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SYNTHESIS OF 2-OXAZOLIDINONES FROM (1*S*,2*S*)-2-AMINO-1-(4-NITROPHENYL)-1,3-PROPANEDIOL

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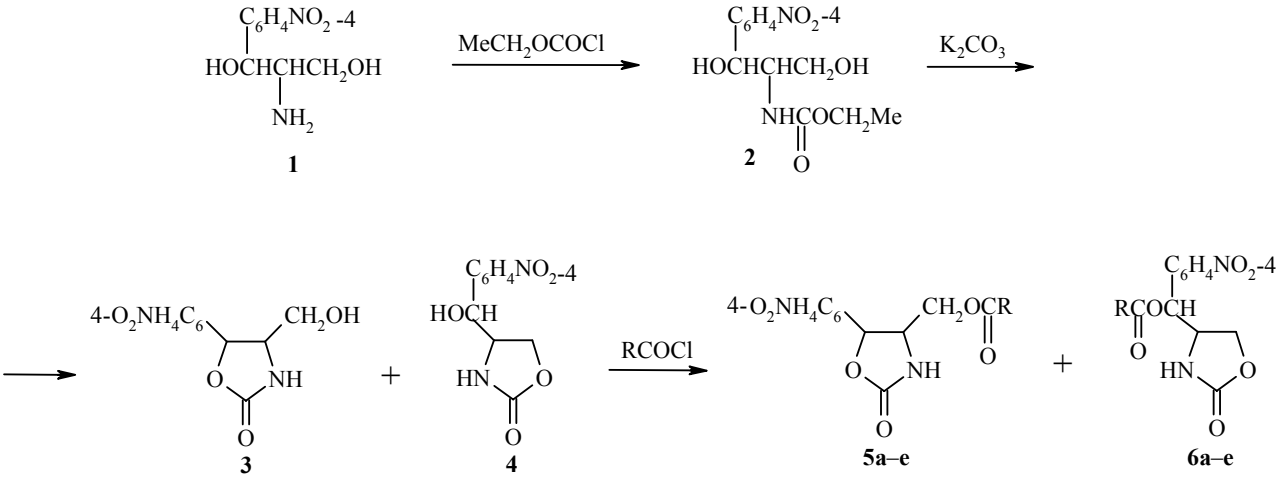
A series of isomeric 2-oxazolidinones has been synthesized from (1S,2S)-2-amino-1-(4-nitrophenyl)-1,3-propanediol.

Keywords: (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol, 2-oxazolidinone.

In recent years there has been a marked upsurge of interest in the chemistry of 2-oxazolidinones. This can be explained, particular by their high biological activity. 2-Oxazolidinones have been patented as antibacterial preparations [1, 2] and as substances effective in the treatment of atherosclerosis, arthritis, and Alzheimer, Krebs [3], or Parkinson [4] deseases. In addition, 2-oxazolidinones are used in asymmetric synthesis [5] and as starting materials for subsequent reactions [6, 7].

In the majority of literature reports 2-oxazolidinones are prepared from the corresponding 3-amino-1,2-diols [1-4]. 2-Amino-1,3-diols are used very rarely for this purpose.

(1*S*,2*S*)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol (**1**) [8] is a convenient and accessible reagent for the synthesis of 2-oxazolidinones. In this work we have prepared a series of 2-oxazolidinones by the following scheme:



5, **6 a** R = Me, **b** R = Et, **c** R = Pr, **d** R = $Cl(CH_2)_3$, **e** R = PhCHCl

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Reaction of compound **1** with ethyl chloroformate was carried out in methylene chloride. The (1*S*,2*S*)-2-carbethoxyamino-1-(4-nitrophenyl)-1,3-propanediol (**2**) obtained was treated for 5 days with a 1:1 mixture of saturated potassium carbonate solution in methanol and water to give the oxazolidinones **3** and **4**. The compound formed in greater amount has a lower chromatographic mobility, on the basis of which it is assigned the structure **3**. This conclusion could be made from later, additional evidence.

