

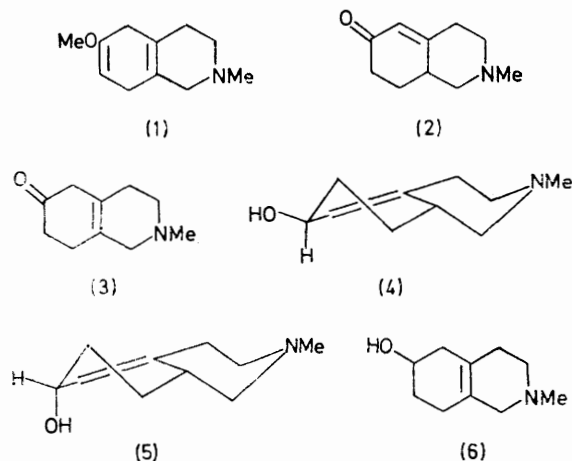
## Synthesis of Hexahydroisoquinolines

By T. A. Crabb\* and J. R. Wilkinson, Department of Chemistry, Portsmouth Polytechnic, Portsmouth, Hampshire

Hexahydroisoquinolines have been synthesised by a reduction–dehydration sequence beginning with octahydro-2-methyl-6-oxo- and 7-oxo-isoquinolines.

A ROUTE to hexahydroisoquinolines is suggested by the readiness with which dienol ethers [*e.g.* (1)] are converted into enones by treatment with aqueous acid. The carbonyl group of the derived enone may then be reduced to the corresponding unsaturated hydroxy-compound which, on dehydration, should yield a hexahydroisoquinoline.

The  $\alpha\beta$ -unsaturated ketone (2), together with a small amount of the  $\beta\gamma$ -unsaturated ketone (3), was prepared in 85% yield by heating the dienol ether (1) with 10% sulphuric acid.<sup>1</sup> Reduction of (2) with lithium aluminium hydride proceeded smoothly to give a mixture of two diastereoisomeric  $\alpha\beta$ -unsaturated hydroxy-compounds, (4) and (5), and a small amount of the  $\beta\gamma$ -unsaturated alcohol (6), derived from the enone (3),

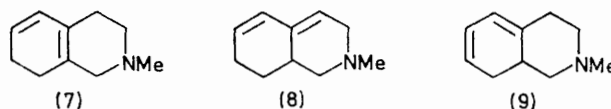


which were separated by column chromatography over alumina. The major product was different from that obtained<sup>1</sup> by reduction of the enone (2) with aluminium isopropoxide in isopropyl alcohol, and since reductions of cyclohexanones by lithium aluminium hydride normally result in a predominance of the equatorial alcohol, whereas Meerwin–Ponndorf reductions often give axial alcohols preferentially, structures (4) and (5) were tentatively assigned to the major and minor isomers, respectively. Support for these assignments is provided by the magnitudes of  $J_{5,6}$  in the <sup>1</sup>H n.m.r. spectra of (4) and (5) (*ca.* 0 and 5 Hz, respectively), on the assumption that the cyclohexene ring is in a half-chair conformation.

Dehydration of (4) by formic acid afforded a mixture of conjugated dienes, which were separated by preparative g.l.c. to give two major products (B and C), together with a very small quantity of a minor component A (retention times  $A < B < C$ ).

The u.v. absorption [ $\lambda_{\max}$  263 nm ( $\epsilon$  5 300)] of component B indicates homoannular conjugation and the

n.m.r. singlet at  $\delta$  5.60 represents only two olefinic protons, consistent with structure (7). The u.v. absorption [ $\lambda_{\max}$  236 nm ( $\epsilon$  18 400)] of component C is typical of a heteroannularly conjugated diene and this, together with a three-proton multiplet ( $\delta$  5.25–6.05) in its n.m.r. spectrum, shows the structure of this product to be (8). These dienes [(7) and (8)] can arise by loss of a proton from an intermediate allylic cation.



The u.v. spectrum of the minor component A displays  $\lambda_{\max}$  265 ( $\epsilon$  5 500) and 272sh nm (4 900). In the n.m.r. spectrum, a multiplet centred at  $\delta$  5.55 represents three olefinic protons. Component A was therefore assigned structure (9) (calc.  $\lambda_{\max}$  273 nm).

It seemed probable that a preferable route to the diene (7) might proceed *via* the  $\beta\gamma$ -unsaturated ketone (3) and the derived hydroxy-compound (6). With aqueous oxalic acid at 0 °C the enol ether (1) gave a mixture of the enones (2) and (3), but a more satisfactory procedure for the preparation of the pure enone (3) involved conversion of the picrate of (1) into the picrate of (3) by prolonged boiling of its solution in aqueous ethanol.

