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.

Acknowledgment.—The authors express their appreciation to Dr. J. A. Montgomery for encouragement in this work and to Mr. W. E. Fitzgibbon and associates of the Organic Preparations Section for preparing large quantities of some of the required intermediates.

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]

Y. FULMER SHEALY AND JOE D. CLAYTON

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama

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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

(1) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. PH-43-64-51, and by the C. F. Kettering Foundation.

(2) Y. F. Shealy and C. A. O'Dell, *J. Org. Chem.*, **29**, 2135 (1964).

(3) Y. F. Shealy and J. D. Clayton, *ibid.*, **28**, 1491 (1963).

(4) H. Auterhoff and M. F. Hebler, *Arzneimittel-Forsch.*, **9**, 621 (1959).

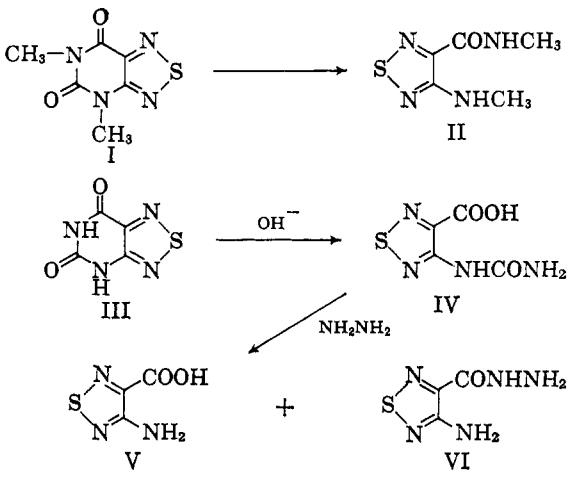
(5) (a) A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 2066 (1956); (b) G. P. G. Dick, H. C. S. Wood, and W. R. Logan, *ibid.*, 2131 (1956); (c) E. C. Taylor, Jr., C. K. Cain, and H. M. Loux, *J. Am. Chem. Soc.*, **76**, 1874 (1954); (d) E. C. Taylor, Jr., H. M. Loux, E. A. Falco, and G. H. Hitchings, *ibid.*, **77**, 2243 (1955); (e) R. B. Angier and W. V. Curran, *J. Org. Chem.*, **27**, 892, 1366 (1962).

(6) J. Weijlard, M. Tishler, and A. E. Erickson, *J. Am. Chem. Soc.*, **67**, 802 (1945); R. C. Ellingson, R. L. Henry, and F. G. McDonald, *ibid.*, **67**, 1711 (1945); *cf.* Ref. 5c and d.

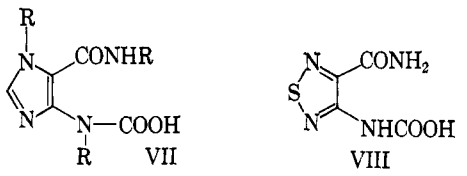
(7) (a) J. S. Webb and A. S. Tomcufcik, U. S. Patent 2,714,110. (July 26, 1955); (b) L. L. Bennett, Jr., and H. T. Baker, *J. Org. Chem.*, **22**, 707 (1957).

(8) R. Maly and R. Andreasch, *Monatsh. Chem.*, **4**, 369 (1883); E. Fischer and O. Bromberg, *Ber.*, **30**, 219 (1897); H. Biltz and H. Rakett, *ibid.*, **61**, 1409 (1928); A. Einhorn and E. Baumeister, *ibid.*, **31**, 1138 (1898).

(VII) sufficiently stable to be isolated; warming these imidazoles in water caused decarboxylation to the amino carboxamides. The carbamic acid VIII, which would have the same composition as the ureido acid (IV), is analogous to the imidazole derivatives



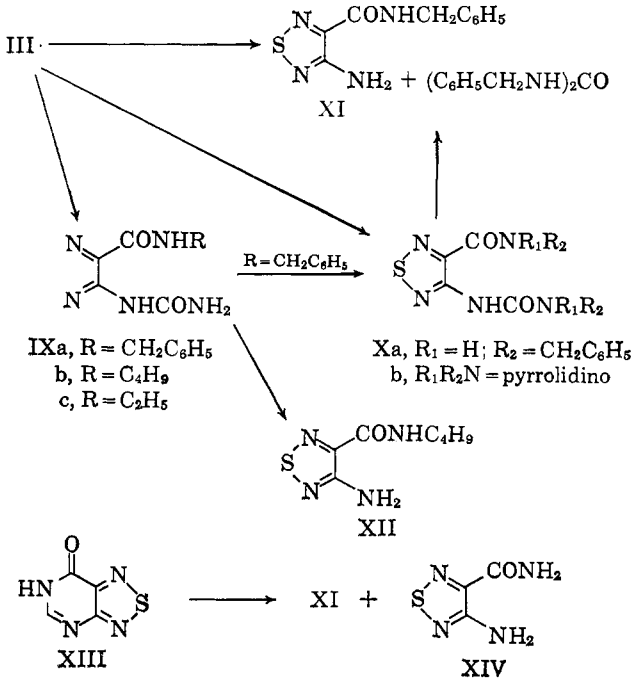
(VII). When the thiadiazole obtained from the alkaline cleavage of III was heated in boiling water for 2 hr., 86% of the compound was recovered. This result supports the ureido acid structure (IV) rather than the carbamic acid structure (VIII). In addition, treatment of the ureido acid with hydrazine afforded 4-



