The authors wish to express their gratitude to N. G. Ageev for carrying out the HPLC analyses.

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SYNTHESIS OF 2-METHYL-4-AMINO-5-tert-BUTOXYMETHYLPYRIMIDINE AND SPLITTING OF ITS ETHER BOND

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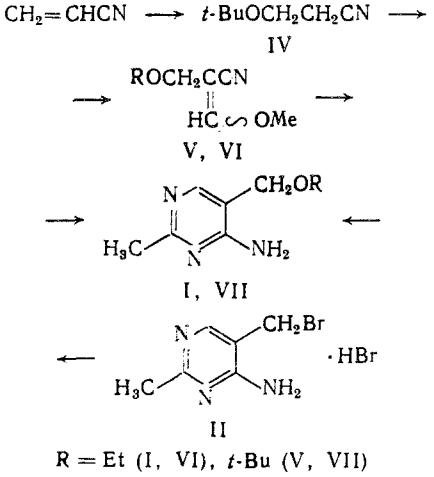
UDC 615.356:577.164.111].012.1.07

One of the steps in the synthesis of vitamin B_1 includes the transformation of 2-methyl-4-amino-5-ethoxymethylpyrimidine (I) into the corresponding hydrohalide of 5-bromomethyl- and 5-chloromethyl-2-methyl-4-aminopyrimidines (II and III) [1, 8]. The conditions are fairly rigorous: a high concentration of the hydrogen halides, high temperature (65-70°C), long reaction time (5-6 h in the case of the synthesis of bromide II, and 20-24 h in the preparation of chloride III). A side-reaction thus takes place – the replacement of the amino group by halogen [4]. All this results in definite difficulties in the synthesis of compounds II and III under industrial conditions.

In the present work, the synthesis of 2-methyl-4-amino-5-tert-butoxymethylpyrimidine (VII) and the investigation of its transformation on treatment with hydrohalic acids are reported. The sequence of stages in the synthesis of tert-butoxymethylpyrimidine VII is shown in the scheme, which is analogous to a similar scheme for the preparation of compound I [1].



Belgorod Branch of All-Union Scientific Research Vitamin Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 23, No. 11, pp. 1374-1377, November, 1989. Original article submitted February 8, 1989.

β-tert-Butoxypropionitrile (IV) was obtained by cyanoethylation of tert-butanol in the presence of 10^{-4}-10^{-2} equivalents of t-BuONa or EtONa. The reaction is complicated by the formation of a considerable amount of yellow colored (polymeric) by-products of the transformation of acrylonitrile, which precipitate. After the separation of the precipitate, the solution was subjected to distillation; the yield of IV was 30%. Neutralization of the reaction mixture by acetic acid before separation reduced the yield of the desired end product.

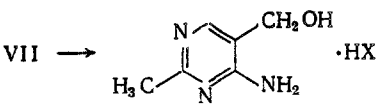
Condensation of nitrile IV with HCOOEt in the presence of EtONa, followed by the methylation of the reaction mixture with dimethyl sulfate led, as expected, to a mixture of α-methoxy-methylene-β-tert-butoxypropionitrile (V) and α-methoxymethylene-β-ethoxypropionitrile (VI), present in the form of cis- and trans-isomers (GLC). Treatment with acetamide of the reaction mixture obtained gave a mixture of pyrimidines I and VII with a considerable preponderance of I (GLC). When a similar sequence of reactions was carried using finely divided Na or t-BuONa as the condensing agent, compounds I and VII were also produced, but in this case they were obtained in commensurable amounts (GLC). Despite the cocrystallization of compounds I and VII, the required tert-butoxy methylpyrimidine could be purified to a considerable extent by fractional crystallization. tert-Butoxymethylpyrimidine VII can possibly be obtained exclusively, by using tert-butyl formate in the synthesis, but the latter was found to be rather difficult to obtain for laboratory use [6]. The structure of the compound VII was confirmed by PMR spectrum, as well as by alternate synthesis (see scheme), starting from bromomethylpyrimidine II and t-BuONa or finely divided Na in tert-butanol at 40-50°C, whereby a better yield of VII (15.3%) can be obtained by using Na. Alcoholysis of II in tert-butanol, in contrast to that in ethanol, proceeds very slowly.

