293. *The Isolation and Synthesis of* 13-*Hydroxy*-14-*isopropylpodocarpa*-8,11,13-*trien*-16-*oic Acid and Some Related Compounds.*

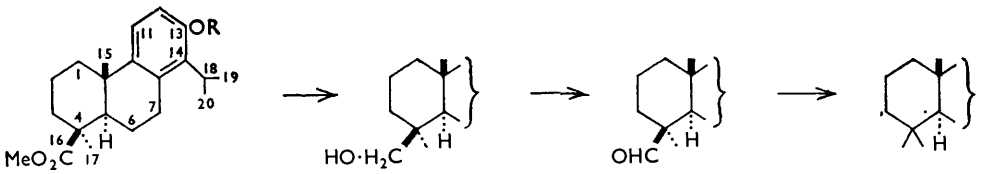
By D. A. H. Taylor.

A resin acid isolated from the timber of *Podocarpus mannii* Hook f. has been shown to be 13-hydroxy-14-isopropylpodocarpa-8,11,13-trien-16-oic acid (I). The corresponding primary alcohol and aldehyde have also been isolated. The structures assigned to these compounds have been confirmed by total synthesis. Two other compounds which have been obtained from *Podocarpus mannii* are also described.

The genus *Podocarpus* consists of some sixty species, mostly occurring in the southern hemisphere. Several have been found to contain diterpenes, of which totarol, ferruginol, and podocarpic acid are the most important. Two species occur in West Africa, where they are the only conifers. One of these, *Podocarpus mannii* Hook f., which only occurs naturally in the small coastal island of Sao Thome, has now been investigated. The specimen used was from the trunk of a tree some 35 years old, grown by the Forestry Research Department in their collection at Sapoba, Western Nigeria.

Extraction of the pulverised timber with light petroleum gave a resin which was distilled in vacuum to give a main fraction, b. p. *ca.* 200°/2 mm., and a less volatile residue. The main fraction crystallised readily, and the solid part was identified as totarol (IVa). During the purification two other compounds A and B were obtained.

Compound A is a dihydroxy-diterpene, $C_{20}H_{30}O_2$, m. p. 227°, $[\alpha]_D^{20}$ +44°, which gave a diacetate. The spectral properties of this compound are very similar to those of totarol, and it seemed probable that it is a hydroxy-derivative. This was confirmed by methylation of the phenolic hydroxyl group with potassium t-butoxide and methyl iodide, oxidation of the aliphatic hydroxyl group to a carbonyl group with chromic acid in acetone, and removal of the carbonyl group by Wolff–Kishner reduction. The product was a mixture which on remethylation gave totarol methyl ether (IVb), identical with an authentic specimen. The intermediate carbonyl compound shows a sharp absorption band at 2700 cm.$^{-1}$, which suggests that it is an aldehyde, and that the original compound is a primary alcohol.



(I) (II) (III) (IV)

Compound B, $C_{20}H_{28}O_2$, m. p. 185° $[\alpha]_D^{20}$ +76°, has a carbonyl group absorbing at 1690 cm.$^{-1}$, and its acetate, though not the free phenol, shows the characteristic aldehyde band at 2700 cm.$^{-1}$. This suggested that B is the aldehyde corresponding to the primary alcohol A, and this was supported by reduction of B with lithium aluminium hydride, which gave compound A.

The less volatile fraction of the resin was separated into acidic and neutral fractions; the acidic fraction on esterification gave a crystalline methyl ester, reduced by lithium aluminium hydride to compound A, thus identifying the acid as an oxidation product of totarol, and confirming that compound A is a primary alcohol and compound B an aldehyde.

