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TETRACYCLIC TETRAAMINES BY GLYOXAL-MACROCYCLIC TETRAAMINE CONDENSATION

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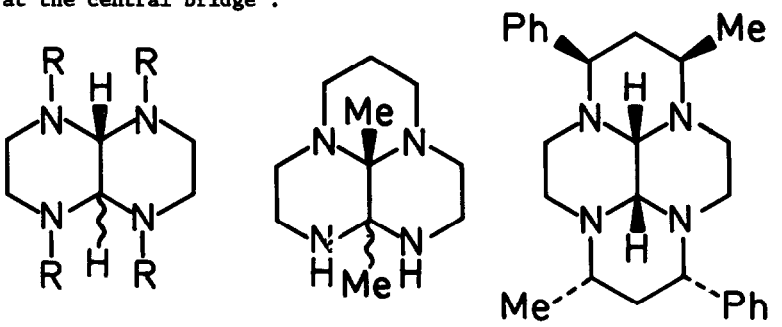
A series of new tetracyclic tetraamines have been synthesized in good to moderate yield by glyoxal-macrocyclic tetraamine condensation.

Isolated reports of bicyclic (1a)[1,2] and tricyclic (2)[3] tetraaminoethanes have appeared in the chemical literature over the past few decades. Recently, Katritzky and coworkers have carried out a detailed conformational investigation of the cis:trans (2:3) mixture 1b, which was prepared in 53% yield by condensation of glyoxal with N,N'-dimethyl ethylenediamine[4]. The first report of a tetracyclic derivative appeared in 1977. Turner and coworkers isolated 3 in 75% yield upon reaction of glyoxal with a substituted 1,4,8,11-tetraazacyclotetradecane ("cyclam"). X-ray crystallographic study demonstrated that 3 had the indicated cis-fused stereochemistry at the central bridge[5].

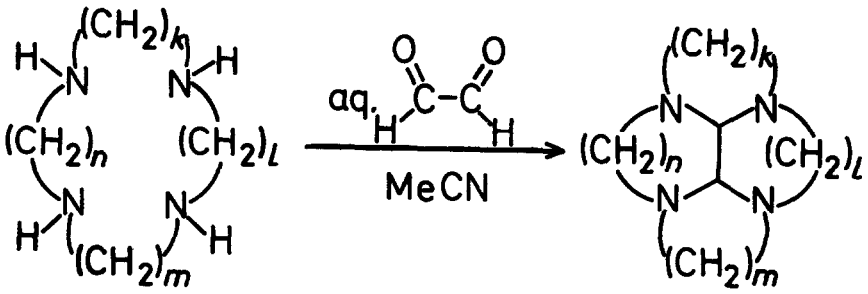


1 a: R=H
b: R=Me

2

3

As part of a general program of research into the stereochemistry, conformations, and reactivity of polycyclic polyamines, we have investigated the condensation of aldehydes with macrocyclic polyamines. We now wish to report that a wide variety of tetracyclic tetraamines may be prepared in moderate to high yield by glyoxal-macrocyclic tetraamine condensation. Our results for reactions of a homologous series of macrocyclic tetraamines, 4, are summarized in Fig. 1.



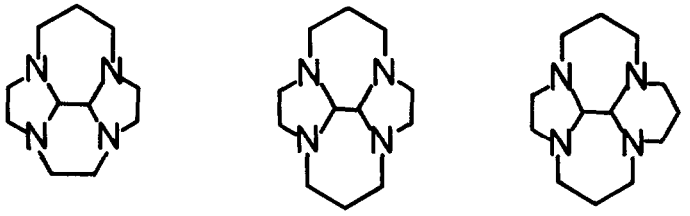
4 5

Reaction	Starting Material	k	l	m	n	Products (% yield)
a	4a	2	2	2	2	5a (91)
b	4b	3	2	2	2	cis-5b (74) + 6 (18)
c	4c	3	3	2	2	5c (94)
d	4d	3	2	3	2	cis-5d (75)
e	4e	3	3	3	2	5e-isomer A (46) 5e-isomer B (44)
f	4f	3	3	3	3	5f (62)

Fig. 1

Typically, a mixture of 1-3 moles of 4 (prepared by the general procedures of Richman[6] and Raymond[7]) and a slight molar excess of 40% aq glyoxal in 25-50 ml MeCN was stirred at 50-65°C for 1-2 hr under nitrogen. After removal of solvent, the residue was stirred with $CHCl_3$ and filtered. The $CHCl_3$ soluble crude product(s) was further purified by alumina chromatography or sublimation. Proposed product structures are consistent with IR, mass spectral[8], ^1H and ^{13}C NMR, and analytical data[8]. NMR and melting point data are given in Table 1.

