Synthesis of Isoquinoline Derivatives related to the *endo*-6,14-Etheno-tetrahydrothebaines. Part 2 [1]

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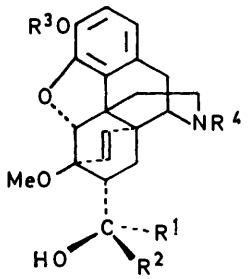
A series of secondary and tertiary alcohols have been prepared by the action of Grignard reagents on *exo*- and *endo*-7-acetyl-1,2,3,4,6,7,8,8a-octahydro-6-methoxy-2-methyl-6,8a-ethanoisoquinolines and on *exo*- and *endo*-6-acetyl-1,2,3,4,4a,5,6,7-octahydro-7-methoxy-2-methyl-4a,7-ethanoisoquinolines. Structures have been assigned to these on the basis of their n.m.r. and i.r. spectra and the analgetic activity of the compounds is described.

THE high analgetic potency of many carbinols of the general structure (1), as well as the influence of the C-7 substituents on activity,[2-10] has led to the postulate that the analgetic receptor is more extensive than originally proposed and contains an area capable of independently

[1] Part 1, T. A. Crabb and J. R. Wilkinson, *J.C.S. Perkin I*, 1976, 644.
[2] K. W. Bentley, D. G. Hardy, and B. Meek, *J. Amer. Chem. Soc.*, 1967, **89**, 3273.
[3] W. Fulmor, J. E. Lancaster, G. O. Morton, J. J. Brown, C. H. Howell, C. T. Nora, and R. A. Hardy, *J. Amer. Chem. Soc.*, 1967, **89**, 3322.
[4] J. H. van den Hende and N. R. Nelson, *J. Amer. Chem. Soc.*, 1967, **89**, 2901.
[5] K. W. Bentley and D. G. Hardy, *J. Amer. Chem. Soc.*, 1967, **89**, 3281.
[6] J. W. Lewis and M. J. Readhead, *J. Medicin. Chem.*, 1970, **13**, 525.
[7] K. W. Bentley and J. W. Lewis, reported to the Committee on Problems of Drug Dependence, 1968.
[8] J. W. Lewis, M. J. Readhead, I. A. Selby, A. C. B. Smith, and C. A. Young, *J. Chem. Soc.* (*C*), 1971, 1158.
[9] J. W. Lewis and M. J. Readhead, *J. Chem. Soc.* (*C*), 1971, 1161.
[10] K. W. Bentley, J. D. Bower, and J. W. Lewis, *J. Chem. Soc.* (*C*), 1969, 2569.

mediating analgetic effects through suitable C-7 groups.[7] It follows that destruction of the aromatic nucleus in certain derivatives might not result in complete loss of



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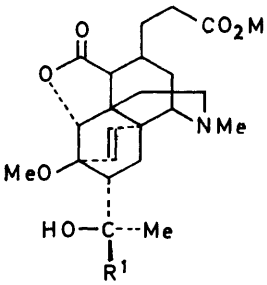

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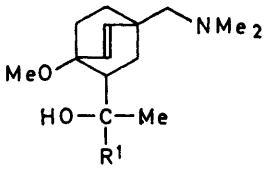

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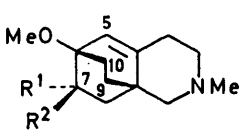
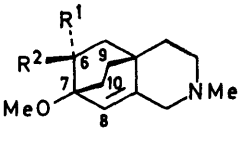
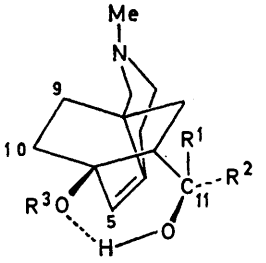




(4) R^1 = CO_2Et, R^2 = H
(5) R^1 = COMe, R^2 = H
(6) R^1 = H, R^2 = COMe
(7) R^1 = CH_2·OH, R^2 = H

(8) R^1 = CO_2Et, R^2 = H
(9) R^1 = COMe, R^2 = H
(10) R^1 = H, R^2 = COMe
(11) R^1 = CH_2·OH, R^2 = H



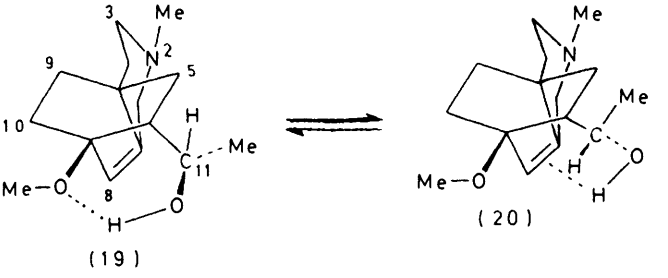
(12) R^1 = R^3 = Me, R^2 = H
(13) R^1 = H, R^2 = R^3 = Me
(14) R^1 = R^2 = Me, R^3 = Et
(15) R^1 = Ph, R^2 = Me, R^3 = Et
(16) R^1 = Me, R^2 = Ph, R^3 = Et
(17) R^1 = Pr^n, R^2 = Me, R^3 = Et
(18) R^1 = H, R^2 = Me, R^3 = Et

analgetic activity. This prediction has been verified by fission of the aromatic nucleus between C-3 and C-4 in the carbinols by ozonolysis to give lactonic esters (2; R^1 = Pr^n, Bu^n, or n-pentyl) having activities comparable with that of morphine.[11] Isomeric mixtures of simpler carbinols (3; R^1 = Me, Pr^n, or $Me_2CH·CH_2·CH_2$) showed no analgetic activity.[11]

To explore further the relevance of the aromatic nucleus as a structural requirement for morphine-like narcotic activity, the octahydroethanoisoquinolines (4)—(6) and (8)—(10) [1] were converted into alcohols by reactions with lithium aluminium hydride and with Grignard reagents. These derivatives bear some structural resemblances to the 6,14-ethenotetrahydrothebaines but lack an aromatic nucleus.