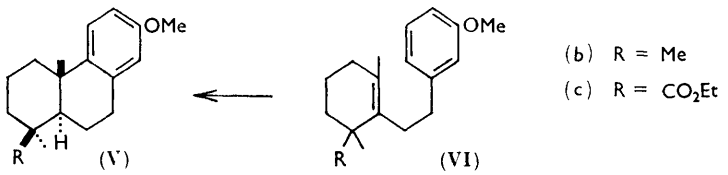
It remained to decide which of the methyl groups in totarol is oxidised in these compounds. By analogy with known resin acids it seemed very probable that the carboxyl group in the acid is attached to position 4 of the nucleus, and the resistance of the ester to hydrolysis suggested that the ester group is in the axial β position, so that the acid is (Ia). This assignment is supported by the optical rotatory dispersion curve of the aldehyde (IIIa), measured by Professor Klyne,[1] which shows a negative Cotton effect, the reverse of that given by 4α-aldehydes of the triterpene series.[2]

A preliminary account of this work has already been published,[3] a description of compound A has also been published by Wenkert and Beak,[4] and compounds A and B have been described by Cambie and Mander.[5] These authors deduce the same stuctures as given here.

The argument given above depends on the unproved assumption that the carboxyl group in the acid is attached to C-4. Confirmation of this was therefore sought in a total synthesis. Haworth and Moore [6] have synthesised the corresponding deisopropyl compound by cyclisation of the olefin (VIc), and although the configuration of the product

[1] Klyne, personal communication.
[2] Djerassi, Osiecki, and Closson, *J. Amer. Chem. Soc.*, 1959, **81**, 4587.
[3] Taylor, *Chem. and Ind.*, 1961, 1712.
[4] Wenkert and Beak, *Tetrahedron Letters*, 1961, 358.
[5] Cambie and Mander, *Chem. and Ind.*, 1961, 1877.
[6] Haworth and Moore, *J.*, 1946, **633**.

was not investigated only one isomer was obtained. Barltrop and Day [7] have repeated this work in more detail, and using a different method of cyclisation obtained two isomers, of which one was shown to be (Vc), having the configuration ascribed here to the acid from *Podocarpus mannii*. The 12-methoxy-isomer of (Vc) was also synthesised by Haworth and Moore,[6] who again obtained only one isomer. This has been re-investigated by King, King, and Topliss,[8] who showed that other isomers were also produced, and that one of the products is ethyl *O*-methylpodocarpate, which has the same stereochemistry.



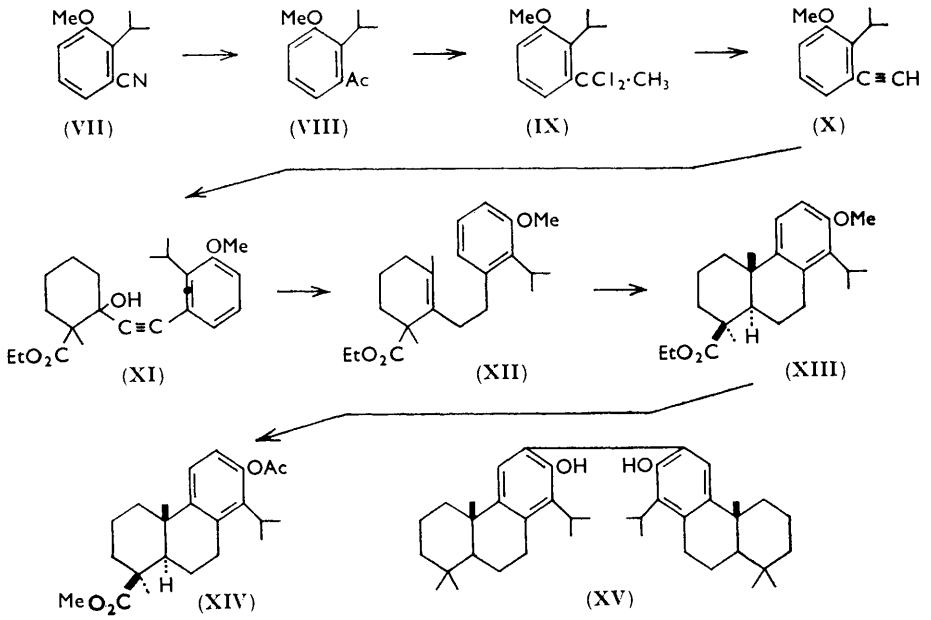
Haworth and Moore synthesised the intermediate olefin (VIc) by the reaction of ethyl 1,3-dimethyl-2-oxocyclohexane-1-carboxylate with *m*-methoxyphenethylmagnesium bromide, but the Grignard reaction with such hindered ketones gives only a small yield, and it has been shown by Barltrop and Day that a much better yield is obtained by the use of the magnesium derivative of *m*-methoxyphenylacetylene. Metal derivatives of the appropriate acetylene have also been used by Barltrop and Rogers [9] in the case of compound (VIb) and by King, King, and Topliss [10] in the case of the *p*-methoxy-isomer of (VIb). This method was therefore followed.

