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STEREOSPECIFICITY OF THE REACTION OF (+)-(4*S*, 5*S*)-4-(4-NITROPHENYL)-1-AZA-3,7-DIOXABICYCLO[3.3.0]OCTANE WITH METHYL IODIDE

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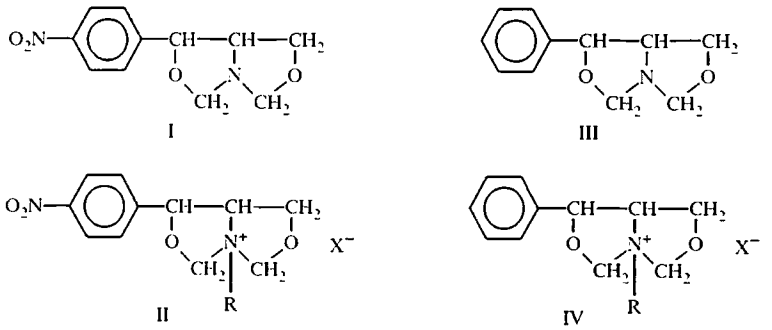
The MINDO3, MNDO, AM1, and PM3 methods have been used to optimize the geometries of (+)-(4S,5S)-4-(4-nitrophenyl)-1-aza-3,7-dioxabicyclo[3.3.0]octane and (+)-(4S,5S)-4-phenyl-1-aza-3,7-dioxabicyclo-[3.3.0]octane. It has been shown that the stereospecificity of the reaction of the former with methyl iodide is due to the high stability of one of the possible conformers.

Quaternary ammonium salts with an asymmetric nitrogen atom find application in medicinal practice and are usually used as a mixture of stereoisomers [1]. Bearing in mind that quaternary ammonium salts II obtained by us before [2] and based on (+)-(4*S*,5*S*)-4-(4-nitrophenyl)-1-aza-3,7-dioxabicyclo[3.3.0]octane (I) show a range of biological activity, we decided to determine whether this would occur in a mixture of (1*S*,4*S*,5*S*)- and (1*R*,4*S*,5*S*)-stereoisomers and allow us to study the structure of their active centers. With this in view we have examined the conformational stability of compound I and its analog (+)-(4*S*,5*S*)-4-phenyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (III) as well as their stereoisomeric cations II and IV together with carrying out the synthesis of the dioxabicyclooctane IIa and a PMR spectroscopic study of the obtained products.



I III

II IV

a R = Me; b R = $PhCH_2$; X = I

Evaluation of the stability for compound III and the corresponding quaternary ammonium salt cations IV was carried out *via* the geometric optimization of the indicated compounds using the MINDO3, MNDO, AM1, and PM3 programs within the Hyper Chem program package. All four programs could be used for compounds III and IV which did not contain a nitro group in the benzene ring whereas, for the nitro derivatives I and II, the MINDO3 and MNDO methods led to an optimization result with the nitro groups placed perpendicularly to the plane of the benzene ring (which is incorrect, in principle). Hence the AM1 and PM3 methods were used for these nitro derivatives.

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Using the MINDO3, MNDO, and AM1 methods for compound III, it was possible to observe on the screen display the transformation of the (1*S*,4*S*,5S)- stereoisomer to the (1*R*,4*S*,5*S*)- stereoisomer *via* an intermediate form corresponding to the planar configuration of the nitrogen atom. Using the PM3 method, this transition could not be achieved. A similar result was obtained by using the AM1 and PM3 methods for compound I.

The difference in energy between the (1*R*,4*S*,5*S*)- stereoisomer III and the transition form is considerable (Table 1) and can virtually guarantee the absence of the (1*S*,4*S*,5*S*)- stereoisomer in the equilibrium mixture [3]. The significant difference in energy between the (1*R*,4*S*,5*S*)- and (1*S*,4*S*,5*S*)- stereoisomers of III (Table 1) does not, in this case, have a physical sence since the energy reported for the (1*S*,4*S*,5*S*)- stereoisomer corresponds to a highly distorted conformer. At the same time, the difference in energy between the optimized (1*S*,4*S*,5*S*)- and (1*R*,4*S*,5*S*)- stereoisomers of cations IIa and IVa (Tables 1 and 2) is evidently the nearest to the difference in energy for the analogous stereoisomers of compounds I and III respectively (Tables 1 and 2), which must be close to 25 kcal/mole (the energy values reported in Tables 1 to 4 are rounded off to whole numbers).

