A NEW SYNTHESIS OF dl-3-METHOXY-17β-CARBOXY-1,3,5(10),6,8-ESTRAPENTAENE (1).

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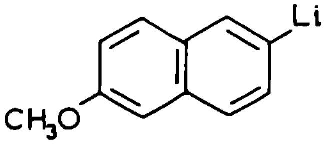
ABSTRACT

3-Methyl-4-carboxy-2-(2'-methoxy-6'-naphthyl)cyclopenten-3-acetic acid, prepared from <u>trans</u> methyl 2-methyl-3-carbomethoxycyclopentanon-2-acetate and 2-methoxy-6-lithionaphthalene, on ring closure and catalytic hydrogenation gave dl-3-methoxy-17β-carboxy-1,3,5(10),6,8-estrapentaene.

A synthesis of dl-3-methoxy-17β-carboxy-1,3,5(10),6,8-estrapentaene (VII) was reported (2) earlier by Banerjee and Johnson et al. We presently describe a new short synthesis of the compound (VII).

In 1952, Banerjee and Das Gupta (3) published the details of the preparation of cis and trans 2-methyl-3-carboxycyclopentanon-2-acetic acids as possible intermediates for the synthesis of steroids. Condensation of the methyl ester (II) of the trans keto diacid with 2-methoxy-6-lithionaphthalene (I) following the procedure of Newman et al.(4), followed by treatment with p-toluenesulfonic acid in benzene and subsequent saponification with 10% alcoholic potassium hydroxide furnished dl-3-methyl-4-carboxy-2-

-(2'-methoxy-6'-naphthyl)cyclopenten-3-acetic acid (IIIa) in 25% yield. Treatment of the acid (IIIa) with diazomethane gave the dl-ester (IIIb), preparation of the latter being reported by Harnik *et al.*(5). The point of attachment of the cyclopentane ring to the naphthalene nucleus was proved by oxidizing (IIIb) to 2-methoxy-6-naphthoic acid (IV) (6). Treatment (7) of a solution of the diacid (IIIa) in phosphorous oxychloride with polyphosphoric acid gave the dl--unsaturated keto acid (Va) in 73% yield; a much lower yield was obtained when either (IIIa) or the diester (IIIb) was directly treated with polyphosphoric acid. Ring closure of the acid chloride of (IIIa) with anhydrous aluminium chloride furnished (Va) in 47% yield. Hydrogenation of (Va) with Raney nickel (8) furnished the dl-saturated keto acid (VI) in 70% yield; use of 5% Pd-charcoal and stopping the hydrogenation after absorption of 1 mole of hydrogen gave an 83% yield. When the hydrogenation in presence of 30% Pd-charcoal was allowed to proceed until the uptake of hydrogen stopped, 3 moles of hydrogen were absorbed to afford dl-3-methoxy-17β-carboxy-1,3,5(10),6,8-estrapentaene (VII) in 60% yield. The compound (VII) was found to be identical with that synthesized earlier by Banerjee and Johnson (2), the configuration of the latter compound being proved by direct comparison with an authentic specimen (2) prepared from *dl*-equilenin methyl ether (9).



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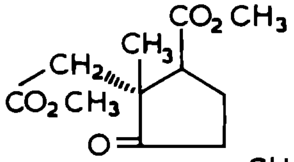

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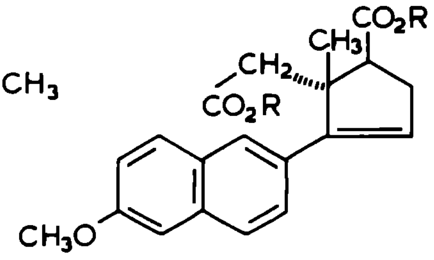

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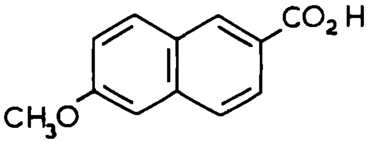

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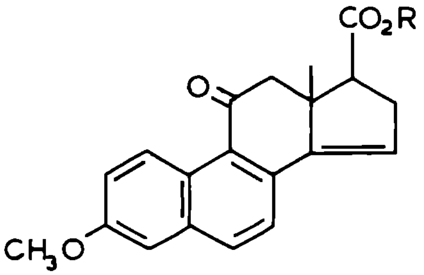

V

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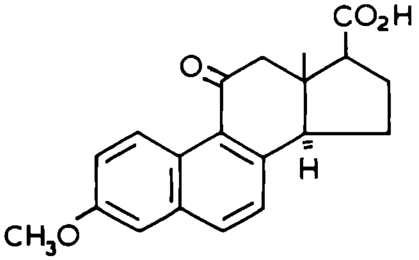
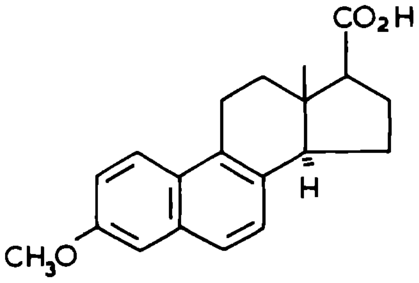


