An Improved Synthesis of 6-Amino-1,2,3,4-tetrahydro-2-methylisoquinoline: Elucidation of the Stereochemistry of Some Diastereoisomers of 6-Amino-2-methyldecahydroisoquinoline

By **Ian W. Mathison*** and **Richard R. Tidwell**, Department of Medicinal Chemistry, College of Pharmacy, University of Tennessee Center for the Health Sciences, Memphis, Tennessee 38163, U.S.A.

An improved synthesis of 6-amino-1,2,3,4-tetrahydro-2-methylisoquinoline is reported, along with the synthesis, isolation, and elucidation of the stereochemistry of three of the four possible diastereoisomers of the previously unreported 6-amino-2-methyldecahydroisoquinoline. Stereochemical assignments were made from a combination of chemical evidence, involving conversion of the amines into the corresponding known alcohols and oxidation of the alcohols to the corresponding ketones, and spectral data.

THE synthesis and stereochemistry of the diastereoisomers of 6-amino- and 6-hydroxy-2-methyldecahydroisoquinoline is reported here as part of a study on structure–activity relationships (in regard to antiarrhythmic activity) of variously substituted decahydroisoquinolines.[1] 6-Amino-2-methyldecahydroisoquinoline has not been previously described, but several investigators have described the isolation and elucidation of the structures of the four diastereoisomers of 6-hydroxy-2-methyldecahydroisoquinoline and the two diastereoisomers of the 6-oxo-analogue.[2] Some discrepancies exist amongst the m.p.s reported (Table). 6-Hydroxy-2-methyldecahydroisoquinoline can be obtained in fair yields by a series of reactions involving a ring closure.[2a,b,g,3] It occurred to us that since alicyclic amines can be converted into alcohols with retention of configuration (thereby limiting the need for separation of isomers to the amines alone), and since we required both amino- and hydroxy-decahydroisoquinolines, it would be preferable to synthesize the amines and convert them into the alcohols rather than to convert known hydroxy-compounds into amines.

For the synthesis of 6-amino-2-methyldecahydroisoquinoline we required 6-amino-1,2,3,4-tetrahydro-2-methylisoquinoline (VII), which had been reported previously only in minor yields.[4] The latter was synthesised by a better procedure as shown in the Scheme. Low pressure catalytic hydrogenation of (VII) over platinum oxide in acid then gave a mixture of diastereo isomers of 6-amino-2-methyldecahydroisoquinoline (VIII). G.l.c. indicated that in addition to a small amount of deaminated product three components were present in the ratio 52 (VIIIa) : 43 (VIIIb) : 5 (VIIIc). This mixture was acetylated and the individual components were separated by repeated fractional recrystallizations.

Acidic hydrolysis of the acetamide (IXa) obtained in largest quantity to the amine (VIIIa), followed by deamination with nitrous acid, gave a high yield (82%) of the corresponding alcohol (Xa). It is well documented that high yields of alcohols are obtained from this conversion only when the amino-substituent is in the equatorial position.[5] The broad peak at δ 3.77 [half-width at baseline ($W/2$) 28 Hz] in the n.m.r. spectrum of the alcohol (Xa) indicated that H-6 was axial and therefore that the hydroxy-substituent (and thus the amino-substituent in the amine from which it was derived) occupied the equatorial position.[2h,6] The C–O (*ca.* 1 000 cm^{-1}) stretching region in the i.r. spectrum of the alcohol (Xa) was identical with that reported[6] for 6β-hydroxy-2-methyl-*cis*(4aα,8aα)-decahydroisoquinoline. The m.p.s of the picrate and methiodide of (Xa) coincided with the literature values (Table).

[1] (*a*) I. W. Mathison and R. C. Gueldner, *J. Org. Chem.*, 1968, **33**, 2510; (*b*) I. W. Mathison, R. C. Gueldner, J. W. Lawson, S. J. Fowler, and E. R. Peters, *J. Medicin. Chem.*, 1968, **11**, 997; (*c*) I. W. Mathison, P. H. Morgan, R. R. Tidwell, and C. R. Handorf, *J. Pharm. Sci.*, 1972, **61**, 637; (*d*) I. W. Mathison and P. H. Morgan, *J. Org. Chem.*, 1974, **39**, 3210; (*e*) I. W. Mathison and P. H. Morgan, *J. Medicin. Chem.*, 1974, **17**, 1136.

