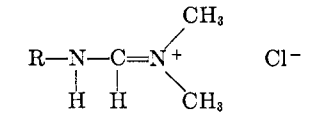
TABLE I

FORMAMIDINIUM CHLORIDES FROM AMIDES[a]



R	M.p., °C.	Yield, %	Calcd., % C	H	Cl	N	Found, % C	H	Cl	N
$C_6H_5C(=O)-$	173–175 dec.	68	56.47	6.16	16.67	13.17	56.3	6.3	17.0	12.9
$CH_3C(=O)-$	188–190 dec.	71	39.87	7.36	23.54	18.60	40.0	7.5	...	18.6
$C_6H_5CH_2C(=O)-$	128–132	59	58.28	6.67	15.64	12.36	58.0	7.0	15.2	12.0
$CH_2=C(CH_3)-C(=O)-$	121–125	62	47.60	7.42	20.07	15.86	47.2	7.8	20.8	15.2

[a] These salts are extremely hygroscopic, and good melting points and analyses were difficult to obtain even when precautions were taken to prevent contact with air.

The reaction mixture was poured, with vigorous stirring, into a mixture of 250 ml. each of dry benzene and ether. After cooling the mixture at 5° in a refrigerator for several hours, the product crystallized. The formamidinium chlorides were recrystallized from hot benzene–dimethylformamide.

Hydrolysis of N,N-Dimethyl-N′-benzoylformamidinium Chloride.—To 15 ml. of water was added 4.0 g. of the formamidinium chloride. After a few minutes, a white crystalline precipitate formed. After 1 hr. the solid was filtered off and dried. The yield of N-formylbenzamide was 2.8 g. (99%), m.p. 107–108°. Authentic N-formylbenzamide was prepared by the method of Thompson,[5] m.p. 106–108°. The infrared spectrum was identical with the product obtained from the hydrolysis of N,N-dimethyl-N′-benzoylformamidinium chloride and a mixture melting point was undepressed.

Hydrolysis of N,N-Dimethyl-N′-phenylacetylformamidinium Chloride.—The hydrolysis was carried out exactly as above. The yield was 93%, m.p. 129–131°.

Anal. Calcd. for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.7; H, 5.5; N, 8.3.

Tribenzamide.—A reaction was carried out as given for the preparation of formamidinium salts except that N,N-dimethylacetamide replaced the dimethylformamide. After the reaction was complete, the mixture was poured into 150 ml. of water and was allowed to stand for 1 hr. The precipitated solid was filtered off, washed with ether, and dried. A 41% yield of tribenzamide, m.p. 209–210° (lit.[6] 208–210°), was obtained which proved to be identical with an authentic sample.

(5) Q. E. Thompson, *J. Am. Chem. Soc.*, **73**, 5914 (1951).
(6) C. Blacher, *Ber.*, **28**, 432 (1895).

The Synthesis of 3,5-Diaminoisoxazoles

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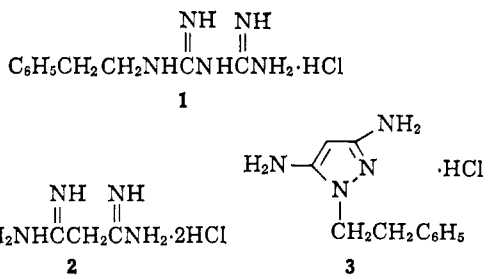
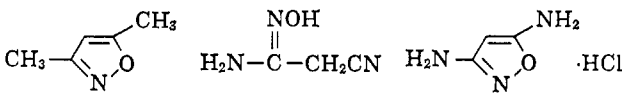
Phenethylbiguanide hydrochloride (**1**) is a clinically effective drug for the control of selected cases of diabetes.[1] We have sought to prepare novel related compounds for evaluation as hypoglycemic agents and have already reported the syntheses of phenethylmalonamidine dihydrochloride (**2**)[2] and 3,5-diamino-1-phenethylpyrazole hydrochloride (**3**).[3] We now wish to describe the synthesis of some representatives of 3,5-diaminoisoxazole, a new system related to **3**.



1 **2** **3**

Added impetus was given to this investigation by the recent[4] report of hypoglycemic activity for 3,5-dimethylisoxazole (**4**).



