927. *Synthetical Studies of Terpenoids. Part VI.*[1] *Synthesis of* (±)-*Nimbiol Methyl Ether.*

By P. K. Ramachandran and Phanindra Chandra Dutta.

The (±)-form of nimbiol methyl ether has been synthesised and its structural identity with the (+)-form has been established by infrared studies.

The bark of *Melia Azadirachta* L., which is extensively used in the indigenous system of medicine in India, contains[2] as a component the phenolic ketone (I) whose structure was established by degradation. We now record the synthesis of its (±)-methyl ether (II).

The ketone[3] (III) was prepared in improved yield from the acid chloride of the arylbutyric acid[4] by ring-closure with stannic chloride and was allowed to react with methylmagnesium iodide. The hydrocarbon (IV) was obtained, dehydration occurring during distillation (the presence of iodine formed by decomposition of the Grignard complex with mineral acids should be avoided as it would lead to the formation of the naphthalene derivative). The hydrocarbon (IV) with perbenzoic acid gave a crude epoxide which on isomerisation with dilute sulphuric acid[5] afforded the tetralone (V) in an excellent yield. This was condensed with 2-chloroethyl ethyl ketone in presence of sodium methoxide, giving the crystalline unsaturated ketone (VI). Methylation by the standard procedure[6] afforded the tetramethyl ketone (VII), which did not crystallise but was characterised by lack of absorption at 220—250 mμ and by a yellow 2,4-dinitrophenylhydrazone. This in turn was reduced catalytically to the crystalline octahydro-ketone (VIII) with a *trans*-ring junction arising from 1,3-diaxial interaction.[7] The saturated ketone (VIII) was then subjected to Huang-Minlon reduction and the viscous product was oxidised with chromic acid. The desired ketone (II) was obtained, which was characterised by a red 2,4-dinitrophenylhydrazone and absorption maxima in ethanol at 231 and 279 mμ (log ε 4·1, 4·1). Isolation of a monoketone (II) further corroborates the *trans*-ring junction, being a diagnostic procedure for determining the nature of the ring junction in octahydrophenanthrenes.[8] The ketone (II) melts at 118—119° and the mixed melting point with

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[1] Part V, Narang and Dutta, *J.*, 1960, 2842.

[2] Bhattacharji, Mitra, and Siddiqui, *J. Sci. Ind. Res., India*, 1949, **8**, *B*, 188; 1953, **12**, *B*, 154; Choudhuri, Khastagir, and Sen Gupta, *Chem. and Ind.*, 1958, 861; 1959, 634, 1284.

[3] Buu-Hoï, Cagniant, Hoán, and Khoi, *J. Org. Chem.*, 1950, **15**, 950.

[4] Desai and Wali, *Proc. Indian Acad. Sci.*, 1937, **6**, *A*, 144.

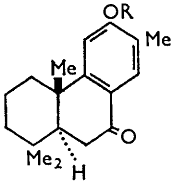
[5] Howell and Taylor, *J.*, 1958, 1248.

[6] Conia, *Bull. Soc. chim. France*, 1954, 690, 943.

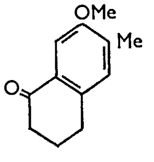
[7] Stork and Schulenberg, *J. Amer. Chem. Soc.*, 1956, **78**, 250.

[8] Wenkert and Chamberlin, *J. Amer. Chem. Soc.*, 1959, **81**, 698.