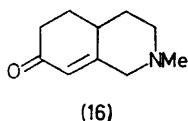
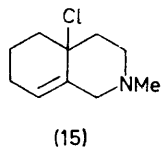
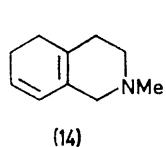
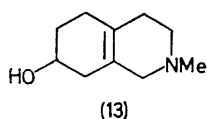
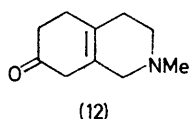
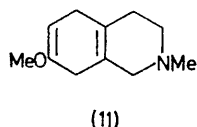
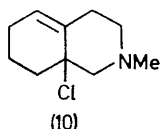
Reduction of the non-conjugated enone (3) with lithium aluminium hydride gave the  $\beta\gamma$ -unsaturated hydroxy-compound (6), which resisted all attempts at dehydration by formic acid. Treatment of (6) with phosphoryl chloride in pyridine solution produced an oil estimated by u.v. and n.m.r. spectroscopy to contain *ca.* 30% of the conjugated diene (7). The oil formed the methiodide of 1,2,3,4,5,8-hexahydroisoquinoline<sup>2</sup> together with a methiodide,  $C_{11}H_{19}ClIN$ , showing no u.v. absorption characteristic of a 1,3-diene. The presence of one olefinic proton, as well as the absence of a methine proton attached to a chloro-substituted carbon, was shown by the n.m.r. spectrum. This suggests the methiodide to be derived from the chloro-compound (10). The dienol ether (11) can similarly be converted, *via* the enone (12) and the hydroxy-compound (13), into the conjugated diene (14), the unconjugated diene (19), and the chloro-compound (15).

Finally, the  $\alpha\beta$ -unsaturated ketone (16) was investigated as a possible source of new hexahydroisoquinolines. This rather unstable enone was obtained by treatment of the dienol ether (11) with dilute sulphuric acid. Reduction of the enone (16) with lithium aluminium hydride

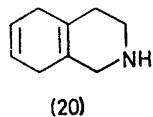
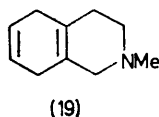
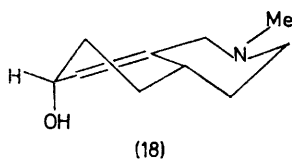
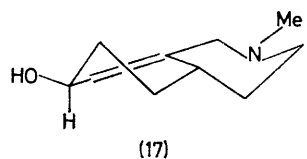
<sup>1</sup> A. Marchant and A. R. Pinder, *J. Chem. Soc.*, 1956, 327.

<sup>2</sup> T. A. Crabb and J. R. Wilkinson, *J.C.S. Perkin I*, 1975, 58.

gave a mixture containing two diastereoisomeric  $\alpha\beta$ -unsaturated 7-hydroxy-compounds (17) and (18). Configurational assignments were made as for (4) and (5).



The alcohol (17) was resistant to dehydration by formic acid, despite prolonged heating at 100 °C, and attempted dehydration of (17) with phosphoryl chloride in pyridine yielded a mixture of (14) and (15).



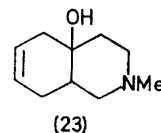
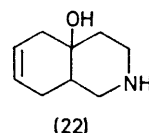
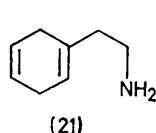
The diene (19) was obtained<sup>2</sup> by reduction of 1,2,3,4-tetrahydro-*N*-methylisoquinoline with lithium and ethanol in liquid ammonia, and the secondary base (20) was prepared by a similar reduction of 1,2,3,4-tetrahydroisoquinoline. In the n.m.r. spectrum of (20), the two olefinic protons give rise to a singlet ( $\delta$  5.62) and the NH proton to a singlet at  $\delta$  1.5. Analytical data for the picrate (m.p. 158°) and the *N*-acetyl derivative (m.p. 56°) are in good accord with the assignment of structure (20) to the secondary base. *N*-Methylation of the secondary base (20) yielded the tertiary base (19).

The secondary base (20) (picrate m.p. 158°) and the tertiary base (19) (picrate m.p. 164°) have thus been unequivocally characterised. However, Grewe and Otto<sup>3</sup> have reported the synthesis of compounds (20) and (19) by alternative routes and recorded picrates of m.p.s. 123–124 and 133°, respectively. The sequence of reactions described by these workers was therefore investigated.

On treatment of the diene (21) with formaldehyde followed by hydrochloric acid, a viscous oil was obtained to which Grewe and Otto<sup>3</sup> had assigned structure (22). After heating this oil with formic acid, distillation of the crude product was accompanied by extensive decomposition and production of an impure liquid in poor

yield. This liquid was found by examination of its spectra to contain little, if any, of the earlier described diene (19).

