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EXPERIMENTAL STUDIES OF THE ANOMERIC EFFECT. PART 2 RING INVERSION AND NITROGEN INVERSION EQUILIBRIA IN CIS- DECAHYDROQUINAZOLINES

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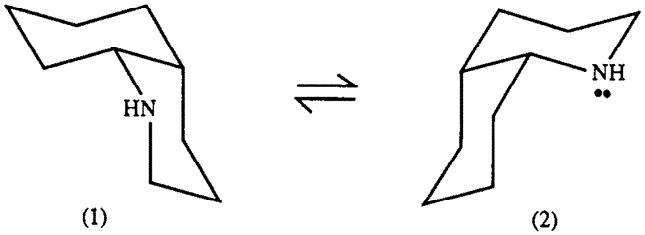
Abstract - The positions of conformational equilibria due to the double ring inversion in cis-decahydroquinazoline (7 ⇌ 8) and cis-decahydro-3-methylquinazoline (9 ⇌ 10) were determined by ^{13}C n.m.r. spectroscopy in the range 215-225 K. In both cases there is a very strong preference ($-\Delta G^{o}_{7\rightarrow 8}$ 1.08 kcal mol^{-1}; $-\Delta G^{o}_{9\rightarrow 10}$ 1.10 kcal mol^{-1}) for the conformation which would allow the lone pairs on N(1) and N(3) to lie on the hindered 'inside' face of the molecules. However, the values of ^{3}J(CHNH) coupling constants for both cis-decahydro-3-methylquinazoline (10) and cis (4aH, 8aH) cis (2H, 8aH)-decahydro-2,3-dimethylquinazoline (14) show that the N-inversion equilibrium at N(1) prefers the conformation in which N(1)-H is 'inside' (axial), and N(1)-lone pair equatorial, thus demonstrating the ability of the anomeric effect to outweigh steric repulsions.

Introduction

^{13}C n.m.r. experiments in non-polar solvents in the range 173-225 K have established that cis-decahydroquinoline (1 ⇌ 2) strongly prefers conformation (2)[1,2] (93.5% at 199 K; $\Delta G^{o}_{1\rightarrow 2}$ -1.10 kcal mol^{-1}) whilst cis-decahydroisoquinoline (3 ⇌ 4) prefers conformation (3)[3] (70.0% at 215 K; $\Delta G^{o}_{3\rightarrow 4}$ 0.37 kcal mol^{-1}). From n.m.r. experiments using N-alkyl derivatives of the two cyclic bases,[4,5] it was concluded[5] that the dominant factor controlling the position of equilibria was a steric one; it was argued that the gauche butane (GB) repulsive interaction [cf.(5)] is more severe than the gauche propylamine (GP) repulsive interaction [cf.(6)] possibly because the latter allows the nitrogen lone pair to be orientated on the hindered 'inside face' of cis-fused bicyclic molecules possessing a twin-chair conformation. Conformation (1) suffers 3GB whilst conformation (2) has 1GB and 2GP interactions. Conformation (4) suffers 3GB whereas conformation (3) has 2GB and 1GP interactions.

The preceding arguments suggest a preference for conformation (8) in cis-decahydroquinazoline (7 ⇌ 8). Moreover, whereas (8c) is preferred on purely steric grounds, (8a) and (8b) are favoured by a stabilising endo-anomeric effect,[6] since an equatorially disposed nitrogen lone pair lies anti-periplanar to a ring C-N bond.[7]



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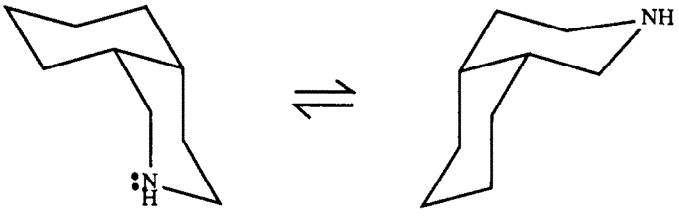

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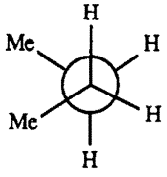

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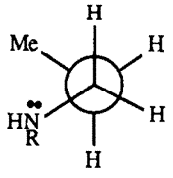


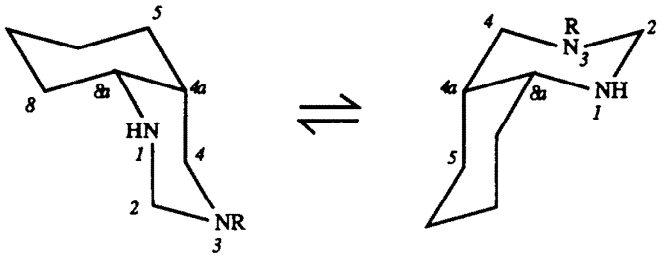
(6)

Results and Discussion

The aim of the present investigation was to determine the position of equilibrium due to nitrogen inversion in (8a ⇌ 8b ⇌ 8c) and in the corresponding 3-methyl- (10a ⇌ 10b ⇌ 10c) and 2,3-dimethyl- (14a ⇌ 14b ⇌ 14c) derivatives. In these three examples, anomeric effects are balanced against steric effects.