amino-1,2,5-thiadiazole-3-carboxylic acid (V), which must have been formed by cleavage of the ureido group, and 4-amino-1,2,5-thiadiazole-3-carboxylic acid hydrazide (VI), which could have arisen by reaction of hydrazine at both the ureido and the carboxyl carbon atoms.

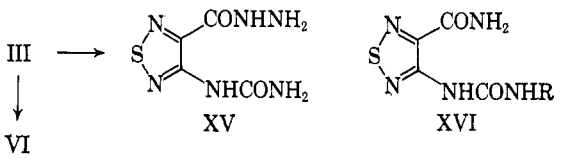
Three thiadiazoles were isolated, depending on reaction conditions, from reactions of III with benzylamine. Treatment of III with refluxing benzylamine for 6.5 hr. resulted in the formation of 4-amino-*N*-benzyl-1,2,5-thiadiazole-3-carboxamide (XI); the by-product, *N*,*N*′-dibenzylurea, was also isolated in high yield. *N*-Benzyl-4-(3-benzylureido)-1,2,5-thiadiazole-3-carboxamide (Xa) was isolated following interaction of III and refluxing benzylamine for 1 hr., and, finally, *N*-benzyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXa) was obtained by treating III with benzylamine at 75–80°. The reaction conditions that produced the 4-benzylureido derivative (Xa) from III also gave this compound from the 4-ureido derivative (IXa), and the 4-benzylureido derivative, in turn, yielded the 4-amino derivative (XI) under the conditions that effected the formation of XI from III.

4-Amino-*N*-benzyl-1,2,5-thiadiazole-3-carboxamide (XI) was identical with a specimen obtained by treating [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one (XIII) with benzylamine. 4-Amino-1,2,5-thiadiazole-3-carboxamide (XIV) was isolated as a second product of the interaction of XIII and benzylamine; this reaction,



therefore, parallels reactions[3] of XIII with butylamine and with methylamine, both of which gave XIV plus the appropriate *N*-alkyl amide.

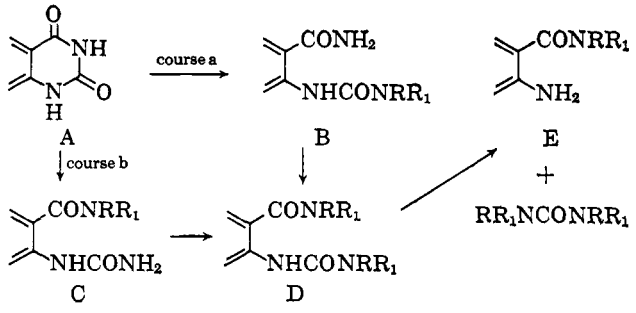
Other amino compounds gave results similar to those obtained with benzylamine. Reactions of III with boiling butylamine and with ethylamine at 50–60° afforded, respectively, *N*-butyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXb) in 79% yield and *N*-ethyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXc) in 89% yield. Further treatment of the *N*-butyl derivative with butylamine under more strenuous conditions gave 4-amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamide[3] (XII). Xb was isolated from a reaction of III with pyrrolidine; no attempt was made to obtain derivatives analogous to IX or XI. Either 4-ureido-1,2,5-thiadiazole-3-carboxylic acid hydrazide (XV) or 4-amino-1,2,5-thiadiazole-3-carboxylic acid hydrazide (VI) could be obtained from reactions of III with hydrazine. The ureido derivative was formed at 50–60°; the amino derivative was isolated by employing a higher temperature.



The ureido thiadiazoles obtained as initial products of ring opening of III were assigned structures IXa–c and XV, rather than the isomeric structures represented by XVI, by analogy to the structure of the ureido acid (IV). The formation of Xa and XII from the initially formed ureido thiadiazoles does not confirm structure IX because Xa might be formed by reaction of benzylamine at the amide group of XVI (R = $CH_2C_6H_5$) and XII might result from attack by butylamine at both the amide and the ureido groups of XVI (R = C_4H_9). Confirmation of the assigned structures (IX and XV) was obtained by preparing a representative of XVI. 4-(3-Ethylureido)-1,2,5-

thiadiazole-3-carboxamide (XVI, R = C_2H_5), prepared from the amino amide XIV and refluxing ethyl isocyanate, was shown to be different from the product (IXc) obtained from III and ethylamine.

