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TRANS-1,4,5,8-TETRACARBOETHOXY- AND 1,4,5,8-TETRAMETHYL-1,4,5,8-TETRAAZADECALIN (TAD)[1,2]

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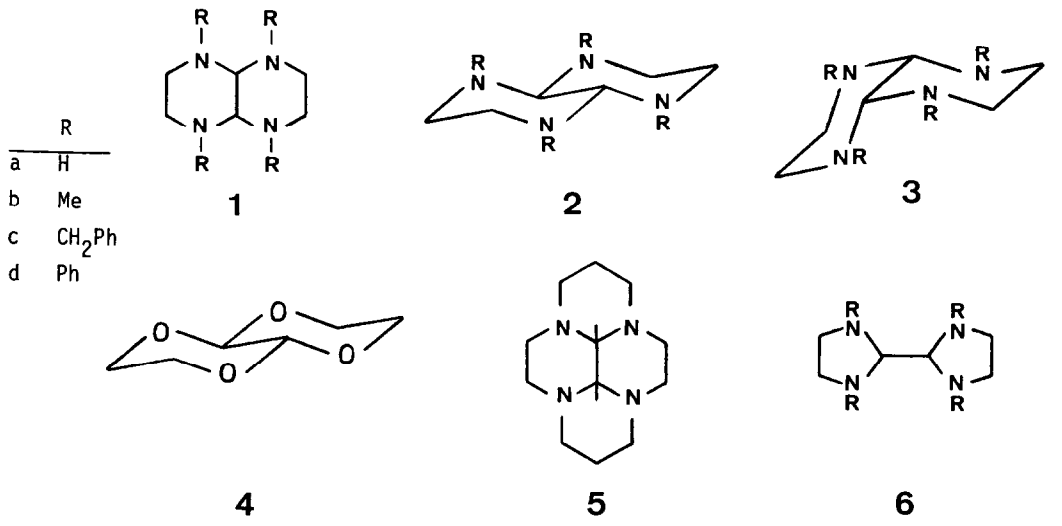
Abstract - Chemical correlation between the title compounds (7 and 8) was performed. X-ray crystallographic analysis of the novel tetraurethane (7) proved the trans configuration of (7) and indirectly that of tetramethyl TAD (8). The latter's chemical and conformational behavior is examined and discussed.

The 1,4,5,8-tetraazadecalin (TAD) system 1 has recently become the subject of sustained interest as such[1,4] or when incorporated into tri- or tetracyclic frameworks[1,5-8].

The Tel-Aviv group has reported[1] the preparation of various TAD derivatives (1) and elaborated on their stereochemistry, emphasizing that they (including the mother molecule (1a)) occur mainly as trans diastereomers (2). The rationalization of this behavior was that N-inversion enables the system to obviate the destabilizing double anomeric effect, which makes the 1,4,5,8-tetraoxadecalin analog (4) completely elusive[3]. Certain tetra-N-substituted derivatives (1c) and bridged compounds[1,5-8] e.g. (5)[6-8], were found, however, to occur as cis structures (3) or sometimes even as the isomeric biimidazolidin-2-yl structures (6c,d)[1].

The Norwich group had carried out[4] the reaction of glyoxal with N,N'-dimethyl ethylenediamine and examined by nmr the reaction product, considered to be a mixture of trans- (2b) and cis-1,4,5,8-tetramethyl-1,4,5,8-tetraazadecalin (3b). The stereochemical assignment was made on the strength of the mixture's variable-temperature ^{1}H- and ^{13}C-nmr (methyl signals) behavior: free energies for inversion of $\Delta G^{\ddagger}$ 9.1 and 11.6 kcal/mol were derived and suggested to represent, respectively, nitrogen and ring inversion. The Tel-Aviv findings (vide supra), however, along with the known (high) conformational free-energy differences for N-Me (e.g., in N,N'-dimethylpiperazine ΔG^{o}_{eq-ax}=2.96[9]) were taken[1] to cast some doubt on the above assignment.

The main worry of the Tel-Aviv authors was the thought that a trans double chair structure (2b) would have a prohibitively high heat-content to make it viable, since parallel equatorial



1,3 N,Me bonds must be accompanied by strongly destabilising peri interactions and lone pair--lone pair interactions (generalized anomeric effect), while any alleviation of those would demand unstable axial N-Me conformations. We present now unequivocal evidence vindicating, in fact, the original assignment[4] and providing new insight in and rationale for what we take to be rather subtle and unusual behavior.

