[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Studies on Condensed Pyrimidine Systems. XIV. Some Pyrido[3,2-d]pyrimidines

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The fusion of urea with 3-aminopicolinic acid yields 2,4-dihydroxypyrido[3,2-d]pyrimidine (V). This substance has served as a starting material from which there has been prepared a variety of pyrido[3,2-d]pyrimidines with one or two functional groups in the pyrimidine moiety. Some comparative studies of these with the corresponding pyrido[2,3-d]-pyrimidines are reported.

Studies in this Laboratory of condensed pyrimidine systems as antagonists of purines, pyrimidines and pteridines recently led to an investigation of the pyrido[2,3-d] ring system.[2] The isomeric pyrido-[3,2-d]pyrimidines are of equivalent interest, and the preparation of functionally-substituted derivatives of this system is the subject of the present communication.

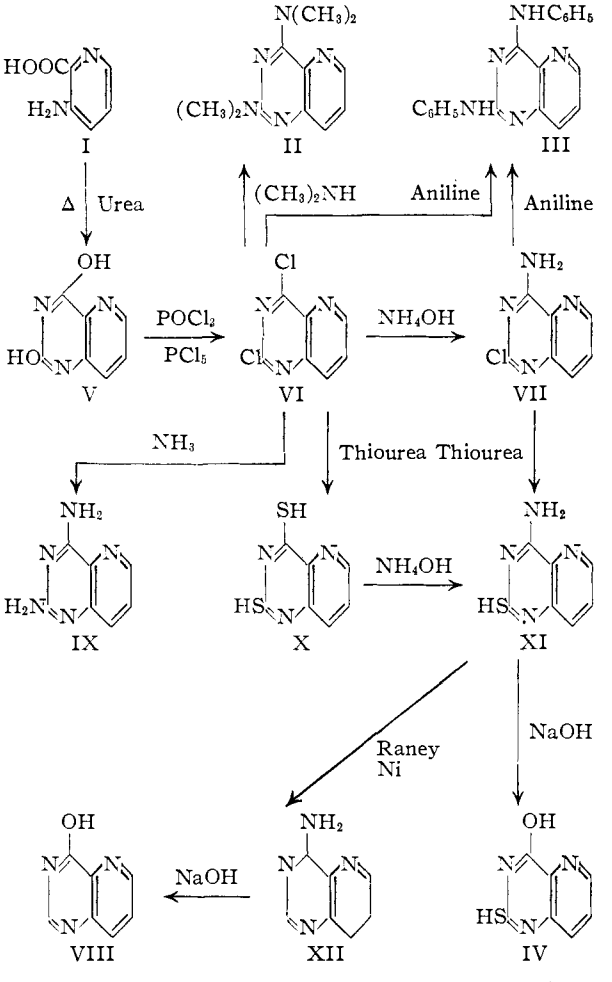
When the present investigation was initiated, the only known derivative of the pyrido(3,2-d) series was the 4-hydroxy compound, prepared by Price and Curtin[3] by the reaction of 3-aminopicolinic acid with formamide. During the course of the present work, Korte[4] added the 2,4-dihydroxy and 2-mercapto-4-hydroxy derivatives, prepared by cyclization of the 3-ureidopyridine-2-carboxylic acid.

In the present studies, 2,4-dihydroxypyrido(3,2-d)pyrimidine (V) served as the starting material from which various derivatives were prepared. The method employed for its preparation, fusion of 3-aminopicolinic acid with urea, produced 3-aminopicolinamide as a by-product; however, the latter was also convertible to 2,4-dihydroxypyrido(3,2-d)-pyrimidine by fusion with urea and the over-all yield was excellent.

The ultimate precursor of many of the derivatives is the 2,4-dichloropyrido(3,2-d)pyrimidine (VI), as shown in the reaction scheme. It is noteworthy that the transformation of the dihydroxy V to the dichloro derivative does not occur with phosphoryl chloride alone, as in the 2,3-d series, but only after the addition of phosphorus pentachloride. The 4-hydroxy derivative VIII is even more refractory; the present authors were just as unsuccessful as Price and Curtin[3] in the chlorination of this compound. Similarly, neither the mono- nor the dimercapto derivative was readily prepared by reaction of the hydroxyl derivatives with phosphorus pentasulfide, although some evidence of reaction was observed. All the above reactions take place without difficulty with the corresponding pyrido(2,3-d)pyrimidines.[2]