[2] (*a*) A. Marchant and A. R. Pinder, *J. Chem. Soc.*, 1956, 327; (*b*) S. M. McElvain and P. H. Parker, *J. Amer. Chem. Soc.*, 1956, **78**, 5312; (*c*) S. Durand-Henchoz and R. C. Moreau, *Bull. Soc. chim. France*, 1966, 3422; (*d*) S. Durand-Henchoz and R. C. Moreau, *ibid.*, p. 3416; (*e*) C. A. Grob and R. A. Wohl, *Helv. Chim. Acta*, 1965, **48**, 1610; (*f*) S. M. McElvain and R. C. Remy, *J. Amer. Chem. Soc.*, 1960, **82**, 3960; (*g*) S. Kimoto and M. Okamoto, *Chem. and Pharm. Bull. (Japan)*, 1962, **10**, 362; (*h*) S. Kimoto and M. Okamoto, *ibid.*, 1967, **15**, 1045.

[3] L. Helfer, *Helv. Chim. Acta*, 1924, **7**, 945.

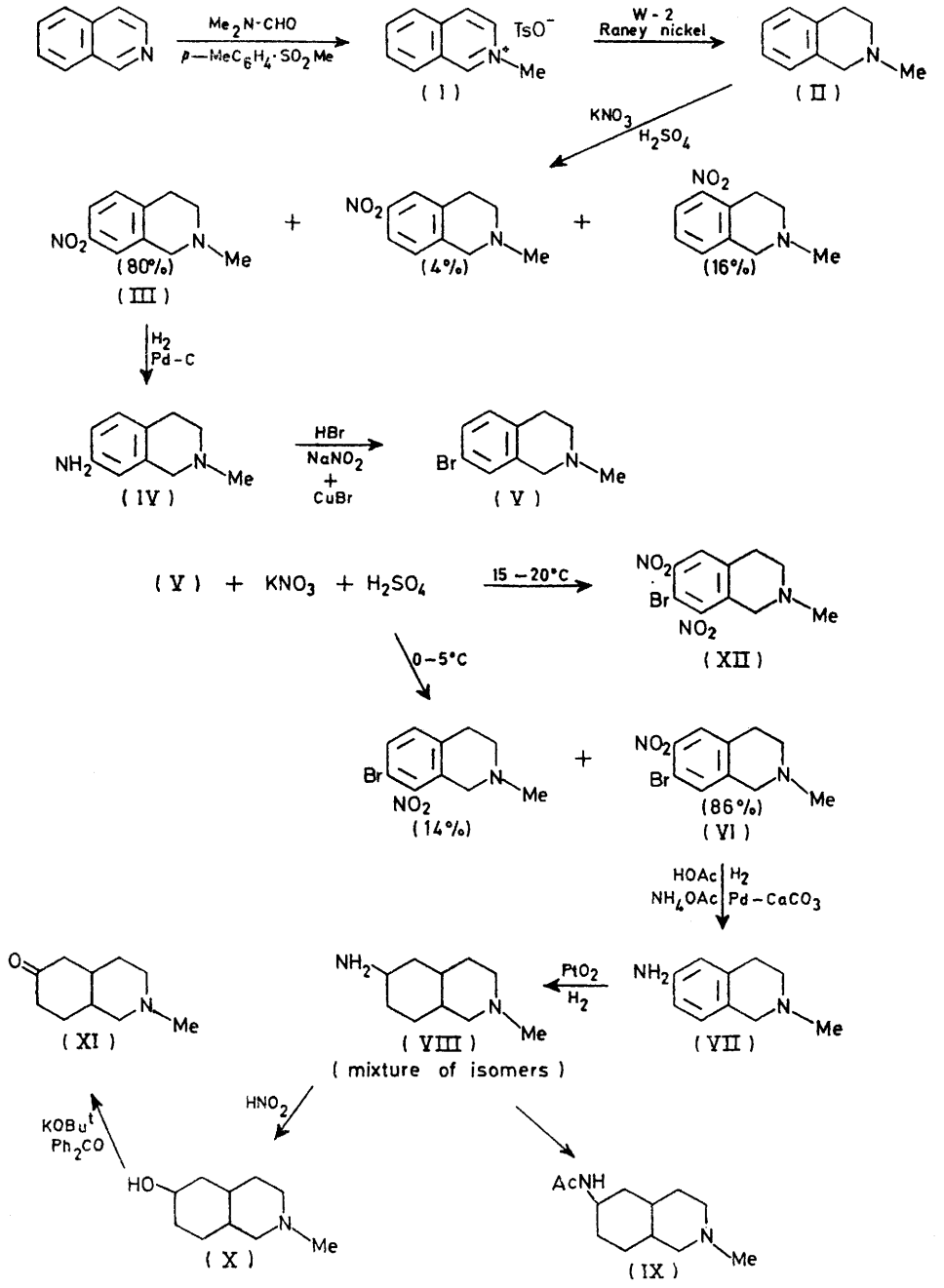
[4] S. Durand-Henchoz and R. C. Moreau, *Bull. Soc. chim. France*, 1966, 3413.

