Studies on the Syntheses of Heterocyclic Compounds. Part 680.† Abnormal Formation of Aporphine Derivatives by Grewe Cyclisation

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Grewe cyclisation of 1,2,3,4,5,8-hexahydro-1-(4-hydroxybenzyl)-2-methylisoquinoline (5) under various conditions gave the aporphines (11), (12), and (14); the structures of (11) and (12) were confirmed by alternative syntheses.

APORPHINE-TYPE compounds [1,2] have been synthesised usually by Pschorr reactions [3] of 1-(2-aminobenzyl)-1,2,3,4-tetrahydroisoquinolines, but recently several modified synthetic methods have been reported: photo-Pschorr reactions of 1-(2-aminobenzyl)-1,2,3,4-tetrahydroisoquinolines,[4] photocyclisations [4] or benzyne reactions [5] of 1-(2-halogenobenzyl)-1,2,3,4-tetrahydro-7-hydroxyisoquinolines, and phenolic oxidations [6] of diphenolic isoquinolines. We now report a new route to aporphines by application of Grewe cyclisation,[7] which has been used widely in syntheses of morphinan-type compounds such as morphine,[8] levorphanol,[9,10] and pentazocine.[11,12]

Our aim in this study was a synthesis of morphinan-3-ol (10) [13] from 1,2,3,4,5,8-hexahydro-1-(4-hydroxybenzyl)-2-methylisoquinoline (5) and its methyl ether (4) by Grewe cyclisation; the starting materials were prepared as follows.

Although Sugasawa [14] had reported that a Bischler–Napieralski reaction of *N*-(2-cyclohexa-1,4-dienylethyl)-4-methoxyphenylacetamide (1) with phosphoryl chloride in boiling benzene gave the 3,4-dihydroisoquinoline (6) by cyclisation and aromatisation, the reaction in our hands with the same reagent in acetonitrile at 47—49 °C gave the expected 3,4,5,8-tetrahydroisoquinoline (2), which without isolation was reduced with sodium borohydride to afford the 1,2,3,4,5,8-hexahydroisoquinoline (3), characterised as the hydrochloride, in 30% yield. The n.m.r. spectrum of (3) showed signals for two olefinic protons at δ 5.66 as a singlet and four aromatic protons at δ 6.72 (2 H) and 7.05 (2 H) as doublets (*J* 9 Hz). An Eschweiler–Clarke reaction of the hexahydroisoquinoline (3) with formic acid and 37% formalin provided the 1,2,3,4,5,8-hexahydro-2-methylisoquinoline (4), characterised as the oxalate, in 85% yield. An attempted synthesis of (4) from 1,2,3,4-tetrahydro-1-(4-methoxybenzyl)-2-methylisoquinoline (7) [15] by Birch reduction with metallic lithium in liquid ammonia and ethanol failed, giving instead 1,2,3,4,5,8-hexahydro-1-(4-methoxycyclohexa-1,4-dienylmethyl)-2-methylisoquinoline (9) [$\nu_{max.}$ 1 685 and 1 655 cm^{-1} (enol ether); [16] δ 3.53 (HC:C·O*Me*), 4.62 (C*H*:C·OMe), and 5.71 (olefinic H-6 and -7) (no aromatic proton signals)]. However, Birch reduction of the phenolic base (8), prepared by demethylation of (7) with 48% hydrobromic acid,[15] under the same conditions, afforded the expected 1,2,3,4,5,8-hexahydro-1-(4-hydroxybenzyl)-2-methylisoquinoline (5) in 52% yield [δ 5.63 (2 H, s, :CH) and 6.45 and 6.93 (each 2 H, d, *J* 9 Hz, aromatic)].