Thus, the synthesis of 2-methyl-4-amino-5-tert-butoxymethylpyrimidine, an analog of an intermediate for the preparation of vitamin B_1 was effected starting from acrylonitrile in four steps, and also from bromomethylpyrimidine II in one step.

We further studied the splitting of the ether bond in tert-butoxymethylpyrimidine VII by the action of HBr and HCl.

Compound VII was treated by a 20% solution of HBr in acetic acid and the heterogeneous mass obtained was allowed to stand at 20°C. The crystalline product was then filtered, the solvents were removed, and the product was analyzed by PMR in two solvents: DMSO-d_6 made it possible to avoid the hydrolysis of bromomethylpyrimidine II [5], when it is formed, while recording of the spectra in ^2H_2O enabled the determination of the integral intensities of signals of the methyl and tert-butyl groups in a strong field, the chemical shifts of which are similar to those of DMSO protons, and thus the splitting of the ether bond could be ascertained.

From the analysis of the PMR spectra of the samples obtained and their comparison with the spectra of authentic samples of compounds II and III, it follows that during the treatment with HBr (4 h), the sample was mainly in the form of a hydrobromide of the initial VII. After 24 h, total splitting of the tert-butyl group was observed and 2-methyl-4-amino-5-hydroxymethylpyrimidine hydrobromide (VIII) was formed.



X = Br (VIII), Cl (IX)

When compound VII was treated with a 25% solution of HCl in 2-butanol (this solvent was chosen because it is used for the industrial synthesis of III) at 20°C, the ether bond was split more slowly: after 24 h, the presence of the tert-butyl group was still noted in the sample. After 4 days, the only crystalline reaction product was 2-methyl-4-amino-5-hydroxymethylpyrimidine hydrochloride (IX).

A similar experiment using an equimolar mixture of ethoxymethylpyrimidine I and tert-butoxypyrimidine VII, showed, on the basis of the results of PMR spectra of the samples obtained that during the time when the tert-butyl group has been completely eliminated, the ethoxyl group remained practically unaffected.

Thus, the synthesis of tert-butoxymethylpyrimidine VII was carried out for the first time, and it was shown that the splitting of its ether bond by the action of hydrohalic acids, in contrast to ethoxymethylpyrimidine I, proceeds in the direction of formation of alcohols VIII, IX, and not of halides II, III. As should be expected [3], the splitting of the ether bond in VII proceeds under milder conditions than in its ethyl analog I. In turn, alcohols VIII and IX can be converted into the corresponding bromoethyl- [2] and chloromethylpyrimidines [4] II and III under milder conditions than I.

EXPERIMENTAL

The PMR spectra were run on a "Tesla BS-567 A" spectrometer (100 MHz) (CSSR). The melting points were determined on a Koffler block and the GLC analysis was carried out on a LKhM-8MD chromatograph with a heat conductivity detector. The length of the column was 2 m, internal diameter 2.5 mm. The sorbent was chromaton N-AW (the 0.16-0.20 mm fraction), impregnated with 5% KhE-60; carrier gas helium. Conditions of analysis: temperature of the columns thermostat 190°C, of the evaporator 200°C, and of the detector 200°C, current strength of the detector bridge 105 mA, velocity of the diagram tape 1800 mm/h.

2-Methyl-4-amino-5-bromomethylpyrimidine hydrobromide (II) was obtained according to [7], and was additionally washed with a benzene–ethanol mixture (1:2 by volume) to a bromine content of 56.5% (according to Volhard).

