# *Sesquiterpenoids. Part V.* The Stereochemistry of the Tricyclic Derivatives of Caryophyllene.*

By A. Aebi, D. H. R. Barton, A. W. Burgstahler, and A. S. Lindsey.

[Reprint Order No. 5580.]

The degradation of 4 : 4 : 8-trimethyl*tricyclo*[6 : 3 : 1 : $0^{1:5}$]dodecane-2β : 9α-diol (clovane-2β : 9α-diol), the acid-catalysed hydration product of caryophyllene oxide, has been continued in a stepwise manner to afford *p*-cymene as final product. By oxidative fission of the five-membered ring of the glycol and removal of the 9α-hydroxyl group, clovenic acid has been obtained, thus providing final confirmation of the constitution already proposed for clovene.

The stereochemistry of the caryolane and of the clovane series of tricyclic caryophyllene derivatives has been rationalised in terms of a difference in stereochemistry of the bridging methylene group. Conformational arguments provide support for this hypothesis.

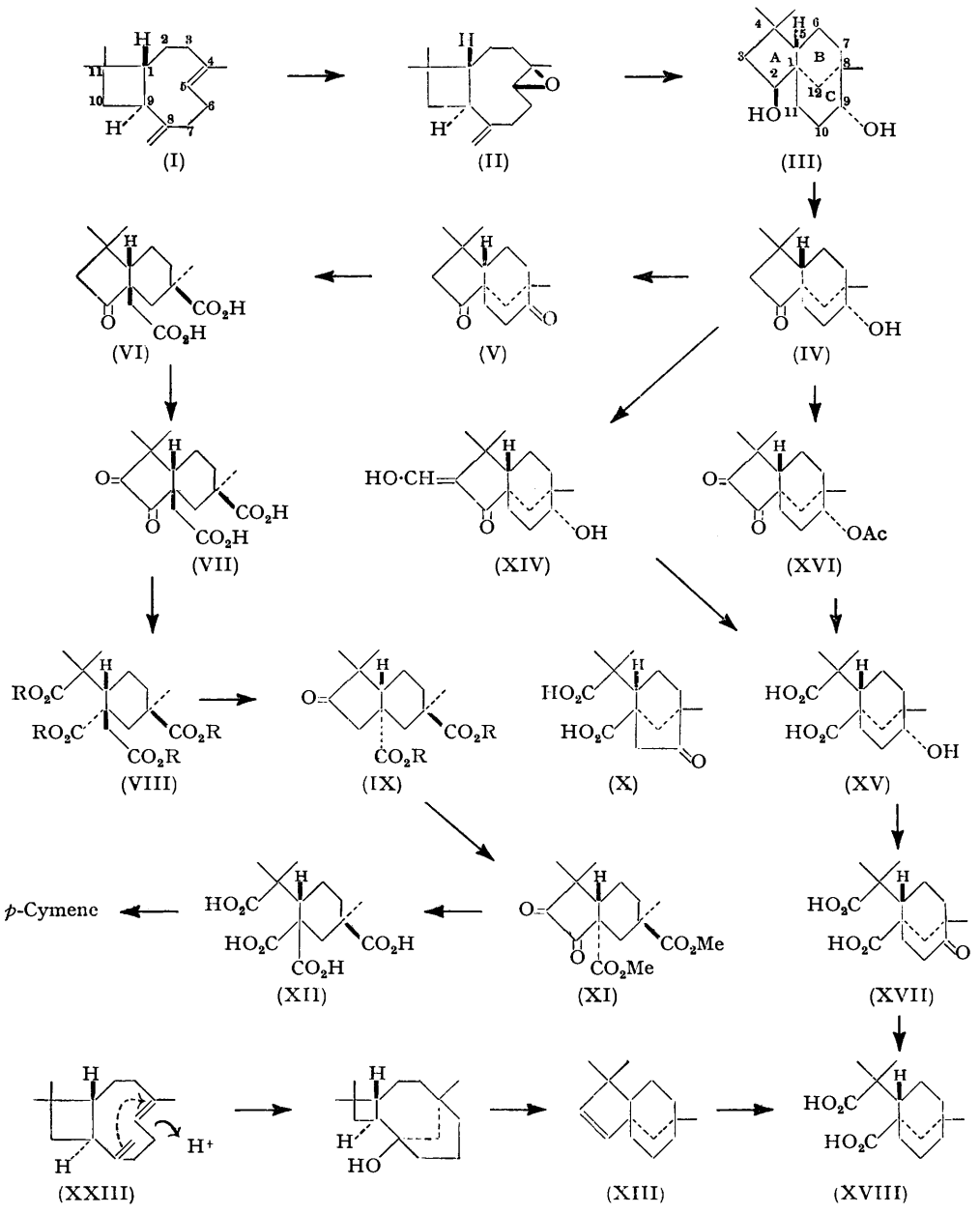
A preliminary communication summarising the more important of our conclusions has already appeared (Aebi, Barton, and Lindsey, *Chem. and Ind.*, 1953, 748).

