TABLE IV
EFFECTS ON BLOOD PRESSURE AND RESPIRATION RATE[a]

Compd[b]	Dose, mg/kg	Blood pressure Decrease, mm	Blood pressure Duration, min	Respiration rate increase, % of control
I	1	0		14
	2	5	1	30
	4	5	1	36
	6	130	3	50
VIII	1	0		0
	2	0		5
	4	0		6
	6	0		60
IX	1	30	4	22
	2	40	4	35
	4	70	20	83
	6	100	60	81
XIV	1	20	2	41
	2	30	2	40

[a] Figures represent mean values obtained from at least two separate experiments for each dose level. No change in the heart rate was observed in all experiments. [b] Compound III did not cause any significant drop in blood pressure.

***p*-Trimethylsilylhydrocinnamoyl chloride** was similarly obtained in 75% yield, bp 112–114° (2 mm). *Anal.* ($C_{12}H_{17}ClOSi$) C, H, Cl.

Typical examples for the preparation of the amides are given below; the rest are summarized in Table I.

***p*-Trimethylsilylbenz-*p*-anisidide (I).**—A solution of *p*-trimethylsilylbenzoyl chloride[5] (2.12 g, 0.01 mole) in $CHCl_3$ (10 ml) was dropped into a cooled solution of *p*-anisidine (2.46 g, 0.02 mole) in dry $CHCl_3$ (30 ml) and stirred for 20 hr. The $CHCl_3$ was driven off *in vacuo*, and Me_2CO was added to the residue. The precipitated *p*-anisidine hydrochloride was filtered off and washed thoroughly (Me_2CO). The combined Me_2CO solutions were evaporated *in vacuo*, H_2O was added, and I was filtered off and washed (5% HCl, H_2O); yield 2.7 g (90%), mp 126° (from EtOH–H_2O). *Anal.* ($C_{17}H_{21}NO_2Si$) C, H, N, Si.

***p*-Trimethylsilylphenylacetylpiperidide (II).**—A solution of *p*-trimethylsilylphenylacetyl chloride (2.26 g, 0.01 mole) in $CHCl_3$ (15 ml) was dropped into a cooled solution of piperidine (1.68 g, 0.02 mole) in $CHCl_3$ (25 ml) and stirred for 15 hr at room temperature. The solvent was driven off *in vacuo* and the residue was taken up in ether and H_2O. The ethereal layer was separated, washed (dilute HCl, NaOH), and dried ($MgSO_4$). The ether was removed *in vacuo* and II (2.4 g, 87%) was collected at 164–166° (1 mm). *Anal.* ($C_{16}H_{25}NOSi$) C, H, N, Si.

***p*-Trimethylsilylphenylacetyl Hydrazide (III).**—A mixture of *p*-trimethylsilylphenylacetic acid (10.4 g, 0.05 mole), 1-butanol (15 ml), hydrazine hydrate (4 ml), and activated alumina (2 g) (100–150 mesh) were stirred and heated to reflux. C_6H_6 (10 ml) was then added, and the mixture was distilled azeotropically for 5 hr, the temperature being kept below 95° by occasional addition of C_6H_6. The hot reaction mixture was filtered and evaporated *in vacuo*. Petroleum ether (bp 40–60°) was added to the residue and III (8.2 g, 80%) crystallized out; mp 118° (from EtOH–H_2O). *Anal.* ($C_{11}H_{18}N_2OSi$) C, H, N, Si.

***p*-Trimethylsilylphenylacetylurea (IV.)**—A solution of *p*-trimethylsilylphenylacetyl chloride (2.26 g, 0.01 mole) in C_6H_6 (3 ml) was heated with urea (2 g, 0.033 mole) until reaction set in, and then on a steam bath for 2 hr. The C_6H_6 was driven off *in vacuo*, and H_2O was added to the residue, which was filtered off and washed (NaOH, H_2O); yield 1.9 g (76%), mp 176° (from EtOH–H_2O). *Anal.* ($C_{12}H_{18}N_2OSi$) C, H, N, Si.

