of the appropriate amine were employed for the preparation of compounds XV and XVI, XVII, XVIII, respectively. Compound XX was obtained when equimolecular amounts of XI, *o*-chloroaniline, and triethylamine reacted at 0°. Crude XX was isolated by separation of the solids from the ethereal reaction mixture, evaporation of the ether, extraction of the residue with refluxing benzene, and addition of ligroin to the benzene extract. For the preparation of 2-amino-4,6-difluoro-*s*-triazine (XXII) ammonia was passed for 1 hr. into an ice-cold solution of 13.5 g. of cyanuric fluoride in 100 ml. of ether. The excess ammonia was removed by passing air through the ice-cold reaction mixture. The solid was then filtered by suction and the filter cake washed several times with ether. The dry filter cake (14.0 g.) consisted mainly of ammonium fluoride from which 3.1 g. of crude XXII was extracted with hot dioxane. Another crop of crude XXII (2.65 g.) was obtained when the solvent was removed from the ether filtrate, thus resulting in an over-all yield of 45.6%. Compound XXII was purified by sublimation under normal pressure at a bath temperature of 120–130°. XXII seems to split off hydrogen fluoride upon heating to give a polymeric material which does not melt up to 300°. If XXII is put on a plate, preheated to 270°, it first melts and then forms a white solid within a few seconds. XXII is a sternutator and produces burns on contact with the skin.

The synthesis of XXIV and the conversion of this compound into XXV and XXVI was accomplished according to the procedures described for the preparation of the corresponding 4,6-dichloro-*s*-triazines.[9]

Pertinent data for these compounds are listed in Table I.

Trichlorophosphazotrifluoroacetyl (XXIX).—Trifluoroacetamide (45.2 g.) was mixed with thoroughly powdered phosphorus pentachloride (83.4 g.) and heated. At 40°, evolution of hydrogen chloride started. The mixture was completely liquefied at 50°. Heating was continued for 4 hr. at 72° and the reaction mixture finally fractionated. After a small forerun, the principal product distilled at 146–149° (750 mm.); yield: 73.2 g. (73.6%); $n^{25}D$ 1.4341.

Anal. Calcd. for $C_2Cl_3F_3NPO$: N, 5.64; Cl, 42.83. Found: N, 5.03; Cl, 43.03.

Upon exposure to air, XXIX formed ***N*-trifluoroacetylphosphoramidic acid dichloride,** m.p. 76–77°.

Anal. Calcd. for $C_2HCl_2F_3NPO_2$: C, 10.45; H, 0.43; Cl, 30.84; N, 6.09; P, 13.48. Found: C, 10.45; H, 0.39; Cl, 29.50; N, 6.44; P, 13.45.

2,4,6-Tris(trifluoromethyl)-*s*-triazine (XXVIII).—Trichlorophosphazotrifluoroacetyl (XXIX, 24.85 g., 0.1 mole) was refluxed with 3 equivalents of silver fluoride (37.8 g.) for 2 hr. A considerable amount of low boiling material, consisting mainly of phosphoryl fluoride, was condensed in a carbon dioxide–acetone cooled trap which was connected with the reaction flask through the outlet of the reflux condenser. Fractionation of the reaction mixture yielded—besides 6.1 g. of unchanged XXIX—4.1 g. of XXVIII, b.p. 93° (lit.: 96–98°); $n^{28}D$ 1.3209.

Anal. Calcd. for $C_6F_9N_3$: C, 25.28; N, 14.74. Found: C, 24.91; N, 14.53.

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Synthesis of Polyfluorinated Heterocycles by Indirect Fluorination with Silver Fluorides. II. Fluoropyrimidines[1-3]

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Tetrachloropyrimidine was converted with silver fluoride into 5-chloro-2,4,6-trifluoropyrimidine, but all attempts to replace the chlorine atom in 5-position with fluorine failed. 2,4,6-Trichloropyrimidine gave upon treatment with silver fluoride 2,4,6-trifluoropyrimidine which reacted with silver difluoride (AgF_2) in perfluorinated diluents to form tetrafluoropyrimidine. Numerous derivatives of the new halopyrimidines are described.

