Conformational Equilibria due to Ring Inversion in *N*-Alkyl-*cis*-decahydroisoquinolines

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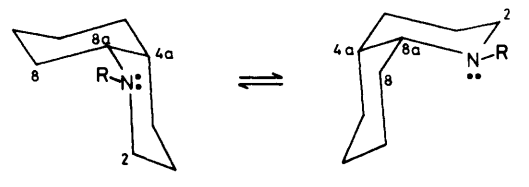
The position of conformational equilibria due to ring inversion in *N*-alkyl-*cis*-decahydroisoquinolines (alkyl = Me, Et, Pr^i, CH_2CF_3, or CH_2CCl_3) has been assessed directly from ^{13}C and/or ^{19}F n.m.r. spectra recorded at temperatures between 173 and 253 K. The measured equilibrium constants are related to the inductive effect of the *N*-substituent which produces an increase (Me, Et, Pr^i) or decrease (CH_2CF_3, CH_2CCl_3) in the magnitude of the *gauche* propylamine-type repulsive interaction. ^{13}C Chemical shifts are tabulated for the carbon atoms of the two twin-chair conformations undergoing exchange.

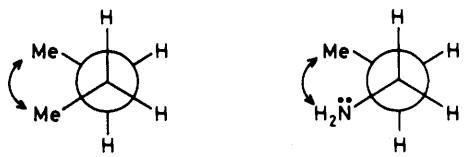
In previous work [1,2] it was shown from ^{13}C n.m.r. spectra recorded at 199—223 K that the position of equilibrium, due to a double ring inversion, in *N*-substituted *cis*-decahydroquinolines [(1) ⇌ (2)] shifted from a preference for conformation (2) [3] (' type 2 ' allowing the nitrogen lone pair to be ' inside ') when R = H [93.5% (2)] or R = Me [70% (2)] to a preference for conformation (1) (' type 1 ') when R = CD_2CH_3 [86% (1)] or R = CH_2CF_3 [83% (1)]. In *cis*-decahydroquinoline itself the preference for (2) was rationalised [4] on the reasonable assumption that a *gauche* butane (GB) type interaction [*cf.* (3)] is greater than a *gauche* propylamine [5] (GP) type interaction [*cf.* (4)] and that (1) suffers three GB-type interactions whereas (2) suffers one GB- and two GP-type interactions. It may be recalled that the experimentally determined difference in enthalpy between *trans*- and *cis*-decalin is 2.69—2.75 kcal mol^{-1}; [6] this value is approximately equal to three GB-type interactions, since the conformational free energy difference for methyl in methylcyclohexane (1.75 kcal mol^{-1}; ref. 7) represents two GB-type interactions.

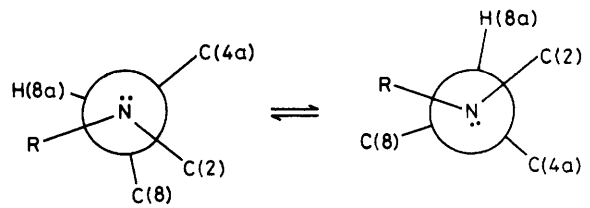
It was suggested previously [2] that the shortness of the C–N bond, as compared with the C–C bond, leads to ring puckering around the nitrogen atom in (1) and (2). The resulting Newman projections [for views along the N–C(8a) bond] may be drawn as (5) and (6), for (1) and (2), respectively. When R is H or Me, the dominant *gauche* repulsion is between C(2) and C(8), making (6) [≡ (2)] the preferred conformation. However, when R is CD_2CH_3 and CH_2CF_3 the *gauche* interaction between R and C(8) becomes dominant, leading to a preference for conformation (5) [≡ (1)].

It is now seen that the increasing preference for (1), as R is altered from H through Me to CD_2CH_3, may also be explained by the increasing electron repulsion of the alkyl substituent, causing an increase in the GP interaction in (2). The fact that the trend is reversed when R is CH_2CF_3 lends some support to this second explanation.

The purpose of the present study was to attempt to distinguish between the two explanations by an investigation of the position of conformational equilibrium in a series of *N*-substituted *cis*-decahydroisoquinolines, (7) ⇌ (8). In this case (8) suffers three GB-type interactions whereas (7) suffers two GB- and one GP-type interactions. If ring puckering round the nitrogen is again assumed to occur, the Newman projections [for views along the N–C(1) bond] may be drawn as (9) and (10), corresponding to (7) and (8), respectively. In contrast to the situation in *cis*-decahydroquinolines [(5) ⇌ (6)], the repulsive *gauche* interactions involving R are identical in (9) and (10) because the nitrogen atom is remote from the ring junction. Consequently, ring puckering effects can no longer affect the conformational equilibrium, whereas the inductive effect of the *N*-substituent R, which alters the magnitude of the GP interaction with C(8), remains a significant factor.



