# Constituents of *Erythroxylon monogynum* Roxb. Part III.[1] Erythroxytriols P and Q[2]

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Structures for erythroxytriol P and erythroxytriol Q acetate, which occur in the heartwood of *E. monogynum*, are suggested on the basis of spectroscopic and chemical evidence. Ozonolysis of erythroxydiol X acetonide leads to an α-cyclopropyl ketone and unexpectedly to an α-ketol.

THE light-petroleum-soluble extractive of the trunk-wood of *E. monogynum* affords [1] a mixture of diols and triols that can be separated by gradient elution of the derived acetonides from silver nitrate-impregnated silica gel. The most polar fractions from this chromatogram contain the acetonides, triol P acetonide (PA) (1a), $C_{23}H_{40}O_3$, m. p. 142—143°, $[\alpha]_D$ +31°, and triol Q acetonide acetate (2c), $C_{23}H_{40}O_4$, m. p. 111—113°, $[\alpha]_D$ −17°. This Paper is concerned with the structure elucidation of these two compounds. Triol Q acetonide (QA) (2a), $C_{23}H_{38}O_3$, had m. p. 103—105°; 115—116°, $[\alpha]_D$ +5°, triol Q* (2b), $C_{20}H_{34}O_3$, had m. p. 181—183°, $[\alpha]_D$ −10° (EtOH).

In the n.m.r. spectrum of QA (2a), two regions are virtually identical with those attributable to the acetonide and cyclopropane functions in the n.m.r. spectrum of erythroxydiol X acetonide (3),[2] suggesting that these functions and their immediate environment are common to the two compounds.

Oxidation of QA (2a) with the Sarett reagent afforded the corresponding ketone (4), $C_{23}H_{36}O_3$, m. p. 92—93°, $[\alpha]_D$ +124°, $\nu_{max.}$ ($CCl_4$) 1704 cm.$^{-1}$, $\lambda_{max.}$ 296 mμ (ε 55), whose n.m.r. spectrum clearly indicated retention of the acetonide (3H multiplet τ 5·95—6·40) and cyclopropane ring (1H doublets at τ 9·43 and 9·92). The mass spectrum had a strong peak (50%) at *m/e* 101, corresponding to $C_5H_9O_2^+$, characteristic of the acetonide function,[4] and this was absent in the mass spectrum of the derived diol (5), m. p. 167—169°, $\nu_{max.}$ ($CCl_4$) 1704, 3580, and 3631 cm.$^{-1}$. Huang-Minlon reduction of the acetonide ketone (4) afforded diol X acetonide (3) as the sole product. Triol Q is therefore a monohydroxylated diol X in which the additional hydroxyl function is secondary.

The environment of the secondary hydroxyl group in (2a) can be deduced from the n.m.r. spectra of QA acetate (2c), the epimeric acetate (6), and the acetonide ketone (4), and from deuteriation experiments with the last compound.

Thus QA acetate (2c), exhibited in the n.m.r. spectrum a one-proton quartet centred at τ 5·07 (>C*H*–OAc) arising from an axial proton ($J$ = 10, 6 c./sec.) so that the acetate residue must be equatorial. Borohydride reduction of the ketone (4) afforded exclusively the epimeric alcohol (7), $C_{23}H_{38}O_3$, m. p. 113—115°, $[\alpha]_D$ +36°, $\nu_{max.}$ ($CCl_4$) 3632 cm.$^{-1}$. The derived acetate (6), $C_{25}H_{40}O_4$, m. p. 119—121°, $[\alpha]_D$ +34°, had in its n.m.r. spectrum a one-proton triplet, centred at τ 5·12 [$W_{\frac{1}{2}}$ 9 c./sec.[3]] arising from an equatorial proton, so that the acetate must here be axial. In accordance with these assignments the peak at *m/e* 344 ($P$ − 18) in the mass

* Hydroxydevadarool, m. p. 181·5—182°, $[\alpha]_D$ −3·75 (EtOH), also isolated from *E. monogynum*, is probably identical with erythroxytriol Q (ref. 3).

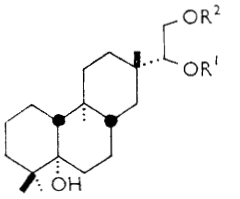
[1] Part II, J. D. Connolly, R. McCrindle, R. D. H. Murray, A. J. Renfrew, K. H. Overton, and A. Melera, *J. Chem. Soc.* (*C*), 1966, 268.

[2] Preliminary communications: (*a*) J. D. Connolly, R. McCrindle, R. D. H. Murray, and K. H. Overton, *Tetrahedron Letters*, 1964, 1859; (*b*) J. D. Connolly, D. M. Gunn, R. McCrindle, R. D. H. Murray, and K. H. Overton, *ibid.*, 1966, 2109.

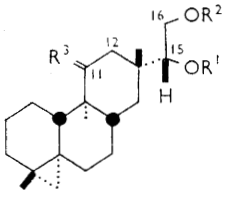
[3] A. H. Kapadi and Sukh Dev, *Tetrahedron Letters*, 1964, 1171, 1902.

[4] D. C. de Jongh and K. Biemann, *J. Amer. Chem. Soc.*, 1964, **86**, 67.

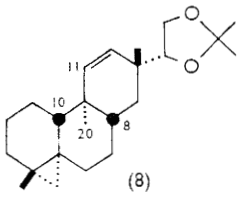
spectrum of the axial alcohol (7) was much more abundant (1800 × *P*) than in that of the equatorial alcohol (2a) (12 × *P*); further support comes from the respective dehydration products of the two alcohols discussed below. The n.m.r. spectra of both acetates strongly



(1a) $R^1 + R^2 = Me_2C=$
(1) $R^1 = R^2 = H$



(2) $R^1 = R^2 = H$; $R^3 = \alpha$-OAc, $\beta$-H
(2a) $R^1 + R^2 = Me_2C=$; $R^3 = \alpha$-OH, $\beta$-H
(2b) $R^1 = R^2 = H$; $R^3 = \alpha$-OH, $\beta$-H
(2c) $R^1 + R^2 = Me_2C=$; $R^3 = \alpha$-OAc, $\beta$-H
(3) $R^1 + R^2 = Me_2C=$; $R^3 = H_2$
(3a) $R^1 = R^2 = H$; $R^3 = H_2$
(4) $R^1 + R^2 = Me_2C=$; $R^3 = O$
(5) $R^1 = R^2 = H$; $R^3 = O$
(6) $R^1 + R^2 = Me_2C=$; $R^3 = \beta$-OAc, $\alpha$-H
(7) $R^1 + R^2 = Me_2C=$; $R^3 = \beta$-OH, $\alpha$-H



