5-SUBSTITUTED PYRIMIDINE DERIVATIVES

II. Synthesis of 5,6-Dihydropyrrolo[2,3-d]pyrimidines (5,7-Diazaindolines)*

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The properties and reactivities of 4-hydroxy- and 2,4-dihydroxy-5-(β-hydroxyethyl)pyrimidines and of the products of their transformations have been studied. 4-Chloro- and 2,4-dichloro-5-(β-chloroethyl)pyrimidines have been obtained. A number of 4-alkyl(aryl)amino-5-(β-chloroethyl)pyrimidines have been synthesized, and they have been converted into derivatives of 5,6-dihydropyrrolo[2,3-d]pyrimidine.

In the preceding communication, the synthesis and some properties of 5-(β-hydroxymethyl) derivatives of 2-hydroxy-, 2-mercapto-, 2-amino-, and 2-methyl-4-hydroxypyrimidines were described [1]. The continuation of work in this direction has enabled us to obtain a number of new data relating to the properties and reactivity of the 4-hydroxy- and 2,4-dihydroxy-β-hydroxyethylpyrimidines (I and II) and the products of their transformations. (For convenience of illustration, the derivatives of 4-oxo- and 2,4-dioxopyrimidines are given in their tautomeric hydroxy forms.)

During the work it was possible, with no reduction in the yield, to simplify the synthesis of 2,4-dihydroxy-5-(β-hydroxyethyl)pyrimidine (II) and 4-hydroxy-5-(β-hydroxyethyl)-2-mercaptopyrimidine (III) by performing the preparation of the α-sodioformyl-γ-butyrolactone in absolute ethanol, which has made these compounds still more accessible. The 2-mercapto derivative III was converted by a known method [2] into the previously unreported 4-hydroxy-5-(β-hydroxyethyl)pyrimidine (I).

A comparative study of the reactions of I and II with thionyl chloride and halogen compounds of phosphorus has shown that the presence of the hydroxy group in position 2 lowers the activity of the compound with respect to these reagents. Thus, II does not react with $SOCl_2$ at room temperature in chloroform in the presence of pyridine, while under the same conditions I readily reacts and is converted into 5,6-dihydrofuro-[2,3-d]pyrimidine (IV). The reaction of the hydroxy derivatives I and II with phosphorus oxychloride also gave different results. While II did not dissolve in $POCl_3$ even on prolonged heating, I readily reacted with phosphorus oxychloride to form 4-chlor-5(β-chloroethyl)pyrimidine (V). 2,4-Dichloro-5-(β-chloroethyl)pyrimidine (VI) could be obtained from II only by the action on the latter of a mixture of $POCl_3$ and PCl_5.

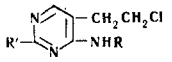
The formation of the above-mentioned 5,6-dihydrofuro[2,3-d]pyrimidine (IV) by the reaction of I with $SOCl_2$ was not unexpected, since a similar reaction is described in the literature for the 2-amino and 2-amino-6-substituted derivatives of I [1,3]. However, we are the first to have obtained the bicycle IV free from substituents. Its structure was confirmed by PMR spectroscopy. In the PMR spectrum of IV there are four resonance signals—two singlets and two triplets with relative intensities of 1 : 1 : 2 : 2 which therefore cover all six protons of the compound. The singlets in the weak-field region (8.64 and 8.38 ppm) relate to the less-shielded isolated protons at C_2 and C_4 of the pyrimidine nucleus. The triplets at 4.72 ppm (I ~ 8 Hz) and 3.33 ppm (I ~ 8 Hz) correspond to the protons of the two neighboring methylene groups of the dihydrofuran ring. The absence from the IR spectrum of IV of the absorption band of a hydroxy group is also in favor of the dihydrofuran structure.

