SYNTHETIC STUDIES ON TERPENOIDS - PART IV[1,2] SYNTHESIS OF (±)-PODOCARPA-8,11,13-TRIENE-13-METHOXY-19,20-DIOIC ACID.

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Abstract- An alternate approach for the titled compound (I), a potential intermediate for the synthesis of racemic atisine and veatchine is described.

A number of ingenious methods[3] developed towards the construction of the nitrogen bridge, present in diterpene alkaloids, can broadly be divided into two classes: (i) to functionalize the inactive C-10 methyl group in podocarpic acid system. (ii) synthesize compounds having C-10 functionalized group directly. From these considerations the dicarboxylic acid I becomes a key intermediate for entry into diterpene alkaloids. Two syntheses[4,5] of dicarboxylic acid I on different building principles and its transformation[4] to tetracyclic acetylamine II were reported. In addition, dicarboxylic acid I possess all the structural and stereochemical characteristics for the synthetic entry into N-acetyl phenol III whose synthesis[6] from podocarpic acid has already been achived. In connection with other works on diterpene alkaloids carried out in this laboratory[7] an alternative approach for the synthesis of I was desired. The synthesis of I is the subject of the present paper.

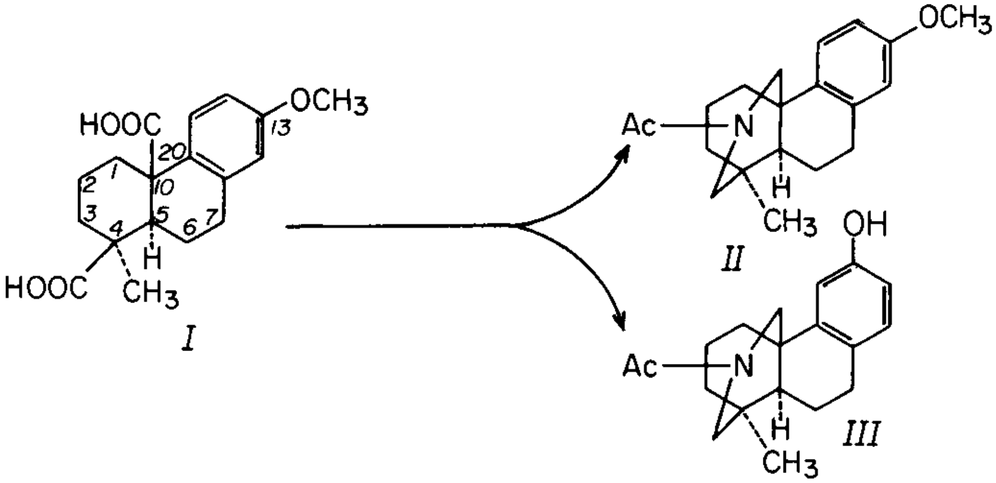
Ketone IV, prepared by the published procedure[8], was converted to the oily olefin V in 83% yield by the Clemmensen reduction.[9] Hydroboration-oxidation[10,11] of the olefin V with 9-BBN yielded 65% of the oily alcohol X which in the NMR spectrum exhibited a multiplet at δ 3.35 with half-width ($W_{1/2}$) of 16 Hz and thus indicated the axial nature[12] of the proton at C-4 of X. Alcohol X on oxidation with Jones reagent (-12°) afforded ketone[13] VIII in quantitative yield which on equilibration with acid and base at refluxing temperature was recovered unchanged and thus indicated that the A/B ring fusion of ketone VIII is in the more stable trans configuration.

Reduction of VIII with $LiAlH_4$ in tetrahydrofuran afforded 50% of the alcohol

XI which in the NMR spectrum showed a multiplet at δ 4.35 with half-width ($W_{1/2}$) of 6 Hz and thus provided evidence of the equatorial nature[12] of the proton at C-6 of XI. In order to oxygenate C-10β-methyl group by intramolecular, transannular oxidation[14], the alcohol XI was oxidized in cyclohexane with lead tetraacetate in presence of iodine. The resulting product after chromatographic purification afforded the cyclic ether XII and the ketone VIII in 10% and 85% yields respectively. The structure of XII was confirmed by the appearance of two doublets at δ 4.62 (1H, J= 8 Hz) and δ 4.74 (1H, J= 8 Hz) (2H at C-20) and by the disappearance of C-10 methyl group in the NMR spectrum. Oxidation of the cyclic ether XII with chromic acid in acetic acid afforded the oily lactone XIII and the oily keto-acid XV in 20% and 12% yield respectievly. Besides the lactone, and keto-acid, a small amount of an oily material was obtained which had molecular ion m/e 272 (M^+) and exhibited two bands at 1765 (γ-lactone) and 1710 (CO) cm^{-1} in the IR spectrum. Based on these spectroscopic data the oily material was assigned to structure XIV. The rest of the oxidized material (63%) was a mixture of complex products and thus could not be identified. Treatment of the sodium salt of keto-acid XV with MeI in methylphosphoramide[15] afforded keto-ester XVI.