2-Isopropyl-3-methoxybenzonitrile (VII) is readily available [11] by the action of isopropylmagnesium bromide on 2,3-dimethoxybenzonitrile. The nitrile group in this compound is very unreactive, but with methyl-lithium 2-isopropyl-3-methoxyacetophenone (VIII) was obtained. This was converted into 3-ethynyl-2-isopropylanisole (X) by reaction first with phosphorus pentachloride in benzene, and then with sodamide in liquid ammonia. The acetylene was then treated with ethyl 1,3-dimethyl-2-oxocyclohexane-1-carboxylate. Unfortunately, reaction occurred to a large extent between the ethynyl group and the ester carbonyl group rather than the ketone. This was shown by the fact that the crude product contained an unsaturated carbonyl group, absorbing strongly in the infrared region, which could not have arisen in any other simple way. The relative intensity of the infrared absorption of this unsaturated carbonyl grouping and the saturated ester group which characterised the required product varied with the conditions used for the reaction, and trials indicated that sodamide in liquid ammonia gave the most favourable results. A considerable amount of the acetylene was recovered unchanged, indicating that in this case, as in the Grignard reactions referred to, the ketone reacts largely in the enolic form.

Distillation of the product gave two fractions, the lower-boiling one containing more of the unsaturated carbonyl compound than the other. The separation was only partial, but it was considered that a complete separation could be obtained more easily later by use of the fact that only the required product contained an ester group. The higher-boiling fraction was therefore hydrogenated over palladised charcoal to give the saturated alcohol. This was dehydrated with formic acid to the olefin (XII), which was cyclised with sulphuric acid in acetic acid.[6] The crude cyclisation product (XIII) was dealkylated with pyridinium chloride, and the acidic fraction of the product isolated. This crystallised readily, but as the acetate methyl ester of the natural product was known to crystallise much better than the free hydroxy-acid, the crude product was acetylated and then

[7] Barltrop and Day, *J.*, 1959, 671.
[8] King, King, and Topliss, *Chem. and Ind.*, 1956, 113.
[9] Barltrop and Rogers, *J.*, 1958, 2566.
[10] King, King, and Topliss, *J.*, 1957, 573.
[11] Richtzenhain and Nippus, *Chem. Ber.*, 1944, **77**, 566.

esterified with diazomethane. Crystallisation from methanol then gave methyl (±)-13-acetoxy-14-isopropylpodocarpa-8,11,13-trien-16-oate (XIV). The infrared spectrum of this compound in methylene chloride was identical with that of the optically active isomer. No other isomer was obtained from the mother liquors. Hydrolysis with 10% alcoholic



potash removed the acetyl group, giving methyl (±)-13-hydroxy-14-isopropylpodocarpa-8,11,13-trien-16-oate (IVa). The infrared spectrum of this compound in methylene chloride was also identical with that of its optically active isomer. Reduction of the (±)-acetate methyl ester with lithium aluminium hydride gave (±)-14-isopropylpodocarpa-8,11,13-triene-13,16-diol (IIIa). The spectrum of this in a Nujol mull was very similar to that of the optically active isomer, but the compound was not soluble enough to permit measurement of the spectrum of a solution. Acetylation gave the (±)-diacetate, the spectrum of which in methylene chloride was identical with that of the natural isomer.