β-tert-Butoxypropionitrile (IV). A 1.85 g portion (0.027 mole) of NaOEt was added at 20°C in the course of 10 min, with stirring, to a solution of 150 ml (2.28 mole) of acrylonitrile and 300 ml (3.19 mole) of tert-butanol. As a result, the temperature of the solution rose rapidly to 40°C, and the mixture acquired a yellow color. The reaction mixture was held at 30-40°C for 4 h, then cooled to 10°C and filtered from the yellow precipitate. The filtrate was fractionally distilled without neutralization of the base. First, the unreacted tert-butanol and acrylonitrile were distilled off on a boiling water bath, and then at 210°C nitrile IV was distilled on a Wood's alloy bath, collecting the fraction boiling at 190-193°C, n_D^{20} 1.4160. Yield 87 g (30%). The product is pure according to the GLC data. PMR spectrum, δ, ppm: 3.47 t (J = 6 Hz, 2H, CH_2CN or OCH_2), 2.44 t (J = 6 Hz, 2H, OCH_2 or CH_2CN), 1.14 s [9H, $C(CH_3)_3$].

Synthesis of a mixture of 2-methyl-4-amino-5-tert-butoxymethylpyrimidine (VII) and 2-methyl-4-amino-5-tert-ethoxymethylpyrimidine (I) was conducted using the condensing agents: Na (A), t-BuONa (B), and Na (A), t-BuONa (B), and NaOEt (C).

A) A mixture of 25.4 g (0.20 mole) of nitrile IV and 30 ml (0.35 mole) of ethyl formate was added in the course of 2 h, with stirring, to 5.5 g (0.24 mole) of finely divided Na in 100 ml of kerosene ("illuminating"), while the temperature was maintained at 25-30°C. The mixture was then stirred for 3 h at the above temperature. During this time, Na dissolved, and the mixture was in the form of a yellow-brown oil. The mixture was cooled to 10°C, and after adding 20 ml of acetonitrile, was methylated by adding, with stirring, 24.5 ml (0.24 mole) of dimethyl sulfate in one portion. The temperature thus rose to 35-40°C, was maintained at this level for another 3 h, and then was raised to 55°C. To the vinyl ethers V, VI (GLC) thus formed, acetamidine base, obtained by mixing solid acetamidine hydrochloride (28.4 g or 0.30 mole) and NaOEt (20.4 g or 0.30 mole) in 35 ml of acetonitrile, was added in one portion. The reaction mixture was then allowed to stand for 4 h at 55-60°C, the salts were filtered, and the filtrate was evaporated to the cessation of the distillation of ethanol and acetonitrile, without allowing the temperature of the concentrate to rise above 100°C. From the residue, by extraction with kerosene (5 × 50 ml) at 75°C, followed by crystallization at 0-5°C, 10 g of a mixture (1:1 GLC) of tert-butoxymethylpyrimidine VII and ethoxymethylpyrimidine I was isolated in the form of a white amorphous powder, mp 90-105°C. A triple crystallization from a hexane–ether mixture gave VII with a slight admixture of I, mp 120-127°C. PMR spectrum (for VII=), $CDCl_3$, δ, ppm: 7.92 s (1H, =CH), 5.73 br. s (2H, NH_2), 4.30 s (2H, CH_2O), 2.41 s (3H, CH_3), 1.22 s [9H, $C(CH_3)_3$]. PMR spectrum, DMSO-d_6, δ, ppm: 7.95 s (1H, =CH), 6.46 br. s (2H, NH_2), 4.22 s (2H, CH_2O), 2.31 s (3H, CH_3), 1.21 s [9H, $C(CH_3)_3$].

B) A mixture of 12.7 g (0.10 mole) of nitrile IV and 15.4 ml (0.18 mole) of ethyl formate was added in the course of 1.5 h to a suspension of t-BuONa, prepared from 2.3 g (0.10 mole) of Na and 20 ml of tert-butanol in 50 ml of kerosene, while the temperature maintained at 25-30°C, and the mixture was then allowed to stand at 30°C for 3 h. The synthesis was then continued as described in experiment A. Yield, 4 g of a mixture of VII and I (1:1, GLC), mp 90-102°C.

