IMPROVEMENT OF THE SYNTHESIS OF DICAIN

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At present, two methods for the synthesis of dicain [p-(butylamino)benzoic acid β-(dimethylamino)ethyl ester hydrochloride (I)] are known [2-4]. In the first method p-nitrobenzoic acid (II) is reduced, the resulting p-amino-benzoic acid (III) is alkylated to IV, IV is chlorinated, and acid chloride V is used to acylate β-(dimethylamino)ethanol [3].

$$p\text{-}O_2NC_6H_4COOH \xrightarrow{} p\text{-}H_2NC_6H_4COOH \xrightarrow{n\text{-}C_4H_9Br}$$
II III

$$\xrightarrow{} p\text{-}(n\text{-}C_4H_9)NHC_6H_4COOH \xrightarrow{SOCl_2} p\text{-}(n\text{-}C_4H_9)NHC_6H_4COCl\cdot HCl \xrightarrow{HOCH_2CH_2N(CH_3)_2}$$
IV V

$$\xrightarrow{} p\text{-}(n\text{-}C_4H_9)NHC_6H_4COOCH_2CH_2N(CH_3)_2\cdot HCl$$
I

The yield of I was 28% based on III.

In the second method ethyl p-nitrobenzoate (VI), which was synthesized from II, is reduced to VII, VII is converted to β-(dimethylamino)ethyl p-aminobenzoate (VIII), and I is obtained by reductive alkylation of VIII [2, 4].

$$p\text{-}O_2NC_6H_4COOH \xrightarrow[H_2SO_4]{C_2H_5OH} p\text{-}O_2NC_6H_4COOC_2H_5 \xrightarrow{}$$
II VI

$$\xrightarrow{} p\text{-}H_2NC_6H_4COOC_2H_5 \xrightarrow{HOCH_2CH_2N(CH_3)_2}$$
VII

$$\xrightarrow{} p\text{-}H_2NC_6H_4COOCH_2CH_2N(CH_3)_2 \xrightarrow[Zn;\ CH_3COOH]{CH_3CH_2CH_2C(=O)H}$$
VIII

$$p\text{-}(n\text{-}C_4H_9)NHC_6H_4COOCH_2CH_2N(CH_3)_2 \xrightarrow{HCl}$$
IX

$$\xrightarrow{} p\text{-}(n\text{-}C_4H_9)NHC_6H_4COOCH_2CH_2N(CH_3)_2\cdot HCl$$
I

The overall yield of I via this scheme in many respects is determined by the transesterification step (the transformation VII→VIII). In [4] it is pointed out that this reaction proceeds in 80% yield; however, the qualitative and quantitative indexes of VIII, the method used to purify it, and the results of elementary analysis are not presented. We reproduced the synthesis of VIII from VII by the method in [4] and analyzed the product by gas-liquid chromatography (GLC). We found that unpurified VIII contains a significant number of impurities, including 15-20% starting VII.

According to the data in [2], the yield of VIII based on VII is 49.24%, while the yield of I based on starting II does not exceed 23.9%.

We investigated the possibility of obtaining I by a new method in which, in contrast to the first scheme, the acylation of β-(dimethylamino)ethanol is carried out with the more active p-nitrobenzoyl chloride (X).

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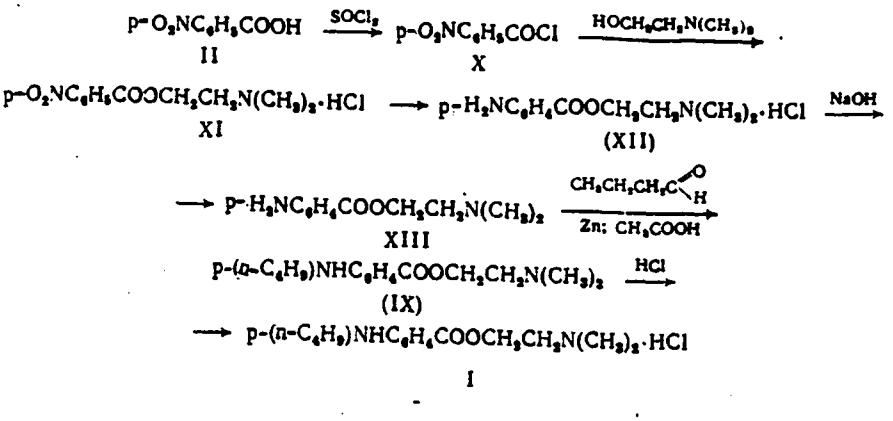
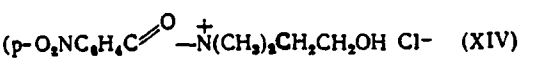