The 2,4-dimercapto derivative X was obtained from the dichloro compound through reaction of the latter with thiourea. In both the dimercapto and dichloro derivatives the group at the 4-position is more reactive than that at the 2-position (as with quinazolines[5,6] and pyrido(2,3-d)pyrimidines[2]) yielding the 4-amino-2-chloro (VII) and 4-amino-2-mercapto (XI) derivatives, respectively. The latter was prepared from the former with thiourea, and its structure was established in two ways; by conversion to the known 4-hydroxy-2-mercaptopyrido-(3,2-d)pyrimidine[4] (IV) and 4-hydroxypyrido-(3,2-d)pyrimidine (VIII).[3]

REACTION SCHEME



Despite the selectivity shown in the reactions with ammonia, only 2,4-bis-dimethylaminpyrido-(3,2-d)pyrimidine (II) could be obtained through the reaction of the dichloro compound with dimethylamine under a variety of conditions.

When 4-amino-2-chloropyrido(3,2-d)pyrimidine (VII) was heated with aniline in an attempt to prepare the 4-amino-2-anilino derivative, the product was found by analysis to contain two phenyl moieties. Since the same product was formed by the reaction of 2,4-dichloropyrido(3,2-d)pyrimidine

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(2) R. K. Robins and G. H. Hitchings, THIS JOURNAL, **77**, 2256 (1955).

(3) C. C. Price and D. Y. Curtin, *ibid.*, **68**, 914 (1946).

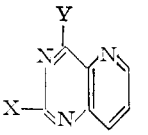
(4) F. Korte, *Ber.*, **85**, 1012 (1952).

(5) F. J. Wolf, R. H. Beutel and J. R. Stevens, THIS JOURNAL, **70**, 4264 (1948).

(6) N. J. Leonard and D. Y. Curtin, *J. Org. Chem.*, **11**, 349 (1946).

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF PYRIDO[3,2-d]PYRIMIDINES



X	Y	pH 1.0 Max., mμ	pH 1.0 E_m × 10³	pH 1.0 Min., mμ	pH 1.0 E_m × 10³	pH 11.0 Max. mμ	pH 11.0 E_m × 10³	pH 11.0 Min., mμ	pH 11.0 E_m × 10³
H	OH	265	4.93	250	4.5	282	5.34	253	2.9
		300	4.85	285	4.3	310	5.90	292	4.7
OH	OH	315	6.37	270	1.4	265	7.50	250	5.71
						315	6.37	285	1.7
H	NH_2	305	14.3	250	3.4	235	21.9	260	4.1
						280	6.4	290	5.8
						310	8.76		
NH_2	NH_2	250–270	6.4–5.2	288	4.6	235	20.9	293	1.2
		316	7.25			260–270[a]	7.2		
						340	5.18		
SH	NH_2	287	26.4	245	4.4	295	21.4	255	5.7
						330–350	3.5		
Cl	SH	255	9.68	290	1.7	245	9.08	295	1.5
		372	6.75			370	9.7		
SH	OH	290	28.7	245	5.5	295	23.3	250	6.4
SH	SH	252	8.97	267	7.1	253	10.04	278	4.5
		295	10.02	326	4.6	305	9.67	360	3.2
		350	5.32			390	3.95		
Cl	NH_2	275	5.32	250	3.7	237	9.04	260	3.17
		310	4.34	298	3.4	275	4.34	300	2.9
						310	3.7		
$N(CH_3)_2$	$N(CH_3)_2$	305	11.4	270	3.95	276	19.8	255	9.78
						360	6.05	330	3.9
C_6H_5NH	C_6H_5NH	333	13.92	290	7.04	248	23.78	270	12.5
						296	29.42	340	9.1
						368	11.11		
NHC_6H_4-Cl-2	NHC_6H_4-Cl-2	330	13.5	285	9.2	240	25.6	265	14.3
						288	22.9	325	7.8
						360	11.3		
2,5-$(CH_3)_2C_6H_3NH$	2,5-$(CH_3)_2C_6H_3NH$	327	14.12	285	1.08	240	36.7	270	21.5
						282	27.8	328	10.3
						368	15.04	237	34.4

[a] Shelf.

with aniline, it is highly probable that this substance is the 2,4-dianilino derivative (III).

