Radioactivity Measurements.—All C^{14} counting was done with a Packard-Tri-Carb liquid scintillation counter, Model 314X. The scintillation mixture contained 4 g. of 2,5-diphenyloxazole and 0.1 g. of 1,4-bis-2-(phenyloxazolyl)benzene/l. of toluene. For compounds **1a**, **3**, and **7**, all of which have strong absorption at 400 mμ, counting efficiency was too low to permit direct counting. In these cases samples were oxidized to carbon dioxide by a standard chromic acid wet combustion technique, and barium carbonate was counted in a thixotropic scintillation gel. For all other compounds, weighed samples were counted directly in the scintillation solution. All samples were counted five times, usually for 10 min., and for each sample the efficiency was determined by adding a benzoic acid-C^{14}-1 standard; efficiencies ranged from 44–58%. The specific activities reported below are corrected for background and counting loss.

1-Diazo-3-methyl-4-phenyl-3-buten-2-one C^{14}-1 (17).—Diazomethane-C^{14} was prepared by the standard procedure[31] from 21.5 g. (0.2 moles) of N-methyl-C^{14}-N-nitroso-*p*-toluenesulfonamide[32] containing 0.1 mc. of C^{14} activity. The yield by titration was 71%. To this diazomethane was added a solution of 5.90 g. of freshly crystallized α-methylcinnamoyl chloride. After standing at room temperature for 5 hr., the solution was evaporated at reduced pressure and the diazo ketone was collected in three crops, total yield 4.1 g. (61%), m.p. 85–89°; specific activity 9.33×10^4 d.p.s./mmole.

This diazo ketone was converted to the pyrazoline **18** with nonradioactive diazomethane in 48% yield by the usual procedure; **18** had m.p. 92–95°. This product was then diluted with unlabeled **18** to give 3.9 g., m.p. 92–93°; specific activity 2.30×10^4 d.p.s./mmole. The radioactive pyrazoline was converted to **1a** in 70% yield, and the product was again diluted with unlabeled material to give 7.7 g. of **1a**, m.p. 151–152°; specific activity 1.27×10^3 d.p.s./mmole.

Subsequent steps were then carried out by the procedures described above without further dilutions of radioactivity. Compounds **3**, **7**, **8**, and **12** had specific activities ranging from 100–103% of that of **1a**. In the decarboxylation of **12**, a slow stream of nitrogen was bled into the sublimer and the entrained carbon dioxide was absorbed in sodium hydroxide solution and then precipitated by addition of barium chloride. The barium carbonate had specific activity 1.21×10^3 d.p.s./mmole; the picrate of **13** had specific activity 85 d.p.s./mmoles.

(31) T. J. deBoer and H. J. Backer, *Org. Syn.*, **36**, 16 (1956).

(32) Obtained from New England Nuclear Corp.

Acknowledgment.—We wish to thank Dr. J. M. Vandenbelt and Mrs. Carola Henrich Spurlock, Parke, Davis and Company, for the pK_A and ultraviolet data.

Thiadiazoles. III. Amino-Group Exchange and Ring-Cleavage Reactions of 7-Amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidines[1]

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Displacement of the amino group of 7-amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (I) by secondary amines was shown to occur with the formation of 7-(disubstituted amino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidines (V–VIII). Primary amines were likewise shown to effect displacement of the amino group, but cleavage of the pyrimidine ring to a 1,2,5-thiadiazole may ensue. The structure of the amino-group exchange product from I and butylamine was shown to be 7-(butylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine, rather than the 6-butyl derivative, by reduction to 4,5-diamino-6-(butylamino)pyrimidine and by independent synthesis. Products of ring cleavage of I were shown to be *N*-substituted amidines, *e.g.*, 4-amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamidine (XIV). The formation of the thiadiazolopyrimidines resulting from exchange of amino groups could be favored over the formation of 1,2,5-thiadiazoles by limiting the reaction time. Exchange of one mono- or disubstituted amino group for another and the reversibility of this type of reaction were also demonstrated. Evidence that these amine-exchange reactions are influenced by the relative basicities of the attacking and departing amines and by steric effects was obtained. It is suggested that the exchange of amino groups occurs by direct displacement and that ring cleavage is an independent process.

Facile nucleophilic displacement from position 7 of substituents commonly subject to expulsion from heterocyclic rings was observed during the course of investigations on the synthesis of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines.[2] These displacements were effected by aniline generated during the formation of the thiadiazole ring by *N*-sulfinylaniline (III). Evidence was subsequently obtained that trace amounts of 7-anilino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (IV) may be formed during the preparation of 7-amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (I) from 4,5,6-triaminopyrimidine (II, $R_1 = R_2 =$ H) and *N*-sulfinylaniline. Moreover, cleavage of the pyrimidine ring of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines bearing oxygen functions was found to proceed under comparatively mild conditions.[3] These reactions indicate an unusual lability of the pyrimidine ring that is probably ascribable to electron localization at the hetero atoms. The lability of the ring system suggested that additional studies of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines might contribute to further elucidation of the course of amino-group exchange and ring-opening reactions of fused pyrimidine heterocycles.

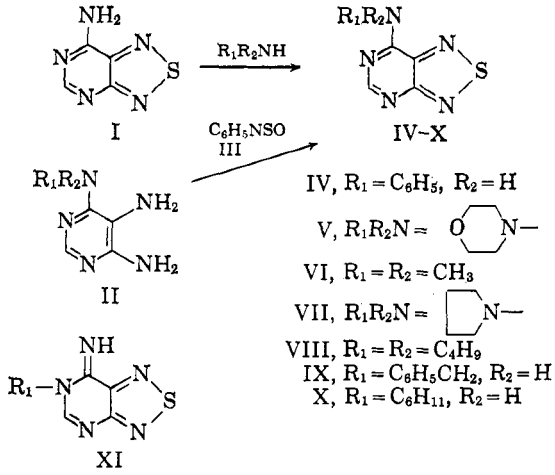
Paper chromatographic evidence for the formation of trace amounts of the 7-anilino derivative (IV) during the preparation of the 7-amino derivative (I) was confirmed by showing that a small amount of the 7-anilino derivative (IV) could be isolated by greatly prolonging the reaction time. Interaction of pure I and refluxing aniline afforded IV in low yield. From reactions of I with refluxing morpholine and with dimethylamine at 100°, 7-morpholino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (V) and 7-(dimethylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (VI) were isolated and were shown to be identical with specimens of these compounds that had been prepared[2] from reactions of the appropriate 6-substituted 4,5-diaminopyrimidines (II) and N-sulfinylaniline (III). Similarly, reactions of I with pyrrolidine, with dibutylamine, and with certain primary amines gave the 7-(substituted amino) derivatives VII–X (Chart I).

(1) This investigation was supported by the C. F. Kettering Foundation and by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. SA-43-ph-1740.

(2) Y. F. Shealy, J. D. Clayton, and J. A. Montgomery, *J. Org. Chem.*, **27**, 2154 (1962).