In the first paper of this series[2] the synthesis of certain perfluorinated derivatives of 1,3,5-triazine was described. It was demonstrated that silver difluoride and especially silver fluoride are excellent agents for the replacement of nuclear bound chlorine by fluorine in the *s*-triazine system.

The objective of the present investigation was the preparation of polyfluoropyrimidines, especially tetrafluoropyrimidine, and derivatives thereof. Based on our experience in the triazine series, the reaction of silver fluoride and silver difluoride with chloropyrimidines appeared to offer the most promising route of synthesis, especially since it had been shown that tetrachloropyrimidine was not affected at all by the "Swarts reagent" (SbF_3Cl_2).[5] Partial fluorination of 2,4,6-trichloropyrimidine by means of sulfur tetrafluoride has been reported recently.[6] This method gave a mixture of 4,6-dichloro-2-fluoropyrimidine and 2,6-dichloro-4-fluoropyrimidine when the reaction was carried out at 225°.

The perchlorinated pyrimidine, 2,4,5,6-tetrachloropyrimidine[7] (I), appeared to be the obvious

(1) This article is based on work performed during 1956 and 1957 under Project 116-B of The Ohio State University Research Foundation sponsored by the Olin Mathieson Chemical Corporation, New York, N. Y.

(2) Preceding communication: E. Kober, H. Schroeder, R. Rätz, H. Ulrich, and C. Grundmann, *J. Org. Chem.*, **27**, 2577 (1962).

(3) Preliminary publication: H. Schroeder, *J. Am. Chem. Soc.*, **82**, 4115 (1960).

(4) Present address: Olin Mathieson Chemical Corporation, New Haven, Conn.

(5) E. Kober and Ch. Grundmann, *J. Am. Chem. Soc.*, **81**, 3769 (1959).

(6) C. W. Tullock, R. A. Carboni, R. J. Harder, W. C. Smith, and D. D. Coffman, *J. Am. Chem. Soc.*, **82**, 5107 (1960).

(7) S. J. Childress and R. C. McKee, *J. Am. Chem. Soc.*, **72**, 4271 (1950).

starting material for our study. Treatment with silver fluoride converted it in a smooth reaction into 5-chloro-2,4,6-trifluoropyrimidine (II), thus replacing the activated chlorine atoms, namely those which are attached to the carbon atoms in α-position to the electron withdrawing nitrogen atoms.

To achieve also replacement of the chlorine atom in 5-position, II was refluxed with silver difluoride in the presence of perfluorotributylamine. The powerful oxidizing silver difluoride however, did not effect fluorination but destroyed part of the starting material. Fluorination did also not occur when II was heated with silver fluoride in an autoclave at 290° for twenty-four hours. In another attempt, compound I was treated directly with silver difluoride. Even under carefully controlled conditions approximately 70% of the pyrimidine compound decomposed. The product recovered consisted of II and a low-boiling compound, formed from II by addition of fluorine to one of its double bonds, to which we tentatively assign the structure of 5-chloro-2,4,4,5,6-pentafluoro-4,5-dihydropyrimidine (III).

The failure to replace the chlorine atom in the 5-position prompted us to approach our goal by a different route. Since compound I easily exchanged its chlorine atoms in the 2,4- and 6-position for fluorine, and since the same behavior could be anticipated for 2,4,6-trichloropyrimidine (IV), use of the latter compound would give rise to the possibility of replacing hydrogen rather than chlorine in the peculiar 5-position. As expected, IV and silver fluoride reacted in good yield to form 2,4,6-trifluoropyrimidine (V). The final fluorination, namely the conversion of V into tetrafluoropyrimidine (VI), required the direct substitution of a hydrogen atom by fluorine without addition of fluorine to the double bonds of the pyrimidine ring. Silver difluoride was selected to meet this objective, although it had been used hitherto only for the synthesis of saturated perfluorinated compounds,[8-10] usually by reaction in the gas phase. Upon heating a mixture of V and silver difluoride, an exothermic reaction started at 90° and was completed in a few minutes. The product obtained did not contain any fluorine-addition products but a minor amount of tetrafluoropyrimidine (VI) which could not be separated completely from unchanged starting material. Similar results were obtained when V was passed in a nitrogen stream over silver difluoride at 200° or when it was treated with silver difluoride in an autoclave at 280°. A considerable improvement of the yield of VI was finally achieved by carrying out the reaction in high-boiling inert diluents—*e.g.*, perfluorinated amines or perfluoro cyclic ethers.

