Compounds with Bridgehead Nitrogen. Part 41.[1] The Reaction between *trans*-2-Aminocycloalkanols and Formaldehyde

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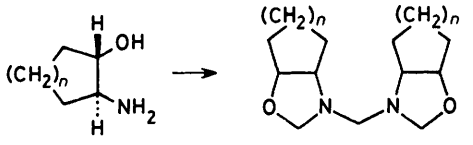
trans-2-Aminocyclopentanol and *trans*-2-aminocyclohexanol condense with formaldehyde to give single isomers of *NN'*-methanoperhydrocycloalkano[*d,i*][1,6,3,8]dioxadiazecines whereas *trans*-2-aminocycloheptanol and *trans*-2-aminocyclo-octanol give 1 : 1 mixtures of two isomeric bis(perhydrocycloalkano-oxazol-3-yl)methanes. The formation of the two types of dimer is explained in terms of differences in ring fusion strain.

trans-2-AMINOCYCLOALKANOLS of the type (1) may condense with excess of formaldehyde to give either a bis-(perhydro-oxazol-3-yl)methane (2) or a perhydro-3,8-methano[1,6,3,8]dioxadiazecine (3). This work was aimed at exploring the effect of ring size in the amino-alcohols (1; $n = 1$—4) and of possible substituent effects [Me group in (4)] on the course of dimerisation.



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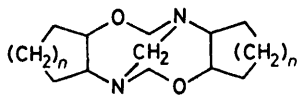
or 

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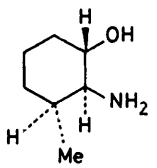

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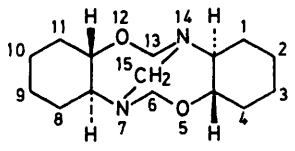
1. *Reaction between* trans-2-*Aminocyclohexanols or* trans-2-*Aminocyclopentanol and Formaldehyde.*—The structure of the crystalline compound, m.p. 157—158 °C,† obtained from the reaction between *trans*-2-aminocyclohexanol and formaldehyde had been assigned [2] as *r*-4a,*t*-7a,*c*-11a,*t*-14a-7,14-methanoperhydrodibenzo[*d,i*]-[1,6,3,8]dioxadiazecine (5) on the basis of 60 MHz ^{1}H n.m.r. data rather than the previously assigned [3] bis(perhydrobenzoxazol-3-yl)methane structure (2; n = 2). Confirmation of structure (5) was provided by the 270 MHz ^{1}H (Table 1) and ^{13}C n.m.r. spectra (Table 2).

Analysis of the OCH_2N signals gave a geminal coupling constant of −11.5 Hz in strong contrast to the J_{gem} of *ca.* −2.5 Hz observed for *N*-substituted perhydrobenzoxazoles (6). Thus the oxazolidine structure (2; n =2) proposed by Crandall and van Hoozer [3] is ruled out. The observed J_{gem} resembles that (−11.1 to −12.8 Hz) in seven-membered ring systems (7) [4] and accordingly the dimer must possess structure (5).

The symmetrical nature (plane containing NCN) of the dimer is also shown (^{1}H n.m.r.) by the single AB quartet



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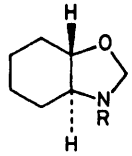

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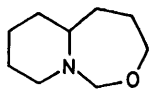

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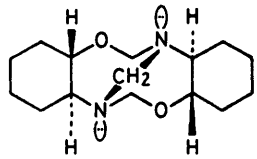

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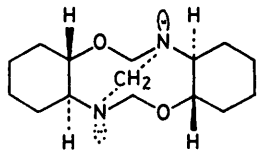

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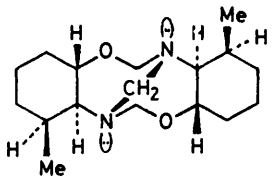


(10)

(δ 4.48 and δ 4.05) for the two sets of NCH_2O methylene protons, by the singlet absorption for the NCH_2N methylene protons at δ 4.28, and by the single absorptions for the angular OCH protons (4a- and 11a-H) and for the NCH protons (7a- and 14a-H). This is confirmed by the simplicity of the ^{13}C n.m.r. spectrum (Table 2) which shows seven different carbon nuclei. C(**2**), C(**3**), C(**9**), and C(**10**) all absorb at δ 24.6 p.p.m. and C(**4**) and C(**11**)

† °C = K −273.15.

