Tetrahedron, 1963, Vol. 19, pp. 985 to 994. Pergamon Press Ltd. Printed in Northern Ireland

SYNTHETIC STUDIES ON RESIN ACIDS—V[1]

SYNTHESIS OF THREE ISOMERS OF DEHYDROABIETIC ACID[1a]

M. SHARMA[1b], U. RANJAN GHATAK[1c] and P. CHANDRA DUTTA[1d]

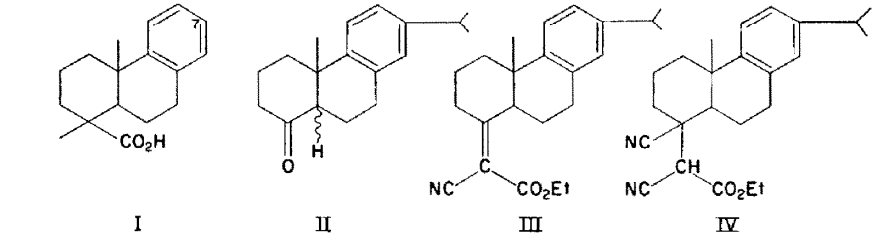
Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta-32

Abstract—Synthesis of three stereoisomers of dehydroabietic acid has been described and these together with the isomer, synthesized by Stork consitute the entire series, theoretically possible. Stereochemistry of these isomers has been placed on a firm basis.

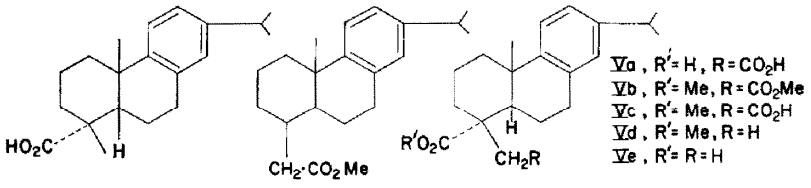
IN PREVIOUS publications[1,2], the synthesis of the four theoretically possible stereoisomers of desisopropyldehydroabietic acid (I) has been described and their stereochemistry determined. Preliminary studies[1] in the synthesis of dehydroabietic acid and its three stereoisomers by the introduction of the isopropyl group at C_7- in I were not encouraging and different routes for the synthesis of the three stereoisomers of dehydroabietic acid were developed. These acids together with the isomer synthesized by Stork *et al*[3], constitute the entire series.

For the synthesis of one of these isomers, the following scheme is presented:

The ketone (II), synthesized by Stork[4] was found in subsequent studies to be



I II III IV



Ia VI

[1] Part IV. U.R. Ghatak, D. K. Datta and S. C. Ray, *J. Amer. Chem. Soc.*, **82**, 1728 (1960).

[1a] A preliminary report on a part of this investigation has already been published (M. Sharma, *Tetrahedron Letters*, **23**, 1, 1960).

[1b] Present address: Department of Chemistry, Tufts University, Medford 55, Mass., U.S.A.

[1c] Present address: Department of Chemistry, St. John's University, Jamaica-32., N.Y., U.S.A.

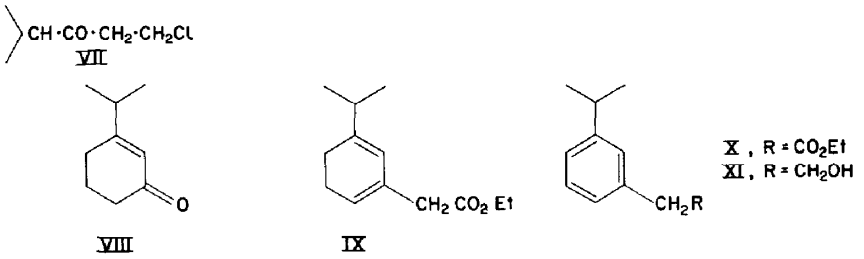
[1d] Any communication regarding this paper may be sent to this author.

[2] N. N. Saha, B. K. Ganguli and P. C. Dutta, *J. Amer. Chem. Soc.*, **81**, 3670, (1959).

[3] G. Stork and J. W. Schulenberg, *J. Amer. Chem. Soc.*, **84**, 284 (1962).

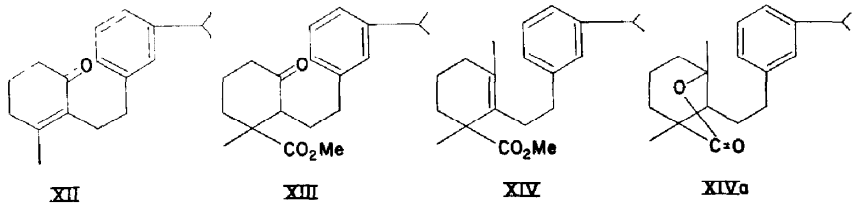
[4] G. Stork and A. Burgstahler, *J. Amer. Chem. Soc.* **73**, 3544, (1951).

stereochemically heterogeneous[5]. Considerable quantities of the ketone (II) as well as the unsaturated ketone (XII) were necessary, and the original method[4] has been modified with improvement in yield, and simplification of the experimental procedures. An important starting material, *β*-(*m*-isopropylphenyl)-ethyl alcohol (XI)[6], was made by reduction of the ester (X) which in turn was prepared in good yield according to the following scheme:



Condensation of *β*-chloroethyl isopropyl ketone (VII) with ethyl acetoacetate afforded the ketone[7] (VIII) on acidic hydrolysis and simultaneous ring-closure. This was condensed with ethyl bromoacetate to afford the doubly unsaturated ester (IX) and this was next dehydrogenated[8] by heating with sulphur.

