CONFORMATIONAL STUDY OF CYCLIC 2-AMINO AND 2-DIMETHYLAMINO ALCOHOLS WITH SIX-MEMBERED RING BY ^{1}H-NMR SPECTROSCOPY

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Conformation of thirty vicinal amino alcohols with six-membered ring was studied by ^{1}H-NMR spectroscopy and the results were compared with those obtained by IR-spectroscopic study of hydrogen bonding. The results of both methods are in good agreement.

In the course of the last years the conformation of various vicinal amino alcohols with six-membered ring was investigated using infrared spectroscopic determination of hydrogen bond between the functional groups[1-7]. Although the results of this method seem convincing, it was nevertheless felt that a comparison with results obtained by an independent method would be of great value. In the present communication we investigate conformations and conformational equilibria in some amino alcohols by means of ^{1}H-NMR spectroscopy and compare the results with those obtained[8] by the mentioned IR spectroscopic approach.

The use of the ^{1}H-NMR spectroscopy in the elucidation of conformations and evaluation of conformational equilibria in cyclohexane derivatives is well known (see *e.g.* ref.[9-13]). In the determination of conformational equilibria usually a comparison of chemical shifts (δ) or coupling constants, either as such (J) or represented by signal widths (W), has been used. In our present study we use the latter two parameters.

Two aspects were investigated: *1*) conformational equilibria between "diaxial" chair form and the corresponding boat (Scheme 1) or the "diequatorial" chair form (Scheme 2), and *2*) deformation of the ring in a particular conformer, *i.e.* the deviation of the dihedral angle between the vicinal substituents from the normal value (60° or 180°). For the semiquantitative evaluation of conformational equilibria we chose the compounds *I* and *XII* as standards for a "diaxial" and "diequatorial" conformation, respectively. Both these compounds are known to be conformationally homogeneous.

Since the conformationally mobile compounds exhibit averaged spectra at room temperature, we attempted to measure several selected compounds at low tempera-

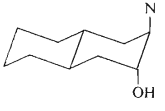
$N = NH_2$ or $N(CH_3)_2$; $n = 1$ or 2

SCHEME 1

IX: $R^1 = R^2 = CH_3$
X: $R^1 = i\text{-}C_3H_7$, $R^2 = H$
XI: $R^1 = H$, $R^2 = i\text{-}C_3H_7$

In the formulae $N = NH_2$ or $N(CH_3)_2$

SCHEME 2



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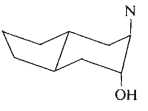

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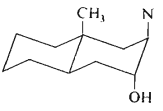

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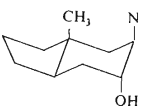

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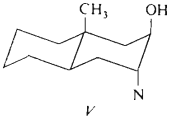

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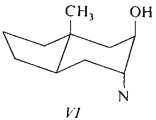

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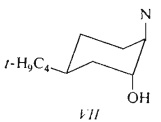

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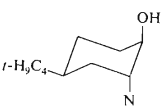

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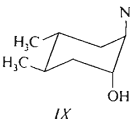

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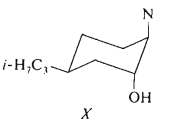

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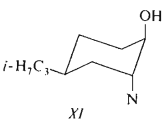

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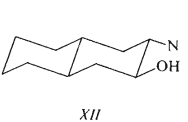
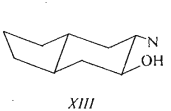


XII



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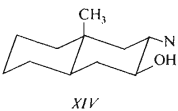

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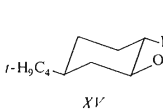

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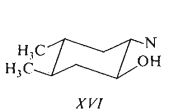


XVI

In the formulae: *a*, $N = NH_2$; *b*, $N = N(CH_3)_2$

SCHEME 3

tures in order to separate the signals of the single conformers. Unfortunately, even at the lowest attained temperature (−80°C), the conformational equilibration was still too rapid to allow the signal resolution.

Measurement of the tetradeuterio amino alcohols derived from the compounds *I*, *XII*, *XXI* and *XXVII* afforded the corresponding coupling constants J_{aa}, J_{ee} and J_{ae}.

The coupling constants obtained for the other two series of amino alcohols (3-amino-4-hydroxy-*trans*-bicyclo[4,3,0]nonanes and 2-amino-*trans*-4,5-dimethylcyclohexanols) confirmed the presence of conformational equilibria found by the method of signal widths.

trans-*Amino Alcohols*

The diaxial and diequatorial amino alcohols investigated (*I*–*XVI*) are listed in Scheme 3. The ^{1}H-NMR data are given in Table I and the coupling constants of the

TABLE I

Methine Proton Characteristics of the *trans*-Amino (*a*) and *trans*-Dimethylamino (*b*) Alcohols *I*–*XVI* (in $CDCl_3$)

Compound	*a*				*b*			
	H/OH		H/NH_2		H/OH		$H/N(CH_3)_2$	
	δ^a	W^{*b}	δ^a	W^{*b}	δ^a	W^{*b}	δ^a	W^{*b}
I	3·74	8	3·01	8·5	4·09	9	2·09	9
II	3·76	7	3·03	8·5	4·11	11	2·15	—
III	3·69	10	3·03	12	3·88	20	2·51	24
IV	3·79	16	3·03	16	3·93	22	2·69	24
V	3·75	9·5	3·04	9	3·95	17·5	2·30	—
VI	3·77	11	3·10	11	3·87	23	2·64	23
VII	3·78	8	2·91	9	3·98	14	2·05	14
VIII	3·63[d]	9[d]	3·03[d]	10[d]	3·96	11	2·15[c]	—
IX	3·51	16	2·81	17	3·67	21·5	2·33[c]	—
X	3·41	21	2·58	21	3·52	24	2·20[c]	—
XI	3·25	20	2·70	21	3·38	24	2·30[c]	—
XII	3·17	24	2·52	24[c]	3·36	24	2·10[c]	—
XIII	3·23	24	2·51	24	3·39	24	2·30[c]	—
XIV	3·15	24	2·74	24	3·36	25	2·47	25
XV	3·16	24	2·40[c]	—	3·35	24	2·14[c]	—
XVI	3·18	24	2·49	24	3·37	24	2·17[c]	—

