ETHADEN SYNTHESIS

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Ethaden, or 6-amino-8-(β-hydroxyethylamino)purine hydrobromide hydrate (Xa), is an original Russian drug used as a stimulator of reparative processes in the human organism. The drug is administered in cases of ulceration in the stomach and duodenum, thermal and radiation skin damage, and leukopenia [1 – 3].

Ethaden as a chemical compound was obtained in the form of free base (X) by interaction of 8-bromoadenine with 2-aminoethanol [4]. Because adenine is not commercially produced in Russia, a special procedure was developed in the State Chemico-Pharmaceutical Academy (St.-Petersburg) for ethaden synthesis proceeding from cyanoacetic acid ethyl ester. The method is based on the well-known scheme involving intermediate adenine and 8-bromoadenine. The process includes nine stages, providing a target product yield of about 4% (calculated for the initial ester).

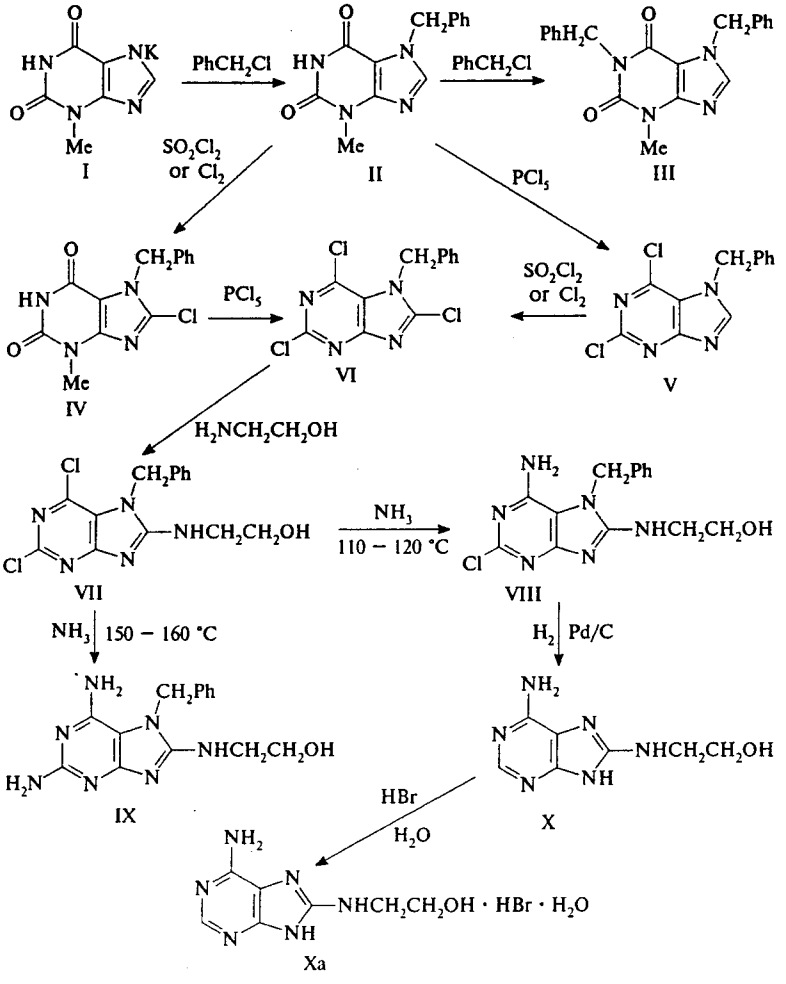
Within the framework of creating a combined scheme of production of a series of medicinal preparations on the basis of commercially available 3-methylxanthine (a semiproduct in the production of caffeine and theobromine), we have developed a new method for ethaden synthesis.

According to the procedure described previously [5], we used a potassium salt of 3-methylxanthine (I) and benzyl chloride to obtain 3-methyl-7-benzylxanthine. Note that a large excess of benzyl chloride is not allowed, since otherwise compound II is subjected to further benzylation in position 1 under the reaction conditions with the formation of 1,7-dibenzyl-3-methylxanthine (III).

The main semiproduct in the proposed scheme of ethaden synthesis is previously unreported 2,6,8-trichloro-7-benzylpurine (VI). We have elaborated three variants of obtaining this compound.

