## A NEW METHOD OF PREPARING SYNTHOMYCIN\*

# V. I. Isagulyants and V. R. Melikyan

Synthomycin is a highly effective antibiotic. There are several means of preparing it, from acetanilide, styrene, or p-nitrobenzoic acid [2]. At present, synthomycin is most often prepared on an industrial scale from styrene; however, the multistage manufacture (11 stages) leads to a comparatively low overall yield of final product (8-10%, based on starting material). The basic compound in the synthesis of synthomycin is d1-threo-1-(p-nitrophenyI)-2-amino-1,3-propanediol "threoamine" (I), which is convertible by further dichloroacetylation to synthomycin, or after separation into optical antipodes, into levomycetin.

As a result of study of the chemical transformations of substituted 1,3-dioxanes, we have synthesized I by the following scheme:



By condensation of trans- $\beta$ -bromostyrene (II) with formaldehyde in the presence of KU-2 cationexchange resin, 4-phenyl-5-bromo-1,3-dioxane (III) was obtained, upon nitration of which 4-(p-nitrophenyl)-5-bromo-1,3-dioxane (IV) was formed.

By amination of the latter, 4-(p-nitrophenyl)-1.5-amino-1.3-dioxane (V) was obtained in 50% yield.

Methanolysis of V on KU-2 resin by the well-known method of [3] led to cleavage of the 1,3-dioxane ring, with formation of I.

It is to be noted that the proposed method requires only six stages to prepare the amine, while ten stages are usually required to prepare it from styrene.

#### EXPERIMENTAL

<u>Preparation of 4-Phenyl-5-bromo-1,3-dioxane (III)</u>. A mixture of 18.3 g of trans- $\beta$ -bromostyrene [4], 6 g of paraformaldehyde, 10 g of KU-2 ion-exchange resin, and 20 ml of dioxane was stirred for 10 h at the bp. An 80% yield of trans-III was isolated by vacuum distillation of the mixture, bp 110-115° (2 mm), n<sub>D</sub><sup>20</sup> 1.5580, d<sub>4</sub><sup>20</sup> 1.4700. Lit. [5]: bp 120-123° (3 mm), n<sub>D</sub><sup>19</sup> 1.5598. Found, %: C 50.05; H 4.78; Br 31.86. C<sub>10</sub>H<sub>11</sub>BrO<sub>2</sub>. Calculated, %: C 49.4; H 5.56; Br 32.87.

The trans-structure of III was demonstrated by IR and UV spectroscopy [6].

<u>Preparation of 4-(p-Nitrophenyl)-5-bromo-1,3-dioxane (IV)</u>. A mixture of 24.3 g of III and 50 ml of acetic anhydride was cooled to  $-5^{\circ}$  with stirring, after which 45 g of fuming nitric acid (sp. gr. 1.5) was added over a 2-h period, and stirring was continued for a few hours longer at  $-5^{\circ}$ . The reaction mixture

## \* See [1].

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was allowed to stand for a day to partially remove nitrogen oxides, after which it was poured into ice and water. The oily layer was extracted with ether (after salting-out with sodium chloride), and the ether layer was separated; the latter was washed with water to a neutral reaction. After the solution had been dried with calcium chloride and the ether had been distilled off, a very viscous yellow mass was obtained, from which crystals of trans-IV separated after standing several days, mp 131-132°, yield, 38%. Lit. [5]: mp 133.5-134°.

Preparation of 4-(p-Nitrophenyl)-5-amino-1,3-dioxane (V). Into an autoclave provided with a mechanical stirrer and an electrical heater were charged 18.3 g IV and 100 ml of absolute alcohol which had been saturated with gaseous ammonia (molar ratio of dioxane to ammonia, 1:2.5-5). The reaction was heated for 9-10 h at 95-100°. At the end of the reaction, the alcohol was distilled off on a water bath; dilute hydrochloric acid was added to the residue, and the undissolved oil was extracted with ether. After cooling, the hydrochloric acid solution was basified with NaOH solution, the base which separated was extracted with ether, and the extract was dried with sodium sulfate. After the ether had been distilled, the crystals which fell were extracted with ethanol. The yield of V was 50% (mp 115-118°).

Preparation of 1-p-Nitrophenyl-2-amino-1,3-propanediol (I). Compound V (37 g), 20 ml of methanol, and 10 g of dry KU-2 ion-exchange resin were mixed, and reaction was carried out by the previously described method [3]. After removal of the catalyst and evaporation of the solution, crystals of I precipitated, mp 138-141°, yield 37%. Lit. [2]: mp 140-141°.

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