34. *The Triterpene Group. Part IX. The Constitution of Breïn and Maniladiol.*

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It is shown that a close structural relationship probably obtains between breïn and maniladiol, the two principal diols of *Manila elemi* resin. Both isomerides are singly unsaturated, pentacyclic, di-secondary glycols; they probably differ in the location of their ethenoid linkages, but it is possible that their hydroxylated positions are identical. There is no close association either between the hydroxyl groups themselves, or between these and the double bond, in either diol. Efforts to establish an experimental relationship between the diols and either of the amyrins have been unsuccessful. The *methyl ethers* of α- and β-amyrin have been prepared, and also β-*amyrin* p-*toluenesulphonate*; the latter compound is unexpectedly stable in acid media.

In previous papers (Morice and Simpson, J., 1940, 795; 1941, 181) we have shown that *Manila elemi* resin is a remarkably prolific source of triterpene alcohols, the two principal diols being the isomeric substances breïn and maniladiol. We now describe experiments which we have recently carried out with a view to the elucidation of the structure of these two diols.

Breïn.—Vesterberg (*Ber.*, 1906, **39**, 2467) suggested on biogenetic grounds that breïn is probably a hydroxyamyrin. In the work here described we have found that the diol is pentacyclic, that it resembles

α- rather than β-amyrin, that both hydroxyls are secondary, and that only one of them can be in ring A; we have, however, been unable to convert breïn into any known derivative of the amyrins.

The similarity between breïn and α-amyrin is indicated by the reluctance of the diacetate to react with perbenzoic acid. In one experiment, in which a 0·25N-solution of the acid in chloroform was used, only 0·03 atom of oxygen was absorbed during 14 days, and the diacetate was recovered in practically quantitative yield. In other experiments, small but appreciable amounts of oxygen were absorbed, but the only material recovered was the rather impure diacetate. The diol, however, is undoubtedly unsaturated (tetranitromethane), so the double bond is evidently of the extremely inert type present in α-amyrin, in contrast to the comparatively reactive unsaturated position characteristic of β-amyrin (Ruzicka, Silbermann, and Furter, *Helv. Chim. Acta*, 1932, **15**, 482). Furthermore, treatment of breïn dibenzoate with sulphur in boiling benzyl acetate leads to general decomposition of part of the ester, the remainder being recoverable, but in an impure condition; this behaviour would be unexpected if the diol were a β-amyrin derivative, but is not inconsistent with the view that the double bond may occupy the position characteristic of α-amyrin, because the methyl ester of acetyl-β-boswellic acid, which belongs to the α-amyrin group (Ruzicka and Wirz, *Helv. Chim. Acta*, 1939, **22**, 948), is largely unattacked under these conditions (Simpson and Williams, J., 1938, 1712).

Oxidation of breïn diacetate with chromic anhydride gives a good yield of a new *diacetate*, $C_{34}H_{52}O_5$, which shows the absorption spectrum of an αβ-unsaturated ketone, and gives no colour with tetranitromethane. It follows that breïn contains only a single ethenoid linkage (which must be of the type $>C{=}CH{-}CH_2-$), and the diol is therefore pentacyclic. Alkaline hydrolysis of the keto-diacetate yields the corresponding keto-diol, *breienediolone*, m. p. 249°.

The secondary nature of both hydroxyl groups in breïn is suggested by the fact that we have been unable to obtain any evidence of selective hydrolysis of breïn diacetate, and by the extremely smooth oxidation of the diol with chromic anhydride at room temperature to the corresponding dicarbonyl compound. This substance, which we now name breienedione, was originally obtained in very poor yield by Rollett (*Monatsh.*, 1929, **53—54**, 231) by oxidation with the same reagent on the water-bath. This author, on the basis of his analytical data and of the formation from the compound of only a monoxime, was unable to decide whether one or both of the hydroxyl groups had undergone oxidation. We have confirmed the formation of the monoxime, but we regard the compound as a diketone in view of its reduction by aluminium *iso*propoxide to a mixture of two keto-alcohols, *breieneonol*-A and -B, each of which has been characterised as a monohydric alcohol by the preparation of the corresponding *acetate*. These keto-alcohols are probably epimeric, and may be considered to result from the reduction of the C_2-carbonyl of breienedione (this also is presumably the carbonyl group of the diketone which reacts with hydroxylamine). Reduction of the C_2-carbonyl group by aluminium *iso*propoxide has already been observed in the case of nor-β-boswellanedione (Simpson and Williams, *loc. cit.*). Breienedione exhibits weak selective absorption in the ultra-violet which is indicative of isolated carbonyl groups; these, therefore, cannot be conjugated either with each other or with the double bond.

