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DIASTEREOSELECTIVE REACTION OF (1*S*,2*S*)-2-AMINO-1-(4-NITROPHENYL)-1,3-PROPANEDIOL WITH AROMATIC ALDEHYDES. SYNTHESIS OF (1*R*,2*R*,4*S*,5*S*,8*S*)-2,8-DIARYL-4-(4-NITROPHENYL)-1-AZA-3,7-DIOXABICYCLO[3.3.0]OCTANES

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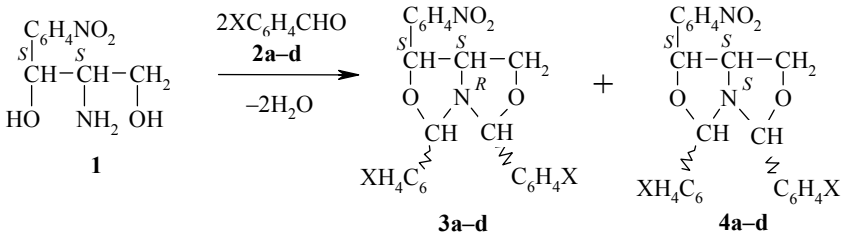
We have synthesized a series of (1R,2R,4S,5S,8S)-2,8-diaryl-4-(4-nitrophenyl)-1-aza-3,7-dioxabicyclo[3.3.0]octanes as a result of reaction of (1S,2S)-2-amino-1-(4-nitrophenyl)-1,3-propanediol with aromatic aldehydes. The structure of the compounds obtained was established on the basis of ^{1}H NMR data.

Keywords: (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol, (1*R*,2*R*,4*S*,5*S*,8*S*)-2,8-diaryl-4-(4-nitrophenyl)-1-aza-3,7-dioxabicyclo[3.3.0]octane, oxazolidine, diastereoselectivity, ^{1}H NMR.

Many cases are described in the literature of synthesis of compounds containing an oxazolidine ring that are of practical interest due to their biological activity [1]. Their spatial structure has accordingly been studied [2,3], and correlations have been made between structure and biological activity [4]. At the same time, the indicated compounds are useful synthetically and are used in asymmetric synthesis [3, 5, 6].

As the starting material for synthesis of compounds containing an oxazolidine ring, we can use (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol (**1**), a byproduct of production of the antibiotic levomycetin [7].

The aim of this work was to study the feasibility of synthesis of compounds containing an oxazolidine ring from compound **1**, according to the following scheme:



2–4 **a** X = H, **b** X = 4-Me, **c** X = 4-MeO, **d** X = 4-Cl

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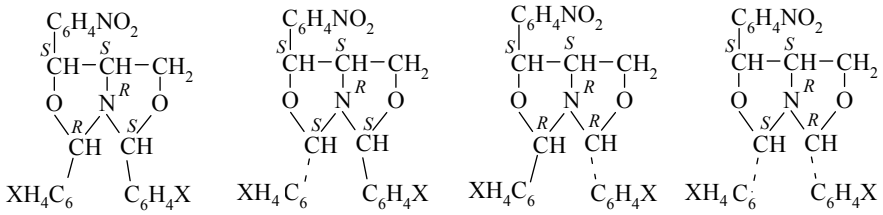
When stereoisomers **3** and **4** are formed, three new asymmetric atoms appear: a nitrogen atom and two carbon atoms. Thus eight stereoisomeric compounds **3** and **4** can possibly be formed. We represent the stereoisomers of **3** as follows:



3.1 **3.2** **3.3** **3.4**

Stereoisomers **3.1-3.4** are characterized by the same structure for the bicyclic system. In these compounds, the unshared electron pair of the nitrogen atom and the "original" benzene ring are located on the same side of the bicyclic system.