(3) (a) Y. F. Shealy and J. D. Clayton, *ibid.*, **28**, 1491 (1963); (b) Y. F. Shealy and J. D. Clayton, *ibid.*, **29**, 2141 (1964).

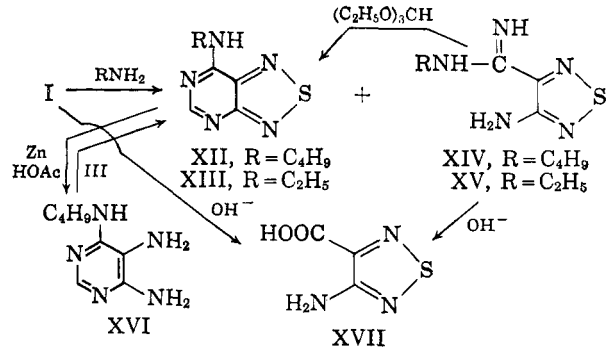
CHART I



The structural assignments (VII–X) for the products of these reactions are based on their composition, characteristic ultraviolet spectra, and analogy to V–VI. However, if amino-group exchange proceeds by a ring-opening and reclosure mechanism,[4,5] 6-substituted 7-imino[1,2,5]thiadiazolo[3,4-*d*]pyrimidines (XI) are possible products of exchange by primary amines. During studies of the interaction of benzylamine and of cyclohexylamine with the 7-amino derivative (I), the ultraviolet long-wave-length absorption maximum of [1,2,5]-thiadiazolo[3,4-*d*]pyrimidines was observed to move hypsochromically, during long-term reactions, toward that of certain 1,2,5-thiadiazoles.[3a] Both the possibility of pyrimidine ring cleavage and the structure of products of exchange with primary amines were investigated more fully by employing butylamine as the nucleophile.

Two compounds were detected in and isolated from crude products of reactions of 7-amino[1,2,5]thiadiazolo-[3,4-*d*]pyrimidine (I) with refluxing butylamine that were allowed to proceed for 1–2 days. The higher-melting product had the composition of 7-(butylamino)-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (XII) and exhibited ultraviolet absorption consistent with this structure. The second, lower-melting product had the composition of 4-amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamidine (XIV) and, like other derivatives[3a] of 4-amino-1,2,5-thiadiazole-3-carboxylic acid, showed an absorption maximum near 320 mμ. In contrast to 4-amino-1,2,5-thiadiazole-3-carboxamide,[3a] but, in accord with the presence of the basic amidine group, the second product formed a stable hydrochloride. Reduction of the higher-melting compound with zinc and acetic acid[6] gave 4,5-diamino-6-(butylamino)pyrimidine (XVI), identical with a specimen prepared by reducing 4-amino-6-butylamino-5-nitropyrimidine. The higher-melting compound was synthesized by treating 4,5-diamino-6-(butylamino)pyrimidine (prepared from the 5-nitropyrimidine) with *N*-sulfinylaniline. These interconversions excluded 6-butyl-6,7-dihydro-7-imino-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (XI, $R_1 = C_4H_9$), a potential product of opening and subsequent reclosure of the pyrimidine ring, and they confirmed the structure (XII) assigned to the higher-melting product. The structure (XIV) assigned to the second, lower-melting product was confirmed by the following reactions: (1) basic hydrolysis gave 4-amino-1,2,5-thiadiazole-3-carboxylic acid[3a] (XVII); and (2) an acid-catalyzed reaction with triethyl orthoformate reclosed the pyrimidine ring, giving 7-(butylamino)[1,2,5]thiadiazolo-[3,4-*d*]pyrimidine (XII). Further studies of the interaction of I and butylamine showed that XII could be obtained in 84% crude yield by limiting the reaction time to 7 hr.; 4-amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamidine (XIV) could be isolated free of XII in 40–50% yield by prolonging the reaction time to 90–120 hr. (Chart II).

CHART II



Reactions of I with ethylamine gave analogous results. The structural assignments for the higher-melting thiadiazolopyrimidine (XIII) and the lower-melting thiadiazole (XV) are based on elemental analyses, analogy to the products formed by butylamine, and ultraviolet spectra. The formation of XIII was also favored by reaction periods shorter than those that afforded the best yields of the thiadiazole (XV). The 1,2,5-thiadiazoles obtained from I are closely related to those isolated from reactions of [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one with amines, hydrazine, or aqueous base.[3a] Ring opening also resulted from the action of aqueous base on I; the final product of a prolonged reaction at room temperature was 4-amino-1,2,5-thiadiazole-3-carboxylic acid (XVII). An analogous ring opening is the cleavage of 4-aminopteridine by hydrazine and by aqueous base[8]; other examples of the formation of ring-cleavage products from variously substituted heterocycles have been cited previously.[3a] Compound XVII might be the hydrolysis product of an intermediate thiadiazole formed by ring opening of I, or I might first be hydrolyzed to the 7(6*H*)-one, which can be cleaved to XVII by aqueous base.[3a] Evidence has been presented by Brown and Jacobsen[9] that both of these pathways are followed, depending on reaction conditions, in the alkaline cleavage of an *N*-

(4) E. C. Taylor, Jr., and C. K. Cain, *J. Am. Chem. Soc.*, **73**, 4384 (1951).

(5) E. C. Taylor, Jr., *ibid.*, **74**, 1648 (1952).

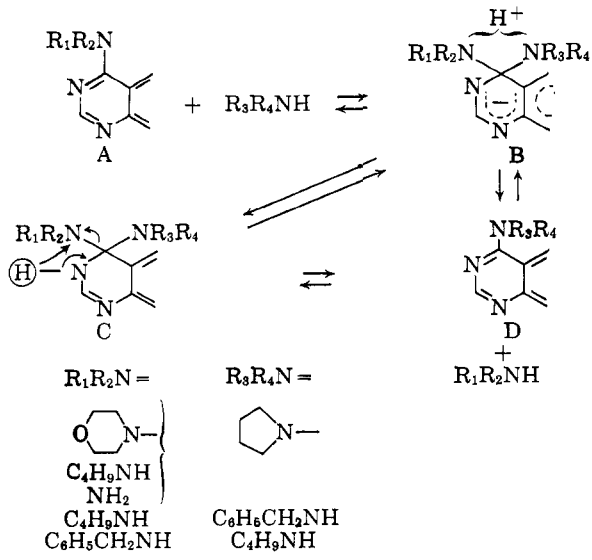
(6) The reduction of XII is another example of reductive cleavage, by a different reagent, of the thiadiazole ring of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines.[2] D. C. Sen [*J. Indian Chem. Soc.*, **15**, 537 (1938)] reported the reduction of bornylene-1,2,5-thiadiazole to bornylene-2,3-diamine by zinc and acetic acid. 2,1,3-Benzothiadiazoles are reduced to *o*-phenylenediamines by tin or zinc in acidic media. Iron and acetic acid or sodium dithionite reduce certain nitro- and phenylazo-2,1,3-benzothiadiazoles to amino derivatives without cleaving the thiadiazole ring. See V. G. Pesin, A. M. Khaletskii, and V. A. Sergeev, *Zh. Obshch. Khim.*, **32**, 181 (Eng. transl.,[7] p. 177) (1962), and preceding publications.

