Thiadiazoles. II. Formation of 4-Amino-1,2,5-thiadiazole-3-carboxylic Acid and Its Derivatives by Ring-Cleavage of [1,2,5]Thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one[1,2]

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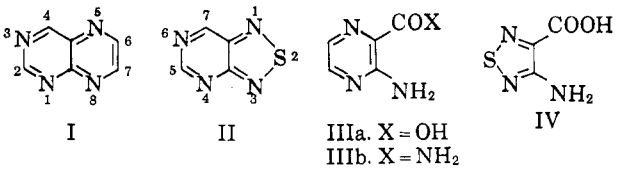
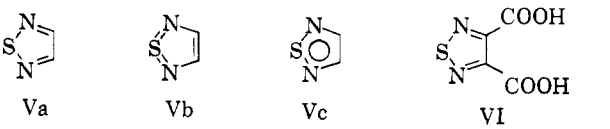
Basic reagents cleave the pyrimidine ring of [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one (VII) under mild conditions. The products of these reactions are derivatives of the recently described 1,2,5-thiadiazole ring. These reactions, which afford 4-amino-1,2,5-thiadiazole-3-carboxylic acid (IV) and its derivatives, comprise a new method for the synthesis of 1,2,5-thiadiazoles. The mode of ring-opening and the properties of the thiadiazoles are discussed.

The isoelectronic relationship between the pteridine ring (I) and the [1,2,5]thiadiazolo[3,4-*d*]pyrimidine ring (II) was shown to be manifested in similarities in a number of properties of derivatives of these two ring systems.[2] Under basic conditions, certain pteridines suffer cleavage of the pyrimidine ring, giving rise thereby to derivatives of 3-aminopyrazinoic acid (IIIa).[3,4] Confirmation[2] of the predicted resemblance of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines and pteridines indicated that 4-amino-1,2,5-thiadiazole-3-carboxylic acid (IV) and its derivatives would be formed by the action of basic reagents on [1,2,5]thiadiazolo[3,4-*d*]pyrimidines. Ring-opening reactions of 4-quinazolones[5] provided a further precedent for this projected transformation.

Until recent years, the 1,2,5-thiadiazole ring (Va–c) was known only in compounds, such as the 2,1,3-benzothiadiazoles, in which it is fused to another ring system.[6,7] The first monocyclic 1,2,5-thiadiazoles[8] were obtained by oxidation of 2,1,3-benzothiadiazoles.[9–11] A study by Khaletskiĭ, Pesin, and Chou[9] of the effect of oxidizing agents on 2,1,3-benzothiadiazoles led to the isolation of 1,2,5-thiadiazole-3,4-dicarboxylic acid (VI), its 1,1-dioxide, and the semicarbazone of 1,2,5-thiadiazole-3,4-dicarboxaldehyde. The oxidation of 2,1,3-benzothiadiazoles to 1,2,5-thiadiazole-3,4-dicarboxylic acid (VI), the conversion of this compound to various carboxylic acid derivatives, and the obtaining of 1,2,5-thiadiazole-3-carboxylic acid and its derivatives *via* decarboxylation of VI have been reported by Carmack, Weinstock, and Shew[7,10] and by Sekikawa.[11] In addition, the former investigators have prepared the parent compound 1,2,5-thiadiazole (V).





Reaction of [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one (VII) with ethanolic ammonia at 80° gave a compound with the composition of 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII). 4-Amino-1,2,5-thiadiazole-3-carboxylic acid (IV) was isolated after treatment of VII with aqueous potassium hydroxide, and the hydrazide (IX) of this acid was obtained in 95% yield by treating VII with hydrazine. The compounds represented by structures[12] IV, VIII, and IX are the products expected by analogy with ring-cleavage reactions of pteridines[4] and other fused-ring heterocycles.[5] Confirmation of the structure of the amino carboxamide (VIII) was obtained by reclosing the pyrimidine ring, to VII, with ethyl orthoformate containing a catalytic amount of *p*-toluenesulfonic acid. The amino acid (IV) was related structurally to the carboxamide VIII by alkaline hydrolysis of the latter compound to IV.

Two products were isolated from the reaction of VII with refluxing butylamine: one of these was 4-amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamide (X), isolated in 45% yield; the second product proved to be 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII), isolated in 37% yield. Similarly, anhydrous methylamine gave a