Having obtained the desired keto-ester XVI in desired stereochemistry, the next operation concerned the conversion of C-4 ketonic carbonyl to aldehyde following the procedure of Levine.[16] Thus treatment of XVI with methoxymethyltriphenylphosphorane, generated from methoxymethyltriphenylphosphonium chloride and potassium t-butoxide in ether, produced XVII which on hydrolysis with perchloric acid yielded an aldehydic compound as evidenced by its IR data and this without purification was alkylated with MeI in presence of potassium t-butoxide. The high stereoselectivity of the present methylation was expected from the result of previous studies.[17,18] The resulting methylated aldehyde XVIII on oxidation with Jones reagent followed by hydrolysis[19] with potassium t-butoxide afforded the crystalline dicarboxylic acid I, m.p. 229° (decomp) whose identity was confirmed by mixed m.p. determination with an authentic specimen[4] and also corresponding dimethyl ester.[4] The dicarboxylic acid I has been converted[4] to the tetracyclic acetylamine II which represented a potential synthon for the total synthesis of racemic atisine and veatchine.

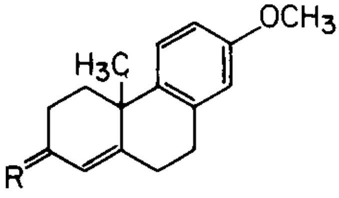
In conclusion the present synthesis of dicarboxylic acid I constitutes an additional approach towards the synthesis of amine II and thereby the synthesis



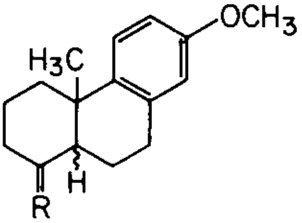
I

II

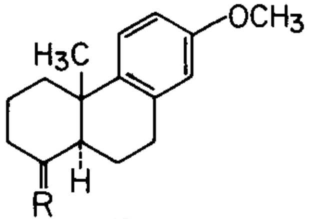
III



IV; $R = O$
V ; $R = H,H$

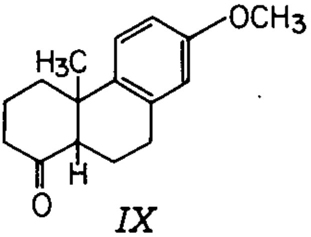


VI; $R = \sim OH, H$
VII; $R = O$

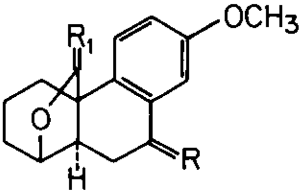


VIII; $R = O$
X; $R = \langle^{OH}_{H}$

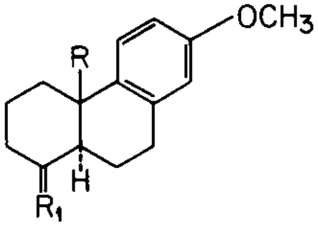
XI; $R = \langle^{OH}_{H}$



IX



XII; $R = R_1 = H, H$
XIII; $R_1 = O$, $R = H,H$
XIV; $R_1 = R = O$



XV; $R = COOH$, $R_1 = O$
XVI; $R = COOCH_3$; $R_1 = O$
XVII; $R = COOCH_3$; $R_1 = CHOCH_3$
XVIII; $R = COOCH_3$; $R_1 = \langle^{CH_3}_{CHO}$

of atisine and veatchine.

EXPERIMENTAL[20]

Olefin V

Ketone IV (10 g) suspended in 20% HCl (200 ml) was heated under reflux for 7 hr in the presence of amalgamated mossy Zn |273 g, shaken for 15 min with $HgCl_2$ soln (210 ml containing 18 g $HgCl_2$ and 14 ml conc HCl)|. After cooling, the mixture was extracted with ether, washed, dried and concentrated in vacuo to give the oily olefin V (7.81%, 83%), b.p. 88-94°/0.8 mm (bath) m/e 228 (M^+), IR (film) 1615 (C=C), NMR: δ 1.21 (3H, s, 10-CH_3), 3.65 (3H, s, OCH_3) and 5.25 (1H, m, 4-H). (Found: C, 84.11; H, 8.76. $C_{16}H_{20}O$ requires: C, 84.16; H, 8.83%).

