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SYNTHESIS AND STEREOCHEMISTRY OF (1*S*,3*S*,4*S*,7*R*,11*R*)-3-(4-NITROPHENYL)-11-AZA-2,6-DIOXATRICYCLO-[5,3,1,$0^{4,11}$]UNDECANE

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The reaction of (1S,2S)-2-amino-1-(4-nitrophenyl)-1,3-propanediol with glutaraldehyde has been studied. It has been established on the basis of AM1 and PM3 calculations and ^{1}H NMR spectra recorded in the presence of the shift reagent Eu(fod)$_3$ that (1S,3S,4S,7R,11R)-3-(4-nitrophenyl)-11-aza-2,6-dioxatricyclo[5,3,1,$0^{4,11}$]undecane is formed as the result of the reaction.

Keywords: (1*S*,3*S*,4*S*,7*R*,11*R*)-3-(4-nitrophenyl)-11-aza-2,6-dioxatricyclo[5,3,1,$0^{4,11}$]undecane.

Enantiomerically pure compounds have potential as medicinals, insecticides, and materials for new technologies [1, 2]. A special place for solving problem and for the preparation of such compounds is reserved for stereoselective and stereospecific reactions.

We have shown [3] that the reaction of (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol (**1**) with paraformaldehyde occurs stereospecifically because of the considerably greater stability of one of the possible stereoisomers. The results of further investigation of the chemical properties of compound **1** [3, 4] and a study of its reaction with glutaraldehyde indicate the possibility of forming eight stereoisomeric 3-(4-nitrophenyl)-11-aza-2,6-dioxatricyclo[5,3,1,$0^{4,11}$]undecanes **2** (Table 1).

TABLE 1. Results of Optimization of the Geometry of the Stereoisomers of Compound **2**

Method	Configurations of atoms 1-C and 7-C (energy, kcal/mol*)			
	RS	*SS*	*SR*	*RR*
AM1	-3696 -3709	-3721 -3681*[2]	-3735 -3688*[2]	-3720 -3685
PM3	-3726 -3737	-3744 -3716*[2]	-3755 -3729*[2]	-3743 -3717

* In the numerator values of the energies of stereoisomers with the *R*-configuration of nitrogen are given, in the denominator, for the *S*-configuration.

*[2] Energies of structures with planar configuration of the nitrogen atom.

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On the basis of quantum-chemical calculations using the AM1 and PM3 methods, two of the stereoisomers appear to be unstable and should be transformed to the corresponding stereoisomers with the *R*-configuration of the nitrogen atom, which is observed on the screen display. These energy values correspond to the structures with a planar configuration of the nitrogen atom (Table 1). Comparison of the energy values for the stereoisomers permits to indicate the degree of strain in the structures and, as these compounds consist of the same functional groups and differ only by their configuration, corresponding to correlation of their activation energies of formation. Consequently only the three compounds with the *R*-configuration of the nitrogen atom and the greatest stability should be retained for discussion. The formation of the others, if they are produced at all, will only be in trace amounts.

In view of the fact that the signals of diastereotopic protons in the ^{1}H NMR spectra in similar structures differ considerably [3, 4] (e.g., the protons of the CH_2 group in position 5) it may be suggested that the signals of the protons in positions 1 and 7 of different stereoisomers of compound **2**, if they are formed, should be observed in different regions of the spectrum. However it seems that signals of only one stereoisomer are present in the ^{1}H NMR spectrum (Fig. 1a).

