132. *Podocarpic Acid. Synthesis of* 6- *and* 7-*Methoxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic Acids.*

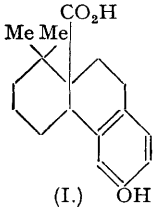
By Robert D. Haworth and Barry P. Moore.

6-*Methoxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic acid* and the isomeric 7-*methoxy acid* have been synthesised from ethyl 2 : 6-dimethyl*cyclo*hexanone-2-carboxylate and β-(4-methoxyphenyl)ethyl bromide and β-(3-methoxyphenyl)ethyl bromide respectively by applications of the method used by Haworth and Barker (*J.*, 1939, 1299) in the synthesis of dehydroabietic acid. The constitutions of both acids have been confirmed

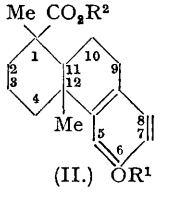
by dehydrogenation with selenium to the 6- and 7-methoxy-1-methylphenanthrenes, which have been identified by comparison with authentic specimens.

The absorption spectra of the two acids have been determined and compared with that of *O*-methylpodocarpic acid. 6-Methoxy-1 : 12-dimethyloctahydrophenanthrene-1-carboxylic acid and *O*-methylpodocarpic acid yield identical curves, and are therefore regarded as stereoisomers.

OUDEMANS (*Ber.*, 1873, **6**, 1122; *Annalen*, 1873, **170**, 214; *J. pr. Chem.*, 1874, **9**, 385) first isolated podocarpic acid, $C_{17}H_{22}O_3$, from the resin of *Podocarpus cupressinus*, and the acid was subsequently isolated (Easterfield and Aston, *Trans. New Zealand Inst.*, 1904, **36**, 483; 1910, **42**, 53; 1911, **43**, 53) from other members of the Podocarpus and Dacrydium species. Oudemans showed that podocarpic acid was a monobasic hydroxy-acid capable of nitration and sulphonation, which yielded "methanthrene," $C_{15}H_{12}$, on distillation with zinc dust, and a variety of products, including *p*-cresol, on distillation of the calcium salt. Radcliffe, Sherwood, and Short (*J.*, 1931, 2293) showed that "methanthrene" was identical with 1-methylphenanthrene, and later (*J.*, 1938, 1006) Sherwood and Short established the phenolic character of podocarpic acid and their studies on the molecular refraction of the acid indicated a tricyclic system containing three ethylenic linkages. The production of 6-methoxy-1-methylphenanthrene by dehydrogenation of the *O*-methyl ether of podocarpic acid was explained by formula (I) or (II; $R^1 = R^2 = H$) of which the former was preferred by Sherwood and Short on account of the inert character of the carboxyl group in podocarpic acid.



(I.)



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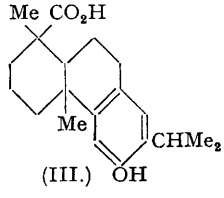
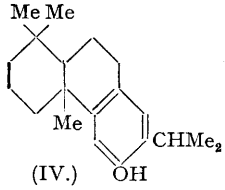
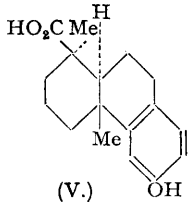


(III.)

Fieser and Campbell (*J. Amer. Chem. Soc.*, 1939, **61**, 2528) suggested that structure (II; $R^1 = R^2 = H$) had several advantages, and that 7-*iso*propylpodocarpic acid might be identical with 6-hydroxydehydroabietic acid (III). Campbell and Todd (*ibid.*, 1940, **62**, 1287) converted methyl *O*-methylpodocarpate (II; $R^1 = R^2 =$ Me) into 7-*iso*propylpodocarpic acid which differed from 6-hydroxydehydroabietic acid (III), but subsequently (*ibid.*, 1942, **64**, 928) it was shown that the two acids both yielded ferruginol (IV) when the carboxyl group was converted, *via* the aldehyde, into the methyl group. Consequently, podocarpic acid must be represented



(IV.)



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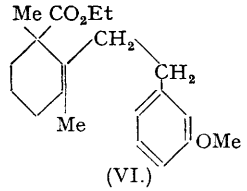
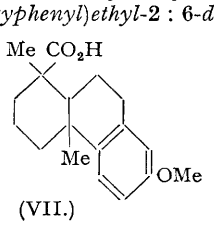


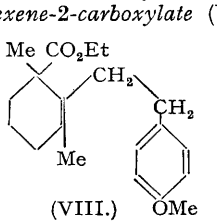
(VI.)

either by formula (II; $R^1 = R^2 = H$) or by an alternative obtained by interchanging the carboxyl and the angle methyl group. Reduction of podocarpic acid to the corresponding carbinol, followed by Wagner–Meerwein rearrangement and selenium dehydrogenation, yielded 6-methoxy-1-ethylphenanthrene. Campbell and Todd concluded therefore that podocarpic acid has structure (II; $R^1 = R^2 = H$), which conforms to the general structure of the resin acids, and they suggest that podocarpic and dehydroabietic acids both contain the *trans*-decalin structure but differ in configuration at carbon atom 1. In order to account for marked steric hindrance in podocarpic acid the configuration shown in (V) was suggested.