VI



VII

EXPERIMENTAL (10)

dl-3-Methyl-4-carboxy-2-(2'-methoxy-6'-naphthyl)cyclopenten-2-acetic acid (IIIa).- Into a cooled (-5° to -10°) and stirred solution of methyl 2-methyl-3-carbomethoxycyclopentanon-2-acetate (II, 18.4 g, 1 mole) (3) in dry ether (100 ml) was slowly forced under nitrogen a solution of 2-methoxy-6-lithionaphthalene, prepared by treating a solution of one equivalent of butyl lithium (11) in dry ether (90 ml) with a solution of 2-methoxy-6-bromonaphthalene (19 g, 1 mole) (12) in 1:1 ether-benzene (160 ml) under nitrogen. The mixture was stirred for 2 hr, left for 15 hr at room temperature and then poured into dilute sulfuric acid. The organic layer was separated and the aqueous solution extracted twice with ether. The combined organic solution was washed with water, aqueous sodium bicarbonate, ice-cold 5% aqueous potassium hydroxide and water. A solution of the residue (20 g), obtained after removal of the solvent, in benzene (100 ml) and p-toluenesulfonic acid (0.5 g) was heated under reflux for 1½ hr. The solution was cooled, washed with aqueous sodium bicarbonate and water, the benzene removed and the gummy residue heated under reflux for 20 hr with potassium hydroxide (12.5 g) in ethanol (110 ml). The alcohol was removed and the residue was treated with water and ether. The aqueous layer, after thorough extraction with ether, was acidified. The precipitated semisolid was extracted with benzene, the extract washed with water and concentrated to a small volume to furnish a solid which on recrystallization from benzene afforded the pure unsaturated diacid (IIIa, 5.7 g, 25%), m.p. 201-3° (vac); UV λmax 235 (log ε 4.6), 285 (log ε 3.8), 320 (log ε 3.2), 329 mμ (log ε 3.2); IR ν max (nujol) 2600, 1704, 1631-1634, 1600, 1250, 830 cm^{-1}.

Anal. Calcd. for $C_{20}H_{20}O_5$: C, 70.58; H, 5.88. Found: C, 70.45; H, 6.18%.

The *dl-dimethyl ester (IIIb)*, prepared in the usual way from the diacid (IIIa, 2 g) and diazomethane (from 3 g of nitrosomethylurea) in ether (100 ml), was crystallized from methanol to give 1.8 g (80%) of the pure product, m.p. 109-10°; UV λmax 235 (log ε 4.1), 285 (log ε 3.6), 320 (log ε 2.9), 329 mμ (log ε 2.9); IR ν max (nujol) 1745, 1645, 1613, 1258, 814 cm^{-1}.

Anal. Calcd. for $C_{22}H_{24}O_5$: C, 71.54; H, 7.50. Found: C, 71.41; H, 6.60%.

Oxidation of the dl-diester (IIIb).- A mixture of the unsaturated diester (IIIb, 0.2 g), sodium carbonate (0.5 g), potassium permanganate (2.1 g) and water (65 ml) was heated under reflux for 2 hr. Sulfur dioxide was passed through the cooled reaction mixture and the clear solution was allowed to stand in the cold for 2 hr. The separated solid was crystallized from aqueous ethanol to furnish 69 mg of a product, m.p. 197-8°, found to be identical with an authentic specimen (6) of 2-methoxy-6-naphthoic acid (IV).

dl-3-Methoxy-11-keto-17β-carboxy-1,3,5(10),6,8,14-estrahexaene (Va) and its methyl ester (Vb).- (a) A solution of the diacid (IIIa, 1 g) in phosphorus oxychloride (15 ml) was added to polyphosphoric acid, prepared from phosphorus pentoxide (10 g) and orthophosphoric acid (10 ml, d, 1.75), and the mixture heated on a steam-bath for 6 min. The deep red solution was poured into ice and water. The precipitated solid was filtered, dried, and crystallized from benzene to obtain the pure unsaturated keto acid (Va) (695 mg, 73%), m.p. 258-60° (vac); UV λmax 238 (log ε 4.4), 273 (log ε 4.6), 312 (log ε 3.8), 375 mμ (log ε 3.8); IR ν max (nujol) 1724, 1678, 1629-1634, 1603, 1245, 809 cm^{-1}.

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.16; H, 5.62%.