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

(3) For example: (a) J. Weijlard, M. Tishler, and A. E. Erickson, *J. Am. Chem. Soc.*, **67**, 802 (1945); (b) J. H. Mowat, J. H. Boothe, B. L. Hutchings, E. L. R. Stokstad, C. W. Waller, R. B. Angier, J. Semb, D. B. Cosulich, and Y. Subba Row, *ibid.*, **70**, 14 (1948); (c) E. C. Taylor, Jr., *ibid.*, **74**, 1651 (1952); (d) E. C. Taylor, Jr., *ibid.*, **74**, 2380 (1952); (e) E. C. Taylor, Jr., J. A. Carbon, and D. R. Hoff, *ibid.*, **75**, 1904 (1953); (f) E. C. Taylor, O. Vogl, and P. K. Loeffler, *ibid.*, **81**, 2479 (1959); (g) A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 4219 (1952); (h) A. Albert, *ibid.*, 2690 (1955); (i) A. Albert, D. J. Brown, and H. C. S. Wood, *ibid.*, 2066 (1956); (j) D. J. Brown and N. W. Jacobsen, *ibid.*, 1978 (1960); (k) W. V. Curran and R. B. Angier, *J. Org. Chem.*, **26**, 2364 (1961); (l) W. V. Curran and R. B. Angier, *ibid.*, **27**, 1366 (1962).

(4) E. C. Taylor, Jr., "Chemistry and Biology of Pteridines, Ciba Foundation Symposium," G. E. W. Wolstenholme and M. P. Cameron, Ed., Little, Brown and Co., Boston, Mass., 1954, pp. 2–34.

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

(6) L. L. Bambas, "The Chemistry of Heterocyclic Compounds," Vol. 4, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1952 pp. 205–211.

(7) W. R. Sherman, "Heterocyclic Compounds," Vol. 7, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, pp. 579–586.

(8) However, a fused-ring derivative in which the thiadiazole ring has aliphatic substituents, derived from the bornane skeleton, had been claimed earlier: D. C. Sen, *J. Indian Chem. Soc.*, **15**, 537 (1938). Other than this claim, only three 1,2,5-thiadiazoles[9] had been reported in the periodical literature prior to the initiation of our work.

(9) (a) A. M. Khaletskiĭ, V. G. Pesin, and T. Chou, *Dokl. Akad. Nauk SSSR*, **114**, 811 (1957); *Chem. Abstr.*, **52**, 4605i (1958); (b) V. G. Pesin, A. M. Khaletskiĭ, and T. Chou, *Zh. Obshch. Khim.*, **28**, 2089 (1958); see English translation, *J. Gen. Chem. USSR*, **28**, 2126 (1958), Consultants Bureau, Inc., New York, N. Y.

(10) (a) M. Carmack, L. M. Weinstock, and D. Shew, Abstracts of Papers, 136th National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1959, p. 37P; (b) M. Carmack, D. Shew, and L. M. Weinstock, U. S. Patent 2,980,687 (April 18, 1961); *Chem. Abstr.*, **55**, 21147h (1961); U. S. Patents 2,990,408 and 2,990,409 (June 27, 1961); *Chem. Abstr.*, **56**, 4775 (1962).

(11) I. Sekikawa, *Bull. Chem. Soc. Japan*, **33**, 1229 (1960).

(12) Although structures Vb and Vc may be more nearly in accord with evidence[13] that 1,2,5-thiadiazole is aromatic, structure Va is used for the sake of simplicity throughout this discussion.

(13) R. A. Bonham and F. A. Momany, *J. Am. Chem. Soc.*, **83**, 4475 (1961).

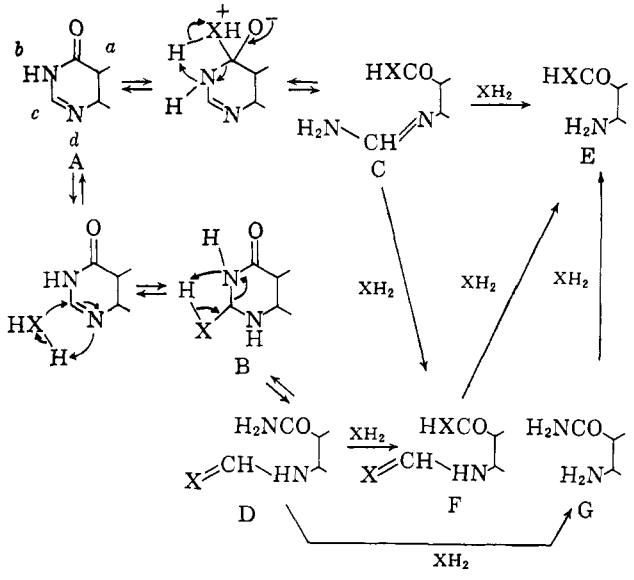
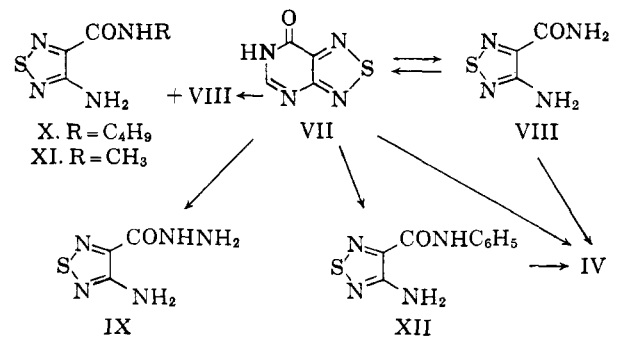


Fig. 1.—X = RN, O, HN, NH_2N. *a* = position 7 of VII or 4 of 4-pteridinones. *c* = position 5 of VII or 2 of 4-pteridinones.

crude product that was predominantly the *N*-methyl amide (XI), but paper chromatography revealed the presence of some 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII). The pure *N*-methyl amide was obtained in 41% yield, and a small amount of the unsubstituted amide (VIII) was also isolated.