As a first step in the synthetical confirmation of their views, an optically inactive form of *6-methoxy-1 : 12-dimethyloctahydrophenanthrene-1-carboxylic acid* (II; $R^1 = Me$; $R^2 = H$) has been synthesised by the reactions previously employed (Haworth and Barker, *J.*, 1939, 1299) in the synthesis of a racemic modification of dehydroabietic acid. Preliminary experiments made with β-(3-methoxyphenyl)ethylmagnesium bromide and ethyl 2 : 6-dimethyl*cyclo*hexanone-2-carboxylate yielded a carbinol, which was dehydrated by boiling with formic acid to *ethyl* 1-β-(3-*methoxyphenyl*)*ethyl*-2 : 6-*dimethyl*-Δ⁶-cyclo*hexene*-2-*carboxylate* (VI). Cyclisation of this



(VII.)



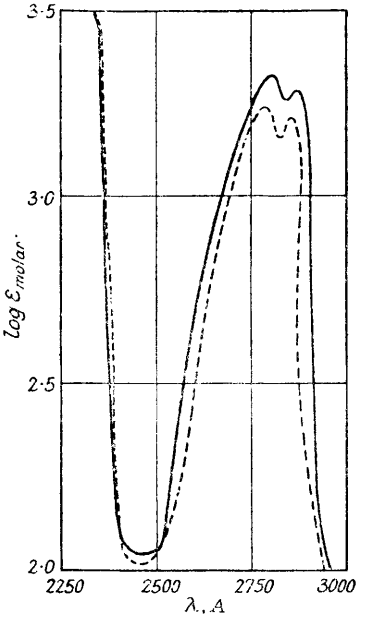
(VIII.)

*cyclo*hexene proceeded readily with acetic–sulphuric acid to give *7-methoxy-1 : 12-dimethyloctahydrophenanthrene-1-carboxylic acid* (VII), m. p. 171—173°, which yielded 7-methoxy-1-methylphenanthrene on selenium

dehydrogenation, thus excluding the alternative structure with a 5-methoxyl group. The absorption spectrum (Figure) determined in methyl alcoholic solution, whilst similar to that of *O*-methylpodocarpic acid, shows sufficient displacement to justify this method of comparison as a criterion of structural identity or divergence.

The Grignard reagent from β-(4-methoxyphenyl)ethyl bromide reacted with ethyl 2 : 6-dimethyl*cyclo*hexanone-2-carboxylate to yield a carbinol which gave *ethyl* 1-β-(4-*methoxyphenyl*)*ethyl*-2 : 6-*dimethyl*-Δ^6-cyclo*hexene*-2-*carboxylate* (VIII) on dehydration with formic acid. Owing to the unfavourable position of the methoxyl group, cyclisation of this *cyclo*hexene derivative was expected to occasion some difficulty. This was indeed the case, and ring closure necessitated prolonged boiling with acetic–sulphuric acid. The resultant 6-*methoxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic acid* (II; R^1 = Me; R^2 = H) gave 6-methoxy-1-methylphenanthrene on selenium dehydrogenation, and the absorption spectrum, determined in methyl alcoholic solution by Dr. F. B. Strauss (Oxford), was indistinguishable from that of *O*-methylpodocarpic acid under similar conditions (Figure). Demethylation of 6-methoxy-1 : 12-dimethyloctahydrophenanthrene-1-carboxylic acid proved unexpectedly difficult, and could only be effected smoothly by treatment with boiling hydriodic acid and acetic anhydride in an atmosphere of carbon dioxide. 6-*Hydroxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic acid* (II; R^1 = R^2 = H), m. p. 258°, was obtained and exhibited close chemical similarity with podocarpic acid.

Resolution experiments are in progress but until these are completed it is not possible to decide whether the synthetic acid (II; R^1 = R^2 = H) represents racemic podocarpic acid or a diastereoisomeric modification.



—— O-*Methylpodocarpic acid and* 6-*methoxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic acid*

------ 7-*Methoxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic acid.*

Experimental.