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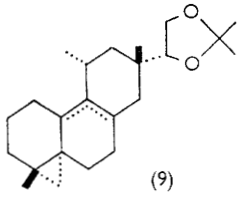
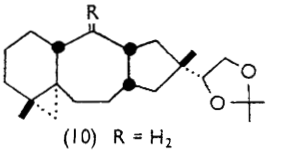


(9)

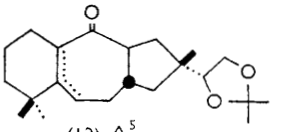
suggest that the nuclear hydroxyl of triol Q has only two hydrogens on adjacent carbon and this is supported by base-catalysed deuterium exchange of the ketone (4) [16% $d_0$, 61% $d_1$, 12% $d_2$, 0% $d_3$ after 96 hr. at 60° in NaOD/$D_2O$–dioxan]. Moreover the n.m.r. spectrum of this ketone shows that both hydrogens are attached to the *same* α-carbon atom, since two one-proton doublets at τ 7·08 and 8·23 (both disappear on deuterium exchange) are mutually coupled (n.m.d.r.) and must, from their coupling constant ($J$ = 13 c./sec.) and the fact that they show virtually no other coupling, be geminal and isolated. Monitoring of the exchange reaction by n.m.r. shows that the hydrogen resonating at τ 7·08 is exchanged first. This could mean, in agreement with previous observations,[5] that the axial hydrogen is exchanged first, although it cannot safely be assumed that of two protons situated on the same carbon atom adjacent to carbonyl the one resonating at lower field is necessarily axial.[6]

These observations lead to the functional sequence ·C·CHOH·$CH_2$·C· and this can be fitted into the structure of diol X acetonide (3) only if the secondary hydroxyl is placed at either position 11 or 12. A number of observations would support such a hindered location. Thus reduction of the ketone (4) exclusively to the axial alcohol is reminiscent of the classical precedent of 11-oxo-steroids.[7] Lack of reactivity both at the carbonyl carbon and the adjacent methylene carbon in ketone (4) is apparent in its inertness when subjected to conditions that could lead to ketal formation, diosphenolation, α-bromination, or α-acetoxylation and condensation with benzaldehyde (see Experimental section).

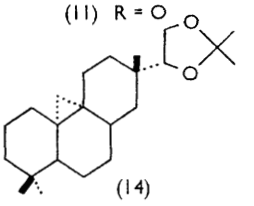
Of the two available positions, the secondary hydroxyl must be attached to C-11 rather than C-12 for the following reasons. Dehydration of the epimeric alcohols (2a) and (7) with thionyl chloride in cold pyridine led in each case to one major product. Thus the axial alcohol (7) afforded the olefin (8) $C_{23}H_{36}O_2$ (in 75% yield by g.l.c.) which was separated from the two minor dehydration products by preparative t.l.c. on silver nitrate–silica gel. As expected, this showed in its n.m.r. spectrum, in addition to multiplets characteristic of the acetonide and cyclopropane functions, an AB quartet arising from the vinyl protons at τ 4·03 and 4·69 ($J$ = 9·6 c./sec.) with subsidiary coupling (1 c./sec.) of the proton at τ 4·69 (homoallylic coupling of H-11 with H-8, H-10, or H-20). One of the two minor dehydration products [obtained about 90% pure (g.l.c.) from the preparative chromatoplate] showed in its n.m.r. spectrum two tertiary and one secondary methyl groups and no vinyl protons, and might therefore be formulated as (9). Hydrogenation of the olefin (8) with palladised carbon (10%) in ethanol led to diol X acetonide (3).



(10) R = $H_2$
(11) R = O



(12) $\Delta^5$
(13) $\Delta^{5(10)}$



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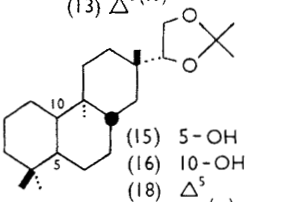
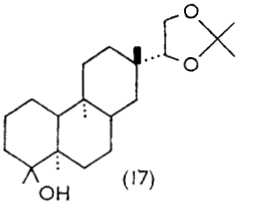


(15) 5-OH
(16) 10-OH
(18) $\Delta^5$
(19) $\Delta^{5(10)}$
(19a) $\Delta^{1(10)}$



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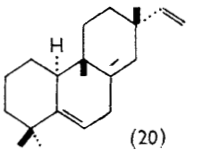


(20)

Dehydration of the equatorial alcohol (2a) under the same conditions gave as major product (90% by g.l.c.) the olefin (10), $C_{23}H_{36}O_2$. Its structure is assigned on the

[5] (*a*) D. H. Williams, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, 1963, **85**, 2091. (*b*) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, 1962, p. 241.

[6] N. S. Bhacca, J. E. Gurst, and D. H. Williams, *J. Amer. Chem. Soc.*, 1965, **87**, 302.