[5] W. G. Dauben, R. C. Tweit, and C. Mannerskantz, *J. Amer. Chem. Soc.*, 1954, **76**, 4420.

[6] S. Durand-Henchoz and R. C. Moreau, *Bull. Soc. chim. France*, 1966, 3428.

Confirmation of the *cis*-stereochemistry at the ring junction was obtained by oxidation of (Xa) to the ketone. The m.p. of the ketone methiodide coincided with literature values (see Table) for the *cis*-isomer.

equatorial position.[2h,6] The C–O stretching region of the i.r. spectrum of the alcohol (Xb) showed little difference from the published spectrum for 6α-hydroxy-2-methyl-*trans*(4aβ,8aα)-decahydroisoquinoline.[6] The



SCHEME Synthesis of 6-amino- and 6-hydroxy-2-methyl decahydroisoquinolines

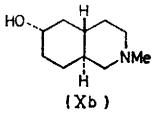
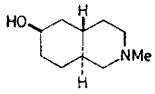
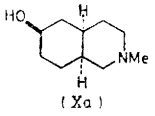
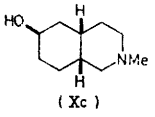
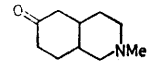
The acetamide (IXb) isolated in second highest yield was converted *via* the amine (VIIIb) as described above to yield the alcohol (Xb) in 94% yield. This high yield together with the broad peak at δ 3.56 (*W*/2 33 Hz) in the n.m.r. spectrum indicated that the hydroxy-substituent (and thus the amino-group) occupied the

m.p.s of the picrate and the methiodide were similar to those reported for this isomer (see Table). Oxidation to the ketone confirmed a *trans*-ring junction; the m.p. of the methiodide coincided with those reported for the *trans*-compound (Table).

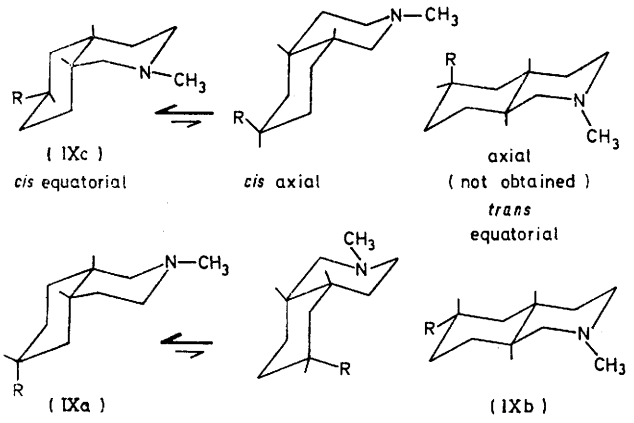
The third acetamide isomer, isolated in only small

quantity, was also converted into the amine and thence into the alcohol (Xc). The high yield of the alcohol (79%) coupled with n.m.r. and i.r. spectral data indicated once more that the substituent was in an equatorial position. The m.p. of the picrate (169—171°) was only slightly less than that reported [2h] (178°) for 6β-hydroxy-2-methyl-*cis*(4aβ,8aβ)-decahydroisoquinoline. The m.p. for the methiodide of the *cis*-ketone (Table). A mixture of the methiodides of the ketones obtained from the acetamides (IXa) and (IXc) showed no m.p. depression. Since the two ketones were obtained from different hydroxy-isomers, each with the hydroxy-group equatorial, the ketones, and thus the two alcohols, must possess *cis*-ring junctions.

M.p.s of 6-substituted 2-methyldecahydroisoquinolines (°C)

Structure		Ref: 2e	2h	2g	2d	2c	2a	2b	This work
 (Xb)	Free base	40—43	64			45			44—46
	Picrate	191—193	180—181			193	178		188—190
	Methiodide		259	256—258		280	273		247—276
	Free base	68	68			63			
	Picrate		228	228—230		235			
	Methiodide		263			265			
 (Xa)	Free base		(Oil)			(Oil)			(Oil)
	Picrate		190—191			196			193—194
	Methiodide		251	259—261		286			280—282
 (Xc)	Free base		(Oil)			(Oil)			(Oil)
	Picrate		178						169—171
	Methiodide		282	255—256		305			290—292
	*trans*-Methiodide			244—246	256		243		249—251
	cis-Methiodide			257—259	270—272			271—273	269—271

of the methiodide (290—292°) however was between the values reported by Moreau (lit.,[2c] 282°) and by Kimoto (lit.,[2h] 282°). To clarify this situation the ketone was prepared; the m.p. of the methiodide (270—271°) was in close agreement with those reported



Diastereoisomeric 6-substituted 2-methyldecahydroisoquinolines (R = AcNH)

From the chemical, physical, and spectral evidence cited above, the stereochemical configurations of the 6-amino-2-methyldecahydroisoquinolines isolated are those shown in the Figure.

