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Polyazamacrocycles. V. Structure of Isomeric 3,5,7,7,10,12,14,14-Octamethyl-1,4,8,11-tetraazacyclotetradecanes

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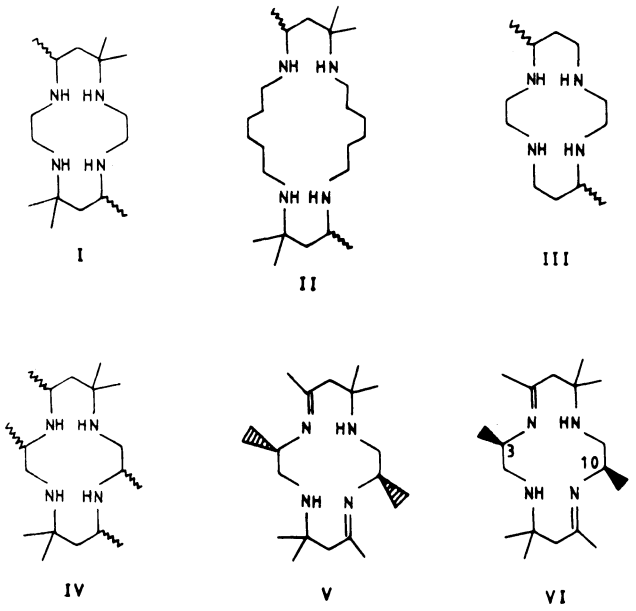
Reduction of 3,5,7,7,10,12,14,14-octamethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene (Me8[14]diene) with sodium borohydride yields three diastereomeric Me8[14]anes. These diastereomers can be separated through fractional crystallization from xylene. The structure of these isomers has been established on the bseis of their NMR spectra. The structure of one isomer has been confirmed by X-ray crystallography.

The importance of polyaza macrocycles is now well-documented and needs no elaboration. These macrocycles and their metal complexes present intriguing stereochemical problems. The stereochemistry of Me6[14]anes[1] (**I**), Me6[22]anes[2] (**II**), and Me2[14]-anes[3,4] (**III**), all of which give two isomers, the C-meso and C-rac forms, has been quite comprehensively investigated. No isomers of Me8[14]ane (**IV**) have been isolated, although this macrocycle with four chiral centers is expected to give several isomeric species. However, some reports have indeed appeared on the isomeric nickel(II) complexes of Me8[14]anes.[5] These species have been prepared by the reduction of the nickel(II) complex of 3,10-*C-rac*-Me8[14]diene (**V**). In this paper we report the isolation and characterization of three isomeric 3,10-*C-meso*-Me8[14]anes.



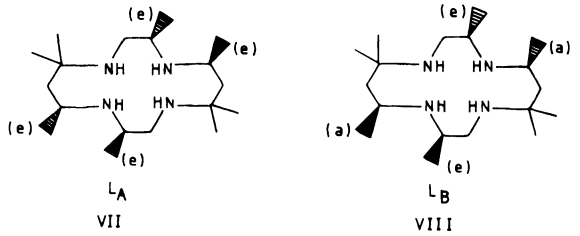
Results and Discussion

Synthesis. 1,2-Propanediamine reacts with acetone to yield Me8[14]diene, an octamethyl derivative of the 14-membered tetraaza macrocycle. The reaction is completely stereospecific and yields Me8[14]diene (**VI**) with the methyls at 3,10 positions in a meso-configuration. This assignment has been confirmed by X-ray studies.[6] The 3,10-*C-rac*-isomer (**V**) cannot be recovered from the mother liquor. The IR spectra of **VI** shows $\nu_{C=N}$ band at 1660 cm^{-1}. This C=N bond can be readily reduced with sodium borohydride to yield the corresponding saturated macrocycles. The infrared spectrum of the product shows no band around 1650 cm^{-1} assignable to $\nu_{C=N}$ and shows a ν_{NH} band at 3200 cm^{-1}. The reduction of **V**, which has a 3*S**,10*R** configuration, generates two new chiral carbons at positions 5 and 12. During the course of reduction, the 3*S**,10*R** configuration is retained. As a consequence, 3,10-*C-meso*-Me8[14]diene (**V**) would give three isomeric 3,10-*C-meso*-Me8[14]anes. These isomers, L_A, L_B, and L_C have been separated by fractional crystallization from xylene. Each isomer gave (i) a single spot on thin-layer chromatograms (TLC) using 80:20% methanol–chloroform mixture as a developing solvent, (ii) a distinct mp, and (iii) showed differences in solubilities in some common solvents like chloroform, methanol, xylene, and trifluoroacetic acid. Isomer L_A showed very low solubility in these solvents except for trifluoroacetic acid.