4 **5** **6**

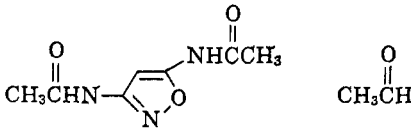
An obvious precursor to 3,5-diaminoisoxazole is 2-cyanoacetamidoxime (**5**), whose synthesis had been described by Schmidtmann[5] in 1896. Since the compound is isomeric with 3,5-diaminoisoxazole and the only characterization published was an elemental analysis, verification of the structure appeared to be warranted. The infrared spectrum of 2-cyanoacetamidoxime exhibits a weak nitrile band at 4.40 μ, and the ultraviolet spectrum fails to show a maximum above 210 mμ. These data are consistent with the nonconjugated structure **5** which was confirmed by the n.m.r. spectrum, which displays singlets at τ 0.75

(1) G. Ungar, L. Freedman, and S. L. Shapiro, *Proc. Soc. Exptl. Biol. Med.*, **95**, 190 (1957).
(2) W. J. Fanshawe, V. J. Bauer, E. F. Ullman, and S. R. Safir, *J. Org. Chem.*, **29**, 308 (1964).
(3) W. J. Fanshawe, V. J. Bauer, and S. R. Safir, *ibid.*, **29**, 942 (1964).
(4) W. E. Dulin and G. C. Gerritsen, *Proc. Soc. Exptl. Biol. Med.*, **113**, 683 (1963).
(5) H. Schmidtmann, *Ber.*, **29**, 1168 (1896).

(1H, very broad, =NOH), 4.28 (2H, broad, NH_2), and 6.63 (2H, sharp, CH_2).[6]

When treated with triethylamine, 2-cyanoacetamidoxime (**5**) was converted to a new compound which was characterized as the crystalline hydrochloride. The identity of this salt as 3,5-diaminoisoxazole hydrochloride (**6**) was established from its elemental analysis and its n.m.r. spectrum, which displays a one-proton singlet at τ 4.92 that is unaffected by deuterium exchange.[7]

The reaction of crude 3,5-diaminoisoxazole base with 1 equiv. of acetic anhydride provided a monoacetyl derivative. Further acetylation gave a diacetyl derivative, 3,5-bisacetamidoisoxazole (**7**). Two structures, 3-acetamido-5-amino- (**8**) or 5-acetamido-3-aminoisoxazole (**9**), were entertained for the monoacetyl



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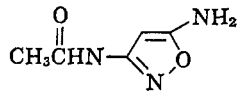

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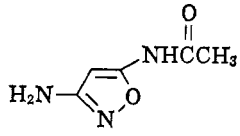
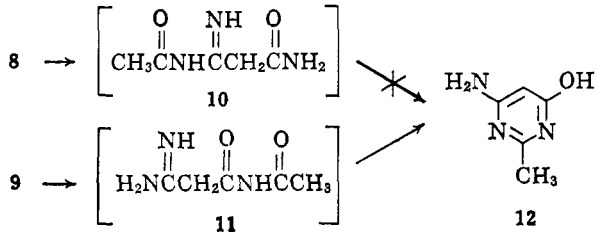


9

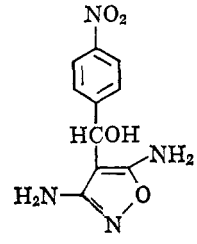
compound. To differentiate between these possibilities, the compound was hydrogenated[8] in ethanol solution with platinum oxide catalyst. The product was shown to be 4-amino-6-hydroxy-2-methylpyrimidine (**12**) by comparison with an authentic sample. Although both postulated reduced intermediates **10** and **11** contain a sequence of atoms which could lead to **12**, cyclization



10 **11** **12**

of the bisamide **10** in neutral ethanol solution appears unlikely, while the amidine and imide groups of **11** are exceptionally well suited for ring formation. Although not unequivocal, the 5-acetamido-3-aminoisoxazole structure **9** has therefore been assigned to the monoacetyl derivative.

The reactivity of 3,5-diaminoisoxazole toward *p*-nitrobenzaldehyde was investigated. Instead of one of the expected Schiff bases, a product was isolated which retained the elements of water. The n.m.r. spectrum of the compound displays doublets at τ 1.77 (2H, J = 8 c.p.s., phenyl), 2.23 (2H, J = 8 c.p.s., phenyl), 4.02 (1H, J = 4 c.p.s., OH), and 4.22 (1H, J = 4 c.p.s., OCH), and singlets at τ 3.78 (2H, NH_2) and 5.09 (2H, NH_2). After deuterium exchange, the signals at τ 3.78, 4.02, and 5.09 disappear, and the signal at τ 4.22 becomes a singlet. These observations demonstrate the presence of one H–C–OH and two NH_2 groups and the absence of a 4-isoxazolyl proton, and are best accommodated by structure **13**, 3,5-diamino-α-(*p*-nitrophenyl)-4-isoxazolemethanol.