The reaction of glyoxal with N,N'-dimethyl ethylendiamine was repeated using the published procedure[4] but the work up was fast and at a temperature between 0-20, to give one practically pure product which could also be distilled in vacuo almost in pure state (b.p. 56/0.7 torr). Its mass-spectrum shows a relative abundance ratio of $[M^+]/[M/2^+]$ = 1.3 indicating a tetra-azadecalin gross structure[1]. The ^{1}H-NMR spectrum exhibits a methyl singlet at 2.32 ppm followed by a multiplet of both methylene and methine protons. The ^{13}C-NMR spectrum exhibits three signals at 36.85 ($\underline{C}H_3$), 50.0 ($\underline{C}H_2$) and 73.4 ($\underline{C}H$) ppm. On standing at room temperature the ^{1}H-NMR spectrum changes in that a new methyl singlet develops at 2.40 ppm while in the ^{13}C NMR spectrum a new set of three signals grow gradually at 42.1 ($\underline{C}H_3$), 48.25 ($\underline{C}H_2$) and 76.7 ($\underline{C}H$) ppm. On prolonged standing, after more than one half-life-time and while the process still continues, the mixture deteriorates and spurious signals develop. Thus we could not determine whether we were dealing with a reversible isomerization leading to a stationary state or with a one way process.

Variable temperature NMR measurements in the ^{13}C-mode, scrutinising the two ^{13}C-methyl resonances[4], were repeated. The results[4] were, in fact reproduced, viz. the two above described species undergo fast inversion processes with $\Delta G^{\ddagger}$ 9.6 and 11.6 kcal/mol, respectively consistent with restricted nitrogen inversion in a trans species (2a) and with ring inversion in a cis isomer (3a),[11] but not enough to provide irrefutable proof for the above assignments.

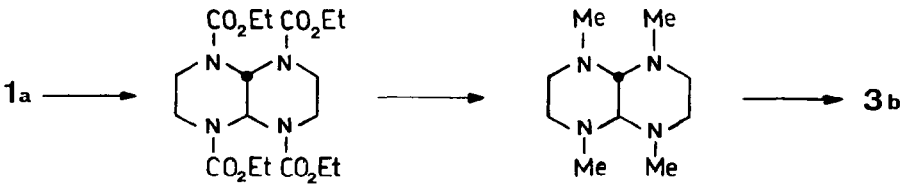
Such unequivocal proof was eventually obtained from the following train of events. The reaction of TAD (1a)[1] (0.01 mol) with ethyl chloroformate (0.045 mol) in 50 ml aq. Na_2CO_3 (0.1 mol) at 0°C gave, after suitable work-up a nearly quantitative yield of 1,4,5,8-tetra-ethoxycarbonyl -1,4,5,8-tetraazadecalin (7), m.p. 102°; m/e 430; ν_{max} 1705, 1690 cm^{-1}; δ 1.20 (t, 12H), 3.70 (m,8H), 4.04 (q,8H), 5.08 (s,2H).

This tetraurethane was subjected to an X-ray diffraction study which showed it to have a trans fused structure (cf. 7). The experimental work was performed with the aid of a CAD4 diffractometer. Thus, the crystal is monoclinic, with unit cell dimensions: a = 8.605(2)Å, b = 10.213(1)Å, c = 12.596(4)Å and β = 100.69(2)° space group $P2_1/c$ and two molecules of $C_{18}H_{30}N_4O_8$ in the unit cell. Since this space group requires the presence of four asymmetric units in the unit cell, the molecules must be located on twofold special positions and the only such positions available in $P2_1/c$ are centers of symmetry. It follows that the molecules must be centrosymmetric and this is consistent only with a trans fused arrangement (7). The above conclusion was confirmed by the determination of the structure, the refinement of which is in progress. At the present stage (overall isotropic, R = 0.19) we can affirm that the TAD skeleton occurs in the crystal as two trans fused twist boats related by a molecular center of symmetry. Further work on this crystal is in progress, and will be communicated elsewhere.

On a reduction of the tetraurethane (7) with a large excess of $LiAlH_4$ in ether at 0° followed by careful work up (without exceeding 4°C), a tetramethyl TAD derivative was obtained identical with that isolated as described above as judged by all physical measurements, particularly NMR, proving that we were dealing indeed with trans-1,4,5,8-tetramethyl-1,4,5,8-tetraazadecalin(8)

It is in our opinion noteworthy how 8 behaves, equipped as it is with a peculiar combination of static and dynamic stereochemical and electronic effects.

Nitrogen inversion and limited ring inversion may enable it to escape such destabilizing factors as peri-interactions, anomeric interactions and 1,3-diaxial interactions by assuming twist-boat conformations (in analogy to 7). Even so, it prefers to escape eventually via another, chemical path of isomerization (to 3b) available by virtue of its aminal character[1]. This subtle behavior provides additional impetus to further investigation of the interesting and versatile TAD system, now in course.



7 8

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