(7) *J. Gen. Chem. USSR*, Consultants Bureau Enterprises, Inc., New York, N. Y.

(8) R. M. Evans, P. G. Jones, P. J. Palmer, and F. F. Stephens, *J. Chem. Soc.*, 4106 (1956).

(9) D. J. Brown and N. W. Jacobsen, *ibid.*, 1978 (1960).

CHART III



substituted pteridine, 1,4-dihydro-4-imino-1-methylpteridine; 4-aminopteridine has been hydrolyzed by aqueous base to 4-hydroxypteridine.[10]

Because of its relatively strong basic properties, pyrrolidine was chosen for a study of exchange of substituted amino groups. Reactions of pyrrolidine with 7-morpholino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (V) and with 7-(butylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (XII) both gave 7-pyrrolidino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (VII) at the temperature of refluxing pyrrolidine. Thus, a secondary amine effected displacement, as summarized in Chart III, of ammonia, a primary amine, and another secondary amine. In addition, exchange of one primary amine for another[11] was demonstrated by the isolation in low yield of 7-(butylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (XII) from a reaction of the 7-benzylamino derivative (IX) with butylamine. Considerable IX (52%) was recovered, and chromatographic evidence of slight ring opening to XIV was obtained. The reversibility of these exchange reactions was shown by reversing the roles of benzylamine and butylamine. A small quantity of the 7-benzylamino derivative (IX) was isolated by treating the 7-butylamino derivative (XII) with benzylamine. However, when the roles of pyrrolidine and morpholine were reversed by treating the 7-pyrrolidino derivative (VII) with morpholine, the 7-pyrrolidino derivative (VII) was recovered[12] after a much longer reaction period than that required at the same temperature for the formation of the 7-pyrrolidino derivative (VII) in high yield from the 7-morpholino derivative (V).

The basicity[13] (in water) of the four bases involved in reactions of pyrrolidine with the three thiadiazolopyrimidines (Chart III) increases in the order morpholine < ammonia < butylamine < pyrrolidine. The rate of formation of VII in relation to the basicity of the amine displaced would be expected to decrease in the order morpholine > ammonia > butylamine. The butylamino group was displaced by pyrrolidine much less readily than the morpholino and amino groups, both of which were displaced almost quantitatively after reaction periods of 1–2 hr. Our observations of shifts of the long-wave-length ultraviolet absorption maximum during the formation of VII do not show a clear distinction between displaceability of the amino and morpholino groups by pyrrolidine; steric effects or volatilization of the displaced ammonia may have counteracted the difference in base strength. The failure of morpholine (pK_a 8.36) to effect any appreciable displacement of pyrrolidine (pK_a 11.27) from VII under comparable conditions is consistent with the difference in base strength of the two amines. Reactions of I with pyrrolidine, morpholine, and dibutylamine represent a variation of the attacking amine. The 7-pyrrolidino derivative (VII) was formed more rapidly than the 7-morpholino derivative (V), even though the temperature of the morpholine reaction was higher. This difference may be due to either steric or basic effects, but steric effects must be responsible for the fact that the dibutylamino derivative (VIII) formed more slowly than either V or VII, even though the attacking amine is comparable in basicity[13] to pyrrolidine.[14] Although these observations are qualitative, they are consistent with the expectation that, other factors being equal, diplaceability of amino groups by amines depends on both steric effects and the relative basicities (or nucleophilicities) of the attacking and departing amines.

Amino-group exchange reactions, some of which were acid catalyzed, of 2,4-diaminopteridines[4,5,15,16] and 2,4-diaminoquinazolines,[17] as well as 2,4-disubstituted pteridines[4,16] and quinazolines[18] having one amino substituent, have been described. In addition, acid-catalyzed exchange of amino groups of pyrimidines[19,20] and of purines[19,21] has been reported. Most of these reactions were conducted at temperatures of 130–200°, whereas exchange of amino groups at position 7 of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines was effected without acid catalysis and frequently at temperatures below 100°; for example, the benzylamino derivative (IX) was obtained from I in 88% yield after a 16-hr. reaction at 80–85° and the pyrrolidino derivative (VII) was obtained in nearly quantitative yields from either I or V after approximately 2 hr. at 85–90°. Taylor[4,5] proposed a mechanism based on ring opening and subsequent reclosure for amino-group exchange reactions of 2,4-disubstituted pteridines. A similar course had been proposed by Leonard and co-workers[22] for amine exchange involving a ring-nitrogen atom of

(10) A. Albert, D. J. Brown, and G. Cheeseman, *J. Am. Chem. Soc.*, 474 (1951).

(11) Exchange of one primary amine for another has been previously observed with certain bifunctional pteridines,[4] quinazolines,[17] and pyrimidines.[19]

(12) A trace amount of the 7-morpholino derivative (V) was detected chromatographically in the recovered VII (*cf.* ref. 42).

(13) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5441 (1957), and references cited therein.

(14) Diisopropylamine failed to displace chlorine from a 6-chloropurine nucleoside, although a number of other primary and secondary amines effected this displacement; see L. Goldman and J. W. Marsico, *J. Med. Chem.*, **6**, 413 (1963).

(15) B. Roth, J. M. Smith, Jr., and M. E. Hultquist, *J. Am. Chem. Soc.*, **73**, 2864 (1951).

(16) M. D. Potter and T. Henshall, *J. Chem. Soc.*, 2000 (1956).

(17) F. H. S. Curd, E. Hoggarth, J. H. Landquist, and F. L. Rose, *ibid.*, 1766 (1948).

(18) R. J. Grout and M. W. Partridge, *ibid.*, 3540 (1960).

(19) C. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.*, **82**, 3971 (1960).

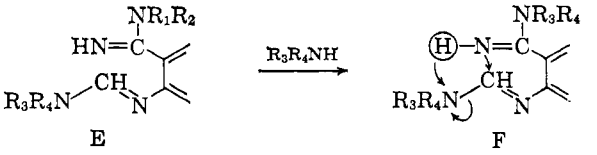
(20) W. V. Curran and R. B. Angier, *J. Org. Chem.*, **28**, 2672 (1963).

(21) N. J. Leonard and J. A. Deyrup, *J. Am. Chem. Soc.*, **84**, 2148 (1962).

(22) N. J. Leonard and D. Y. Curtin, *J. Org. Chem.*, **11**, 341 (1946); N. J. Leonard, W. V. Ruyle, and L. C. Bannister, *ibid.*, **13**, 617 (1948); N. J. Leonard and W. V. Ruyle, *ibid.*, **13**, 903 (1948).