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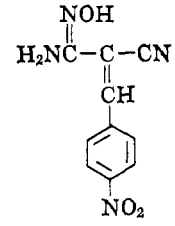
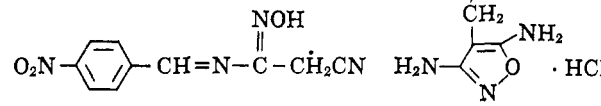


14



15 **16**

The synthesis of 4-alkylated 3,5-diaminoisoxazoles was also accomplished by another route. The reaction of 2-cyanoacetamidoxime (**5**) and *p*-nitrobenzaldehyde provided a benzylidene compound whose n.m.r. spectrum (in pyridine-d_5) displays doublets at τ 1.78 (2H, J = 9 c.p.s., phenyl) and 2.03 (2H, J = 9 c.p.s., phenyl) and singlets at τ −3.10 (1H, very broad, =NOH), 1.95 (1H, = CHAr), and 3.28 (2H, broad, NH_2). The signals at τ −3.10 and 3.28 disappear after deuterium exchange. These data are consistent with structure **14**, 2-cyano-2-*p*-nitrobenzylideneacetamidoxime, and exclude the alternative **15**. Treatment of **14** with sodium borohydride effected reduction and concomitant cyclization to provide 3,5-diamino-4-*p*-nitrobenzylisoxazole, isolated as the hydrochloride **16**. The n.m.r. spectrum of **16** exhibits doublets at τ 1.73 (2H, J = 8 c.p.s., phenyl) and 2.33 (2H, J = 8 c.p.s., phenyl) and singlets at τ 2.07 (5H, broad, NH_2) and 6.01 (2H, CH_2Ar). The signal at τ 2.07 disappears after deuterium exchange. Further confirmation of structures **13** and **16** is found in the similarity of their ultraviolet spectra under both acidic and basic conditions.

Experimental[9]

2-Cyanoacetamidoxime (**5**).—A modification of the procedure of Schmidtmann[5] was used. To a solution of 50 g. (0.75 mole) of malononitrile and 52.5 g. (0.75 mole) of hydroxylamine hydrochloride in 600 ml. of methanol was added slowly with stirring at 0° a mixture of 40.5 g. (0.75 mole) of sodium methoxide and 350 ml. of methanol. The mixture was filtered. Upon standing, 15.5 g. (21%) of a light gray solid, m.p. 135–138°, separated

(6) For comparison, the ultraviolet spectrum of 2-cyano-N-phenethylacetamidine, which as the base exists in the conjugated form, displays a maximum at 258 mμ,[2] and the n.m.r. spectrum of its hydrochloride salt, which exists in the nonconjugated form, displays a CH_2 resonance at τ 5.70.[3]

(7) As a model for 3,5-diaminoazoles, the n.m.r. spectrum of 3,5-diamino-1-phenethylpyrazole hydrochloride (**3**) displays a singlet at τ 4.97.[3]

(8) G. Shaw and G. Sugowdz [*J. Chem. Soc.*, 665 (1954)] have shown that hydrogenation of 5-acetamidoisoxazoles leads to the formation of pyrimidines.

(9) Melting points were determined in a Hershberg apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff. N.m.r. spectra were determined by Mr. W. Fulmor and staff on a Varian A-60 spectrometer in dimethyl-d_6 sulfoxide solution (unless otherwise stated) with tetramethylsilane as an internal standard.

from the filtrate. The filter cake, 60 g. of a light brown solid, was treated with ethanol and filtered. An additional 16.3 g. (22%) of gray crystals, m.p. 136–139°, separated from the filtrate. Recrystallization of the combined crops from ethanol gave long colorless prisms, m.p. 138–140°.

The literature procedure[5] employs an aqueous medium for this reaction. It was found that **5**, which is unstable in water, could not be dried quickly enough when prepared on a large scale in aqueous solution to permit isolation in reasonably pure quality. The infrared spectrum of a sample, m.p. 129–131°, prepared by the literature method was identical with that of the compound prepared above.