In Part III of this series (Aebi, Barton, and Lindsey, *J.*, 1953, 3124) we described the conversion of caryophyllene (I), *via* caryophyllene oxide (II), into the tricyclic glycol (III). The systematic name for this glycol is cumbersome (see Summary); to effect a simplification we propose that it should be regarded as a dihydroxy-derivative of the saturated hydrocarbon clovane, a trivial name already in current use (see Lutz and Reid, *Chem. and*

* Part IV, *J.*, 1954, 3492.

*Ind.*, 1953, 749). We commence the present paper by the description of a stepwise degradation of this glycol.

As reported previously (Aebi, Barton, and Lindsey, *loc. cit.*), the glycol (III) is




oxidised by chromic acid in two stages : to the ketol (IV) and then to the dione (V). Further oxidation of the dione has now been demonstrated to afford the keto-dicarboxylic acid (VI). The latter showed (in Nujol) bands at 1688 (carboxyl) and at 1728 cm.$^{-1}$ (five-ring ketone) in agreement with the assigned structure. It was oxidised by selenium dioxide to the diketo-dicarboxylic acid (VII), which on fission with alkaline hydrogen

peroxide furnished the tetracarboxylic acid (VIII; R = H). Although the latter was amorphous, it could be characterised as the crystalline tetramethyl ester (VIII; R = Me). On pyrolysis at 260—270° the tetracarboxylic acid (VIII; R = H) was smoothly converted into a keto-dicarboxylic acid (IX; R = H), characterised as the dimethyl ester (IX; R = Me) and as the dimethyl ester 2 : 4-dinitrophenylhydrazone. The infra-red spectrum of (IX; R = H) (in Nujol) disclosed bands at 1730 (five-ring ketone) and at 1702 $cm.^{-1}$ (carboxyl). The constitution (IX; R = H) is assigned, rather than the alternative (X), on the following basis. All compounds with two carboxyl groups derived from the original five-membered ring of (III) decompose on melting to afford the corresponding anhydrides. A careful comparison of the melting of (IX; R = H) relative to that of clovenic acid (see below) showed that there was no decomposition or anhydride formation at the m. p. This is nicely explained by the structure (IX; R = H) where the two carboxyls are necessarily *trans* in a *six*-membered ring and thus could not afford a monomeric anhydride. It would not be explained by the alternative formula (X). Oxidation of (IX; R = Me) with selenium dioxide afforded a non-crystalline diketo-ester (XI). On fission with alkaline hydrogen peroxide and hydrolysis this gave a crude product (XII; or equivalent structure). Dehydrogenation of this with palladised charcoal furnished *p*-cymene, identified by its ultra-violet and infra-red spectra and by oxidation to terephthalic acid. This degradational sequence provides an independent confirmation of the correctness of structure (III).

The glycol (III) is closely related in constitution to the structure (XIII) proposed (Barton, Bruun, and Lindsey, *Chem. and Ind.*, 1951, 901; *J.*, 1952, 2210; Eschenmoser and Günthard, *Helv. Chim. Acta*, 1951, **34**, 2338) for clovene. A confirmation of this relationship has now been secured.* The ketol (IV) was smoothly converted into the the hydroxymethylene derivative (XIV) which on fission with alkaline hydrogen peroxide afforded the hydroxy-acid (XV). The latter was also available from the oxidation of the acetate of (IV) with selenium dioxide to give (XVI), which was split by alkaline hydrogen peroxide with concomitant hydrolysis. Chromic acid oxidation of (XV) gave the keto-acid (XVII) which afforded clovenic acid (XVIII) on Wolff–Kishner reduction.

