N-(4-PYRIMIDYL)ETHYLAMINE DERIVATIVES

V. N. Sokolova and O. Yu. Magidson

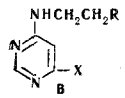
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 2, pp. 343–347, 1968

UDC 547.853.7'857'751

In order to find antitumoral agents, a number of new N-(4-pyrimidyl) ethylamine derivatives have been synthesized from 4,6-dichloropyrimidine, 6-amino-4-chloropyrimidine, 4-chloro-6-hydroxypyrimidine, and various ethylamines substituted in the β position.

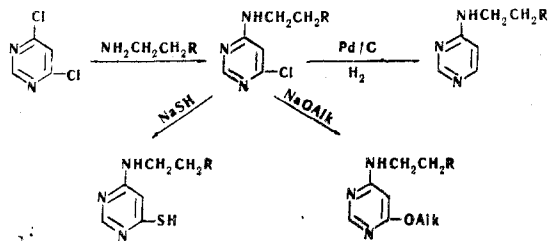
In 1960 a paper by Lettré and Ballweg [1] appeared on the selective action with regard to malignant cells of purine derivatives of biogenic amines of type A.

Some of the compounds they obtained interfered with the process of cell division in malignant tumors and did not exhibit such an action on the cells of normal tissue. The most interesting compound was 6-[β-(4'-imidazolyl)-ethylamino]purine. It appeared of interest to obtain pyrimidine derivatives of an analogous type both with biogenic amines and with nonbiogenic amines of closely similar structures, since it was not clear what was responsible for the physiological activity: the type of compound or the presence of a biogenic amine residue in the molecule. Some pyrimidine derivatives of histamine were described by Ballweg in 1964 [2]. It also appeared of interest to elucidate the influence of various substituents in positions 5 and 6 on the possible physiological activity of the compounds mentioned. In the present communication we report compounds of type B (see table).



As the starting compounds for the syntheses we used β-substituted ethylamines and halogen derivatives of pyrimidine: 4,6-dichloropyrimidine [3], 6-amino-4-chloropyrimidine [4], and 4-chloro-6-hydroxypyrimidine [5], which were prepared from 4,6-dihydroxypyrimidine by known methods [6, 7] with some modifications. 4,6-Dichloropyrimidine was purified by vacuum sublimation [8].

The reaction of 4,6-dichloropyrimidine (1 mole) with an amine (2 moles) in boiling benzene led to the replacement of only one chlorine atom in the 4(6) position.



The second chlorine atom, in position 6(4), was replaced by hydrogen or an alkoxy or mercapto group, The replacement of the second chlorine atom by hydrogen was carried out in acetic acid (99%) with a catalyst containing 1.7% palladium on carbon. When 6-chloro-4-[β-(1'-cyclohexenyl)ethylamino]pyrimidine was hydrogenated, the double bond in the cyclohexene ring was retained if the reaction was stopped after the absorption of the amount of hydrogen necessary for replacing the chlorine. The presence of the double bond was confirmed by its quantitative bromination. The introduction of alkoxy and mercapto groups was carried out under selected conditions by the usual methods with sodium alkoxides in the corresponding alcohols with heating or with sodium hydrogen sulfide in dimethylformamide.

EXPERIMENTAL

4,6-Dihydroxypyrimidine. With stirring, 61.2 g (0.6 mole) of malondiamide and 54 g (1.2 mole) of formamide were added to a solution of sodium methoxide in methanol prepared from 27.6 g (1.2 g-atom) of sodium and 600 ml of ethanol. The mixture was heated to the boil for 4 hr and then the methanol was distilled off. The residue was dissolved in 300 ml of water and acidified with hydrochloric acid (17%) to pH 3. The 4,6-dihydroxypyrimidine was filtered off from the cooled mixture, washed with water, and dried at 50°–60° C. Yield 54–55%.

