm.$^{-1}$, $\nu_{max.}$ (mull) 1672 (C=O) cm.$^{-1}$. Haller and LaForge [19,20] give m. p. 156°, $[\alpha]_D^{34}$ −26·5° (*c* 5·86 in $CHCl_3$), $[\alpha]_D^{20}$ −92·5° (*c* 2 in C_6H_6), for material made in this way and m. p. 155—156°, $[\alpha]_D^{20}$ −104° (*c* 4 in C_6H_6), for (−)-4′,5′-dihydrodeguelin from natural sources.

(−)-4′,5′-Dihydrodeguelin (600 mg.) was refluxed with potassium carbonate in acetone for 1½ hr. Working up in the usual way gave (±)-4′,5′-dihydrodeguelin (460 mg.), m. p. 173·5—174·5° (from methanol–chloroform) (Found: C, 69·25; H, 6·3%), $[\alpha]_D^{19}$ 0°, $\lambda_{max.}$ 234 (4·21) and 288 (4·30) mμ, $\nu_{max.}$ 1669 (C=O) cm.$^{-1}$. From the mother-liquors a second form, m. p. 155°, was isolated. The forms were interconverted by seeding and had the same infrared spectrum. The infrared spectra (mulls) of the specimen, m. p. 173·5—174·5°, and naturally derived (±)-4′,5′-dihydrodeguelin were identical. The infrared spectra of (−)- and (±)-4′,5′-dihydrodeguelin in chloroform were identical. Haller and LaForge [22a] give m. p. 171° for "(±)-β-dihydrorotenone," but report that one specimen softened at 171° and melted at 176°.

Reduction of (−)- *and* (±)-4′,5′-*Dihydrodeguelin with Lithium Aluminium Hydride.*—(*a*)

[47] (*a*) LaForge and Smith, *J. Amer. Chem. Soc.*, 1929, **51**, 2574; (*b*) Haller and Schaffer, *ibid.*, 1933, **55**, 3495.

[48] Brochet and Cornubert, *Compt. rend.*, 1921, **172**, 1499; *Bull. Soc. chim. France*, 1922, **31**, 1280.

[49] Dann, Volz, and Huber, *Annalen*, 1954, **587**, 16.

(−)-4′,5′-Dihydrodeguelin (430 mg.) in dry tetrahydrofuran was added to lithium aluminium hydride (70 mg.) in tetrahydrofuran (10 ml.), and the mixture was stirred under nitrogen for 2 hr. Ethyl acetate, water, and N-sodium potassium tartrate solution were added and the mixture was extracted with chloroform. The extract was dried and evaporated to give a gum which crystallised (330 mg.) when treated with methanol. These crystals appear to be solvated for they have m. p. 90° with frothing, and one crystallisation raised the m. p. to 155—157°. In two other runs the (−)-12-*hydroxy-compound* (IXe; R = H), m. p. 160°, was obtained immediately, from methanol; this m. p. was raised to 163·5—165° by further crystallisation (Found: C, 69·0; H, 6·35. $C_{23}H_{26}O_6$ requires C, 69·35; H, 6·55%); the alcohol had $[\alpha]_D^{25}$ −46·2° (*c* 2·4 in C_6H_6), $\lambda_{max.}$ 288 (3·82) mμ, $\nu_{max.}$ 1623, 1597, and 1499 cm.$^{-1}$ (aryl bands). The infrared spectrum (chloroform) of the whole crude product was closely similar to that of the purified material.

(±)-4′,5′-Dihydrodeguelin (890 mg.) was similarly reduced with lithium aluminium hydride (400 mg.) and gave the (±)-12-*hydroxy-compound* (IXe; R = H) [*trans*-arrangement of 12-hydroxyl to 12a-hydrogen], m. p. 177—178° (from methanol) (Found: C, 69·25; H, 6·55%), $\lambda_{max.}$ 228 (3·78) mμ. The infrared spectrum (chloroform) was identical with that of the (−)-compound.