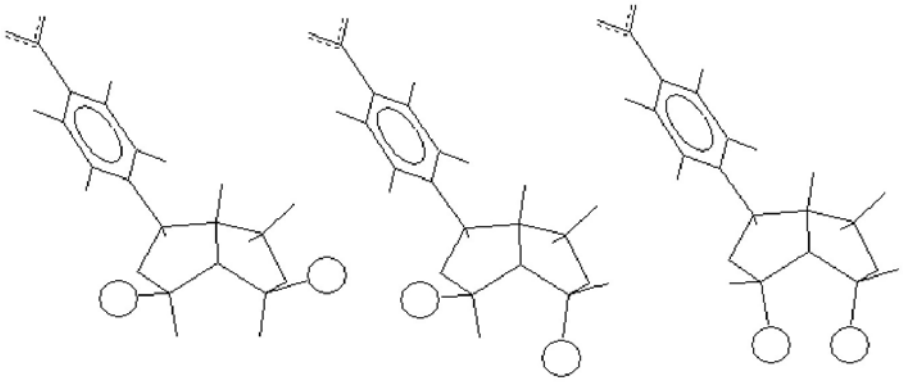
In the following, we will consider an orientation of the bicyclic system of isomers **3.1-3.2** where the "original" benzene ring and the unshared electron pair of the nitrogen are positioned above the bicyclic structure (Fig. 1). The aromatic rings in the 2 and 8 positions of stereoisomers **3.2** and **3.3** occupy alternative positions.

Four more stereoisomers **4** have an *S*-configuration for the nitrogen atom.

We showed previously that (1*S*,4*S*,5*S*)-4-(4-nitrophenyl)-1-aza-3,7-dioxabicyclo[3.3.0]octane (**5**) is unstable and the equilibrium is almost completely (by more than 99.9%) shifted toward the corresponding stereoisomer with an *R*-configuration for the nitrogen atom [8].

Optimization of the geometry for stereoisomers **4** (performed by the AM1 method, included in the Hyperchem Pro 7.0 software package) showed that these stereoisomers, like compound **5**, are unstable, and during optimization of their geometry, they go to the more stable, corresponding stereoisomers **3.1-3.4** that have an *R*-configuration for the nitrogen atom.

The energy difference between the conformation with a planar configuration for the nitrogen atom and the corresponding conformation with an *R*-configuration for the nitrogen atom is equal to approximately 25 kcal/mol, regardless of the nature of the substituents at the 2 and 8 positions, and thus it is determined by the nature of the bicycle, as in the case of compound **5** [8]. This allows us to assume that formation of stereoisomers **4** is unlikely in practice [8, 9].



3.1 **3.3** **3.4**

Fig. 1. Three-dimensional optimized models of stereoisomers **3.1, 3.3**, and **3.4**. ◯ = an aromatic ring.

The results of optimization of the geometry for stereoisomers **3** are shown in Table 1. From those results we see that stereoisomer **3.4**, with a *cis* arrangement of the introduced aromatic rings, is energetically unfavorable and should not be formed in practice. From this it follows that when this reaction is carried out, we should expect formation of at most only three stereoisomers: **3.1**, **3.2**, and **3.3** (Fig. 1).

Of the three remaining stereoisomers **3**, two of them (**3.2** and **3.3**) have approximately equal stabilities. Stereoisomer **3.1** is less stable. The difference in stability between stereoisomers **3.1**, **3.2**, and **3.3** is slight, but enough for their content in the reaction mixture to be substantially different [9].

Reaction of compound **1** with aldehydes was carried out in boiling benzene in a device fitted with a Dean–Stark trap. The reaction was considered complete when distillation of water stopped. This did not always correspond to 100% conversion of the material; but boiling further, replacing benzene by toluene, or increasing the excess of the aldehyde did not lead to additional distillation of water. Most complete conversion occurred for benzaldehydes **2a** and **2b**; in the rest of the cases, we could not achieve distillation of water in an amount close to the theoretical value. After the reaction was complete, the benzene was driven off on a rotary evaporator, and the remaining reaction mixture spontaneously crystallized after a certain amount of time.

An attempt to purify the reaction products obtained by column chromatography on aluminum oxide or silica gel was unsuccessful, due to their instability (compound **3a** is more stable than **3b**).