[7] L. H. Sarett, M. Feuer, and K. Folkers, *J. Amer. Chem. Soc.*, 1951, **73**, 1777; S. Bernstein, R. H. Lenhard, and J. W. Williams, *J. Org. Chem.*, 1953, **18**, 1168.

basis of its n.m.r. spectrum (only two tertiary methyl groups but in addition a two-proton doublet at $\tau$ 5·16 and 5·20, characteristic of a vinylidene group), the geometry of its precursor (2a) which would be expected to lead to such a structure, and the formation and nature of the derived nor-ketone (11). Thus osmylation of olefin (10) and cleavage with periodate of the resulting mixture of diols, afforded the nor-ketone (11), $C_{22}H_{34}O_3$, m. p. 142—143°, $[\alpha]_D$ +67°, $\nu_{max.}$ ($CCl_4$) 1696 (cycloheptanone) cm.$^{-1}$. In the n.m.r. spectrum the low-field doublet present in its precursor (10) was replaced by a diffuse two-proton multiplet ($\tau$ 6·8—7·4; 2 >C*H*·CO·). Under basic catalysis the nor-ketone (11) smoothly exchanged two protons for deuterium (11% $d_0$, 18% $d_1$, 71% $d_2$, 0% $d_3$ after 72 hr. at 70° in NaOD/$D_2O$–dioxan). Exposure of the nor-ketone to a solution of hydrogen chloride in chloroform at 20° and replacement of the acetonide function, led to a mixture of two unsaturated ketones (9 : 1 by g.l.c.), $\nu_{max.}$ 1700 and 1670 cm.$^{-1}$, presumably to be formulated as (12) and (13), with the unconjugated ketone preponderating ($\lambda_{max.}$ 254 m$\mu$, $\varepsilon \sim 1000$), as previously noted [8] in a cycloheptenone.

The highly stereoselective dehydration paths followed by the two alcohols which substantiate the configurations assigned to them, entirely accord with established precedent [9] and do not require further comment.

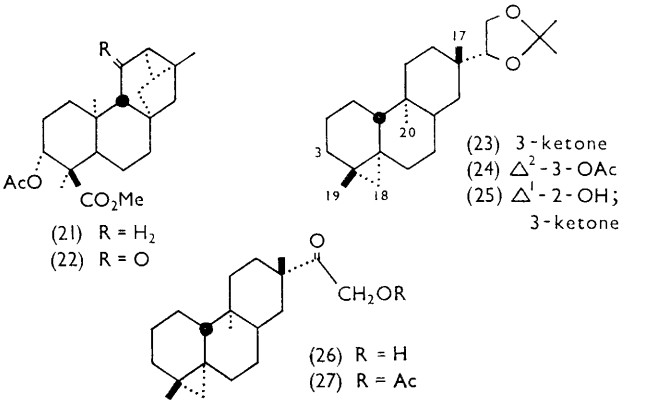
We have—on the basis of our previous work—favoured [2] the 4,5- (3) over the alternative 9,10-cyclopropane structure (14) for erythroxydiol X. The definitive distinction between these alternatives, which was previously lacking is now supplied by the reactions of erythroxytriol Q, when taken in conjunction with its conversion by two routes into erythroxydiol-X.

A recent *X*-ray structure determination [10] confirms in every detail formulation of the triol as in (2a) and hence of diol X [2] as (3a). It also provides definitive support for the configuration at C-10, formerly inferred on biogenetic grounds, and at C-15, previously undefined.

Triol P acetonide (PA) (1a), has in its n.m.r. spectrum signals typical of the acetonide function present in triol Q acetonide (2a). It lacks cyclopropyl proton signals but instead has a fourth tertiary methyl group. In place of an olefinic double-bond (absence of signals in the n.m.r. below $\tau$ 6; transparent in the u.v. above 200 m$\mu$; tetranitromethane negative), it contains a tertiary hydroxyl group [$\nu_{max.}$ ($CCl_4$) 3625 cm.$^{-1}$; no C*H*·OH signal in the n.m.r.; appreciable peak in the mass spectrum at *m/e* 346 (*P* — 18)]. These properties suggest the alternative structures (15), (16), or (17). A low-field n.m.r. methyl signal to be expected if the structure were (17) is absent (3H singlets at $\tau$ 8·98, 9·06, 9·10, and 9·13).

Strong support for the suggested structure (15) comes from dehydration of PA (1a) with thionyl chloride in cold pyridine. The major product (18) (88% by g.l.c.), $C_{23}H_{38}O_2$, m. p. 85—86°, $[\alpha]_D$ —29°, is accompanied (12%) by the previously obtained [2] isomer (19). Isomerisation of the olefin (18) with a solution of hydrogen chloride in chloroform at 20° afforded a mixture of (18) (53%), (19) (34%), and two minor products that were not further investigated.

Of the two possible structures for the major olefin, (18) is preferred to (19a) because of two properties that resemble rimuene (20).[11] Thus in the n.m.r. spectrum there is a signal from a tertiary methyl group at high-field ($\tau$ 9·35) ascribed here, as in rimuene ($\tau$ 9·38) to the shielding effect of the $\Delta^5$-olefinic bond on the C-9 methyl group. Furthermore two major fragments in the mass spectrum of (18) at *m/e* 136 and 121 arise, as in rimuene, from retro-Diels–Alder fission of ring-B.




We comment in conclusion on the results obtained when diol X acetonide (3) was ozonised in methylene chloride–pyridine (2 : 1) at —70°. This reaction was undertaken during the early stages of this work in the hope of obtaining the two α-cyclopropyl ketones at positions 3 and 6 for comparison with QA-ketone (4). Moreover the novel conversion of the ester (21) into the corresponding α-cyclopropyl ketone (22), reported by Ourisson [12] and apparently relatively specific to the trachylobane system, appeared to us of sufficient intrinsic interest to merit further investigation with the readily accessible diol X acetonide (3). When this was ozonised under the conditions of Ourisson, and the product separated by preparative thin-layer chromatography, the cyclopropyl ketone (23), $C_{23}H_{36}O_3$, m. p. 125—126°, was obtained in 33% yield, allowing for recovered starting material. There was no evidence that the 6-ketone had been formed.

The new ketone has $\nu_{max.}$ ($CCl_4$) 1683 cm.$^{-1}$ (α-cyclopropyl ketone). The n.m.r. solvent shifts [13] ($CDCl_3$ to benzene) were particularly informative in distinguishing

[8] W. S. Johnson, M. Neeman, S. P. Birkeland, and N. A. Fedoruk, *J. Amer. Chem. Soc.*, 1962, **84**, 989; G. Snatzke, B. Zech, and E. Muller, *Tetrahedron Letters*, 1963, 1425.

[9] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, 1966, p. 291.

[10] G. Ferguson, J. W. B. Fulke, and R. McCrindle, *Chem. Comm.*, 1966, 691.