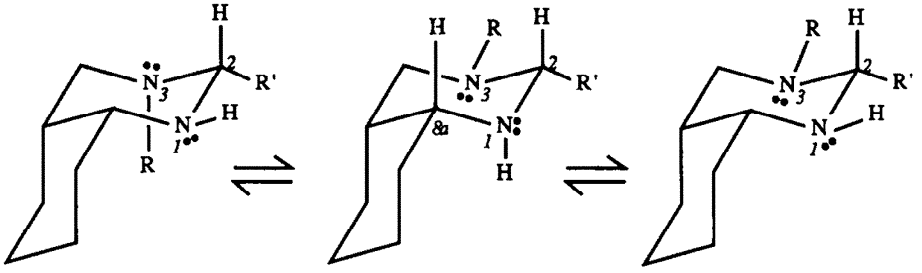
In early work on cis- decahydroquinazoline involving the analysis of ^{1}H nmr spectra at room temperature, Armarego and Kobayashi[8] came to the reasonable conclusion that (8) was the dominant conformation in the equilibrium (7 ⇌ 8). These workers also observed a reversible collapse of the AB quartet assigned to the protons at 2-C when the temperature was raised to 160°, a phenomenon explained in terms of the interconversion (7 ⇌ 8). Such an explanation implies an exceptionally high activation energy for the double ring inversion (7 ⇌ 8) and it seems more likely that the dynamic effect observed is due to a reversible fission of a C(2)-N bond to give a methyleneimine. The authors' further conclusion, that the N-inversion equilibrium in cis- decahydroquinazoline favoured conformation (8c), is also of doubtful value because it is based on the observation in the ^{1}H nmr spectrum of a sharp singlet for the N-H protons. When amines are examined at room temperature in solvents which have not been intensively dried, intermolecular exchange of N-attached protons of the molecule with exchangeable protons present either in different molecules of the amine, or in molecules of water, is fast enough to produce a coalesced signal in the ^{1}H nmr spectrum.

Armarego and Reece[9] interpreted the room temperature ^{1}H nmr spectrum of cis-decahydro-3-methylquinazoline in terms of a preponderance of conformation (10) in the ring-inversion equilibrium (9 ⇌ 10).



(7; R = H)
(9; R = Me)

(8; R = H)
(10; R = Me)



(8a; R = R' =H)
(10a; R = Me; R' = H)
(14a; R = R' = Me)

(8b; R = R' = H)
(10b; R = Me; R' = H)
(14b; R = R' = Me)

(8c; R = R' = H)
(10c; R = Me; R' = H)
(14c; R = R' = Me)

In the present study, cis-decahydroquinazoline (7 ⇌ 8) was prepared in six stages from cis- tetrahydrophthalic anhydride by combining work by Plieninger and Schneider[10] with work by Armarego and Kobayashi.[8] cis- Decahydro-3-methylquinazoline (9 ⇌ 10) was synthesised by making use of work by Kricheldorf[11,12] and by Armarego and Reece.[9] The cis- stereochemistry of the starting tetrahydrophthalic anhydride was largely preserved throughout the eight reactions involved. cis (4aH, 8aH), cis (2H, 8aH)-Decahydro-2,3-dimethylquinazoline (13 ⇌ 14) was similarly prepared, substituting ethanal for methanal in the final ring closure reaction with cis-1-amino-2-methylaminomethylcyclohexane.

The ^{1}H nmr spectrum of cis-decahydroquinazoline agreed with the details recorded in the literature.[8] The ^{13}C nmr spectrum was recorded at 318 K, 258 K and 219 K in $CFCl_3/CDCl_3$ (85/15 by volume). At 318 K the spectrum showed eight sharp lines, six of which were considerably broadened at 258 K, demonstrating a slowing of the double ring inversion (7 ⇌ 8). At 219 K the spectrum included eight sharp signals assigned to the major conformation (8) and several weak signals due to the minor conformation (7) (Table 1). The 'calculated' ^{13}C shifts for (7) and (8) were deduced from the known ^{13}C shifts in the two conformations (3) and (4) of cis- decahydroisoquinoline,[3,5] modified by the 'substituent' α-parameter (+ 20 ppm) which accompanies the replacement of $-CH_2-$ by -NH- [2] (β- and γ-parameters are small[2] and may be neglected). For conformation (8), agreement between observation and calculation is reasonable except for carbon-2, for which distortions of ring geometry are expected to make such calculations unsatisfactory. Indeed, the observed chemical shift of 62.7 ppm for 2-C in (8) is

close to that recorded during the present investigation for 2-C in hexahydropyrimidine (63.1 ppm).