Acknowledgment.—We wish to express our thanks to "Yissum" Research Development Co. for the grant which enabled us to carry out this research. We wish to thank Dr. H. Edery and Dr. Y. Grunfeld of the Israel Institute for Biological Research, Ness-Ziona, and the Pharmacological Institute of the National Council for Research and Development for carrying out the pharmacological tests.

Syntheses and Hypotensive Activities of 3-Amino-4H-pyrrolo[3,4-*c*]isoxazoles and Derivatives

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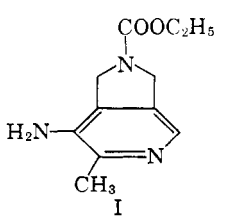
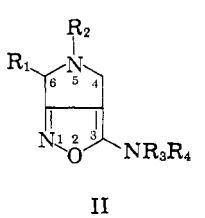
A series of novel 3-amino-4H-pyrrolo[3,4-*c*]isoxazoles and their derivatives have been synthesized and evaluated for their biological activity. Some of the compounds caused hypotension, tyrosine hydroxylase inhibition, and catecholamine and serotonin depletion.

Previous reports[1] from these laboratories have disclosed the chemistry and pharmacology of a series of pyrrolo[3,4-*c*]pyridines, which included 7-amino-2-carbethoxy 6-methylmerimine (I). Since it is known[2] that isoxazoles and pyridines exhibit many similar chemical properties (*e.g.*, basicities, polarities, boiling points, and dielectric constants), it was decided to prepare derivatives of 3-amino-4H-pyrrolo[3,4-*c*]isoxazoles (II) for pharmacological evaluation.

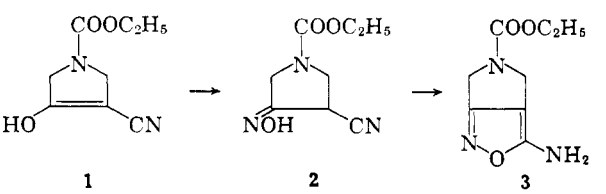


I



II

Chemistry.—Utilizing a key intermediate in the synthesis of merimines, ethyl 3-cyano-4-hydroxy-3-pyrroline-1-carboxylate (**1**)[3] was condensed with hydroxylamine to afford the oxime (**2**), which following



1 2 3

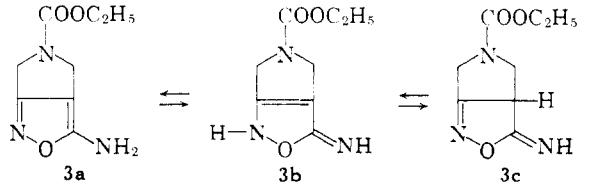
(1) (a) W. B. Wright, Jr., J. S. Webb, and J. M. Smith, Jr., *J. Am. Chem. Soc.*, **79**, 2199 (1957); (b) S. M. Gadekar, J. L. Frederick, J. Semb, and J. R. Vaughan, Jr., *J. Org. Chem.*, **26**, 468 (1961).

(2) N. K. Kuchetkov and S. D. Sokolov, *Advan. Heterocyclic Chem.*, **2**, 365 (1963).

(3) J. Song, U. S. Patent 3,024,243 (1962).

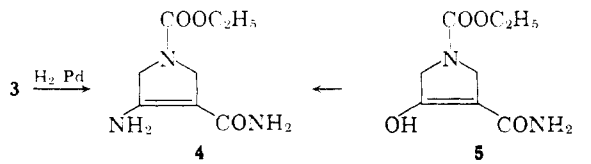
base treatment formed ethyl 3-amino-4H-pyrrolo[3,4-*c*]-isoxazole-5(6H)-carboxylate (**3**).

Because of the novelty of this heterocycle, the spectral properties of **3** were studied in detail to compare it with the simple 5-aminoisoxazoles. In particular, we were concerned with the possible tautomeric forms **3a**, **b**, and **c**.