Examination of the mother liquors from the crystallisation of totarol gave mostly more totarol, but a small amount of another substance was obtained as a crystalline acetate, $C_{18}H_{24}O_3$, m. p. 245°. The infrared spectrum of this compound indicated that it was a phenolic acetate and contained another carbonyl group. Nothing is yet known of its structure. The infrared spectrum of the final residues after repeated chromatography showed bands suggesting the presence of a phenol different from totarol, ferruginol, or the above compound, but this has not been obtained crystalline.

The non-acidic fraction of the involatile resin gave a crystalline phenol after chromatography; the analytical results agree with the formula $C_{40}H_{56}O_2$. The ultraviolet spectrum showed maxima at 213, 254, and 289 mμ, similar to that of 2,2-dihydroxybiphenyl, which has maxima at 211, 242, and 283 mμ. The spectrum of the acetate was quite different, showing a maximum at 218 mμ, with a shoulder at 274 mμ. This suggests that the compound is a biphenyl derivative, and that, in the acetate, steric hindrance prevents conjugation of the rings. 2,2-Dihydroxybiphenyl diacetate has a maximum at 231 mμ; clearly the extent of conjugation and hence the spectrum will depend on the nature of the other substituents in the molecule. It is considered that this substance is probably 12,12′-bitotaryl (XV).

Addendum.—The author is grateful to one of the Referees for pointing out that the

assigned configurations at C-4 are in agreement with the known molecular rotation difference for 4-carboxylic acids in the ferruginol series.[12] In this series [13-OH, 14-Pr^i) the $[M]_D$ values are: 4,4-dimethyl, +123°; 4-methoxycarbonyl, +409°. In the ferruginol series (12-OH, 13-Pr^i) $[M]_{5461}$ values are: 4,4-dimethyl, +106°; 4β-methoxycarbonyl (12-OMe) +426°; 4α-methoxycarbonyl (12-OMe), +299°.

Experimental

Extraction of Podocarpus mannii.—Finely powdered timber of *Podocarpus mannii* (223 kg.; Herbarium specimens are preserved as Forest Herbarium Ibadan No. 51693) was percolated exhaustively with boiling light petroleum (b. p. 60—80°). The extract was concentrated and the gummy residue (1895 g.; 0·85%) was distilled in a vacuum. After a small forerun, a main fraction (1380 g., 0·62%) was collected at 210—240°/5 mm. The residue after cooling was a hard resin. The distillate, which crystallised on cooling, was recrystallised from heptane to give a solid, m. p. 120—154°. This was placed on a column of alumina (1 kg.) and percolated with benzene until no more was eluted. Concentration of the eluate and crystallisation from heptane gave totarol (IVa) (620 g.) as massive prisms, m. p. and mixed m. p. 127—128°. The column was then stripped with ethyl acetate giving a crystalline mixture (40 g.) which was chromatographed on alumina (1 kg.). Benzene–ether eluted crystalline material of variable m. p.; ether eluted 14-*isopropylpodocarpa*-8,11,13-*triene*-13,16-*diol* (IIa) (22·7 g.; 0·01%) which crystallised from toluene as very long needles, m. p. 225—227° (Found: C, 79·4; H, 9·8. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%), $\lambda_{max.}$ (in methanol) 280 mμ (log ε 3·19), $[\alpha]_D^{22}$ (in methanol) +44°. The *diacetate* crystallised from methanol in plates, m. p. 131—132° (Found: C, 74·5; H, 9·0. $C_{24}H_{34}O_4$ requires C, 74·6; H, 8·9%), $[\alpha]_D^{22}$ (in methanol) +46°.

The more readily eluted material was combined and chromatographed again on alumina. The first fractions, eluted with benzene–hexane, gave totarol (12·6 g.); benzene–ether then gave a substance crystallising from heptane in needles (3·3 g.), m. p. 170—175°, which showed a strong carbonyl band in the infrared spectrum. This was rechromatographed on alumina (100 g.); benzene–hexane eluted small amounts of totarol; benzene–ether eluted 16-*oxototarol* (IIIa) (1·075 g., 0·0005%), rhombs, m. p. 185—187° (from heptane–toluene) (Found: C, 79·75; H, 9·2. $C_{20}H_{28}O_2$ requires C, 79·95; H, 9·4%), $[\alpha]_D^{20}$ (in methanol) +76°, $\nu_{max.}$ (in Nujol) 1690 cm.$^{-1}$. The *acetate* formed prisms, m. p. 135—136°, from methanol (Found: C, 76·6; H, 8·75. $C_{22}H_{30}O_3$ requires C, 77·15; H, 8·8%), $[\alpha]_D^{20}$ (in methanol) +75°, $\nu_{max.}$ (in Nujol) 1700, 1750, 2700 cm.$^{-1}$.