The absence of an aldehydic carbonyl in breienedione is confirmed by the stability of the compound towards chromic anhydride, by which it is attacked extremely slowly at temperatures below 55—60°. At about 65° the diketone yields a mixture of acid and neutral resins, the latter predominating. No crystalline substance could be obtained from the acid fraction, but the neutral material on treatment with semicarbazide furnished a yellow, crystalline *semicarbazone*, m. p. 194°. The formula of this substance suggested by analysis is $C_{31}H_{49}O_3N_3$, but the amount available was too small to permit further investigation.

The foregoing evidence clearly indicates that breïn cannot be an α-glycol. A primary-secondary β-glycol grouping of the hederagenin type is similarly excluded, and in agreement with this conclusion we find that the diol does not yield an acetonyl derivative in presence of hydrochloric acid. It may be noted in passing that condensation with acetone is not rigidly indicative of the presence of the system $CH_2(OH)\cdot\overset{|}{C}\cdot CH(OH)-$ in a triterpene diol, because, although hederagenin and bassic acid both form acetonyl derivatives (Jacobs, *J. Biol. Chem.*, 1925, **63**, 631; Heywood, Kon, and Ware, J., 1939, 1124), soyasapogenol-B, in which the same system is present (Tsuda and Kitagawa, *Ber.*, 1938, **71**, 790, 1604), does not do so. The possibility that breïn might be a disecondary β-glycol can also be eliminated for the reason that breienedione would then be a β-diketone, a formulation which is inconsistent with the reluctance of the compound to undergo further oxidation. It therefore follows that the second hydroxyl group of breïn cannot be in ring A.

In attempting to relate breïn to either α- or β-amyrin, we at first sought to effect the removal of hydroxyl groups from the diol by means of phosphorus pentachloride, the dehydrating action of which

upon triterpene alcohols has been frequently observed (compare Vesterberg, *Ber.*, 1887, **20**, 1247; Nojd, *Arch. Pharm.*, 1927, **265**, 381) In the case of breïn, however, uncrystallisable resins resulted, and milder conditions were apparently required. We considered that *p*-toluenesulphonyl chloride might fill this need, because this reagent forms reactive esters with cholesterol and other sterols (Stoll, *Z. physiol. Chem.*, 1932, **207**, 147), which readily undergo double decomposition in alcoholic solution. Although the reactivity of these steroid tosylates is evidently dependent on the proximity of the 5 : 6 double bond to the tosyl group, it nevertheless seemed possible that the more readily dehydrated triterpene alcohols might undergo spontaneous dehydration, or at least yield reactive tosylates which could be broken down to the sulphonic acid and unsaturated hydrocarbons. To test this hypothesis, the tosylation of β-amyrin was carried out, with the result that *β-amyrin p-toluenesulphonate* was isolated in high yield. This ester, however, proved to be unexpectedly stable, and highly resistant to fission in acid media; experiments in this direction were therefore discontinued.

The reduction of breienedione by the Clemmensen method furnished a poor yield of a *hydrocarbon*, m. p. 143°, analysis of which suggested the molecular formula $C_{30}H_{48}$ rather than the expected composition $C_{30}H_{50}$. The physical constants of the compound, however, are not in agreement with those of any of the known amyrilenes or amyrenes.

As an alternative means of establishing a relationship between breïn and the amyrins, we considered that methylation of breieneonol-A, followed by Clemmensen reduction, might give rise to the methyl ether of α- or β-amyrin. These *ethers*, hitherto unknown, were accordingly prepared from the corresponding alcohols by means of emulsified potassium and methyl iodide; the alkylations were extremely sluggish in comparison with those of ergosterol derivatives by the same method (Heilbron and Simpson, J., 1932, 268). Each ether was stable towards the Clemmensen reagent under the conditions employed in the preparation of the hydrocarbon from breienedione. When, however, the methylation of breieneonol-A was attempted *via* the potassium derivative, decomposition rapidly set in with production of a resin, and further search for the correct methylation conditions was prevented by lack of material.

Finally, the reduction of breienedione with hydrazine and sodium ethoxide was investigated; here again, however, resinification occurred, and no serviceable product could be isolated.

