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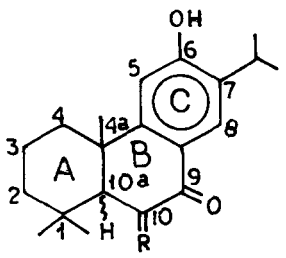
STEREOSELECTIVE SYNTHESIS OF CIS-A/B OCTAHYDROPHENANTHRENE SKELETON RELATED TO DITERPENES VIA REDUCTIVE ALKYLATION IN ANHYDROUS AMMONIA

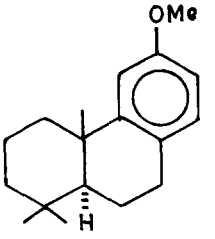
Sukanta Bhattacharyya and Debabrata Mukherjee*
Department of Organic Chemistry
Indian Association for the Cultivation of Science, Calcutta 700032, India

Summary : 7-Methoxy-1,1,4aβ-trimethyl-1,2,3,4,4aβ,9,10,10aβ-octahydrophenanthrene (5), a skeletal representative of several diterpenes, has been synthesised stereoselectively through reductive methylation of the α,β-unsaturated ketone 14 in anhydrous ammonia followed by Huang-Minlon reduction.

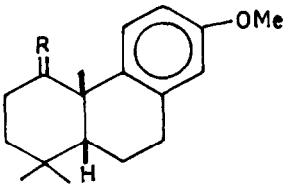
The tricyclic diterpenes sugiol (1)[1] and xanthoperol (2)[1] incorporate respectively A/B-trans and A/B-cis fused octahydrophenanthrene skeleta, the ring C of the natural products (1) and (2) being aromatic. Recently Davis et al[2] reported a clean, high-yield synthesis of the ring C-aromatic trans-A/B tricyclic molecule 3 through acid-catalysed cyclisation of trans-1-(p-methoxyphenylethyl)-2,2,6-trimethylcyclohexanol. As complementary to their method, we now wish to report a stereoselective synthesis of the cis-A/B octahydrophenanthrene 5 through reductive methylation of the α,β-unsaturated ketone 14 in anhydrous ammonia. Ring system analogous to 5 is present in several diterpenoid artefacts, e.g. cis-A/B-Coleon V[3] and cis-A/B-6,7-dioxoroyleanon[3].



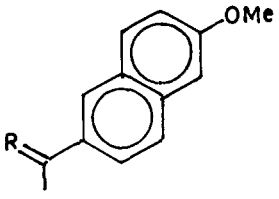
1, A/B Trans, R = H_2
2, A/B Cis; R = O



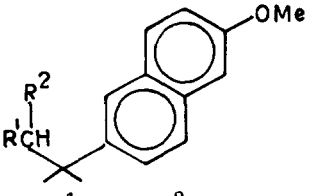
3



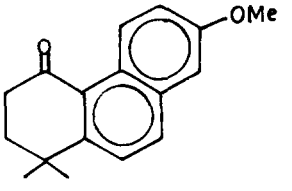
4, R = O
5, R = H_2



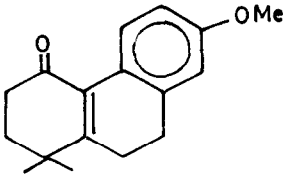
6, R = O
7, R = C(CN)CO_2Et



8, R^1 = CN; R^2 = CO_2Et
9, R^1 = H; R^2 = CO_2H
10, R^1 = H; R^2 = $COCHN_2$
11, R^1 = H; R^2 = CH_2CO_2Me
12, R^1 = H, R^2 = CH_2CO_2H



