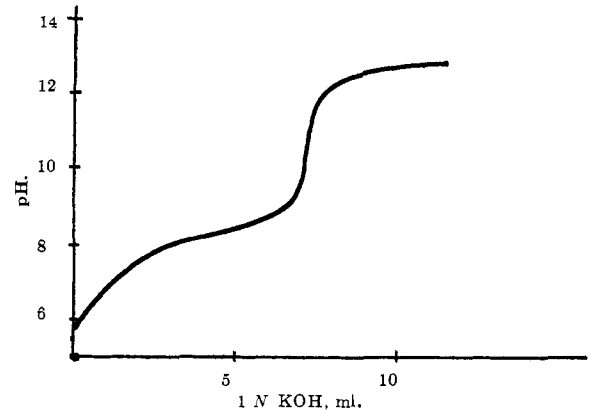

Figure 1.

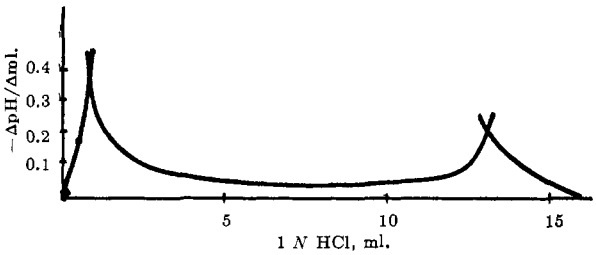

Figure 2.

The hydrazide was crystallized from ethanol.

Anal. Calcd.: C, 63.98; H, 6.71; N, 18.66; O, 10.65. Found: C, 64.10; H, 6.75; N, 18.47; O, 10.58.

Thin layer chromatography on silica gel with various solvents showed one spot.

Acknowledgment.—The authors are indebted to Dr. G. Tosolini for chromatography and to Mr. G. E. Gradogna for technical collaboration.

Acidic Cleavage of Amino[1,2,5]thiadiazolo[3,4-*d*]- and -*v*-triazolo[4,5-*d*]pyrimidines to 1,2,5-Thiadiazole-[1] and *v*-Triazolecarboxamidines[2]

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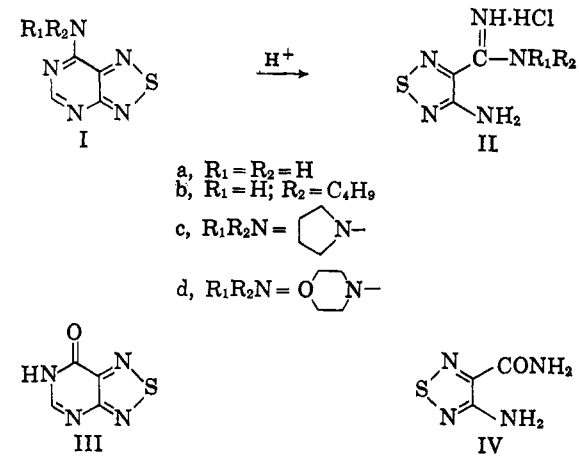
The pyrimidine ring of 7-amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (Ia) has been opened by aqueous base and by primary amines, the latter agents producing N-alkyl carboxamidines.[3] During studies on possible modes of ring cleavage, 7-pyrrolidino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (Ic) was treated with dilute hydrochloric acid in dioxane at 85°. The product had the composition of the hydrochloride of the amino carboxamidine IIc, and the ultraviolet absorption properties were consistent with this structure. In order to gain additional support for the formation of this type of product, 7-(butylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (Ib) was cleaved under the same conditions to the known[3] 4-amino-N-butyl-1,2,5-thiadiazole-3-carboxamidine (IIb). This reaction occurred much more rapidly than the formation of IIb in the reaction of Ia with butylamine, a reaction that evidently proceeds *via* the 7-butylamino derivative (Ib).[3] The acidic cleavage reaction was also successfully applied to the 7-amino (Ia) and the 7-morpholino (Id) derivatives; however, the yield of the amidine (IId) from the 7-morpholino derivative was lowered by a competing hydrolytic reaction that produced [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7(6H)-one (III) and 4-amino-1,2,5-thiadiazole-3-carboxamide (IV). Examination of aliquots from such a reaction by thin layer chromatography indicated that IId and III were formed simultaneously and that IV was then formed from III. The yields of the carboxamidines, with the exception of IId, were 68–82%. Further confirmation of the aminocarboxamidine structures was obtained by recyclizing 4-amino-1,2,5-thiadiazole-3-carboxamidine (IIa) to the thiadiazolopyrimidine (Ia) with ethyl orthoformate. In addition, alkaline hydrolysis of IIc gave 4-amino-1,2,5-thiadiazole-3-carboxylic acid.