Maniladiol.—The fact that breïn and maniladiol occur in very close association in *Manila elemi* resin (Morice and Simpson, *locc. cit.*) is suggestive of a correspondingly intimate chemical relationship between them. The physical constants of corresponding derivatives of the two isomerides are, indeed, strikingly similar in many instances, as may be seen from the accompanying Table.

	Maniladiol.		Breïn.	
	M. p.	$[\alpha]_D$.	M. p.	$[\alpha]_D$.
Diol	220—221°	+68°	221—222°	+63·5°
Diacetate	193—194	+80	197—198	+70
Diformate	191—192	+84	220—221	+67
Dibenzoate	233—234	+63·5	209—210	+58
Diketone	209—210	+48	159—160	+66
Oxime of diketone	272—274	—	250—252	—
Keto-diacetate	224—225	+93	222—223	+90
Keto-diol	240—241	+88	247—249	+82

The diols, however, appear to differ in the reactivity, and therefore probably also in the location, of their unsaturated centres. For instance in a perbenzoic acid titration, conditions being used under which breïn diacetate absorbed only 0·03 atom of oxygen, maniladiol diacetate reacted with 0·53 atom of oxygen; the product was a mixture which still gave a positive tetranitromethane reaction, although the melting point was depressed by the parent diacetate. That maniladiol contains only one unsaturated position, and is therefore pentacyclic, follows from the ready oxidation of the diacetate to a *compound*, $C_{34}H_{52}O_5$, which shows the absorption spectrum of an αβ-unsaturated ketone and gives a negative tetranitromethane reaction. As in the case of the breïn derivative, this new diacetate easily yields the related *keto-diol* on hydrolysis.

Oxidation of the free diol at room temperature proceeds smoothly, as with breïn, to the corresponding diketone, *maniladione*, the absorption spectrum of which indicates the absence of conjugation, and closely resembles that of breienedione. Maniladione forms a *monoxime*, fails to react with Schiff's reagent, and is stable to chromic anhydride below 50°. At 63° it yields on oxidation an *acid* of probable formula $C_{30}H_{46}O_5$, presumably formed by fission of ring A at C_2–C_3, together with a yellow neutral *substance*, $C_{30}H_{44}O_3$. The colour of the latter persists after treatment with charcoal and activated alumina, and we therefore regard it as characteristic of the compound.

For the reasons given in the section dealing with breïn, it follows from the above facts that manila-

diol is a disecondary glycol in which ring A can contain only one hydroxyl group (presumably attached to C_2). No acetonyl derivative could be obtained from maniladiol.

Unsuccessful attempts were made to reduce maniladione to a hydrocarbon. With hydrazine and sodium ethoxide a low yield of a crystalline *substance* was obtained, but the analytical values were approximately those of a monohydric alcohol; lack of material prevented further characterisation of the product. The Clemmensen procedure, as with breienedione, furnished a mixture, but in this case no oxygen-free substance could be isolated.

Although the war has prevented the completion of this investigation, the evidence here recorded is indicative of a close structural relationship between breïn and maniladiol, and is consistent with the provisional hypothesis that the two diols differ in the location of their unsaturated centres, although it is possible that their hydroxylated positions may be identical.

We are indebted to Dr. R. A. Morton for the spectrographic data.

Experimental.

(Melting points are uncorrected, and specific rotations were measured in chloroform solution.)

Oxidation of Breïn with Chromic Anhydride.—(*A*) *Breienedione.* A solution of chromic anhydride (2 g.) in water (5 c.c.) and glacial acetic acid (195 c.c.) was added with stirring to a solution of breïn (4 g.) in acetic acid (1 l. of 95%) at room temperature during 3 hours. After a further 3 hours the solution was diluted with water (3 vols.), and the precipitate collected and washed. It was then taken up in ether, and the solution, after being washed with aqueous sodium hydroxide (no acid fraction was present) and with water, was dried and evaporated. Two crystallisations of the residue from aqueous methanol yielded the pure diketone (2·7 g.), which formed both octahedra, m. p. 150—151°, $[\alpha]_D^{16°}$ + 67° (l = 1, c = 2·81), and long prisms, m. p. 159—160°, $[\alpha]_D^{17°}$ + 66° (l = 1, c = 2·435), either form being obtainable from a solution of the other by nucleation (Found: C, 82·0, 82·1; H, 10·5, 10·5. Calc. for $C_{30}H_{48}O_2$: C, 81·7; H, 11·0%. Calc. for $C_{30}H_{46}O_2$: C, 82·1; H, 10·6%). *Light absorption in alcohol:* Maximum at 2950 A., log ε = 1·833.

