THE REACTION OF BENZYLIDENEACETONE WITH ETHYLENEDIAMINE. EVIDENCE FOR THE PRODUCTION OF TWO ISOMERIC 1,4,8,11-TETRA-AZACYCLOTETRA-DECA-4,11-DIENES

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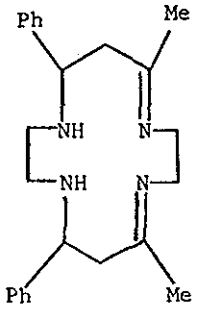
Summary. The reduction of the 1,4,8,11-tetra-azacyclo-tetradeca-4,11-diene product from benzylidene acetone and ethyl-enediamine to give two isomeric 1,4,8,11-tetra-azacyclotetra-decanes is reported. X-ray data for the condensation product of the minor isomer and glyoxal is described. The assignment of the transoid structure, (9) to the minor isomer suggests that the initial tetra-azacyclotetradeca-4,11-diene is a mixture of the diastereoisomers (2) and (3).

Reaction of benzylideneacetone with ethylenediamine under basic conditions gives rise to a 1,4,8,11-tetra-aza-cyclotetradeca-4,11-diene product, which was initially assigned the cisoid structure, (1) on the basis of its chemical properties.[1] Recent work reported by this laboratory[2] and two other groups of workers[3],[4] suggested that the alternative transoid structure, (2) was the correct assignment. Evidence is presented in this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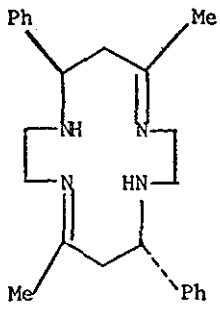
(1)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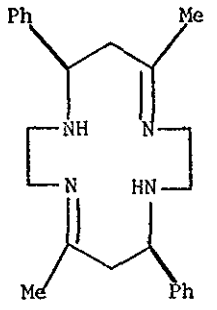
(2)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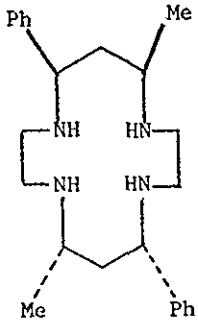
(3)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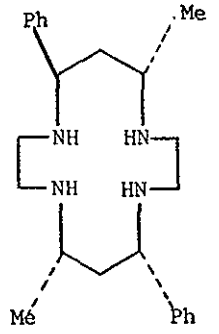
(4)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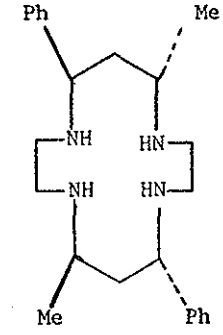
(5)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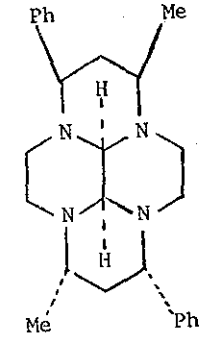
(6)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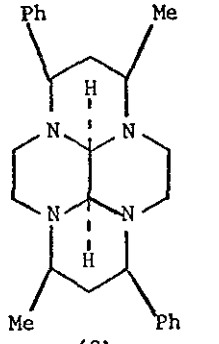
(7)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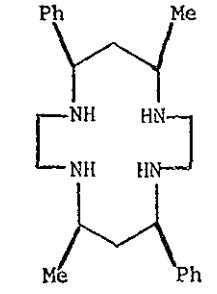
(8)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(9)

communication that the aza-cyclotetradecadiene product is in fact a mixture of the diastereoisomers (2) and (3).

Lloyd[5] found that sodium borohydride reduction of the aza-cyclotetradecadiene product provided a 1,4,8,11-tetra-azacyclotetradecane (m.p. 197° - 199°), which has been shown by X-ray studies[2], [3], [4] to possess structure, (4). In our hands the reduction gave rise to two isomeric compounds. The major product, identical to (4), was produced in 60% yield and the minor isomer (m.p. 129° - 131°) in 15% yield. The two tetra-amines showed identical N.M.R. spectra, [5] but could be readily differentiated using thin layer chromatography.† Recently Cook [3] has claimed the isolation of three isomers from the reduction of Lloyd's macrocycle and from this observation Hay[6] has suggested that the macrocycle is the pure diastereoisomer, (2) since reduction would be expected to give three isomeric tetra-amines, (4), (5) and (6). The minor isomer isolated in our reduction should, therefore, possess either structure, (5) or (6).

The two isomers obtained from the sodium borohydride reduction both reacted with glyoxal to give $C_{26}H_{34}N_4$ condensation products. We have shown by X-ray crystallographic studies [2] that the compound derived from the major isomer, (4) possessed the novel 3a, 5a, 8a, 10a - tetra-azapyrene structure (7).

The condensation product derived from the minor isomer and glyoxal was readily obtained by reaction in ethanol at 25°, m.p. 165° - 167° (recrystallised from ethyl acetate). The ^{1}H.N.M.R. spectrum (deuteriochloroform)

† Merck silica $60F_{254}$ plates developed with a mixture of toluene/ethanol/ethyl acetate/0.88 ammonia solution in the ratio 6:4:2:1.

showed the aminal protons as a sharp singlet at 3.42 δ and the methyl groups as one doublet centred at 1.05 δ. Neither of the 3a, 5a, 8a, 10a -tetra-azapyrenes, related to (7), derived from the macrocycles, (5) and (6) would be expected to give N.M.R. data like this. Accordingly an X-ray crystallographic study on the $C_{26}H_{34}N_4$ compound derived from the minor isomer was undertaken.