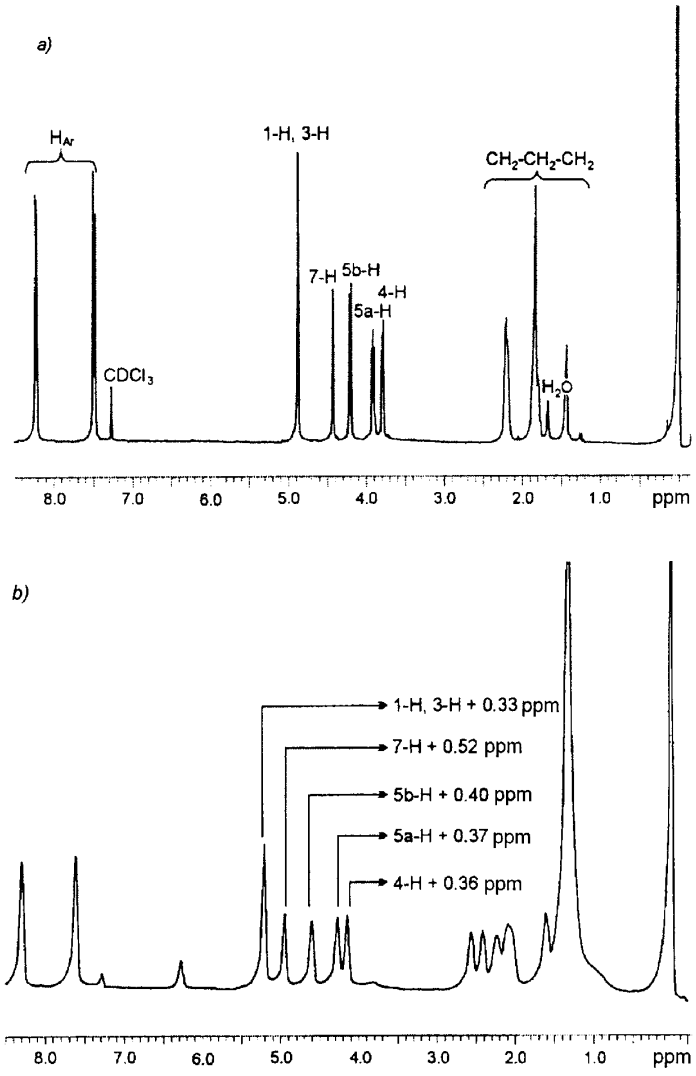
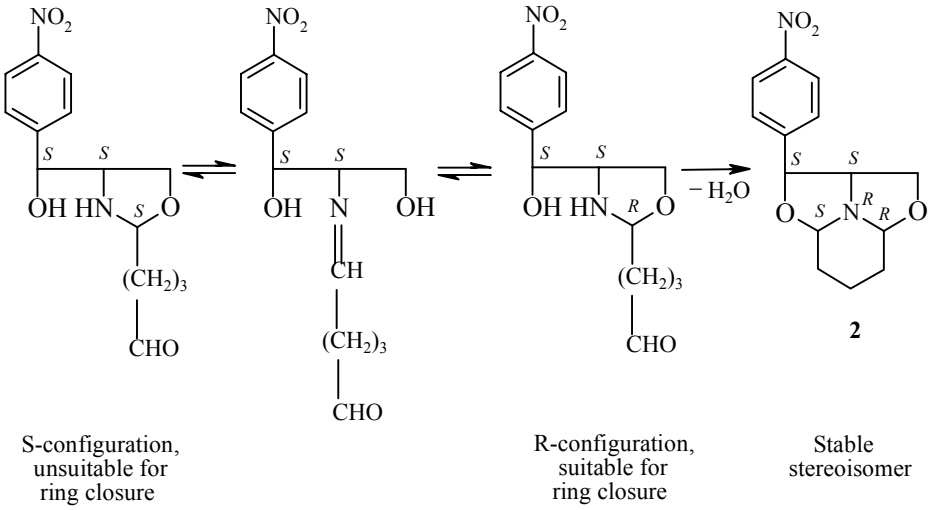


Fig. 1 . (a) ^{1}H NMR spectrum of compound **2**.
(b) ^{1}H NMR spectrum of compound **2** in the presence of $Eu(fod)_3$. [$(Eu(fod)_3)$/**2** 0.69].