The action of amines on pteridine-2,4(1*H*,3*H*)-diones gave either 3-aminopyrazinamides (pyrazine corresponding to E) or 3-(3-substituted ureido)pyrazinamides (pyrazine corresponding to D), and further treatment of the 3-substituted ureido derivatives with the appropriate amine gave the amino derivatives.[9] Taylor[9a] proposed two pathways, designated as courses a and b, between pteridine-2,4(1*H*,2*H*)-diones and 3-aminopyrazinamides and cited evidence in support of course b, although intermediates of type C were not isolated and could not be prepared.[10] The isolation of 4-ureido-1,2,5-thiadiazole-3-carboxylic acid (IV) and its derivatives (IXa–c and XV) represents the isolation of intermediates of type C; the sequence III → IXa → Xa → XI, found in the reactions of III with benzylamine, exemplifies course b.



It was observed that *N*-butyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXb) is unstable in dilute aqueous base. The product isolated, in 90% yield, from a solution of IXb in 0.1 *N* sodium hydroxide at room temperature was 4-ureido-1,2,5-thiadiazole-3-carboxylic acid (IV), but closer examination of this facile conversion revealed that it is not a simple hydrolysis of an *N*-alkylamide to a carboxylic acid. Changes in the ultraviolet absorption of a 0.1 *N* sodium hydroxide solution of IXb indicated that it cyclized to III with the elimination of butylamine and that IV then formed from III. (See the Experimental for details.) A re-examination of the reaction of III with aqueous base under similar conditions showed, as mentioned above, that IV is formed in high yield at room temperature. Finally, additional evidence for this course was obtained by quenching the reaction by acidifying a 0.1 *N* sodium hydroxide solution of IXb and lyophilizing. Paper chromatograms of the crude product obtained after 0.5 hr. showed spots with R_f values, in four solvent systems, corresponding to III and IXb. Quenching after 70 min. gave a mixture in which III, IXb, and a small amount of IV were detected chromatographically. From this mixture a specimen of III was isolated and identified by its infrared spectrum.

(9) (a) E. C. Taylor, Jr., *J. Am. Chem. Soc.*, **74**, 1651 (1952); (b) E. C. Taylor, Jr., J. A. Carbon, and D. R. Hoff, *ibid.*, **75**, 1904 (1953); (c) G. P. G. Dick, D. Livingston, and H. C. S. Wood, *J. Chem. Soc.*, 3730 (1958).

(10) Under the conditions used to obtain certain pyrazines of types D and E from pteridinediones (A), a 3-aminopyrazinamide[9a] (E, R = R_1 = H) and an *N*-methyl-3-(methylamino)pyrazinamide[9c] failed to undergo amine exchange at the amide group. These failures have been cited[9a,c] as evidence to exclude course a, but this type of evidence is not unequivocal. Amine exchange at the amide group of an *o*-aminocarboxamide (E) may require more drastic conditions, because of the electron-donating *o*-amino group, than the exchange represented by B → D.

Experimental

Melting temperatures, infrared and ultraviolet spectra, and paper chromatographic data were determined by methods outlined previously.[3] Principal infrared absorption bands are listed only in the 1700–1400- and 900–650-cm.$^{-1}$ regions. In contrast to the usual blue or violet fluorescence of spots of 4-amino-1,2,5-thiadiazole-3-carboxylic acid derivatives[3] and of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines,[11] all of the ureido carboxamides (IX, X, and XVI) appeared on paper chromatograms as yellow or orange fluorescent spots under 254-mμ light, the ureido acid (IV) as bluish yellow spots, and the ureido acid hydrazide (XV) as a dull reddish orange fluorescence. These ureido derivatives were not detectable with 365-mμ light. XV was apparently degraded partly to blue fluorescent materials in the 2-propanol–ammonia and the acetate buffer (pH 6.7) solvent systems.

***N*-Methyl-4-(methylamino)-1,2,5-thiadiazole-3-carboxamide (II).**—A mixture of 396 mg. of 4,6-dimethyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (I) and 40 ml. of 0.1 *N* potassium hydroxide solution was heated in a boiling water bath for 3 hr. Chilling the reaction mixture at 5° overnight produced a crop of 145 mg. of white needles: m.p. 96° (with sublimation). A second crop of 58 mg. (m.p. 95°) of product (total yield 59%) was obtained by concentrating the filtrate. The compound may be purified by recrystallization from water or by sublimation: m.p. 96° (with sublimation). λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 219 (11.9), 345 (5.9) in 0.1 *N* hydrochloric acid and at pH 7; 344 (5.9) in 0.1 *N* sodium hydroxide. ν in cm.$^{-1}$ was 1670 s, 1570 ms, 1550 s, 1480 m, 1415 ms; 895 m, 855 m, 810 ms, 795 mw, 750 w.