In order to study the aminolysis of the 4-chloro- and 2,4-dichloro-5-(β-chloroethyl)pyrimidines (V, VI), we took two primary alkylamines (methylamine and butylamine) with approximately the same basicity but with alkyl chains of different lengths and a primary aromatic amine—aniline. It was established that both chlorine derivatives V and VI react with alkylamines at room temperature with the predominant formation of the monoalkylamino derivatives (VII–X). The yields of reaction products were 45–75%. The structure of the monoalkylamino derivatives was shown in the following way. Compound VII, obtained by the reaction of V with CH_3NH_2, was subjected to the action of ethanolic alkali. The reaction product (XI) differed in respect to its empirical formula ($C_7H_9N_3$) from the starting material ($C_7H_{10}ClN_3$) by a molecule of HCl. The substance gave positive reactions for a double bond with potassium permanganate and bromine. The PMR spectrum of the compound confirmed the presence of a vinyl group in it. The protons of the CH_2 group attached to the double bond appeared as doublets: the cis-proton at 5.41 ppm with a spin-spin coupling constant I ~ 11 Hz and the trans-proton at 5.64 ppm with I ~ 18 Hz. The methyl proton gave a quadruplet in the 6.55 ppm region with I constants of 11 and 18 Hz. The formation of methylaminovinylpyrimidine (XI) unambiguously determined the structure of the aminolysis product VII as 5-(β-chloroethyl)-4-methylaminopyrimidine.

In order to establish the position of the methylamino group in the monomethylamino derivative VIII obtained from VI, it was subjected to reductive dehalogenation by hydrogenation over a palladium catalyst. The reaction mixture yielded VII and a chlorine-free compound with the composition $C_7H_{17}N_3$ (XII). The formation of VII in the reduction process establishes the structure of VIII as 2-chloro-5-(β-chloroethyl)-4-methylaminopyrimidine. The second hydrogenation product,

*For part I, see [1].

Table 1



Compound	R	R′	Mp, °C (from benzene)	R_f	Empirical formula	Found, %				Calculated, %				Yield, %
						C	H	Cl	N	C	H	Cl	N	
VII*	CH_3	H	115—116.5	0.56	$C_7H_{10}ClN_3$	49.08	5.51	21.17	24.90	48.98	5.87	20.67	24.48	69.5
VIII*	CH_3	Cl	132—133	0.86	$C_7H_9Cl_2N_3$	41.24	4.49	34.65	20.23	40.80	4.40	34.41	20.39	61.2
X (hydrochloride)	C_4H_9	Cl	164—165**	0.93	$C_{10}H_{15}Cl_2N_3 \cdot HCl$	42.34	5.80	37.85	14.71	42.19	5.67	37.37	14.77	44.7

*Reaction performed in aqueous ethanolic solution.
**From a mixture of absolute ethanol and acetone.

compound XII, possessed the properties of a strong dibasic amine containing no conjugated double bonds and could be a product of the further reduction of both VIII and VII. To confirm this hypothesis the hydrogenation of VII was carried out under the same conditions. The reduction products proved to be two substances. One of them (XIII) had the composition $C_7H_{16}ClN_3$, and the second was identical with XII. It is known from the literature that the hydrogenation of pyrimidine derivatives in a neutral or acid medium may lead to both the partial and to the complete reduction of the pyrimidine nucleus with the formation of the corresponding 1,4,5,6-tetrahydropyrimidines [4] or hexahydropyrimidines [5]. Since the PMR spectrum of the hydrochloride of XIII lacked a resonance signal in the weak-field region (6—7 ppm) characteristic for a proton attached to a carbon connected by a double bond with nitrogen, it may be assumed that the hydrogenation led to the hexahydro derivative. Apparently, in the catalytic reduction of VIII, because of the elimination of the chlorine in position 2, complete hydrogenation of the pyrimidine nucleus took place with the formation of XIII and the latter, as a result of the replacement of the chlorine in the side chain by hydrogen, was finally converted into 5-ethyl-4-methylaminohexahydropyrimidine (XII).