EXPERIMENTAL

M.p.s were determined with a Buchi apparatus. I.r. spectra were obtained with either a Perkin-Elmer 137B Infracord or a Beckman IR-33 grating spectrophotometer. N.m.r. spectra were recorded with either a Varian A60-A or a Hitachi–Perkin-Elmer R-24 spectrometer. Tetramethylsilane was used as internal standard and deuterium oxide exchange was performed on all compounds possessing labile hydrogen atoms. G.l.c. was carried out on a Varian Aerograph A-700 with helium as carrier gas and a column (20 ft × ¾ in) packed with 20% SE30 on Chromosorb W. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee, and Chemalytics, Inc., Tempe, Arizona.

Analytical t.l.c. was carried out on aluminum-supported, precoated sheets of aluminum oxide F-254, neutral type E, layer thickness 0.20 mm (Merck), developed with 9 : 11 chloroform–methanol. The spots were located by spraying with Dragendorff's reagent (orange colour with amines).

For column chromatography, aluminium oxide (Matheson, Coleman, and Bell Activated Alumina, Chromatographic Grade, 80—200 mesh) was used after activation by heating at 150 °C for 6 h.

2-*Methylisoquinolinium Toluene*-p-*sulphonate* (I).—Isoquinoline (100 g, 0.774 mol) was dissolved in dimethylformamide (DMF) (750 ml), methyl toluene-*p*-sulphonate (158.5 g, 0.853 mol) was added, and the solution was stirred until no further heat was evolved. The solution was then allowed to cool; crystals were filtered off, the filtrate was evaporated, and a further crop was collected. Recrystallization from ethanol to give white *needles* (231.0 g, 95%), m.p. 160—161° (Found: C, 64.55; H, 5.5; N, 4.6. $C_{17}H_{17}NO_3S$ requires C, 64.4; H, 5.55; N, 4.45%).

1,2,3,4-*Tetrahydro*-2-*methylisoquinoline* (II).—Compound (I) (200.0 g, 0.635 mol) dissolved in water (200 ml) was hydrogenated over W-2 Raney Nickel [7] (45 g) at 1 000 lb in^{-2} for 18 h at room temperature. The mixture was washed out with hot water. Filtration and evaporation afforded a white solid which was dissolved in water, made alkaline with sodium hydroxide solution, and extracted with ether. The extract was dried (Na_2SO_4) and evaporated and the resulting oil was distilled (60—65° and 0.45 mmHg) to give pure (II) (90.0 g, 95%) (lit.,[4] b.p. 107—108° at 12 mmHg).

1,2,3,4-*Tetrahydro*-2-*methyl*-7-*nitroisoquinoline* (III).—Compound (II) (300 g, 2.02 mol) was dissolved in concentrated sulphuric acid (700 ml) and cooled to 0 °C. A solution of potassium nitrate (206 g, 1% excess) in sulphuric acid (750 ml) was then added dropwise during 3 h with the temperature kept between 5 and −5 °C. The mixture was stirred until room temperature was reached; it was then stirred in a solid CO_2–acetone bath during slow addition (5 h) of concentrated sodium hydroxide. The solution was then extracted with ether until the extracts no longer showed a positive reaction with Dragendorff's reagent. The extracts were dried and evaporated, leaving a dark brown oil (500 ml). G.l.c. indicated three components, identified as 7-nitro- (82%), 5-nitro- (15%), and 6-nitro- (3%) 1,2,3,4-tetrahydro-2-methylisoquinoline. The oil was extracted with warm petroleum (b.p. 30—60°) and the extract evaporated, leaving a reddish-brown oil (*ca.* 90% of the original oil) which partially crystallized at 0 °C. The mixture was filtered and the crystals were washed with cold petroleum until no oil remained. The solid was recrystallized from ether–petroleum (b.p. 30—60°) to give compound (III) (101 g) as yellow needles, m.p. 50—52° (lit.,[4] 53°). The remaining oil afforded a further crop of pure (III) (23 g) in addition to the 6-nitro-derivative (0.45 g), obtained as a pale yellow solid, m.p. 89—91° (lit.,[4] 90—92°). By fractionally recrystallizing the hydrochloride salt of the residual oil [ethanol–water (3 : 1)] and conversion back into the free base, a further crop of (III) (12 g), the 6-nitro-derivative (1.2 g), and the 5-nitro-derivative (18 g) was obtained. The m.p.s of the hydrochloride salts were: 7-nitro-, 252—254°; 5-nitro-, 235—236°; and 6-nitro-, 222° [total yield of (III) 35%].