Compound **4** partially (and in a virtually pure state) begins to crystallize from the reaction mixture after 4 days and, hence, can be isolated. However it was more effective to obtain a mixture of compounds **3** and **4** and then to treat it with the corresponding acid chloride to give a mixture of compounds **5** and **6** which could be easily separated by column chromatography. Even after 5 days compound **2** is present in the reaction mixture as clearly revealed by TLC. Since its content in the reaction mixture changes insignificantly during the fourth and fifth days a more prolonged hold of the reaction mixture was regarded as unhelpful. After completion of the reaction the methanol was distilled off on a rotary evaporator and the residue was treated with water. The mixture of compounds **3** and **4** was filtered off, dried in air, and treated at room temperature with the corresponding acid chloride in chloroform in the presence of pyridine. Reaction between the indicated compounds occurs virtually instantaneously as indicated by the rapid loss of the odor of the acid chloride in the reaction mixture. In the acylation a mixture with different **3** and **4** content was used hence the ratio of yields of compounds **5** and **6** in the experiments carried out was not the same. The acid chloride was added dropwise to the reaction mixture in two steps, the first with an equivalent amount and the second portionwise in an amount sufficient for full reaction of compounds **3** and **4**. The need for the addition of a significant excess of the acid chloride is evidently associated with the fact that compounds **3** and **4** contain crystallization water which is difficult to remove. The TLC method was used to monitor the course of the initial reaction after addition of an equivalent amount of acid chloride and then after each further addition to avoid an undesirable excess of acid chloride and the consequent possibility of acylation of the nitrogen atom.

The oxazolidinones **3** and **4** react with the acid chloride at a different rate, as confirmed by chromatographic analytical data, and with the more rapidly reacting base product being assigned structure **3** since a primary alcohol group is taking part in the reaction in this instance.

Compounds **5** and **6** are separated by column chromatography, after which they are additionally purified by recrystallization and holding in a vacuum desiccator for several days where this is necessary. Similarly, compounds **3** and **4** were purified before carrying out the elemental analysis, melting point determination, and recording of the ^{1}H NMR spectra.

Isomers **5** and **6** have characteristic ^{1}H NMR spectra in the 4-5 δ region from which they can be reliably identified (see Fig. 1). This proved important for the identification of compounds **5a** and **6a** since they were obtained in virtually equal yield. As noted above, the chromatographic mobility of compound **3** is lower than compound **4**. Conversely, compound **5a** has a greater chromatographic mobility than **6a**.

The complexity of the proton signals for the methylene and neighboring methine protons in compound **6a** (Fig. 1) is related to the fact that in compounds **6** the nonequivalence of the diastereotopic methylene protons is greater than in compounds **5** since, in compounds **6**, they occupy a fixed position in space on different sides of the cyclic structure.

The chemical shifts observed correlate only partially with the values of the charges on the hydrogen atoms as obtained for the structure optimized by the AM1 method (HYPERCHEM program package, see Table 1). Thus the signal for the methine CH–O proton in compounds **3** and **6** is found at lower field when compared with the signal for the corresponding proton in compounds **4** and **5**. The difference in chemical shifts of the CH_2–O methylene and CH–N protons is greater for compound **5**. In this case the large difference in chemical shifts agrees with the larger difference in the charges on the indicated hydrogen atoms (see Fig. 1 and Table 1).

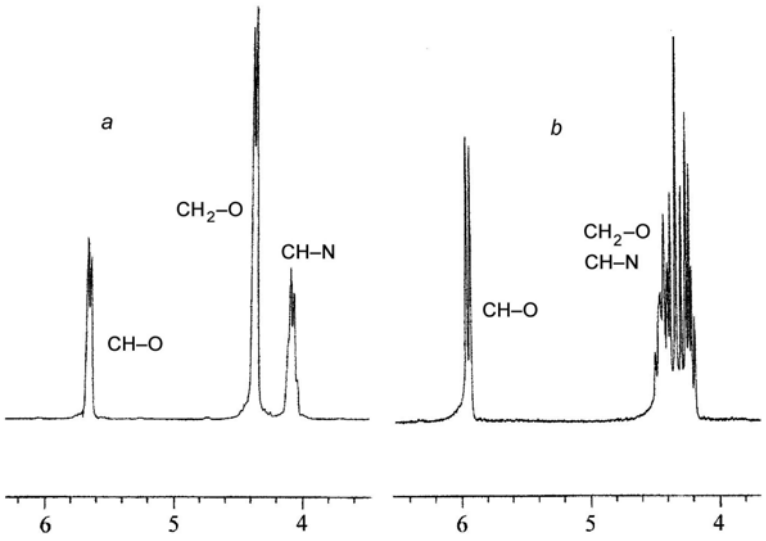

Fig. 1. ^{1}H NMR Spectrum of compounds **5a** (a) and **6a** (b) in acetone-d_6.