Structure Assignment. On the basis of the overall macrocyclic structure, some broad conclusions about the expected patterns of the ^1H NMR spectra can be made. The most prominent feature of ^1H NMR spectra of these macrocycles would be that the geminal dimethyl groups would give two singlet signals corresponding to six protons each. The chiral methyl groups should appear as doublets due to coupling with the protons attached to the adjacent carbon. The upfield doublet would be due to an equatorially oriented methyl group, while the downfield doublet would be due to an axially oriented methyl group. The various methylene protons on the macrocyclic ring would appear as multiplets due to complicated coupling patterns. On the other hand, on the basis molecular models, the chiral methyls can be assigned to be equatorial or axial. In each molecular model structure, the ring is placed in a chair form with minimum hydrogen–hydrogen interactions and two adjacent carbons in a gauche conformation. Compar-

ison of the predicted space orientations with the conclusions drawn from ^{1}H NMR spectra, permit assignment of structures to these isomers. A similar method has been successfully used in assigning the isomeric structures of the Co(III) complexes with *C-meso-* and *C-rac-*Me$_2$[14]anes.[7,8]

The 400 MHz ^{1}H NMR spectrum of isomer $\mathbf{L_A}$ (Fig. 1a) shows a sharp methyl singlet at δ 1.6 and an unresolved multiplet at δ 1.7. The singlet at δ 1.6 can be assigned to an equatorial methyl of the gem-dimethyl groups. The other methyl of the gem-dimethyl which is expected to appear at a position downfield in comparison, overlaps with doublets arising from the methyls at C_3, C_5, C_{10}, and C_{12} positions. This type of pattern is suggestive of a completely symmetrical C-meso structure in which C_3, C_5, C_{10}, and C_{12} methyls are all equatorial. This conclusion is based on the fact that a similar assignment has been made for [Ni(tet'a')](ClO$_4$)$_2$[9] (**I**); where the two chiral methyls have an equatorial orientation. It has been concluded that those isomers which show only one methyl singlet for the gem-dimethyl group and an unresolved multiplet, must be meso or racemic diastereomers with all the methyls equatorial. Since in the case of Me$_8$[14]anes, C_3 and C_{10} must have only a meso-configuration by virtue of the method of the synthetic procedure adopted,[6] occurence of a racemic diastereomers is ruled out. Therefore, isomer $\mathbf{L_A}$ is assigned a completely C-meso configuration with the ring lying in a chair form and the four chiral methyls in an equatorial position (**VII**). This requires these centers to be C_3,*S**; C_5,*S**; C_{10},*R**; C_{12},*R**. An X-ray crystal structure determination of the cobalt(III) complexes of $\mathbf{L_A}$ showed complete agreement with the above configuration of the chiral methyls. Details of this work will be published elsewhere.



L_A VII L_B VIII

Isomer $\mathbf{L_B}$ shows two singlets at δ 1.08 and 1.16 (Fig. 1b) corresponding to 6 protons each that can be assigned to the gem-dimethyl groups. The spectrum also shows two doublets at δ 0.99 and 1.03, each corresponding to 6 protons. This requires that the C_3, C_{10} and C_5, C_{12} methyl groups should be in a pairwise equivalent configuration. The upfield doublet at δ 0.99 can be assigned to equatorial methyls and downfield doublet at δ 1.03 to axial methyls. A diequatorial-diaxial arrangement is possible in the structure in which the C_5, C_{12} methyls occupy a meso-configuration (**VIII**) opposite to that in $\mathbf{L_A}$.

