2-Amino-5-allyl-4-pyrimidone (IX) *by rearrangement.* A mixture of 5.0 g. of XIV and 15 ml. of *N,N*-diethylaniline was heated in an oil bath. When XIV had melted, the mixture was swirled to insure complete solution. The solution was refluxed for 4 hr. at a bath temperature of 240°. On cooling a black oil separated. Most of the solvent was removed by vacuum distillation, and the tarry residue rinsed with a little ether, then extracted with five 50-ml. portions of boiling water. The aqueous extracts were concentrated to about 50 ml. and refrigerated. The product crystallized in slender needles as a hydrate. Additional material was obtained by concentrating the filtrate. The weight of efflorescent hydrate obtained varied from 0.12 g. to 0.80 g. An additional crystallization from isopropyl alcohol gave anhydrous IX.

2-Methyl-5-allyl-4-pyrimidone (X) *and 2-trifluoromethyl-5-allyl-4-pyrimidone* (XI) *by rearrangement.* Because the corresponding 4-alloxypyrimidines XV and XVI had boiling points lower than the temperature at which rearrangement occurred, they were heated with diethylaniline in a sealed tube at 240° for 8 hr. Examination of the reaction mixtures did not indicate the presence of any more than a trace of product along with tars and oils.

BUFFALO, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF BUFFALO]

Phosphorylated Pyrimidines[1]

JAMES J. HODAN[2] AND HOWARD TIECKELMANN

Received May 8, 1961

Several phosphorylated pyrimidines have been prepared from 5-hydroxymethyl- (I), 5-bromomethyl- (II), and 5-formyl-4-amino-2-methylthiopyrimidine (III). 5-Phosphonylmethylpyrimidines have been synthesized from II and trialkyl phosphites; 5-phosphonylhydroxymethylpyrimidines have been synthesized from III. Phosphorus oxychloride and thiophosphoryl chloride with I gave phosphorodichloridates and phosphorodichlorothioates, respectively. These latter compounds were converted to diamidates. Dialkyl chlorophosphates and thionochlorophosphates and I gave the corresponding tertiary phosphate esters.

Interest in 2-methylthio-4-amino-5-hydroxymethylpyrimidine (I, methioprim) and related compounds has led to the synthesis of several related pyrimidines in this laboratory.[3] These compounds have been assayed in experimental rodent tumors and in microbiological systems. The results were encouraging to the extent that the synthesis of further related compounds seemed pertinent.

In clinical trial I was found to be inactive as a tumor inhibitor.[4] Experiments with rat liver homogenates have shown that in this system I was rapidly oxidized to the corresponding 5-formylpyrimidine and 5-hydroxymethylpyrimidine.[5] This suggested that those derivatives of I which are less susceptible to oxidation, might be better candidates for cancer chemotherapy. In a previous paper esters of I were reported.[3] The present paper deals with phosphonates, phosphates and phosphorodiamidates of I and related pyrimidines. As compounds of phosphorus that contain the ethyleneimine group such as triethylene phosphoramide and triethylene thiophosphoramide are of chemotherapeutic interest, it also seemed pertinent to incorporate this type of structure into methioprim.

The pyrimidine phosphonates were synthesized from 4-amino-5-formyl-2-methylthiopyrimidine (III)[6] and 4-amino-5-bromomethyl-2-methylthiopyrimidine hydrobromide (II).[6,7] Dialkyl and diaryl phosphites and III gave 5-(4-amino-2-methylthiopyrimidyl)hydroxymethylphosphonates (IV-VII). The ethyl ester (V) was formed in good yield and was used in further syntheses. Treatment of V with hydrochloric acid in ethanol gave diethyl 5-(4 - amino - 2 - hydroxypyrimidyl)hydroxymethylphosphonate hydrochloride (VIII). V and concentrated hydrochloric acid resulted in hydrolysis of the ester and the methylthio group to give 5-(4-amino - 2 - hydroxypyrimidyl)hydroxymethylphosphonic acid (IX).

