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DITERPENOID TOTAL SYNTHESIS—III*

RESIN ACID ANALOGUES WITHOUT ANGULAR METHYL GROUP

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Abstract—Synthesis of some resin acid analogues without angular methyl group is described.

IN CONNECTION with synthetic work on the gibberellins,[1] some resin acid analogues without angular methyl groups were prepared. These seemed appropriate starting materials for the synthesis of gibberellins by contraction of ring B to a five-membered ring with extrusion of a carboxyl group. Since then three successful conversions of hydrophenanthrenes into hydrofluorenes have been published.[2-4] Although this conversion could not be realized with our materials, the synthesis of several resin acid analogues will be recorded here.

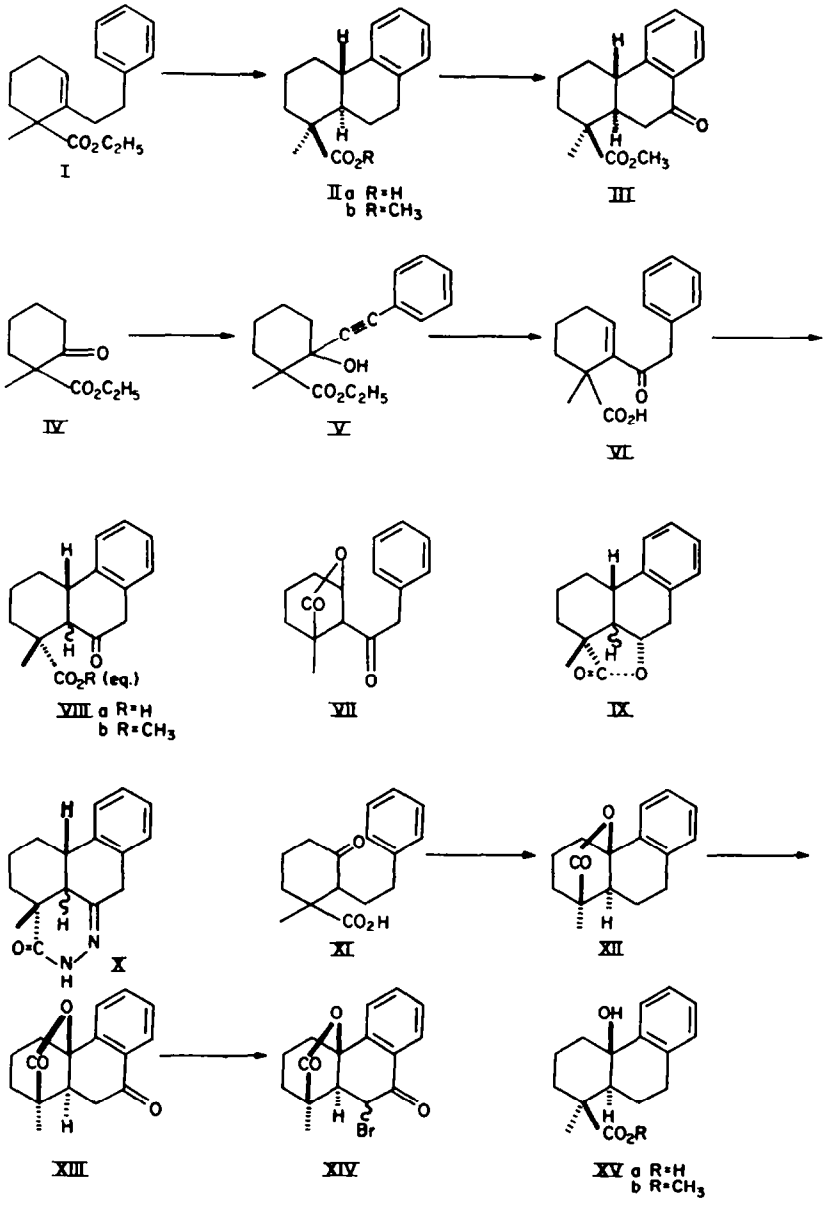
(±)-12-*Demethyldesoxypodocarpic acid.* An isomer of 1-methyl-1,2,3,4,9,10,11,12-octahydrophenanthrene-1-carboxylic acid (IIa)† was synthesized by acid-catalysed cyclization of ethyl 1-methyl-2-β-phenylethylcyclohex-2-ene-1-carboxylate (I) according to Haworth and Barker.[5] The stereochemistry depicted in IIa was based on the following facts. Firstly in the corresponding methyl ester (IIb), an equatorial carbomethoxy group was saponified with 0·5N ethanolic potassium hydroxide while an axial one survived.[6] In our case less than 5% of the added alkali was consumed, indicating the axial configuration of the carbomethoxy group. Secondly, the methyl ester was treated with chromic acid to give a monoketone (III). If it can be assumed that according to Wenkert and Jackson[7] the relationship between the stereochemistry of A/B ring fusion and the oxidation product is applicable to the demethyl analogue, this ester (IIb) possesses A/B *trans*-fused stereochemistry. Thus the parent acid (IIa) was shown to be (±)-12-demethyldesoxypodocarpic acid (phenanthrene numbering).