Acidic cleavage of the thiadiazolopyrimidines (I) appears to be less complicated than acidic degradation of certain related heterocycles. Although the formation of III and IV, in addition to IId, from the 7-morpholino derivative is reminiscent of the acidic hydrolysis of 4-aminopteridine to 4(3H)-pteridinone and further degradation products,[4] the derivative (Ia) comparable to 4-aminopteridine gave a high yield of the amidine (IIa). Adenine, the purine analog of Ia, has been degraded under acidic conditions to glycine and ammonia,[5,6] and heating adenine at 150° for 2 hr. with 6 *N* hydrochloric acid gave only a 10% yield of 5-(or 4-) aminoimidazole-4- (or 5-) carboxamidine.[5,7]

(1) Part V on Thiadiazoles. Part IV: Y. F. Shealy and J. D. Clayton, *J. Org. Chem.*, **29**, 2141 (1964).

(2) 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.

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

(4) A. Albert, D. J. Brown, and G. Cheesman, *J. Chem. Soc.*, 474 (1951).

(5) L. F. Cavalieri, J. F. Tinker, and G. B. Brown, *J. Am. Chem. Soc.*, **71**, 3973 (1949).

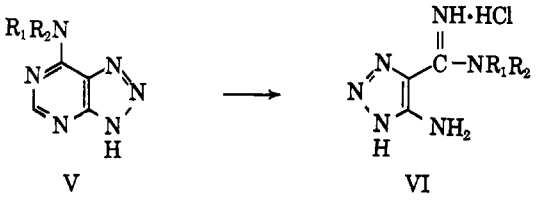
(6) R. H. Lindsay, W. K. Paik, and P. P. Cohen, *Biochem. Biophys. Acta*, **58**, 585 (1962).

(7) However, substituents on the adjacent ring-nitrogen atom facilitate this cleavage; 1-methyladenine and adenine N-oxide were cleaved by hydrochloric acid under milder conditions to 5- (or 4-) amino-N-methylimidazole-4- (or 5-) carboxamidine[8] and to 5- (or 4-) aminoimidazole-4- (or 5-) carboxamidoxime,[9] respectively. Similarly, 7-amino-*v*-triazolo[4,5-*d*]pyrimidine N-oxide (6-oxide of Va) was easily cleaved to the corresponding *v*-triazolecarboxamidoxime (VI, R_1 = H; R_2 = OH) by concentrated hydrochloric acid.[10]

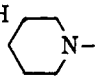
(8) P. Brookes and P. D. Lawley, *J. Chem. Soc.*, 539 (1960).

(9) M. A. Stevens and G. B. Brown, *J. Am. Chem. Soc.*, **80**, 2759 (1958).

(10) M. A. Stevens, H. W. Smith, and G. B. Brown, *ibid.*, **82**, 3189 (1960).



V VI

a, $R_1=R_2=H$
b, $R_1R_2N=$ 

The procedure employed in the formation of the thiadiazolecarboxamidines (IIa–d) was successfully extended to *v*-triazolo[4,5-*d*]pyrimidines devoid of substituents (other than hydrogen) on the ring-nitrogen atoms.[7] Both 7-amino-*v*-triazolo[4,5-*d*]pyrimidine (Va) and the 7-piperidino[11] derivative (Vb) were cleaved to aminocarboxamidines (VIa–b). Treatment of 5-amino-*v*-triazole-4-carboxamidine (VIa) hydrochloride with ethyl orthoformate re-formed the triazolopyrimidine (Va) in 92% yield. The *v*-triazoleamidines appeared to form more slowly than did the 1,2,5-thiadiazole derivatives, but the yields indicate that acidic cleavage has preparative significance for both types of aminoamidines.

Experimental[12]

4-Amino-1,2,5-thiadiazole-3-carboxamidines and 5-Amino-*v*-triazole-4-carboxamidines.—Data on the preparation and characterization of the carboxamidines II and VI are tabulated in Table I. The following procedure for the preparation of 4-amino-1,2,5-thiadiazole-3-carboxamidine hydrochloride (IIa) is typical of procedures employed in the acidic cleavage reactions. The proportions of dioxane and water varied somewhat depending on the starting material.