To confirm that only a single stereoisomer was formed, we converted compound **2** into the quaternary ammonium salt, the iodide of (1*S*,3*S*,4*S*,7*R*,11*R*)-11-methyl-3-(4-nitrophenyl)-11-azonia-2,6-dioxatricyclo-[5,3,1,$0^{4,11}$]undecane (**3**), with an excess of methyl iodide. The corresponding quaternary ammonium salts are more distinguishable by ^{1}H NMR spectroscopy because of the simplicity, isolated position, and intensity of the methyl group signal. Moreover such approach leads to the change in position of other signals. However, the spectrum of compound **3** contains only one methyl signal and the other signals are also not doubled. So the reaction of compound **1** with glutaraldehyde leads to the formation of the single most stable stereoisomer with the stereospecific formation of three new chiral centers. The formation of this stereoisomer evidently occurs via the following mechanism:



Reaction of glutaraldehyde with the aminoalcohol **1** occurs in benzene at room temperature to give a product, soluble in benzene, and insoluble product of polycondensation, which was not studied further. Compound **2** readily reacts with methyl iodide analogously to (1*R*,3*S*,4*S*)-1-aza-3,7-dioxabicyclo[3,3,0]octane (**4**). We associate that with the rigid structure of the latter and the fixed configuration of the nitrogen atom [3], but unlike compound **4** it does not react with ethyl iodide, with difficulty with benzyl chloride and propargyl bromide and better with allyl bromide. Evidently this is explained by the difficulty of nucleophilic attack at a nitrogen atom in the center of a practically planar tricyclic structure (Fig. 2) by molecules more complex than methyl iodide. In the three latter cases (unlike ethyl iodide) the reactions obviously proceed by another mechanism, (e.g., S_N1).

To obtain direct proof of the structure of compound **2** its ^{1}H NMR spectrum was recorded in the presence of the shift reagent Eu(fod)$_3$ (Fig. 1b). A spatial model of the stable stereoisomer of **2** is shown in Fig. 2. It is known from literature data that nitrogen atom forms a more stable bond with Eu(fod)$_3$ than an oxygen atom [5].

If the Eu(fod)$_3$ molecule is coordinated to the nitrogen atom, it should be shifted under the influence of the benzene ring towards the 7-H proton, which should experience the greatest shift of its signal. Protons 1-H and 4-H are in approximately the same positions relative to Eu(fod)$_3$ and should have approximately equal shifts of their signals, which is observed in fact. The relative shift of signals is especially conclusive: while in the spectrum of **2** the difference in shifts of the protons in positions 3 and 7 is 0.45 ppm, in the presence of Eu(fod)$_3$ at a ratio Eu(fod)$_3$/**2** equal to 0.69, the difference is 0.26 ppm, i.e., it shows unambiguously that compound **2** has the *R*-configuration at atom 7-C and, since only one stereoisomer is formed, this compound at atom 1-C has the *S*-configuration, which corresponds to the more stable stereoisomer. The value of the shift of the proton signal at position 1 is in complete agreement with this choice of configuration.

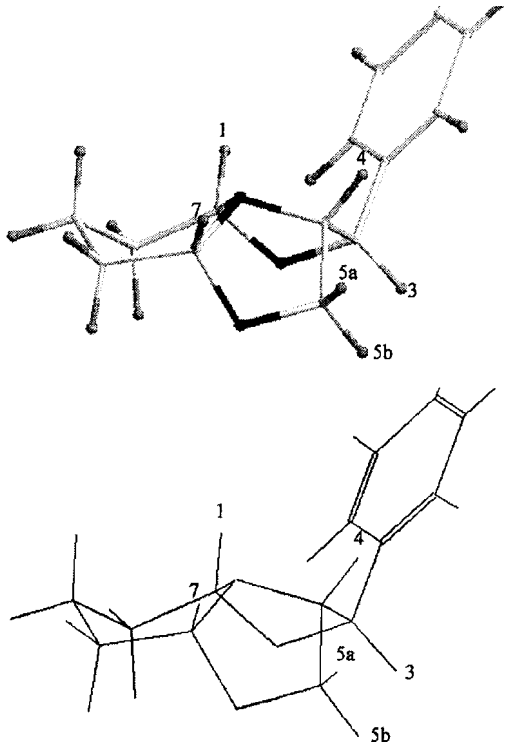


Fig. 2. Spatial model of the stable stereoisomer of compound **2**.