Grewe cyclisation of 1,2,3,4,5,8-hexahydro-1-(4-methoxybenzyl)-2-methylisoquinoline (4) was examined under various conditions, but a pure product could not be isolated. Similarly, Grewe cyclisation of the phenolic base (5) was investigated; only a reaction with 85% phosphoric acid at 120—130 °C gave a pure product, in 13.3% yield, identified as the 1,2,3,11b-tetrahydroaporphine (11). The expected morphinan (10) was not obtained. The n.m.r. spectrum of the product (11), showed signals for three aromatic protons at δ 6.37—7.07 (multiplet) but lacked an olefinic proton resonance. The structure (11) was proved by an alternative synthesis as described later. Its formation may be explained in terms of acid-catalysed isomerisation of the unconjugated diene (5) to give the conjugated diene (5a), in which the less hindered carbon atom is attacked by the aromatic ring (Scheme).

Treatment of the oxalate of (5) with 85% phosphoric acid at 120—130 °C afforded 6-methylaporphin-10-ol (12), together with the 1,2,3,3a,6b,11b-hexahydro-derivative (14), in the ratio 3 : 4. The product (12) exhibited a typical aporphine u.v. spectrum ($\lambda_{max.}$ 267, 270sh, 292, and 310 nm) [17] and signals for six aromatic protons in the n.m.r. spectrum. The product (14) showed n.m.r. signals for three aromatic protons but no olefinic protons. The reaction of the phenolic isoquinoline (5) with 85% phosphoric acid in the presence of formic acid gave a mixture of (12) and (14) in the

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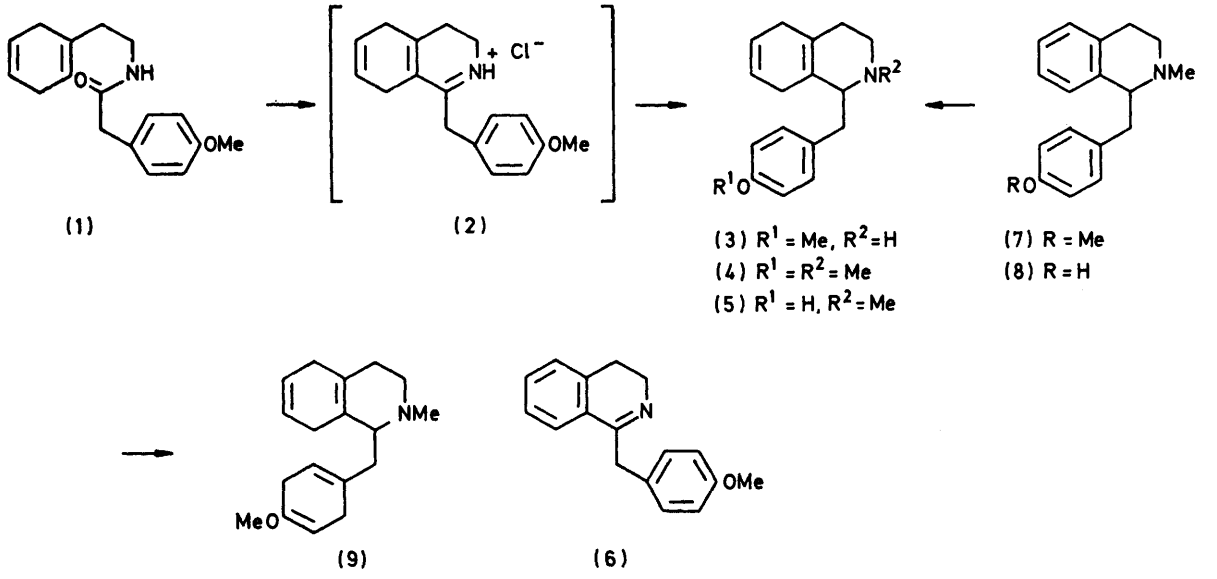
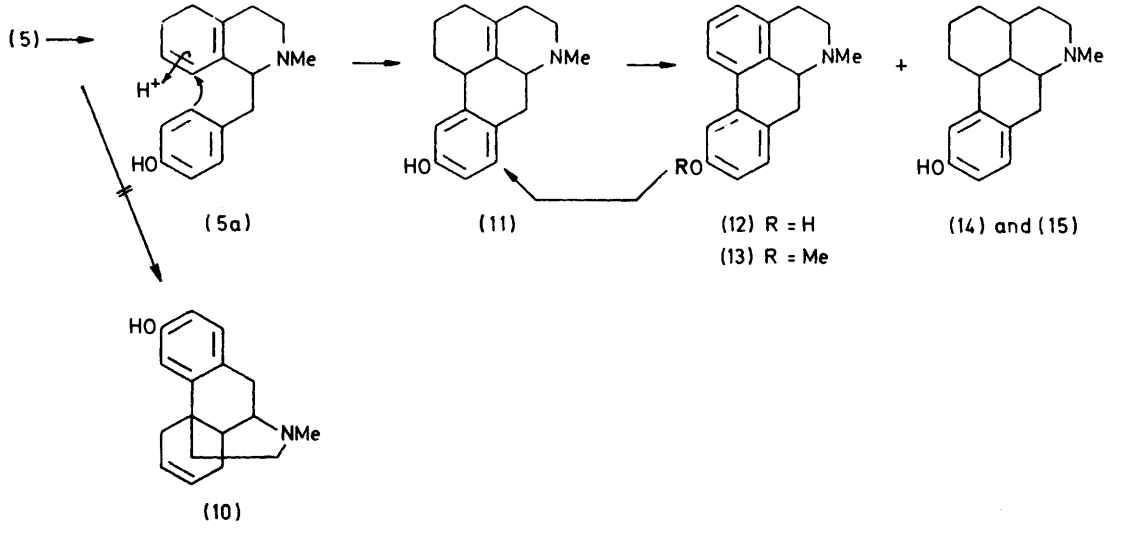
ratio 3 : 4. These observations suggested that the hexahydroaporphine (14) was formed by reduction of the first-formed tetrahydroaporphine (11) with formic acid (present in the reaction medium or generated from oxalic acid); the formation of the aporphine (12) could then be due to aromatisation of (11) by aerial oxidation. However, disproportionation of the tetrahydroaporphine (11) to the aporphine (12) and the hexahydroaporphine (14) could not be ruled out. The structure (12) was also proved by an alternative synthesis as described later.