Anal. Calcd. for $C_5H_8N_4OS$: C, 34.87; H, 4.68; N, 32.54; S, 18.62. Found: C, 35.12; H, 4.83; N, 32.49; S, 18.66.

4-Ureido-1,2,5-thiadiazole-3-carboxylic Acid (IV).—In initial experiments on the cleavage of [1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione[11] (III) with aqueous base, reaction temperatures near 100° were applied. From a reaction of III with 1 *N* sodium hydroxide in a boiling water bath for 2 hr., a 41% yield of IV was obtained. A second crop of solid (18% yield) from this reaction was shown by its infrared and ultraviolet spectra to be principally 4-amino-1,2,5-thiadiazole-3-carboxylic acid[3] (V). Heating III and 15 *N* aqueous ammonia in a bomb at 100–110° for 5 hr. yielded 91% of the calculated amount of IV. After evidence was obtained, as described below, that the mild alkaline hydrolysis of *N*-butyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXb) proceeds by way of III, the following experiment was performed.

A solution of 340 mg. (2 mmoles) of III in 125 ml. of 0.1 *N* sodium hydroxide was stirred at 23–24° for 8.5 hr. and then acidified with 7 ml. of 2 *N* hydrochloric acid. The precipitated solid was collected by filtration, washed twice with water, and dried *in vacuo* at 78° over phosphorus pentoxide: yield 327 mg. (87%), m.p. 234–235° dec. A sample for analysis was recrystallized from a 1:1 mixture of dimethylformamide and water. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 220 (sh), 231 (12.3), 302 (7.2) in 0.1 *N* hydrochloric acid; 224 (13.6), 297 (8.2) at pH 7 and in 0.1 *N* sodium hydroxide. ν in cm.$^{-1}$ was 1680 s, 1640 s, 1560 s, 1530 sh, 1505 s, 1450 m, 1400 ms; 860 m, 815 m, 800 mw, 760 mw, 730 ms, 700 w, 675 w.

Anal. Calcd. for $C_4H_4N_4O_3S$: C, 25.52; H, 2.14; N, 29.78; S, 17.04. Found: C, 25.74; H, 2.21; N, 29.59; S, 16.75.

A solution of the ureido acid (IV) in water was boiled under reflux for 2 hr. in order to determine whether decarboxylation would occur. The ureido acid was recovered in 86% yield and identified by its infrared and ultraviolet spectra.

Cleavage of the Ureido Group of IV with Hydrazine.—A solution of 565 mg. of 4-ureido-1,2,5-thiadiazole-3-carboxylic acid (IV) and 10 ml. of hydrazine was heated at the reflux temperature for 5.25 hr. Water (10 ml.) was added to the solid remaining after the hydrazine had been evaporated *in vacuo*. The insoluble portion was separated by filtration, washed with water, and dried at 78° *in vacuo*: wt. 190 mg. (40% yield). The ultraviolet and infrared spectra and the melting point of this material were the same as those of **4-amino-1,2,5-thiadiazole-3-carboxylic acid**

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

hydrazide (VI) obtained from III (below) and from [1,2,5-thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one.[3]

The aqueous filtrate was acidified to pH 1 and evaporated to a solid residue. A 10-ml. water solution of this residue, after filtration and chilling, deposited 134 mg. (31%) of crystals that were identified by their infrared and ultraviolet spectra and by paper chromatography as 4-amino-1,2,5-thiadiazole-3-carboxylic acid[3] (V).

***N*-Benzyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXa).**—A solution consisting of 5.10 g. of [1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7-(4*H*,6*H*)-dione and 200 ml. of benzylamine (distilled from and dried over calcium hydride) was heated at 75–80° for 4 hr. The starting material and the apparatus were thoroughly dried before being used, and the reaction mixture was protected from atmospheric moisture with a tube of calcium sulfate. The solid remaining after the benzylamine had been evaporated *in vacuo* was slurried with ethanol (100 ml.), removed by filtration, washed with ethanol, and dried *in vacuo:* wt. 7.92 g. Although the melting point (177–179°) indicated that this material was essentially pure, paper chromatograms showed the presence of some of the starting material. Paper chromatograms of the residual oil from the filtrate showed that it contained III, IXa, and Xa. The crude solid was recrystallized twice from ethanol, an ethanol-insoluble fraction being removed each time. The yield of purified IXa was 4.35 g. (52%). A sample for analysis was recrystallized from benzene: m.p. 179°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 233 (16.0), 305 (8.7) in 0.1 *N* hydrochloric acid; 233 (16.7), 304 (8.8) at pH 7. $\bar{\nu}$ in cm.$^{-1}$ was 1700 s, 1640 s, 1575 ms, 1540 ms, 1520 m, 1490 m, 1450 w, 1435 m, 1400 ms; 840 m, 815 m, 795 w, 755 ms, 725 m, 700 ms, 650 w.