[11] J. D. Connolly, R. McCrindle, R. D. H. Murray, and K. H. Overton, *J. Chem. Soc.* (*C*), 1966, 273.

[12] G. Hugel, L. Lods, J. M. Mellor, and G. Ourisson, *Bull. Soc. chim. France*, 1965, 2894.

[13] J. D. Connolly and R. McCrindle, *Chem. and Ind.*, 1965, 379.

between the 3- and 6-positions for the carbonyl groups. Thus the cyclopropyl proton at $\tau$ 9·25 experienced a large positive shift (+0·50 $\tau$) and the shifts of the methyl groups, C-20 (+0·20 $\tau$), C-19 (−0·24 $\tau$), and C-17 +0·05 $\tau$) were all in accordance with prediction [13] for a C-3 but not for a C-6 ketone.

The following further properties of ketone (23) accorded with the assigned structure. Huang-Minlon reduction smoothly afforded diol X acetonide (3). Two hydrogens were exchanged for deuterium under basic catalysis (2% $d_0$, 6% $d_1$, 91% $d_2$, 1% $d_3$ after 72 hr. with NaOD in $D_2O$–dioxan at 60°). With isopropenyl acetate and toluene-*p*-sulphonic acid, the ketone (23) formed an enol acetate (24), $C_{25}H_{38}O_4$, m. p. 110—111°, $\nu_{max.}$ ($CCl_4$) 1759 and 1215 cm.$^{-1}$ (enol acetate), one proton quartet in the n.m.r. at $\tau$ 5·12 ($J = 7$ c./sec. with proton at $\tau$ 8·13, 2 c./sec. with proton at $\tau$ 8·30) (vinyl proton coupling with two neighbouring allylic protons). Reaction of ketone (23) with oxygen and potassium t-butoxide in t-butyl alcohol, afforded the diosphenol (25), $C_{23}H_{34}O_4$, m. p. 168—170°, $\lambda_{max.}$ 268 (ε 3500), 240 (ε 3650) (EtOH), and 314 mμ (ε 3130) (0·1N-NaOH/EtOH), $\nu_{max.}$ ($CCl_4$) 1653 (C=C), 1673 (CO), and 3448 (bonded OH) cm.$^{-1}$; one proton in the n.m.r. at $\tau$ 4·36 (doublet $J = 3·2$ c./sec.; H-1) coupling with one proton at $\tau$ 7·55 (H-10). The solvent shifts [13] ($CDCl_3 \longrightarrow$ benzene; see Experimental section) are in accord with the suggested structure.

A second major product (25%) from the ozonolysis of diol X acetonide (3) is formulated as the α-ketol (26), $C_{20}H_{32}O_2$, m. p. 82—84°, $\nu_{max.}$ ($CCl_4$) 1705 (CO) and 3484 (bonded OH) cm.$^{-1}$; n.m.r. signals at $\tau$ 8·78 (3H, $CH_3$C·CO) and 5·57 (2H, singlet HOC$H_2$·CO), since on acetylation it afforded the known [2] acetate (27), m. p. 93—95°; 103—104°. The rather unexpected formation of an α-ketol CO·$CH_2$OH from the acetonide of the related α-glycol CHOH·$CH_2$OH under conditions of ozonolysis is of mechanistic interest and may have practical utility in the steroid field.

## EXPERIMENTAL

For general experimental see Part II.[1]

*Isolation of Triol P Acetonide and Triol Q Acetonide Acetate.*—Triol P and triol Q acetate were isolated as the acetonides as previously described.[1] Chromatography of the mixture (10 g.) on alumina (500 g., Grade H) afforded on elution with ether–light petroleum (1 : 24) *triol Q acetate acetonide* (2c) (6·21 g.), prisms from methanol, m. p. 111—113°, $[\alpha]_D$ −17° (*c* 1·32); $\nu_{max.}$ ($CCl_4$) 1740 and 1246 (acetate), 860 (acetonide) cm.$^{-1}$; mass-spectral peaks at *m/e* 404 (*P*), 389 (*P* − 15), 344 (*P* − 60, 35%), 101 ($C_5H_9O_2$, 70%), and 60 ($CH_3$·$CO_2$H, 100%); n.m.r. signals at $\tau$ 9·84, 9·48 (1H doublets; $J = 4·8$ c./sec., cyclopropyl H's), 9·09, 9·02, 9·00 (3H singlets; tertiary methyls), 8·68, 8·62 (3H singlets; acetonide methyls), 8·08 (3H singlet, O·CO·C$H_3$), and 5·07 (1H quartet; $J = 10$, 6 c./sec.; >C*H*–OAc) (Found: C, 74·0; H, 9·8. $C_{25}H_{40}O_4$ requires C, 74·2; H, 9·95%).

Elution with ether–light petroleum (1 : 9) eluted *triol P acetonide* (1a) (275 mg.), prisms from light petroleum, m. p. 142—143°, $[\alpha]_D$ +31° (*c* 0·91), $\nu_{max.}$ ($CCl_4$) 3625 (hydroxyl) and 860 (acetonide) cm.$^{-1}$; mass-spectral peaks at *m/e* 364 (*P*), 349 (*P* − 15), 346 (*P* − 18), and 101 ($C_5H_9O_2$); n.m.r. signals at $\tau$ 9·14, 9·10, 9·06, 8·98 (3H singlets; tertiary methyls), 8·64, 8·58 (3H singlets; acetonide methyls), and 6·18 (3H multiplet; acetonide H's) (Found: C, 75·6; H, 11·0. $C_{23}H_{40}O_3$ requires C, 75·75; H, 11·05%).

Elution with methanol–ether (1 : 1) afforded more polar materials (2·1 g.) that were not further investigated.