A discussion of the stereochemistry of the tricyclic derivatives of caryophyllene commences logically with the stereochemistry (XIX; R = H) of caryolan-1-ol ("β-caryophyllene alcohol"†) elucidated by Robertson and Todd (*Chem. and Ind.*, 1953, 437). In all discussions of stereochemistry we may take the hydrogen atom at position 1 of caryophyllene [see (I)] as reference centre, since this is unchanged in all transformations. Substituents or bonds on the same side of the plane of the main ring as this hydrogen may be called β- (thickened bonds), those on the opposite side α- (broken bonds). It is now recognised that acid-catalysed dehydration of caryolan-1-ol does not afford clovene (Lutz and Reid, *Chem. and Ind.*, 1953, 437; *J.*, 1954, 2265) as would be expected if the methylene bridge had the same configuration in both compounds. Similarly we have shown that the glycol (XIX; R = OH) (Barton, Bruun, and Lindsey, *loc. cit.*) cannot be an intermediate in the formation of (III). The obvious rationalisation of these facts is that caryolan-1-ol and clovane belong to different stereochemical families as already indicated in formulae (XIX; R = H) and (XIII). Supporting evidence is available in terms of conformational analysis.

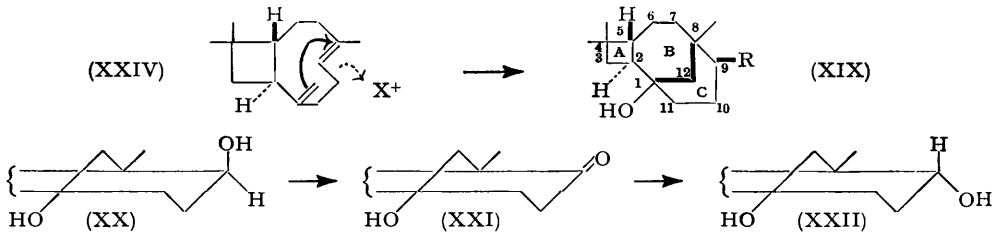
If the methylene bridge in the glycol (III) is α, it must have been derived by the opening (with inversion) of a β-oxide (II). The stereochemistry of the 9-hydroxyl group is thus defined (note apparent inversion due to the *trans*-endocyclic double bond in caryophyllene) as α. Whilst ring B in (III) is possibly a boat form, ring C is free to take up the preferred chair conformation. The 9α-hydroxyl group must therefore be axial and the epimeric β-hydroxyl group, derived from *iso*caryophyllene oxide (see Aebi, Barton,

* Lutz and Reid (*Chem. and Ind.*, 1953, 749; *J.*, 1954, 2265) have also provided a link between clovene and the glycol (III). We thank Dr. Evans B. Reid cordially for his kindness in sending us a copy of his paper before its publication.

† We propose that the saturated tricyclic hydrocarbon on which "β-caryophyllene alcohol" is based should be called caryolane, a name kindly suggested to us by Dr. Alex Nickon of these laboratories. This avoids the confusion of α, β stereochemical nomenclature (see below) with trivial naming and circumvents cumbersome systematic nomenclature.

and Lindsey, *loc. cit.*) must be equatorial. In agreement (see Barton, *Experientia*, 1950, **6**, 316) 9α-hydroxy-compounds are oxidised more rapidly by chromic acid than are the 9β-analogues (see Experimental section). Furthermore, the alcohol (IV) shows a C–OH stretching frequency at 1031 cm.$^{-1}$, whilst the 9-epimer of (IV) has the corresponding band at 1053 cm.$^{-1}$. The difference is indicative that (IV) has an axial, and its epimer an equatorial hydroxyl group (see, for summary, Barton, *J.*, 1953, 1027).