TABLE 1

The ^1H n.m.r. spectra ($CDCl_3$) of 7,14-methanoperhydrodibenzo- (5), 1,8-dimethyl-7,14-methanoperhydrodibenzo- (10), and 6,12-methanoperhydrodicyclopentano-[*d*,*i*][1,6,3,8]dioxadiazecine (11)

	Chemical shifts (δ)					Coupling constants (Hz)
Compound	NCH_2O		NCH_2N	OCH	NCH	NCH_2O
(5)	4.48	4.05	4.28	3.40	2.78	−11.5
(10)	4.35	4.00	4.25	3.43	2.73	−11.5
(11)	4.42	4.10	4.33	3.78	3.65	−11.2

TABLE 2

^{13}C N.m.r. spectrum ($CDCl_3$) of 7,14-methanoperhydrodibenzo[*d*,*i*][1,6,3,8]dioxadiazecine (5)

Carbon nuclei	Chemical shift δ (p.p.m.)	Multiplicity	Relative intensity	$J_{^{13}C-H}$/Hz
C(2), (3), (9,10)	24.6	t	4	126
C(1), (8)	33.9 *	t	2	126
C(4), (11)	34.3 *	t	2	126
C(14a), (7a)	64.2	d	1—2	136
C(4a), (11a)	80.9	d	2	136
C(13), (6)	86.2	t	2	153
C(15)	67.9	t	1	146

* These assignments may be reversed. † t = Triplet, d = doublet.

show identical chemical shifts (δ 34.3 p.p.m.) as do C(1) and C(8) (δ 33.9 p.p.m.). Both these latter two sets of nuclei absorb at lower field than C(2), C(3), and equivalent nuclei, due to their proximity to the heteroatoms. The bridgehead carbon nuclei next to nitrogen [C(7a) and C(14a)] show the same chemical shift (δ 64.2 p.p.m.) with multiplicities of two as do the carbon nuclei [C(4a) and C(11a)] adjacent to the oxygen atoms (δ 80.9 p.p.m.). The NCH_2O carbon nuclei [C(13) and C(6)] both absorb at δ 86.2 p.p.m. as triplets and the NCH_2N nucleus at C(15) absorbs as a triplet at δ 67.9 p.p.m.

Examination of Dreiding models of the two symmetrical isomers (8) and (9) of *r*-4a,*t*-7a,*c*-11a,*t*-14a-7,14-methanoperhydrodibenzo[*d*,*i*][1,6,3,8]dioxadiazecine consistent with the n.m.r. data suggests that isomer (8) represents the most favourable structure of the dimer.

Similar dimeric structures (10) and (11) may be assigned to the products arising from *r*-1,*t*-2,*t*-3-*trans*-2-amino-3-methylcyclohexanol (4) and from *trans*-2-aminocyclopentanol (1; $n = 1$) on the basis of the ^1H n.m.r. data (Table 1). The axial orientation of the methyl group in (10) is shown by the magnitude of the coupling constants ($J_{7a,11a}$ 10.5, $J_{7a,8eq}$ 4.0 Hz) extracted from the doublet of doublets at δ 2.73 arising from 7a-H.