7-*Amino*-1,2,3,4-*tetrahydro*-2-*methylisoquinoline* (IV).—To compound (III) (50 g, 0.26 mol) dissolved in ethanol (250 ml) was added palladium–charcoal (5 g, 5%) suspended in water (50 ml). The mixture was hydrogenated at 50 lb in^{-2} for 12 h. Filtration and evaporation left an oil which was distilled (109° and 0.25 mmHg); the resulting oil solidified on cooling. Recrystallization from ether–petroleum (b.p. 60—90°) gave (IV) as clear prisms, m.p. 91—92° (lit.,[4] 90—92°) (40.5 g, 95%).

7-*Bromo*-1,2,3,4-*tetrahydro*-2-*methylisoquinoline* (V).—Compound (IV) (62 g, 0.38 mol) was dissolved in 48% hydrobromic acid (104 ml) and cooled to 4 °C, and sodium nitrite (28 g, 0.38 mol) in water (60 ml) was added, with the temperature kept below 10 °C. The solution was then kept at 0 °C without stirring, and added dropwise (during *ca.* 20 min) to a boiling solution of copper(I) bromide (32 g, 0.22 mol) in hydrobromic acid (30 ml, 0.23 mol). The resulting solution was allowed to cool to room temperature and then made alkaline with concentrated sodium hydroxide solution. The solution was extracted with ether until the extracts no longer gave a positive reaction with Dragendorff's reagent. The extracts were dried and evaporated and the resulting oil was distilled (86° and 0.5 mmHg) to give (V) as a pale yellow oil (71.5 g, 87%). The *hydrobromide* of (V) crystallized from ethanol–water to give a buff-coloured solid, m.p. 285—286° (Found: C, 39.05; H, 4.4; Br, 51.85; N, 4.75. $C_{10}H_{13}Br_2N$ requires C, 39.1; H, 4.25; Br, 52.05; N, 4.55%).

7-*Bromo*-1,2,3,4-*tetrahydro*-2-*methyl*-6,8-*dinitroisoquinoline* (XII).—The tetrahydroisoquinoline (V) (13.4 g, 0.059 mol) was dissolved in concentrated sulphuric acid (45 ml) and cooled to 17 °C. Potassium nitrate (6.43 g, 0.075 mol) dissolved in concentrated sulphuric acid (40 ml) was added dropwise during 1 h. The mixture was then allowed to warm to room temperature, cooled again in a solid CO_2–acetone bath, and basified by careful addition of concentrated sodium hydroxide solution. The solution was extracted with ether until the extracts no longer showed a positive reaction with Dragendorff's solution. The extracts were dried and evaporated and the residue was recrystallized from methanol–acetone to give (XII) (7.4 g, 39.5%) as light yellow *needles*, m.p. 160—162°, δ ($CDCl_3$) 7.80 (1 H, s, ArH) (Found: C, 37.7; H, 3.1; Br, 25.55; N, 13.25. $C_{10}H_{10}BrN_3O_4$ requires C, 38.0; H, 3.2; Br, 25.55; N, 13.3%).

7-*Bromo*-1,2,3,4-*tetrahydro*-2-*methyl*-6-*nitroisoquinoline* (VI) *and its* 8-*Nitro-isomer*.—Compound (V) (50 g, 0.22 mol) was dissolved in concentrated sulphuric acid (300 ml) * and cooled to −5 °C (acetone–solid CO_2). Potassium nitrate (24 g, 0.22 mol) dissolved in concentrated sulphuric acid (250 ml) was then added dropwise and the stirred mixture was allowed to warm to room temperature. The solution was re-cooled and basified by dropwise addition of concentrated sodium hydroxide solution. The mixture was extracted with ether until the extracts no longer gave a positive reaction with Dragendorff's reagent. The extracts were dried (Na_2SO_4) and evaporated and the residue was recrystallized from petroleum (b.p. 60—90°) to give (VI) (44.7 g, 78%) as yellow *needles*, m.p. 96—97°, δ ($CDCl_3$) 7.35 (1 H, s, H-8) and 7.65 (1 H, s, H-5) (Found: C, 44.25; H, 4.05; Br, 29.65; N, 10.25. $C_{10}H_{11}BrN_3O_2$ requires C, 44.3; H, 4.1; Br, 29.45; N, 10.35%).

The mother liquors were evaporated to give a solid, m.p. 50—73°. G.l.c. indicated two components (*ca.* 2 : 1). Slow crystallization from petroleum (b.p. 30—60°) (twice) gave the 8-*nitro-isomer* as light yellow needles (1.8 g, 3%), m.p. 100—102°, δ ($CDCl_3$) 7.30 (2 H, q, H-5 and -6) (Found: C, 44.35; H, 3.95; Br, 29.5; N, 10.25%).