[a] Centers of multiplets; [b] terminal line separation; [c] very approximate value, signal overlapping; [d] reported[12] $\delta = 3{\cdot}62$, $W^* = 9$ Hz for H/OH, and $\delta = 3{\cdot}03$, $W^* = 10$ Hz for H/NH_2.

TABLE II

Coupling Constants J (Hz) between the Methine Protons in Some Tetradeuterio Amino (*a*) and Dimethylamino (*b*) Alcohols (in $CDCl_3$, internal standard tetramethylsilane)

Compound	$I-d_4$	$II-d_4$	$IX-d_4$	$XII-d_4$	$XX-d_4$	$XXI-d_4$	$XXII-d_4$	$XXVII-d_4$
a	2·6	2·7	6·5	10	—	4	4	2·7
b	3·2	4	9	10	9·15	5·6	6	3

TABLE III

Conformational Equilibria in Amino (*a*) and Dimethylamino (*b*) Alcohols *I*—*VI* and *IX*—*XI*, Calculated from ^{1}H-NMR and IR (in parentheses) Data

Chair–boat equilibria (Scheme 1)

Compound	% Boat form		Compound	% Boat form	
	a	*b*		*a*	*b*
I	0 (0)	5—10[a] (7)	*IV*	50[b] (27)	85—90[b] (86)
II	5—10[a] (10)	15—20[a] (26)[c]	*V*	5—10[b] (14)	55—60[b] (45)
III	10—15[b] (19)	70—85[b] (66[c], ~50[d])	*VI*	15—20[b] (19)	90—95[b] (81)

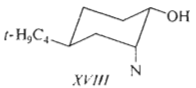
Chair–chair equilibria (Scheme 2)

Compound	% N[e]O[e] Conformer	
	a	*b*
IX	45—60[a] (51—53)[e]	80—85[a] (72—77)[e]
X	80—85[b] (70—73)[e]	90—95[b] (84—85)[e]
XI	75[b] (71—75)[e]	90—95[b] (82—89)[e]

[e] Calculated from the coupling constants obtained for the tetradeuterio compounds (Table II) using the formula $K = (J_{mob} - J_{ee})/(J_{aa} - J_{mob})$; [b] calculated from the signal widths using the formula $K = (W_{mob} - W_e)/(W_a - W_{mob})$ with compounds *I* and *XII* as standards (W_a and W_e, respectively); [c] taken from ref.[8]; [d] taken from ref.[7]; [e] taken from ref.[5].

fifteen tetradeuterio amino alcohols in Table II. The quantitative data on chair–boat equilibria (Scheme 1) in the compounds *I* – *VI* and chair–chair equilibria (Scheme 2) in the compounds *IX* – *XI* as calculated from the ^{1}H-NMR data are presented in Table III, together with the results of the IR measurements from our previous paper[8]. It is evident that compounds *I*, *II*, *IIIa*, *Va*, *VIa*, *VII* and *VIII* exist mainly in the diaxial conformation whereas compounds *IIIb* – *VIb* are present predominantly in the boat form[2]. In the chair–chair equilibrium in the compounds *IXb* – *XI* the diequatorial chair form predominates; all these results are in accord with the earlier

XVII

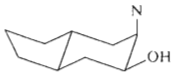


XVIII

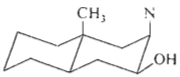
XIX

XX

XXI



XXII



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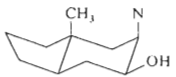

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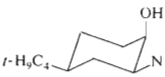

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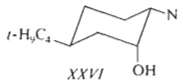
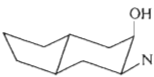


XXVI

XXVII



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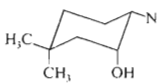
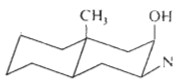


XXIX



XXX

In the formulae: *a*, N = NH_2; *b*, N = $N(CH_3)_2$

SCHEME 4

findings[5]. Compounds *VIIb* and *VIIIb* exhibit large *W* values (14 and 11 Hz, respectively) indicative of the presence of a conformational equilibrium[1]; however, it cannot be concluded whether this equilibrium is of a chair–chair or a chair–boat type.

cis-*Amino Alcohols*

The ^{1}H-NMR data for twenty three amino alcohols (Scheme 4) with *cis*-functional groups are listed in Table IV. The chemical shifts and signal widths for the methine protons in the compounds *XVIIa*–*XXIIa* are in accord with the $NH_2^eOH^e$ chair conformation and in *XXVIIa*, *XXVIIIa* and *XXXa* with the $NH_2^eOH^a$ conformation. For dimethylamino derivatives the signal of the OH-methine proton in *XXVb* to *XXVIIIb* and *XXXb* indicates that these compounds exist in the chair conformer. The coupling constant ($J = 3$ Hz) for *XXVIId*$_4$ (Table II) is in accord with this conclusion. The value 11 Hz observed for *XXIXb* indicates a certain deformation of the ring, compatible with the flattening assumed previously on the basis of IR

