46.6% urea are added with stirring, and 59 ml of water are bulk-distilled in vacuum of 25 mm at 50°C. The syrupy mass obtained is cooled to 35°C, and then 70 ml of acetic anhydride are added; the temperature raises spontaneously to 60°C. The reaction mixture is heated to 80°C, left to stand for 2 h, then cooled to 65°C, and 30 ml of 95% acetic acid are distilled at 30 mm Hg. To the residue, 31 ml of water are added, and 30 ml of 30% acetic acid are distilled at 30 mm Hg at 65°C. To the reaction mixture 170 ml of water are added, the mixture is stirred, and the precipitate is filtered and dried at 70°C. The yield of III is 40.1 g (81% of theoretical, calculated on I), and the content of the main compound is 96%.

RESOLUTION OF dl-1-PHENOXY-2-HYDROXY-3-AMINOPROPANE INTO ENANTIOMERS

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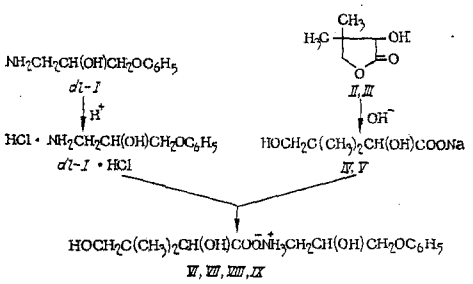
At present a large number of compounds have been synthesized, which are analogs of the group of aryloxypropanolamines, used in medical practice as β-adreno-blocking agents. A characteristic feature of these compounds is that in their structure they contain an asymmetric carbon atom and can be present in the form of a racemate or d- and l-isomers. The biological activity of most of the compounds synthesized was studied in the racemic form. However, recently, great attention is being paid to problems of the interrelationship between the stereochemistry and the pharmacological action of the above group of compounds. A study of the biological activity of the optical isomers known in medical practice showed that they differ considerably. It was shown that the l-isomer of propranolol, a preparation used for medicinal purposes in the form of a racemic compound, is 60 times more active than the d-isomer. The isomers also exhibit considerable metabolic differences [1]. The study of the metabolism of bunolol showed that the l-isomer is nearly 2.5 times more active than the dl-preparation in the inhibition of tachycardia [2]. Prenalterol was found to be highly stereospecific in the manifestation of the β_2-antagonistic activity, and l-prenalterol is 100 times more active than the d-enantiomer [3].

It was therefore interesting to resolve compounds of this group into optical isomers.

To prepare the isomers of propranolol, we used (+)- and (−)-di-(p-tolyl)tartaric acids [1]. The levorotating isomer of 1-(o-methoxyphenoxy)-3-isopropylamino-2-propanol, used as a β-blocking agent (the moprolol preparation), was obtained by resolution of the racemic compound by means of L(+)-glutamic acid [4].

In the present work, we resolved dl-1-phenoxy-2-hydroxy-3-aminopropane (1) into enantiomers by means of D- and L-pantolactones (α-hydroxy-β,β-dimethyl-γ-butyrolactones) (II), (III), which are intermediate products in the preparation of pantothenic acid (vitamin B_3), according to the following scheme:



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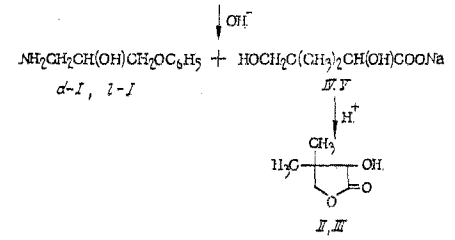

By heating with sodium hydroxide, D- and L-pantolactones II and III were converted into salts of D- and L-pantothenic acid (**α,γ-dihydroxy-β,β-dimethylbutyric acid**) (IV, V), which in the reaction with the hydrochloride salt of d*l*-1 formed diastereomeric salts: when II was used – d-1-phenoxy-2-hydroxy-3-ammoniumpropane-D-pantoate (VI) and *l*-1-phenoxy-2-hydroxy-3-ammoniumpropane-D-pantoate (VII); when III was used – d*l*-1-phenoxy-2-hydroxy-3-ammoniumpropane-L-pantoate (VIII) and *l*-1-phenoxy-2-hydroxy-3-ammoniumpropane-L-pantoate (IX) were obtained. The diasteromeric pairs of salts (VI and VII) and (VIII and IX) were separated by crystallization of an **alcoholic solution of the less** soluble salts VI and IX. After treatment of VI and IX separated from the solution, and salts VII and VIII, remaining in the filtrate, with an aqueous solution of sodium hydroxide, d- and *l*-isomers of 1-phenoxy-2-hydroxy-3-aminopropane (d-I and *l*-I) were obtained, which after recrystallization from methanol had a specific rotation of +15.91° and –16.12°, respectively, in water, and were identified by melting point, R_f value, IR spectra, and the elemental analysis.

The asymmetric reagents II and III were regenerated by heating in a mineral acid solution the salts IV and V, formed after the preparation and isolation of d-I and *l*-I from the **diastereomeric salts VI-IX,** and extracting by an organic solvent.