Treatment of VII with aniline in the presence of a small quantity of hydrochloric acid gave 4-amino-1,2,5-thiadiazole-3-carboxanilide (XII). Under comparable conditions, ring-opening was not effected either by anhydrous aniline or by aniline containing a small amount of water. The carboxanilide has also been isolated when the preparation of VII from 5,6-diaminopyrimidin-4(3*H*)-one sulfate has been conducted on a large scale. Aniline, formed in the reaction from *N*-sulfinylaniline, must have reacted with VII through the intervention of protons, originating from the pyrimidine sulfate, and water added during the isolation. The formation of XII during the preparation of VII has not been observed when the pyrimidine free base was used as the starting material and the product isolated without adding water. In the reaction of VII with the weak base aniline, it seems likely that equilibria established between VII and ring-opened intermediates are overwhelmingly in favor of VII and that the addition of aqueous acid shifts the equilibria by hydrolyzing a ring-opened intermediate to XII. The carboxanilide was hydrolyzed by aqueous base to 4-amino-1,2,5-thiadiazole-3-carboxylic acid (IV).



Basic cleavage of the pyrimidine ring of quinazolines,[5] purines[14] (especially *N*-substituted purines), *v*-triazolo-[4,5-*d*]pyrimidines,[15] and other heterocyclic systems, besides the pteridines, is known; and rearrangement and amine-exchange reactions of such fused heterocycles and of pyrimidines have been explained by postulating opening and reclosure of the pyrimidine ring.[5,14,16] Ring-opening of VII is, however, more appropriately compared with ring-opening of its electronic analogs, the 4-pteridinones. The 1,2,5-thiadiazoles were formed from VII under milder conditions than those reported[3h,4] for the cleavage of 4-pteridinones not substituted on the ring-nitrogen atoms. For example, aqueous base cleaved VII within one-half hour at 100° and in less than three hours at 50°, whereas several hours of refluxing were required for the cleavage of 4-pteridinone.[3i] (*N*-substituted 4-pteridinones are more easily cleaved than are those without substituents on the ring-nitrogen atoms.[3d,3i])

The isolation of 4-amino-1,2,5-thiadiazole-3-carboxylic acid (IV) from the alkaline cleavage of VII under mild conditions suggests superficially that initial attack occurred at position 7. On the other hand, it is difficult to see how 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII) could be formed by initial attack of butylamine or methylamine at position 7. In Fig. 1 the transformations depicted with partial structures A–G, representing VII or 4-pteridinones and 1,2,5-thiadiazoles or pyrazines, show pathways by which the terminal products E and G (*e.g.*, IV and VIII–XII) may be formed by initial attack of the nucleophilic agent at either position 5 (*c* of A) or position 7 (*a* of A), the later stages (E, F, G) resulting from hydrolysis or amine-exchange reactions of formamidine and amide groups. Evidence for reaction at *c* or at both *a* and *c* is available from the pteridine series.[17]

Alkaline hydrolysis, mentioned previously, of 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII) to the carboxylic acid IV was conducted under the same conditions used to prepare IV from VII. This reaction not only related the amide and the acid structurally, but also demonstrated that the amide might have been an intermediate[19] in the formation of IV from VII. In order to determine whether 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII) might be a precursor of the *N*-alkyl amides (X and XI), an amide-exchange reaction was attempted by treating VIII with butylamine under the conditions used in the reaction of butylamine with VII.

(14) E. Shaw, *J. Org. Chem.*, **27**, 883 (1962), and references cited therein; G. B. Elion, *ibid.*, **27**, 2478 (1962); E. Fischer, *Ber.*, **31**, 3266 (1898).

(15) L. L. Bennett, Jr., and H. T. Baker, *J. Org. Chem.*, **22**, 707 (1957); J. S. Webb and A. S. Tomcufcik, U. S. Patent 2,714,110 (July 26, 1955).

(16) D. J. Brown, *Nature*, **189**, 828 (1961); E. C. Taylor and P. K. Loeffler, *J. Am. Chem. Soc.*, **82**, 3147 (1960).

