1550 (C=C), 1315, 1125 cm^{-1} (SO_2); λ_{max} 246 mμ (ε 8800) and 311 mμ (ε 6500). The compound was only sparingly soluble in the usual nmr solvents; hence, the data for the minor component are not reliable. The major component shows broad singlets at δ 2.09 (CH_3) and 3.70 (CH_2). The olefinic protons appear as a broad singlet at δ 5.33 and a weakly split multiplet at 6.10. The spectrum indicates that the minor component is present in about 15%. Acid hydrolysis of the mixture afforded the ketone **7** in good yield.

Anal. Calcd for $C_{10}H_{15}NO_3S$: C, 52.38; H, 6.59. Found: C, 52.23; H, 6.44.

B. A solution of 1.6 g (7 mmoles) of the enamine **9** and five drops of triethylamine in 50 ml of dioxane was heated under reflux for 24 hr. From the reaction mixture 1.1 g (69%) of a mixture of compounds **4c** and **5c**, mp 194–196°, was isolated.

Maleic Anhydride Adduct.—The above mixture (800 mg, 3.5 mmoles) and 340 mg (3.5 mmoles) of maleic anhydride in 20 ml of xylene was heated under reflux for 2 hr. When cold, the precipitate was filtered and washed with ethanol yielding 800 mg of product: mp 254–255°; ν_{max} 1780, 1810 cm^{-1} (anhydride C=O). The substance was insoluble in all common solvents. It formed a homogeneous solution with aqueous sodium hydroxide.

Anal. Calcd for $C_{14}H_{17}NO_6S$: C, 51.37; H, 5.23; N, 4.28; O, 29.32. Found: C, 51.15; H, 5.20; N, 4.31; O, 29.22.

2-N-Morpholinyl-1-(2-propynylsulfinyl)propene (10).—To a solution of 2.5 g (20 mmoles) of the sulfoxide **2** in 20 ml of dry ether was added dropwise 3.5 g (40 mmoles) of morpholine. The reaction mixture was left at room temperature overnight. Filtration gave 3.3 g (78%) of the adduct **10**, mp 108–110°. An analytical sample was obtained by recrystallizations from ethanol: mp 118°; ν_{max} 3200 (C≡CH), 1560 (C=C–N) 1005 cm^{-1} (SO); nmr, singlet at δ 2.27 (CH_3), triplet at 2.42 (C≡CH), doublet at 3.56 (CH_2), singlet at 5.25 (CH), and characteristic absorption due to the morpholine protons (the peak area ratio is 3:1:2:2, respectively).

Anal. Calcd for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09. Found: C, 56.36; H, 7.04.

Registry No.—**2**, 15292-69-0; **3**, 14039-88-4; **4a**, 15292-71-4; **4b**, 15292-72-5; **4c**, 15292-73-6; **6**, 15292-74-7; **7**, 15292-75-8; **7** 2,4-dinitrophenylhydrazone, 15268-82-3; **7** oxime, 15268-83-4; **8b**, 15268-58-3; **9**, 15268-59-4; **10**, 15268-60-7; **6**·HCl, 15268-54-9; **5a**, 15268-55-0; **5b**, 15268-56-1; **5c**, 15268-57-2.

The Preparation and Properties of Some Acylguanidines[1a]

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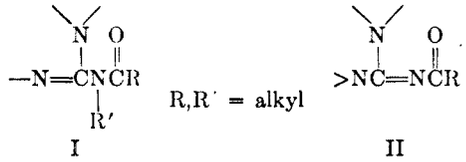
The preparation and properties of a number of monoacylguanidines are described. Ultraviolet spectral studies in aqueous and ethanolic solutions as a function of pH and observation of hydrolytic behavior have been found to be useful in distinguishing between acylguanidines of the acylamino and acylimino types. Examination of their pK_a's revealed significant differences with specific series. However, the wide range of values obtained made the pK_a's of little utility for structural correlations among the various acylguanidines.

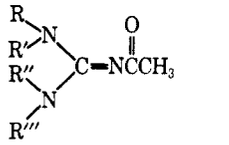
Our interest in acylguanidines was stimulated by the possible presence of such a moiety in a natural substance and its degradation products. There exist two possible substituted monacylguanidine types, but a literature search revealed that no clear distinction has been made between the acylamino (I) and acylimino (or potential acylimino) (II) forms. In particular, we were interested in the ultraviolet spectral behavior of the two types as a function of pH and in their pK's.



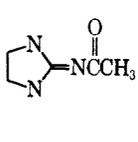
I II

A series of substituted guanidines has been monoacetylated, and the resulting derivatives are reported[2] to absorb in the ultraviolet between 230–235 mμ. Since neither guanidine nor primary or secondary amides absorb strongly above 210 mμ, this absorption was interpreted to indicate conjugation of the acetyl carbonyl with the guanidine moiety. Further, from this evidence it was concluded that monoacetylguanidines exist in the acetylimino form. Although our present work confirms these structural assignments, it also clearly demonstrates the difference in ultraviolet absorption of types I and II. Since there are only a few reported[3-9] compounds of the acylamino type and no spectral and limited pK data for them, we have synthesized a series of suitable compounds for comparison with some acyliminoguanidines of proven structure.

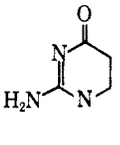
Synthesis of Acylimino Type.[10]—Compounds III, V, VII, and VIII were prepared as reported;[2,11,12] creatinine (IX) was a commercial sample. Acetyl-N,N,-



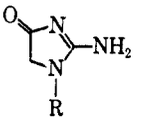
III, R = R' = R'' = R''' = H
IV, R = R''' = CH_3; R' = R'' = H
VI, R = R' = R'' = R''' = CH_3



V



VII



VIII, R = H
IX, R = CH_3

(1) (a) Supported in part by the U. S. Army Research Office, Durham, N. C.; (b) National Institutes of Health Predoctoral Fellow.

(2) R. Greenhalgh and R. A. B. Bannard, *Can. J. Chem.*, **39**, 1017 (1961).

(3) T. B. Johnson and B. H. Nicolet, *J. Am. Chem. Soc.*, **37**, 2416 (1915).

(4) K. Zeile and H. Meyer, *Z. Physiol. Chem.*, **252**, 101 (1938).

(5) G. Korndorfer, *Arch. Pharm.*, **242**, 620 (1904).

(6) A. F. McKay and M. E. Kreling, *Can. J. Chem.*, **40**, 1160 (1962).

(7) A. F. McKay and M. E. Kreling, *ibid.*, **35**, 1438 (1957).

(8) A. F. McKay and M. E. Kreling, *ibid.*, **40**, 205 (1962).

(9) A. F. McKay, W. G. Hatton, and R. O. Braun, *J. Am. Chem. Soc.*, **78**, 6144 (1956).