The ester (X) was isolated in pure state free from sulphur by boiling with freshly precipitated copper in benzene and after reduction the alcohol (XI) was converted to bromide[6] and the latter condensed with 4-carbethoxy-3-methyl-Δ^2-cyclohexenone in the presence of potassium-t-butoxide to yield after hydrolysis the unsaturated ketone[4] (XII). This was cyclized to the ketone[4] (II) and condensed[9] with ethyl cyanoacetate

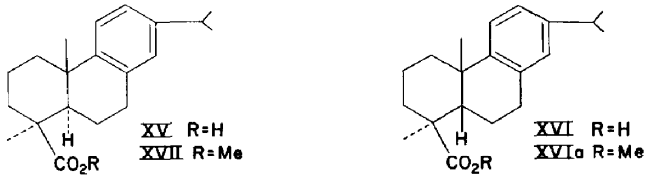


to yield III, isolated in moderate yield as a highly viscous gum. 1:4-Addition of hydrocyanic acid to III was difficult but hydrolysis of the dicyano-ester (IV) gave the dibasic acid (Va) melting at 202°. No isomeric acids could be detected in the mother liquors. The dibasic acid was esterfied to Vb and the latter on partial hydrolysis under mild alkaline conditions yielded the half-ester (Vc), which was converted to the silver salt. The dry silver salt was subjected to Hunsdiecker's degradation[10] but as most of the starting material was recovered, this was again treated but only a poor yield of the desired neutral material was obtained. This was heated

[5] J. A. Barltrop and N. A. J. Rogers, *J. Chem. Soc.*, 2566 (1958), and the references cited therein.
[6] R. D. Haworth and R. L. Barker, *J. Chem. Soc.* 1299 (1939).
[7] A. J. Birch and S. M. Mukherjee, *J. Chem. Soc.* 2531 (1949).
[8] J. C. Bardhan and D. Nasipuri, *J. Chem. Soc.* 350, (1956).
[9] E. J. Cragoe, Jr., C. M. Robb and J. M. Sprague, *J. Org. Chem.*, **15**, 381 (1950).
[10] cf. R. G. Johnson and R. K. Ingham, *Chem. Rev.*, 219 (1956).

with zinc dust in acetic acid to remove aliphatic bromine but it was also necessary to heat with freshly distilled acetamide and zinc dust[11] to remove bromine in the aromatic nucleus. The product was refluxed with methanolic potassium hydroxide to remove VI, which may have been formed by trans-esterification of succinic acid half-ester residue (Vc). The gummy residue finally obtained, analysed well for the methyl ester (Vd), although it could not be obtained in a crystalline state, but hydrolysis under vigorous alkaline conditions yielded the desired acid (Ve) melting at 167–168°. This acid melts at 130–135° and 147–154° when mixed with the isomeric acids, melting at 155° and 202° respectively (*vide infra*). Its non-identity with the isomer of dehydroabietic acid synthesized by Stork[3] has been established by Prof. Burgstahler by mixed melting point and determination of a different crystalline structure. As the diagnostic procedure developed by Wenkert[12] for detecting *cis*-locking of rings in octahydrophenanthrenes is not decisive in all cases, the stereoformula (Ia) was assigned by a process of elimination, after direct comparison with the other isomers. This conclusion is supported by the fact that desisopropyl tricyclic ketone, after a similar sequence of reactions, yields an acid[2] melting at 146–147° and having the *cis* ring-junction.

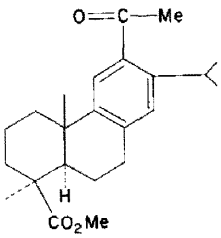
The synthesis of the two isomeric acids XV and XVI, in which the carboxyl group and the angular methyl group are *cis*, was achieved according to the following scheme and the related stereochemistry has been established.



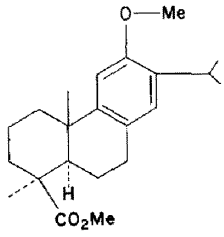
The addition of potassium cyanide to the ketone[4] (XII) followed by alkaline hydrolysis and subsequent esterification with diazomethane[1,13] afforded the ester (XIII) in good yield. After reaction with methylmagnesium iodide the crude carbinol was dehydrated[14] with oxalic acid in boiling toluene solution. The product, a complex mixture from infra-red studies, exhibited a band at 5·67 μ, characteristic of a γ-lactone and indicating the presence of XIVa in appreciable amounts. It was cyclized by heating with polyphosphoric acid and the neutral and acidic fractions were separated. The acidic fraction was separated into two acids melting at 202° and 155°, and further characterized by their methyl esters melting at 98–99° and 62° respectively. From the rate of hydrolysis[15] of the methyl ester (XVII), m.p. 98–99°, it appeared that the acid melting at 202°, is represented by the stereoformula XV. This assignment is supported by oxidation[12] with chromic acid to the mono-keto ester (XX), characterized by the 2,4-dinitrophenylhydrazone and suggesting thereby a *trans*-locking of the rings as proposed earlier. From the methyl ester, m.p. 62°, when subjected to oxidation under identical conditions, no α-diketone[12] could be isolated, considerable decomposition

[11] D. Heyl and A. C. Cope, *J. Amer. Chem. Soc.*, **65**, 669 (1943).
[12] E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.* **80**, 211 (1958).
[13] J. O. Jilek and M. Protiva, *Coll. Czeck. Chem. Comm.*, **23**, 692 (1958).
[14] Y. Klibansky and D. Ginsburg, *J. Chem. Soc.*, 1293 (1957).
[15] W. P. Campbell and D. Todd, *J. Amer. Chem. Soc.*, **64**, 928 (1942).