(17) Although the formation of 3-aminopyrazinoic acids and *N*-substituted 3-aminopyrazinamides from 4-pteridinones also suggests reaction at *a*, this obvious interpretation was contradicted by Taylor's finding[4] that ring-opening of a 4-pteridinone by isopropylamine, which gave the *N*-isopropyl amide at 200°, gave the unsubstituted amide at a lower temperature (150°). The formation of both 3-amino-*N*-methylpyrazinamide and 3-aminopyrazinoic acid from 3-methyl-4(3*H*)-pteridinone under conditions that did not hydrolyze the amide to the acid was cited by Wood[18] as evidence for ring-opening at both *a* and *c*. More recently, Curran and Angier[3k] have obtained *N*-substituted 3-formamidopyrazinamides by basic cleavage of 3-substituted 4-pteridinones and, though they do not rule out two modes of fission, favor one mode, namely, reaction at *c*. *Cf.* E. C. Taylor, R. J. Knopf, J. A. Cogliano, J. W. Barton, and W. Pfleiderer, *J. Am. Chem. Soc.*, **82**, 6058 (1960); **83**, 2786 (1961).

(18) H. C. S. Wood, pp. 35–42 of reference cited in footnote 4; *cf.* ref. 3i.

(19) Both 3-aminopyrazinamide (IIIb) and 3-aminopyrazinoic acid (IIIa) have been obtained[3h] from an alkaline hydrolysis of 4-pteridinone.

TABLE I

PHYSICAL PROPERTIES OF 1,2,5-THIADIAZOLES

Compound	pH	Ultraviolet data[a] λ_{max} in mμ ($\epsilon \times 10^{-3}$)[b]	Infrared data[c] $\bar{\nu}$ in cm.$^{-1}$ 1700–1400-cm.$^{-1}$ region	Infrared data[c] $\bar{\nu}$ in cm.$^{-1}$ 900–650-cm.$^{-1}$ region	Paper chromatographic data[d] R_f values A	B	C	D	Color of fluorescence[e]
VIII	1	214 (10.9), 326 (6.2)	1700s, 1605s	865ms, 850ms	0.68	0.79	0.73	0.59	BL
	7	213 (11.0), 326 (6.2)	1510w, 1470s	800ms, 730w					BS
	13	326 (6.2)	1400ms	680s					
	1 *N* HCl	213 (10.6), 325 (6.1)							
	5.4 *N* HCl	216 (9.5), 263 (2.3), 326 (5.2)							
	6 *N* HCl[i]	263 (4.0), 323 (4.3)							
XI	1	326 (7.0)	1665s, 1605s	860ms, 810ms	.79	.86	.81	.70	BL
	7	325 (7.0)	1550s, 1500w	790w, 750w					BS
	13	326 (7.0)	1445ms 1400mw						
X	1	213 (11.4), 326 (7.4)	1655s, 1600s	855ms, 820ms	.90	.93	.89	.73	BL
	7	213 (11.4), 326 (7.4)	1535s, 1500w	795w, 750ms					BS
	13	326 (7.4)	1460sh., 1450ms 1420m, 1400w	705w, 650m					
IX	1	215 (11.1), 331 (7.0)	1665ms, 1600s	895m, 855ms	.84	...	...	.62	BL
	7	212 (11.0), 326 (7.4)	1555ms, 1500w	815m, 760m					BS
	13	325 (10.0)	1445m	670mw					
XII	1	232 (11.2), 280 (3.7), 336 (10.3)	1675s, 1605s 1540s, 1490mw	900mw, 855m 840m, 800m	.88	.93	.86	...	VL VS
	7	232 (11.3), 280 (3.8), 336 (10.2)	1450s, 1435sh 1400w	790mw, 755s 690m					
	13	230 (sh), 330 (10.0)							
IV	1	328 (6.3)	1690s, 1600s	850ms, 810ms	.13	.76	.47	.79	BL or VL[f]
	7	316 (6.7)	1515mw, 1465s	710s					VS
	13	316 (6.7)							
K salt of IV			1620s, 1510m 1445m	880w, 860m 825m, 810m 755m					
3-Aminopyrazinamide (IIIb)	1	241 (12.1), 352 (6.8)	1690s, 1610s	900m, 850m					
	7	246 (11.5), 350 (6.4)[g]	1555ms, 1520w	815ms, 770mw					
	13	245 (12.8), 350 (6.4)	1440ms	740m, 650m					
	1 *N* HCl[h]	241 (12.6), 352–353 (7.1)							
	6 *N* HCl[h]	242 (12.6), 354 (7.1)							