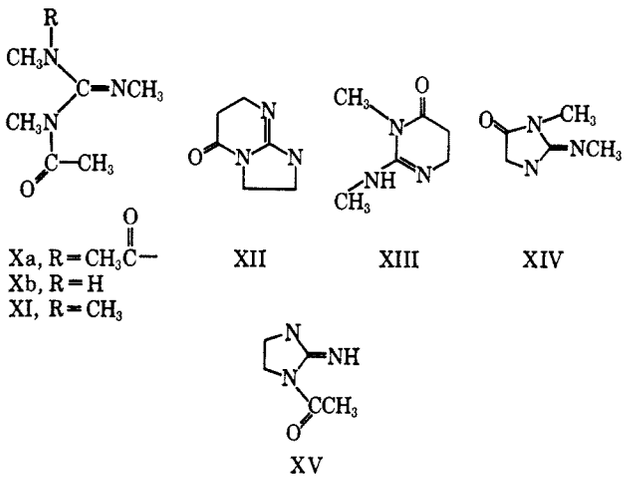
(10) Where tautomeric structures are possible, we have adopted the following convention in drawing and naming compounds: (a) acylimino forms are used whenever possible, (b) the exocyclic double bond isomer is preferred for five-membered ring compounds, and (c) the endocyclic double bond isomer is preferred for six-membered ring compounds.

(11) F. H. Holm, *Arch. Pharm.*, **242**, 612 (1904).

(12) I. S. Bengelsdorf, *J. Am. Chem. Soc.*, **75**, 3138 (1953).

N′,N′-tetramethylguanidine was prepared by reaction of commercially available N,N,N′,N′-tetramethylguanidine with acetic anhydride. Although N-acetyl-N′,N″-dimethylguanidine (IV) has been reported,[2] its method of preparation and characterization were not described. We prepared it by reaction of N,N′-dimethylguanidine with ethyl acetate, analogously to the procedure for the preparation of a series of monoacetylguanidines.[2] Its structure can be assigned from its nmr spectrum which reveals only a sharp singlet integrating for six protons in the N-methyl region (δ 3.0). The isomeric structure in which the acetyl group is attached to the methylated nitrogen would be expected to show two different N-methyl absorptions, as has been shown to be the case with acetyl-N,N′,N″-trimethylguanidine and acetyl-N,N,N′,N″-tetramethylguanidine, and which will be discussed later. The structure of V likewise can be assigned as 2-acetyliminoimidazolidine from its nmr spectrum, a sharp singlet for the equivalent ethylene protons as opposed to a multiplet for the other isomer. Its structure was confirmed by direct synthesis of the other isomer.

Synthesis of Acylamino Type.—The acylaminoguanidines are new compounds except XII, which was synthesized as reported.[13] The methods for preparing monoacylguanidines include (1) acylation of a guanidine with an anydride,[2,14-18] acyl halide,[18,19] or ester,[2,7-9,20-24] (2) deacylation of a di- or triacyl guanidine in abolute ethanol,[15] and (3) cyclization of a guanidino acid with concentrated hydrochloric acid.[5,11,12] The parent guanidines of X and XI were synthesized as previously reported.[25-27] Attempted monoacetylation of N,N′,N″-trimethylguanidine with ethyl acetate in ethanol at room temperature or under reflux gave only unchanged starting material. Reactions at room temperature using either a large excess or 50 mole % of acetic anhydride afforded a mixture of acetate salt and diacetyl and monoacetyl derivatives as shown by paper chromatography. Since the diacetyl derivative could be prepared in good yield by prolonged treatment with acetic anhydride, deacetylation to Xb, analogous to the reported[15] selective deacetylation of triacetylguanidine with absolute ethanol, was investigated. By following the deacetylation with paper chromatography and ultraviolet absorption (disappearance of the 233-mμ absorption in acid of the diacetyl compound Xa) a 41% yield of Xb was obtained, the other products being a minor amount of diacetyl compound Xa and the unacetylated guanidine. The nmr spectrum of Xb revealed that the N-methyl

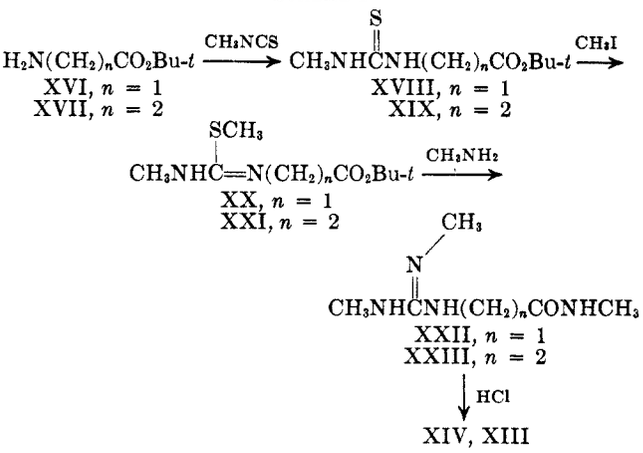


group on the acetylated nitrogen was shifted downfield 0.1 δ unit from the other two equivalent N-methyl groups.

N,N,N′,N″-Tetramethylguanidine was generated from its hydriodide salt[26] by ion exchange. Subsequent reaction with acetic anhydride and vapor phase chromatographic purification afforded XI in 47% yield. Its nmr spectrum also revealed that the methyl group on the acetylated nitrogen was shifted slightly downfield relative to the remaining N-methyl groups.

Several attempts to prepare the appropriately substituted β-guanidinopropionic[28] and -acetic[29] acid intermediates for the synthesis of 2-methylamino-3-methyl-4-oxo-3,4,5,6-tetrahydropyrimidine (XIII) and 1-methyl-2-methyliminoimidazolidin-5-one (XIV) by the usual reaction of an isothiourea and an amino acid failed. We then proceeded to build the guanidino moiety *via* a protected amino acid, according to Scheme I.

SCHEME I

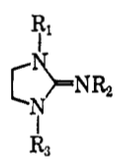


The *t*-butyl ester was employed to minimize side reactions of both inter- and intramolecular nature and the preparation of *t*-butyl glycinate (XVI) was carried out as previously reported,[30] beginning with bromoacetyl bromide, in over-all 62% yield. *t*-Butyl β-alaninate (XVII) was prepared in poor yield beginning with β-alanine and isobutylene in diglyme, analogous to a reported[31] procedure on the preparation of *t*-

(13) A. F. McKay and M. E. Kreling, *Can. J. Chem.*, **38**, 1819 (1960).
(14) W. F. Cockburn and R. A. B. Bannard, *ibid.*, **35**, 1285 (1957).
(15) R. Greenhalgh and R. A. B. Bannard, *ibid.*, **37**, 1810 (1959).
(16) A. A. Ryabinin, *J. Gen. Chem. USSR*, **22**, 541 (1952).
(17) C. Grundmann and E. Beyer, *Ber.*, **83**, 452 (1952).
(18) G. Korndorfer, *Arch. Pharm.*, **241**, 449 (1903).
(19) M. Necki, *Ber.*, **7**, 1584 (1874).
(20) R. R. Burtner, U. S. Patent 2,734,904; *Chem. Abstr.*, **50**, 13,095*i* (1956).
(21) J. K. Simons and W. I. Weaver, U. S. Patent 2,408,694; *Chem. Abstr.*, **41**, 1239*i* (1946).
(22) W. N. Oldham, U. S. Patent 2,378,724; *Chem. Abstr.*, **39**, 5088 (1945).
(23) W. Traube and R. Ascher, *Ber.*, **46**, 2077 (1913).
(24) A. Ostrogovich, *Chem. Zentr.*, II, 1358 (1905),
(25) M. L. Moore and F. S. Crossley, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1963, p 617.
(26) J. D. Mold, J. M. Ladino, and E. J. Schantz, *J. Am. Chem. Soc.*, **75**, 6321 (1953).
(27) S. J. Angyal and W. K. Warburton, *J. Chem. Soc.*, 2492 (1951).
(28) M. Mourgue, *Bull. Soc. Chim. France*, 181 (1948).
(29) E. Brand and F. C. Brand, ref 25, p 441.
(30) A. Vollmar and M. S. Dunn, *J. Org. Chem.*, **25**, 387 (1960).
(31) R. W. Roeske, *Chem. Ind.* (London), 1121 (1959).

