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SYNTHESIS OF MEDIUM-RING BICYCLIC BRIDGEHEAD DIAMINES FROM MONOCYCLIC DIAMINES VIA α-AMINOAMMONIUM IONS

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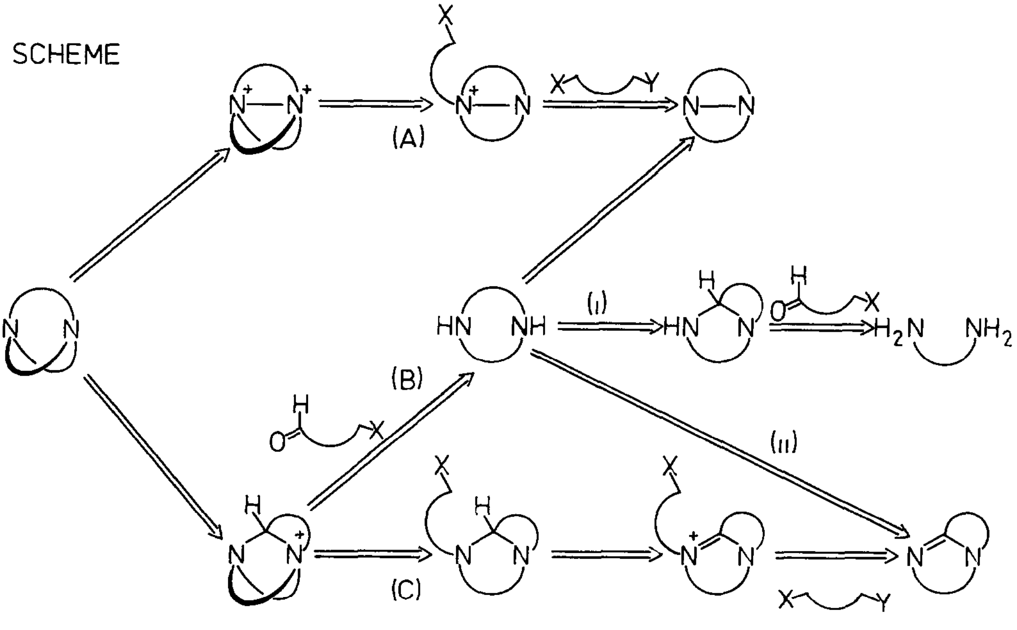
Summary Condensation of 4-chlorobutanal and 5-chloropentanal with six cyclic diamines gave twelve α-aminoammonium salts, cleavage of these with $LiAlH_4$ gave medium-ring bicyclic diamines

The Scheme below summarises the progress we have made in developing routes to bicyclic diamines with bridgehead nitrogens and built from medium rings (7-12 membered) Routes (A) and (C) have been described previously [1,2] Route (A) is limited by the ring sizes which can be created in the cyclo-alkylation of the hydrazines Route (C) is limited to the introduction of 2- and 3-carbon fragments in the alkylation/reduction/cyclo-alkylation of the amidines The third and most versatile route (B) involves the condensation of an ω-haloaldehyde with a monocyclic diamine as the key step



We find that mixing the six medium-ring monocyclic diamines (**1**) - (**6**) shown in the Table with 4-chlorobutanal (**7**) and 5-chloropentanal (**8**) in CH_2Cl_2 solution containing suspended $MgSO_4$ produces the six 2-aminopyrollidinium and six 2-aminopiperidinium salts listed in good yields *

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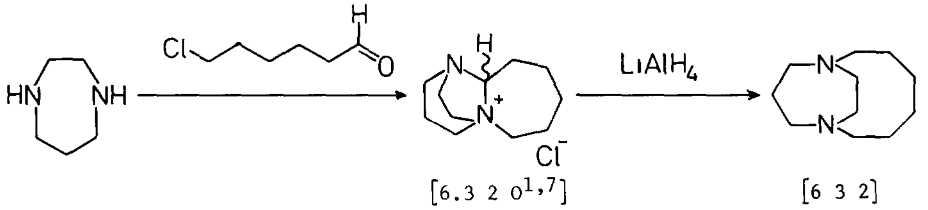
*All new compounds gave satisfactory analytical and spectroscopic data