1-*Methyl*-10-*oxo*-1,2,3,4,9,10,11,12-*octahydrophenanthrene*-1-*carboxylic acid.* This acid was synthesized by a procedure similar to that described by Parham *et al.*[8] for

* Part II, *Tetrahedron* **22**, 879 (1966).

† Although the formulae depicted represent only one enantiomer, they represent a racemate in every case.

[1] cf. K. Mori, M. Matsui and Y. Sumiki, *Tetrahedron Letters* No. 27, 1803 (1964).
[2] J. F. Grove and B. J. Riley, *J. Chem. Soc.* 1105 (1961).
[3] A. Tahara, *Chem. Pharm. Bull.* **9**, 252 (1961).
[4] R. H. B. Galt and J. R. Hanson, *J. Chem. Soc.* 1565 (1965).
[5] R. D. Haworth and R. L. Barker, *J. Chem. Soc.* 1299 (1939).
[6] I. R. Sherwood and W. F. Short, *J. Chem. Soc.* 1006 (1938).
[7] E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.* **80**, 211 (1958).
[8a] W. E. Parham, E. L. Wheeler, R. M. Dodson and S. W. Fenton, *J. Amer. Chem. Soc.* **76**, 5380 (1954); [b] R. M. Dodson, W. E. Parham and E. L. Wheeler, *Ibid.* **77**, 1166 (1955).



resin acids. Treatment of ethyl 1-methylcyclohexan-2-one-1-carboxylate (IV) with phenylethynyl magnesium bromide afforded ethyl 1-methyl-2-phenylethynylcyclohexan-2-ol-1-carboxylate (V). The Rupe rearrangement of V with 80% formic acid yielded 1-methyl-2-phenylacetylcyclohex-2-ene-1-carboxylic acid (VI), together with a crude oily lactone (VII). Cyclization of VI with aluminum chloride afforded an oxohydrophenanthrene acid (VIIIa). The corresponding methyl ester (VIIIb) rapidly consumed alkali when boiled with 0·5 N ethanolic potassium hydroxide, while the ester (IIb) did not. This indicated the equatorial configuration of the carbomethoxy

group. Two attempts to transform VIIIa into the corresponding desoxo acid failed. The Clemmensen reduction of VIIIa unexpectedly afforded a lactone (IX). The Wolff-Kishner reduction of VIIIa gave a neutral compound to which was assigned the formula X on the basis of its IR spectrum (ν_{max} (Nujol) 3270, 3120, 1669, 1635 (sh) cm^{-1}) and elemental analysis. An analogous compound (X, C-12 CH_3 instead of H) had previously been obtained by the Wolff-Kishner reduction of VIIIa (C-12 CH_3 instead of H).[8b] Inspection of the molecular models of IX and X revealed that both rings A/B *trans* and *cis* structures were possible with an equatorial carboxyl group. A fact favoring the A/B *trans* stereochemistry was the equilibration of VIIIa with boiling hydrochloric acid from which unchanged starting ketone was recovered. However, cyclization of this type was known to afford *cis*-fused compounds as evidenced by Dodson.[9] So no definite conclusion could be drawn concerning the stereochemistry of A/B ring junction.