A solution consisting of 5.0 g. of 7-amino[1,2,5]thiadiazolo-[3,4-*d*]pyrimidine[14] (Ia), 180 ml. of purified dioxane, 25 ml. of 6 *N* hydrochloric acid, and 50 ml. of water was heated in a nitrogen atmosphere at 82–85° for 4 hr. The solution was cooled to room temperature and concentrated to dryness *in vacuo*. The residual solid was triturated with 25 ml. of ethanol, collected by filtration, and dried *in vacuo* at 60°, yield 4.7 g. (81%), m.p. 230–235° dec. Dilution with ether of a hot solution of 4.5 g. of the amidine hydrochloride in 75 ml. of methanol gave 3.6 g. of white platelets, m.p. 235–240° dec.

III and IV from 7-Morpholino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (Id).—When extension of the reaction time to 24 hr. (*cf.* Table I) failed to improve the yield of IId, 500 mg. of Id was added to a solution of 40 ml. of dioxane, 3 ml. of 6 *N* hydrochloric acid, and 10 ml. of water at 82–85°. Aliquots were withdrawn at 2 min. and 2, 4, 5.5, and 7 hr. and subjected to thin layer chromatography on silica gel in chloroform–methanol, and the chromatograms were examined under ultraviolet light (365 mμ). Both IId and III, as well as Id, were detected at 2 min. and 2 and 4 hr.; Id, IId, III, and IV were all detected at 5.5 hr.; and at 7 hr. the amount of IV had increased and very little Id remained. In the same manner IId and IV, but not III, were detected in a 24-hr. aliquot from an earlier run. These results indicate that the carboxamidine (IId) and III are formed simultaneously and that IV is formed more slowly from III.

Cyclization of 4-Amino-1,2,5-thiadiazole-3-carboxamidine (IIa) to Ia.—A mixture of 600 mg. of IIa hydrochloride and 25 ml. of ethyl orthoformate was heated at the reflux temperature for 3 hr. under anhydrous conditions. The reaction mixture, which contained a yellow solid, was chilled in an ice bath and filtered to remove the precipitate (533 mg.). The crude product was, at

TABLE I

4-AMINO-1,2,5-THIADIAZOLE-3-CARBOXAMIDINES AND 5-AMINO-*v*-TRIAZOLE-4-CARBOXAMIDINES (AS HYDROCHLORIDES). PREPARATION AND CHARACTERIZATION

Compd.	Reaction time, hr.	Yield, %	Recrystn. solvent[a]	M.p.,[b] °C.	Formula	Calcd., % C	H	N	Cl	Found, % C	H	N	Cl	λ_{max}, mμ (ε × 10⁻³) pH 1	pH 7	pH 13
IIa	4	81	A + B	235–240	$C_3H_5N_5S\cdot HCl$	20.07	3.37	39.00	19.8	20.28	3.48	38.82	19.8	216 (9.8), 324 (5.6)	216 (9.8), 324 (5.9)	319 (7.4)
IIb	3	82[c]														
IIc	28	68	A + B	>260	$C_7H_{11}N_5S\cdot HCl$[d]	35.93	5.17	29.96	15.2	35.98	4.83	29.78	15.4	240 (sh), 315 (6.0)	240 (sh), 315 (6.0)	305 (7.4)
IId	5.5	27	A + B	>270	$C_7H_{11}N_5OS\cdot HCl$	33.53	4.44	28.05	14.2	33.61	4.72	27.81	14.4	240 (sh), 317 (6.0)	240 (sh), 316 (6.0)	306 (7.3)
VIa[e]	26	89	A + B	268–270	$C_3H_6N_6\cdot HCl$	22.16	4.34	51.70	21.8	22.36	4.14	51.73	21.9	225 (sh), 271 (7.7)	230 (sh), 274 (7.6)	262 (7.8)
VIb	312	33	C + D	248–250	$C_8H_{14}N_6\cdot HCl$	41.64	6.56	36.43	15.4	41.80	6.30	36.48	15.6	227 (12.6), 272 (6.7)	225 (sh), 277 (6.4)	234 (10.8)

[a] A = methanol, B = ether, C = ethanol, D = ethyl acetate. [b] Melting points of IIa and VIa determined with a Mel-Temp melting point apparatus. The remaining melting temperatures were determined with a Kofler Heizbank apparatus. [c] Isolated as the free base and identified by infrared and ultraviolet spectra; see ref. 3. [d] *Anal.* Calcd.: S, 13.7. Found: S, 13.9. [e] The free base has been prepared by reduction of 5-amino-*v*-triazole-4-carboxamidoxime.[10]

(11) Y. F. Shealy, J. D. Clayton, C. A. O'Dell, and J. A. Montgomery, *J. Org. Chem.*, **27**, 4518 (1962).