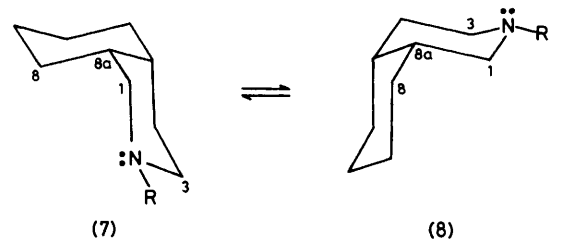




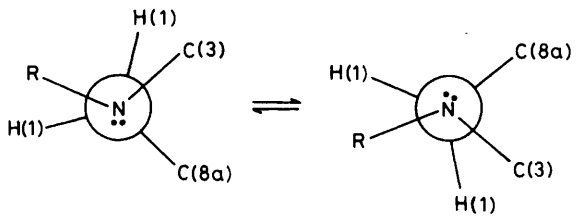
cis-Decahydroisoquinoline (11) ⇌ (12) was prepared as described in earlier work,[8] and also by *N*-demethylation of a pure sample of *N*-methyl-*cis*-decahydroisoquinoline (13) ⇌ (14) [9] by successive treatments with ethyl chloroformate and concentrated hydrochloric acid.[10] *N*-Methyl-*cis*- and *trans*-decahydroisoquinoline (23) were prepared by *N*-methylation of a mixture of isomeric secondary amines,[8] and separation of the products by preparative g.l.c.

Hydrogenation of isoquinoline over Raney nickel in cyclohexane and ethanol gave a mixture of *cis*- [(15) ⇌ (16)] and *trans*-*N*-ethyldecahydroisoquinoline (24) which resisted attempts at separation by preparative g.l.c. When isoquinoline in propan-2-ol was hydrogenated over Raney nickel, the product was exclusively *N*-isopropyl-*trans*-decahydroisoquinoline (25). However, direct alkylation of pure *cis*-decahydroisoquinoline with isopropyl methanesulphonate in benzene and triethylamine gave the required *N*-isopropyl-*cis*-decahydroisoquinoline (17) ⇌ (18) in good yield.

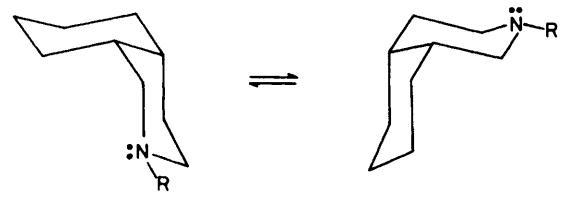
N-(2,2,2-Trifluoroethyl)-*cis*-decahydroisoquinoline (19) ⇌ (20) was obtained in 79% yield by direct alkylation



(7) (8)



(9) (10)



(11) R = H
(13) R = Me
(15) R = Et
(17) R = Pr^i
(19) R = CH_2CF_3
(21) R = CH_2CCl_3

(12) R = H
(14) R = Me
(16) R = Et
(18) R = Pr^i
(20) R = CH_2CF_3
(22) R = CH_2CCl_3

(23) R = Me
(24) R = Et
(25) R = Pr^i
(26) R = CH_2CF_3

using 2,2,2-trifluoroethyl trifluoromethanesulphonate (' triflate '). An alkylation using the corresponding methanesulphonate gave only a 47% yield of product, despite a longer reaction time, presumably because in this case the charge on the leaving group is less delocalised. The effectiveness of the methods of alkylation just described had been established by experiments using 1,2,3,4-tetrahydroisoquinoline as a model compound. However, an attempt to synthesise *N*-trichloroethyl-1,2,3,4-tetrahydroisoquinoline by alkylation of the secondary amine with 2,2,2-trichloroethyl methanesulphonate failed, the product consisting almost entirely of *N*-methylsulphonyl-1,2,3,4-tetrahydroisoquinoline. In this instance nucleophilic attack at sulphur is preferred to attack at carbon. A different approach was therefore adopted for the synthesis of *N*-(2,2,2-trichloroethyl)-*cis*-decahydroisoquinoline (21) ⇌ (22). The action of hexachloroacetone on *cis*-decahydroisoquinoline gave a good yield of *N*-trichloroacetyl-*cis*-decahydroisoquinoline from which the required *N*-trichloroethyl amine was obtained by reduction with diborane. The method had been checked previously on 1,2,3,4-tetrahydroisoquinoline.