Anal. Calcd. for $C_{11}H_{11}N_5O_2S$: C, 47.64; H, 4.00; N, 25.26; S, 11.56. Found: C, 47.88; H, 4.09; N, 25.17; S, 11.7.

***N*-Benzyl-4-(3-benzylureido)-1,2,5-thiadiazole-3-carboxamide (Xa).** **A. From III.**—The procedure used in the preparation of IXa was duplicated with 510 mg. of III except that the reaction time was 1 hr. and the reaction temperature was that of the refluxing solution. The sirup remaining from the evaporation of the solvent was slurried with toluene, and a crop of 656 mg. of crystals was filtered from the chilled mixture and washed with hexane. Trituration of the syrupy residue from the filtrate with ethanol yielded a second crop of 115 mg. of crystals. Two recrystallizations of the combined crops from ethanol gave 340 mg. (31%): m.p. 147–148°. A yield of 51% of analytically pure Xa was obtained, after several recrystallizations, from a larger scale preparation in which no special precautions, other than the use of freshly distilled benzylamine, were taken to exclude moisture. Specimens of Xa recrystallized from ethanol–hexane mixtures were observed to melt at 143–144°; the molten material resolidified and remelted at 147–148° when seeded with the higher melting crystals. Solid-state infrared spectra of the two crystal forms were similar although they displayed some differences. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 232 (20.2), 311 (8.4) in ethanol. $\bar{\nu}$ in cm.$^{-1}$ (higher melting form) was 1680 s, 1660 sh, 1640 vs, 1590 w, 1560 s, 1515 s, 1500 w, 1455 m, 1440 w, 1410 m; 890 w, 850 w, 825 m, 800 w, 765 w, 740 m, 720 m, 700 ms, 670 w.

Anal. Calcd. for $C_{18}H_{17}N_5O_2S$: C, 58.83; H, 4.67; N, 19.06; S, 8.73. Found: C, 58.92; H, 4.49; N, 19.36; S, 8.74.

B. From IXa.—Treatment of 555 mg. of *N*-benzyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXa) with benzylamine by the same procedure gave, after purification, 160 mg. (22%) of Xa. The infrared spectrum and melting point behavior (143–144° and 147–148°) were the same as those of specimens obtained from III.

4-Amino-*N*-benzyl-1,2,5-thiadiazole-3-carboxamide (XI). A. From III.—A solution consisting of 1.02 g. of the 5,7(4*H*,6*H*)-dione (III) and 20 ml. of benzylamine (redistilled and dried over calcium hydride) was heated at the reflux temperature for 6.5 hr. The reactants and apparatus were thoroughly dried prior to being used, and the reaction mixture was protected from atmospheric moisture with a tube of calcium sulfate. The reaction solution was diluted with 20 ml. of toluene, chilled in an ice bath, and filtered to remove 1.23 g. of white crystals: m.p. 167–172°. A second crop of 152 mg. (m.p. 165–170°) was obtained by further chilling the combined filtrate and toluene washings (5 ml.). The two crops of crystals were crude *N,N'*-dibenzylurea (total yield 95%). A sample that gave satisfactory analytical data for carbon, hydrogen, and nitrogen and that melted at 171.5–172° was obtained by recrystallizing a specimen of crude material from 50% aqueous ethanol.

The filtrate, combined with the solvent washings, from the second crop of dibenzylurea was evaporated *in vacuo* to a sirup. Crude XI (959 mg., m.p. 76–81°) crystallized in two crops from a solution of the syrup in 2 ml. of toluene and 8 ml. of cyclohexane and was recrystallized from an isopentyl acetate–cyclohexane (1:3) solution. A crop of 409 mg. of crystals (m.p. 79–81°) was obtained, and recrystallization of the filtrate residue from an ethyl acetate–cyclohexane solution furnished an additional 180 mg. (m.p. 80–82°). The crystals from a second isopentyl acetate–cyclohexane recrystallization of the combined crops were dissolved in ethyl acetate and cyclohexane, a small crop of amorphous solid was filtered from the cooled solution, and the residue from this filtrate was recrystallized from ethyl acetate–cyclohexane (1:10). The white crystals melted at 80–81°. (Difficulties were experienced in raising the melting point of crude XI to this value regardless of the starting material used.) λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 225 (slight shoulder), 326 (7.2) in 0.1 *N* hydrochloric acid, pH 7 phosphate buffer, and 0.1 *N* sodium hydroxide solution. $\bar{\nu}$ in cm.$^{-1}$ was 1660 s, 1600 s, 1530 s, 1450 m, 1420 mw; 860 m, 810 m, 800 w, 755 m, 730 m, 720 m, 695 m, 670 w.