(i) *Reductions with lithium aluminium hydride.* The primary alcohols (7) and (11) were readily obtained on reduction of the esters (4) and (8) with an excess of lithium aluminium hydride.

Reduction of the *endo*-ketone (5) afforded a carbinol in the n.m.r. spectrum of which the high-field OH resonance at δ 1.49 indicates the absence of strong intramolecular hydrogen bonding with the C-6 methoxy-group.[2] However, in the i.r. spectrum (CCl_4 solution), a broad concentration-independent band at 3 520 cm^{-1} is characteristic of a weak intramolecular hydrogen bond. A Dreiding model * of one diastereoisomer (12) of the alcohol shows little apparent steric constraint to the formation of a hydrogen bond between the hydroxylic hydrogen and the methoxylic oxygen, whereas in the diastereoisomer (13) the C-11 methyl group is in a hindered environment in the hydrogen-bonded conformation. This suggests that the reduction product is the alcohol (13), in which intramolecular hydrogen



(19) (20)

bonding involving the methoxy-group is expected to be weaker than for the other possible alcohol (12).

Reduction of the *endo*-ketone (9) also yielded one product, which was isolated as a crystalline solid (m.p. 66°) by column chromatography over neutral alumina. Structure (19), rather than the epimeric structure, was assigned to this secondary alcohol on the basis of n.m.r. and i.r. data. The n.m.r. spectrum is similar to that of the alcohol (13), and suggests that both alcohols belong to the same stereochemical series. In the i.r. spectrum (CCl_4 solution), bands at 3 520 and 3 570 cm^{-1} (independent of concentration) may be attributed to weak hydrogen bonding with the methoxy-group as in (19) or with the π-electron cloud of the C=C bond in an alternative conformer (20).

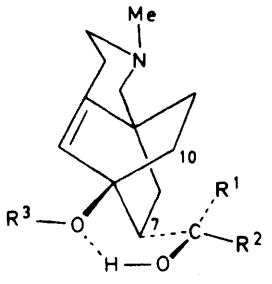
When the *exo*-ketone (6) was reduced with lithium

* For ease of representation some distortion of perspective has been introduced in many of the structures depicted in this paper, particularly of the trigonal geometry at C-4a in compounds of the type (12)—(18).

[11] K. W. Bentley, D. G. Hardy, and P. A. Mayor, *J. Chem. Soc.* (*C*), 1969, 2385.

aluminium hydride, a mixture of the two diastereoisomeric alcohols (21) and (25) was obtained (ratio *ca.* 5 : 3, as shown by t.l.c. and the n.m.r. spectrum). These were separated by column chromatography over neutral alumina to give the major isomer as a viscous liquid and the minor isomer as a crystalline solid (m.p. 95°).

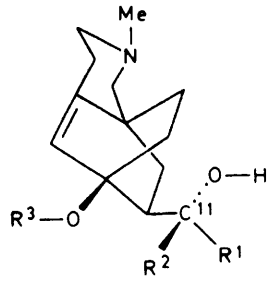
In the 60 MHz n.m.r. spectrum of the major isomer, a low-field OH resonance at δ 5.05 (removed by D_2O) is indicative of hydrogen bonding. This is confirmed by a broad i.r. band at 3 460 cm^{-1} (independent of concentration) which suggests that there is a strong intramolecular hydrogen bond between the hydroxylic hydrogen and the methoxy-group. Dreiding models show that such hydrogen bonding should occur readily



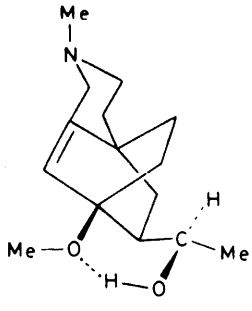
(21) R^1 = H, R^2 = R^3 = Me
(22) R^1 = R^2 = Me, R^3 = Et
(23) R^1 = Me, R^2 = Ph, R^3 = Et
(24) R^1 = Me, R^2 = Pr^n, R^3 = Et

Reduction of the corresponding *exo*-ketone (10) similarly yielded a *ca.* 65 : 35 mixture of diastereoisomeric secondary alcohols. These were separated by chromatography over alumina and are represented by structures (27) and (28). The major isomer was obtained as a viscous liquid and the minor isomer as a crystalline solid (m.p. 93°).

The spectral characteristics [δ 5.00 (OH); $\nu_{max.}$ 3 460 cm^{-1} (concentration independent)] of the major isomer closely resemble those of the alcohol (21), indicating the stereochemically analogous structure (27). The hydroxylic proton of the minor isomer gives rise to a high field singlet at δ 1.83 and a sharp i.r. band at 3 610 cm^{-1} (free O–H stretching), supporting the assignment of the non-hydrogen-bonded structure (28).