It was intended to synthesise hexafluoroisopropyldecahydro-*cis*-isoquinoline, but model reactions of 1,2,3,4-tetrahydroisoquinoline with the hexafluoroisopropyl esters of methanesulphonic and trifluoromethanesulphonic acids were failures. The sole products were identified, by unambiguous syntheses, as the *N*-methylsulphonyl- and *N*-trifluoromethylsulphonyl derivatives of 1,2,3,4-tetrahydroisoquinoline. As in the earlier example, the preference for nucleophilic attack at sulphur, rather than carbon, is partly due to steric hindrance.

Differentiation of *N*-substituted *cis*- and *trans*-decahydroisoquinolines proved straightforward. The room temperature ^{13}C spectrum of a *cis*-decahydroisoquinoline always shows signals which are broadened owing to the relatively slow exchange between the twin-chair conformations (7) and (8). On the other hand, a *trans*-decahydroisoquinoline (23) reveals ^{13}C signals which are all as sharp as that due to the reference tetramethylsilane. In some cases, additional evidence was provided by ^1H n.m.r. spectra (see Experimental section). The ^{13}C n.m.r. spectra of the *cis*-bases, recorded at temperatures between 173 and 235 K, showed signals for both conformations (7) and (8). ^{13}C Chemical shifts for the *cis*- and some of the *trans*-decahydroisoquinolines are listed in Table 1. Line assignments depended on the multiplicities in off-resonance ^1H-decoupled spectra, and on comparisons with shifts calculated from the shifts in the unsubstituted decahydroisoquinolines, together with the substituent chemical shift parameters for the *N*-alkyl group.[11] Parameters for the *N*-(2,2,2-trifluoroethyl) substituent were based on published shifts of the corresponding *cis*- and *trans*-decahydroquinoline derivatives.[2] Parameters for the *N*-(2,2,2-trichloroethyl) substituent were not available, and assignment of ring carbons relied on comparisons with the ^{13}C shifts for the analogous *N*-trifluoroethyl conformations.

Integration of several pairs of signals in the low temperature ^{13}C spectra of the *N*-substituted *cis*-decahydroisoquinolines (7) ⇌ (8) gave the proportions of conformations which are listed in Table 2, along with the corresponding equilibrium constants and conformational free energy differences. The precautions to be taken when determining meaningful integration from ^{13}C spectra have been noted earlier.[4,7] The position of equilibrium in *N*-trifluoroethyl-*cis*-decahydroisoquinoline was also determined from ^{19}F n.m.r. spectra at 235.19 MHz. The spectrum at room temperature (298 K) already showed two broad signals for the fluorine nuclei in the two conformations (19) and (20). At lower temperatures the signals became much sharper, but whereas the major signal (69.5 p.p.m. to high field of $CFCl_3$) was the expected triplet, the minor signal (68.5 p.p.m.) remained too broad to show the vicinal HF coupling. Integration of the signals at five temperatures gave the results shown in Table 2.

Table 2 reveals that successive replacement of N–H by N–Me, N–Et, and N–Pr^i causes a decrease in the preference for conformation (7), with the lone pair ' inside ' the fold of the molecule. As argued earlier, ring puckering cannot be responsible for these observations. On the other hand, the findings are readily explained in terms of an increase in electron repulsion from the *N*-substituent, which must lead to a more severe GP repulsive interaction in (7). The trend disfavouring (7) with respect to (8) should be reversed when the *N*-substituent is an electronegative group such as CH_2CCl_3 or CH_2CF_3. This was observed (Table 2). However, since fluorine is more electronegative than chlorine, the finding that the *N*-trichloroethyldecahydroisoquinoline displays a stronger preference for (7) than the corresponding *N*-trifluoroethyl derivative appears anomalous. With this single exception, the conformational equilibria in *N*-substituted *cis*-decahydroquinolines and *cis*-decahydroisoquinolines can be adequately explained by the inductive effect of the *N*-substituent, which

Table 1. ^{13}C Chemical shifts for decahydroisoquinolines in $CFCl_3$–$CDCl_3$ (p.p.m. downfield from Me_4Si) (calculated shifts in parentheses)