Crystal data: $C_{26}H_{34}N_4$, M = 402.6, a = 12.56(1), b = 10.90(1), c = 16.80 A° orthorhombic, $Pbc2_1$; U = 2300(1) $A^{\circ 3}$, D_c = 1.162g cm^{-3} for Z = 4, MoK_α radiation (Nb filter).

Cell dimension and three-dimensional intensity ($2\theta < 50°$) were measured on a Picker automatic diffractometer. Although systematic absences were compatible with either Pbcm or $Pbc2_1$, the second, non-centrosymmetric, space group was chosen because behaviour suggestive of piezoelectricity had been observed under the microscope. The structure was solved by direct methods (MULTAN) and refined with isotropic temperature factors to R = 0.104 for 1654 reflections. All the peaks on an electron density difference map were less than 0.7e, and they were mostly in plausible positions for hydrogen atoms. All bonds in the tetracyclic group were close to the expected values, C-C 1.54A° and C-N 1.47A°, for C-C and C-N single bonds, and the bond angles were close to tetrahedral values. A three-dimensional view of the molecule is shown in the Figure.

Both glyoxal condensation products thus possessed the same 3a, 5a, 8a, 10a-tetra-azapyrene ring system. The rings are all chair-shaped, though not

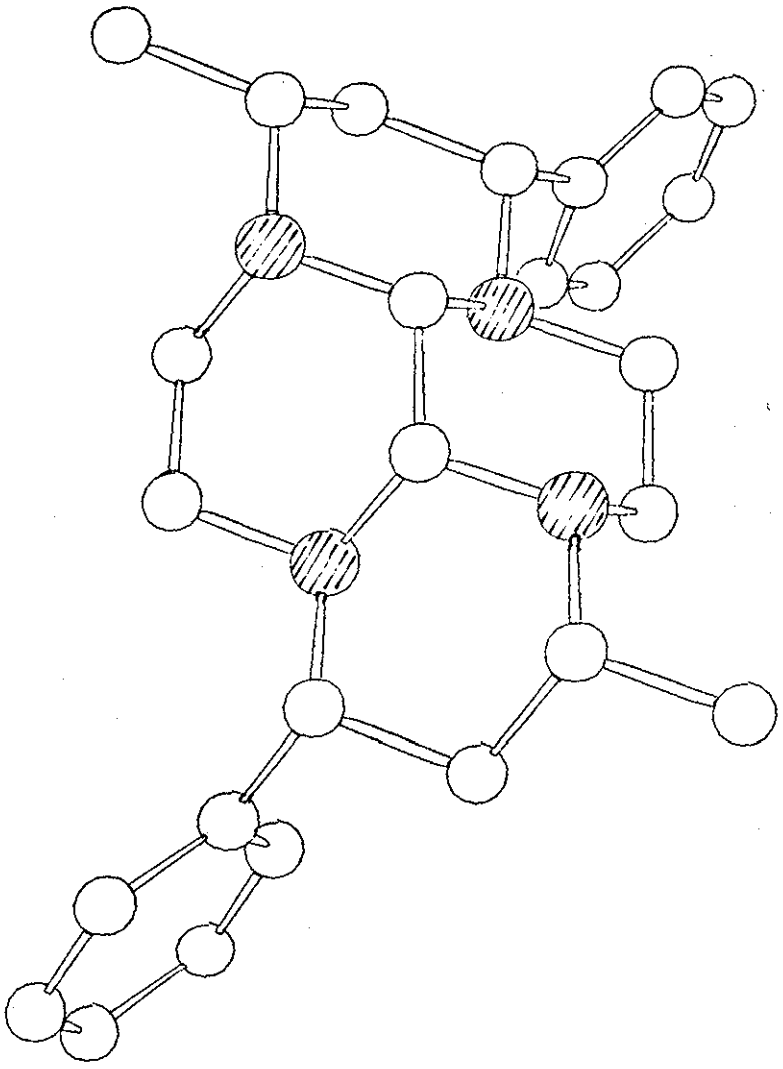

FIGURE. Molecule of the Glyoxal product $C_{26}H_{34}N_4$

all in the same orientation and the aminal hydrogen atoms are in a cis-relationship. In contrast to (7), the minor isomer/glyoxal product, (8) has all four ring substituents in equatorial positions. This X-ray data also implied that the minor isomer obtained from the sodium borohydride reduction had the structure (9) unless an unprecedented rearrangement occurred during the reaction with glyoxal.

The formation of the isomer, (9) by reduction of the tetra-azacyclotetradecadiene (2) is impossible. The initial benzylidene acetone/ethylenediamine product obtained by Lloyd must be a mixture of the isomers, (2) and (3). This was confirmed by a ^{13}C.N.M.R. study on it. The spectrum (deuteriochloroform solution) displayed a duplication of signals, showing a minor and major signal for the imine carbon atom at 169.2 and 168.0 δ_{TMS}, for the benzylic carbon atom at 60.1 and 59.2 δ_{TMS} and for the methyl carbon atom at 18.7 and 18.4 δ_{TMS}. All the attempts to separate the mixture of isomers, (2) and (3) by thin layer chromatography failed.

References

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