554. *The Structure and Stereochemistry of the Rotenolones, Rotenolols, Isorotenolones, and Isorotenolols.**

By L. Crombie and P. J. Godin.

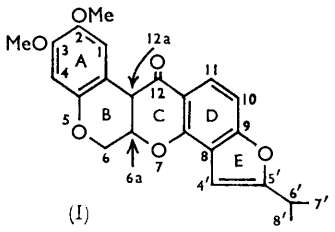
(±)-Isorotenolone A and B, formed by alkaline oxygenation of (−)-isorotenone, are *cis*- and *trans*-12a-hydroxy-derivatives respectively. Optically active forms are made by oxidation with dichromate in acetic acid, and their absolute stereochemistry is established. Reduction of (±)-isorotenolone A (*cis*-B/C) gives one (±)-diol, whilst (±)-isorotenolone B (*trans*-B/C) gives two. The configurations of these are established, and the work is extended to deal with the absolute stereochemistry of corresponding optically active diols. The stereochemistry of (±)-tephrosin and (±)-isotephrosin is also elucidated.

Alkaline oxygenation of natural rotenone gives four diastereoisomers (all 5′β), instead of the two racemates above. By direct and indirect means these are isolated and stereochemically identified. The absolute stereochemistry of their reduction products is then worked out.

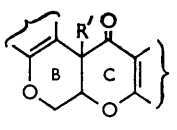
(±)-Isorotenolone C which results when (−)-isorotenone is treated with alkaline hydrogen peroxide is the spiro-hydroxy-compound (XXXIV).

The isorotenolones, four racemic hydroxy-derivatives of (±)-isorotenone (I), were investigated by LaForge and Haller [1] but they were unable to propose definite structures. In this paper the status of the four compounds is examined, structural and stereochemical proposals are made, and the treatment is then extended to optically active isorotenolones. Later, the more complex case of the rotenolones is cleared up and stereochemical work is developed to deal with the diols produced by reduction of the isorotenolones and rotenolones (isorotenolols and rotenolols).

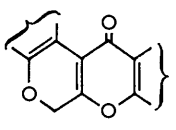
LaForge and Haller [1] listed isorotenolones I (m. p. 203—204°), II (m. p. 193—194°), C (m. p. 210—212°) and D (m. p. 188—189°). The first two can be made by aerating an alkaline suspension of isorotenone; isorotenolone I is also obtained when (±)-12a-acetoxyisorotenone (IIc; R′ = OAc),† which is isolated together with 6a,12a-dehydroisorotenone (IIIc) when (−)- or (±)-isorotenone is treated with iodine and sodium acetate, is hydrolysed. Isorotenolone C and D were encountered when (−)- or (±)-isorotenone in alkaline methanol was treated with 30% aqueous hydrogen peroxide.



(I)



(II)†



(III)

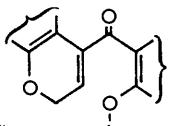
† In order to conserve space, the letter following the Roman numeral indicates that the complete structural series to which the compound belongs is as follows: a, 5′β-rotenone; b, 6′,7′-dihydro-5′β-rotenone; c, isorotenone; d, deguelin (R = H) or toxicarol (R = OH); e, 4′,5′-dihydrodeguelin (R = H) or 4′,5′-dihydrotoxicarol (R = OH); f, 6a,12a-dihydro-6*H*-rotoxen-12-one; g, dihydrorotenonic acid (1′,5′-*seco*); h, rotenonic acid (1′,5′-*seco*). The omitted pieces of the structures are on p. 2846.

Pure isorotenolone I has m. p. 208—209° and is now referred to as (±)-isorotenolone A. The preparation [1] of isorotenolone II is reproducible, but the product of m. p. 193—194° is a mixture of (±)-isorotenolone A and a new isomeric hydroxy-derivative, m. p. 243°, namely, (±)-isorotenolone B. The mixture of (±)-isorotenolone A and B can also be made by treating the 6a,12a-dehydro-6a,7-*seco*-acetate (IVc) with t-butyl hydroperoxide and Triton B, and has been encountered in the treatment of isorotenone with alkaline

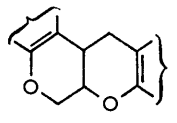
* For a preliminary communication see Crombie and Godin, *Proc. Chem. Soc.*, 1960, 276.

[1] LaForge and Haller, *J. Amer. Chem. Soc.*, 1934, **56**, 1620.

hydrogen peroxide. Hydrolysis of crystalline (±)-12a-acetoxyisorotenone gives, besides (±)-isorotenolone A, a little (±)-isorotenolone B. LaForge and Haller reported that oxidation of isorotenone with alkaline peroxide gave mainly (±)-isorotenolone C with only small quantities of D. Careful search of a number of preparations revealed no (±)-isorotenolone D, only C (m. p. 211—212°). But on one occasion the whole product had m. p. 189—190° in agreement with that reported for D; this compound is, however, only a polymorph of C, for although its spectrum as a mull differs slightly, in solution it is identical with that of C; also the low-melting form reverted to the high-melting form after one crystallisation from chloroform–methanol. The existence of isorotenolone D is thus doubtful but it must be pointed out that LaForge and Haller state that their specimen gave a methyl ether different from that of C. It will emerge that isorotenolones A and B are based on an unaltered isorotenone skeleton, whereas C involves a spiro-system. Although (−)-isorotenone can be used as a starting material in the above preparation, the isorotenolones obtained are (±)-compounds because the basic conditions racemise centres 6a and 12a. Nonetheless, optically active forms of isorotenolone A and B can be made in another way and are discussed below.

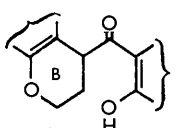


(IV)

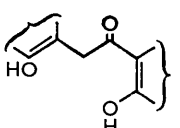


(V)

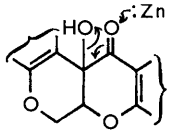
The hydroxyl group in (±)-isorotenolone A and B is located on the B/C ring junction since brief refluxing with 10% sulphuric acid converts either into 6a,12a-dehydroisorotenone (IIIc): also neither ketol is dehydrogenated by active manganese dioxide under conditions which readily give 6a,12a-dehydroisorotenone from isorotenone. Specifically, the 12a-position is implicated by the absence of enolisation reactions. Thus only a monoacetyl derivative is formed under conditions which, if there were a 12a-hydrogen atom, would lead to a diacetyl derivative (one enol acetate group). The preparation of (±)-acetylisorotenolone A by the iodination technique, or by treatment of (±)-isorotenone with lead tetra-acetate, also indicates substitution at position 12a. The conversion of (±)-isorotenolone B methyl ether into the corresponding A compound, and the formation of (±)-acetylisorotenolone A when (±)-isorotenolone B is acetylated, have been mentioned earlier.[2] (±)-Isorotenolone A and B are thus represented by (IIc; R′ = OH). In agreement, vigorous catalytic hydrogenation produces either the bis-deoxygenated compound (Vc) or (Vb) by hydrogenolysis of one actual and one potential benzylic hydroxyl group. When treated with zinc and alkali, (±)-isorotenolone A and B each give isorotenol (VIc) and isoderritol (VIIc): this is as expected since the 12a-hydroxyl group is eliminated as in (VIIIc) and degradation as explained elsewhere [3] ensues.



(VI)



(VII)



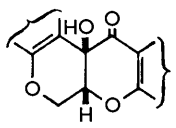
(VIII)

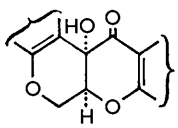
(±)-Isorotenolone A and B must be represented by one or other of the *cis*-B/C racemate (IX—Xc) or the *trans*-B/C racemate (XI—XIIc), and the immediate problem is to assign the correct fusion to each compound.

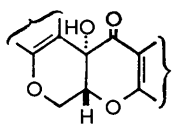
(±)-Isorotenolone B, which is dehydrated by acid rather faster than A, is less soluble than A in most solvents, including carbon tetrachloride, and infrared examination indicates intramolecular hydrogen bonding of only a very weak kind. In fairly concentrated

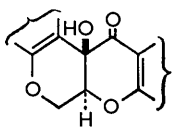
[2] Büchi, Crombie, Godin, Kaltenbronn, Siddalingaiah, and Whiting, preceding paper.
[3] Crombie, Godin, Siddalingaiah, and Whiting, following paper.

solution (*ca.* 5%) a free or lightly bonded hydroxyl group is indicated by absorption at 3610 (±10) cm.$^{-1}$, and a strong intermolecular-bonding band at ~3310 cm.$^{-1}$ (broad) (NaCl, $CHCl_3$). In dilute solution only a lightly bonded hydroxyl group is revealed, at 3593 cm.$^{-1}$ (LiF, CCl_4 < ~0·005M). (±)-Isorotenolone A has, in fairly concentrated solution, an intramolecularly bonded hydroxyl at 3497 (± ~10) cm.$^{-1}$ (NaCl,$CHCl_3$) and shows no intermolecular bonding. In dilute solution the situation is virtually unchanged, with only an intramolecularly bonded hydroxyl at 3506 cm.$^{-1}$ (LiF, CCl_4 < ~0·005M).

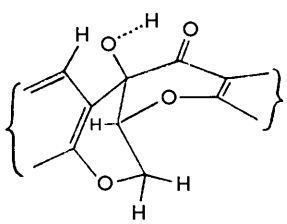

(IX)

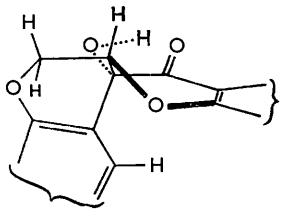

(X)

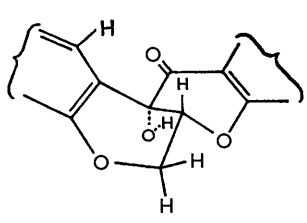

(XI)


(XII)

For the A isomer the strength of the intramolecular bond is considerably greater than expected for aryl or ether bonding [4] in a molecule such as (±)-isorotenolone and suggests that the ketone group must be involved. This is confirmed: whereas the ketone stretching vibration in (±)-isorotenolone B (1697 cm.$^{-1}$) is higher than that of its methyl ether (1688 cm.$^{-1}$) or the parent ketone (I) (1677 cm.$^{-1}$), in (±)-isorotenolone A (1676 cm.$^{-1}$) it is lowered relative to that of its methyl ether (1683 cm.$^{-1}$) (CaF_2, $CHCl_3$). Hydrogen bonding to a ketone group is known to lower the stretching frequency.[5] In (±)-*trans*-isorotenolone (XV) the hydroxyl group is badly oriented towards the ketonic oxygen and the situation is similar in one *cis*-conformation (XIII). The other *cis*-conformation (XIV)


(XIII)


(XIV)


(XV)

has the hydroxyl group approaching co-planarity with the carbonyl lone-pair orbitals,[6] and the hydroxyl-hydrogen atom is closer to the oxygen atom than in (XIII) or (XV). This satisfactorily accounts for the intramolecular bond in (±)-isorotenolone A. In agreement, the ketol (XVI), in which there is a very similar relationship (XVII) between the ketone and the hydroxyl group to that in (XIV), shows the hydroxyl frequency at 3500 cm.$^{-1}$ (CS_2).[7] (±)-Isorotenolones A and B are thus assigned *cis*- and *trans*-fusions respectively.