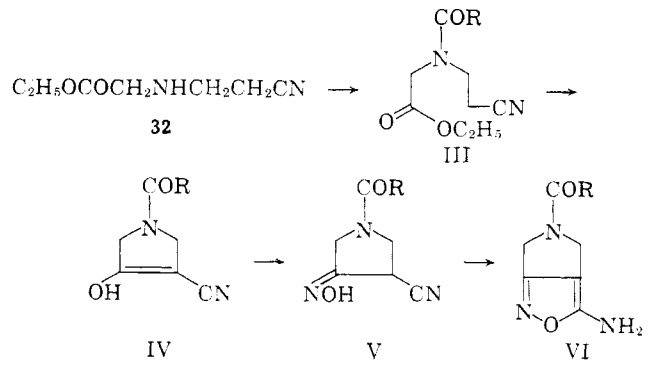
Using in part the same methodology as employed by Boulton and Katritzky[4] in establishing the "amino" rather than the "imino" form of 5-aminoisoxazoles, we have evidence that **3a** is the major contributing structure. The ir, uv, and nmr data are presented in the Experimental Section.

The gross structure of **3** was established by hydrogenation to cleave the isoxazole ring and form ethyl 3-amino-4-carbamoyl-3-pyrroline-1-carboxylate (**4**). An independent synthesis of **4** was accomplished by treating **5** with ammonium formate in ethanol.



Structural variations on the nitrogen at position 5 to form the products listed in Table I were made by the sequence shown in Scheme I. Treating ethyl

SCHEME I



N-(2-cyanoethyl)glycinate (**32**)[5] with the appropriate acyl halide followed by basic ring closure yielded the pyrroline IV. Oxime formation and subsequent alkaline treatment afforded the product VI. When methyl N-(2-cyanoethyl)-α-alaninate was the starting material, the 6-methyl compound **11** was formed.

Modifications at the 3 position to yield compounds **12**–**16** in Table II were accomplished by acylation of the appropriate amines in Table I.

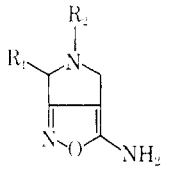
The reactions of **3** with trimethyl orthoacetate and acetic anhydride yielded the "imino ether" (**31**),

(4) A. J. Boulton and A. R. Katritzky, *Tetrahedron*, **12**, 51 (1961).

(5) A. P. Terent'ev and P. F. Butskus, *Zh. Obshch. Khim.*, **23**, 1230 (1953); *Chem. Abstr.*, **47**, 12237 (1953).

TABLE I

5-SUBSTITUTED 3-AMINO-4H-PYRROLO[3,4-*c*]ISOXAZOLES

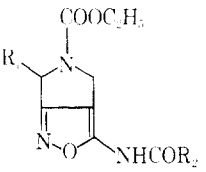


Compd	R_1	R_2	Mp, °C	Yield, %	Formula[c]
3	H	$COOC_2H_5$	177–179	72	$C_8H_{11}N_3O_3$
6	H	$COOC_4H_9$-*i*	125–127[a]	30	$C_{10}H_{15}N_3O_3$
7	H	$COOCH_2C_6H_5$	139–141[c]	51	$C_{13}H_{13}N_3O_3$
8	H	$COCH_3$	178–180[b]	43	$C_7H_9N_3O_2$
9	H	$COC_6H_2(OCH_3)_3$	172–173[c]	65	$C_{15}H_{17}N_3O_5$
10	H		188–189	67	$C_9H_8N_5OCl$
11	CH_3	$COOC_2H_5$	115–117[d]	80	$C_9H_{13}N_3O_3$

[a] Recrystallized from aqueous EtOH. [b] From EtOH. [c] From Me_2CO. [d] From H_2O. [e] All compounds were analyzed for C, H, N.