3,5-Diaminoisoxazole Hydrochloride (**6**).—A solution of 10 g. (0.1 mole) of 2-cyanoacetamidoxime and 1.0 g. (0.01 mole) of triethylamine in 300 ml. of methanol was stored at room temperature overnight and then concentrated under reduced pressure to 10 g. of a brown liquid. The liquid was dissolved in isopropyl alcohol and acidified with ethanolic hydrogen chloride. Addition of ether to the solution effected the separation of 9 g. (67%) of a light brown crystalline solid, m.p. 125–126° dec.

Anal. Calcd. for $C_3H_6ClN_3O$: C, 26.57; H, 4.43; Cl, 26.20; N, 31.00. Found: C, 26.74; H, 4.56; Cl, 26.02; N, 30.99.

The ultraviolet spectrum exhibits λ_{max}^{MeOH} 244 mμ (ε 25,000), which shifts to 228 mμ (ε 13,000) upon the addition of base.

One attempt to distill the crude base resulted in a violent explosion.

5-Acetamido-3-aminoisoxazole (**9**).—A solution of 10 ml. (0.1 mole) of acetic anhydride and 10 ml. of pyridine was added dropwise with stirring during 30 min. to a cold solution of 10 g. (0.1 mole) of crude 3,5-diaminoisoxazole and 10 ml. of pyridine. The off-white solid, 6.1 g., m.p. 184–192°, which separated was collected. Four recrystallizations from methanol provided the analytical sample, m.p. 195–197° dec.

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.88; H, 5.05; N, 29.57.

The ultraviolet spectrum exhibits λ_{max}^{MeOH} 239 mμ (ε 17,000), which shifts to λ_{max}^{MeOH} 248 mμ (ε 19,000) upon addition of ethanolic hydrogen chloride. The n.m.r. spectrum exhibits singlets at τ −1.15 (1H, NH—C=O), 4.18 (1H, 4-isoxazolyl H), 4.52 (2H, NH_2), and 7.88 (3H, $NC(=O)CH_3$).

3,5-Bisacetamidoisoxazole (**7**). **A.**—A solution of 1.0 g. (0.01 mole) of crude 3,5-diaminoisoxazole, 2.0 g. (0.02 mole) of acetic anhydride, and 10 ml. of pyridine was allowed to stand at room temperature for 15 hr. The colorless solid, 0.73 g., m.p. 185–205°, which separated was collected. Three recrystallizations from methanol provided colorless prisms, m.p. 203–205°.

Anal. Calcd. for $C_7H_9N_3O_3$: C, 45.90; H, 4.95; N, 22.94. Found: C, 46.15; H, 4.87; N, 22.90.

The ultraviolet spectrum exhibits λ_{max}^{MeOH} 227 mμ (ε 11,500) and 246 mμ (ε 11,600). The n.m.r. spectrum exhibits singlets at τ −1.45 (1H, NH—C=O), −0.74 (1H, NH—C=O), 3.25 (1H, 4-isoxazolyl H), 7.85 (3H, $NC(=O)CH_3$), and 7.88 (3H, $NC(=O)CH_3$).

B.—A mixture of 0.12 g. of 5-acetamido-3-aminoisoxazole, 0.11 g. of acetic anhydride, and 2 ml. of pyridine was stirred at room temperature for 3 days and concentrated under reduced pressure to a colorless solid. Recrystallization from methanol provided 0.05 g. of colorless prisms, m.p. 203–205°. The infrared spectrum was identical with that of material prepared in method A, above.

Hydrogenation of 5-Acetamido-3-aminoisoxazole. 4-Amino-6-hydroxy-2-methylpyrimidine (**12**).—A solution of 0.50 g. (3.5 mmoles) of 5-acetamido-3-aminoisoxazole in 20 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure with platinum oxide catalyst. During 2.25 hr., 3.7 mmoles of hydrogen was taken up. A colorless solid separated during the hydrogenation. After warming to dissolve the solid, the mixture was filtered. Upon cooling, 0.19 g. of colorless microcrystals, m.p. 298–303°, separated from the filtrate. The infrared spectrum was identical with that of authentic 4-amino-6-hydroxy-2-methylpyrimidine (Aldrich Chemical Co.).

3,5-Diamino-α-(*p*-nitrophenyl)-4-isoxazolemethanol (**13**).—A solution of 1.1 g. (0.01 mole) of crude 3,5-diaminoisoxazole, 3.0 g. (0.02 mole) of *p*-nitrobenzaldehyde, and 110 ml. of ethanol was allowed to stand at room temperature overnight. A yellow solid, 1.7 g., m.p. 156–160°, separated and was collected. Two recrystallizations from acetone–carbon tetrachloride provided yellow microcrystals, m.p. 164–165°.