(±)-Tephrosin and (±)-isotephrosin [8] result when (±)-deguelin (XVIII; R = H) is aerated in alkaline solution. On dehydration, both give 6a,12a-dehydrodeguelin (IIId; R = H) and their reactions in general parallel those of (±)-isorotenolones A and B. By applying the above spectroscopic criteria, (±)-tephrosin is assigned the *cis*-B/C fusion (IX—Xd; R=H) since it possesses the intramolecularly bonded hydroxyl group [3498 (CaF_2, CCl_4; < ~0·005M) and 3509 cm.$^{-1}$ (NaCl, $CHCl_3$; ~5%)] and ketone (1675 cm.$^{-1}$; cf. deguelin,

[4] *Inter al.*, Fales and Wildman, Abs. Amer. Chem. Soc. 138th Meeting, Sept. 11–16, 1960, p. 19P; Brimacombe, Foster, Stacey, and Whiffen, *Tetrahedron*, 1958, **4**, 351; Barker, Brimacombe, Foster, Whiffen, and Zweifel, *Tetrahedron*, 1959, **7**, 10; Kuhn, *J. Amer. Chem. Soc.*, 1958, **80**, 5950, and earlier papers.

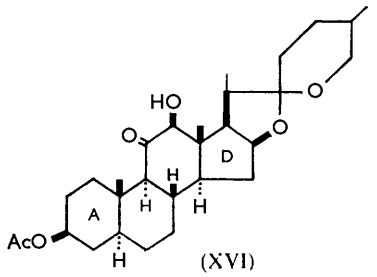
[5] Cole and Müller, *J.*, 1959, 1224; Pickering and Werbin, *J. Amer. Chem. Soc.*, 1958, **80**, 680.

[6] Schneider, *J. Chem. Phys.*, 1955, **23**, 26.

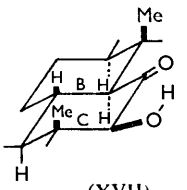
[7] Elks, Phillipps, Walker, and Wayman, *J.*, 1956, 4330.

[8] (*a*) Clark, *J. Amer. Chem. Soc.*, 1931, **53**, 729; (*b*) Clark and Claborn, *ibid.*, 1932, **54**, 4454; (*c*) Clark, *ibid.*, 1943, **65**, 27; (*d*) Boam, Cahn, and Stuart, *J. Soc. Chem. Ind.*, 1937, 91T.

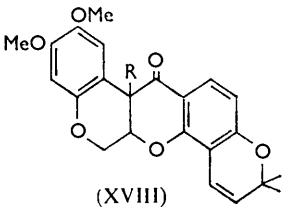
1669 cm.$^{-1}$). (±)-Isotephrosin has a free (3597 cm.$^{-1}$) and intermolecularly bonded hydroxyl group (3311 cm.$^{-1}$, broad) in chloroform solution (NaCl), and its 12-ketone vibration is at 1695 cm.$^{-1}$: it is less soluble than (±)-tephrosin in carbon tetrachloride. These facts are consistent with the *trans*-B/C assignment (XI—XIId; R = H).



(XVI)



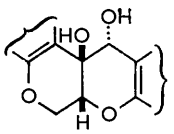
(XVII)



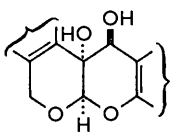
(XVIII)

The key to the preparation of optically active isorotenolones is contained in a paper by Clark who noticed that treatment of (±)-toxicarol with dichromate in acetic acid gave a (±)-hydroxytoxicarol.[9] When applied to (—)-6aβ,12aβ-isorotenone, this reagent gave two 12a-hydroxy-compounds; because of the acid conditions the 6a-centre is not racemised. The first product, m. p. 97° (methanol solvate), $[\alpha]_D^{16}$ —52° (in $CHCl_3$), has a *cis*-B/C junction (infrared criteria) and is thus ketol (IXc). The second, m. p. 220°, $[\alpha]_D^{19}$ +366° (in $CHCl_3$), formed in small yield, is much less soluble and as again the configuration at position 6a is β, it is the ketol (XIc), in agreement with infrared data. Similar oxidation of (+)-6aα,12aα-isorotenone [2,10] gave the *cis*-isorotenolone (Xc), m. p. 96° (methanol solvate), $[\alpha]_D^{16}$ +53° (in $CHCl_3$), enantiomorphic with (IXc). When crystallised together, the enantiomorphs gave (±)-isorotenolone A.

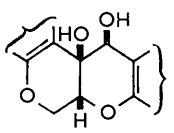
The diols obtained by reducing isorotenolones with borohydride will next be considered. (±)-Isorotenolone B gave two diols, (±)-B_1, m. p. 263°, and (±)-B_2, m. p. 213°. The *trans*-B/C junction must be maintained and one must have a *cis*- and the other a *trans*-12,12a-diol arrangement. Because it is cleaved almost instantly with lead tetra-acetate, and because it results when the 12,12a-unsaturated racemate (XXVII—XXVIIIc) is



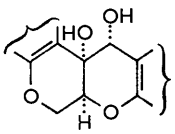
(XIX)



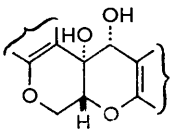
(XX)



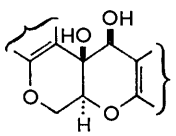
(XXI)



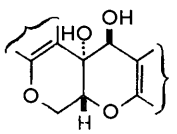
(XXII)



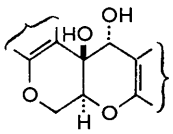
(XXIII)



(XXIV)



(XXV)



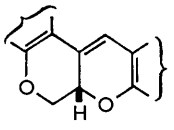
(XXVI)

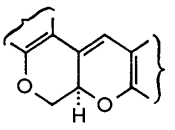
cis-hydroxylated with osmium tetroxide, the (±)-B_1-diol must be the *cis*-12,12a-diol racemate (XXIII—XXIVc). The (±)-B_2-diol is thus the *trans*-12,12a-racemate (XXV—XXVIc) and, as expected, reacts more slowly with lead tetra-acetate. Both diols (±)-B_1 and (±)-B_2 re-formed (±)-isorotenolone B when treated with manganese dioxide, showing that the B/C fusion is unaltered. When (±)-isorotenolone A (IX—Xc), with a *cis*-B/C fusion, was reduced either by borohydride or catalytically, only one diol, (±)-A, m. p. 218°, was isolated. This reacted with lead tetra-acetate more slowly than the *cis*-12,12a-diol

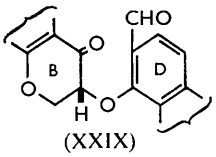
[9] Clark, *J. Amer. Chem. Soc.*, 1934, **56**, 987.
[10] Cahn, Phipers, and Boam, *J.*, 1938, 513.

(±)-B_1, though faster than the (±)-B_2-diol. Structure (XIX—XXc) is consistent with this as (XXI—XXIIc) would react almost instantaneously. On oxidation with manganese dioxide, the (±)-A-diol formed (±)-isorotenolone A. This formation of racemate (XIX—XXc) alone or dominantly is as expected, for the α-face in rotenone and derivatives with *cis*-B/C fusion (XIII—XIVc) is hindered and attack by borohydride ion or catalytic hydrogenation would give predominantly an α-oriented hydroxyl at position 12. The *trans*-B/C fusion is open to attack from each face. Diols (±)-A and B_1 each gave (±)isorotenone, presumably by intervention of the 12a-carbonium ion, when treated with acid.

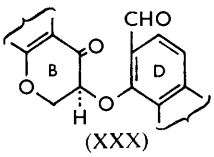
Similar work has been carried out on optically active *cis*-B/C isorotenolones. Thus the 6aβ,12aβ-ketol (IXc) gave the 12α-diol (6aβ,12aβ; XIXc), m. p. 176°, $[\alpha]_D^{20}$ −157° (in $CHCl_3$) whilst the 6aα,12aα-ketol (Xc) gave the 12β-diol (6aα, 12aα; XXc), m. p. 176°, $[\alpha]_D^{20}$ +160° (in $CHCl_3$). Crystallised together, the two enantiomorphs formed the (±)-diol A, m. p. 218°. Each of the racemic diols (±)-A, (±)-B_1, and (±)-B_2 could be degraded to the same racemic keto-aldehyde (XXIX—XXXc), m. p. 182°, when treated with periodic acid in aqueous methanol. Effectively the (±)-B_2-racemate resembles a diaxial diol and it seems likely that the cleavage is preceded by acid-catalysed epimerisation at position 12a. The enantiomorphs (XXIXc), m. p. 190°, $[\alpha]_D^{21}$ +205° (in $CHCl_3$), and (XXXc), m. p. 190°, $[\alpha]_D^{21}$ −202° (in $CHCl_3$), were obtained by treating the diols (XIXc) and (XXc) with periodic acid.


(XXVII)


(XXVIII)

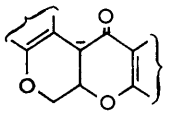


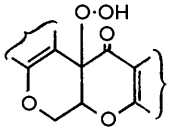
(XXIX)



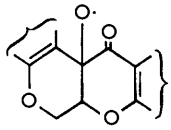
(XXX)

In the absence of definite information, the formation of isorotenolones by aerial oxidation in alkaline medium can be viewed as resulting from attack by molecular oxygen on the ion (XXXIc) to give hydroperoxide ion. The hydroperoxide (XXXIIc) thus formed may react with ion (XXXIc) or with hydroxyl ion [11] to give an isorotenolone, or, less probably, may break down homolytically to (IIc; R′ = OH) *via* the radical (XXXIIIc).