According to the first variant, xanthine II was chlorinated with chlorine or sulfuryl chloride with the formation of 3-methyl-7-benzyl-8-chloroxanthine (IV). This compound was treated with PCl_5 to yield the target 7-benzyltrichloropurine VI.

In the second variant, 7-benzylxanthine II was initially chlorinated with PCl_5 by the method described in [5]. The resulting 2,6-dichloro-7-benzylpurine (V) was treated with chlorine or sulfuryl chloride, smoothly forming trichloride VI.



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A most technologically simple procedure for the synthesis of trichloride III was offered by the reaction of xanthine II with chlorine and PCl_5 in $POCl_3$ as a solvent. The first stage of this process is the formation of 8-chloroxanthine IV under the action of Cl_2. Compound IV is treated (without isolation) with PCl_5, which results in the splitting of methyl chloride and the formation of trichloride VI.

The above syntheses of the trichloride derivative of purine have demonstrated the different reaction abilities of chlorine atoms in positions 8, 6, and 2 (with the maximum mobility in the nucleophilic substitution reaction observed for the chlorine atom in position 8, and the minimum in position 2). This feature was employed in the proposed ethaden synthesis.

Boiling 7-benzyltrichloropurine VI with aminoethanol in ethyl alcohol leads to the formation of 2,6-dichloro-6-amino-7-benzyl-8-(β-hydroxyethylamino)purine (VII). This compound, on heating with 12.5% aqueous ammonia at 110–120°C, is converted into 2-chloro-6-amino-7-benzyl-8-(β-hydroxyethylamino)purine (VIII). Under more rigid conditions (150–160°C), the nucleophilic substitution involves chlorine atoms in position 2 as well, which results in the formation of a side product, 2,6-diamino-7-benzyl-8-(β-hydroxyethylamino)purine (IX).

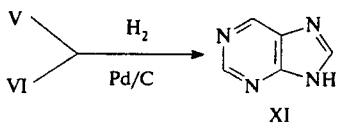
To obtain ethaden X, compound VIII was hydrogenated in ethanol solution in the presence of a palladium catalyst. This interaction led to removal of the benzyl protection and conversion of the C–Cl bonds into C–H in position 2. The role of hydrogen chloride acceptors in this reaction can be performed by NaOH, CH_3COONa, or other bases.

The last stage of ethaden synthesis is very simple, consisting in the conversion of base X into its hydrobromide Xa.

Thus, the investigation described above allowed us to develop a new preparative method for ethaden synthesis, not involving expensive and relatively unavailable reagents – adenine and bromine.

It was reported that purine XI can be obtained by a catalytic dechlorination of 6-chloropurine [6, 7], 2,6-dichloropurine [7], or 2,6,8-trichloropurine [7] in the presence of a palladium catalyst.

Once the di- and trichloro-7-benzylpurine derivatives (V, VI) are readily available, we have performed hydrogenation of these compounds and obtained purine, a valuable chemical reagent, with a yield on the order of 70%.



XI

EXPERIMENTAL CHEMICAL PART

The IR spectra of the synthesized compounds were measured on a Perkin-Elmer Model 682 spectrophotometer using samples prepared as nujol mulls. The ^1H NMR spectra were obtained with a Tesla-6-spectrometer using DMSO-d_6 as the solvent and TMS as the internal standard.

The purity of the reaction products was checked by TLC on Silufol UV-254 plates eluted in *n*-butanol – acetic acid – water, 4 : 1 : 5 (system 1) and chloroform – ethyl alcohol – ammonia, 30 : 20 : 1 (system 2) solvent mixtures and developed by exposure to UV light or iodine vapors.

The data of elemental analyses for both previously unreported compounds (III, IV, VI – IX) and the known substance X and its hydrobromide Xa agree with the results of calculations according to the empirical formulas.

In all stages of the ethaden synthesis, except for the last one (base to hydrobromide Xa conversion), the intermediate compounds II, IV – VIII were used in the form of technical products without any additional purification.

3-Methylxanthine potassium salt (I). Commercial product, preliminarily dried at 120 – 130°C to constant weight (the main substance content, not less that 96%).

7-Benzyl-3-methylxanthine (II). Compound II was obtained as described in [5]; R_f, 0.56 (system 1).

