Compounds with Bridgehead Nitrogen. Part 47.[1] The Reaction between *trans*-1-Aminobenzocycloalkan-2-ols and Formaldehyde

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The reaction between *trans*-1-aminoindan-2-ol and formaldehyde and between *trans*-1-amino-1,2,3,4-tetrahydronaphthalen-2-ol and formaldehyde yields 5,*r*-5a,*t*-8a,13,*c*-13a,*t*-16a-hexahydro-8,16-methanodi-indeno[1,2-*d*:1′,2′-*i*][1,6,3,8]dioxadiazecine and 5,6,*r*-6a,*c*-9a,14,15,*t*-15a,*t*-18a-octahydro-9,18-methanodinaphtho[1,2-*d*:1′,2′-*i*][1,6,3,8]dioxadiazecine respectively whereas the reaction between *trans*-1-amino-2-hydroxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptane and formaldehyde yields bis(1,3a,4,5,6,10b-hexahydro-2*H*-benzo[6,7]cyclohept[1,2-*d*]oxazol-1-yl)methanes.
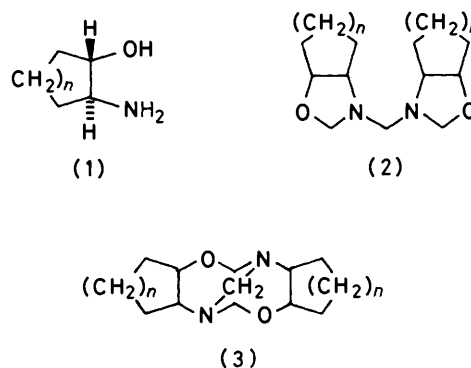
The condensation reaction between *trans*-2-aminocycloalkanols (1) and formaldehyde to give either bis(perhydrocycloalkano-oxazol-3-yl)methanes (2) or *N*,*N*′-methanoperhydrodicycloalkano[*d*,*i*][1,6,3,8]dioxadiazecines (3) is dependent upon ring fusion strain in the two types of dimer.[2] In order to investigate this further, the reactions between various 1-aminobenzocycloalkan-2-ols (4)—(6) and formaldehyde were chosen for study.

(1)　　　　(2)

(3)

(i) *Reaction between* trans-1-*Aminoindan-2-ol and Formaldehyde.*—The reaction between *trans*-1-aminoindan-2-ol (4) and formaldehyde gave a crystalline product, m.p. 205—206 °C, with the empirical formula $C_{21}H_{22}N_2O_2$ (M^+ 334) consistent with a dimeric product of structure (7) or (10).

Analysis of the ^1H n.m.r. spectrum (Table 1) reveals an AB quartet (δ 4.92, 4.57, J_{gem} −11.0 Hz) equivalent to four protons, assigned to the OCH_2N methylene protons. J_{gem} Values for the NCH_2O protons in 1,3-oxazolidines have been shown[3] to lie between −2.5 and −6.2 Hz, while values in hexahydro-1,3-oxazepines[4] lie in the range −11.0 to −12.8 Hz. The observed J_{gem} of −11.0 Hz is therefore consistent with structure (7) rather than (10). The NCH_2N protons absorb as a singlet equivalent to two protons at δ 4.65. The angular CHN protons are represented by a doublet equivalent to two protons at δ 4.69 (J 9.4 Hz) and the angular CHO protons by a multiplet at δ 4.39. Analysis of these angular proton signals gives $J_{NCH,OCH}$ of 9.8 Hz confirming the *trans* ring fusion. The methylene protons in the five-membered ring give rise to two multiplets centred at δ 3.13 and 3.00. The simplicity of this spectrum is indicative of C_2 symmetry with each proton in one half of the molecule in an identical environment to its counterpart in the other half. Thus the spectral evidence leads to the assignment of structure 5,*r*-5a,*t*-8a,13,*c*-13a,*t*-16a-hexahydro-8,16-methanodi-indeno[1,2-*d*:1′,2′-*i*][1,6,3,8]dioxadiazecine (13) to the product of the reaction between *trans*-1-aminoindan-2-ol and formaldehyde.