Dehydrohalogenation and reduction of the products gave the known 6-amino- (VII) and 8-amino-1,2,3,4-tetrahydro-2-methylisoquinolines (described below).

* A large dilution of the base gave higher yields of the desired product.

[7] R. Mozingo, *Org. Synth.*, 1955, Coll. Vol. III, p. 181.

6-*Amino*-1,2,3,4-*tetrahydro*-2-*methylisoquinoline* (VII).—Compound (VI) (25 g, 0.092 mol) was dissolved in glacial acetic acid (250 ml), and ammonium acetate (25 g) and 5% palladium–calcium carbonate (20 g) were added. The mixture was then hydrogenated at 50 lb in^{-2} for 24 h. The mixture was filtered and the filtrate basified with concentrated sodium hydroxide solution. The solution was extracted with ether and the extract dried (Na_2SO_4) and evaporated. The residue was recrystallized from acetone–petroleum (b.p. 60—90°) to give (VII) as white platelets (13.0 g, 86%), m.p. 129—131° (lit.,[4] 129—130°).

6-*Amino*-2-*methyldecahydroisoquinoline* (VIII).—To compound (VII) (28 g, 0.172 mol) dissolved in glacial acetic acid (350 ml) were added concentrated sulphuric acid (0.7 ml) and platinum oxide (5 g). The mixture was hydrogenated at 50 lb in^{-2} for 72 h at room temperature, then filtered, and the filtrate was concentrated to 100 ml, made alkaline with ammonium hydroxide, and extracted with ether. The extract was dried (Na_2SO_4) and distilled, leaving a light brown oil. G.l.c. showed three components with similar retention times (two major and one minor) together with two components of very short retention time. The latter two peaks represented 5% of the total material and were presumed to be *cis*- and *trans*-2-methyldecahydroisoquinoline.[1d] The former peaks were subsequently shown to be the 6β-amino-*cis*(4aα,8aα)-isomer (52%), the 6α-amino-*trans*(4aβ,9aα)-isomer (43%), and the 6β-amino-*cis*(4aβ,8aβ)-isomer (5%) of 6-amino-2-methyldecahydroisoquinoline. Most of the deamination products were removed by extracting the aqueous alkaline solution of the crude product mixture with ether (3 × 75 ml). G.l.c. of the extract showed that little loss of the aminoisoquinolines occurred.

The 6-*Acetamido*-2-*methyldecahydroisoquinolines* (IXa—c).—The isomeric mixture of 6-amino-2-methyldecahydroisoquinolines (50 g, 0.27 mol) was dissolved in dry DMF (400 ml) and cooled to 10 °C with stirring. Acetic anhydride (50 g, 0.49 mol) in dry benzene was added over 20 min and the mixture was stirred at room temperature for 24 h. Solvents were evaporated off and the remaining oil was dissolved in water and made alkaline with ammonium hydroxide. The solution was extracted with ether and the extract dried ($MgSO_4$) and evaporated to give the mixed acetamide diastereoisomers as a solid (44 g, 77%). Several fractional recrystallizations of the mixture (80 g) from ethyl acetate or ether–petroleum (b.p. 30—60°) gave pure 6β-*acetamido*-2-*methyl*-cis(4aα,8aα)-*decahydroisoquinoline* (IXa) (12 g) as white layered crystals, m.p. 130—131°, $\nu_{max.}$ ($CHCl_3$) 1 655 (C=O of amide I), 1 505 (amide II), 3 440 (free N–H str.), and 3 310 cm^{-1} (bonded N–H str.), δ ($CDCl_3$) 5.70br [1 H, half-width at baseline (*W*/2) 25 Hz, CONH], 3.76br (1 H, *W*/2 28 Hz, C*H*·NHAc), 2.30 (3 H, s, NCH_3), and 2.00 (3 H, s, $CO{\cdot}CH_3$) (Found: C, 68.75; H, 10.55; N, 13.3. $C_{12}H_{22}N_2O$ requires C, 68.5; H, 10.55; N, 13.3%).