(25) R^1 = R^3 = Me, R^2 = H
(26) R^1 = Me, R^2 = H, R^3 = Et



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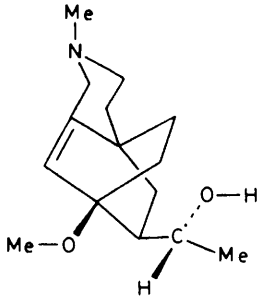

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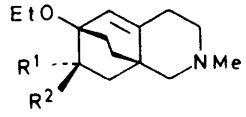


(29) R^1 = H, R^2 = COMe
(30) R^1 = COMe, R^2 = H

in the alcohol (21), but would involve steric interaction between the C-11 methyl group and the ethano-bridge in the alcohol (25). The major isomer is therefore assigned structure (21).

The assignment of stereochemistry to the minor isomer (25) is supported by the high-field OH resonance at δ 1.40 and a sharp i.r. absorption band at 3 610 cm^{-1} (independent of concentration) characteristic of free O–H stretching. It is therefore considered that in the preferred conformation of the alcohol (25), the C-11 methyl group takes up a position involving minimum steric hindrance so that hydrogen bonding between the hydroxy- and methoxy-groups does not occur.

(ii) *Grignard reactions.* The *exo*-ketone (29) and the *endo*-ketone (30) [1] were used as starting materials for Grignard reactions.

(a) *Reaction with methylmagnesium iodide.* The tertiary alcohol (14), m.p. 74°, was prepared by the reaction of the *endo*-ketone (30) with methylmagnesium iodide in ether solution. In the i.r. spectrum of the alcohol (14), a strong, sharp band at 3 490 cm^{-1} (independent of concentration) indicates intramolecular hydrogen bonding involving the OH and OEt groups. This is supported by an n.m.r. singlet due to OH at relatively low field (δ 5.07). The two C-11 methyl groups give two singlets of very similar chemical shifts

(δ 0.99 and 1.00) and the one-proton triplet at δ 2.09 ($'J'_{7\alpha,8\alpha} = {}'J'_{7\alpha,8\beta} = 8.5$ Hz) is attributed to the 7β-methine proton.

Similar treatment of the *exo*-ketone (29) with methylmagnesium iodide yielded the tertiary alcohol (22). Clear evidence of intramolecular hydrogen bonding in the *exo*-carbinol (22) is provided by a strong, concentration-independent i.r. band at 3 480 cm^{-1} and a one-proton n.m.r. singlet at δ 5.22. A significant aspect of the n.m.r. spectrum, as compared with that of the *endo*-carbinol (14), is the difference in chemical shifts (δ 1.08 and 1.37) of the two C-11 methyl groups. The lower field singlet at δ 1.37 is considered to arise from the methyl group lying near to the ethano-bridge in the conformation involving hydrogen bonding between the hydroxy- and ethoxy-groups. Another characteristic feature of the n.m.r. spectrum of the *exo*-carbinol (22) is the signal at δ 1.83 attributed to the 7α-proton. The observed splitting is considered to approximate to vicinal coupling with H-8α ($'J'_{7\alpha,8\alpha}$ 11.5 Hz) and H-8β ($'J'_{7\alpha,8\beta}$ 7.5 Hz) as well as long-range coupling with H-10 (J 2 Hz).

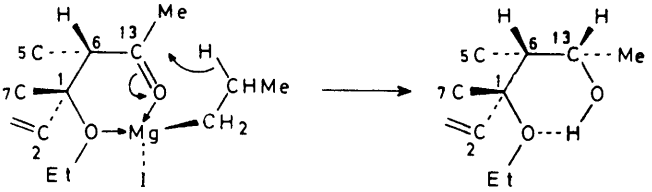
(b) *Reaction with phenylmagnesium bromide.* The reaction of the *endo*-ketone (30) with phenylmagnesium bromide occurred readily to give only one (m.p. 102°) of the two possible diastereoisomeric carbinols. Intramolecular hydrogen bonding in this carbinol [strong i.r. absorption at $\nu_{max.}$ 3 460 cm^{-1}; δ 5.52 (OH)] suggests that the probable stereochemistry is that represented by structure (15), in which hydrogen bonding between the hydroxy- and ethoxy-groups involves less steric hindrance of the phenyl group than in structure (16). Further evidence supporting the assignment of stereochemistry (15) is provided by the 220 MHz n.m.r. spectrum. The resonance due to the olefinic proton is at slightly lower field (δ 5.98) than those for the other *endo*-carbinols [*e.g.* δ 5.90 for (14)]. In the hydrogen-bonded conformation (15), the phenyl group points away from the olefinic proton, which lies almost in the plane of the aromatic ring and may experience a small deshielding effect. The corresponding most likely hydrogen-bonded conformation of the diastereoisomeric carbinol (16) requires the phenyl group to be disposed closer to the olefinic proton which lies above the aromatic ring. A strong shielding effect on the olefinic proton in the carbinol (16) would therefore be anticipated.

The high degree of stereoselectivity observed in these Grignard reactions has been attributed to the formation of a six-membered intermediate in which magnesium completes its outer electron shell by co-ordination with the oxygen atoms of the carbonyl group and the adjacent alkoxy-group.[2] Assuming that the reaction of the *endo*-ketone (30) with phenylmagnesium bromide involves co-ordination of magnesium with the C-11 carbonyl and C-6 ethoxy-oxygen atoms, the expected product is the carbinol (15), since approach from the other side of the carbonyl group is more hindered.