(ii) *Reaction between* trans-1-*Amino-1,2,3,4-tetrahydronaphthalen-2-ol and Formaldehyde.*—The reaction between *trans*-1-amino-1,2,3,4-tetrahydronaphthalen-2-ol and excess of aqueous formaldehyde gave a crystalline product, m.p. 186 °C with the molecular formula $C_{23}H_{26}N_2O_2$ (M^+ 362). Thus, ignoring stereochemistry at the ring junctions, a dimer of the type (8) or (11) was indicated.

The ^1H n.m.r. spectrum of the reaction product (the Figure shows the spectrum recorded in C_6D_5N) was much more complicated than that of (13) and selective decoupling experi-

ments were necessary in order to analyse the spectrum (CDCl$_3$ solution).

Irradiation of the doublets at δ 5.1 and 4.4 caused the peaks centred at δ 4.6 and 4.1 to collapse to singlets, thus locating the position of two NCH_2O AB quartets (J_{gem} −11.1 and −11.4 Hz respectively). The magnitudes of these J_{gem} values indicate structure (8) rather than (11). A third AB quartet (δ 4.4, 4.1, J_{gem} −14.7 Hz) was assigned to the NCH_2N protons in (8).
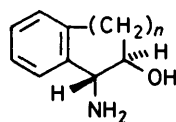
Irradiation of the doublet centred at δ 4.3 caused the triplet of doublets centred at δ 3.7 to collapse to a doublet of doublets. Thus the δ 4.3 doublet may be assigned to the angular CHN proton (9a-H) and the triplet of doublets at δ 3.7 to the angular CHO proton (6a-H). Similarly the doublet at δ 4.4 and the (masked) triplet of doublets at δ 4.6 may be assigned to the remaining angular CHN (18a-H) and CHO (15a-H) protons, respectively. The value of the vicinal coupling constant involving both the CHN protons was found to be 10.2 Hz. Analysis of the signals arising from the angular CHO protons gave J_{vic} 10.2, 10.2, and 4.9 Hz for 6a-H and J_{vic} 10.2, 10.2, and 4.4 Hz for 15a-H. The large coupling values support the *trans* arrangement of the bridgehead hydrogens. The 6-H$_{ax}$ and 15-H$_{ax}$ protons absorbed as separate multiplets at δ 2.05 and 1.8 with the corresponding equatorial protons absorbing at δ 2.15. The remaining C(5) and C(14) methylene protons absorbed together at δ 3.0 (H$_{eq}$) and 2.8 (H$_{ax}$).

The appearance of two AB quartets for the NCH_2O protons, the doubling of the signals for the angular CHO and CHN protons as well as the observed AB quartet for the NCH_2N protons indicate the assignment of the 5,6,*r*-6a,*c*-9a,14,15,*t*-15a,*t*-18a-octahydro-9,18-methanodinaphtho[1,2-*d*:1′,2′-*i*]-[1,6,3,8]dioxadiazecine structure (14) to the dimer. This structure is clearly supported by the ^{13}C n.m.r. spectrum
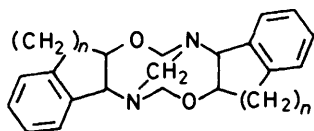
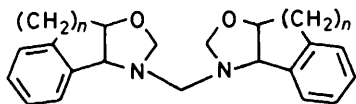**Table 1.** ^{1}H N.m.r. spectra (CDCl$_3$) of dimers (13), (14), (15), and (16)

| Compound	Chemical shift (δ)			
	NCH$_2$O	NCH$_2$N	CHO	CHN
(13)	4.92, 4.57	4.65	4.39	4.69
	(J_{gem} −11.0) *		(J 9.4, 9.8, 7.4)	
(14)	5.1, 4.6	4.4, 4.1	3.7 (6a-H)	4.3 (9a-H)
	(J_{gem} −11.4)	(J_{gem} −14.7)	(J 10.2, 10.2, 4.9)	
	4.4, 4.1		4.6 (15a-H)	4.4 (18a-H)
	(J_{gem} −11.1)		(J 10.2, 10.2, 4.4)	
(15)	4.97, 4.73	3.58	3.38	3.88
	(J_{gem} −4.9)			(J 8.8)
(16)	4.74, 4.41	3.97, 3.66	3.20	3.69
	(J_{gem} −6.3)	(J_{gem} −7.8)		(J 8.8)

* J in Hz.