13



14

2-Acetyl-6-methoxynaphthalene (6) was condensed with ethyl cyanoacetate in the presence of NH_4OAc to afford the unsaturated cyano-ester 7 as a mixture of geometrical isomers in 75% yield, IR (Film): 2220, 1725, 1627, 1600, 1588 cm^{-1}; ^{1}H-NMR (CCl_4): δ 1.03, 1.37(2t, 3H, J = 7 Hz), 2.53, 2.7(2s,3H), 3.87(s,3H), 3.99, 4.27(2q,2H,J = 7 Hz), 6.93-7.83(m,6H). Conjugate addition of CH_3MgI to 7 in the presence of CuI furnished the saturated compound 8 contaminated with ca. 25% of the starting material 7. In order to separate 8 from 7, the mixture was treated with calculated quantity of the sodium salt of cyanoacetamide in EtOH at room temperature for several hours. On dilution with water, 7 was removed completely as a water-soluble salt[4] and pure 8 was recovered unchanged in 58% overall yield, b.p.(bath temp.) 182-185°/0.1 mm, IR(Film): 2250, 1740, 1630, 1605 cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.88(t,3H,J = 7 Hz), 1.67(s,6H), 3.65(s,1H), 3.85(s,3H), 3.86(q,2H,J = 7 Hz), 6.92-7.73 (m,6H). Hydrolysis of 8 with 20% KOH in refluxing ethylene glycol:water (5:1) for 20 hr and subsequent decarboxylation at 200° for ½ hr afforded the acid 9 in 76% yield, m.p. 140°. The acid 9 was converted into the corresponding diazomethyl ketone 10 which underwent rearrangement to the homologous methyl ester 11 in 72% overall yield on treatment with silver benzoate in CH_3OH in the presence of Et_3N[5]. Hydrolysis of 11 with 10% methanolic KOH furnished the acid 12 (95%), m.p. 136°; IR ($CHCl_3$): 1708, 1630, 1604 cm^{-1}. The acid chloride, prepared from 12 with $(COCl)_2$, was treated with anhydrous $AlCl_3$ in $C_6H_5NO_2$ at 10° for 20 hr to afford the ketone 13 in 75% yield (two steps), b.p. (bath temp.) 170°/0.1 mm; IR(Film): 1672, 1620, 1600 cm^{-1}, ^{1}H-NMR(CCl_4): δ 1.4(s,6H), 1.99(m,2H), 2.72(m,2H), 3.83(s,3H), 6.9-7.47(m,3H), 7.73(d,1H,J = 8 Hz), 9.1(d,1H,J = 10 Hz). Birch reduction[6] of 13 with Na and EtOH in distilled liquid ammonia furnished the α,β-unsaturated ketone 14 (80%), m.p. 98°; IR($CHCl_3$): 1665, 1608 cm^{-1}; ^{1}H-NMR($CDCl_3$): δ 1.23(s,6H), 1.87(m,2H), 2.23-2.78(m,6H), 3.77(s,3H), 6.65(overlap, 1H), 6.73(d of d,1H,J = 8,2.5 Hz), 7.87(d of d,1H,J = 8,1.5 Hz). Reductive methylation of 14 in anhydrous ammonia afforded the saturated ketone 4 as the only product in 86% yield, b.p.(bath temp.) 160-162°/0.1 mm; IR(Film): 1710, 1608 cm^{-1}; ^{1}H-NMR(CCl_4). δ 0.92 (s,3H), 1.0(s,3H), 1.27(s,3H), 1.5-3.02(m,9H), 3.72(s,3H), 6.4-6.7(m,3H). The ketone 4 was found homogeneous on TLC and VPC analyses. Conclusive evidence for the cis stereochemistry of the A/B ring fusion of 4 was obtained by the conversion of 4 through Huang-Minlon reduction into the known[7] compound 5 in 78% yield, b.p.(bath temp.) 140-142°/0.2 mm, ^{1}H-NMR(CCl_4): δ 0.88(s,3H), 0.92(s,3H), 1.12(s,3H), 1.18-2.99(m,11H), 3.70(s,3H), 6.45(overlap,1H), 6.53(d of d,1H,J = 8,2.5 Hz), 7.05(d,1H,J = 8 Hz). The appearance of the ^{1}H-NMR signals at δ 0.88 and 0.92 ppm for the gem-dimethyl group at C-1 is a characteristic feature[8] in this series for the A/B-cis isomers.

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