butyl esters of amino acids; *t*-butyl glycinate (XVI) also was obtained in extremely poor yield using this method. The subsequent conversions to the thiourea (XVIII, XIX) and S-methyl (XX, XXI) derivatives were quantitative. Orginally we planned to treat the S-methyl compounds with methylamine to form the corresponding guanidino *t*-butyl esters which could subsequently be converted to the acids and cyclized. However, reaction of both isothioureas XX and XXI with excess methylamine invariably led to loss of the *t*-butyl group and isolation of the corresponding amides XXII and XXIII. Presumably this came about *via* first reaction of methylamine with the isothiuronium portion to form the strongly alkaline guanidine moiety which subsequently underwent ring closure. Reaction with excess methylamine could then cause ring opening to yield the products obtained. The intramolecular path is supported by the fact that both *t*-butyl β-alaninate and *t*-butyl glycinate are completely stable under the conditions used, *i.e.*, treatment with excess methylamine. Conversion to the corresponding amides was not detrimental to the synthesis since the ensuring reactions with concentrated hydrochloric acid would lead to the cyclized products whether the compounds were guanidino acids or amides. Ring closures with concentrated hydrochloric acid afforded the cyclized products XIII and XIV plus methylamine hydrochloride which was easily separated by ion exchange.

Synthesis of 1-acetyl-2-iminoimidazolidine (XV) was first attempted *via* deacetylation of either diacetyl derivative, XXX or XXXI. Reaction of 2-imino-



XXIV, $R_1 = R_2 = R_3 = H$
XXVI, $R_1 = R_3 = H$; R_2 = Cbo
XXVII, $R_1 = R_2 = H$; R_3 = Cbo
XXVIII, $R_1 = R_3 = CH_3CO$; R_2 = Cbo
XXIX, $R_1 = R_2 = CH_3CO$; R_3 = Cbo
XXX, $R_1 = R_3 = CH_3CO$; $R_2 = H$
XXXI, $R_1 = R_3 = CH_3CO$; $R_3 = H$
XXXII, R_1 = CH CO; R_2 = Cbo; $R_3 = H$

imidazolidine (XXIV)[32] and benzyloxycarbonyl chloride (XXV) in aqueous tetrahydrofuran afforded a low yield after chromatography of the two monobenzyloxycarbonyl derivatives XXVI and XXVII in a ratio of 1:2. The isomers were readily distinguishable by their nmr spectra which revealed a sharp singlet for the ethylene protons in XXVI and a multiplet for the ethylene protons in XXVII. The monobenzyloxycarbonyl derivatives were converted to the corresponding diacetylbenzyloxycarbonyl compounds XXVIII and XXIX with acetic anhydride and then smoothly hydrogenolyzed to the corresponding diacetyl derivatives XXX and XXXI. Deacetylation of 1-acetyl-2-acetyliminoimidazolidine (XXXI) with absolute ethanol under a variety of conditions led only to the acetylimino compound V as established by thin layer chromatography and ultraviolet absorption. Deacetylation of 1,3-diacetyl-2-iminoimidazolidine (XXX) also under a variety of conditions led to a mixture of products, a significant amount of which was V as shown by thin layer chromatography, nmr, and ultraviolet absorption. Thus rearrangement to the apparently more stable 2-acetyliminoimidazolidine (V) must have taken place.

In view of the deacetylation results a nonhydrolytic procedure was sought which would eliminate the possibility of rearrangement. The alkalinity of 2-benzyloxycarbonyliminoimidazolidine (XXVI) should be greatly reduced by the addition of an acetyl group and hence monoacetylation should be possible. This was the case when XXVI was treated with excess acetyl chloride and triethylamine in tetrahydrofuran to yield 1-acetyl-2-benzyloxycarbonyliminoimidazolidine (XXXII). Subsequent hydrogenolysis to XV proceeded smoothly with no rearrangement. Its nmr spectrum displayed a multiplet for the ethylene protons which readily distinguishes XV from its isomer V; the latter has a sharp singlet for the equivalent ethylene protons.

Discussion of Results

The ultraviolet spectra of the various acylguanidines were taken as a function of pH in the hope of more completely differentiating the acylamino from the acylimino types. Examination of the spectra in acidic ethanol and aqueous (pH 3 and 7) solutions frustrated this objective due to frequent end absorptions and random positioning of the maxima. The important data are the aqueous pH 12 and alkaline ethanolic spectra (see Table I). The only compound which does not possess an absorption maximum, N-acetyl-N′,N″-dimethylguanidine (IV), does show end absorption which probably is not due to hydrolysis since at 230 mμ the extinction is ~10,000. Simple guanidines and their salts are reported[33] to absorb below 215 mμ with ϵ_{max} <1000. Also, the end absorption is stable at pH 12 for at least 1 hr which would not be the case if hydrolysis were taking place.

The most striking difference between the acylamino and acylimino types of acylguanidines can be seen in the cyclic cases (which include endo- and exocyclic acylguanidines). Here, the difference lies in the hydrolytic behavior which is conveniently observed in the aqueous pH 12 spectra. Hydrolysis proceeds with simple pseudo-first-order kinetics and can be conveniently followed by observing the decrease in optical density. In all cases the cyclic acylamino compounds were extremely labile to hydrolysis as demonstrated by their relatively short half-lives. In contrast, the acylimino compounds were completely stable for at least 1 hr at pH 12 with the exception of β-alacreatinine (VII) which hydrolyzes at a much slower rate ($t_{1/2}$ = 4 hr) than XIII which has a half-life of only 8 min. This contrast also can be shown between VIII or IX, which are stable, and XIV which has a half-live of 70 min, and between V, which is stable, and XV, which has a half-life of only 1 min.

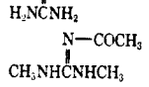
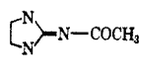
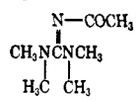
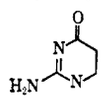
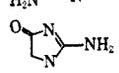
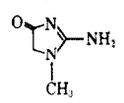
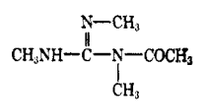
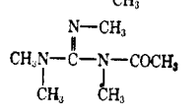
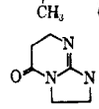
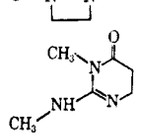
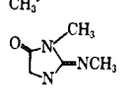
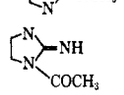
Although in aqueous solution of pH 12, the absorption maxima for the cyclic acylamino compounds generally occur at lower wavelength than for the cyclic acylimino compounds, this criterion alone cannot be used to differentiate the two types since an anomalous situation exists with the two acetyl derivatives of 2-iminoimidazolidine, XV and V; both absorb in the 230-mμ region. The alkaline ethanol spectra of the

(32) M. P. Pierron, *Ann. Chim.* (Rome), **11**, 361 (1919).

(33) I. Szilagyi, T. Valyi-Nagy, and T. Keresztes, *Nature*, **196**, 376 (1962).