When the reaction was carried out with *p*-methoxybenzaldehyde (**2c**) and *p*-chlorobenzaldehyde (**2d**), spontaneous crystallization of the reaction mixture did not occur after driving off the benzene. Since the extent of conversion in the reactions with these aldehydes was low and the reaction mixtures contained the starting materials and probably the corresponding Schiff's bases, we had to use chromatography on a short silica gel column under pressure in order to purify their reaction mixtures. After driving off the solvent, the residue was crystallized only after treatment with isopropyl alcohol.

The compounds obtained retain both alcohols and hexane well, and so they were dried in a vacuum desiccator for a few days.

When the reaction was carried out with 3,4-dimethoxybenzaldehyde and 2-thiophenecarbaldehyde, we could not achieve crystallization of the reaction mixture, and the corresponding products were not obtained in pure form.

According to ^{1}H NMR data, the content of the major stereoisomer in the reaction mixture is 85-93%.

The ^{1}H NMR spectrum of the reaction mixture has a characteristic shape. The most informative portion of the spectrum is the 4.5-6.5 ppm region (Fig. 2*a*).

Judging from the optimization results, we thought the considered compounds could be conveniently studied by ^{1}H NMR spectroscopy. In these stereoisomers, the signals from the protons at the 2, 4, and 8 positions should be singlets and, due to the adjacent position of the benzene rings, they should be found downfield from the signals for other aliphatic protons. The proton at the 4 position should give a doublet.

When the indicated mixture of stereoisomers is formed, the ^{1}H NMR spectrum of the mixture should contain three doublets and six singlets in the aliphatic region, as we in fact observed (Fig. 2*a*).

TABLE 1. Results of Optimization of the Geometry by the AM1 Method for Stereoisomers **3.1-3.4**

Compound	Stereoisomer energy, kcal/mol			
	3.1	**3.2**	**3.3**	**3.4**
3a	-5407.5	-5408.4	-5408.3	-5401.5
3d	-5375.3	-5376.2	-5376,0	-5369.4
3b	-5973.0	-5973.7	-5974.0	-5967.1
3c	-6152.8	-6153.9	-6153.9	-6146.8

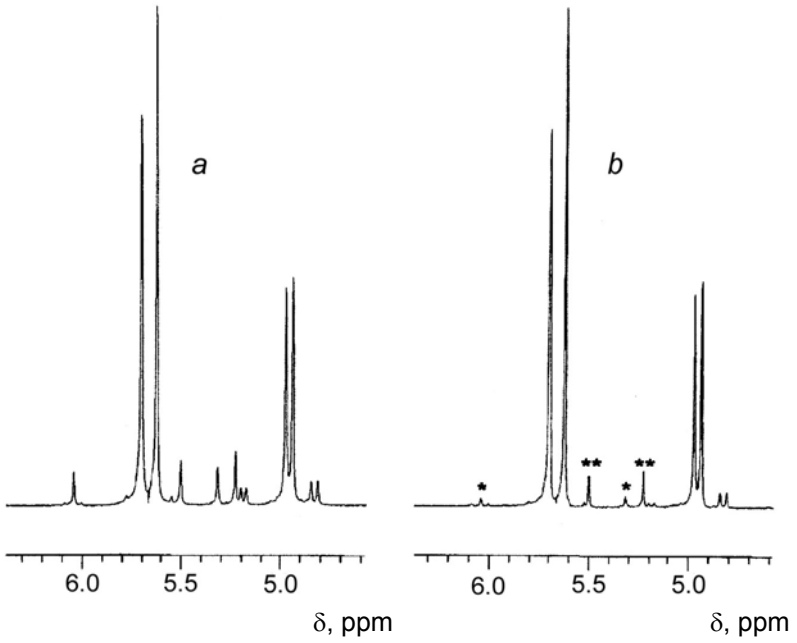


Fig. 2. ^{1}H NMR spectrum of the reaction product of compounds **1** and **2d**:
a) crude product; *b*) after recrystallization from hexane (there are three groups of signals for stereoisomers **3.1**, **3.2**, and **3.3** in the isolated region).