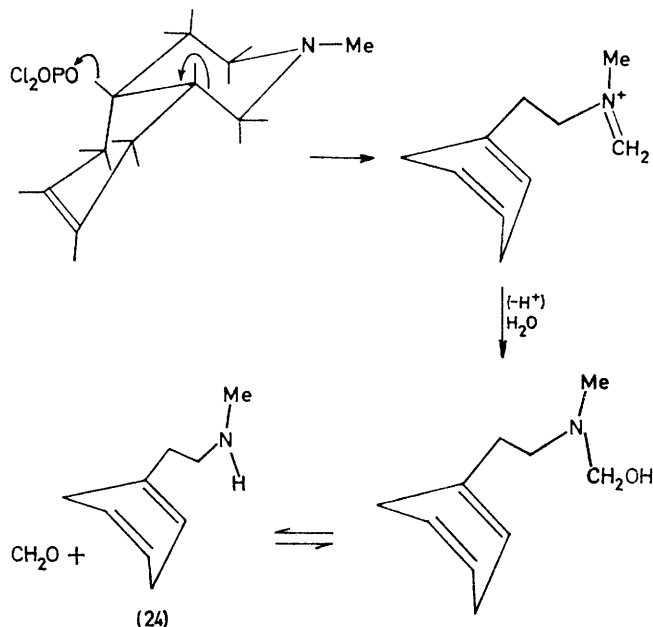
It had also been reported<sup>3</sup> that the tertiary base (19) was prepared by heating the viscous oil containing (22) with formaldehyde and formic acid. When this was attempted, by the published procedure,<sup>3</sup> a small quantity



of a liquid was obtained together with a white crystalline solid (m.p. 94°) to which structure (23) was assigned.

The n.m.r. spectrum of (23) showed two olefinic protons ( $\delta$  5.59 and 5.49;  $J$  10 Hz) together with  $NCH_3$  ( $\delta$  2.17) and OH ( $\delta$  2.44). The absence of signals between  $\delta$  3.0 and 5.0 showed the tertiary nature of the OH group and the location of the hydroxy-group at C-4a rather than C-8a was suggested on mechanistic grounds and by the reactions outlined below.

The alcohol (23) resisted all attempts at dehydration by formic acid, and treatment with phosphoryl chloride in pyridine gave the conjugated diene (9) (ca. 25%) and  $\beta$ -(cyclohexa-1,4-dienyl)-*N*-methylethylamine (24). The production of (24) on treatment of (23) with phosphoryl chloride suggests that in the alcohol (23) the cyclohexene and piperidine rings are *cis*-fused. If (23) adopts the conformation shown in the Scheme, the C(4a)-O and C(8a)-C(1) bonds are *trans*-coplanar and



elimination with C(8a)-C(1) bond rupture can occur, followed by loss of formaldehyde.

The impure liquid formed as a minor product along

<sup>3</sup> R. Grewe and H. Otto, *Chem. Ber.*, 1959, **92**, 644.

with the crystalline hydroxy-base (23) was next examined. It formed a picrate (m.p. 133°) presumed to correspond to the picrate (m.p. 133°) described<sup>3</sup> as that of the diene (19). However the n.m.r. spectrum of the pure liquid (picrate m.p. 138°) showed it to be  $\beta$ -(cyclohexa-1,4-dienyl)-*NN*-dimethylethylamine.

The hydroxy-compound (23), characterised here as a crystalline solid (m.p. 94°) unaffected by formic acid, had been described<sup>3</sup> as a liquid (b.p. 80–84° at 12 mmHg) which could be dehydrated by formic acid to the diene (19) (b.p. 80–85° at 12 mmHg). The published method<sup>3</sup> for the preparation of (23) involved treatment of the secondary base (24) with formaldehyde followed by cyclisation in the presence of hydrochloric acid. When this sequence of reactions was repeated, the crystalline hydroxy-compound (23), m.p. 94°, was again obtained, together with a small quantity of impure liquid. Grewe and Otto<sup>3</sup> had apparently obtained impure (23) as a liquid since their value for the m.p. of the picrate (177°) agrees with the value (179°) found for the picrate of the crystalline hydroxy-compound (23).

#### EXPERIMENTAL

Elemental analyses were carried out by Drs. F. and E. Pascher, Microanalytical Laboratory, Bonn, Germany, and also by the Analytical Section, Department of Chemistry, Portsmouth Polytechnic. U.v. spectra were obtained with a Unicam SP 800 spectrophotometer for solutions in absolute ethanol, i.r. spectra were determined with a Perkin-Elmer 237 spectrometer, and n.m.r. spectra were recorded with a Varian T 60 spectrometer for solutions in carbon tetrachloride, with tetramethylsilane as internal reference. An Aerograph Autoprep instrument was employed in g.l.c. separations.

*trans*(6-H,8a-H)-(4) and *cis*(6-H,8a-H)-1,2,3,4,6,7,8,8a-Octahydro-2-methylisoquinolin-6-ol (5).—The conjugated enone (2) (18.0 g) in dry ether (200 ml) was added dropwise, with constant stirring, to a suspension of lithium aluminium hydride (5 g) in dry ether (200 ml). The grey mixture was stirred for 1 h, and wet ether (100 ml), followed by water (ca. 20 ml), was then cautiously added with ice-cooling until coagulation occurred. The ethereal solution was filtered, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. A mixture (15.6 g) of the diastereoisomeric alcohols (4) and (5), was obtained by vacuum distillation; b.p. 104–106° at 0.4 mmHg.