The reaction of V and VI with primary alkylamines showed that the chlorine atom on carbon atom 4 of the pyrimidine nucleus is the more reactive with respect to nucleophilic substitution. This is in full agreement with literature data [6]. When V and VI were heated with aniline hydrochloride in an aqueous ethanolic medium, 5-(β-chloroethyl)-4-phenylaminopyrimidine XIV and 5-(β-chloroethyl)-2,4-di(phenylamino)pyrimidine (XV), respectively, were obtained with yields of about 75%. The activation of the chlorine in position 2 in the formation of XV was possibly the consequence of the protonation of the nitrogen of the pyrimidine nucleus [7].

The study of the properties of the 4-alkyl(aryl)-amino-5-(β-chloroethyl)pyrimidines (VII–X, XIV, XV) showed that when they were heated in ethylene glycol above their melting points a molecule of hydrogen chloride split off with cyclization into the corresponding 7-alkyl(aryl)-5,6-dihydropyrrolo[2,3-d]pyrimidines (5,7-diazaindolines). A similar closure of the pyrroline ring has been described in the literature for the synthesis of derivatives of 7-azaindoline by the reaction of a number of 2-chloro-3-(β-chloroethyl)-pyridines with primary or secondary amines [8]. The transition from 5-substituted pyrimidines to the bicyclic system of 5,6-dihydropyrrolo[2,3-d]pyrimidine may be of interest since it opens up the possibility of a search for accessible routes of synthesis of analogs of the biologically active antibiotics Tubercidin and Toyocamicin [9]. It is interesting to note that when XIV and XV are heated in ethanolic alkali the reaction leads almost quantitatively to 7-phenyl-5,6-dihydropyrrolo[2,3-d]pyrimidine (XVI) and 7-phenyl-2-phenylamino-5,6-dihydropyrrolo[2,3-d]pyrimidine (XVII) while, under similar conditions the 4-alkylamino derivatives are converted into 4-alkylamino-5-vinylpyrimidines.

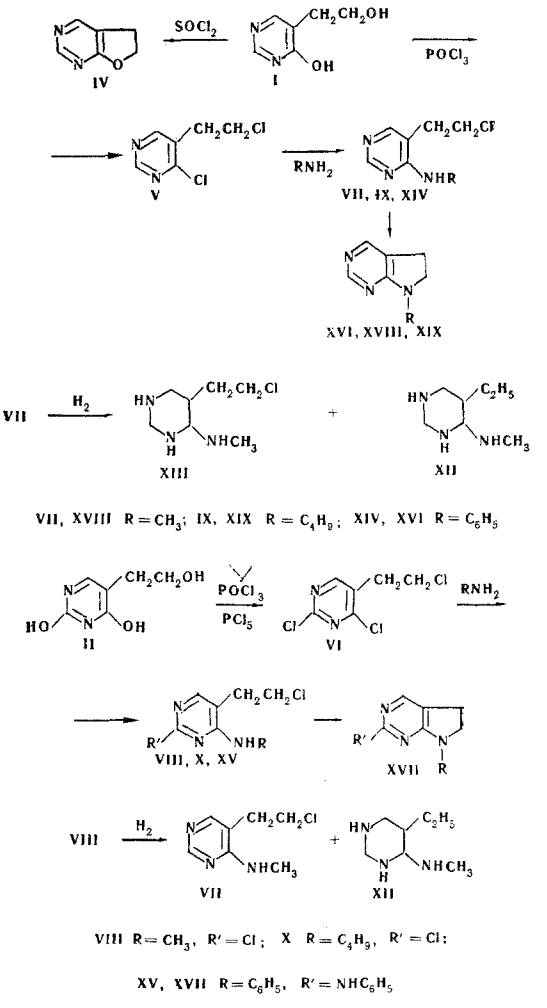
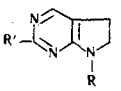