The *exo*-ketone (29) also reacted with phenylmagnesium bromide, to give only one carbinol which was isolated as a crystalline solid (m.p. 105°) by chromatography over neutral alumina. On mechanistic grounds the expected product is the carbinol (23). Intramolecular hydrogen bonding in (23) is indicated by a strong i.r. band at 3 460 cm^{-1} (independent of concentration) and OH absorption at δ 5.66. Comparison of Dreiding models of the two possible structures in hydrogen-bonded conformations shows less hindrance involving the phenyl group in the isomer (23) than in its epimeric structure.

(c) *Reaction with n-propylmagnesium iodide.* Reaction of the *endo*-ketone (30) with n-propylmagnesium iodide was found to be highly stereoselective, producing only one of the two possible tertiary alcohols (m.p. 86°), which was assigned the stereochemistry shown in (17) by analogy with the corresponding phenyl carbinols and the assumption of similar stereochemistry in their synthesis, since the n.m.r. spectrum afforded no clear indication of configuration at C-11.

The initial product obtained from the reaction between the ketone (30) and n-propylmagnesium iodide contained another carbinol (m.p. 51°) in addition to (17). This was assigned the secondary alcoholic structure (18) arising from Grignard reduction of the *endo*-ketone since a cyclic intermediate [in which magnesium co-ordinates with both oxygen atoms of the ketone (30)] is involved in the Grignard reduction [see



(31) (32)

(31) ⟶ (32)]. In addition, the i.r. and n.m.r. spectra of the carbinols (13) and (18) are very similar and verify that both compounds have the same configuration at C-11.

Chromatographic separation of the products of the reaction between the *exo*-ketone (29) and n-propylmagnesium iodide afforded a tertiary carbinol (Grignard product) (24) and a secondary alcohol (reduction product) (26).

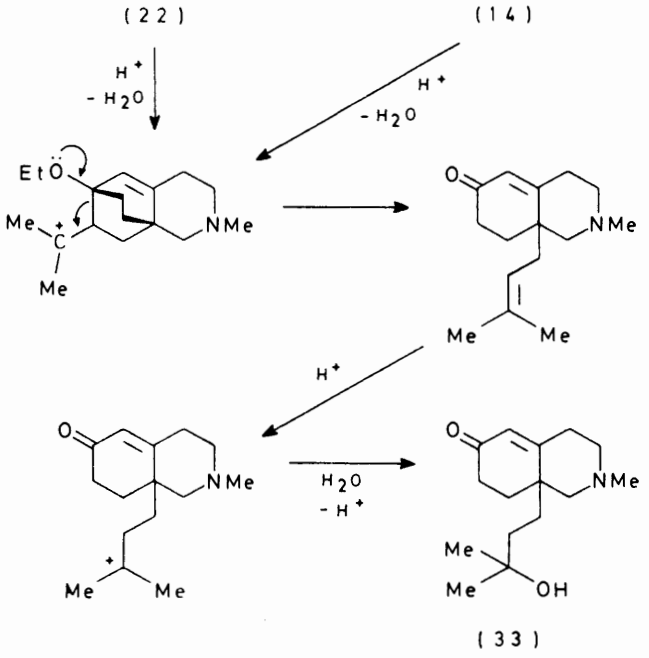
Intramolecular hydrogen bonding in the tertiary carbinol (24) is indicated by i.r. absorption at $\nu_{max.}$ 3 480 cm^{-1} and the chemical shift of the hydroxy-proton (δ 5.07). Support for the suggested configuration at C-11 is provided by a comparison of the C-11 methyl resonance for the carbinol (24) (δ 1.37) with those for the dimethyl carbinol (22) (δ 1.37 and 1.08). In each hydrogen-bonded carbinol one of the C-11 methyl groups occupies a similar environment (close to the ethano-bridge) resulting in the observed relative deshielding.

The assignment of structure (26) to the accompanying reduction product was verified by comparison of spectral

data for the stereochemically analogous secondary alcohol (25).

(iii) *Acid-catalysed rearrangements.* Most of the carbinols described above are unstable in the presence of acid: dehydration and rearrangement can occur. Alcohols of the 6,14-*endo*-ethenotetrahydrothebaine series,[2] which are structurally related to these carbinols, also undergo acid-catalysed dehydration and rearrangement, the course of which depends on the nature of the hydroxy-substituted group and the conditions of the reaction.[12] The results of such rearrangements have been investigated extensively.[12-14]

Rearrangement of the *exo*-dimethyl carbinol (22) by the action of 2N-hydrochloric acid at 100 °C occurred smoothly to give a viscous oil, $C_{15}H_{25}N_2O$ [on the basis of analytical data for the picrate, m.p. 200° (decomp.)]. The rearrangement product was a hydroxy-compound



SCHEME Rearrangement of the epimeric tertiary carbinols (22) and (14) in 2N-hydrochloric acid at 100 °C

which exhibited strong i.r. absorption at $\nu_{max.}$ 3 400 cm^{-1} (broad). In the n.m.r. spectrum, a singlet at δ 2.10 (removed by D_2O) represented the hydroxylic proton and a resonance at δ 5.80 was attributed to one olefinic proton. A three-proton singlet at δ 2.27 was characteristic of an *N*-methyl group and a six-proton singlet at δ 1.27 was assigned to two methyl groups. U.v. absorption at $\lambda_{max.}$ 235 nm (ε 11 000) and a strong i.r. band at 1 660 cm^{-1} indicated the presence of an αβ-unsaturated ketone.

