2- AND 4-SUBSTITUTED 5-FLUOROPYRIMIDINES

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2- and 4-substituted 5-fluoropyrimidines were synthesized by the reaction of 2,4-dichloro-5-fluoropyrimidine with alkoxides, phenols, and aromatic and heterocyclic amines.

2-Chloro-4-alkoxy- (II) and 2,4-dialkoxy-5-fluoropyrimidines (III) [3] were obtained by the reaction of 2,4-dichloro-5-fluoropyrimidine (I) [1,2] with one or two equivalents of sodium alkoxide. The replacement of chlorine in I by one or two aroxy groups was carried out in an excess of the corresponding phenols by heating with the calculated amount of anhydrous potassium carbonate [4, 5]. The yields of 2-chloro-4-aroxy-5-fluoropyrimidines (IVa, b) were considerably higher in this case than in the synthesis of these same compounds with an equivalent amount of the corresponding phenoxides [3]. 2,4-Diaroxy-5-fluoropyrimidines (IVc-h) were obtained in high yields (Table 1) via this method.

In analogy with the products of the reaction of I with amino acids [6] and amines [7], the 2-chloro-4-alkoxy- and 2-chloro-4-aroxy-5-fluoropyrimidine structures were adopted for II and IVa, b, the products of the reaction of I with 1 mole of sodium alkoxide or phenol.

Compounds V, which contain residues of aromatic or heterocyclic amines, were obtained by heating an excess of the appropriate amines with I. All of the compounds obtained form hydrochlorides (Table 1).

We were unable to obtain 2-arylamino-4-phenoxy-5-fluoropyrimidines from IVa by heating with an excess of the amines, since the phenoxy group in the 4 position is replaced in addition to the chlorine in the 2 position to give V.

Compound II reacts very vigorously with excess piperidine (the temperature of the reaction mixture rises to 100°C) to give 2-piperidyl-4-alkoxy-5-fluoropyrimidines (VI), which react with alcoholic hydrogen chloride solution to give hydrochlorides that readily yield the bases in aqueous solution.

EXPERIMENTAL

2-Chloro-4-methoxy-5-fluoropyrimidine (IIa). A solution of sodium methoxide, obtained from 0.23 g (0.01 mole) of sodium in 30 ml of absolute methanol, was added by drops in the course of 10 min to a solution of 1.66 g (0.01 mole) of I in 30 ml of absolute methanol, and the mixture was stirred for 1 h, diluted with water, and extracted with ether. The ether solution was dried with anhydrous sodium sulfate, the solvent was removed by distillation, and the residue was vacuum distilled.

Compounds IIb-d were similarly obtained.

2,4-Dimethoxy-5-fluoropyrimidine (IIIa). A sodium methoxide solution, obtained from 2.3 g (0.1 mole) of sodium in 50 ml of absolute methanol, was added in the course of 30 min to a solution of 8.3 g (0.05 mole) of I in 50 ml of absolute methanol, and the mixture was heated at 40° for 30 min. The mixture was then worked up as in the preparation of IIa. The reagent ratio for IIIb, c, d was similar to that in the preparation of IIIa, but the mixture was refluxed for 19 h in the preparation of IIIb, held at 100° for 30 min for the preparation of IIIc, and held at 120° for 1 h for the preparation of IIId.

2-Methoxy-4-ethoxy-5-fluoropyrimidine (IIIe). This compound was obtained by refluxing equimolar amounts of IIb and sodium methoxide in absolute methanol for 6 h with subsequent workup as in the preparation of IIa.

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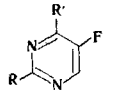
TABLE 1. 2,4-Substituted 5-Fluoropyrimidines