TABLE IV

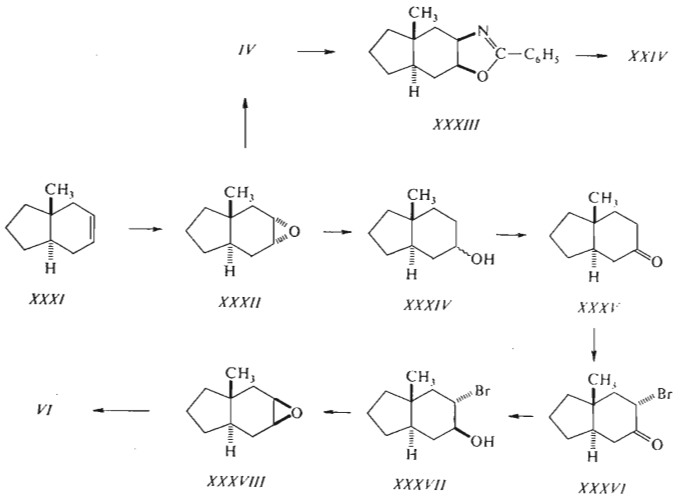
Methine Protons Characteristic for the *cis*-Amino (*a*) and *cis*-Dimethylamino (*b*) Alcohols *XVII* to *XXX* (in $CDCl_3$, TMS)

Compound	*a*				*b*			
	H/OH		H/NH_2		H/OH		$H/N(CH_3)_2$	
	δ^a	W^{*b}	δ^a	W^{*b}	δ^a	W^{*b}	δ^a	W^{*b}
XVII	3·52	20	3·06	10	3·62	21	2·59	13
XVIII	3·50	19	3·15	8	3·64	21	2·60	13
XIX	3·54	19	3·07	10	3·83	15	2·30[c]	—
XX	3·56	20	3·08	8	3·78	18	2·40[c]	—
XXI	3·55	19	3·09	10	3·63	22	2·73	12
XXII	3·63	20	3·16	9	3·64	18·5	2·79	12
XXIII	—	—	—	—	4·14	15	2·15	—
XXIV	—	—	—	—	4·19	14	2·10	—
XXV	—	—	—	—	3·98	8	2·00[c]	—
XXVI	—	—	—	—	4·07	8	2·10[c]	—
XXVII	3·75	8·6	2·83	18·5	4·10	8	2·00[c]	—
XXVIII	3·60	8·5	2·85	18	4·05	8	2·10[c]	—
XXIX	—	—	—	—	4·00	9	1·85	11
XXX	3·80	9·5	2·82	19	4·01	9	1·94	15

[a] Centers of multiplets: [b] terminal line separation; [c] approximate values, signal overlapping; [d] reported[1,2] $\delta = 3·5$ for H/OH and 3·15 for H/NH_2.

data[6]. In the series of N^aO^e dimethylamino derivatives (*XVIIb*, *XVIIIb*, *XXIb*, *XXIIb*) the signal widths ($W = 12-13$ Hz) found for the methine protons under the $N(CH_3)_2$ groups indicate a deformation of the ring, again in agreement with the assumption made on the basis of an infrared spectral study[6]. This conclusion is also supported by the fact that the coupling constants for the tetradeuterio compounds *XXId*-d_4 and *XXIIb*-d_4 ($J = 5{\cdot}6$ Hz and 6 Hz, respectively) are greater than those for the amino compounds *XXIa* ($J = 4$ Hz) and *XXIIa* ($J = 4$ Hz). The derivatives *XXIIIb* and *XXIVb* clearly show the presence of a boat form, as already indicated by the infrared spectrum[6]. Finally, the data for the monocyclic compounds *XIXb* and *XXb* are compatible with the expected conformational equilibrium $N^aO^e \rightleftharpoons N^eO^a$, as shown also by the coupling constant ($J = 9{\cdot}1$ Hz) found for the tetradeuterio derivative *XXb*-d_4.

In conclusion, it can be said that the ^{1}H-NMR method supports the results obtained by the IR spectroscopy. Since it was not possible to study the compounds at low enough temperatures, the method gives only approximate values and therefore the infrared hydrogen bond determination appears to be a more suitable approach.

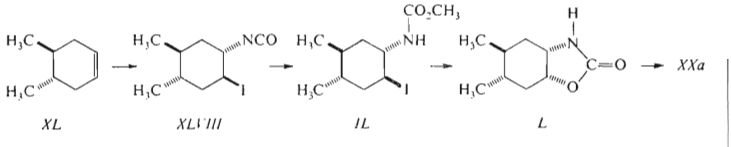


SCHEME 5

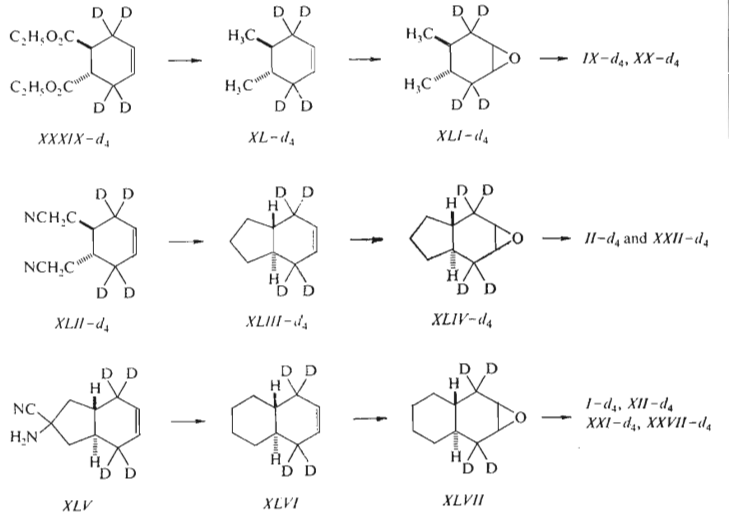
Synthesis of the Compounds

Most of the compounds are already known[1-8,14-17]. Compounds *IVa,b*, *VIa,b* and *XXIVa,b* were synthesized starting from 1-methyl-*trans*-bicyclo[4,3,0]non--3-ene[18,19] (*XXXI*) as shown in Scheme 5, compounds *XXa,b* were prepared from *trans*-4,5-dimethylcyclohexene (Scheme 6).