The picrate (8.5 g), m.p. 179°, of the major isomer (4) was isolated by treatment of this mixture (5.0 g), in ethanolic solution, with picric acid (6.8 g) followed by two recrystallisations from ethanol (Found: C, 48.8; H, 5.2; N, 14.1. C<sub>16</sub>H<sub>20</sub>N<sub>4</sub>O<sub>8</sub> requires C, 48.5; H, 5.1; N, 14.1%). The pure alcohol (4) was obtained as a viscous liquid (3.1 g), b.p. 104° at 0.2 mmHg, by breakdown of a solution of the picrate (8.0 g) in acetone on neutral alumina, followed by elution with ether;  $\delta$  5.33br (s, olefinic proton) [methiodide (from EtOH), m.p. 250° (decomp.)].

The two  $\alpha\beta$ -unsaturated alcohols (4) and (5), were also separated by chromatography. A solution of the mixture (5.0 g) in benzene (5 ml) was applied to an alumina column [Wöelm neutral (activity III; 200 g)] and eluted with benzene, chloroform, and ether. The combined early fractions (monitored by t.l.c. on alumina plates with chloroform as eluant) were of the less viscous minor alcohol

(5) (0.5 g), b.p. 104° at 0.4 mmHg (Found: C, 71.7; H, 10.3; N, 8.4. C<sub>10</sub>H<sub>17</sub>NO requires C, 71.8; H, 10.25; N, 8.4%),  $\delta$  5.50 (*J* 5 Hz, olefinic proton). Later fractions, eluted with chloroform and ether, were composed of the major alcohol (4) (3.5 g). The acetyl derivative of the alcohol (4) was prepared by heating with an excess of acetic anhydride in refluxing pyridine for 20 min, removal of pyridine, and distillation to give an oil, b.p. 108–110° at 1 mmHg (Found: C, 68.6; H, 9.3; N, 6.6. C<sub>12</sub>H<sub>19</sub>NO<sub>2</sub> requires C, 68.9; H, 9.15; N, 6.7%);  $\nu_{\max}$ . 1735 cm<sup>-1</sup> (ester C=O);  $\delta$  1.97 (3H, s, OAc).

*Dehydration of trans*(6-H,8a-H)-1,2,3,4,6,7,8,8a-Octahydro-2-methylisoquinolin-6-ol (4).—The  $\alpha\beta$ -unsaturated hydroxy-compound (4) (5.0 g) was heated with 90% formic acid (20 ml) on a water-bath for 4 h. The mixture was basified and extracted with ether, and the extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was distilled to give a mobile oil, b.p. 88–92° at 5 mmHg (3.8 g). This contained the conjugated dienes, 1,2,3,4,8,8a-hexahydro-2-methylisoquinoline (9) (minor product), 1,2,3,4,7,8-hexahydro-2-methylisoquinoline (7), and 1,2,3,7,8,8a-hexahydro-2-methylisoquinoline (8) (major products), which were separated by preparative g.l.c. The homoannular diene (9) boiled at 88–90° at 5 mmHg (Found: C, 80.3; H, 10.1; N, 9.5. C<sub>10</sub>H<sub>15</sub>N requires C, 80.5; H, 10.1; N, 9.4%). The methiodide (recrystallised from ethanol) of the homoannular diene (7) melted at 173° (Found: C, 45.5; H, 6.4; N, 4.6. C<sub>11</sub>H<sub>18</sub>IN requires C, 45.4; H, 6.2; N, 4.8%). The methiodide (recrystallised from ethanol) of the heteroannular diene (8) melted at 218° (Found: C, 45.2; H, 6.4; N, 4.8%. C<sub>11</sub>H<sub>18</sub>IN requires C, 45.4; H, 6.2; N, 4.8%).

2,3,4,5,7,8-Hexahydro-2-methylisoquinolin-6(1H)-one (3).—The picrate (m.p. 126°) of the enol ether (1), made by mixing cold, ethanolic solutions of (1) (18.8 g) and picric acid (24.1 g), was filtered off and refluxed with aqueous ethanol (200 ml) for 8 h to give, on cooling, the picrate of the unconjugated enone (3), m.p. 156° (Found: C, 48.9; H, 4.8; N, 14.2. C<sub>16</sub>H<sub>18</sub>N<sub>4</sub>O<sub>8</sub> requires C, 48.7; H, 4.6; N, 14.2%). The dried picrate (32.3 g) was dissolved in the minimum volume of acetone and the solution was poured onto a column of neutral alumina. Elution with ether afforded the unconjugated enone (3) as an almost colourless oil (12.1 g). The methiodide had m.p. 218° (from ethanol) (Found: C, 43.1; H, 5.9; N, 4.6. C<sub>11</sub>H<sub>18</sub>INO requires C, 43.0; H, 5.9; N, 4.6%).