Catalytic reduction of the tetrahydroaporphine (11) in acetic acid in the presence of platinum oxide gave the hexahydroaporphine (15), a stereoisomer of the hexahydroaporphine (14). The stereochemistry of the tetrahydroaporphine (11) and the hexahydroaporphines (14) and (15) was not determined.

The alternative syntheses of the aporphine (12) and the tetrahydroaporphine (11) were carried out as follows. 10-Methoxy-6-methylaporphine (13) [18] was demethylated with a mixture of 47% hydrobromic acid and 57% hydriodic acid at 110—120 °C to give the 10-hydroxyaporphine (12). Birch reduction of (12) with metallic lithium in liquid ammonia in the presence of ethanol then afforded the tetrahydroaporphine (11).





SCHEME

Both products were identical with those already mentioned.

EXPERIMENTAL

M.p.s were measured with a Yanagimoto micro apparatus, u.v. spectra with a Hitachi 124 spectrophotometer, i.r.

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spectra with a Hitachi 215 spectrophotometer, n.m.r. spectra with a JEOL JNM-PMX-60 spectrometer, and mass spectra with a Hitachi RMU-7 spectrometer. High-pressure liquid chromatography (h.p.l.c.) was carried out with a Waters Associates ALC/GD 202/instrument (6 000 pumping system).

