STEREOSELECTIVE SYNTHESIS OF (±)-*threo*-2-AMINO-1-(4-NITROPHENYL)-1,3-PROPANEDIOL

Otakar ČERVINKA[a], Václav DUDEK[a], Anna FÁBRYOVÁ[a], Jiří KOLÁŘ[b], Juraj LUKÁČ[b], Jan ŠIMON[b] and Martin VIKTORIN[b]

[a] *Department of Organic Chemistry, Prague Institute of Chemical Technology, 166 28 Prague 6 and*
[b] *Léčiva, Dolní Měcholupy, 109 02 Prague 10*

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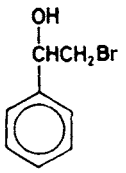
Addition of hypobromic acid to styrene afforded styrene bromohydrin (*I*) which was dehydrated to ω-bromostyrene (*II*). Prince reaction of *II* with aqueous formaldehyde gave 5-bromo-4-phenyl-1,3-dioxane (*III*). The bromine atom in *III* was replaced with amino group by treatment with methanolic ammonia at 150°C and 6–8 MPa and the obtained *threo*-5-amino-4-phenyl-1,3-dioxane (*IVa*) was hydrolyzed to give (±)-*threo*-2-amino-1-phenyl-1,3-propanediol (*V*). Suitably chosen method of nitration converted the free base *IVa* or its N-acetyl derivative *IVb* into 5-amino-4-(4-nitrophenyl)-1,3-dioxane (*VIa*) or its N-acetyl derivative *VIb* which without isolation were hydrolyzed to *threo*-2-amino-1-(4-nitrophenyl)-1,3-propanediol (*VII*), isolated as hydrochloride. The liberated base was resolved into enantiomers and dichloroacetylated in the known manner to give D-(−)-*threo*-2-dichloroacetylamino-1-(4-nitrophenyl)-1,3-propanediol (chloramphenicol).

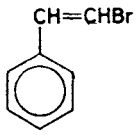
The antibiotic chloramphenicol (D-(−)-*threo*-2-dichloroacetylamino-1-(4-nitrophenyl)-1,3-propanediol), used at present predominantly in the veterinary medicine, is obtained exclusively by chemical synthesis. Of the known synthetic methods the most suitable one is based on *p*-nitroacetophenone. Our present communication describes the synthesis of the most common key intermediate, (±)-*threo*-1-(4-nitrophenyl)-2-amino-1,3-propanediol (*V*), starting from styrene. This approach is more advantageous than the other existing methods because the starting material is available and cheap. Owing to its technological importance, our synthesis was hitherto described only in the patent literature. Compound *V* is then readily converted into chloramphenicol by the usual optical resolution and dichloroacetyation.

Reaction of styrene with hypobromic acid, generated from hydrobromic acid and 30% hydrogen peroxide, afforded styrene bromohydrin (*I*). Dehydration of compound *I* to ω-bromostyrene (*II*) is complicated by easy polymerization of the product, induced by the acid catalyst. Attempted discontinuous liquid-phase dehydration under atmospheric pressure in the presence of SO_4^{2-}, Cl^-, PO_4^{3-}, or HSO_4^- ions was not satisfactory[1]. Better results were obtained with continuous gas phase dehydration

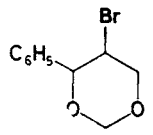
in a flow reactor on phosphorus pentoxide on Celite in a stream of nitrogen. Eventually, we suppressed the polymerization by working in a rotatory evaporator (ensuring a good mixing) with gradual addition of the reaction components in the presence of a polymerization inhibitor and under continuous removal of the product by distillation. Potassium hydrogen sulfate proved to be the catalyst of choice[2].



I

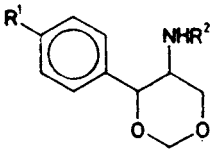


II

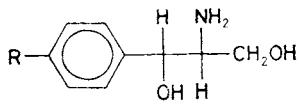


III

In the Prince reaction of ω-bromostyrene[3], leading to 5-bromo-4-phenyl-1,3--dioxane (*III*), we replaced the commonly used paraformaldehyde or trioxane by aqueous formaldehyde. The reaction was catalyzed with sulfuric acid and gave the product in high yield. The subsequent amination with methanolic ammonia under pressure was stereoselective (with configurational inversion on the halogen-bearing carbon atom) and afforded (±)-*threo*-5-amino-4-phenyl-1,3-dioxane[4] (*IVa*) which was hydrolyzed to yield (±)-*threo*-2-amino-1-phenyl-1,3-propanediol (*V*).



