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REGIOSELECTIVITY OF THE INTERACTION OF (1*S*,2*S*)-2-AMINO-1-(4-NITROPHENYL)-1,3-PROPANEDIOL WITH SOME SYMMETRICAL KETONES

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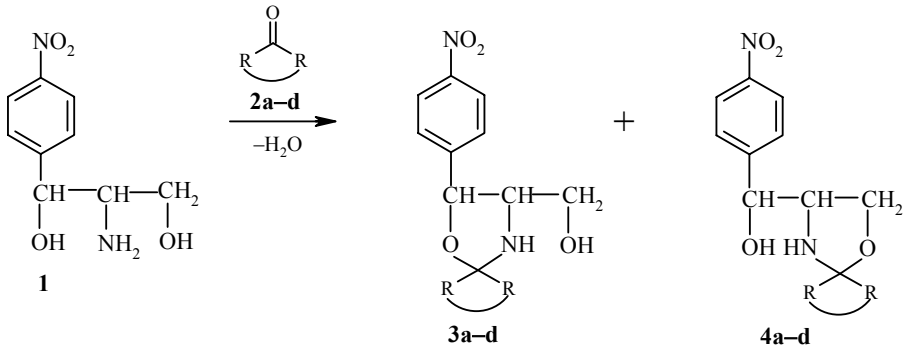
The interaction of (1S,2S)-2-amino-1-(4-nitrophenyl)-1,3-propanediol with a series of symmetrical ketones has been studied. As a result isomeric oxazolidines are formed in a ratio of 85:15. These oxazolidines were shown to decompose readily under the action of hydrazine.

Keywords: (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol, acetone, oxazolidine, cyclohexanone, cyclopentanone, symmetrical ketones, regioselectivity.

Study of the regioselectivity of organic reactions is of considerable interest. We showed previously that (1*S*,2*S*)-2-arylmethylamino-1-(4-nitrophenyl)-1,3-propanediols interact regioselectively with paraformaldehyde [1]. The first step of the method proposed for using the side product of the manufacture of the levomycetin analog thiamphenicol is based on the regioselectivity of the interaction of (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol with acetone [2].

On interacting (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol (**1**) with the symmetrical ketones **2a-d** it is possible to form two isomeric oxazolidines **3** and **4**.



2–4 a R+R = $(CH_2)_5$, **b** R+R = $(CH_2)_4$, **c** R+R = $(CH_2)_6$, **d** R = Me

The use of this reaction [2] assumes a high degree of regioselectivity for it with the preferential formation of isomer **3,** but there are no data in this work on the regioselectivity of the reaction. Meanwhile it is known that secondary alcoholic groups of 1,2-diols are more inclined than primary to form cyclic acetals [3].

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Symmetrical ketones are frequently used to form O-alkylidene protection, possessing various stability depending on the structure of the ketone used [3]. In the present work we have investigated the conditions of interaction of a series of symmetrical ketones **2a-d** with 2-amino-1,3-propanediol **1**, the regioselectivity of this reaction, and the stability of oxazolidines obtained towards hydrazinolysis [4].

The interaction of compound **1** with ketones was carried out in boiling benzene with azeotropic distillation of water. The criterion for completion of the reaction is the dissolution of the solid and cessation of water distillation, after which the reaction mixture was boiled for a further 30 min. Benzene was then distilled off on a rotary evaporator and the excess of ketone on vacuum equipment to constant weight, which corresponded to quantitative conversion of 2-amino-1,3-propanediol. The compounds obtained were spectrally pure and were not subjected to additional purification before assessing regioselectivity. As is evident from Table 1, the reactivity of ketones falls in the series, cyclohexanone > cyclopentanone >> cycloheptanone. In the reaction cyclic ketones were taken in 30% excess in the case of cyclohexanone and cyclopentanone and in 80% excess in the case of cycloheptanone. Since the boiling point of acetone is less than the boiling point of benzene and it accumulates in the Dean–Stark stillhead, acetone is introduced into the reaction in a large excess. Under the conditions indicated it displays a greater reactivity than cycloheptanone but less than cyclopentanone.