The above information provides convincing evidence for structure (33) (Scheme). The corresponding *endo*-carbinol (14) also underwent rearrangement to the hydroxy-enone (33), but required more prolonged heating for complete conversion. Rearrangement of the carbinols (22) and (14) to give the same product (33) is a further demonstration that these carbinols are C-11 epimers.

Biological Activity.—The antinociceptive activities of the compounds are summarised in the Table. None of

Biological activities [a] [antagonism of phenylquinone-induced writhing (PQ) [15] and hot plate test (HP) [16]]

Compound	PQ (100 mg per kg body weight orally)	HP (50 mg per kg body weight s.c.)
Codeine	++ (20 mg per kg)	++
(14)	± (50 mg per kg)	−
(15)	− (50 mg per kg)	−
(17)	− (50 mg per kg)	±
(19)	+	−
(23)	−	−
(24)	+	−

[a] Details of tests are given in ref. 1.

the compounds tested showed potent analgetic activity; two were weakly active. This lack of activity as compared with thebaine suggests that the aromatic ring is important for efficient binding to the biological receptor.

EXPERIMENTAL

Elemental analyses were carried out by the Analytical Section, Department of Chemistry, Portsmouth Polytechnic. I.r. spectra were determined for liquid films or solutions in carbon tetrachloride with a Perkin-Elmer 237 spectrometer. N.m.r. spectra were determined with a Varian T60 or HR-220 spectrometer for solutions in deuteriochloroform. U.v. spectra were recorded with a Unicam SP 800 A instrument for solutions in ethanol.

Reduction of the Esters (4) *and* (8) *with Lithium Aluminium Hydride.*—A solution of the *endo*-ester (0.35 g) in dry ether (10 ml) was added, with continuous stirring, to a suspension of lithium aluminium hydride (0.2 g) in dry ether (20 ml). After 2 h, wet ether and water were added and the ethereal solution was filtered from inorganic material. The dried ethereal extract was evaporated to leave the primary alcohol (7) or (11), as a viscous oil. 1,2,3,4,6,7,8,8a-*Octahydro-7α-hydroxymethyl-6-methoxy-2-methyl-6,8a-ethanoisoquinoline* (7) (0.19 g) distilled at 110 °C and 0.05 mmHg (Found: C, 70.9; H, 9.4; N, 13.3. $C_{14}H_{23}NO_2$ requires C, 70.8; N, 9.7; N, 13.5%). 1,2,3,4,4a,5,6,7-*Octahydro-6α-hydroxymethyl-7-methoxy-2-methyl-4a,7-ethanoisoquinoline* (11) (0.17 g) distilled at 114—116 °C and 0.07 mmHg (Found: C, 70.6; H, 9.5; N, 13.5. $C_{14}H_{23}NO_2$ requires C, 70.8; H, 9.7; N, 13.5%).

Reduction of Ketone Adducts with Lithium Aluminium Hydride (General Procedure).—A solution of the methoxy-ketone (1.0 g) in dry ether (20 ml) was added dropwise, with continuous stirring, to a suspension of lithium aluminium hydride (0.5 g) in dry ether (50 ml). The mixture was stirred for 2 h and the reduction product was then liberated by addition of wet ether followed by water. The

[12] K. W. Bentley, D. G. Hardy, and B. Meek, *J. Amer. Chem. Soc.*, 1967, **89**, 3293.

[13] K. W. Bentley, D. G. Hardy, C. F. Howell, W. Fulmor, J. E. Lancaster, J. J. Brown, G. O. Morton, and R. A. Hardy, *J. Amer. Chem. Soc.*, 1967, **89**, 3303.

[14] K. W. Bentley, D. G. Hardy, B. Meek, J. B. Taylor, J. J. Brown, and G. O. Morton, *J. Chem. Soc.* (*C*), 1969, 2229.

[15] L. C. Hendershot and J. Forsaith, *Proc. Soc. Exp. Biol. Med.*, 1959, **125**, 237.

[16] G. Woolfe and A. D. MacDonald, *J. Pharmacol.*, 1944, **80**, 300.

ethereal solution was decanted and the inorganic residue was thoroughly washed with ether. The combined ethereal extracts were dried (Na_2SO_4) and evaporated and the remaining liquid was distilled under reduced pressure.

1,2,3,4,6,7,8,8a-*Octahydro*-7α-[(S)-1-*hydroxyethyl*]-6-*methoxy*-2-*methyl*-6,8a-*ethanoisoquinoline* (13), b.p. 114—116° at 0.01 mmHg (0.8 g), was obtained by reduction of the *endo*-ketone (5) (1.0 g); δ 5.90 (1 H, s, olefinic), 3.98 (1 H, m, $J_{CH,Me}$ 6.5, $J_{CH,H\text{-}7}$ 2 Hz, C*H*·CH$_3$), 3.37 (3 H, s, OMe), 2.30 (3 H, s, NMe), 2.08 (1 H, t, $'J'_{7\beta,8\beta} = 'J'_{7\beta,8\alpha} =$ 8 Hz, H-7), 1.01 (3 H, d, J 6.5 Hz, CH*Me*), and 1.49 (1 H, s, OH). The *methiodide* had m.p. 178° (from ethanol) (Found: C, 48.9; H, 7.4; N, 3.3. $C_{16}H_{28}NO_2I$ requires C, 48.8; H, 7.1; N, 3.6%).