Probably the presented ^{1}H NMR spectra are enough to establish the structure of the most stable stereoisomer. Here two approaches are possible, which increases the reliability of the conclusions drawn.

1. As we see (Fig. 2*a*), the stereoisomers are present in the reaction mixture in a ratio which we may approximately give as 12:1:1. This significantly simplifies the problem, since we need to separate one stereoisomer from the other two, and the latter should be similar in steric interactions and consequently in stability. Obviously stereoisomer **3.1** is such a form. This stereoisomer lacks the steric interactions between the hydrogen atom and the benzene ring at positions 2 and 8 that occur in stereoisomers **3.2** and **3.3**. We have every reason to assume that this steric interaction makes the decisive contribution to the stability of the considered stereoisomers. And these stereoisomers are equal in stability. The distance between the hydrogen atom at the 2 position and the hydrogen atom at the *ortho* position of the benzene ring in the *trans* position (stereoisomer **3c**) is equal to 0.06 nm, if the indicated atom is located in the plane of the benzene ring, and the covalent radius of the hydrogen atom is equal to 0.11 nm.

Examination of BUCHI stick models (Switzerland) also shows that rotation of the benzene rings in the 2 and 8 positions for stereoisomers **3.2** and **3.3** is impossible due to steric hindrances caused by the hydrogen atoms under the plane of the bicyclic system in *cis* positions relative to the considered aromatic rings. Such hindrances do not arise in stereoisomer **3.1**, where all the benzene rings can freely rotate.

2. After recrystallization of the crude product from hexane or ethyl alcohol, the stereoisomeric composition of the reaction mixture changes, which made it possible to allocate the remaining signals between the two stereoisomers (Fig. 2).

From examination of three-dimensional models of stereoisomers **3** (Fig. 1), we see that the protons at the 2 and 8 positions are positioned identically with respect to the adjacent benzene ring in stereoisomer **3.1**, and should have approximately identical chemical shifts due to identical deshielding caused by the aromatic rings, which we also in fact observe (Δδ 0.08 ppm, Fig. 2*b*). These signals are the maximum signals, i.e., they

belong to the major stereoisomer. At the same time, in stereoisomers **3.2** and **3.3**, the protons at the 2 and 8 positions are identically shielded by the adjacent aromatic rings, but are shielded differently by the aromatic rings in the *trans* positions. This means that the chemical shifts for the indicated protons are considerably different (Δδ* 0.72 ppm and Δδ* 0.28 ppm, Fig. 2*b*).

Thus the major stereoisomer in the reaction mixture is **3.1**, which does not correspond to the energy values for the stereoisomers obtained as a result of optimization of the geometry.

Probably in this case we can cite imperfections in the method and possible error in optimization of the geometry [4]. But we can also point to another reason for the lack of agreement between the experimental data and the calculations. In the optimization of the geometry, we neglect the fact that in one case there may be a tremendous number of conformations for the stereoisomer that are close in stability to the optimal conformation, but in the other case the number of these conformations is limited. In other words, we need to compare either identically rigid structures or identically flexible structures, since the entropic contribution to the stability of the stereoisomers is not taken into account during optimization of the geometry. Obviously the stability of the stereoisomers and the stability of their most preferred conformations are not the same thing.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker Avance 200 (200 MHz) spectrometer in $CDCl_3$, internal standard TMS. The melting points were determined on a Kofler apparatus. In this work, we used Merck Al_2O_3 and SiO_2 chromatography plates, Fluka Al_2O_3 powder (Brockmann standard activity I), and SiO_2 powder from SDS. Compound **1** was supplied by the Akrikhin plant; the aldehydes were supplied by Janssen Chimika and Acros.