Table 2



Compound	R	R′	Mp (bp, °C) (solvent for crystallization	R_f	Empirical formula	Found, %				Calculated, %				Yield, %
						C	H	Cl	N	C	H	Cl	N	
XVII	C_6H_5	NHC_6H_5	213.5—215 (benzene)	0.78	$C_{18}H_{16}N_4$	74.98	5.56	—	19.43	74.98	5.59	—	19.43	77.3 (82.7)*
XVII (hydrochloride)	C_6H_5	NHC_6H_5	257—258.5 (abs. ethanol)	0.78	$C_{18}H_{16}N_4 \cdot HCl$	66.90	5.40	11.29	17.43	66.56	5.28	10.91	17.25	—
XVIII (hydrochloride)	CH_3	H	233—234 (abs. ethanol—acetone)	0.15	$C_7H_9N_3 \cdot HCl$	—	—	20.67	24.22	—	—	20.67	24.48	13.3
XIX**	C_4H_9	H	134—135 (5 mm) n_D^{20} 1.542	0.57	$C_{10}H_{15}N_3$	—	—	—	—	—	—	—	—	31.87
XIX (picrate)	C_4H_9	H	105.5—107 (ethanol)	0.74	$C_{10}H_{15}N_3 \cdot C_6H_3N_3O_7$	47.35	4.59	—	20.95	47.29	4.47	—	20.68	—

*By method (b).
**The reaction was carried out at 195° C

EXPERIMENTAL

The PMR spectra were taken on a JEOL 4H-100 instrument in $CDCl_3$ with tetramethylsilane as internal standard (we express our deep gratitude to Yu. N. Sheinker and G. P. Syrova for recording the PMR spectra and assisting with their interpretation).

Chromatography was carried out with the n-butanol—5% acetic acid (1:1) system on type "M" paper of the Leningrad No. 2 mill. The spots were revealed in UV light and with Dragendorff's reagent.

4-Hydroxy-5-(β-hydroxyethyl)-2-mercaptopyrimidine (III). With stirring at a temperature not exceeding 5° C, a mixture of 43 g (0.5 mole) of γ-butyrolactone and 48 g (0.64 mole) of ethyl formate was added to a solution of 12.3 g (0.53 g-at) of sodium in 230 ml of absolute ethanol cooled to −5° C. The mixture was stirred at 5° C for 3 hr and was left at room temperature for 3 days. The resulting solution of α-sodioformyl-γ-butyrolactone was treated with 38 g (0.5 mole) of thiourea dissolved in 200 ml of hot ethanol and the mixture was boiled for 5 hr. After 12 hr, the precipitate was filtered off and dissolved in 150 ml of water and the solution was decolorized with activated carbon and, after filtration, acidified with hydrochloric acid. The yield of **III** was 46 g (53.5%), mp 248–249° C (from water) [1], R_f 0.51.

2,4-Dihydroxy-5-(β-hydroxyethyl)pyrimidine (II). To an ethanolic solution of α-sodioformyl-γ-butyrolactone prepared as described above was added a 30% ethanolic solution of sulfuric acid at a temperature not exceeding 30° C and then a solution of 30 g (0.5 mole) of urea in 160 ml of hot ethanol. The mixture was boiled for 8 hr and, after the solvent had been distilled off in vacuum, the residue was treated with 100 ml of water. Acidification yielded 32.85 g of α-(1-carbamoylimino-methyl)-γ-butyrolactone with mp 245–246° C (R_f 0.47), which was cyclized by being boiled in methanol (500 ml) containing 20 g of caustic potash for 4 hr. The precipitate was filtered off and dissolved in 100 ml of hot water, the solution was decolorized with carbon, and the **II** was precipitated with hydrochloric acid. Yield 24.8 g (31.8%), mp 259–261° C [1], R_f 0.32.