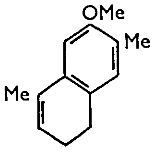
the (+)-methyl ether (m. p. 141—142°) is 118—120°. The infrared spectra (KBr disc) of the two are superimposable, thereby establishing their identity. Fetizon [9] has also synthesised the (±)-ether (II) but found m. p. 108—110°. The mixed melting point of the two synthetic specimens is 108—112°, indicating that the ether may exist in polymorphic forms although it is possible that Fetizon's sample is slightly impure. Occurrence of sugiol [10] along with nimbiol (I) in the bark suggests a common pathway for the biogenesis of these compounds from diterpenoid intermediates.[11]



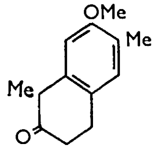
(I) R = H
(II) R = Me



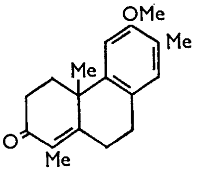
(III)



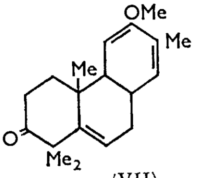
(IV)



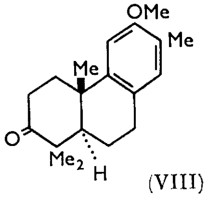
(V)



(VI)



(VII)



(VIII)

EXPERIMENTAL

Ultraviolet spectra were measured for ethanol solutions. Light petroleum was a fraction with b. p. 40—60°.

1,2-*Dihydro*-6-*methoxy*-4,7-*dimethylnaphthalene* (IV).—To a solution of 7-methoxy-6-methyl-1-tetralone (75 g.) in ether (100 c.c.) was slowly added a Grignard reagent from magnesium (11·4 g.), methyl iodide (30 c.c.), and ether (300 c.c.) with stirring. The complex was decomposed after 3 hr. with ice-cold dilute sulphuric acid. The ethereal layer was separated and the aqueous solution extracted with ether. The combined ethereal solutions were washed with 5% sodium hydrogen sulphite solution and water and on distillation afforded the *ether* (IV) (66·5 g., 89·6%), b. p. 140—145°/6 mm. (Found: C, 82·9; H, 8·7. $C_{13}H_{16}O$ requires C, 82·9; H, 8·5%).

7-*Methoxy*-1,6-*dimethyl*-2-*tetralone* (V).—The preceding ether (IV) (22·5 g.) was oxidised with perbenzoic acid (22·5 g.) in chloroform (300 c.c.) at 0°. The solution was washed with 8N-sodium hydroxide and evaporated. The residue was refluxed with ethanol (150 c.c.), water (120 c.c.), and concentrated sulphuric acid (15 c.c.) for 4 hr., then cooled, diluted with water, and extracted with ether. On distillation the extract yielded the ketone (V) (19 g., 77·8%), b. p. 125—135°/0·4 mm. This material was converted into its semicarbazone which was crystallised once from alcohol and then decomposed by refluxing 10% oxalic acid solution (200 c.c.). The recovered *ketone* (13·2 g., 69·4%) had 128—132°/0·4 mm. (Found: C, 75·9; H, 7·8. $C_{13}H_{16}O_2$ requires C, 76·4; H, 7·9%). The *semicarbazone* (crystallised from ethanol) had m. p. 212° (Found: C, 64·4; H, 7·5; N, 16·4. $C_{14}H_{19}N_3O_2$ requires C, 64·3; H, 7·3; N, 16·1%).

2,3,4,4a,9,10-*Hexahydro*-6-*methoxy*-1,4a,7-*trimethyl*-2-*oxophenanthrene* (VI).—The ketone (V) (5 g.) in methanol (10 c.c.) was condensed at 0° with freshly distilled 2-chloroethyl ethyl ketone (3 g.) in presence of sodium methoxide [prepared from sodium (1·15 g.) and methanol (25 c.c.)] under nitrogen. After 2 hr. at 0° the mixture was refluxed for 1 hr., cooled, poured into acidified water, and worked up as usual. The residue (3·5 g.) distilled at 180—185°/0·4 mm. It was chromatographed through alumina (100 g.) and eluted with light petroleum–benzene (4 : 1); the *phenanthrene* separated from light petroleum in needles, m. p. 87°, $\lambda_{max.}$ 246 mμ (log ε 4·2)

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[9] Fetizon, personal communication; cf. *Tetrahedron Letters*, 1960, No. 9, 16.