The structure assigned to $\mathbf{L_B}$ on the basis of its ^{1}H NMR spectra is in complete agreement with the one obtained from X-ray crystallographic studies. A perspective view of the molecule is presented in Fig. 2.

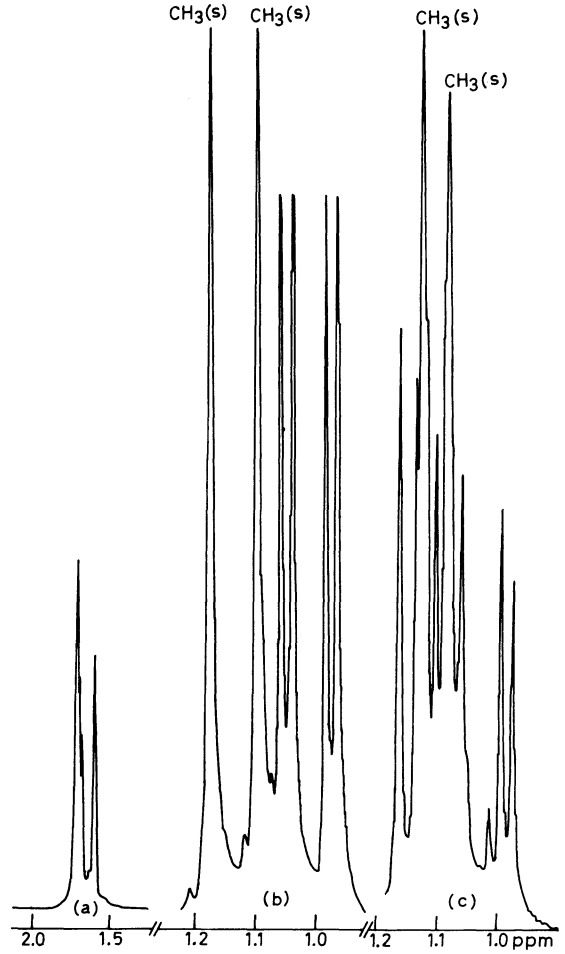


Fig 1. 400 MHz ^{1}H NMR spectrum of $\mathbf{L_A}$ (in CF_3COOH), $\mathbf{L_B}$, and $\mathbf{L_C}$ (both in $CDCl_3$).

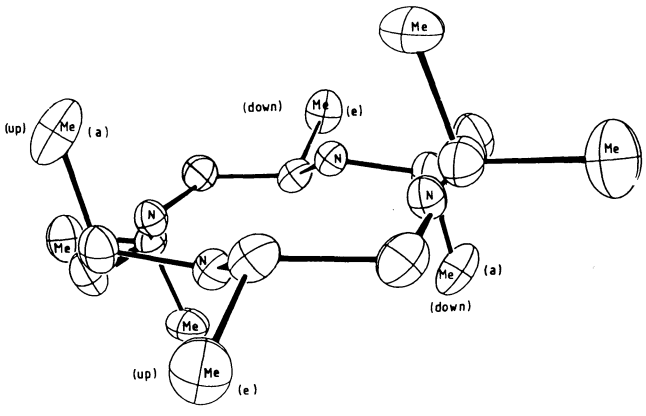
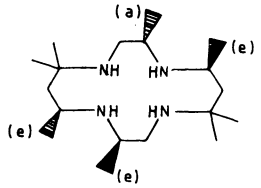


Fig 2. ORTEP perspective view of $\mathbf{L_B}$. Atoms are represented at 50% probability level. Hydrogen atoms have been omitted for clarity.

Included in the unit cell is a water molecule of solvation sitting on a crystallographic two fold center. The molecule is located at an inversion center. This determination shows that the ring lies in a chair form. The bond distances, bond angles, and torsion angles for L_B are presented in Tables 1—4.