6-Chloro-4[β-(1'-cyclohexenyl)ethylamino]pyrimidine (I). A mixture of 14.9 g (0.1 mole) of 4,6-dichloropyrimidine, 25 g (0.2 mole) β-(1'-cyclohexenyl)-ethylamine and 250 ml of benzene was boiled with stirring for 1 hr. After cooling, the amine hydrochloride that had deposited was filtered off and washed with benzene. The benzene solution was evaporated to dryness in vacuum, and the residue was triturated with water and extracted with ether. After the ether had been driven off, the substance was purified by recrystallization from solvents (table). Compounds **IX, XII, XVI, XXI,** and **XXIII** were obtained under analogous conditions with the difference that some of them required heating for 2–4 hr and in the case of 5-methoxytryptamine the amount of benzene was increased to 450 ml. Compound XVIII was obtained in butanol (397 ml). Compounds **XII, XVIII,** and **XXIII** were not extracted with ether but, after trituration with water, were filtered off and purified by recrystallization from solvents. Compound IX is sparingly soluble in benzene and therefore the bulk of it was obtained from its mixture with β-phenylethylamine hydrochloride after the latter had been dissolved in water.

6-Amino-4-[β-(1'-cyclohexenyl)ethylamino]pyrimidine (V). A mixture of 2 g (0.016 mole) of 6-amino-4-chloropyrimidine, 4 g (0.032 mole) of β-(1'-cyclohexenyl)ethylamine, and 250 ml of toluene was boiled with stirring for 12 hr. After cooling, the precipitate was filtered off, washed with toluene, dried, triturated with water, and filtered off again. It was purified by recrystallization from ethyl acetate.

Compounds **XXVI** and **XXVII** were obtained under the conditions given for **V** but the time of heating the mixture was increased to 8 hr. Compound XXVII was subjected to additional purification before crystallization, for which prupose it was converted into the hydrochloride and the base liberated from the salt was washed with ethyl acetate.

4-[β-(1'-Cyclohexenyl)ethylamino]-6-hydroxypyrimidine (VI). A mixture of 1 g (0.0077 mole) of 4-chloro-6-hydroxypyrimidine, 2 g