(4) n = 1
(5) n = 2
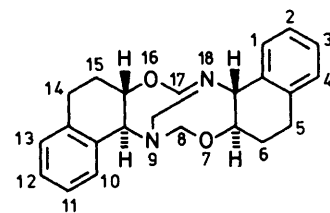(6) n = 3

(7) n = 1
(8) n = 2
(9) n = 3

(10) n = 1
(11) n = 2
(12) n = 3

Table 2. ^{13}C N.m.r. spectrum of 5,6,r-6a,c-9a,14,15,t-15a,t-18a-octa-hydro-9,18-methanodinaphtho[1,2-d:1′,2′-i][1,6,3,8]dioxadiazecine (14)

Carbon nucleus	Chemical shift (δ)	J (^{13}C–H) (Hz)
C(8), C(17)	83.0	152.5
	83.6	152.5
C(6a), C(15a)	82.4	136.0
	78.3	136.0
C(19)	69.7	145.0
C(9a), C(18a)	65.0	136.0
	64.7	136.0
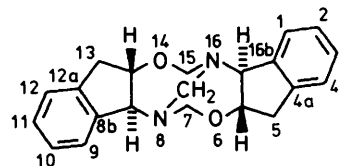
(13)

(14)

(Table 2). The ^{13}C n.m.r. proton-decoupled spectrum showed absorptions for twenty-three carbon nuclei. The four quaternary aromatic nuclei absorbed downfield of the remaining eight aromatic carbons. Of the remaining nuclei C(5), C(6), C(14), and C(15) absorbed between δ 28.5—31.4 which are typical shift values for such nuclei. The remaining signals were assigned on the basis of the known electronegativity effects on ^{13}C chemical shifts.[5] The C(9a) and C(18a) angular CHN nuclei were observed at δ 64.7 and 65.0, ca. 15 p.p.m. upfield from the angular CHO nuclei [C(6a) and C(15a)] which absorbed at δ 78.3 and 82.4. The NCH$_2$O nuclei absorbed at δ 83.0 and 83.6 with the NCH$_2$N carbon nucleus at δ 69.7.

(iii) *Reaction between* trans-1-*Amino*-6,7,8,9-*tetrahydro*-5H-*benzocyclohepten*-2-*ol and Excess of Formaldehyde.*—The condensation between *trans*-1-amino-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-ol (6) and excess of formaldehyde gave a

crystalline product, m.p. 167—170 °C with the empirical formula $C_{25}H_{30}N_2O_2$ (M^+ 390), indicating a dimeric structure (9) or (12). The 270 MHz ^{1}H n.m.r. spectrum showed some considerable differences from those obtained for the dimers (13) and (14) with doubling of most of the signals (Table 1).

The two downfield AB quartets at δ 4.97 and 4.73 (J_{gem} −4.9 Hz) and at δ 4.74 and 4.41 (J_{gem} −6.3 Hz) gave chemical shifts consistent with NCH$_2$O methylene protons. The J_{gem} values are not in agreement with a dimeric structure containing a central perhydro-3,8-methano[1,6,3,8]dioxadiazecine ring as in (13) and (14), but are consistent with NCH$_2$O protons in 1,3-oxazolidines.[3]

