DERIVATIVES OF N-(4-PYRIMIDYL)ETHYLAMINE

II. 5-Allyl- and 5-p-Chlorophenylpyrimidines*

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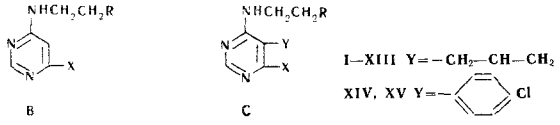
In order to find antitumoral substances, a number of new derivatives of N-(4-pyrimidyl)ethylamine with an allyl or p-chlorophenyl group in position 5 of the pyrimidine nucleus has been synthesized. The starting materials were 5-allyl-4,6-dichloropyrimidine and 5-(p-chlorophenyl)-4,6-dichloropyrimidine and various ethylamines substituted in the β-position.

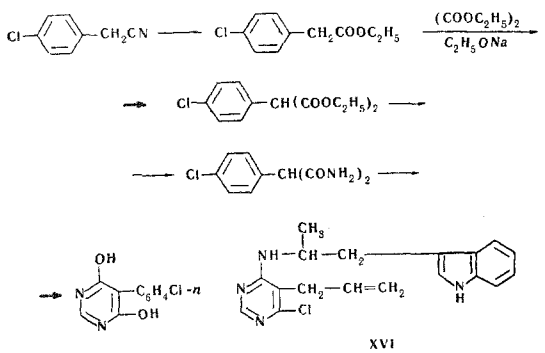
In the preceding communication we described the synthesis of various derivatives of N-(4-pyrimidyl)-ethylamine of type B not containing substituents in position 5 of the pyrimidine nucleus.



Continuing our study of compounds of similar structure, in the present paper we describe the preparation of derivatives of the analogous type C bearing an allyl or a p-chlorophenyl group as substituent in position 5.

Starting materials for the synthesis were, in addition to β-substituted ethylamine derivatives (see table), 5-allyl-4,6-dichloropyrimidine and 5-(p-chlorophenyl)-4,6-dichloropyrimidine which, in their turn, were obtained by a known method from the corresponding 4,6-dihydroxypyrimidines [2,3]. The reaction of allylmalondiamide with formamide in methanol in the presence of sodium methoxide led to 5-allyl-4,6-dihydroxypyrimidine with a yield of 79.4%, i.e. considerably higher than was achieved in the preparation of 4,6-dihydroxypyrimidine.

The synthesis of 5-(p-chlorophenyl)-4,6-dihydroxy-pyrimidine was effected by the following method:



By using the conditions for preparing ethyl phenyl-acetate and phenyl malonate [4,5], p-chlorophenyl-acetonitrile [6] was converted into ethyl p-chloro-phenylacetate and then into p-chlorophenylmalonate. The latter was converted almost quantitatively at room temperature with a solution of ammonia in methanol into p-chlorophenylmalondiamide. The closure of the pyrimidine ring with ethyl formate was carried out in analogy with known examples [2].

The reaction of 5-allyl- and 5-(p-chlorophenyl)-4,6-dichloropyrimidines with amines was carried out under the same conditions (boiling point of benzene) as the reactions of 4,6-dichloropyrimidine unsubstituted in position 5 [1] with the formation of derivatives monosubstituted in position 4. The second chlorine atom in position 6 was replaced by an alkoxy or mercapto group with a sodium alkoxide or sodium hydrogen sulfide, but in the case of 4-[β-(1'-cyclohexenyl)-ethylamino]-5-(p-chlorophenyl)-6-chloropyrimidine, the chlorine could not be replaced by a mercapto group.