The mother liquors from all fractions of the distillate were combined and acetylated; crystallisation of the product from methanol gave totarol acetate (445 g.), m. p. 121—122°. The mother liquors were combined and chromatographed in hexane on alumina. The main part was eluted very easily and remained gummy. Ether–hexane eluted a *substance* (450 mg.) crystallising from methanol in needles, m. p. 245° (Found: C, 75·1, 74·85; H, 8·3, 8·5; O, 16·7; 16·75%; sap. equiv., 300. $C_{18}H_{24}O_3$ requires: C, 75·0; H, 8·4; O, 16·6%; *M*, 288), $\nu_{max.}$ (in Nujol) 1695, 1760 cm.$^{-1}$; $\lambda_{max.}$ (in methanol) 266 mμ (log ε 3·0). Hydrolysis of this with alkali gave an amorphous phenol; $\nu_{max.}$ (in Nujol) 1680 cm.$^{-1}$; $\lambda_{max.}$ (in methanol) 277mμ (log ε 3·7), from which the original substance was recovered on acetylation.

The easily eluted fraction was hydrolysed; chromatography gave a further amount of totarol (total yield including that isolated as acetate 1095 g., 0·49%) and amorphous material.

The resinous distillation residue (515 g.) was dissolved in benzene and extracted with aqueous sodium hydroxide. Acidification of the extract gave an amorphous solid (107 g.) which was dissolved in methanol (100 ml.) and water (100 ml.) containing potassium hydroxide (28 g.). Dimethyl sulphate (50 ml.) was then added and the solution boiled briefly. The acidic fraction was separated and treated again in the same way. The combined neutral product was crystallised from methanol to give *methyl* 13-*hydroxy*-14-*isopropylpodocarpa*-5,11,13-*trien*-16-*oate* (Ia) (14·1 g.) as prisms, m. p. 198° (Found: C, 76·0; H, 9·0. $C_{21}H_{30}O_3$ requires: C, 76·3; H, 9·15%), $[\alpha]_D^{20}$ (in methanol) +124°. The *acetate* crystallised from methanol in prisms, m. p. 160—161° (Found: C, 73·9; H, 9·0. $C_{23}H_{32}O_4$ requires C, 74·2; H, 8·7%), $[\alpha]_D^{20}$ (in methanol) +121°. The mother liquors from the crystalline ester were chromatographed in hexane on alumina. Hexane eluted methyl 13-methoxy-14-isopropylpodocarpa-8,11,13-trien-16-oate (Ib) (980 mg.), identical with a specimen described later; benzene eluted more of the hydroxy-acid methyl ester (2·1 g.). The noncrystalline fractions were acetylated;

[12] Campbell and Todd, *J. Amer. Chem. Soc.*, 1940, **62**, 1287; 1942, **64**, 928.

crystallisation from methanol–methylene chloride gave the methyl ester acetate (5·75 g.: total yield calculated as hydroxy-ester 22·2 g., 0·01%).

