Isomerisation of 1,2,3,4,5,8-Hexahydroisoquinolines to Hexahydroisoquinolines containing a 1,3-Diene System

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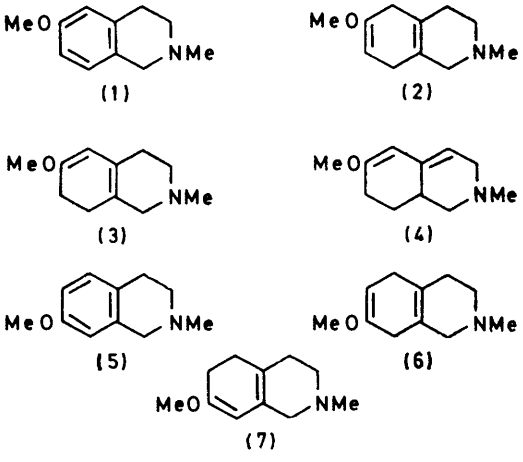
Hexahydro-2-methylisoquinolines containing a conjugated diene system have been synthesised by isomerisation of 1,2,3,4,5,8-hexahydro-2-methylisoquinolines formed by Birch reduction of 1,2,3,4-tetrahydro-2-methylisoquinoline, 1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline, and 1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinoline.

THE Birch reduction of tetrahydro-6-methoxy-2-methylisoquinoline (1) with sodium and methanol in liquid ammonia [1] readily provides 1,2,3,4,5,8-hexahydro-6-methoxy-2-methylisoquinoline (2).

Isomerisation of compound (2) by treatment with potassamide in liquid ammonia [2,3] gave a complex mixture of products from which three compounds were isolated by preparative g.l.c. The major product proved to be the conjugated diene (3); the n.m.r. spectrum showed a one-proton singlet at δ 4·62 (H-5) and the u.v. spectrum showed $\lambda_{max.}$ 271 nm (ε 5200) (*cf.* $\lambda_{max.}$ 279 nm calculated by the Woodward–Fieser rules). The u.v. absorption [$\lambda_{max.}$ 245 nm (ε 7100)] of one of the two minor products indicated heteroannular conjugation as in structure (4) (calc. $\lambda_{max.}$ 240 nm) and the two singlets at δ 4·62 (sharp) and 5·11 (broad) in the n.m.r. spectrum were respectively assigned to H-5 and -4. The second minor product was considered to be an octahydroisoquinoline.

When the isomerisation was attempted with sodamide in liquid ammonia and the red mixture was left overnight,[3] aromatisation occurred to give compound (1), but a 1 h isomerisation period gave a mixture containing *ca.* 79% of (3), 25% of (2), and 5% of (1).

An alternative isomerisation procedure, for obtaining the conjugated diene (3), involved the use of potassium t-pentyl oxide in t-pentyl alcohol.[4,5] When the unconjugated diene (2) was heated in this system at 100° for 4 h, a mixture consisting of 70% of (3), 20% of (2), and 10% of (1) was obtained.



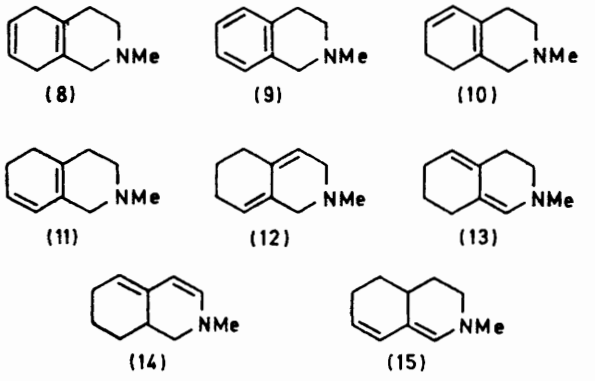
Birch reduction of 1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinoline (5) with sodium and methanol in liquid ammonia produced the expected diene (6) as a crystalline solid (m.p. 51°).[6] This was readily isomerised by potassium t-pentyl oxide in t-pentyl alcohol to give a mixture composed of 70% of (7), 25% of (6), and 5% of (5), from which the conjugated diene (7) crystallised.