Table 1. Carbon -13 chemical shifts (δ/ppm from Me_4Si) at 62.9 MHz for cis- decahydroquinazoline (7 ⇌ 8) and cis-decahydro-3-methylquinazoline (9 ⇌ 10) in $CFCl_3/CDCl_3$, (85/15; v/v).

Formula	7 ⇌ 8	7	7[a]	8	8[a]	9	9[a]	10	10[a]
T/K	318	219	-	219	-	221	-	221	-
Carbon									
2	62.7	55.8	60.9	62.7	67.0	63.9	64.7	70.8	71.8
4	50.9	44.4	45.1	51.0	52.2	53.7	53.5	60.3	60.1
4a	36.2	37.3	35.4	35.1	35.8	35.2	36.1	34.8	33.9
5	25.0[b]	d	29.8	23.9	26.0	28.7	28.6	24.7[b]	22.5
6	25.7[b]	d	21.2	25.9	26.5	20.4	21.0	25.2[b]	25.9
7	21.2	d	c	20.3	20.5	23.8	c	19.7	20.3
8	32.1	d	25.1	32.3	31.9	25.4	25.0	30.6	32.3
8a	53.8	d	53.8	53.1	54.1	50.7	52.6	51.5	51.7
CH_3	-	-	-	-	-	42.0	-	42.0	-

a calculated (see discussion)
b assignments may need to be exchanged
c corresponding signal in cis- decahydroisoquinoline not observed (see discussion)
d not observed clearly

Owing to the high noise level of the ^{13}C spectrum of (7 ⇌ 8), only the signals at 55.8 (2-C), 44.4 (4-C) and 37.3 (4a-C) ppm could be identified with certainty as arising from conformation (7). Since an accurate integration was not possible, a sample of cis- decahydroquinazoline was prepared in which 2-C was specifically enriched in ^{13}C. The ^{13}C nmr spectrum of [2-^{13}C]-cis-decahydroquinazoline at 225 K showed 2-C of (8) at 62.4 ppm and 2-C of (7) at 55.6 ppm. Direct integration of the signals gave the equilibrium constant 8/7 as 13.18 at 225 K and 13.73 at 215 K. The corresponding free energy differences ($\Delta G^{o}_{7\to8}$) were calculated to be -1.04 kcal mol^{-1} (225 K) and -1.12 kcal mol^{-1} (215 K). These values were supported by a slightly less accurate assessment of the position of equilibrium (7 ⇌ 8) at 277 K which made use of the line broadening technique described independently by Anet and Basus[13] and by Okazawa and Sorensen.[14] The maximum broadening of the signal for 2-C occurred at 277 K and the half-intensity width ($W_{\frac{1}{2}}$) of this signal (43.25 Hz), relative to that of tetramethylsilane (W_o, 2.11 Hz), was used in the 'accurate' equation of Okazawa and Sorensen to calculate an equilibrium constant for 8/7 of 9.05, corresponding to a $\Delta G^{o}_{7\to8}$ value of -1.20 kcal mol^{-1} at 277 K. Unfortunately we were unable to assess the position of equilibrium (8a ⇌ 8b ⇌ 8c), due to nitrogen inversion; the 2-H region of the ^1H n.m.r. spectrum was excessively complicated when recorded at temperatures low enough to allow -CH-NH- coupling to be observed.

Attention was then directed to cis- decahydro-3-methylquinazoline (9 ⇌ 10), for which the low temperature ^1H nmr spectrum was expected to be simpler than that for cis- decahydroquinazoline itself. The ^{13}C nmr spectrum of cis-decahydro-3-methylquinazoline at 297 K showed broad lines for all carbons, indicating a relatively slow rate of twin-chair interconversion (9 ⇌ 10) at that temperature. At lower temperatures, the broadening increased, but at 221 K 17 sharp signals were observed, 9 from the major conformation (10) and only 8 from the minor