Anal. Calcd. for $C_{10}H_{10}N_4OS$: C, 51.25; H, 4.30; N, 23.92; S, 13.69. Found: C, 51.60; H, 4.37; N, 23.51; S, 13.7.

B. From Xa.—The procedure used in the conversion of III to XI was applied to a solution of 735 mg. of *N*-benzyl-4-(3-benzylureido)-1,2,5-thiadiazole-3-carboxamide (Xa) in 15 ml. of dry benzylamine. The benzylamine was evaporated *in vacuo* until crystallization began, toluene was added, and the white crystalline *N,N'*-dibenzylurea (85% yield) was removed by filtration. The yellow oil obtained by evaporating the filtrate was dissolved in hot toluene, the solution was diluted with cyclohexane and seeded with XI, and crystals (278 mg., m.p. 75–80°) were filtered from the chilled mixture and recrystallized from cyclohexane: m.p. 79°. The infrared and ultraviolet spectra were identical with those of the analytical sample of XI prepared from III.

The Reaction of [1,2,5]Thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one (XIII) with Benzylamine.—A solution of 925 mg. of XIII and 15 ml. of redistilled benzylamine (dried with calcium hydride) was heated at 80° for 3.5 hr. and then concentrated *in vacuo* to a syrup. Trituration of the syrup with 8 ml. of xylene caused the crystallization of 214 mg. (25%) of crude **4-amino-1,2,5-thiadiazole-3-carboxamide (XIV)**: m.p. 165–168°. Recrystallization from ethanol–hexane (1:1) gave crystals with melting point (170°) and infrared spectrum identical with specimens obtained previously.[3]

The xylene filtrate and washings from the crude XIV were concentrated to a syrup. Dissolution of this material in a mixture of 2 ml. of toluene, 2 ml. of ethyl acetate, and 8 ml. of cyclohexane and seeding of the solution with the product obtained from III gave 512 mg. (36%) of crude **4-amino-*N*-benzyl-1,2,5-thiadiazole-3-carboxamide** (m.p. 70–75°). Recrystallization of this material from ethyl acetate–cyclohexane solution and from a large volume of hexane gave white crystals (m.p. 77–79°) having an infrared spectrum identical with that of the pure specimen of XI obtained from III.

***N*-Butyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXb).**—A mixture of 1.02 g. of III and 40 ml. of redistilled *n*-butylamine was heated at the reflux temperature for 200 min. The reaction mixture became homogeneous during the heating period. Evaporation of the butylamine left a crystalline solid that was recrystallized from aqueous ethanol: yield 1.15 g. (79%), m.p. 151°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 217 (sh), 232 (14.9), 304 (8.3) in 0.1 *N* hydrochloric acid and at pH 7. $\bar{\nu}$ in cm.$^{-1}$ was 1695 s, 1650 s, 1605 ms, 1550 s, 1520 sh, 1500 m, 1460 w, 1400 ms; 860 m, 830 m, 790 m, 740 w, 710 w, 650 w.

Anal. Calcd. for $C_8H_{12}N_5O_2S$: C, 39.49; H, 5.38; N, 28.78; S, 13.18. Found: C, 39.56; H, 5.39; N, 28.79; S, 13.39.

4-Amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamide (XII) from IXb.—A solution of 500 mg. of *N*-butyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXb) and 50 ml. of redistilled butylamine was heated in a stainless steel bomb at 200° for 14 hr. Concentration of the reaction mixture gave a yellow oil that crystallized when it was chilled. The crystalline residue, which was probably a mixture of XII and the urea by-product, was slurried with 15 ml. of water, collected by filtration, and dried *in vacuo* at 56°: wt. 660 mg., m.p. 63–77°. Two recrystallizations from hexane gave 226 mg. (55%) of crystals identical by melting point (82–83°, oil bath), mixture melting point, and infrared and ultraviolet spectra with 4-amino-*N*-butyl-1,2,5-thiadiazole-3-carbox-

amide[3] obtained from [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one.