Compound VI is very volatile and is a strong lachrymator. Its structure was confirmed by the reaction with di-*n*-butylamine in boiling toluene to give 2,4-bisdi-*n*-butylamino-5,6-difluoropyrimidine (VId) which was converted with di-*n*-butylamine at 220° into tetradi-*n*-butylaminopyrimidine (VII). By the same series of reactions VII was also obtained from I and di-*n*-butylamine *via* 2,4-bisdi-*n*-butylamino-5,6-dichloropyrimidine (Ic) as an intermediate.

The fluorine resonance spectrum of 2,4,6-trifluoropyrimidine (V) consisted of two lines in a ratio of 1:2. The chemical shifts relative to trifluoroacetic acid are −35.6 p.p.m. and −22.9 p.p.m. for the 2 fluorine and the 4,6 fluorines, respectively. The fluorine resonance of the tetrafluoropyrimidine (VI) exhibited three lines in an intensity of 1:2:1. The chemical shifts are −31.3 p.p.m. for the 2 fluorine, −6.3 p.p.m. for the 4,6 fluorines, and +95.2 p.p.m. for the 5 fluorine.

Some monosubstituted derivatives of VI—*e.g.*, 4-amino-2,5,6-trifluoropyrimidine (VIa) and 4-hydroxy-2,5,6-trifluoropyrimidine (VIb)—were prepared by its reaction with nucleophilic reagents at 10–20°. The fluorine NMR spectrum of the amino compound (VIa) exhibited three lines of equal intensity. The amino substituent therefore must be at C-4, since any other structure would not contain three nonequivalent fluorines. The chemical shifts for the 2,6 and 5 fluorines are −28.0 p.p.m., +10.7 p.p.m., and +103.0 p.p.m., respectively.

The reaction of VI with diethylaminoethanol resulted in the formation of 4-β-diethylaminoethoxy - 2,5,6 - trifluoropyrimidine (VIc). Surprisingly, VIc, a liquid easily soluble in common organic solvents, solidified within 24 hr. to give a sharp melting product which was found to be only soluble in water and slightly soluble in alcohols. As the analytical data were still in accordance with the formula of VIc, probably an internal quaternary ammonium salt (VIII) had been formed. β-Dimethylaminoethanol reacted with VI at 25° to give 2,4-bis-β-dimethylaminoethoxy-5,6-difluoropyrimidine (VIe).[11] Other disubstituted compounds were obtained with dimethylamine and sodium ethylate.

Trifluoropyrimidine (V) and 5-chloro-2,4,6-trifluoropyrimidine (II) showed a similar reactivity toward nucleophilic substitution, giving monosubstituted derivatives at a reaction temperature

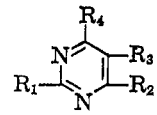
(8) F. B. Stilmar, W. S. Struve, and W. V. Wirth, *Ind. Eng. Chem.*, **39**, 348 (1947).

(9) E. T. McBee *et al.*, U. S. Patents 2,459,780, 2,459,781, 2,459,782, and 2,614,129; *Ind. Eng. Chem.*, **39**, 380 (1947).

(10) C. Slesser and S. R. Schram, "Preparation, Properties and Technology of Fluorine and Organic Fluoro Compounds," McGraw-Hill Book Company, Inc., New York (1951).