In the absence of a directive methoxy-substituent, isomerisation of a non-conjugated hexahydroisoquinol-

[1] A. Marchant and A. R. Pinder, *J. Chem. Soc.*, 1956, 327.
[2] A. J. Birch, *J. Chem. Soc.*, 1950, 1551.
[3] A. J. Birch, *J. Chem. Soc.*, 1947, 1642.
[4] R. B. Bates, R. H. Carnighan, and C. E. Staples, *J. Amer. Chem. Soc.*, 1963, **85**, 3030.
[5] A. A. Othman, M. A. Qasseem, and N. A. J. Rogers, *Tetrahedron*, 1967, **23**, 87.
[6] C. B. Clarke and A. R. Pinder, *J. Chem. Soc.*, 1958, 1967.

ine [*e.g.* (8)] might be expected to give rise to a wider variety of conjugated products than do compounds (2) and (6). The diene (8) was readily obtained by reduction of the aromatic precursor (9) with lithium and ethanol in liquid ammonia. However its isomerisation with sodamide or potassamide in liquid ammonia was not found to be a useful procedure for the preparation of conjugated hexahydroisoquinolines, since the reaction was accompanied by extensive aromatisation to (9) and when the mixture was left overnight complete conversion into (9) took place.

When potassium t-pentyl oxide in t-pentyl alcohol was used as reagent, it was possible to limit and control the isomerisation products by variation of the temperature and duration of isomerisation. Isomerisation at 100 °C for 2 h or less gave mixtures of the starting material (8) and the two homoannular dienes, (10) and (11). For example, in a 1 h isomerisation period (8) gave a mixture [$\lambda_{max.}$ 263 nm (ε 3000)] containing 44% of (8), 28% of (10), and 28% of (11).



Isomerisation of the diene (8) with potassium t-pentyl oxide in t-pentyl alcohol for 4 h at 100 °C yielded a mixture containing the dienes (10) and (11) together with another diene which was isolated by preparative g.l.c. This diene showed $\lambda_{max.}$ 238 nm (ε 5250), characteristic of heteroannular conjugation. In the n.m.r. spectrum a sharp singlet at δ 5·67 and a broad signal at δ 5·37 corresponded to two olefinic protons, and a singlet at δ 2·25 to an *N*-methyl group. Thus this heteroannular diene was assigned the structure (12) (calc. $\lambda_{max.}$ 244 nm). The approximate composition of the isomerisation mixture was estimated as 55% (12), 20% (10), 15% (11), 10% other products.

These results indicate that reversible and comparatively rapid conversion of the diene (8) into the homoannular dienes (10) and (11) is accompanied by slower isomerisation of (11) to the more stable heteroannular diene (12). Similar transformations have been observed in the isomerisation of hexahydronaphthalenes.[4] In order to obtain an equilibrium mixture of hexahydroisoquinolines, the isomerisation of (8) was carried out under reflux for 12 h. By means of preparative g.l.c., two major products were obtained. The u.v. absorption [$\lambda_{max.}$ 291 (ε 9600)] of the first fraction off the column showed it to be a dienamine since extension of the diene chromophore to include the tertiary nitrogen atom would be expected to give rise to a large bathochromic shift relative to the conjugated hexahydroisoquinolines so far encountered. The n.m.r. spectrum showed olefinic proton signals at δ 5·47 (1H, s) and 4·98 (broad) (total 2H). The only structure consistent with the spectroscopic data is that of the dienamine (13) (calc. $\lambda_{max.}$ 299 nm), which possesses only two olefinic protons, one of which would be expected to give rise to the observed low-field singlet.

The other g.l.c. fraction showed $\lambda_{max.}$ 283 nm (ε 8500) and therefore must also be a dienamine. The calculated value of $\lambda_{max.}$ is 289 nm for both of the two remaining possible dienamines, (14) and (15). In the n.m.r. spectrum, the ' AB ' quartet at δ 5·67 and 4·87 (*J* 8 Hz) corresponds to two adjacent olefinic protons and the broad signal at δ 5·07 was attributed to a third olefinic proton. The assignment of structure (14) to this fraction is therefore supported by the n.m.r. parameters for these olefinic protons. The low-field doublet at δ 5·67, which forms half the ' AB ' quartet (*J* 8 Hz), must be due to the enamine olefinic proton adjacent to the tertiary nitrogen atom [*cf.* the H-1 signal at δ 5·47 for the dienamine (13)] and its doublet nature is only reconcilable with structure (14), in which the enamine C-3 olefinic proton can couple with the adjacent olefinic proton at C-4.