EXPERIMENTAL

Allylmalondiamide. A solution of 47 g (0.235 mole) of diethyl allylmalonate [7] in 150 ml of methanol saturated with dry ammonia at 0° C was kept at room temperature for 4 days. The precipitate that deposited was filtered off. Evaporation of the mother liquor gave a further small amount of material. The two precipitates were recrystallized from water. Yield 24.2 g (72.6%), mp 167°-168° C. Found, %: C 50.56; H 7.23; N 19.34. Calculated for $C_6H_{10}N_2O_2$, %: C 50.70; H 7.04; N 19.71.

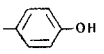
5-Allyl-4,6-dihydroxypyrimidine. To an ethanolic solution of sodium ethoxide [6.5 g (0.28 g-atom) of metallic sodium and 170 ml of absolute ethanol] were added 20 g (0.14 mole) of allylmalondiamide and 9.5 g (0.21 mole) of formamide. The mixture was boiled for 4 hr and the alcohol was distilled off. The residue was dissolved in water and the solution was decolorized with carbon, filtered, and acidified with hydrochloric acid (1 : 1) to pH 3. The precipitate that deposited was filtered off, washed with water, and dried. Yield 17 g (79.4%). The substance began to decompose at 240° C and was converted into a yellow resin at 250°-255° C. Recrystallization from water did not change the decomposition temperature. Found, %: C 55.15; H 5.13; N 18.43; Calculated for $C_7H_8N_2O_2$, %: C 55.26; H 5.26; N 18.42.

5-Allyl-4,6-dichloropyrimidine. A mixture of 26.2 g (0.14 mole) of 5-allyl-4,6-dihydroxypyrimidine, 375 ml of phosphorus oxychloride, and 14 ml of dimethylaniline was heated at the boil for 4 hr. The excess of phosphorus oxychloride was distilled off in vacuum; the residue was poured onto ice and the substance that separated out was extracted with ether. After evaporation of the ether, the residue was distilled in vacuum. Bp 96°-98° C (8 mm). Yield 29.18 g (89.7%). Found, %: Cl 38.10. Calculated for $C_7H_6Cl_2N_2$, %: Cl 37.56.

Ethyl p-chlorophenylacetate [8,9] was obtained with a yield of 94.1% from p-chlorophenylacetonitrile. Bp 128°-131° C (10 mm). Found, %: C 60.03; H 5.33; Cl 18.16. Calculated for $C_{10}H_{11}ClO_2$, %: C 60.45; H 5.54; Cl 17.88;

*For part I, see [1].

Ethylamino Pyrimidine Derivatives of Type C

Compound	R	X	Mp, °C (solvent for crystallization)	Empirical formula	Found, %				Calculated, %				Yield, %
					C	H	Cl	N	C	H	Cl	N	
I		Cl	84—85 (70% ethanol)	$C_{15}H_{20}ClN_3$	64.74	7.19	13.01	—	64.86	7.20	12.79	—	78
II	„ „	—OCH_3	—	$C_{16}H_{23}N_3O$*	70.34	8.33	—	—	70.32	8.42	—	—	85.3
III	„ „	SH	203—205.5 (ethanol)	$C_{15}H_{21}N_3S$[2]*	65.34	7.77	—	—	65.45	7.63	—	—	31.2
IV	„ „	—OC_4H_9	—	$C_{19}H_{29}N_3O$[3]*	72.40	9.28	—	13.71	72.38	9.20	—	13.33	75.1
V	„ „	OCH_2—CH=CH_2	—	$C_{18}H_{25}N_3O$[4]*	72.42	8.33	—	13.65	72.24	8.36	—	14.04	78.5
VI	„ „	SC_4H_9	—	$C_{19}H_{29}N_3S$[5]*	68.89	8.86	—	—	68.88	8.76	—	—	54.3
VII		Cl	92—93 (70% ethanol)	$C_{16}H_{18}ClN_3O$	63.27	5.97	11.63	—	63.26	5.93	11.79	—	84.1
VIII	„ „	OCH_3	—	$C_{17}H_{21}N_3O_2$[6]*	68.58	7.10	—	—	68.22	7.02	—	—	63
IX	„ „	SH	173—175.5 (ethanol, ethyl acetate)	$C_{16}H_{19}N_3OS$[7]*	63.77	6.43	—	—	63.78	6.31	—	—	44
X		Cl	109—110 (70—90% ethanol)	$C_{15}H_{16}ClN_3$	65.79	5.80	12.94	—	65.81	5.85	12.97	—	88.5
XI	„ „	OCH_3	—	$C_{16}H_{19}N_3O$[8]*	71.16	6.93	—	—	71.37	7.06	—	—	76
XII		Cl	143—144 (50% ethanol)	$C_{15}H_{16}ClN_3O$	61.85	5.33	12.08	—	62.17	5.52	12.26	—	78.3
XIII	„ „	OCH_3	121—123 (40% ethanol)	$C_{16}H_{19}N_3O_2$	67.18	6.67	—	14.77	67.36	6.66	—	14.73	53.3
XIV		Cl	94—97 (75% ethanol)	$C_{18}H_{19}Cl_2N_3$	61.99	5.73	—	—	62.06	5.45	—	—	61
XV	„ „	OCH_3	116—118 (90% ethanol)	$C_{19}H_{22}ClN_3O$	66.37	6.36	10.41	—	66.37	6.40	10.33	—	60