The monoxime, prepared in aqueous-alcoholic solution, separated from methanol in shining leaflets, m. p. 250—252° (decomp.) (Found: C, 79·2; H, 10·4; N, 3·6. Calc. for $C_{30}H_{47}O_2N$: C, 79·4; H, 10·5; N, 3·1%).

(*B*) A solution of the diol (0·5 g.) in acetic acid (50 c.c. of 95%) was treated with a solution of chromic anhydride (0·5 g.) in water (5 c.c.) and acetic acid (45 c.c.), added with stirring at 63° during 1 hour. After a further hour, most of the solvent was removed under reduced pressure, water added to the residue, and the precipitate collected and washed. It was then dissolved in ether and separated into acid and neutral fractions with 2% aqueous sodium hydroxide.

The acid fraction, obtained by acidification of the alkaline washings with dilute hydrochloric acid and extraction with ether, was a resin which could not be crystallised. It was methylated with ethereal diazomethane, but again no crystalline material could be obtained.

The ethereal solution containing the neutral material, after being washed, dried, and evaporated, yielded a yellow resin (0·36 g.). After unsuccessful attempts at crystallisation, this material was refluxed with semicarbazide hydrochloride (0·4 g.) and sodium acetate (0·6 g.) in aqueous alcohol (45 c.c.) for 4 hours; water was then added, and the product extracted with ether. The residue from the washed and dried extract crystallised from benzene–ligroin, and after several crystallisations the *semicarbazone* separated in small yellow prisms, m. p. 193—194° (decomp.), $[\alpha]_D^{17°}$ + 111° (l = 1, c = 0·415) (Found: C, 72·0; H, 9·5; N, 8·6. $C_{31}H_{49}O_3N_3$ requires C, 72·7% H, 9·7; N, 8·2%).

The same compound was also obtained by an analogous oxidation of breienedione.

Reduction of Breienedione.—(A) *By the Clemmensen method.* A solution of the diketone (0·6 g.) in glacial acetic acid (52 c.c.) was refluxed for 10 hours with amalgamated zinc dust (22 g.) and concentrated hydrochloric acid (22 c.c.). Water was then added, and the precipitated organic material extracted with ether. The extract was washed with water, aqueous sodium carbonate, and again with water, dried and evaporated. The residue crystallised from acetone, and after six crystallisations from this solvent, which involved heavy losses of material, shining leaflets (30 mg.) of a *hydrocarbon* were obtained, m. p. (constant) 142—143°, $[\alpha]_D^{13°}$ + 40° (l = 1, c = 1·035). The addition of tetranitromethane to a solution of the hydrocarbon in chloroform produced a yellow colour, and in the Liebermann–Burchard test the colour changed from pink through orange to brown (Found: C, 88·4; H, 11·85. $C_{30}H_{48}$ requires C, 88·15; H, 11·85%. $C_{30}H_{50}$ requires C, 87·7; H, 12·3%).

The crystalline material in the mother-liquors was a mixture; one fraction was isolated which melted constantly at 129—131°, but analysis showed this to be a mixture of hydrocarbon and oxygenated material (Found: C, 86·0, 86·2; H, 11·9, 11·8%).

(B) *With hydrazine and sodium ethoxide.* The reduction was carried out as described for maniladione (*q.v.*). No crystalline product could be obtained from the resultant resin, either directly or by adsorption on activated alumina.

(C) *With aluminium* iso*propoxide.* A solution of breienedione (2·6 g., dried at 130° in a vacuum) in *iso*propyl alcohol (220 c.c.) was refluxed for 3½ hours with aluminium *iso*propoxide (11 g.). Water and dilute sulphuric acid were added, and the precipitated material extracted with ether. The residue from the washed,

dried, and evaporated extract could not be satisfactorily purified by crystallisation; it was therefore dissolved in benzene, and the solution was drawn through a column (1·4 × 67 cm.) of activated alumina (100 g.). The bulk of the material was only weakly adsorbed, and on recrystallisation from methanol yielded lustrous plates (0·48 g.) of *breieneonol*-A, m. p. 208—209°, $[\alpha]_D^{17°}$ + 37° (l = 1, c = 2·385) (Found: C, 81·7; H, 11·0. $C_{30}H_{48}O_2$ requires C, 81·75; H, 11·0%). The keto-alcohol was characterised by the preparation of the *acetate* (pyridine and acetic anhydride); this separated from aqueous methanol in clusters of prisms, m. p. 133—135°, $[\alpha]_D^{22°}$ − 13° (l = 1, c = 0·555) (Found: C, 79·4; H, 10·35. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·45%).