The tetradeuterio amino alcohols were prepared using classical synthetic methods. All the synthetic procedures started from 1,1,4,4-tetradeuteriobuta-1,3-diene[20]



SCHEME 6



SCHEME 7

which by Diels–Alder addition gave the olefins *XL*–d_4, *XLIII*–d_4 and *XLVI*–d_4 and these were transformed into the desired amino alcohols (Scheme 7). The *trans*-bicyclo-[4,4,0]decane system was synthesized by deamination of the α-diamine[21] prepared by reduction of the amino nitrile *XLV*. This reaction, involving an extension of the five-membered ring, was performed in perchloric rather than in acetic acid in order to avoid side reactions which occurred in the latter acid.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. The IR spectra were taken on a Beckmann IR 8 instrument .The gas–liquid chromatographic analyses were carried out on a Girdel 75 FH chromatograph equipped with a flame ionisation detector, on a 3 m column (3 mm diameter) packed with 5% Carbowax 20M on Chromosorb W 60—80, flow rate 20 ml/min. Preparative gas–liquid chromatography was performed on an Autoprep-Aerograph A 700 apparatus, using a 3 m column (9 mm diameter) with 30% Carbowax 20M on Chromosorb W; nitrogen flow rate 250 ml/min.

The ^{1}H-NMR spectra were measured in 0·5M solutions on a Varian HR-100 spectrometer and are given in δ-scale with tetramethylsilane as internal standard. Mass spectra were measured on a JEOL-JMS-D 100 spectrometer in the Laboratory of Physical Measurement, Languedoc University, Montpellier. The microanalyses were performed in the Microanalytical Laboratory CNRS, Chemical University, Montpellier.

2α-Dimethylamino-3β-hydroxy-9β-methyl-*trans*-bicyclo[4,4,0]decane (*XIVb*)

Prepared from *XIVa* (ref.[16]) by Clarke-Eschweiler methylation; b.p. 115°C/0·15 Torr. For $C_{13}H_{25}NO$ (211·3) calculated: 73·88% C, 11·92% H, 6·63% N; found: 73·56% C, 11·83% H, 6·81% N.

3α,4α-Epoxy-1-methyl-*trans*-bicyclo[4,3,0]nonane (*XXXII*)

Epoxidation of 1-methyl-*trans*-bicyclo[4,3,0]non-3-ene (*XXXI*) (10 g, 0·07 mol) with *p*-nitroperoxybenzoic acid afforded the title compound in 84% yield; b.p. 95—100°C/15 Torr. This product contained 17% of the epimeric epoxide *XXXVIII*, according to the gas–liquid chromatography of the alcohols after reduction. IR spectrum (film, cm^{-1}): 2941, 2874, 1447 and 1429, 1260, 975, 935, 872 and 792. ^{1}H-NMR spectrum ($CDCl_3$): 0·72 (s, CH_3), 3·15 (m, 1 H, $W\,1/2$ = = 7·5 Hz), 3·07 (m, 1 H, W 1/2 = 6·5 Hz). For $C_{10}H_{16}O$ (152·2) calculated: 78·89% C, 10·59% H; found: 79·15% C, 10·48% H.

4-Hydroxy-1-methyl-*trans*-bicyclo[4,3,0]nonane (*XXXIV*)

A solution of the epoxide *XXXII* (3 g, 0·05 mol) in ether (50 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (3 g) in ether (100 ml) and the resulting mixture was refluxed for 1 h. The usual work up procedure and distillation at 118—120°C/17 Torr afforded in 89% yield a product containing 43% of the axial 4α-alcohol (α-*XXXIV*), 40% of the equatorial 4β-isomer (β-*XXXIV*) and 17% of a mixture of epimeric 3-hydroxy-1-methyl-*trans*-bicyclo-[4,3,0]nonanes formed by reduction of the β-epoxide *XXXVIII* which was present in *XXXII*. The alcohols were separated by preparative gas–liquid chromatography at 150°C. Isomer

α-*XXXIV*: IR spectrum (film, cm^{-1}): 3378, 1058, 992, 985, 974. ^{1}H-NMR spectrum ($CDCl_3$): 0·68 (s, CH_3), 4·10 (m, H/OH, $W1/2 = 11$ Hz). For $C_{10}H_{18}O$ (154·2) calculated: 77·86% C, 11·76% H; found: 77·64% C, 11·58% H. Isomer β-*XXXIV*: IR spectrum (film, cm^{-1}): 3322, 1107, 1074, 1032, 1007, 990, 950. ^{1}H-NMR spectrum ($CDCl_3$): 0·74 (s, CH_3), 3·63(m, H/OH, $W1/2 = 23$ Hz). For $C_{10}H_{18}O$ (154·2) calculated: 77·86% C, 11·76% H; found: 77·55% C, 11·48% H.

1-Methyl-*trans*-bicyclo[4,3,0]nonan-4-one (*XXXV*)

A mixture of the alcohols *XXIV* (8 g, 0·05 mol) in acetone (100 ml) was treated by Jones solution (15 ml). After 12 hours' stirring the product was isolated as usual, b.p. 112°C/13 Torr, yield 80%. IR spectrum (CCl_4): 1720 cm^{-1}. For $C_{10}H_{16}O$ (152·2) calculated: 78·89% C, 10·59% H; found: 79·22% C, 10·45% H.