When V was heated with alcoholic ammonia in a sealed tube, no reaction occurred. Oxidation of V in absolute ethanol by chlorine gave diethyl 5-(4 - amino - 2 - methylsulfonylpyrimidyl)hydroxymethylphosphonate (X). Treatment of X with alcoholic ammonia in a sealed tube gave diethyl 5 - (2,4 - diaminopyrimidyl)hydroxymethylphosphonate (XI).

5 - (4 - Amino - 2 - methylthiopyrimidyl)methylphosphonates (XII–XVI) were prepared from II and trialkyl phosphites by the Michaelis-Arbuzov reaction.

The reaction of phosphorus oxychloride with I gave 5 - (4 - amino - 2 - methylthiopyrimidyl)-methyl phosphorodichloridate (XVII). This served

(1) Supported by a Grant CY-2857, from the National Cancer Institute of the National Institutes of Health U. S Public Health Service.

(2) Present address: Hooker Chemical Corp., Niagara Falls, N. Y.

(3) For leading references, see J. G. Nairn and H. Tieckelmann, *J. Org. Chem.*, **25**, 1127 (1960).

(4) James F. Holland, Roswell Park Memorial Institute, unpublished results.

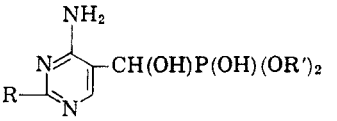
(5) I. J. Slotnick, A. W. Spears, and H. Tieckelmann, *Proc. Soc., Exptl. Biol. Med.*, 102, 239 (1959).

(6) T. Okuda and C. C. Price, *J. Org. Chem.*, **23**, 1738 (1958).

(7) B. Blank and W. T. Caldwell, *J. Org. Chem.*, **24**, 1137 (1959).

TABLE I

SUBSTITUTED PYRIMIDYLHYDROXYMETHYLPHOSPHONATE DERIVATIVES

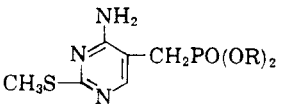


No.	R	R′	Yield, %	M.P.	Ultraviolet Spectra, 95% Ethanol λ_{max} (mμ)	Log ε	Formula		Calcd., %	Found, %
IV	CH_3S	CH_3	34	109–112	248	4.26	$C_8H_{14}N_3O_4PS$	C	34.40	34.29
								H	5.06	5.19
								P	11.09	11.18
V	CH_3S	C_2H_5	62	120–122	254	4.09	$C_{10}H_{18}N_3O_4PS$	C	39.08	39.17
								H	5.91	5.42
								N	13.67	13.88
								P	10.08	9.80
VI	CH_3S	C_4H_9	36	171–173 dec.	254	4.18	$C_{14}H_{26}N_3O_4PS$	C	46.29	46.45
								H	7.22	6.96
								P	8.52	8.49
VII	CH_3S	C_6H_5	10	134–136	292	3.97	$C_{18}H_{18}N_3O_4PS$	P	7.68	7.84
					254	4.17		S	7.95	8.02
					228	4.34				
VIII[a]	OH	C_2H_5	95	88–91	246	4.12	$C_9H_{17}ClN_3O_5P$	C	34.46	33.91
								H	5.46	5.79
								P	9.87	9.78
IX	OH	OH	77	300–303 dec.	285	3.81	$C_5H_8N_3O_5P$	C	27.15	27.40
								H	3.66	4.16
								N	19.01	19.18
								P	14.01	14.05
X	CH_3SO_2	C_2H_5	50	181–183	290	3.62	$C_{10}H_{18}N_3O_6PS$	C	35.39	35.92
					248	3.96		H	5.35	5.53
								P	9.14	9.36
XI[b]	NH_2	C_2H_5	45	>220 dec.	284	3.79	$C_9H_{17}N_4O_4P$	C	39.12	39.56
								H	6.21	5.90
								N	20.28	20.03
								P	11.21	10.87

[a] This compound was isolated as a hydrochloride. [b] Decomposed slowly above 220°.