The non-acidic fraction of the resin was chromatographed in hexane on alumina. The early fractions crystallised from hexane to give fine needles, m. p. 200—220°. Rechromatography of this material and elution with hexane gave a compound, probably 12,12′-*bitotaryl* (XV) (21 g.), which formed fine needles, m. p. 229—231° from heptane (Found: C, 81·45; H, 10·2; O, 8·6. $C_{40}H_{58}O_2,H_2O$ requires C, 81·6; H, 10·3; O, 8·15%. Found, after being dried in a vacuum: C, 83·7; H, 10·1; O, 6·2. $C_{40}H_{58}O_2$ requires C, 84·15; H, 10·2; O, 5·6%); $\lambda_{max.}$ (in methanol) 218 mμ (log ε 4·52), 254 mμ (log ε 4·03), 289 mμ (log ε 3·75); $[\alpha]_D^{20}$ (in chloroform) +41°. The *acetate* crystallised from pyridine in needles, m. p. 235° (Found: C, 81·0; H, 9·4; O, 9·8. $C_{44}H_{62}O_4$ requires C, 80·7; H, 9·5; O, 9·8%); $\lambda_{max.}$ (in methanol) 218 mμ (log ε 4·43), shoulder 272—276 mμ (log ε 3·11); $[\alpha]_D^{20}$ (in chloroform) +55°.

14-*Isopropylpodocarpa*-8,11,13-*triene*-13,16-*diol* (IIa).—(*a*) Methyl 13-hydroxy-14-isopropylpodocarpa-8,11,13-trien-16-oate (Ia) (1·0 g.) in ether was added to lithium aluminium hydride (1·0 g.) in ether. The mixture was decomposed with dilute hydrochloric acid, and the ether layer washed with water and evaporated. Crystallisation from toluene gave the diol (800 mg.) as needles, m. p. and mixed m. p. 222—227°, identical in infrared spectrum (in Nujol) with the first sample.

(*b*) 16-Oxototarol (IIa) (132 mg.) in ether was added to lithium aluminium hydride (100 mg.) in ether as above. Crystallisation from benzene gave the diol (120 mg.), m. p. and mixed m. p. 227°. The infrared spectrum (in Nujol) was identical with that of the original sample.

Methyl 14-*Isopropyl*-13-*methoxypodocarpa*-8,11,13-*trien*-16-*oate* (Ib).—Potassium (1 g.) was dissolved in t-butyl alcohol (100 ml.) and the hydroxy-ester (Ia) (3·0 g.) added, followed by methyl iodide (10 ml.). After ½ hr. the solvent was removed in a vacuum, and the residue taken up in ether and water. Evaporation of the ether layer left a residue which crystallised from pentane to give the *methyl* 13-*methoxy-ester* (Ib) (2·04 g.) as fluffy needles, m. p. 56° (Found: C, 76·6; H, 9·3. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·4%). This ester is very soluble and difficult to crystallise.

14-*Isopropyl*-13-*methoxypodocarpa*-8,11,13-*trien*-16-*ol* (IIIb).—(*a*) Potassium (0·3 g.) was dissolved in t-butyl alcohol (30 ml.), and the diol (IIa) (1·2 g.) added, followed by methyl iodide (3 ml.). After 2 hr. the solution was evaporated, the residue taken up in water and ether, and the ether layer evaporated The residue was chromatographed on alumina (35 g.). Hexane–ether eluted the 13-*methoxy–alcohol* (IIb) (0·75 g.), crystallising from methanol in fine matted needles, m. p. 128—130° (Found: C, 79·1; H, 10·1. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%), $[\alpha]_D^{20}$ (in methanol) +38°.

(*b*) The methyl ether methyl ester (Ib) (1·0 g.) in ether was added to a solution of lithium aluminium hydride (1·0 g.) in ether. The product (850 mg.) was isolated in the usual way and was identical with the above sample.

14-*Isopropyl*-13-*methoxypodocarpa*-8,11,13-*trien*-16-*one* (III).—The methoxy-alcohol (IIb) (700 mg.) was dissolved in acetone (10 ml.) and oxidised with chromic acid solution (8N; 0·6 ml.). After ½ hr. the solution was diluted with water and ether, the ether layer evaporated, and the product crystallised from propanol to give 14-*isopropyl*-13-*methoxypodocarpa*-8,11,13-*trien*-16-*one* (III) (475 mg.) as prisms, double m. p. 88—90° and 108° (Found: C, 80·2; H, 9·5. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%); $[\alpha]_D^{22}$ (in methanol) +76°, $\nu_{max.}$ (in Nujol) 1708, 2700 cm.$^{-1}$.

