Identification of the Transformation Products. The transformation products were extracted from the beer and identified by TLC by the scheme described in Part I. The relative chromatographic mobilities of the substances are summarized in Table 2.

11α-Deuterocortisol (VII). Following the method of [5], the 17,20,20,21-bismethylenedioxy derivative of cortisone (3 g) was reduced with $LiAlD_4$ (isotopic purity > 95%), oxidized with active manganese dioxide, and hydrolyzed, yielding the crude product (2 g). It was refluxed with chloroform (10 ml) and left overnight in a refrigerator. The precipitate (0.94 g) was filtered off and dissolved in a mixture of chloroform (9.4 ml) and methanol (2.4 ml). Water (50 ml) was gradually stirred into the solution, which was stirred for a further 2 h and then left overnight in a refrigerator; filtration gave chromatographically pure VII (0.71 g), mp 212°C.

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SYNTHESIS OF D(+)-PANTHENOL

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One of the most important biologically active derivatives of pantothenic acid is pantothenyl alcohol (panthenol), α, γ-dihydroxy-N-(3-hydroxypropyl)-β,β-dimethylbutyramide (I).

$$HOCH_2C(CH_3)_2CH(OH)CONHCH_2CH_2CH_2OH$$
I

In its biological action in humans and animals D-panthenol displays the vitamin activity of D-pantothenic acid [1-3], being simultaneously a strong inhibitor of pantothenic acid in bacteria [4, 5]. L-Panthenol is biologically inactive; the racemate has one half the activity of the D isomer [6].

Many authors [7-9] have attributed the pantothenic acid activity displayed by this alcohol to its oxidation to the acid in experiments *in vivo*, which showed that pathenol administered to rats orally or parenterally is excreted in the urine as pantothenic acid. Japanese workers [10] have provided direct evidence for the enzymic conversion of the alcohol to pantothenic acid *in vitro* in rat liver extract. The identity of the enzyme that catalyzes the oxidation of pantothenyl alcohol with liver alcohol dehydrogenase has been demonstrated. The enzymic oxidation of the alcohol was NAD-dependent and was accompanied by the absorption of oxygen.

Because of their important metabolic role pantothenic acid and panthenol are widely used in therapy.

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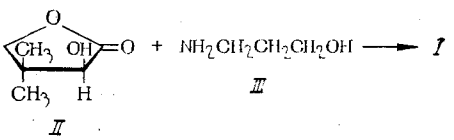
D-Panthenol displays a specifically dermotropic action, being distributed in the skin and mucosae; as a result it is used in dermatology for various dermatoses and dermatitises (resulting from intoxication, infection, metabolic disorders, and radiation), in the treatment of eczemas of various origins, burns, and various types of wounds. Panthenol is used in cosmetics prescribed for skin and scalp disorders that arise from a deficiency of pantothenic acid [11, 12].

The known methods of synthesis of panthenol comprise the condensation of 1,6-diamino-3-hexene with pantolactone [13], the reaction of α-γ-dihydroxy-β,β-dimethylbutyramide with allyl alcohol [14], and the condensation of pantolacetone (II) with 3-aminopropyl alcohol [15].

In view of the availability of the starting materials and its technical simplicity, our chosen method for synthesizing D(+)-panthenol is the condensation of D-pantolactone (II) with 3-aminopropyl alcohol (III).



The reaction was carried out by heating the reactants in a medium of the lowest aliphatic alcohols. To determine the optimum conditions we studied the influence of the reaction time, temperature, and reactant ratio on the yield and quality of the product.

Conversions were determined quantitatively by measuring the content of III in the reaction solution by titration with 0.1 N hydrochloric acid.

When equimolar quantities of the reactants were used, 90.17% of the 3-aminopropyl alcohol had reacted after 2 h at 70°C in methanol; 94.7% of pathenol had formed after 2 h at 80°C in ethyl alcohol (Fig. 1). The resulting linear dependence of $C_0 - C/C_0C$ on time implies a second-order reaction (Fig. 2).