TABLE 1. Results of the Geometric Optimization for Compound III and Cation IVa

Method	Energy of compound III, kcal/mole			Energy of cation IVa, kcal/mole	
	1*S*,4*S*,5*S*	4*S*,5*S*	1*R*,4*S*,5*S*	1*S*,4*S*,5*S*	1*R*,4*S*,5*S*
MINDO3	-2760	-2820	-2833	-2959	-2981
MINDO	-2779	-2824	-2839	-2956	-2985
AM1	-2765	-2804	-2829	-2964	-2990
PM3	-2789	—	-2837	-2971	-2998

TABLE 2. Results of the Geometric Optimization for Compound I and Cation IIa

Method	Energy of compound I, kcal/mole			Energy of cation IIa, kcal/mole	
	1*S*,4*S*,5*S*	4*S*,5*S*	1*R*,4*S*,5*S*	1*S*,4*S*,5*S*	1*R*,4*S*,5*S*
AM1	-2815	-2980	-3005	-3132	-3158
PM3	-2894	—	-3026	-3152	-3179

TABLE 3. Results of the Geometric Optimization for Cation IVb

Method	Energy of cation IVb, kcal/mole (conformation)					
	A		B		C	
	1*S*,4*S*,5*S*	1*R*,4*S*,5*S*	1*S*,4*S*,5*S*	1*R*,4*S*,5*S*	1*S*,4*S*,5*S*	1*R*,4*S*,5*S*
MINDO3	-4158	-4182	-4158	-4180	-4160	-4181
MINDO	-4158	-4189	-4158	-4182	-4161	-4189
AM1	-4169	-4199	-4169	-4197	-4174	-4199
PM3	-4177	-4208	-4177	-4206	-4182	-4208

TABLE 4. Results of the Geometric Optimization for Cation IIb

Method	Energy of cation IIb, kcal/mole (conformation)					
	A		B		C	
	1*S*,4*S*,5*S*	1*R*,4*S*,5*S*	1*S*,4*S*,5*S*	1*R*,4*S*,5*S*	1*S*,4*S*,5*S*	1*R*,4*S*,5*S*
AM1	-4338	-4368	-4338	-4369	-4343	-4368
PM3	-4359	-4389	-4358	-4390	-4363	-4389

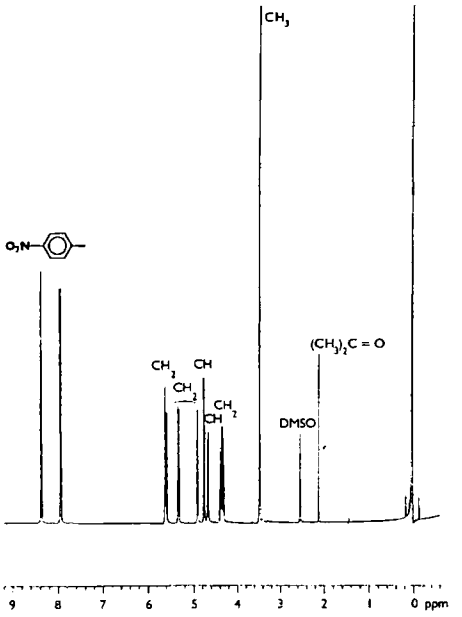

Fig. 1. PMR Spectrum of compound IIa.

For cations IIb and IVb, thanks to rotation of the benzyl substituent about the C–N bond joining it to the bicyclic system, there arises the possibility of a larger number of conformers than for cations IIa and IVa. The difference in energy between the three conformers (A, B, C) that would be formed by rotation through each of 120° (Tables 3 and 4) is close to the value observed for cations IIa and IVa and this is not unexpected since, in all of the conformations, the benzene ring of the $PhCH_2$ radical is separated from the bicyclic system and the second benzene ring.

The obtained energy value points (see [3]) to a increasing (more than 99.9%) of the (1*R*,4*S*,5*S*)-stereoisomer content for compounds I and III in the equilibrium mixture. This explains their high reactivity towards nucleophilic substitution [2] and can lead exclusively to one of the stereoisomers in their reaction with alkyl halides.

By reaction of compound I with methyl iodide we were able to synthesize the salt IIa. Work up of the PMR spectrum (Fig. 1) of the latter using the MESTREC computer program showed the signals for only one stereoisomer and this probably has the (1*R*,4*S*,5*S*)- configuration.

EXPERIMENTAL

PMR Spectra were taken on a Bruker AC-400 spectrometer for DMSO-d_6 solutions with TMS internal standard. Work up of the spectra was carried out using the MESTREC computer program.

(+)-(4*S*,5*S*)-4-(4-Nitrophenyl)-1-aza-3,7-dioxabicyclo[3.3.0]octane (I) and (+)-(4*S*,5*S*)-1-methyl-4-(4-nitrophenyl)-1-azonium-3,7-dioxabicyclo[3.3.0]octane iodide (IIa) were prepared by method [2].

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