(XXXI)



(XXXII)



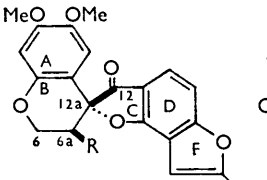
(XXXIII)

(±)-Isorotenolone C is made by heating a solution of (−)-isorotenone in 5% methanolic potassium hydroxide with 30% hydrogen peroxide at 60°: conditions are rather critical. Analogous compounds can be obtained from deguelin [1] and from dihydrorotenone. (±)-Isorotenolone C is isomeric with A and B and contains one hydroxyl group (Zerewitinoff) which forms a methyl ether, a toluene-*p*-sulphonate and, by treatment with keten or refluxing sodium acetate–acetic anhydride, a monoacetate. The latter conditions gave an enol acetate when applied to isorotenone, so position 12a probably carries no hydrogen atom: this is supported by the failure to iodinate (±)-isorotenolone C. The compound is insoluble in alkali, gives no ferric reaction, and is not methylated on prolonged contact with diazomethane, and its acetate has its C–O stretching frequency at 1230 $cm.^{-1}$ (in acetonitrile). These facts suggest that the hydroxyl group is not aromatic (aromatic acetates absorb near 1205 $cm.^{-1}$, steroid acetates near 1240 $cm.^{-1}$). A benzylic placing is not satisfactory as the compound is not oxidised by manganese dioxide or catalytically hydrogenolysed under rather severe conditions. Dehydration is difficult.

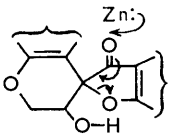
[11] Howe and McQuillen, *J.*, 1958, 1513.

The infrared spectrum of (±)-isorotenolone C shows an intermolecularly bonded hydroxyl at 3378 cm.$^{-1}$ (NaCl, $CHCl_3$) and in dilute solution a " free " (3609 cm.$^{-1}$) and a bonded (3578 cm.$^{-1}$) hydroxyl group (LiF, CCl_4; $< \sim 0{\cdot}005$M). Compared with that of isorotenone (1680 cm.$^{-1}$), the ketone frequency for (±)-isorotenolone C (1706 cm.$^{-1}$) suggests that it is in a five-membered environment. A relationship with the spiro-compound (XXXIV; R = H) ($\nu_{max.}$ 1709 cm.$^{-1}$), the structure of which is dealt with elsewhere,[3] is at once suggested and is supported by the close similarity of their ultraviolet spectra (which are virtually unchanged by acid or alkali). As required, position 12a is blocked. The formation of analogues from deguelin and dihydrorotenone makes it highly unlikely that ring E or its addendum carries the hydroxyl group: this leaves only positions 6 and 6a. In the former case the compound would be a hemiketal, but (±)-isorotenolone C shows none of the expected properties. When treated with phosphorus oxychloride in pyridine it forms a chloro-derivative which is very stable to base and is thus much more in accord with a β- than an α-halogeno-ether formulation.

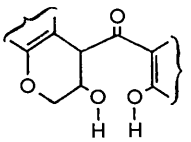
In agreement with (XXXIV; R = OH; and enantiomorph), (±)-isorotenolone C gives isorotenol (VIc) and isoderritol (VIIc) when treated with zinc and alkali. This is readily



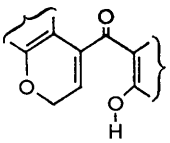
(XXXIV)



(XXXV)

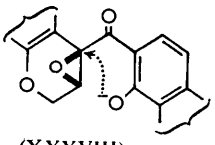


(XXXVI)



(XXXVII)

explained by attack as in (XXXVc) to give the β-hydroxy-compound (XXXVIc) which can yield the first intermediate (XXXVIIc) of the rotenol–derritol change discussed later.[3] (±)-Isorotenolone C is reduced to a diol by borohydride: as expected, oxidation of this diol with manganese dioxide gives back the original ketol. The formation of (±)-isorotenolone C from (−)-isorotenone may be viewed as attack by $^-O{\cdot}OH$ on the ion of (XXXVIIc), which is available in an alkaline solution of isorotenone,[3] to give an epoxide [12] which is attacked intramolecularly as in (XXXVIIIc).[12b] Consequently the hydroxyl group may be *cis*- to the keto-group in the spiro-system. It is not optimally placed for bonding to the ketone, so the hydroxyl stretching frequency (above) does not necessarily conflict with this stereochemistry.


(XXXVIII)

Takei and his colleagues [13] have reported that alkaline oxygenation of natural (−)-rotenone gives two products, rotenolone I, m. p. 137—138°, and rotenolone II, m. p. 210°, and this has been confirmed by Miyano and Matsui.[14] These compounds are accepted by them as individuals: but because there is an optical centre at 5′(β) four diastereoisomeric ketols (IX—XIIa) must be produced instead of the two pairs of enantiomorphs (IX—Xc) and (XI—XIIc) obtained when isorotenone is similarly treated. The two expected *trans*-B/C ketol diastereoisomers, 6aβ,12aα,5′β (XIa), m. p. 251°, $[\alpha]_D^{15}$ +420° (in $CHCl_3$), and 6aα,12aβ,5′β (XIIa), m. p. 212°, $[\alpha]_D^{19}$ −78° (in $CHCl_3$), could in fact be separated by fractional crystallisation of the higher-melting and less soluble rotenolone II. As the mixture of *cis*-B/C ketol diastereoisomers contained in rotenolone I did not part cleanly on crystallisation, they were made in another way (the presence of the two diastereoisomers in rotenolone I was, however, shown indirectly by examination of the products obtained by reduction with borohydride). The 6aβ,12aβ,5′β (IXa) compound, m. p. 88° (methanol solvate), $[\alpha]_D^{16}$ −189° (in $CHCl_3$), was the major product when natural rotenone was treated

[12] (*a*) Payne, *J. Org. Chem.*, 1958, **23**, 310; (*b*) Vander Werf, Heisler, and McEwen, *J. Amer. Chem. Soc.*, 1954, **76**, 1231.
[13] Takei, Miyajima, and Ono, *Ber.*, 1933, **66**, 482.
[14] Miyano and Matsui, *Chem. Ber.*, 1959, **92**, 1438.

with dichromate–acetic acid, whilst the 6aα,12aα,5′β (Xa) diastereoisomer was formed by similar treatment of an epirotenone [10] concentrate. The second ketol was amorphous, $[\alpha]_D^{18}$ +26° (in $CHCl_3$), but yielded crystalline degradation products (below). Assignment of structure to these compounds rests on criteria similar to those used for isorotenolones above and emerges in the degradations below. Assignment of ring fusion depends on hydroxyl-to-ketone hydrogen-bonding criteria. The configuration of the two *cis*-B/C diastereoisomers at 6a is apparent from that of their precursors, whilst that of the two *trans*-B/C diastereoisomers at this centre is shown below by degradation. In all four compounds the configuration (β) at 5′ remains the same.

As in the case of the isorotenolones, each *trans*-B/C rotenolone diastereoisomer gave a separable pair of 12,12a-diols when reduced with borohydride. Thus the 6aβ,12aα,5′β-ketol (XIa) gave the 6aβ,12aα,12α,5′β-diol (XXIIIa) and the 6aβ,12aα,12β,5′β-diol (XXVa), whilst the 6aα,12aβ,5′β-ketol (XIIa) gave the 6aα,12aβ,12β,5′β-diol (XXIVa) and the 6aα,12aβ,12α,5′β-diol (XXVIa). The *cis*-12,12a-diol structure is assigned to compounds (XXIIIa) and (XXIVa) because they are cleaved almost instantaneously with lead tetra-acetate, whilst reaction of the *trans*-12,12a-diols (XXVa) and (XXVIa) is considerably slower. On preparative cleavage with periodic acid the diols (XXIIIa) and (XXVa) gave the keto-aldehyde (XXIXa) of known β-configuration at positions 6a and 5′ (below), whilst the diols (XXIVa) and (XXVIa) gave the keto-aldehyde (XXXa) of known α-configuration at 6a and β at 5′ (below). These diols were oxidised back to their parent ketols by manganese dioxide, and the information given allows complete definition of their stereochemistry.

Only one diol was isolated from each of the two *cis*-B/C rotenolone diastereoisomers on reduction with borohydride. The 6aβ,12aβ,5′β-ketol (IXa) gave the 6aβ,12aβ,12α,5′β-diol (XIXa) (methanol solvate), and the 6aα,12aα,5′β-ketol (Xa) gave the 6aα,12aα,12β,5′β-diol (XXa) (methanol solvate).* The *trans*-12,12a-diol arrangement is assigned to each because, although they are cleaved more rapidly than the " *trans*-diaxial " diols, the rate is considerably slower than that of the *cis*-12,12a-diols above. The configurations at positions 6a and 5′ follow from the stereochemistry of their precursors, and thus the configurations of the keto-aldehyde (XXIXa) (6aβ,5′β) isolated by periodate treatment of diol (XIXa), and the keto-aldehyde (XXXa) (6aα,5′β) similarly isolated from diol (XXa), are known. These are the reference substances used above.

In a recent paper by Miyano and Matsui [14] assignments for the rotenolones and rotenolols were made, but differently from those above. Experimental differences apart, our interpretations diverge on the following main points. First, we recognise four diastereoisomeric ketols obtained on alkaline oxygenation of rotenone, not two (these are mixtures). Secondly, our assignments of configuration to the B/C fusions are opposite to those claimed. Thirdly, the stereochemical position regarding the rotenolols does not seem to be properly appreciated by Miyano and Matsui—a total of eight forms is possible with the natural configuration at 5′. In two cases, because in our submission their interpretation is incorrect, Miyano and Matsui have to postulate an unexpected epimerisation at position 6a during borohydride reduction. This, they admit, they do not understand, and no such epimerisations are required in our treatment. Recent assignments [14,15] to tephrosin and isotephrosin also differ from ours above. Biological evidence cited [16] in favour of a *trans*-B/C configuration for " rotenolone I," if accepted as valid, is just as easily interpreted in favour of a *cis*-B/C configuration, for it suggests only that " rotenolone I " [*i.e.*, (IXa) and (Xa)] and natural rotenone possess the same B/C fusion.

* Among the rotenolols, pairs which would be enantiomorphic but for the possession by each of the same 5′β-isopropenyl group, have virtually indistinguishable solution spectra, *e.g.*, (XIXa)–(XXa), (XXIIIa)–(XXIVa), and (XXVa)–(XXVIa). In other cases the diastereoisomers have distinctly different solution spectra.

[15] Miyano, Nishikubo, and Matsui, *Chem. Ber.*, 1960, **93**, 1746.
[16] Miyano and Matsui, *Bull. Agric. Chem. Soc. Japan*, 1958, **22**, 335.

Experimental

For general working procedures see the preceding paper.