***N*-Ethyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXc).**—A suspension of 510 mg. of III in 40 ml. of anhydrous 1-butanol and 30 ml. of commercial, anhydrous, liquid ethylamine was heated at 50–60° for 37.5 hr. The mixture was homogeneous after about 28 hr. A condenser supplied with solid carbon dioxide was used to contain the ethylamine in the reaction mixture. The reaction mixture, which deposited white needles upon cooling to room temperature, was reduced in volume to 15 ml. *in vacuo* and stored at 5°. The crystals were collected by filtration, washed with 10 ml. of 9:1 hexane–ethanol, and dried *in vacuo* at 56°: wt. 578 mg. (89%), m.p. 192–194°. Two recrystallizations from ethanol gave 367 mg. (57%), m.p. 196°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 218 (sh), 232 (14.6), 304 (8.1) in 0.1 *N* hydrochloric acid and at pH 7. $\bar{\nu}$ in cm.$^{-1}$ was 1690 ms, 1640 s, 1610 s, 1545 ms, 1510 ms, 1440 m, 1400 ms; 890 w, 860 m, 820 m, 800 w, 775 mw, 740 mw, 730 mw, 695 w, 670 w.

Anal. Calcd. for $C_6H_9N_5O_2S$: C, 33.48; H, 4.22; N, 32.54; S, 14.90. Found: C, 33.48; H, 4.39; N, 32.62; S, 14.8.

***N*-(4-Pyrrolidinocarbonyl-1,2,5-thiadiazolyl)-1-pyrrolidinecarboxamide (Xb)** was isolated from a reaction of III with pyrrolidine at 75–80° for 10 days and was obtained pure in 18% yield by recrystallization from cyclohexane: m.p. 150–151°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 242 (14.4), 298 (6.9) in 0.1 *N* hydrochloric acid and at pH 7. $\bar{\nu}$ in cm.$^{-1}$ was 1690 s, 1620 ms, 1540 s, 1490 w, 1455 ms; 885 w, 850 w, 820 m, 790 m, 750 w, 730 w, 715 m, 680 w.

Anal. Calcd. for $C_{12}H_{17}N_5O_2S$: C, 48.79; H, 5.80; N, 23.71; S, 10.85. Found: C, 48.83; H, 5.80; N, 23.72; S, 10.5.

4-Ureido-1,2,5-thiadiazole-3-carboxylic Acid Hydrazide (XV).—A solution of 5.1 g. of the 5,7(4*H*,6*H*)-dione (III) in 150 ml. of hydrazine was heated at 50° for 20 hr. Evaporation of the hydrazine *in vacuo* at 30–35° left a solid that was triturated with ethanol and then recrystallized from acetic acid. The fine white crystals were collected in two crops totaling 3.11 g. (51%), m.p. 245° dec. A specimen for analysis was recrystallized from water: m.p. 246–247° dec. (The decomposition temperature was variable; the readings reported here were made by sprinkling a specimen along the surface of a Kofler Heizbank melting point apparatus.). λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 235 (14.7), 306 (7.9) in 0.1 *N* hydrochloric acid; 232 (13.5), 305 (7.9) at pH 7; 235 (slight shoulder), 315 (7.6) in 0.1 *N* sodium hydroxide. $\bar{\nu}$ in cm.$^{-1}$ was 1720 s, 1680 ms, 1630 s, 1600 ms, 1510 s, 1490 m; 870 ms, 830 m, 800 m, 775 m, 720 w, 690 m.

Anal. Calcd. for $C_4H_6N_6O_2S$: C, 23.76; H, 2.99; N, 41.57; S, 15.86. Found: C, 23.74; H, 2.92; N, 41.39; S, 15.95.

4-Amino-1,2,5-thiadiazole-3-carboxylic Acid Hydrazide (VI).—A solution of 5.10 g. of the 5,7(4*H*,6*H*)-dione and 30 ml. of hydrazine was heated at 90° for 3 hr. and then diluted with 50 ml. of warm water. A crystalline solid was removed by filtration, washed with water, and dried *in vacuo* at 56°: wt. 4.31 g., m.p. 202–212°. Sublimation of the crude product at 0.3 mm. (130–150°) gave 2.61 g. (55%) of white sublimate: m.p. 204–206°. The infrared and ultraviolet spectra were identical with those of VI obtained from [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7-(6*H*)-one.[3]

4-(3-Ethylureido)-1,2,5-thiadiazole-3-carboxamide (XVI, R = C_2H_5).—A suspension of 288 mg. of 4-amino-1,2,5-thiadiazole-3-carboxamide[3] (XIV) in 15 ml. of ethyl isocyanate was heated, with stirring, for 66.5 hr. at the reflux temperature and then filtered, and the solid residue was washed with toluene. Recrystallization of the solid (340 mg.) from ethyl acetate gave 244 mg. (57%) of white needles; the melting point (192°) was unchanged after a second recrystallization. λ_{max} in mμ ($\epsilon \times 10^{-3}$) was 221 (sh), 234 (16.6), 307 (7.4) in 0.1 *N* hydrochloric acid and at pH 7; unstable in 0.1 *N* sodium hydroxide. $\bar{\nu}$ in cm.$^{-1}$ was 1690 m, 1660 vs, 1560 ms, 1515 s, 1450 m; 845 m, 820 m, 810 sh, 780 w, 755 mw, 705 m, 655 w.