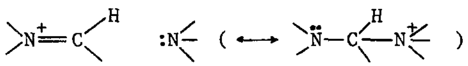
These α-aminoammonium salts are efficiently cleaved to bicyclic diamines by stirring with $LiAlH_4$ in 1,2-dimethoxyethane (room temperature, 24h)[2] Eight of the amines are new compounds* and, with one exception,[3] represent the first example of the ring system. The new preparations of the known [4 3.2] , [4 3 3] and [4.4.3]diamines[1,2] are substantial improvements on earlier methods The full scope of this route remains to be explored especially with regard to the ring size of the monocyclic diamine and the chain length of the ω-haloaldehyde Piperazine fails to form tricyclic α-aminoammonium salts containing a bicyclo[2 2.1] subunit with either 4-chlorobutanal or 5-chloropentanal However reaction of 1,4-diazacycloheptane (**1**) with 6-chlorohexanal does produce 8-aza-1-azoniatricyclo[6 3.2 $0^{1,7}$]tridecane chloride (35% yield, chemical shifts for CH (D_2O) $\delta^{13}C$ 97.0, $\delta^{1}H$ 4.8) which can be reduced to 1,8-diazabicyclo[6 3 2]tridecane in 65% yield, equation (1).



(1)

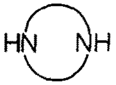
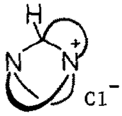
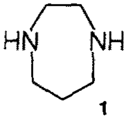
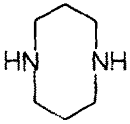
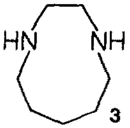
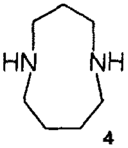
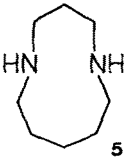
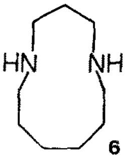
Tricyclic salt formation proceeds via a bicyclic aminal (nmr monitoring indicates that this is formed rapidly in the cases studied here), followed by a slower cycloalkylation step In all cases studied so far aminal formation creates at least one 5- or 6-membered ring, we anticipate difficulties when both the new rings created during aminal formation lie in the medium-ring range.

The tricyclic α-aminoammonium salts derived from unsymmetrical diamines (i e all those in the Table except (**2**)) may exist as two diastereomers differing in the stereochemistry at the methine carbon In practice diamines (**1**), (**3**) and (**6**) produce a single isomer within the limits of ^{13}C detection, while (**4**) and (**5**) give mixtures Assignment of stereochemistry is no simple matter, but we presume that the tricycles formed from 4-chlorobutanal (**7**) and diamines (**1**) and (**3**) contain a <u>cis</u>-, rather than <u>trans</u>-fused [3 3 0] subunit, this would be in accord with the stereochemistry of the product from (**1**) and acetaldehyde[4] As can be seen (Table), the chemical shifts of the methine group in these tricyclic salts varies widely $\delta^{13}C$ 70-105 ppm, $\delta^{1}H$ 4-6 ppm. The chemical shifts of both nuclei will be sensitive to the degree of immonium ion character



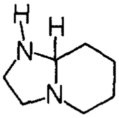
in the salt; there is X-ray evidence for delocalisation in a related α-aminoammonium salt derived from a natural product[5] The degree of delocalisation is likely to depend critically on the lone pair/$C—N^+$ dihedral angle about the N—CH bond The lone pair/CH dihedral angle about the same bond may also have a direct effect on the proton chemical shift[6] We intend to study the spectroscopic and chemical properties of these salts more thoroughly

TABLE

1,x-Diazacycloalkane			y-Aza-1-azoniatricyclo[ ]-alkane chloride	>CH $\delta^{13}C$	>CH $\delta^{1}H$		1,k+2-Diazabicyclo[k.1 m]alkane	$\delta^{13}C$
			 Cl⁻					
 **1**	7	86%	$[4.3.2.0^{1,5}]$	97.6	5.04	78%	[4.3.2]	30.0, 33.3, 53.6, 54.1, 54.8
	8	74%	$[5.3.2.0^{1,6}]$	91.2	5.26	70%	[5.3.2]	25.6, 32.5, 33.4, 54.4, 55.4, 58.2
 **2**	7	74%	$[4.3.3.0^{1,5}]$	85.0	5.13	62%	[4.3.3]	30.0, 30.3, 52.0, 54.5
	8	82%	$[5.3.3.0^{1,6}]$	82.9	4.83	73%	[5.3.3]	25.2, 30.4†, 52.0, 57.0
 **3**	7	89%	$[5.4.2.0^{1,8}]$	100.0	5.86	65%	[5.4.2]	28.0†, 30.3, 51.1, 56.1, 57.2
	8	85%	$[5.5.2.0^{1,6}]$	84.4	4.62	71%	[5.5.2]	23.3, 29.1, 51.3, 55.7
 **4**	7	82%	$[4.4.3.0^{1,5}]$	94.9 87.0	5.16 4.65	72%	[4.4.3]	30.5, 32.8, 55.6, 59.6
	8	92%	$[5.4.3.0^{1,6}]$	90.3 81.6	5.0 4.8	80%	[5.4.3]	25.1, 29.9, 31.0, 31.8, 55.2, 58.5, 58.6
 **5**	7	73%	$[5.4.3.0^{1,8}]$	90.7 80.6	5.14 4.97	60%		
	8	65%	$[5.5.3.0^{1,6}]$	88.2 74.9	5.03 4.36	67%	[5.5.3]	23.4, 29.4, 29.6, 53.7, 57.2
 **6**	7	94%	$[6.4.3.0^{1,9}]$	80.4	5.18	70%	[6.4.3]	25.4, 26.7, 30.5, 31.2, 55.2, 59.6, 60.0
	8	88%	$[6.5.3.0^{1,9}]$	72.8	≤4.05	70%	[6.5.3]	23.2, 25.1, 26.0, 27.7, 28.2, 54.4, 55.5, 56.4