(b) The diacid (IIIa, 0.2 g) was added to a freshly prepared polyphosphoric acid, from phosphorus pentoxide (2 g) and orthophosphoric acid (1.2 ml), thoroughly mixed and heated for 1½ hr on a steam-bath. Crushed ice was added and the mixture warmed on a steam-bath. After cooling, the solid was filtered, dried, and crystallized to afford (Va) (48 mg, 25%), m.p. 255-7° (vac).

(c) The diester (IIIb, 1 g) was treated with polyphosphoric acid, from phosphorus pentoxide (10 g) and orthophosphoric acid (6 ml), as before to furnish a solid which on crystallization from ethanol yielded pure dl-3-methoxy-11-keto-17β-carbomethoxy-1,3,5(10),6,8,14-estrahexaene (Vb) (0.32 g, 36%), m.p. 168-9°; UV λmax 240 (log ε 4.5), 316 (log ε 3.8), 322 (log ε 3.8), 326 (log ε 3.8), 372 mμ (log ε 3.8); IR ν max (nujol) 1748, 1684, 1629, 1608, 1244, 809 cm^{-1}.

Anal. Calcd. for $C_{21}H_{20}O_4$: C, 75.00; H, 5.90. Found: C, 75.37; H, 5.90%.

(d) To a suspension of the diacid (IIIa, 0.5 g) in dry ether (45 ml) was added oxalyl chloride (3 ml) and the mixture allowed to stand overnight. The ether and the excess of oxalyl chloride were removed from the clear solution under diminished pressure. Dry benzene (10 ml) was added to the residue and the process repeated to ensure complete removal of the oxalyl chloride. To a cooled solution of freshly sublimed aluminium chloride (2.8 g) in dry nitrobenzene (15 ml) was added with swirling a solution of the above crude acid chloride in nitrobenzene (10 ml). After standing at room temperature for 20 hr, the dark green reaction mixture was poured into ice and hydrochloric acid. The nitrobenzene layer was separated and the aqueous layer extracted with ether-benzene. The combined organic solution was extracted with aqueous sodium bicarbonate (3 x 100 ml). Acidification of the bicarbonate extract and crystallization of the precipitated solid gave pure (Va) (225 mg, 47%), m.p. 253-5° (vac).

dl-3-Methoxy-11-keto-17β-carboxy-1,3,5(10),6,8-estrapentaene (VI).- (a) A mixture of a solution of the unsaturated keto acid (Va, 0.7 g) in dioxan (70 ml) and Raney nickel catalyst (0.5 g) (8) was stirred in an atmosphere of hydrogen until the absorption of hydrogen (*ca.* 1 mole) ceased. The catalyst was filtered and the solid obtained after removal of the solvent was crystallized from ethanol to afford the saturated keto acid (VI) (0.5 g, 70%), m.p. 279-80° (vac); UV λmax 220 (log ε 4.7), 248 (log ε 4.5), 279.5 (log ε 3.6), 282 (log ε 3.6), 284 (log ε 3.6), 316 (log ε 3.8), 355 mμ (log ε 3.5); IR ν max (nujol) 2660, 1718, 1661, 1623, 1597, 1245 cm^{-1}.

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22. Found: C, 73.65; H, 6.31%.

(b) A solution of (Va) (0.5 g) in ethanol (50 ml) was hydrogenated in the presence of prereduced 5% Pd-charcoal (0.5 g) in ethanol (25 ml) until 42.5 ml (1 mole) of hydrogen was absorbed. On working up as before the keto acid (VI) (0.42 g, 83%), m.p. 279-80° (vac) was obtained.

dl-3-Methoxy-17β-carboxy-1,3,5(10),6,8-estrapentaene (VII).- A solution of (Va) (0.5 g) in ethanol (50 ml) was hydrogenated in the presence of prereduced 30% Pd-charcoal (0.5 g) in ethanol until the absorption of hydrogen (*ca.* 3 moles) ceased. On working up as before and crystallizing the product from ethanol, there was obtained 0.3 g (62%) of the acid (VII), m.p. 281-2° (vac); UV λmax 231 (log ε 4.8), 268 (log ε 3.7), 278 (log ε 3.7), 323 (log ε 3.3), 338 mμ (log ε 3.4); IR ν max (nujol) 2833, 1700, 1623, 1598, 1244 cm^{-1}, identical with the IR spectrum of a genuine specimen.

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.28; H, 7.17%.

ACKNOWLEDGEMENTS

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10. Recorded temperatures are uncorrected. UV spectra were determined in 95 percent ethanol using a Beckman model DU spectrophotometer. IR spectra were taken with a Perkin-Elmer infracord model 137 B. Microanalyses were carried out by Mr. R.R. Seetharamia of this department. A few exploratory experiments were carried out by Dr. K.N. Rangammal.

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