Synthetic Study on Zizaane-type Sesquiterpenoids [1]

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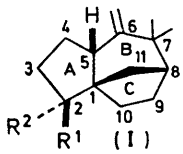
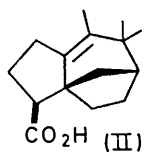
The total synthesis of epizizanoic acid (7,7-dimethyl-6-methylenetricyclo[6,2,1,$0^{1,5}$]undecane-2α-carboxylic acid) from (+)-3,3-dimethyl-2-methylenenorbornan-1-ylmethanol (XIII) is described. Hydrocyanation of 4-(3,3-dimethyl-2-methylenenorbornan-1-yl)but-3-en-2-one (XV) derived from the alcohol (XIII), followed by ozonolysis and cyclisation, gave 7,7-dimethyl-4-oxotricyclo[6,2,1,$0^{1,6}$]undec-5-ene-2-carbonitrile (XVII), which was converted into methyl 5,6-dihydroxy-7,7-dimethyltricyclo[6,2,1,$0^{1,6}$]undecane-2-carboxylate (XXIII). The monomethanesulphonate of (XXIII) was submitted to solvolytic rearrangement to afford the 5-epimers of methyl 7,7-dimethyl-6-oxotricyclo[6,2,1,$0^{1,5}$]undecane-2-carboxylate, (XXIV) and (XXVa), which have the desired zizaane skeleton. Finally, the epimer (XXVa) was converted into epizizanoic acid (Ib).

In recent years a new class of sesquiterpenoids, the zizaane group, has been isolated from vetiver oil. These sesquiterpenoids contain a tricyclo[6,2,1,$0^{1,5}$]undecane system with four one-carbon substituents situated at the C-7 (as a geminal dimethyl group), C-6, and C-2. Zizanoic acid [2-4] (Ia), epizizanoic acid [5] (Ib), isokhusenic acid [6] (II), and zizanol [7] (III), *inter alia*, have been recorded as members belonging to this group. Formulae previously proposed for tricyclovetivene (zizaene) and khusimol (also vetiver constituents) have been revised to the zizaane structures (Ic and d).[2,8,9]

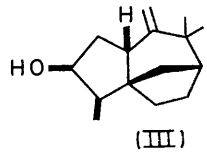


(I)

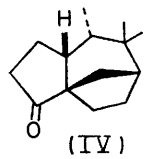
a; $R^1 = CO_2H$, $R^2 = H$
b; $R^1 = H$, $R^2 = CO_2H$
c; $R^1 = Me$, $R^2 = H$
d; $R^1 = CH_2OH$, $R^2 = H$



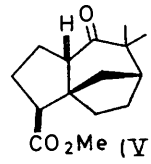
(II)



(III)



(IV)



(V)

In our study on the structure of zizanoic acid (Ia), the stereochemistry was investigated chiefly by rotatory dispersion of the norketones (IV) and (V), derived from (Ia).[3] Lack of suitable model compounds, however, left some uncertainty as to the stereochemistry.† Thus we set about the stereoselective total synthesis of the zizaane sesquiterpenoids.

Our first project was the ring expansion of suitably substituted camphene derivatives, which would lead to bicyclo[3,2,1]octane systems corresponding to rings B and C in the zizaane skeleton. Two methods have been recorded for such ring expansion of camphene (VIa). Matsubara obtained the homo-ketone (VIII) from (VIa) in good yield on treatment with lead tetra-acetate.[11] Several derivatives of camphene, substituted at the bridgehead, were submitted to this oxidative rearrangement, but all the compounds examined (VIb—e), however, were recovered unchanged. Probably the bridgehead substituents sterically retard the reaction.

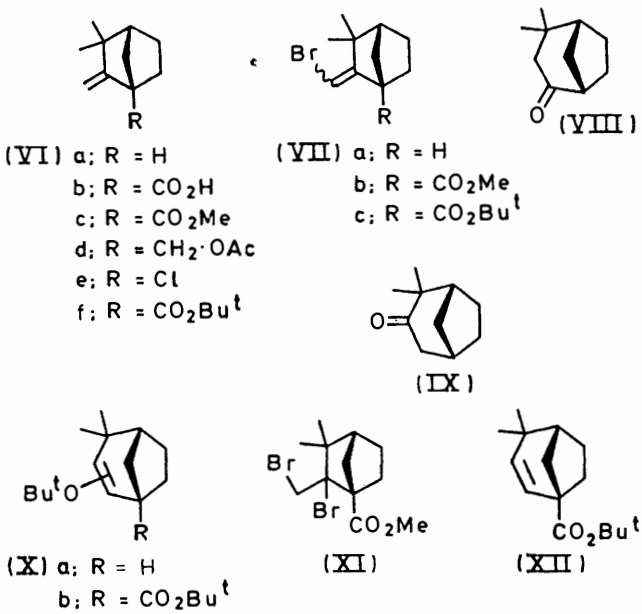
The 3-bromomethylene-norbornane (VIIa) has been reported to be transformed into a mixture of the ketones (VIII) and (IX) on treatment with base followed by hydrolysis of the vinyl ethers (Xa) so formed,[12] and a carbene mechanism has been proposed for the rearrangement (VIIa) ⟶ (Xa).[13] Bromination of the ester (VIc) gave the dibromide (XI), which was dehydrobrominated to the bromomethylene-ester (VIIb). The latter was heated with potassium t-butoxide in toluene giving a mixture, which showed four peaks in the ratio of 8 : 10 : 3 : 12 on g.l.c. The four compounds were separated by preparative g.l.c., and their structures were examined. The compound eluted most quickly was identified as the t-butyl ester (VIf) by comparison with an authentic sample. The product corresponding to the second peak showed two olefinic proton signals of an AB-type in the n.m.r. spectrum. This and other evidence seemed to support the ring-expanded structure (XII) for the product. Since the third product, formed in the least amount, indicated the presence of an olefinic proton and two t-butyl groups in the n.m.r. spectrum, it was tentatively identified as the desired vinyl ether (Xb).