Ethyl 1-β-(3-*methoxyphenyl*)*ethyl*-2 : 6-*dimethyl*-Δ^6-cyclo*hexene*-2-*carboxylate* (VI). Th Grignard reagent from β-(3-methoxyphenyl)ethyl bromide (6 g.), magnesium (0·66 g.), and ether (40 c.c.) was cooled in ice, and an ice-cold solution of ethyl 2 : 6-dimethyl*cyclo*hexanone-2-carboxylate (3 g.) in ether (5 c.c.) was added during 15 minutes. The mixture, after being kept at 0° for 15 minutes and overnight at room temperature, was decomposed with ice and ammonium chloride, volatile by-products were removed, and the residue distilled. The fraction, b. p. 170—180° (oil-bath)/0·1 mm., was refluxed with anhydrous formic acid (20 c.c.) for 30 minutes, poured into water, and the product isolated with ether. The *ester* (VI) was isolated as an oil, b. p. 130—140° (oil-bath)/0·1 mm., which decolourised bromine in chloroform solution (Found: C, 76·8; H, 8·9. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·8%).

7-*Methoxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic acid* (VII). Cyclisation of the above ester (VI) (2 g.) was readily effected by refluxing with glacial acetic acid (20 c.c.) and concentrated sulphuric acid (½ c.c.) for 1 hour. The mixture was poured into water, partially neutralised with sodium hydroxide, and the product isolated with ether. Removal of the ether gave an oil containing both the required acid and its ethyl ester. The mixture was hydrolysed by heating with excess of 25% alcoholic potassium hydroxide for 12 hours at 150°, poured into water, and neutral impurities removed in ether. Acidification of the alkaline layer afforded the crude acid, which was distilled in a vacuum. 7-*Methoxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic acid* (VII), b. p. 170—180° (oil-bath)/0·005 mm., crystallised from aqueous methyl alcohol in colourless prisms (0·5 g.), m. p. 171—173° (Found: C, 75·4; H, 8·5. $C_{18}H_{24}O_3$ requires C, 75·0; H, 8·3%). The acid was soluble in aqueous alkali to give a crystalline sodium salt (plates from brine), and did not decolourise bromine solutions. The methoxy-acid (VII) (0·1 g.) was heated with selenium (0·125 g.) for 46 hours at 320—340°, cooled, and extracted with chloroform. The extract was distilled over sodium in a vacuum and yielded 7-methoxy-1-methylphenanthrene, m. p. 132—133°, undepressed by admixture with an authentic specimen.

Ethyl 1-β-(4-*methoxyphenyl*)*ethyl*-2 : 6-*dimethyl*-Δ^6-cyclo*hexene*-2-*carboxylate* (VIII). The Grignard reagent, prepared from β-(4-methoxyphenyl)ethyl bromide (9 g.) and magnesium (1 g.), in ether (30 c.c.), was condensed with ethyl 2 : 6-dimethyl*cyclo*hexanone-2-carboxylate (4·5 g.) in ether (10 c.c.) exactly as in the previous series, and the product distilled. The fraction distilling at 170—180° (oil-bath)/0·1 mm. was refluxed with anhydrous formic acid (20 c.c.) for 30 minutes, and the mixture was poured into water. The *ester* (VIII) (3 g.), isolated with ether, was obtained as an oil, b. p. 135—145° (oil-bath)/0·1 mm., which decolourised bromine in chloroform solution (Found: C, 75·7; H, 8·6. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·8%).

6-*Methoxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic acid* (II; R^1 = Me; R^2 = H). The above unsaturated ester (VIII) was unaffected by stannic chloride in carbon disulphide solution. Treatment with aluminium chloride in carbon disulphide solution, followed by hydrolysis of the product with alkali under pressure, gave a small yield of the required acid. Cyclisation was best effected by refluxing the ester (VIII) (2 g.) with glacial acetic acid (12 c.c.) and concentrated sulphuric acid (½ c.c.) for 5 hours. The product was hydrolysed by heating with excess of 25% alcoholic potassium hydroxide for 12 hours at 150°, poured into water, and neutral impurities extracted with ether. Acidification of the alkaline layer afforded the crude acid, which was distilled in a vacuum. The saturated *acid* (II; R^1 = Me; R^2 = H), b. p. 190—200° (oil-bath)/0·005 mm., crystallised from ligroin (b. p. 60—80°) or aqueous methyl alcohol in colourless prisms, m. p. 194—195° (Found: C, 74·7; H, 8·4. $C_{18}H_{24}O_3$ requires C, 75·0; H, 8·3%). The acid was soluble in aqueous sodium bicarbonate solution to give a crystalline sodium salt (colourless plates from water). The *methyl* ester (II; R^1 = R^2 = Me), prepared in quantitative yield from the acid and diazomethane in ethereal solution, crystallised from ligroin in colourless plates, m. p. 128—129° (Found: C, 75·2; H, 8·7. $C_{19}H_{26}O_3$ requires C, 75·5; H, 8·6%). The *p-nitrobenzyl* ester, prepared from the sodium salt and *p*-nitrobenzyl bromide, crystallised from methyl alcohol in colourless plates, m. p. 128° (Found: C, 70·9; H, 7·1. $C_{25}H_{29}O_5N$ requires C, 70·9; H, 6·9%). The methoxy-acid (II; R^1 = Me; R^2 = H) (0·1 g.) was heated with selenium (0·125 g.) for 46 hours at 320—340°, cooled, and the residue extracted