TABLE II

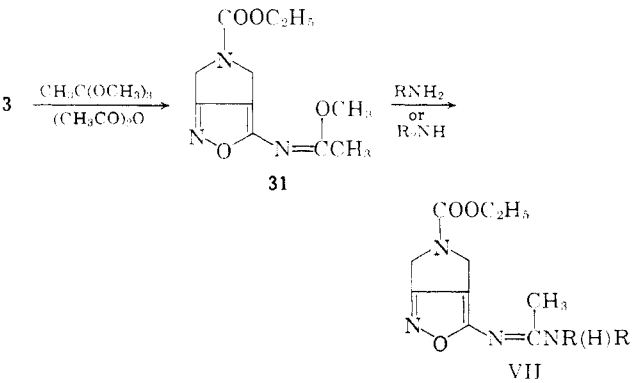
ETHYL 3-ACYLAMINO-4H-PYRROLO[3,4-*c*]ISOXAZOLE-5(6H)-CARBOXYLATES



Compd	R_1	R_2	Mp, °C	Yield, %	Formula[a]
12	H	CH_3	195–196	63	$C_{10}H_{13}N_3O_4$
13	H	C_2H_5	203–204	52	$C_{11}H_{15}N_3O_4$
14	H	CF_3	185–187	58	$C_{10}H_{10}F_3N_3O_4$[b]
15	H	H	177–178	53	$C_9H_{11}N_3O_4$
16	CH_3	CH_3	148–150	51	$C_{11}H_{15}N_3O_4$

[a] All compounds were analyzed for C, H, N. [b] C: calcd, 41.0; found, 41.6.

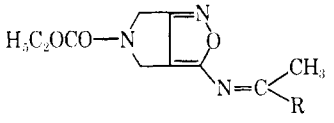
which when treated with various amines afforded a series of amidines VII listed in Table III.



Biological Activity.[6]—Hypotensive effects were determined in conscious normotensive male albino rats of the Wistar strain and in normotensive and renal hypertensive dogs. Rats were fastened to a board in a supine position, and their femoral arteries were exposed and catheterized under local anesthesia. Dogs were trained to lie on a table so that their femoral artieries could be punctured percutaneously with a 26-gauge needle. Mean arterial blood pressure was

(6) No other significant activity was found in the other screening programs at Lederle Laboratories.

TABLE III
3-AMIDINO-4H-PYRROLO[3,4-c]ISOXAZOLES



Compd	R	Mp, °C[b]	Yield, %	Method[a]	Formula[d]
17	NH_2	160–161	58	A	$C_{10}H_{14}N_4O_3$
18	$NHCH_3$	141–145	29	A	$C_{11}H_{16}N_4O_3$
19	$N(CH_3)_2$	100–102	50	C	$C_{12}H_{18}N_4O_3$
20	NHC_2H_5	152–154	63	C	$C_{12}H_{18}N_4O_3$
21	$NHOCH_3$	179–181	66	A	$C_{11}H_{16}N_4O_4$
22	NHCN	197–200	11	B	$C_{11}H_{13}N_5O_3$
23	$NHNHCOOC_2H_5$	206–209	79	B	$C_{13}H_{19}N_5O_5$
24		118–121	56	A	$C_{19}H_{20}N_4O_3$
25		167–171	45	A	$C_{16}H_{24}N_4O_3$
26		205–208	24	B	$C_{16}H_{17}ClN_4O_3$
27		226–229	31	B	$C_{17}H_{17}F_3N_4O_3$[c]
28	$NHCH_2C_6H_5$	148–152	53	A	$C_{17}H_{20}N_4O_3$
29		125–127	44	A	$C_{16}H_{19}N_5O_3$
30	NHC_6H_5	212–214	59	B	$C_{16}H_{18}N_4O_3$

[a] Method A = room temperature for 20 hr in ethanol; B = refluxing for 3 hr in ethanol; C = room temperature for 20 hr in $CHCl_3$. [b] All the compounds were recrystallized from H_2O or EtOH or aqueous EtOH. [c] H: calcd, 4.48; found, 4.95. [d] All compounds were analyzed for C, H, N.

recorded in both species during a 24-hr period following drug administration by means of a pressure transducer-polygraph recorder system. The compounds were given to the rats by gavage and to the dogs in hard-shell capsules. In other experiments, dogs were anesthetized with chloralosane, and various sympathomimetic agents were given before and after parenteral injections of 1–10 mg/kg of the selected pyrroloisoxazoles.