1,2,3,4,5,6,7,8-Octahydro-2-methylisoquinolin-6-ol (6).—The non-conjugated enone (3) (10.0 g) in dry ether (100 ml) was added dropwise, with stirring, to a suspension of lithium aluminium hydride (2.5 g) in dry ether (100 ml). After 1 h, wet ether (50 ml) and water were cautiously added to the ice-cooled mixture and the ethereal solution was filtered. After drying (Na<sub>2</sub>SO<sub>4</sub>), ether was evaporated off and the hydroxy-compound was distilled to give a viscous oil (9.6 g), b.p. 102–104° at 0.05 mmHg. This was purified by column chromatography on Wöelm neutral alumina (activity III) (elution with petroleum and ether) to give the crystalline  $\beta\gamma$ -unsaturated hydroxy-compound (6), m.p. 64° (Found: C, 72.0; H, 10.4; N, 8.2. C<sub>10</sub>H<sub>17</sub>NO requires C, 71.8; H, 10.25; N, 8.4%). The methiodide had m.p. 227° (from ethanol) (Found: C, 42.4; H, 6.8; N, 4.3. C<sub>11</sub>H<sub>20</sub>INO requires C, 42.7; H, 6.5; N, 4.5%).

*Dehydration of 1,2,3,4,5,6,7,8-Octahydro-2-methylisoquinolin-6-ol (6).*—Phosphoryl chloride (1.66 g) was added dropwise, with swirling, to a solution of the  $\beta\gamma$ -hydroxy-compound (6) (1.2 g) in dry pyridine (10 ml) at 0°C. The

mixture was left at room temperature overnight and then heated for 2 h on a water-bath. After cooling and pouring onto crushed ice, the solution was made alkaline with aqueous 10% sodium hydroxide, pyridine was removed *in vacuo* and the product was extracted with ether. The extract was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated and the liquid residue was distilled; b.p. 80–85° at 2 mmHg (0.2 g). This liquid was estimated from its spectra to contain the conjugated diene (7) (*ca.* 30%), the non-conjugated diene (19), and 8a-chloro-1,2,3,4,6,7,8,8a-octahydro-2-methylisoquinoline (10). The liquid formed the methiodide (m.p. 194°) of the diene (19),<sup>2</sup> verified by mixed m.p., which was recrystallised from ethanol (Found: C, 45.0; H, 6.2; N, 4.5. Calc. for  $\text{C}_{11}\text{H}_{18}\text{IN}$ : C, 45.4; H, 6.2; N, 4.8%). The methiodide mother liquor yielded the *methiodide* (m.p. 150°) of (10) (Found: C, 40.7; H, 6.1; Cl, 10.4; I, 38.4; N, 4.1.  $\text{C}_{11}\text{H}_{19}\text{ClIN}$  requires C, 40.3; H, 5.8; Cl, 10.8; I, 38.8; N, 4.3%).

2,3,4,5,6,8-Hexahydro-2-methylisoquinolin-7(1H)-one (12).—The picrate (18.3 g), m.p. 140°, of the enol ether (11) was made by mixing ice-cooled ethanolic solutions of (11) (9.0 g) and picric acid (11.5 g). This picrate was converted into the *picrate*, m.p. 160°, of the  $\beta\gamma$ -unsaturated ketone (12) by refluxing in aqueous ethanol (100 ml) (Found: C, 48.3; H, 4.75; N, 13.9.  $\text{C}_{16}\text{H}_{18}\text{N}_4\text{O}_8$  requires C, 48.7; H, 4.6; N, 14.2%). Breakdown of the picrate (15.0 g) of (12) on neutral alumina afforded the free non-conjugated enone (12) (5.2 g).

1,2,3,4,5,6,7,8-Octahydroisoquinolin-7-ol (13).—The non-conjugated enone (12) (5.0 g) in dry ether (50 ml) was reduced with lithium aluminium hydride (1 g) in dry ether, by the same procedure as for the preparation of the hydroxy-compound (6). The crude product (4.8 g) was purified by column chromatography on Wöelm neutral alumina (activity III) to produce the  $\beta\gamma$ -unsaturated hydroxy-compound (13) as a viscous oil (4.1 g), b.p. 85° at 0.02 mmHg. The methiodide, m.p. 173° (from ethanol), was made in ethanol-ether solution by addition of methyl iodide (Found: C, 42.6; H, 6.3; N, 4.6.  $\text{C}_{11}\text{H}_{20}\text{INO}$  requires C, 42.7; H, 6.5; N, 4.5%).

Dehydration of 1,2,3,4,5,6,7,8-Octahydro-2-methylisoquinolin-7-ol (13).—The  $\beta\gamma$ -unsaturated hydroxy-compound (13) (1.2 g) was dehydrated with phosphoryl chloride (1.6 g) in pyridine solution, by the procedure described earlier for dehydration of the analogous hydroxy-compound (6). The liquid product (0.3 g), b.p. 70–75° at 1 mmHg,  $\lambda_{\text{max}}$  263 nm ( $\epsilon$  1800) was estimated to contain the conjugated diene (14) (*ca.* 35%)  $\delta$  5.55 (olefinic protons), the diene (19), and 4a-chloro-1,2,3,4,4a,5,6,7-octahydro-2-methylisoquinoline (15),  $\delta$  5.65 (olefinic proton). The last formed a *methiodide*, m.p. 187° (from ethanol) (Found: C, 40.7; H, 5.75; N, 4.1.  $\text{C}_{11}\text{H}_{19}\text{ClIN}$  requires C, 40.3; H, 5.8; N, 4.3%).