*Triol Q Acetonide* (2a).—A solution of triol Q acetonide acetate (2c) (380 mg.) and lithium aluminium hydride (200 mg.) in dry ether (15 ml.) was refluxed for 1 hr. Addition of saturated aqueous sodium sulphate and evaporation of solvent from the dried ethereal solution left triol Q acetonide (2a) (310 mg.), prisms from aqueous methanol, m. p. 115—116°, $[\alpha]_D$ +5° (*c* 0·86); $\nu_{max.}$ ($CCl_4$) 3617 (free hydroxyl), 3051 (cyclopropane), and 866 cm.$^{-1}$ (acetonide); mass-spectral peaks at *m/e* 362 (*P*; 95%), 347 (*P* − 15), 344 (*P* − 18; 12%), and 101 ($C_5H_9O_2$; 100%) (Found: C, 75·95; H, 10·8. $C_{23}H_{38}O_3$ requires C, 76·2; H, 10·6%).

*Triol Q Acetate* (2).—Triol Q acetate acetonide (2c) (50 mg.) was refluxed in aqueous dioxan (1 : 5; 10 ml.) with Amberlite 120 I.R. (150 mg.) for 2 hr. Filtration and evaporation of solvent yielded a residue (45 mg.) which after purification by preparative t.l.c. afforded *triol Q acetate* (2) (24 mg.) as a colourless oil, $[\alpha]_D$ −14° (*c* 1·49); $\nu_{max.}$ ($CCl_4$) 3640, 3610 (free OH), 3470 (bonded OH), 3048 (cyclopropane), 1730, and 1238 cm.$^{-1}$ (acetate); n.m.r. signals at $\tau$ 9·86, 9·46 (1H doublets; $J = 4·8$ c./sec.; cyclopropyl H's), 9·05 (3H), 8·98 (6H; tertiary methyls), 6·2—6·9 (5H multiplet; C$H_2$OH, C*H*OH, 2O*H*), and 5·17 (1H quartet; $J = 10·2$, 6·6 c./sec.; C*H*·OAc) (Found: C, 72·3; H, 9·85. $C_{22}H_{36}O_4$ requres C, 72·5; H, 9·95%).

*Triol Q* (2b).—Triol Q (2b) was regenerated from triol Q acetonide acetate (2c) (100 mg.) by refluxing it with aqueous acetic acid (1 : 19) for 4 hr., removal of acetic acid *in vacuo*, and reaction of the product dissolved in tetrahydrofuran with an excess of lithium aluminium hydride to destroy any acetates initially formed. *Triol Q* (2b) (65 mg.) thus obtained crystallised in needles from ethyl acetate, m. p. 181—183°, $[\alpha]_D$ −10° (*c* 0·81, EtOH); n.m.r. signals at $\tau$ 9·87, 9·43 (1H doublets; $J = 4·8$ c./sec; cyclopropyl H's), 9·17, 9·02, 8·96 (3H singlets; tertiary methyls), 6·35 (4H multiplet; >C*H*·OH) (Found: C, 74·15; H, 10·5. $C_{20}H_{34}O_3$ requires C, 74·5; H, 10·65%).

*Attempted regeneration of Triol P* (1) *from its Acetonide.*—Reaction of triol P acetonide (1a) (30 mg.) with aqueous acetic acid (1 : 19) for 4 hr. at reflux, followed by removal of solvent *in vacuo* and reduction of the product in tetrahydrofuran with lithium aluminium hydride, afforded an oily product (21 mg.), n.m.r. signals at 9·36, 9·10, 9·00, 8·94 (3H singlets; tertiary methyls), 4·47 (1H multiplet; vinylic proton). This was acetonised in the usual way, and the product analysed by g.l.c. (1% SE 30 at 175° with C-20 and C-24 n-hydrocarbons as standards). It consisted of two components, the olefins (19) (17%) and (18) (83%). Olefin (18) crystallised on standing, m. p. and mixed m. p. 84—86° with olefin (18) obtained from dehydration of triol P acetonide (see p. 673).

*The Ketone* (4).—Triol Q acetonide (2a) (200 mg.) and AnalaR chromium trioxide (350 mg.) in AnalaR pyridine (10 ml.) were kept at 20° for 48 hr. The single product, (t.l.c.) obtained in the usual way, afforded from aqueous methanol the *ketone* (4) (160 mg.), m. p. 92—93°, $[\alpha]_D$ +124° (*c* 1·10); $\nu_{max.}$ ($CCl_4$) 1704 (cyclohexanone) cm.$^{-1}$; $\lambda_{max.}$

(EtOH) 296 mμ (ε 55); mass-spectral peaks at *m/e* 360 (*P*), 345 (*P* − 15), 101 ($C_5H_9O_2$, acetonide residue); n.m.r. resonances in $CDCl_3$ at τ 9·92, 9·42 (1H doublets; $J = 5$ c./sec.; cyclopropyl H's), 9·12, 8·97, 8·82 (3H singlets; tertiary methyls), 8·62, 8·58 (3H singlets; acetonide methyls), 7·08, 8·23 (1H doublets, $J = 13$ c./sec.; C-12 hydrogens) and in benzene at τ 10·0, 9·48, 9·26, 8·98, 8·93, 8·70, 8·63, 7·10, 8·10 with the same assignments; rotatory dispersion (MeOH); $[\Phi]_{400}$ +950°, $[\Phi]_{312}$ +2800°, $[\Phi]_{276}$ +1560°, $[\Phi]_{217}$ +6350° (Found: C, 76·9; H, 9·8. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·05%).

The dihydroxy-ketone (5), obtained from the above acetonide by aqueous acetic acid (1 : 19) treatment, and reduction of the product with lithium aluminium hydride in tetrahydrofuran had (from light petroleum) m. p. 167—169°, mass spectrometric *M* 320 ($C_{20}H_{32}O_3$ requires 320); $\nu_{max.}$ ($CCl_4$) 1704 (cyclohexanone), 3041 (cyclopropane), 3631 (free OH), and 3580 (bonded OH) cm.$^{-1}$.

*Deuterium Exchange of Ketone* (4).—The ketone (4) (60 mg.) was dissolved in dry dioxan (10 ml.) and deuterium oxide (3 ml.). To this solution was added sodium (100 mg.) in small pieces under nitrogen, and the solution stirred for 96 hr. at 60° in a nitrogen atmosphere. The solvents were removed *in vacuo*, the residue extracted with dry ether (3 × 10 ml.), and the combined extracts washed with deuterium oxide (2 × 2 ml.), dried, and the ether removed. The crystalline residue (46 mg.) had by mass spectrometry, 16% $d_0$, 61% $d_1$, 13% $d_2$, and 0% $d_3$. In the n.m.r. spectrum the doublet centred at τ 7·08 (12α-H?) has virtually disappeared.