The glycol (XIX; R = OH), which is isolated as a by-product in the preparation of caryophyllene oxide, has a β-methylene bridge. In order to ensure *trans*-electrophilic addition, it must be produced by α-attack by $OH^+$ on the endocyclic ethylenic linkage. The configuration of the secondary hydroxyl group must therefore be β (note, again, apparent inversion). Now Robertson and Todd (*loc. cit.*) have shown from their important *X*-ray studies that ring C of (XX) adopts the expected chair conformation. The β-configuration of the secondary hydroxyl must therefore be axial in character [see (XX)]. This has been confirmed experimentally. Oxidation of (XIX; R = OH) afforded




the corresponding ketone [see (XXI)] (Barton, Bruun, and Lindsey, *loc. cit.*), which on reduction with sodium and propan-1-ol furnished the expected epimeric equatorial alcohol (XXII). In the infra-red, the diol (XX) showed C–OH stretching bonds at 1094 and at 1050 cm.$^{-1}$, whilst the isomer (XXII) had the corresponding bands at 1094 (unchanged) and at 1058 cm.$^{-1}$. The difference for the stretching frequencies of the secondary alcohols again demonstrates (see above) that (XX) has the axial and (XXII) the equatorial hydroxyl group.

A conformational study of the caryophyllene molecule shows that, because it is *trans* within a $C_9$ ring, the endocyclic ethylenic linkage must lie with its plane perpendicular to that of the four-membered ring. If the 4-methyl group projects downwards (relative to the upward β-hydrogen atom at position 1), then only β-attack is possible, which will lead [see (XXIII)] to clovane-type cyclisation, whilst if it projects upwards only α-attack is possible leading [see (XXIV)] to caryolane-type cyclisation. In conclusion we note that the β-configuration of the secondary 2-hydroxyl group in (III) necessarily follows from the well-appreciated requirements of Walden inversion at this carbon atom in the ring expansion.

## Experimental

For general experimental directions see *J.*, 1952, 2339. Infra-red spectra, in $CS_2$ solution, were kindly determined by Messrs. Glaxo Laboratories Ltd., except where noted otherwise. Unless specified to the contrary $[\alpha]_D$ are in $CHCl_3$; ultra-violet absorption spectra were determined in ethanol.

*Chromic Acid Oxidation of Clovane-2 : 9-dione* (V).—The diketone (1·0 g.) in glacial acetic acid (60 ml.) was treated with chromium trioxide (3·0 g.), dissolved in the minimum of water, at room temperature for 72 hr. Crystallisation of the product from water gave the *keto-dicarboxylic acid* (VI) as colourless needles (550 mg.). Recrystallised from light petroleum (b. p. 100—120°) containing a trace of methanol, this had m. p. 230—231°, $[\alpha]_D$ +7° (*c*, 1·50 in EtOH) (Found : C, 63·9; H, 8·2%; equiv., 142. $C_{15}H_{22}O_5$ requires C, 63·85; H, 7·9%; equiv., 141). The dicarboxylic acid was more conveniently prepared by applying the same oxidation technique to clovane-2β : 9α-diol (III). For large-scale preparations cooling is necessary during the addition of the chromium trioxide.

*Selenium Dioxide Oxidation of the Keto-dicarboxylic Acid* (IV).—The acid (see above)

(500 mg.) was refluxed with selenium dioxide (250 mg.) in "AnalaR" acetic acid (25 ml.) for 4 hr. Crystallisation of the product from water gave the *diketo-dicarboxylic acid* (VII) (400 mg.). Recrystallised from light petroleum (b. p. 100—120°) containing a trace of methanol this (long slender needles) had m. p. 207°, $[\alpha]_D$ −37° (*c*, 1·02 in EtOH) (Found: C, 60·9; H, 7·0%; equiv., 148. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8%; equiv., 148).