4-Hydroxy-5-(β-hydroxyethyl)pyrimidine (I). A mixture of 15 g (0.087 mole) of **III** in 220 ml of water and 25 ml of concentrated aqueous ammonia was boiled with 30 ml of an aqueous suspension of Raney nickel for 3 hr with stirring. The nickel was filtered off and extracted with hot water (2 × 40 ml). The combined aqueous solutions were evaporated in vacuum to dryness and the residue was treated with 20 ml of absolute ethanol. The crystals of **I** were filtered off with suction. Yield 10.9 g (89.3%), mp 153–155° C (from absolute ethanol), R_f 0.43. Found, %: C 51.80; H 5.82; N 19.79. Calculated for $C_6H_8N_2O_2$, %: C 51.42; H 5.75; N 19.99.

5,6-Dihydrofuro[2,3-d]pyrimidine (IV). In drops, 3.47 g (0.029 mole) of thionyl chloride in 7 ml of $CHCl_3$ was added at 5° C to 2.8 g (0.02 mole) of **I** and 1.67 g (0.021 mole) of pyridine in 30 ml of $CHCl_3$. After 3 hours' stirring at 20° C, the precipitate was filtered off and washed with chloroform. This gave the hydrochloride of **IV**, yield 2.14 g (67.5%), mp 111.5–112.5° C (from 2% ethanolic hydrogen chloride), R_f 0.12. Found, %: C 45.57; H 4.43; Cl 22.55; N 17.58. Calculated for $C_6H_6N_2O \cdot HCl$, %: C 45.44; H 4.45; Cl 22.36; N 17.67.

In 50 ml of water, 1.15 g of the hydrochloride of **IV** was shaken with an excess of moist silver oxide for 2 hr, the AgCl was filtered off, the aqueous solution was evaporated in vacuum to dryness, and the residue was extracted with ether. This gave **IV** with a yield of 0.6 g (67.8%), mp 78–80° C (from a mixture of benzene and petroleum ether), R_f 0.57. Readily soluble in water and organic solvents. Found, %: C 58.87; H 5.00; N 22.80. Calculated for $C_6H_6N_2O$, %: C 59.01; H 4.95; N 22.94.

4-Chloro-5-(β-chloroethyl)pyrimidine (V). A mixture of 5.6 g (0.04 mole) of **I** and 40 ml of $POCl_3$ was boiled for 1 hr 30 min. The excess of $POCl_3$ was distilled off in vacuum, the residue was poured into 50 ml of a mixture of ice and water, and, after standing for 40 minutes, the solution was made alkaline with saturated potassium carbonate and exhaustively extracted with chloroform. The extract was dried with $MgSO_4$ and, after the chloroform had been driven off, the residue was fractionated in vacuum. The yield of **V** was 6.09 g (86.1%); bp 92–94° C (2 mm), n_D^{20} 1.549. Found, %: C 40.68; H 3.45; Cl 39.48; N 15.75. Calculated for $C_6H_6Cl_2N_2$, %: C 40.70; H 3.42; Cl 40.35; N 15.87. **Hydrochloride of V,** mp 138–140° C (from absolute ethanol). Found, %: Cl 49.51 (of which 16.51 ionic). Calculated for $C_6H_6Cl_2N_2 \cdot HCl$, %: Cl 49.82 (of which 16.61 ionic).

2,4-Dichloro-5-(β-chloroethyl)pyrimidine (VI). A mixture of 6.24 g (0.04 mole) of **II**, 60 ml of $POCl_3$, and 25 g of PCl_5 was boiled for 4 hr. The reaction mixture was treated in the same way as in the preparation of **V**. The yield of **VI** was 5.6 g (66.3%), bp 112–115° C (2 mm), n_D^{20} 1.564. Found, %: Cl 50.43; N 13.37. Calculated for $C_6H_5Cl_3N_2$, %: Cl 50.30; N 13.25.