† The crystal structure of khusimyl *p*-bromobenzoate was recently analysed, and the stereoformula proposed by us was confirmed.[10]

[1] Preliminary report, F. Kido, H. Uda, and A. Yoshikoshi, *Chem. Comm.*, 1969, 1335.
[2] F. Kido, H. Uda, and A. Yoshikoshi, *Tetrahedron Letters*, 1967, 2815.
[3] F. Kido, H. Uda, and A. Yoshikoshi, *Tetrahedron Letters*, 1968, 1247.
[4] I. C. Nigam, H. Komae, G. A. Neville, C. Redecka, and S. K. Paknikar, *Tetrahedron Letters*, 1968, 2497, and references cited therein.
[5] N. Hanayama, F. Kido, R. Sakuma, H. Uda, and A. Yoshikoshi, *Tetrahedron Letters*, 1968, 6099.
[6] H. Komae and I. C. Nigam, *J. Org. Chem.*, 1968, **33**, 1771.
[7] A. Homma, M. Kato, M.-D. Wu, and A. Yoshikoshi, *Tetrahedron Letters*, 1970, 231; N. H. Andersen, *ibid.*, p. 1755.
[8] R. Sakuma and A. Yoshikoshi, *Chem. Comm.*, 1968, 41.
[9] D. C. Umarani, K. G. Gore, and K. K. Chakravarti, *Perfumery Essent. Oil Record*, 1969, **60**, 307.
[10] R. M. Coates, R. F. Farney, S. M. Johnson, and I. C. Paul, *Chem. Comm.*, 1969, 999.
[11] Y. Matsubara, *Nippon Kagaku Zasshi*, 1955, **76**, 1088.
[12] J. Wolinsky, *J. Org. Chem.*, 1961, **26**, 704.
[13] K. L. Erickson and J. Wolinsky, *J. Amer. Chem. Soc.*, 1965, **87**, 1142.

The last fraction was a mixture, as its n.m.r. spectrum indicated.

Although the structures of the products and the mechanism had been insufficiently investigated, we discontinued further elaboration of this scheme because of the poor yields.



We adopted, as the second scheme, base-induced rearrangement of the monosulphonate of a suitably substituted tricyclo[6,2,1,$0^{1,6}$]undecanediol, such as (XXIII). Judging from the well-documented stereoselective course of this rearrangement,[14] one may presume that the monosulphonate of the diol (XXIII), for example, rearranges to a tricyclo[6,2,1,$0^{1,5}$]undecanone with the stereochemistry shown in (XXIV). Although the 7-hydrogen atom of the predicted rearrangement product is epimeric with that of zizaane, it has been found that the product may equilibrate with its 7-epimer in base, as experienced with the keto-ester (XXVa), a degradation product of epizizanoic acid (Ib).[5] Thus, we decided to examine the base-induced rearrangement of the α-hydroxy-sulphonate.

The alcohol (XIII), which was obtained from (+)-carboxylic acid (VIb) *via* the methyl ester (VIc), afforded the aldehyde (XIV) on treatment with dicyclohexylcarbodi-imide and phosphoric acid in dimethyl sulphoxide [15] in 80% yield. The aldehyde was condensed with acetone in the presence of sodium ethoxide to give the *trans*-enone (XV), which was hydrocyanated [16] and the resulting keto-nitrile, without purification, was ozonised to the diketo-nitrile (XVI) in 44% yield. The fact that the product was homogeneous (t.l.c. and n.m.r.) demonstrated stereoselective introduction of the nitrile group into the enone (XV), although its orientation could not be established. In order to cyclise the diketo-nitrile without elimination of hydrogen cyanide, several catalysts (*e.g.*, benzoic acid–pyrrolidine, acetic acid–pyrrolidine, benzoic acid–piperidine, *etc.*) were examined with a variety of reaction times and molar ratios. The highest yield (62%) of the cyclisation product (XVII) was obtained when the diketo-nitrile was heated in benzene with 2 mol. equiv. of benzoic acid and piperidine, with azeotropic removal of the water formed during the reaction. The n.m.r. spectrum of the product (XVII) showed a doublet at δ 2·66 p.p.m. indicating that the nitrile group was quasi-equatorial.*

We attempted to prepare the unsaturated ester (XXII) from the keto-nitrile (XVII). Desulphurisation of the thioacetal (XVIII), derived from (XVII), gave poor and variable yields of the unsaturated nitrile (XIX), depending upon the activity of the Raney nickel used, while hydrolysis of the nitrile group of (XVIII), prior to desulphurisation, resulted in the formation of a complex mixture. The keto-nitrile (XVII) was treated with sodium borohydride, and the resulting hydroxy-nitrile was hydrolysed with potassium hydroxide. The crude product was treated with diazomethane followed by Jones oxidation giving the keto-ester (XX) in 74% overall yield. The thioacetal (XXI), obtained from (XX) without purification, was smoothly desulphurised with Raney nickel to the desired unsaturated ester (XXII) in 73% yield.