conformation (9) because the N-methyl carbons had identical chemical shifts in the two conformations. The assignment of signals to carbon atoms in conformations (9) and (10) relied on 'calculated' shifts (Table 1) which were obtained by combining either the observed shifts for cis- decahydroquinazoline (Table 1) or, in the absence of observed shifts, the calculated shifts for cis- decahydroquinazoline (Table 1) with the known chemical shift parameters (α + 9.1); β-1.2; γ -1.4 ppm) for replacement of NH by NMe in piperidine (solvent $CDCl_3$).[15] Direct integration of the spectrum at 221 K gave an equilibrium constant (= 10/9) of 12.21, equivalent to a $\Delta G^{\circ}_{9\rightarrow 10}$ value of -1.10 kcal mol^{-1}. The ^1H nmr spectrum of (9 ⇄ 10), recorded at 90 MHz and 308 K agreed with that reported by Armarego and Reece.[9] However, the spectrum recorded at 250 MHz and 297 K showed broad lines for all protons except 8a-H and N-CH_3 because the rate of exchange (9 ⇄ 10) is now comparable with chemical shift differences ν_9-ν_{10} (Hz) for exchanging protons. The low temperature ^1H nmr spectrum provided additional evidence for the presence of the minor conformation (9). At 241 K the spectrum (details in Table 2)

Table 2. ^1H nmr data (250 MHz, 241 K) for cis- decahydro-3-methylquinazoline [conformation (10), unless stated otherwise] in $CFCl_3/CDCl_3$ (85/15, v/v).

Chemical Shifts (δ/ppm)

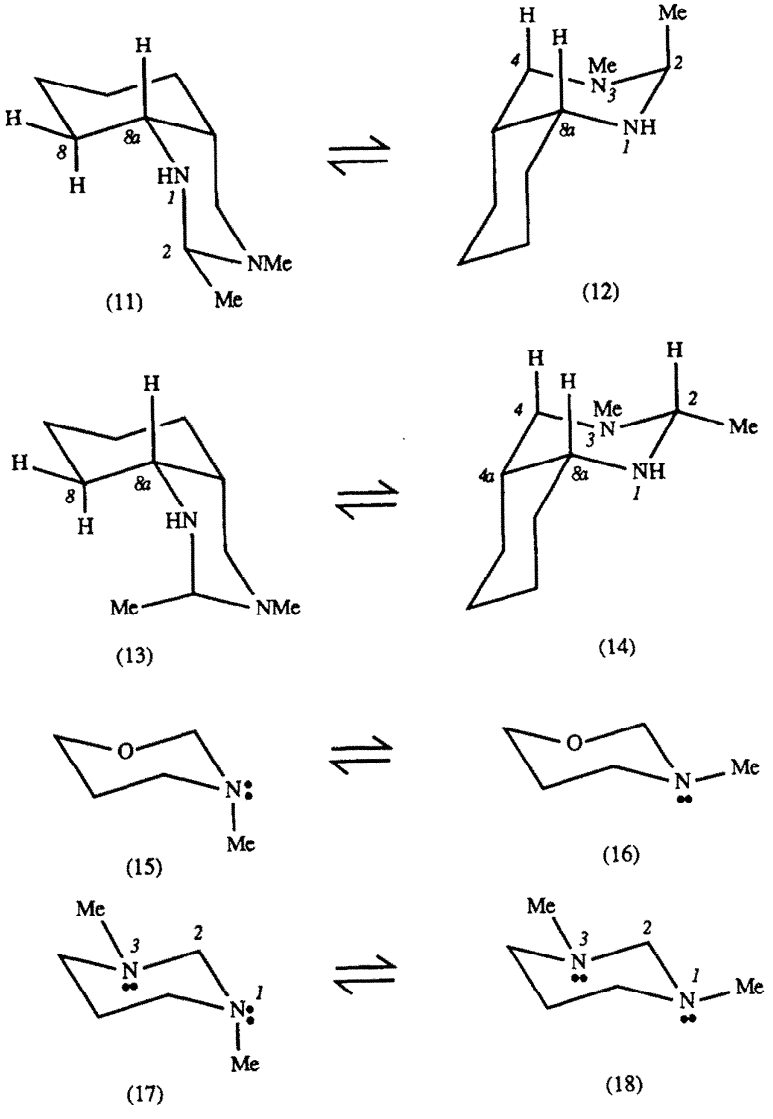
2-H_{eq}	3.81	4-H_{eq}	2.72
2-H_{eq}	3.96*	4-H_{ax}	2.18
2-H_{ax}	2.89	Me-N	2.10
8a-H	2.85	4a,5,6,7,8-H	1.10-2.00

Coupling Constants (J/Hz)

$^2J(2_{eq}2_{ax})$	11.0	$^4J(2_{eq}4_{eq})$	1.7
$^2J(2_{eq}2_{ax})$	10.0*	$^2J(4_{eq}4_{ax})$	11.4
	$^3J(4_{ax}4a)$	3.2	