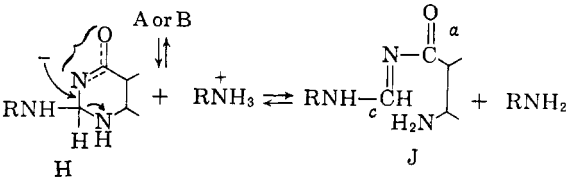
[a] Only VIII, IX, and X in neutral and acidic solutions were examined in the region 220–210 mμ. Spectra of 1 *N* and 6 *N* hydrochloric acid solutions were determined by dissolving specimens directly in these solvents, determining the spectra within 5 min., and redetermining the spectra 10 min. later as a test of stability. [b] A slight shoulder appears at 225–230 mμ in all of the thiadiazole spectra except those of IV at pH 7 and 13, that of VIII in 6 *N* HCl, and those of XII, in which a plateau or maximum is present at 230–232 mμ. [c] s = strong, m = medium, w = weak. [d] Solvent systems A, B, C, D are defined in ref. 26. [e] BL = Blue fluorescence in long wave length light (365 mμ), BS = blue fluorescence in short wave length light (254 mμ), VL and VS have the same meaning for violet fluorescence. [f] Violet in solvent D. [g] Data at pH 7 in agreement with data of Albert[3h] at pH 6. [h] In over-all shape, the differences among the three curves produced by the acidic solutions are much less than the difference between the spectra given by the neutral and the 0.1 *N* hydrochloric acid solutions. [i] Not determined in the region 220–210 mμ

The pure amide VIII was recovered in 90% yield. The reaction G → E (X = RN) is, therefore, not essential in the formation of the *N*-alkyl amides (X and XI).[20] Failure of the transamidation may be interpreted as evidence for separate and simultaneous attack at both *a* and *c*, but this evidence is not unequivocal for at least two reasons. First, the *N*-alkyl amides might be formed by the route B → D → F → E (X = RN), the transamidation occurring prior to the liberation of the amino group. The finding of Curran and Angier[3k] that 3-formamidopyrazinamides are more easily hydrolyzed than 3-aminopyrazinamides is consistent with this possibility and also provides a possible explanation for the results of Wood.[17] Secondly, attack at *c* could lead to fission of the *c*–*d* bond and generate an intermediate from which both VIII and the *N*-alkyl amides might be formed.[21]

(20) This conversion may have occurred to some extent during the reaction of methylamine with VII since the latter reaction was allowed to proceed for a longer period of time than the reaction with butylamine.

Some of the physical properties of the 1,2,5-thiadiazoles are summarized in Table I. The ultraviolet spectra of 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII) at pH 1, 7, and 13 are identical. The *N*-methyl (XI) and *N*-butyl (X) amides likewise give identical spectra at these three pH values, and the spectra of all

(21) In basic solution, A should be present partly or entirely, depending on the basic strength of the medium, as the anion. Species H may be formed from the anion of A or by ionization of B (Fig. 1). The acylformamidine (J) should react at the carbonyl carbon atom (*a*), this course



giving the *N*-alkylamides (X and XI). The amide VIII may be formed simultaneously by attack at the formamidine carbon atom (*c*) or by the amidine-exchange reaction D → G (Fig. 1), if initial attack at *c* of A were to give both D and J.

three amides, as well as that of the acid hydrazide (IX) at pH 7, are essentially the same except for slight differences in intensity. The spectrum of 4-amino-1,2,5-thiadiazole-3-carboxamide in 1 *N* hydrochloric acid is also unchanged. All of these spectra display an absorption maximum at 326 mμ. When the spectra of the amide (VIII), the *N*-butyl amide (X), and the acid hydrazide (IX) at pH 1 and 7 were examined between 220 and 210 mμ, a maximum was found near 214 mμ.

The constancy of the spectra of VIII, X, and XI within a broad range of pH values suggests that the neutral molecules are present in the acidic solutions and that these amino carboxamides, therefore, are very weak bases. This evidence is supported by the failure of VIII to form an isolable hydrochloride with anhydrous hydrogen chloride in ethanol. However, the presence of both the cation and the neutral molecule of VIII in strong hydrochloric acid (5.4–6*N*) is indicated by decreased intensity of the ultraviolet maxima at 326 mμ and 214 mμ and by the appearance of a maximum at 263 mμ. In comparison, 3-aminopyrazinamide (IIIb), the pyrazine analog[22] of VIII, must be present chiefly as the cation in 0.1 *N* hydrochloric acid since its spectrum in this solution differs slightly, but palpably, from the spectra given by neutral and alkaline solutions and undergoes little additional change as the acidity is increased to 1 *N* and 6 *N* hydrochloric acid. By utilizing generalizations[24] for protonation of π-deficient heterocycles, these data may be interpreted further. The slight change in the spectrum of 3-aminopyrazinamide (IIIb) in acidic solution suggests protonation on a ring-nitrogen atom,[25] whereas the large change represented by the appearance of a maximum at 263 mμ in the spectrum of 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII) in strong acid suggests protonation on the amino-nitrogen atom. The spectra of VIII and the pyrazine derivative (IIIb) are otherwise similar in appearance, but the maxima of the thiadiazole derivative (VIII) are displaced hypsochromically by approximately 25 and 32 mμ, respectively, from the long and short wave length maxima of the pyrazine analog in neutral solution. The absorption maximum (316 mμ) of the amino acid (IV) at pH 7 shows a similar hypsochromic shift with respect to that reported[3h] (340 mμ) for 3-aminopyrazinoic acid at pH 6.