†Double intensity, presumed coincidence

The medium-ring monocyclic diamines (**2**) - (**6**) required for these syntheses were prepared in a number of ways, but all the routes involved cleavage of a bicyclic precursor Diamine (**2**) came from hydrogenolysis of 1,5-diazabicyclo[3.3.0]octane [7] The discovery by Yamamoto and Maruoka[8] that aminals and amidines are regioselectively cleaved by di-isobutylaluminium hydride as in (i) or (ii) in the Scheme, has proved very useful Thus (**4**) and (**6**) derive from the commercially-available amidines DBN and DBU respectively. Diamines (**3**) and (**5**) were made by di-isobutylaluminium hydride cleavage of aminals (**9**) and (**10**). These aminals were made by simple condensation/cycloalkylation from 5-chloropentanal (**8**) and 1,2-diaminoethane and 1,3-diaminopropane respectively. The reaction of (**8**) and 1,2-diaminoethane in CH_2Cl_2 solution containing excess powdered K_2CO_3 gave (**9**) in 41% yield. Reaction of (**8**) with 1,3-diaminopropane in CH_2Cl_2 containing $MgSO_4$ gave (**10**) as the hydrochloride in 86% yield, attempts to isolate (**9**) as the hydrochloride were unsuccessful.



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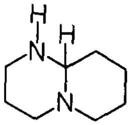

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Our syntheses of the bicyclic diamines [5 4.2], [5.5 2], [5 4 3] and [5 5 3] are particularly economical and flexible in that the bicyclic structure is constructed in only four steps with each bridge derived from a simple acyclic precursor

We have now prepared 16 of the 27 conceivable bicyclic ring systems built entirely from medium (7- to 12-membered) rings in the form of bridgehead diamines The routes shown in the Scheme should allow the preparation of many of the remainder We are actively studying the redox and proton encapsulation chemistry of these molecules [1,2,9]

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References

1 (a) R W. Alder, R.B Sessions, J M Mellor, M F.Rawlins, J C S Chem Comm 747 (1977),
(b) R W Alder,R.B Sessions, J Amer Chem.Soc. 101, 3651 (1979),
(c) R.W Alder, R B Sessions, A.J Bennet, R.E Moss, J C S Perkin I, 603 (1982)

2 R.W.Alder, R B Sessions, Tetrahedron Letters, 23, 1121 (1982)

3 L A Paquette, J.M Photis, R P.Micheli, J.Amer.Chem Soc 99, 7899 (1977)

4 S.F Nelson, P J. Hintz, R T Landis, II, J Amer.Chem Soc. 94, 7105 (1972).

5 G.I Birnbanm, K.K Cheung, M Wiewiorowski,M.D Bratek-Wiewiorowska, J.Chem Soc (B), 1368 (1967)

6. T J Atkins, J.Amer Chem Soc., 102, 6364 (1980), J M.Erhardt, E R Glover, J.D Wuest, ibid, 102, 6365 (1980), G.R.Weisman, V Johnson, R.E Fiala, Tetrahedron Letters, 3635 (1980)

7 H. Stetter, K Findeisen, Chem. Ber , 98, 3228 (1965)

8 H Yamamoto, K Maruoka, J.Amer Chem Soc , 103 , 4186 (1981)

9. R W Alder, A Casson, R.B.Sessions, J Amer.Chem Soc 101, 3652 (1979); R.W Alder, R J Arrowsmith, A.Casson, R B.Sessions, E Heilbronner, B Kovač, H Huber, M.Taagepera, J Amer Chem.Soc. 103, 6137 (1981), S F. Nelsen, R.W Alder, R.B.Sessions, K -D Asmus, K.O. Hiller, M.Gobl, J Amer Chem Soc 102, 1429 (1980).

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