Isomer L_C shows two singlets at δ 1.07 and 1.11 (Fig. 1c) corresponding to six protons, each assignable to gem-dimethyl groups. The spectrum also shows three doublets at δ 0.99, 1.08, and 1.14 in the ratio of 2:1:1, corresponding to 6, 3, and 3 protons each. The signal at δ 0.99 can be assigned to a pair of equivalent equatorial methyls. The δ 1.08 doublet appears due to an equatorial methyl and the δ 1.14 doublet due to an axial methyl. Such an arrangement is possible if the C_5, C_{12} methyls are in a diequatorial configuration and C_3, C_{10} methyls in an equatorial-axial configuration (IX). The chiral centers then have the forms: C_3,*S**; C_5,*S**; C_{10},*R**; C_{12},*R**. This assignment of the configuration of chiral methyl groups is confirmed by the X-ray structure determination of the Nickel(II) complex of L_C. Details of this work will also be published elsewhere.



L_C

IX

Table 1. Positional ($\times 10^4$) and Thermal ($\times 10^2$) Parameters

Atom	x	y	z	U/Å²
O	5000	4967(2)	2500	4.4(1)
N(1)	5395(2)	3746(1)	715(1)	2.53(6)
N(2)	3370(2)	4518(2)	−640(2)	2.63(7)
C(1)	4504(3)	3156(2)	88(2)	3.15(9)
C(2)	4824(3)	2824(2)	−991(3)	4.8(1)
C(3)	3308(3)	3650(2)	−68(2)	3.60(9)
C(4)	2305(2)	5111(2)	−759(2)	3.00(8)
C(5)	1185(3)	4608(2)	−1301(3)	4.8(1)
C(6)	2116(3)	5453(2)	359(3)	4.2(1)
C(7)	2524(2)	5917(2)	−1494(2)	2.96(8)
C(8)	3427(2)	6658(2)	−1040(2)	2.80(8)
C(9)	3466(3)	7393(2)	−1903(3)	4.1(1)

The equivalent isotropic thermal parameter is given by: $U=1/3\Sigma r_i^2$ were r_i are the root-mean-square amplitudes of vibration. Those parameters without an esd were not refined.

Table 2. Bond Distances (Å) of $^1{}_B$

Atom 1	Atom 2	Distance
N(1)	C(1)	1.459 (2)
N(1)	C(8)	1.462 (2)
N(2)	C(3)	1.462 (2)
N(2)	C(4)	1.477 (2)
C(1)	C(2)	1.529 (3)
C(1)	C(3)	1.527 (3)
C(4)	C(5)	1.532 (3)
C(4)	C(6)	1.530 (3)
C(4)	C(7)	1.536 (3)
C(7)	C(8)	1.538 (2)
C(8)	C(9)	1.526 (3)

Numbers in parentheses are estimated standard deviations in the least significant digits.

^{13}C NMR Spectra. ^{13}C NMR spectra gives a separate resonance for each stereochemically distinct carbon atom. Therefore, the method is a sensitive means of characterizing isomers.[10] However, a major problem encountered is that the resonances observed for the methyl carbons cannot be assigned to a particular group on the basis of ^{13}C NMR spectra alone. This is a real limitation on the method for assigning isomeric structures.[11]

The ^{13}C NMR spectra (Figs. 3—5) of the three isomers, L_A, L_B, and L_C show nine, nine and eighteen resonances respectively. The macrocycles contain

Table 3. Bond Angles (°) of L_B

Atom 1	Atom 2	Atom 3	Angle
C(1)	N(1)	C(3)	116.0 (1)
C(3)	N(2)	C(4)	116.9 (1)
N(1)	C(1)	C(2)	114.6 (2)
N(1)	C(1)	C(3)	108.6 (1)
C(2)	C(1)	C(3)	111.8 (2)
N(2)	C(3)	C(1)	111.0 (1)
N(2)	C(4)	C(5)	112.1 (1)
N(2)	C(4)	C(6)	109.4 (1)
N(2)	C(4)	C(7)	107.4 (1)
C(5)	C(4)	C(6)	109.2 (2)
C(5)	C(4)	C(7)	107.9 (2)
C(6)	C(4)	C(7)	110.7 (2)
C(4)	C(7)	C(8)	118.9 (1)
N(1)	C(8)	C(7)	110.3 (1)
N(1)	C(8)	C(9)	110.5 (2)
C(7)	C(8)	C(9)	109.2 (2)

Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 4. Torsional Angles (°) of L_B

Atom 1	Atom 2	Atom 3	Atom 4	Angle	Atom 1	Atom 2	Atom 3	Atom 4	Angle
C(4)	N(2)	C(3)	C(1)	−174.58 (0.29)	C(2)	C(1)	C(3)	N(2)	−67.86 (1.02)
C(3)	N(2)	C(4)	C(5)	−55.13 (0.41)	N(2)	C(4)	C(7)	C(8)	−71.94 (0.32)
C(3)	N(2)	C(4)	C(6)	66.28 (0.51)	C(5)	C(4)	C(7)	C(8)	167.00 (0.27)
C(3)	N(2)	C(4)	C(7)	−173.47 (0.33)	C(6)	C(4)	C(7)	C(8)	47.50 (0.59)
N(1)	C(1)	C(3)	N(2)	59.60 (0.38)	C(4)	C(7)	C(8)	C(9)	−178.57 (0.81)

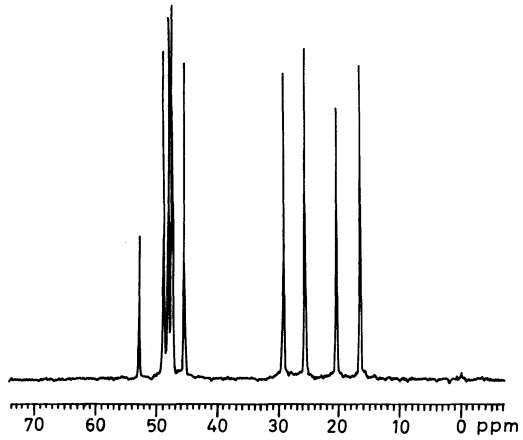


Fig 3. ^{13}C NMR spectrum of L_A (in CF_3COOH).

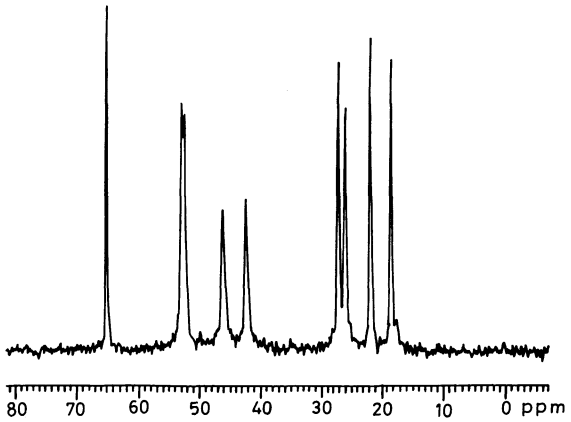


Fig 4. ^{13}C NMR spectrum of L_B (in $CDCl_3$).

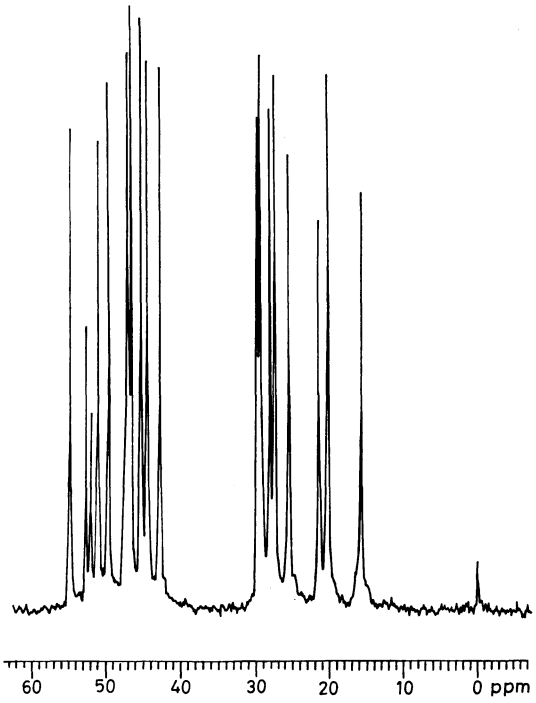
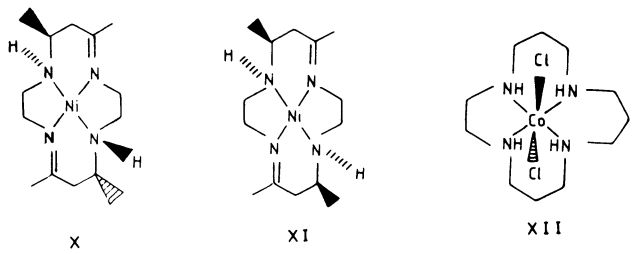