*Huang-Minlon Reduction of the Ketone* (4).—The ketone (4) (40 mg.) and sodium (100 mg.) in dry ethanol (2 ml.), with added hydrazine hydrate (0·3 ml.) and triethylene glycol (5 ml.) were kept at 200° for 1 hr. in a nitrogen atmosphere. The product (28 mg.), obtained in the usual way, purified by preparative t.l.c., crystallised from methanol–ether to afford diol X acetonide (3) (12 mg.), m. p. and mixed m. p. 87—89°. Mass, n.m.r., and i.r. spectra and t.l.c. behaviour on silver nitrate–silica gel were indistinguishable from those of authentic material.[1]

*Borohydride Reduction of the Ketone* (4).—The ketone (4) (210 mg.) and sodium borohydride (250 mg.) were kept in aqueous methanol (1 : 19; 20 ml.) at 20° for 3½ hr. Dilution with water and ether extraction afforded an oil (140 mg.). Adsorption from benzene on to activated alumina (neutral, III) and elution with benzene–chloroform (1 : 1) afforded the *alcohol* (7) (105 mg.), m. p. (from methanol) 113—115°, $[\alpha]_D$ +36° (*c* 0·86); $\nu_{max.}$ ($CCl_4$) 3632 (free OH), 3050 (cyclopropane), and 864 (acetonide) cm.$^{-1}$; mass-spectral peaks at *m/e* 362 (*P*), 347 (*P* − 15), 344 (*P* − 18), 101 (acetonide residue) (Found: C, 76·35; H, 10·7. $C_{23}H_{38}O_3$ requires C, 76·2; H, 10·6%).

Oxidation of alcohol (7) with the Sarett reagent under the usual conditions afforded the ketone (4) as the sole product.

*The Acetate* (6).—The alcohol (7) obtained in the previous experiment (30 mg.) was kept in AnalaR pyridine (2 ml.) and AnalaR acetic anhydride (3 ml.) at 20° for 16 hr. Removal of solvents *in vacuo* and isolation of the product by preparative t.l.c. afforded the *acetate* (6) (26 mg.), m. p. (from methanol) 119—121°, $[\alpha]_D$ +34° (*c* 0·83); $\nu_{max.}$ ($CCl_4$) 1743 and 1243 (acetate) cm.$^{-1}$; n.m.r. peaks at τ 9·84, 9·47 (two 1H doublets; $J = 4·7$ c./sec.; cyclopropyl protons), 9·16, 9·02, 8·97 (three 3H singlets; tertiary methyls), 8·67, 8·62 (two 3H singlets; acetonide methyls), 7·94 (3H singlet; OCO·C*H*$_3$), 5·12 (1H triplet, $J = 3$ c./sec.; C*H*·OAc) (Found: C, 74·2; H, 10·0. $C_{25}H_{40}O_4$ requires C, 73·9; H, 9·9%).

*Unsuccessful Attempts to React the Ketone* (4).—The ketone (4) was recovered substantially unchanged from the following experiments:

(*a*) Ketalisation. Excess of ethylene glycol and benzene in the presence of β-naphthalenesulphonic acid under reflux.

(*b*) Diosphenolation. Under conditions [14] which converted the ketone (23) and α-onocerindione [15] into the corresponding diosphenols.

(*c*) Reaction with benzaldehyde. Under conditions [16] that were effective with α-onocerindione.

(*d*) Enol acetylation. With acetic anhydride–pyridine, unchanged ketone was the sole product. Acetic anhydride–toluene-*p*-sulphuric acid afforded the 16,17-diacetate and isopropenyl acetate–toluene-*p*-sulphonic acid a mixture of ketone acetonide and ketone diacetate.

(*e*) α-Acetoxylation.[17] The only identifiable product was the 17-nor-16-aldehyde formed by removal of the acetonide with $BF_3$ and cleavage by lead tetra-acetate of the glycol formed.

*Dehydration of Alcohol* (7).—The alcohol (7) (70 mg.) was kept in AnalaR pyridine (10 ml.) and redistilled thionyl chloride (1 ml.) at 20° for 20 min. Working up in the usual way afforded a residue (55 mg.) consisting of one major product (70% by g.l.c. on 2% 20M PEG at 200°) and two minor products. Isolation of the major product by extraction with cold chloroform saturated with nitrogen from silver nitrate–silica gel chromatophate, afforded the *olefin* (8) (20 mg.) as a colourless oil; n.m.r. signals at τ 9·90, 9·42 (1H doublets; $J = 4·2$ c./sec.; cyclopropyl H's), 9·15 (3H), 8·96 (6H) (tertiary methyls), 8·68, 8·60 (3H singlets; acetonide methyls), 6·15 (3H multiplet; acetonide H's), 4·69 (1H quartet, $J = 9·6$; <1 c./sec), 4·03 (1H doublet; $J = 9·6$ c./sec.) (olefinic protons) (Found: C, 80·1; H, 10·75. $C_{23}H_{36}O_2$ requires C, 80·2; H, 10·55%).

One of the two minor dehydration products (9?), separated by preparative t.l.c. on silver nitrate–silica gel, had n.m.r. peaks at τ 9·15, 8·92 (3H singlets; tertiary methyls), 8·98 (3H doublet; $J = 6$ c./sec.; secondary methyl), 8·66, 8·58 (3H singlets; acetonide methyls), and 6·12 (3H multiplet; acetonide H's).

*Hydrogenation of the Olefin* (8).—The olefin (8) (5 mg.) in ethanol (15 ml.) was hydrogenated over 10% palladium–charcoal (25 mg.) in a microhydrogenator for 2 hr. The mixture obtained after removal of catalyst and solvent was compared on g.l.c. (2% 20M PEG at 200° with $C_{24}$ and $C_{30}$ n-hydrocarbons as standards) with olefin (8) and diol X acetonide (3) with the following results: Olefin (8); Rt 12·15 min. [Rt/Rt($C_{30}$) 0·476]; Diol X acetonide; Rt 9·65 min. [Rt/Rt($C_{30}$) 0·512]; Hydrogenation Product; Rt 9·45 min. [Rt/Rt($C_{30}$) 0·511].

