sym-**Dibenzyl-N,N,N′,N′-tetrakis-(2-chloroethyl) Pyrophosphorodiamidate (XLIX).**—A mixture of 0.99 g. of the benzyl phosphoramidic chloride X, 0.34 ml. of 2,6-lutidine and 0.03 ml. of water was agitated until solid separated from the mixture. After refrigeration overnight and dilution with ether the oily solid precipitate that formed was removed by filtration. The filtrate was evaporated leaving an oily residue which after washing several times with petroleum ether was taken up in ether. The ether extracts treated with Norit after evaporation gave 0.62 g. of oily product, $n^{25}D$ 1.5320.

Anal. Calcd. for $C_{22}H_{30}Cl_4N_2O_5P_2$: N, 4.62; Cl, 23.43. Found: N, 4.7; Cl, 23.70.

sym-**Diphenyl-N,N,N′,N′-tetrakis-(2-chloroethyl) Pyrophosphorodiamidate (XLVIII).**—This compound was prepared in the same manner as XLIX. Reaction of 1 g. of the phenyl phosphoramidic chloride (IX), 0.36 ml. of 2,6-lutidine and 0.057 ml. of water yielded 0.86 g. (48%) of oily product.

Anal. Calcd. for $C_{20}H_{26}Cl_4N_2O_5P_2$: C, 41.52; H, 4.5; N, 4.84; P, 10.73; Cl, 24.57. Found: C, 41.98; H, 4.62; N, 4.74; P, 10.42; Cl, 23.84.

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2-Amino-5-pyrimidinesulfonamides

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2-Amino-5-pyrimidinesulfonamides have been prepared from 2-(5-chlorosulfonylpyrimidyl)-phosphoramidic dichloride, readily obtainable from 2-aminopyrimidine in two steps.

When 2-chloro-5-pyrimidinesulfonyl chloride, recently described by Caldwell and Jaffe,[1] was treated with ammonia or amines, both halogens were replaced; hence this intermediate is not suited to the preparation of compounds of the type 2-aminopyrimidine-5-(N-phenyl)sulfonamide, an isomer of sulfadiazine. The object of the work described here was to obtain an intermediate from which a variety of 2-amino-5-pyrimidinesulfonamides could be prepared readily.

Like pyridine, pyrimidine is resistant to electrophilic attack and, as yet, a simple mononitropyrimidinesulfonic acid has not been described. Substituted nitropyrimidines, pyrimidinesulfonic acids or sulfonyl chlorides are known[2-7] but, unless prepared from pyrimidines containing at least two such substituents as hydroxyl or amino groups, have not been obtained by either direct nitration or sulfonation. The compounds described by Caldwell and Jaffe are the first to have been made by direct electrophilic action upon a monoaminopyrimidine.

Preparation of 1-aminobenzene-2,4,6-trisulfonyl chloride by Lustig and Katscher[8] and the report of the formation of sulfanilyl chloride directly from aniline[9] gave support to the thought that 2-amino-5-pyrimidinesulfonyl chloride might be obtained since it also had been shown previously[10-12] that a strongly electron-withdrawing group in position 5 of the pyrimidine nucleus deactivates an amino group in position 2 toward electrophilic attack. The normal incompatibility to be expected in the simultaneous existence of free primary amino and sulfonyl chloride groups might not prevail in this particular case.

Attempts to acetylate 2-amino-5-pyrimidinesulfonic acid or its sodium salt by methods analogous to those by which 2-acetamido-5-nitropyrimidine was prepared[12] from 2-amino-5-nitropyrimidine failed in our hands; furthermore, we obtained only 2-amino-5-pyrimidinesulfonic acid upon treating 2-acetamidopyrimidine with chlorosulfonic acid.

We therefore turned to a reaction between the sodium salt of 2-amino-5-pyrimidinesulfonic acid and phosphorus pentachloride from which we derived, not the expected 2-aminopyrimidinesulfonyl chloride but, instead, 2-(5-chlorosulfonylpyrimidyl)phosphoramidic dichloride (I) by a sequence of reactions presumably like those given by Bieber and Kane[13] for an analogous reaction between sodium sulfanilate and phosphorus pentachloride. Its preparation and conversion to the desired compounds are shown.

We wish to thank Eli Lilly and Co. for carrying out pharmacological tests and the Temple University Committee on Research and Publications for a grant-in-aid.