4-quinazolones. Likewise, base-catalyzed rearrangements of certain purines,[23-27] pyrazolopyrimidines,[27,28] pteridines,[29,30] quinazolines,[18,31] and pyrimidines[9,32,33] in which an alkyl or aryl group appears to migrate from a ring-nitrogen atom to an exocyclic nitrogen or in which an amino group and another substituent appear to exchange positions have been explained[26-28,31,34] by sequences consisting of ring opening and recyclization. This course has been validated for a pyrimidine by the use of an N^{15}-label,[35] and a ring-opened intermediate has been isolated from a "normal" hydrolytic replacement of chlorine from the purine ring.[36]

The apparent relationship between amino-group exchange and ring opening may be questioned on the basis of the facts (1) that reactions of I with butylamine and ethylamine resulted in both displacement of an amino group and ring opening by the same reagent under the same conditions except for reaction time and (2) that one secondary amine (pyrrolidine) displaced another (morpholine).[37] The fact that the thiadiazoles (XIV–XV) were most easily isolated after reaction periods much longer than those that favored the formation of the corresponding 7-(substituted amino)-[1,2,5]thiadiazolo[3,4-*d*]pyrimidines (XII–XIII) indicated that the thiadiazoles must have been formed chiefly, if not entirely, from the 7-(substituted amino)-[1,2,5]thiadiazolo[3,4-*d*]pyrimidines and, consequently, that the *isolated* products of ring opening were formed *after* amino-group exchange had already occurred. Evidence in support of this conclusion was furnished by ultraviolet spectra of aliquots from reactions of I with butylamine. The observed long-wave-length absorption maximum shifted from the position of maximum absorption of I (340 mμ at pH 7) to approximately that of XII (357 mμ), and then it broadened and moved near that of the thiadiazole (XIV) at 320 mμ. Exchange of the 7-morpholino group for a 7-pyrrolidino group would be possible either by direct displacement at position 7 (Chart III) or by ring opening at position 5 (E from A) and subsequent reclosure (F), but not by ring opening at position 7. On the premise that ring opening as a prerequisite of amine exchange would proceed by fission of the N-6–C-7 bond,[38]



E F

the exchange of one secondary amine for another argues for direct displacement rather than ring opening and reclosure. In addition, the influence of basicity and steric factors on the exchange of amino groups of [1,2,5]thadiazolo[3,4-*d*]pyrimidines is reminiscent of aromatic nucleophilic substitution,[39] and acid catalysis[5,17,19] of other amino-group exchange reactions is also reminiscent of acid-catalyzed displacement of halogens from certain heterocycles.[40] In the absence of knowledge of the rate-controlling processes, it is not possible to exclude ring opening (E), amidine exchange, and reclosure (F) as the basis for exchange of amino groups, but it is suggested that amino-group exchange occurs by direct nucleophilic displacement (Chart III) and that ring opening is an independent process.

Experimental[41]

7-Anilino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (IV).—A solution of 200 mg. of 7-amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (I) in 10 ml. of redistilled aniline was heated at the reflux temperature for 1.5 hr., concentrated to about 3 ml., diluted with 1 *N* hydrochloric acid to approximately pH 2, and extracted continuously with benzene. Concentration of the benzene extract to dryness gave 84 mg. (28%) of crude IV (m.p. 168–169°). Recrystallization of this material from benzene–cyclohexane gave a 12% yield of pure IV, which was identical by melting point (179–180°), ultraviolet spectra, and paper chromatography with specimens prepared from other starting materials.[2]

7-Anilino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (IV) was also isolated in 12% yield from a reaction of 4,5,6-triaminopyrimidine and *N*-sulfinylaniline that was allowed to proceed for 50 hr. in refluxing pyridine. Yields of crude I as high as 95% are obtained by this method after a reaction period of 4–5 hr. at 110°. Trace amounts of IV detectable by paper chromatography may be present in crude specimens of I. (IV has been easily detected chromatographically by its bright yellow fluorescence in ultraviolet light in synthetic mixtures of IV and I containing 1% of IV.)

7-Morpholino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (V).—A reaction solution consisting of 500 mg. of I and 60 ml. of redistilled morpholine was heated, in an atmosphere of nitrogen and with the exclusion of moisture, for 24 hr. at the reflux temperature. Ultraviolet spectra of aliquots removed from the reaction mixture showed that the observed long-wave-length maximum at pH 7 had shifted from that of I (340 mμ) to 357 and to 363 mμ after 5 hr. and 6.5 hr., respectively, and to that of V (369–370 mμ) after 24 hr. The yellow solid remaining after the solvent had been evaporated under reduced pressure was washed well with water and dried *in vacuo* at 55°: wt. 600 mg. (82%), m.p. 154–155°. The yellow crystalline product (58% yield) obtained by recrystallizing the crude product from water melted at 155–156°; its infrared and ultraviolet absorption spectra were identical with those of a specimen[2] of V prepared from 4,5-diamino-6-morpholinopyrimidine.

(23) E. Fischer, *Ber.*, **31**, 542 (1898).
(24) G. B. Elion, *J. Org. Chem.*, **27**, 2478 (1962).
(25) P. Brookes and P. D. Lawley, *J. Chem. Soc.*, 539 (1960).
(26) H. G. Windmueller and N. O. Kaplan, *J. Biol. Chem.*, **236**, 2716 (1961).
(27) E. C. Taylor and P. K. Loeffler, *J. Am. Chem. Soc.*, **82**, 3147 (1960).
(28) C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **24**, 1570 (1959).
(29) W. V. Curran and R. B. Angier, *J. Am. Chem. Soc.*, **80**, 6095 (1958); R. B. Angier and W. V. Curran, *J. Org. Chem.*, **27**, 892 (1962); R. B. Angier, *ibid.*, **28**, 1509 (1963).
(30) W. Pfleiderer, E. Liedek, R. Lohrmann, and M. Rukwied, *Chem. Ber.*, **93**, 2015 (1960).
(31) E. C. Taylor and R. V. Ravindranathan, *J. Org. Chem.*, **27**, 2622 (1962).
(32) H. C. Carrington, F. H. S. Curd, and D. N. Richardson, *J. Chem. Soc.*, 1858 (1955).
(33) D. J. Brown, E. Hoerger, and S. F. Mason, *ibid.*, 4035 (1955); D. J. Brown and J. S. Harper, *ibid.*, 1298 (1961); D. J. Brown, *J. Appl. Chem.*, **9**, 203 (1959).
(34) E. C. Taylor and M. J. Thompson, *J. Org. Chem.*, **26**, 5224 (1961).
(35) D. J. Brown, *Nature*, **189**, 828 (1961); J. Goerdeler and W. Roth, *Chem. Ber.*, **96**, 534 (1963).
(36) E. Shaw, *J. Org. Chem.*, **27**, 883 (1962).
(37) Exchange of one secondary amine for another does not appear to have been reported previously.
(38) Mechanisms proposed for ring opening of variously substituted fused pyrimidine heterocycles at the position corresponding to 7 of V have been based on rupture of the C–N bond corresponding to the N-6–C-7 bond of V; see ref. 4, 5, 22, 23, 28, 31, 34, 36.
(39) J. F. Bunnett, *Quart. Rev.* (London), **12**, 1 (1958); J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951).
(40) For example: C. K. Banks, *J. Am. Chem. Soc.*, **66**, 1127 (1944); J. S. Morley and J. C. E. Simpson, *J. Chem. Soc.*, 1014 (1949); N. B. Chapman and C. W. Rees, *ibid.*, 1190 (1954); N. B. Chapman and D. Q. Russell-Hill, *ibid.*, 1563 (1956).
(41) Melting points, infrared and ultraviolet spectra, and paper chromatographic data were determined by methods outlined previously.[3a] Paper chromatography was performed by Miss Kathleen Hewson, Miss Mary Broadaway, and Mrs. Dottye Searcy. Microanalyses and spectral determinations were by Drs. W. J. Barrett, W. C. Coburn, Jr., and P. D. Sternglanz, and associates of the Analytical Section of this institute. Some of the elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