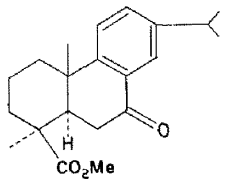
taking place. The acid, m.p. 155°, yields retene on selenium dehydrogenation and this reveals the presence of a perhydrophenanthrene nucleus in the molecule. As the monoketo-compound[16] can also be isolated from a *cis*-octahydrophenanthrene derivative, the stereo-chemistry of the acid melting at 202° was established by converting XVII to XIX by the following series of reactions:



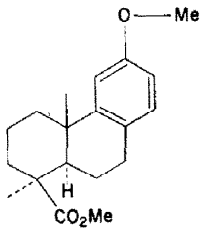
XVIII



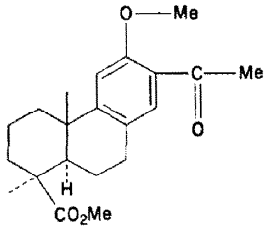
XIX



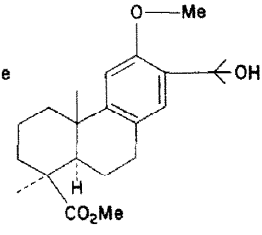
XX



XXI

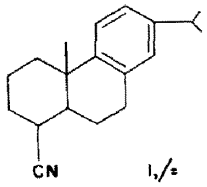


XXII

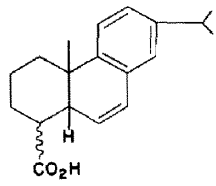


XXIII

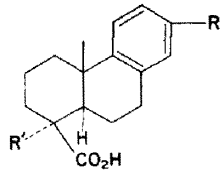
The methyl ester (XVII) reacted with acetyl chloride to afford XVIII which was subjected to oxidation,[17] the acetoxy derivative hydrolysed and the product on treatment with diazomethane yielded XIX after purification. An authentic specimen of XIX was prepared by condensing the methyl ether of methyl DL-podocarpate[1] (XXI) with acetyl chloride and reacting the acetyl compound (XXII) with methylmagnesium iodide to form XXIII. This was dehydrated[18] and the unsaturated compound on catalytic hydrogenation afforded (XIX) identical in all respects with XIX previously prepared and, therefore, establishing the stereoformula XV for the acid, m.p. 202°.



XXIV



XXV

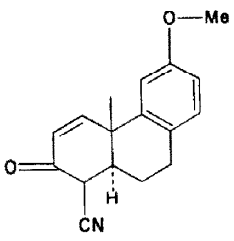


XXVI, R'= Me, R = H
XXVIa, R'= H, R = P_{γ}^{β}

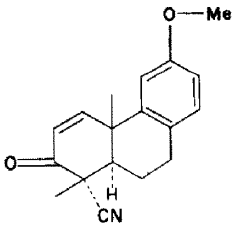
This assignment was further substantiated by measurement of the apparent dissociation constant, kindly carried out by Dr. Simon.[19] The acid, m.p. 202°, has pK_a 8·46; comparable to the value, 8·4–8·5, recorded for the podocarpic acid system as

[16] J. A. Barltrop and A. C. Day, *J. Chem. Soc.*, 671, (1959).
[17] S. L. Friess, *J. Amer. Chem. Soc.*, **71**, 14 (1949).
[18] W. P. Campbell and D. Todd, *J. Amer. Chem. Soc.* **62**, 1287 (1940)
[19] P. F. Sommer, V. P. Arya and W. Simon, *Tetrahedron Letters*, No. **20**, 18 (1960).

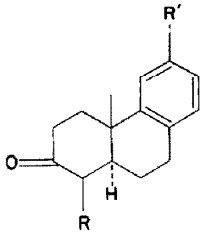
distinct from the value, 8·0–8·1, exhibited by abietic acid and its congeners. The measurement of the dissociation constant of the acid, m.p. 155°, did not lead to any definite conclusion. Few comparable standards are as yet available for *cis*-locked analogous resin acids. Moreover, synthesis of the methyl ester corresponding to XIX could not be achieved utilizing the acid, m.p. 207[1] which has the stereochemical formula XXVI. An independent synthesis of the acid, m.p. 155°, was developed according to the reactions successfully applied for the synthesis of XXVI[1].



XXVII



XXVIII



XXIX , R = CN , R' = OMe
XXX , R = CO_2Me, R' = H

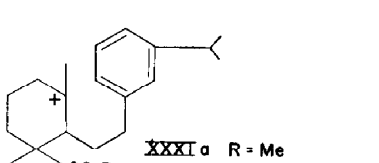
The crude unsaturated nitrile (XXIV) obtained from the ketone (II), by dehydration of the corresponding cyanhydrin, was hydrolysed to the acid (XXV), m.p. 178°, with U.V. absorption at 268 mμ, characteristic of the styrene system and a *cis*[1,20,21] ring junction. The acid was reduced catalytically to XXVIa and the latter methylated at the α-position[1], through its t-amyl ester leading ultimately to an acid, melting at 155°, alone or mixed with the sample already described. This not only establishes definitely the *cis* ring-junction of the acid (XVI), but also the *cis*-relationship of the angular methyl and the tertiary carboxyl group as depicted in the structure XVI, arising as it does from approach of the entering methyl group at α-position of the carboxylic group from the side opposite to the angular methyl group, although the methylation step may not be entirely stereospecific.