The crude reduction product of breienedione contained a small amount of material which was strongly adsorbed on alumina. On recrystallisation of this from methanol, prisms of *breieneonol*-B were obtained (0·16 g.), m. p. 226—227°, $[\alpha]_D^{18°}$ + 48° (l = 1, c = 2·65) (Found: C, 81·9; H, 11·1. $C_{30}H_{48}O_2$ requires C, 81·75; H, 11·0%). The *acetate* formed prismatic needles from methanol, m. p. 212—213°, $[\alpha]_D^{22°}$ + 46° (l = 1, c = 1·47) (Found: C, 79·5; H, 10·2. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·45%).

Oxidation of Breïn Diacetate.—A solution of chromic anhydride (0·15 g.) in water (1 c.c.) and acetic acid (6·5 c.c.) was added during ½ hour at 95° to a solution of breïn diacetate (0·3 g.) in acetic acid (15 c.c. of 95%) with continuous stirring. After a further ½ hour, the solution was diluted with water (3 vols.), and the resultant precipitate collected, washed, and dissolved in ether. The solution was washed with aqueous sodium hydroxide (no acid fraction was present), and again with water. After drying and evaporation, a crystalline residue was obtained, which after one crystallisation from aqueous methanol yielded *breienediolone diacetate* in prisms (0·27 g.), m. p. 222—223°, $[\alpha]_D^{17°}$ + 90° (l = 1, c = 1·87). The compound gave no coloration with tetranitromethane in chloroform. *Light absorption in alcohol:* Maxima at 2470 and 3320 A., log ε = 4·094 and 1·672 (Found: C, 75·6, 75·75; H, 10·0, 9·9. $C_{34}H_{52}O_5$ requires C, 75·5; H, 9·7%).

Breienediolone.—The foregoing compound (170 mg.) was refluxed for 2 hours with 0·1N-alcoholic potassium hydroxide (35 c.c.); the solution was then concentrated to half volume, diluted with water, and extracted with ether. The residue from the washed, dried, and evaporated extract was crystallised from methyl alcohol and then from benzene, yielding rosettes of needles of *breienediolone*, m. p. 247—249° (efferv.), $[\alpha]_D^{21°}$ + 82° (l = 1, c = 1·01) (Found: C, 79·45; H, 10·9. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%).

Attempted Methylation of Breïn.—A solution of the diol (0·2 g.) in benzene (5 c.c.) was refluxed for 4½ hours with 0·2 g. of "emulsified" potassium in benzene (5 c.c.). Methyl iodide (5 c.c.) was then added, and refluxing continued for a further 3 hours. Alcohol and water were then added, and the precipitated material isolated by extraction with ether. The product, though crystalline, was a mixture which could not be separated; after crystallisation, twice from methanol and twice from acetone, it had m. p. 194—207°, but consisted mainly of ummethylated material (Found: OMe, 1·4%).

Attempted Methylation of Breieneonol-A.—A solution of the keto-alcohol (0·4 g.) in benzene (5 c.c.) was treated successively with potassium and methyl iodide under conditions identical with those described above; the solution rapidly darkened on addition of the potassium. Since only a trace (*ca.* 5 mg.) of crystalline substance (m. p. 199—207°) could be isolated, the whole product (0·4 g.) was refluxed for 10 hours in glacial acetic acid (40 c.c.) with concentrated hydrochloric acid (18 c.c.) and amalgamated zinc dust (18 g.); the product, however, was still an intractable resin.

Methylation of α- and β-Amyrin.—α-Amryin (1 g., dried at 130° in a vacuum) was dissolved in benzene (55 c.c.), the solution mixed with a suspension of emulsified potassium (0·4 g.) in benzene (15 c.c.), and the whole refluxed for 3¼ hours. Methyl iodide (10 c.c.) was then added and the refluxing was continued for a further 3 hours. The product, isolated as already described, was crystallised thrice from benzene–alcohol, *α-amyrin methyl ether* separating in lustrous plates (0·25 g.), m. p. 221—222°, $[\alpha]_D^{16°}$ + 93° (l = 1, c = 2·765) (Found: C, 84·3; H, 11·8; OMe, 7·0. $C_{31}H_{52}O$ requires C, 84·45; H, 11·9; OMe, 7·1%).