TABLE 1. Hydrogen Atom Charges

Compound	Hydrogen atom positive charge		
	CH–O	CH–N	CH_2–O
3	0.143	0.134	0.080
4	0.103	0.134	0.110
5a	0.139	0.143	0.107
6a	0.148	0.133	0.120
5b	0.139	0.142	0.105
6b	0.148	0.132	0.120
5c	0.134	0.142	0.106
6c	0.149	0.133	0.119
5d	0.139	0.142	0.107

For all of the compounds the signal for the CH–N methine proton is found to the right of the signal for the CH_2–O methylene protons. The absence of a correlation with the value of the charges in this case is evidently related to the difference in deshielding by the aromatic ring which determines the values for the chemical shifts of indicated protons.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker Avance 200 (200 MHz) spectrometer with TMS as internal standard and using the MESTREC program. Melting points were determined on a Kofler stage. Merck SDS grade silica powder plates were used in the work. (1*S*,2*S*)-2-Amino-4-(4-nitrophenyl)-1,3-propanediol was supplied by the Akrikhin company and the acid chlorides by Acros. The chromatographic separation of all of the products was carried out on a column filled with SiO_2 (3 × 45 cm), the eluent is specified in each case. The compounds obtained were named using the recommended ACD Labs and ChemOffice 2004 programs.

(1*S*,2*S*)-2-Carbethoxyamino-1-(4-nitrophenyl)-1,3-propanediol (2). Compound **1** (42.4 g, 200 mmol), sodium carbonate (40 g, 380 mmol), and methylene chloride (300 ml) were placed in a 1 liter round bottomed flask fitted with a reflux condenser and magnetic stirrer, cooled in ice to 5-10°C, and ethyl chloroformate (22.8 g, 210 mmol) was added dropwise with stirring at such a rate that the temperature did not exceed 15°C. The stirred reaction mixture was left overnight and then diluted with ethyl acetate in a quantity sufficient to dissolve compound **2** which was filtered using a Büchner funnel. The inorganic precipitate was washed on the filter several times with ethyl acetate. The mother liquor was evaporated on a rotary evaporator to leave a small amount of solvent. Compound **2** crystallized and the residue in the flask was left overnight in a fridge, filtered on a Büchner funnel, washed with a small amount of methylene chloride, and dried. The yield of raw product was 48.4 g (85%); mp 118°C (methylene chloride). Found, %: C 50.79; H 5.71; N 9.97. $C_{12}H_{16}N_2O_6$. Calculated, %: C 50.70; H 5.67; N 9.86.

(*S*)-4-(*S*)-Hydroxy(4-nitrophenyl)methyloxazolidin-2-one (4). Compound **2** (17 g, 60 mmol), water (50 ml), and a saturated solution of K_2CO_3 (50 ml) in methanol were placed in a 250 ml round bottomed flask fitted with a magnetic stirrer. The flask was stoppered and the reaction mixture was stirred, periodically checking the pH which was held at 9.5 by addition of solid NaOH as needed. After 4 days a precipitate formed in the flask was filtered off. The material separated is virtually pure compound **4**. The yield of raw product was 1.65 g (11.7%); mp 206-207°C (ethyl acetate–acetone). ^{1}H NMR spectrum (acetone-d_6), δ, ppm (*J*, Hz): 7.74-8.28 (4H, H_{arom}); 6.76 (1H, s, NH); 5.29 (1H, d, *J* = 5.0, OH); 4.94-4.98 (1H, m, CH–O): 4.19-4.34 (3H, m, CH_2 and CH–N). Found, %: C 50.72; H 4.17; N 11.80. $C_{10}H_{10}N_2O_5$. Calculated, %: C 50.42; H 4.23; N 11.76.

(4*S*,5*S*)-4-Hydroxymethyl-5-(4-nitrophenyl)oxazolidin-2-one (3). The mother liquor from the previous experiment was stirred for a further day and the methanol was removed on a rotary evaporator after which the reaction mixture separated into two layers. Water (100 ml) was added and the precipitated crystalline product was filtered off, washed with water, and dried. The separated product is a mixture of compounds **3** and **4** with a predominance of **3**. Yield 6.6 g (46.7%). Compound **3** was purified by column chromatography using a silica column and ethyl acetate–methanol (15:1) as eluent and then recrystallized from ethyl acetate; mp 137-138°C (ethyl acetate). ^{1}H NMR spectrum (acetone-d_6), δ, ppm (*J*, Hz): 7.72-8.36 (4H, H_{arom}); 6.95 (1H, s, NH); 5.61 (1H, d, *J* = 3.8, CH–O); 4.44-4.49 (1H, m, OH); 3.80-3.82 (3H, m, CH_2 and CH–N). Found, %: C 50.44; H 4.14; N 11.69. $C_{10}H_{10}N_2O_5$. Calculated, %: C 50.42; H 4.23; N 11.76.