We now considered the configuration of the methoxycarbonyl group of the unsaturated ester (XXII) because this determined whether the final product of the synthesis is zizanoic acid (Ia) or epizizanoic acid (Ib). In the n.m.r. spectrum of (XXII), the proton α to the ester group was observed as a quartet (J 4 and 10 Hz) at δ 2·63 p.p.m. thus demonstrating a quasi-axial configuration.* Two conformations (XXVIa) and (XXVIb) are possible for the cyclohexene ring of the unsaturated ester. In both cases, the groups attached to C-1 and -2 are staggered or nearly eclipsed with respect to each other, as seen in (XXVIa) and (XXVIb). Hence we concluded that the more stable conformation of the cyclohexene ring must be the former and, consequently, that the configuration of the methoxycarbonyl group is α. We thus expected to obtain epizizanoic acid as the final product of this synthesis.

Oxidation of (XXII) with osmium tetroxide afforded a diol, believed to be (XXIII), by oxidation on the less-hindered *exo*-face. Assuming that the dihydroxy-cyclohexane ring of (XXIII) adopts a chair conformation, the 5-hydroxy-group is equatorial. This configuration is favourable for the simple rearrangement of the central 1,6-bond, in terms of an anticoplanar steric relationship. In fact, the monomethanesulphonate of the diol (XXIII)

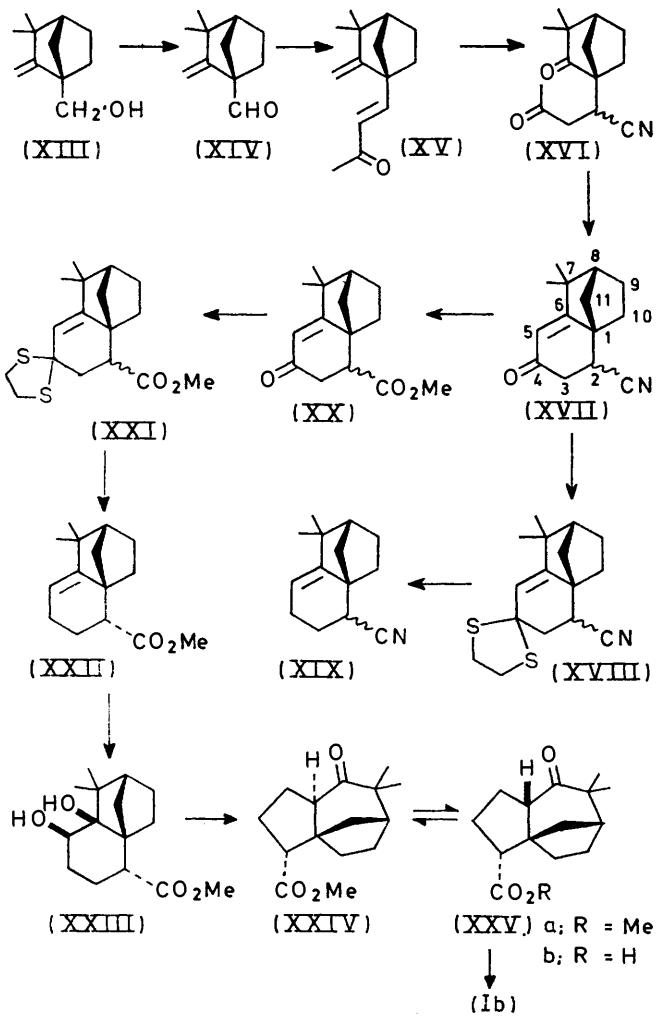
* The stereochemical assignment based on n.m.r. spectra was derived from an examination of molecular models and the Karplus relationship between coupling constants and dihedral angles.

[14] C. D. Gutsche and D. Redmore, 'Carbocyclic Ring Expansion Reactions,' Academic Press, New York and London, 1968, pp. 101—103, and references therein.

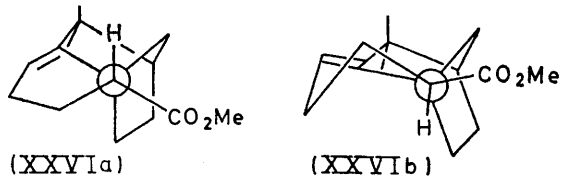
[15] K. E. Pfitzner and H. G. Moffat, *J. Amer. Chem. Soc.*, 1963, **85**, 3207.