Preparation of (±)-Isorotenolone A and B by Alkaline Oxygenation.—(−)-Isorotenone (18 g.) was suspended in ethanol (450 ml.) containing N-aqueous potassium hydroxide (15 ml.), and a rapid stream of air was passed through the mixture for 6 hr. Next morning a granular precipitate (13 g.) was obtained which crystallised as prisms, m. p. 192°, from chloroform–methanol. Continued crystallisation from chloroform gave *(±)-isorotenolone B* (2·33 g.), prisms, m. p. 242—243° (decomp.; pre-heated Kofler hot-stage) (Found: C, 67·5; H, 5·4; active H, 0·25. $C_{23}H_{22}O_7$ requires C, 67·3; H, 5·4; active H, 0·25%), $\lambda_{max.}$ (in $CHCl_3$) 246 (4·69), 248 (4·69), 262 (4·25), 283 (4·16), and 335 (3·70), $\lambda_{max.}$ (alkaline ethanol) 242 (4·69), 260 (4·18), 278 (4·03), and 330 (3·54) mμ. Methylation with methyl iodide and silver oxide gave a little dehydroisorotenone (m. p. and mixed m. p. 195°) together with *(±)-isorotenolone B methyl ether*, m. p. 166° (Found: C, 67·75; H, 5·8. $C_{24}H_{24}O_7$ requires C, 67·9; H, 5·7%). A second form, m. p. 145°, of the ether was also encountered.

The mother-liquors from the chloroform crystallisation were diluted with methanol and concentrated, to give crystals which when recrystallised from chloroform–methanol formed needles of (±)-isorotenolone A, m. p. 208—209° (8·8 g.) (Found: C, 67·3; H, 5·55; active H, 0·27%), $\lambda_{max.}$ (in $CHCl_3$) 246 (4·76), 252 (4·76), 264 (4·32), 285 (4·25), 297 (3·98), and 335 (3·72), $\lambda_{max.}$ (alkaline ethanol) 243 (4·84), 247 (4·82), 260 (4·39), 279 (4·21), and 332 (3·83) mμ. Methylation as above gave (±)-isorotenolone A methyl ether, m. p. 152°, together with a little dehydroisorotenone. Neither (±)-isorotenolone formed a toluene-*p*-sulphonyl derivative, or an acetyl derivative (with keten): both were recovered unchanged after 6 hours' refluxing with active manganese dioxide in acetone; both failed to react with iodine and sodium acetate in dioxan in 12 hr. at 20°. LaForge and Haller [1] give m. p. 203—204° (methyl ether, m. p. 153°) for (±)-isorotenolone I, and m. p. 193—194° (methyl ether, m. p. 133—134°) for (±)-isorotenolone II. The former is almost pure isorotenolone A, but the latter corresponds to our material of m. p. 192° (the infrared spectrum of the authentic sample kindly supplied by Dr. H. L. Haller was identical) and is a mixture of (±)-isorotenolone A and B, as was shown spectroscopically and by methylation. Isorotenolone II (0·7 g.), when methylated as above, gave, after chromatography on alumina (N3) from benzene, (±)-isorotenolone A and B methyl ethers, m. p. and mixed m. p. 152—153° and 144—145° (second form), respectively; a little dehydroisorotenone was also formed.

(±)-Isorotenolones by Treatment of 6a,12a-*Dehydroisorotenol Acetate* (IVc) *with t-Butyl Hydroperoxide.*—The acetate (150 mg.) in benzene (0·5 ml.) was treated with t-butyl hydroperoxide (0·5 ml.) and Triton-B reagent (0·25 ml.). After 12 hr. more hydroperoxide (0·5 ml.) was added. After a further 3 hr. the mixture was washed with brine and chromatographed from benzene–chloroform (1 : 1) on alumina (K1), to give a mixture of (±)isorotenolones A and B, m. p. 187—190° not depressed on admixture with " isorotenolone II; " the infrared curves (mull) were almost superimposable.

Oxidation of (±)- and (−)-Isorotenone with Dichromate in Acetic Acid.—(−)-6aβ,12aβ-Isorotenone (7 g.) in acetic acid (175 ml.) was added to a warm solution of sodium dichromate (3·5 g.) in acetic acid (35 ml.) and kept for 12 hr. The product was poured into water and chromatographed from benzene–light petroleum (b. p. 60—80°) (1 : 1) on alumina (A5). The gum was treated with methanol. The insoluble solid, crystallised from chloroform–benzene, gave 6aβ,12aα-*isorotenolone B* (XIc) (50 mg.), plates, m. p. 220° (decomp.; br.), $[\alpha]_D^{19}$ +366° (*c* 1·5 in $CHCl_3$) (Found: C, 67·1; H, 5·6%; *M*, 416. $C_{23}H_{22}O_7$ requires C, 67·3; H, 5·4%; *M*, 410). The infrared spectrum (chloroform) was identical with that of (±)-isorotenolone B.

Concentration of the methanol solution and crystallisation at 0° gave 6aβ,12aβ-*isorotenolone A* (IXc) as the methanol solvate (4·2 g.), m. p. 96—97° (decomp.), $[\alpha]_D^{25}$ −83·5° (*c* 2 in C_6H_6), $[\alpha]_D^{16}$ −52° (*c* 2 in $CHCl_3$) (Found: C, 64·9, 65·2; H, 6·0, 5·9; OMe, 20·5. $C_{23}H_{22}O_7$, $CH_3{\cdot}OH$ requires C, 65·15; H, 5·9; OMe, 21·05%), $\lambda_{max.}$ (in $CHCl_3$) 246, 252, 264, 285, 298, and 336 mμ. In the infrared (CaF_2, CCl_4; < ~0·005M) there were bands at 3645 (free primary OH of methanol) and 3503 $cm.^{-1}$ (intramolecularly bonded hydroxyl) and also (NaCl,$CHCl_3$) 1675 (aryl conj. ketone), 1613, 1595, and 1502 (aryl) $cm.^{-1}$. When heated *in vacuo* at 105—110° the substance frothed slowly and the glass did not crystallise again although its infrared spectrum in chloroform was the same as that of (±)-isorotenolone A. The solvate was heated at 120° and the distillate identified as methanol (α-naphthylurethane, m. p. and mixed m. p. 123°).

(±)-Isorotenone (500 mg.) was treated with potassium dichromate (200 mg.) in warm acetic acid (20 ml.) and kept overnight. Working up as above gave, after chromatography from benzene–chloroform (3 : 1) on alumina (A3) and crystallisation from chloroform–methanol, (±)-isorotenolone A, m. p. and mixed m. p. 208—209°.

Oxidation of (+)-Isorotenone with Dichromate in Acetic Acid.—(+)-6aα,12aα-Isorotenone [2] (10 g.) {m. p. 183—184°, $[\alpha]_D^{18}$ +82° (*c* 2 in C_6H_6)} in glacial acetic acid (200 ml.) was treated with potassium dichromate (6 g.) in water (20 ml.) at 60° for 30 min. After being kept overnight the mixture was worked up as above and chromatographed from benzene on alumina (N3). The resulting glass was dissolved in methanol, and (±)-isorotenolone A (730 mg.), m. p. and mixed m. p. 209—210°, crystallised and was removed. (+)-6aα,12aα-*Isorotenolone A* (Xc) crystallised as the methanol solvate (4·7 g.), m. p. 96° (decomp.) (Found: C, 65·6; H, 5·7%), $[\alpha]_D^{19}$ +81° (*c* 2 in C_6H_6), $[\alpha]_D^{16}$ +53° (*c* 2 in $CHCl_3$). When (+)- and (−)-isorotenolone A methanol solvates (100 mg.) were crystallised together from chloroform–methanol, (±)-isorotenolone A (unsolvated; 186 mg.) was isolated, with m. p. and mixed m. p. 209—210°.

(±)-*Isorotenolone A Acetate.*—(*a*) Isorotenone (2 g.) in glacial acetic acid (80 ml.) was shaken at 20° for 48 hr. with glacial acetic acid (100 ml.) saturated with lead tetra-acetate. The product was poured into water (1 l.), and the solid was filtered off and warmed with methanol. Crystallisation of the insoluble material (from chloroform–methanol) gave isorotenonone (76 mg.), m. p. and mixed m. p. 251°, $\lambda_{max.}$ (in $CHCl_3$) 295 (4·36), 274 (4·40), 261 (4·38), and 403 (3·88) mμ, $\nu_{max.}$ 1733 (unsaturated lactone), 1650 (C=O), 1613, 1587, 1563, and 1527 (aryl) cm.$^{-1}$. The methanolic solution crystallised, to give (±)-*isorotenolone A acetate* (920 mg.), m. p. and mixed m. p. 165° (Found: C, 66·6; H, 5·35%; *M*, 447. $C_{25}H_{24}O_8$ requires C, 66·4; H, 5·3%; *M*, 452). A second form, diamonds, m. p. 179°, was also encountered: its solution spectrum is identical with that of the form, m. p. 165°.

(*b*) Iodine (8 g.) in ethanol (100 ml.) was added to (−)-isorotenone (12 g.) in ethanol (300 ml.) containing sodium acetate (30 g.) and kept at 60°. The solution was partly evaporated, allowed to crystallise, and filtered, to give 6a,12a-dehydroisorotenone (6 g.), m. p. and mixed m. p. 196° (decomp.). The filtrate was poured into water, and the precipitated solid was dried and chromatographed from benzene–chloroform (3 : 1) on alumina (N1), to give more dehydroisorotenone, (±)-isorotenone, and (±)-isorotenolone A acetate (340 mg.), m. p. and mixed m. p. 165°. [For the direct acetylation of (±)-isorotenolone A and B see elsewhere.[2]]

(±)-Isorotenolone A acetate (1 g.) was treated with ethanolic 10% sodium hydroxide (50 ml.) at 40° for 2 hr., then poured into water, and the suspension was extracted with chloroform. The extract was dried and evaporated. The residue was chromatographed from benzene–chloroform (3 : 1) on alumina (N3), to give (±)-isorotenolone A (116 mg.), needles (from chloroform–methanol), m. p. and mixed m. p. 206—207°, and (±)-isorotenolone B (27 mg.), m. p. 239° (decomp.) (from the same solvents): the infrared spectrum of the latter was identical with that of an authentic specimen.