TABLE II

5-(4-AMINO-2-METHYLTHIOPYRIMIDYL)METHYLPHOSPHONATES

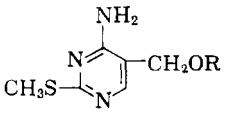


No.	R	Yield, %	M.P.	Ultraviolet Spectra, 95% Ethanol λ_{max} (mμ)	Log ε	Formula		Calcd., %	Found, %
XII[a,f]	CH_3	52	281–284 dec.	247	4.06	$C_8H_{14}N_3O_3PS$	C	36.49	36.83
							H	5.37	5.64
							N	15.96	15.84
							P	11.77	11.63
XIII[b,g]	C_2H_5	52	268–270 dec.	252	4.15	$C_{10}H_{18}N_3O_3PS$	N	14.42	14.19
							P	10.63	10.71
XIV[c,h]	i-C_3H_7	47	286–289 dec.	254	4.06	$C_{12}H_{22}N_3O_3PS$	P	9.70	9.80
							S	10.04	10.13
XV[d,i]	C_6H_{13}	47	121–123	251	4.15	$C_{18}H_{34}N_3O_3PS$	P	7.68	7.65
							S	7.94	8.05
XVI[e,j]	C_6H_5	43	197–200 dec.	281	4.00	$C_{18}H_{18}N_3O_3PS$	N	10.85	11.00
							P	8.00	7.90
							S	8.27	8.15

[a] Heated on a steam bath for 6 hr. [b] Heated at 120° for 4 hr. [c] Heated at 120° for 6 hr. [d] Heated at 130° for 6 hr. [e] Heated at 180° for 6 hr. [f] Recrystallization solvents: Methanol-acetone. [g] Ethanol-ether. [h] Ethanol-acetone. [i] Benzene–petroleum ether (b.p. 30–60°). [j] Ethanol-water.

TABLE III

PHOSPHORIC ACID DERIVATIVES OF METHIOPRIM



No.	R	Yield, %	M.P.	Ultraviolet Spectra, 95% Ethanol λ_{max} (mμ)	Log ε	Formula		Calcd., %	Found, %
XVII[a]	$POCl_2$	71	260 dec.	—	—	$C_6H_8Cl_2N_3O_2PS$	C	24.99	24.50
							H	2.80	3.29
							N	14.59	14.39
							P	10.75	10.67
XVIII	$PO(NHCH_3)_2$	42	198–200 dec.	292	3.31	$C_8H_{16}N_5O_2PS$	C	34.64	34.61
				248	3.60		H	5.83	6.20
							P	11.17	10.90
XIX	$PO(NCH_2CH_2)_2$	61	176–179 dec.	288	3.30	$C_{10}H_{16}N_5O_2PS$	C	39.85	40.01
				229	3.66		H	5.36	5.72
							P	10.28	10.42
							S	10.64	10.99
XX	$PO(NH_2)_2$	43	254–256 dec.	255	3.59	$C_6H_{12}N_5O_2PS$	N	28.10	27.61
				230	3.49		P	12.43	12.61
XXI[b]	$PO(OC_2H_5)_2$	37	>200 dec.	253	4.31	$C_{10}H_{18}N_3O_4PS$	C	39.08	39.58
							H	5.92	5.72
							P	10.08	10.35
XXII	$PO(OC_4H_9)_2$	33	87–90	253	4.35	$C_{14}H_{26}N_3O_4PS$	C	46.26	46.68
				229	4.31		H	7.22	7.29
							P	8.52	8.12
							S	8.82	8.71
XXIII[c]	$PSCl_2$	55	231–234 dec.	—	—	$C_6H_8Cl_2N_3OPS_2$	N	13.82	13.32
							P	10.18	10.53
XXIV[c]	$PS(NCH_2CH_2)_2$	52	193–196	—	—	$C_{10}H_{16}N_5OPS_2$	C	37.84	37.28
							H	5.09	5.50
							P	9.76	9.65
XXV[d]	$PS(OC_2H_5)_2$	43	157–159 dec.	249	4.22	$C_{10}H_{19}ClN_3O_3PS_2$	C	33.37	33 75
							H	5.32	4.67
							P	8.61	8.99
XXVI[d]	$PS(OCH_3)_2$	26	149–152	252	4.26	$C_8H_{15}ClN_3O_3PS_2$	N	12.67	12.45
							P	9.34	9.67