*conformation (9)

included a doublet at δ3.81 assigned to 2-H_{eq} in conformation (10). A weak doublet ($^2J \sim 10$ Hz) at δ3.96 was assigned to 2-H_{eq} in the minor conformation (9), and integration gave 11.3 for the approximate ratio of area of δ3.81 signal to area of δ3.96 signal. In addition to the 2-H_{eq} signal at δ3.81 the spectrum at 241 K revealed for the major conformation (10) a doublet at δ2.89 due to 2-H_{ax}, overlapped by a relatively narrow signal at δ2.85 due to the ring junction proton 8a-H. Temperatures below 210 K were required to slow N-H exchange sufficiently to allow C<u>H</u>-N<u>H</u> coupling to be observed (cf.[16]). At an intermediate temperature of 218 K, the 3 signals 2-H_{eq}, 2-H_{ax} and 8a-H showed broadening and a further lowering of temperature caused a re-sharpening. At 203 K, 2-H_{eq} remained a doublet (^2J 11.1 Hz), with each component slightly broadened compared to the signal at 241 K, but the pattern of sharpened signals in the region δ2.80-2.95 can only be interpreted as a triplet (J ≃ 11.3 Hz) due to 2-H_{ax}, overlapped by a doublet (J ≃ 11.3 Hz) due to 8a-H. The observation of additional couplings of about 11 Hz, due to $^3J_{HCNH}$ in the signals for both 2-H_{ax} and 8a-H points to (10b), with N(1)-H axial, as the dominant conformation. Clearly the anomeric effect, which in this case is the stabilising overlap of the equatorial N(1) lone pair with the antibonding orbital of the C(2)-N(3) bond, overcomes the destablilising repulsions associated with the 'inside' axial hydrogen at N(1).



The ^{1}H n.m.r. spectral details for the isolated cis-decahydro-2,3-dimethylquinazoline are summarised in Table 3. The signal assigned to 8a-H at δ2.90 is an unresolved multiplet with a half-intensity width of only 9.5 Hz, thus excluding appreciable proportions of conformations (11) and (13) in which 8a-H suffers a large axial: axial coupling (10-12 Hz) with 8-H_{ax}, in addition to a small axial: equatorial coupling (2-4 Hz) with 8-H_{eq}. The chemical shifts of 8a-H (2.90) and 4-H_{ax} (2.28) are almost identical to those of the corresponding protons in the major conformation (10) of cis-decahydro-3-methylquinazoline (see Table 2). Conformation (12) in thus excluded, since the axial methyl group at 2-C is expected to exert a deshielding effect of about 0.25 ppm on syn-axial protons at 8a-C and 4-C.[17] These arguments establish the preferred conformation of the molecule as (14), and therefore the configuration of the synthesised compound as cis(4aH, 8aH), cis(2H, 8aH)-decahydro-2,3-dimethylquinazoline.

Table 3 ^{1}H nmr data (250 MHz, 280 K) for cis(4aH, 8aH) cis(2-H, 8aH) decahydro-2,3-dimethylquinazoline (13 ⇌ 14) in $CFCl_3/CDCl_3$ (7/3, v/v).

Chemical Shifts (δ/ppm)

2-H_{ax}	2.79	4-H_{ax}	2.28
8a-H	2.90*	Me-N	2.11
4-H_{eq}	2.64	Me-C	1.24
	4a,5,6,7,8-H	1.2-1.9	

Coupling Constants (J/Hz)

$^2J(4_{eq}4_{ax})$	11.3	$^3J(4_{ax}4a)$	3.3
$^3J(4_{eq}4a)$	1.3	$^3J(2_{ax}CH_3)$	5.8

*$W_{\frac{1}{2}}$ 9.5 Hz

That the highly preferred conformation in the equilibrium (13 ⇌ 14) is (14) is not surprising in view of the severe non-bonded repulsions suffered by the 'inside' axial methyl group of (13).

The preferred orientation of the N(1)-H bond in (14) was clearly established by observing the effect of reduced temperature on the nmr signals for 8a-H (broad singlet, $W_{\frac{1}{2}}$ 9.5 Hz at 280 K) and 2-H (1,3,3,1-quartet, ^3J 5.8 Hz, at 280 K). At 250 K the N-H exchange rate had decreased to such an extent that the signals for 8a-H and 2-H showed extensive broadening, whilst all other signals were unchanged. At 223 K the 8a-H signal was now a doublet (^3J 11.5 Hz) whilst the 2-H signal was a sextet (separation 5.8 Hz), simplifying to a doublet (^3J 11.5 Hz) after irradiation of the C-methyl signal at δ1.24. Evidently both 2-H_{ax} and 8a-H are now coupled to the N-H by about 11.5 Hz, thus identifying the major conformation as (14b). As with cis-decahydro-3-methylquinazoline (10b), the stabilising anomeric effect in (14b) outweighs the destabilising steric repulsions due to the 'inside' axial N-H. Although conformations (10a) and (14a) also benefit from an anomeric effect, they are strongly disfavoured by the steric repulsions suffered by an 'inside' axial N-Me group.