(*b*) (−)-4′,5′-Dihydrodeguelin (600 mg.), dissolved in dry tetrahydrofuran (10 ml.), was refluxed under nitrogen for 15 min. with lithium aluminium hydride in tetrahydrofuran. Ethyl acetate, water, and N-sulphuric acid were added and the solution was extracted with chloroform. Drying and evaporation gave a gum which, when chromatographed on alumina (K1) and triturated with light petroleum, crystallised to give the (−)-12,12a-*olefin* (XXIe; R = H) (120 mg.), m. p. 177·5—179·5° (from chloroform–methanol), identical (mixed m. p. and infrared solution spectrum) with the specimen of $[\alpha]_D^{25}$ −122° (*c* 1·93 in C_6H_6) below, except for its rotation $[\alpha]_D^{20}$ −82° (*c* 1·44 in C_6H_6) (Found: C, 72·45; H, 6·3. $C_{23}H_{24}O_5$ requires C, 72·6; H, 6·35%).

(±)-4′,5′-Dihydrodeguelin (920 mg.) was dissolved in tetrahydrofuran (30 ml.) and heated under reflux for 1 hr. with lithium aluminium hydride (670 mg.) in tetrahydrofuran. The product was worked up as above to give, after crystallisation from methanol–chloroform, the (±)-12,12a-*olefin* (XXIe; R = H) (350 mg.), m. p. 184—185° (Found: C, 72·45; H, 6·55%). Its infrared solution spectrum was identical with that of the (−)-specimen recorded above.

Dehydration of the (−)-6aβ,12aβ-12α-*Hydroxy-compound* (IXe; R = H).—The (−)-hydroxy-compound (500 mg.) was heated for 1 hr. at 100° with pyridine (5 ml.) and phosphorus oxychloride (2 ml.), then poured on ice, and the whole was extracted with ether. The extract was washed with dilute hydrochloric acid, dried, and evaporated: the residual gum crystallised, having m. p. 169—171° (330 mg.) (from chloroform–methanol). Chromatography of this product from benzene on alumina (K1) gave the (−)-12,12a-olefin (XXIe; R = H) (see above), m. p. 177·5—179·5° (180 mg.) (from chloroform–methanol), $[\alpha]_D^{25}$ −122° (*c* 1·93 in C_6H_6), $\lambda_{max.}$ 254 (4·24), 258 (4·28), 264 (4·23), 361 (4·49), and 380 (4·45) mμ. Another preparation gave material of m. p. 176° but $[\alpha]_D^{22}$ −30° (*c* 1·42 in C_6H_6).

Low-pressure Catalytic Hydrogenation of 6a,12a-*Dehydro*-6′,7′-*dihydro*-5′(R)-*rotenone* (VIIIb).—The dehydro-compound [50] had m. p. 226—228° (Found: C, 69·7; H, 5·75. Calc. for $C_{23}H_{22}O_6$: C, 70·05; H, 5·6%), $\lambda_{max.}$ 240 (4·37), 280 (4·30), and 310 (4·19) mμ, $\nu_{max.}$ 1628 cm.$^{-1}$ (C=O) (lit., m. p. 228—230°). The ketone (500 mg.) in glacial acetic acid (100 ml.) was hydrogenated over Adams platinum (35 mg.) until 49 ml. of hydrogen (N.T.P.) had been absorbed. The mixture was filtered and evaporated, the gummy residue triturated with methanol (50 ml.), and unchanged ketone (21 mg.) filtered off. On concentration, the methanol solution gave crystals (294 mg.), m. p. 120—127°, $[\alpha]_D^{17}$ −64° (*c* 2 in C_6H_6) (positive Durham test).[51] Another crystallisation led to m. p. 130—135°. Both specimens had infrared spectra almost identical with " mutadihydrorotenone " (see below). Repeated crystallisation from benzene–methanol then gave (−)-6′,7′-dihydrorotenone (18 mg.), m. p. and mixed m. p. 213—214°, $[\alpha]_D^{19}$ −215° (*c* 2 in C_6H_6). An authentic specimen of the latter [47b] had m. p. 212°, $[\alpha]_D^{20}$ −222·5° (*c* 2 in C_6H_6), $\lambda_{max.}$ 237 (4·23) and 295 (4·28) mμ, $\nu_{max.}$ 1667 (C=O) cm.$^{-1}$.