The infrared spectra of all of the 1,2,5-thiadiazoles have bands of medium or medium-strong intensity at 860–850 cm.$^{-1}$ and 820–800 cm.$^{-1}$, as does 3-aminopyrazinamide; a strong band, presumably due to NH_2-deformation vibrations, at 1610–1600 cm.$^{-1}$; the expected bands in the 3-μ and 6-μ regions corresponding to N—H and C=O stretching vibrations; and, except for IV and VIII, a band at 1555–1535 cm.$^{-1}$ in the region of secondary amide II bands.

Experimental[26]

4-Amino-1,2,5-thiadiazole-3-carboxamide (VIII).—A mixture of 308 mg. of [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one (VII), 15 ml. of absolute ethanol, and 15 ml. of liquid ammonia was heated in a 50-ml. stainless steel bomb at 80° for 18 hr. (On a larger scale the proportion of starting material was increased almost fourfold.) The reaction solution was removed from the chilled bomb and concentrated *in vacuo* at room temperature to approximately 5 ml. The crystalline precipitate (m.p. 164–166°) amounted to 197 mg. after it had been washed with ethanol (2 ml.) and dried *in vacuo* at 56°; a second crop (m.p. 168–169°), which was obtained by evaporating the solvent *in vacuo* from the filtrate and recrystallizing the residue from ethanol–hexane, raised the yield of crude product to 82%. Recrystallization from ethanol–hexane (1:1) or sublimation (*e.g.*, at 0.15–0.2 mm. and 100–105°) gave pure VIII; yields, 61–66%; m.p. 170–171°.

Anal. Calcd. for $C_3H_4N_4OS$: C, 24.99; H, 2.80; N, 38.87; S, 22.24. Found: C, 25.27; H, 2.67; N, 39.03; S, 22.35.

No precipitate was formed when a large excess of dry hydrogen chloride was passed into an ethanol solution of VIII. The free base was recovered (97%) by concentrating the solution *in vacuo*.

4-Amino-1,2,5-thiadiazole-3-carboxylic Acid (IV). a. From VII.—A solution of 462 mg. (3.0 mmoles) of [1,2,5]thiadiazolo-[3,4-*d*]pyrimidin-7(6*H*)-one (VII) in 10 ml. of 1.2 *N* aqueous potassium hydroxide was heated at the reflux temperature for 30 min., filtered, and acidified to pH 1.6 with 6 *N* hydrochloric acid. The crystalline precipitate that formed at pH 3–1.6 melted at 220° and depressed the melting point of the starting material; yield, 282 mg. (65%). The product was recrystallized from water; m.p. 220–221° (with sublimation); recovery, 80%.

Anal. Calcd. for $C_3H_3N_3O_2S$: C, 24.83; H, 2.09; N, 28.95; S, 22.09. Found: C, 24.86; H, 2.07; N, 29.01; S, 22.05.

b. From 4-Amino-1,2,5-thiadiazole-3-carboxamide.—A mixture of 288 mg. (2 mmoles) of 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII), 10 ml. of 2 *N* aqueous potassium hydroxide, and 10 ml. of ethanol was heated at the reflux temperature for 30 min. Acidification of the reaction mixture to pH 1.2 with 6 *N* hydrochloric acid and concentration of the acidified mixture afforded 210 mg. (72%) of a white crystalline solid (m.p., 220–222° subl.) that produced infrared and ultraviolet absorption spectra identical with those of 4-amino-1,2,5-thiadiazole-3-carboxylic acid obtained from VII.

c. From 4-Amino-1,2,5-thiadiazole-3-carboxanilide (XII).—A solution of 42.5 g. of XII, 1 l. of absolute ethanol, and 400 ml. of 4 *N* aqueous potassium hydroxide was heated at the reflux temperature for 2.5 hr. The potassium salt separated from the cold reaction mixture in 94% yield (33.19 g.), and a portion was recrystallized from water–ethanol; m.p. 338–340° dec. (Al block).

Anal. Calcd. for $C_3H_2N_3OSK$: C, 19.67; H, 1.10; N, 22.93; S, 17.50. Found: C, 19.73; H, 1.38; N, 23.09; S, 17.3.

The remainder of the potassium salt (31.4 g.) was dissolved in 500 ml. of warm water, and the solution was filtered and acidified with 6 *N* hydrochloric acid. The white crystalline product, consisting of a first crop of 20.36 g. (82%) and a second crop of 1.8 g. (7%), was identified by melting point (221°) and by infrared and ultraviolet spectra as 4-amino-1,2,5-thiadiazole-3-carboxylic acid.

4-Amino-1,2,5-thiadiazole-3-carboxylic Acid Hydrazide (IX).—A solution of 462 mg. of VII in 27 ml. of anhydrous hydrazine was heated at 95–100° for 105 min. and then evaporated to dryness *in vacuo*. The residue was triturated with 5 ml. of ethanol and with 10 ml. of hexane and dried *in vacuo* over phosphorus pentoxide; yield, 452 mg. (95%); m.p. 202–204° dec. (oil bath). Recrystallization from water gave yellow needles that melted at 206°.