* Purified by vacuum distillation, bp 178° C (2 mm). 2*Found, %: S 11.53, calculated, %: S 11.63. 3*Bp 206–207° C (2–3 mm). 4*Bp 202–203° C (2 mm). 5*Bp 201–202° C (2 mm). 6*Found, %: S 9.35. Calculated, %: S 9.66. 7*Bp 195–197° C (1–2 mm). Found, % OCH_3 20.60. Calculated %: OCH_3 20.73. 8*Found, %: S 10.66. Calculated, %: S 10.66. 9*Bp 173–175° C (3 mm).

Diethyl p-chlorophenylmalonate [5]. After the addition of the initial esters to a solution of sodium ethoxide in absolute ethanol, the sodium salt of diethyl p-chlorophenyloxaloacetate did not precipitate from the solution. The ethanol was evaporated off from the solution in vacuum and the residue was dissolved in water and treated as described for the preparation of the phenylmalonic ester. yield 30%. Bp 175°-181° C (10 mm). Found, %: C 57.82; H 5.54; Cl 13.63. Calculated for $C_{13}H_{15}ClO_4$, %: C 57.67; H 5.54; Cl 13.12.

p-Chlorophenylmalondiamide. This was obtained under the same conditions as allylmalondiamide with a yield of 95%. Mp 210°-212° C. Found, %: C 51.19; H 4.17; N 13.42. Calculated for $C_9H_9ClN_2O_2$, %: C 50.82; H 4.23; N 13.17.

5-(p-Chlorophenyl)-4,6-dihydroxypyrimidine. To a solution of sodium ethoxide prepared from 5.4 g (0.235 g-atom) of Na in 92 ml of absolute ethanol were added 18.3 g (0.09 mole) of p-chlorophenylmalondiamide and 17.5 g (0.235 mole) of ethyl formate. The mixture was boiled for 4 hr and the ethanol was evaporated off. The residue was dissolved in water (160 ml) and acidified with hydrochloric acid (1 : 1) to pH 3. The precipitate that deposited was filtered off, washed with water, stirred in water (250 ml), and treated with concentrated caustic soda solution until it dissolved completely, and then the solution was decolorized with carbon and filtered. The purified substance was precipitated from the filtrate with hydrochloric acid. The precipitate was filtered off and washed with distilled water until the filtrate no longer contained chloride ion. Yield 16.88 g (88.3%). Found, %: Cl 16.24. Calculated for $C_{10}H_7ClN_2O_2$, %: Cl 15.95.