IV a, $R^1 = R^2 = H$
IV b, $R^1 = H$; $R^2 = COCH_3$
VI a, $R^1 = NO_2$; $R^2 = H$
VI b, $R^1 = NO_2$; $R^2 = COCH_3$



V, R = H
VII, $R = NO_2$

It was desirable to introduce the nitro group into the *para*-position of the aromatic nucleus, with minimal formation of the undesired *ortho*-derivative. However, we have found that the *para* : *ortho* isomer ratio remains almost constant (65 : 35) with various nitration reagents as well as various experimental conditions. Best results were obtained when the acetyl derivative *Vb* was nitrated with nitration mixture in nitromethane, contingently in the presence of phosphoric acid on Celite or anhydrous copper sulfate and alumina[5]. The isomer ratio was determined by comparison of the IR spectra with those of standard mixtures. The pure *ortho*- and *para*- isomers were obtained by chromatographic separation of the crude nitration product on a column of silica gel in methyl acetate–benzene (1 : 1). Cleavage or the

dioxane ring in compound *VI* represented the most difficult step. Unlike ketone acetals, acetals of formaldehyde are known to be unusually resistant to hydrolysis. Attempted acetolysis with acetic anhydride and sulfuric acid or with acetic anhydride and zinc chloride gave no satisfactory results; on the other hand, quantitative hydrolysis was achieved with 30% hydrochloric acid if the equilibrium was shifted by removal of the arising formaldehyde by distillation. Thus, hydrochloric acid was added dropwise to the dioxane derivative *VI* at 160–170°C with simultaneous distillation of the formaldehyde together with some hydrochloric acid. The reaction was monitored by the Schiff's reagent[6]. It appeared advantageous to hydrolyse the crude nitration product without previous removal of the undesired *ortho*- isomer which was then separated in the stage of hydrochlorides of nitrated 2-amino-1--phenyl-1,3-propanediols. The hydrochloride of the base *VII* could be easily isolated in the pure state by crystallization from the reaction mixture. In this manner we achieved yields of 50%, calculated for both the reaction steps (nitration and hydrolysis).

EXPERIMENTAL

The melting and boiling points are uncorrected. The analytical samples were dried for 6 h at room temperature in vacuo (oil pump).

2-Bromo-1-phenylethanol (Styrene Bromohydrin, *I*)

Hydrogen peroxide (30%, 704 g, 6·2 mol) was added dropwise at 90–95°C to a stirred mixture of hydrobromic acid (2 400 ml, 6 mol) and styrene (623 g, 6 mol) during 3 h. After cooling, the reaction mixture separated into two layers. The bottom layer was distilled to give 1 158 g (96%) of the pure product *I*, boiling at 133°C/1·6 kPa. For C_8H_9BrO (201·1) calculated: 47·78% C, 4·51% H, 39·73% Br; found: 48·02% C, 4·63% H, 39·52% Br.

ω-Bromostyrene (*II*)

Distilled styrene bromohydrin (*I*, 201 g), containing trace of hydroquinone, and a solution of crystalline potassium hydrogen sulfate (66 g) in water (200 ml) were divided into four parts. The first part of the potassium hydrogen sulfate solution was injected into rotatory evaporator flask at 1·6–2·0 kPa and 130°C. After evaporation of water at 150°C, the first portion of *I* was added. At this temperature the product began to distil; after the reaction had ceased, further portions of the reaction components were alternately added. Finally, at 185°C all the product was distilled. The distillate (164 g; 89%) contained, according to chromatographic analysis, 84% of ω-bromostyrene (80% *trans* and 20% *cis*) and was fractionated, b.p. 108°C/2·6 kPa (reported[7] b.p. 110–112°C/2·7 kPa. For C_8H_7Br (183·0) calculated: 52·50% C, 3·86% H, 43·66% Br; found: 52·38% C, 3·82% H, 43·71% Br.

5-Bromo-4-phenyl-1,3-dioxane (*III*)

Aqueous formaldehyde solution (30%, 1 800 g) was placed into a reactor. Sulfuric acid (2 060 g) was added under vigorous stirring at such a rate as to keep the temperature below 50°C. ω-Bromostyrene (755 g) was added at this temperature during 3 h. The reaction mixture was then stirred

for 3·5 h at 50°C, cooled to room temperature and poured with stirring on crushed ice (5 kg). After separation of the layers, the product was extracted with tetrachloromethane, the organic extract was washed successively with water, 10% sodium carbonate solution and water, and dried over calcium chloride. The solvent was evaporated and the product distilled to give 822 g (90%) of product *III*, b.p. 90–110°C/50·67 kPa (reported[8] b.p. 120°C/60 kPa). For $C_{10}H_{11}BrO_2$ (243·1) calculated: 49·40% C, 4·58% H, 32·87% Br; found: 49·73% C, 4·80% H, 32·56% Br. A small amount of ω-bromostyrene (38 g; 5%) was recovered.

(±)-*threo*-5-Amino-4-phenyl-1,3-dioxane (*IVa*)

Crude 5-bromo-4-phenyl-1,3-dioxane (*III*, 122 g, 0·5 mol) in methanol (200 ml) was mixed with anhydrous ammonia (190–200 g) in a stainless 1 litre autoclave. The mixture was stirred at 150 C and 6–7 MPa for 14 h. After the end of the reaction the mixture was evaporated to dryness and the residue was treated with dilute hydrochloric acid (1 : 4) to acid reaction. After extraction with tetrachloromethane (3 × 30 ml) and liberation with aqueous sodium hydroxide, the separated amine was extracted with ether. The ethereal extract was dried over potassium carbonate, the solvent was evaporated and the product distilled; yield 67·5 g (75%), b.p. 97–100°C/270 kPa (reported[8] b.p. 113°C/350 kPa). For $C_{10}H_{13}NO_2$ (179·2) calculated: 67·02% C, 7·31% H, 7·82% N; found: 67·22% C, 7·12% H, 7·89% N.