Formula	Ring fusion	T/K	Ring carbon atoms 1	3	4	5	6	7	8	4a	8a	Side-chain carbons N–C	N–C–C
(11)	*c*	215	52.2	47.0	24.6	31.9	20.5	26.5	26.0	34.1	35.8		
(12)	*c*	215	45.1	40.9	32.3	25.1	*a*	21.2	29.8	33.8	35.4		
(23)	*t*	294	62.8	56.6	33.0	33.3	26.6	26.2	30.8	41.5	42.1	46.5	
			(62.0)	(56.1)	(32.7)	(33.5)	(26.5)	(26.2)	(29.8)	(41.7)	(42.1)		
(13) ⇌ (14)	*c*	321	59.9	54.7	28.0 [b]	29.1	23.3	24.8	28.3 [b]	33.7	36.2	46.9	
(13)	*c*	221	62.3	56.8	25.4	31.2	20.6	26.6	26.0	32.5	36.1	47.0	
			(61.3)	(56.1)	(23.4)	(31.9)	(20.5)	(26.5)	(25.3)	(32.7)	(34.6)		
(14)	*c*	221	55.0	50.5	30.3	24.9	26.2	21.3	29.7	32.8	34.4	46.4	
			(54.2)	(50.0)	(31.1)	(25.1)		(21.2)	(29.1)	(32.4)	(34.2)		
(24)	*t*	321	60.3	54.2	34.4	33.2	26.6	26.2	30.9	42.0	42.2	52.9	12.1
			(60.4)	(54.5)	(33.7)	(33.5)	(26.5)	(26.2)	(30.6)	(42.5)	(43.1)		
(15) ⇌ (16)	*c*	321	56.9	52.1	28.2	28.7	23.6	24.6	28.8	33.2	36.0	52.7	12.1
(15)	*c*	221	59.1	55.5	25.9 [b]	32.7	20.6	26.6 [b]	25.6 [b]	33.3 [c]	36.0 [c]	52.8	12.3
			(59.6)	(54.4)	(24.1)	(31.9)	(20.5)	(26.5)	(26.1)	(34.2)	(35.3)		
(16)	*c*	221	52.8	48.4	31.3	25.0 [b]	25.9 [b]	21.4	29.9	32.7 [c]	36.0 [c]	52.8	12.3
			(52.5)	(48.3)	(31.8)	(25.1)		(21.2)	(29.9)	(33.9)	(34.9)		
(25)	*t*	321	55.8	49.6	33.2 [b]	33.6 [b]	26.7 [c]	26.3 [c]	31.0	42.4	42.4	54.6	18.4, 18.5
			(55.3)	(49.4)	(33.4)	(33.5)	(26.5)	(26.2)	(30.3)	(42.1)	(42.8)		
(17) ⇌ (18)	*c*	298	52.3	48.1	29.2	28.7	23.1	25.0	27.7	36.4 [b]	34.8 [b]	54.6	18.5, 18.6
(17)	*c*	225	54.3	51.1	24.7	31.1	20.5	26.3	25.6	34.3	35.9	53.9	18.2, 17.7
			(54.5)	(49.3)	(23.7)	(31.9)	(20.5)	(26.5)	(25.7)	(33.9)	(35.1)		
(18)	*c*	225	47.5	43.4	31.4	25.8	26.3	21.1	29.7	33.2	34.4	53.9	18.2, 18.1
			(47.4)	(43.2)	(31.6)	(25.1)		(21.2)	(29.5)	(33.8)	(34.7)	(54.6)	
(26)	*t*	293	61.1	55.0	33.2 [b]	33.1 [b]	26.6 [c]	26.2 [c]	30.6	42.1 [d]	41.5 [d]	59.2 [e]	*e*
(19) ⇌ (20)	*c*	293	58.8	53.5	28.0 [b]	29.7	22.8	25.2	27.2 [b]	33.8	36.5	59.2 [e]	125.9 [g]
(19)	*c*	223	60.5	55.2	25.2	31.0	20.3	26.3	25.5	33.2	36.3	58.4 [f]	125.4 [g]
			(60.0)	(54.8)	(24.1)	(31.9)	(20.5)	(26.5)	(24.9)	(33.0)	(35.3)		
(20)	*c*	223	53.6	49.1	31.2 [b]	24.6 [c]	26.3 [c]	21.1	29.4 [b]	32.4	34.2	*a*	125.3 [h]
			(53.5)	(49.3)	(31.8)	(25.1)		(21.2)	(28.6)	(32.6)	(34.9)		
(21) ⇌ (22)	*c*	298	60.1	54.9	26.9 [b]	30.3	22.3	25.7 [b]	27.8 [b]	34.0	37.2	76.1	101.6
(21)	*c*	223	61.5	56.1	26.5 [b]	31.4	20.5	26.1 [b]	25.4 [b]	33.6	37.3	75.3	101.3
(22)	*c*	223	54.5	49.9	31.4	25.0	25.9	21.5	29.8	32.8	34.1		

[a] Not seen clearly. [b] Assignments exchangeable. [c] Assignments exchangeable. [d] Assignments exchangeable. [e] Quartet, $^2J_{CF}$ 29 Hz. [f] Quartet, $^2J_{CF}$ 31 Hz. [g] Quartet, $^1J_{CF}$ 280 Hz. [h] Quartet, $^1J_{CF}$ 281 Hz.

controls the magnitude of the *gauche* propylamine (GP) interaction. However, in the case of *cis*-decahydroquinolines, it is clearly impossible to exclude the possibility that some ring puckering is involved, resulting from the replacement of *N*–H by *N*-alkyl.