(11) It is deduced from analogous nucleophilic displacement reactions of trihalopyrimidines and tetrahalopyrimidines that the halogen atom in position 4 is replaced first followed by replacement of that in position 2. Unequivocal proof for the assigned structures was obtained only for those compounds examined by NMR spectrometry. The other assignments must be considered tentative but probable. The halogen at the 5-position is deemed the least reactive since unlike all the others it is attached to a carbon atom which is not influenced by an adjacent nitrogen atom [S. J. Childress and R. L. McKee, *J. Am. Chem. Soc.*, **72**, 4271 (1950)].

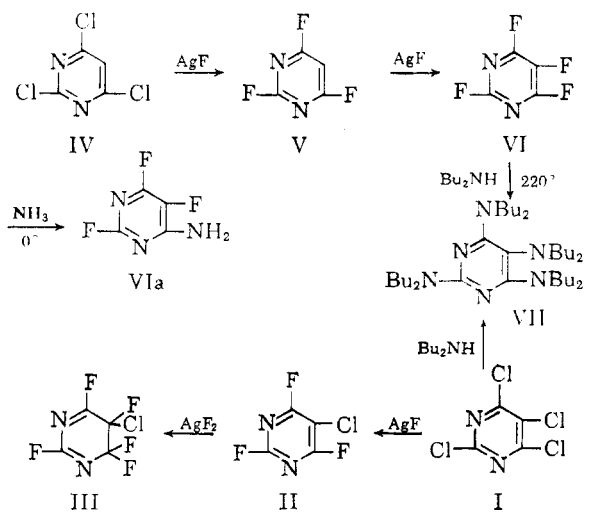
TABLE I
HALOPYRIMIDINES AND DERIVATIVES



	R_1	R_2	R_3	R_4	M.P.	B.P. (mm.)		$n^{25}D$	Yield, %
Ia	Cl	OC_2H_5	Cl	Cl	66				75.3
Ib	Cl	OC_4H_9	Cl	Cl		120	(3.5)	1.5325	39.6
Ic	$N(C_4H_9)_2$	$N(C_4H_9)_2$	Cl	Cl		180	(0.4)	1.5250	57
Id	$N(C_2H_5)_2$	$N(C_2H_5)_2$	Cl	Cl		160–162	(2.3)	1.5607	85
Ie	OC_5H_{11}	OC_5H_{11}	Cl	Cl		112–115	(3)	1.4781	5
II	F	F	Cl	F		114–115	(760)	1.4390	84
IIa	OC_2H_5	OC_2H_5	Cl	F	71–73				42
IIb	OC_4H_9	OC_4H_9	Cl	F		112–114	(0.5)	1.4815	23
IIc	OC_4H_9	F	Cl	OC_4H_9		68–70	(1)	1.4760	3.5
IId	$N(C_2H_5)_2$	$N(C_2H_5)_2$	Cl	F		117–119	(2)	1.5350	54.6
V	F	F	H	F		98	(760)	1.4047	82
Va	F	$N(CH_3)_2$	H	F	85–86				62
Vb	$N(C_2H_5)_2$	$N(C_2H_5)_2$	H	F	23	110	(0.65)	1.5410	85
Vc	$N(CH_2CH_2)$	$N(CH_2CH_2)$	H	F	61				91
Vd	$OCH_2CH_2N(CH_3)_2$	$OCH_2CH_2N(CH_3)_2$	H	F		127	(0.3)	1.4830	60.5
Ve	OC_2H_5	OC_2H_5	H	F		59	(0.25)	1.4709	58.8
VI	F	F	F	F		89	(760)	1.3875	30.4
VIa	F	NH_2	F	F	158				36
VIb	F	OH	F	F	121				31
VId	$N(C_4H_9)_2$	$N(C_4H_9)_2$	F	F		157	(0.3)	1.4962	55
VIe	$OCH_2CH_2N(CH_3)_2$	$OCH_2CH_2N(CH_3)_2$	F	F		129	(0.25)	1.4750	51.5
VIf	OC_2H_5	OC_2H_5	F	F	43	58	(0.3)		46
VIg	$N(CH_3)_2$	$N(CH_3)_2$	F	F	96–97				47
VII	$N(C_4H_9)_2$	$N(C_4H_9)_2$	$N(C_4H_9)_2$	$N(C_4H_9)_2$		196	(0.3)	1.5030	69

below 10° and disubstituted derivatives at approximately 25°. The fluorine NMR spectrum of one of these compounds, 2,4-diethoxy-6-fluoropyrimidine (Ve), was obtained and had one line as expected and a chemical shift of −811 cycles/sec. or −13.67 p.p.m. relative to trifluoroacetic acid.