The amino, mercapto and hydroxypyrido(3,2-d)-pyrimidines have the low solubilities and high melting (or decomposition) points characteristic of related compounds. They exhibit equally strikingly the effect of replacement of the hydrogen atoms of such functional groups by alkyl radicals. Thus the melting points of 2,4-diaminopyrido(3,2-d)pyrimidine and the corresponding 2,4-bis-dimethylamino derivative differ by about 250° as in the pyrido(2,3-d)pyrimidine series.[2] Such data provide additional exemplification of the probable role[7] of hydrogen bonding in these physical properties.

The ultraviolet absorption spectra (Table I) of the pyrido(3,2-d)pyrimidines resemble those of the 2,3-d series rather closely.

Acknowledgment.—The authors wish to thank S. W. Blackman, N. Martinez, Jr., and Pauline Kulka for the microanalyses reported here. This work was supported by a grant from the Charles F. Kettering Foundation.

(7) A. Albert, D. J. Brown and G. Cheeseman, *J. Chem. Soc.*, 4227 (1952).

Experimental[8]

3-Aminopicolinic Acid Amide.—Dry hydrogen chloride gas was passed into a solution of 5 g. of 3-aminopicolinic acid[9] in 75 ml. of dry methanol while the solution was refluxed gently for 4 hours. The solution was then concentrated to about 15 ml. by evaporation under reduced pressure and the sirup poured into 150 ml. of cold concentrated ammonium hydroxide. This solution was heated carefully to 50° on the steam-bath and then refrigerated for 4 days. The crude precipitate was filtered off and recrystallized from water. The yield was 1.4 g., m.p. 180–181°; a second recrystallization from water raised the m.p. to 181–182°.

Anal. Calcd. for $C_6H_7N_3O$: C, 52.3; H, 5.1; N, 30.7. Found: C, 52.28; H, 4.78; N, 30.65.

2,4-Dihydroxypyrido(3,2-d)pyrimidine (V). A.—A mixture of 33 g. of 3-aminopicolinic acid and 70 g. of urea was heated at 160° until the clear melt partially resolidified (about 20 minutes). The temperature was gradually raised to 180° and the heating discontinued. To the cooled solid was added 400 ml. of 2 *N* sodium hydroxide and the mixture heated to 70°, at which point there was complete solution. The solution was allowed to cool gradually to 25°

(8) All melting points are uncorrected.

(9) E. Sucharda, *Ber.*, **58**, 1727 (1925).

TABLE II

2,4-DIANILINOPYRIDO[3,2-d]PYRIMIDINES

Aniline	M.p., °C.	Yield, %[a]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Unsub.	168–170	83.2	72.8	73.0	4.8	5.30	22.4	22.3
4-Chloro	215–217	51.6	59.7	59.3	3.4	3.54	20.2	20.1
2-Chloro	143–145	63.0	59.7	59.4	3.4	3.44		
2,5-Dimethyl	176–178	36.0	74.9	75.2	6.26	6.42	18.85	18.85

[a] Method A, see text.

and to remain at 25° for one hour before filtration. (At temperatures lower than 25°, some sodium salt of 2,4-dihydroxypyrido(3,2-d)pyrimidine precipitated.) The precipitate (19.2 g.) consisted of 3-aminopicolinic acid amide, m.p. 175–177°, which after two recrystallizations from water gave a m.p. of 181–182° and a mixed m.p. of 181–183° with authentic 3-aminopicolinic acid amide. The filtrate was warmed on the steam-bath while being saturated with a stream of carbon dioxide to precipitate the 2,4-dihydroxypyrido(3,2-d)pyrimidine (14.7 g.) which was collected after cooling. It failed to melt at 360°. A small amount of the product was recrystallized for analysis from glacial acetic acid.

Anal. Calcd. for $C_7H_5N_3O_2$: C, 51.5; H, 3.07; N, 25.8. Found: C, 51.6; H, 3.04; N, 25.7.

B.—A mixture of 10 g. of 3-aminopicolinic acid amide and 30 g. of urea was heated at 190° until the clear melt solidified (about 30 minutes). The solid was dissolved in 300 ml. of 2 *N* sodium hydroxide by heating to 70°. After being kept at 25° for one hour no precipitate formed. The solution was then heated to boiling and acidified with glacial acetic acid. The precipitate (8.5 g.) of 2,4-dihydroxypyrido(3,2-d)pyrimidine was filtered from the hot solution. After solution in hot dilute sodium hydroxide and reprecipitation with acetic acid, the yield was 6.3 g. It was identical in all respects with the product made by method A.