(12) Melting points and infrared and ultraviolet spectra were determined by methods outlined previously.[13]

(13) Y. F. Shealy and J. D. Clayton, *J. Org. Chem.*, **28**, 1491 (1963).

(14) Y. F. Shealy, J. D. Clayton, and J. A. Montgomery, *ibid.*, **27**, 2154 (1962).

least partially, the hydrochloride of Ia and was recrystallized from water containing a small amount of triethylamine. The yellow crystals (69% yield) were identified as 7-amino[1,2,5]thiadiazolo-[3,4-*d*]pyrimidine (Ia) by their melting point (250–252°) and infrared and ultraviolet spectra.[14]

Hydrolysis of IIc.—A mixture of 100 mg. of IIc and 10 ml. of 1 *N* sodium hydroxide was stirred at room temperature for 24 hr., heated under reflux for 4.5 hr., cooled, and acidified to pH 1. Concentration of the solution yielded 40 mg. (65%) of 4-amino-1,2,5-thiadiazole-3-carboxylic acid,[13] which was identified by its melting point (220–222°) and infrared spectrum.

Cyclization of 5-Amino-*v*-triazole-4-carboxamidine (VIa) to Va.—A mixture of 500 mg. of VIa hydrochloride and 20 ml. of triethyl orthoformate heated under anhydrous conditions at the reflux temperature for 7 hr. and then chilled yielded 477 mg. of a white precipitate. A suspension of the precipitate in water was adjusted to pH 7 with sodium bicarbonate, stirred for 0.5 hr., and filtered. The white solid, which amounted to 385 mg. (92% yield) after it had been washed with water and dried, was identified as Va by its ultraviolet and infrared spectra.

Acknowledgment.—The authors express their appreciation to Drs. W. J. Barrett, W. C. Coburn, Jr., P. D. Sternglanz, and associates of the Analytical Section of this Institute for microanalyses and spectral determinations and to Dr. J. A. Montgomery for encouragement in this work.

Derivatives of 6-Hydroxyhomoveratramide

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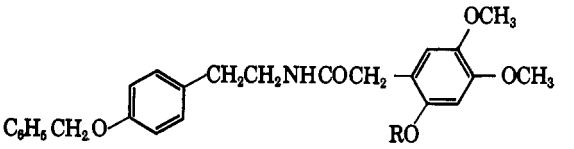
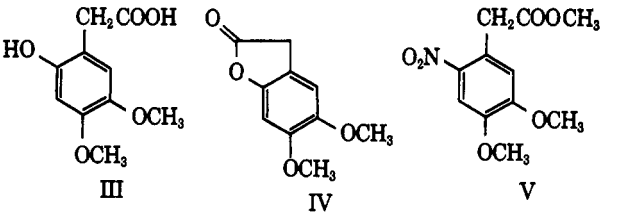
In connection with an investigation since discontinued, we prepared amide I and its benzyl ether II. The amine component of these amides, β-(*p*-benzyloxyphenyl)ethylamine, was prepared from the known[2] *p*-benzyloxybenzaldehyde. Base-catalyzed condensation of the aldehyde and nitromethane led to *p*-benzyloxy-β-nitrostyrene. Reduction of this latter material with lithium aluminum hydride in refluxing ether yielded the desired amine, which was conveniently purified as the hydrochloride.

For acylation of this amine the most convenient derivative of 6-hydroxyhomoveratric acid (III) appeared to be the corresponding lactone IV.[3,4] A suitable route to this compound entailed the following steps. Methyl 6-nitrohomoveratrate (V), available through Fischer esterification of the easily accessible[5] acid, was hydrogenated in benzene solution over 5% palladium on carbon to give the corresponding amino ester. This was diazotized and the diazonium salt was hydrolyzed in boiling aqueous sulfuric acid to hydroxy acid III. Acid-catalyzed dehydration to lactone IV proceeded smoothly in hot benzene solution with continuous removal of the water formed. This procedure from V led to IV in an over-all yield of 47% without purification of intermediates; the assigned



I, R=H

II, R=$C_6H_5CH_2$



III IV V

structure of this lactone is supported by infrared carbonyl absorption at 5.57 μ.