Physical and analytical data for the halopyrimidines II, V, and VI and the products of performed reactions are compiled in Table I. Several new derivatives of tetrachloropyrimidine (I), which were prepared for comparative studies, are also included in this table.



It is interesting to note that only in one experiment, namely by treating I with two molar equivalents of sodium butylate, isomeric products were isolated. The structure of 5-chloro-6-fluoro-2,4-dibutoxypyrimidine (IIb) has been tentatively assigned to the main product; consequently the by-product (3% yield) should be 5-chloro-2-fluoro-4,6-dibutoxypyrimidine (IIc).

Compounds I, IV, and VI were treated with diazomethane under the same conditions as described for cyanuric chloride.[12] In each case, the starting material was recovered to a large extent and only minute amounts of reaction products, probably monodiazomethylsubstituted compounds, were obtained.

Experimental[13]

2,4,6-Trifluoropyrimidine (V).—A mixture of 2,4,6-trichloropyrimidine[14] (IV, 92 g., 0.5 mole) and silver fluoride (420 g., 3.3 moles) was warmed slowly in a flask equipped with an efficient condenser. At a bath temperature of approx. 90°, a vigorous exothermic reaction started which necessitated removal of the oil bath to prevent loss of product through the condenser. When the reaction moderated, the mixture was refluxed for 1 hr. and the liquid components were stripped off to give a mixture, 73 g., $n^{29}D$ 1.4465.

(12) C. Grundmann and E. Kober, *J. Am. Chem. Soc.*, **79**, 944 (1957).

(13) Melting points were determined with the Fisher-Johns apparatus. Microanalyses were by the Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(14) H. Langermann and K. C. Nanks, *J. Am. Chem. Soc.*, **73**, 3012 (1951).

TABLE I (*continued*)

Formula	Mol. Wt.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Fluorine Calcd.	Fluorine Found
$C_6H_5Cl_3N_2O$	227.5	31.67	31.56	2.22	2.22	12.32	12.84	46.76	46.96		
$C_8H_9Cl_3N_2O$	255.5	37.60	37.59	3.55	3.42	10.97	11.06	41.62	41.30		
$C_{20}H_{36}Cl_2N_4$	403.4							17.58	17.39		
$C_{12}H_{20}Cl_2N_4$	291.2	49.49	49.48	6.92	6.67	19.24	19.21	24.35	24.64		
$C_{14}H_{22}Cl_2N_2O_2$	321.2	52.34	53.76	6.90	7.28			22.07	21.93		
$C_4N_2ClF_3$	168.5	28.52	29.06			16.62	16.39	21.04	20.74	33.82	33.05
$C_8H_{10}ClFN_2O$	204.6	43.57	43.75	4.57	4.59	12.42	12.78	16.08	16.08	8.61	8.55
$C_{12}H_{18}ClFN_2O_2$	276.7	52.08	52.11	6.56	6.28	10.12	10.75	12.81	13.35		
$C_{12}H_{18}ClFN_2O_2$	276.7					10.12	10.77	12.81	13.34		
$C_{12}H_{20}ClFN_4$	274.8	52.45	52.24	7.33	7.10	20.40	20.51	12.91	13.13	6.91	6.71
$C_4HF_3N_2$	134.1	35.84	36.01	0.75	1.05	20.90	20.56				
$C_6H_7F_2N_3$	159.1	45.28	45.16	4.43	4.52	26.41	26.40			24.18	23.81
$C_8H_{13}FN_4$	184.2	52.16	52.15	7.11	7.38	30.42	30.26			10.31	10.16
$C_8H_9FN_4$	180.2	53.32	53.57	5.04	4.97	31.10	29.51			10.54	11.19
$C_{12}H_{21}FN_4O_2$	272.3	52.92	53.19	7.77	7.86	20.58	20.68			6.98	6.77
$C_8H_{11}FN_2O_2$	186.2	51.61	51.54	5.96	5.99	15.05	14.92			10.20	10.10
$C_4F_4N_2$	152.1	31.60	31.66			18.42	18.25			49.98	49.70
$C_4H_2F_3N_3$	149.1	32.22	32.23	1.35	1.73	28.20	28.63				
$C_4HF_3N_2O$	150.1	32.01	32.22	0.67	1.21	18.67	18.82			37.98	37.85
$C_{20}H_{36}F_2N_4$	370.5					15.12	15.69				
$C_{12}H_{20}F_2N_4O_2$	290.3	49.65	49.73	6.95	7.05	19.30	19.29			13.09	13.28
$C_8H_{10}F_2N_2O_2$	204.2	47.06	47.12	4.94	4.70	13.72	13.58				
$C_8H_{12}F_2N_4$	202.2	47.52	47.54	5.98	5.99	27.71	27.03				
$C_{36}H_{72}N_6$	589.0	73.40	72.74	12.32	12.37						