7-(Dimethylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (VI).—A solution of 500 mg. of I and 50 ml. of an anhydrous dimethylamine–pyridine solution, containing a large excess of dimethylamine, was heated in a 100-ml. stainless steel bomb at 125° for 24 hr. The reaction mixture was freed of volatile components under reduced pressure. Recrystallization of the residual yellow solid (588 mg.) from water gave 300 mg. (51%) of 7-(dimethylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine, identical according to its melting point (172–173°), paper chromatograms, and infrared and ultraviolet spectra with a specimen prepared[2] from 4,5-diamino-6-(dimethylamino)pyrimidine.

7-(Dibutylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (VIII) was isolated in 55% yield by recrystallizing (from 50% aqueous ethanol) the crude product obtained from a reaction of refluxing dibutylamine (redistilled) with I for 55 hr. The bathochromic shift of the long-wave-length maximum corresponding to the conversion of I to VIII was incomplete at 32 hr. and complete at 55 hr. Recrystallization of a specimen from 50% aqueous ethanol gave the analytical sample: m.p. 86–87°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 229 (12.9), 265 (4.7), 355 (17.0) in 0.1 *N* hydrochloric acid; 235 (15.7), 275 (3.9), 285 (sh), 374 (11.9) at pH 7; 235 (15.8), 276 (4.0), 285 (sh), 374 (12.0) in 0.1 *N* sodium hydroxide; 234 (16.2), 277 (4.5), 287 (3.2), 378 (11.7) in ethanol.

Anal. Calcd. for $C_{12}H_{19}N_5S$: C, 54.30; H, 7.22; N, 26.39; S, 12.08. Found: C, 54.23; H, 7.34; N, 26.43; S, 12.05.

7-Pyrrolidino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (VII).—A solution of 4.93 g. of I and 150 ml. of redistilled pyrrolidine was heated at the reflux temperature for 4.5 hr. The mixture, which contained yellow needles after it had been allowed to stand at room temperature overnight, was cooled in an ice bath and filtered. The precipitate was analytically pure after it had been washed with water and dried *in vacuo* at 50°: wt. 3.25 g. (49%), m.p. 179°. An additional portion (m.p. 178–179°) amounting to 1.75 g. (26%) was isolated by evaporating the solvent from the filtrate and slurrying the residue with water. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 227 (13.3), 265–270 (4.3, plateau), 347 (17.1) in 0.1 *N* hydrochloric acid; 234 (16.9), 275 (4.0), 285 (sh), 368 (12.6) at pH 7; 234 (17.1), 275 (4.1) 285 (sh), 368 (12.6) in 0.1 *N* sodium hydroxide.

Anal. Calcd. for $C_8H_9N_5S$: C, 46.35; H, 4.35; N, 33.78; S, 15.45. Found: C, 46.20; H, 4.36; N, 33.87; S, 15.55.

In order to compare displaceability of amino groups, I was treated with dry pyrrolidine by the exact procedure described below for the reaction of V with pyrrolidine. The observed long-wave-length maximum at pH 7 shifted from 340 (I) to 368 mμ (VII) within 1–1.5 hr. (Reaction was incomplete after 0.5 hr.) The product obtained after 1.5 hr. amounted to a 97% yield, m.p. 177–178°. Recrystallization from ethanol–water gave VII (72%), pure by melting point and ultraviolet data.

7-(Benzylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (IX).—A solution of 6.0 g. of I in 120 ml. of redistilled benzylamine was heated at 80–85° for 16 hr., cooled to room temperature, and added dropwise to 275 ml. of phosphate buffer (pH 7). The pale yellow crystalline solid that formed was separated by filtration, washed with water, and dried *in vacuo* at 60°: yield 8.37 g. (88%), m.p. 202–203°. A specimen was recrystallized from aqueous ethanol. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 219 (16.0), 264 (5.0), 342 (18.6) in 0.1 *N* hydrochloric acid; 222 (16.8), 272 (5.1), 280 (sh), 353 (12.3) at pH 7; 265–70 (sh), 280 (sh), 358 (9.8) in 0.1 *N* sodium hydroxide; 223 (16.8), 274 (5.4), 282 (sh), 360 (11.8) in ethanol.

Anal. Calcd. for $C_{11}H_9N_5S$: C, 54.29; H, 3.74; N, 28.78; S, 13.18. Found: C, 54.43; H, 3.95; N, 28.91; S, 13.25.

During a preliminary experiment at 80° for 78 hr., a decrease in the ultraviolet absorption at 355–360 and an increase at 320–330 mμ, suggestive of thiadiazole formation,[3a] was noted. A small amount of IX was isolated.

7-(Cyclohexylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (X).—A solution of 1.0 g. of I in 50 ml. of redistilled cyclohexylamine was heated at 90° for 30 hr. Half of the reaction solution was removed and concentrated *in vacuo* to an oil that solidified after several portions of water were added and evaporated. Recrystallization of the solid from aqueous ethanol gave yellow crystals: yield 35%, m.p. 164°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 222 (12.2), 263 (4.3), 270 (sh), 344 (16.9) in 0.1 *N* hydrochloric acid; 226 (13.7), 272 (4.6), 280 (sh), 359 (11.7) at pH 7; 272 (4.4), 280 (sh), 360 (11.1) in 0.1 *N* sodium hydroxide; 225 (13.8), 274 (4.8), 283 (4.0), 363 (11.0) in ethanol.

Anal. Calcd. for $C_{10}H_{13}N_5S$: C, 51.03; H, 5.57; N, 29.74; S, 13.63. Found: C, 50.73; H, 5.34; N, 29.66; S, 13.6.