Compound	R	R′	mp, °C,* bp, °C (mm)	n_D^{20}	Empirical formula	Found, %				Calc., %				Yield, %	Hydrochlorides †	
						C	H	Cl	N	C	H	Cl	N		mp, °C	yield, %
IIa	Cl	OCH_3	67 (5)	—	$C_5H_4ClFN_2O$	—	—	21,76	17,54	—	—	21,81	17,23	85	—	—
IIb	Cl	OC_2H_5	82 (3)	—	$C_6H_6ClFN_2O$	—	—	19,83	16,91	—	—	20,08	16,80	83	—	—
IIc	Cl	$O(CH_2)_2CH_3$	85—86 (5)	1,4900	$C_7H_8ClFN_2O$	—	—	18,72	15,03	—	—	18,62	14,69	80	—	—
IId	Cl	$O(CH_2)_3CH_3$	128—129 (25)	1,4865	$C_8H_{10}ClFN_2O$	—	—	17,09	13,78	—	—	17,34	13,68	82	—	—
IIIa	OCH_3	OCH_3	48—50	—	$C_6H_7FN_2O_2$	45,47	4,21	—	17,68	45,57	4,46	—	17,71	95	—	—
IIIb	OC_2H_5	OC_2H_5	148—150 (88)	1,4770	$C_8H_{11}FN_2O_2$	51,45	5,90	—	15,21	51,60	5,95	—	15,04	87	—	—
IIIc	$O(CH_2)_2CH_3$	$O(CH_2)_2CH_3$	117 (8)	1,4750	$C_{10}H_{15}FN_2O_2$	55,95	7,00	—	13,37	56,06	7,05	—	13,07	90	—	—
IIId	$O(CH_2)_3CH_3$	$O(CH_2)_3CH_3$	141 (9)	1,4730	$C_{12}H_{19}FN_2O_2$	59,13	7,61	—	11,79	59,37	7,88	—	11,54	85	—	—
IIIe	OCH_3	OC_2H_5	45—47	—	$C_7H_9FN_2O_2$	48,51	5,11	—	16,52	48,83	5,26	—	16,26	72	—	—
IVa	Cl	OC_6H_5	71—71,5	—	$C_{10}H_6ClFN_2O$	—	—	15,83	12,68	—	—	15,77	12,51	95	—	—
IVb	Cl	$OC_6H_4CH_3$-*o*	68,5—69,5	—	$C_{11}H_8ClFN_2O$	—	—	14,95	12,14	—	—	14,85	11,73	85	—	—
IVc	OC_6H_5	OC_6H_5	91—93	—	$C_{16}H_{11}FN_2O_2$	67,91	3,60	—	9,86	68,08	3,92	—	9,92	79	—	—
IVd	$OC_6H_4CH_3$-*o*	$OC_6H_4CH_3$-*o*	55—57	—	$C_{18}H_{15}FN_2O_2$	69,32	4,55	—	9,22	69,66	4,87	—	9,02	90	—	—
IVe	$OC_6H_4CH_3$-*m*	$OC_6H_4CH_3$-*m*	66—68	—	$C_{18}H_{15}FN_2O_2$	69,53	4,59	—	9,26	69,66	4,87	—	9,02	95	—	—
IVf	$OC_6H_4CH_3$-p	$OC_6H_4CH_3$-p	82—83	—	$C_{18}H_{15}FN_2O_2$	69,37	4,39	—	9,08	69,66	4,87	—	9,02	96	—	—
IVg	OC_6H_4F-*o*	OC_6H_4F-*o*	80—82	—	$C_{16}H_9F_3N_2O_2$	60,07	2,80	—	8,66	60,38	2,85	—	8,80	89	—	—
IVh	OC_6H_4F-p	OC_6H_4F-p	153—155	—	$C_{16}H_9F_3N_2O_2$	60,21	2,73	—	8,54	60,38	2,85	—	8,80	95	—	—
IVi	OC_6H_5	OC_2H_5	69—70	—	$C_{12}H_{11}FN_2O_2$	61,37	4,58	—	12,09	61,53	4,73	—	11,95	73	—	—
Va	HNC_6H_5	HNC_6H_5	166—167	—	$C_{16}H_{13}FN_4$	68,43	4,51	—	19,73	68,55	4,67	—	19,99	92	226—228	92
Vb	$HNC_6H_4CH_3$-*o*	$HNC_6H_4CH_3$-*o*	103—106	—	$C_{18}H_{17}FN_4$	70,23	5,67	—	17,67	70,11	5,55	—	18,16	89	232—233	83
Vc	HNC_6H_4F-p	HNC_6H_4F-p	213—215	—	$C_{16}H_{11}F_3N_4$	60,79	3,57	—	17,43	60,75	3,51	—	17,71	83	255	70
Vd	$N(CH_2)_2O(CH_2)_2$	$N(CH_2)_2O(CH_2)_2$	115—116	—	$C_{12}H_{17}FN_4O_2$	53,88	6,45	—	20,51	53,72	6,38	—	20,88	99	226	88
Ve	NC_5H_{10}	NC_5H_{10}	166—167 (4)	1,5680	$C_{14}H_{21}FN_4$	63,73	8,25	—	21,03	63,61	8,01	—	21,12	62	98—100	62
VIa	NC_5H_{10}	OCH_3	120—121 (3)	1,5330	$C_{10}H_{14}FN_3O$	56,63	6,71	—	19,64	56,86	6,68	—	19,80	70	92—93	90
VIb	NC_5H_{10}	OC_2H_5	143—145 (8)	1,5270	$C_{11}H_{16}FN_3O$	58,86	6,94	—	17,84	58,65	7,15	—	18,65	63	123—125	70
VIc	NC_5H_{10}	$O(CH_2)_2CH_3$	145 (5)	1,5200	$C_{12}H_{18}FN_3O$	60,01	7,63	—	17,54	60,23	7,58	—	17,56	60	105—106	76
VId	NC_5H_{10}	$O(CH_2)_3CH_3$	165—167 (11)	1,5170	$C_{13}H_{20}FN_3O$	61,25	7,85	—	16,54	61,63	7,95	—	16,58	85	103,5—105	65
VIe	Cl	NC_6H_{10}	52—53	—	$C_9H_{11}ClFN_3$	—	—	16,58	19,54	—	—	16,43	19,48	60	—	—