*Fission of the Diketo-dicarboxylic Acid* (VII) *with Alkaline Hydrogen Peroxide.*—The diketo-dicarboxylic acid (see above) (2·5 g.) in aqueous sodium hydroxide (10%; 30 ml.) was treated at room temperature with hydrogen peroxide (30%; 25 ml.). After 48 hr. at the same temperature the product was recovered by acidification with concentrated hydrochloric acid, saturation with solid ammonium sulphate, and thorough extraction with ether. Crystallisation of the product from benzene containing a little methanol gave the tetracarboxylic acid (VIII; R = H) as a white amorphous powder, m. p. *ca.* 154° (decomp.), $[\alpha]_D$ −16° (*c*, 1·16 in EtOH), for which satisfactory analytical data could not be obtained. Treatment of the tetracarboxylic acid (500 mg.) with excess of ethereal diazomethane, chromotography of the oily product over alumina, and elution with light petroleum (b. p. 40—60°) (14 fractions) gave the crystalline *tetramethyl ester* (VIII; R = Me) (300 mg.). Recrystallised from light petroleum (b. p. 40—60°) this formed prisms, m. p. 61—62°, $[\alpha]_D$ −32° (*c*, 1·48) (Found: C, 59·5; H, 7·8. $C_{19}H_{30}O_8$ requires C, 59·1; H, 7·8%).

*Preparation of the Keto-dicarboxylic Acid* (IX).—The tetracarboxylic acid (VIII; R = H) (see above) (1·30 g.) in a small Pyrex tube was heated gently over a free flame until water evolution ceased. The tube was then sealed off and heated by total immersion in a Wood's metal bath at 260° for 6 hr. The product in ethanol (50 ml.) and potassium hydroxide (3·0 g.) was heated under reflux for 1 hr., the ethanol removed *in vacuo*, and the residue acidified with concentrated hydrochloric acid and extracted with ether. The resulting yellow oil readily crystallised on addition of benzene. It was purified by chromatography (in benzene solution) over silica gel (32 fractions), being eluted with benzene containing 20% of ether. Recrystallisation from ethyl acetate–benzene gave the pure *keto-dicarboxylic acid* (IX; R = H) (800 mg.) as prisms, m. p. 110—115° and then 173—174° (after drying at 80° *in vacuo*, only the m. p. at 173—174° was observed), $[\alpha]_D$ +81° (*c*, 1·19 in EtOH) (Found: C, 62·2; H, 7·7%; equiv., 135. $C_{14}H_{20}O_5$ requires C, 62·7; H, 7·5%; equiv., 134). Treatment with ethereal diazomethane in the usual way gave the *dimethyl ester* (IX; R = Me), m. p. [prisms from light petroleum (b. p. 40—60°)] 88—89°, $[\alpha]_D$ +56° (*c*, 4·50) (Found: C, 65·3, 65·15; H, 8·35, 7·9. $C_{16}H_{24}O_5$ requires C, 64·85; H, 8·15%). The *dimethyl ester* 2 : 4-*dinitrophenylhydrazone*, prepared and purified in the usual way, had m. p. (from benzene–methanol) 168—169° (Found: C, 55·15; H, 5·9; N, 12·2. $C_{22}H_{28}O_8N_4$ requires C, 55·45; H, 5·9; N, 11·75%).

The keto-dicarboxylic acid (IX; R = H) (50 mg.) was heated at 195—200° for 1½ hr. Crystallisation of the product from dry ethyl acetate–benzene gave back starting material (45 mg.), identified by m. p. and mixed m. p. Clovenic acid, heated under the same conditions, lost water as soon as it melted and gave [from light petroleum (b. p. 40—60°)] the anhydride. The anhydride is obtained with equal ease if the melt is cooled after 1 min.