Fig 5. ^{13}C NMR spectrum of L_C (in $CDCl_3$).



X XI XII

eighteen carbons each. In case of L_A and L_B, only nine peaks are observed due to pairwise equivalence of carbon atoms. This observation is in support of the symmetric 'all equatorial' and 'diaxial-diequatorial' arrangements as has already been assigned on the basis of ^1H NMR spectra. The symmetry of structure L_B has also been confirmed by X-ray crystallography. In contrast, isomer L_C gives eighteen peaks which corresponds to eighteen nonequivalent carbon atoms indicating no symmetry in the molecule.[11-13] The results of ^1H NMR spectra also show that this isomer lacks symmetry. These conclusions are supported by similar observations with Me_4[14]dienes. Two isomeric nickel(II) complexes of Me_4[14]diene (ttcd), *Aα*-$[Ni(ttcd)]^{2+}$ (**X**) and *Bα*-$[Ni(ttcd)]^{2+}$ (**XI**) both containing fourteen carbon atoms show fourteen and seven peaks respectively.[11] Similar observations have been obtained in the case of two isomers[12] of *trans*-$[Co([15]ane)Cl_2]^+$ (**XII**). In another study, the *C-meso*- and *C-rac*-Me_6[22]ane (**II**) are also found to show twelve peaks, equivalent to half the number of total carbon atoms[2] due to the pairwise equivalence of each carbon atom.

In case of ligand L_A and L_B, the first four peaks can be assigned to the eight carbons (pairwise equivalent) of peripheral methyl groups and the next five peaks to the remaining ten carbons (pairwise equivalent) in the ring. On the other hand, the first eight peaks observed in the case of L_C correspond to the eight nonequivalent carbon atoms of peripheral methyl groups and the remaining ten resonances to ten different carbon atoms of the macrocyclic ring. The range of chemical shifts assigned for the peak positions of methyl carbons (δ 15—30) and ring carbons (δ 40—65) is the one which has already been reported for similar type of ligands and for their complexes.[11]

Experimental

Microanalysis, ^{13}C NMR, and the mass spectral measurements were carried out at the University of Stirling, Scotland. 400 MHz ^1H NMR were recorded at the Regional Sophisticated Instrumentation Centre, Central Drug Research institute, Lucknow, India. IR spectra were run on a Beckman IR 20 Spectrophotometer as KBr discs. TLC was performed on 8×2.5 cm glass plates coated with a 0.25—0.5 mm layer of silica gel (BDH, without binder).

Synthesis: 3,10-*C-meso*-Me$_8$[14]diene (**VI**) was prepared as described.[6] 10.5 g of 3,10-*C-meso*-Me$_8$[14]diene suspended in 400 cm^3 of hot 1:1 water–methanol mixture was reduced by the slow addition of 15 g of sodium borohydride with constant stirring and heated for 2 h on a steam bath. Methanol was then removed on a rotatory evaporator and the pH raised to above 12 with solid NaOH. The solution was again heated on a steam bath for about half an hour and the reduced material extracted several times with chloroform from the hot mixture. The chloroform extracts were dried over anhydrous sodium sulfate and the chloroform stripped off on a rotatory evaporator leaving behind a yellow oily liquid which on cooling gave a white solid. The product of the reduction process consists of a mixture of isomeric 3,10-*C-meso*-Me$_8$[14]anes.