*Compounds IVa-i were recrystallized from n-hexane; IVg was recrystallized from n-hexane–acetone (5:1); IVh was recrystallized from acetone; Va, b were recrystallized from benzene; and Vc was recrystallized from ether–benzene (1:1).

†The hydrochloride of Va was washed with acetone; Vb, c, e were washed with ether–acetone (1:1); and Vd and VIa-d were washed with ether. The results of the analysis for chlorine and nitrogen were close to the theoretical values.

2-Chloro-4-phenoxy-5-fluoropyrimidine (IVa). A mixture of 10 g (0.06 mole) of I, 28.2 g (0.3 mole) of phenol, and 4.14 g (0.03 mole) of anhydrous potassium carbonate was heated at 80° for 1 h and then at 100° for 1.5 h. The cooled mass was mixed with an aqueous solution of 16.2 g (0.3 mole) of potassium hydroxide, and the precipitated crystalline substance was removed by filtration, washed with water, dried, and recrystallized.

Compound IVb was similarly obtained.

Compound I and potassium carbonate (1:2) and an excess of the appropriate phenol were used for the synthesis of IVc-h, and the mixture was heated at 140° for 3 h. The excess material in the preparation of IVi was IIb.

2,4-Diphenylamino-5-fluoropyrimidine (Va). A 1.66-g (0.01 mole) sample of I or 2.24 g (0.01 mole) of IVa was mixed with 9.3 g (0.1 mole) of aniline, and the mixture was heated at 100° for 1 h and at 150° for 2 h. It was then cooled, 10 ml of water and 10 ml of methanol were added, and the product, which began to crystallize, was removed by filtration, dried, and recrystallized. Compounds Vb, c were similarly obtained. Compound Vd was isolated after dilution of the reaction mixture with water.

2,4-Dipiperidyl-5-fluoropyrimidine (Ve). A mixture of 3.34 g (0.02 mole) of I and 10.2 g (0.12 mole) of piperidine in 25 ml of ethanol was heated for 3 h, after which the piperidine hydrochloride was removed by filtration, the solvent was removed by distillation, and the residue was treated with ether. The ether was removed by distillation, and the final product was vacuum distilled.

2,4-Diarylamino-5-fluoropyrimidine Hydrochlorides. These were obtained by mixing equimolar amounts of acetone solutions of V and an alcohol solution of hydrogen chloride.

2-Piperidyl-4-methoxy-5-fluoropyrimidine (VIa). A mixture of 8.61 g (0.053 mole) of IIa and 21.5 g (0.25 mole) of piperidine was stirred with water cooling until the mixture no longer warmed up. It was then mixed with water and extracted with ether. The ether extract was dried with anhydrous sodium sulfate, the solvent was removed by distillation, and the residue was vacuum distilled.

Compounds VIb-d were similarly obtained.

Hydrochlorides of VIa-d. These were obtained by a method similar to that used for the hydrochlorides of V, but absolute ethanol was used as the solvent.

2-Chloro-4-piperidyl-5-fluoropyrimidine (VIe). A solution of 1.7 g (0.02 mole) of piperidine in 20 ml of ether was added in the course of 30 min to a solution of 3.34 g (0.02 mole) of I and 2.02 g (0.02 mole) of triethylamine in 30 ml of ether. The triethylamine hydrochloride was removed by filtration, and the solvent was removed by distillation. Dilution of the oily substance with petroleum ether and cooling of the mixture precipitated the crystalline product.

LITERATURE CITED

1. C. Hennart and E. Merlin, Bull. Soc. Chim. France, 741 (1959).
2. L. D. Protsenko and Yu. I. Bogodist, Zh. Obshch. Khim., 33, 537 (1963).
3. E. Profft and H. Raddatz, Arch. Pharm., 295, 649 (1962).
4. T. Mattsukawa and K. Shirakawa, J. Pharm. Soc. Japan, 71, 1313 (1951).
5. D. Ghosh and M. Mukherjee, J. Med. Chem., 11, 1237 (1968).
6. R. A. Paégle, M. G. Plata, and M. Yu. Lidak, Khim. Geterotsikl. Soedin., 475 (1966).
7. Yu. I. Bogodist and L. D. Protsenko, Ukr. Khim. Zh., 36, 1142 (1970).