[a] Insoluble in 95% ethanol, decomposed slowly above 260°. [b] Decomposed slowly above 200°. [c] Insoluble in 95% ethanol. [d] This compound was isolated as a hydrochloride.

as an intermediate for reaction with amines and ammonia to give the corresponding phosphorodiamidates (XVIII and XX). XVII and ethyleneimine gave 5-(4-amino-2-methylthiopyrimidyl)-methyl *N,N'* - diethylenephosphorodiamidate (XIX). Thiophosphoryl chloride and I gave 5-(4 - amino - 2 - methylthiopyrimidyl)methyl phosphorodichlorothioate (XXIII). This was used as an intermediate to form 5-(4-amino-2-methylthiopyrimidyl)methyl *N,N'*-diethylenephosphorodiamidothioate (XXIV).

Dialkyl chlorophosphates were treated with I in the presence of triethylamine to give tertiary phosphate esters (XXI and XXII). Dialkyl chlorothiophosphates and methioprim in the presence of triethylamine gave tertiary thiophosphate esters (XXV and XXVI). These compounds were isolated as hydrochloride salts; the bases were oils or solids which crystallized with difficulty.

Screening data for these compounds in experimental rodent tumors will be reported elsewhere.[8]

EXPERIMENTAL[9]

Dimethyl 5-(4-amino-2-methylthiopyrimidyl)hydroxymethylphosphonate (IV). A solution of 2.0 g. (0.012 mole) of 4-amino-5-formyl-2-methylthiopyrimidine (III), 0.20 g. (0.020 mole) of triethylamine and 2.6 g. (0.024 mole) of dimethyl hydrogen phosphite in 40 ml. of dry methanol was refluxed with stirring for 10 hr. After removing the solvent under reduced pressure an oil formed. Fifteen milliliters of water was added to the oil. Unchanged III (0.5 g.) precipitated. The filtrate was evaporated under reduced pressure. The resulting oil solidified in a vacuum desiccator with phosphorus pentoxide after 24 hr. Recrystallization from an ethanol-ether mixture gave 1.12 g. of yellow solid.

Diethyl 5-(4-amino-2-methylthiopyrimidyl)hydroxymethyl phosphonate (V). A solution of 10 g. (0.059 mole) of III, 1.00 g. (0.099 mole) of triethylamine and 16 g. (0.0116 mole) of diethyl hydrogen phosphite in 125 ml. of absolute ethanol was refluxed, with stirring, for 18 hr. Unchanged III which

(8) E. Mihich, Roswell Park Memorial Institute, unpublished results.

(9) Melting points are uncorrected. Analyses were by Galbraith Laboratories, Knoxville, Tenn.; Geller Microanalytical Laboratories, Bardonia, N. Y.; and Donald A. Levine, University of Buffalo.

precipitated on cooling (2.60 g.) was separated. The solvent was evaporated under reduced pressure. The remaining oil solidified upon the addition of 25 ml. of cold water. Recrystallization from an ethanol-water mixture gave 11.3 g.

Di-n-butyl 5-(4-amino-2-methylthiopyrimidyl)hydroxymethylphosphonate (VI). Dibutyl hydrogen phosphite (2.0 g., 0.010 mole) triethylamine (0.20 g., 0.20 mole) and III (2.3 g., 0.014 mole) were heated in a 125° oil bath for 8 hr. Upon cooling, an amber solid remained. Recrystallization from an ethanol–water mixture gave 1.53 g. of tan solid.

Diphenyl 5-(4-amino-2-methylthiopyrimidyl)hydroxymethylphosphonate (VII). A solution of 3.0 g. (0.018 mole) of III, 0.30 g. (0.0030 mole) of triethylamine and 4.7 g. (0.020 mole) of diphenyl hydrogen phosphite in 125 ml. of absolute ethanol was refluxed with stirring for 9 hr. Unchanged III which precipitated on cooling (2.0 g.) was separated and the filtrate evaporated under reduced pressure. The oil solidified upon the addition of 25 ml. of dry ether. Recrystallization from an ethanol-water mixture gave 0.69 g.