EXPERIMENTAL

Elemental analyses were carried out by Drs. F. Pascher and E. Pascher, Microanalytical Laboratory, Bonn, and by Portsmouth Polytechnic analytical service. U.v. spectra were obtained (Unicam SP 800 spectrophotometer) for solutions in absolute ethanol. I.r. spectra were determined for liquid films and/or solutions in carbon tetrachloride with a Perkin-Elmer 237 spectrometer. N.m.r. spectra were recorded on a Varian T60 spectrometer for solutions in carbon tetrachloride, with tetramethylsilane as internal reference. An Aerograph Autoprep instrument was employed in g.l.c. separations. Unless otherwise stated, ' light petroleum ' refers to the fraction of b.p. 40—60°.

1,2,3,4,5,8-*Hexahydro*-6-*methoxy*-2-*methylisoquinoline* (2). —Sodium (24 g) was added during 1 h with stirring to 1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (20·0 g) in methanol (100 ml) and liquid ammonia (500 ml).[1] After cautious addition of ether and water, the ammonia was allowed to evaporate off and the product was extracted with ether. The dried extract was evaporated and the residue distilled to give 1,2,3,4,5,8-hexahydro-6-methoxy-2-methylisoquinoline (19·4 g) as an oil, b.p. 114—116° at 5 mmHg; $\nu_{max.}$ 1670 cm^{-1} (non-conj. C=C); δ 3·50 (OMe), 2·24 (NMe), and 4·52 (1H, olefinic). The *methiodide*, m.p. 218—220° (decomp.), was formed by treatment with methyl iodide in ethanol–ether and recrystallisation from ethanol (Found: C, 44·8; H, 5·9; N, 4·5. $C_{12}H_{20}INO$ requires C, 44·8; H, 6·2; N, 4·4%). The *picrate*, m.p. 128°, was made by treatment of the free base with an equimolar quantity of picric acid in cold, absolute ethanol followed by recrystallisation from absolute ethanol (Found:

C, 50·3; H, 5·1; N, 13·6. $C_{17}H_{20}N_4O_8$ requires C, 50·0; H, 4·9; N, 13·7%).

Isomerisation of the Hexahydroisoquinoline (2). (*a*) Potassium (5·5 g) was added in small portions, with stirring, to liquid ammonia (200 ml) containing a trace of hydrated iron(III) nitrate. When the grey suspension of potassamide had formed, the nonconjugated diene (20·0 g) was added and the deep red mixture stirred for 30 min. Ethanol (2 ml) was then added dropwise, followed by water when the red colour had disappeared. After extraction with ether and drying (Na_2SO_4), evaporation and distillation of the residue yielded a mixture (18·7 g), b.p. *ca.* 85—110° at 4 mmHg. Fractional distillation of this mixture (16·5 g) (Nester–Faust spinning band column) gave fractions (6·1 g), b.p. 95—100° at 4 mmHg, which were enriched in conjugated isomerisation products. The lower-boiling fractions (3·0 g), b.p. 85—95° at 4 mmHg, were composed mainly of aromatic material and later fractions (6·2 g), b.p. 100—110° at 4 mmHg, contained the non-conjugated diene (2) and its precursor (1). A fraction (2·0 g), b.p. 98—100° at 4 mmHg, was dissolved in light petroleum (5 ml) and chromatographed on Wöelm neutral alumina (activity II; 100 g), with light petroleum and benzene as eluants. Pure 1,2,3,4,7,8-hexahydro-6-methoxy-2-methylisoquinoline (3) was isolated as an oil (1·4 g), b.p. 104—106° at 5·5 mmHg, which formed a *methiodide*, m.p. 210° (decomp.) (from ethanol–ether) (Found: C, 44·8; H, 5·8; N, 4·3. $C_{12}H_{20}INO$ requires C, 44·8; H, 6·2; N, 4·4%).