4-Butylamino-5-(β-chloroethyl)pyrimidine (IX), hydrochloride. A mixture of 1.77 g (0.01 mole) of **V** and 3 ml of n-butylamine in 15 ml of ethanol was kept at room temperature for three days. The ethanol was distilled off in vacuum and the residue was dissolved in 5 ml of water, made alkaline with saturated potassium carbonate solution, and extracted with ether. The extract was dried over $MgSO_4$ and, after the ether had been driven off, the residue—an oily substance—was treated with ethanolic hydrogen chloride to give the crystalline hydrochloride. The yield of the hydrochloride of **IX** was 1.9 g (75.9%), mp 151.5–153° C (from a mixture of absolute ethanol and ether). Found, %: C 48.37; H 6.66; Cl 28.33, (of which 14.07 ionic); N 16.96. Calculated for $C_{10}H_{16}ClN_3 \cdot HCl$, %: C 48.01; H 6.85; Cl 28.35 (of which 14.27 ionic); N 16.80.

5-(β-Chloroethyl)-4-methylaminopyrimidine (VII), 2-chloro-5-(β-chloroethyl)-4-methylaminopyrimidine (VIII), and 4-butylamino-

2-chloro-5-(β-chloroethyl)-pyrimidine (X) were obtained under similar conditions (Table 1).

4-Methylamino-5-vinylpyrimidine (XI). A mixture of 1 g (0.0058 mole) of **VII** and 0.75 g (0.013 mole) of caustic potash in 15 ml of absolute ethanol was boiled for 3 hr. The potassium chloride was filtered off, the ethanol was evaporated in vacuum, and the residue was extracted with boiling benzene. The benzene extract was passed through a column containing 20 g of Al_2O_3, and the material was eluted with benzene, which gave 0.64 g (81.3%) of **XI** with mp 105–106° C (from a mixture of benzene and petroleum ether), R_f 0.55. Found, %: C 62.21; H 6.53; N 31.64. Calculated for $C_7H_9N_3$, %: C 62.20; H 6.71; N 31.09.

Catalytic hydrogenation of VIII. A solution of 0.5 g of $PdCl_2$ in 5 ml of boiling 8% hydrochloric acid was added to 1.03 g (0.005 mole) of **VIII** in 15 ml of ethanol. Hydrogenation was carried out at room temperature and a pressure of 15–20 cm of water until the absorption of hydrogen ceased. The catalyst was filtered off and the solution was evaporated to small volume, made alkaline with saturated potassium carbonate solution, and extracted with ether. The ethereal extract yielded 0.14 g (16.3%) of **VII**. The aqueous alkaline solution was evaporated in vacuum and the residue was extracted with absolute ethanol. From the ethanolic solution **5-ethyl-4-methylaminohexahydropyrimidine (XII)** was isolated in the form of the crystalline dipicrate. Yield 0.77 g (25.7%), mp 229–230° C (from water), R_f of the base 0.04. Found, %: C 37.93; H 3.40; N 21.31. Calculated for $C_7H_{17}N_3 \cdot 2C_6H_3N_3O_7$, %: C 37.94; H 3.85; N 20.96.

Catalytic hydrogenation of VII. One gram (0.0058 mole) of **VII** was hydrogenated under the conditions of the preceding experiment. The resulting ethanolic solution was saturated with hydrogen chloride, and 0.8 g of the dihydrochloride of **5-(β-chloroethyl)-4-methylaminohexahydropyrimidine (XIII)** with mp 150–152° C, R_f 0.07, was isolated Found, %: C 33.36; H 6.94; Cl 43.13 (of which 28.68 ionic); N 16.83. Calculated for $C_7H_{16}ClN_3 \cdot 2HCl$, %: C 33.55; H 7.24; Cl 42.44 (of which 28.30 ionic); N 16.77. From the mother liquors after the recrystallization of **XIII** was isolated 0.2 g (5.7%) of a picrate with mp 228.5–229° C giving no depression of the melting point in admixture with the picrate of **XII**.