[16] W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *J. Org. Chem.*, 1968, **30**, 2307.

smoothly yielded, on treatment with potassium t-butoxide, the keto-ester (XXIV) as the sole product

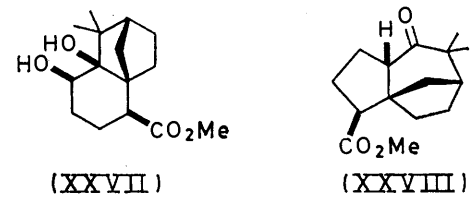


under mild conditions, while prolonged exposure to the base gave not only (XXIV) but its epimerisation product (XXVa). The keto-ester (XXVa) was separated from



the mixture and identified by comparison with an authentic sample previously prepared from epizizanoic acid.[5]

Ramage and McSweeney have recently described the total synthesis of zizanoic acid.[17] These authors also utilised the diol (XXIII) and its epimer (XXVII) as the key intermediates in their synthesis. They used pyridine–triethylamine to effect rearrangement of the monomethanesulphonates of the diols into the keto-esters (XXVa) and (XXVIII), respectively. Since pyridine–triethylamine is not sufficiently strong to cause isomerisation of the keto-esters,[17]* how the isomeric keto-esters (XXVa) and (XXVIII) were formed in contrast to our results remains unexplained.



The final step of the synthesis was introduction of an *exo*-methylene group at the 6-position of the keto-carboxylic acid (XXVb) by a Wittig reaction. In order to obtain (XXVb) without isomerisation at epimerisable centres, the ester (XXVa) was reduced with lithium aluminium hydride and then oxidised with Jones reagent. The sodium salt of the keto-acid (XXVb) was treated with methylenetriphenylphosphorane in dimethyl sulphoxide. Although the carbonyl group was unreactive, a large excess of the reagent and prolonged treatment afforded epizizanoic acid (Ib) in 10% yield.

Since the transformations of epizizanoic acid into zizanoic acid [5] (Ia), khusimol [2] (Id), and zizaene [2,8] (Ic) have been reported, the synthesis of epizizanoic acid amounts to the synthesis of these zizaane sesquiterpenoids.

EXPERIMENTAL

All m.p.s and b.p.s are uncorrected. U.v. spectra were taken on a Cary Model 14 spectrophotometer. I.r. spectra were run on a Hitachi EPI-S2 or G-2 spectrophotometer. N.m.r. spectra of carbon tetrachloride solutions (unless otherwise stated) were recorded on a Varian A-60 spectrometer with tetramethylsilane as an internal standard, and coupling constants are given in Hz. Optical rotatory dispersions of methanolic solutions and mass spectra were obtained on JASCO Model ORD/UV-5 and Hitachi RMU-6D instruments, respectively.

3,3-Dimethyl-2-methylenenorbornane-1-carboxylic Acid (VIb).—This was prepared according to the method of Houben [18] from (+)- or (±)-bornan-2-one (camphor) in *ca.* 70% yield: the (+)-acid, m.p. 75—78°, $[\alpha]_D^{22}$ +83·2° (*c* 1·9) (lit.,[18] m.p. 83—84°, $[\alpha]_D^{19}$ +95·5°), $\nu_{max.}$ (KBr) 1697, 1650, and 896 cm^{-1}, δ ($CDCl_3$) 1·10 (6H, s) and 4·68 and 4·98 p.p.m. (1H, s, each) (Found: C, 73·45; H. 9·0. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·95%); the (±)-acid, m.p. 107·5—108·5° (lit.,[18] 109—110°).

Methyl 3,3-Dimethyl-2-methylenenorbornane-1-carboxylate (VIc).—The (+)- or (±)-acid (VIb) was esterified with an excess of ethereal diazomethane to give *methyl ester* (VIc), b.p. 79—83° at 4 mmHg, $\nu_{max.}$ (film) 1735 cm^{-1}, δ 1·10 (6H, s), 3·67 (3H, s), and 4·62 and 4·80 (1H, s, each) (Found: C, 74·45; H, 9·55. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·35%).

Methyl 2-Bromo-2-bromomethyl-3,3-dimethylnorbornane-1-carboxylate (XI).—Bromine (8·2 g) was added dropwise to

* Professor Ramage is now investigating the stereochemistry of these diols (personal communication).

[17] D. F. McSweeney and R. Ramage, *Tetrahedron*, 1971, **27**, 1481.

[18] J. Houben and E. Pfankuch, *Annalen*, 1930, **483**, 271.

a stirred solution of the foregoing ester * (VIc) (10 g) in dry ether (50 ml) at ice-bath temperature during 1·5 h. The solution was washed with aqueous sodium thiosulphate solution, water, and brine. Removal of the ether left crystals (5·55 g) of the *dibromo-ester* (XI), m.p. 102—102·5° (from methanol), $\nu_{max.}$ (KBr) 1710 cm^{-1}, δ 1·32 (6H, s), 3·67 (3H, s), and 3·94 p.p.m. (1H, d, *J* 12) (Found: C, 40·5; H, 5·05; Br, 44·75. $C_{12}H_{17}Br_2O_2$ requires C, 40·75; H, 5·1; Br, 45·15%).