Alcohol X

To a soln of 9-BBN in tetrahydrofuran (10 ml, 0.5 M) was added with a syringe a soln of the olefin V (1 g) in tetrahydrofuran (3 ml). After heating under reflux for 8 hr, the borane complex was oxidized by adding successively ethanol (3 ml), a soln of NaOH (2 ml, 6N) and 30% H_2O_2 (2 ml). The mixture was heated for 1 hr, cooled and the organic layer was separated. The aqueous layer was saturated with K_2CO_3 and extracted with tetrahydrofuran. The combined organic extract was washed and dried. Evaporation of the solvent afforded an oily material which was chromatographed over silica. Elution with benzene:ether (85:15) yielded alcohol X (695 mg, 65%); m/e 246 (M^+), IR (film) 3375 (OH), NMR: δ 1.22 (3H, s, 10-CH_3), 3.35 (m, 1H, 4-H, $W_{1/2}$ = 16 Hz), 3.76 (3H, s, OCH_3) and 6.57-7.18 (m, 3H, aromatic protons). (Found: C, 77.86; H, 8.96. $C_{16}H_{22}O_2$ requires: C, 78.01; H, 9.00%).

Ketone VIII

Jones chromic acid reagent (3 ml) was added to an ice-cold soln of the alcohol X (557 mg) dissolved in acetone (3 ml) and the mixture was left at room temp for 10 min. 2-Propanol was added to destroy the excess of oxidant, diluted with water, extracted with ether. The organic extract was washed, dried and evaporated. Ketone VIII (551 mg; 99%) was obtained as oily liquid, b.p. 168-172°/0.6 mm (bath), 2,4-dinitrophenylhydrazone, m.p. 204-205° |lit.[13] b.p. 165-170°/0.5 mm (bath), 2,4-dinitrophenylhydrazone, m.p. 205°|, m/e 244 (M^+), IR (film) 1710 (CO), NMR: δ 1.33 (3H, s, 10-CH_3), 3.78 (3H, s, OCH_3) and 6.58-7.23 (3H, m, aromatic protons). (Found: C, 78.49; H, 8.12. $C_{16}H_{20}O_2$ requires: C, 78.65; H, 8.25%).

Alcohol XI

To $LiAlH_4$ (1.98 g) in tetrahydrofuran (30 ml) was added the ketone VIII (925 mg) dissolved in tetrahydrofuran (8 ml). After heating the resulting mixture for 6 hr, water was added. The precipitate was filtered and the filtrate was dried. Removal of the solvent afforded a thick oil which was chromatographed over alumina. Benzene:ether (90:10) eluted the alcohol XI (462 mg, 50%); m/e 246 (M^+), IR (film) 3440 (OH), NMR: δ 1.18 (3H, s, 10-CH_3), 3.78 (3H, s, OCH_3) and 4.35 (1H, m, 4-H, $W_{1/2}$ = 6 Hz). (Found: C, 77.88; H, 8.94. $C_{16}H_{22}O_2$ requires: C, 78.01; H, 9.00%).

Lead tetraacetate oxidation of alcohol XI

A mixture of lead tetraacetate (910 mg) and anhydrous calcium carbonate (910 mg) was dried under reduced pressure and then heated in cyclohexane (10 ml) under reflux for 30 min with stirring. A soln of the alcohol XI (350 mg) in cyclohexane was added to the above suspension followed immediately by iodine (120 mg). After heating the mixture under reflux for 1 hr with two Philips 500-W photolamps, the reaction mixture was cooled, filtered followed by washing the filtered cake with ether. The combined organic extracts were washed with 1% sodium hydroxide soln, brine and dried. Evaporation of the solvent afforded an oily material which was chromatographed over alumina. Elution with hexane:ether (6:4) produced the cyclic ether XII (34 mg; 10%) m/e 244 (M^+), NMR: δ 3.65 (3H, s, OCH_3), 4.62 (d, 1H, J=8 Hz) and 4.74 (d, 1H, J=8 Hz) (2H, C-20). (Found: C, 78.48; H, 8.19. $C_{19}H_{20}O_2$ requires: C, 78.65; H, 8.25%). Elution with hexane:ether (1:1) gave ketone VIII (284 mg, 85%).

Oxidation of the cyclic ether XII

To the ether XII (120 mg) in acetic acid (2 ml, 98%) was added a soln of chromic acid (110 mg) in acetic acid (2 ml, 80%). The reaction mixture was stirred at room temperature for 60 hr. The usual workup produced the acid XV (16 mg, 12%), which did not solidify, m/e 274 (M^+) and 229 (M^+-COOH), IR (film) 1720 (unresolved acid and ketonic carbonyl). (Found: C, 69.94; H, 6.52. $C_{16}H_{18}O_4$ requires: C, 70.05; H, 6.61%).

To a soln of XV (97 mg) dissolved in HMPA (3 ml) was added NaOH (52 mg) in water (4 ml) and after stirring the mixture for 1.2 hr at room temperature methyl iodide (750 mg) was added. The resulting soln after stirring for 2 hr at room temperature, was acidified and extracted with ether. By the usual workup the neutral and acidic fractions were separated. The neutral fraction afforded the oily ester XVI (71 mg, 70%) m/e 288 (M^+). (Found: C, 70.72; H, 6.91. $C_{17}H_{20}O_4$ requires: C, 70.81; H, 6.99%).