(±)-*threo*-5-Acetylamino-4-phenyl-1,3-dioxane (*IVb*)

5-Amino-4-phenyl-1,3-dioxane (*IVa*, 17·9 g) was added at 25–35°C during 15 min to a stirred and cooled mixture of sodium carbonate (15·8 g) and acetic anhydride (16·2 g). The reaction mixture was diluted with water (50 ml), stirred at room temperature for 2 h, extracted with chloroform and the extract was dried over magnesium sulfate. After evaporation of the chloroform, ether (20 ml) was added and the separated crystals were collected and washed with ether; yield 16·3 g (74%) of *IVb*, m.p. 101–104°C. For $C_{12}H_{15}NO_3$ (221·3) calculated: 65·14% C, 6·83% H, 6·33% N; found: 65·28% C, 7·01% H, 6·12% N.

(±)-*threo*-2-Amino-1-phenyl-1,3-propanediol (*V*)

A solution of compound *IVa* (17·9 g) in water (60 ml) was mixed with a cation-exchanging resin (Ostion KS, 200 ml) and steam was introduced into the mixture at 120°C. After all the formaldehyde had been distilled off (about 4 000 ml of water), the resin was transferred into a chromatographic column, washed with water (1 000 ml) and the product was eluted with 2% ammonium hydroxide. Evaporation of the eluate afforded 15·2 g (91%) of the crystalline product *V*, m.p. 80–82°C. For $C_9H_{13}NO_2$ (167·2) calculated: 64·65% C, 7·83% H, 8·38% N; found: 64·84% C, 7·65% H, 8·27% N.

(±)-*threo*-2-Amino-1-(4-nitrophenyl)-1,3-propanediol (*VII*)

A) A nitration mixture (prepared from 7·5 ml of nitric acid, $h = 1{\cdot}52$ g cm^{-3}, and 7·5 ml of 96% sulfuric cid) was mixed with nitromethane (10 ml) and cooled to −20°C. A solution of 5-acetylamino-4-phenyl-1,3-dioxane (4 g) in nitromethane (15 ml) was added dropwise under stirring during 30 min. After stirring for 1 h, the reaction mixture was poured into water (100 ml) and extracted with chloroform (3 × 40 ml). The extract was dried over magnesium sulfate, evaporated and the residue was dissolved in 30% hydrochloric acid (50 ml). The solution was heated to 160–170°C and hydrochloric acid (160–170 ml) was added dropwise at this temperature under simultaneous distillation of the formed formaldehyde. When the distillate gave a nega-

tive reaction with Schiff's reagent, the solution was concentrated to 35 ml. After cooling, the separated crystals were collected on filter and washed with 2-propanol (10 ml); yield 2·3 g (50·8%) of hydrochloride of compound *VII*, m.p. 176–8°C. For $C_9H_{13}ClN_2O_4$ (248·7) calculated: 43·47% C, 5·27% H, 11·27% N; found: 43·67% C, 5·31% H, 11·47% N.

B) Distilled acetic anhydride (183·6 g) was slowly added dropwise to a cooled and stirred 5-amino-4-phenyl-1,3-dioxane (17·9 g) so as the temperature did not exceed 20°C. The mixture was cooled to 0°C and fuming nitric acid (64 g) was added dropwise at 0°C during 30 minutes under cooling and stirring. The stirring was continued for further 30 min at 0°C and for 2 h at 20°C. The mixture was poured on ice (200 g), neutralized with 10% sodium carbonate solution (250 ml), extracted with dichloromethane (3 × 100 ml) and the combined organic phases were washed with water. Evaporation of the solvent gave a deep yellow oil, containing both isomers (according to spectral analysis), which was directly hydrolyzed by heating to 166–170°C with 30% hydrochloric acid (232 g). At this temperature, hydrochloric acid was added dropwise with simultaneous distillation. After collecting 700 g of the distillate, no reaction with Schiff's reagent was observed. The mixture was concentrated to 150 ml, filtered with charcoal and inoculated. The nitration product was filtered, washed with cold ether (20 ml) and dried over phosphorus pentoxide in vacuo for 24 h. Yield 8·9 g (40%) of hydrochloride of *VII*, m.p. 177°C. On treatment with an alkali, the hydrochloride liberated the base *VII* which was taken up in ethyl acetate. After evaporation of the solvent, the product was crystallized from ethanol, m.p. 142 to 144°C (reported[9] m.p. 141–143°C). For $C_9H_{12}N_2O_4$ (212·2) calculated: 50·94% C, 5·70% H, 13·20% N; found: 51·08% C, 5·85% H, 13·01% N.

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