1,2,3,4,5,8-*Hexahydro*-1-(4-*methoxybenzyl*)*isoquinoline* (3).—A mixture of *N*-(2-cyclohexa-1,4-dienylethyl)-4-methoxyphenylacetamide (1) [14] (9.17 g) and phosphoryl chloride (10.4 g) in acetonitrile (120 ml) was heated at 47—49 °C for 2 h. After cooling, the mixture was poured into an excess of water and extracted with chloroform. The organic layer was washed with water, dried (Na_2SO_4), and evaporated and the residue was dissolved in methanol (120 ml). To the stirred solution was added sodium borohydride (4.5 g) in small portions at 5—10 °C during 40 min. After stirring at the same temperature for 2 h, the solvent was evaporated off and the residue was extracted with benzene. The extract was washed with water, and re-extracted with 5% hydrochloric acid. The aqueous layer was basified with 28% ammonium hydroxide and then extracted with chloroform. The chloroform layer was washed with water, dried (Na_2SO_4), and evaporated to give a syrup (2.66 g), $\nu_{max.}$ ($CHCl_3$) 1 680 cm^{-1} (C=C), δ ($CDCl_3$) 3.71 (3 H, s, OMe), 5.66 (2 H, s, 6- and 7-H), and 6.72 and 7.05 (each 2 H, each d, *J* 9 Hz, ArH). The hydrochloride was recrystallised from methanol–ether to give *needles*, m.p. 189—191° (Found: C, 69.9; H, 7.65; N, 4.7. $C_{17}H_{21}NO$,HCl requires C, 69.95; H, 7.6; N, 4.8%).

1,2,3,4,5,8-*Hexahydro*-1-(4-*methoxybenzyl*)-2-*methylisoquinoline* (4).—A mixture of the isoquinoline (3) (1.83 g), 99% formic acid (1.65 g), and 37% formaldehyde (1.20 g) was kept at room temperature for 2 h, and then heated at 95—100 °C for 14 h. The mixture was then poured into 3% hydrochloric acid (30 ml) and the solution was washed with benzene. The aqueous layer was basified with 28% ammonium hydroxide and extracted with benzene. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a syrup, $\nu_{max.}$ ($CHCl_3$) 1 650 cm^{-1} (C=C), δ ($CDCl_3$) 2.37 (3 H, s, NMe), 3.73 (3 H, s, OMe), and 6.67 and 7.14 (each 2 H, each d, *J* 9 Hz, ArH). The oxalate was recrystallised from propan-2-ol–ether to give *plates* (1.98 g), m.p. 188—188.5° (Found: C, 66.5; H, 7.15; N, 3.80. $C_{18}H_{23}NO$,$C_2H_2O_4$ requires C, 66.85; H, 7.0; N, 3.9%).

Birch Reduction of 1,2,3,4-*Tetrahydro*-1-(4-*methoxybenzyl*)-2-*methylisoquinoline* (7).—To a solution of the tetrahydroisoquinoline (7) (700 mg) in liquid ammonia (80 ml) and ethanol (3.6 g) was added lithium (550 mg) in small portions with stirring during 40 min. Stirring was continued for a further 30 min, until decolourisation occurred. The solvent was then removed and the residue was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a syrup, which was chromatographed on silica gel (10 g) with benzene–ethyl acetate (95 : 5 v/v) as eluant. Evaporation of the eluate gave 1,2,3,4,5,8-*hexahydro*-1-(4-*methoxycyclohexa*-1,4-*dienylmethyl*)-2-*methylisoquinoline* (9) (250 mg) as a syrup (Found: C, 79.5; H, 9.35; N, 4.7. $C_{18}H_{25}NO$ requires C, 79.65; H, 9.3; N, 5.15%), $\nu_{max.}$ ($CDCl_3$) 1 685 and 1 655 cm^{-1} (C=C), δ ($CDCl_3$) 2.37 (3 H, s, NMe), 3.53 (3 H, s, OMe), 4.62br (1 H, s, 5′-H), 5.46br (1 H, s, 2′-OH), and 5.71 (2 H, s, 6- and 7-H).