The distillate was refluxed with 180 g. of silver fluoride for 2 hr. and again distilled to give crude V, 64 g., $n^{29}D$ 1.4135.

The crude product was refluxed with 100 g. of silver fluoride for 1 hr. to give 61.5 g. of product, $n^{29}D$ 1.4100. Fractionated distillation yielded 55 g. of pure V, b.p. 64° (180 mm.).

5-Chloro-2,4,6-trifluoropyrimidine (II).—Similar to the above procedure, tetrachloropyrimidine[7] (I, 109 g., 0.5 mole) reacted with silver fluoride (560 g., 4.4 moles) to give 80 g. of a mixture, $n^{25}D$ 1.4453. The second treatment with 150 g. of silver fluoride gave 74 g. of crude II, $n^{25}D$ 1.4390, which was refluxed again with 100 g. of silver fluoride. Fractionation of the distillate gave 70.5 g. of pure II.

Preparation of II by Means of Silver Difluoride.—Silver difluoride (300 g.) was added in 50-g. portions to 95 g. of I. After each addition, the reaction mixture was heated to 100° and, after the reaction had ceased, cooled to add the next portion of silver difluoride. After the addition of silver difluoride was completed, the reaction mixture was kept at 150° for 1 hr. and then distilled at 200 mm. The distillate (37 g.) was refluxed with and distilled from two 50-g. portions of fresh silver difluoride. The final distillate (18.5 g.) was subjected to fractional distillation to yield a main fraction II (13.2 g., 20%), b.p. 114–115° (760 mm.), and a forerun consisting of 5-chloro-2,4,4,5,6-pentafluoro-4,5-dihydropyrimidine (III, 3.1 g.), $n^{25}D$ 1.3945; b.p. 78–82° (760 mm.).

Anal. Calcd. for $C_4ClF_5N_2$: C, 24.77; Cl, 17.84; F, 43.10; N, 13.85. Found: C, 24.26; Cl, 17.17; F, 46.00; N, 13.57.

Tetrafluoropyrimidine (VI).—A mixture of trifluoropyrimidine (V, 26.8 g., 0.2 mole), silver difluoride (44 g., 0.3 mole), and perfluorotributylamine (27 ml.) was heated with stirring. An exothermic reaction lasting 5 min. was noted at a bath temperature of approx. 90°. The mixture was then heated at a bath temperature of 130° for 15 min. The reaction mixture was carefully stripped at 200 mm. to give crude VI (20 g.) and high-boiling amine (5 g.). The latter was easily separated from VI, since both compounds are immiscible and the perfluorinated amine has a higher specific gravity. Distillation of the crude VI, first at reduced and then at normal pressure, gave 9.2 g. of pure VI, b.p. 65° (220 mm.) and 7 g. of a mixture of V and VI, b.p. 89° (760 mm.).