Diethyl 5-(4-amino-2-hydroxypyrimidyl)hydroxymethylphosphonate hydrochloride (VIII). A solution of 1.5 g. (0.005 mole) of V and 1.18 g. (0.012 mole) of concd. hydrochloric acid in 20 ml. of absolute ethanol was refluxed with stirring, for 17 hr. Upon removal of the solvent under reduced pressure, a white solid remained. Recrystallization from an absolute ethanol-ether mixture gave 1.45 g. of white hygroscopic solid.

5-(4-Amino-2-hydroxypyrimidyl)hydroxymethylphosphonic acid. (IX). A solution of 2.0 g. (0.006 mole) of V in 20 ml. of concd. hydrochloric acid was refluxed, with stirring, for 5 hr. Upon removal of the solvent under reduced pressure, an oil remained which solidified slowly after addition of 10 ml. of water. Recrystallization from water gave 1.10 g.

Diethyl 5-(4-amino-5-methylsulfonylpyrimidyl)hydroxymethylphosphonate (X). Chlorine gas was bubbled slowly through a stirred solution of 4.0 g. (0.013 mole) of V in 30 ml. of 1% hydrochloric acid for 15 min. The temperature was kept below 5°. Sodium bisulfite (0.35 g., 0.003 mole was then added slowly so as not to exceed this temperature. The precipitate was washed with 50 ml. of cold water and recrystallized from absolute ethanol to give 2.22 g.

Diethyl 5-(2,4-diaminopyrimidyl)hydroxymethylphosphonate (XI). A solution of 0.88 g. (0.003 mole) of X in 20 ml. of absolute ethanol was saturated with ammonia. The mixture was heated in a sealed tube at 110° for 6 hr. Solvent was removed under reduced pressure. Recrystallization of the residue from a 1-propanol-ethyl acetate mixture gave 0.32 g. of tan solid.

5-(4-Amino-2-methylthiopyrimidyl)methylphosphonates (XII–XVI). The trialkyl phosphite (0.012 mole) and II were heated at 100–180° for 4–6 hr. The amber solid, which formed on cooling, was purified by recrystallization.

5-(4-Amino-2-methylthiopyrimidyl)methyl phosphorodichloridate, (XVII). Solid 4-amino-5-hydroxymethyl-2-methylthiopyrimidine (I) (10.0 g., 0.058 mole) was added slowly to 25.00 g. (0.163 mole) of stirred phosphorus oxychloride. An exothermic reaction resulted with the formation of an insoluble oil. After cooling, the mixture was poured into 150 ml. of dry ether. The oil solidified and was separated by filtration. The hygroscopic solid, insoluble in organic solvents and hydrolyzed by water was purified by washing with hot toluene and absolute ethanol to give 11.9 g.

5-(4-Amino-2-methylthiopyrimidyl)methyl N,N'-dimethylphosphorodiamidate, (XVIII). Methylamine was slowly passed into a stirred slurry of 1.7 g. (0.006 mole) of XVII in 75 ml. of dry methanol for 15 min. The reaction was slightly exothermic and the pyrimidine went into solution. The solvent was removed under reduced pressure. The remaining oil solidified upon the addition of 25 ml. of acetone and was extracted with dry 1-propanol. After removal of the solvent under reduced pressure the residue was recrystallized from an ethanol-ethyl acetate mixture to give 0.67 g.

5-(4-Amino-2-methylthiopyrimidyl)methyl N,N'-diethyl enephosphorodiamidate (XIX). Dry XVII (3.0 g., 0.010 mole) was added slowly to a stirred solution of 4.0 g. (0.093 mole) of ethyleneimine in 20 ml. of dry ether. The resulting oil solidified when added to 50 ml. of dry ether. The solid was extracted with dry 1-propanol. Removal of the solvent under reduced pressure left a tan solid, which gave 1.93 g. of light tan hygroscopic solid, after recrystallization from ethanol-ethyl acetate.