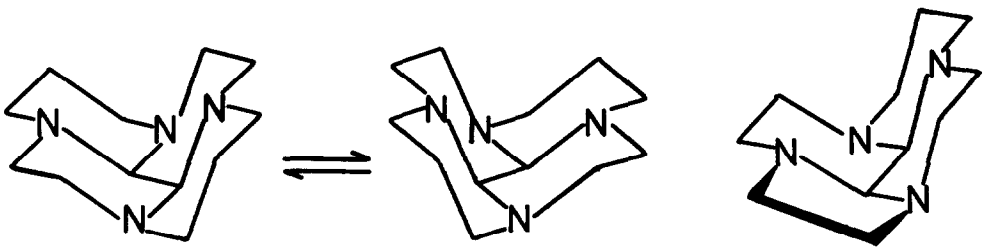
Symmetry considerations dictate that structural isomers 5a, 5c, and 5f are the only reasonable monomeric tetraamine products possible for reactions a, c, and f, respectively. For reactions b, d, and e, however, 6, 7, and 8 respectively represent possible products in addition to isomers 5. While 6 was obtained as a minor product of reaction b, no evidence for either 7 or 8 could be found.



6 7 8

Dynamic ^{13}C NMR results (Table 1) allow unambiguous assignment of cis stereochemistry to product 5d. Interconversion between enantiomeric diamond lattice configurations cis-5d and cis-5d', which must involve net inversion of all four nitrogens, is slow on the ^{13}C NMR timescale at room temperature resulting in two pairs of $-CH_2-N$ carbon resonances. At higher temperatures, each of the two pairs coalesces into a single resonance and sharpens. Application

of the coalescence temperature approximation[9] for an equally populated, two-site system yields $\Delta G^{\ddagger}$ of 15.36 ± 0.2 kcal/mole (at 57.5 ± 3°C; $\Delta\nu$ = 213 Hz) for this unusual process. Similarly, three of the four $-\underline{CH_2}-N$ carbon resonances of 5b are intermediate-exchange broadened at room temperature but sharpen at higher temperature indicating the cis stereochemistry.



cis-5d cis-5d′ cis-5b

We are unable to make reliable stereochemical assignments for other members of the series based on present data. Although we have isolated both diastereomers of 5e, assignment of isomers A and B without additional evidence is unwarranted. Inspection of molecular models provides guidance only in the case of 5a: trans product is seen to be severely strained compared to cis.

The tetracyclic structure imparts relative hydrolytic stability to bis-aminals 5[5,10]. 5d, for instance, is quantitatively recovered from aq. HCl-MeCN. Isomers A and B of 5e are equilibrated in aq. MeCN (6 hr at reflux) without formation of sideproducts.

Future work on this interesting class of compounds will include conformational analysis by low temperature ^{13}C NMR and studies toward reduction to unusual new bicyclic tetraamines.

Table 1

Product	mp (°C)	^1H NMR(δ)	^{13}C NMR(δc)($CDCl_3$) N-CH-N	$-CH_2-N$	$CH_2CH_2CH_2$
5a	90-94	2.34-3.01(m, 16H) 3.10 (s, 2H)	77.63	50.44, 51.25	-----
cis-5b	oil	1.02-1.40(m, 1H) 1.9-3.5(m, 18H) 3.35(d, 1H, J = 3Hz)	76.13 78.17	49.82(br), 50.41 50.97, 53.83	20.35
6	oil	2.36-3.44(m, 18H) 3.55 (s, 2H)	-----	-------	-----
5c	oil	1.15-3.75(m)	81.91 84.46	48.00, 50.16 52.33, 52.71 53.04, 55.58 55.80, 56.99	23.94 30.61

Table 1 (Continued)

Product	mp (°C)	^{1}H NMR(δ)	N-CH-N	^{13}C NMR(δc)(CDCl$_3$) -CH$_2$-N	CH$_2$CH$_2$CH$_2$
				amb. temp. (DMSO-d$_6$)	
cis-5d	82.5-85	0.80-1.55(m, 2H) 1.70-3.90(m, 18H) 3.04 (s, 2H)	77.11	44.80(br), 52.55(br) 54.39(br), 56.07(br)	19.66
				100°C (DMSO-d$_6$)	
				49.66(br), 54.32(br)	
5e isomer A	70-72	1.1-3.4(m) 3.03 (s, ∿ 2H)	80.78	49.57, 49.79 54.66, 55.75	20.70 22.86 (2C)
5e isomer B	oil	1.1-3.5(m) 2.94 (s, ∿ 2H)	81.97	50.65, 53.04 (2C) 53.74	23.19 (2C) 26.33
5f	99.5-101.5	0.9-3.65(m, 24H) 3.77 (s, 2H)	84.57	51.85, 55.48	20.04 22.05

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(8) All mass spectra exhibited appropriate molecular ions. Suitable C, H, and N analyses were obtained for all compounds except 5a, which was extremely hygroscopic (but not hydrolytically unstable), 6, which was hydrolytically unstable, and 5e isomer B, which equilibrated with isomer A on the laboratory timescale.

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