DERIVATIVES OF N-(PYRIMID-4-YL)ETHYLAMINE

III. 2,5,6-Substituted Derivatives*

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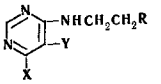
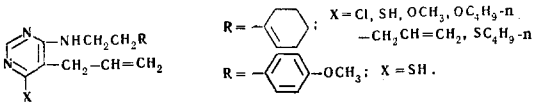
In order to find compounds possessing antibacterial activity, a number of new derivatives of N-(pyrimid-4-yl)ethylamine have been synthesized from 5-amino-4,6-dichloropyrimidine, 2-amino-4,6-dichloropyrimidine, 4,6-dichloro-2-phenylpyrimidine, and 2,4-dichloro-6-methylpyrimidine and various ethylamines substituted in the β-position. Several derivatives of 4-(4'-methylpiperazinyl)pyrimidine have also been obtained. Results of a biological study of the compounds obtained are presented.

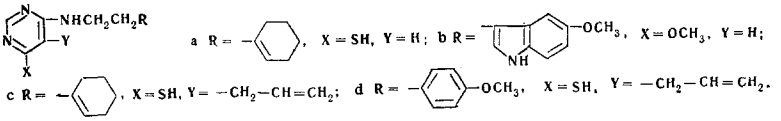
The synthesis of pyridine derivatives of type C containing no substituents in position 2 has been reported in previous papers [1, 2].



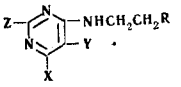
Some of them, in a study of their bacteriostatic and antimetabolic action, exhibited an antibacterial activity with respect to the tubercle bacillus of the human type strain $H_{37}Rv$. The growth of the bacteria was suppressed fairly strongly by compounds which had the general formula:



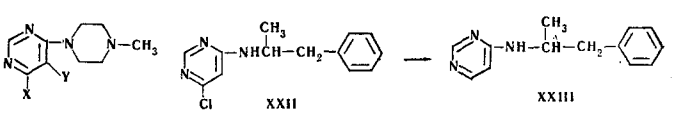
However, this action fell sharply in the presence of horse serum. Bacteriostatic activity with respect to the lactic acid bacteria L. casei strain 7469 was shown by the following compounds:



The antibacterial activity of the compounds synthesized served as a basis for the continuing search for new pyrimidine derivatives **I–XVI** of type D bearing an amino group in position 5 or various substituents in position 2 (Table 1).



Compounds **XVII–XXI** (Table 2) with various substituents in positions 5 and 6 were also synthesized, starting from 4-chloro-6-(4'-methylpiperazinyl)-pyrimidine (**E**), and so was 4-(α-methyl-β-phenylethylamino)pyrimidine (**XXIII**).



*For part II, see [1].

The starting materials for the syntheses, apart from the β-substituted ethylamine derivatives, N-methylpiperazine and α-methyl-β-phenylethylamine, were dihalogen-substituted pyrimidines: 4,6-dichloropyrimidine |3|, 5-amino-4,6-dichloropyrimidine |4|, 2-amino-4,6-dichloropyrimidine, 2,4-dichloro-6-methylpyrimidine |5,6|, and 4,6-dichloro-2-phenylpyrimidine |7|, obtained from the corresponding dihydroxypyrimidines by known methods.

There are a few papers in the literature on the preparation of 2-amino-4,6-dichloropyrimidine by heating malonylguanidine either with phosphorus oxychloride alone |8| or with the addition of dimethylaniline, giving a yield of more than 80% |9|. Brown |10| assumes that this yield relates to the unpurified compounds; he considers the best reaction conditions to be heating malonylguanidine with phosphorus oxychloride alone, and even under these conditions the pure substance is obtained with a yield of only 25%. We obtained 2-amino-4,6-dichloropyrimidine by heating malonylguanidine with phosphorus oxychloride alone for 30 min. The substance was purified either by sublimation (with a yield of 41.4%) or by the extraction of the technical product with large volumes of benzene (with a yield of 55.3% of theory). The malonylguanidine was obtained from malonic ester and guanidine sulfate in an ethanolic solution of sodium ethoxide.