2,3,4,4a,5,6-Hexahydro-2-methylisoquinoline-7(1H)-one (16).—The enol ether (11) (10.0 g) was boiled under reflux with 2*N*-sulphuric acid (100 ml) through which nitrogen was bubbled. The free conjugated enone (16) was obtained by basification, extraction with ether, drying ( $\text{Na}_2\text{SO}_4$ ), and removal of ether. The pale yellow oil (8.7 g) was used in this form when subsequently reduced with lithium aluminium hydride. [Substantial loss of enone (16) by decomposition occurred during vacuum distillation; b.p. 74–76° at 0.05 mmHg (lit.,<sup>4</sup> b.p. 58–60° at 0.05 mmHg);  $\nu_{\text{max}}$  1665  $\text{cm}^{-1}$  (conj. C=O);  $\delta$  5.70 (1H, s, olefinic), and 2.27 (3H, s, NMe)].

trans(4a-H,7-H)- (17) and cis(4a-H,7-H)-1,2,3,4,4a,5,6,7-

Octahydro-2-methylisoquinolin-7-ol (18).—The conjugated enone (16) (8.0 g) in dry ether (100 ml) was reduced with a suspension of lithium aluminium hydride (2 g) in dry ether (100 ml) as described for reduction of the enone (2) to the alcohols (4) and (5). A viscous oil (7.3 g) was obtained which contained the two diastereoisomeric alcohols (17) and (18). These were separated by column chromatography on Wöelm neutral alumina (activity III) (light petroleum and ether as eluents) to give first the minor isomer (18) (0.6 g), b.p. 90° at 0.05 mmHg,  $\delta$  5.60 (*J* 5 Hz, olefinic protons), and then the major isomer (17) (4.9 g), b.p. 92° at 0.05 mmHg,  $\delta$  5.43br (s, olefinic protons). The *acetyl derivatives* of alcohols (18) (b.p. 100–102° at 1 mmHg) (Found: C, 68.8; H, 9.2; N, 6.7.  $\text{C}_{12}\text{H}_{19}\text{NO}_2$  requires C, 68.9; H, 9.15; N, 6.7%) and (17) (b.p. 102–104° at 1 mmHg) (Found: C, 68.7; H, 9.3; N, 6.6%) were prepared by heating under reflux with an excess of acetic anhydride in pyridine for 20 min, followed by removal of pyridine and distillation. The *methiodide* (m.p. 197°) of alcohol (17) crystallised from ethanol (Found: C, 42.4; H, 6.3; N, 4.6.  $\text{C}_{11}\text{H}_{20}\text{INO}$  requires C, 42.7; H, 6.5; N, 4.5%).

Dehydration of trans(4a-H,7-H)-1,2,3,4,4a,5,6,7-Octahydro-2-methylisoquinoline-7-ol (17).—The  $\alpha\beta$ -unsaturated hydroxy-compound (17) (1.0 g) was dehydrated with phosphoryl chloride (1.5 g) in pyridine as described for dehydration of the unsaturated alcohols (6) and (13). The resultant mobile oil (b.p. 70–75° at 1 mmHg), obtained in poor yield (0.1 g), was found by comparison of spectroscopic data to resemble closely the mixture [containing diene (14) and the derived chloro-compound (15)] produced by dehydration of the  $\beta\gamma$ -unsaturated alcohol (13).

1,2,3,4,5,8-Hexahydroisoquinoline (20).—1,2,3,4-Tetrahydroisoquinoline (15.0 g) in liquid ammonia (1 l) and ether (300 ml) was partially reduced by addition of lithium (12 g) and ethanol (*ca.* 200 ml) as described<sup>2</sup> for partial reduction of 1,2,3,4-tetrahydro-*N*-methylisoquinoline. The diene (20) distilled as a liquid (13.2 g), b.p. 105° at 11 mmHg; 96° at 8 mmHg; 90° at 3 mmHg (lit.<sup>3</sup> b.p. 80–85° at 15 mmHg). The *picrate*, m.p. 158° (from ethanol), was readily prepared in hot ethanolic solution (Found: C, 49.7; H, 4.4; N, 15.4.  $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_7$  requires C, 49.45; H, 4.4; N, 15.4%) (lit.,<sup>3</sup> m.p. 123–124°).

The *N*-acetyl derivative of the secondary base (20) (10 g) was made by adding an excess of acetic anhydride (10 g) dropwise to its solution in pyridine (20 ml) and heating on a water-bath for 30 min. Pyridine and the excess of acetic anhydride were removed *in vacuo* and the acetyl derivative (12.3 g) was distilled at reduced pressure (b.p. 130° at 0.1 mmHg). On cooling, crystallisation occurred and the pure *acetyl derivative* (m.p. 56°) was obtained by recrystallisation from light petroleum (Found: C, 74.7; H, 8.7; N, 7.6.  $\text{C}_{11}\text{H}_{15}\text{NO}$  requires C, 74.5; H, 8.5; N, 7.9%),  $\delta$  2.00 (Nac) and 5.68 (2H, olefinic).