The reaction product, obtained after removal of the solvent by distillation, is contaminated by up to 4% of the original reactants. Removal of the contaminating D-pantolactone is technically difficult; we examined this problem on a suitable scale by introducing excess III into the reaction, in view of the possibility of separating it from the reaction product with cation-exchange resin. We found that a 5% excess of III leads to the formation of 99.6% D-panthenol after 2 h at 80°C (Fig. 1).

We used KU-23 sulfonate-type cation-exchange resin (30% divinylbenzene) to remove the contaminating aminoalcohol. We determined the exchange capacity of the resin in ethyl alcohol (3.53 mg-eq/g) and methanol (3.67 mg-eq/g). The resin was used in the theoretical quantity (air-dry basis). The contaminating III in the final product was determined by titration and by thin-layer chromatography on Silufol plates in butanol–acetic acid–water (20:15:5). Panthenol had R_f 0.79 and 3-aminopropanol had R_f 0.24.

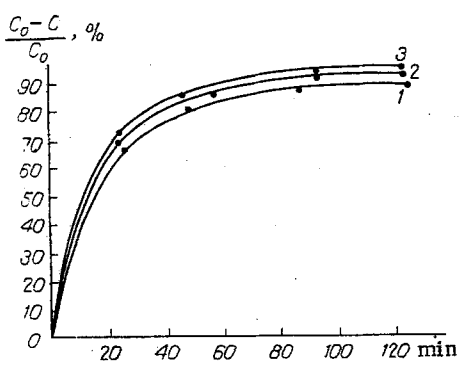


Fig. 1

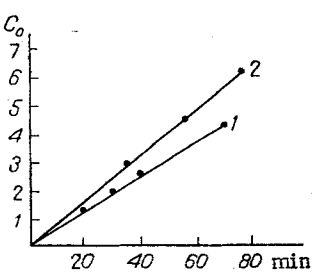


Fig. 2

Fig. 1. Consumption of III versus time: 1) at 70°C with equimolar ratio of reactants; 2) at 80°C with equimolecular ratio of reactants; 3) at 80°C and 5% excess of III.

Fig. 2. Dependence of $C_0 - C/C_0C$ on time at 1) 70°C, and 2) 80°C.

The process gave chromatographically pure D-panthenol; its IR spectrum lacked the 1780-cm^{-1} band that is characteristic for the ester group of pantolactone.

EXPERIMENTAL

After addition of III (4.61 g, 0.062 mole) to a solution of D-pantolactone (7.61 g, 0.058 mole) in ethyl alcohol (30 ml), the reaction mixture was stirred at 78-80°C for 2 h. After cooling to 20°C, KU-23 cation-exchange resin (1.5 g) was added and the mixture was stirred for 30 min. The resin was filtered off and washed with ethyl alcohol (15 ml). The combined filtrate was evaporated to dryness at 60-65°C. The yield of D-panthenol was 11.8 g (98.6%), $[\alpha]^{20}$ +31.5° (C 5; water), n_D^{20} 1.4965. Found, %: C 52.37; H 9.27; N 6.91. $C_9H_{19}NO_4$. Calculated, %: C 52.66; H 9.33; N 6.96. IR spectrum, cm^{-1}: 1540, 1650.

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PREPARATION OF CHLOROACETMESIDIDE

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The most complex stage in the production of the local anesthetic trimecaine is the preparation of chloroacetmesidide (III) by chloroacetylation of mesidine (I).

Use of chloroacetyl chloride (IIa) gives the maximum yields of III [1, 2] but because of the limited availability of this material methods have been proposed that stipulate the use of a mixture of monochloroacetic acid and phosphorus trichloride [3] and phosphorus oxychloride [4]. The acylating agent is again IIa.

In addition to the use of monochloroacetyl chloride attempts have been made to carry out the reaction with mixed acetic-chloroacetic anhydride (IIb), using a mixture of monochloroacetic acid and acetic anhydride [5].

This variant has become widely used in the commerical process, despite the comparatively low yield of III, which is attributed to the parallel acetylation reaction. The technical product III contains up to 30% of acetmesidide. Increase in the yield of the desired product in this variant obviously requires removal from the reaction mixture of acetic anhydride and

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