1-Methyl-12-hydroxy-1,2,3,4,9,10,11,12-octahydrophenanthrene-1-carboxylic acid lactone. 2-β-Phenylethyl-3-methyl-3-carboxycyclohexanone (XI)[10] was treated with polyphosphoric acid to give a hydrophenanthrene lactone (XII). As a monoketone (XIII) was obtained by chromic acid oxidation of XI, its A/B ring junction was *trans*. The lactone (XII) could not be hydrolysed by dilute aqueous alkali.[11] Hydrolysis was accomplished by fusion with potassium hydroxide to give the corresponding hydroxy acid (XVa), m.p. 108–110°(dec) while the corresponding methyl ester melted at 146–147° (dec). Bromination of the keto lactone (XIII) afforded a crude bromoketone (XIV). Attempted quasi-Favorskii rearrangement of XIV was unsuccessful.

EXPERIMENTAL

All m.ps and b.ps were uncorrected. IR spectra refer to Nujol mulls for solid samples and films for liquid samples.

1-Methyl-1,2,3,4,9,10,11,12-octahydrophenanthrene-1-carboxylic acid (IIa). This was synthesized according to Haworth and Barker,[5] m.p. 185–187°. ν_{max} 1694, 752 cm^{-1}. Treatment with diazomethane afforded the *methyl ester* (IIb), m.p. 75–76°, ν_{max} 1722, 1604, 748 cm^{-1}.

Methyl 1-methyl-9-oxo-1,2,3,4,9,10,11,12-octahydrophenanthrene-1-carboxylate (III). To a solution of IIb (500 mg) in acetic acid (5 ml), CrO_3 (1 g) in water (1 ml) and acetic acid (5 ml) was added. The mixture was warmed at 60° for 1·5 hr and then left to stand overnight at room temp. MeOH was added to destroy excess CrO_3. The mixture was concentrated *in vacuo*, diluted with water and extracted with ether. The ether extract was washed with Na_2CO_3aq, dried over Na_2SO_4 and concentrated *in vacuo* to give 150 mg (29%) of III as prisms from ethyl acetate–pet. ether, m.p. 102–103°; ν_{max} 1722, 1684, 1600, 780 cm^{-1}. (Found: C, 74·43; H, 7·27. $C_{17}H_{20}O_3$ requires: C, 74·97; H, 7·40%.)

Ethyl 1-methyl-2-phenylethynylcyclohexan-2-ol-1-carboxylate (V). To an ether solution of EtMgBr prepared from EtBr (25 g), Mg (5·6 g) and ether (56 ml) was added phenylacetylene (23 g) in ether (30 ml). The mixture was stirred and refluxed for 1 hr, and then IV (41 g) was added dropwise during 1 hr and stirring and refluxing continued for 1·5 hr after the addition. After cooling, sat NH_4Claq and ice were added. The ether layer was separated, dried over $MgSO_4$ and concentrated. The residue was distilled *in vacuo*, b.p. 168–170°/0·3 mm, yield, 27 g (42%), n_D^{20} 1·5325, ν_{max} 3490, 3560 (sh), 1730, 1700, 1598, 754, 685 cm^{-1}. (Found: C, 75·28; H, 7·83. $C_{18}H_{22}O_3$ requires: C, 75·49; H, 7·74%.)

1-Methyl-2-phenylacetylcyclohex-2-ene-1-carboxylic acid (VI). A solution of V (20 g) in 80% formic acid (500 ml) was refluxed for 70 hr, poured into water and then extracted with ether. The extract was washed with water, dried over Na_2SO_4 and concentrated. The residue was triturated with benzene to give 4·5 g (25%) of VI which crystallized as elongated prisms from ethyl acetate–pet.