2,4-Dichloropyrido(3,2-d)pyrimidine (VI).—Ten grams of 2,4-dihydroxypyrido(3,2-d)pyrimidine (V) and 50 g. of phosphorus pentachloride were added to 150 ml. of phosphorus oxychloride. The mixture was refluxed for two hours and the excess phosphorus oxychloride removed under reduced pressure. The residue was added to 200 g. of crushed ice and allowed to stand for 15 minutes. The cold aqueous solution was then extracted with chloroform and the chloroform extract washed with water and dried over anhydrous magnesium sulfate. Evaporation of the chloroform left 5.1 g. of slightly yellow product, m.p. 170–175°. A small amount was recrystallized from Skellysolve C to yield colorless crystals, m.p. 177°.

Anal. Calcd. for $C_7H_3N_3Cl_2$: C, 42.0; H, 1.50; N, 21.1. Found: C, 41.9; H, 1.62; N, 21.0.

2,4-Diaminopyrido(3,2-d)pyrimidine (IX).—To 20 ml. of alcohol, saturated with dry ammonia at 0°, was added 2.5 g. of crude 2,4-dichloropyrido(3,2-d)pyrimidine (VI), and the solution was heated at 155–160° for 18 hours in a sealed tube. The cooled solution was added to an equal volume of water, made strongly basic with sodium hydroxide and allowed to stand overnight. The filtered product was recrystallized from 50% ethanol to give 1.1 g. of fine needles, m.p. 317–319°.

Anal. Calcd. for $C_7H_7N_5$: N, 43.5. Found: N, 43.4.

2,4-Dimercaptopyrido(3,2-d)pyrimidine (X).—Six grams of thiourea was dissolved in 200 ml. of absolute ethanol and 6.0 g. of 2,4-dichloropyrido(3,2-d)pyrimidine was added and the mixture was heated under a reflux condenser for five hours. The green precipitate was recovered by filtration, dissolved in 2 *N* sodium hydroxide and precipitated by the addition of acetic acid. The filtered precipitate was washed and dried to yield 4.3 g. of yellow-green amorphous powder. Two grams of this product was purified by Soxhlet extraction using absolute ethanol to give 1.6 g. of yellow-orange crystals which decomposed at 335–340°.

Anal. Calcd. for $C_7H_5N_3S_2$: C, 43.0; H, 2.58; N, 21.5. Found: C, 43.1; H, 2.62; N, 22.0.

4-Amino-2-chloropyrido(3,2-d)pyrimidine (VII).—Two grams of finely powdered 2,4-dichloropyrido(3,2-d)pyrimidine (VI) was added to 100 ml. of concentrated ammonium hydroxide and heated for 1.5 hours on the steam-bath. The white product was filtered and washed with distilled water, m.p. 264–265°; the yield was 1.3 g.

Anal. Calcd. for $C_7H_5N_4Cl$: C, 46.6; H, 2.78; N, 31.0. Found: C, 46.6; H, 2.87; N, 30.6.

4-Amino-2-mercaptopyrido(3,2-d)pyrimidine (XI). A.—2,4-Dimercaptopyrido(3,2-d)pyrimidine (X) (2.3 g.) was dissolved in 100 ml. of concentrated ammonium hydroxide and heated on the steam-bath. After one hour an additional 100 ml. of ammonium hydroxide was added and the heating continued for a further 2 hours. The solution was filtered while hot and the precipitate was washed with cold ammonium hydroxide to give 1.8 g. of small yellow-green needles, m.p. 340–345° dec.

Anal. Calcd. for $C_7H_6N_4S$: C, 47.2; H, 3.37; N, 31.5. Found: C, 47.5; H, 3.63; N, 32.0.

B.—To a solution of 0.5 g. of thiourea in 250 ml. of absolute ethanol was added 0.5 g. of 4-amino-2-chloropyrido-(3,2-d)pyrimidine (VII). The solution was refluxed for 4 hours, cooled and filtered to yield 0.3 g. of product, m.p. 340–345° dec. The ultraviolet absorption spectra, decomposition points and mixed decomposition points of the two preparations were identical.

4-Hydroxy-2-mercaptopyrido(3,2-d)pyrimidine (IV).—To 25 ml. of 10 *N* sodium hydroxide was added 0.5 g. of XI and the solution was heated for 3 hours on the steam-bath. The clear solution was diluted to 50 ml. and acidified with acetic acid. The light green product gradually decomposed above 300° and was found to be identical to 4-hydroxy-2-mercaptopyrido(3,2-d)pyrimidine (IV) prepared by the method of Korte[2] as judged by identical ultraviolet absorption spectra. Hydrolysis of XI to IV was equally well accomplished with 6 *N* hydrochloric acid on the steam-bath.