2. *Reaction between* trans-2-*Aminocycloheptanol or* trans-2-*Aminocyclo-octanol and Formaldehyde.*—The reaction between *trans*-2-aminocycloheptanol (1; $n = 3$) and formaldehyde gave a viscous oil, unlike the crystalline products (5) and (11) obtained from *trans*-2-aminocyclohexanol and *trans*-2-aminocyclopentanol. The mass spectrum gave a molecular weight of 294 with elemental analysis revealing an empirical formula of $C_{17}H_{30}N_2O_2$ consistent with a dimeric structure. The ^1H n.m.r. spectrum (Table 3) was markedly different from the spectra of 7,14-methanoperhydrodibenzo[*d*,*i*][1,6,3,8]dioxadiazecine (5) and of 6,12-methanoperhydrodicyclopentano[*d*,*i*][1,6,3,8]dioxadiazecine (11). The spectrum showed doubling of most peaks with two AB quartets at δ 4.30 and 4.60 and at δ 4.26 and 4.67 both with J_{gem} −4.0 Hz. These chemical shift values are characteristic of NCH_2O methylene protons but the J_{gem} values are inconsistent with the NCH_2O moiety in a perhydro-3,8-methano[1,6,3,8]dioxadiazecine ring as in the dimers (5) and (11). The value of J_{gem}, however, lies within the range for NCH_2O protons in *N*-alkylperhydrocycloheptano-oxazoles.[5] The NCH_2N protons absorbed at higher field than in (5) and (11) as an AB quartet (δ 3.24, 3.40, J_{gem} −9.6 Hz) equivalent to two protons and as a two proton singlet at δ 3.20. A four proton multiplet centred at δ 3.58 was assigned to the angular CNO protons and two doublets of triplets centred at δ 2.38 and δ 2.26, each equivalent to two protons, was assigned to the angular CHN protons. Thus the spectrum is consistent with equal proportions of two isomers (12) and (13) of bis(perhydrocycloheptano-oxazol-3-yl)methane (2; $n = 3$). In the depicted conformation (13) there is a plane of symmetry containing the NCN atoms. In such a conformation the NCH_2N protons are non-equivalent although each NCH_2O methylene proton in one half of the molecule is in an equivalent position to its counterpart in the other half. In contrast in an alternative conformation (14) to (12) the NCH_2N protons are in a symmetrical environment. Thus in the ^1H n.m.r. spectrum the NCH_2N singlet can be assigned to isomer (12) and the NCH_2N AB quartet to isomer (13).

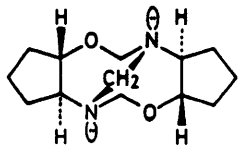
The reaction between *trans*-2-aminocyclo-octanol (1; $n = 3$) and formaldehyde gave a 1 : 1 mixture of

TABLE 3

270 MHz ^1H N.m.r. spectra of bis(perhydrocycloheptano-oxazol-3-yl)methanes (12) and (13) and bis(perhydrocyclooctano-oxazol-3-yl)methanes (15) and (16)

	Chemical shifts (δ)							Coupling constants (Hz)	
Compound	NCH_2O			NCH_2N		CHO	CHN	NCH_2O	NCH_2N
(12) [a]	4.67		4.26	3.20		3.58	2.26	−4.0	
(13) [a]	4.60		4.30	3.40	3.24	3.58	2.38	−4.0	−9.6
(15)		4.41		3.30		3.70	2.65		
(16)	4.57		4.40	3.42	3.30	3.70	2.50	−5.4	−8.4

[a] $J_{8a,8eq}$ 5.1, $J_{3a,4ax}$ 9.2, $J_{3a,4eq}$ 5.1 Hz.



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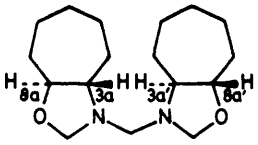

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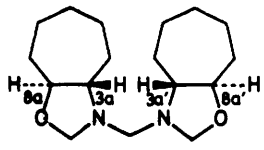

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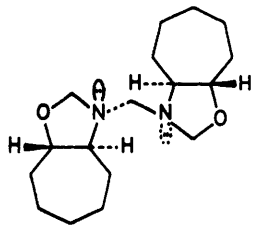

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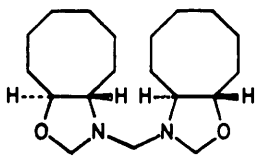

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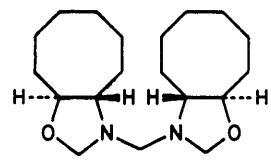
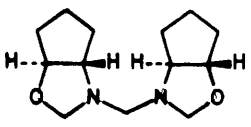


(16)

isomeric bis(perhydrocyclo-octano-oxazol-3-yl)methanes (15) and (16).