O-*Methyltotarol* (Ib).—The methoxy-aldehyde (IIIb) (800 mg.), hydrazine hydrate (1 ml.), and diethylene glycol (10 ml.) were refluxed briefly, potassium hydroxide (2 g.) was added, and the whole refluxed for 2 hr. The solution was diluted with ether and dilute hydrochloric acid, the ether layer evaporated, and the partly crystalline residue remethylated with potassium t-butoxide and methyl iodide. After the addition of water and ether, the ether layer was evaporated, and the residue crystallised from propanol, giving totarol methyl ether (Ib) (450 mg.) as prisms, m. p. 90—93° (m. p. of a mixture with material prepared by methylation of totarol with potassium t-butoxide and methyl iodide, 92—95°) (Found: C, 83·9; H, 10·7. Calc. for $C_{21}H_{32}O$: O, 83·9; H, 10·7%). The infrared spectrum in Nujol was identical with that of the authentic specimen.

2-*Isopropyl*-3-*methoxyacetophenone* (VIII).—2-Isopropyl-3-methoxybenzonitrile (VII) (142 g.) [11] was added to a solution of methyl-lithium [from lithium (17 g.) and excess of methyl bromide in ether (1 l.)]. After 1 hr., dilute hydrochloric acid was added, and the ether layer washed with water and evaporated. Distillation of the residue gave 2-isopropyl-3-methoxyacetophenone

(VIII) (86 g., 55%) as an oil, b. p. 140°/5 mm., $\nu_{max.}$ (film) 1685 cm.$^{-1}$ (no nitrile band). The *dinitrophenylhydrazone* crystallised from methanol in yellow prisms, m. p. 157—158° (Found: C, 58·0; H, 5·5; N, 15·1. $C_{18}H_{20}N_4O_5$ requires C, 58·1; H, 5·4; N, 15·05%). The *semicarbazone* formed fine matted needles, m. p. 210—212°, from methanol (Found: C, 62·1; H, 7·4; N, 16·75. $C_{13}H_{19}N_3O_2$ requires C, 62·6; H, 7·7; N, 16·9%).

3-*Ethynyl*-2-*isopropylanisole* (X).—To a mixture of the ketone (VIII) (85 g.) and benzene (25 ml.) was added phosphorus pentachloride (100 g.). Reaction proceeded slowly with a slight rise in temperature, and after 8 hr. most of the phosphorus pentachloride had dissolved. The reaction mixture was then poured on ice and ether, and the organic layer washed with ice–water, dried, and concentrated under reduced pressure. The residue in ether (500 ml.) was addded slowly to a suspension of sodamide [prepared from sodium (32 g.) and liquid ammonia (1·5 l.) with a little ferric chloride]. After 2 hr. ammonium chloride (100 g.) was added, and then water. The ether layer was separated, washed with water, and concentrated. Distillation of the residue gave 3-*ethynyl*-2-*isopropylanisole* (X) (60 g., 77%), b. p. 112°/10 mm. (Found: C, 82·4; H, 8·4. $C_{12}H_{14}O$ requires C, 82·7; H, 8·1%); $\nu_{max.}$ (film) 3300 cm.$^{-1}$; $\lambda_{max.}$ (in methanol) 240 mμ (log ε 3·79), 290 mμ (log ε 3·14), 297 mμ (log ε 3·14); η_D^{20} 1·5410. The *mercuric derivative* formed needles, m. p. 150°, from benzene (Found: C, 52·7; H, 4·8. $C_{24}H_{26}O_2Hg$ requires C, 52·7; H, 4·75%).