4-Aminopyrido(3,2-d)pyrimidine (XII).—Five grams of 4-amino-2-mercaptopyrido(3,2-d)pyrimidine was suspended in 1800 ml. of absolute ethanol and 200 ml. of concentrated ammonium hydroxide, approximately 15 g. of Raney nickel was added and the reaction mixture was heated under reflux conditions for 30 hours. The mixture was filtered hot and the filtrate concentrated to 250 ml. and allowed to cool. The yield of almost colorless needles was 1.2 g., m.p. 221–222°.

Anal. Calcd. for $C_7H_6N_4$: C, 57.5; H, 4.15; N, 38.4. Found: C, 57.7; H, 4.24; N, 37.9.

4-Hydroxypyrido(3,2-d)pyrimidine (VIII).—To 10 ml. of 10 *N* sodium hydroxide was added 150 mg. of XII and the solution was heated for 4 hours on the steam-bath. The suspended starting material was gradually replaced by long colorless needles of the sodium salt of 4-hydroxypyrido(3,2-d)pyrimidine (VIII). This product was filtered and dissolved in a little water and the solution acidified with acetic acid to yield 10 mg. of VIII, m.p. 345–346° dec. This product did not depress the melting point of VIII, m.p. 345–346° dec., prepared by the method of Price and Curtin.[3] The ultraviolet absorption spectra of the two preparations were found to be identical.

2,4-Dianilinopyrido(3,2-d)pyrimidines. A.—The dianilinopyrido(3,2-d)pyrimidines which are listed in Table II were prepared by the reaction of the dichloro derivative with the appropriate aniline in the absence of added solvent. This general method is illustrated with the preparation of the dianilino compound III. To 3 g. of aniline heated on the steam-bath was carefully added, a little at a time with shaking, 1.0 g. of 2,4-dichloropyrido(3,2-d)pyrimidine (VI). The reaction mixture was heated for 12 hours, cooled, and the solid residue dissolved in hot 50% ethanol with sufficient sodium hydroxide to make the solution strongly basic. The cooled solution yielded 1.3 g. of tan needles, m.p. 168–170°. Recrystallization from ethanol did not change the m.p.

B.—To 10 ml. of refluxing aniline was carefully added 2.0 g. of 4-amino-2-chloropyrido(3,2-d)pyrimidine (VII) and the heating was continued for 30 minutes. After cooling, the product was treated with 10 ml. of 50% ethanol containing a little sodium hydroxide, and filtered. The solid was recrystallized from ethanol to yield 0.6 g. of tan needles, m.p. 168–170°. A mixed melting point of this product with that of III prepared by method A was 168–170°.

2,4-Bis-(dimethylamino)-pyrido(3,2-d)pyrimidine (II).—This product was prepared from 2,4-dichloropyrido(3,2-d)-pyrimidine (VI) and dimethylamine by three different procedures. The products were identical as judged by ultraviolet absorption spectra, melting points and mixed melting points.

A.—A mixture of 2 g. of VI and 30 ml. of a 20% solution of dimethylamine in alcohol was heated in a sealed tube at 150° for 8 hours. The solution was evaporated to dryness on the steam-bath and the residue dissolved in 20 ml. of 2 *N* sodium hydroxide at 40°. After chilling overnight at 4°, the precipitate was collected, washed with water and dried at room temperature. The crude product was extracted with 100 ml. of boiling hexane (Skellysolve B). The solution gave 1.7 g. of product, m.p. 61–63°. Recrystallization from a small amount of pentane (Skellysolve A) raised the m.p. to 65–66°.

Anal. Calcd. for $C_{15}H_{15}N_5$: C, 60.9; H, 6.89; N, 32.3. Found: C, 61.39; H, 6.48; N, 32.6.

B.—A mixture of 1 g. of VI and 30 ml. of 20% alcoholic dimethylamine was heated on the steam-bath until dry. The residue was worked up as in method A and gave 0.9 g. of product, m.p. 61–63°.

C.—A mixture of 1.5 g. of VI and 75 ml. of 20% aqueous dimethylamine was heated on the steam-bath until dry (8 hours). The residue was worked up as in method A and gave 1.1 g. of product, m.p. 60–63°.