The neutral fraction obtained from XV on purification by preparative thin layer chromatography (silica gel 60 F_{234}, eluent benzene) yielded (i) the oily lactone XIII (25 mg, 20%), m/e 258 (M^+) and IR (film) 1765 (γ-lactone), (ii) keto-lactone XIV (7 mg, 5%), a thick oily material, m/e 272 (M^+) and IR (film) 1710 (CO) and 1765 (γ-lactone).

(±)-Podocarpa-8,11,13-triene-13-methoxy-19,20-dioic acid (I)

To a suspension of methoxymethyltriphenylphosphonium chloride (513 mg) in dry ether (10 ml) was added potassium t-butoxide (153 mg). To the resulting red soln was added ester XVI (108 mg) in dry ether (8 ml). The reaction mixture was stirred for 30 hr under nitrogen, decomposed with water (3 ml) and extracted with ether. The organic extract was washed with brine, dried and evaporated. A dark red oily material was obtained which was partitioned between petroleum ether and aqueous methanol (1:4), the aqueous layer was separated and extracted with ether. The combined ether extract was washed, dried and evaporated. The residue on being chromatographed on alumina (eluent-benzene:ether (9:1) afforded XVII (102 mg), a dense liquid, m/e 316 (M^+), IR (film) 1720 (ester CO) and 1675 ($C=CHOCH_3$).

Methoxymethylene derivative XVII (98 mg) in ether (15 ml) was treated with 70% perchloric acid (3 ml) and stirred at room temperature for 3 hr. The reaction mixture was diluted with ether, washed with brine, dried and evaporated. The resulting aldehyde, m/e 302 (M^+), without purification, was dissolved in benzene:t-butyl alcohol (20 ml, 1:1) followed by treatment with potassium t-butoxide (220 mg). After stirring the mixture for 10 min at room temperature, methyl iodide (560 mg) was added and the whole mixture was stirred at room temperature for 20 hr under nitrogen. To the resulting dark red mixture was added potassium t-butoxide (120 mg) followed by addition of methyl iodide (280 mg). After stirring for an additional 4 hr, the reaction mixture was diluted with water, extracted with ether, washed the ethereal extract with brine and dried. The oily material was chromatographed over Florisil. Elution with ether:hexane (10:90) afforded XVIII (52 mg), a very low melting yellowish-white solid m/e 316 (M^+) and 242 (M^+-COOH- CHO), IR (KBr) 2700, 1715 (CHO) and 1735 (ester CO). The aldehyde XVIII was found unstable at room temperature as evidenced by its change of colour from yellow to green.

The low melting aldehyde XVIII (45 mg) dissolved in acetone (5 ml) was treated with Jones reagent (5 ml) and stirred at 25° for 10 hr (occasionally cooling). The mixture was stirred for 2 additional hr at 30-35°, diluted with water and extracted several times with chloroform. The organic extract was washed several times with sodium carbonate solution (5%). The alkaline extract after acidification afforded a gummy acidic material (48 mg) which dissolved in dimethyl sulfoxide (5 ml) was treated with potassium-t-butoxide (40 mg) and heated in an oil bath (bath temp 90°) for 55 min. The usual workup afforded I (32 mg, 26% from XVI), m.p. 229 (decomp) (from tetrahydrofuran) |lit[4] 228-230° (decomp)|; m/e 228 (M^+-2 COOH) and 213 (M^+-2 COOH- CH_3), IR (KBr) 1702 (CO). (Found: C, 68.11; H, 7.22. $C_{18}H_{22}O_5$ requires: C, 67.91; H, 6.97%). The dimethyl ester (from diazomethane treatment) melted at 113-114° (from petroleum), |lit[4] 114°|. The mp.s of acid I and its dimethyl ester were not depressed on admixture with authentic samples.[4] The IR spectra of I and its dimethyl ester was indistinguishable from the IR spectra of authentic specimen.[4]

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11. Hydroboration-Oxidation reaction of the olefin V with diborane (B_2H_6) generated from boron trifluoride etherate and sodium borohydride afforded a mixture of alcohols VI whose separation by column chromatography was found very laborious. Oxidation of VI with Jones reagent produced a mixture of ketones VII which on chromatographic purification over alumina yieldes 60% and 40% respectively. The oily ketone IX, m/e 244 (M^+), IR (film) 1710 (CO), NMR: δ 1.25 (3H, s, 10-CH_3), 3.74 (3H, s, OCH_3) and 6.59-7.12 (3H, aromatic protons), on heating with p-toluenesulfonic acid in methanol resulted 70% of its conversion to VIII.

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