We found that the reaction of X and β-(dimethylamino)ethanol in benzene, toluene, dichloroethane, and chlorobenzene proceeds to give XI in ~ 63% yield based on II. The relatively low yield is evidently explained by the fact that the acylation reaction is complicated by a side process that results in the formation of a rather stable acylammonium salt.



This is confirmed by the fact that XIV is rapidly hydrolyzed to give β-(dimethylamino) ethanol hydrochloride and II when the precipitated mixture of XI and XIV formed in the acylation is treated with water.

The realization of the indicated process in chloroform made it possible to obtain XI in high yield. Considering the ability of chloroform to form donor—acceptor complexes with organic bases [1, 5, 6], it may be assumed that β-(dimethylamino)ethanol also reacts with chloroform. The tertiary amino group in the resulting $Cl_3C...H...N(CH_3)_2CH_2CH_2OH$ complex is probably blocked, and acylation is directed unambiguously to the alcohol hydroxy group. Thus in this case chloroform has a positive regulating effect on the course of the reaction itself.

After the acylation step, XI was extracted with water and reduced in solution with powdered iron; it is not necessary to introduce an electrolyte, since starting salt XI plays this role. The reduction of XI to XII proceeds rapidly and quantitatively and is easily monitored by TLC. We carried out the subsequent synthesis of I by the reductive alkylation of XIII by the method in [2] with several changes. The entire synthesis of I, beginning with II up to the production of the crude preparation, can be accomplished without isolation of the intermediates. Thus by a technologically simple method we obtained I in 51.8% yield (based on II), which exceeds the yields previously obtained [2-4] by a factor of almost two.

The compositions and structures of the obtained and isolated XI and XIII were confirmed by the results of elementary analysis and by the IR, PMR, and UV spectra.

EXPERIMENTAL

Chromatography of the reaction products was carried out on Silufol UV-254 plates (Czechoslovakia) with elution with chloroform (saturated with ammonia)—n-butanol (1:1) and development with UV light and iodine vapors. The IR spectra of suspensions in mineral oil were recorded with a UR-20 spectrometer (East Germany). The UV spectra of solutions in water were obtained with an SF-16 spectrophotometer. The PMR spectra of solutions in CDCl3 were recorded with a Tesla BS 487 spectrometer (Czechoslovakia) with an operating frequency of 80 MHz; the internal standard was hexamethyldisiloxane (HMDS).

p-(Butylamino)benzoic Acid β-(Dimethylamino)ethyl Ester Hydrochloride (I). A mixture of 30 g (0.18 mole) of II, two drops of dimethylformamide, and 30 ml (0.42 mole) of thionyl chloride was refluxed for 1 h, after which the excess thionyl chloride was removed by distillation, and 50 ml of chloroform that did not contain ethanol was added to the resulting acid chloride X. The solution of X in chloroform was added with cooling (the temperature in the mass was no higher than 30°C) to a solution of 16 g (0.18 mole) of β-(dimethylamino)ethanol in 125 ml of chloroform, after which the mixture was refluxed for 1 h, cooled, and treated

with 75 ml of water. After the precipitated XI had dissolved in the water, the organic layer was separated, and XI was extracted repeatedly from it with 25 ml of water. The combined aqueous extracts of XI were then subjected to reduction.