Monosubstitution Products of Tetrafluoropyrimidine. 4-Amino-2,5,6-trifluoropyrimidine (VIa).—An ice-cold solution of ammonia in ether (30 ml.) was added, with stirring, to tetrafluoropyrimidine (VI, 3.0 g.) in ether (10 ml.). After 30 min., the precipitated crude VIa was filtered and the filtrate was evaporated in vacuo to regain 1 g. of VI. Compound VIa was recrystallized from benzene and chloroform; m.p. 158°.

4-Hydroxy-2,5,6-trifluoropyrimidine (VIb).—A solution of 1.5 g. of water in 10 ml. of tetrahydrofuran was added at 20° to 3.0 g. of tetrafluoropyrimidine (VI) in 10 ml. of tetrahydrofuran. The mixture was allowed to stand for 2 hr., then the solvent was evaporated. The residual VIb, which solidified slowly and sublimed partially despite careful distillation, was recrystallized from ligroin; m.p. 121°.

Reaction of β-Diethylaminoethanol with VI.—A solution of diethylaminoethanol (6.5 g., 0.06 mole) in ligroin (20 ml.) was added, with stirring, at 10° to a solution of VI (4.6 g., 0.03 mole) in ligroin (20 ml.). After keeping the mixture at 15° for 2 hr., the ligroin was evaporated. The residue was distilled *in vacuo* to give 4-diethylaminoethoxy-2,5,6-trifluoropyrimidine (VIc), 5.3 g. (70.5%), b.p. 80° (0.2 mm), $n^{25}D$ 1.4551. Compound VIc solidified overnight to give VIII, which was purified by dissolving in methanol and subsequent precipitation with ether, m.p. 245°.

Anal. Calcd. for $C_{10}H_{14}F_3N_3O$: C, 48.14; H, 5.66; N, 16.86. Found: C, 47.44; H, 5.50; N, 16.06.

Alkoxylation of Halopyrimidines.—Two illustrative examples are given below, describing the employment of sodium bicarbonate or sodium as hydrogen halide acceptors.

4-Butoxy-2,5,6-trichloropyrimidine (Ib).—Tetrachloro-

pyrimidine (I, 21.8 g., 0.1 mole) was added at room temperature, with stirring, to a mixture of sodium bicarbonate (8.4 g., 0.1 mole), *n*-butyl alcohol (110 ml.), and water (20 ml.). Evolution of carbon dioxide was observed when the reaction mixture was heated, with stirring, at 90° for 6 hr. Then 100 ml. of ether was added and the mixture was extracted three times with water. After drying over sodium sulfate, the organic solvents were evaporated *in vacuo* and the residue was distilled *in vacuo* to give Ib (10.1 g., 39.6%).

2,4-Diamyloxy-5,6-dichloropyrimidine (Ie) contained traces of the monosubstituted compound and had to be subjected three times to fractional distillation for purification. **4-Ethoxy-2,5,6-trichloropyrimidine** (Ia) and **2,4-diethoxy-5-chloro-6-fluoropyrimidine** (IIa) separated as solids from the reaction mixture and were recrystallized from 80% ethanol and ligroin, respectively. The products of the reaction of 5-chloro-2,4,6-trifluoropyrimidine (II) with *n*-butyl alcohol in the presence of two molecular equivalents of sodium bicarbonate, namely **2,4-dibutoxy-5-chloro-6-fluoropyrimidine** (IIb, b.p. 112–114° (0.5 mm.) and **4,6-dibutoxy-5-chloro-2-fluoropyrimidine** (IIc, b.p. 68–70° (1 mm.), could be easily separated by fractional distillation.