5-(4-Amino-2-methylthiopyrimidyl)methyl phosphorodiamidate (XX). Ammonia was bubbled slowly through a stirred slurry of 2.0 g. (0.007 mole) of XVII in 50 ml. of dry methanol. The pyrimidine dissolved and after a few minutes a deep yellow solid formed. After dilution with water, the solid was separated and washed with 50 ml. of water. Recrystallization from a methanol-water mixture gave 0.65 g.

Diethyl 5-(4-amino-2-methylthiopyrimidyl)methyl phosphate (XXI). Diethyl chlorophosphate (3.0 g., 0.018 mole) in 20 ml. of 1,4-dioxane was added dropwise to a stirred solution of I (3.0 g., 0.018 mole) and triethylamine (3.5 g., 0.034 mole) in 30 ml. of 1,4-dioxane and refluxed for 2 hr. After cooling, the triethylamine hydrochloride was separated by filtration. Solvent was removed from the filtrate under reduced pressure. The remaining oil was added to 25 ml. of water and a solid formed which was separated by filtration and recrystallized from an ethanol–acetone mixture to give 1.98 g. of light yellow solid.

Di-n-butyl 5-(4-amino-2-methylthiopyrimidyl)methyl phosphate (XXII). Dibutyl chlorophosphate (4.0 g., 0.018 mole) in 20 ml. of 1,4-dioxane was added dropwise to a stirred solution of I (3.0 g., 0.018 mole) and triethylamine (3.5 g., 0.034 mole) in 30 ml. of 1,4-dioxane. The mixture was refluxed for 2 hr. After cooling, the triethylamine hydrochloride was separated by filtration and the solvent was removed under reduced pressure. The remaining oil solidified after remaining for 24 hr. in a vacuum desiccator containing phosphorus pentoxide. Recrystallization from an ethanol-acetone mixture gave 2.12 g. of tan solid.

5-(4-Amino-2-methylthiopyrimidyl)methyl phosphorodichlorothioate (XXIII). A solution of I (2.0 g., 0.012 mole) and triethylamine (2.0 g., 0.020 mole) in 25 ml. of 1,4-dioxane was added dropwise to 10.0 g., (0.059 mole) of stirred thiophosphoryl chloride. The resulting tan solid was filtered and the residue washed with 75 ml. of cold water. Purification was accomplished by washing with hot acetone and methanol to give 1.96 g.

Tris[5-(4-amino-2-methylthiopyrimidyl)methyl]phosphorothioate. When thiophosphoryl chloride (1.0 g., 0.006 mole) in 5 ml. of pyridine was added dropwise to a solution of I (1.0 g., 0.006 mole) in 5 ml. of pyridine and the resulting mixture added to 100 ml. of dry ether, a solid was formed which corresponded closely to tris[5-(4-amino-2-methylthiopyrimidyl)methyl]phosphorothioate. It was insoluble in organic solvents but was partially purified by washing with hot chloroform, acetone and ethyl alcohol. Compared to other compounds reported in this paper this material was remarkable because of its acute toxicity. Mice and rats die within 3–10 min. after interperitoneal injection of toxic doses (60–80 mg./kg.) by respiratory block.[8]

Anal. Calcd. for $C_{18}H_{24}N_9O_3PS_4$: C, 37.68; H, 4.22; P, 5.40. Found: C, 38.54; H, 4.45; P, 5.32.

5-(4-Amino-2-methylthiopyrimidyl)methyl N,N'-diethylenephosphorodiamidothioate (XXIV). Dry XXIII (1.0 g., 0.003 mole) was added slowly to 4.0 g. (0.093 mole) of stirred ethyleneimine. An oil formed which solidified when added to 15 ml. of methanol. The precipitate was washed with 75 ml. of water, hot methanol, acetone and chloroform to give 0.54 g.