The methylation of β-amyrin was very incomplete under the above conditions, and unchanged material was easily isolated from the recrystallisation mother-liquors. By the use of smaller quantities of solvent (0·6 g. of the alcohol in 12 c.c. of benzene mixed with 0·4 g. potassium in 10 c.c. of benzene), *β-amyrin methyl ether* was obtained in a yield of 20%; it crystallised from benzene–alcohol in lustrous plates, m. p. 247—248°, $[\alpha]_D^{16°}$ + 98° (l = 1, c = 1·545) (Found: C, 84·1; H, 11·8; OMe, 6·9, 7·1%). Both ethers are considerably less soluble than the parent alcohols.

β-Amyrin p-Toluenesulphonate.—A solution of β-amyrin (0·5 g.) in pyridine (7·5 c.c.) was heated with *p*-toluenesulphonyl chloride (1 g.) on the water-bath for 4 hours; the solution was then diluted with water and extracted with ether. The extract was washed with 2% sodium bicarbonate solution and water, dried, and evaporated. A solution of the residue in acetone deposited dense prisms of the *ester*, m. p. 132—138° (decomp.) (Found: C, 76·5; H, 9·9; S, 5·7. $C_{37}H_{56}O_3S$ requires C, 76·5; H, 9·7; S, 5·5%).

The ester was recovered unchanged from the following experiments: (i) 0·26 G. was refluxed for 4 hours in methyl alcohol (25 c.c.) and benzene (12 c.c.).

(ii) 0·2 G. was refluxed for 2 hours with benzene (5 c.c.) and a 2% solution of concentrated hydrochloric acid in alcohol (30 c.c.). The solution was then made neutral to Congo-red with sodium acetate, the benzene removed, water added, and the precipitate collected and washed.

(iii) 0·19 G. was refluxed for 2 hours with benzene (10 c.c.) and a 10% solution of concentrated hydrochloric acid in alcohol (30 c.c.), the product being isolated as described above.

Finally, the ester (90 mg.) was refluxed for 2 hours with concentrated hydrochloric acid (2 c.c.) in glacial acetic acid (20 c.c.). The solvent was removed under reduced pressure, water added, and the suspension extracted with ether; no crystalline material could be isolated from the resultant resin.

Maniladione.—A solution of maniladiol (1 g.) in 95% acetic acid (150 c.c.) was oxidised with chromic anhydride (0·4 g.) in water (1 c.c.) and acetic acid (49 c.c.), added at room temperature with stirring during 1 hour. After a further hour the product was precipitated with water, filtered off, and dissolved in ether. The extract was washed successively with water, 2% aqueous sodium hydroxide (no acids were present), and water; it was then dried and evaporated. A solution of the residue in aqueous alcohol deposited shining plates (yield, 82%) of *maniladione*, m. p. 209—210°, $[\alpha]_D^{17°}$ + 48° (l = 1, c = 2·39). The compound gave no colour with Schiff's reagent; it gave a yellow colour with tetranitromethane in chloroform, and in the Liebermann–Burchard reaction a pink coloration, changing to orange, was produced. *Light absorption in alcohol :* Maximum at 2925 A., log ε = 1·92 (Found : C, 82·5; H, 10·9. $C_{30}H_{46}O_2$ requires C, 82·1; H, 10·6%).

The *monoxime*, prepared under the usual conditions, separated from aqueous alcohol in shining leaflets, m. p. 272—274° (decomp.) (Found : C, 79·6; H, 10·5; N, 3·2. $C_{30}H_{47}O_2N$ requires C, 79·4; H, 10·5; N, 3·1%).