Methyl 2-*Bromomethylene*-3,3-*dimethylnorbornane*-1-*carboxylate* (VIIb).—The dibromo-ester (XI) (5·55 g) was heated with a solution of potassium t-butoxide [prepared from potassium (0·55 g) and dry t-butyl alcohol (40 ml)] for 3·5 h. The solution was poured into water and extracted with ether. The extracts were washed with water and brine. Removal of the solvent left an oil (4·0 g), which was chromatographed on a silica gel column. Chloroform–n-hexane eluted the *bromomethylene-ester* (VIIb), an oil (2·41 g), $\nu_{max.}$ (film) 1734 and 1634 cm^{-1}, δ 1·31, 1·35, 3·67 (3H, s, each), and 5·95 p.p.m. (1H, s) (Found: C, 53·05; H, 6·05. $C_{12}H_{17}BrO_2$ requires C, 52·75; H, 6·25%).

Reaction of the Bromomethylene-ester (VIIb) *with Potassium t-Butoxide*.—A solution of the ester (VIIb) (1·5 g) in dry toluene (8 ml) was added dropwise to a suspension of potassium t-butoxide [prepared from potassium (1 g)] in dry toluene (120 ml) at room temperature over 20 min, then the solution was heated under reflux for an additional 4 h. The mixture was washed with water and brine. Evaporation gave an oil (1·05 g), which showed four major peaks on g.l.c. (column: Carbowax 20M, 3 mm × 3 m; column temp. 213°; helium press. 1·5 kg cm^{-2}) with retention times of 3·8, 4·3, 5·6, and 6·2 min (designated as A, B, C, and D). The compounds were separated by preparative g.l.c.

Fraction A. This was identified as t-butyl 3,3-dimethyl-2-methylenenorbornane-1-carboxylate (VIf) by comparison (i.r. and n.m.r.) with an authentic sample, whose preparation is described later.

Fraction B. This may be designated as *t-butyl* 4,4-*dimethylbicyclo*[3,2,1]*oct*-2-*ene*-1-*carboxylate* (XII) from the following data: $\nu_{max.}$ (film) 1725 cm^{-1}, δ 0·99 and 1·02 (3H, s, each), 1·25 (9H, s), 5·08br (1H, d, *J* 10), and 5·90 p.p.m. (1H, dd, *J* 10 and 1) (Found: C, 76·5; H, 10·0. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·25%).

Fraction C. This fraction was tentatively identified as *t-butyl* 4,4-*dimethyl*-2(or 3)-*t-butoxybicyclo*[3,2,1]*oct*-2-*ene*-1-*carboxylate*, $\nu_{max.}$ (film) 1730 and 1665 cm^{-1}, δ ($CDCl_3$) 1·00 and 1·07 (3H, s, each), 1·37 and 1·47 (9H, s, each), and 5·12br p.p.m. (1H, s).

Fraction D. The n.m.r. spectrum showed this fraction to be a mixture.

t-Butyl 3,3-*Dimethyl*-2-*methylenenorbornane*-1-*carboxylate* (VIf).—A mixture of the methyl ester (VIc) (60 mg), potassium t-butoxide (25 mg), and dry toluene (2 ml) was heated under reflux for 3·5 h. Toluene (0·5 ml) was distilled from the mixture, and the heating was continued for an additional 2 h. The mixture was poured into water, and the organic layer was washed with brine and dried. Removal of the solvent left an oil (56 mg), $\nu_{max.}$ (film) 3050, 1723, 1660, and 885 cm^{-1}, δ 1·08 (6H, s), 1·45 (9H, s), and 4·58 and 4·85 p.p.m. (1H, s, each) (Found: C, 76·55; H, 10·2. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·25%).

3,3-*Dimethyl*-2-*methylenenorbornan*-1-*ylmethanol* (XIII).—A solution of the methyl (+)-ester † (VIc) (20 g) in dry ether (80 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (7 g) in dry ether (300 ml) during 45 min, and the solution was heated under reflux for 4 h. Sufficient water to destroy the excess of reagent was added with cooling (an ice-bath), and the resulting suspension was filtered. The filtrate was washed with water and dried ($MgSO_4$). The ether was evaporated to leave a residue, which solidified. An analytical sample of the *alcohol* (XIII), m.p. 31°, $\nu_{max.}$ (CCl_4) 3400, 1655, and 885 cm^{-1}, δ 1·03 and 1·06 (3H, s, each), 3·69 (2H, d, *J* 3), and 6·26 p.p.m. (2H, s), was obtained on sublimation *in vacuo* (Found: C, 78·1; H, 10·95. $C_{11}H_{18}O$ requires C, 79·45; H, 10·9%).

3,3-*Dimethyl*-2-*methylenenorbornane*-1-*carbaldehyde* (XIV).—A solution of the alcohol (XIII) (16·4 g) and dicyclohexylcarbodi-imide (61·8 g) in dimethyl sulphoxide (200 ml) was cooled in an ice-bath, and 100% phosphoric acid (5 g) was added.[15] The solution was stirred at room temperature overnight. Dilute hydrochloric acid (100 ml) was added to the solution at ice-bath temperature, and the solution was stirred for 1 h. The precipitated dicyclohexylurea was filtered off and washed with light petroleum three times. Water was added into the combined filtrates, and the mixture was extracted with ether–light petroleum (1 : 1) three times. The combined extracts were washed with water and brine. Evaporation gave the crude product, which was distilled *in vacuo* to obtain the *aldehyde* (XIV) (13·1 g, 81%), b.p. 81—85° at 5 mmHg, $\nu_{max.}$ (film) 2700, 1717, 1650, and 888 cm^{-1}, δ 1·13 (6H, s), 4·73 (2H, s), and 9·83 p.p.m. (1H, s). The 2,4-*dinitrophenylhydrazone*, yellowish orange crystals, melted at 140—142° (Found: C, 59·1; H, 5·7; N, 16·2. $C_{17}H_{20}N_4O_4$ requires C, 59·3; H, 5·85; N, 16·25%).

