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Abstract

Full Text

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ETHAMBUTOL AND RELATED COMPOUNDS

SYNTHESIS AND STEREOCHEMICAL RELATIONSHIPS

(Presented by Academician A. N. Nesmeyanov, February 19, 1962)

Recently a brief communication appeared ([1]) on the synthesis of a representative of a new group of antitubercular compounds, (+)-1′,2′-bis-(2-iminobutanol-1)-ethane, "ethambutol" (Ia). This preparation possesses high activity (in *in vitro* tests and in experiments on animals) toward strains of tubercle mycobacteria resistant to other types of antitubercular drugs (streptomycin, phthivazide). It is noteworthy that, among the stereoisomers of 1′,2′-bis-(2-iminobutanol-1)-ethane formed in the reaction of 2-aminobutanol-1 with dichloroethane, only the (+)-isomer, obtained from (+)-2-aminobutanol-1, is highly active. At the same time, its antipode is devoid of antibacterial activity, while the activity of the meso form is only one tenth of the activity of Ia. The high stereospecificity of the preparation makes it possible to suppose that the mechanism of its action may be connected with the metabolic processes of certain optically active substances that are of essential importance for the vital activity of the tubercle bacillus, for example, α-amino acids.*

In approaching the elucidation of the mechanism of action of the preparation, it was first of all desirable to compare the configurations of the asymmetric centers of Ia, responsible for its antibacterial activity, with the configuration of natural α-amino acids. Such a comparison could be made by proving the absolute configuration of optically active 2-aminobutanols-1 ([4,5]), by obtaining one of them from α-aminobutyric acid of known spatial structure (cf. ([6–10])).

To solve the problem posed, the hydrochloride of optically pure *D*-α-aminobutyric acid, obtained by resolution of the benzyl ester of *DL*-α-aminobutyric acid with dibenzoyl-*D*-tartaric acid (cf. ([11])), was converted by us into the ethyl ester of *D*-α-aminobutyric acid, which was reduced with lithium aluminum hydride to *D*-2-aminobutanol-1. The isolated amino alcohol had $[\alpha]_D^{24} - 10.2^\circ$ and, in its properties, coincided with (−)-2-aminobutanol obtained by us by resolution of 2-aminobutanol-1 (see ([5])). Thus, the previously described (+)- and (−)-2-aminobutanols-1 ([4,5]) should be assigned the *L*- and, respectively, *D*-configurations (or the *S*- and, respectively, *R*-configurations, according to the universal system proposed by Cahn, Ingold, and Prelog ([11])),

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and the two asymmetric centers of ethambutol the *L*- or, according to the universal system, *S*-configuration, corresponding to the configurations of the α-carbon atoms in natural amino acids.

To obtain analogs and homologs of Ia, the study of which could provide further information on the relationship between structure and antibacterial activity in this series, we successfully applied a new synthetic route, which also gives good results in obtaining Ia itself. On interaction of racemic 2-aminobutanol (IIb) with diethyl oxalate in 95% yield there was obtained a mixture of the racemate and meso form of the corresponding oxamides (IIIb, c), which, without separation, was reduced

* The presence of an α-aminobutyric acid, structurally related to ethambutol, in the products of vital activity of the tubercle bacillus has been noted repeatedly before ([2,3]).

with lithium aluminum hydride to a mixture of racemate Iv (37%) and meso form Ig (35%); the latter were readily separated on the basis of the more difficult solubility of Ig in most common solvents.

$$\underset{\text{(II)}}{\begin{matrix}\mathrm{HOCH_2}\\ \mathrm{C_2H_5}\end{matrix}\!\!>\mathrm{CH-NH_2}} \xrightarrow{(\mathrm{C_2H_5OCO-})_2} \underset{\text{(III)}}{\left[\begin{matrix}\mathrm{HOCH_2}\\ \mathrm{C_2H_5}\end{matrix}\!\!>\mathrm{CH-NH-CO-}\right]_2} \xrightarrow{\mathrm{LiAlH_4}} \longrightarrow \underset{\text{(I)}}{\left[\begin{matrix}\mathrm{HOCH_2}\\ \mathrm{C_2H_5}\end{matrix}\!\!>\mathrm{CH-NH-CH_2-}\right]_2}$$

a—*L*-form; b—*D*-form; v—racemate; g—meso form.

The optically active forms of 2-aminobutanol-1 (IIa, b) (see (5)) were smoothly converted into the corresponding oxamides (IIIa, b), reduction of which led to the optically active diamines Ia and Ib in an overall yield of about 65%. Ia was identical with the substance obtained by us according to (1).

By an analogous route, a series of compounds related to ethambutol was also obtained, which will be described in another communication. Chemotherapeutic investigations of the synthesized substances were carried out in the chemotherapy department of the institute by M. A. Breger and G. Ya. Kivman.