1,2,3,4,5,8-*Hexahydro*-1-(4-*hydroxybenzyl*)-2-*methylisoquinoline* (5).—To a solution of the tetrahydroisoquinoline (8) (8 g) in liquid ammonia (300 ml) and ethanol (43.6 g) was added lithium (6.6 g) in small portions with stirring during 1.5 h. Stirring was continued for 30 min until decolourisation occurred. The solvent was then removed and the residue was treated with an excess of saturated ammonium chloride solution, and extracted with chloroform. The chloroform layer was washed with water, dried (Na_2SO_4), and evaporated to give an oil, which was recrystallised from benzene to afford the *hexahydroisoquinoline* (5) as prisms (4.21 g), m.p. 112—113° (Found: C, 79.85; H, 8.3; N, 5.5. $C_{17}H_{21}NO$ requires C, 79.95; H, 8.3; N, 5.5%), $\lambda_{max.}$ (MeOH) 280 nm (log ε 3.31), $\nu_{max.}$ ($CHCl_3$) 3 600 (OH) and 1 650 cm^{-1} (C=C), δ ($CDCl_3$) 2.28 3 H, s, NMe), 5.63 (2 H, s, 6- and 7-H), 6.38 (1 H, s, OH), and 6.45 and 6.93 (each 2 H, each d, *J* 9 Hz, ArH). The *oxalate* was recrystallised from ethanol to give prisms, m.p. 199—201° (Found: C, 65.8; H, 6.6; N, 4.15. $C_{17}H_{21}NO$,$C_2H_2O_4$ requires C, 66.05; H, 6.7; N, 4.05%).

Grewe Cyclisation of 1,2,3,4,5,8-*Hexahydro*-1-(4-*hydroxybenzyl*)-2-*methylisoquinoline* (5) *with* 85% *Phosphoric Acid*.—(*a*) A mixture of the hexahydroisoquinoline (5) (4.5 g) and 85% phosphoric acid (90 ml) was heated at 120—130 °C for 21 h. The mixture was then diluted with water, basified with 28% ammonium hydroxide, and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a gum, which was chromatographed on silica gel (90 g) with benzene–methanol (97 : 3 v/v) as eluant. Evaporation of the eluate gave 1,2,3,11b-*tetrahydro*-6-*methylaporphin*-10-*ol* (11) (605 mg) as needles, m.p. 199—202° (from benzene) (Found: C, 80.15; H, 8.25; N, 5.35. $C_{17}H_{21}NO$ requires C, 79.95; H, 8.3; N, 5.5%), $\lambda_{max.}$ (MeOH) 281 (log ε 3.44) and 286sh nm (3.42), $\nu_{max.}$ ($CHCl_3$) 3 600 cm^{-1} (OH), δ ($CDCl_3$) 2.48 (3 H, s, NMe) and 6.37—7.07 (3 H, m, ArH), *m/e* 255 (M^+), 254 (base peak), and 212. The hydrochloride formed needles, m.p. 251—252° (decomp.) (from propan-2-ol).

(*b*) A mixture of the hexahydroisoquinoline (5) oxalate (3 g) and 85% phosphoric acid (60 ml) was heated at 120—130 °C for 15 h and worked up as above. The resulting gum was chromatographed on silica gel (50 g); elution with benzene–methanol (97 : 3 v/v) (fractions 7—10; each 50 ml) gave 6-*methylaporphin*-10-*ol* (12) (85 mg) as prisms, m.p. 169—170° (from benzene) (Found: C, 79.8; H, 7.1; N, 5.1. $C_{17}H_{17}NO$ requires C, 81.25; H, 6.8; N, 5.55%), $\lambda_{max.}$ (MeOH) 267 (log ε 4.16), 270sh (3.75), 292 (3.69), and 310 nm (3.75), $\nu_{max.}$ ($CHCl_3$) 3 590 cm^{-1} (OH), δ ($CDCl_3$) 2.53 (3 H, s, NMe) and 6.17—7.25 (6 H, m, ArH), *m/e* 251 (M^+), 250 (base peak), and 208. Fractions 17—21 gave 1,2,3,3a,6b,11b-*hexahydro*-6-*methylaporphin*-10-*ol* (14) (116 mg) as needles, m.p. 218—220° (from benzene) (Found: C, 80.0; H, 8.75; N, 5.25. $C_{17}H_{23}NO$,0.17C_6H_6 requires C, 79.95;H, 8.95; N, 5.2%), $\lambda_{max.}$ (MeOH) 281 (log ε 3.45), and 288sh nm (3.41), $\nu_{max.}$ ($CHCl_3$) 3 600 cm^{-1} (OH), δ ($CDCl_3$) 2.35 (3 H, s, NMe), 6.43—7.10 (3 H, m, ArH), and 7.37 (1 H, s, 1/6 C_6H_6), *m/e* 257 (M^+, base peak) and 256. The hydrochloride formed needles, m.p. 265—268° (from ethanol).