Methyl (±)-13-*Acetoxy*-14-*isopropylpodocarpa*-8,11,13-*trien*-16-*oate* (XIV).—Sodium (8 g.) was dissolved in liquid ammonia (1 l.) containing a small amount of ferric chloride. To the suspension of sodamide thus obtained 3-ethynyl-2-isopropylanisole (58 g.) in ether (200 ml.) was added, followed by ethyl 1,3-dimethyl-2-oxocyclohexanecarboxylate (75 g.) in ether (200 ml.). The mixture was left for 2 hr., acidified with ammonium chloride, and diluted with water. The organic layer was separated, washed with water, and distilled. The condensation product (58 g.) was collected at *ca.* 200°/3 mm. Unchanged ethynylisopropylanisole (22 g.) was recovered from the low-boiling fraction by way of the mercuric derivative. Redistillation of the condensation product gave two fractions; the first (26 g.), b. p. 180°/2 mm., showed very intense absorption at 1670 cm.$^{-1}$; the second (30 g., 22%), b. p. 200—210°/2 mm., had less strong absorption at this wave-number. This fraction was dissolved in methanol and hydrogenated over palladised charcoal; after filtration and evaporation of the solvent the product was refluxed with formic acid (200 ml.) for 45 min., the solution diluted with water, and benzene, and the organic layer washed until neutral and evaporated. Distillation of the residue gave an oil (22 g.), b. p. 195—204°/1 mm., that showed no hydroxyl band in the infrared region. This was dissolved in acetic acid (180 ml.) and sulphuric acid (7 ml.) and refluxed for 1 hr. The solution was diluted with ether and water, and the ether layer washed with small amounts of sodium hydroxide until neutral. The sodium hydroxide washings were acidified, and the oil which separated was isolated with ether, esterified with diazomethane, and added to the main neutral fraction. This was evaporated, and the residue distilled in a vacuum. The product (16 g.), b. p. 190°/1 mm., was mixed with pyridinium chloride (16 g.) and refluxed for 1 hr. The product was taken up in methanol, the solution diluted with benzene and water, and the acidic fraction isolated with aqueous sodium hydroxide. There was also a large neutral fraction which showed no carbonyl band in its infrared spectrum. The acidic fraction, which crystallised, was acetylated with pyridine and acetic anhydride, and the crystalline acetate acid esterified with diazomethane. Crystallisation from methanol gave *methyl* (±)-13-*acetoxy*-14-*isopropylpodocarpa*-8,11,13-*trien*-16-*oate* (XIV) (2·70 g., 12% on the crude condensation product) as prisms, m. p. 157—158° (Found: C, 74·1; H, 8·7. $C_{23}H_{32}O_4$ requires C, 74·2; H, 8·7%). The infrared spectrum in methylene chloride was identical with that of the natural isomer.

Methyl (±)-13-*Hydroxy*-14-*isopropylpodocarpa*-8,11,13-*trien*-16-*oate* (Ia).—The acetoxy-ester (XIV) (0·4 g.), potassium hydroxide (1·0 g.), and ethanol (95%; 10 ml.) were refluxed for 1 hr. The solution was diluted with water and ether, the ether layer concentrated, and the residue crystallised from methanol to give *methyl* (±)-13-*hydroxy*-14-*isopropylpodocarpa*-8,11,13-*trien*-16-*oate* (Ia) (310 mg.) as prisms, m. p. 186—187° (Found: C, 76·8; H, 9·1. $C_{21}H_{30}O_3$ requires: C, 76·3; H, 9·15%). The infrared spectrum in methylene chloride was identical with that of the natural isomer.

14-*Isopropylpodocarpa*-8,11,13-*triene*-13,16-*diol* (IIa).—The acetoxy-ester (XIV) (262 mg.) in ether was added to a solution of lithium aluminium hydride (200 mg.) in ether (20 ml.). After ½ hr. the mixture was decomposed with dilute hydrochloric acid, and the ether layer was

evaporated. The product was taken up in benzene and chromatographed on alumina (10 g.). Ether eluted the (±)-13,16-*diol* (IIa) (195 mg.), crystallising from toluene in needles, m. p. 205° (Found: C, 79·3; H, 10·15. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%). The infrared spectrum in Nujol was very similar to, but not identical with that of the natural isomer. The (±)-diacetate formed plates, m. p. 123—124°, from methanol. The infrared spectrum of this in methylene chloride was identical with that of the natural isomer.

DEPARTMENT OF CHEMISTRY,
UNIVERSITY COLLEGE, IBADAN, NIGERIA.

[*Received, March 22nd,* 1962.]