Ethylamino Derivatives of Pyrimidine of Type B

Compound	R	X	Mp, °C (solvent for crystallization)	Empirical formula	Found, %					Calculated, %					Yield, %
					C	H	Cl	N	S	C	H	Cl	N	S	
I		Cl	96-97 (benzene-petroleum ether)	$C_{12}H_{16}ClN_3$	60.34	6.78	15.07	17.73	—	60.63	6.73	14.94	17.68	—	76.1
II	,, ,,	OCH_3	55-56 (petroleum ether	$C_{13}H_{19}N_3O$*	—	—	—	18.21	—	—	—	—	18.02	—	57.1
III	,, ,,	H	47[2]*	$C_{12}H_{17}N_3$[3]*	70.59	8.60	—	—	—	70.93	8.37	—	—	—	80.0
IV	,, ,,	SH	147.5-150 (50% ethyl acetate)	$C_{12}H_{17}N_3S$	—	—	—	17.61	13.54	—	—	—	17.87	13.61	61.2
V	,, ,,	NH_2	144.5-145.5 (ethyl acetate)	$C_{12}H_{18}N_4$	65.84	8.30	—	25.69	—	66.05	8.29	—	25.65	—	70
VI	,, ,,	OH	177-178 (30% ethanol)	$C_{12}H_{17}N_3O$	—	—	—	19.09	—	—	—	—	19.17	—	28
VII	,, ,,	OC_4H_9	63-64 (75% ethanol	$C_{16}H_{25}N_3O$	69.85	9.18	—	15.52	—	69.81	9.09	—	15.27	—	80
VIII	,, ,,	$OCH_2—CH=CH_2$	57-58 (75% ethanol	$C_{15}H_{21}N_3O$	69.77	8.25	—	15.79	—	69.49	8.10	—	16.21	—	73.6
IX		Cl	119-120 (70% ethanol	$C_{12}H_{12}ClN_3$	61.78	5.29	15.09	—	—	61.67	5.13	15.20	—	—	66.0
X	,, ,,	OCH_3	56-58 (petroleum ether and benzene)	$C_{13}H_{15}N_3O$[4]*	68.37	6.47	—	—	—	68.12	6.55	—	—	—	76.5
XI	,, ,,	SH	175-176 (ethyl acetate)	$C_{12}H_{13}N_3S$	61.66	6.09	—	—	13.62	62.31	5.65	—	—	13.86	53.0
XII		Cl	91-92 (benzene and petroleum ether)	$C_{13}H_{14}OClN_3$	—	—	13.52	—	—	—	—	13.47	—	—	88.2
XIII	,, ,,	OCH_3	72-74 (benzene)	$C_{14}H_{17}N_3O_2$[5]*	—	—	—	16.16	—	—	—	—	16.21	—	80.0
XIV	,, ,,	H	120-121 (10% ethanol)	$C_{13}H_{15}N_3O$[6]*	68.04	6.73	—	18.37	—	68.12	6.55	—	18.34	—	76.9
XV	,, ,,	OH	187 (50% ethanol)	$C_{13}H_{15}N_3O_2$	63.63	5.97	—	—	—	63.67	6.12	—	—	—	40.0
XVI		Cl	91-92.5 (benzene and petroleum ether)	$C_{14}H_{16}ClN_3O_2$	—	—	12.26	—	—	—	—	12.09	—	—	76.4
XVII	,, ,,	H	113.5-115.5 (benzene and petroleum ether)	$C_{14}H_{17}N_3O_2$[7]*	64.85	6.61	—	16.09	—	64.82	6.59	—	16.19	—	80.6
XVIII		Cl	175-176 (50% ethanol)	$C_{12}H_{12}ClN_3O$	57.62	5.03	14.01	—	—	57.71	4.80	14.22	—	—	77.6
XIX	,, ,,	OCH_3	116-117.5 (36% ethanol)	$C_{13}H_{15}N_3O_2$[8]*	63.73	6.09	—	16.77	—	63.67	6.12	—	17.14	—	84.7
XX	,, ,,	SH	218-220 (50% ethanol	$C_{12}H_{13}N_3OS$	58.56	5.04	—	—	12.84	58.29	5.26	—	—	12.95	
XXI		Cl	99-100 (benzene)	$C_{11}H_{11}ClN_4$	—	—	15.19	23.96	—	—	—	15.13	23.88	—	69.6
XXII	,, ,,	H	82-83 (benzene)	$C_{11}H_{12}N_4$	—	—	—	27.84	—	—	—	—	28.00	—	76.8
XXIII		Cl	140-140.5 (50% ethanol)	$C_{15}H_{15}ClN_4O$	—	—	11.80	18.39	—	—	—	11.73	18.51	—	74.0
XXIV	,, ,,	H	129-130.5 (benzene and petroleum ether)	$C_{15}H_{16}N_4O$[9]*	—	—	—	20.79	—	—	—	—	20.89	—	61.0
XXV	,, ,,	OCH_3	125-126 (benzene)	$C_{16}H_{18}N_4O_2$[10]*	—	—	—	18.80	—	—	—	—	18.77	—	81
XXVI	,, ,,	NH_2	185.5-186.5 (ethanol)	$C_{15}H_{17}N_5O$	63.68	6.02	—	—	—	63.57	6.03	—	—	—	25
XXVII		NH_2	212-213 (50% ethanol)	$C_{15}H_{17}N_5O$	63.57	5.99	—	24.50	—	63.60	6.00	—	24.73	—	50

*Found, %: OCH_3 13.09. Calculated, %: OCH_3 13.30. Hydrochloride, mp 128° C. Found, %: Cl 13.51. Calculated, %: Cl 13.17.

2*Purified by vacuum distillation. Bp 150–153° C (2 mm).

3*Hydrochloride, mp 123–126° C. Found, %: Cl 14.91. Calculated, %: Cl 14.82.

4*Found, %: OCH_3 13.51. Calculated, %: OCH_3 13.53.

5*Found, %: OCH_3 23.52. Calculated, %: OCH_3 23.93. Hydrochloride, mp 115–116° C.

6*The hydrochloride contains 1 mole of water of crystallization, mp 109–110° C. Found, %: Cl 12.53. Calculated, %: Cl 12.52. Mp of the anhydrous salt 141–142° C.

7*Hydrochloride, mp 173–175° C. Found, %: Cl 11.86. Calculated, %: Cl 11.97.

8*On recrystallization from 36% ethanol, it contains 1 mole of water of crystallization.

9*Found, %: OCH_3 11.49. Calculated, %: OCH_3 11.56. Hydrochloride. Found, % Cl 11.40. Calculated, %: Cl 11.49.

10*Found, %: OCH_3 20.59. Calculated, %: OCH_3 20.70. Hydrochloride. Found, %: Cl 10.05. Calculated, %: Cl 10.61.