((4*S*,5*S*)-5-(4-Nitrophenyl)-4-propionyloxymethyl)oxazolidin-2-one (5b), (S)-4-(S)-(4-Nitrophenyl-propionyloxy)methyloxazolidin-2-one (6b). A mixture of compounds **3** and **4** (1.1 g, 4.6 mmol), chloroform (25 ml), and pyridine (1.7 g, 22 mmol) was placed in a 50 ml round bottomed flask fitted with a magnetic stirrer and propionyl chloride (0.85 g, 92 mmol) was added slowly with stirring and then stirred for 1 h. Water (15 ml) was added and stirring was continued for a further 1 h. The reaction mixture was transferred to a separating funnel, chloroform (30 ml) was added, and the organic layer was separated. It was washed with dilute hydrochloric acid solution, sodium bicarbonate solution and then water, and dried over sodium sulfate. The chloroform was distilled off and the raw product was purified on a silica chromatographic column using ethyl acetate–cyclohexane (6:4) as eluent. The fractions containing **5** and **6** were separated, solvent was distilled off on a rotary evaporator, and the crystals were washed on the filter with a mixture of ethyl acetate and cyclohexane (4:6).

Compound 5b. Yield 0.63 g (46.7%); mp 149-150°C. ^{1}H NMR spectrum, (acetone-d_6), δ, ppm (*J*, Hz): 7.53-8.36 (4H, H_{arom}); 7.15 (1H, s, NH); 5.63 (1H, d, *J* = 4.8, CH–O); 4.36 (2H, d, *J* = 4.6, CH_2O); 4.07 (1H, t, *J* = 4.9, CH–N); 2.39 (2H, q, *J* = 7.5, CH_2); 1.09 (3H, t, *J* = 7.5, CH_3). Found, %: C 53.09; H 4.81; N 9.61. $C_{13}H_{14}N_2O_6$. Calculated, %: C 53.06; H 4.80; N 9.52.

Compound 6b. Yield 0.16 g (11.8%); mp 105°C (hexane). ^{1}H NMR spectrum, (acetone-d_6), δ, ppm (*J*, Hz): 7.75-8.29 (4H, H_{arom}); 7.10 (1H, s, NH); 5.96 (1H, d, *J* = 5.6, CH–O); 4.19-4.46 (3H, m, CH–N, CH_2–O); 2.44-2.57 (2H, double q, *J* = 2.6, *J* = 7.6, CH_2); 1.07-1.14 (3H, t, *J* = 7.6, CH_3). Found, %: C 53.21; H 4.84; N 9.64. $C_{13}H_{14}N_2O_6$. Calculated, %: C 53.06; H 4.80; N 9.52.

(4*S*,5*S*)-4-Acetoxymethyl-5-(4-nitrophenyl)oxazolidin-2-one (5a), (*S*)-4-(*S*)-Acetoxymethyl(4-nitrophenyl)oxazolidin-2-one (6a) were prepared similarly by treating the mixture of compounds **3** and **4** (1 g, 4.2 mmol) with acetyl chloride (0.63 g, 8.0 mmol). The raw product was purified on a silica chromatographic column using ethyl acetate–cyclohexane (8:2) as eluent.

Compound 5a. Yield 0.38 g (32.2%); mp 68°C. ^{1}H NMR spectrum, ($CDCl_3$), δ, ppm (*J*, Hz): 7.57-8.29 (4H, H_{arom}); 6.99 (1H, s, NH); 5.47 (1H, d, *J* = 5.4, CH–O); 4.25-4.43 (2H, m, CH_2–O); 3.96-4.04 (1H, m, CH–N); 2.15 (3H, s, CH_3). Found, %: C 51.53; H 4.55; N 9.68. $C_{12}H_{12}N_2O_6$. Calculated, %: C 51.43; H 4.31; N 9.99.