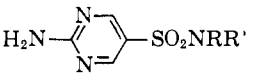
Experimental

2-Amino-5-pyrimidinesulfonic Acid.—This compound was prepared by a modification of the method of Caldwell and Jaffe.[1] To 100 ml. (1.5 moles) of chlorosulfonic acid was added, with stirring, 16.0 g. (0.168 mole) of 2-aminopyrimidine and the

(1) W. T. Caldwell and G. E. Jaffe, *J. Am. Chem. Soc.*, **81**, 5166 (1959).
(2) N. V. Khromov-Borisov and R. S. Karlinskaya, *J. Gen. Chem. U.S.S.R.* (Eng. Transl.), **24**, 2185 (1954).
(3) A. Boehringer, E. Boehringer, I. Liebert, and J. Liebert, British Patent 753,317, July 25, 1956.
(4) F. C. Fischer, J. Rock, and W. P. Neumann, German Patent 927,631, May 12, 1955.
(5) R. O. Roblin, Jr., and J. W. Clapp, *J. Am. Chem. Soc.*, **72**, 4890 (1950).
(6) R. O. Roblin, Jr., and J. W. Clapp, U.S. Patent 2,577,231, Dec. 4, 1951.
(7) R. R. Herr, T. Enkoji, and T. J. Bardos, *J. Am. Chem. Soc.*, **78**, 401 (1956).
(8) O. Lustig and E. Katscher, *Monatsh.*, **48**, 91 (1927).
(9) M. C. Marques, *Bol. Soc. Quim. Peru*, **6**, 89 (1940).
(10) R. O. Roblin, Jr., and J. English, *J. Am. Chem. Soc.*, **64**, 567 (1942).
(11) J. English and J. Clark, *ibid.*, **68**, 453 (1946).
(12) W. T. Caldwell, *ibid.*, **73**, 2357 (1951).
(13) T. I. Bieber and B. Kane, *J. Org. Chem.*, **21**, 1198 (1956).

TABLE I

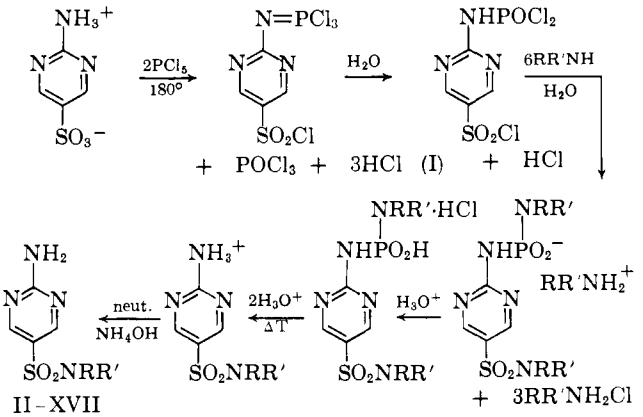
2-AMINOPYRIMIDINE-5-SULFONAMIDE AND SOME OF ITS SUBSTITUTED DERIVATIVES[a]



II–XVII

	Reagent	M.p., °C.	Yield, %	Crystn. solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
II	Ammonia	283–284[1]							
III	Dimethylamine	240–241	46	MeOH	$C_6H_{10}N_4O_2S$	35.63	35.69	4.98	4.92
IV	Diethylamine	174–175	71	*i*-PrOH	$C_8H_{14}N_4O_2S$	41.72	42.15	6.13	6.17
V	Diethanolamine	188–189	47	H_2O	$C_8H_{14}N_4O_4S$	36.63	36.91	5.38	5.41
VI	Ethylamine	226–228	59	EtOH	$C_6H_{10}N_4O_2S$	35.65	35.85	4.98	5.20
VII	*n*-Propylamine	235–236	61	EtOH-H_2O	$C_7H_{12}N_4O_2S$	38.87	38.82	5.59	5.71
VIII	*n*-Butylamine	239–241	51	EtOH-H_2O	$C_8H_{14}N_4O_2S$	41.72	41.44	6.13	6.35
IX	Ethanolamine	210–212	57	H_2O	$C_6H_{10}N_4O_3S$	33.02	32.84	4.58	4.91
X	*tert*-Butylamine	186–187	53	H_2O	$C_8H_{14}N_4O_2S$	41.72	41.88	6.13	6.40
XI	Allylamine	225–226	76	*i*-PrOH	$C_7H_{10}N_4O_2S$	39.24	39.65	4.71	4.84
XII	Cyclohexylamine	205–206	32	EtOH-H_2O	$C_{10}H_{16}N_4O_2S$	46.86	47.39	6.29	6.31
XIII	Benzylamine	255–257	35	EtOH	$C_{11}H_{12}N_4O_2S$	49.99	49.60	4.58	4.55
XIV	Aniline	244	13	H_2O	$C_{10}H_{10}N_4O_2S$	48.00	48.20	4.00	4.04
XV	*p*-Toluidine	247–249	15	H_2O	$C_{11}H_{12}N_4O_2S$	50.00	49.86	4.55	4.32
XVI	3-Aminopyridine	281	35	EtOH-H_2O	$C_9H_9N_5O_2S$	43.02	43.00	3.61	3.71
XVII	Piperidine	249–250	47	EtOH-H_2O	$C_9H_{14}N_4O_2S$	44.61	44.52	5.82	6.07