Absorption for two sets of NCH$_2$N protons was observed as an AB quartet at δ 3.97 and 3.66 (J_{gem} −7.8 Hz) and a singlet at δ 3.58. Two sets of doublets arising from the angular CHN protons appeared at δ 3.88 and 3.69 with J_{vic}
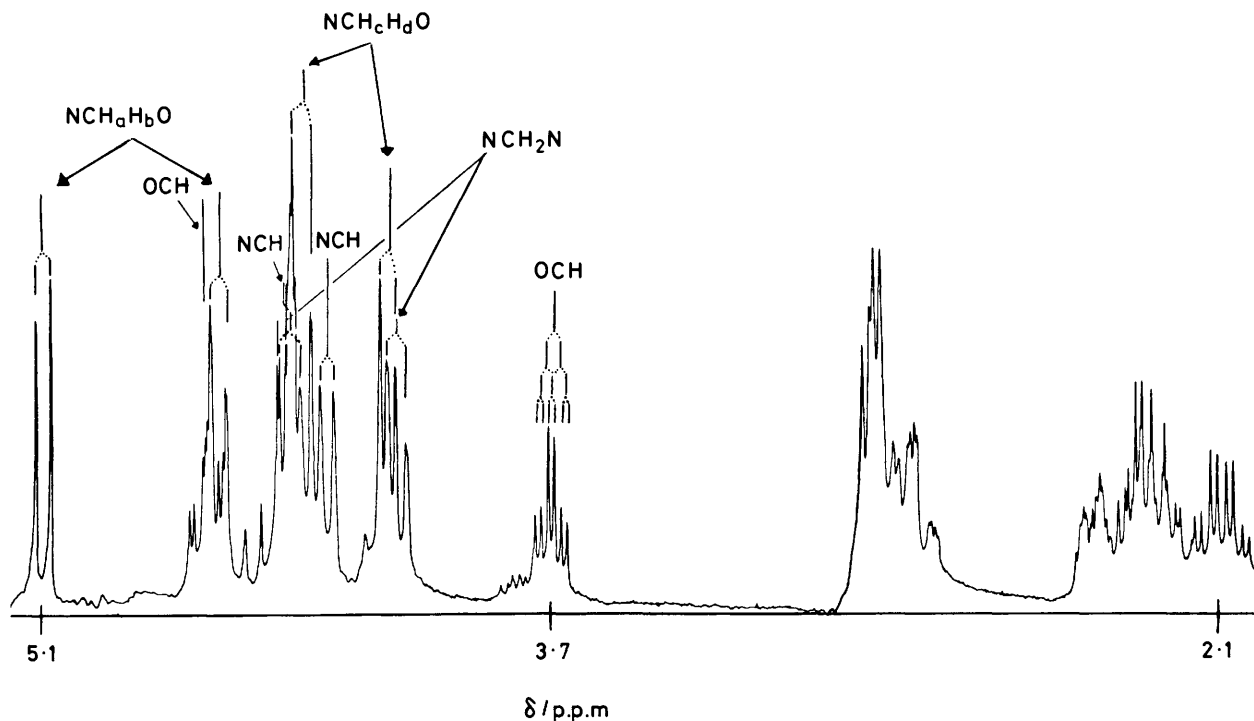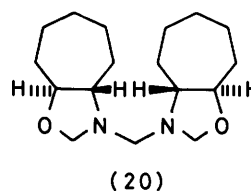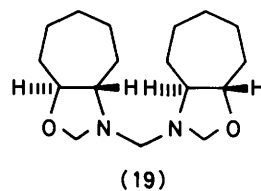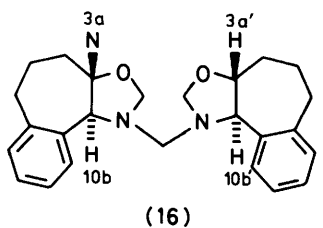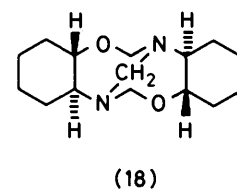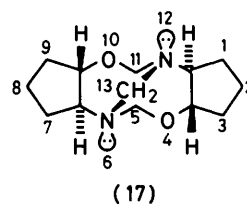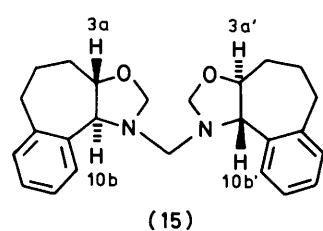
Figure. 270 MHz ^{1}H N.m.r. spectrum of 5,6,r-6a,c-9a,14,15,t-15a,t-18a-octahydro-9,18-methanodinaphtho[1,2-d:1',2'-i][1,6,3,8]-dioxadiazecine (8) in C_6D_5N (δ 5.2—2.0)

(15)

(16)

(17)

(18)

(19)

(20)

8.8 Hz. The angular CHO protons absorb as two sets of doublets of triplets at δ 3.38 and 3.20. The near *trans*-diaxial arrangement of the CHN and CHO angular protons is demonstrated by the vicinal coupling of 8.8 Hz. The observation of two separate sets of signals for each type of proton, the equal intensities of these, and the values of J_{gem} for the NCH_2O protons indicate the formation of a 50 : 50 mixture of the two isomers (15) and (16) of bis(1,3a,4,5,6,10b-hexahydro-2*H*-benzo[6,7]cyclohept[1,2-d]oxazol-1-yl)methane.