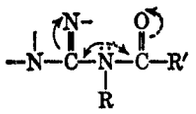
TABLE I

ULTRAVIOLET SPECTRA[a] AND pK_a's OF ACYLGUANIDINES

Compd		Aqueous Buffer,[b] pH 12 λ_{max}, mμ (ε)	0.01 *N* NaOH in absolute ethanol λ_{max}, mμ (ε)	pK_a[h]
		A. Acylimino		
	III	228 (16,200)[c] ($t_{1/2}$ = 5.5 hr)	231 (16,400)	8.33[i]
	IV	*d*	235 (16,000)	7.50
	V	230 (19,000)	230 (19,600)	7.48
	VI	234 (14,400)	238 (15,000)	7.50
	VII	233 (10,870)[c] ($t_{1/2}$ = 4 hr)	237 (13,100)	7.05[j]
	VIII	225 (8,125)	228 (7,410)	4.80[k]
	IX	235 (7,060)	230 (9,600)	4.83[l]
		B. Acylamino		
	Xb	213 (9,500)[e]	216 (8,550)	8.93
	XI	220 (9,050)[e]	225 (8,950)	9.10
	XII	212 (7,850)[e,f] ($t_{1/2}$ = 8 min)	218 (7,070) broad 228 (7,070) broad	8.25[m]
	XIII	210 (10,700)[e,f] ($t_{1/2}$ = 8 min)	213 (7,350)	9.48
	XIV	207 (5,450)[e,f] ($t_{1/2}$ = 70 min)	223 (2,700)	7.96
	XV	208 (2,160) 234 (7,970)[e,f] ($t_{1/2}$ = 1 min)	213 (4,520)[g] 231 (7,650)[e] ($t_{1/2}$ = 4 min)	9.06

[a] All maxima unchanged for 1 hr in solvent used unless otherwise indicated. [b] Phosphate buffer. [c] Hydrolyzes slowly. [d] End absorption only. [e] Taken in 0.01 *N* NaOH. [f] Rapid hydrolysis; extinction coefficients are extrapolated values. [g] This low wavelength absorption is due to the hydrolysis product 2-iminoimidazolidine as evidenced by the fact that it absorbs at λ_{max} 213 mμ (ε 4250) in 0.01 *N* ethanolic NaOH. [h] Potentiometric titrations at 25° unless otherwise indicated. [i] At 20°; A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948). [j] T. Goto, Y. Kishi, S. Takahashi, and Y. Hirata, *Tetrahedron Letters*, 779 (1964). [k] C. F. Failey and E. Brand, *J. Biol. Chem.*, **102**, 767 (1933). [l] A. K. Grzybowski and S. P. Datta, *J. Chem. Soc.*, 187 (1964). [m] At 30.5°; A. F. McKay and M. E. Kreling, *Can. J. Chem.*, **40**, 1160 (1962).

cyclic compounds reveal no hydrolytic behavior except for XV but are less useful than the aqueous pH 12 data. McKay and Kreling[8] also report similar lability for a number of bicyclic acylguanidines of the acylamino type in aqueous solution. From a theoretical standpoint, the labile nature of the cyclic acylaminoguanidines can be looked upon as resulting from amidine resonance opposing normal amide resonance, while for the acylimino compounds normal amide



R, R′ = alkyl

resonance is reinforced or extended through the other two nitrogens.

For the acyclic acylguanidines, differentiation can most conveniently be made in ethanolic sodium hydroxide since all compounds possess absorption maxima. The acylimino compounds III, IV, and VI cover the extremes of substitution and absorb in the region 231–238 mμ (ε 16,000–20,000). This is in contrast to the acyclic acylamino compounds Xb and XI which absorb at 216–225 mμ (ε ~9000). It can be seen that the absorption maximum for acetylguanidine (III) is quite close to that of acetyl-N,N,N′,N″-tetramethylguanidine (XI). In this regard, the degree of substitution becomes important since the absorption maxima of both acylimino and acylamino compounds

shift bathochromically with increasing alkyl substitution. The only labile acylic acylguanidine was acetylguanidine (III) which hydrolyzes very slowly in aqueous pH 12 solution with pseudo-first-order kinetics.

Thus a combination of data which includes absorption maximum in both alkaline ethanolic and aqueous solutions as well as observation of any hydrolytic behavior can be generally diagnostically definitive in differentiating acylamino- and acyliminoguanidines.

It is of interest that the ultraviolet spectra of two diacetylguanidines, 1,3-diacetyl-2-iminoimidazolidine (XXX) and 1-acetyl-2-acetyliminoimidazolidine (XXXI) did not possess two absorption maxima in the regions 212–225 mμ and 243–263 mμ as would be predicted from previous data.[2] Compound XXX possessed λ_{max}^{EtOH} 221 mμ (ε 15,750) and XXXI λ_{max}^{EtOH} 244 mμ (ε 18,950). These results clearly demonstrate that differentiation between mono- and diacetylguanidines solely on the basis of ultraviolet absorption is unreliable.

An examination of the infrared spectra of the monoacylguanidines revealed strong absorption(s) in the region 5.7–6.2 μ (taken as the hydrochlorides either in chloroform or potassium bromide) and failed to serve any differentiating purpose between the two types discussed. The spectra in fact were very similar to those of simple substituted guanidines reported in the literature.[34]

The opportunity also was taken to examine the pK_a's of the compounds synthesized. The pK_a values for the compounds quoted in the literature are cited and are in agreement with values found in our titrations. It can be seen from the wide range of values that pK_a's cannot be used as a diagnostic tool in distinguishing between acylimino and acylamino guanidines in general. However, there are some interesting points to note. For acyclic guanidines, it has been reported[27] that the pK_a changes very little with increasing alkyl substitution (pK_a = 13.4–13.9). The same relatively small changes can be seen in acyclic compounds III, IV, and VI, which are acylimino types, and Xb and XI, which are acylamino types. In the acyclic and exocyclic acylguanidines, the pK_a's in general are 0.5–1.5 pK_a units higher for the acylamino types. The largest differences can be found in the endocyclic cases. In comparing compound VII to XIII, an increase of 2.5 pK_a units is seen. An even more pronounced difference, greater than 3 pK_a units, is seen when comparing compounds VIII and IX to XIV.

The increase in pK_a in going from acylimino- to acylaminoguanidines can be explained by conjugation with the acetyl group. For the acylamino compounds, normal amide resonance is opposed by amidine resonance, thus leading to a decrease of the normal base-weakening effect of acylation. On the other hand, for the acylimino compounds normal amide resonance is extended *via* the other two nitrogens and the base-weakening effect is reinforced.

Experimental Section[35]

N-Acetyl-N′,N″-dimethylguanidine (IV) Nitrate.—The hydrobromide salt of N,N′-dimethylguanidine,[26] (5.0 g, 29.8 mmoles), was dissolved in 50 ml of absolute ethanol and applied to a Bio Rad AG1 X-8 column in the OH^- form. Elution with 200 ml of absolute ethanol and evaporation of the solvent afforded a clear liquid to which was added 10 ml (2.9 ml theoretical) of ethyl acetate. After overnight setting at room temperature, the excess ethyl acetate was removed *in vacuo* to afford a hygroscopic solid weighing 3.6 g (94%). The free base was difficult to analyze and therefore was converted to the nitrate salt using concentrated nitric acid in absolute ethanol. Recrystallization of the white solid from ethanol–ether afforded the nitrate salt of IV: mp 98–100°; $\lambda_{max}^{0.01\ N\ NaOH,\ C_2H_5OH}$ 235 mμ (ε 16,000); nmr absorption (D_2O) showed $CH_3C(=O)$– at δ 2.3 (s) and 2 CH_3N– at 3.0 (s).