Theoretical Implication of Results

Previously reported cases in which anomeric effects dominate steric effects include tetrahydro-1,3-oxazine,[16] tetrahydro-2-methyl-1,3-oxazine,[16] and 1-methylhexahydropyrimidine.[16] Anomeric effects and steric effects appear to be evenly balanced in 3-methyltetrahydro-1,3-oxazine (15 ⇌ 16), which shows a slight preference ($\Delta G^\circ \simeq 0.16$ kcal mol^{-1} at 138 K) for (15), with axial N-methyl, i.e. the anomeric effect just retains control,[18] (see also ref.19). In 1,3-dimethylhexahydropyrimidine (17 ⇌ 18), however, the anomeric effect in (17) is weaker than in (15) because the C(2)-N(3) bond in (17) is a weaker acceptor than the C(2)-O bond in (15); steric effects are now dominant and (18) is preferred by as much as 0.65 kcal mol^{-1} at 123 K.[20] However, in a recent investigation of nitrogen inversion by X-ray analysis, crystalline 1,3,5-tribenzyl-1,3,5-triazacyclohexane was shown to exist exclusively at 127 K as the conformation with two substituents axial and one equatorial;[21] higher temperatures favoured an increase in conformations possessing more equatorial substituents.

EXPERIMENTAL

General - ^{1}H n.m.r. spectra were recorded on a Perkin-Elmer R.32 spectrometer (90 MHz) at 305 K and a Bruker WM 250 PFT spectrometer (250 MHz) at 294 K, unless stated otherwise.

^{13}C n.m.r. spectra were recorded on a Bruker WM 250 PFT spectrometer (62.9 MHz) at the stated temperature. The thermocouple reading of the Bruker WM 250 spectrometer was accurate to ± 0.5 K over the range 145-294 K when checked against a gold/gold-doped iron thermocouple.

The following abbreviations are used in describing n.m.r. spectra: b (broad), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). ^{1}H n.m.r. spectra were analysed by a first-order approach and therefore most reported coupling constants are approximate.

Mass spectra were recorded on either a VG Micromass 70E (7070E) or an A.E.I. MS 902 spectrometer.

cis-Hexahydrophthalamic acid. - cis-1,2,3,6-tetrahydrophthalic anhydride (20 g) was converted by the literature method[10] into cis-1,2,3,6-tetrahydrophthalamic acid (19.8 g., 97%), m.p. 139-142° (H_2O) (lit.,[10] 147-149°). Hydrogenation of the product (10 g) in ethanol (100 cm^3) over 10% Pt/C at room temperature and atm. pressure gave cis-hexahydrophthalamic acid (9.2 g., 91%), m.p.160-162° (EtOH) (lit.,[10] 167-168°).

Ethyl cis-2-aminocyclohexanecarboxylate. - Bromine (10 g.) was added, with stirring, to an ice-cold solution of NaOH (12 g.) in water (48 cm^3). To this solution, at 0°C, was added finely powdered cis-hexahydrophthalamic acid (10 g.) and the resulting mixture was poured into a cold solution of NaOH (88 g.) in water (32 cm^3). The resulting mixture was warmed to 75° for 2 min. and filtered. The filtrate was cooled to 10°C, neutralised with concentrated hydrochloric acid, and evaporated to dryness under reduced pressure. The residue was extracted with dry ethanol (3 x 30 cm^3), after which the combined extracts were filtered and diluted with ethanol (80 cm^3) containing anhydrous hydrogen chloride (10% w/v). The mixture was heated under reflux for 3 hr., cooled and evaporated to dryness under reduced pressure. The residue was dissolved in the minimum volume of water, basified with a saturated aqueous solution of K_2CO_3 and extracted with ether (3 x 40 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated to leave crude ester as an oil. Distillation gave ethyl cis-2-aminocyclohexane-carboxylate (8.2 g., 75%), b.p. 137-139°/61 mm Hg (lit.,[22] 103-104°/11 mm Hg). The ^{1}H n.m.r. spectrum agreed with the details published,[8] although weak signals due to the trans- isomer were also visible.