3α-Bromo-1-methyl-*trans*-bicyclo[4,3,0]nonan-4-one (*XXXVI*)

A solution of bromine (6·48 g, 0·081 mol) in acetic acid (12 ml) was added dropwise to a stirred solution of *XXXV* (5·4 g; 0·036 mol) in acetic acid (40 ml). The mixture was poured on ice and the product isolated in the usual manner, m.p. 86—88°C (light petroleum), yield 70%. IR spectrum (CCl_4): 1745 cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$): 1·05 (s, CH_3), 4·80 (q, H/Br, $J_{AX} + J_{BX} = 13$ Hz). For $C_{10}H_{15}BrO$ (231·1) calculated: 51·96% C, 6·54% H, 34·57% Br; found: 52·15% C, 6·43% H, 34·40% Br.

3α-Bromo-4β-hydroxy-1-methyl-*trans*-bicyclo[4,3,0]nonane (*XXXVII*)

A suspension of sodium borohydride (4·5 g; 0·12 mol) in 2-propanol (100 ml) was added in small portions to a stirred solution of *XXVI* (3 g; 0·012 mol) in 2-propanol (30 ml). The mixture was stirred for 4 h at 20°C and the product was isolated. The residue (3 g) was chromatographed on a silica gel column (75 g). Elution with light petroleum containing 1% ether afforded 0·8 g of 3α-bromo-4α-hydroxy-*trans*-bicyclo[4,3,0]nonane. IR spectrum (CCl_4, cm^{-1}): 3450, 1010 and 875. ^{1}H-NMR spectrum ($CDCl_3$): 0·75 (s, CH_3), 4·05 (q, H/OH, $W1/2 = 8$ Hz), 4·47 (sextuplet, H/Br, $W1/2 = 20$ Hz). Elution with light petroleum–5% ether afforded 1·5 g of *XXXVII*, m.p. 42°C. IR spectrum (CCl_4, cm^{-1}): 3445, 1110, 1060, 1035, 1000, 953. ^{1}H-NMR spectrum ($CDCl_3$): 0·79 (s, CH_3), 3·68 (m, H/OH, $W1/2 = 24$ Hz), 4·20 (octet, H/Br, $W1/2 = 26$ Hz). For $C_{10}H_{17}BrO$ (233·1) calculated: 51·51% C, 7·34% H, 34·27% Br; found: 51·19% C, 7·18% H, 34·10% Br.

3β,4β-Epoxy-1-methyl-*trans*-bicyclo[4,3,0]nonane (*XXXVIII*)

The bromo alcohol *XXXVII* (5 g, 0·021 mol) was refluxed with a solution of potassium tert-butoxide (0·025 mol in 50 ml of tert-butyl alcohol) for 3 h. The work-up procedure afforded *XXXVIII*, b.p. 90—95°C/13 Torr, in 70% yield. IR spectrum (film, cm^{-1}): 2933, 1449, 1253, 1058, 992, 975, 795. For $C_{10}H_{16}O$ (152·2) calculated: 78·89% C, 10·59% H; found 78·65% C, 10·42% H.

3β-Amino-4α-hydroxy-1-methyl-*trans*-bicyclo[4,3,0]nonane (*IVa*)

This compound, m.p. 115°C/0·5 Torr, was prepared by ammonolysis of the epoxide *XXXII* and was purified by preparative gas–liquid chromatography at 200°C. For $C_{10}H_{19}NO$ (169·3)

calculated: 70·96% C, 11·31% H, 8·27% N; found: 70·91% C, 10·98% H, 8·40% N. N-Benzoyl derivative, m.p. 186°C (methanol). For $C_{17}H_{23}NO_2$ (273·4) calculated: 74·69% C, 8·48% H, 5·12% N; found: 74·80% C, 8·35% H, 5·21% N. N,N-Dimethyl derivative *IVb*, b.p. 78°C/1 Torr. For $C_{12}H_{23}NO$ (197·3) calculated: 73·04% C, 11·75% H, 7·10% N; found: 72·95% C, 11·58% H, 7·22% N.

4α-Amino-3β-hydroxy-1-methyl-*trans*-bicyclo[4,3,0]nonane (*VIa*)

Prepared by ammonolysis of the epoxide *XXXVIII*; m.p. 126°C (light petroleum). For $C_{10}H_{19}NO$ (169·3) calculated: 70·96% C, 11·31% H, 8·27% N; found: 71·07% C, 10·92% H, 8·20% N. N,N-Dimethyl derivative *VIb*, m.p. 74°C (light petroleum). For $C_{12}H_{23}NO$ (197·3) calculated: 73·04% C, 11·75% H, 7·10% N; found: 73·10% C, 11·55% H, 6·52% N.

3β-Amino-4β-hydroxy-1-methyl-*trans*-bicyclo[4,3,0]nonane (*XXIVa*)

This compound was prepared from *IVa* by benzoylation, cyclisation of the benzoyl derivative by $SOCl_2$ to oxazoline and subsequent acid hydrolysis; b.p. 95°C/0·5 Torr. For $C_{10}H_{19}NO$ (169·3) calculated: 70·96% C, 11·31% H, 8·27% N; found: 71·05% C, 11·18% H, 8·35% N. N,N-Dimethyl derivative *XXIVb*, m.p. 80°C (ethanol). For $C_{12}H_{23}NO$ (197·3) calculated: 73·04% C, 11·75% H, 7·10% N; found: 72·50% C, 11·62% H, 7·02% N.