*Dehydration of Alcohol* (2a).—Alcohol (2a) (200 mg.), was dehydrated as for alcohol (7) above and the product recovered as before. This (165 mg.) consisted of one

[14] D. H. R. Barton, S. K. Pradhan, S. Sternhell, and J. F. Templeton, *J. Chem. Soc.*, 1961, 255.
[15] D. H. R. Barton and K. H. Overton, *J. Chem. Soc.*, 1955, 2639.
[16] D. H. R. Barton, A. J. Head, and P. J. May, *J. Chem. Soc.*, 1957, 935.
[17] H. B. Henbest, D. N. Jones, and G. P. Slater, *J. Chem. Soc.*, 1961, 4472.

major (90% by g.l.c. on 2% 20M PEG at 200°) and two minor components. The major product was again unstable in solutions containing oxygen and was therefore recovered from a silver nitrate–silica gel chromatoplate with cold oxygen-free chloroform, affording the *olefin* (10) (115 mg.), as a colourless oil; n.m.r. signals at τ 10·04, 9·56 (1H doublets; $J = 4{\cdot}8$ c./sec.; cyclopropyl H's), 9·02, 8·91 (3H singlets; tertiary methyls), 8·64, 8·58 (3H singlets; acetonide methyls), 6·17 (3H multiplet; acetonide H's), 4·17 (2H doublet; $J = 2{\cdot}4$ c./sec.; $=CH_2$) (Found: C, 79·8; H, 10·4. $C_{23}H_{36}O_2$ requires C, 80·2; H, 10·55%).

*The Ketone* (11).—The olefin (10) (55 mg.) and osmium tetroxide (70 mg.) in dry ether (3 ml.) and pyridine (1·5 ml.) were kept at 0° for 18 hr. in the dark. The solution was saturated with hydrogen sulphide, the osmium sulphide removed by filtration, and the residue (45 mg.) obtained after solvent removal, purified by t.l.c. The mixed diols (32 mg.) so obtained were kept with sodium metaperiodate (100 mg.) in methanol (3 ml.) and water (1 ml.) at 20° for 36 hr. The product, obtained as usual, was separated by preparative t.l.c. into unreacted diols (14 mg.) and the *ketone* (11) (13 mg.), colourless plates, from methanol–chloroform, m. p. 142—143°, $[\alpha]_D$ +67° (*c* 1·05); $\nu_{max.}$ ($CCl_4$) 1696 cm.$^{-1}$; n.m.r. signals at τ 10·04, 9·34 (1H doublets; $J = 4{\cdot}2$ c./sec.; cyclopropyl H's), 9·05, 8·90 (3H singlets; tertiary methyls), 8·66, 8·60 (3H singlets; acetonide methyls), 6·08 (3H multiplet; acetonide H's); mass-spectral peaks at 346 (*P*), 331 (*P* − 15), 288 (100%; *P* − $C_3H_6O$) (Found: C, 76·2; H, 10·0. $C_{22}H_{34}O_3$ requires C, 76·25; H, 9·9%).

*Deuterium Exchange of Ketone* (11).—The ketone (11) (5 mg.) was treated with sodium in deuterium oxide–dioxan and the product recovered as described for the ketone (4) above, after 48 hr. The process was repeated on the same sample for a further 24 hr. Mass spectrometry of the crystalline product showed the following incorporations:— after 48 hr., 20% $d_0$; 30% $d_1$; 50% $d_2$; 0% $d_3$: after 72 hr. 11% $d_0$; 18% $d_1$; 71% $d_2$; 0% $d_3$.

*Isomerisation of Ketone* (11) *with a Solution of Hydrogen Chloride in Chloroform.*—Dry hydrogen chloride was passed into the ketone (11) (6 mg.), in AnalaR chloroform (5 ml.) for 10 min. and the solution kept at 20° for 1 hr. Solvent and hydrogen chloride were removed *in vacuo* and the residue was stirred with anhydrous copper sulphate in AnalaR acetone for 2 hr. at 20°. Filtration and evaporation yielded an oil (4·5 mg.), homogeneous by t.l.c., but g.l.c. (2% 20M PEG at 200°) revealed the presence of two compounds (12) and (13) (9 : 1), differing from starting material. The i.r. spectrum of the mixture had bands at 1700 (ketone), 1670 (unsaturated ketone), and 870 (acetonide) cm.$^{-1}$; $\lambda_{max.}$ 254 mμ (ε ~1000) (4 mg. oil in 10 ml. EtOH).

*Dehydration of the Alcohol* (1a).—The alcohol (1a) (40 mg.) was dehydrated with thionyl chloride and pyridine and the product recovered as in the dehydration of alcohols (2a) and (7) above. G.l.c. analysis of the product (31 mg.) (1% SE 30 at 175°) showed it to consist of the olefin (18) (88%) and the isomeric olefin (19) (12%).

*The olefin* (18) (20 mg.) crystallised from the oil and had, recrystallised from methanol, m. p. 85—86°, $[\alpha]_D$ −29° (*c* 0·68); n.m.r. signals at τ 9·35, 9·10, 9·00, 8·94 (3H singlets; tertiary methyls), 8·65, 8·60 (3H singlets; acetonide methyls), 6·21 (3H multiplet; acetonide H's), 4·52 (1H multiplet; vinylic proton) (Found: C, 79·3; H, 11·35. $C_{23}H_{38}O_2$ requires C, 79·7; H, 11·05%).



The minor product had the same retention time as the known [1] olefin (19) on 1% SE 30 at 175°.

*Isomerisation of Olefin* (18).—Dry hydrogen chloride was passed through a solution of the olefin (18) (5 mg.) in dry chloroform at 20° for 5 min., and the solution kept for 20 hr. The solvent and hydrogen chloride were removed at 20°, and the residue dissolved in AnalaR acetone (10 ml.) and shaken with anhydrous copper sulphate (20 mg.) for 2 hr. at 20°. The oily product consisted (g.l.c. on 1% SE 30 at 175°) of olefin (18) (53%), olefin (19) (34%), and two unknown isomers.