Anal. Calcd for $C_5H_{12}N_4O_4$: C, 31.3; H, 6.3; N, 29.2. Found: C, 31.0; H, 6.1; N, 29.2.

Acetylguanidine (III) was prepared as previously reported:[2] mp 188–190° (lit.[2] mp 188–190°); λ_{max}^{pH3} 203 mμ (ε 19,200); λ_{max}^{pH7} 205 (13,000); λ_{max}^{pH12} 228 (16,200); $\lambda_{max}^{0.01\ N\ NaOH,\ C_2H_5OH}$ 231 (16,400).

2-Acetyliminoimidazolidine (V) was prepared as previously reported:[2] mp 223–235° (lit.[2] mp 227–229°); λ_{max}^{pH3} 201 mμ (ε 17,050); λ_{max}^{pH7} 205 (12,150); λ_{max}^{pH12} 230 (19,000); $\lambda_{max}^{0.1\ N\ NaOH,\ C_2H_5OH}$ 230 (19,600); nmr absorption ($CDCl_3$) showed $CH_3C(=O)$– at δ 2.05 (s) and $-CH_2CH_2-$ at 3.65 (s).

Acetyl-N,N,N′,N′-tetramethylguanidine (VI).—To 10.0 g (0.115 mole) of N,N,N′,N′-tetramethylguanidine was slowly added 50 ml of acetic anhydride. After the initial exothermic reaction had subsided, the solution was heated at 100° for 6 hr, cooled, and excess acetic anhydride removed *in vacuo* at 30° for 5 hr. Preparative vpc on 60–70 mesh HMDS Chromosorb W coated with 15% SF 96 afforded pure acetyl-N,N,N′,N′-tetramethylguanidine (VI) as a liquid: λ_{max}^{pH3} 210 mμ (ε 12,100), 248 (6900); λ_{max}^{pH7} 212 (10,600), sh 234 (7920); λ_{max}^{pH12} 234 (14,400); $\lambda_{max}^{0.01\ N\ HCl,\ C_2H_5OH}$ 213 (11,400), sh 233 (7440); $\lambda_{max}^{0.01\ N\ NaOH,\ C_2H_5OH}$ 238 (15,100); nmr absorption (CCl_4) showed $CH_3C(=O)$– at δ 1.90 (s) and 4 CH_3N– at 2.80 (s).

Anal. Calcd for $C_7H_{15}N_3O$: C, 53.5; H, 9.6; N, 26.7. Found: C, 53.1; H, 9.9; N, 27.2.

β-Alacreatinine (VII) hydrochloride was prepared as previously reported:[11] mp 270–275° dec (lit.[11] mp 268–271°); λ_{max}^{pH12} 233 mμ (ε 10,870); $\lambda_{max}^{0.01\ N\ NaOH,\ C_2H_5OH}$ 237 (13,100).

Glycocyamidine (VIII) hydrochloride was prepared as previously reported:[12] mp 211–212° dec (lit.[12] mp 208–210° dec); λ_{max}^{pH7} 223 mμ (ε 9350); λ_{max}^{pH12} 225 (8125); $\lambda_{max}^{0.01\ N\ NaOH,\ C_2H_5OH}$ 228 (7410).

Creatinine (IX) hydrochloride was purchased from Eastman Organic Chemicals: mp 260–261° dec; λ_{max}^{pH3} 215 mμ (ε 4940); λ_{max}^{pH7} 234 (6950); λ_{max}^{pH12} 235 (7060); $\lambda_{max}^{0.01\ N\ HCl,\ C_2H_5OH}$ 215 (5130); $\lambda_{max}^{0.01\ N\ NaOH,\ C_2H_5OH}$ 230 (9600).

Diacetyl-N,N′,N″-trimethylguanidine (Xa).—To 615 mg (6.1 mmoles) of N,N′,N″-trimethylguanidine, generated from the nitrate salt[36] by elution with ethanol through a Bio Rad AG1 X-8 column in the OH^- form, was added 30 ml of acetic anhydride and the solution was heated at 100° for 6 hr and cooled and excess acetic anhydride removed *in vacuo* at room temperature for 3 hr. The residue was distilled at 50° (1 mm) to afford 960 mg (85%) of diacetyl-N,N′,N″-trimethylguanidine (Xa): λ_{max}^{pH3} 233 mμ (ε 9500); λ_{max}^{pH7} 212 (12,050); λ_{max}^{pH12} 220 (8900); nmr absorption (CCl_4) showed $CH_3C(=O)$– at δ 1.95 (s) and 215 (s), 3 CH_3N– at 2.90 (s), 3.02 (s), and 3.08 (s).

Anal. Calcd for $C_8H_{15}N_3O_2$: C, 51.9; H, 8.2; N, 22.7. Found: C, 52.1; H, 8.1; N, 22.7.

Acetyl-N,N′,N″-trimethylguanidine (Xb).—A solution of 1.77 g (9.56 mmoles) of diacetyl-N,N′,N″-trimethylguanidine (Xa) and 10 ml of absolute ethanol was heated under nitrogen at 75° for 1.5 hr. Evaporation of the solvent and examination of the residue by ultraviolet spectrometry (disappearance of 233-mμ acid spectrum of diacetyl compound) and paper chromatography using butanol–acetic acid–water (4:1:5) revealed mostly starting material and very little monoacetyl compound. The residue was taken up again in 10 ml of absolute ethanol and heated again to 75° for 1 hr. After evaporation of the ethanol, paper chromatography revealed a minor amount of diacetyl compound and approximately a 60:40 mixture of monoacetyl compound and the guanidine free base. The mixture was dissolved in 50 ml of ether and applied to a column of 54 g of Woelm neutral alumina,

(34) T. Goto, K. Nakanishi, and M. Ohashi, *Bull. Chem. Soc. Japan*, **30**, 723 (1957).

(35) All melting points are corrected; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley. Ultraviolet spectra were taken in water unless otherwise noted; nmr values are reported in δ units referred to TMS, δ = 0.

(36) T. L. Davis and R. C. Elderfield, *J. Am. Chem. Soc.*, **54**, 1499 (1932).

activity IV. Elution with 4:1 ether–hexane removed the diacetyl compound; the monoacetyl compound was eluted with 9:1 ether–hexane. Fractions containing the monoacetyl compound were combined and molecularly distilled at 50–70° (1 mm) to afford 565 mg (41%) of pure acetyl-N,N′,N″-trimethylguanidine (Xb): $\lambda_{max}^{pH3.7}$ 209 mμ (ε 11,330); $\lambda_{max}^{0.01\ N\ NaOH}$ 213 (9500); $\lambda_{max}^{0.01\ N\ HCl,\ C_2H_5OH}$ 212 (13,150); $\lambda_{max}^{0.01\ N\ NaOH,\ C_2H_5OH}$ 216 (8550); nmr absorption (CCl_4) showed $CH_3C(=O)$– at 1.90 (s), 2 CH_3N– at 2.78 (s), and CH_3N–Ac at 2.90 (s).

Anal. Calcd for $C_6H_{13}N_3O$: C, 50.3; H, 9.2; N, 29.4. Found: C, 50.4; H, 9.0; N, 29.9.