Conversion of the Secondary Base (20) into the Tertiary Base (19).<sup>2</sup>—A mixture of the secondary base (20) (6.7 g), 90% formic acid (6.4 g), and 35% aqueous formaldehyde (4.7 g) was heated on a water-bath for 8 h. Sodium hydroxide solution was added and the liberated base was extracted with ether. The dried extract was evaporated and the residual tertiary base (19) distilled at 93° and 7 mmHg (6.2 g);  $\nu_{\text{max}}$  (film) 1655 (C=C) and 3020  $\text{cm}^{-1}$  (C–H);  $\delta$  5.63 (2H, s, olefinic) and 2.23 (3H, s, NMe).

$\beta$ -(Cyclohexa-1,4-dienyl)ethylamine (21).—Lithium metal (15 g) was added to a solution of  $\beta$ -phenylethylamine

<sup>4</sup> C. B. Clarke and A. R. Pinder, *J. Chem. Soc.*, 1958, 1967.

(20.0 g) in liquid ammonia (1 l) and ether (300 ml). Absolute ethanol (*ca.* 200 ml) was then introduced dropwise until the deep blue colour had faded, with stirring continuously throughout. After evaporation of ammonia and addition of water, the primary amine (21) was isolated with ether and distilled at 74° and 6 mmHg (lit.,<sup>3</sup> b.p. 80° at 12 mmHg) as an oil (18.6 g);  $\nu_{\max}$  (film) 3 360 and 3 270 (NH<sub>2</sub>), 1 645 (C=C), 3 020 (=CH), and 670 cm<sup>-1</sup> (=CH),  $\delta$  5.43 (1H) and 5.64 (2H).

$\beta$ -(Cyclohexa-1,4-dienyl)-N-methylethylamine (24).—N-Methyl- $\beta$ -phenylethylamine (10.0 g) in liquid ammonia (1 l) and ether (300 ml) was partially reduced by addition of lithium (8 g) and ethanol (*ca.* 150 ml) to give the diene (24), by the general procedure described above for synthesis of the dienes (19)—(21). The secondary base (24) was isolated with ether and distilled as an oil (8.8 g), b.p. 112° at 10 mmHg (lit.,<sup>3</sup> b.p. 78—80° at 12 mmHg),  $\nu_{\max}$  (film) 3 300 (NH), 3 040 (=CH), 1 660 (C=C), and 680 cm<sup>-1</sup> (=CH);  $\delta$  1.43 (1H, s, NH), 2.34 (3H, s, NMe), 5.60 (2H, s, olefinic), and 5.38 (1H, s, olefinic). The picrate had m.p. 150° (from ethanol).

1,2,3,4,4a,5,8,8a-Octahydroisquinolin-4a-ol (22).—The primary amine (21) (20.0 g) was mixed with aqueous 40% formaldehyde (16.8 g) and 5N-hydrochloric acid (38 ml) was slowly added without allowing the temperature of the mixture to rise above 5°. The resulting solution was heated for 30 min on a water-bath, neutral substances were extracted with ether and the free base was liberated by addition of ammonia solution and extracted with ether. The extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give the crude hydroxy-base (22) as a gum (17.4 g). This product was not amenable to purification by vacuum distillation, during which extensive decomposition occurred.

1,2,3,4,4a,5,8,8a-Octahydro-2-methylisquinolin-4a-ol (23).—(a) A mixture of the crude hydroxy-base (22) (15.0 g), 85% formic acid (20 g), and aqueous 40% formaldehyde (17 g) was heated on a water-bath for 4 h, concentrated hydrochloric acid (10 ml) was added, and the mixture was left overnight. Neutral substances were removed with ether, ammonia solution was added, and the liberated base was extracted thoroughly with ether. The dried extract was evaporated and the residue partially crystallised on cooling in ice. The crystalline hydroxy-base (23) (10.3 g) was filtered off and the accompanying liquid (1.4 g) distilled to give two fractions, b.p. 80—90° at 7 mmHg (0.6 g) and 120—125° at 7 mmHg (0.5 g). The higher boiling fraction crystallised on cooling to give the tertiary hydroxy-base (23) which was obtained as prisms, m.p. 94° (from light petroleum) (Found: C, 71.6; H, 10.2; N, 8.4. C<sub>10</sub>H<sub>17</sub>NO requires C, 71.8; H, 10.25; N, 8.4%).