[9] S. N. Mahapatra and R. M. Dodson, *Chem. & Ind.* 253 (1963).
[10] U. R. Ghatak, D. K. Datta and S. C. Ray, *J. Amer. Chem. Soc.* **82**, 1728 (1960).
[11] cf. E. E. Fleck and S. Palkin, *J. Amer. Chem. Soc.* **61**, 3197 (1939).

ether, m.p. 146–147°, ν_{max} 1696, 1674, 1634, 1606, 768, 730 cm^{-1}. (Found: C, 74·20; H, 7·17. $C_{16}H_{18}O_3$ requires: C, 74·39; H, 7·02%.) The mother liquor, when concentrated, gave a crude oily lactone (VII), ν_{max} 1774, 1710, 1600, 750, 700 cm^{-1}.

1-*Methyl*-10-*oxo*-1,2,3,4,9,10,11,12-*octahydrophenanthrene*-1-*carboxylic acid* (VIIIa). To a suspension of $AlCl_3$ (10 g) in benzene (50 ml) was added with stirring and refluxing a solution of VI (4 g) in benzene (100 ml) during 30 min and stirring and refluxing continued for further 2 hr. During these 2·5 hr dry HCl was bubbled into the reaction mixture. After cooling, ice-water and dil. HClaq were added. Then benzene layer was separated, and the aqueous layer extracted with $CHCl_3$. The combined extract was washed with water, dried over $MgSO_4$ and concentrated to give 2·5 g (62%) of VIIIa which crystallized as prisms from ethyl acetate–pet. ether, m.p. 188–189° (dec; sinter at 184°), ν_{max} 1700, 1690 (sh), 760 cm^{-1}. (Found: C, 74·27; H, 6·87. $C_{16}H_{18}O_3$ requires: C, 74·39; H, 7·02%.) Treatment with ethereal diazomethane afforded a *methyl ester* (VIIIb) as stout prisms from ethyl acetate–pet. ether, m.p. 98–100°, ν_{max} 1716 (1708 sh), 1606, 760 cm^{-1}. (Found: C, 74·86; H, 7·37. $C_{17}H_{20}O_3$ requires: C, 74·97; H, 7·40%.)

The Clemmensen reduction of the acid (VIIIa). The keto acid (VIIIa, 1 g) was added to a mixture of water (3 ml), conc. HCl (5 ml), toluene (10 ml) and mossy Hg–Zn (2·4 g). The mixture was refluxed for 30 hr. During the reaction period 1 ml portions of conc. HCl were added to the mixture at 6-hr intervals. The mixture was diluted with water and extracted with ether. The extract was washed, dried and concentrated to give an oil. This was chromatographed over silicic acid to afford IX (10 mg) as needles from pet. ether, m.p. 192–194°, ν_{max} 1781, 712 cm^{-1}. (Found: C, 79·24; H, 6·88. $C_{16}H_{18}O_2$ requires: C, 79·34; H, 7·44%.)

The Wolff-Kishner reduction of the acid (VIIIa). A solution of VIIIa (800 mg) and 80% hydrazine hydrate (8 ml) in diethylene glycol (24 ml) was refluxed for 30 min and KOHaq (2·4 g in 2 ml) added and the refluxing continued for another 30 min. Water and excess of hydrazine hydrate was distilled off. The bath temp was raised to 200° and kept there for 3·5 hr. After cooling, the mixture was diluted with water and extracted with ether. The extract was washed with water followed with saturated brine, dried and concentrated to give 150 mg of X as rods from ethyl acetate–pet. ether, m.p. 194–195°, ν_{max} 3270, 3120, 1669, 1635, 755 cm^{-1}. (Found: C, 75·44; H, 6·96; N, 10·86. $C_{16}H_{19}ON_2$ requires: C, 75·59; H, 7·08; N, 11·02%.) Acidification of the aqueous layer afforded an intractable gum which was not further investigated.