50 g of the reduced material obtained above was suspended in 200 cm^3 of xylene and heated on a steam bath for about half an hour at 80—85 °C. The solution was filtered hot and the insoluble white product was washed with hot xylene. The product is Me$_8$[14]aneA (**L$_A$**); yield 9.59 g (19%), mp 350 °C (decomp) (Found: C, 69.2; H, 12.9; N, 17.9%. Calcd for $C_{18}H_{40}N_4$: C, 69.2; H, 12.9; N, 17.9%).

The filtrate from above on standing overnight at room temperature yielded needle shaped crystals of Me$_8$[14]aneB (**L$_B$**). The isomer **L$_B$** was filtered off, washed thoroughly with cold xylene and dried in vacuum. The product was recrystallized from hot ether; yield 19 g (38%), mp 122 °C; (Found: C, 65.7; H, 12.9; N, 17.1%. Calcd for $C_{18}H_{40}N_4 \cdot H_2O$: C, 65.5; H, 12.7; N, 17.0%).

The filtrate after removal of isomer **L$_A$** and isomer **L$_B$** was allowed to stand in the open for several days, when cubic shaped crystals of Me$_8$[14]aneC (**L$_C$**) were deposited. Another crop of isomer **L$_C$** could be collected on standing the mother liquor for another two days. The isomer **L$_C$** was recrystallized from hot ethers; yield 11 g, (22%), mp 85 °C; (Found: C, 69.1; H, 12.9; N, 17.9%. Calcd for $C_{18}H_{40}N_4$: C, 69.2; H, 12.9; N, 17.9%).

The purity of the isomers was checked on thin-layer chromatographic plates of 8 cm×2.5 cm coated with silica gel without any binder. The chromatograms were eluted with 80:20% methanol–chloroform mixture and exposed to iodine vapor. Each isomer gave a single spot on these plates.

The mass spectra of each isomer showed M^+ peak at m/z 312 for $C_{18}H_{40}N$. An additional (M^++1) peak at m/z 313 is observed in case of **L$_B$**.

X-Ray Crystallography.[14] Crystals of **L$_B$** for X-ray crystallography were grown by slow evaporation of its dilute solution in xylene.

Crystal Data. Me$_8$[14]aneB (**L$_B$**), $C_{18}H_{42}N_4O$, M=330.56. Monoclinic, a=11.391(3), b=14.596(4), c=12.481(4) Å, β=99.23(2)°, V=2048(1) Å^3 (by least squares refinement on diffractometer angles for 21 reflections in the range $10<2\theta<32°$), Mo $K\alpha$ radiation, λ=0.71073 Å, space group $C2/c$, Z=4, D_c=1.072 g cm^{-3}. Crystal dimensions: 0.37×0.42×0.26 mm, μ=0.63 cm^{-1}.

Data Collection and Processing. CAD4 automated diffractometer, $\omega/2\theta$ mode with scan width=0.60+0.35 tan θ, speed 10.1 to 1.6 deg min^{-1}, graphite-monochromated Mo $K\alpha$ radiation; 2552 reflections measured, 2431 unique [merging R=0.020] giving 1376 with $I>\sigma(I)$.

Structure Analysis and Refinement.[15] Direct methods program MITHRIL[16] was used. Full matrix least squares refinement on F_o minimising the function where $|F_o|$ and $|F_c|$ are the observed and calculated structure factor amplitudes respectively and the weighting factor is given by $\omega=4F_o^2/\sigma^2(F_o^2)|$. The neutral atom scattering factors were calculated from the analytical expression for the scattering factor curves.[17] The f' and f'' components of anomalous dispersion[18] were included in the calculation for all non-hydrogen atoms.

All hydrogen atoms were included at their idealized calculated positions, assuming C–H 0.95 Å and appropriate sp^2 or sp^3 geometries. The methyl hydrogens were fitted by least squares to peaks observed in a difference Fourier. These atoms were then included in the calculations with fixed, isotropic thermal parameters 1.2 times that of the attached atom and constrained to 'ride' with this atom. The largest shift in any parameter was 0.03 times its estimated standard deviation and the error in an observation of unit weight was 2.71 e.

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