(*c*) A mixture of the hexahydroisoquinoline (5) (402 mg), 85% phosphoric acid (4 ml), and 99% formic acid (87 mg) was treated as above to give the aporphine (12) (18 mg) and the hexahydroaporphine (14) (24 mg), identical with the samples obtained by method (*b*) (spectral and m.p. comparisons).

Reduction of 1,2,3,11b-*Tetrahydro*-6-*methylaporphin*-10-*ol* (11).—A mixture of the tetrahydroaporphine (11) (30 mg),

platinum oxide (15 mg), and acetic acid (2 ml) was shaken in hydrogen for 5 h at 80—90 °C. The solvent was evaporated off to leave a gum, which was basified with 5% ammonium hydroxide and extracted with chloroform. The chloroform layer was washed with water, dried (Na_2SO_4), and evaporated to give a gum. Chromatography on silica gel (5 g) with benzene–methanol (97 : 3 v/v) as eluant gave 1,2,3,3a,6b,11b-*hexahydro*-6-*methylaporphin*-10-*ol* (15) (5 mg) as needles, m.p. 216—218° (from benzene) (Found: C, 79.35; H, 9.0; N, 4.95. $C_{17}H_{23}NO$ requires C, 79.35; H, 9.0; N, 5.45%), $\lambda_{max.}$ (MeOH) 282 nm (log ε 3.42), $\nu_{max.}$ ($CHCl_3$) 3 600 cm^{-1} (OH), δ ($CDCl_3$) 2.37 (3 H, s, NMe) and 6.37—7.10 (3 H, m, ArH), *m/e* 257 (M^+, base peak) and 256. The hydrochloride formed prisms, m.p. 300° (from ethanol).

6-*Methylaporphin*-10-*ol* (12).—A mixture of the tetrahydroaporphine (13) [18] (140 mg), 47% hydrobromic acid (1.4 ml), and 57% hydriodic acid (1.4 ml) was heated for 2 h at 110—120 °C, then basified with 28% ammonium hydroxide and extracted with chloroform. The chloroform layer was washed with water, dried (Na_2SO_4), and evaporated to give the phenolic aporphine (12) (108 mg) as prisms, m.p. 168—170° (from benzene), identical with the sample prepared from (5) (spectra and m.p.).

1,2,3,11b-*Tetrahydro*-6-*methylaporphin*-10-*ol* (11).—To a solution of the aporphine (12) (152 mg) in liquid ammonia (70 ml) and ethanol (840 mg) was added lithium (130 mg) in small portions with stirring during 15 min. Stirring was continued for 10 min, until decolourisation occurred. The solvent was removed and the residue was extracted with water. The solution was washed with ether, treated with an excess of crystalline ammonium chloride, and extracted with chloroform. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to give an oil, which was chromatographed on silica gel (3 g) with benzene–methanol (97 : 3 v/v) as eluant. Evaporation of fractions 5—12 (each 10 ml) gave a syrup, which was further purified by h.p.l.c. {column (1 ft × 1/4 in) packed with μ-Bondapak C_{18}; elution with methanol–water [2 : 1 v/v, $(NH_4)_2CO_3$ 0.5% w/v] at 2 ml min^{-1}}. The material with retention time 4.2 min gave the tetrahydroaporphine (11) (22 mg), which was converted into the hydrochloride [needles, m.p. 250—251° (decomp.) (from propan-2-ol)]. This product was identical with the tetrahydroaporphine prepared from (5) (spectra and m.p.).

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