Anal. Calcd. for $C_{10}H_{10}N_4O_4$: C, 48.00; H, 4.02; N, 22.39. Found: C, 47.90; H, 4.14; N, 22.07.

The ultraviolet spectrum exhibits λ_{max}^{MeOH} 232 mμ (ε 10,800) and 269 mμ (ε 8400), which changes to λ_{max}^{MeOH} 249 mμ (ε 25,000)[10] upon addition of hydrogen chloride.

2-Cyano-2-*p*-nitrobenzylideneacetamidoxime (**14**).—A solution of 10 g. (0.1 mole) of 2-cyanoacetamidoxime, 30 g. (0.2 mole) of *p*-nitrobenzaldehyde, and 750 ml. of methanol was allowed to stand at room temperature for 2 days and was then concentrated under reduced pressure to a tacky orange solid. Recrystallization from acetonitrile provided 9.3 g. (40%) of yellow crystals, m.p. 189–191° dec. Two additional recrystallizations gave the analytical sample as orange prisms, m.p. 190–192° dec.

Anal. Calcd. for $C_{10}H_8N_4O_3$: C, 51.72; H, 3.47; N, 24.13. Found: C, 51.97; H, 3.02; N, 24.22.

The ultraviolet spectrum exhibits $\lambda_{max}^{CH_3CN}$ 294 mμ (ε 13,700) and 346 mμ (ε 11,900).

3,5-Diamino-4-*p*-nitrobenzylisoxazole Hydrochloride (**16**).—A solution of 0.76 g. (0.02 mole) of sodium borohydride in 10 ml. of methanol was added to a stirred suspension of 0.47 g. (0.002 mole) of 2-cyano-2-*p*-nitrobenzylideneacetamidoxime in 20 ml. of methanol. After 2 hr. at room temperature, the yellow solution was acidified with ethanolic hydrogen chloride. The mixture was filtered, and the filtrate was concentrated under reduced pressure to 0.75 g. of a yellow solid. The solid was treated with hot ethanol. The mixture was filtered, and the filtrate was concentrated to 0.51 g. of an off-white solid, m.p. 150–155°. This solid was dissolved in isopropyl alcohol and precipitated with hexane, to yield 0.33 g. of a cream-colored solid, m.p. 153–156° dec.

Anal. Calcd. for $C_{10}H_{11}ClN_4O_3$: C, 44.36; H, 4.07; Cl, 13.12; N, 20.70. Found: C, 44.47; H, 4.16; Cl, 13.02; N, 20.95.

The ultraviolet spectrum exhibits λ_{max}^{MeOH} 252 mμ (ε 16,900), which changes to λ_{max}^{MeOH} 234 mμ (ε 10,600) and 272 mμ (ε 8700) upon addition of sodium hydroxide.

(10) The intensity of the maximum is dependent upon the amount of acid present.

Steric Enhancement of Resonance. III. Absorption Spectra of the 1-Alkyl-2,4-dinitrobenzenes[1]

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Received January 26, 1965.

We have suggested that progressive bathochromic displacements of ultraviolet maxima and longer wave length band edges in the series, 1,3,5-trinitrobenzene, 2,4,6-trinitrotoluene, 1-ethyl-2,4,6-trinitrobenzene, 1-isopropyl-2,4,6-trinitrobenzene, 1-*t*-butyl-2,4,6-trinitrobenzene, might be ascribed to a phenomenon which we have characterized as steric diminution of electronic suppression of resonance interaction or, more succinctly, *steric enhancement of resonance.*[3] In the system I, as the bulk of R increased, the nitro groups in positions 2 and 6 were forced increasingly from coplanarity, and steric inhibition of ($R—C_1^+ \rightarrow C_2=NO_2^-$) and ($R—C_1^+ \rightarrow C_6=NO_2^-$) resonance resulted in successively lowered intensity of the band deriving from these electronic transitions. The same

(1) Part II: M. J. Kamlet, H. G. Adolph, and J. C. Hoffsommer, *J. Am. Chem. Soc.*, **86**, 4018 (1964).

(2) Work done in part while M. J. K. was attached to the Embassy of the United States, Office of Naval Research, London.

(3) M. J. Kamlet, J. C. Hoffsommer, and H. G. Adolph, *J. Am. Chem. Soc.*, **84**, 3925 (1962).