4-(3,3-*Dimethyl*-2-*methylenenorbornan*-1-*yl*)*but*-3-*en*-2-*one* (XV).—A solution of the aldehyde (XIV) (10·5 g) in ethanol (30 ml) was added to a stirred mixture of acetone (20 ml) and ethanolic sodium ethoxide [prepared from sodium (1·0 g) and ethanol (200 ml)]. After 19h at room temperature, water was added, and the solution was concentrated by evaporation. The residue was poured into water and extracted with ether. The ether extracts were washed and evaporated to leave an oily product (16·2 g). A fraction (10·0 g, 76%), b.p. 134—136° at 5 mmHg, of the *ketone* (XV) was collected, $\lambda_{max.}$ (MeOH) 230 nm (ε 9900), $\nu_{max.}$ (film) 1670 and 1625 cm^{-1}, δ 1·08, 1·12, and 2·18 (3H, s, each), 4·57 and 4·60 (1H, s, each), and 6·00 and 6·93 p.p.m. (1H, d, *J* 17 each) (Found: C, 82·1; H, 9·9. $C_{14}H_{20}O$ requires C, 82·3; H, 9·85%).

2-(3,3-*Dimethyl*-2-*oxonorbornan*-1-*yl*)-4-*oxopentanonitrile* (XVI).—A solution of the unsaturated ketone (XV) (14·0 g) in dimethylformamide (20 ml) was added to a stirred suspension of potassium cyanide (9·1 g) and ammonium chloride (5·6 g) in a mixture of water (45 ml) and dimethylformamide (350 ml),[16] and the mixture was stirred for 10 h at 76—81°. The mixture was diluted with water and extracted with ether. The ether extracts were combined and washed with dilute hydrochloric acid, water, and brine. Evaporation gave the oily crude hydrocyanation product (13 g), $\nu_{max.}$ (film) 2230, 1722, 1653, and 880 cm^{-1}.

Ozonised air was passed through a solution of the crude product (13 g) in ethyl acetate (400 ml) at −70 to −50°, and the resulting ozonide solution was treated with hydrogen over palladium–carbon (10%; 100 mg) at room

* In this series of preparations, the (±)-ester (VIc) was used as the starting material.

† The (+)-isomer was used in this series.

temperature. The catalyst was filtered off, and the filtrate was washed with aqueous sodium hydrogen carbonate. The ethyl acetate was evaporated to leave an oil, which was chromatographed on a silica gel column. Chloroform–ether (4 : 1) eluted the *diketo-nitrile* (XVI) (7·05 g), $\nu_{max.}$ (film) 2240, 1723, and 1714 cm^{-1}, δ ($CDCl_3$) 1·07 (6H, s), 2·22 (3H, s), and 3·44 p.p.m. (1H, q, *J* 4 and 10) (Found: C, 71·75; H, 8·2; N, 5·95. $C_{14}H_{19}NO_2$ requires C, 72·0; H, 8·2; N, 6·0%).

Cyclisation of the Diketo-nitrile (XVI).—A solution of the diketo-nitrile (XVI) (3·43 g), piperidine (2·5 g), and benzoic acid (3·59 g) in dry benzene was heated under reflux under nitrogen for 96 h, while azeotropically removing the water formed during the reaction with a Dean–Stark head. The solution was washed with dilute hydrochloric acid, 5% aqueous potassium hydroxide, and water. Removal of the solvent gave an oil (4 g), which was distilled *in vacuo* to remove a non-volatile portion. The distillate was poured onto an active alumina column and eluted with ether to give 7,7-*dimethyl*-4-*oxotricyclo*[6,2,1,$0^{1,6}$]*undec*-5-*ene*-2-*carbonitrile* (XVII) [1·68 g, 62% on the basis of the (XVI) consumed] and the unchanged diketo-nitrile (XVI) (0·47 g). The nitrile (XVII) was recrystallised from light petroleum to give crystals, m.p. 62—62·5°, $\lambda_{max.}$ (MeOH) 240 nm (ε 13,300), $\nu_{max.}$ ($CHCl_3$) 2250 and 1665 cm^{-1}, δ ($CDCl_3$) 1·18 (6H, s), 2·64 (1H, d, *J* 11), 2·66 (1H, d, *J* 8), 3·44 (1H, q, *J* 8 and 11), and 5·75 p.p.m. (1H, s) (Found: C, 77·8; H, 8·25; N, 6·65. $C_{14}H_{17}NO$ requires C, 78·1; H, 7·95; N, 6·5%).