*Ozonolysis of the Acetonide* (3).—The acetonide (3) (1·00 g.) in methylene chloride (50 ml.) and dry pyridine (25 ml.) was ozonised for 3 hr. at −70°. Water (25 ml.) was added and the mixture kept at 20° for 16 hr. Working up in the usual way furnished an oily residue (820 mg.) consisting (t.l.c.) of starting material and two more polar products. Preparative t.l.c. afforded, in order of increasing polarity, recovered starting material (400 mg.), the hydroxy-ketone (26) (145 mg.), and the ketone (23) (200 mg.).

The *hydroxy-ketone* (26), crystallised from petroleum, had m. p. 82—84°; $\nu_{max.}$ ($CCl_4$) 1705 (carbonyl), 3049 (cyclopropane), 3484 (bonded OH) cm.$^{-1}$; n.m.r. signals at τ 9·45 (1H doublet; one of the cyclopropyl H's), 9·22, 8·99, 8·78 (3H singlets; tertiary methyls), 5·57 (2H singlet; $CO{\cdot}CH_2{\cdot}OH$); mass-spectral bands at *m/e* 304 (*P*), 289 (*P* − 15), 245 (95%; *P* − 59; loss of side chain) (Found: C, 78·7; H, 10·6. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6%). Acetylation of the hydroxy-ketone (26) under the usual conditions afforded the known [1] acetate (27), m. p. and mixed m. p. 93—95°; 103—104°; i.r. (solution), mass, and n.m.r. spectra were indistinguishable from those of authentic material; $\nu_{max.}$ ($CCl_4$) 1728 (ketonic carbonyl), 1756 and 1236 (acetate), 3046 (cyclopropane) cm.$^{-1}$; mass-spectral peaks at *m/e* 346 (*P*), 331 (*P* − 15), 245 (*P* − 101; 70% loss of side chain); n.m.r. signals at τ 9·88, 9·47 (1H doublets; $J = 5$ c./sec.; cyclopropyl H's), 9·22, 8·98, 8·74 (3H singlets; tertiary methyls), 7·84 (3H singlet; acetate methyl), 5·10 (2H singlet; $CO{\cdot}CH_2OAc$) (Found: C, 76·05; H, 9·65. Calc. for $C_{22}H_{34}O_3O$: C, 76·25; H, 9·9%).

*The ketone* (23) had (from aqueous acetone) m. p. 125—126°, $\nu_{max.}$ ($CCl_4$) 1683 (α-cyclopropyl-cyclohexanone) cm.$^{-1}$; mass-spectral peaks at *m/e* 360 (*P*), 345 (*P* − 15), and 101 ($C_5H_9O_2$); n.m.r. signals in $CDCl_3$ at τ 9·25 (1 H doublet, $J = 5$ c./sec.; one of the cyclopropyl H's), 9·18, 9·07, 8·79 (3H singlets; tertiary methyls), 8·65, 8·60 (3H singlets; acetonide methyls) and in benzene at τ 9·75, 9·38, 9·12, 8·55, 8·72, 8·64; with the same assignments (Found: C, 76·8; H, 9·8. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·05%).

*Deuterium Exchange of Ketone* (23).—The conditions were those used for ketone (4). Mass-spectrometric analysis showed: after 48 hr.; 4% $d_0$, 16% $d_1$, 80% $d_2$, 0% $d_3$. After 72 hr.; 2% $d_0$, 6% $d_1$, 91% $d_2$, 1% $d_3$.

*Huang-Minlon Reduction of Ketone* (23).—Under the conditions used for ketone (4), ketone (23) afforded as the only major product, material identical (mixed t.l.c. on silver nitrate–silica gel and g.l.c. on 2% 20M PEG at 200°) with authentic diol X acetonide.

*Enol Acetate* (24) *of Ketone* (23).—The ketone (90 mg.) and a trace of toluene-*p*-sulphonic acid were refluxed in redistilled isopropenyl acetate (5 ml.) for 6 hr. Preparative t.l.c. afforded the *enol acetate* (24) (50 mg.), m. p. (from methanol) 110—111°; $\nu_{max.}$ ($CCl_4$) 1759, 1215 (acetate), 1680

(olefinic double bond) cm.$^{-1}$; n.m.r. signals at $\tau$ 9·46 (1H doublet; one of the cyclopropyl H's), 9·20, 9·08, 8·97 (3H singlets; tertiary methyls), 8·67, 8·61 (3H singlets; acetonide methyls), 7·89 (3H singlet; acetate methyl), 5·12 (1H quartet; vinyl H) (Found: C, 74·4; H, 9·8. $C_{25}H_{38}O_4$ requires C, 74·6; H, 9·5%).

*The Diosphenol* (25).—The ketone (23) (50 mg.) in 1N-potassium t-butoxide in t-butyl alcohol (10 ml.) was shaken in 1 atm. oxygen in a hydrogenation apparatus for 3 hr. Dilution, acidification, and extraction afforded the product (45 mg.), which on preparative t.l.c. afforded the *diosphenol* (25) (26 mg.), m. p. (from methanol) 168—170°, $\lambda_{max.}$ (EtOH) 268 mμ (ε 3500) 240 mμ (ε 3650); $\lambda_{max.}$ (0·1N-NaOH/EtOH) 314 mμ (ε 3130); $\nu_{max.}$ ($CCl_4$) 1653 (olefinic double bond), 1673 (enone carbonyl), 3448 (bonded OH) cm.$^{-1}$; n.m.r. signals in $CDCl_3$ at $\tau$ 9·20, 9·08, 8·70 (3H singlets; tertiary methyls), 8·69, 8·62 (3H singlets; acetonide methyls), 7·62 (1H doublet; $J$ = 3·2 c./sec; H-10), 4·35 (1H doublet; $J$ = 3·2 c./sec; H-1), and in benzene at $\tau$ 9·44, 9·19, 8·58, 8·74, 8·67, 8·17, 4·50, with the same assignments (Found: C, 73·45; H, 9·15. $C_{23}H_{34}O_4$ requires C, 73·75; H, 9·15%).

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