Discussion

The reaction between the *trans*-1-aminobenzocycloalkan-2-ols (4), (5), and (6) and formaldehyde gives rise to dimeric products of different structures [(13)—(16)]. The structures of these dimers may be compared to those [(17)—(20)] obtained

from the analogous *trans*-1-aminocycloalkan-2-ols (1; $n = 1, 2,$ or 3).

The formation of the dimers (13), and (15) and (16), are exactly analogous to the formation of dimers (17), and (19) and (20), from the corresponding aminocycloalkanols. The formation of the different dimers are again attributed to differences in ring fusion strain[2] and require no further comment.

In contrast, whereas *trans*-2-aminocyclohexanol (1; $n = 2$) condenses with formaldehyde to form the dimer (18) possessing C_2 symmetry, *trans*-1-amino-1,2,3,4-tetrahydronaphthalen-2-ol (5) condenses with formaldehyde to form the asymmetric dimer (14). This difference in the stereochemistry of the condensation products must reflect changes in non-bonding interactions between the two systems resulting from replacement of the cyclohexane ring in (18) by a half-chair in (14) and from the presence of interactions involving the C(1)–H and C(10)–H bonds of the aromatic rings in the

r-6a,*t*-9a,*c*-15a,*t*-18a-isomer of (14). A close examination of the Figure shows minor peaks throughout the spectrum possibly due to the presence of a small amount of this isomer.

Experimental

Elemental analyses were carried out by the Butterworth Microanalytical Consultancy, Teddington, Middlesex. The ¹H n.m.r. spectra were recorded on Varian T60, Jeol PMX-60, and Bruker WH 270 spectrometers as 10% solutions with tetramethylsilane as internal reference. The ¹³C n.m.r. spectrum was obtained from Jeol (U.K.) Ltd, Colindale, London, on a Jeol FX200 spectrometer operating at 50.184 MHz; spectral width 12 000 Hz (decoupled) and 6 000 Hz (coupled) with 6 000 data points, pulse width 9 μs. Samples were dissolved in equal volumes of CDCl₃ or C₆D₅N with SiMe₄ as an internal reference. Mass spectra were obtained at 70 eV on a MSE20 Organic Mass Spectrometer. Ether refers to diethyl ether.

trans-1-*Aminoindan*-2-*ol*.—1,2-Epoxyindan (0.38M, 50 g) was heated with aqueous ammonium hydroxide (*d* 0.88; 54.6M; 370 ml) and ethanol (75 ml) in a high pressure steel autoclave at 120—140 °C for 4 h. Solvents were removed by distillation and the product recrystallised from water to yield *trans*-1-aminoindan-2-ol (32.6 g, 57.7%), m.p. 123—124 °C (lit.,⁶ 128—129 °C) (Found: C, 72.1; H, 7.3; N, 9.6. Calc. for C₉H₁₁NO: C, 72.4; H, 7.4; N, 9.4%).

trans-1-*Amino*-1,2,3,4-*tetrahydronaphthalen*-2-*ol*.—1,2-Epoxy-1,2,3,4-tetrahydronaphthalene (0.1 mol, 14.6 g) was shaken with aqueous ammonium hydroxide (*d* 0.88; 0.3 mol; 21.5 ml) in a stainless steel autoclave for 3 h at a temperature of 120 °C. The solvent was removed by distillation and the residue distilled under reduced pressure to yield a colourless liquid which solidified rapidly on cooling. The solid was recrystallised from cyclohexane to yield *trans*-1-amino-1,2,3,4-tetrahydronaphthalen-2-ol (9 g, 55%), m.p. 115—116 °C (lit.,⁷ 116.5—117.5 °C) (Found: C, 73.3; H, 8.1; N, 8.3. Calc. for C₁₀H₁₃NO: C, 73.6; H, 8.0; N, 8.6%).