Experimental part*

Ethyl ester of *D*-α-aminobutyric acid. To a suspension of 3 g of *D*-α-aminobutyric acid hydrochloride, having $[\alpha]_D^{22} - 14.2^\circ$ (*C* 2; water) (10, 13), in 25 ml of absolute alcohol, with good cooling, 1.65 ml of thionyl chloride was added dropwise. The reaction mass was left for 3 days at room temperature, the alcohol was distilled off, the residue was dissolved in 10 ml of chloroform, and, with good cooling, 20 ml of chloroform saturated at 0° with ammonia was added

SovietRxiv

to the resulting solution. Ammonium chloride was filtered off, the chloroform was distilled off at a temperature not above 20°, the residue was dried by adding and evaporating dry benzene, and distilled in vacuo, collecting the fraction with b.p. 55.5–56°/11 mm; n_D^{22} 1.4230; yield 2.29 g (81%); $[\alpha]_D^{24} - 12.6°$ (neat liquid); $[\alpha]_D^{24} - 18.2°$ (C 2.2; alcohol).

Found %:	C 54.56, 54.55; H 10.06, 9.96
$C_6H_{13}O_2N$. Calculated %:	C 54.93; H 9.99

***D*-2-Aminobutanol-1.** To a solution of 1 g of lithium aluminum hydride in 30 ml of ether, with stirring, 1.7 g of ethyl *D*-α-aminobutyrate in 20 ml of ether was added dropwise. The reaction mixture was boiled for 1 hour and then, with good cooling, decomposed by successive addition of 1.4 ml of water, 0.8 ml of 20% sodium hydroxide, 3.8 ml of water, and 4.6 ml of 40% sodium hydroxide. The ethereal solution was separated, and the precipitate was extracted several times with chloroform. The extracts were evaporated, the residue was distilled off with dry benzene and distilled in vacuo, collecting the fraction with b.p. 51–52°/2 mm. Yield 0.6 g (51%); n_D^{22} 1.4522; $[\alpha]_D^{24} - 10.2°$ (neat liquid). Literature data (4): b.p. 81°/11 mm; $[\alpha]_D^{24} - 9.8°$.

Acid oxalate was obtained by mixing alcoholic solutions of the base with an excess of oxalic acid. M.p. 139–141°; $[\alpha]_D^{23} - 8.3°$ (C 3; water).

Found %:	C 40.20, 40.36; H 7.36, 7.28
$C_6H_{13}O_5N$. Calculated %:	C 40.21; H 7.31

Identical with a sample of the salt obtained by us from (−)-2-aminobutanol-1 (5) by an analogous method.

* The melting points given are uncorrected.

Oxalyl-bis-(2-iminobutanol-1) (mixture of racemate and meso form). To 3 g of freshly distilled racemic 2-aminobutanol-1, with stirring, 2.46 g of diethyl oxalate was added. The reaction mixture warmed up and a crystalline precipitate separated, which was washed with dry acetone, filtered off, and dried in vacuo. Yield of the mixture of racemate and meso form 3.7 g (95%). M.p. 166–173°. The mixture was reduced without separation (see below).

Found, %:	C 51.77, 51.63;	H 8.39, 8.77;	N 22.15, 12.00
$C_{10}H_{20}O_4N_2$. Calculated, %:	C 51.76;	H 8.68;	N 12.06

Oxalyl-bis-(L-2-iminobutanol-1). Obtained from 3 g of *L*-2-aminobutanol-1 ($[\alpha]_D^{21} + 9.8°$) (5) and 2.46 g of diethyl oxalate by the method described above. Yield 3.7 g (95%); m.p. 203.5–204.5°; $[\alpha]_D^{21} - 46°$ (C 0.4; ethanol).

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After recrystallization from alcohol, thin needles with m.p. 205.5–206° were obtained. The angle of rotation did not change.

Found, %:	C 51.74, 51.75;	H 8.71, 8.61;	N 12.05, 12.16
$C_{10}H_{20}O_4N_2$. Calculated, %:	C 51.76;	H 8.68;	N 12.06

Oxalyl-bis-(D-2-iminobutanol-1). Obtained analogously from 2 g of *D*-2-aminobutanol-1 ($[\alpha]_D^{21} - 9.8°$) (5) and 1.64 g of diethyl oxalate. Yield 2.47 g (95%); m.p. 205–206°; $[\alpha]_D^{21} + 46°$ (*C* 0.4; ethanol). After recrystallization from alcohol, thin needles with m.p. 206–206.5° were obtained. The angle of rotation did not change.