EXPERIMENTAL

The optical activity was measured in aqueous solution on the Polamat A polarimeter (GDR). The IR spectra were run on the Perkin-Elmer spectrometer, model 180 (USA) in the form of a paste in mineral oil. The chromatography was carried out on Silufol UV-254 plates in a butanol–acetic acid–water system (10:7:3). The plates were developed by UV light and alcoholic solution of ninhydrin. The melting points were determined on a Koffler block.

d*l*-1-Phenoxy-2-hydroxy-3-aminopropane (d*l*-I). This was synthesized by the reaction of epichlorohydrin with phenol, followed by treatment of phenoxyglicidic ester obtained with ammonia [3].

d-1-Phenoxy-2-hydroxy-3-ammoniumpropane-D-pantoate (VI). A 3.4 ml portion of hydrochloric acid (sp. gr. 1.19) is added to a solution of 6.3 g (0.037 mole) of compound d*l*-I in 20 ml of ethanol to form a solution of d*l*-I hydrochloride. A 1.52 g portion (0.037 mole) of sodium hydroxide is added to a solution of 4.96 g (0.037 mole) of compound II in 20 ml of ethanol, and the mixture is stirred for 30 min at 70-72°C. A solution of compound IV is obtained, to which a solution of d*l*-I-hydrochloride is added, and the mixture is stirred for 1 h at 50°C. The precipitate is filtered from sodium chloride, and the filtrate is left to stand for 10-15 h at 5-7°C. The precipitate is filtered, washed with 30 ml of cold ethanol, and dried. Yield, 5.19 g (88.5%) of VI, mp 132-133°C; $[\alpha]_D^{20}$ +4° (c 2; water). Found, %: C 57.31; H 8.93; N 4.30. $C_{15}H_{26}NO_6$. Calculated, %: C 56.94; H 8.28; N 4.43.

d-1-Phenoxy-2-hydroxy-3-aminopropane (d-I). A 5.19 g portion (0.016 mole) of VI is added to a solution of 0.75 g (0.019 mole) of sodium hydroxide in 15 ml of water. The mixture is stirred for 1 h at 65°C, and then cooled to room temperature, and extracted with chloroform (4 times with 40 ml portions). The chloroform is distilled, and the residue is dried *in vacuo.* Yield: 2.57 g (40.8% based on d*l*-I) of d-I, $[\alpha]_D^{20}$ +14.1° (c 2; water). After recrystallization from methanol, d-I is obtained, mp 98-100°C, $[\alpha]_D^{20}$ +15.91° (c 2; water), R_f 0.48. Found, %: C 63.93; N 8.67 $C_9H_{13}NO_2$. Calculated, %: C 64.62; N 8.37. IR spectrum, ν, cm^{-1}: 3500-3300 (OH, NH), 1600, 1590, 1500 (C=C), 1250(C–O).

Hydrochloride of d-I: mp 132-133°C. Found, %: C 53.10; H 6.97; N 6.73. $C_9H_{14}NO_2Cl$. Calculated, %: C 53.08; H 6.93; N 6.87.

The filtrate of VII obtained after separation of VI is evaporated to dryness *in vacuo* The residue is dissolved in 20 ml of water, 0.8 g of sodium hydroxide is added, and the mixture is stirred for 1 h at 65°C, and then cooled, and extracted with chloroform (3 times with 30 ml portions). The chloroform is distilled, and 2.82 g of I, $[\alpha]_D^{20}$ −5.26° (c 2; water), are obtained.

l-1-Phenoxy-2-hydroxy-3-ammoniumpropane-L-pantoate (IX). This is obtained similarly to VI. Yield, 4.65 g (78%). mp 132-133°C, $[\alpha]_D^{20}$ −4.1° (c 2; water. Found, %: C 55.95; H 8.56; N 4.25, $C_{15}H_{26}O_6N$. Calculated, %: C 56.94; H 8.28; N 4.43.

1-Phenoxy-2-hydroxy-3-aminopropane (l-I). This is obtained similarly to d-I. Yield, 2.65 g (42.06%, calculated on dl-I). mp 98-100°C, α_D^{20} −16.12° (c 2; water); R_f 0.48. Found, %: C 64.63; N 8.49; $C_9H_{13}NO_2$. Calculated, %: C 64.62; N 8.37.

Hydrochloride of l-I: mp 132-133°C, $[\alpha]_D^{20}$ +12° (c 2; water). Found, %: C 53.14; H 7.02; N 6.79. $C_9H_{14}NO_2Cl$. Calculated, %: C 53.08; H 6.93; N 6.87.

After heating with sodium hydrochloride and extraction with chloroform, from the filtrate of VIII, compound I, $[\alpha]_D^{20}$ +10.22° (c 2; water), is isolated.

Regeneration of D-Pantolactone (II). To an aqueous solution obtained after the separation of d-I, 10 ml of hydrochloric acid (sp. gr. 1.19) are added, and the mixture is stirred for 30 min at 80-85°C. The reaction mixture is then cooled, and extracted with 4 × 50 ml portions of chloroform. Chloroform is distilled, and 1.99 g of II are obtained. From the aqueous solution obtained after the separation of I ($[\alpha]_D^{20}$ −5.26°), 2.01 g of II are isolated as above. A total of 4.0 g of II were regenerated.

The regeneration of L-pantolactone (III) is carried out from an aqueous solution after the separation of I ($[\alpha]_D^{20}$ +10.22°) as in the regeneration of II. A total of 4.03 g of III was regenerated.

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