1,2,3,4,4a,5,6,7-*Octahydro*-6α-[(S)-1-*hydroxyethyl*]-7-*methoxy*-2-*methyl*-4a,7-*ethanoisoquinoline* (19) was similarly formed by reduction of the *endo*-ketone (5) (1.0 g). When the resultant viscous liquid (0.8 g) was purified by column chromatography on Wöelm neutral alumina (activity III; eluants light petroleum and ether) the secondary carbinol (19) was isolated as a crystalline solid (0.5 g), m.p. 66° (from light petroleum) (Found: C, 71.5; H, 10.1; N, 5.4. $C_{15}H_{25}NO_2$ requires C, 71.7; H, 10.0; N, 5.6%); δ 5.90 (1 H, s, olefinic), 3.36 (3 H, s, OMe), 3.15 (2 H, m, J_{gem} −15, $J_{1\text{-}H,8\text{-}H}$ 2 Hz, C-1 methylene), 2.28 (3 H, s, NMe), 1.01 (3 H, d, J 6.5 Hz, CH*Me*), 3.96 (1 H, m, C*H*OH), and 1.56 (1 H, s, OH).

1,2,3,4,6,7,8,8a-*Octahydro*-7β-[(S)-1-*hydroxyethyl*]-6-*methoxy*-2-*methyl*-6,8a-*ethanoisoquinoline* (21) and its R-*isomer* (25) were obtained as a mixture (0.9 g) (ratio 5 : 3) by reduction of the *exo*-ketone (6) (1.0 g). Separation by column chromatography on Wöelm neutral alumina (activity III; eluants light petroleum and ether) afforded first the intramolecularly hydrogen-bonded carbinol (21) as a viscous liquid (0.4 g), b.p. 112° at 0.01 mmHg (Found: C, 71.5; H, 10.2; N, 5.5. $C_{15}H_{25}NO_2$ requires C, 71.7; H, 10.0; N, 5.6%) and then the epimeric carbinol (25) (0.2 g) as a crystalline solid, m.p. 95° (from light petroleum) (Found: C, 71.6; H, 10.1; N, 5.6%); δ for carbinol (21) 6.05 (1 H, s, olefinic), 3.42 (3 H, s, OMe), 2.30 (3 H, s, NMe), 1.18 (3 H, d, J 6 Hz, CH*Me*), 3.80 (1 H, m, C*H*OH), and 5.05 (1 H, s, OH); δ for carbinol (25) 6.05 (1 H, s, olefinic), 3.35 (3 H, s, OMe), 2.30 (3 H, s, NMe), 1.20 (3 H, d, J 6.5 Hz, CH*Me*), 4.20 (1 H, m, C*H*OH), 2.45 (2 H, J −12 Hz, C-1 methylene), and 1.40 (1 H, s, OH).

1,2,3,4,4a,5,6,7-*Octahydro*-6β-[(S)-1-*hydroxyethyl*]-7-*methoxy*-2-*methyl*-4a,7-*ethanoisoquinoline* (27) and its R-*isomer* (28) were similarly produced as a mixture (0.9 g) by reduction of the *exo*-ketone (10) (1.0 g). The two diastereoisomers were again separated by chromatography on neutral alumina (elution with light petroleum and ether). The hydrogen-bonded carbinol was eluted first as a viscous liquid (0.4 g), b.p. 114° at 0.01 mmHg (Found: C, 71.7; H, 10.05; N, 5.7. $C_{15}H_{25}NO_2$ requires C, 71.7; H, 10.05; N, 5.6%), δ 5.97 (1 H, s, olefinic), 3.40 (3 H, s, OMe), 2.30 (3 H, s, NMe), 1.18 (3 H, d, J 6 Hz, CH*Me*), 3.80 (1 H, m, C*H*OH), and 5.00 (1 H, s, OH). The isomeric carbinol (28) (0.2 g) had m.p. 93° (from light petroleum) (Found: C, 71.9; H, 9.9; N, 5.4%); δ 6.07 (1 H, s, olefinic), 3.37 (3 H, s, OMe), 2.33 (3 H, s, NMe), 1.23 (3 H, d, J 6.5 Hz, CH*Me*), 4.20 (1 H, m, C*H*OH), and 1.83 (1 H, s, OH).

Reactions of the Ketones (29) *and* (30) *with Methylmagnesium Iodide.*—A solution of methylmagnesium iodide (in excess) in dry ether was prepared by dropwise addition of methyl iodide (1.42 g) in dry ether (20 ml) to clean magnesium turnings (0.25 g) in dry ether (40 ml), followed by heating under reflux on a water-bath to ensure complete formation of the Grignard reagent. After cooling to room temperature, a solution of the ethoxy-ketone (1.0 g) in dry ether (20 ml) was added dropwise with stirring. The mixture was heated under reflux on a water-bath for 2 h and then carefully poured into ammonium chloride solution (5 g in 10 ml of water) to liberate the tertiary carbinol. The ethereal solution was separated from the aqueous layer, which was further extracted with ether. The combined ethereal extracts were dried (Na_2SO_4) and evaporated and the product was distilled under reduced pressure.