5-(p-Chlorophenyl)-4,6-dichloropyrimidine was obtained in the same way as 5-allyl-4,6-dichloropyrimidine. In ice water, the substance precipitated in the form of a fine powder; it was filtered off and recrystallized from petroleum ether. Mp 89°-91° C. Yield 84.4%. Found. %: Cl 40.88. Calculated for $C_{10}H_5Cl_3N_2$, %: Cl 41.04.

5-Allyl-4-[β-(1'-cyclohexenyl)ethylamino]-6-chloropyrimidine (I). A mixture of 18.9 g (0.1 mole) of 5-allyl-4,6-dichloropyrimidine, 25 g (0.2 mole) of β-(1'-cyclohexenyl)ethylamine, and 155 ml of benzene was boiled for 4 hr. The precipitate of the amine hydrochloride that deposited was filtered off and washed with benzene. The benzene solutions were evaporated in vacuum and the solid residue was washed with petroleum ether, triturated with water, filtered off, and purified by recrystallization from a solvent.

Compounds VII, X, XII, XIV, and XVI were obtained similarly from the corresponding amines (see table).

Substance XVI was obtained from 5-allyl-4,6-dichloropyrimidine and β-(3-indolyl)-α-methylethylamine. It was purified by recrystallization from 70% ethanol. Mp 97°-99° C, giving a turbid melt which became clear at about 105° C. Yield 77.2%. Found, %: C 66.04; H 5.84; Cl 11.00. Calculated for $C_{18}H_{19}ClN_4$, %: C 66.15; H 5.81; Cl 10.87.

5-Allyl-4-[β-(1'-cyclohexenyl)ethylamino]-6-methoxypyrimidine (II). Compound I (2.77 g; 0.01 mole) was added to a solution of sodium methoxide prepared from 0.75 g (0.05 g-atom) of sodium and 25 ml of methanol. The mixture was boiled for 4 hr and the ethanol was evaporated in vacuum. The residue was triturated with water and extracted with ether. After the elimination of the ether, the substance was distilled in vacuum. Substances VIII, XI, XIII, and XV were obtained similarly. Compound XV was obtained in the form of a solid with mp 60°-71° C. When it was recrystallized from 75-90% ethanol, the low-melting form with mp 65°-69° C underwent a transition into the high-melting form with mp 116°-118° C.

5-Allyl-4-[β-(1'-cyclohexenyl)ethylamino]-6-butoxypyrimidine (IV). To a solution of sodium butoxide prepared from 2 g (0.08 g-atom) of sodium and 40 ml of butanol was added 2.7 g (0.01 mole) of I, and the mixture was boiled for 5 hr. The product was isolated in the same way as II. 5-Allyl-4-[β-(1'-cyclohexenyl)ethylamino)-6-allyloxypyrimidine (V) was obtained similarly, with the reaction mixture being boiled for 2 hr.

5-Allyl-4-[β-(1'-cyclohexenyl)-ethylamino]-6-mercaptopyrimidine (III). A mixture of 27.75 g (0.01 mole) of I, 19.6 g (0.35 mole) of sodium hydrogen sulfide, and 200 ml of dimethylformamide was heated at 145°-147° C for 1 hr 30 min in a current of nitrogen. The reaction mixture was cooled to room temperature and 174 ml of water was added; the insoluble residue was filtered off and the filtrate was decolorized with carbon. After filtration, the solution was neutralized with hydrochloric acid (1 : 1) to pH 4. The substance was purified by recrystallization from solvents. Compound IX was obtained similarly.

5-Allyl-4-[β-(1'-cyclohexenyl)ethylamino]-6-butylthiopyrimidine (VI). A solution of 2.75 g (0.01 mole) of III in 15.7 ml of 1 N caustic soda (0.015 mole) was treated with 4 ml of water and 2 g (0.014 mole) of butyl bromide, and the mixture was stirred at room temperature for 5-6 hr. The oil that separated out was extracted with ether. After evaporation of the ether, the residue was distilled in vacuum.

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