1,7-Dibenzyl-3-methylxanthine (III). A mixture of 2.56 g (0.1 mole) of compound II, 2.0 g (0.125 mole) of 25% NaOH, and 1.5 ml (1.65 g, 0.13 mole) of benzyl chloride in 20 ml DMF was boiled for 4.5 h, cooled, poured into water, and allowed to stand overnight for precipitation. The precipitate was filtered, washed with water and ether, and suspended in 150 ml of 0.5 N NaOH. The insoluble precipitate was filtered, washed with water and ether, and dried to obtain 2.67 g (77%) of compound III; m.p., 108 – 111°C. A white powder with m.p. = 108 – 111°C, obtained upon reprecipitation from acetone with water, is soluble in most of the common organic solvents.

7-Benzyl-3-methyl-8-chloroxanthine (IV).

(A) A mixture of 5.0 g of compound II and 50 ml of SO_2Cl_2 was stirred for 5 h at 10 – 12°C and allowed to stand overnight. The precipitate was filtered, transferred into a glass with ice, and neutralized with aqueous ammonia (to pH 7). The precipitate was filtered, washed with water, and dried to obtain 4.45 g (78%) of compound IV with m.p. = 233 – 236°C. A white powder with m.p. = 238 – 239°C, obtained upon reprecipitation from acetone, is poorly soluble in most of the common organic solvents and soluble in DMF.

(B) A solution of 1.3 g of compound II in 15 ml of $POCl_3$ was purged with stirring at room temperature with a weak flow of chlorine for 1h. Then $POCl_3$ was distilled off in vacuum. The residue was decomposed in ice-cold water and neutralized with aqueous ammonia (to pH 7). The precipitate was filtered, washed with water, and dried to obtain 1.1 g (76%) of compound IV with m.p. = 232 – 236°C. A sample obtained by mixing compounds IV obtained by methods A and B showed no evidence of depression in the melting temperature.

7-Benzyl-2,6-dichloropurine (V). Compound V was obtained as described in [5].

7-Benzyl-2,6,8-trichloropurine (VI).

(A) A mixture of 1.0 g (0.0034 mole) of monochloride IV and 80 ml of $POCl_3$ was boiled for about 2.5 h, until complete dissolution of precipitate, and cooled. To this solution was added 1.43 g (0.0035 mole) of PCl_5 and the boiling was continued for 4 h. Then the reaction mixture was slowly, with constant stirring, decomposed with ice-cold water and then treated with aqueous ammonia (to alkaline reaction). The precipitate was filtered, washed with water, and dried to obtain 1.0 g (93.5%) of compound VI with m.p. = 134 – 137°C. A light-yellow powder with m.p. = 138 – 139°C, obtained upon reprecipitation from 0% ethanol, is soluble in most of the common organic solvents; R_f = 0.56 (system 1).

(B) A mixture of 2.8 g of dichloride V in 30 ml of SO_2Cl_2 was treated as described for compound IV (method A). Yield of compound VI, 2.8 g (90%); m.p., 133 – 137°C.

(C) A solution of 2.8 g of dichloride V in 30 ml of $POCl_3$ was treated with chlorine as described for compound IV (method B). Yield of compound VI, 2.7 g (87%); m.p., 134 – 137°C.

(D) Technical phosphorus oxychloride (1400 ml) was boiled for 2.5 – 3 h (to remove HCl), cooled to 15 – 20°C, and saturated with chlorine (100 g, 1.41 mole). To the resulting solution was gradually added (during 1.5 – 2 h) by small portions with stirring 325 g (1.27 mole) of compound II (after which the temperature increases to 40 – 50°C). Then the reaction mixture was stirred for 1.5 – 2 h at 68 – 72°C, boiled for 5 – 6 h, and cooled to 15 – 20°C. To this mixture was gradually added by small portions with stirring 528 g (2.54 mole) of PCl_5, after which the temperature was gradually (over 2 – 2.5 h) increased to 70°C and then to the boiling temperature. The solution was boiled for 3 – 4 h with simultaneous distillation of $POCl_3$ (1600 ml, to be repeatedly used in the same reaction), after which the residue was cooled to 18 – 20°C. The precipitate was filtered and transferred in small portions with stirring into a glass with crushed ice and 25 – 30 ml of 25% aqueous ammonia. The crushed ice was added (so as to ensure that the temperature would not rise above 15°C) and aqueous ammonia was added to a total volume of about 185 ml to obtain the reaction mass with pH 8. The precipitate was filtered, washed with water, and dried to obtain 358 g (90%) of technical-purity compound VI with m.p. = 135 – 137°C. A sample obtained by mixing compounds VI obtained by methods A – D showed no evidence of depression in the melting temperature.