It is important to note that methylation of the unsaturated keto-nitrile (XXVII) gave only one crystalline product (XXVIII)[22] in 80% yield where the attaching methyl group is from the same side as the axial methyl group. This may be attributed to the presence of the double bond which causes flattening of the ketonic ring. Shielding from alkylation by the angular methyl group thereby becomes sufficiently low to permit the electronically favoured axial attack to take place. In the saturated β-keto nitrile[22] (XXIX) or ester[23] (XXX) hindrance by the angular methyl group is increased, but not sufficiently to permit complete stereospecificity of the alkylation process, i.e. only from the less hindred equatorial side. This may be due to the presence of the β-carbonyl group. The axial attack is being favoured by maximum charge[24] overlap with the carbonyl and nitrile or ester of the carbanion from XXIX or XXX. This decreases the importance of steric repulsion of the angular methyl group as the only factor

[20] E. Wenkert and T. E. Stevens, *J. Amer. Chem. Soc.*, **78**, 2318 (1956).
[21] E. M. Fry, *J. Org. Chem.*, **22**, 1710 (1957).
[22] M. E. Kuehne, *J. Amer. Chem. Soc.*, **83**, 1492 (1961). cf. W. S. Johnson and D. Allen, Jr. *ibid*, **78**, 1261 (1957).
[23] E. Wenkert and A. Tahra, *J. Amer. Chem. Soc.* **82**, 3229 (1960).
[24] W. S. Johnson, *Chem. and Ind.*, 167 (1956).

in controlling the methylation. It may be that the alkylation of the carbanion from the ester of XXVIa is controlled only by the steric factor of the axial angular methyl group because of the absence of possible distortion arising from the double bond or the keto-group in the ring. The only crystalline product from the alkylation of t-amyl ester of XXVIa is from the equatorial methylation. Although no other alkylation product was isolated, the poor yield does not rule out the possibility of another isomer arising from axial alkylation.

The stereochemistry of the two acids (XV) and (XVI) is elucidated by the ring closure reaction with polyphosphoric acid. The acidic product isolated from the reaction mixture or from hydrolysis of the neutral material left after separation of the acidic product, reveals the presence of only two isomers (XV) and (XVI). Extensive chromatography of the crude methyl ester did not disclose the presence of any other product related to the two remaining isomers. This observation is quite significant because only a podocarpic acid system[25] could be generated from this reaction so far as the spatial orientation of the angular methyl and the tertiary carboxyl group is concerned. Appearance of *cis* and *trans* ring junction in the acids (XV) and (XVI) may arise from the comparative stability of the tertiary carbonium ion (XXXIa)



XXXI a R = Me
XXXI b R = Phosphoric acid residue

formed as a result of protonation of the double bond in XIV or with the opening of the lactone ring in XIVa leading to XXXIb.

EXPERIMENTAL

3-Isopropyl-Δ²-cyclohexenone (VIII). β-Chloroethyl isopropyl ketone (106 g, b.p. 117–125°/35–40 mm), prepared by passing dry ethylene gas through an ice-cooled solution of isobutyryl chloride (110 g) in dry chloroform (350 ml) containing anhydrous aluminium chloride (132 g), was condensed with ethyl acetoacetate (156 g) in the presence of sodium ethoxide from sodium (23 g) and ethanol (350 ml). The mixture was refluxed for 2 hr after standing at room temperature for 6 hr. It was cooled and poured into water containing hydrochloric acid (70 ml) and extracted with ether. The ethereal extract was washed with water, dried (Na_2SO_4) and the product (80 g) distilling at 80–120°/6–7 mm. collected. This was heated with a mixture of sulphuric acid (4 ml) and acetic acid (80 ml) until the evolution of carbon dioxide ceased, poured into ice-cold water (300 ml), neutralized with a conc sodium carbonate solution and extracted with ether. The product (60 g) distilled at 80–90°/6–7 mm. The 2,4-dinitrophenylhydrazone, m.p. 155°, was crystallized from ethyl acetate as red needles (Lit. m.p. 155°).

Ethyl isopropyl-cyclohexa-Δ¹,³-diene-3-acetate and/or its bond isomer (IX). To a mixture of isopropylcyclohexene-3-one (25 g) in benzene (100 ml) and zinc-wool (12·5 g), ethyl bromoacetate (25 g) was added and the mixture slowly heated on a water-bath till a vigorous reaction ensued. The reaction having slowed down, another lot of zinc (12·5 g) and ethyl bromoacetate (25 g) were added and the refluxing continued for 4 hr. It was decomposed with ice-cold dil. sulphuric acid. The desired product (30 g) was obtained, b.p. 125–130°/6–7 mm. (Found: C, 75·1; H, 9·3; $C_{13}H_{20}O_2$ requires: C, 75·0; H, 9·6%).

Ethyl m-*isopropylphenylacetate* (X). The above unsaturated ester (25 g) was heated with powdered

[25] S. A. Narang, and P. C. Dutta, *J. Ind. Chem. Soc.*, **38**, 576 (1961) and references cited therein.

sulphur (4·1 g) at 240–260° for 2 hr. The product was dissolved in benzene (100 ml) and boiled for 6 hr with freshly precipitated copper powder (5 g). The solution was filtered and the solvent evaporated. On distillation, it yielded a colourless product (15 g) at 105–110°/3–4 mm. (Found: C, 75·5; H, 8·6; $C_{13}H_{18}O_2$ requires C, 75·7; H, 8·7%).

1-*Keto*-7-*isopropyl*-12-*methyl*-1,2,3,4,9,10,11,12,-*octahydrophenanthrene* (II). To a solution of lithium aluminium hydride (3 g) in dry ether (150 ml), the above ester (20 g) was slowly added at room temp and the mixture refluxed for 3 hr. The product was worked up and on removal of the unreduced ester through hydrolysis with an excess of alcoholic potassium hydroxide solution (10%), the desired alcohol (13·5 g) distilled at 95–100°/3–4 mm. (Lit. 134–138°/20 mm).