5-(β-Chloroethyl)-4-phenylaminopyrimidine (XIV). A mixture of 1.77 g (0.01 mole) of **V** and 1.52 g (0.012 mole) of aniline hydrochloride in 20 ml of 50% aqueous ethanol was boiled for 2 hr. The solution was evaporated in vacuum to half its original volume, and the residue was made alkaline with saturated potassium carbonate solution; the oily substance that separated out crystallized on rubbing. The yield of **XIV** was 1.8 g (77%), mp 75–77° C (from a mixture of acetone and benzene), R_f 0.82. Found, %: C 62.15; H 5.24; Cl 14.90; N 18.24. Calculated for $C_{12}H_{12}ClN_3$, %: C 61.67; H 5.18; Cl 15.17; N 17.98. **Hydrochloride of XIV,** mp 170–171° C (from ethanol). Found, %: C 52.95; H 4.78; Cl 26.42 (of which 13.36 ionic); N 15.31. Calculated for $C_{12}H_{12}ClN_3 \cdot HCl$, %: C 53.35; H 4.85; Cl 26.25 (of which 13.12 ionic); N 15.55.

5-(β-Chloroethyl)-2,4-di(phenylamino)pyrimidine (XV). This was obtained by the reaction of **VI** with aniline hydrochloride under the conditions of the preceding experiment. The yield of **XV** was 71.9%, mp 135.5–136° C (from benzene), R_f 0.83. Found, %: C 66.92; H 5.08; Cl 11.01; N 17.00. Calculated for $C_{18}H_{17}ClN_4$, %: C 66.56; H 5.28; Cl 10.91; N 17.25. **Hydrochloride of XV,** mp 188–190° C (from 0.1 N hydrochloric acid). Found, %: C 59.69; H 4.99; Cl 19.50 (of which 10.00 ionic); N 15.69. Calculated for $C_{18}H_{17}ClN_4 \cdot HCl$, %: C 59.84; H 5.02; Cl 19.63 (of which 9.81 ionic); N 15.51.

7-Phenyl-5,6-dihydropyrrolo[2,3-d]pyrimidine (XVI). a) A mixture fo 1.0 g (0.0043 mole) of **XIV** in 5 ml of ethylene glycol was kept at 140–150° C for 2 hr. After cooling, 15 ml of water was added to the mixture and it was made alkaline with a concentrated solution of potassium carbonate. The precipitate of **XVI** was washed with water. Yield 0.7 g (82.04%), mp 105–106° C (from aqueous methanol) R_f 0.70. Found, %: C 73.13; H 5.40; N 21.50. Calculated for $C_{12}H_{11}N_3$, %: C 73.07; H 5.62; N 21.31. **Hydrochloride of XVI,** mp 262–263° C (from absolute ethanol). Found, %: Cl 15.16; N 17.88. Calculated for $C_{12}H_{11}N_3 \cdot HCl$, %: Cl 15.17; N 17.99. The PMR spectrum of **XVI** has the following signals: triplets in the strong-field region (3.08 and 4.02 ppm) with I ~ 8 Hz (neighboring CH_2 groups of a pyrroline ring); doublets at 7.07 ppm (I ~ 6 Hz) and 7.77 ppm (I ~ 7 Hz), and a triplet at 7.38 ppm (I ~ 7 and 6 Hz) (protons of a phenyl nucleus), singlets at 8.06 and 8.55 ppm (hydrogens of the pyrimidine ring).

b) A mixture of 0.5 g (0.0021 mole) of **XIV** and 0.25 g (0.0045 mole) of KOH in 10 ml of absolute ethanol was boiled for 2 hr. The ethanol was evaporated off in vacuum, the residue was treated with 5 ml of water, and the crystals of **XVI** were filtered off and washed with water, yield 0.37 g (87.7%).

The following compounds were obtained under similar conditions: by methods (a) and (b)—**7-phenyl-2-phenylamino-5,6-dihydropyrrolo-[2,3-d]pyrimidine (XVII)**; and by method (a)—**7-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidine (XVIII)** and **7-butyl-5,6-dihydropyrrolo-[2,3-d]pyrimidine (XIX)** (Table 2).

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