DISCUSSION

The course of the dimerisation reaction between *trans*-2-aminocycloalkanols and formaldehyde has been shown to be sensitive to the size of the cycloalkane ring with the cyclopentane and cyclohexane derivatives (1; $n = 1$) and (1; $n = 2$) giving perhydro-3,8-methano[1,6,3,8]-dioxadiazecines (3; $n = 1$) and (3; $n = 2$) and the



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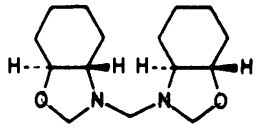

(18)

cycloheptane and cyclo-octane derivatives giving oxazolidines (2; $n = 3$) and (2; $n = 4$). The ring size dependency of reaction may be explained in terms of ring fusion strain. Thus ring closure of *trans*-2-aminocyclopentanol with formaldehyde leading to bis(perhydrocyclopentano-oxazol-3-yl)methane (17) will not occur due to the strain involved in the *trans*-fusion of two five-membered rings (*cf.* $\Delta H°$ 6.0 kcal mol^{-1} * between *cis*- and *trans*-bicyclo[3.3.0]octane [6]). Since ring fusion strain has also been invoked to explain the small free energy difference (0.24—0.38 kcal mol^{-1} at 25 °C) between *cis*- and *trans*-hydrindan [7] (*cf.* $\Delta G°_{25°}$ 2.7 kcal mol^{-1} for *cis*- and *trans*-decalin [7]) then the formation of (18) from *trans*-2-aminocyclohexanol should also be disfavoured by ring fusion strain. Thus the alternative dimerisation process to the perhydro-3,8-methano[1,6,3,8]dioxadiazecines (5) and (11) is favoured since ring fusion strain in a *trans*-fusion between five- and seven-membered rings and between six- and seven-membered rings may be minimised by the flexibility of the seven-membered ring.

The formation of bis(perhydrocycloheptano-oxazol-3-yl)methane (12) and (13), and bis(perhydrocyclo-octano-oxazol-3-yl)methane (15) and (16) from the reaction between *trans*-2-aminocycloheptanol and *trans*-2-aminocyclo-octanol and formaldehyde becomes possible since *trans*-fusion of the five-membered oxazolidine rings to seven- and eight-membered rings involves no fusion strain since the large carbocyclic rings are much more flexible than the five- and six-membered rings.

EXPERIMENTAL

General experimental details are as given in previous Parts.[1]

3-Methylcyclohexene Oxide.—3-Methylcyclohexene (0.26 mol, 25 g) was added slowly to a mixture of *N*-bromosuccinimide (0.25 mol, 45 g) in water (100 ml) † with constant stirring. The mixture was stirred at room temperature for 6 h.‡ The organic layer was separated from the aqueous layer which was extracted with ether. The ether extracts were combined with the organic phase and dried (Na_2SO_4), and the ether removed by distillation. The resultant oil was added slowly to a cooled solution of sodium hydroxide (0.75 mol, 30 g) in water (100 ml) with constant stirring and stirred for a further 2 h. The supernatant oily layer was separated off from the residual aqueous layer which was extracted with ether. The combined ether extracts and oily layer were dried (Na_2SO_4) and the ether removed by distillation. The residual oil was distilled *in vacuo* to yield 3-methylcyclohexene oxide (15 g, 52%), b.p. 50—52 °C at 3.00 mmHg § (lit.,[8] 142 °C at 15 mmHg) (Found: C, 74.7; H, 10.9. Calc. for $C_7H_{12}O$: C, 74.9; H, 10.8%).