The condensation product (51 g) from Hagemann's ester (44 g) and β-(*m*-isopropylphenyl)-ethyl bromide (51 g) in presence of potassium t-butoxide (potassium, 9 g) in t-butanol, was decarboxylated by refluxing with an ethanolic solution of potassium hydroxide (130 ml, 15%) for 12 hr under a nitrogen atmosphere. The unsaturated ketone (30 g, b.p. 155–160°/0·2 mm) was cyclized by heating with a mixture of sulphuric acid (35 ml) and phosphoric acid (175 ml) at 120–125° for 12 hr. The product (20 g) distilled at 150–155°/0·25 mm. (Lit.[4] 155–160°/0·3 mm) and furnished an yellow 2,4-dinitrophenylhydrazone, m.p. 189° (Lit.[4] 189–190°).

Ethyl 7-*isopropyl*-12-*methyl*-1,2,3,4,9,10,11,12-*octahydrophenanthrylidene*-1-*cyanoacetate* (III). A mixture of the above tricyclic ketone (36 g), ethyl cyanoacetate (37 g), glacial acetic acid (16 ml.), benzene (70 ml) and ammonium acetate (2 g) was refluxed for 60 hr with constant separation of water, formed during the reaction. During this period, 2 g lots (total 12 g) ammonium acetate were added after every 12 hr. It finally afforded a pale-yellow viscous liquid (15 g), b.p. 205–210°/0·3 mm; λ_{max}^{alc} 234 mμ; log ε 4·1. (Found: C, 79·0; H, 8·6; $C_{23}H_{29}O_2N$ requires: C, 78·6; H, 8·3%).

Ethyl 7-*isopropyl*-12-*methyl*-1,2,3,4,9,10,11,12-*octahydrophenanthrene*-1-*cyano*-1-*cyanoacetate* (IV). Potassium cyanide (9 g) dissolved in water (20 ml) and diluted with ethanol (50 ml) was added to the above unsaturated cyano-ester (15 g) and the whole refluxed for 24 hr. Conc hydrochloric acid (8 ml) was added to the cooled mixture and after 30 min excess dil. hydrochloric acid was added and the reaction mixture extracted with chloroform. On removal of the solvent and evaporative distillation of the residue, the dicyano-ester (10 g) was obtained as a thick glassy solid boiling at 200–215°/0·4 mm. (Found: C, 75·8; H, 8·3; $C_{24}H_{30}O_2N_2$ requires: C, 76·1; H, 8·0%).

7-*Isopropyl*-12-*methyl*-1,2,3,4,9,10,11,12-*octahydrophenanthrene*-1-*carboxy*-1-*acetic acid* (Va). A solution of the above dicyano-ester (15 g), in conc sulphuric acid (60 ml), water (60 ml). and glacial acetic acid (60 ml) was slowly refluxed in an oil-bath for 7 hr. It was cooled and poured into ice-cold water and extracted with chloroform. The acidic product was isolated by repeatedly washing with 10% aqueous sodium carbonate solution. The alkaline washings were acidified with hydrochloric acid and the acidic material was crystallized from acetic acid. From the residue after evaporation of the chloroform layer, further quantity of the acidic material was obtained on repeated treatment with potassium cyanide as before and subsequent acidic hydrolysis. Total yield of the acid was 7 g, m.p. 202°. (Found: C, 73·1; H, 8·0; $C_{21}H_{28}O_4$ requires: C, 73·2; H, 8·1%).

Methyl 7-*isopropyl*-12-*methyl*-1,2,3,4,9,10,11,12-*octahydrophenanthrene*-1-*methoxycarbonyl*-1-*acetate* (Vb). The above dicarboxylic acid (7 g) was dissolved in methanol (20 ml) and esterified with an ethereal solution of diazomethane. The ester was isolated as a colourless highly viscous mass (6·5 g), b.p. 175–180°/0·2 mm. (Found: C, 74·1; H, 8·8; $C_{23}H_{32}O_4$ requires: C, 74·2; H, 8·6%).

7-*Isopropyl*-12-*methyl*-1,2,3,4,9,10,11,12-*octahydrophenanthrene*-1-*carbomethoxy*-1-*acetic acid*(Vc). A mixture of potassium hydroxide (1·4 g) in water (1·4 ml) and the above diester (6 g) in methanol (25 ml) was allowed to stand at room temp for 2 hr and then refluxed on a steam-bath for 2 hr. Steam was passed through the acidified mixture to remove methanol and the reaction mixture extracted with ether. The ethereal extract was washed with 5% aqueous sodium carbonate solution. On acidification of the alkaline extract, the white crystalline solid (5 g) separated and was crystallized from methanol; m.p. 159–160°. (Found: C, 73·9; H, 8·5; $C_{22}H_{30}O_4$ requires: C, 73·7; H, 8·4%).