In a second experiment the product from the dehydro-compound (500 mg.) was freed from unchanged material and poured into water. The whole solid product (411 mg.; negative ferric reaction) had $[\alpha]_D^{22}$ −21° (*c* 2 in C_6H_6) and still contained a little dehydro-compound.

[50] LaForge and Smith, *J. Amer. Chem. Soc.*, 1930, **52**, 1091.
[51] Jones and Smith, *Ind. Eng. Chem., Analyt.*, 1933, **5**, 75.

When racemised at positions 6a,12a by means of sodium acetate in the usual way, the whole product had $[\alpha]_D^{24}$ −77°. (−)-6′,7′-Dihydrorotenone (100 mg.) was refluxed for 18 hr. with ethanol (25 ml.) containing sodium acetate (1 g.). The whole product, isolated by pouring of the mixture into water, had $[\alpha]_D^{20}$ −94·5° (*c* 2 in C_6H_6). Dann and Volz [37] report $[\alpha]_D^{20}$ −87° (in C_6H_6) for the equilibrium mixture. It does not follow that the latter is exactly a 1 : 1 mixture but a value of $[\alpha]_D$ −85·6° (in C_6H_6) can be calculated from 6′,7′-dihydrorotenone (6aβ,12aβ,5′β), $[\alpha]_D^{20}$ −222·5°, and 6′,7′-dihydroepirotenone (6aα,12aα,5′β), $[\alpha]_D$ +51·4°,[36] so that it is approximately so.

(±)- *and* (−)-6,6aβ,12,12aβ,4′,5′-*Hexahydro*-2,3-*dimethoxy*-6′,6′-*dimethyl*-4H-*pyrano*-(3′,2′-8,9)*rotoxen* (XXVe; R = H).—(a) *By hydrogenolysis of* 4′,5′-*dihydrodeguelin.* The (−)-ketone (Xe; R = H; 6aβ,12aβ) (210 mg.), was hydrogenated over Adams platinum (100 mg.) in acetic acid (15 ml.) until 2 mol. of hydrogen had been absorbed. After filtration, the solution was poured into water and extracted with ether. The extracts were washed with sodium carbonate solution and water, dried, and evaporated to a gum which crystallised from methanol (m. p. 117—120°; 95 mg.); there followed a second crop, m. p. 100—105° (95 mg.), with an infrared spectrum closely similar to that of the first. Crystallisation from methanol gave pure 12-*deoxy-compound* (XXVe; R = H; 6aβ,12aβ), m. p. 122—122·5° (Found: C, 72·4; H, 6·6. $C_{23}H_{26}O_5$ requires C, 72·25; H, 6·85%), $[\alpha]_D^{25}$ −115° (*c* 0·63 in C_6H_6), $\lambda_{max.}$ 288 (3·85) mμ, $\nu_{max.}$ 1621, 1595, and 1511 cm.$^{-1}$. Similarly the (±)-ketone (Xe; R = H) (260 mg.) gave, on hydrogenation, solid (250 mg.), m. p. 151—152° (150 mg., from methanol) (Found: C, 72·0; H, 7·0%), $\lambda_{max.}$ 288 (3·89) mμ, $\nu_{max.}$ 1621, 1595, and 1511 cm.$^{-1}$. The infrared spectrum (chloroform) was identical with that of the (−)-12aβ-form (as mulls there were recognisable differences) and the spectrum of the whole crude product was nearly identical with that of the pure compound.

(b) *By hydrogenolysis of the hydroxy-compound* (IXe; R = H). The (−)-hydroxy-compound (IXe; R = H; 6aβ,12aβ) (390 mg.) was hydrogenated over Adams catalyst (200 mg.) in acetic acid (15 ml.) until 1 mol. of hydrogen was absorbed. Working up gave a solid of m. p. 112—114° (332 mg.), raised by crystallisation from methanol to m. p. 122° (150 mg.), $[\alpha]_D^{25}$ −115° (*c* 1·6 in C_6H_6), identical with the (−)-specimen described in (a) above. The spectrum of the crude whole product was identical with that of the purified material, and the stability of the (−)-hydroxy-compound towards dehydration under the reaction conditions was checked.