Acetyl-N,N′,N″-tetramethylguanidine (XI).—In 100 ml of absolute ethanol was dissolved 6.55 g (26.9 mmole) of N,N′,N″-tetramethylguanidine hydriodide[27] and the solution was applied to a Bio Rad AG1 X-8 column in the OH^- form. The column was washed with an additional 200 ml of absolute ethanol and the combined eluates evaporated *in vacuo* to afford a clear oil. This residue was acetylated with 20 ml of acetic anhydride at 100° for 6 hr. Most of the acetic anhydride was removed *in vacuo* at room temperature for 5 hr. The viscous liquid residue was purified by preparative vpc on an SF 96 on firebrick column and molecularly distilled at 40° (0.1 mm) to afford 1.96 g (47%) of analytically pure acetyl-N,N,N′,N″-tetramethylguanidine (XI); $\lambda_{max}^{pH3.7}$ 217 mμ (ε 12,300); λ_{max}^{pH12} 220 (9050); $\lambda_{max}^{0.01\ N\ HCl,\ C_2H_5OH}$ 218 (12,150); $\lambda_{max}^{0.01\ N\ HCl,\ C_2H_5OH}$ 225 mμ (8950); nmr absorption (CCl_4) showed $CH_3C(=O)$– at δ 1.85 (s), 3 CH_3N– at 2.80 (s), CH_3NAc at 2.85 (s).

Anal. Calcd for $C_7H_{15}N_3O$: C, 53.5; H, 9.6; N, 26.7. Found: C, 53.2; H, 9.6; N, 26.5.

5-Oxo-2,3,6,7-tetrahydro-1H,5H-imidazo[1,2-*a*]pyrimidine (XII) was prepared as previously reported:[13] mp 138–140° (lit.[13] mp 141°); λ_{max}^{pH3} 214 mμ (ε 15,380); λ_{max}^{pH7} 214 (12,000); $\lambda_{max}^{0.01\ N\ NaOH}$ 212 (7850); $\lambda_{max}^{0.01\ N\ HCl,\ C_2H_5OH}$ 21 (15,700); $\lambda_{max}^{0.01\ N\ NaOH,\ C_2H_5OH}$ 218 (7070), 228 (7070); nmr absorption (D_2O), C-6 H_2 at 2.6 (t), C-2, -3, -7 H_6 at 3.3–4.0 (m).

***t*-Butyl glycinate (XVI)** was prepared as previously reported:[30] bp 68–70° (21 mm) (lit.[30] bp 68° (21 mm)); nmr absorption (neat) showed $(CH_3)_3CO$– at δ 1.4 (s), NH_2 at 1.49 (s), and $-CH_2-$ at 3.2 (s).

***t*-Butyl β-Alaninate (XVII).**—To a pressure bottle was added 8.9 g (0.1 mole) of β-alanine, 75 ml of diglyme, 9 ml of concentrated sulfuric acid, and 120 ml (*ca.* 1.4 moles) of isobutylene and the bottle was shaken for 48 hr at room temperature. The contents of six such bottles were poured into 500 ml of cold 2 *N* sodium hydroxide. The pH was adjusted to 3.8 with phosphate buffer and continuously extracted with methylene chloride for 2 days. The pH was then adjusted to 10 and continuously extracted for 2 more days. Drying the methylene chloride layer over magnesium sulfate and evaporating the solvent afforded 12.2 g (8.4%) of a liquid: bp 58–61° (7 mm); nmr absorption (neat) showed H_2N– at δ 1.26 (s), $(CH_3)_3CO$– at 1.42 (s), $-CH_2CO$ at 2.28 (t), $-NCH_2-$ at 2.81 (t).

N-Methyl-N′-(*t*-butoxycarbonylmethyl)thiourea (XVIII).—To 5.0 g (38.15 mmoles) of *t*-butyl glycinate in 10 ml of absolute methanol cooled to 0° was added 2.80 g (38.15 mmoles) of methyl isothiocyanate[37] over a 20-min period. Stirring for an additional 2 hr at 0° and removing the solvent *in vacuo* afforded a quantitative yield of the viscous thiourea (XVIII): λ_{max}^{pH3} 205 mμ (ε 13,700), 237 (12,000); λ_{max}^{pH12} 228 (12,000); nmr absorption ($CDCl_3$) showed $(CH_3)_3CO$– at δ 1.5 (s), CH_3N–H at 2.97 (d, J = 5 cps), $-CH_2-$ at 4.3 (d, J = 5 cps), and NH at ~7 (broad).

Anal. Calcd for $C_8H_{16}N_2O_2S$: C, 47.0; H, 7.9; N, 13.7. Found: C, 47.2; H, 7.9; N, 13.9.

Reaction at room temperature results in intramolecular condensation and loss of the *t*-butyl group.

N-Methyl-N′-(2-*t*-butoxycarbonylethyl)thiourea (XIX).—To 5.0 g (34.5 mmoles) of *t*-butyl β-alaninate in 5 ml of water was added 2.52 g (34.5 mmoles) of methyl isothiocyanate over a 30-min period. Two layers were formed and the mixture was heated on the steam bath for 5 min. Removal of the water *in vacuo* afforded a quantitative yield of XIX as a viscous liquid: λ_{max}^{pH3} 209 mμ (ε 14,000), 236 (12,950); λ_{max}^{pH12} 235 (13,100); nmr absorption ($CDCl_3$) showed $(CH_3)_3CO$– at δ 1.48 (s), $-CH_2CO$ at 2.58 (t), CH_3NH at 2.97 (d, J = 5 cps), $-NCH_2-$ at 3.80 (q), and 2 N–H at 6.9 (broad).

Anal. Calcd for $C_9H_{18}N_2O_2S$: C, 49.5; H, 8.3; N, 12.8. Found: C, 49.8; H, 8.1; N, 13.0.

(37) M. L. Moore and F. S. Crossley, ref 25, p 599.

S,N-Dimethyl-N′-(*t*-butoxycarbonylmethyl)isothiourea (XX) Hydriodide.—To 5.61 g (27.5 mmoles) of the thiourea XVIII dissolved in 50 ml of absolute methanol was added 6.0 g of methyl iodide and the solution was refluxed for 1 hr. Evaporation of the solvent *in vacuo* afforded a quantitative yield of the viscous isothiuronium salt of XX: λ_{max} 223 mμ; nmr absorption ($CDCl_3$) showed $(CH_3)_3CO$– at δ 1.4 (s), CH_3N or CH_3S at 2.7 (s) or 3.1 (broad), $-CH_2-$ at 3.9 (broad), 2 NH at 7.9 (broad).

Anal. Calcd for $C_9H_{19}N_2O_2SI$: C, 31.2; H, 5.5; N, 8.1. Found: C, 31.7; H, 5.3; N, 8.2.

S,N-Dimethyl-N′-(2-*t*-butoxycarbonylethyl)isothiourea (XXI) hydriodide was prepared as above in quantitative yield from the thioureido compound (XIX) in absolute ethanol: λ_{max} 223 mμ; nmr absorption ($CDCl_3$) showed $(CH_3)_3CO$– at δ 1.45 (s), $C-CH_2-CO$ at 2.80 (t), CH_3N or CH_3S at 2.90 (s) or 3.2 (broad), and $N-CH_2-C$, at 3.8 (broad).