7-*Isopropyl*-1,12-*dimethyl*-1,2,3,4,9,10,11,12-*octahydrophenanthrene*-1-*carboxylic acid* (Ve). The above ester-acid (7·2 g) dissolved in methanol (80 ml) was neutralized with N NaOH. Silver nitrate (4 g) in water (100 ml) was added slowly under constant stirring. The precipitated salt was washed repeatedly until free from nitrate and finally dried *in vacuo*, at 100° for 8 hr. To the dry silver salt (8 g) suspended in dry carbon tetrachloride (150 ml), a solution of bromine (1·2 ml) in carbon tetrachloride (10 ml) was slowly added with constant stirring under reflux. Refluxing was continued until the colour of bromine completely disappeared. The precipitated silver bromide was filtered off

and washed with carbon tetrachloride. The residue left after removal of the solvent was dissolved in ether and washed with a solution of sodium carbonate (10%), water and dried. The crude neutral material (1·3 g) was boiled for 7 hr with acetic acid (20 ml) and zinc-dust (2 g). The mixture was cooled, diluted with water and extracted with ether. The ethereal solution was washed with sodium carbonate solution (5%), dried (Na_2SO_4) and the solvent evaporated. The residue was then heated with a mixture of freshly distilled acetamide (3 g) and zinc-dust (1 g) at 200–205° for 3 hr and the product worked up. The neutral fraction was again boiled with methanolic potassium hydroxide (10 ml, 10%) for 3 hr and the product worked up in the usual way. The neutral residue on evaporative distillation at 120–130°/0·2 mm afforded a clear thick liquid (1 g). (Found: C, 80·2; H, 9·5; $C_{21}H_{30}O_2$ (methyl ester) requires: C, 79·9; H, 9·7%). This was refluxed for 6 hr under nitrogen with a solution of potassium hydroxide (0·6 g) in water (0·6 ml) and ethylene glycol (4 ml). The reaction mixture was cooled, poured into dil. hydrochloric acid and extracted with ether. The ethereal solution was washed with a solution (10%) of sodium carbonate and water. From alkaline washings on acidification with hydrochloric acid, a gummy product was obtained and distilled at 160–180°/0·6 mm. On treatment with methanol, it solidified and on crystallization from the same solvent, it afforded the desired acid, m.p. 167–168°. (Found: C, 80·0; H, 9·5; $C_{20}H_{28}O_2$ requires: C, 80·0; H, 9·3%).

2-(m-*Isopropylphenethyl*)-3-*methyl*-3-*carbomethoxy-cyclohexanone* (XIII). A mixture of 2-(*m*-isopropylphenethyl)-3-methylcyclohexenone (XII, 45 g) in alcohol (400 ml) and potassium cyanide (45 g) in water (200 ml) was refluxed for 10 hr. On cooling a solution of potassium hydroxide (65 g) in water (700 ml) was added and then refluxed for 60 hr. Excess of cold dil. hydrochloric acid was cautiously added and an oily layer separated. The aqueous portion was extracted with ether. The combined organic layer was washed repeatedly with a solution of sodium hydroxide (5%) in order to isolate the acidic material. The combined alkaline washings on acidification were extracted with ether and the solvent removed. The thick residue so obtained was esterified with an ethereal solution of diazomethane. The neutral product (35 g) distilled at 195°/0·4 mm. (Found: C, 75·5; H, 8·7; $C_{20}H_{28}O_2$ requires: C, 75·9; H, 8·9%).

It gave a 2,4-dinitrophenylhydrazone which was obtained as fine yellow needles from ethyl acetate–ethanol, m.p. 151°. (Found: C, 62·9; H, 6·4; N, 11·3; $C_{26}H_{32}O_6N_4$ requires: C, 62·8; H, 6·3; N, 11.27%).

2-(m-*Isopropylphenethyl*)-1,3-*dimethyl*-1-*carbomethoxy*-Δ^2-*cyclohexene* (XIV). To an ice-cold solution of the above keto-ester (34 g) in dry ether (100 ml.), an ethereal solution of Grignard's reagent, prepared from magnesium (3·2 g) and methyl iodide (11 ml), was slowly added with shaking. Stirring was continued for 2 hr more, in the cold. Towards the end, temp was raised to room temp, and the yellow mass decomposed with cold dil hydrochloric acid and extracted with ether. The residue after evaporation of the solvent was dissolved in toluene (120 ml) and refluxed with oxalic acid (15 g) with constant separation of water. The mixture was poured into water, the toluene layer separated and the aqueous layer extracted with benzene. The combined organic layer was washed with a solution of sodium carbonate (10%) and water. On removal of the solvent, the neutral residue distilled at 190–195°/0·4 mm, yield 30 g. (Found: C, 79·6; H, 9·2; $C_{21}H_{30}O_2$ requires: C, 80·2; H, 9·6; $C_{20}H_{28}O_2$. *Lactone* XIVa; requires: C, 80·0; H, 9·4%).

7-*Isopropyl-desoxypodocarpic acid* (XV). To the above unsaturated ester (30 g) was added with vigorous stirring, polyphosphoric acid, prepared from phosphorous pentoxide (75 g) and syrupy phosphoric acid (65 ml, 89%). After keeping at 90–100° for 1 hr the mixture was poured into ice-cold water and extracted with ether. The ethereal solution was washed repeatedly with sodium hydroxide solution (5%) and then with water. The alkaline washings were slowly acidified in the cold with conc hydrochloric acid. A white solid (2 g) was crystallized from methanol, m.p. 202°. (Found: C, 80·1; H, 9·2; $C_{20}H_{28}O_2$ requires: C, 80·0; H, 9·4%).

Methyl 7-*isopropyldesoxypodocarpate* (XVII). The methanolic solution of the above acid (XV, 1·3 g) was treated with an ethereal solution of diazomethane in the usual way. The solid neutral product (1·2 g) was crystallized from methanol, m.p. 98–99°. (Found: C, 79·7; H, 9·5; $C_{21}H_{30}O_2$ requires: C, 80·2; H, 9·6%).

7-*Isopropyldesoxy*-cis-*podocarpic acid* (XVI). The mother liquor, after separation of the acid, m.p. 202°, furnished on concentration, another acidic material (1 g) which crystallized from methanol, m.p. 155°. (Found: C, 80·3; H, 9·7; $C_{20}H_{28}O_2$ requires; C, 80·0; H, 9·4%).