(1*R*,2*R*,4*S*,5*S*,8*S*)-4-(4-Nitrophenyl)-2,8-diphenyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (3a). Compound **1** (2.12 g, 10 mmol), benzaldehyde (2.65 g, 25 mmol), and benzene (50 ml) were placed in a round-bottomed flask (100 ml) fitted with a Dean–Stark trap. The reaction mixture was refluxed for 4 h, the benzene was distilled off on a rotary evaporator; after spontaneous crystallization, an equal amount of *i*-PrOH was added to the reaction mixture and it was filtered out and dried. Yield of crude product 3.6 g (92%), with 90% **3a** content; mp 90-91°C (hexane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.23-8.21 (14H, m, H_{arom}); 5.74 and 5.66 (2H, 2 s, H-2 and H-8); 4.95 (1H, d, *J* = 6.8, H-4); 4.07 and 3.87 (2H, two dd, *J* = 2.2, *J* = 8.9 and *J* = 8.8, *J* = 6.2, H-6); 3.72(1H, dt, *J* = 2.1, *J* = 6.4, H-5). Found, %: C 71.15; H 5.16; N 7.23. $C_{23}H_{20}N_2O_4$. Calculated, %: C 71.12; H 5.19; N 7.21.

(1*R*,2*R*,4*S*,5*S*,8*S*)-2,8-Bis(4-methylphenyl)-4-(4-nitrophenyl)-1-aza-3,7-dioxabicyclo[3.3.0]octane (3b) was obtained by a similar method. Yield of crude product 3.2 g (77%), 89% **3b** content; mp 115-116°C (hexane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.08-8.21 (12H, m, H_{arom}); 5.71 and 5.62 (2H, 2 s, H-2 and H-8); 4.94 (1H, d, *J* = 6.8, H-4); 4.05 and 3.88 (2H, two dd, *J* = 2.3, *J* = 8.8 and *J* = 6.2, *J* = 8.8, H-6); 3.67 (1H, dt, *J* = 2.2, *J* = 6.5, H-5); 2.36 and 2.29 (6H, 2s, two CH_3 groups). Found, %: C 72.23; H 5.87; N 6.68. $C_{25}H_{24}N_2O_4$. Calculated, %: C 72.10; H 5.81; N 6.73.

(1*R*,2*R*,4*S*,5*S*,8*S*)-2,8-Bis(4-methoxyphenyl)-4-(4-nitrophenyl)-1-aza-3,7-dioxabicyclo[3.3.0]octane (3c). Compound **1** (3.18 g, 15 mmol), 4-methoxybenzaldehyde (4.69 g, 34.5 mmol), and benzene (50 ml) were placed in a round-bottomed flask (100 ml). The reaction mixture was boiled for 5 h and the benzene was driven off on a rotary evaporator. The crude product was purified by chromatography under pressure for 1.5-2 h on a 3.5 × 8 cm column packed with silica gel (with eluent 8:2 cyclohexane–ethyl acetate). Yield 3.3 g (49%), 93% **3c** content; mp 85-86°C (hexane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.81-8.22 (12H, m, H_{arom}); 5.70 and 5.61 (2H, 2 s, H-2 and H-8); 4.95 (1H, d, *J* = 6.8, H-4); 3.70-4.09 (3H, m, H-5 and H-6); 3.82 and 3.77 (6H, 2s, two CH_3O groups). Found, %: C 66.97; H 5.37; N 6.28. $C_{25}H_{24}N_2O_6$. Calculated, %: C 66.95; H 5.39; N 6.25.

(1*R*,2*R*,4*S*,5*S*,8*S*)- 2,8-Bis(4-chlorophenyl)-4-(4-nitrophenyl)-1-aza-3,7-dioxabicyclo[3.3.0]octane (3d) was obtained by a similar method. Yield 3.2 g (47%), 85% **3d** content; mp 91-92°C (hexane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.26-8.24 (12H, m, H_{arom}); 5.70 and 5.62 (2H, 2 s, H-2 and H-8); 4.96 (1H, d, *J* = 6.9, H-4); 4.09 and 3.85 (2H, two dd, *J* = 2.1, *J* = 8.9 and *J* = 6.2, *J* = 8.9, H-6); 3.75 (1H, dt, *J* = 2.1, *J* = 2.1, *J* = 6.3, H-5). Found, %: C 60.40; H 3.96; N 6.14. $C_{23}H_{18}Cl_2N_2O_4$. Calculated, %: C 60.41; H 3.97; N 6.13.

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