[a] Prepared using crude intermediate, N-(5-chlorosulfonyl-2-pyrimidyl)-phosphoramidic dichloride.



resulting solution was refluxed for 8 hr. Thereupon approximately one-half of the chlorosulfonic acid was removed by distillation at atmospheric pressure. This operation resulted in a three-fold increase in yield. The residual sirupy liquid was added with stirring to approximately 100 g. of crushed ice, and the resulting white solid was filtered off and was washed with cold water. Recrystallization from water afforded 17.1 g. (58%) of white crystals; m.p. 326–328° dec.; lit. m.p.[1] 305–307° dec.

N-(5-Chlorosulfonyl-2-pyrimidyl)phosphoramidic Dichloride (I).—A mixture of 10.0 g. (0.050 mole) of the sodium 2-amino-5-pyrimidinesulfonate and 25.0 g. (0.120 mole) of phosphorus pentachloride was heated in an oil bath at 150° for 1.5 hr. Upon cooling, the reaction mixture was poured on crushed ice. The white solid that formed was collected, washed with cold water and dried in a vacuum desiccator at room temperature; the yield of crude product was 11.1 g. (70.8%); m.p. 185–190°. A sample of this material was recrystallized twice from anhydrous benzene–ligroin; m.p. 202–203°; infrared spectra: λ_{max}^{Nujol} 7.78, 8.84 μ (SO_2); 8.42 μ (P=O).

Anal. Calcd. for $C_4H_3Cl_3N_3O_3PS$: C, 15.45; H, 0.97; N, 13.53; P, 9.98; mol. wt., 311. Found: C, 16.08; H, 1.13; N, 13.34; P, 9.81; mol. wt., 307 (Osmometer, Mechro Lab. Model 310).

2-Aminopyrimidine-5-(N-phenyl)sulfonamide.—Three grams (9.6 mmoles) of N-(5-chlorosulfonyl-2-pyrimidyl)phosphoramidic dichloride was added to 15 ml. of water containing 6.4 g. (69.0 mmoles) of aniline and the solution was heated 10 hr. on a steam bath. The solution was cooled in an ice-water bath and slowly acidified with concd. hydrochloric acid to pH 2. The acid solution was heated on a steam bath for 20 min. and filtered. The filtrate was cooled and slowly neutralized by stirring with aqueous ammonia. The solid formed was collected, washed well with water, and recrystallized twice from ethanol-water to give 0.81 g. (30%) of white crystals; m.p. 224°.

1-(2-Amino-5-pyrimidinesulfonyl)piperidine.—Three grams (9.6 mmoles) of N-(5-chlorosulfonyl-2-pyrimidyl)phosphoramidic dichloride was added to 35 ml. of dry ether containing 6.57 g. (77.2 mmoles) of piperidine and refluxed for 12 hr. on a steam bath. Upon removal of the ether, acidification with concd. hydrochloric acid and subsequent neutralization with aqueous ammonia gave 1.10 g. (47%) of white crystals. An analytical sample was obtained by recrystallizing twice from ethanol–water; m.p. 249–250°.

Pharmacological Summary.—Eli Lilly and Co.[14] carried out the pharmacological tests; compounds IV and XIV were ineffective in a screening test designed to uncover antimetabolites by using a minimal medium supplying only the essential levels of amino acids, vitamins, *etc.* Sulfonamide drugs are active in this test but not in the usual antibiotic spectrum screen which employs a medium rich in nutrients. Compounds V and X when tested by the method of Johnson, Simpson and Cline[15] against minimal bacteria, algae and protozoans, were inactive when used on pads dipped in a 500 γ/ml. suspension. XIII was administered to mice at a dose level of 1.7 mg./kg. and found ineffective against P-1534 leukemia. Compound III appeared to be a very weak CNS depressant at a dose level of 400 mg./kg., causing a 15 mg./100 ml. increase in blood glucose when administered orally to rats.

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(14) R. G. Jones and E. C. Kornfeld, personal communication.

(15) I. S. Johnson, P. J. Simpson, and J. C. Cline, *Cancer Research*, **22**, 617 (1962).