The initially distilled complex mixture of products (2·0 g) was subjected to preparative g.l.c. with a Carbowax column at 200 °C (thermal conductivity detector; hydrogen as carrier gas). Fractions A (97 mg), B (788 mg), C (96 mg), and D (591 mg) were obtained (in order of increasing retention times). Fraction A was an octahydro-6-methoxy-2-methylisoquinoline [δ 4·41 (1H, olefinic)], fraction B consisted of the earlier characterised conjugated diene (3), fraction C was 1,2,3,7,8,8a-*hexahydro*-6-*methoxy*-2-*methylisoquinoline* (4), b.p. 98° at 3 mmHg (Found: C, 73·5; H, 9·8; N, 7·7. $C_{11}H_{17}NO$ requires C, 73·7; H, 9·6; N, 7·8%), and fraction D contained the non-conjugated diene (2) and its aromatic precursor (1).

(*b*) Isomerisation by the same procedure as described in (*a*) of the unconjugated diene (10·0 g) was effected with sodamide [from sodium (1·7 g)] in liquid ammonia (400 ml) during 1 h. (When the mixture was left overnight, aromatisation occurred to give 1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline.) The mixture of isomers distilled as a pale yellow oil (9·1 g), b.p. *ca.* 95—105° at 6 mmHg.

(*c*) The unconjugated diene (15·0 g) was dissolved in a solution of potassium t-pentyl oxide [from potassium (7·5 g)] in t-pentyl alcohol and the mixture was heated on a water-bath for 4 h. t-Pentyl alcohol was removed *in vacuo*, water was added, and the organic product was extracted with ether. The dried extract was evaporated and the residue distilled at 90—94° and 2 mmHg (14·5 g). This mixture contained the conjugated diene (3) in good yield (*ca.* 70%).

1,2,3,4,5,8-*Hexahydro*-7-*methoxy*-2-*methylisoquinoline* (6). —Sodium (17 g) was added in small pieces during 1 h, with constant stirring, to a solution of the tertiary base (5) (20 g) in liquid ammonia (1·5 l), methanol (90 ml), and ether (100 ml). After evaporation of ammonia, water was added and the Birch reduction product was extracted with ether. The extract was dried (Na_2SO_4) and evaporated and the residual base was distilled; b.p. 114—116° at 4 mmHg (yield 19·7 g) (lit.,[6] 126° at 8 mmHg). Crystallisation occurred on cooling and recrystallisation from light peroleum gave needles, m.p. 50° (lit.,[6] 50—51°); δ 3·50 (OMe), 2·25 (NMe), and 4·50 (1H, olefinic). The *picrate*, m.p. 142°, was made by mixing, in absolute ethanol solution at 0 °C, with an equimolar quantity of picric acid and recrystallising from absolute ethanol (Found: C, 49·75; H, 4·8; N, 13·8. $C_{17}H_{20}N_4O_8$ requires C, 50·0; H, 4·9; N, 13·7%).

Isomerisation of the Hexahydroisoquinoline (6).—The non-conjugated diene (6) (15·0 g) was dissolved in a solution of potassium t-pentyl oxide [from potassium (7·5 g)] in t-pentyl alcohol and the mixture was heated on a water-bath for 4 h. t-Pentyl alcohol was removed *in vacuo*, water was added, and the organic product was extracted with ether. The dried extract was evaporated and the residue distilled at 104—106° at 2 mmHg (14·4 g). On cooling the mixture, 1,2,3,4,5,6-*hexahydro*-7-*methoxy*-2-*methylisoquinoline* (7) crystallised; m.p. 37° (from light petroleum) (Found: C, 73·4; H, 9·5; N, 7·7. $C_{11}H_{17}NO$ requires C, 73·7; H, 9·6; N, 7·8%); $\lambda_{max.}$ 271 nm (ε 6400); δ 3·53 (OMe), 2·25 (NMe), and 4·57 (1H, olefinic). The *methiodide* had m.p. 195° (decomp.) (from ethanol) (Found: C, 45·2; H, 6·4; N, 4·1. $C_{12}H_{20}INO$ requires C, 44·8; H, 6·2; N, 4·1%).