Compounds **3**, **11**, **12**, and **15** produced hypotension in conscious rats at an oral dose of 100 mg/kg. These agents caused a >30 mm reduction in mean blood pressure 2 hr after treatment. In contrast, the remaining 26 compounds failed to evoke a statistically significant reduction in mean blood pressure under identical conditions.

When the four active compounds were given to conscious renal hypertensive dogs at doses of 10–25 mg/kg, erratic antihypertensive responses were recorded. In 38% of the trials, **11**, **12**, and **15** lowered blood pressure, whereas **3** was always inactive. None of the compounds reduced the mean blood pressure of normotensive dogs. In anesthetized dogs, all four pyrroloisoxazoles reduced the vasopressor responses to epinephrine (2 μg/kg), norepinephrine (2 μg/kg), and phenethylamine (50 μg/kg). However, neither intraperitoneal nor intravenous administrations of 1–10 mg/kg caused hypotension.

The assay procedure for an *in vitro* inhibition of tyrosine hydroxylase has been discussed in detail elsewhere.[7] Five compounds (**3**, **7**, **8**, **13**, and **15**) inhibited the hydroxylation of tyrosine, which is the rate-limiting step in the synthesis of norepinephrine. The concentrations ranged from 1×10^{-4} *M* to 4×10^{-3} *M*. Compound **3** inhibited 50% at 1×10^{-4} *M* and was equal in potency to 3,4-dihydroxyphenylpropylacetamide.[7] Since the present series is not structurally related to either this compound, α-methyl-*p*-tyrosine, or 3-iodotyrosine,[8] it represents a new class of compounds which inhibit tyrosine hydroxylase.

A detailed report on the effect of **12** on tissue levels of catecholamines and serotonin in the rat will appear elsewhere.[9] Briefly, a single intraperitoneal dose of **12** in the rat caused an appreciable lowering of catecholamine levels in the heart and brain, with only a slight effect on brain serotonin. After repetitive doses, an appreciable decline was noted in the levels of catecholamines in the heart, brain, and adrenals and the level of brain serotonin was markedly depressed.

Experimental Section

The melting points were determined in open capillary tubes and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Methyl N-(2-Cyanoethyl)-α-alaninate (33).—To a cold solution (0°) of 2.2 g of NaOH in 5 ml of H_2O was added 7 g (0.05 mole) of methyl α-alaninate·HCl and 3.5 ml (0.035 mole) of acrylonitrile. The mixture was kept at 70–75° for 1.5 hr. After cooling to room temperature, the oil was separated and the aqueous layer was extracted with ether (two 50-ml portions). The oil and ether extracts were dried ($MgSO_4$), concentrated, and distilled giving 1.9 g (25%) of product: bp 95° (0.3 mm), $n^{24}D$ 1.4461. *Anal.* ($C_7H_{12}N_2O_2$) H, N; C: calcd, 53.8; found, 54.5.

Ethyl N-Isocarbobutyloxy-N-(2-cyanoethyl)glycinate (34).—A 13.6-g (0.1 mole) sample of isobutyl chlorocarbonate was added slowly to an ice-cold solution of 8.4 g (0.1 mole) of $NaHCO_3$ and 15.6 g (0.1 mole) of **32** in 60 ml of H_2O. After stirring in ice for 2 hr and at room temperature for 2 hr, the aqueous layer was extracted with ether (two 100-ml portions). The ethereal layer was dried ($MgSO_4$), concentrated, and distilled to yield 20.1 g (79%) of product, bp 144–145° (0.5–0.6 mm), $n^{24}D$ 1.4498. *Anal.* ($C_{12}H_{20}N_2O_4$) C, H, N.