trans-1-*Amino*-6,7,8,9-*tetrahydro*-5H-*benzocyclohepten*-2-*ol*.—1,2-Epoxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (0.05M, 9 g) was heated with aqueous ammonium hydroxide (*d* 0.88; 1.12M; 100 ml) and ethanol (20 ml) at 120 °C for 2 h. The precipitated solid was removed by filtration and recrystallised from ethanol to yield *trans*-1-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-ol (4.7 g, 47.1%), m.p. 160—162 °C (lit.,⁸ 161—162 °C) (Found: C, 74.4; H, 8.4; N, 8.0. Calc. for C₁₁H₁₅NO: C, 74.5; H, 8.3; N, 7.9%).

5,5a,8a,13,13a,16a-*Hexahydro*-8,16-*methanodi-indeno*-[1,2-d:1′,2′-i][1,6,3,8]*dioxadiazecine*.—*trans*-1-Aminoindan-2-ol (0.02M; 3 g) suspended in water (10 ml) was shaken with 40% aqueous formaldehyde solution (0.06M; 4.5 ml) at room temperature for 0.5 h. The mixture was basified with 50% aqueous sodium hydroxide and extracted with ether. The combined ether extracts were dried (Na₂SO₄) and the ether removed by distillation to yield a white solid which on

recrystallisation from ethanol gave 5,*r*-5a,*t*-8a,13,*c*-13a,*t*-16a-*hexahydro*-8,16-*methanodi-indeno*[1,2-d:1′,2′-i][1,6,3,8]*dioxadiazecine* (1.1 g, 32.7%), m.p. 205—206 °C (Found: C, 75.3; H, 6.7; N, 8.2. C₂₁H₂₂N₂O₂ requires C, 75.4; H, 6.6; N, 8.4%).

5,6,6a,9a,14,15,15a,18a-*Octahydro*-9,18-*methanodinaphtho*-[1,2-d:1′,2′-i][1,6,3,8]*dioxadiazecine* (14).—*trans*-1-Amino-1,2,3,4-tetrahydronaphthalen-2-ol (0.025M; 4 g) suspended in water (12.5 ml) was shaken with 40% aqueous formaldehyde solution (0.1M; 7.5 ml) for 0.5 h at room temperature. The mixture was basified with 50% aqueous sodium hydroxide and extracted with ether. The combined ether extracts were dried (Na₂SO₄) and the ether removed by distillation to yield a white solid which on recrystallisation from ethanol gave 5,6,*r*-6a,*c*-9a,14,15,*t*-15a,*t*-18a-*octahydro*-9,18-*methanodi-naphtho*[1,2-d:1′2′-i][1,6,3,8]*dioxadiazecine* (14) (1.5 g, 16.6%), m.p. 184—185 °C (Found: C, 74.9; H, 7.0; N, 8.0. C₂₃H₂₆N₂O₂ requires C, 76.2; H, 7.2; N, 7.7%).

Bis(1,3a,4,5,6,10b-*hexahydro*-2H-*benzo*[6,7]*cyclohept*-[1,2-d]*oxazol*-1-*yl*)*methanes* (15) *and* (16).—*trans*-1-Amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-ol (0.03M; 5 g) dissolved in water (10 ml) was shaken with 40% aqueous formaldehyde solution (0.07M; 5 ml) at room temperature for 0.5 h. The mixture was basified with 50% aqueous sodium hydroxide and extracted with ether. The combined ether extracts were dried (Na₂SO₄) and the ether removed by distillation to yield a white solid which on recrystallisation from ethanol gave a 50 : 50 mixture of isomeric *bis*(1,3a,4,5,-6,10b-*hexahydro*-2H-*benzo*[6,7]*cylohept*[1,2-d]*oxazol*-1-*yl*)-*methanes* (15) and (16) (2.0 g, 36.3%), m.p. 167—170 °C (decomp.) (Found: C, 76.7; H, 7.9; N, 7.0. C₂₆H₃₀N₂O₂ requires C, 76.9; H, 7.7; N, 7.2%).

Acknowledgements

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