Acid-catalysed Dehydration of the Isorotenolones.—(*a*) (±)-Isorotenolone A (50 mg.) was refluxed for 15 min. with 10% sulphuric acid in methanol (5 ml.). After cooling, recrystallisation of the crystals from chloroform–methanol gave 6a,12a-dehydroisorotenone (39 mg.), m. p. and mixed m. p. 195° (decomp.). Similarly (±)-isorotenolone B (50 mg.), (+)-isorotenolone B (5 mg.), and (−)-isorotenolone A (10 mg.) gave dehydroisorotenone (41, 4, and 6 mg., respectively). (*b*) The isorotenolone (*ca.* 10 mg.) was dissolved in a 10% solution of sulphuric acid in tetrahydrofuran, with shaking for the first 5 min. Light absorption readings at 316 mμ were then taken with the following results (density increments in parentheses): (±)-isorotenolone A (10·77 mg.: initial dens. 0·392), 20 (0·014), 30 (0·019), 40 (0·024), 60 (0·032), 90 (0·039), 120 (0·042), 180 (0·046) min.; (±)-isorotenolone B (10·57 mg.: initial dens. 0·380), 10 (0·032), 20 (0·043), 50 (0·058), 70 (0·062), 95 (0·067), 115 (0·070), 140 (0·078), 170 (0·087), 195 (0·092) min. The absorption at 316 mμ (ε 2300) of a 10% solution of dehydroisorotenone in tetrahydrofuran was stable; so was that of (±)-isorotenolone A (ε 400) and B (ε 370) at 316 mμ in tetrahydrofuran.

Degradation of (±)-Isorotenolone A and B with Zinc Dust and Alkali.—(±)-Isorotenolone A (1 g.) was refluxed and stirred with zinc dust (2·5 g.), 15% aqueous potassium hydroxide (15 ml.), and ethanol (35 ml.) for 3 hr. The mixture was cooled, filtered, acidified, and evaporated, and the residue was extracted with ether. The ethereal extracts were themselves extracted with 2% aqueous potassium hydroxide. The residual ethereal solution was evaporated, to give isorotenol (135 mg.), plates (from methanol), m. p. 131°, $\lambda_{max.}$ (in acid

ethanol), 243 (4·58), 250 (4·56), 263 (4·05), 284 (4·05), and 338 (3·46) mμ, $\nu_{max.}$ 1631 (chelated C=O), 1621, 1597, and 1499 (aryl) cm.$^{-1}$; the chelated-hydroxyl absorption is a broad band emerging from both sides of the C–H stretching complex. The alkaline extracts were acidified, to give isoderritol, yellow needles (314 mg.) (from methanol), m. p. 148°, $\lambda_{max.}$ (in $CHCl_3$), 242 (4·53), 252 (4·46), 291 (4·32) and 368 (4·00) mμ, $\nu_{max.}$ 1631 (chelated C=O), 1605, 1582, and 1497 (aryl) cm.$^{-1}$ (chelated hydroxyl as above plus intermolecularly bonded hydroxyl 3330 cm.$^{-1}$). Under the same conditions (±)-isorotenolone B (1 g.) gave isorotenol (58 mg.), m. p. 131° and isoderritol (160 mg.), m. p. 148°.

Pressure Hydrogenation of (±)-*Isorotenolone A and B.*—(±)-Isorotenolone A (1 g.) was hydrogenated in ethyl acetate (25 ml.) over Adams platinum catalyst (200 mg.) at 95°/50 atm. for 6 days. Working up gave a gum which on chromatography from benzene on alumina (A3) gave the *deoxy-compound* (Vb; but without stereochemical implications) (29 mg.), m. p. 160° (Found: C, 72·25, 72·2; H, 6·9, 7·05. $C_{23}H_{26}O_5$ requires C, 72·25; H, 6·85%), $\nu_{max.}$ 1621, 1610, and 1495 (aryl) cm.$^{-1}$. The infrared spectrum (chloroform) was very closely similar to that of (Vb; 6aβ,12aβ,5′β), m. p. 172°. It may be the same as the product, m. p. 160°, obtained when 6a,12a-dehydroisorotenone was catalytically hydrogenated.[17] Similarly hydrogenated, (±)-isorotenolone B gave the *deoxy-compound* (Vc) (27 mg.), m. p. 149° (from ethanol), in which ring E has not been reduced (Found: C, 72·7; H, 6·4. $C_{23}H_{24}O_5$ requires C, 72·6; H, 6·35%), $\nu_{max.}$ 1621, 1592, and 1497 cm.$^{-1}$.

(±)-*Tephrosin and* (±)-*Isotephrosin.*—(±)-Deguelin (200 mg.) in ethanol (20 ml.) and N-sodium hydroxide (1 ml.) was aerated for 24 hr. After 12 hr. at 0° crystals (150 mg.), m. p. 192—195°, had been deposited; they were chromatographed from benzene–chloroform (1 : 1) on alumina (K1), to give (±)-isotephrosin (14 mg.), prisms, m. p. 253—254° (lit.,[8b,18] m. p. 252°, 260°), and then (±)-tephrosin (82 mg.), plates (from methanol), m. p. 201°. An authentic specimen of the latter from natural sources had m. p. 197° (mixed m. p. 198—199°; lit.,[8a,18] m. p. 197°, 201°). (±)-Tephrosin had $\lambda_{max.}$ 238 (4·36), 251 (4·37), 271 (4·47), 300 (4·02), and 317 (3·97) mμ.

Dehydration of (±)-*Tephrosin.*—(*a*) (±)-Tephrosin (100 mg.) was refluxed with a 10% solution (3 ml.) of sulphuric acid in methanol for 30 min. The crystals which separated recrystallised from chloroform–methanol, to give 6a,12a-dehydrodeguelin (64 mg.), pale yellow rods, m. p. 230—231°, $\lambda_{max.}$ 220, 236, 259, 278, and 314 mμ. (*b*) (±)-Tephrosin (100 mg.) was warmed at 60—65° for 20 min. with sulphuric acid (0·5 ml.) in glacial acetic acid (1 ml.). The product was chromatographed from benzene–chloroform (1 : 1) on alumina (A1), to give 6a,12a-dehydrodeguelin, m. p. and mixed m. p. 228—229°. (*c*) (±)-Tephrosin (100 mg.) was heated under reflux with sodium acetate (100 mg.) in acetic anhydride (1 ml.) for 2 hr. Methanol was added and the solid which separated was chromatographed as above, to give 6a,12a-dehydrodeguelin, m. p. and mixed m. p. 231°. These three specimens had identical ultraviolet and infrared properties [$\nu_{max.}$ 1637 (C=O), 1621, 1603, 1572, 1502 (aryl) cm.$^{-1}$]. This agrees with the view of Boam and his co-workers [8d] on earlier claims.[19]

Reduction of (±)-*Isorotenolone A with Borohydride.*—(±)-Isorotenolone A (1 g.) in tetrahydrofuran–water (1 : 1; 50 ml.) was kept with potassium borohydride (3 g.) at 0° for 36 hr. The mixture was refluxed for 1 hr., 20% aqueous potassium carbonate (20 ml.) was added, and refluxing was continued for 3 hr. The product was poured on ice and filtered off (970 mg.; m. p. 206°). Crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave the (±)-*A diol* (XIX—XXc), m. p. 218° (632 mg.) (Found: C, 67·3; H, 5·9. $C_{23}H_{24}O_7$ requires C, 67·0; H, 5·85%), $\lambda_{max.}$ (in $CHCl_3$) 253 (4·24), 260 (4·24), 281i (3·83), 291 (3·97), and 299 (3·78) mμ, $\nu_{max.}$ (mull) 3483 (OH), 1618, 1605, 1590, and 1508 (aryl) cm.$^{-1}$. Another preparation was worked up chromatographically but a second diol was not found. When shaken with active manganese dioxide in acetone for 48 hr. the (±)-A diol was reconverted into (±)-isorotenolone A. Reduction of (±)-isorotenolone A (2·7 g.) with sodium borohydride (2·7 g.) gave the (±)-A-diol (2·17 g.), plates, m. p. 216—218° (decomp.). The diol was unchanged after 48 hours' refluxing with sodium ethoxide in ethanol.

Reduction of (±)-*Isorotenolone B with Borohydride.*—(±)-Isorotenolone B (1 g.) in tetrahydrofuran (50 ml.) and ethanol (100 ml.) was kept with sodium borohydride (1 g.) at 50° for 30 min. The mixture was cooled, then set aside for 12 hr., and acetone (25 ml.) was added.

[17] Butenandt and Hildebrandt, *Annalen*, 1930, **477**, 245.
[18] Clark, *J. Amer. Chem. Soc.*, 1943, **65**, 27.
[19] Merz and Schmidt. *Arch. Pharm.*, 1935, **273**, 1.

After evaporation, the residue was extracted with chloroform, and the extract was washed with 2N-hydrochloric acid and water and dried. Evaporation and crystallisation from chloroform–methanol gave the (±)-*B_1 diol* (XXIII—XXIVc) (405 mg.), plates m. p. 251—252° (decomp.; pre-heated block at 220°) or 263° (decomp.; preheated block at 250°) (Found: C, 67·2; H, 5·8. $C_{23}H_{24}O_7$ requires C, 67·0; H, 5·85%), $\lambda_{max.}$ (in $CHCl_3$) 253 (4·28), 258 (4·28), 280i (3·88), 290 (3·95), and 296i (3·85) mμ, $\nu_{max.}$ (mull) 3425i, 3356 (OH), 1610, 1600, 1582, and 1511 (aryl) cm.$^{-1}$. The chloroform mother-liquors were concentrated, methanol was added, and the concentration was repeated. This was done several times and the methanol solution was then set aside for 2 days. After filtration from a small amount of crystalline material, the solution was evaporated. The glassy product, crystallised from benzene–cyclohexane, gave the (±)-*B_2 diol* (XXV—XXVIc) (216 mg.), prisms, m. p. 213° (decomp.; br.) (Found: C, 66·85; H, 6·0%), $\nu_{max.}$ (mull) 3497, 3333 (OH), 1623i, 1613, 1600, 1587, and 1505 (aryl) cm.$^{-1}$. The mull spectra of (±)-A, (±)-B_1, and (±)-B_2 diols, although having a general similarity, are distinguishable from each other. When shaken with active manganese dioxide (1·5 g.) in acetone for 48 hr. the (±)-B_1 diol (152 mg.) gave (±)-isorotenolone B (143 mg.). The (±)-B_2 diol (50 mg.) was resistant to oxidation at 20° but, when refluxed in acetone with active manganese dioxide (1 g.) for 24 hr., gave (±)-isorotenolone B (18 mg.).