The picrate, m.p. 179°, was made by mixing hot, ethanolic solutions of the hydroxy-base (23) and picric acid, followed by recrystallisation from ethanol (Found: C, 48.6; H, 5.0; N, 14.2. C<sub>16</sub>H<sub>20</sub>N<sub>4</sub>O<sub>8</sub> requires C, 48.5; H, 5.1; N, 14.1%). The acetyl derivative, b.p. 70° at 1.5 mmHg, was prepared by refluxing a solution of the hydroxy-base (23) in pyridine and an excess of acetic anhydride for 20 min, followed by removal of pyridine and vacuum distillation (Found: C, 68.6; H, 8.8; N, 6.6. C<sub>12</sub>H<sub>19</sub>NO<sub>2</sub> requires C, 68.9; H, 9.15; N, 6.7%).

The impure liquid (b.p. 80—90° at 7 mmHg), formed with the hydroxy-base (23) as a side-product, gave a picrate (m.p. 133°) which corresponded to a picrate (m.p. 133°) (Found: C, 50.7; H, 5.0; N, 14.8%)<sup>3</sup> assumed by Grewe and Otto<sup>3</sup> to be derived from the diene (19) (C<sub>10</sub>H<sub>15</sub>N-

C<sub>6</sub>H<sub>3</sub>N<sub>3</sub>O<sub>7</sub> requires C, 50.8; H, 4.8; N, 14.8%). The liquid was purified by preparative g.l.c. on a Carbowax column at 160 °C and the pure g.l.c. fraction found to be  $\beta$ -(cyclohexa-1,4-dienyl)-NN-dimethylethylamine,  $\delta$  2.11 (6H, NCH<sub>3</sub>) and 5.59 (3H, olefinic); Picrate, m.p. 138° (Found: C, 50.7; H, 5.1; N, 14.6. C<sub>16</sub>H<sub>20</sub>N<sub>4</sub>O<sub>7</sub> requires C, 50.5; H, 5.3; N, 14.75%).

(b) The primary amine (21) (7.3 g) was dissolved in 85% formic acid (12 g), aqueous 40% formaldehyde (10 g) was added, and the mixture was left for 45 min. After heating for 4 h on a water-bath and cooling, concentrated hydrochloric acid (5 ml) was added. The mixture was left overnight and heated for 5 min on a water-bath. Neutral substances were removed with ether, the solution was made alkaline with ammonia, and organic, basic material was thoroughly extracted with ether. Evaporation of the dried extract and cooling to induce crystallisation, followed by filtration and vacuum distillation of liquid material, afforded the crystalline hydroxy-base (23) (5.2 g) and an impure liquid (1.6 g) [from which a picrate (m.p. 133°) was isolated] of the same composition as the liquid obtained as a side-product by method (a). Breakdown of the picrate (m.p. 133°) on alumina gave a mixture (*ca.* 2 : 1) of  $\beta$ -(cyclohexa-1,4-dienyl)-NN-dimethylethylamine and (24).

(c) The secondary amine (24) (8.0 g) was mixed with aqueous 40% formaldehyde (7.6 ml) and 5N-hydrochloric acid (16 ml) was added under ice-cooling.<sup>3</sup> When dissolution was complete, the mixture was heated for 30 min on a water-bath and neutral substances were removed with ether. After addition of ammonia solution, extraction with ether, and evaporation of the extract, the crystalline hydroxy-base (23) (4.7 g) was separated from liquid material (3.1 g) as described above.

Attempted Dehydration of the Tertiary Hydroxy-base (23).—(a) The hydroxy-base (23) (1.45 g) was dissolved in 85% formic acid (10 ml) and heated on a water-bath for 4 h.<sup>3</sup> After cooling, concentrated hydrochloric acid (1 ml) was added and the solution left overnight. The free base was liberated with ammonia solution and thoroughly extracted with ether. Evaporation of the dried extract afforded starting material (23) (0.87 g) and a small quantity (<0.1 g) of liquid similar in composition to the side-product obtained in methods (a) and (b) for the synthesis of the alcohol (23). Attempted dehydration of (23), using 90 and 98% formic acid, was also unsuccessful.

(b) The hydroxy-base (24) (11.5 g) was dissolved in dry pyridine (71 g) and phosphoryl chloride (15.5 g) was added slowly, with thorough mixing, to the ice-cooled solution. After heating for 1½ h on the water-bath and cooling, the mixture was poured into cracked ice, the solution was made alkaline with sodium hydroxide solution, and the liberated base was extracted with ether. Evaporation of ether from the dried extract and removal of pyridine *in vacuo* left an oil, b.p. 102—104° at 7.5 mmHg (2.7 g), which contained the conjugated diene (9) and the ring-opened secondary base (24) (separable by preparative g.l.c. on a Carbowax column at 150 °C).

(c) Dehydration of the hydroxy-base (23) *via* the tosyl derivative was next attempted. A solution in dry pyridine (10 ml) of the alcohol (23) (1.5 g) and toluene-*p*-sulphonyl chloride (5 g) was heated on a water-bath for 8 h and left overnight. The mixture was poured into water (20 ml), ammonia solution was added, and the product was extracted with ether. The dried extract was evaporated and pyridine was removed *in vacuo* to leave a viscous liquid (*ca.* 1 g).

The previously characterised heteroannular diene (8) was isolated in low yield when this liquid was subjected to preparative g.l.c. (Carbowax column at 150 °C).

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