(22) The isoelectronic relationship of the 1,2,5-thiadiazole ring and the pyrazine ring has been noted by Carmack[10a] and by Koutecky.[23]

(23) R. Zahradník and J. Koutecký, *Collection Czech. Chem. Commun.*, **26**, 156 (1961).

(24) A. Albert, "Heterocyclic Chemistry," The Athlone Press, University of London, 1959, pp. 49, 302.

(25) *Cf.* G. W. H. Cheeseman, *J. Chem. Soc.*, 242 (1960), for protonation of 2-aminopyrazines.

(26) Unless otherwise noted, melting points were determined with a Kofler Heizbank melting point apparatus and are corrected. Infrared spectra were determined with samples in pressed potassium bromide disks and with a Perkin-Elmer Model 221G spectrophotometer with the sodium chloride prism–grating interchange. Ultraviolet spectra were determined with a Cary Model 14 recording spectrophotometer. Solutions for ultraviolet determinations were prepared by dissolving the sample in water or ethanol and diluting 5-ml. aliquot portions to 50 ml. with 0.1 *N* hydrochloric acid, pH 7 phosphate buffer, and 0.1 *N* sodium hydroxide. Spectra given by these solutions of a compound are considered to be its spectra at pH 1, 7, and 13. Paper chromatography was performed by the descending technique on Whatman no. 1 paper in the following solvent systems: (A) butanol saturated with water, (B) butanol–acetic acid–water (5:2:3 by volume), (C) 2-propanol–water–concentrated aqueous ammonia (70:25:5 by volume), and (D) acetate buffer (pH 6.7). Spots were detected with two ultraviolet lamps that emit light principally at 365 and 254 mμ.

Anal. Calcd. for $C_3H_5N_5OS$: C, 22.63; H, 3.17; N, 44.00; S, 20.13. Found: C, 22.75; H, 3.27; N, 43.73; S, 20.31.

Reaction of [1,2,5]Thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one with Butylamine.—A solution of 2.31 g. of VII (m.p. 234° dec., 98% pure by ultraviolet absorption) and 35 ml. of dry, redistilled butylamine was heated at the reflux temperature for 3 hr. and then concentrated *in vacuo* to a sirup. The residue was slurried with a mixture of ethanol (3 ml.) and hexane (10 ml.). A white crystalline solid that formed in the slurry was separated by filtration and washed with 6 ml. of hexane. This fraction was chromatographically homogeneous and was shown by melting point (169–170°, not depressed by VIII), infrared spectrum, and paper chromatographic characteristics to be **4-amino-1,2,5-thiadiazole-3-carboxamide (VIII)**; yield, 800 mg. (37%).

The filtrate combined with the washings deposited 1.34 g. (45%) of chromatographically homogeneous **4-amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamide (X)** (m.p., 79–80°). An analytical sample was obtained as white needles by recrystallization from hexane; m.p. 82–84°.

Anal. Calcd. for $C_7H_{12}N_4OS$: C, 41.98; H, 6.04; N, 27.98; S, 16.01. Found: C, 42.21; H, 5.77; N, 27.79; S, 15.83.

4-Amino-N-methyl-1,2,5-thiadiazole-3-carboxamide (XI).—The conditions for the reaction of VII with anhydrous methylamine were identical with those employed in the preparation of VIII. Evaporation of the volatile components from the reaction mixture and sublimation of the residue at 90° and 0.2 mm. gave a white sublimate, in 70% yield calculated as XI, that melted at 122–124°. Paper chromatography showed the presence of two components: the preponderant component was identical with pure XI obtained subsequently; the minor, more slowly moving spot had the same R_f values in four solvent systems as 4-amino-1,2,5-thiadiazole-3-carboxamide (VIII). Recrystallization of the sublimate from water gave white needles; m.p. 136–137°; yield from VII, 41%.

Anal. Calcd. for $C_4H_6N_4OS$: C, 30.37; H, 3.82; N, 35.42; S, 20.27. Found: C, 30.39; H, 3.78; N, 35.58; S, 20.20.

4-Amino-1,2,5-thiadiazole-3-carboxamide (VIII) was isolated in 10% yield from a larger reaction by extracting XI from the total reaction residue with hexane in a Soxhlet extractor.

4-Amino-1,2,5-thiadiazole-3-carboxanilide (XII).—A mixture consisting of 308 mg. (2 mmoles) of VII, 10 ml. of aniline, and 0.2 ml. of 12 *N* hydrochloric acid was heated at 100° for 4.5 hr. The ultraviolet spectrum at pH 1 of an aliquot removed after 3 hr. of heating showed that ring-opening was essentially complete. Concentration of the reaction mixture *in vacuo* left an orange oil that solidified when 20% ethanol was added. The crystalline product (m.p. 137–140°) was filtered from the cold mixture, washed with 10% ethanol, and dried *in vacuo* at 78°; yield, 274 mg. (62%). Beige crystals obtained by recrystallization from 60% ethanol melted at 141°.