Evaporation of the mother liquors from the recrystallization produced a solid, m.p. 89—111°. When this was dissolved in ether and allowed to crystallize by slow evaporation at room temperature, two types of crystals were distinguishable: flat platelets (IXa) and a larger quantity of white felted needles. The platelets were removed mechanically and the needles were recrystallized twice from ethyl acetate to give pure 6α-*acetamido*-2-*methyl*-trans(4aβ,8aα)-*decahydroisoquinoline* (IXb) (10 g), m.p. 180—183°, $\nu_{max.}$ ($CHCl_3$) 1 660 (C=O of amide I), 1 510 (amide II), 3 440 (free N–H str.), and 3 310 cm^{-1} (bonded N–H str.), δ ($CDCl_3$) 5.50br (1 H, *W*/2 30 Hz, CONH), 3.80br (1 H, *W*/2 28 Hz, C*H*·NHAc), 2.28 (3 H, s, NCH_3), and 1.98 (3 H, s, $CO{\cdot}CH_3$) (Found: C, 68.35; H, 10.4; N, 13.2%).

Evaporation of the filtrate from the recrystallizations of (IXb) yielded white needles (2.5 g), which were recrystallized from ether to give pure 6β-*acetamido*-2-*methyl*-cis(4aβ,8aβ)-*decahydroisoquinoline* (IXc) (2 g), m.p. 168—169°, $\nu_{max.}$ ($CHCl_3$) 1 660 (C=O of amide I), 1 510 (amide II), 3 415 (free N–H str.), and 3 320 cm^{-1} (bonded N–H str.), δ ($CDCl_3$) 5.30br (1 H, *W*/2 28 Hz, CO·NH), 3.90br (1 H, *W*/2 28 Hz, C*H*·NHAc), 2.20 (3 H, s, NCH_3), and 1.95 (3 H, s, $CO{\cdot}CH_3$) (Found: C, 68.7; H, 10.55; N, 13.2%). Mixed m.p. determinations showed that three different isomers had been obtained.

Hydrolysis of the Acetamido-derivatives (IX).—Compound (IXa) (2.00 g, 0.0095 mol) was dissolved in 10% sulphuric acid (100 ml) and heated under reflux for 48 h. The solution was made alkaline with concentrated sodium hydroxide solution and extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated to yield the amine (VIIIa) as an oil (1.46 g, 91%). All attempts to crystallize the oil failed. G.l.c. indicated that the compound was pure; $\nu_{max.}$ ($CHCl_3$) 3 368 (free N–H str.), 3 265 and 3 150 (bonded N–H str.), 1 580 (N–H bend), and 1 100 cm^{-1} (C–N). 6β-*Amino*-2-*methyl*-cis(4aα,8aα)-*decahydroisoquinoline* (VIIIa) *dihydrobromide* had m.p. 262—264° (from acetonitrile–ethyl acetate) (Found: C, 36.0; H, 6.5; Br, 48.6; N, 8.55. $C_{10}H_{22}Br_2N_2$ requires C, 36.4; H, 6.7; Br, 48.4; N, 8.5%).

Compound (IXb) (2.00 g, 0.0095 mol) in 10% sulphuric acid (175 ml) under reflux for 72 h similarly afforded the amine (1.52 g, 93%) as an oil. The oil was thoroughly dried and purged with nitrogen but showed no signs of crystallizing; $\nu_{max.}$ ($CHCl_3$) 3 365 (free N–H str.), 3 278 and 3 160 (bonded N–H str.), 1 584 (N–H bend), and 1 100 cm^{-1} (C–N). 6α-*Amino*-2-*methyl*-trans(4aβ,8aα)-*decahydroisoquinoline* (VIIIb) *dihydrobromide* had m.p. 289—291° (from ethyl acetate–methanol) (Found: C, 36.4; H, 6.6; Br, 48.25; N, 8.5%).

Compound (IXc) (2.00 g, 0.0095 mol), hydrolysed as described for (IXb), yielded the amine (1.30 g, 81%) as an oil, which g.l.c. indicated to be a single component; $\nu_{max.}$ ($CHCl_3$) 3 370 (free N–H str.), 3 284 and 3 157 (bonded N–H str.), 1 580 (N–H bend), and 1 105 cm^{-1} (C–N). 6β-*Amino*-2-*methyl*-cis(4aβ,8aβ)-*decahydroisoquinoline* (VIIIc) *dihydrobromide* had m.p. 272—274° (from acetonitrile–ethyl acetate) (Found: C, 36.35; H, 6.7; Br, 48.4; N, 8.45%).