Diethyl 5-(4-amino-2-methylthiopyrimidyl)methyl phosphorothioate hydrochloride (XXV). Diethyl thionochlorophosphate (3.3 g., 0.018 mole) in 20 ml. of 1,4-dioxane was added dropwise to a stirred solution of I (3.0 g., 0.018 mole) and triethylamine (3.5 g., 0.034 mole) in 30 ml. of 1,4-dioxane and refluxed for 1 hr. After cooling, the triethylamine hydro-

chloride was separated by filtration. The solvent was removed from the filtrate under reduced pressure. Five milliliters of 10% hydrochloric acid was added to the remaining oil. Solvent was removed under reduced pressure. The residue was recrystallized from chloroform to give 2.70 g. of yellow solid.

Dimethyl 5-(4-amino-2-methylthiopyrimidyl)methyl phosphorothioate hydrochloride (XXVI). Dimethyl thionochlorophosphate (2.8 g., 0.018 mole) in 20 ml. of 1,4-dioxane was added dropwise to a stirred solution of I (3.0 g., 0.018 mole) and triethylamine (3.4 g., 0.034 mole) in 30 ml. of 1,4-dioxane. The mixture was refluxed for 2 hr. After cooling, solvent was removed under reduced pressure. The semisolid was treated with isopropyl alcohol. The residual triethylamine hydrochloride was separated by filtration. The solid formed on adding 5 ml. of 10% hydrochloric acid was separated by filtration and recrystallized from a methanol-ether mixture to give 1.52 g. of tan hygroscopic solid.

BUFFALO 14, N. Y.

[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY, SOUTHERN RESEARCH INSTITUTE]

v-Triazolo[4,5-d]pyrimidines. I. Synthesis and Nucleophilic Substitution of 7-Chloro Derivatives of 3-Substituted v-Triazolo[4,5-d]pyrimidines[1]

Y. FULMER SHEALY, ROBERT F. STRUCK, JOE D. CLAYTON, AND JOHN A. MONTGOMERY

Received May 17, 1961

3-Substituted 5-amino-7-chloro-v-triazolo[4,5-d]pyrimidines have been synthesized from the appropriate 2,5-diamino-4-chloro-6-alkyl(or aryl)aminopyrimidines. Retention of the chloro group until the v-triazolo[4,5-d]pyrimidine ring has been formed permits the introduction, by nucleophilic displacement, of a wide variety of substituents at position 7.

The synthesis of the v-triazolo[4,5-d]pyrimidine (8-azapurine) analogs of the principal purines of nucleic acids was reported[2] in 1945. Prior to that publication, only two derivatives of this ring system were known, but many have since been synthesized, chiefly as potential purine antagonists. The usual method of synthesis[3] depends on the preparation of a 4,5-diaminopyrimidine bearing the substituents at positions 2 and 6 desired in the v-triazolo[4,5-d]pyrimidine at positions 5 and 7, respectively; treatment of the pyrimidine with nitrite in acidic solution forms the triazole ring. v-Triazolo[4,5-d]pyrimidines have also been synthesized by cyclizing appropriately substituted v-triazoles[4,5c] and—for 2-substituted derivatives—by oxidizing 4-amino-5-arylazopyrimidines.[5,3q] The synthetic sequence described in this report was designed to produce the v-triazolo[4,5-d]pyrimidine ring with a replaceable chlorine atom at position 7 in order that a variety of derivatives might be synthesized by nucleophilic substitution.[6] The method, applied to the preparation of 3-substituted 3*H* - *v* - triazolo[4,5 - *d*]pyrimidines, is depicted in Chart I.

2-Amino-4-chloro-6-ethylaminopyrimidine (IIa) and the corresponding butylamino derivative (IIb) were obtained from 2-amino-4,6-dichloropyrimidine and an excess of the appropriate amine. The *p*-anisidino derivative (IIc) was prepared by the fusion method of Basford, Curd, Hoggarth, and Rose.[7] Disubstitution products (III) were ob-

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(6) Amino derivatives have been converted to oxo derivatives with nitrous acid and oxo derivatives to thiones with phosphorus pentasulfide (ref. 3). Recently, Weiss, Robins, and Noell have prepared amino derivatives from 7-alkylthio-v-triazolo[4,5-d]pyrimidines (ref. 3j).

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