Oxidation of Maniladione.—The diketone (0·2 g.) was dissolved in 95% acetic acid (20 c.c.) and treated with a solution of chromic anhydride (50 mg.) in water (1 c.c.) and acetic acid (4 c.c.), added during ½ hour at 48—50° with continuous stirring. As no perceptible reaction occurred, the temperature was slowly raised to 63°; oxidation then set in. After being maintained at this temperature for 1 hour, most of the solvent was removed under reduced pressure, and water added to the residue. The precipitate was filtered off, dissolved in ether, and separated into acid and neutral fractions with 2% aqueous sodium hydroxide. Continued crystallisation of the neutral fraction from methyl alcohol gave a yellow product which melted rather indefinitely at 217—222°. The whole of the neutral material was therefore united, dissolved in benzene, and filtered through a column of activated alumina. By this means the mixture was separated into (i) unchanged maniladione, and (ii) a *compound* which crystallised from methanol in bright yellow, prismatic needles, m. p. 227—229·5°, $[\alpha]_D^{15°}$ + 155° (l = 1, c = 1·97) (Found : C, 79·9; H, 9·9. $C_{30}H_{44}O_3$ requires C, 79·6; H, 9·8%).

The alkaline washings from the oxidation were acidified with dilute hydrochloric acid and extracted with ether. The solution was washed, dried, and evaporated, and the residue crystallised twice from aqueous acetic acid, from which the *acid* separated in fluffy needles, m. p. 270—272° (decomp.). Both this acid and also the yellow neutral compound were obtained from an analogous oxidation of maniladiol (Found : C, 73·2; H, 9·6. $C_{30}H_{46}O_5$ requires C, 74·0; H, 9·5%); $[\alpha]_D^{15°}$ + 23° (l = 1, c = 0·51).

Reduction of Maniladione.—(*A*) A solution of the diketone (0·77 g.) in glacial acetic acid (70 c.c.) was refluxed for 10 hours with amalgamated zinc dust (30 g.) and concentrated hydrochloric acid (30 c.c.). The product was isolated as described in the analogous reduction of breienedione; after three crystallisations from acetone there were obtained 90 mg. of prisms which had the constant m. p. 175—176°, $[\alpha]_D^{13°}$ + 32° (l = 1, c = 2·505), but appeared from analysis to be a mixture (Found : C, 86·1; H, 11·9%).

(*B*) The diketone (0·1 g.), hydrazine hydrate (1 c.c. of 95%), and a solution of sodium (0·5 g.) in absolute alcohol (12 c.c.) were heated in a bomb-tube at 190—200° for 16 hours. The reduction product was isolated by extraction with ether, the extract being washed with dilute hydrochloric acid and water, dried, and evaporated. The residual resin was dissolved in benzene (20 c.c.) and filtered through a column (16·5 × 0·9 cm.) of activated alumina. The filtrate contained 70 mg. of crystalline material, which after three crystallisations from aqueous alcohol yielded prisms, m. p. 160—162°, $[\alpha]_D^{22°}$ + 72° ± 10° (l = 1, c = 0·125), in quantity too small for analysis. Concentration of the mother-liquors gave a *substance* which formed rosettes of tiny prisms, m. p. 177—179°, $[\alpha]_D^{22°}$ + 50° (l = 1, c = 1·02); it gave a yellow colour with tetranitromethane in chloroform, and depressed the m. p. of the mixture from the Clemmensen reduction of the diketone (Found : C, 84·0; H, 11·5. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%).

Oxidation of Maniladiol Diacetate.—A solution of the diacetate (0·6 g.) in acetic acid (30 c.c. of 95%) was treated at 95° with a solution of chromic anhydride (0·3 g.) in water (3 c.c.) and acetic acid (12 c.c.), added with stirring during ½ hour. After a further ½ hour the product was precipitated with water and filtered off. It was dissolved in ether, and traces of acid material removed with 2% sodium hydroxide solution. Complete purification of the neutral product by crystallisation was tedious and wasteful; after five crystallisations from methanol the *keto-acetate* was obtained (0·2 g.), m. p. 223—224°, and after several more crystallisations the pure compound separated in needles, m. p. 224—225°, $[\alpha]_D^{16°}$ + 93° (l = 1, c = 1·48), which showed no colour with tetranitromethane (Found : C, 75·65; H, 9·8. $C_{34}H_{52}O_5$ requires C, 75·5; H, 9·7%). *Light absorption in alcohol :* Maxima at 2480 and 3325 A., log ε = 4·059 and 1·625.

Hydrolysis of this diacetate (90 mg., refluxed for 2 hours with 18 c.c. of 0·1N-alcoholic potassium hydroxide, followed by precipitation and ether-extraction) furnished the corresponding *keto-diol*, which crystallised from benzene in rosettes of needles (50 mg.), m. p. 240—241° (efferv.), $[\alpha]_D^{21°}$ + 88° (l = 1, c = 1·29) (Found : C, 79·0; H, 10·85. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%).

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