SYNTHESIS OF PTEROIC ACID

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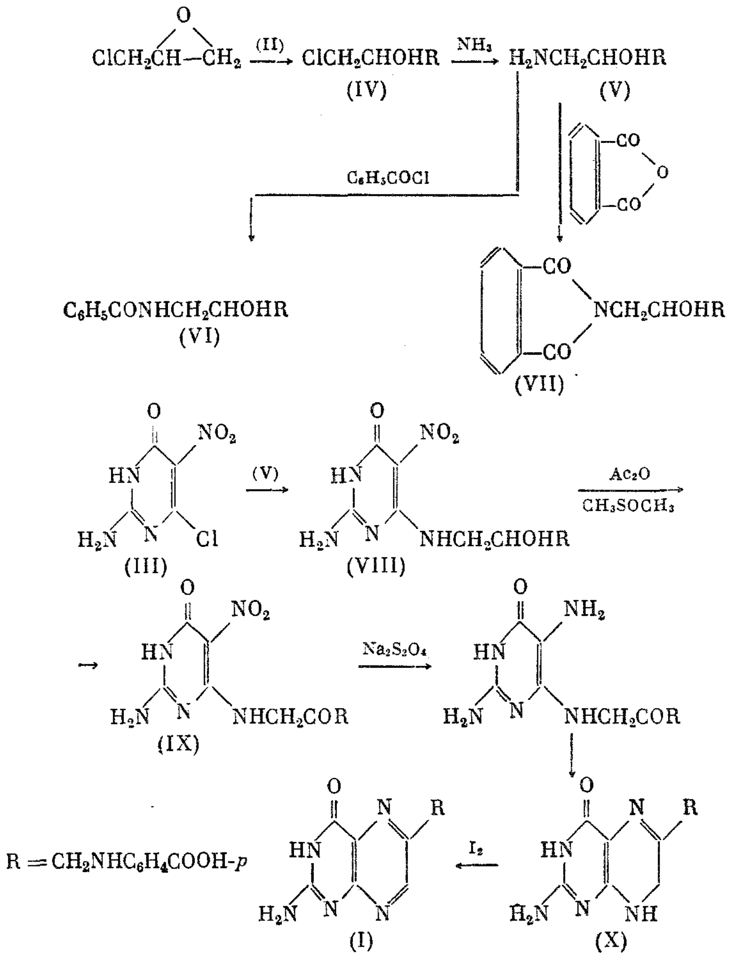
Pteroic acid (I) is a growth factor of certain microorganisms [1]. For a further study of the biological properties of (I) we effected a simple synthesis of (I) by starting with epichlorohydrin, p-aminobenzoic acid (II), and 2-amino-4-hydroxy-5-nitro-6-chloropyrimidine (III) [2] via the following scheme.



p-(β-Hydroxy-γ-chloropropylamino)benzoic acid (IV) was obtained when (II) is heated with epichlorohydrin, which with aqueous NH_3 in the presence of NH_4Cl gives p-(β-hydroxy-γ-aminopropylamino)benzoic acid (V). The structure of the latter was confirmed by conversion to the N-benzoyl and phthaloyl derivatives (VI) and (VII).

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The reaction of (III) with (V) in the presence of $NaHCO_3$ leads to the formation of 2-amino-4-hydroxy-5-nitro-6-(β-hydroxy-γ-(p-carboxyphenylamino)propylamino)pyrimidine (VIII). The sought (I) was isolated by oxidizing nitro derivative (VIII) with dimethyl sulfoxide and Ac_2O, reduction of the nitro group with $Na_2S_2O_4$, closure of the dihydropyrazine ring, and subsequent dehydrogenation.

EXPERIMENTAL

The UV spectra of alcohol solutions of the compounds were taken on a Specord UV-VIS instrument.

p-(β-Hydroxy-γ-chloropropylamino)benzoic Acid (IV). A mixture of 5.64 g of epichlorohydrin and 8.28 g of (II) in 50 ml of alcohol was refluxed for 15 h, evaporated in vacuo, the residue was treated with ether, and the precipitate was filtered and dried in the air. We obtained 10.6 g (76%) of (IV), mp 156-157°. Found: C 52.59; H 5.37; N 6.84%. $C_{10}H_{12}ClNO_3$. Calculated: C 52.29; H 5.23; N 6.31%.

p-(β-Hydroxy-γ-aminopropylamino)benzoic Acid (V). A mixture of 4 g of (IV) and 8 g of NH_4Cl in 60 ml of 28% NH_3 solution was kept at ~20°C for ~100 h, after which it was evaporated in vacuo, the residue was dissolved in 100 ml of boiling water, filtered hot, and the filtrate was cooled to ~20° and transferred to a column containing Dowex-50 (200 ml). The chloride ions were eluted with 500 ml of distilled water, and then the reaction product was eluted with 500 ml of 1 N NH_3 solution. After evaporation, the residue was dried in vacuo over P_2O_5 to give 3.01 g (80%) of (V), mp 236-238° (decompn.). Found: C 57.13; H 6.67; N 12.85%. $C_{10}H_{14}N_2O_3$. Calculated: C 57.14; H 6.67; N 13.19%.

Benzoyl Derivative (VI). With stirring, to a solution of 0.86 g of Na_2CO_3 in 15 ml of water were gradually added 1.4 g of (V) and 0.96 g of C_6H_5COCl (temperature kept below 20°), after which the mixture was stirred for another 2 h at 20°, and then it was acidified with conc. HCl to pH 3, 10 ml of AcOEt was added, and it was let stand at 20° for 12 h. The precipitate was filtered and dried in the air to give 0.89 g (44%) of (VI) with mp 194-196°; λ_{max} 227 and 303 nm. Found: 64.61; H 5.88; N 9.03%. $C_{18}H_{18}N_2O_4$. Calculated: C 64.97; H 5.73; N 8.92%.