Ethyl N-Carbobenzyloxy-N-(2-cyanoethyl)glycinate (35).—The reaction with carbobenzyloxy chloride (0.05 mole) and **32** (0.05 mole) was run as described above to yield 7.7 g (54%) of product, bp 204–205° (1.5 mm), $n^{25}D$ 1.5072. *Anal.* ($C_{15}H_{18}N_2O_4$) C, H, N.

Ethyl β-(2-Cyanoethyl)-3,4,5-trimethoxyhippurate (36).—A clear solution of 11.5 g (0.05 mole) of trimethoxybenzoyl chloride in 35 ml of *p*-dioxane was added to a cold solution of 7.8 g (0.05 mole) of **32** and 7.3 ml of Et_3N in 20 ml of *p*-dioxane. The mixture was stirred at room temperature for 5 hr, filtered, concentrated, and chilled to yield 9.5 g (54%) of product, mp 87–88°. *Anal.* ($C_{17}H_{22}N_2O_6$) C, H, N.

Ethyl N-(5-Chloro-2-pyrimidinyl)-N-(2-cyanoethyl)glycinate (37).—A mixture of 31.2 g (0.2 mole) of **32** and 14.9 g (0.1 mole) of 2,5-dichloropyrimidine was heated at 130–140° for 4 hr. The mixture was cooled and 450 ml of Et_2O was added. After filtering the insoluble solid, the filtrate was concentrated giving a waxy solid which was crystallized from aqueous EtOH to form 14.8 g (56%) of product, mp 54–56°. *Anal.* ($C_{11}H_{13}ClN_4O_2$) C, H, N.

4-Hydroxy-1-(3,4,5-trimethoxybenzoyl)-3-pyrroline-3-carbonitrile (38).—To a stirred mixture of 2.7 g (0.05 mole) of $NaOCH_3$ in 100 ml of dry toluene was added 18 g (0.05 mole) of **36**. After stirring at room temperature for 5 hr, the salt was filtered and washed with hexane, dissolved in H_2O, and acidified with 5 *N* HCl to form an oil. The oil was extracted with $CHCl_3$, concentrated, and crystallized from C_6H_6 giving 6.4 g (43%) of a white solid, mp 76–78°. *Anal.* ($C_{15}H_{16}N_2O_5$) C, H, N.

1-(5-Chloro-2-pyrimidinyl)-4-hydroxy-3-pyrroline-3-carbonitrile (39).—Following the method used to prepare **38**, **37** was cyclized giving 2.6 g (46%) of a white solid which was recrystallized from EtOH, mp 218–220°. *Anal.* ($C_9H_7ClN_4O$) C, H, N.

(7) R. J. Taylor, Jr., and L. Ellenbogen, *Life Sci.*, **6**, 1463 (1967).

(8) S. Udenfriend, P. Zaltzman-Nirenberg, and T. Nagatsu, *Biochem. Pharmacol.*, **14**, 837 (1965).

(9) W. Lippmann and M. Wishnick, *J. Pharm. Pharmacol.*, **19**, 855 (1967).

1-Acetyl-4-hydroxy-3-pyrroline-3-carbonitrile (40).—Ac_2O (20 ml) was added with cooling to 15.6 g (0.1 mole) of **32**. The mixture was stirred for 24 hr at room temperature and concentrated and the oily residue was treated with 6.0 g (0.11 mole) of $NaOCH_3$ in 50 ml EtOH. The mixture was heated for 2 hr and cooled and the resulting salt was collected and washed with Et_2O. This salt was treated with 200 ml of cold 1 *N* HCl giving a solid which was recrystallized (H_2O) to yield 6.0 g (40%) of product, mp 172–175°, lit.[10] mp 171–172°.

Ethyl 4-Cyano-3-hydroxy-2-methyl-3-pyrroline-1-carboxylate (41).—Following the general procedure 5.0 g (0.02 mole) of **33** was converted to 2.7 g (63%) of the 3-pyrroline **41**, mp 85–87°. *Anal.* ($C_9H_{12}N_2O_3$) H, N; C: calcd, 55.1; found, 55.6.