The reaction of the 2,4- or 4,6-dichloropyrimidine derivatives (1 mole) with amines (2 moles) in boiling benzene or toluene (compounds **XV** or **XVI**) led to the replacement of only the chloride atom in position 4 (6). The second chlorine atom in position 6 (4) was replaced by an n-butoxy or mercapto group, and that in position 2 by an n-butoxy, methoxy, hydroxy, or mercapto group. We effected the introduction of the n-butoxy, methoxy, and mercapto groups under selected conditions by general methods with sodium butoxide or methoxide with heating in n-butanol or methanol, or with sodium hydrogen sulfide in formamide. The chlorine in position 2 was replaced by a hydroxyl group by heating the 2-chloro derivative with concentrated HCl.

All the new compounds obtained, like those described previously, were studied for their bacteriostatic and antimetabolic action with the following strains of bacteria:

1) Escherichia coli strain No. 335;

2) the human type tubercle bacillus, strain $H_{37}Rv$; and

3) lactic acid bacteria of the strain L. casei 7469 and Strept. faecalis 8043.

The experiments showed that a number of the compounds suppressed the growth of the human type tubercle bacillus strain $H_{37}Rv$. Among them were the following compounds with a high tuberculostatic activity: **V**, **VIII**, **X**, and **XIV**.

The following compounds exhibited bacteriostatic activity with respect to the lactic acid bacteria L. casei strain 7469: **XV**, **XXI**, **XIV**, **VIII**, **IX**, and **XI**. The compounds synthesized had no effect on the growth of Escherichia coli.

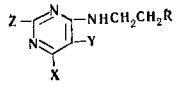
EXPERIMENTAL

2-Amino-4,6-dihydroxypyrimidine.* To a solution of sodium ethoxide prepared from 6.3 g (0.27 g-at.) of sodium ethanol were added 10.7 g (0.068 mole) of guanidine sulfate and 8.0 g (0.05 mole) of malonic ester. The mixture was heated at the boil for 30 min. After cooling, the precipitate was filtered off and dissolved in water (100 ml) and the solution was acidified with HCl (17%) to pH 5. The 2-amino-4,6-dihydroxypyrimidine that deposited was filtered off, washed with water, and dried. Yield 86.7%. It did not melt below 320° C.

2-Amino-4,6-dichloropyrimidine. A mixture of 10 g (0.08 mole) of 2-amino-4,6-dihydroxypyrimidine and 52 ml of phosphorus oxychloride was heated at the boil for 30 min, by which time the solid matter had dissolved. The cooled reaction mixture was poured onto ice and the substance that separated out was filtered off, washed with water, and dried in a vacuum desiccator. The yield was 8.3 g. The filtrate, after neutralization with concentrated NaOH and cooling, yielded an additional 2 g of 2-amino-4,6-dichloropyrimidine. The substance was purified either by sublimation in the absence of a vacuum (yield 41.4%), or by extraction with a large amount of benzene (55.3%). Mp 221° C.

* A method of obtaining 2-amino-4,6-dihydroxypyrimidine either from guanidine thiocyanate or from guanidine carbonate with a yield of 54% is described in the literature |10|. We performed this reaction with guanidine sulfate (yield about 87%).