Reduction of (+)- *and* (−)-*Isorotenolone A with Borohydride.*—(−)-6aβ,12aβ-Isorotenolone A (methanol solvate; 1·5 g.) in ethanol (30 ml.) was reduced with sodium borohydride. Chromatography from chloroform on alumina (K3) gave the (−)-6aβ,12aβ,12α-*diol* (XIXc) (1·19 g.), m. p. 175—177° [from chloroform–light petroleum (b. p. 60—80°)], $[\alpha]_D^{20}$ −157° (*c* 2 in $CHCl_3$) (Found: C, 66·8; H, 5·7. $C_{23}H_{24}O_7$ requires C, 67·0; H, 5·85%). (+)-6aα,12aα-Isorotenolone A (methanol solvate; 1·5 g.) similarly gave the (+)-6aα,12aα,12β-*diol* (XXc) (1·24 g.), m. p. 175—176°, $[\alpha]_D^{20}$ +160° (*c* 2 in $CHCl_3$) (Found: C, 66·7; H, 5·95%). Each diol was oxidised back to its ketol precursor, m. p. and mixed m. p. 97—98°, when shaken for 1 hr. with active manganese dioxide in acetone. The diols, crystallised together from chloroform, gave the (±)-A-diol, m. p. and mixed m. p. 216° (decomp.). The infrared solution spectra of the (±)-, (+)-, and (−)-A-diols are identical. Those of the (+)- and (−)-diols as mulls (identical) show only minor differences from the mull spectrum of the (±)-compound.

Catalytic Hydrogenation of (±)-*Isorotenolone A and B.*—(*a*) (±)-Isorotenolone A (1 g.) in glacial acetic acid (50 ml.) was hydrogenated over Adams platinum catalyst (250 mg.) at atmospheric pressure for 6 hr. The mixture was filtered into water, and the precipitated solid was crystallised from ethyl acetate–light petroleum (b. p. 60—80°), to give the (±)-A-diol (657 mg.), m. p. and mixed m. p. 216—217° (infrared confirmation). (*b*) (±)-Isorotenolone B (1 g.) in ethyl acetate (25 ml.) was hydrogenated over Adams catalyst (200 mg.) at 60°/80 atm. for 2 days. Working up and crystallisation from ethyl acetate–ethanol gave the (±)-B_1-diol (452 mg.), needles, m. p. 263—264° (decomp.; br): identity was established by comparison of mull spectra.

Treatment of the (±)A- *and* (±)B_1-*Diols with Acid.*—(*a*) The (±)-A-diol (100 mg.) was refluxed with 10% methanolic sulphuric acid (5 ml.) for 1 hr. and the product was poured into water and extracted with chloroform. The extract yielded (±)-isorotenone (33 mg.), needles (from methanol), m. p. and mixed m. p. 171°. The mother-liquors gave no precipitate with Brady's reagent. (*b*) The (±)-B_1-diol (200 mg.) similarly gave a product (no precipitate with Brady's reagent) which after chromatography from benzene–chloroform (3 : 1) on alumina (N1) gave (±)-isorotenone (26 mg.), m. p. and mixed m. p. 171°. A second experiment worked up as in (*a*) gave (±)-isorotenone (44 mg.) from (±)-B_1-diol (100 mg.).

The (±)-6,6a-*Dihydrorotoxen Derivative* (XXVII—XXVIIIc).—The 12β-hydroxy-compound, m. p. 193° (4 g.), made by reducing (±)-isorotenone with borohydride,[2] was treated with phosphorus oxychloride (12 ml.) in dry pyridine (30 ml.) at 80° for 90 min. The mixture was poured into water and extracted with chloroform. After being washed with 4N-hydrochloric acid and water the extract was dried and evaporated, and the residue was chromatographed from benzene–chloroform (3 : 1) on alumina (A1) and crystallised from chloroform–methanol, to give the (±)-6,6a-*dihydrorotoxen derivative* (XXVII—XXVIIIc) (2·13 g.), plates, m. p. 180° (Found: C, 72·75; H, 5·8. $C_{23}H_{22}O_5$ requires C, 73·0; H, 5·85%), $\lambda_{max.}$ 255 (4·50), 267 (4·48), 277 (4·49), 312 (3·93), 338i (4·29), 357 (4·49), and 376 (4·40) mμ, $\nu_{max.}$ 1623, 1595, and 1502 (aryl and C=C) cm.$^{-1}$.

Isorotenone Enol-acetate.—This *acetate* was prepared by the sodium acetate–acetic anhydride technique for the purposes of ultraviolet comparison; it had m. p. 134° (Found: C, 68·5; H,

5·5. $C_{25}H_{24}O_7$ requires C, 68·8; H, 5·55%), $\lambda_{max.}$ 255 (4·49), 265 (4·38), 274 (4·30), 312 (3·85), 333i (4·11), 352 (4·31), and 370 (4·24) mμ, $\nu_{max.}$ 1763 cm.$^{-1}$ (Ac).

Treatment of the (±)-6,6a-*Dihydrorotoxen Derivative* (XXVII—XXVIIIc) *with Osmium Tetroxide*.—The (±)-6,6a-dihydrorotoxen (600 mg.) and osmium tetroxide (500 mg.) in dry dioxan (20 ml.) and pyridine (2 drops) were kept in the dark for 20 days. The osmium complex was decomposed by passage of hydrogen sulphide (12 hr.), the osmium sulphide was filtered off, and the filtrate was poured into water. After 12 hr. the product was filtered off and crystallised from ethyl acetate, to give the (±)-B_1-diol (272 mg.) having an infrared spectrum (mull) identical with that of the authentic specimen above. Oxidation with active manganese dioxide gave isorotenolone B, m. p. and mixed m. p. 241° (decomp.) (infrared confirmation). Addition of light petroleum to the ethyl acetate mother-liquors gave unchanged 6,6a-dihydrorotoxen precursor (78 mg.).

Oxidation of the Isorotenolols with Lead Tetra-acetate.—The diol (20 mg.) and 0·1N-lead tetra-acetate in acetic acid (2 ml.) were rapidly and accurately made up to 10 ml. with acetic acid. At intervals 1 ml. portions were removed and titrated against 0·1N-sodium thiosulphate. The (±)-B_1-diol had completely reacted before a reading at 2 min. The $t_{1/2}$ and $t_{3/4}$ for the (±)-B_2- diol were 8½ and 16 min., respectively; for the (±)-A diol they were 2 and 3½ min., respectively.

Oxidation of the Isorotenolols with Periodic Acid.—Periodic acid (1 g.) in 50% aqueous solution was diluted with methanol (5 ml.) and added to the (±)-A-diol (XIX—XXc) (250 mg.) in dioxan (25 ml.). The mixture was shaken for 24 hr. and poured into water (100 ml.). The precipitate was filtered off and crystallised from acetone–methanol, to give the (±)-*keto-aldehyde* (XXIX—XXXc) (228 mg.), needles, m. p. 182° (Found: C, 67·05; H, 5·4. $C_{23}H_{22}O_7$ requires C, 67·3; H, 5·4%), $\lambda_{max.}$ (CaF_2, $CHCl_3$) 1675 cm.$^{-1}$ (ketone and aldehyde not resolved). The (±)-B_1-diol (250 mg.) gave an identical keto-aldehyde (172 mg.), m. p. and mixed m. p. 182°. The (±)-B_2-diol (50 mg.) gave the same keto-aldehyde (19 mg.), m. p. 179—180°, mixed m. p. 180—181°. The infrared spectra (mulls) of the three specimens were the same.

The (−)-6aβ,12aβ,12α-diol (XIXc) (250 mg.) gave the 6aβ-*keto-aldehyde* (XXIXc) (172 mg.), needles (from acetone–methanol), m. p. 189—190° (Found: C, 66·5, 66·5; H, 5·2, 5·4. $C_{23}H_{22}O_7,\frac{1}{2}CH_3{\cdot}OH$ requires C, 66·25; H, 5·65%), $[\alpha]_D^{21}$ +205° (*c* 2 in $CHCl_3$). The (+)-6aα,12aα,12β-diol (XXc) (250 mg.) gave the 6aα-*keto-aldehyde* (XXXc) (165 mg.), m. p. 190° (from the same solvent mixture) (Found: C, 66·5, 66·6; H, 5·35, 5·7%), $[\alpha]_D^{21}$ −202° (*c* 2 in $CHCl_3$). Crystallised together the enantiomorphs gave the (±)-keto-aldehyde, m. p. and mixed m. p. 182°. The chloroform infrared spectra of the three keto-aldehydes were identical except for a band due to methanol in the solvates.

Reduction of (±)-*Isorotenolone B Methyl Ether with Sodium Borohydride*.—The ether (1·5 g.; m. p. 145°) in ethanol (150 ml.) was reduced with sodium borohydride (1·5 g.) in the usual way and gave the (±)-12a-*monomethyl ether* of isorotenolol B (XXIII—XXIVc) (1·42 g.) (Found: C, 67·55; H, 6·25. $C_{24}H_{26}O_7$ requires C, 67·6; H, 6·15%), m. p. 262° (decomp.; br). The ether could be chromatographed on alumina (K1) but in one experiment in which chromatography on " acid " alumina was employed the 12a-ether and (±)-isorotenone were found. Refluxing the ether (100 mg.) with 5% hydrochloric acid in dioxan gave (±)-isorotenone (64 mg.), m. p. and mixed m. p. 171°.

The stereochemistry of the 12a-monomethyl ether was decided by methylation to the dimethyl ether, m. p. 172° (decomp.) (from pentane), identical (mixed m. p.) with the dimethyl ether from (±)-isorotenolol B_1, m. p. 170°, and different from (±)-isorotenolol B_2 dimethyl ether, m. p. 89° (decomp.).