Preparation of Oximes. Ethyl 3-Cyano-4-oxo-1-pyrrolidinecarboxylate Oxime (42).—To a solution of 8.0 g (0.04 mole) of **1**[3] in 100 ml of 95% EtOH was added 2.8 g (0.04 mole) of $HONH_2 \cdot HCl$ and 3.3 g (0.04 mole) of anhydrous NaOAc. After refluxing for 1 hr, the NaCl was filtered and the filtrate was evaporated to dryness. The solid residue was recrystallized (hexane–EtOAc) to give 3.3 g (42%) of **42**, mp 131–132°. *Anal.* ($C_9H_{11}N_3O_3$) C, H, N.

The following compounds were prepared by the same general procedure.

4-Oxo-1-(3,4,5-trimethoxybenzoyl)-3-pyrrolidinecarbonitrile oxime (43), yield 20%, mp 206–208°. *Anal.* ($C_{15}H_{17}N_3O_5$) C; H: calcd, 5.37; found, 5.87; N: calcd, 13.2; found, 12.6.

1-(5-Chloro-2-pyrimidinyl)-4-oxo-pyrrolidinecarbonitrile oxime (44), yield 80%, mp 183–185°. *Anal.* ($C_9H_8ClN_5O$), C, H, N.

Ethyl 4-cyano-3-oxo-2-methylpyrrolidinecarboxylate oxime (45), yield 6%, mp 123–125°. *Anal.* ($C_9H_{13}N_3O_3$) C, H, N.

Model Procedure for Preparation of Pyrrolo[3,4-*c*]isoxazoles. Ethyl 3-Amino-4H-pyrrolo[3,4-*c*]isoxazole-5(6H)-carboxylate (3).—A 1.1-g sample of the oxime **42** was dissolved in 25 ml of 0.1 *N* NaOH, and the product (**3**) precipitated almost immediately. Compounds **9–11** were made from their requisite oxime. Compounds **6–8** were made by the previously described procedures but the intermediates were not isolated and identified.

Model Procedure for Preparation of Acylamino Compounds. Ethyl 3-Acetamido-4H-pyrrolo[3,4-*c*]isoxazole-5(6H)-carboxylate (12).—A 2.0-g (0.01 mole) sample of **3** was suspended in 5 ml of Ac_2O, stirred, and refluxed for 5–10 min. Upon cooling the mixture, the product precipitated and was recrystallized from ethanol. Compound **13** was recrystallized from Me_2CO, **14** from EtOH, **15** from aqueous EtOH, and **16** from C_6H_6.

Ethyl 4-Amino-3-carbamoyl-3-pyrroline-1-carboxylate (4). (a) From Reduction of 3.—To a solution of 0.2 g (0.001 mole) of **3** in 15 ml of Methyl Cellosolve was added 0.02 g of 10% Pd–C. The mixture was hydrogenated for 25 min while 26.3 ml of H_2 was absorbed. The catalyst was filtered off and the filtrate was concentrated to dryness. The resulting solid was recrystallized (EtOH) to yield 0.15 g (75%) of **4**, mp 225–228°, identical with sample prepared from **5**, no depression of melting point when admixed with material obtained from **5**.

(b) From Ethyl 3-Carbamoyl-4-hydroxy-3-pyrroline-1-carboxylate (5).—A mixture of 0.2 g (0.001 mole) of **5** and 0.126 g (0.002 mole) of ammonium formate in 5 ml of EtOH was refluxed for 24 hr. The product precipitated when the mixture was cooled to yield 0.18 g (90%) of **5**, mp 222–225°. *Anal.* ($C_8H_{13}N_3O_3$) C, H, N.

Ethyl 3-Carbamoyl-4-hydroxy-3-pyrroline-1-carboxylate (5).—A 5-g (0.025 mole) sample of **1** was added to 50 ml of 98% H_2SO_4. The mixture was heated for 2 hr (55–60°), cooled, and added to 200 ml of ice water. The material was extracted with $CHCl_3$, concentrated, and treated with 125 ml of petroleum ether (bp 30–60°) to precipitate 4.8 g (96%) of **5**, mp 155–158° (EtOH). *Anal.* ($C_8H_{12}N_2O_4$) C, H; N: calcd, 14.0; found, 13.3.