The purity of the compounds *IVa,b VIa,b* and *XXIVa,b* was checked by gas–liquid chromatography (Firebrick 20% KOH, 1% Carbowax 20 M); the retention times of *IVa*, *VIa* and *XXIVa*, and also of *IVb*, *VIb* and *XXIVb*, were different.

r-1-Iodo-*trans*-2-methoxycarbonylamino-*cis*-4-*trans*-5-dimethylcyclohexane (*IL*)

trans-4,5-Dimethylcyclohexene (*XL*) (7·7 g) was added dropwise at −20°C to a stirred mixture of silver isocyanate (22·23 g) and iodine (22·85 g) in ether (200 ml). The mixture was stirred for 3 h at −20°C and for 15 h at room temperature. The precipitate was filtered off, washed with ether and the filtrate was used in the subsequent experiment. A small sample was evaporated, leaving the crude iodo isocyanate *XLVIII*. IR spectrum (film): 1247 and 1718 cm^{-1}; ^{1}H-NMR spectrum (CCl_4, δ): 4·02 (q, C<u>H</u>—NCO, $W\,1/2 = 12$ Hz) 4·45 (C<u>H</u>—I, $W\,1/2 = 12$ Hz). The ethereal solution was treated with methanol (200 ml) in which lithium (70 mg) was dissolved. The mixture was set aside for 24 h at room temperature and refluxed for 4 h. After cooling, it was washed with sodium thiosulphate solution and water, dried over sodium sulphate and taken down, affording 15 g (70%) of *IL*, m.p. 133°C (methanol). IR spectrum (KBr), cm^{-1}: 3285, 1520 (NH), 1706, 1675 (C=O), 1248 (C—O—C). ^{1}H-NMR spectrum ($CDCl_3$, δ): 4·04 (sext., C<u>H</u>—NHCOCH$_3$, $W\,1/2 = 13$ Hz), 4·60 (m, C<u>H</u>—I, $W\,1/2 = 9$ Hz). For $C_{10}H_{18}INO_2$ (311·1) calculated: 38·60% C, 5·82% H, 4·50% N; found: 38·65% C, 5·77% H, 4·56% N.

cis-2-Amino-*trans*-4-*cis*-5-dimethylaminocyclohexan-*r*-1-ol (*XXa*)

Heating of *IL* (6·2 g) to 160—170°C at 0·01 Torr for 30 min afforded 3·2 g (91%) of the oxazoline *L*, m.p. 66°C (ether). IR spectrum (KBr), cm^{-1}: 1022 (C—O—C), 1739 (C=O), 3005 (NH). ^{1}H-NMR spectrum ($CDCl_3$, δ): 3·53 (m, C<u>H</u>—NH, $W\,1/2 = 13$ Hz), 4·51 (m, C<u>H</u>—O, $W\,1/2 = 22$ Hz). For $C_9H_{15}NO_2$ (169·2) calculated: 63·88% C, 8·94% H, 8·28% N; found: 63·95% C, 8·91% H, 8·14% N. The oxazoline *L* (2·5 g) was hydrolysed by boiling with a solution of potassium hydroxide (11 g) in water (20 ml) and ethanol (180 ml). The work-up procedure afforded 2 g (91%) of *XXa*, m.p. 93°C (ethanol). For $C_8H_{17}NO$ (143·2) calculated: 67·09% C,

11·96% H, 9·78% N; found: 67·34% C, 12·07% H, 9·92% N. Hydrochloride, m.p. 184°C (ethanol–ether). For $C_8H_{18}ClNO$ (179·8) calculated: 53·47% C, 10·08% H, 7·78% N; found: 53·25% C, 9·91% H, 7·73% N. N,N-Dimethyl derivative *XXb*, b.p. 92°C/0·8 Torr, was prepared by Clarke–Eschweiler methylation of *XXa* in 85% yield. For $C_{10}H_{21}NO$ (170·2) calculated: 70·12% C, 12·35% H, 8·17% N; found: 69·97% C, 12·35% H, 8·21% N.

3,3,6,6-Tetradeuteric-*trans*-4,5-bis(methoxycarbonyl)cyclohexene (*XXXIX*—d_4)

Condensation of 1,1,4,4-tetradeuterio-1,3-butadiene (obtained by pyrolysis of 2,2,5,5-tetradeuteriosulfolene[20]) with dimethyl fumarate was carried out[22] in 80% yield. Mass spectrum of the adduct shows the presence of 90% d_4-species.

3,3,6,6-Tetradeuterio-*trans*-4,5-dimethylcyclohexene (*XL*—d_4)

The diester *XXXIX*—d_4 (66 g) in ether (150 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (19 g) in ether (1 000 ml). The mixture was refluxed for 48 h, decomposed with 10% H_2SO and worked up, yielding 3,3,6,6-tetradeuterio-*trans*-4,5-bis(hydroxymethyl) cyclohexene, b.p. 135°C/0·25 Torr, m.p. 46°C, yield 75%. IR spectrum (film): 3 280 and 1 026 cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$): 1·68 (m, 2 H), 3·60 (m, 4 H), 5·62 (s, 2 H). No molecular peak in the mass spectrum. For $C_8H_{10}D_4O_2$ (146·2) calculated: 21·88% O; found: 22·04% O.