Continued heating of the second half of the reaction mixture at 90–100° for several days caused the observed long-wave-length ultraviolet absorption maximum to approach that of certain 1,2,5-thiadiazoles.[3a]

Interaction of Butylamine and I.—From several reactions of refluxing butylamine with I for periods of 20–32 hr. both the 7-butylamino derivative (XII) and the thiadiazole XIV were obtained and were separated by subliming XIV from the mixture at 100° under reduced pressure (0.5 mm.). The residue was essentially pure XII and was obtained in 50–60% yields from the shorter reactions. At higher temperatures some of XII, as well as XIV, sublimed. In order to define more exactly the conditions favoring amino-group exchange and those favoring 1,2,5-thiadiazole formation, the following experiments were performed.

Interaction of 6.5 g. of I and 200 ml. of refluxing butylamine (freshly distilled, but not otherwise dried) was allowed to proceed for 120 hr., and the butylamine was evaporated *in vacuo*. A solution of the residual oil in 150 ml. of 50% aqueous ethanol yielded two crops of yellow solid (m.p. 52–55°) amounting to 4.7 g. and 1.96 g. Recrystallization of the first crop from 50% aqueous ethanol gave 3.15 g. of crystals, m.p. 58–59°. Sublimation of the second crop and recrystallization of the sublimate from 50% aqueous ethanol gave an additional 900 mg., m.p. 59–60°, total yield 49%. The analytical sample of **4-amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamidine (XIV)** was prepared by recrystallizing a crude specimen from 50% aqueous ethanol and subliming the resulting precipitate. The white sublimate melted at 60–61°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 215 (9.5), 320 (6.2) in 0.1 *N* hydrochloric acid; 215 (9.4), 320 (6.2) at pH 7; 317 (8.5) in 0.1 *N* sodium hydroxide; 260–280 (2.9 plateau), 325 (9.6) in ethanol.

Anal. Calcd. for $C_7H_{13}N_5S$: C, 42.19; H, 6.57; N, 35.16; S, 16.08. Found: C, 42.37; H, 6.50; N, 34.90; S, 16.24.

A pure hydrochloride of XIV was prepared by introducing hydrogen chloride into an ethanol solution of XIV, evaporating the ethanol, adding ether to the residual oil, chilling, and reprecipitating the resulting solid from ethanol with a large volume of ether. λ_{max} was 322 mμ (ϵ 6400) in ethanol.

Anal. Calcd. for $C_7H_{13}N_5S \cdot HCl$: C, 35.66; H, 5.99; S, 13.61; Cl, 15.04. Found: C, 35.68; H, 5.70; S, 13.7; Cl, 15.1.

Interaction, under a nitrogen atmosphere and with the exclusion of atmospheric moisture, of 500 mg. of I and 25 ml. of refluxing, dry butylamine (twice distilled from and stored over calcium hydride) was followed by determining the ultraviolet absorption of aliquot residues. The observed long-wave-length maximum at pH 7 shifted from that of I (340 mμ) to that of XII (357 mμ after 6–8 hr.), broadened and moved hypsochromically (338 mμ at 50 hr.), and gradually approached (325 mμ after 90 hr.) that of XIV. Ring opening appeared to be somewhat faster than in the 120-hr. reaction, which had also been followed spectroscopically. The isolated yield of XIV after 90 hr. was 43%. An identical experiment was discontinued after 7 hr. (Ultraviolet absorption reached a maximum at 357 mμ within 6 hr.) The residue remaining after the butylamine had been evaporated *in vacuo* was slurried with water and dried. The yellow crystalline solid, which amounted to 563 mg. (84%) and melted at 138–140°, was **7-(butylamino)[1,2,5]thiadiazolo[3,4-*d*]-pyrimidine (XII)** containing, according to paper chromatography, a trace amount of thiadiazole (XIV). Recrystallization of the solid from aqueous ethanol gave pure XII (66% yield): m.p. 142–143°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 222 (12.8), 264 (4.3), 270 (sh), 342 (16.5) in 0.1 *N* hydrochloric acid; 223 (13.7), 272 (4.9), 280 (sh), 357 (11.4) at pH 7; 272 (4.7), 280 (sh), 357 (10.7) in 0.1 *N* sodium hydroxide; 224 (13.7), 274 (5.1), 283 (4.3), 362 (10.9) in ethanol.

Anal. Calcd. for $C_8H_{11}N_5S$: C, 45.91; H, 5.29; N, 33.47; S, 15.32. Found: C, 45.98; H, 5.22; N, 33.47; S, 15.25.

Reduction of 7-(Butylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (XII).—To a stirred solution that was composed of 860 mg. of the 7-butylamino derivative (XII), 30 ml. of ethanol, 30 ml. of water, and 3 ml. of glacial acetic acid and that was maintained under a nitrogen atmosphere at 70° was added, during 1 hr., 3.13 g. of zinc dust. The reaction mixture was kept under these conditions for an additional 2 hr., filtered to remove unreacted zinc, and made basic to pH 9 with 6 *N* sodium hydroxide. The precipitated zinc hydroxide was removed by filtration, the solvents were evaporated *in vacuo* from the filtrate, and the residual solid was leached with three 25-ml. portions of hot ethyl acetate. A first crop of crude product (m.p. 138–139°) amount-

ing to 520 mg. (70%) crystallized from the combined and concentrated ethyl acetate extracts. Recrystallization of a portion of the crude product gave a 78% recovery of crystals identical by melting point (141–142°), infrared spectrum, and ultraviolet spectra with 4,5-diamino-6-(butylamino)pyrimidine (XVI) prepared from 4-amino-6-butylamino-5-nitropyrimidine.

7-(Butylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (XII) from 4,5-Diamino-6-(butylamino)pyrimidine.—A solution of 500 mg. of 4,5-diamino-6-(butylamino)pyrimidine (prepared from 4-amino-6-butylamino-5-nitropyrimidine), 1.15 g. of *N*-sulfinylaniline, and 50 ml. of anhydrous pyridine was heated at 90–95° for 3.5 hr. Pyridine was evaporated under reduced pressure; water (25 ml.) was added to the residue and its volume was reduced by one-half under reduced pressure; and yellow crystals were collected by filtration, washed with water, and dried *in vacuo* at 56°: yield 560 mg. (97%), m.p. 142°. Recrystallization from 2:1 water–ethanol gave material having a melting point (143°), ultraviolet and infrared spectra, and R_f values identical with those of XII obtained from I.

4-Amino-6-butylamino-5-nitropyrimidine.—A mixture of 3.0 g. of 4-amino-6-chloro-5-nitropyrimidine, 6 ml. of butylamine, and 312 ml. of ethyl acetate was stirred at room temperature overnight. A precipitate was separated by filtration, the filtrate was concentrated to dryness, and the residue was washed with ethyl acetate and combined with the first crop. Washing the combined portions of solid several times with water left 3.22 g. (89%) of yellow solid. A 50% aqueous ethanol solution yielded 2.82 g. (78%) of pale yellow crystals. Specimens of both the crude and recrystallized samples melted principally at 140°, but some crystals persisted to 170°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 241 (24.1), 294 (3.6), 342 (7.1) in 0.1 *N* hydrochloric acid; 342 (9.5) at pH 7; 344 (9.6) in 0.1 *N* sodium hydroxide; 340 (9.9) in ethanol.