Treatment of the 6-*Amino-derivatives* (VIII) *with Nitrous Acid*.—To a stirred solution of compound (VIIIa) (1.50 g, 0.0089 mol) in glacial acetic acid (2.13 g, 0.0356 mol), sodium nitrite (1.23 g, 0.0178 mol) in water (15 ml) was added dropwise. The mixture was heated to 65 °C and a 20% excess (0.43 g) of glacial acetic acid in water (5 ml) was added dropwise. The mixture was heated for a further 4 h and then allowed to cool to room temperature, made strongly alkaline with concentrated sodium hydroxide solution, and refluxed for 1 h. After cooling, the solution was extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated. The resulting oil (1.25 g, 83%) was shown by g.l.c. to contain 82% of the alcohol and 18% of olefins. This oil was subjected to column chromatography and eluted with benzene (to remove olefins) followed

by chloroform, which yielded the pure 6β-hydroxy-2-methyl-*cis*(4aα,8aα)-decahydroisoquinoline (Xa) as an oil (lit.,[2c,h] oil), $\nu_{max.}$ ($CHCl_3$) 3 220 (bonded O–H str.) and 1 058 and 1 022 (equatorial C–O) cm^{-1}, δ ($CDCl_3$) 5.57br (1 H, OH), 3.77br (1 H, *W*/2 28 Hz, C*H*·OH), and 2.23 (3 H, s, NCH_3); picrate, m.p. 193—194° (from 95% ethanol); methiodide, m.p. 280—282° (from ethyl acetate–acetonitrile) (for lit. m.p.s see Table).

The 6-amino-2-methyldecahydroisoquinoline (VIIIb) (2 g, 0.012 mol) was treated similarly. The oil (1.68 g) recovered from the chloroform extract was shown by g.l.c. to contain 94% of the alcohol (Xb) and 6% of deamination products. The oil solidified at 0 °C and was recrystallized from ether–petroleum (b.p. 30—60°) to give transparent platelets of 6α-hydroxy-2-methyl-*trans*-(4aβ,8aα)-decahydroisoquinoline (Xb) (1.41 g, 58%), m.p. 44—46°, $\nu_{max.}$ ($CHCl_3$) 3 280 (bonded O–H str.), and 1 050 and 1 030 cm^{-1} (equatorial C–O), δ ($CDCl_3$) 4.12br (1 H, OH), 3.56br (1 H, *W*/2 33 Hz, C*H*·OH), and 2.22 (3 H, s, NCH_3); picrate, m.p. 188—190° (from 95% ethanol); methiodide, m.p. 274—276° (from ethyl acetate–acetonitrile) (for lit. m.p.s see Table).

The 6-amino-2-methyldecahydroisoquinoline (VIIIc) (1.5 g, 0.0089 mol) was treated similarly to give an oil (1.23 g), shown by g.l.c. to contain 84% (Xc) and 16% olefins. Column chromatography as for (Xa) yielded pure 6β-hydroxy-2-methyl-*cis*(4aβ,8aβ)-decahydroisoquinoline (1.12 g, 74%) as a clear oil (lit.,[2c,h] oil), $\nu_{max.}$ ($CHCl_3$) 3 190 (bonded O–H str.), and 1 050, 1 035, and 1 018 cm^{-1} (equatorial C–O), δ ($CDCl_3$) 5.62br (1 H, OH), 3.59br (1 H, *W*/2 26 Hz, C*H*·OH), and 2.25 (3 H, s, NCH_3); picrate, m.p. 169—171° (from 95% ethanol); methiodide, m.p. 290—292° (from ethyl acetate–acetonitrile) (for lit. m.p.s see Table).

Oxidation of the 6-Hydroxy-derivatives (X).—Compound (Xa) (0.80 g, 0.0047 mol) was dissolved in benzene and refluxed overnight under a Dean–Stark trap to remove all water. To the solution were added benzophenone (4.00 g, 0.022 mol) and potassium t-butoxide (1.25 g, 0.011 mol). The mixture was stirred and heated to reflux for 6 h under nitrogen. After cooling, it was extracted with 10% hydrochloric acid. The extract was made alkaline by slow addition to a cooled stirred solution of ammonium hydroxide. The basic solution was continuously extracted with ether for 12 h. The ethereal extract was washed with saturated aqueous sodium chloride (2 × 100 ml), dried ($MgSO_4$), and distilled to leave the ketone as an oil (0.40 g, 50%), $\nu_{max.}$ (neat) 1 710 cm^{-1} (C=O); methiodide (from ethyl acetate–acetonitrile), m.p. 269—271° (for lit. m.p.s see Table).

Compound (Xb) (0.50 g, 0.0029 mol), oxidized similarly, gave an oil (0.31 g, 62%); methiodide (from ethyl acetate–acetonitrile), m.p. 249—251° (see Table for lit. m.p.s), $\nu_{max.}$ (KBr) 1 705 cm^{-1} (C=O).

Compound (Xc) (0.50 g, 0.0029 mol) similarly afforded an oil (0.24 g, 48%); methiodide (from ethyl acetate–acetonitrile), m.p. 270—271° (see Table for lit. m.p.s), $\nu_{max.}$ (neat) 1 700 cm^{-1} (C=O), identical (mixed m.p.) with that obtained from oxidation of (Xa).

[5/573 *Received, 24th March,* 1975]