6-*Ethoxy*-1,2,3,4,6,7,8,8a-*octahydro*-7α-(1-*hydroxy*-1-*methylethyl*)-2-*methyl*-6,8a-*ethanoisoquinoline* (14), b.p. 120° at 0.02 mmHg, was obtained by the reaction of the *endo*-ketone (30) (1.0 g) with methylmagnesium iodide. The viscous liquid (1.0 g) crystallised on cooling and recrystallisation from light petroleum yielded the pure tertiary carbinol, m.p. 74° (Found: C, 72.9; H, 10.5; N, 5.1. $C_{17}H_{29}NO_2$ requires C, 73.1; H, 10.5; N, 5.0%), δ 5.90 (1 H, s, olefinic), 2.29 (3 H, s, NMe), 3.61 (2 H, q, O·C*H*$_2$·CH$_3$), 1.23 (3 H, t, O·CH$_2$·C*H*$_3$), 0.99 (3 H, s, 11-Me), 1.00 (3 H, s, 11-Me), 5.07 (1 H, s, OH), 2.09 (1 H, t, $J_{7\alpha,8\alpha} = J_{7\alpha,8\beta} =$ 8.5 Hz, H-7β), and 2.28 (2 H, q, J −12 Hz, C-1 methylene).

The 7β-(1-*hydroxy*-1-*methylethyl*) *isomer* (22) was similarly produced by the reaction of the *exo*-ketone (29) (1.0 g) with methylmagnesium iodide. The tertiary carbinol (22) was distilled at 118—120° and 0.02 mmHg (0.8 g), and was purified by chromatography on Wöelm neutral alumina (activity III; elution with light petroleum and ether) to give a viscous oil (0.5 g), b.p. 120° at 0.03 mmHg, δ 6.08 (1 H, s, olefinic), 2.32 (3 H, s, NMe), 3.57 (2 H, q, O·C*H*$_2$·CH$_3$), 1.23 (3 H, t, O·CH$_2$·C*H*$_3$), 1.08 (3 H, s, 11-Me), 1.37 (3 H, s, 11-Me), 5.22 (1 H, s, OH), and 1.83 (1 H, m, $J_{7\alpha,8\alpha}$ 11.5, $J_{7\alpha,8\beta}$ 7.5, $J_{7\alpha,10}$ 2 Hz, 7α-H); *picrate*, m.p. 173° (from ethanol) (Found: C, 54.4; H, 6.2; N, 10.8. $C_{23}H_{32}N_4O_9$ requires C, 54.3; H, 6.3; N, 11.0%).

Reactions of the Ketones (29) *and* (30) *with Phenylmagnesium Bromide.*—A solution of the ethoxy-ketone (1.0 g) in dry ether (20 ml) was added dropwise with stirring to an excess of phenylmagnesium bromide in dry ether (60 ml), prepared from bromobenzene (1.57 g) and magnesium turnings (0.25 g). The mixture was heated under reflux on a water-bath for 2 h, cooled, and slowly poured into ammonium chloride solution (5 g in 10 ml of water). After separation of the ethereal layer, the aqueous layer was extracted with ether and the combined ethereal extracts were dried (Na_2SO_4) and evaporated. The crystalline carbinol was isolated from the residual liquid by column chromatography on Wöelm neutral alumina (elution with light petroleum and ether).

6-*Ethoxy*-1,2,3,4,6,7,8,8a-*octahydro*-7α-[(S)-1-*hydroxy*-1-*phenylethyl*]-2-*methyl*-6,8a-*ethanoisoquinoline* (15) was obtained by the reaction of the *endo*-ketone (30) (1.0 g) with phenylmagnesium bromide. The pure tertiary carbinol (15) (0.8 g) had m.p. 102° (from light petroleum) (Found: C, 77.7; H, 9.3; N, 4.1. $C_{22}H_{31}NO_2$ requires C, 77.4; H, 9.15; N, 4.1%); δ 5.98 (1 H, s, olefinic), 2.21 (1 H, s, NMe), 1.44 [3 H, s, C(OH)*Me*], 7.13—7.44 (5 H, m, aromatic), 3.69 (2 H, q, O·C*H*$_2$·CH$_3$), 1.30 (3 H, t, O·CH$_2$·C*H*$_3$), and 5.52 (1 H, s, OH).

The 7β-[(R)-1-*hydroxy*-1-*phenylethyl*] *isomer* (23) was formed by the reaction of the *exo*-ketone (29) (1.0 g) with phenylmagnesium bromide. The pure carbinol (23), m.p. 105° (0.75 g), crystallised from light petroleum

as needles (Found: C, 77.6; H, 9.35; N, 4.2%); δ 6.08 (1 H, s, olefinic), 2.21 (1 H, s, NMe), 1.80 [3 H, s, C(OH)*Me*], 7.08—7.45 (5 H, m, aromatic), 3.64 (2 H, q, O·C*H*$_2$·CH$_3$), 1.27 (3 H, t, O·CH$_2$·C*H*$_3$), and 5.60 (1 H, s, OH).

Reactions of Ketones (29) *and* (30) *with n-Propylmagnesium Iodide*.—A solution of n-propylmagnesium iodide in dry ether (80 ml) was prepared from 1-iodopropane (1.70 g) and magnesium turnings (0.25 g). The ethoxy-ketone (1.0 g) in dry ether (20 ml) was added dropwise, with stirring. After heating under reflux on a water-bath for 6 h, the cooled mixture was cautiously poured into ammonium chloride solution (5 g in 10 ml of water). The ethereal layer was separated, the aqueous layer was extracted with ether, and the combined ethereal extracts were dried (Na_2SO_4) and evaporated to leave a mixture of Grignard reaction and reduction products.