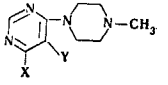
Table 1



Compound	R	X	Y	Z	Mp, °C (solvent for crystallization)	Empirical formula	Found, %					Calculated, %					Yield, %
							C	H	Cl	N	S	C	H	Cl	N	S	
I	Cyclohex-1-enyl	Cl	NH_2	H	129—130 (50% ethanol)	$C_{12}H_{17}ClN_4$	57.01	6.72	14.20	22.44	—	57.02	6.73	14.05	22.17	—	70.6
II	,, ,,	OC_4H_9	NH_2	H	86—87 (50% ethanol)	$C_{16}H_{26}N_4O$	66.12	8.98	—	18.93	—	66.20	8.96	—	19.31	—	34.0
III	,, ,,	SH	NH_2	H	197—198 (ethyl acetate)	$C_{12}H_{18}N_4S$	57.50	7.03	—	22.15	12.59	57.60	7.20	—	22.40	12.80	41.2
IV	,, ,,	Cl	H	NH_2	129—130 (50% methanol)	$C_{12}H_{17}ClN_4$	57.03	6.75	14.11	—	—	57.03	6.77	14.03	—	—	77.8
V	,, ,,	OC_4H_9	H	NH_2	78—79 (50% methanol)	$C_{16}H_{26}N_4O$	66.40	9.00	—	19.36	—	66.18	9.02	—	19.30	—	76.1
VI	,, ,,	SH	H	NH_2	203—204 (methanol)	$C_{12}H_{18}N_4S$	58.66	7.12	—	22.05	12.39	57.57	7.24	—	22.39	12.80	25.0
VII	,, ,,	CH_3	H	Cl	78—79 (25% methanol)	$C_{13}H_{18}N_3Cl$	62.20	7.19	14.10	—	—	62.01	7.20	14.08	—	—	77.1
VIII	,, ,,	CH_3	H	OCH_3	80,5—82 (50% methanol)	$C_{14}H_{21}N_3O$	67.97	8.36	—	16.42	—	67.98	8.55	—	16.99	—	97.0
IX	,, ,,	CH_3	H	OH	192—193 (water)	$C_{13}H_{19}N_3O$	66.93	8.33	—	17.68	—	66.89	8.20	—	18.00	—	21.6
X	,, ,,	CH_3	H	OC_4H_9	71 (50% methanol)	$C_{17}H_{27}N_3O$	70.69	9.15	—	14.49	—	70.52	9.40	—	14.52	—	47.8
XI	,, ,,	CH_3	H	SH	112—113 (50% methanol)	$C_{13}H_{19}N_3S$	62.39	7.35	—	—	12.47	62.62	7.68	—	—	12.86	29.1
XII	,, ,,	Cl	H	C_6H_5	107—108 (90% methanol)	$C_{18}H_{20}ClN_3$	68.95	6.40	11.37	—	—	68.89	6.42	11.30	—	—	71.6
XIII*	,, ,,	OC_4H_9	H	C_6H_5	176—178 (chloroform-petroleum ether)	$C_{22}H_{29}N_3O$	78.05	9.12	—	12.23	—	75.18	8.31	—	11.96	—	98.8
XIV	,, ,,	SH	H	C_6H_5		$C_{18}H_{21}N_3S$	69.78	6.78	—	—	10.07	69.39	6.79	—	—	10.29	54,0
XV	3,4-Dimethoxyphenyl	Cl	NH_2	H	133—134 (50% ethanol)	$C_{14}H_{17}ClN_4O_2$	54.40	5.47	11.67	—	—	54.45	5.51	11.50	—	—	73.1
XVI	4-Hydroxyphenyl	Cl	NH_2	H	197—199 (50% ethanol)	$C_{12}H_{13}ClN_4O$	54.58	5.01	13.56	20.85	—	54.44	4.91	13.42	21.17	—	45.2

*Purified by vacuum distillation, bp 225-227° C (2 mm).

Table 2



Compound	X	Y	Mp, °C (solvent for crystallization)	Empirical formula	Found, %					Calculated, %					Yield, %
					C	H	Cl	N	S	C	H	Cl	N	S	
XVII	Cl	H	78—79 (absolute ethanol)	$C_9H_{13}ClN_4$	50.60	6.25	16.42	—	—	50,80	6,16	16,67	—	—	79.4
XVIII*	OC_4H_9	H		$C_{13}H_{22}N_4O$	62,29	8.90	—	22,07	—	62.37	8.85	—	22.39	—	26.1
XIX**	SH	H	294—296 (50% ethanol, decomp)	$C_9H_{15}N_4S \cdot HCl$	43,23	6.43	14.71	—	12.81	43.78	6.13	14.37	—	12.99	35
XX**	Cl	NH_2	271—272 (ethanol, decomp)	$C_9H_{13}N_5 \cdot HCl$	41.20	5.75	27.21	—	—	40.99	5.68	26.89	—	—	44.4
XXI**	SH	NH_2	299—301 (ethanol, decomp)	$C_9H_{15}N_5S \cdot HCl$	41,20	6.17	13.75	26.80	12.55	41.30	6.50	13.57	26.76	12.23	—

*Purified by vacuum distillation. Bp 150-154° C (2 mm).

**Isolated in the form of the hydrochloride. Decomp p. determined in a copper block.

2-Amino-4-chloro-6-(β-cyclohex-1'-enylethylamino)pyrimidine (IV). A mixture of 1 g (6 mM) of 2-amino-4,6-dichloropyrimidine, 1.62 g (12 mM) of β-(cyclohex-1-enyl)ethylamine, and 20 ml of benzene was boiled with stirring for 4 hr. After cooling, the amine hydrochloride that deposited was filtered off and washed with benzene. The benzene solutions were evaporated to dryness in vacuo, the residue was washed with water and petroleum ether and then purified by recrystallization from solvents (Table 1).