Anal. Calcd. for $C_9H_8N_4OS$: C, 49.08; H, 3.66; N, 25.44; S, 14.56. Found: C, 48.91; H, 3.72; N, 25.13; S, 14.7.

An experiment identical with the one described before except for the omission of hydrochloric acid was performed simultaneously. Ultraviolet spectra at pH 1 of aliquots removed after 3 hr. and 5.5 hr. of heating were essentially identical with the spectrum of the starting material (VII). Additional heating up to 70 hr. caused slow deterioration of the reaction mixture, although ultraviolet absorption characteristic of VII was still observable after 22 hr. No evidence for the formation of XII could be gleaned from the ultraviolet examination of the reaction mixture.

A third experiment that was identical with the first except for the addition of 0.2 ml. of water instead of hydrochloric acid showed that the starting material was practically unaffected up to 25 hr. after heating was begun. Continued heating caused the long wave length maximum to shift toward longer wave lengths, but after several days it was still about 15 mμ from that of XII.

The carboxanilide (XII) was also isolated from certain reactions carried out to prepare VII on a large scale (see subsequent description).

Cyclization of 4-Amino-1,2,5-thiadiazole-3-carboxamide (VIII) to [1,2,5]Thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one (VII).—A mixture of 288 mg. of 4-amino-1,2,5-thiadiazole-3-carboxamide, 20 ml. of triethyl orthoformate, and a crystal of *p*-toluenesulfonic acid monohydrate was heated at the reflux temperature for 3 days. Ten milliliters of triethyl orthoformate was added to the heterogeneous mixture, and heating was continued for 4 days. A small amount of suspended white solid (19 mg.; m.p. 230–250° dec.) was removed by filtration, and the filtrate was evaporated to dryness. The yellow crystalline residue was triturated with 1:1 hexane–ethanol, separated by filtration, and dried *in vacuo* at 65° for 2 hr.; wt., 160 mg. (52% yield); m.p. 229–232° dec. (oil bath) (lit.[2] m.p. 234°). Ultraviolet spectra at pH 1, 7, and 13 and the infrared spectrum were identical with those of [1,2,5]-thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one.

Attempted Transamidation of 4-Amino-1,2,5-thiadiazole-3-carboxamide.—A mixture of 288 mg. of VIII and 10 ml. of dry, redistilled butylamine was heated at the reflux temperature for 3 hr. and then concentrated *in vacuo* to dryness. The crystalline residue was slurried with a mixture of ethanol (3 ml.) and hexane (10 ml.) and was then collected by filtration; wt., 258 mg. (90% recovery); m.p. 172°. The infrared spectrum and paper chromatograms of this material showed that it was pure VIII. A small fraction (13 mg., m.p. 162–166°) obtained from the filtrate was shown by paper chromatography to be VIII contaminated with small amounts of impurities, one of which may have been the *N*-butyl amide (X).

[1,2,5]Thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one (VII).—Although VII was prepared[2] on a small scale from *N*-sulfinylaniline and either 5,6-diaminopyrimidin-4(3*H*)-one free base or its sulfate, large-scale reactions utilizing the sulfate afforded large amounts of 4-amino-1,2,5-thiadiazole-3-carboxanilide (XII) as well as VII. The isolation procedure included the evaporation of pyridine from the reaction mixture followed by the addition and re-evaporation of water to aid in the removal of traces of pyridine and aniline (formed in the reaction from *N*-sulfinylaniline). Under the catalytic influence of protons originating from the pyrimidine sulfate, aniline may have reacted with VII during the prolonged evaporation of pyridine from the large reaction mixtures, or water added during the isolation may have participated in the ring-opening of VII. The following steps carried out in accordance with the general procedure[2] for the preparation of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines constitute an improved procedure for preparing VII from the pyrimidine free base.

A mixture of 30 ml. of *N*-sulfinylaniline, 300 ml. of anhydrous pyridine, and 11.0 g. of 5,6-diaminopyrimidin-4(3*H*)-one free base (obtained by dissolving 17.5 g. of the sulfate in 900 ml. of boiling water, neutralizing the hot solution with 6 *N* ammonia, and recrystallizing the cream colored crystals from water) was heated at the reflux temperature for 1.75 hr., cooled, stirred with activated carbon, concentrated *in vacuo* to about 150 ml., and chilled (−12°). The white crystalline precipitate was washed with benzene; wt., 9.56 g. (71%); m.p. 234° dec. A second portion of 1.48 g. (11%) was obtained by recrystallizing, from water, second and third crops (total crude yield, 93%) obtained by diluting the filtrate from crop 1 with water and benzene. Both crop 1 and the second portion had ultraviolet maxima and extinction coefficients essentially identical with those of the analytical sample.[2]

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