A solution of the diol (46·8 g; 0·3 mol) in pyridine (70 ml) was added dropwise at −10°C to a solution of *p*-toluenesulphonyl chloride (150 g; 0·78 mol) in pyridine (180 ml). After stirring for 24 h at 20°C, the usual isolation afforded 3,3,6,6-tetradeuterio-4,5-bis(-*p*-toluenesulphonyloxymethyl)cyclohexene; m.p. 98°C, in 83% yield. IR spectrum (KBr, cm^{-1}): 1 600, 1 490, 1 458, 935, 815. ^{1}H-NMR spectrum (CCl_4): 1·93 (m, 4 H), 2·47 (s, 6 H), 3·87 (m, 4 H), 7·51 (q, 8 H). No molecular peak in the mass spectrum. For $C_{22}H_{22}D_4O_6S_2$ (454·6) calculated: 21·11% O; found: 20·92% O.

The above di-*p*-toluenesulphonate (9·94 g, 0·022 mol) was slowly extracted in a Soxhlet apparatus into a boiling solution of lithium aluminium hydride (2·6 g) in ether (240 ml). The extraction was complete in 24 h. The work up procedure afforded *XL*—d_4; b.p. 126°C/760 Torr, in 60% yield. IR spectrum (film, cm^{-1}): 1 639, 3021. ^{1}H-NMR spectrum (CCl_4): 0·9 (d, 6 H), 1·30 (m, 2 H), 5·55 (s, 2 H). It contains 85% d_4 and 10% d_3 species (mass spectroscopy).

3,3,6,6-Tetradeuterio-1,2-epoxy-*trans*-4,5-dimethylcyclohexene (*XLI*—d_4)

Treatment of *XL*—d_4 (0·1 mol) with *p*-nitroperoxybenzoic acid in chloroform afforded in 80% yield the epoxide *XLI*, boiling at 65°C/15 Torr. IR spectrum (film, cm^{-1}): 940, 825, 800. ^{1}H-NMR spectrum ($CDCl_3$): 0·83 (t, 6 H), 1·10 (m, 2 H), 3·09 (s, 2 H). For $C_8H_{10}D_4O$ (130·2) calculated: 12·28% O; found: 12·03% O.

trans-2-Amino-3,3,6,6-tetradeuterio-*cis*-4-*trans*-5-dimethylcyclohexan-*r*-1-ol (*IXa*—d_4)

Prepared from *XLI*—d_4 according to ref.[5]; b.p. 140°C/12 Torr, m.p. 55°C. IR spectrum (film, cm^{-1}): 3 226, 2 179, 2 105, 1 060, 1 030, 960. Mass spectrometry: 82% $d_4$species, 13% $d_3$species. N,N-Dimethyl derivative *IXb*—d_4 prepared according to ref.[5], b.p. 128°C/12 Torr. IR (film, cm^{-1}): 3 226, 2 179, 2 105, 1 075, 1 040, 960. Mass spectroscopy: 78% of $d_4$species, 10% $d_3$species.

cis-2-Amino-3,3,6,6-tetradeuterio-*trans*-4-*cis*-5-dimethylcyclohexan-*r*-1-ol (*XXa*—d_4)

Prepared as described for the non-deuterated compound; m.p. 93—94°C (ethanol). IR spectrum (film, cm^{-1}): 3289, 1160, 1115, 1001, ν(C—D) 2197, 2105. Mass spectrometry: 75% d_4-species, 22% d_3-species. N,N-Dimethyl derivative *XXb*—d_4, b.p. 101°C/12 Torr. IR spectrum (film, cm^{-1}): 3279, 2198, 2105, 1190, 1170, 1124. Contains 85% $d_4$species and 12% $d_3$species.

trans-4,5-Bis(cyanomethyl)-3,3,6,6-tetradeuteriocyclohexene (*XLII*—d_4)

A solution of *trans*-4,5-bis(*p*-toluenesulphonylmethyl)cyclohexene (40 g; 0·08 mol) in dimethyl sulphoxide (150 ml) was slowly added under stirring to potassium cyanide (13 g) in boiling (85°C) dimethyl sulphoxide (150 ml). The mixture was heated to 85°C for 2 h, cooled, poured on ice and the product extracted with benzene, affording 95% of *XLII*—d_4, m.p. 80°C (benzene–hexane). IR spectrum (KBr): 2247 cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$); 2·11 (m, 2 H) 2·48 (m, 4 H), 5·66 (s, 2 H). Mass spectrum: 85% $d_4$species, 15% $d_3$species.

2,2,5,5-Tetradeuterio-*trans*-bicyclo[4,3,0]non-3-ene (*XLIII*—d_4)

A mixture of *XLII*—d_4 (11 g) and 33% potassium hydroxide (100 ml) was refluxed for 48 h. 3,3,6,6-Tetradeuteriocyclohexane-*trans*-4,5-diacetic acid, m.p. 195°C (methanol) was obtained by the usual procedure in 70% yield. IR spectrum (KBr, cm^{-1}): 2941, 1695, 950. ^{1}H-NMR spectrum (pentadeuteriopyridine): 2·65 (m, 6 H), 6·13 (s, 2 H). For $C_{10}H_{10}D_4O_4$ (202·2) calculated: 31·64% O; found: 31·51% O. This acid (60 g) was heated with barium hydroxide (5 g) to 300°C till the end of distillation. The obtained 2,2,5,5-tetradeuterio-*trans*-bicyclo[4,3,0]non-3-en-8-one, m.p. 69°C, solidified in the receiver; yield 95%. IR spectrum (KBr): 1724cm^{-1} ^{1}H-NMR spectrum: ($CDCl_3$): 2·16 (m, 6 H), 5·75 (s, 2 H). Mass spectrometry: 91% d_4, 8% d_3-species. This ketone (42·4 g; 0·28 mol) was refluxed with potassium hydroxide (47·6 g; 0·827 mol) and 99% hydrazine hydrate (37·2 ml, 0·76 mol) in diethylene glycol (320 ml) for 6 h. The mixture was distilled and the product *XLIII*—d_4 isolated, b.p. 120°C/760 Torr, yield 80%. IR spectrum (film): 1626, 3021 cm^{-1}, ^{1}H-NMR spectrum ($CDCl_3$): 1·5 (m, 8 H), 5·60 (s, 2 H). Mass spectrum: 89% d_4 and 10% d_3 species.