The acid (200 mg, m.p. 155°) was heated with selenium (500 mg) at 340–350° for 12 hr and the hydrocarbon was found to be retene (30 mg), m.p. 97°, alone or mixed with an authentic sample.

Ether was distilled off from the ethereal solution left after removal of acids, m.p. 202° and 155°, described above. The neutral glassy residue (10 g), b.p. 180–190°/0·3 mm., was refluxed with a butanolic solution of potassium hydroxide (18 g, 10%) for 10 hr. The reaction mixture, on acidification and removal of butanol by steam distillation, was extracted with ether and the acidic material obtained as a glassy mass on evaporative distillation at 180–200°/0·3 mm. This crystallized from methanol in the cold, m.p. 155° (750 mg). The acidic mother-liquor (1·8 g) left after separation of the above crystals was converted to methyl ester by treatment with diazomethane and purified by chromatography through neutral alumina (50 g). A white crystalline solid (XVIa, 800 mg) was crystallized from methanol m.p. 62.° (Found: C, 80·5; H, 9·4; $C_{21}H_{30}O_2$ requires: C, 80·2; H, 9·6%).

The neutral gummy residue (2 g) left after hydrolysis with butanolic potassium hydroxide, was again hydrolysed by heating with potassium hydroxide (2 g) and diethylene glycol (20 ml) for 5 hr under a nitrogen atmosphere. The acidic portion afforded the acid (200 mg), m.p. 202°, alone or mixed with the sample, described before.

Methyl-9-keto-7-isopropyl-desoxypodocarpate (XX). To the methyl ester (200 mg; m.p. 98–99°) dissolved in acetic acid (5 ml) was slowly added with occasional shaking, a solution of chromium trioxide (250 mg) in acetic acid (3 ml) and the solution, left at room temp for 18 hr. The mixture was poured into water (25 ml), saturated (sodium chloride) and extracted with chloroform. The chloroform layer was washed with a cold solution (5%) of sodium hydroxide and water. On evaporation the residue furnished an orange-red 2,4-dinitropehnylhydrazone, (ethyl acetate), m.p. 200°. (Found: C, 64.1; H, 6·2; N, 10·8; $C_{27}H_{32}O_6N_4$ requires: C, 63·8; H, 6·3; N, 11·1%).

Methyl 7-isopropyl-6-acetyl-desoxypodocarpate (XVIII). To an ice-cold solution of methyl 7-isopropyldesoxypodocarpate (1·1 g) in nitrobenzene (8 ml.), anhydrous aluminium chloride (1·3 g) was added slowly. The mixture was stirred thoroughly and acetyl chloride (0·6 ml.) added dropwise in the cold and left for an hr and at room temp for 17 hr. It was poured into ice-cold dil. hydrochloric acid (50 ml, 10%) and nitrobenzene removed by steam distillation. The ethereal extract was washed with a solution (5%) of sodium carbonate, water and dried (Na_2SO_4). The crude neutral product was converted to the semicarbazone (m.p. 255°). The semicarbazone was washed with light petroleum ether and then decomposed by refluxing with dil. hydrochloric acid (10%) for 2 hr and finally extracted with ether yielding a white crystalline solid (0·5 g). It was crystallized from methanol, m.p. 141°, λ_{max}^{alc} 257 mμ, log ϵ 3·9. (Found: C, 77·4; H, 8·8; $C_{23}H_{32}O_3$ requires: C, 77·5; H, 9·0%).

It formed a 2,4-dinitrophenylhydrazone, orange needles (ethyl acetate), m.p. 214°. (Found: C, 64·8; H, 6·8; $C_{29}H_{36}O_6N_4$ requires: C, 64·9; H, 6·7%).

Methyl O-methyl-7-isopropylpodocarpate (XIX). To a cold solution of methyl 7-isopropyl-6-acetyl-desoxy-podocarpate (0·5 g) in chloroform (10 ml) was added a chloroform solution of perbenzoic acid (0·7 g) with shaking. The mixture was kept in the dark at 10° for 48 hr and afterwards at room temp for 72 hr. The chloroform solution was washed with a solution (5%) of sodium carbonate and then with water. The gummy residue left after removal of chloroform was refluxed with a solution of potassium hydroxide (500 mg) dissolved in water (30 ml) and ethanol (500 ml) for 4 hr. The mixture was cooled, added to dil. hydrochloric acid and extracted with ether. The residue after removal of the solvent was dissolved in methanol and treated with an ethereal solution of diazomethane. The neutral product was obtained as a clear glassy solid (140–160°/0·3 mm) on evaporative distillation, and finally afforded a crystalline solid (50 mg) when purified by passing through neutral alumina (10 g) and on eluting with petroluem ether (40–60°). It crystallized from methanol as flakes, m.p. 130–132°. (Found C, 76·4; H, 9·6; $C_{22}H_{32}O_3$ requires: C, 76·6; H, 9·4%).

Methyl O-methyl-7-acetylpodocarpate (XXII). Methyl O-methylpodocarpate (3 g) obtained from methyl podocarpate by treatment with diazomethane was dissolved in nitrobenzene (30 ml) containing acetyl chloride (1·8 ml). Anhydrous aluminium chloride (3 g) was added slowly in small portions to the above reaction mixture cooled to 0° during 15 min with constant shaking, and finally kept in the cold (10–15°) for 100 hr. Towards the end of the reaction, the mixture turned dark red and was kept at room temp for 5 hr. It was poured into ice-cold dil. hydrochloric acid (150 ml; 10%) and nitrobenzene removed by distilling with steam. The product was extracted with ether, and converted to a semicarbazone. The semicarbazone was decomposed by refluxing with dil. hydrochloric acid (30 ml; 10%) for 2 hr. The oily product was extracted with ether and distilled (200–220°/0·6 mm). It afforded a white crystalline solid (1 g) from methanol, m.p. 124°. (Found: C, 73·4; H, 8·3; $C_{21}H_{28}O_4$ requires: C, 73·2; H, 8·1%).