Anal. Calcd. for $C_8H_{13}N_5O_2$: C, 45.49; H, 6.20; N, 33.16. Found: C, 45.53; H, 6.19; N, 33.09.

4,5-Diamino-6-(butylamino)pyrimidine (XVI).—4-Amino-6-(butylamino)-5-nitropyrimidine (2.57 g.) in 225 ml. of ethyl acetate was reduced with hydrogen and about 1 g. of Raney nickel catalyst. When the consumption of hydrogen ceased, additional catalyst was added to complete the hydrogenation. The ethyl acetate filtrate, after having been concentrated, deposited 1.53 g. (69%) of crystals, m.p. 139–140°. Recrystallization of 1 g. of this material from ethyl acetate gave 320 mg. of XVI: m.p. 143°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 222 (20.5), 283 (11.1) in 0.1 *N* hydrochloric acid; 218 (28.2), 279 (10.8) at pH 7; 279 (10.5) in 0.1 *N* sodium hydroxide; 218 (29.4), 283 (10.5) in ethanol.

Anal. Calcd. for $C_8H_{15}N_5$: C, 53.01; H, 8.34; N, 38.64. Found: C, 53.14; H, 8.18; N, 38.37.

Hydrolysis of 4-Amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamidine (XIV).—A mixture of 500 mg. of XIV and 65 ml. of 1 *N* sodium hydroxide was heated at the reflux temperature for 2.5 hr., cooled, acidified to pH 2, concentrated to approximately one-half the original volume, and refrigerated. The precipitate, which contained inorganic salts, was washed well with water and dried: 64% yield of white crystals, m.p. 220–221° (sublimation). The ultraviolet spectra, R_f values, and melting point of this material were identical with those of 4-amino-1,2,5-thiadiazole-3-carbo ylic acid (XVII) obtained by ring cleavage of [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one.[38]

Cyclization of 4-Amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamidine (XIV to XII).—A solution of 199 mg. of XIV, 10 ml. of triethyl orthoformate, and a small crystal of *p*-toluenesulfonic acid monohydrate was heated at the reflux temperature for 4 hr.; the reaction mixture was concentrated to dryness *in vacuo;* and the yellow crystalline residue was triturated with water. Pure 7-(butylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (XII), identical by melting point (142–143°) and by infrared and ultraviolet spectra with specimens prepared from I and from 4,5-diamino-6-(butylamino)pyrimidine (XVI), was obtained in 63% yield by recrystallizing the crude product (84% yield, m.p. 137–138°) from 50% aqueous ethanol.

7-(Ethylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (XIII).—Several experiments indicated that both 7-(ethylamino)[1,2,5]-thiadiazolo[3,4-*d*]pyrimidine (XIII) and 4-amino-*N*-ethyl-1,2,5-thiadiazole-3-carboxamidine (XV) were formed from I and ethylamine in proportions depending on the reaction time and the concentration of I. The following procedure favored the formation and isolation of XIII. A mixture consisting of 1.0 g. of I, 20 ml. of ethylamine, and 20 ml. of methanol was heated in a 100-ml. stainless steel bomb at 80° for 12.5 hr. Yellow crystals were filtered from the reaction mixture and washed with ethanol: wt. 450 mg. (38%), m.p. 202–203°. Purification of additional crops from the filtrate gave 385 mg. (32%) with the same melting point. Pale yellow needles of the 7-ethylamino derivative (XIII) crystallized from ethanol or from 75% ethanol: m.p. 202–203°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 220 (13.1), 263 (4.4), 270 (sh), 339 (16.1) in 0.1 *N* hydrochloric acid; 224 (13.5), 272 (4.9), 280 (sh), 355 (11.0) at pH 7; 224 (13.9), 274 (5.1), 283 (4.4), 360 (10.5) in ethanol.

Anal. Calcd. for $C_6H_7N_5S$: C, 39.75; H, 3.90; N, 38.64; S, 17.69. Found: C, 39.93; H, 3.82; N, 38.45; S, 17.6.

4-Amino-*N*-ethyl-1,2,5-thiadiazole-2-carboxamidine (XV).—The procedure used to prepare XIII was repeated except that the reaction time was 48 hr. The dark gum remaining after volatile components had been evaporated *in vacuo* was dissolved in 40% aqueous ethanol. The ethanol solution, after treatment with a small quantity of activated carbon, deposited 355 mg. (36%) of crystals with a melting point of 80–82°. A second crop (175 mg., m.p. 85–140°) was a mixture of XV and XIII according to paper chromatography. Recrystallization of the first crop from 40% ethanol gave white needles: m.p. 83°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 321 (6.0) in 0.1 *N* hydrochloric acid; 321 (6.1) in pH 7 buffer; 318 (8.1) in 0.1 *N* sodium hydroxide; 265 (2.5), 325 (9.1) in ethanol.

Anal. Calcd. for $C_5H_9N_5S$: C, 35.12; H, 5.30; N, 40.89; S, 18.72. Found: C, 35.49; H, 5.20; N, 40.85; S, 18.8.

4-Amino-1,2,5-thiadiazole-3-carboxylic Acid from I.—A solution of 500 mg. of I in 65 ml. of 0.2 *N* sodium hydroxide (4 equiv.) was stirred at room temperature for 18 days. Crude XVII, identified by its infrared spectrum, was obtained in 55% yield by the isolation procedure used in the hydrolysis of XIV. Recrystallization from water gave a 79% recovery: m.p. 220° (sublimation), neut. equiv. 148 (calcd. 145.2).

Displacement of Substituted Amino Groups. A. Morpholino by Pyrrolidine.—A solution (protected from atmospheric moisture with a tube of calcium sulfate) of 300 mg. of 7-morpholino-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine[42] (V) in 15 ml. of dry pyrrolidine (twice distilled from and stored over calcium hydride) was heated at the reflux temperature for 2.5 hr. Reaction was incomplete after 0.75 hr. and appeared, as judged by ultraviolet spectra of aliquots determined in 0.1 *N* hydrochloric acid, to be essentially complete within 1–2 hr. Concentration of the reaction mixture to dryness *in vacuo* left a yellow crystalline solid: m.p. 178°, yield 270 mg. (98%). (A small amount of product was lost in aliquots removed from the reaction mixture for ultraviolet examination.) Paper chromatography of this material showed that it was 7-pyrrolidino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (VII) containing a trace amount of the 7-morpholino derivative (V). Recrystallization of the crude product from aqueous ethanol gave an 82% recovery of crystals with melting point of 178° and infrared and ultraviolet spectra identical with those of the 7-pyrrolidino derivative (VII) prepared from I.