Found, %:	C 51.91, 52.07;	H 8.76, 8.89;	N 12.12, 11.91
$C_{10}H_{20}O_4N_2$. Calculated, %:	C 51.76;	H 8.68;	N 12.06

Racemate and meso form of 1′,2′-bis-(2-iminobutanol-1)-ethane. To 3.1 g of a well-ground mixture of the racemate and meso form of oxalyl-bis-2-iminobutanol-1 (see above), a solution of 1.5 g of lithium aluminum hydride in 45 ml of ether was added. The ether was replaced with tetrahydrofuran (60 ml), and the reaction mixture was stirred under reflux for 10 h and then decomposed by successive addition of 2.1 ml of water, 1.1 ml of 20% sodium hydroxide, 5.8 ml of water, and 6.9 ml of 40% sodium hydroxide. To the reaction mixture an additional 40 ml of tetrahydrofuran was added, it was boiled for 20 min, and the hot solution was filtered. On cooling the filtrate, crystals of the meso form separated. Yield 0.95 g (35%), m.p. 135–136°.

Found, %:	C 58.92, 59.14;	H 11.90, 11.73;	N 13.44, 13.35
$C_{10}H_{24}O_2N_2$. Calculated, %:	C 58.82;	H 11.85;	N 13.73

Dihydrochloride was obtained by mixing an alcoholic solution of the base with an ethereal solution of hydrogen chloride. A white crystalline substance with m.p. 199–201.5°.

Found, %:	Cl′ 25.57, 25.51
$C_{10}H_{26}O_2N_2Cl_2$. Calculated, %:	Cl′ 25.62

Literature data (1): m.p. of the base 135.8–136.5°; m.p. of the dihydrochloride 203.5–204.6°.

The tetrahydrofuran mother liquor (see above) was evaporated. The residue crystallized on standing. After recrystallization from ether, 1 g (37%) of racemic 1′,2′-bis-(2-iminobutanol-1)-ethane was obtained with m.p. 73–74°.

SovietRxiv

Found, %:	C 58.50, 58.98; H 11.72, 11.78; N 13.43, 13.21
$C_{10}H_{24}O_2N_2$. Calculated, %:	C 58.82; H 11.85; N 13.73

Dihydrochloride, m.p. 175-176.5°.

Found, %:	Cl′ 25.80, 25.91
$C_{10}H_{26}O_2N_2Cl_2$. Calculated, %:	Cl′ 25.62

Literature data ([1]): m.p. of the base 75–76°; m.p. of the dihydrochloride 179–180°.

1,2′-Bis-(L-2-iminobutanol-1)-ethane. To 3.1 g of well-pulverized oxalyl-bis-(L-2-iminobutanol-1) was added a solution of 1.5 g of lithium aluminum hydride in 45 ml of absolute ether. The ether was replaced by tetrahydrofuran (60 ml), and the reaction mixture was boiled for 16 h. The base was isolated in the same way as described above. Yield 1.94 g (72%); m.p. 85.5–86°; $[\alpha]_D^{25}$ + 26.8° (C 5; alcohol).

Found, %:	C 58.56, 58.45; H 11.81, 11.67; N 13.80, 13.89
$C_{10}H_{24}O_2N_2$. Calculated, %:	C 58.82; H 11.85; N 13.73

Dihydrochloride. A white crystalline substance, readily soluble in water and methanol, somewhat less soluble in alcohol. M.p. 196–197.5°, $[\alpha]_D^{24} + 6.0°$ (C 5, water).

Found, %:	C 43.34, 42.95; H 9.30, 9.45; Cl′ 25.39, 25.54
$C_{10}H_{26}O_2N_2Cl_2$. Calculated, %:	C 43.32; H 9.38; Cl′ 25.62

Literature data ([1]): base, m.p. 87.5–88.8°; dihydrochloride, m.p. 198.5–200.3°; $[\alpha]_D^{25} + 5.5° \pm 0.4°$ (water).

1,2′-Bis-(D-2-iminobutanol-1)-ethane. Obtained analogously from 1.8 g of oxalyl-bis-(D-2-iminobutanol-1). Yield 1.05 g (66%); m.p. 85.5–86.5°; $[\alpha]_D^{24}$ − 26.7° (C 5; alcohol).

Found, %:	C 58.74, 58.62; H 11.64, 11.77; N 13.47, 13.49
$C_{10}H_{24}O_2N_2$. Calculated, %:	C 58.82; H 11.85; N 13.73

Dihydrochloride: m.p. 196–198°; $[\alpha]_D^{24} - 5.5°$ (C 5; water).

SovietRxiv

Found, %:	Cl′ 25.67; 25.80
$C_{10}H_{26}O_2N_2Cl_2$. Calculated, %:	Cl′ 25.62

Literature data ([1]): base, m.p. 89–90°; dihydrochloride, m.p. 200.5–201.5°; $[\alpha]_D^{25} - 4.7^\circ \pm 0.4^\circ$ (water).

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