Similarly, the (±)-hydroxy-compound (109 mg.) on hydrogenolysis gave a glass (105 mg.) which, crystallised from methanol, had m. p. 151° (55 mg.), identical with the (±)-material described in paragraph (a).

(c) *By catalytic hydrogenation of the* (±)- *and* (−)-12,12a-*dehydro*-6aβ-*compound* (XXIe; R = H). The 12,12a-dehydro-compound (116 mg.; $[\alpha]_D^{22}$ −30°) was hydrogenated over Adams catalyst (80 mg.) in acetic acid (10 ml.) until 1 mol. of hydrogen had been absorbed. Working up gave a glass (107 mg.), $[\alpha]_D^{17}$ −24° (*c* 1·06 in C_6H_6), which when carefully crystallised gave the deoxy-compound (XXVe; R = H) in (±)-form, m. p. 149·5—150·5° (50 mg.), $[\alpha]_D$ 0°: mixed m. p. and infrared comparison established identity with the material described above. There followed a crop, m. p. 134—138° (15 mg.), $[\alpha]_D^{17}$ −2·5° (*c* 0·89 in C_6H_6), and finally a crop, m. p. 110° (8 mg.), $[\alpha]_D^{17}$ −106° (*c* 0·58 in C_6H_6). The infrared spectrum (mull) of the latter was indistinguishable from that of the (−)-form above, but this specimen was not optically pure. Infrared examination of the original glass gave no evidence of products other than the (−)- and (±)-compound (XXVe; R = H).

Similar hydrogenation of the (±)-12,12a-dehydro-compound (102 mg.) gave a gum which crystallised from methanol, to give the (±)-compound (XXVe; R = H), m. p. 149—150° (50 mg.), identical (mixed m. p. and infrared criteria) with the specimen just noted. No second compound could be traced in the crude product.

Reduction of 6a,12a-*Dehydrorotenone with Lithium Aluminium Hydride.*—The ketone (2 g.) in dry dioxan was heated with lithium aluminium hydride (1 g.), added in portions. After 1 hour's refluxing, the product was cooled, 2N-sulphuric acid was added, and the mixture was extracted with chloroform. The extracts were dried and evaporated, and the gum was chromatographed on alumina (N) to give, after crystallisation from benzene–methanol, the 12,12a-dehydro-compound (XXIa) (150 mg.), m. p. and mixed m. p. 164—165° with the specimen described below.

The 12,12a-*Dehydro-compound* (XXIa).—The hydroxy-compound (IXa; glass) (700 mg.) in dry pyridine (5 ml.) was heated at 100° with phosphorus oxychloride (2 ml.) for 1¼ hr. and

then poured on ice. Extraction with ether gave the dehydro-compound (XXIa) (510 mg.), which crystallised from benzene–light petroleum (b. p. 40—60°), m. p. 163—164° (Found: C, 73·05; H, 6·00. Calc. for $C_{23}H_{22}O_5$: C, 73·0; H, 5·85%), $[\alpha]_D^{23}$ −272·5° (*c* 2 in C_6H_6), $\lambda_{max.}$ 255 (4·15), 265 (4·12), 360 (4·47), and 375 (4·41) mμ (lit.,[16] m. p. 160—161°).

(−) - 6,6aβ,12,12aβ,4′,5′ - *Hexahydro* - 2,3 - *dimethoxy* - 5′β - *isopropylfurano*(3′,2′ - 8,9)*rotoxen* (XXVb).—(a) *By hydrogenolysis of rotenone.* Rotenone (1 g.) in glacial acetic acid (20 ml.) was hydrogenated over Adams catalyst (250 ml.) until 3 mol. of hydrogen had been absorbed. Working up gave the deoxy-compound (XXVb) (650 mg.), m. p. 172—173° (from ethanol) (Found: C, 72·0; H, 7·0. $C_{23}H_{26}O_5$ requires C, 72·25; H, 6·85%), $[\alpha]_D^{22}$ −150·5° (*c* 2 in $CHCl_3$), $\lambda_{max.}$ 290 (3·88) mμ, $\nu_{max.}$ 1616, 1602, and 1500 cm.$^{-1}$. The same compound (m. p. and mixed m. p. 175°) was also obtained by reduction of rotenone in ethyl acetate over Adams catalyst at 50°/30 atm. for 7 days. Butenandt [38] gives m. p. 168°.