Recently, semiempirical quantum-mechanical methods of calculation, particularly AM1 and PM3, have been widely used to predict the results of reactions and the structure of the resulting products [5,6]. We selected isomers **3a** and **4a**, the products of the interaction of compound **1** with cyclohexanone, as model compounds. Four optimal conformers were considered for each of the isomers, two with *R* and *S* configuration of the nitrogen atom, and the following energy values (kcal/mol) were obtained for the conformers being considered:

AM1 (**3a**): -4144.1; -4146.2; -4146.5; -4147.8; PM3 (**3a**): -4152.5; -4153.8; -4155.1; -4158.2.

AM1 (**4a**): -4146.7; -4147.7; -4147.7; -4147.8; PM3 (**4a**): -4155.6; -4156.5; -4157.2; -4157.4.

It is evident that the difference in energy values will be of the same order for other pairs of compounds **3** and **4**.

In spite of the fact that the energy values obtained indicate some preference for isomer **4a**, it is impossible from these data to draw a conclusion on the preference of forming one of the isomers, since the difference in the obtained values is less than the admissible error of the calculation, which may reach 5 kcal/mol [7]. However it is possible to conclude from these data that the regioselectivity of this reaction may not be high [8].

The ^{1}H NMR spectra of the reaction products were taken for an experimental assessment of the regioselectivity of the reaction. It turned out that the spectra taken in $CDCl_3$ and DMSO-d_6 differed strongly (Fig. 1). The signals of the Ar–CH and N–CH methine protons of isomers **3** and **4** have different chemical shifts only in deuterochloroform, so it is possible to assess the regioselectivity of the reaction investigated by the ^{1}H NMR spectrum of the reaction mixtures in deuterochloroform. Independent on the nature of ketone taken the ratio of isomers was approximately 85:15 (Fig. 1, Table 1) and did not change with time or after purification on a chromatographic column.

TABLE 1. Data on the Interaction of Compound **1** (2.1 g, 0.01 mol) with Ketones **2a-d**

Ketone **2**	Amount of ketone, g (mol)	Reaction time, min*	Ratio of isomers **3** and **4**, as % (data of ^{1}H NMR)
Cyclohexanone (**a**)	1.3 g (0.013)	15/45	84 : 16
Cyclopentanone (**b**)	1.1 g (0.013)	45/75	85 : 15
Cycloheptanone (**c**)	2.1 g (0.018)	180/210	83 : 17
Acetone (**d**)	10 ml (0.14)	60/90	83 : 17

* The time required for complete solution of **1** is given in the numerator, the total reaction time is given in the denominator.

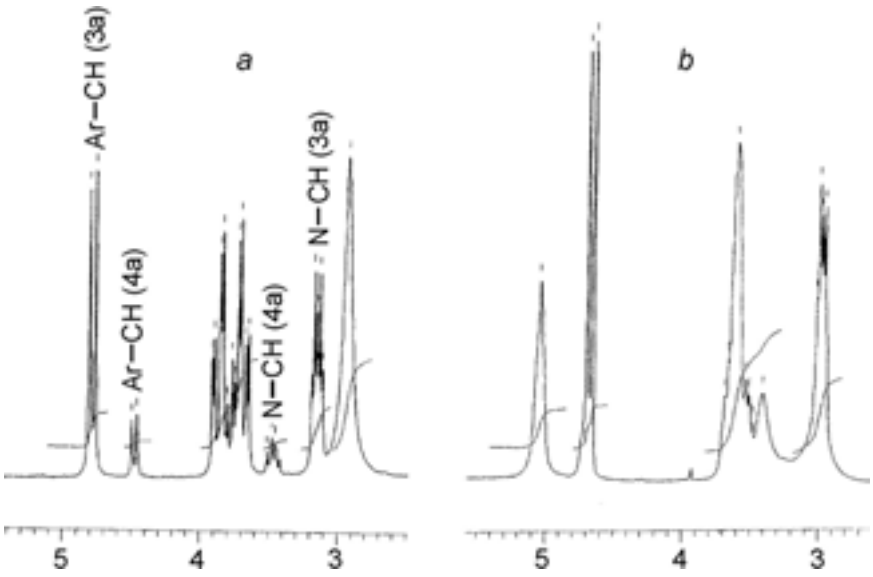


Fig. 1. Region of the ^{1}H NMR spectrum of the interaction products of compound **1** with cyclohexanone used for assessment of the regioselectivity of the reaction, a) in $CDCl_3$ and b) in DMSO-d_6.