2,4-Diethoxy-5,6-difluoropyrimidine (VIf).—A solution of sodium (1.84 g., 0.08 mole) in absolute ethanol (35 ml.) was added to a solution of tetrafluoropyrimidine (VI, 6.1 g., 0.4 mole) in ethanol (10 ml.) at 20°. The reaction mixture was neutral after 20 min. and was evaporated *in vacuo*. The residue was dissolved in petroleum ether, filtered, and, after evaporation of the petroleum ether, distilled *in vacuo*. The distillate (5.1 g.) solidified and was recrystallized from petroleum ether to give pure VIf (3.8 g., 46%), m.p. 43°.

The following two examples are representative for the preparation of **bisdialkylaminomono(or di-)halopyrimidines**:

5-Chloro-2,4-bis-diethylamino-6-fluoropyrimidine (IId).—5-Chloro-2,4,6-trifluoropyrimidine (II, 33.7 g., 0.2 mole) in 130 ml. of ether was added at 10°, with stirring, to the solution of diethylamine (44 g., 0.6 mole) in 270 ml. of ether. The reaction mixture was allowed to warm up and was kept, with stirring, at 30° for 12 hr. The diethylamine hydrofluoride formed during the reaction had separated as an oil from which the ether layer was decanted. After evaporation of the ether, the residue was subjected to fractionated distillation to give IId, b.p. 117–119° (2 mm).

2,4-Bisdimethylamino-5,6-difluoropyrimidine (VIg), prepared accordingly, was recrystallized from petroleum ether. In the preparation of **2,4-diaziridino-6-fluoropyrimidine** (Vc), triethylamine was used as a hydrogen fluoride acceptor instead of an excess of ethyleneimine; the reaction product was recrystallized from ligroin.

2,4-Bis-β-dimethylaminoethoxy-5,6-difluoropyrimidine (VIe).—A solution of β-dimethylaminoethanol (10.6 g., 0.12 mole) in petroleum ether (20 ml.) was added slowly, with stirring, to the solution of tetrafluoropyrimidine (VI, 4.6 g., 0.03 mole) in petroleum ether (15 ml.) maintaining a temperature of 25° by external cooling. After keeping the mixture at 35° for 20 min., the petroleum ether was decanted from dimethylaminoethanol hydrochloride which had separated as a liquid at the bottom of the flask. The petroleum ether was evaporated and the residue was distilled *in vacuo* to give 4.5 g. of VIe (51.5%), b.p. 129° (0.25 mm.).

The water-soluble **2,4-bis-β-dimethylaminoethoxy-6-fluoropyrimidine** (Vd) was prepared in the same manner as the previous compound by the reaction of trifluoropyrimidine with dimethylaminoethanol.

Monodialkylaminopolyhalopyrimidines were prepared by the following procedure:

4-Dimethylamino-2,6-difluoropyrimidine (Va).—A solution of dimethylamine (4.5 g., 0.1 mole) in 30 ml. of ether was added with ice-cooling to a solution of 2,4,6-trifluoropyrimidine (V, 4 g., 0.03 mole) in 10 ml. of ether. After keeping the mixture at 0–3° for 1 hr., it was filtered and evaporated *in vacuo*. The residue was recrystallized from petroleum ether to give 2.9 g. of Va (62%), m.p. 85–86°.

Tetradi-*n*-butylaminopyrimidine (VII).—A mixture of 2,4-bisdibutylamino-5,6-dichloropyrimidine (Ic, 10.1 g., 0.025 mole) and dibutylamine (19.4 g., 0.15 mole) was kept in a sealed tube at 220° for 4 hr. The product obtained was extracted with ligroin (50 ml.), filtered, evaporated, and distilled to give 10.1 g. of VII (69%). Compound VII was prepared in the same manner from 2,4-bisdibutylamino-5,6-difluoropyrimidine (VId).

F^{19} NMR Spectra.—A Varian high-resolution NMR spectrometer was used at 56.4 Mc. The spectra of the liquids were obtained neat with a sealed capillary containing trifluoroacetic acid as the external reference. The amino compound was run as a solution in acetone. The chemical shifts were measured using the side-band technique.

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