r-1,t-2,t-3-trans-2-*Amino*-3-*methylcyclohexanol.*—3-Methylcyclohexene oxide (0.1 mol, 10 g) was heated with ammonium hydroxide solution (*d* 0.88; 4.6 mol, 300 ml) and ethanol (50 ml) in a high pressure stainless steel autoclave at 120—150 °C for 3 h. Solvents were removed by distillation and the product purified by distillation *in vacuo* to yield *r*-1,*t*-2,*t*-3-*trans*-2-amino-3-methylcyclohexanol (9.3 g, 79%), b.p. 80—82 °C at 0.07 mmHg (lit.,[8] 130 °C at 15 mmHg) (Found: C, 64.8; H, 11.8; N, 10.7. Calc. for $C_7H_{15}NO$: C, 65.1; H, 11.7; N, 10.4%).

Reaction between trans-2-*Aminocyclopentanol* (1; n = 1), trans-2-*Aminocyclohexanols* (1; n = 2) *or* (4) *and Formaldehyde.*—40% Aqueous formaldehyde solution (0.16 mol, 12 ml) was added slowly with constant stirring to *trans*-2-aminocycloalkanol (0.074 mol) in water (25 ml) and the mixture was shaken for 0.5 h. The crystalline mass which was deposited was filtered off and dried *in vacuo*. The dry crystals were recrystallised from the minimum quantity of methanol to yield 6,12-*methanoperhydrodicyclopentano*[d,i]-[1,6,3,8]*dioxadiazecine* (28%), m.p. 72—74 °C (Found: C, 65.8; H, 9.5; N, 12.1. $C_{13}H_{22}N_2O_2$ requires C, 65.5; H,

* 1 cal = 4.184 J.

† 1 l = 10^{-3} m^3.

‡ 1 h = 3 600 s.

§ 1 mmHg ≈ 133.322 387 Pa.

9.3; N, 11.7%), 7,14-methanoperhydrodibenzo[*d*,*i*][1,6,3,8]-dioxadiazecine (60%), m.p. 153—155 °C (lit.,[3] 157—158 °C) (Found: C, 67.6; H, 9.5; N, 10.6. Calc. for $C_{15}H_{26}N_2O_2$: C, 67.7; H, 9.8; N, 10.5%), and 1,8-*dimethyl*-7,14-*methano-perhydrodibenzo*[d,i][1,6,3,8]*dioxadiazecine* (24%), m.p. 135—137 °C (Found: C, 69.0; H, 10.4; N, 9.4. $C_{17}H_{30}N_2O_2$ requires C, 69.3; H, 10.3; N, 9.5%).

Reaction between trans-2-*Aminocycloheptanol* (1; n = 3) *or* trans-2-*aminocyclo-octanol* (1; n = 4) *and Formaldehyde.*—40% Aqueous formaldehyde solution (0.16 mol, 12 ml) was added slowly to the *trans*-2-aminocycloalkanol (0.07 mol) in water (40 ml) with constant stirring and the mixture was shaken for 0.5 h. The mixture was basified with 50% aqueous sodium hydroxide solution and extracted with ether. The combined ether extracts were dried (Na_2SO_4), the ether removed by distillation, and the resulting oil purified by distillation *in vacuo* to yield *bis*(*perhydrocycloheptano-oxazol*-3-*yl*)*methane* (70%), b.p. 172—174 °C at 0.1 mmHg (Found: C, 69.7; H, 10.4; N, 9.6. $C_{17}H_{30}N_2O_2$ requires C, 69.3; H, 10.3; N, 9.5%) and *bis*(*perhydrocyclo-octano-oxazol*-3-*yl*)*methane* (8.8 g), b.p. 166—168 °C at 0.15 mmHg (Found: C, 70.6; H, 10.7; N, 8.9. $C_{19}H_{34}N_2O_2$ requires C, 70.8; H, 10.6; N, 8.7%).

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