cis-1-Amino-2-aminomethylcyclohexane. - The published method[8] was used to convert the foregoing ester (5 g.) into cis-2-aminocyclohexanecarbohydrazide (3 g., 66%), m.p. 60-65° (lit.,[8] 69-70°). The ^{1}H n.m.r. spectral parameters agreed with those published.[8] Reduction of the product (3.5 g.) with lithium aluminium hydride (4 g.) in ether, as described,[8] gave cis-1-amino-2-aminomethylcyclohexane (1.10 g., 38%), which was not distilled. The dipicrate, from EtOH, had m.p. 230-235° (lit.,[8] 234-235°) (Found: C, 38.92; H, 3.80; N, 18.9. Calc. for $C_{19}H_{22}N_8O_{14}$: C, 38.91; H, 3.75; N, 19.1%).

cis-Decahydroquinazoline and [2-^{13}C]-cis-decahydroquinazoline. - Following the published method,[8] the foregoing crude sample (0.90 g.) of cis-1-amino-2-amino-

methylcyclohexane was converted by aqueous formaldehyde (methanal) (0.80 g., 37% w/v) into cis- decahydroquinazoline (0.22 g., 22%), a pale yellow oil which was not distilled but which gave a ^{1}H n.m.r. spectrum (100 MHz) which was identical to that described.[8] The ^{13}C n.m.r. spectral details are given in Table 1. When the synthesis was repeated using aqueous methanal containing [^{13}C] methanal (90.0 ^{13}C atom %), the resulting pale yellow oil was crude [2-^{13}C]decahydroquinazoline (0.48 g., 48%). In the ^{1}H n.m.r. spectrum ($CDCl_3$), the protons at 2-C gave the typical 8-line pattern for the AB part of an ABX spin system (X=^{13}C), with a J_{AB} (= $^{2}J_{2eq2ax}$) of 12.4 Hz).

Trimethylsilyl cis-2-isocyanato-4-cyclohex-1-ene carboxylate. Trimethylsilyl azide (17.7 g, 62%), b.p. 95-97°, was prepared[2] from sodium azide (17.9 g.) and trimethylchlorosilane (27.15 g.). Commercial 1,2,3,6-tetrahydrophthalic anhydride (40 g.) was purified by being heated under reflux for 3 hr with acetic anhydride (72 g.) and petroleum ether (210 cm^3), b.p.100-120°. The mixture was allowed to cool during 12 h. The white needles which crystallised were filtered, washed with dry diethyl ether (100 cm^3) and dried, giving pure 1,2,3,6-tetrahydrophthalic anhydride, m.p. 101-102° (26.3 g.).

A mixture of the pure anhydride (18.4 g.), trimethylsilyl azide (18.4 g.) and dry dioxane (100 cm^3) was heated to 70-80° in an oil-bath. A vigorous reaction occurred, with evolution of nitrogen, and the flask was periodically removed from the oil-bath. After 2 hr. the mixture was boiled for 10 min. and then distilled at atmospheric pressure to remove trimethylsilyl azide and dioxane. Distillation of the residue through a short Vigreux column afforded trimethylsilyl cis-2-isocyanato-4-cyclohex-1-ene carboxylate (2.50 g, 86%) as a colourless liquid, b.p. 100°/1.2 mm Hg (lit.,[11] 82-84°/0.4 mm Hg).

cis-2-Aminocyclohexanecarboxylic acid hydrochloride. - The foregoing product (12.25 g.) was converted by the published method[12] into cis-2-aminocyclohex-4-enecarboxylic acid hydrochloride (8.15 g., 90%), m.p. 214-216° (lit.[12] 210-213°). The product (12.0 g.), in methanol (150 cm^3) containing Adam's PtO_2 catalyst (1.2 g), was hydrogenated at 293 K and 760 mm Hg. The uptake of hydrogen was 1744 cm^3 (theory 1625 cm^3). The usual method of recovery gave white crystals (10.42 g., 86%) of cis-2-aminocyclohexanecarboxylic acid hydrochloride, m.p. 220-222° (EtOH) (lit.,[12] 219-221°). The ^{1}H n.m.r. spectrum (90 MHz, D_2O) included signals at δ3.50 (m; 2-H), 2.95 (q, J ~ 5 Hz; 1-H) and 1.10-1.20 (m; 3,4,5,6-H).

cis-2-(4'-Methylbenzenesulphonylamino)cyclohexanecarboxylic acid. - The foregoing product (7.28 g.) was converted by the published procedure[9] into cis-2-(4'-methylbenzenesulphonylamino)cyclohexanecarboxylic acid (11.3 g., 94%), m.p. 167-168° (lit.,[9] 172°). The ^{1}H n.m.r. spectrum (90 MHz, $CDCl_3$) included signals at δ7.84 (d, J 7.8 Hz; aromatic 2',6'-H), 7.37 (d, J 7.8 Hz; aromatic 3',5'-H), 6.7-7.1 (b; OH), 6.06 (d, J 9 Hz; NH), 3.25-3.70 (m; 2-H), 2.80 (q, J 5 Hz; 1-H), 2.45 (s; Me) and 1.05-2.25 (m; 3,4,5,6-H).