(±)-*Isorotenolone C*.—(−)-Isorotenone (10 g.) in 5% methanolic potassium hydroxide (130 ml.) was warmed to 60° and 30% hydrogen peroxide (14 ml.) was added in portions. Heating was continued for 30 min. and the whole was set aside for 12 hr. and then filtered, to give (±)-isorotenolone C (6·4 g.), m. p. 209° raised to 211—212° (plates) after crystallisation from chloroform–methanol. It did not depress the m. p. of LaForge and Haller's original specimen [1] m. p. 210—212° (we thank Dr. Haller for this). (±)-Isorotenolone C (Found: C, 67·15; H, 5·6. Calc. for $C_{23}H_{22}O_7$: C, 67·3; H, 5·4%) had $[\alpha]_D^{20}$ 0°, $\lambda_{max.}$ (in $CHCl_3$) 241 (4·76), 247i (4·69), 264i (4·07), 281 (4·11), 292i (3·98), and 335 (3·74) mμ, $\lambda_{max.}$ (in alkaline ethanol) 239 (4·72), 245 (4·64), 259i (4·02), 281 (4·02), 290i (3·95), and 333 (3·70) mμ (the curve in acid ethanol was very similar), $\nu_{max.}$ ($CHCl_3$) 1706, $\nu_{max.}$ (mull) 1684 (C=O) cm.$^{-1}$. On methylation with methyl iodide–silver oxide the methyl ether was obtained, having m. p. 157°, $\lambda_{max.}$ 240 (4·69), 246 (4·62), 278

(4·06), 282 (4·07), and 333 (3·73) mμ, $\nu_{max.}$ (in $CHCl_3$) 1706 (C=O), 1629, 1597, and 1504 (aryl) $cm.^{-1}$, $\nu_{max.}$ (mull) 1706 (C=O), 1623, 1585, and 1506 (aryl) $cm.^{-1}$ (lit.,[1] m. p. 160°). Refluxing sodium acetate and acetic anhydride or keten gave the monoacetate, m. p. 142—143°, $\nu_{max.}$ 1742 (OAc), 1704 (C=O), 1626, 1592, and 1502 (aryl) $cm.^{-1}$ (lit.,[1] m. p. 145°). By heating the alcohol with toluene-*p*-sulphonyl chloride in pyridine the *toluene*-p-*sulphonate* was obtained as prisms [from benzene–light petroleum (b. p. 60—80°)], m. p. 187° (Found: C, 63·65; H, 5·1. $C_{30}H_{28}O_9S$ requires C, 63·9; H, 5·0%), $\nu_{max.}$ 1706 (C=O) $cm.^{-1}$. The derivative was recovered in poor yield after treatment with sodium n-butoxide in butan-1-ol.

(±)-Isorotenolone C was unaffected by refluxing 10% ethanolic potassium hydroxide or 1 : 2 sulphuric–acetic acid. It gave no ferric chloride colour. When dissolved in concentrated sulphuric acid and poured into water it gave a deep green precipitate, soluble in methanol to a deep blue solution; adding ethanolic sodium hydroxide discharged the blue colour. (±)-Isorotenolone C was unchanged after attempted hydrogenation over Adams platinum at 95°/55 atm. for 12 hr. The substance was not oxidised by lead tetra-acetate, sodium bismuthate, chromium trioxide–pyridine, or chromium trioxide in concentrated sulphuric acid and acetone at 20°. More severe oxidative conditions gave no identifiable product. (±)-Isorotenolone C was not affected by iodination in dioxan at 20° (24 hr.), by refluxing it with an acetone suspension of manganese dioxide, or by keeping it with ethereal diazomethane at 0° for 60 days.

In one preparation (±)-isorotenolone C, m. p. 189—190°, was isolated. One crystallisation from chloroform–methanol raised the m. p. to 209—210°. The two forms had identical infrared solution spectra and nearly identical mull spectra. LaForge and Haller [1] give m. p. 188—189° for isorotenolone D. If the temperature in the preparation is not sufficiently high, isorotenolones A and B can be isolated.

6′,7′-Dihydrorotenolone C.—Dihydrorotenone (2 g.) was treated with 30% hydrogen peroxide (5 ml.) in 5% methanolic potassium hydroxide, as above. After being kept at 0°, the mixture was poured into water; extraction with ether gave a glass which was extracted with hot light petroleum (b. p. 100—120°). The petroleum extracts were kept at 0°; after 3 months *6′,7′-dihydrorotenolone C* crystallised; it had m. p. 187° (800 mg.) (Found: C, 66·75; H, 6·0. $C_{23}H_{24}O_7$ requires C, 67·0; H, 5·85%), $[\alpha]_D^{18}$ −79° (*c* 0·9 in $CHCl_3$), $\nu_{max.}$ (in $CHCl_3$) 3586, 3381 (OH), 1698 (C=O), 1621, 1600, and 1486 (aryl) $cm.^{-1}$, $\nu_{max.}$ (mull) 1692 (C=O) $cm.^{-1}$.

Degradation [1] of (±)-Isorotenolone C to Isorotenol (VIc) *and Isoderritol* (VIIc).—Isorotenolone C (2 g.) was treated under reflux for 3½ hr. with 15% aqueous potassium hydroxide (30 ml.), ethanol (70 ml.), and zinc dust (5 g.). Working up gave isorotenol [3] (0·26 g.), m. p. 132°, and isoderritol (0·72 g.), m. p. 148°, both identical with authentic specimens.

The Chloro-derivative of (±)-Isorotenolone C.—(±)-Isorotenolone C (1 g.) was refluxed with dry γ-collidine (15 ml.) and phosphorus oxychloride (4 ml.) for 2 hr. The mixture was poured on ice and extracted with chloroform. The extract was washed with 4N-hydrochloric acid and water, dried, and evaporated. Chromatography of the residual gum from benzene–chloroform (3 : 1) on alumina (A1) and crystallisation from light petroleum (b. p. 60—80°) gave the *monochloro-derivative* (XXXIV; R = Cl), m. p. 171°, $\nu_{max.}$ (in $CHCl_3$), 1711 (C=O), 1629, 1593, and 1505 (aryl) $cm.^{-1}$, $\nu_{max.}$ (mull) 1708 $cm.^{-1}$ (Found: C, 64·45; H, 5·0; Cl, 8·15. $C_{23}H_{21}ClO_6$ requires C, 64·4; H, 4·95; Cl, 8·25%).

Reduction of (±)-Isorotenolone C with Borohydride.—(±)-Isorotenolone C (1 g.) and potassium borohydride (3 g.) in tetrahydrofuran–ethanol (1 : 1; 75 ml.) were kept at 0° for 6 days. The solution was refluxed for 2 hr. and then refluxed overnight with 20% aqueous potassium carbonate (10 ml.). Working up gave the *diol* (840 mg.), plates [from ethyl acetate–light petroleum (b. p. 60—80°)], m. p. 197—198° (Found: C, 67·2; H, 6·0. $C_{23}H_{24}O_7$ requires C, 67·0; H, 5·85%), $\lambda_{max.}$ (in $CHCl_3$) 252 (4·29), 259 (4·27), 289 (4·06), and 295 (4·09) mμ, $\nu_{max.}$ (CaF_2, CCl_4; $< \sim 0{\cdot}005$M) 3606 and 3574 $cm.^{-1}$, $\nu_{max.}$ (NaCl, $CHCl_3$), 3616, 3390 (OH), 1634i, 1621, 1590, and 1504 $cm.^{-1}$. When the diol was shaken with active manganese dioxide in acetone at 20°, (±)-isorotenolone C was formed almost quantitatively.

Preparation of Rotenolones by Alkaline Oxygenation.—Natural rotenone (50 g.) was suspended in 95% ethanol (1·5 l.), aqueous N-potassium hydroxide (30 ml.) was added, and a rapid stream of air was passed through the mixture for 3 days. The rotenone first dissolved and a granular precipitate was then formed. The latter (6·1 g.) was filtered off and crystallised from chloroform–ethanol to give rotenonone (19 mg.), yellow plates, m. p. 295° (mixed m. p. 296—297°), and crystals (4·9 g.), m. p. 207—219° (decomp.). The latter were further crystallised

from chloroform–ethanol, to give 6aβ,12aα,5′β-*rotenolone* (XIa) (1·8 g.), large plates, m. p. 249—251° (decomp.) (Found: C, 67·0; H, 5·3. $C_{23}H_{22}O_7$ requires C, 67·3; H, 5·4%), $[\alpha]_D^{20}$ +420° (*c* 2 in $CHCl_3$), $\nu_{max.}$ (CaF_2, CCl_4; < ~0·005M) 3603 cm.$^{-1}$ (there were signs of a very weak band at 3556 cm.$^{-1}$), $\nu_{max.}$ (NaCl, $CHCl_3$) 3584 (OH), 3344 (intermolecularly bonded OH), 1692 (C=O), 1616, and 1504 (aryl) cm.$^{-1}$. The mother-liquors from the crystallisation were diluted with methanol and evaporated several times *in vacuo*, the methanol being renewed each time. Finally the product was recrystallised from ethanol, to give 6aα,12aβ,5′β-*rotenolone* (XIIa) (104 mg.), needles, m. p. 211—212° (Found: C, 67·3; H, 5·15%), $[\alpha]_D^{19}$ −78° (*c* 2 in $CHCl_3$). The solution infrared spectra of the two diastereoisomers were virtually the same.

The original filtrate from the aeration was just acidified with acetic acid and poured into water. The precipitate was filtered off, dried, and treated with ether. There remained material which contains a new substance which will not be considered here: the ether solution was dried and on refrigeration gave crystals, m. p. 132—135°, which when crystallised from methanol gave a mixture of 6aβ,12aβ,5′β- and 6aα,12aα,5′β-rotenolones (16·1 g.), prisms, m. p. 139—140° (Found: C, 67·25; H, 5·3%), $[\alpha]_D^{15}$ −140° (*c* 2 in $CHCl_3$), $\nu_{max.}$ (CaF_2, CCl_4, < ~0·005M) 3509 cm.$^{-1}$, $\nu_{max.}$ (NaCl, $CHCl_3$) 3521 (intramolecularly bonded OH), 1672 (C=O), 1616, and 1504 (aryl) cm.$^{-1}$ [rotenone has $\nu_{max.}$ 1674 (C=O) cm.$^{-1}$].

Oxidation of Natural Rotenone with Dichromate in Acetic Acid.—Rotenone (10 g.) in acetic acid (250 ml.) was treated with potassium dichromate (7 g.) in glacial acetic acid (100 ml.) and water (10 ml.) and kept at 50° for 30 min. and then at 20° for 24 hr. Pouring the solution into water (1 l.) gave a precipitate that was chromatographed from benzene–chloroform (1 : 1) on alumina (K1), elution being with chloroform. In order of elution there were obtained: rotenone (29 mg.), m. p. and mixed m. p. 296°; dehydrorotenone (262 mg.), m. p. and mixed m. p. 216°; a mixed fraction separable by treatment with hot methanol into dehydrorotenone (38 mg.) and solvated 6aβ,12aβ,5′β-rotenolone (IXa) (24 mg.); and a glass. The glass gave solvated 6aβ,12aβ,5′β-*rotenolone* (IXa) (5·7 g.) as large prisms, m. p. 88°, when crystallised from methanol (Found: C, 65·1; H, 5·9. $C_{23}H_{22}O_7$,CH_3·OH requires C, 65·1; H, 5·9%), $[\alpha]_D^{16}$ −189° (*c* 2 in $CHCl_3$).