Compound 6a. Yield 0.41 g (34.8%); mp 156°C. ^{1}H NMR spectrum, ($CDCl_3$), δ, ppm (*J*, Hz): 7.56-8.29 (4H, H_{arom}); 6.99 (1H, s, NH); 5.82 (1H, d, *J* = 6.6, CH–O); 4.07-4.36 (3H, m, CH–N, CH_2–O); 2.19 (3H, s, CH_3). Found, %: C 51.59; H 4.65; N 9.79. $C_{12}H_{12}N_2O_6$. Calculated, %: C 51.43; H 4.31; N 9.99.

(4*S*,5*S*)-4-Butanoyloxymethyl-5-(4-nitrophenyl)oxazolidin-2-one (5c) was prepared similarly by treatment of the mixture of compounds **3** and **4** (1.5 g, 6.3 mmol) with butanoyl chloride (1.34 g, 12.6 mmol). The raw product was purified chromatographically using ethyl acetate-cyclohexane (4: 6) as eluent. Yield of compound **5c** 1.11 g (57%); mp 100-101°C. ^{1}H NMR spectrum, (acetone-d_6), δ, ppm (*J*, Hz): 7.75-8.36 (4H, H_{arom}); 7.15 (1H, s, NH); 5.63 (1H, d, *J* = 5.0, CH–O); 4.35-4.38 (2H, m, CH_2–O); 4.02-4.10 (1H, m, CH–N); 2.36 (2H, t, *J* = 7.3, CH_2); 1.62 (2H, q, *J* = 7.3, CH_2); 0.93 (3H, t, *J* = 7.3, CH_3). Found, %: C 54.49; H 5.32; N 9.26. $C_{14}H_{16}N_2O_6$. Calculated, %: C 54.54; H 5.23; N 9.09.

(4*S*,5*S*)-4-(4-Chlorobutanoyloxymethyl)-5-(4-nitrophenyl)oxazolidin-2-one (5d) was prepared similarly by treatment of the mixture of compounds **3** and **4** (1.5 g, 6.3 mmol) with 4-chlorobutanoyl chloride (1.78 g, 12.6 mmol). The raw product was purified chromatographically using ethyl acetate–cyclohexane (5:5) as eluent. Yield of compound **5d** 0.91 g (42.1%). Mp 129-130°C (benzene). ^{1}H NMR spectrum, (acetone-d_6), δ, ppm (*J*, Hz): 7.75-8.37 (4H, H_{arom}); 7.18 (1H, s, NH); 5.65 (1H, d, *J* = 5.0, CH–O); 4.38-4.41 (2H, dd, *J* = 1.3, *J* = 5.1, CH_2–O); 4.05-4.12 (1H, dq, *J* = 1.0, *J* = 5.0, CH–N); 2.68 (2H, t, *J* = 6.5, CH_2–Cl); 2.58 (2H, t, *J* = 7.2, CH_2–CO); 2.01-2.08 (2H, CH_2, obscured by the water signal). Found %: C 48.76; H 4.48; N 8.27. $C_{14}H_{15}ClN_2O_6$. Calculated, %: C 49.06; H 4.41; N 8.17.

(4*S*,5*S*)-5-(4-Nitrophenyl)-(*R*,*S*)-4-phenylchloroacetoxymethyloxazolidin-2-one (5e), (*S*)-4-(*S*)-(4-Nitrophenyl)-(*R*,*S*)-phenylchloroacetoxymethyloxazolidin-2-one (6e) were prepared similarly by treatment of the mixture of compounds **3** and **4** (1.5 g, 6.3 mmol) with racemic 2-chloro-2-phenylacetyl chloride (2.38 g, 12.6 mmol). The raw product was purified chromatographically using ethyl acetate–cyclohexane (4:6) as eluent.

Compound 5e. Yield 1.25 g (50.8%); mp 132-133°C. ^{1}H NMR spectrum, (acetone-d_6), δ, ppm (*J*, Hz): 7.41-8.31 (9H, H_{arom}); 7.14 (1H, s, NH); 5.78 (1H, s, CH–Cl); 5.55 (1H, d, *J* = 4.9, CH–O); 4.46-4.51 (2H, m, CH_2–O); 4.05-4.09 (1H, m, CH–N). Found, %: C 55.48; H 3.95; Cl 9.19; N 7.40. $C_{18}H_{15}ClN_2O_6$. Calculated, %: C 55.32; H 3.87; Cl 9.07; N 7.17.

Compound 6e. Yield 0.55 g (22.4%); mp 72-73°C (in a capillary). Found, %: C 55.54; H 4.20; Cl 9.37; N 7.15. $C_{18}H_{15}ClN_2O_6$. Calculated, %: C 55.32; H 3.87; Cl 9.07; N 7.17.

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