Experimental

General details for determination of ^1H and ^{13}C n.m.r. spectra have been given earlier.[11] ^{19}F N.m.r. spectra were measured in the Fourier transform mode at 235.19 MHz with a Bruker WM-250 spectrometer.

cis-*Decahydroisoquinoline*.—*N*-Methyl-*cis*-decahydroisoquinoline[9] (10 g) dissolved in toluene (50 cm³), was heated to boiling and treated with ethyl chloroformate (10 cm³). The mixture was heated under reflux for 3 h, cooled and washed successively with 2M-hydrochloric acid (2 × 40 cm³) and water (2 × 30 cm³). The organic layer was dried ($MgSO_4$), filtered, and evaporated, leaving crude *N*-ethoxycarbonyl-*cis*-decahydroisoquinoline (11.5 g, 91%) as a yellow oil, b.p. 62—66 °C at 5 mmHg, $\nu_{max.}$ 1 705 cm^{-1}, *m/z* 211.1572 (M^+) (Calc. for $C_{12}H_{21}NO_2$: *M*, 211.1549), δ_H (100 MHz; $CDCl_3$) 1.20 (3 H, t, *J* 7 Hz), 3.96 (2 H, q, *J* 7 Hz) and broad envelopes at 0.8—1.80, 2.4—3.0, and 3.4—3.8. The foregoing compound (9 g) was dissolved in concentrated hydrochloric acid (300 cm³) and the mixture was heated under reflux for 10 h. The solution was cooled, basified with aqueous 20% sodium hydroxide (30 cm³) and shaken with ether (4 × 50 cm³). The combined ethereal extracts were dried ($MgSO_4$), evaporated, and distilled, giving pure *cis*-decahydroisoquinoline as an oil (4.60 g, 78%), b.p. 97—99 °C at 29 mmHg. The picrate (yellow needles from EtOH), had m.p. 148—150 °C (lit.,[8] 152—154 °C) (Found: C, 49.2; H, 5.7; N, 14.8. Calc. for $C_{15}H_{20}N_4O_7$: C, 48.9; H, 5.4; N, 15.2%).

N-*Methyl*-cis- *and* trans-*decahydroisoquinoline*.—A mixture of *cis*- and *trans*-decahydroisoquinoline[8] (10 g) was dissolved, with cooling, in formic acid (40 cm³; 98%) and treated with aqueous formaldehyde (30 cm³; 40%). The mixture was heated under reflux for 20 h, cooled, acidified with hydrochloric acid (70 cm³; 30%), and evaporated to a thick oil. The oil was treated with aqueous sodium hydroxide (75 cm³; 40%) with cooling in ice, and extracted with ether (4 × 70 cm³). The combined ethereal extracts were dried (KOH pellets), filtered, evaporated, and distilled, giving a mixture of *N*-methyl-*cis*- and *trans*-decahydroisoquinoline (6.7 g, 60%), b.p. 99—101 °C at 16 mmHg. The mixture was separated by preparative g.l.c. (Varian Aerograph series 700) on a 35 ft × 1/4 in column of 20% Carbowax 20M on alkali-washed Chromosorb W.

N-*Ethyl*-cis- *and* trans-*decahydroisoquinoline*.—Isoquinoline (25 g) dissolved in cyclohexane (300 cm³) and ethanol (20 cm³) was hydrogenated over Raney nickel (*ca.* 5 g; grade T-1 [12]) at 180 °C and 60 atm initial pressure of H_2. After 48 h the mixture

Table 2. Proportions of conformations, equilibrium constants, and conformational free energy differences for equilibria in 1-substituted *cis*-decahydroisoquinolines (7) ⇌ (8) (from ^{13}C spectra, unless otherwise indicated)