B. Butylamino by Pyrrolidine.—A solution of 344 mg. of 7-(butylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine[42] (XII) in 18 ml. of pyrrolidine (distilled from sodium hydroxide and dried with calcium hydride) was heated at the reflux temperature with the exclusion of atmospheric moisture. The observed long-wavelength ultraviolet absorption maximum at pH 7 displayed a slow bathochromic shift from that of the 7-butylamino derivative (357 mμ), but it did not reach the maximum of VII (368 mμ) within 13.5 hr. The reaction mixture was cooled, and a precipitate of VII, identified by melting point and ultraviolet spectra, was collected by filtration: yield 75 mg. (23%). Fractions, totaling 242 mg., from the filtrate were shown by paper chromatography to contain additional VII, unreacted 7-butylamino derivative (XII), and an unidentified compound.

C. Attempted Displacement of the Pyrrolidino Group by Morpholine.—The procedure described above for the conversion of the 7-morpholino derivative (V) to the 7-pyrrolidino derivative (VII) was employed in heating a solution of 400 mg. of VII in 20 ml. of dry morpholine at 85° for 72 hr. The infrared spectrum of the yellow solid (352 mg., 88% recovery, m.p. 178°) was identical with that of pure VII. The recovery of VII was not quantitative owing to losses in aliquots (an estimated 4.5%) removed during

(42) The specimens of V, VII, IX, and XII used as starting materials for exchange of substituted amino groups were prepared from I, but they contained no I detectable by paper chromatography. If any I had been present as a contaminant, it would have reacted with the attacking amine to form the corresponding 7-(substituted amino)[1,2,5]thiadiazolo[3,4-*d*]-pyrimidine.

the course of the attempted reaction and in water washings. The 7-pyrrolidino and 7-morpholino derivatives may be separated by paper chromatography in pH 6.7 acetate buffer and detected as blue fluorescent spots by ultraviolet light.[2,3a] A paper chromatogram of the recovered material and of pure specimens of V and VII for reference showed VII together with a very weak spot corresponding to V.[42]

D. Butylamino by Benzylamine.—Heating a solution of 400 mg. of the 7-butylamino derivative[42] (XII) in 10 ml. of redistilled benzylamine at 80–85° for 74 hr. and isolation and purification of the product, as described for IX from I, gave a 16% yield of material identical by infrared spectrum and melting point (202°) with the 7-benzylamino derivative (IX) obtained from I.

E. Benzylamino by Butylamine.—A solution of 500 mg. of the 7-benzylamino derivative[42] (IX) in 25 ml. of butylamine (distilled from and stored over calcium hydride) was heated for 6 hr. at the reflux temperature with the exclusion of atmospheric moisture. The residue obtained by evaporating the butylamine was heated in a sublimation apparatus at 125° (0.1 mm.). The principal (solid) fraction (175 mg.) was resublimed in the same way. A small, oily forerun was collected from both sublimations; paper chromatograms of the oily forerun from the second sublimation had a weak spot (in addition to a spot that was either IX or XII) corresponding to 4-amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamidine (XIV). The residue (260 mg.) from the first sublimation was shown by its melting point (200–202°) and infrared spectrum to be the starting material (IX). Recrystallization of the second sublimate from aqueous ethanol gave 43 mg. (10%) of 7-(butylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (XII), identical by melting point and infrared spectrum with specimens obtained from I, from XVI, and XIV.

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Thiadiazoles. IV. 4-Ureido- and 4-Amino-1,2,5-thiadiazole-3-carboxylic Acid Derivatives from [1,2,5]Thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-diones[1]

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4-Ureido-1,2,5-thiadiazole-3-carboxylic acid is formed from [1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (III) by the action of aqueous base, and *N*-methyl-4-(methylamino)-1,2,5-thiadiazole-3-carboxamide is similarly obtained from 4,6-dimethyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione. Either 4-ureido-, 4-(3-benzylureido)-, or 4-amino-*N*-benzyl-1,2,5-thiadiazole-3-carboxamide may be obtained by interaction of III and benzylamine. Similarly, these three types of thiadiazole derivatives were isolated, depending on reaction conditions, from reactions of III with other alkylamines or with hydrazine. The isolation of 4-ureido derivatives unsubstituted on the ureido group provides proof of one of two alternative courses for the formation of *o*-aminocarboxylic acid derivatives from fused pyrimidine heterocycles of type III. 4-Ureido-*N*-butyl-1,2,5-thiadiazole-3-carboxamide was shown to be easily hydrolyzed by base to 4-ureido-1,2,5-thiadiazole-3-carboxylic acid, and evidence that III is an intermediate in this facile hydrolysis is presented.

The formation of 1,2,5-thiadiazole derivatives by cleavage of the pyrimidine ring of [1,2,5]thiadiazolo-[3,4-*d*]pyrimidines bearing amino[2] or oxygen[3] functions at position 7 has been described previously. We have extended the investigation of this method for the preparation of 1,2,5-thiadiazoles by employing [1,2,5]thiadiazolo[3,4-*d*]pyrimidines having oxygen functions at both positions 5 and 7. The previously observed ease of nucleophilic attack on this thiadiazolopyrimidine ring system suggested that mild conditions might be employed to isolate intermediates that would provide proof for the course of ring opening of this type of disubstituted pyrimidine heterocycles.

Treatment of 4,6-dimethyl[1,2,5]thiadiazolo[3,4-*d*]-pyrimidine-5,7(4*H*,6*H*)-dione (I, 8-thiatheophylline) with 0.1 *N* potassium hydroxide solution gave *N*-methyl-4-(methylamino)-1,2,5-thiadiazole-3-carboxamide (II). This reaction is analogous to the cleavage of theophylline to *N*-methyl-5- (or 4-) (methylamino)-imidazole-4- (or 5-) carboxamide[4] and of 1,3-dimethylpteridine-2,4(1*H*,3*H*)-diones to *N*-methyl-3-(methylamino)pyrazinamides.[5] [1,2,5]Thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (III) was cleaved by boiling 1 *N* sodium hydroxide solution to a compound with the composition, after acidification, of 4-ureido-1,2,5-thiadiazole-3-carboxylic acid (IV). A second compound formed in small quantity from this reaction was subsequently identified as 4-amino-1,2,5-thiadiazole-3-carboxylic acid[3] (V). Reaction of III with concentrated aqueous ammonia in a sealed vessel at 100–110° afforded a better yield (91%) of the ureido acid (IV). Subsequently it was shown, as explained below, that III is cleaved by dilute aqueous base at room temperature. Pteridine-2,4(1*H*,3*H*)-diones have been cleaved by aqueous alkali at higher temperatures, usually 170° or above, to 3-aminopyrazinoic acids,[6] and *vic*-triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione has been cleaved to an amino amide, 5-amino-*vic*-triazole-4-carboxamide, under similar conditions by concentrated aqueous ammonia[7] and to the corresponding acid by refluxing aqueous alkali.[7a]

Alkaline degradation of certain purine-2,6(1*H*,3*H*)-diones with methyl groups on the ring-nitrogen atoms has been reported[8] to yield carbamic acid derivatives

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