(10) T. Sheradsky and P. Southwick, *J. Org. Chem.*, **30**, 194 (1965).

Ethyl 3-[(1-Methoxyethylidene)amino]-4H-pyrrolo[3,4-*c*]-isoxazole-5(6H)-carboxylate (31).—A mixture of 2 g (0.01 mole) of **3**, 3 ml of Ac_2O, and 4 ml of trimethyl orthoacetate was refluxed for 3 hr. After cooling and concentrating the mixture, it was extracted with hot hexane. The hexane was cooled to give 1.3 g (52%) of **31**, mp 86–87°. *Anal.* ($C_{11}H_{15}N_3O_4$) C, N; H: calcd, 5.97; found, 6.41.

Model Procedure for Preparation of the Amidines Listed in Table III. Ethyl 3-(Acetimidoylamino)-4H-pyrrolo[3,4-*c*]-isoxazole-5(6H)-carboxylate (17).—A mixture of 3.94 g (0.02 mole) of **3**, 6.2 ml of Ac_2O, and 4 ml of trimethyl orthoacetate was refluxed for 3 hr. The resulting mixture was concentrated and the residue was treated with 10 ml of 7% (by weight) ethanolic NH_3. After allowing the mixture to remain at room temperature for 20 hr, the solid which precipitated was filtered and recrystallized from H_2O.

Evidence for Structure of Tautomer 3a.—In the uv, **3** had λ_{max}^{EtOH} 252 mμ (ε 1150) with a bathochromic shift in 6 *N* HCl to λ_{max} 265 mμ (ε 1350). Katritzky[4] reported that 5-amino-3,4-dimethylisoxazole absorbs at $\lambda_{max}^{H_2O}$ 244 mμ (ε 8230) and $\lambda_{max}^{2\,N\,H_2SO_4}$ 263 mμ (ε 13,800). Interestingly, due to the weak basicity of **3**, no ring protonation occurs in 2 *N* acid as evident by the uv spectrum of **3** being the same in neutral and 2 *N* acid solution. Adembri, *et al.*,[11] report results similar to Katritzky in their uv study of tautomers of 5-aminoisoxazoles.

A comparison of the ir spectrum of **3** with that of 5-amino-3,4-dimethylisoxazole[4,12] showed that the positions of all major bands attributable to ring stretching modes, ring deformation, and NH stretching by the amino group were similar. The band due to NH_2 scissor in the 6.2-μ region, however, was to some extent obscured by the high intensity broad band (5.85–6.10 μ) of the carbethoxy and C=N functions.

A deuteration experiment to further establish the existence of **3** in the "amino" form **3a** by determining the ir spectrum in $CHCl_3$ was not possible due to the insolubility of **3** in $CHCl_3$. However, it was possible to use the 6-methyl homolog (**11**) of **3**. Boulton and Katritzky[4] found in the spectrum of partially deuterated 5-amino-3-methylisoxazole that bands due to NHD are located at 2.9 and 3.95 μ (between those of NH_2 at 2.85 and 2.95 μ and those of ND_2 at 4.0 and 4.05 μ). This indication of an amino form with two available hydrogens is only compatible with our structure **3a** (or **11a**) and indeed partially deuterated **11** showed the dimunition of NH_2 bands below 3 μ and the appearance of strong ND_2 band at 4.1 μ.

An nmr spectrum of **3** run in DMSO showed a broad band at τ 3.2 which integrated for two equivalent portions and both were exchanged with CD_3OD. The absence of a lone proton on the carbon at the junction of the two rings eliminates the imino form **3c** from consideration.

The combined (uv, ir, and nmr) spectral evidence is in accord with the evidence presented by Katritzky[4] and Adembri[11] for the preference of aminoisoxazoles rather than iminoisoxazoles and structure **3a** is definitely preferred.

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