(b) *By hydrogenolysis of the hydroxy-compound* (IXa). The glass (500 mg.) obtained by reducing rotenone with lithium aluminium hydride was hydrogenated in acetic acid (10 ml.) over Adams catalyst (100 mg.) until 2 mol. of hydrogen had been absorbed. Working up gave the above deoxy-compound, m. p. 173—174° (300 mg.), $[\alpha]_D^{27}$ −150° (*c* 2 in $CHCl_3$). Crystalline hydroxy-compound (IXa; methanol solvate) (15 mg.) similarly hydrogenated gave the same compound, m. p. and mixed m. p. 173°.

(c) *By hydrogenolysis of the enol-acetate* (XXIIa). The enol-acetate (200 mg.) was hydrogenated as above (3 mol. of hydrogen). Working up gave the above deoxy-compound (90 mg.), m. p. 172°, $[\alpha]_D^{28}$ −148° (*c* 2 in $CHCl_3$).

(d) *By hydrogenation of the* 12,12a-*dehydro-compound* (XXIa). Hydrogenation of the dehydro-compound (300 mg.) as above (2 mol. of hydrogen) gave the deoxy-compound (XXVb) (200 mg.), m. p. 172° (Found: C, 72·25; H, 7·05%; *M*, 394), $[\alpha]_D^{22·5}$ −128·2° (*c* 2 in $CHCl_3$), $\lambda_{max.}$ 290 (3·80) mμ. It did not depress the m. p. of samples of $[\alpha]_D$ −150° and had an identical infrared solution spectrum.

2-(2,4,5-*Trimethoxyphenyl*)*ethanol.*—2,4,5-Trimethoxyphenylacetic acid was made from derritol according to a published degradation sequence [52] and reduced with lithium aluminium hydride in the usual way. Working up gave an alcohol, b. p. 163°/0·06 mm., m. p. 75—76° (from benzene–light petroleum) (Found: C, 61·6; H, 7·85. Calc. for $C_{11}H_{16}O_4$: C, 62·25; H, 7·6%). Apart from the three infrared clear bands, mentioned in the text, a very weak maximum near 3500 cm.$^{-1}$ has been observed: its origin is not known.

3,4-*Dimethoxybenzyl Alcohol.*—Prepared by reduction of veratraldehyde with potassium borohydride this had b. p. 240°/40 mm., n_D^{20} 1·554, m. p. 54° (lit.,[53] b. p. 172°/12 mm., n_D^{17} 1·555).

2-(3,4-*Dimethoxyphenyl*)*ethanol.*—Reduction of 3,4-dimethoxyphenylacetic acid, m. p. 99° (lit.,[53] m. p. 98—99°), with lithium aluminium hydride gave 2-(3,4-dimethoxyphenyl)ethanol, m. p. 46° (lit.,[54] m. p. 47—48°).

(+)-*Isorotenone.*—" *d*-Epirotenone " concentrate [10] {20 g; $[\alpha]_D^{18}$ +25° (*c* 2 in C_6H_6)} in glacial acetic acid (200 ml.) was treated dropwise with concentrated sulphuric acid (150 ml.), the temperature being kept below 65°, and the red product was poured into water. The precipitated solid (17 g.) crystallised from ethanol, to give (+)-6aα,12aα-isorotenone, m. p. 183—184°, $[\alpha]_D^{18}$ +82° (*c* 2 in C_6H_6) {lit.,[10] m. p. 182°, $[\alpha]$ +75° (in C_6H_6)}. When crystallised with (−)-isorotenone, this gave (±)-isorotenone, m. p. and mixed m. p. 172—173°.

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