When β-(*p*-benzyloxyphenyl)ethylamine and III were heated together in benzene solution, the desired amide I formed in 85% yield. It gave a positive ferric chloride test and showed infrared absorption at 6.11 and 6.30 μ. It reacted with benzyl chloride in methanol containing 1 equiv. of lithium methoxide to yield the benzyloxy derivative II.

Experimental[6]

***p*-Benzyloxy-β-nitrostyrene.**—A solution of 12.0 g. of *p*-benzyloxybenzaldehyde[2] in 400 ml. of ethanol was cooled to 5° and 6.85 g. of nitromethane was added. This solution was stirred while a solution of 5.7 g. of sodium hydroxide in 100 ml. of ethanol, precooled to 5°, was added dropwise. The mixture was stirred 30 min. at 5–10° and then poured into a stirred solution of 68 ml. of concentrated hydrochloric acid in 104 ml. of water at room temperature. After 2 hr. the crude product was filtered. Recrystallization from ethanol gave 10.9 g. (75%). Two further recrystallizations from ethanol gave an analytical sample, m.p. 120–121°.

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.84; H, 5.09; N, 5.61.

β-(*p*-Benzyloxyphenyl)ethylamine.—In a Soxhlet apparatus 10.66 g. of *p*-benzyloxy-β-nitrostyrene was extracted over a 9–10-hr. period into 500 ml. of ether containing 6.5 g. of lithium aluminum hydride. The solution was heated at reflux an additional 8 hr. and then worked up with 5.65 ml. of water, 4.5 ml. of 20% aqueous sodium hydroxide, and finally 17 ml. of water. The resulting ether solution was filtered free of salts and dried over potassium carbonate. There was recovered 9.18 g. of colorless crystals (97%). The amine proved difficult to purify and was accordingly converted to the hydrochloride with 0.5 *M* hydrochloric acid for analysis. Three recrystallizations from isopropyl alcohol gave material of analytical purity, m.p. 196–206° dec.

Anal. Calcd. for $C_{15}H_{18}ClNO$: C, 68.30; H, 6.88; N, 5.31. Found: C, 68.12; H, 6.76; N, 5.17.

Methyl 6-Nitrohomoveratrate (V).—A solution of 66.4 g. of 6-nitrohomoveratric acid[5] in 800 ml. of methanol containing 20 ml. of concentrated sulfuric acid was heated under reflux for 18 hr. and then cooled to 0°. There were added 500 ml. of cold 6% aqueous sodium hydroxide and some ice. The resulting precipitate was filtered, dried, and recrystallized from methanol, yield 64.4 g. (91%). A sample was recrystallized further from ethyl acetate and then sublimed for analysis, m.p. 112.5–113°.

Anal. Calcd. for $C_{11}H_{13}NO_6$: C, 51.76; H, 5.13; N, 5.49. Found: C, 51.71; H, 5.11; N, 5.34.

5,6-Dimethoxycoumaran-2-one (IV).—The preparation of this compound was carried out from the above nitro ester without purification of intermediate compounds.

A solution of 5.00 g. of nitro ester in 100 ml. of benzene containing 500 mg. of 5% palladium on carbon was stirred under hydrogen at normal temperature and pressure. The theoretical

(1) The Rockefeller Institute, New York, N. Y. 10021.

(2) E. Wörner, *Ber.*, **29**, 139 (1896).

(3) Compound III itself has been described. *Cf.* L. E. Smith, and F. B. LaForge, *J. Am. Chem. Soc.*, **56**, 2431 (1934); O. Dann, J. Lang, and H. Vohl, *Ann.*, **631**, 116 (1960).

(4) *Cf.* G. Cramer, *Ber.*, **31**, 2813 (1898).

(5) R. K. Callow, J. M. Gulland, and R. D. Haworth, *J. Chem. Soc.*, 658 (1929).

(6) Chemical analyses were performed in the microanalytical laboratory of the University of California. All melting points are corrected.