R	Formula	T/K	% (7)	% (8)	K	ΔG^0/kcal mol^{-1} [(7) ⟶ (8)]
H	(11) ⇌ (12)	173	75.2	25.8	0.33	0.38 ± 0.03
H	(11) ⇌ (12)	215	70.0	30.0	0.43	0.37 ± 0.02
H	(11) ⇌ (12)	235	69.0	31.0	0.45	0.37 ± 0.02
Me	(13) ⇌ (14)	221	62.1	37.9	0.61	0.21 ± 0.01
Et	(15) ⇌ (16)	221	46.1	53.9	1.17	−0.06 ± 0.01
Pr^i	(17) ⇌ (18)	210	47.6	52.4	1.10	−0.04 ± 0.02
Pr^i	(17) ⇌ (18)	225	48.8	51.2	1.05	−0.02 ± 0.02
Pr^i	(17) ⇌ (18)	240	50.0	50.0	1.00	0.00 ± 0.02
CH_2CF_3	(19) ⇌ (20)	197	68.0	32.0	0.47	0.30 ± 0.03
CH_2CF_3 [a]	(19) ⇌ (20)	197	70.4	29.6	0.42	0.34 ± 0.02
CH_2CF_3	(19) ⇌ (20)	208	67.1	32.9	0.49	0.30 ± 0.03
CH_2CF_3 [a]	(19) ⇌ (20)	208	68.5	31.5	0.46	0.32 ± 0.03
CH_2CF_3	(19) ⇌ (20)	223	67.6	32.4	0.48	0.33 ± 0.03
CH_2CF_3 [a]	(19) ⇌ (20)	223	68.5	31.5	0.46	0.34 ± 0.03
CH_2CF_3	(19) ⇌ (20)	238	69.0	31.0	0.45	0.38 ± 0.03
CH_2CF_3 [a]	(19) ⇌ (20)	238	69.4	30.6	0.44	0.39 ± 0.03
CH_2CF_3 [a]	(19) ⇌ (20)	253	70.0	30.0	0.43	0.42 ± 0.03
CH_2CCl_3	(21) ⇌ (22)	223	78.1	21.9	0.28	0.57 ± 0.05

[a] From ^{19}F spectra.

was cooled, filtered, and evaporated to remove ethanol and cyclohexane. The residue of completely reduced bases was purified by preparative g.l c (Varian Aerograph series 700) on a 12 ft × 3/8 in column of 20% Carbowax 20M on alkali-washed Chromosorb W. Only a partial separation of *N*-ethyl-*cis*- and *trans*-decahydroisoquinolines was achieved, and therefore ^{13}C n.m.r. spectra were recorded for mixtures. The signals due to the *trans*-isomer remained sharp at all temperatures used for recording the spectra. The *picrate*, derived from a mixture of isomers, showed two distinct m.p.s, 114—118 and 129—132 °C (Found: C, 51.4; H, 6.2; N, 13.9. $C_{17}H_{24}N_4O_7$ requires C, 51.5; H, 6.1; N, 14.1%).

N-*Isopropyl*-trans-*decahydroisoquinoline*.—Isoquinoline (15 g) in propan-2-ol (300 cm^3) was hydrogenated over Raney nickel (*ca.* 5 g; grade T-1) at 180 °C and 110 atm initial pressure of hydrogen. After 14 days the mixture was filtered and evaporated to remove propan-2-ol. The residue was distilled, giving pure *N*-isopropyl-*trans*-decahydroisoquinoline (10.9 g, 52%), b.p. 144—146 °C at 43 mmHg. Analytical g.l.c. showed a single peak, and the derived *picrate* (yellow needles from EtOH) had m.p. 150—151 °C (Found: C, 52.8; H, 6.1; N, 13.5. $C_{18}H_{26}N_4O_7$ requires C, 52.7; H, 6.3; N, 13.7%).

N-*Isopropyl*-cis-*decahydroisoquinoline*.—*cis*-Decahydroisoquinoline (1.5 g) in dry benzene (60 cm^3) was treated with isopropyl methanesulphonate (2.5 g). The mixture was heated to boiling and treated with triethylamine (15 cm^3) during 5 min. The solution was then heated under reflux for 48 h, cooled, and washed successively with water (2 × 50 cm^3) and 2M-hydrochloric acid (2 × 40 cm^3). The acid extracts were washed with ether (3 × 30 cm^3), cooled in ice and basified with aqueous 20% sodium hydroxide. The liberated base was extracted into ether (3 × 50 cm^3) and the combined extracts were dried ($MgSO_4$), filtered, and evaporated. Distillation of the residue gave N-*isopropyl*-cis-*decahydroisoquinoline* as a colourless oil (1.6 g, 81%), b.p. 85—89 °C at 37 mmHg (Found: C, 78.2; H, 13.8; N, 7.3. $C_{12}H_{23}N$ requires C, 78.8; H, 13.4; N, 7.7%). The *picrate*, yellow needles (EtOH), had m.p. 128—132 °C (Found: C, 52.8; H, 6.5; N, 13.9. $C_{18}H_{26}N_4O_7$ requires C, 52.7; H, 6.3; N, 13.7%).