3,3-*Ethylenedithio*-7,7-*dimethyltricyclo*[6,2,1,$0^{1,6}$]*undec*-5-*ene*-2-*carbonitrile* (XVIII).—To a solution of the nitrile (XVII) (1·68 g) in acetic acid (33 ml) were added ethanedithiol (4·5 ml) and boron trifluoride–ether (4 ml), and the mixture was stirred for 16 h at room temperature. The mixture was diluted with ether and washed with 5% potassium hydroxide, water, and brine. Evaporation left crystals, which gave, on recrystallisation from methanol, the pure *thioacetal* (XVIII) (1·73 g, 76%) as needles, m.p. 118—119°, $\nu_{max.}$ ($CHCl_3$) 2230, 1662, and 860 cm^{-1} (Found: C, 66·15; H, 7·05; N, 4·8. $C_{16}H_{21}NS_2$ requires C, 65·95; H, 7·25; N, 4·8%).

7,7-*Dimethyltricyclo*[6,2,1,$0^{1,6}$]*undec*-5-*ene*-2-*carbonitrile* (XIX).—An excess of Raney nickel (W-2) was deactivated by heating in acetone. The thioacetal (XVIII) (60 mg) was added to the above suspension and heated under reflux for 18 h. The Raney nickel was filtered off, and the filtrate was diluted with water. The product was extracted with ether. Removal of the ether gave an oil (30 mg), which was chromatographed on a silica gel column. Chloroform eluted the unsaturated *nitrile* (XIX) (24 mg), $\nu_{max.}$ 2230 and 800 cm^{-1} (Found: C, 83·35; H, 9·3; N, 7·2. $C_{14}H_{19}N$ requires C, 83·55; H, 9·5; N, 6·95%).

Methyl 7,7-*Dimethyl*-4-*oxotricyclo*[6,2,1,$0^{1,6}$]*undec*-5-*ene*-2-*carboxylate* (XX).—A solution of the nitrile (XVII) (470 mg) and sodium borohydride (150 mg) in methanol (15 ml) was stirred and heated under reflux for 5 h. Water was added, and the product was extracted with ether. The extracts were combined and washed with water and brine. Evaporation of the ether gave an alcohol (480 mg), $\nu_{max.}$ (film) 3380, 3020, and 2230 cm^{-1}. The alcohol was dissolved in a 50% methanol solution (10 ml) of potassium hydroxide (5 g) and heated under reflux for 40 h under nitrogen. The solution was cooled to room temperature and diluted with water. A neutral portion of the product was removed by extracting with ether, and the aqueous layer was acidified with dilute hydrochloric acid. The liberated acid was collected in ether. The ether extracts were washed with water and evaporated to give an oily acid. The crude acid was treated with ethereal diazomethane giving an oily ester (470 mg), $\nu_{max.}$ (film) 3390, 1732, and 786 cm^{-1}.

An excess of Jones reagent (8N) was added to a solution of the above-mentioned ester in acetone (10 ml), and the solution was shaken at room temperature for 5 min. Usual work-up afforded crystalline product (400 mg, 74%). Recrystallisation from light petroleum gave the pure *keto-ester* (XX), m.p. 90—91°, $\lambda_{max.}$ (MeOH) 241 nm (ε 15,400), $\nu_{max.}$ ($CHCl_3$) 1730 cm^{-1}, δ ($CDCl_3$) 1·13 (6H, s), 2·64 (1H, d, *J* 8), 2·67 (1H, d, *J* 10), 3·33 (1H, q, *J* 8 and 10), and 5·80 p.p.m. (1H, s) (Found: C, 72·7; H, 7·9. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·1%).

Methyl 7,7-*Dimethyltricyclo*[6,2,1,$0^{1,6}$]*undec*-5-*ene*-2α-*carboxylate* (XXII).—A solution of the keto-ester (XX) (230 mg), ethanedithiol (0·3 ml), and boron trifluoride–ether (0·5 ml) in acetic acid (6 ml) was left at room temperature for 40 h. The mixture was worked-up in the usual manner to give the crystalline thio-acetal (XXI) (290 mg). The crude thio-acetal (200 mg) was added to a stirred ethanolic suspension of Raney nickel (W-2), deactivated by heating with boiling acetone, and heated under reflux for 20 h. The nickel was filtered off, and the filtrate was diluted with water. Extraction of the product with ether gave the oily unsaturated *ester* (XXII) (83 mg), $\nu_{max.}$ (film) 1735 cm^{-1}, δ ($CDCl_3$) 1·05br (6H, s), 2·63 (1H, q, *J* 4 and 10), 3·70 (3H, s), and 5·20 p.p.m. (1H, d, *J* 4) (Found: C, 77·0; H, 9·4. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·45%).