Oxidation of (" *d-epi* ") 6aα,12aα,5′β-*Rotenone Concentrate with Dichromate in Acetic Acid.*—6aα,12aα,5′β-Rotenone concentrate (12 g.; $[\alpha]_D$ +10°) in glacial acetic acid (250 ml.) was heated at 50°, as above, with potassium dichromate (8 g.) in water (25 ml.). Working up as above by chromatography gave creamy-white solid (2·65 g.) which did not crystallise. It was purified by precipitation from acetone with water, to give powdery 6aα,12aα,5′β-*rotenolone* (Xa) (Found: C, 67·2; H, 5·55. $C_{23}H_{22}O_7$ requires C, 67·3; H, 5·4%), $[\alpha]_D^{18}$ +26° (*c* 1 in $CHCl_3$). The solution infrared spectra of the 6aα,12aα,5′β- and the 6aβ,12aβ,5′β-diastereoisomer, and their mixture formed in the aeration experiment, were virtually identical and showed clear differences from the series with the *trans*-B/C ring junction.

Reduction of cis-B/C *Rotenolones with Borohydride.*—6aβ,12aβ,5′β-Rotenolone (IXa; methanol solvate) (2·6 g.), in ethanol (150 ml.), was kept at 50° with sodium borohydride (1·5 g.) for 30 min. and then at 20° for 12 hr. Acetone (20 ml.) was added and the solvents were evaporated. The residue was dissolved in chloroform and washed with water, 4N-hydrochloric acid, and aqueous potassium carbonate, and then dried. Evaporation gave solid (2·3 g.) which crystallised from carbon tetrachloride and then methanol to give 6aβ,12aβ,12aα,5′β-*rotenolol* (XIXa) as the methanol solvate, prisms, m. p. 125—126° (decomp.) (Found: C, 64·8; H, 6·5. $C_{23}H_{24}O_7$,CH_3·OH requires C, 64·85; H, 6·35%), $[\alpha]_D^{20}$ −152° (*c* 2 in $CHCl_3$).

6aα,12aα,5′β-Rotenolone (Xa) (2 g.) in ethanol (50 ml.) was reduced with sodium borohydride as above, to give 6aα,12aα,12β,5′β-*rotenolol* (XXa) as the methanol solvate (1·3 g.), m. p. 185° (decomp.) (Found: C, 64·95; H, 5·75%), $[\alpha]_D^{20}$ +120° (*c* 1 in $CHCl_3$). The infrared solution spectrum was virtually identical with that of the 6aβ,12aβ,12α,5′β-diastereoisomer.

The mixture (3·5 g.), m. p. 139—140°, of 6aβ,12aβ,5′β- and 6aα,12aα,5′β-rotenolones obtained from the aerial oxidation experiment was reduced with sodium borohydride (0·5 g.). Crystallisations of the product from methanol and chloroform–methanol gave 6aβ,12aβ,12α,5′β-rotenolol (0·8 g.), m. p. 123—124°, $[\alpha]_D^{18}$ −153° (*c* 2 in $CHCl_3$), identical with the specimen above. The mother-liquors were worked up by crystallisation from carbon tetrachloride, to give material of m. p. 147—153° (after softening from 126°). Chromatography from carbon tetrachloride on alumina (K1), and elution with chloroform and then chloroform–acetone, gave impure 6aα,12aα,12β,5′β-rotenolol (127 mg.), m. p. 156—157°, $[\alpha]_D^{20}$ +88·5° (*c* 2 in $CHCl_3$), from

carbon tetrachloride (unsolvated, identified spectroscopically). In another experiment 6aβ,12aβ,12α,5′β-*rotenolol* was also obtained unsolvated by crystallisation from carbon tetrachloride, forming plates, m. p. 191° (Found: C, 67·2; H, 5·9. $C_{23}H_{24}O_7$ requires C, 67·0; H, 5·85%), $[\alpha]_D^{15}$ −150° (*c* 2 in $CHCl_3$). The crude reduction product of the diastereoisomeric mixture, if crystallised several times from carbon tetrachloride, gave plates, m. p. 194°, $[\alpha]_D^{18}$ −40·5°; one recrystallisation from methanol then gave the 6aβ,12aβ,5′β-rotenolol, m. p. 125° (with liberation of methanol), $[\alpha]_D^{18}$ −154°.

Reduction of trans-B/C *Rotenolones with Borohydride.*—6aβ,12aα,5′β-Rotenolone (2 g.) in tetrahydrofuran (100 ml.) and ethanol (150 ml.) was reduced, as above, with sodium borohydride (0·5 g.). Working up by crystallisation from chloroform and then methanol–chloroform gave the 6aβ,12aα,12α,5′β-*rotenolol* (XXIIIa) (800 mg.), plates, m. p. 257° (decomp.) (Found: C, 67·2; H, 6·15. $C_{23}H_{24}O_7$ requires C, 67·0; H, 5·85%), $[\alpha]_D^{17}$ +196° (*c* 0·25 in $CHCl_3$). More (240 mg.) was isolated from the mother-liquors which were then evaporated and dissolved in benzene. Crystals, m. p. 237° (decomp.) (65 mg.), separated and were rejected. The solution was concentrated and cyclohexane was added. 6aβ,12aα,12β,5′β-*Rotenolol* (XXVa) (570 mg.), m. p. 180° (Found: C, 66·7; H, 5·7%), $[\alpha]_D^{17}$ +228° (*c* 1 in $CHCl_3$), crystallised and was further crystallised from the same solvent mixture. The solution infrared spectra of the 6aβ,12aα,12β,5′β- and 6aβ,12aα,12α,5′β-rotenolol are different.

6aα,12aβ,5′β-Rotenolone (100 mg.) in ethanol (25 ml.) was reduced with sodium borohydride (100 mg.) as usual. The product, a glass, partly crystallised from methanol, to give 6aα,12aβ,12β,5′β-*rotenolol* (XXIVa) (23 mg.), plates, m. p. 259° (decomp.; bl. or br.), 251° (decomp.; tube) (Found: C, 67·15; H, 5·55%), $[\alpha]_D^{16}$ −15° (*c* 0·5 in $CHCl_3$). Concentration of the liquors gave more (13 mg.). Finally the liquors were evaporated and chromatographed from benzene–chloroform (3 : 7) on alumina (K1), to give 6aα,12aβ,12α,5′β-*rotenolol* (XXVIa) (17 mg.), m. p. 157° (br) (from chloroform–cyclohexane) (Found: C, 66·95; H, 5·8%), $[\alpha]_D^{16}$ −50° (*c* 0·5 in $CHCl_3$), and further (11 mg.) 6aα,12aβ,12β,5′β-rotenolol. The solution infrared spectra of 6aα,12aβ,12β,5′β- (XXIVa) and 6aα,12aβ,12α,5′β-rotenolol (XXVIa) were different, but the solution spectra of the 6aβ,12aα,12α,5′β- (XXIIIa) and the 6aα,12aβ,12β,5′β-diol (XXIVa) are virtually indistinguishable: this applies also to the 6aβ,12aα,12β,5′β- (XXVa) and 6aα,12aβ,12α,5′β-pair (XXVIa).

Oxidation of Rotenolols with Manganese Dioxide.—6aβ,12aβ,12α,5′β-Rotenolol (100 mg.) was shaken with active manganese dioxide (1 g.) in acetone for 12 hr. Filtration, evaporation, and crystallisation from methanol gave solvated 6aβ,12aβ,5′β-rotenolone (63 mg.), m. p. and mixed m. p. 88°, $[\alpha]_D^{19}$ −185° (*c* 2 in $CHCl_3$). 6aβ,12aα,12α,5′β-Rotenolol (25 mg.) similarly gave 6aβ,12aα,5′β-rotenolone (17 mg.), m. p. and mixed m. p. 245° (decomp.), $[\alpha]_D^{18}$ +430° (*c* 1 in $CHCl_3$). Under the above conditions, 6aβ,12aα,12β,5′β-rotenolol (17 mg.) was unaltered but, after refluxing (48 hr.) 6aβ,12aα,5′β-rotenolone (13 mg.), m. p. and mixed m. p. 245°, $[\alpha]_D^{17}$ +406° (*c* 0·5 in $CHCl_3$), was obtained.

Oxidation of Rotenolols with Lead Tetra-acetate.—By the method described above, the 6aβ,12aβ,12α,5′β- (XIXa) and the 6aα,12aα,12β,5′β-rotenolol (XXa) each had $t_{1/2}$ and $t_{3/4}$ 2 and 3¾ min. The 6aβ,12aα,12β,5′β- (XXVa) and 6aα,12aβ,12α,5′β-diol (XXVIa) had $t_{1/2}$ 5¾ and 6½ min., and $t_{3/4}$ 13 and 14 min., respectively. 6aβ,12aα,12α,5′β- (XXIIIa) and 6aα,12aβ,12β,5′β-Rotenolol (XXIVa) reacted completely in less than 2 min.

Oxidation of Rotenolols with Periodic Acid.—6aβ,12aβ,12α,5′β-Rotenolol (XIXa) (250 mg.) in dioxan (25 ml.) was added to periodic acid (1 g.) in 50% aqueous methanol (5 ml.). The mixture was shaken for 24 hr. and poured into water. Filtration gave the 6aβ,5′β-*keto-aldehyde* (XXIXa) (189 mg.), needles, m. p. 216° (from acetone–methanol) (Found: C, 67·35; H, 5·7. $C_{23}H_{22}O_7$ requires C, 67·3; H, 5·4%), $[\alpha]_D^{18}$ +141° (*c* 2 in $CHCl_3$). 6aβ,12aα,12α,5′β-Rotenolol (250 mg.) gave the same keto-aldehyde (174 mg.), m. p. and mixed m. p. 216° (infrared mull confirmation), $[\alpha]_D^{18}$ +142° (*c* 2 in $CHCl_3$). 6aβ,12aα,12β,5′β-Rotenolol also gave the keto-aldehyde, m. p. and mixed m. p. 213° (infrared mull comparison).

6aα,12aα,12β,5′β-Rotenolol (XXa) (200 mg.) under the same conditions gave the 6aα,5′β-*keto-aldehyde* (XXXa) (162 mg.), needles, m. p. 196—197° (decomp.) (from acetone–methanol) (Found: C, 67·1; H, 5·3%), $[\alpha]_D^{18}$ −245° (*c* 2 in $CHCl_3$). 6aα,12aβ,12β,5′β-Rotenolol (XXIVa) (10 mg.) gave the same keto-aldehyde (6 mg.), m. p. and mixed m. p. 196—197° (infrared mull comparison).

The 6aβ,5′β- and the 6aα,5′β-keto-aldehyde have readily distinguishable mull spectra, but in chloroform solution they are virtually identical.

One of us (P. J. G.) is grateful for a D.S.I.R. post-graduate award and a Shell post-doctoral fellowship.

UNIVERSITY OF LONDON, KING'S COLLEGE,
STRAND, LONDON, W.C.2.
IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

[*Received, December* 16*th*, 1960.]