The reaction of dimethylamine with the dichloro compound was studied, by means of spectrophotometric observations, at lower temperatures and with more dilute dimethylamine solutions. No evidence was obtained for the formation of a 2-chloro-4-dimethylamino derivative.

TUCKAHOE, NEW YORK

[CONTRIBUTION FROM THE MORLEY CHEMICAL LABORATORY, WESTERN RESERVE UNIVERSITY]

Preparation of Some Hexaalkyl-phosphorous, Phosphoric and Phosphorothioic Triamides[1]

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sec-Aliphatic amines react readily with phosphorus trichloride to form hexaalkyl-phosphorous triamides, $(R_2N)_3P$. These phosphorous triamides are easily converted to the corresponding phosphoric triamides, $(R_2N)_3PO$, by oxidation with dilute hydrogen peroxide; or to the corresponding phosphorothioic triamide, $(R_2N)_3PS$, by sulfurization with elemental sulfur. Each of these three types of amides was prepared, using diethyl-, di-*n*-propyl- and di-*n*-butylamines. At temperatures of about 150°, the phosphorous triamides also react with benzyl mercaptan with the evolution of secondary amine to form S-benzyl-N,N′-tetraalkyl-phosphorodiamidothioite esters, $(R_2N)_2PSCH_2C_6H_5$.

Previous work in this Laboratory has shown that primary aliphatic or aromatic amines react with phosphorus pentasulfide to give phosphorodiamidodithioic acids, $(RNH)_2P(S)SH$, or phosphorothioic triamides, $(RNH)_3PS$, depending on mole ratios and reaction conditions.[3a] Phosphorus pentoxide gives similar results with primary aromatic amines, but in very low yields.[3b]

Secondary aliphatic amines, however, react with phosphorus pentasulfide to form N-dialkyl-phosphoroamidotrithioic acids, $R_2NP(S)(SH)_2$, N,N,N′-trialkyl-phosphorodiamidodithioic acids, $R_2N(RNH)P(S)SH$, or N,N′,N″-trialkyl-phosphorothioic triamides, $(RNH)_3PS$, depending again upon mole ratios and reaction conditions.[3c]

Since the reaction of secondary amines with phosphorus pentasulfide did not yield phosphorodiamidodithioic acids or hexaalkyl-phosphorothioic triamides, it was of interest to prepare these compounds by other methods.

Michaelis[4] has reported the preparation of a few phosphoric and phosphorothioic triamides by treating secondary aliphatic amines with phosphoric trichloride or phosphorothioic trichloride and also by the oxidation or sulfurization, respectively, of the corresponding phosphorous triamides. However, Michaelis was not able to purify his products by distillation and the analytical results, when given, are not satisfactory.

Therefore, attempts were made to repeat Michaelis' work. Using the amine with either phosphoric or phosphorothioic trichloride, we found that the crude product was contaminated with chlorine compounds which could not be removed without decomposing the product. However, the reaction of excess secondary aliphatic amines with phosphorus trichloride to form the phosphorous triamides gave satisfactory results, if anhydrous conditions were maintained. The hexaalkyl-phosphorous triamides of diethyl-, di-*n*-propyl- and di-*n*-butylamines were obtained in good yields as water-white, slightly oily liquids. They could be distilled under reduced pressure without decomposition. Treatment of the phosphorous triamides with either hydrogen peroxide or elemental sulfur gave the corresponding phosphoric or phosphorothioic triamides in fair yields (25–80%). They are colorless to light yellow oils and, with the exception of hexa-*n*-butyl-phosphorothioic triamide, were purified by distillation. The latter was purified by crystallization.

Various attempts were then made to prepare the tetraalkyl-phosphorodiamidodithioic acids, but without success. During this work, it was found that at temperatures of 140–150°, benzyl mercaptan reacted smoothly with the phosphorous triamides to form S-benzyl-N,N′-tetraalkyl-phosphorodia-

(1) Nomenclature used is from the report of the A.C.S. Committee on Nomenclature; *Chem. and Eng. News*, **30**, 4515 (1952).

(2) Lubrizol Corp., Cleveland 17, Ohio.

(3a) A. C. Buck, J. D. Bartleson and H. P. Lankelma, THIS JOURNAL, **70**, 744 (1948).

(3b) A. C. Buck and H. P. Lankelma, *ibid.*, **70**, 2398 (1948).

(3c) G. Wise and H. P. Lankelma, *ibid.*, **74**, 529 (1952).

(4) A. Michaelis, *Ann.*, **326**, 129 (1903).