(0.016 mole) of β-(1'-cyclohexenyl)ethylamine, and 20 ml of absolute ethanol was boiled with stirring for 8 hr. The ethanol was distilled off in vacuum. The residue was dissolved in dilute sodium hydroxide solution and extracted with ether. The aqueous layer was acidified with hydrochloric acid (17%) to pH 7.5. The precipitate that deposited was filtered off, washed with water, and purified by recrystallization from a solvent. Compound XV was obtained similarly and was recrystallized immediately after the elimination of the ethanol and washing with water.

4-[β-(1'-Cyclohexenyl)ethylamino]-6-methoxypyrimidine (II). Compound I (2.375 g; 0.01 mole) was added to a solution of sodium methoxide prepared from 0.85 g (0.0369 g-atom) of sodium and 20 ml of anhydrous methanol. The mixture was boiled for 30 min and the ethanol was evaporated off in vacuum. The residue was stirred with water and extracted with ether. The substance obtained after the elimination of the ether was purified by recrystallization from solvents. Compounds XIII and XIX were obtained analogously. Substances X and XXV were obtained with a large excess of sodium (360 and 400%). Compounds XXV and XIX were not extracted with ether but, after trituration with water, were filtered off, washed with ether, and recrystallized.

6-Butoxy-4-[β-(1'-cyclohexenyl)-ethylamino]pyrimidine (VII). Two grams (0.0084 mole) of I was added to a solution of sodium butoxide prepared from 0.75 g (0.032 g-atom) of sodium and 25 ml of dry butanol. The mixture was heated to the boil for 2 hr and the butanol was evaporated off in vacuum. The residue was separated as described for compound II. Substance VIII was obtained analogously in allyl alcohol.

4-[β-(1'-Cyclohexenyl)ethylamino]-6-mercaptopyrimidine (IV). A mixture of 5 g (0.021 mole) of I, 5 g (0.08 mole) of sodium hydrogen sulfide, and 10 ml of ethylene glycol was heated at 155°–162° C (bath temperature) for 30 min. Then the reaction mixture was cooled to below 100° C and was poured into 35 ml of water. The solution was heated to the boil with carbon, filtered, and acidified with acetic acid (80%) until the precipitate ceased to separate. The mercapto derivative was filtered off, washed with water, and dried.

6-Mercapto-4-(β-phenylethylamino)pyrimidine (XI). A mixture of 4 g (0.017 mole) of 6-chloro-4-(β-phenylethylamino)pyrimidine, 5 g (0.08 mole) of sodium hydrogen sulfide, and 30 ml of dimethylformamide was heated at 170°–175° C (bath temperature) in a current of nitrogen for 1 1/2 hr. The reaction mixture was cooled to room temperature and treated with 40 ml of water and then it was filtered and acidified with hydrochloric acid (17%) to pH 4.5. The precipitate that deposited was filtered off and washed with water. Compound XX was obtained under analogous conditions with the difference that in its separation from the alkaline solution this was acidfied to pH 3.

4-[β-(1'-Cyclohexenyl)ethylamino]pyrimidine (III). Compound I (2.375 g; 0.01 mole) in 40 ml of acetic acid (99%) was hydrogenated in the presence of 0.7 g of 1.7% palladium on carbon. The reaction was terminated after the absorption of the calculated amount of hydrogen for the elimination of the chloride (224 ml). The mixture was filtered and the catalyst was washed with a small amount of acetic acid. The acetic acid was evaporated from the filtrate in vacuum. The residue was dissolved in water, neutralized with sodium hydroxide solution (10%) to an alkaline reaction (phenolphthalein) and extracted with ether. The residue after the elimination of the ether was purified. Compounds XIV, XVII, XXII, and XXIV were obtained analogously. Substance XXII was extracted with chloroform instead of ether.

REFERENCES

1. H. Lettré and H. Ballweg, Ann., 633, 171, 1960.
2. H. Ballweg, Ann., 673, 153, 1964.
3. R. Hull, J. Chem. Soc., 2214, 1951.
4. H. Goldner, Chem. Techn., 12, 495, 1960.
5. D. J. Brown and J. S. Horper, J. Chem. Soc., 1298, 1961.
6. D. J. Brown, J. Chem. Soc., 2312, 1956.
7. L. R. Davidenkov, Med. prom., No. 1, 25, 1962.
8. C. Hennart and E. Merlin, Bull., 741, 1959.

7 May 1966

Ordzhonikidze All-Union Chemical and Pharmaceutical Scientific-Research Institute, Moscow