Anal. Calcd. for $C_6H_9N_5O_2S$: C, 33.48; H, 4.22; N, 32.54; S, 14.90. Found: C, 33.53; H, 4.34; N, 32.62; S, 15.1.

The melting point of a mixture of this compound with the product (IXc), of the same composition, obtained from III was depressed (160–164°), and the infrared spectra of the two compounds differed.

Basic Hydrolysis of *N*-Butyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (IXb).—An attempt to determine the ultraviolet spectrum of IXb in 0.1 *N* sodium hydroxide solution revealed that it was unstable in base. A solution of 243 mg. (1 mmole) of *N*-butyl-4-ureido-1,2,5-thiadiazole-3-carboxamide in 5 ml. of ethanol and 25 ml. of 0.12 *N* aqueous sodium hydroxide (3 mmoles) was then stirred at room temperature for 22 hr. The solution was acidified to pH 1 with 1 *N* hydrochloric acid and concentrated *in vacuo* to a volume of 10 ml. The white crystalline precipitate was collected by filtration, washed with 5 ml. of water, and dried *in vacuo* at 56° over phosphorus pentoxide: yield 169 mg. (90%), m.p. 231–233° dec. Ultraviolet spectra at pH 1, 7, and 13, R_f values in four solvent systems, and the infrared spectrum were identical with those of the ureido acid (IV) obtained from the 5,7(4*H*,6*H*)-dione (III).

Further examination of the behavior of IXb in base indicated that the facile formation of IV was not a simple hydrolysis of an amide to an acid. The spectrum of a freshly prepared solution of IXb (4.4×10^{-5} *M*) in 0.1 *N* sodium hydroxide showed absorption maxima at 253 and at 337 and a minimum at 287 mμ. In 0.1 *N* sodium hydroxide the spectrum of the ureido acid (IV) has maxima at 224 and at 297 and a minimum at 253 mμ; and the spectrum of the 5,7(4*H*,6*H*)-dione (III) has maxima at 226, 283, and 356 and minima at 257 and 308 mμ. Observation of the spectral changes occurring at room temperature in a 0.1 *N* sodium hydroxide solution of IXb showed that, as the maximum at 253 mμ decreased in intensity, a shoulder near 240 mμ shifted toward and then appeared as a maximum at 225 mμ. This latter maximum might have been due to either III or IV, but subsequent intensity changes, correlated with changes in the 290–360-mμ region, suggested that initially it was due chiefly to the 5,7(4*H*,6*H*)-dione (III). Simultaneously, the long-wave-length maximum at 337 shifted to a maximum at 355 mμ, ascribable to the 5,7(4*H*,6*H*)-dione, and a new maximum began to appear at 295–300 mμ. After approximately 0.75 hr., maxima or shoulders near 225, 250–255, 295–300, and 350–355 mμ were consistent with the postulate that IXb, III, and IV were present; and after approximately 1.5 hr. the observed spectrum could be explained by assuming that only III and the ureido acid were present. As the maximum at 355 mμ decreased, the maximum at 297 mμ increased, and the spectrum was essentially that of the ureido acid (IV) after 7–8 hr.

These spectral changes strongly suggested that the amide (IXb) initially cyclizes in base to the 5,7(4*H*,6*H*)-dione (III) and that the ureido acid (IV) is then formed from III. Further evidence for this course was obtained from the following experiments. After a solution of *N*-butyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (1 mmole) in 0.1 *N* sodium hydroxide (3 mmoles) had stood at 24° for 30 min., it was acidified to pH 2 and the mixture was lyophilized. Paper chromatograms of the residue developed in four solvent systems showed two spots corresponding to IXb and III. The total residue obtained in the same manner from an identical solution after 70 min. at 28° showed a small amount of the ureido acid (IV) on chromatograms in addition to the strongly fluorescing spots of IXb and III. The organic components were leached from this residue with acetonitrile, and a small amount of III was isolated by precipitating its potassium salt from an ethanol solution and acidifying an aqueous solution of the salt. The infrared spectrum of the isolated specimen was identical with that of an authentic specimen of III. In addition, it was shown that the higher temperatures previously used to prepare IV from III were not required. An experiment, already described above, showed that IV could be obtained from III under conditions similar to those prevailing during the spectroscopically observed formation of IV from *N*-butyl-4-ureido-1,2,5-thiadiazole-3-carboxamide. (The proportion of base was much higher in the spectroscopically observed formation of IV from IXb than in the other experiments in which IV was formed from III or IXb.)

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