N-(2,2,2-*Trifluoroethyl*)-cis-*decahydroisoquinoline*.—(*a*) The foregoing method of alkylation was repeated on *cis*-decahydroisoquinoline (2 g) using 2,2,2-trifluoroethyl trifluoromethanesulphonate (4 g). The product was *N*-(2,2,2-*trifluoroethyl*)-cis-*decahydroisoquinoline* (2.5 g, 79%), b.p. 108—110 °C at 40 mmHg (Found: C, 59.7; H, 8.4; N, 6.4. $C_{11}H_{18}NF_3$ requires C, 59.7; H, 8.2; N, 6.3%); δ_H (250 MHz; $CDCl_3$) 2.86 (2 H, q, *J* 9.7 Hz, CH_2CF_3), 2.68 (1 H, q, separations 10.9 and 4.2 Hz, 1-H), 2.46 (1 H, q, separations 10.8 and 2.6 Hz, 1-H), 2.8 (1 H, m, 3-H), 2.4 (1 H, m, 3-H), and 1.9—1.2 (12 H, m, remaining ring hydrogens). The *picrate* had m.p. 142—144 °C (Found: C, 45.4; H, 4.8; N, 12.2. $C_{17}H_{21}F_3N_4O_7$ requires C, 45.3; H, 4.7; N, 12.4%).

(*b*) When the foregoing method employed 2,2,2-trifluoroethyl methanesulphonate (2.58 g) as alkylating agent, an identical product (1.5 g, 47%) resulted after a reflux time of 2 days.

N-(2,2,2-*Trifluoroethyl*)-1,2,3,4-*tetrahydroisoquinoline*.—The foregoing method was applied to 1,2,3,4-tetrahydroisoquinoline (3 g), 2,2,2-trifluoroethyl trifluoromethanesulphonate (5.5 g), triethylamine (5 cm^3), and benzene (60 cm^3). The product was N-(2,2,2-*trifluoroethyl*)-1,2,3,4-*tetrahydroisoquinoline*, a colourless oil (4.2 g, 77%), b.p. 140—145 °C at 28 mmHg (Found: C, 61.3; H, 5.7; N, 6.3. $C_{11}H_{12}F_3N$ requires C, 61.4; H, 5.6; N, 6.5%); δ_H (100 MHz; $CDCl_3$) 2.8—2.9 (4 H, m, 3-H and 4-H), 3.76 (2 H, s, 1-H), 3.04 (2 H, q, *J* 9 Hz, CH_2-CF_3), and 6.9 (4 H, m, aromatic); δ_C (62.9 MHz; $CDCl_3$) 28.7 (4-C), 51.5 (3-C), 56.0 (1-C), 58.0 (CH_2CF_3, q, J_{CF} 30.5 Hz), 125.6 (CF_3, q, J_{CF} 279.5 Hz), 133.8 (4a-C or 8a-C), 134.0 (8a-C or 4a-C), 125.8, 126.4, 126.5, and 128.8 (aromatic).

N-*Trichloroacetyl*-cis-*decahydroisoquinoline*.—Hexachloroacetone (6 g) in dry tetrahydrofuran (20 cm^3) was cooled in ice and treated slowly with a solution of *cis*-decahydroisoquinoline (3 g) in dry tetrahydrofuran (30 cm^3). The mixture was stirred at room temperature for 48 h, then decanted from a heavy white precipitate. Evaporation left a thick red oil, which solidified after 4 h. Crystallisation of the solid from light petroleum (b.p. 40—60 °C) gave pure N-*trichloroacetyl*-cis-*decahydroisoquinoline* as white needles (3.8 g, 62%), m.p. 80—82 °C (Found: C, 46.6; H, 5.7; N, 5.3. $C_{11}H_{16}Cl_3NO$

requires C, 46.4; H, 5.7; N, 4.9%), $\nu_{max.}$ (KBr) 1 630 cm^{-1} (C=O); δ_H (100 MHz; $CDCl_3$) 3.9—4.3 (2 H, m, 1-H or 3-H), 3.2—3.6 (2 H, m, 3-H or 1-H), and 1.3—2.1 (12 H, m, remaining ring hydrogens).

N-(2,2,2-*Trichloroethyl*)-cis-*decahydroisoquinoline*.—The foregoing product (2 g) was dissolved in dry tetrahydrofuran (50 cm^2) and transferred by syringe, under conditions of nitrogen purging, to a three-necked flask (100 cm^3). Diborane tetrahydrofuran complex (10 cm^3) was added to the solution during 10 min. The mixture was heated under reflux for 20 h, cooled in ice, and treated with water (1 cm^3) to decompose the excess of diborane. The solution was evaporated and the residue was dissolved in water (30 cm^3) and shaken with chloroform (3 × 50 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated, giving crude N-(2,2,2-*trichloroethyl*)-cis-*decahydroisoquinoline* (1.2 g, 63%), which decomposed on attempted distillation; *m/z* 269.0517 (M^+) (Calc. for $C_{11}H_{18}{}^{35}Cl_3N$: *M*, 269.0547); δ_H (100 MHz; CCl_4) 3.24 (2 H, s, CH_2CCl_3), 2.9—3.3 (2 H, m, 1-H or 3-H), 2.5—2.8 (2 H, m, 3-H or 1-H), and 1.0—2.2 (12 H, m, remaining ring hydrogens). The *picrate* (ethanol) had m.p. 155—158 °C (Found: C, 41.2; H, 4.4; N, 11.0. $C_{17}H_{21}Cl_3N_4O_7$ requires C, 41.0; H, 4.2; N, 11.2%).