with chloroform. The extract was distilled over sodium in a vacuum, and yielded 6-methoxy-1-methylphenanthrene, m. p. 85—87°, undepressed by admixture with a specimen obtained from *O*-methylpodocarpic acid.

6-*Hydroxy*-1 : 12-*dimethyloctahydrophenanthrene*-1-*carboxylic acid* (II; $R^1 = R^2 = H$). Demethylation of the above methoxy-acid (II; $R^1 = Me$; $R^2 = H$) (0·05 g.) was satisfactorily effected by boiling with hydriodic acid (*d* 1·7, 5 c.c.), acetic anhydride (2 c.c.), and a trace of red phosphorus for 4 hours in an atmosphere of carbon dioxide. The *product* was sublimed in a vacuum at 160—180° (oil-bath)/0·005 mm., and crystallised from aqueous acetic acid in colourless prisms, m. p. 258° (Found : C, 73·8; H, 8·1. $C_{17}H_{22}O_3$ requires C, 74·4; H, 8·0%). This acid, in alkaline solution, gave with diazotised sulphanilic acid a wine-red colouration which closely resembled that obtained with podocarpic acid.

αδ-*Di*-(4-*methoxyphenyl*)*butane*. (a) During the preparation of ethyl 1-β-(4-methoxyphenyl)ethyl-2 : 6-dimethyl-Δ^6-*cyclo*hexene-2-carboxylate (VIII), a higher fraction, b. p. 190°/0·1 mm., yielded αδ-*di*-(4-*methoxyphenyl*)*butane*, which separated from ligroin in colourless plates, m. p. 78—79° (Found : C, 79·8; H, 7·9. $C_{18}H_{22}O_2$ requires C, 79·9; H, 7·9%). Demethylation with boiling hydriodic acid (*d* 1·7) gave αδ-*di*-(4-*hydroxyphenyl*)*butane*, which separated from hot water in colourless plates, m. p. 154—155° (Found : C, 78·8; H, 7·5. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·4%), and yielded with acetic anhydride a diacetate, obtained as pearly laminæ, m. p. 88—89°, from aqueous methyl alcohol.

(b) β-(4-Methoxybenzoyl)propionic acid (15 g.) was refluxed with concentrated hydrochloric acid (75 c.c.) and amalgamated zinc (75 g.) for 24 hours. The mixture was cooled, extracted with ether, dried, the solvent removed, and the residual crude β-(4-methoxyphenyl)butyric acid (14 g.) treated with excess of freshly distilled thionyl chloride. When the vigorous reaction had subsided, the mixture was refluxed for 1 hour, excess thionyl chloride was removed, and the residue was covered with benzene and heated on the water-bath until free from benzene and thionyl chloride. The residual crude acid chloride (14 g.) was mixed with anisole (15 c.c.), nitrobenzene (25 c.c.), and powdered aluminium chloride (9 g.) and kept overnight. The complex was decomposed with ice and dilute hydrochloric acid, nitrobenzene and excess anisole were removed in steam, and the cooled residue was extracted with ether, dried, and the solvent removed. Distillation of the residue yielded 4-*methoxyphenyl* β-(4-*methoxyphenyl*)*propyl ketone*, b. p. 200—210°/4 mm., which separated from methyl alcohol in colourless plates (10 g.), m. p. 92° (Found : C, 75·2; H, 6·8. $C_{18}H_{20}O_3$ requires C, 75·8; H, 7·0%). The ketone (10 g.) was reduced by heating with amalgamated zinc (50 g.) and concentrated hydrochloric acid (50 c.c.) for 12 hours. The cooled mixture was dried, and the solvent removed; the residue gave, on distillation, αδ-di-(4-methoxyphenyl)butane, b. p. 180°/2 mm., which separated from ligroin in plates (9 g.), m. p. 78—79° (Found : C, 79·9; H, 7·9%), which gave no depression in m. p. when mixed with a specimen obtained as described in (a) above.

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