7-Benzyl-8-(β-hydroxyethylamino)-2,6-dichloropurine (VII). A mixture of 201.6 g (0.64 mole) of trichloropurine VI and 78.3 g (1.28 mole) of aminoethanol in 500 ml of ethyl alcohol was boiled for 3 – 4 h and cooled to 4 – 6°C. The precipitate was filtered, washed with 50% ethanol (2 × 50 ml) and dried to obtain 177 g of the product with m.p. = 178 – 180°C. The mother water – ethanol liquors were evaporated to reduce the volume to 150 – 160 ml and poured into a tenfold excess of water to obtain additionally 28.7 g of the same compound with m.p. = 176 – 178°C. The total yield of technical product VII, 205.7 g (90%). The analytically pure compound VII has m.p. = 189 – 191°C (from 50% ethanol) and R_f = 0.82 (system 1). The compound appears as a light-yellow powder, soluble in most of the common organic solvents.

6-Amino-7-benzyl-8-(β-hydroxyethylamino)-2-chloropurine (VIII). A mixture of 40 g (0.118 mole) of compound VII and 100 ml of 12.5% aqueous ammonia was charged into a 300-ml stainless-steel rotating autoclave, treated for 2 – 24 h at 110 – 120°C, and cooled. The precipitate was filtered, washed with water, and dried to obtain 37.5 g (95%) of technical-purity compound VIII with m.p. = 230 – 233°C. The analytically pure compound VIII has m.p. = 249 – 252°C (from 20% CH_3COOH) and R_f = 0.65 (system 1). The compound appears as a yellow-grey powder, pooorly soluble in lower alcohols.

2,6-Diamino-7-benzyl-8-(β-hydroxyethylamino)purine (IX). Compound IX was obtained similarly to compound VIII, except for the amination process conducted at 150 – 160°C; yield, 51%; m.p., > 300°C (DMF); R_f, 0.45 (system 1).

6-Amino-8-(β-hydroxyethylamino)purine (X). A mixture of 20 g (0.062 mole) of compound VIII, 5.0 g (0.125 mole) of NaOH, and 20 g of 5% palladium on carbon in 400 ml ethanol was hydrogenated at 50 – 60°C and atmospheric pressure until the hydrogen absorption ceased. The process duration was 6 – 8 h. Then the reaction mass was cooled, NaCl and the catalyst were filtered, and the residue washed with ethanol (3 × 30 ml). To the filtrate, acidified with 3 ml of concentrated HCl, was added a few drops of 25% aqueous ammonia to obtain pH 7.5 – 8. The solution was cooled to 4 – 6°C and the precipitate was filtered, washed with cold ethanol (10 ml), and dried to obtain 7.8 g (65%) of the technical-purity base X with m.p. = 256 – 258°C (with decomp.). By evaporating the mother liquor, it is possible to obtain an additional amount of the product. The product reprecipitated from water appears as a white crystalline powder with m.p. = 260 – 262°C (with decomp.) and R_f = 0.21 (system 2); reported m.p. = 262 – 265°C (with decomp.) [4].

6-Amino-8-(β-hydroxyethylamino)purine hydrobromide monohydrate (Xa). Compound Xa was obtained from a pure base X and a pure colorless 40% HBr solution in ethanol with a yield of 80%. The product appears as a white crystalline powder, poorly soluble in water and ethanol; m.p., 240 – 242°C (with decomp.); R_f, 0.21 (system 2). Heating to 105 – 110°C leads to dehydration; staying in air leads to absorption of 1 mole water and conversion to monohydrate. The IR spectrum of compound Xa, KBr disk (ν, cm^{-1}): 3420, 2890, 2790 (NH_2, NH, OH). The melting temperature, TLC pattern, and parameters of the IR an 1H NMR spectra of compound Xa were identical to those of the ethaden sample kindly provided by the State Chemico-Pharmaceutical Academy (St. Petersburg).

Purine (XI). Compound XI was obtained by hydrogenation of dichloropurine V or trichloropurine VI in a water – ethanol mixture in the presence of 5% palladium on carbon and sodium acetate as described in [7]. Yield of compound

XI, 70 – 73%; m.p., 213 – 215°C; reported m.p. = 216°C [6], 213 – 215°C and 217 – 219°C [7].

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