Anal. Calcd for $C_{10}H_{21}N_2O_2SI$: C, 33.3; H, 5.9; N, 7.8. Found: C, 30.0; H, 5.4; N, 8.0.

Although the analysis was repeatedly low in carbon, the nmr indicated the product was pure enough for subsequent reaction. The material was a nearly immobile liquid.

N,N′-Dimethyl-N″-(N‴-methylcarboxamidomethyl)guanidine (XXII) Hydriodide.—To 26.3 g (76 mmoles) of the isothiuronium iodide of XX dissolved in 100 ml of absolute ethanol was added 200 ml of 25% methylamine in absolute ethanol. The dark solution was refluxed on the steam bath for 4 hr with constant introduction of methylamine. Evaporation of the solvent *in vacuo* and two decolorizations with charcoal in ethanol afforded crude yellow crystals. Successive recrystallizations from ethanol afforded 11.1 g (51%) of white crystalline hydriodide of XXII: mp 175° dec; nmr absorption (D_2O) showed CH_3NH-CO at δ 2.85 (s), 2 CH_3N– at 2.95 (s), and $-CH_2-$ at 4.1 (s).

Anal. Calcd for $C_6H_{15}N_4OI$: C, 25.2; H, 5.3; N, 19.6. Found: C, 24.9; H, 5.1; N, 19.3.

N,N′-Dimethyl-N″-[2-(N‴-methylcarboxamido)ethyl]guanidine (XXIII) Hydriodide.—To 6.0 g (16.7 mmoles) of the isothiuronium salt of XXI was added 60 ml of 25% ethanolic methylamine. The clear solution was stirred at room temperature for 22 hr and then heated to reflux for 2.5 hr. Evaporation of the solvent afforded a viscous liquid which later solidified. Successive recrystallizations from ethanol–ether afforded 2.80 g (56%) of crystalline guanidinoamide (XXIII) hydriodide: mp 128–130°; nmr absorption (D_2O) showed $C-CH_2-CO$ at δ 2.6 (t), $-CON-CH_3$ at 2.8 (s), 2 NCH_3 at 2.9 (s), and $N-CH_2-C$ at 3.6 (t).

Anal. Calcd for $C_7H_{17}N_4OI$: C, 28.0; H, 5.7; N, 18.7. Found: C, 27.9; H, 5.6; N, 18.5.

1-Methyl-2-methyliminoimidazolidin-5-one (XIV) Hydrochloride.—A solution of 3.0 g (10.5 mmoles) of the guanidinoamide (XXII) hydriodide in 125 ml of concentrated hydrochloric acid was heated at 115° for 16 hr. Evaporation of the solution afforded a white solid which was taken up in absolute methanol and applied to a column of Bio Rad AG1 X-8, OH^- form. Washing with 200 ml of methanol, combining the eluates, and evaporating *in vacuo* afforded the solid free base. Conversion to the hydrochloride with concentrated hydrochloric acid, evaporation of the solvent, and recrystallization from ethanol–ether yielded 1.42 g (83%) of crystalline hydrochloride of XIV: mp 249–251° dec; λ_{max}^{pH3} 200 mμ (ε 18,220); λ_{max}^{pH7} 206 (13,150); $\lambda_{max}^{0.01\ N\ NaOH}$ 207 (5450) extrapolated value; $\lambda_{max}^{0.01\ N\ NaOH,\ C_2H_5OH}$ 223 (2700); nmr absorption (D_2O) showed N-2 CH_3 at δ 3.16 (s), N-1 CH_3 at 3.24 (s), and $-CH_2-$ at 4.4 (s).

Anal. Calcd for $C_5H_{10}N_3OCl$: C, 36.7; H, 6.2; N, 25.7. Found: C, 36.7; H, 5.7; N, 25.7.

2-Methylamino-3-methyl-4-oxo-3,4,5,6-tetrahydropyrimidine (XIII) hydrochloride was prepared in 78% yield from the guanidinoamide XXIII hydriodide by the same procedure as above: mp 225–226°; λ_{max}^{pH3} 208 mμ (ε 19,100); λ_{max}^{pH7} 208 (18,600); $\lambda_{max}^{0.01\ N\ NaOH}$ 210 (10,700) extrapolated value; $\lambda_{max}^{0.01\ N\ HCl,\ C_2H_5OH}$ 208 (18,500); $\lambda_{max}^{0.01\ N\ NaOH,\ C_2H_5OH}$ 213 (7350); nmr absorption (D_2O) showed C-5 H_2 at δ 2.9 (t), N-2 CH_3 at 3.0 (s), N-3 CH_3 at 3.3 (s), and C-6 H_2 at 3.7 (t).

Anal. Calcd for $C_6H_{12}N_3OCl$: C, 40.6; H, 6.8; N, 23.7. Found: C, 40.7; H, 6.6; N, 23.6.

1-Benzyloxycarbonyl-2-iminoimidazolidine (XXVII) and 2-Benzyloxycarbonyliminoimidazolidine (XXVI).—To a solution of 33.2 g (200 mmoles) of 2-iminoimidazolidine hydrobromide[31] dissolved in 200 ml of 1 *N* sodium hydroxide and 200 ml of tetrahydrofuran, cooled at 0°, was added simultaneously over a 45-min period 200 ml of 1 *N* sodium hydroxide and 34.2 g (200 mmoles) of benzyloxycarbonyl chloride in 200 ml of tetra-

hydrofuran. The resulting heterogenous mixture was stirred at room temperature for 2 hr, the final pH being 8–9. The tetrahydrofuran was evaporated and the aqueous layer extracted with four 200-ml portions of chloroform. Drying over magnesium sulfate and evaporating the solvent afforded 40 g of crude solid. The material was chromatographed on silica gel, eluting with chloroform. A large amount of forerun which contained much solid was separated and not further investigated. Elution with 5% methanol–chloroform afforded 1.64 g (3.7%) of 2-benzyloxycarbonyliminoimidazolidine (XXVI): mp 178–180°; λ_{max}^{EtOH} 218 mμ (ε 31,600); nmr absorption ($CDCl_3$) showed $-CH_2CH_2-$ at δ 3.6 (s), $C_6H_5-CH_2$ at 5.13 (s), C_6H_5- at 7.4 (s), and 2 NH at 8.4 (broad); R_f 0.46 on silica gel tlc, eluting with 5% methanol–chloroform.

Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.3; H, 6.0; N, 19.2. Found: C, 60.1; H, 5.9; N, 19.0.

Further elution with 10–20% methanol–chloroform afforded after recrystallization from chloroform–petroleum ether 31.8 g (7.2%) of 1-benzyloxycarbonyl-2-iminoimidazolidine (XXVII): mp 117–119° partial melt, 183° completely melted; λ_{max}^{EtOH} 208 mμ (ε 17,300); nmr absorption ($CDCl_3$) showed $-CH_2CH_2-$ at δ 3.7 (m), $C_6H_5-CH_2-$ at 5.25 (s), 2 NH at 6.5 (s), and C_6H_5- at 7.4 (s); R_f 0.05 on tlc eluting with 5% methanol–chloroform.

Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.3; H, 6.0; N, 19.2. Found: C, 59.7; H, 5.8; N, 19.2.