It must be noted that we were unable to decide upon the stereochemistry of compounds **2** and **3** by use of the NOE experiments.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AC-400 in DMSO-d_6 (compound **3**) and $CDCl_3$ (compound **2**) with TMS as internal standard. In the presence of $Eu(fod)_3$, the ^{1}H NMR spectra were recorded with molar ratios $Eu(fod)_3$/**2** equal to 0.24 and 0.69. The ^{1}H NMR spectra were worked up with the MESTREC computer program. Specific rotation values were measured with a Jasco DIP-370 polarimeter. Melting points were measured with a Kofler stage. TLC was carried out with SDS silica gel and Merck aluminum oxide. Column chromatography was carried out on a column (3 × 45 cm) of aluminum oxide (ethyl acetate–cyclohexane, 3:7).

(1*S*,3*S*,4*S*,7*R*,11*R*)-11-Aza-3-(4-nitrophenyl)-2,6-dioxatricyclo[5,3,1,$0^{4,11}$]undecane (2). Benzene (150 ml) and 25% aqueous glutaraldehyde (4.5 g, 11 mmol) were placed in a round-bottomed flask equipped with a magnetic stirrer. Compound **1** (2.1 g, 10 mmol) was added in portions over 1 h with rapid stirring. The reaction mixture was then stirred for 1 h until compound **1** had dissolved completely. The benzene fraction was separated from the water layer and insoluble residue. The benzene was evaporated to give crude product (2.1 g, 76%).

Crude **2** was purified on an aluminum oxide column (3 × 45 cm) (ethyl acetate–cyclohexane, 3:7). The fraction containing compound **2** was collected, evaporated to 20 ml and kept overnight. The precipitated crystals were filtered off and washed with a small quantity 3:7 ethyl acetate-cyclohexane, and dried; mp 136-138°C, $[\alpha]_D^{20}$ = 1.0° (*c* 0.50, ethyl acetate). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 7.47-8.23 (4H, q, *J* = 8, H_{arom});

4.87 (2H, s, 1-H and 3-H); 4.43 (1H, s, 7-H); 4.20 (1H, d, J = 9.5, 5b-H); 3.89-3.92 (1H, dd, J = 5,5, J = 9.5, 5a-H); 3.79 (1H, m, 4-H); 1.42-2.20 (6H, three m, CH_2–CH_2–CH_2). Found, %: C 60.71; H 5.67. $C_{14}H_{16}N_2O_4$. Calculated, %: C 60.86; H 5.84.

(1*S*,3*S*,4*S*,7*R*,11*R*)-11-Methyl-3-(4-Nitrophenyl)-11-azonia-2,6-dioxatricyclo[5,3,1,$0^{4,11}$]undecane Iodide (3). Crude **2** was dissolved in acetone (20 ml), methyl iodide (5.5 g, 39 mmol) was added and the mixture was kept overnight. The precipitated crystals were filtered off, washed on the filter with acetone, and dried to give **3** (2.4 g, 75%); mp 256-258°C, $[\alpha]_D^{20}$ = 23.4° (*c* 0.44, water). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, J (Hz): 7.81-8.34 (4H, q, J = 8.8, $H_{arom.}$); 5.90 (1H, s, 3-H); 5.06 (1H, s, 1-H); 5.09 (1H, s, 7-H); 4.92 (1H, d, J = 6.3, 4-H); 4.79 (1H, d, J = 9.5, 5b-H); 4.46 (1H, dd, J = 6.3, J = 9.5, 5a-H); 3.20 (3H, s, CH_3); 1.50-2.32 (6H, three m, CH_2–CH_2–CH_2). Found, %: C 42.91; H 4.67. $C_{15}H_{19}N_2O_4I$. Calculated, %: C 43.08; H 4.58.

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