The aqueous solution of XI was added to a mixture of 30 g of powdered iron and 10 ml of water heated to 80°C at such a rate that the mass boiled gently, after which the mixture was refluxed for 45 min, and the iron sludge was removed by filtration. The aqueous solution was cooled to 0°C and made alkaline to pH 10.5-11.0 with NaOH solution. The precipitated XIII was removed by filtration, washed with cold water, and dissolved in 150 ml of hot (90°C) toluene. The solution was filtered, and the water contained in it was removed in the form of an azeotrope with toluene by distillation. Zinc dust (30 g) was added to the dry toluene solution of XIII, the mixture was heated to the boiling point, and a solution of 14.1 g (0.19 mole) of butyraldehyde in 33 ml of acetic acid was added in portions in the course of 1 h. The mass was refluxed for 20 min, after which a second portion of the "butylating mixture" consisting of 12.7 g (0.18 mole) of butyraldehyde and 3.4 ml of acetic acid was added. After refluxing for 20 min, the hot mass was filtered and cooled, and 84 ml of 25% ammonium hydroxide was added. The toluene layer was separated and washed with water, and I was extracted from it with 50 ml of 18% hydrochloric acid solution. The aqueous extract of I was neutralized to pH 6.0 with 40% NaOH solution, and 0.2 g of $Na_2S_2O_4$ and 60 ml of a saturated aqueous solution of sodium chloride were added. Crude I crystallized at 3-5°C and was filtered and washed with cold water. This procedure gave 36.8 g of a paste of the crude product containing 30.5 g of I.

To obtain the pharmacopeial product, crude I was recrystallized from water and dried to give 27.7 g (27.68 g 100%) of I in the form of colorless crystals with mp 148-150°C. The yield was 51.8% based on II.

p-Nitrobenzoic Acid β-(Dimethylamino)ethyl Ester Hydrochloride (XI). The product was formed as a precipitate in chloroform after acylation of β-(dimethylamino)ethanol with acid chloride X. Filtration and recrystallization from ethanol gave 40.9 g (83% based on II) of XI in the form of colorless crystals with mp 182-183°C. Found: Cl 12.83; N 9.86. $C_{11}H_{15}O_4N_2Cl$. Calculated, %: Cl 12.93; N 10.20. IR spectrum, ν_{max}, cm^{-1}: 1348 (NO_2). PMR spectrum, δ, ppm: 2.25 s [6H, $N(CH_3)_2$], 2.69 t (2H, CH_2N), 4.45 (2H, OCH_2), 8.27 s (4H, aromatic). UV spectrum, λ_{max}, nm (log ε): 263 (4.1). The product has R_f 0.74.

p-Aminobenzoic Acid β-(Dimethylamino)ethyl Ester Hydrochloride (XII). The product was isolated from the toluene solution after the reduction of XI and separation of the iron sludge. The toluene solution of XIII was extracted with 30 ml of 18% hydrochloric acid solution, the extract was made alkaline to pH 10.0-10.5 with 40% NaOH solution, and the precipitated base XIII was removed by filtration, washed with cold water, and dried. The XIII was then dissolved in 50 ml of isopropyl alcohol, 30 ml of a 25% solution of HCl in isopropyl alcohol was added, and the mixture was cooled to 5-10°C. The precipitate was removed by filtration and dried to give 32.9 g (75% based on II) of XII in the form of colorless crystals with mp 184-185°C (from ethanol). Found, %: Cl 14.98; N 11.4. $C_{11}H_{17}O_2N_2Cl$ Calculated, %: Cl 14.50; N 11.36. IR spectrum, ν_{max}, cm^{-1}: 3410, 3510 (NH). PMR spectrum δ, ppm: 2.25 s [6H, $N(CH3)_3)_2$], 2.63 t (2H, CH_2N), 4.33 t (2H, OCH_2), 6.57 d (2H, aromatic), 7.88 d (2H, aromatic). UV spectrum, λ_{max}' nm (log ε): 291 (4.17). The product had R_f 0.39.

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