2,2,5,5-Tetradeuterio-3,4-epoxy-*trans*-bicyclo[4,3,0]nonane (*XLIV*—d_4)

Obtained in 80% yield as described for *XLI*—d_4; b.p. 118—120°C/40 Torr. IR spectrum: (film): 940 and 820 cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$): 1·33 (m, 8 H), 3·10 (s, 2 H). For $C_9H_{10}D_4O$ (142·2) calculated: 11·24% O; found: 10·08% O.

3β-Amino-2,2,5,5-tetradeuterio-4α-hydroxy-*trans*-bicyclo[4,3,0]-nonane (*IIa*—d_4)

Prepared analogously as the non-deuterated compound[3]; m.p. 84°C (benzene), b.p. 115°C/0·1 Torr· IR spectrum (KBr, cm^{-1}): 3356, 3279, 3125, 2183, 2092, 1054, 996, 960, 945. Contains 83% d_4 and 11% d_3 species. N,N-Dimethyl derivative *IIb*—d_4, m.p. 78—79°C (ether). IR spectrum (KBr, cm^{-1}): 3226, 2212, 2105, 1064, 1027, 980, 915. Contains 70% d_4 and 21% d_3 species.

3β-Amino-2,2,5,5-tetradeuterio-4β-hydroxy-*trans*-bicyclo[4,3,0]nonane (*XXIIa*—d_4)

Obtained as described for the non-deuterated compound[3], m.p. 123°C (ethanol). IR spectrum (KBr, cm^{-1}): 3344, 3279, 3125, 2198,, 2083 1099, 1048, 1010, 980, 946. Mass spectrum: 86% d_4 and 11% d_3 species.

N,N-Dimethyl derivative *XXIIb*$-d_4$, b.p. 90°C/0·2 Torr. IR spectrum (film, cm^{-1}): 3344, 1091, 1034, 1027, 1021; 2198, 2105. Contains 80% d_4 and 15% d_3 species.

2,2,5,5-Tetradeuterio-*trans*-bicyclo[4,4,0]dec-3-ene (*XLVI*$-d_4$)

A mixture of 2,2,5,5-tetradeuterio-*trans*-bicyclo[4,3,0]non-3-en-8-one (5·46 g; 0·039 mol), ammonium chloride (5·3 g, 0·1 mol), potassium cyanide (6·5 g; 0·1 mol), 34% aqueous ammonia (50 ml) and ethanol saturated with ammonia (40 ml) was stirred for 5 days. The reaction mixture was extracted with ether and the ether extract concentrated to 50 ml. The presence of 8-amino--8-cyano-2,2,5,5-tetradeuterio-*trans*-bicyclo[4,3,0]non-3-ene (*XLV*$-d_4$) was proved by IR spectrum which showed bands at 2220, 3330 and 3021 cm^{-1}. For $C_{10}H_{10}D_4N_2$ (166·2) calculated: 16·84% N; found: 17·02% N. The above solution of the crude amino nitrile *XLV*$-d_4$ (50 ml) was treated with lithium aluminium hydride (0·2 mol) and refluxed for 4 h. The work-up procedure afforded 5·2 g of the crude α-diamine in 75% yield. IR spectrum (film): 3330, 3021 cm^{-1}. For $C_{10}H_{14}D_4N_2$ (170·3) calculated: 16·44% N; found: 16·23% N. The diamine (5·1 g) was dissolved in dioxane (8 ml), mixed with aqueous solution (8 ml) of sodium nitrite (0·08 mol) and 2M-$HClO_4$ was added to a just acidic reaction. Extraction afforded 3·1 g of 2,2,5,5-tetradeuterio-*trans*--bicyclo[4,4,0]dec-3-en-8-one. IR spectrum (film): 3021, 1715 cm^{-1}. For $C_{10}H_{10}D_4O$ (154·2) calculated: 10·37% O; found: 10·25% O. This ketone (3·0 g) was refluxed with 58% hydrazine hydrate (0·08 mol) and potassium hydroxide (0·07 mol) in diethylene glycol (30 ml) for 48 h and distilled under normal pressure. The distillate afforded 2·1 g (75%) of the hydrocarbon *XLVI*$-d_4$. IR spectrum (film): 3021, 1639 cm^{-1}. Contains 77% d_4 and 21% d_3 species (mass spectrum).

2,2,5,5-Tetradeuterio-3,4-epoxy-*trans*-bicyclo[4,4,0]decane (*XLVII*$-d_4$)

Epoxidation of *XLVI*$-d_4$ (2·1 g) with *p*-nitroperoxybenzoic acid afforded 1·5 g (60%) of the epoxide *XLVII*$-d_4$. IR spectrum (film, cm^{-1}): 2934, 2857, 1437; 1266, 870. For $C_{10}H_{12}D_4O$ (156·2) calculated: 10·24% O; found: 10·13% O.

Stereoisomeric 3-amino-2,2,5,5-tetradeuterio-4-hydroxy-*trans*-bicyclo[4,4,0]decanes *I*$-d_4$, *XII*$-d_4$, *XXI*$-d_4$ and *XXVII*$-d_4$, and their N,N-dimethyl derivatives were prepared according to Saeluzika[23].

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