Phthaloyl Derivative. A mixture of 1.4 g of (V) and 1 g of phthalic anhydride was heated for 1 h at ~160° (bath), after which it was cooled and the residue was recrystallized from methyl cellosolve to give 2 g (94%) of (VII), mp 236-238° (decompn.); λ_{max} 223 and 303 nm. Found: C 63.20; H 4.84; N 8.48%. $C_{18}H_{18}N_2O_5$. Calculated: C 63.52; H 4.74; N 8.23%.

2-Amino-4-hydroxy-5-nitro-6-(β-hydroxy-γ-(p-carboxyphenylamino)-propylamino)pyrimidine (VIII). A stirred mixture of 2.7 g of 2-amino-4-hydroxy-5-nitro-6-chloropyrimidine [2], 2.93 g of (V), and 1.2 g of $NaHCO_3$ in 180 ml of alcohol was refluxed for 60 h, after which it was cooled, acidified with conc. HCl to pH 2, and the precipitate was filtered, washed with water, dissolved in excess 10% Na_2CO_3 solution, and again acidified with conc. HCl to pH 2. The precipitate was filtered, washed with water, then with alcohol, and dried in vacuo over P_2O_5. We obtained 2.8 g (55%) of (VIII), mp ~290° (decompn.). Found: C 44.27; H 4.45%; $C_{14}H_{16}N_6O_6 \cdot H_2O$. Calculated: C 43.98; H 4.75%.

Pteroic Acid (I). To a solution of 1.47 g of (XIII) in 12 ml of dimethyl sulfoxide at ~40° was added 8 ml of Ac_2O, and the mixture was kept at ~20° for 24 h and then poured into 600 ml of water. After 1 h the precipitate was filtered, washed with water and ether, dissolved in 50 ml of 10% NH_3 solution, let stand at 20° for 12 h, and then, with cooling in ice, it was acidified with conc. HCl to pH 3. The precipitate was filtered, washed with water, and dried in the air to give 0.9 g of ketone (IX), which was reduced as such. For this 1 ml of 2 N NaOH solution was added to 0.75 g of (IX) in 45 ml of 0.1 N Na_2CO_3 solution, the mixture was heated to 70° and then, with stirring, 4.5 g of $Na_2S_2O_4$ was added in 15 min. Then the mixture was heated for another hour at 70°, cooled, filtered, and the filtrate was acidified with AcOH to pH 3. The precipitate was filtered, washed in succession with water, alcohol, and ether, and dried in the air. We obtained 0.2 g of dihydropteroic acid (X), which was oxidized as such. A mixture of 0.1 g of (X) and 2 ml of a saturated alcohol solution of I_2 in 2 ml of 0.1 N Na_2CO_3 was kept at ~20° for 24 h, and then it was acidified with AcOH to pH 3. The precipitate was filtered, washed with boiling water, and reprecipitated several times from alkaline solution with dilute HCl solution. We obtained 0.08 g of (I), R_f 0.15 (paper chromatography, 0.1 N $(NH_4)_2CO_3$ solution, Leningrad Factory paper M). λ_{max} 258, 276, and 370 nm. Authentic (I) had the same R_f and UV spectrum [3].

The oxidation of (I) with $KMnO_4$ solution as described in [4] gave pterin-6-carboxylic acid.

We express our gratitude to L. Plante for supplying the sample of (I).

CONCLUSIONS

Pteroic acid was synthesized by starting with 2-amino-4-hydroxy-5-nitro-6-chloropyrimidine, epichlorohydrin, and p-aminobenzoic acid.

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MECHANISM OF INITIATED OXIDATION OF DIMETHYLAMINOETHYL METHACRYLATE

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The rate constants of chain propagation and termination in alkyl methacrylates when oxidized were measured by us previously [1]. A similar study was made in the present paper for an aminoalkyl ester in order to ascertain the specific effect of a tertiary amino group on the oxidation of a methacrylate.

EXPERIMENTAL

Dimethylaminoethyl methacrylate (DMAEM) was purified in an argon stream by passage through a column containing activated Al_2O_3 and subsequent vacuum-distillation. The initiation rate constant (k_i) for azobisisobutyronitrile (ABIN) in the amino ester medium was measured by the consumption rate of 2,2,6,6-tetramethyl-4-oxo-piperidine-1-oxyl in an argon atmosphere employing the EPR method. In DMAEM the quantity k_i (sec^{-1}) obeys the following equation:

$$\lg k_i = (17.2 \pm 0.2) - (34\,000 \pm 400)/4.57\,T$$

in the range 30-60°C. The rate of the AIBN-initiated oxidation of DMAEM (W) was measured by the O_2 absorption. In the range 0.2-1.0 ata (absolute atmosphere) the quantity W is independent of the O_2 pressure, and is directly proportional to the square root of the initiation rate (W_i) and the concentration of the amino ester in benzene (Fig. 1).

The chain termination rate constant (k_6) was determined by the intermittent illumination method [2]. In the range 10-40°, $k_6 = (1.1 \pm 0.2)\cdot 10^7$ liter/mole·sec and $E_6 \simeq 0$.

The amount of titrable peroxides corresponds to the amount of absorbed O_2 ($\geq 92\%$) when the degree of oxidation is less than 1%. To prove the formation of H_2O_2, 1 ml each of saturated aqueous $NaHCO_3$ and catalase solutions [3] were added in succession to 1-2 ml of the oxidate. After 7 min the soda and catalase were added again, and after 10 min the solution was freed of O_2 using an inert gas, followed by the addition of a saturated solution of KI

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