*Dehydrogenation to* p-*Cymene.*—The dimethyl ester (IX; R = Me) (see above) (2·1 g.) in "AnalaR" acetic acid (25 ml.) was refluxed with selenium dioxide (1·0 g.) for 1 hr. The product (XI) (2·05 g.), a yellow viscous oil which did not crystallise, in ethanol (15 ml.) and ethanolic potassium hydroxide (10%; 20 ml.) was treated with hydrogen peroxide (30%; 2 ml.). After 40 min. at room temperature, water (10 ml.) was added and the neutral fraction removed by ether-extraction. Solid potassium hydroxide (6·0 g.) was then added and the solution refluxed on the steam-bath for 24 hr. Acidification with 50% sulphuric acid and ether-extraction gave a yellow viscous oil (1·70 g.) which partly crystallised. This crude hydrolysis product (600 mg.) together with palladised charcoal (Linstead and Thomas, *J.*, 1940, 1128) (150 mg.) was heated in a Carius tube at 300° for 20 hr. The oily product was extracted with light petroleum (b. p. 40—60°) and filtered (205 mg.). A portion of the resulting oil (100 mg.), which smelt strongly of *p*-cymene, was dissolved in light petroleum (b. p. 40—60°) and chromatographed over alumina to give pure *p*-cymene (20 mg.), identified by b. p., ultra-violet absorption spectrum, identical with that of *p*-cymene ($\lambda_{max.}$ 212, 259, 265, 273 mμ, ε 8300, 330 460, and 520 respectively), infra-red absorption spectrum, identical with that of *p*-cymene [bands (kindly determined by Mr. J. L. Hales, C.R.L., Teddington) as follows: 2915 s, 2857 s (hump), 1887 w, 1639 w, 1605 w, 1511 s, 1456 s, 1414 m, 1377 m, 1359 m, 1337 m, 1302 m, 1277 w, 1206 w, 1183 w, 1142 w, 1107 m, 1078 w, 1054 s, 1043 m (hump), 1020 m, 812 s, 720 m], and by oxidation by heating on the steam-bath for 2 hr. with concentrated nitric acid to give terephthalic acid (m. p. and mixed m. p.).

*Preparation of the 9α-Hydroxyclovenic Acid* (XV).—(*a*) 2-Oxoclovan-9α-ol (Aebi, Barton, and Lindsey, *loc. cit.*) (4·3 g.) in *iso*amyl formate (10 ml.) and dry ether (40 ml.) was added slowly to finely divided sodium (2·0 g.) in absolute ethanol (8 ml.). After refluxing for 30 min. and standing overnight, the excess of sodium was destroyed by the addition of methanol. Acidification of the acid fraction of the product gave the hydroxymethylene compound (XIV) as on orange oil (4·4 g.) giving a purple ferric chloride reaction. The oil in ethanol (20 ml.) and aqueous sodium hydroxide (10%; 20 ml.) was treated with hydrogen peroxide (30%; 25 ml.). After 15 min. a further addition of sodium hydroxide solution (10 ml.) and of hydrogen peroxide (10 ml.) was made and the solution refluxed for 15 min. on the steam-bath. Crystallisation of the acidic product from ether–benzene and then from chloroform–methanol gave 9α-hydroxyclovenic acid (XV) (2·6 g.) as needles, m. p. 174—176° (decomp.), $[\alpha]_D$ +2° (*c*, 2·21 in EtOH) (Found: C, 63·3; H, 8·35%; equiv., 139. $C_{15}H_{24}O_5$ requires C, 63·35; H, 8·5%; equiv., 142).

(*b*) 2-Oxoclovan-9α-yl acetate (Aebi, Barton, and Lindsey, *loc. cit.*) (1·5 g.) in "AnalaR" acetic acid (15 ml.) was refluxed with selenium dioxide (1·5 g.) for 1 hr. Crystallisation of the product from benzene–light petroleum (b. p. 40—60°) gave the 2 : 3-dioxoclovan-9α-yl acetate (XVI) (1·0 g.), m. p. 134—136°, $[\alpha]_D$ −6° (*c*, 0·58). This compound (1·0 g.) in methanol (20 ml.) and methanolic potassium hydroxide (10%; 20 ml.) at 0° was treated with hydrogen peroxide (30%; 8 ml.) and left at 0° for 20 hr. The product was refluxed with 2N-aqueous potassium hydroxide for 30 min. and then crystallised from chloroform–methanol, to give the required 9α-hydroxyclovenic acid (800 mg.), undepressed in m. p. on admixture with material prepared by route (*a*).

*Preparation of 9-Oxoclovenic Acid* (XVII).—9α-Hydroxyclovenic acid (see above) (180 mg.) in "AnalaR" acetic acid (10 ml.) was treated with chromium trioxide (50 mg.) in the minimum of water for 5 hr. at room temperature. Crystallisation from ether–light petroleum (b. p. 40—60°) gave the 9-*oxoclovenic acid* (XVII) (180 mg.), m. p. 180° (decomp.), $[\alpha]_D$ +21° (*c*, 1·06 in EtOH) (Found: C, 63·4; H, 7·65. $C_{15}H_{22}O_5$ requires C, 63·8; H, 7·85%). There was a marked depression in m. p. on admixture with starting material.