1-*Methyl*-12-*hydroxy*-1,2,3,4,9,10,11,12-*octahydrophenanthrene*-1-*carboxylic acid lactone* (XII). A mixture of XI (50 g) and polyphosphoric acid (prepared from 240 g of P_2O_5 and 200 ml 85% H_3PO_4) was stirred and set aside for 1 hr at room temp and then warmed at 50° for 30 min. Ice-water was added carefully to destroy polyphosphoric acid. The mixture was extracted with ethyl acetate. The extract was washed with water and $NaHCO_3$aq, dried over Na_2SO_4, decolorized with charcoal and concentrated *in vacuo* to give 24·5 g (53%) of the lactone as elongated prisms from ethyl acetate–pet. ether, m.p. 129–130°, ν_{max} 1764, 1606, 1130, 1114, 913, 906, 764, 757 cm^{-1}. (Found: C, 79·72; H, 7·98. $C_{16}H_{18}O_3$ requires: C, 79·31; H, 7·49%.)

1-*Methyl*-9-*oxo*-12-*hydroxy*-1,2,3,4,9,10,11,12-*octahydrophenanthrene*-1-*carboxylic acid lactone* (XIII). To a solution of XII (20 g) in acetic acid (250 ml) CrO_3 (25 g) in acetic acid (200 ml) and water (40 ml) was added with stirring and cooling (10–20°). After standing overnight at room temp, the mixture was diluted with water and extracted with ethyl acetate. The extract was washed with $NaHCO_3$aq, dried over Na_2SO_4 and concentrated to give 19·5 g (93%) of XIII as leaflets from ethyl acetate–pet. ether, m.p. 179–180°, ν_{max} 1776, 1738 (sh), 1692, 1600, 921, 769 cm^{-1}. (Found: C, 74·88; H, 6·32. $C_{16}H_{16}O_3$ requires: C, 74·98; H, 6·29%.)

1-*Methyl*-9-*oxo*-10-*bromo*-12-*hydroxy*-1,2,3,4,9,10,11,12-*octahydrophenanthrene*-1-*carboxylic acid lactone* (XIV). Bromine (2·2 ml) in acetic acid (20 ml) was added to a solution of XIII (9 g) in acetic acid (200 ml). The red solution turned colorless when it was warmed at 50° for 5 min. The mixture was diluted with water. The precipitated crystals were collected and washed with a small amount of ether, yield, 8·2 g (66%) as a white powder from ethyl acetate–pet. ether, m.p. 146–148° (dec), ν_{max} 1766, 1708 (sh), 1698, 1600, 950, 938, 756 cm^{-1}. (Found: C, 54·80; H, 4·36; Br, 27·06. $C_{16}H_{15}O_3Br$ requires: C, 57·32; H, 4·81; Br, 23·54%.) The analytical date suggested that the product was a mixture of the monobromo derivative and highly brominated compounds.

1-*Methyl*-12-*hydroxy*-1,2,3,4,9,10,11,12-*octahydrophenanthrene*-1-*carboxylic acid* (XVa). The powdered lactone (XIII, 0·5 g) was added to fused KOH (2 g) containing a small amount of water (0·2 ml) at 200°. The mixture was kept at this temp for 15 min with occasional stirring until a white

solid mass formed. After cooling, water was added and the insoluble neutral material was removed by extraction with ethyl acetate. The aqueous layer was acidified to yield 0·4 g (80%) needles, m.p. 108–110° (dec), ν_{max} 3550, 1690 cm^{-1}. (Found: C, 73·07; H, 7·29. $C_{16}H_{20}O_3$ requires: C, 73·82; H, 7·74%.) The acid readily lactonized and its purification was extremely difficult.

Methyl 1-*methyl*-12-*hydroxy*-1,2,3,4,9,10,11,12-*octahydrophenanthrene*-1-*carboxylate* (XVb). The above XVa was esterified with ethereal diazomethane yielding prisms from ethyl acetate–pet. ether, m.p. 146–147° (dec), ν_{max} 3550, 1708, 1140, 762 cm^{-1}. (Found: C, 74·27; H, 7·72. $C_{17}H_{22}O_3$ requires: C, 74·42; H, 8·08%.)