The ^{1}H NMR spectra of the reaction mixture formed on interacting compound **1** with cyclohexanone were taken in the presence of $Eu(fod)_3$ to confirm the structure of the main reaction product. This reaction product was selected because of its better solubility in deuterochloroform. The signals of the methine proton close to the aromatic ring are readily discernible in both cases (Fig. 1a). The proton being considered in isomer **4a** is closer to the shift reagent and under its influence correspondingly must have a larger shift of signal in the ^{1}H NMR spectrum, which is in fact observed (Fig. 2).

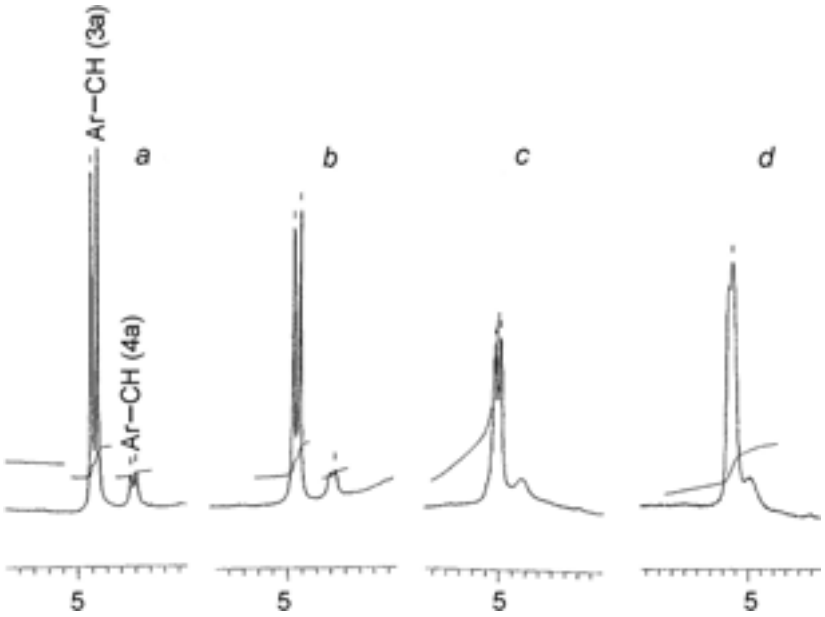
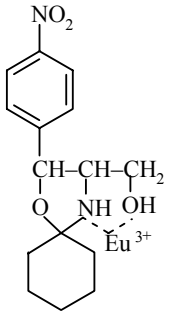
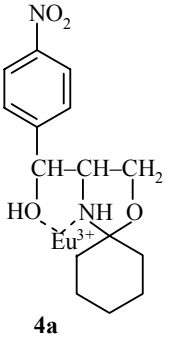


Fig. 2. Signals of the Ar–CH methine proton of isomers **3a** and **4a** in the presence of $Eu(fod)_3$. The molar ratio of $Eu(fod)_3$/substrate is a) 0.03; b) 0.04; c) 0.07; d) 0.09.

This enables structure **3a** to be assigned unequivocally to the main reaction product.



3a



4a

Acetal protection is widely used for the protection of neighboring hydroxyl groups. It is known that acetals formed with 1,2-diols possess differing stability depending on the nature of ketone used. Methylene acetals are the most stable to acid hydrolysis, which also causes their infrequent use [3]. We showed previously that oxazolidines formed on interacting 1,2-amino alcohols with paraformaldehyde are decomposed on treatment with alcoholic solution of hydrazine [4].

In the present work the stability of the various oxazolidine systems has been studied. For this purpose the mixture of oxazolidines formed on interacting compound **1** with cyclohexanone, cyclopentanone, cycloheptanone, and acetone was dissolved in ethyl alcohol and hydrazine hydrate was added. Even after 15-20 min precipitation of the solid initial compound **1** from the reaction mixture had begun, which indicates the low stability of these oxazolidines under hydrazinolysis conditions. In all the experiments the yield of compound **1** was ~80%. The described oxazolidines began to decompose straight away under the action of hydrazine, consequently a quantitative assessment of their relative stability was not carried out.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker Avance DRX 200 (200 MHz) spectrometer in $CDCl_3$, internal standard was TMS. Spectra were processed with the MESTREC computer program. Melting points were determined on a Kofler block. (1*S*,2*S*)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol (**1**) (Akrikhin works (Kupavna, Moscow region)) recrystallized from alcohol was used in the work. Ketones **2a-c** were commercial preparations of Aldrich, silica gel type SDS was from France. Column chromatography was carried out on column (3 × 40 cm) packed with silica gel 35-70 μm. Eluent was ethyl acetate–cyclohexane, 1:1.