6-*Ethoxy*-1,2,3,4,6,7,8,8a-*octahydro*-7α-[(R)-1-*hydroxy*-1-*methylbutyl*]-2-*methyl*-6,8a-*ethanoisoquinoline* (17) and 6-*ethoxy*-1,2,3,4,6,7,8,8a-*octahydro*-7α-[(S)-1-*hydroxyethyl*]-2-*methyl*-6,8a-*ethanoisoquinoline* (18) were obtained as a mixture (1.1 g) from the *endo*-ketone (30) (1.0 g). Chromatography on Wöelm neutral alumina (activity III; eluants light petroleum and ether) gave first the tertiary carbinol (17) (0.7 g) and then the secondary carbinol (18) (0.2 g). The carbinol (17) crystallised from light petroleum as needles, m.p. 86° (Found: C, 74.1; H, 10.9; N, 4.3. $C_{19}H_{33}NO_2$ requires C, 74.2; H, 10.8; N, 4.6%), δ 5.95 (1 H, s, olefinic), 2.36 (3 H, s, NMe), 0.98 [3 H, s, C(OH)*Me*], 0.86 (3 H, t, *J* 7.5 Hz, CH$_2$·CH$_2$·C*H*$_3$), 5.03 (1 H, s, OH), 3.60 (2 H, q, *J* 7 Hz, O·C*H*$_2$·CH$_3$), 1.23 (3 H, t, *J* 7 Hz, O·CH$_2$·C*H*$_3$), 2.14 (1 H, t, *J* 8.5 Hz, H-7β), 2.38 (2 H, *J* −12 Hz, C-1 methylene), 1.00 (3 H, s, 11-Me), and 5.03 (1 H, s, OH); $\nu_{max.}$ 3 480 cm^{-1}. The secondary carbinol (18) had m.p. 51° (from light petroleum) (Found: C, 72.3; H, 10.0; N, 5.4. $C_{16}H_{27}NO_2$ requires C, 72.4; H, 10.2; N, 5.3%); δ 5.87 (1 H, s, olefinic), 2.32 (3 H, s, NMe), 3.57 (2 H, q, O·C*H*$_2$·CH$_3$), and 1.25 (3 H, t, O·CH$_2$·C*H*$_3$); $\nu_{max.}$ 3 520 cm^{-1} (concentration independent).

6-*Ethoxy*-1,2,3,4,6,7,8,8a-*octahydro*-7β-[(S)-1-*hydroxy*-1-*methylbutyl*]-2-*methyl*-6,8a-*ethanoisoquinoline* (24) and 6-*ethoxy*-1,2,3,4,6,7,8,8a-*octahydro*-7β-[(R)-1-*hydroxyethyl*]-2-*methyl*-6,8a-*ethanoisoquinoline* (26) were similarly formed as a mixture (1.0 g) from the *exo*-ketone (29) (1.0 g). Column chromatography on Wöelm neutral alumina (activity III; elution with light petroleum and ether) afforded unchanged ketone (29) (0.2 g), the tertiary carbinol (24) (0.5 g), and the secondary carbinol (26) (0.1 g). The tertiary carbinol (24) was a viscous oil, b.p. 135° at 0.02 mmHg (Found: C, 74.0; H, 10.75; N, 4.4. $C_{19}H_{33}NO_2$ requires C, 74.2; H, 10.8; N, 4.6%); δ 6.10 (1 H, s, olefinic), 2.35 (3 H, s, NMe), 1.37 [3 H, s, C(OH)*Me*], 0.93 (3 H, t, CH$_2$·CH$_2$·C*H*$_3$), 5.07 (1 H, s, OH), 3.60 (2 H, q, O·C*H*$_2$·CH$_3$), and 1.23 (3 H, t, O·CH$_2$·C*H*$_3$). The secondary carbinol (26) was distilled at 118 °C and 0.01 mmHg (Found: C, 72.25; H, 10.4; N, 5.1. $C_{16}H_{27}NO_2$ requires C, 72.4; H, 10.2; N, 5.3%); δ 6.03 (1 H, s, olefinic), 2.32 (3 H, s, NMe), 1.22 [3 H, d, CH(OH)*Me*], 4.20 (1 H, m, C*H*OH), 2.70 (1 H, s, OH), 3.57 (2 H, q, O·C*H*$_2$·CH$_3$), and 1.25 (3 H, t, O·CH$_2$·C*H*$_3$).

Acid-catalysed Rearrangement of the Carbinols (14) *and* (22).—The dimethyl carbinol (0.5 g) was dissolved in 2N-hydrochloric acid (10 ml) and heated on a water-bath for 4 h. After basification with 10% sodium hydroxide solution and extraction with ether, the ethereal solution of the rearrangement product was dried (Na_2SO_4) and evaporated. 1,3,4,7,8,8a-Hexahydro-8a-(3-hydroxy-3-methylbutyl)-2-methylisoquinolin-6(2*H*)-one was obtained as a viscous oil (0.3 g). The *picrate* had m.p. 200° (decomp.) (from ethanol) (Found: C, 52.2; H, 5.5; N, 12.0. $C_{21}H_{28}N_4O_9$ requires C, 52.5; H, 5.8; N, 11.7%).

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