C) A mixture of 26 g (0.20 mole) of nitrile IV and 23.5 ml (0.29 mole) of ethyl formate was added in the course of 1.5 h, with stirring, to a suspension of 16.3 g (0.24 mole) of NaOEt in 70 ml of kerosene and 1 ml of tert-butanol, while the temperature was maintained at 25-30°C. The mixture was then stirred for 3 h at the same temperature. The synthesis was further carried out as described in experiment A. Yield, 9.5 g of a mixture of VII and I (1:4, respectively, GLC), mp, 85-95°C.

2-Methyl-4-amino-5-tert-butoxymethylpyrimidine (VII). A) Synthesis Using Sodium. A 4.74 g portion (16.76 mmoles) of compound II was suspended in 30 ml of tert-butanol, and 0.9 g of a finely divided Na was added with stirring. A vigorous reaction began approximately after 30 min, and the temperature rose to 40-50°C and was maintained at this level for another 3 h. The thickened mixture was diluted with acetonitrile, the salts were filtered, and the filtrate evaporated. From the residue compound VII was isolated by extraction with kerosene (6 × 5 ml) at 70-80°C, followed by crystallization at from 0 to 5°C. Yield, 0.5 g (15.3%) of white powder, mp 120-125°C. After recrystallization, mp 126-127°C (ether–hexane). $C_{16}H_{17}N_3O$. The PMR spectrum was identical with that recorded for a sample obtained from acrylonitrile.

B) Synthesis Using t-BuONa. A 20 ml portion of kerosene was added to a suspension of t-BuONa, prepared from 0.8 g of Na in 30 ml of tert-butanol, and then 4.74 g (16.76 mmoles) of II was added in portions with stirring. The temperature of the mixture thus rose from 27 to 32°C. The reaction mixture was stirred for 3 h at 30-35°C, and VII was isolated as described above. Yield, 0.15 g (4.6%), mp 124-125°C.

2-Methyl-4-amino-5-hydroxymethylpyrimidine Hydrobromide (VIII). A 4.5 ml portion of 20% solution of KBr in acetic acid was added to 0.3 g of tert-butoxymethylpyrimidine VII, and the mixture was allowed to stand at 20°C for 24 h. The crystalline product was filtered off, washed with acetonitrile, ether, and the residue was evaporated in vacuo. Yield, 160 mg (59.3%), white powder, mp 195-200°C, PMR spectrum, DMSO-d_6, δ, ppm: 8.95 and 8.17 2 s (2H, NH_2) [9], 8.07 s (1H, =CH), 4.34 s (2H, CH_2O), 2.47 s (CH_3). PMR spectrum, ^2H_2O, δ, ppm: 8.16 s (1H, =CH), 4.68 s (2H, CH_2O), 2.71 s (3H, CH_3).

The hydrobromide VIII was converted into a base by treatment with an aqueous solution of $NaHCO_3$, followed by concentration and crystallization. mp 190-191°C (187-190°C [2], 190-192°C [7]).

2-Methyl-4-amino-5-hydroxymethylpyrimidine Hydrochloride (IX). A solution of 0.36 g of tert-butoxymethylpyridine VII in 15 ml of 2-butanol was saturated with HCl to a concentration of 25% (according to increase in weight). After 30 min the formation of a white precipitate was observed. The gel-like mass was allowed to stand at 20°C for 4 days, and the crystalline product was filtered, washed with ether, and the solvent residue was evaporated under vacuum. Yield, 280 mg (84.4%), white powder, mp 212-215°C. PMR spectrum, DMSO-d_6, δ, ppm: 8.94 and 8.37 2 s (2H, NH_2) [9], 8.03 (1H, =CH), 4.33 s (2H s (2H, CH_2O), 2.47 s (CH_3). PMR spectrum ^2H_2O, δ, ppm, 8.13 s (1H, =CH), 4.64 s (2H, CH_2O), 2.66 s (3H, CH_3).

Hydrochloride IX was converted into a base, as described for VIII, mp 190-191°C.

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