cis-2-(4'-Methylbenzenesulphonylamino)cyclohexane-N-methylcarboxamide. - The above acid (7.4 g.), treated by the published method,[9] gave the derived N-methylamide (6.5 g., 84%) as white crystals, m.p. 145-146° (lit.,[9] 151°). The ^{1}H n.m.r. spectrum (90 MHz; $CDCl_3$) included signals at δ7.87 (d, J 8 Hz; aromatic 2',6'-H), 7.40 (d, J 8 Hz; aromatic, 3',5'-H), 6.08 (d, J 6 Hz, $-SO_2-NH$), 5.60-5.90 (m; -CONH), 3.25-3.58 (m; 2-H), 2.73 (d, J 5 Hz; NMe), 2.46 (s; aromatic CH_3), 2.30-2.60 (m; 1-H) and 1.10-2.25 (m; 3,4,5,6-H).

cis-2-Aminocyclohexane-N-methylcarboxamide. - The foregoing product (3 g.) was converted by sodium in liquid ammonia (cf.[9]) into cis-2-aminocyclohexane-N-methylcarboxamide (0.8 g., 53%), a viscous oil, b.p. 170°/14 mmHg. The ^{1}H n.m.r. spectrum (90 MHz, $CDCl_3$) included signals at δ8.3 (b; NHCO), 3.31 (q, J 3.6 Hz; 2-H), 2.82 (d, J 4.8 Hz; NMe), 2.26-2.54 (m; 1-H) and 1.12-2.12 (3,4,5,6-H and NH_2).

cis-1-Amino-2-methylaminomethylcyclohexane. - The above amide (3.2 g.) was reduced by the literature method,[9] giving cis-1-amino-2-methylaminomethylcyclohexane as a colourless oil (2.34 g., 80%), b.p. 40-41°/0.25 mmHg (lit.,[9] 58°/0.7 mmHg). The ^{1}H n.m.r. spectrum (250 MHz, $CDCl_3$) showed signals at δ3.10 (q, J 3.6 Hz; 1-H), 2.60 (dd; H_A of $-CH_AH_BN-$), 2.45 (dd; H_B of $-CH_AH_BN-$); 2.42 (s; NMe), 1.18-1.73 (m; 2,3,4,5,6-H) and 1.31 (s; NH and NH_2).

cis-Decahydro-3-methylquinazoline. - Aqueous methanal (1.22 g., 37%) was added to cis-1-amino-2-methylaminomethylcyclohexane (1.76 g.). The mixture was allowed to stand for 2 days at room temperature, cooled to 0°C and saturated with pellets of KOH. The mixture was extracted with ether (3 x 15 cm^3) and the combined extracts were dried (KOH), filtered and distilled. cis-Decahydro-3-methylquinazoline was obtained as a colourless oil (1.04 g., 55%), b.p. 59°/0.8 mmHg (Found: M^+ 154.1430. Calc. for $C_9H_{18}N_2$: 154.1469). Details of the ^{13}C and ^{1}H n.m.r. spectra are listed in Tables 1 and 2, respectively. The derived dipicrate (MeOH) had m.p. 172-173° (lit.,[9] 173-174°) (Found: C,41.2; H, 3.9; N, 18.5. Calc. for $C_{21}H_{24}N_8O_{14}$: C, 41.2; H, 3.95; N, 18.3%).

cis(4aH,8aH), cis(2H,8aH)-Decahydro-2,3-dimethylquinazoline. - The preceding preparation was repeated except that aqueous methanal was replaced by freshly distilled ethanal (acetaldehyde) (0.53 g.) and water (1 cm^3). The product was cis (4aH,8aH), cis (2H, 8aH)-decahydro-2,3-dimethylquinazoline (1.2 g; 60%), a colourless liquid, b.p. 67°/20 mmHg (Found: M^+ 168.1549. $C_{10}H_{20}N_2$ requires M, 168.1626). Details of the ^{1}H n.m.r. spectrum are listed in Table 3. Attempts to prepare a dipicrate in MeOH failed due to ring fission; the isolated compound was the dipicrate of cis-1-amino-2-methylaminomethylcyclohexane, m.p. 200-202° (lit.,[9] 206-210°) (Found: C, 40.1; H 4.1; N, 18.8. Calc. for $C_{20}H_{24}N_8O_{14}$: C, 40.0; H, 4.0; N, 18.7%).

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