[10] Brandt and Thomas, *J.*, 1952, 2442.

[11] Wenkert and Jackson, *J. Amer. Chem. Soc.*, 1958, **80**, 211.

(Found: C, 80·3; H, 8·6. $C_{18}H_{22}O_2$ requires C, 80·0; H, 8·2%). The deep-red 2,4-*dinitrophenylhydrazone*, m. p. 232°, crystallised from ethyl acetate (Found: C, 64·3; H, 5·8. $C_{24}H_{26}N_4O_5$ requires C, 64·0; H, 5·8%).

1,2,3,4,4a,9-*Hexahydro*-6-*methoxy*-1,1,4aβ,7-*tetramethyl*-2-*oxophenanthrene* (VII).—To an ice-cold solution of potassium t-butoxide [from potassium (0·8 g.) in benzene (30 c.c.)] the ketone (VI) (3·5 g.) was added dropwise and the dark solution was stirred at 50—60° for 0·5 hr. under nitrogen, then cooled in ice, treated with methyl iodide (2 c.c.), refluxed for 1 hr., and poured into aqueous acid. Working up as usual gave a crude product that did not crystallise even after chromatography over neutral alumina. The 2,4-*dinitrophenylhydrazone* showed the presence of a trace of the unchanged ketone; the pure, yellow derivative, crystallised from ethanol, had m. p. 206° (Found: C, 64·3; H, 6·2. $C_{25}H_{28}N_4O_5$ requires C, 64·6; H, 6·0%).

(±)-1,2,3,4,4a,9,10,10aα-*Octahydro*-6-*methoxy*-1,1,4aβ,7-*tetramethyl*-2-*oxophenanthrene* (VIII).—The ketone (VII) (3·5 g.) was hydrogenated in ethanol (20 c.c.) in presence of 10% palladium–charcoal (250 mg.) and a drop of perchloric acid. The product (1·2 g.) obtained by chromatography through neutral alumina (100 g.) and elution with light petroleum–benzene (7 : 3) crystallised from a small quantity of light petroleum, affording the *octahydrophenanthrene*, m. p. 104° (Found: C, 80·0; H, 9·4. $C_{19}H_{26}O_2$ requires C, 79·6; H, 9·1%). The 2,4-*dinitrophenylhydrazone* crystallised from ethanol as yellowish-orange flakes, m. p. 186° (Found: C, 64·3; H, 6·5. $C_{25}H_{30}N_4O_5$ requires C, 64·3; H, 6·5%).

(±)-1,2,3,4,4a,9,10,10aα-*Octahydro*-6-*methoxy*-1,1,4aβ,7-*tetramethyl*-9-*oxophenanthrene* [(±)-*Nimbiol Methyl Ether*] (II).—The ketone (VIII) (450 mg.) in distilled diethylene glycol (35 c.c.) was heated under reflux with 100% hydrazine hydrate (0·23 c.c.) and potassium hydroxide (225 mg.) at 150° for 1 hr. and then at 210° for another hour. Dilution with water, acidification, and extraction with ether afforded the crude hydrocarbon (*ca.* 250 mg.). This was dissolved in acetic acid (3 c.c.) and oxidised overnight by chromium trioxide (310 mg.) in water (1 c.c.) and acetic acid (3 c.c.). The product was extracted with chloroform after dilution with water, and was passed through alumina (10 g.). Repeated crystallisation from methanol gave (±)-*nimbiol methyl ether* as needles, m. p. 117—118° (Found: C, 79·5; H, 9·0. $C_{19}H_{26}O_2$ requires C, 79·6; H, 9·1%). The scarlet-red 2,4-*dinitrophenylhydrazone* crystallised from ethyl acetate and had m. p. 231° (Found: C, 64·2; H, 6·3. $C_{25}H_{30}N_4O_5$ requires C, 64·3; H, 6·4%).

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INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE,
CALCUTTA-32, INDIA.

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