9-Oxoclovenic acid (100 mg.) in saturated sodium ethoxide solution (3 ml.) and hydrazine (100%; 1·5 ml.) was heated at 180° overnight. Crystallisation of the product from ether–light petroleum (b. p. 40—60°) gave clovenic acid (80 mg.), m. p. and mixed m. p. 195—196° (decomp.), $[\alpha]_D$ +36° (*c*, 0·42 in EtOH).

*Rates of Chromic Acid Oxidation.*—All oxidations were effected in an ice-bath at the same time. The epimeric clovane-2β : 9-diols (Aebi, Barton, and Lindsey, *loc. cit.*) (45 mg.) in aqueous acetic acid (24 ml.; 80% v/v) were mixed with a stock solution (6 ml.) of chromic acid. The latter was prepared by dissolving chromium trioxide (150 mg.) in aqueous acetic acid (30 ml.; 80% v/v). Aliquot parts were titrated in the usual way with 0·01N-sodium thiosulphate. The results in the Table are illustrative.

The epimeric 2-oxoclovan-9-ols (Aebi, Barton, and Lindsey, *loc. cit.*) (10 ml.) in aqueous acetic acid (13 ml.; 80% v/v) were mixed with a stock solution (2 ml.) of chromic acid. The latter was prepared by dissolving chromium trioxide (16 mg.) in aqueous acetic acid (8 ml.; 80 v/v). Aliquot parts were titrated with 0·001N-sodium thiosulphate. The results in the Table are illustrative.

*Oxidation (% for oxidation to dione).*

| Time (min.) | 6 | 12 | 25 | 40 | 71 | 106 | 151 | 246 | 339 | 476 |
|---|---|---|---|---|---|---|---|---|---|---|
| Clovane-2β : 9α-diol | 24 | 32 | 38 | 45 | 52 | 60 | 64 | 69 | 75 | 79 |
| Clovane-2β : 9β-diol | 24 | 32 | 38 | 45 | 51 | 55 | 61 | 66 | 72 | 73 |

| Time (min.) | 220 | 305 | 395 | 495 | 590 | 720 | 1380 |
|---|---|---|---|---|---|---|---|
| 2-Oxoclovan-9α-ol | 15 | 21 | 34 | 39 | 48 | 57 | 85 |
| 2-Oxoclovan-9β-ol | 7 | 14 | 21 | 27 | 36 | 43 | 76 |

*Caryolane-1 : 9α-diol.*—9-Oxocaryolan-1-ol (Barton, Bruun, and Lindsey, *loc. cit.*) (260 mg.) in propan-1-ol (5 ml.) was treated with sodium under reflux until saturated with the propoxide (1½ hr.). Crystallisation from chloroform–light petroleum gave *caryolane-1 : 9α-diol*, m. p. 162—163°, $[\alpha]_D$ −5° (*c*, 2·39) (Found: C, 75·7; H, 10·75. $C_{15}H_{26}O_2$ requires C, 75·55; H, 11·0%).

*Attempted Rearrangement of Caryolane-1 : 9β-diol.*—Caryolane-1 : 9β-diol (500 mg.) in acetone (4 ml.), water (0·5 ml.), and aqueous sulphuric acid (50% v/v; 0·2 ml.) was heated under reflux for 3 hr. Starting material was recovered almost quantitatively. The experiment

was repeated, more sulphuric acid being added until starting material was no longer recovered. The product was then an intractable gum from which clovane-2β : 9α-diol could not be recovered.

We thank the Government Grants Committee of the Royal Society, the Central Research Fund of London University, and Imperial Chemical Industries Limited for financial assistance. One of us (A. A.) is indebted to the Stiftung für Stipendien auf dem Gebiete der Chemie for a Post-doctorate Fellowship; another (A. W. B.) thanks the National Research Council of the United States for the award of an Eli Lilly Fellowship.

BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, July 22nd,* 1954.]