Compounds **I, XII, VII** and **XXII** were obtained similarly. Compounds **XV** and **XVI** were obtained in toluene, in which they are insoluble, and were filtered off immediately after the reaction. Compound **I** was triturated with water and extracted with ether. Compound **XXII** was purified by recrystallization from 50% methanol. Yield 90.2%, mp 111–112.5° C. Found, %: C 62.90; H 5.73; Cl 14.31. Calculated for $C_{13}H_{14}N_3Cl$, %: C 63.02; H 5.69; Cl 14.31.

5-Amino-4-chloro-6-(4'-methylpiperazinyl)pyrimidine (XX) hydrochloride. A mixture of 3.28 g (0.02 mole) of 5-amino-4,6-dichloropyrimidine, 4 g (0.04 mole) of N-methylpiperazine, and 35 ml of benzene was boiled with stirring for 4 hr. After cooling, the precipitate was filtered off; it was triturated with 16 ml of ethanol, filtered off again, and purified by recrystallization from ethanol. Compound **XVII** was obtained in the form of the free base, which was isolated after the N-methylpiperazine hydrochloride had been filtered off and the benzene had been evaporated.

2-Amino-4-n-butoxy-6-(β-cyclohex-1'-enylethylamino)pyrimidine (V). Compound **IV**, 2.18 g (8.4 mM), was added to a solution of sodium butoxide prepared from 0.66 g (26 mg-at.) of sodium and 44 ml of dry n-butanol. The mixture was heated to the boil for 4 hr, and the butanol was evaporated in vacuo. The residue was stirred with water and extracted with ether. The substance obtained after the elimination of the ether was washed with petroleum ether and purified by recrystallization from solvents. Compounds **II, X,** and **XIII** were obtained similarly. After the distillation of the butanol, compound **XVIII** was dissolved in acetone, the sodium chloride was filtered off, and the residue, after the elimination of the acetone, was distilled in vacuo. Compound **VIII** was obtained similarly in methanol with boiling for 1 hr 30 min.

2-Amino-4-(β-cyclohex-1'-enylethylamino)-6-mercaptopyrimidine (VI). A mixture of 1.26 g (4.9 mM) of **IV**, 1.08 g (17 mM) of sodium hydrogen sulfide and 15 ml of dimethylformamide was heated at 145–147° C in a current of nitrogen for 1 hr 30 min. The reaction mixture was cooled to room temperature and treated with 15 ml of water, the insoluble residue was filtered off, and the filtrate was decolorized with carbon and acidified with HCl (1 : 1) to pH 2. The precipitate was filtered off and purified by recrystallization from solvents. Compounds **III, XI, XIV, XIX,** and **XXI** were obtained similarly. The yield did not increase when compound **III** was prepared from 6.5 moles of sodium hydrogen sulfide. Compounds **XIX** and **XXI** were obtained in the form of the hydrochlorides: the first from 3.2 moles of sodium hydrogen sulfide, and the second using 4 moles. Compound **XIX** was precipitated at pH 4, and **XXI** was precipitated at pH 6.

4-(α-Methyl-β-phenylethylamino)pyrimidine (XXIII). 6-Chloro-4-(α-methyl-β-phenylamino)pyrimidine (**XXII**), 2 g (8 mM), in 55 ml of acetic acid (99%) was hydrogenated in the presence of 0.5 g of palladium on carbon (2%) for 3 hr 30 min until the absorption of hydrogen ceased (180 ml). The mixture was filtered and the catalyst was washed with a small amount of acetic acid. The acetic acid was distilled off from the filtrate in vacuo. The residue was dissolved in water, and the solution was neutralized and made alkaline with caustic soda solution (30%) to pH 10 and then extracted with ether. After the ether had been driven off, the residue was recrystallized from water. Yield 29.2%. Mp 125–126° C. Found, %: C 72.86; H 6.93; N 19.41. Calculated for $C_{13}H_{15}N_3$, %: C 73.20; H 7.09; N 19.71.

4-(β-Cyclohex-1'-enylethylamino)-2-hydroxy-6-methylpyrimidine (IX). A mixture of 0.5 g (2 mM) of **VII** and 5 ml of conc HCl was heated at 95° C for 30 min. The acid was distilled off in vacuo, and the residue was dissolved in water and neutralized with ammonia solution to pH 8.0. Compound **IX** that precipitated was purified by recrystallization from water.

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