Methyl 5β,6β-*Dihydroxy*-7,7-*dimethyltricyclo*[6,2,1,$0^{1,6}$]-*undecane*-2α-*carboxylate* (XXIII).—A solution of the unsaturated ester (XXII) (80 mg) and osmium tetroxide (98 mg) in pyridine (2 ml) was stored at room temperature for 5 days. A saturated aqueous solution of sodium hydrogen sulphite (1 g) was added to the stirred mixture, and the stirring was continued at the same temperature for 3 h. Water was added, and the product was extracted with ether. The extracts were washed with dilute hydrochloric acid, water, and brine. The ether was evaporated to leave a crystalline residue (88 mg), which upon recrystallisation from n-hexane gave the *dihydroxy-ester* (XXIII), m.p. 109—110°, $\nu_{max.}$ ($CHCl_3$) 3600, 3400, and 1728 cm^{-1}, δ ($CDCl_3$) 1·03 and 1·12 (3H, s, each), 3·10 (1H, m), 3·67 (3H, s), and 4·20 p.p.m. (1H, m) (Found: C, 67·3; H, 9·0. $C_{15}H_{24}O_4$ requires C, 67·15; H, 9·0%).

Solvolysis of the Monomethanesulphonate of the Dihydroxy-ester (XXIII).—A solution of the dihydroxy-ester (XXIII) (88 mg) and methanesulphonyl chloride (75 mg) in pyridine (2 ml) was left at room temperature overnight. The oily methanesulphonate (90 mg), $\nu_{max.}$ 3530, 1728, 1350, 1175, and 930 cm^{-1}, was obtained on addition of water followed by extraction with ether. The crude methanesulphonate (20 mg) was dissolved in t-butyl alcohol (0·5 ml), and thereto t-butyl alcohol (2 ml) containing potassium t-butoxide (7 mg) was added. The solution was left at room temperature for 10 min, then water was added. Work-up gave a crystalline residue (12 mg), which was shown to be almost homogeneous on t.l.c. Recrystallisation from light petroleum gave pure *methyl* 7,7-*dimethyl*-6-*oxo*-5αH-*tricyclo*[6,2,1,$0^{1,5}$]*undecane*-2α-*carboxylate* (XXIV), m.p. 92—93°, $\nu_{max.}$ (CCl_4) 1735 and 1697 cm^{-1}, δ ($CDCl_3$) 1·07, 1·17, and 3·67 p.p.m. (3H, s, each), $[\phi]_{310}$ −639° (Found: C, 71·8; H, 8·9. $C_{15}H_{22}O_3$ requires C, 71·95; H, 8·85%).

The mesylate (90 mg) was treated also with potassium

t-butoxide (30 mg) in t-butyl alcohol (4 ml) in a similar manner, except for a longer time (45 min), giving an oily product (70 mg). G.l.c. (Carbowax 20M, 3 mm × 3 m) showed the product to be a 2 : 3 mixture of the 5-epimers (XXIV) and (XXVa). The product was poured onto a silica gel column and eluted with chloroform to afford the 5βH-*ester* (XXVa) (16 mg), the epimeric mixture of (XXVa) and (XXIV), and the keto-ester (XXIV) (5 mg) in that order. The keto-ester (XXVa) was recrystallised from light petroleum to give crystals, m.p. 78—78·5° (lit.,[5] 77·5—78·5°), $[\alpha]_D^{23}$ +33·3° (*c* 0·6), $\nu_{max.}$ (CCl_4) 1738 and 1712 cm^{-1}, δ 1·00, 1·17, and 3·64 p.p.m. (3H, s, each), $[\phi]_{312}$ +6900°, $[\phi]_{269}$ −9400° (*a* +164). The spectra were identical with those of an authentic sample derived from epizizanoic acid,[5] and no depression of the m.p. was observed on admixture.

Epizizanoic Acid (7,7-*Dimethyl*-6-*methylene*-5βH-*tricyclo*-[6,2,1,$0^{1,5}$]*undecane*-2α-*carboxylic Acid*) (Ib).—A mixture of the keto-ester (XXVa) (78 mg) and lithium aluminium hydride (30 mg) in anhydrous ether (4 ml) was heated under reflux for 4 h. The mixture was worked-up in a usual manner to give a diol, an acetone solution of which was treated with an excess of Jones reagent (8N) at room temperature for 7 min. Work-up as before afforded the keto-carboxylic acid (XXVb) (60 mg). A methanolic solution of the keto-carboxylic acid was neutralised with 0·1N-aqueous sodium hydroxide (with phenolphthalein as an indicator), then the solvent was removed *in vacuo*. The residue was dissolved in water, and some insoluble substances were filtered off. The filtrate was evaporated to give a sodium salt. Methylenetriphenylphosphorane solution [prepared from triphenylphosphonium bromide (900 mg) and sodium hydride (60 mg) in dimethyl sulphoxide (2·5 ml)] was added to the sodium salt in dimethyl sulphoxide (1 ml). The mixture was heated at 58° under nitrogen for 7 days and diluted with water. After extracting with ether to remove a neutral portion, the aqueous layer was acidified with dilute hydrochloric acid. Extraction with ether gave an oily product (72 mg), which was chromatographed on a silica gel column. Chloroform–ether (1 : 1) eluted *epizizanoic acid* (Ib) (6 mg), m.p. 108·5—110° (from aqueous methanol) (lit.,[5] 109—110·5°), $\nu_{max.}$ 2600, 1700, 1640, and 898 cm^{-1} (Found: C, 76·55; H, 9·5. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·45%). The i.r. spectrum was identical with that of natural epizizanoic acid.

We thank Mrs. R. Tanaka for the o.r.d. measurements.

[1/2311 *Received*, 6*th December*, 1971]