2,2,2-*Trichloroethyl Methanesulphonate*.—2,2,2-Trichloroethanol (6.5 g), dissolved in dry dichloromethane (20 cm^3), was added slowly to an ice-cold mixture of triethylamine (6 cm^3) and dry dichloromethane (20 cm^3). The resulting mixture was added during 30 min to a stirred solution of methanesulphonyl chloride in dichloromethane at −10 °C. After a further 2 h at −10 °C, the mixture was heated to remove solvent; the residue solidified. Crystallisation of the residue from methanol gave pure 2,2,2-*trichloroethyl methanesulphonate* (7.8 g, 73%), m.p. 40—41 °C (Found: C, 16.1; H, 2.4. $C_3H_5Cl_3O_3S$ requires C, 15.9; H, 2.2%); δ_H (100 MHz; $CDCl_3$) 3.12 (3 H, s, CH_3) and 4.60 (2 H, s, CH_2).

Reaction of 2,2,2-*Trichloroethyl Methanesulphonate with* 1,2,3,4-*Tetrahydroisoquinoline*.—Treatment of 1,2,3,4-tetrahydroisoquinoline (2 g) in benzene (60 cm^3) with 2,2,2-trichloroethyl methanesulphonate (4 g) and triethylamine (10 cm^3) as described earlier for *N*-isopropyl-*cis*-decahydroisoquinoline, and crystallisation of the product from light petroleum (b.p. 60—80 °C), gave *N*-methylsulphonyl-1,2,3,4-tetrahydroisoquinoline (2.1 g), m.p. 124—125 °C (lit.,[13] 129—130 °C), identical with a sample prepared from 1,2,3,4-tetrahydroisoquinoline and methanesulphonyl chloride.

Reaction of Hexafluoroisopropyl Methanesulphonate with 1,2,3,4-*Tetrahydroisoquinoline*.—A solution of hexafluoropropan-2-ol (5 g) in dry dichloromethane (20 cm^3) was mixed with a solution of triethylamine (7 cm^3) in dry dichloromethane (20 cm^3). The resulting mixture, cooled to −10 °C, was added slowly to a solution of methanesulphonyl chloride (4.3 g) in dry CH_2Cl_2 (20 cm^3) at −10 °C. After 2 h at −10 °C, the mixture was heated to remove solvent and then distilled, giving hexafluoroisopropyl methanesulphonate as a colourless liquid (7.5 g, 61%), b.p. 62—64 °C at 30 mmHg (lit.,[14] 157—158 °C at 760 mmHg); δ_H (100 MHz; $CDCl_3$) 3.19 (3 H, s, CH_3) and 5.20 (1 H, septet, CH). Reaction of this ester with 1,2,3,4-tetrahydroisoquinoline in benzene and triethylamine as described earlier for *N*-isopropyl-*cis*-decahydroisoquinoline gave *N*-methylsulphonyl-1,2,3,4-tetrahydroisoquinoline, m.p. 124—125 °C, identical with that already described.

Reaction of Hexafluoroisopropyl Trifluoromethanesulphonate with 1,2,3,4-*Tetrahydroisoquinoline*.—By the method just described, but with dry benzene as solvent, trifluoromethanesulphonyl chloride (4.3 g) and hexafluoropropan-2-ol (4.5 g) gave a solution of crude hexafluoroisopropyl trifluoromethanesulphonate in benzene. The ^1H n.m.r. spectrum (60 MHz; $CDCl_3$) included a septet at δ 4.69 (CH). This solution, from which the pure ester could not be isolated owing to decomposition, was used directly in a reaction with 1,2,3,4-tetrahydroisoquinoline in the presence of Et_3N (for directions, see preparation of *N*-isopropyl-*cis*-decahydroisoquinoline). The product was *N*-trifluoromethylsulphonyl-1,2,3,4-tetrahydroisoquinoline, white crystals, m.p. 192—193 °C, identical with a sample prepared from 1,2,3,4-tetrahydroisoquinoline and trifluoromethanesulphonyl chloride. Elemental microanalysis yielded inconsistent results, but the mass spectrum showed *m/z* 264.0291 ($M^+ - 1$) [Calc. for $C_{10}H_{10}F_3NO_2S$: ($M - 1$) 264.0306].

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