The 2, 4-dinitrophenylhydrazone separated as orange needles (ethyl acetate), m.p. 265°. (Found: C, 61·9; H, 6·3; $C_{27}H_{32}O_7N_4$ requires: C, 61·8; H, 6·1%).

Methyl O-*methyl*-7-(1′-*methyl*-1′-*hydroxyethyl*)-*podocarpate*(XXIII). An ice-cold solution of the above keto-ester (900 mg) in dry ether (20 ml) was treated with an ethereal solution of Grignard reagent prepared from magnesium (0·25 g) and methyl iodide (1 ml) and worked up in the usual way. The product afforded a crystalline solid (500 mg) on treatment with methanol and was re-crystallized from the same solvent, m.p. 148°. (Found: C, 73·3; H, 8·9; $C_{22}H_{32}O_4$ requires: C, 73·3; H, 8·9%).

Methyl O-*methyl*-7-*isopropylpodocarpate* (XIX). The above hydroxy-ester (400 mg) was boiled with glacial acetic acid (15 ml) for 20 min. The mixture was cooled and hydrogenated in presence of palladium-charcoal (100 mg; 10%). After the up-take of the calculated quantity of hydrogen within 15 min, it was poured into water and extracted with ether. The product was crystallized from methanol, m.p. 131–132°, alone or mixed with an authentic sample described earlier; yield 105 mg. (Found: C, 76·6; H, 9·4; $C_{22}H_{32}O_3$ requires: C, 76·7; H, 9·4%).

7-*Isopropyl*-12-*methyl*-1,2,3,4,11,12-*hexahydrophenanthrene*-1-*carboxylic acid* (XXV). 1-Keto-7-isopropyl-12-methyl-1,2,3,4,9,10,11,12-octahydrophenanthrene(II, 15 g) dissolved in ethanol (20 ml) was treated at −10° with hydrocyanic acid from potassium cyanide(100 g) and sulphuric acid (200 ml; 1:1). The crude cyanhydrin (18 g) was dried *in vacuo* and dissolved in pyridine (10 ml) and to the well-cooled solution, thionyl chloride (8 ml) was added slowly with occasional shaking. The mixture was heated gradually over steam-bath for 2 hr. It was poured into ice-cold dil. hydrochloric acid and extracted with chloroform. The unsaturated nitrile (XXIV) (5 g, b.p. 190–200°/0·6 mm) was heated at 200–210° with potassium hydroxide (2 g) in diethylene glycol (18 ml) under nitrogen atmosphere for 6 hr. The mixture was acidified with cold dil. hydrochloric acid, and the gummy acidic material on evaporative distillation at 190–210°/0·5 mm, yielded a hard glassy mass, which crystallized from ethanol, m.p. 178°. λ_{max}^{alc} 268 mμ log ϵ 3·90, yield 3 g. (Found: C, 80·2; H, 8·75; $C_{19}H_{24}O_2$ requires: C, 80·2; H, 8·5%).

7-*Isopropyl*-12-*methyl*-1,2,3,4,9,10,11,12-*octahydrophenanthrene*-1-*carboxylic acid* (XXVIa). The above unsaturated acid (3 g) dissolved in ethanol (30 ml) was hydrogenated over 10% palladium charcoal (200 mg). The product solidified on removal of the solvent and the residue crystallized from aqueous ethanol, m.p. 185°. (Found: C, 79·65; H, 9·04; $C_{19}H_{26}O_2$ requires: C, 79·68; H, 9·15%).

7-*Isopropyl*-1,12-*dimethyl*-1,2,3,4,9,10,11,12-*octahydrophenanthrene*-1-*carboxylic acid* (XVI). To a cooled suspension of potassium-t-amylate (potassium 2·5 g) in ether, an ethereal solution of the acid chloride from the above acid (2·7 g) was added slowly with occasional shaking. It was allowed to stand at room temp for an hr, refluxed for 2 hr, and then decomposed by pouring in water and extracted with ether. On removal of the solvent, the crude t-amyl ester (2·5 g) was dried *in vacuo*, and dissolved in ether (30 ml). This was added with constant stirring to a solution of potassium amide from potassium (2 g) in liquid ammonia (250 ml). The colour turned chocolate-red and after 1 hr methyl iodide (10 ml) in ether (10 ml) was added dropwise whereupon the colour discharged. Ammonia was allowed to evaporate slowly and the residue decomposed with water, and extracted with ether. The resulting product (2 g) was remethylated four times under identical conditions. The product (1·1 g) was finally dissolved in dioxane (10 ml) containing conc. hydrochloric acid (15 ml) and the whole refluxed for 3 hr. The acidic product was obtained as deep-red gummy mass which was further purified by boiling with charcoal in ethanol. It was finally allowed to crystallize in the cold. The crystals (*c* 100 mg) separated slowly and on recrystallization melted at 154–155°, alone or mixed with the acid described before. (Found: C, 80·2; H, 9·6; $C_{20}H_{28}O_2$ requires: C, 80·0; H, 9·4%).

Acknowledgement—Our thanks are due to Dr. W. Simon, E. T. H., Zürich, for pK_a measurements and helpful discussions. One of us (M. S.) thanks the C.S.I.R., Goverment of India for financial assistance. Micro-analyses of the samples described in this communication have been carried out by Mrs. Chhabi Dutta and ultraviolet measurements by Mr. A. Ghosal.