1,3-Diacetyl-2-benzyloxycarbonyliminoimidazolidine (XXVIII).—A solution of 1.00 g (4.56 mmoles) of XXVI in 25 ml of acetic anhydride was heated at 100° for 30 min. Removal of the acetic anhydride *in vacuo* afforded a solid which was recrystallized from chloroform–petroleum ether to yield 1.14 g (82%) of pure XXVIII: mp 125–127°; λ_{max}^{EtOH} 205 mμ (ε 14,200), 233 (17,050); nmr absorption ($CDCl_3$) showed $CH_3C(=O)-$ at δ 2.35 (s), $-CH_2CH_2-$ at 3.85 (s), $C_6H_5-CH_2-$ at 5.15 (s), and C_6H_5- at 7.35 (s).

Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.4; H, 5.7; N, 13.9. Found: C, 59.4; H, 5.5; N, 13.8.

3-Acetyl-1-benzyloxycarbonyl-2-acetyliminoimidazolidine (XXIX) was prepared in quantitative yield by the same method as above from the 1-benzyloxycarbonyl compound (XXVII). A viscous oil was obtained which slowly solidified to a low-melting solid. Further purification was not attempted; nmr absorption ($CDCl_3$) showed $CH_3C(=O)-$ at δ 2.15 (s), $CH_3C(=O)-$ at 2.45 (s), $-CH_2CH_2-$ at 3.78 (s), $C_6H_5CH_2-$ at 5.15 (s), and C_6H_5- at 7.3 (s).

1,3-Diacetyl-2-iminoimidazolidine (XXX).—To 75 ml of tetrahydrofuran was added 1.0 g (3.3 mmoles) of the diacetylbenzyloxycarbonyl compound (XXVIII) and 200 mg of 10% Pd–C. The mixture was hydrogenated at 30 psi for 6 hr. Removal of the tetrahydrofuran and recrystallization of the residue from chloroform–petroleum ether yielded 366 mg (65%) of pure XXX: mp 103–105°; λ_{max}^{EtOH} 221 mμ (ε 15,750); nmr absorption ($CDCl_3$) showed 2-$CH_3C(=O)$ at δ 2.4 (broad) and $-CH_2CH_2-$ at 3.82 (s).

Anal. Calcd for $C_7H_{11}N_3O_2$: C, 49.7; H, 6.6; N, 24.8. Found: C, 49.7; H, 6.6; N, 24.8.

1-Acetyl-2-acetyliminoimidazolidine (XXXI).—This compound was prepared in 61% yield from 3-acetyl-1-benzyloxycarbonyl-2-acetyliminoimidazolidine (XXIX) using the same procedure as above: mp 118–119°; nmr absorption ($CDCl_3$) showed $CH_3C(=O)-$ at δ 2.15 (s), $CH_3C(=O)-$ at 2.65 (s), and $-CH_2CH_2$ at 3.8 (m); λ_{max}^{EtOH} 244 mμ (ε 18,950).

Anal. Calcd for $C_7H_{11}N_3O_2$: C, 49.7; H, 6.6; N, 24.8. Found: C, 49.5; H, 6.3; N, 24.6.

1-Acetyl-2-benzyloxycarbonyliminoimidazolidine (XXXII).—To 75 ml of dry tetrahydrofuran was added 1.00 g (4.37 mmoles) of 2-benzyloxycarbonyliminoimidazolidine (XXVI) and 1.23 ml (8.74 mmoles) of triethylamine. To this stirred mixture was added over a 10-min period, at room temperature, 0.62 ml (8.74 mmoles) of acetyl chloride in 75 ml of tetrahydrofuran. Stirring for additional 40 min and removal of the solvent afforded a solid which was chromatographed on a silica gel column. Elution with chloroform afforded one fraction, the rest of the material remaining on the column. Evaporation of the solvent and recrystallization from chloroform–ether afforded 750 mg (66%) of crystalline XXXII: mp 148–149°; λ_{max}^{EtOH} 230 mμ (ε 24,300); nmr absorption ($CDCl_3$) showed $CH_3C(=O)-$ at δ 2.65 (s), $-CH_2CH_2-$ at 3.8 (m), $C_6H_5-CH_2-$ at 5.15 (s), C_6H_5- at 7.3 (s), NH at 8.7 (broad).

Anal. Calcd for $C_{13}H_{15}N_3O_3$: C, 59.7; H, 5.8; N, 16.1. Found: C, 59.7; H, 5.5; N, 16.1.

1-Acetyl-2-iminoimidazolidine (XV).—To 60 ml of dry tetrahydrofuran was added 400 mg (1.53 mmoles) of 1-acetyl-2-benzyloxycarbonyliminoimidazolidine (XXXII) and 600 mg of 10% palladium on carbon. The mixture was hydrogenated at 35 psi for 6 hr and the solvent removed to afford a crude solid. Recrystallization from chloroform–ether yielded 100 mg (52%) of pure 1-acetyl-2-iminoimidazolidine (XV): mp 203–205° dec; λ_{max}^{pH3} 220 mμ (ε 9400); λ_{max}^{pH7} 220 (4850); $\lambda_{max}^{0.01\ N\ NaOH}$ 208 (2160), 234 (7970) extrapolated value; $\lambda_{max}^{0.01\ N\ HCl,\ C_2H_5OH}$ 220 mμ (10,900); $\lambda_{max}^{0.01\ N\ NaOH,\ C_2H_5OH}$ 213 (4520), 231 (7650) extrapolated value; nmr absorption ($CDCl_3$) showed $CH_3C(=O)-$ at δ 2.20 (s), $-CH_2$ CH_2- at 3.80 (m), 2 NH at 6.12 (broad).

Anal. Calcd for $C_5H_9N_3O$: C, 47.2; H, 7.1; N, 33.1. Found: C, 47.1; H, 7.1; N, 33.2.

Potentiometric Titrations.—Analytically pure acylguanidines (0.50 mmole) were dissolved in 47.5 ml of carbon dioxide free water. These magnetically stirred solutions at a constant temperature of 25° were titrated with 0.1 *N* sodium hydroxide (CO_2-free) using a Beckman "Zeromatic" pH meter equipped with a glass electrode (Beckman No. 41260) and a calomel electrode. The free bases were converted to the hydrochlorides with 1 equiv of standard 0.1 *N* hydrochloric acid and subsequently titrated with standard alkali. This procedure eliminates any hydrolysis in water before beginning the titrations. The validity of this method was checked by titrating two stable acylguanidine free bases with standard 0.1 *N* hydrochloric acid and the results were in agreement within experimental error.

Registry No.—III, 15231-22-8; IV, 15231-23-9; IV nitrate, 15231-24-0; V, 15231-25-1; VI, 15231-26-2; VII, 15231-27-3; VII·HCl, 15231-28-4; VIII, 15231-29-5; VIII·HCl, 15231-30-8; IX, 15231-31-9; IX·HCl, 15275-69-1; Xa, 15275-70-4; Xb, 15231-32-0; XI, 15231-33-1; XII, 15231-34-2; XIII, 15231-35-3; XIII·HCl, 15231-36-4; XIV, 15231-37-5; XIV·HCl, 15231-38-6; XV, 15231-39-7; XVI, 6456-74-2; XVII, 15231-41-1; XVIII, 15231-42-2; XIX, 15231-43-3; XX·HI, 15230-90-7; XXI·HI, 15275-71-5; XXII·HI, 15230-91-8; XXIII·HI, 15230-92-9; XXVI, 15230-93-0; XXVII, 15230-94-1; XXVIII, 15230-95-2; XXIX, 15275-72-6; XXX, 15230-96-3; XXXI, 15230-97-4; XXXII, 15230-98-5.