Interaction of Compound 1 with Ketones 2a-d. Compound **1** (2.1 g, 0.01 mol), cyclohexanone **2a** (1.3 g, 0.013 mol), and benzene (50 ml) were placed in a round-bottomed flask fitted with a Dean–Stark stillhead. The reaction mixture was boiled for 15 min until complete dissolution of compound **1** and then for a further 30 min. Benzene was distilled off on a rotary evaporator, and the excess of cyclohexane on vacuum equipment. Crude product (2.9 g, 100%) was obtained. The ^{1}H NMR spectrum was determined in deuterochloroform to determine the ratio of isomers **3a** and **4a**.

Reactions with cyclopentanone **2b**, cycloheptanone **2c**, and acetone **2d** were carried out by an analogous procedure. The yields of crude product **3b-d** were 98-100%. The crude product was purified by chromatography.

(1*S*,2*S*)-2-Amino-1,2-O,N-cyclohexylidene-1-(4-nitrophenyl)-1,3-propanediol (3a). Oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.53, 8.21 (4H, two d, J = 8, H_{arom}); 4.80 (1H, d, J = 8, CHAr); 3.66-3.92 (2H, two dd, J = 4, J = 12, diastereotopic CH_2); 3.14-3.20 (1H, m, CHN); 2.90 (2H, br. s, OH, NH); 1.49-1.87 (10H, m, $(CH_2)_5$). Found, %: C 61.87; H 7.12. $C_{15}H_{20}N_2O_4$. Calculated, %: C 61.61; H 6.90.

(1*S*,2*S*)-2-Amino-1,2-O,N-cyclopentylidene-1-(4-nitrophenyl)-1,3-propanediol (3b). Oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.57, 8.24 (4H, two d, *J* = 8, H_{arom}); 4.78 (1H, d, *J* = 8, CHAr); 3.70-3.90 (2H, two dd, *J* = 4, *J* = 12, diastereotopic CH_2); 3.16-3.22 (1H, m, CHN); 2.78 (2H, br. s, OH, NH); 1.70-1.93 (8H, m, $(CH_2)_4$). Found, %: C 60.63; H 6.71. $C_{14}H_{18}N_2O_4$. Calculated, %: C 60.40; H 6.52.

(1*S*,2*S*)-2-Amino-1,2-O,N-cycloheptylidene-1-(4-nitrophenyl)-1,3-propanediol (3c). Mp 63-65°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.53, 8.23 (4H, two d, *J* = 8, H_{arom}); 4.74 (1H, d, *J* = 8, CHAr); 3.66-3.92 (2H, two dd, *J* = 4, *J* = 12, diastereotopic CH_2); 3.03-3.09 (1H, m, CHN); 2.90 (2H, br. s, OH, NH); 1.49-1.89 (12H, m, $(CH_2)_6$). Found, %: C 62.92; H 7.39. $C_{16}H_{22}N_2O_4$. Calculated, %: C 62.71; H 7.24.

(1*S*,2*S*)-2-Amino-1,2-O,N-isopropylidene-1-(4-nitrophenyl)-1,3-propanediol (3d). Mp 41-43°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.53-8.23 (4H, two d, *J* = 8, H_{arom}); 4.82 (1H, d, *J* = 8, CHAr); 3.69-3.94 (2H, two dd, *J* = 4, *J* = 12, diastereotopic CH_2); 3.16-3.21 (1H, m, CHN); 2.90 (2H, br. s, OH, NH); 1.56 [6H, s, $C(CH_3)_2$]. Found, %: C 56.91; H 7.23. $C_{12}H_{16}N_2O_4$. Calculated, %: C 56.66; H 7.14.

Hydrazinolysis of the Products of Interaction of Compound 1 with Ketones 2a-d. Mixtures obtained by reacting compound **1** (5 g) with the appropriate quantity of ketones **2a-d** were dissolved in alcohol (10 ml) and hydrazine hydrate (5 ml) was added. The mixtures were left overnight, the precipitated crystals **1** were filtered off, washed with a small amount of alcohol, and dried. Yield for **2a** was 4.05 g (81%), and for **2b-d** (80-82%). In all cases mp 164-166°C (163-164°C [4]).

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