1,2,3,4,5,8-*Hexahydro*-2-*methylisoquinoline* (8).—Lithium metal (15 g) was added with stirring, over 10 min, to a solution of the tertiary base (9) (20·0 g) in liquid ammonia (1 l) and dry ether (300 ml) contained in a 3 l three-necked flask. After further stirring for 5 min, absolute ethanol (*ca.* 200 ml) was added dropwise during *ca.* 30 min until the deep blue colour had disappeared. The flask was fitted with a Bunsen valve and ammonia was allowed to evaporate overnight. Water (*ca.* 200 ml) was added cautiously and the resulting slurry was thoroughly extracted with ether. After evaporation of ether, ethanol was removed *in vacuo* and the product was again extracted with ether. The extract was dried (Na_2SO_4) and evaporated and the residue was distilled to give the non-conjugated diene (8) as a very pale yellow oil (17·8 g), b.p. 98° at 8 mmHg; 88° at 5 mmHg; 75° at 3 mmHg; δ 2·23 NMe) and 5·63 (2H, olefinic). The *picrate* had m.p. 164° (from ethanol) (Found: C, 50·9; H, 4·8; N, 14·8. $C_{16}H_{18}N_4O_7$ requires C, 50·8; H, 4·8; N, 14·8%). The *methiodide* had m.p. 196° (from ethanol) (Found: C, 45·2; H, 6·4; N, 4·7. $C_{11}H_{18}IN$ requires C, 45·4; H, 6·2; N, 4·8%).

Isomerisation of the Diene (8) *with Potassamide in Liquid Ammonia*.—The non-conjugated diene (8) (8·5 g) was added to a suspension of potassamide [from potassium (5 g)] in liquid ammonia (200 ml).[2,3] The red mixture was stirred for 30 min after which ethanol (5 ml) was added dropwise to destroy the red colour. Ether (100 ml) and water (200 ml) were then added cautiously and the product was extracted with ether. The extract was dried (Na_2SO_4) and evaporated and the residual liquid was distilled (b.p. 96—104° at 8 mmHg) to give a complex mixture (7·3 g) of isomerisation products [and the aromatic precursor (9)] which were separated by preparative g.l.c. on a Carbowax column at 150 °C and corresponded with the conjugated hexahydroisoquinolines as characterised below.

Isomerisation of the Diene (8) *with Potassium t-Pentyl Oxide in t-Pentyl Alcohol: General Procedure*.—1,2,3,4,5,8-Hexahydro-2-methylisoquinoline (8) (5·0 g) was thoroughly mixed with a solution of potassium t-pentyl oxide [from

potassium (2·5 g)] in t-pentyl alcohol (50 ml). The temperatures and durations of isomerisation are shown in the Table. t-Pentyl alcohol was then removed *in vacuo*,

Temp. (°C)	Isomerisation period (h)	Products	B.p. (°C) [mmHg]
100	1—2	44% (8), 28% (10), 28% (11)	76—78 [4]
100	4	20% (10), 15% (11), 55% (12)	76—80 [4]
Reflux	12	50% (13), 50% (14)	80—82 [2]

water was added, and the mixture of isomerisation products was extracted with ether. The dried extract was evaporated and the residual liquid was distilled at reduced pressure to give a mixture of hexahydroisoquinolines (*ca.* 4·5 g), which were separated by preparative g.l.c. on a Carbowax column at 150 °C. 1,2,3,4,7,8-*Hexahydro*-2-*methylisoquinoline* (10) and 1,2,3,4,5,6-*hexahydro*-2-*methylisoquinoline* (11) formed a mixed methiodide, m.p. 145° (from ethanol) (Found: C, 45·3; H, 6·3; N, 4·6. Calc. for $C_{11}H_{18}IN$: C, 45·4; H, 6·2; N, 4·8%). 1,2,3,5,6,7-*Hexahydro*-2-*methylisoquinoline* (12) distilled at 80° and 4 mmHg (Found: C, 80·4; H, 10·2; N, 9·4. $C_{10}H_{15}N$ requires C, 80·5; H, 10·1; N, 9·4%). 2,3,4,6,7,8-Hexahydro-2-methylisoquinoline (13) and 1,2,6,7,8,8a-hexahydro-2-methylisoquinoline (14) distilled at 80—82° and 2 mmHg (Found: C, 80·3; H, 10·2; N, 9·3. Calc. for $C_{10}H_{15}N$: C, 80·5; H, 10·1; N, 9·4%).

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