acetate–methanol (100 mL/5 mL, 100 mL/15 mL). Progressive elution from the column gave the following: R_f 0.30 spot, crystalline, 191.0 mg, mp 78–80 °C, methyl 2,6:3,4-dianhydro-α-D-altropyranoside[5] (17); R_f 0.12 spot, crystalline, 113.3 mg, mp 81–82 °C, methyl 2,3-anhydro-α-D-mannopyranoside (16).

Reaction of 3 and Derived Products. A mixture of 3 (2.18 g), dioxane (40 mL), water (10 mL), and 1 N sodium hydroxide (15 mL) was stirred until homogenous (~15 min) and allowed to stand for 5 days. TLC (toluene–ethyl acetate, 1:2 v/v) revealed two areas (three overlapping compounds): R_f 0.41, 0.37. The mixture was neutralized, evaporated to ~15 mL, and transferred to a separatory funnel with water (~100 mL) and dichloromethane (~10 mL). After separation of the organic layer, the aqueous layer was extracted with ten 10-mL portions of dichloromethane. The combined organic extracts were dried and evaporated to a syrup (1.7 g). This syrup was dissolved in dioxane (25 mL), and pyridine (2 mL) and acetic anhydride (1 mL) were added. After the mixture was allowed to stand overnight, TLC (toluene–ethyl acetate, 1:2 v/v) revealed three spots: *Rf* 0.64, 0.55, 0.37. Excess acetic anhydride was destroyed with water (1 mL) by allowing the mixture to stand ~20 h. Evaporation left a syrup that was placed on a dry column chromatograph (3.8 × 47 cm) and developed with toluene–ethyl acetate (600 mL/300 mL, 500 mL/500 mL, 300 mL/600 mL). Progressive elution from the column gave the following. R_f 0.64 spot: crystalline, 240 mg, mp 99–100 °C, methyl 4-*O*-acetyl-3-deoxy-2,6-di-*O*-mesyl-α-D-*arabino*-hex-2-enopyranoside (19). Anal. Calcd for $C_{11}H_{18}O_{10}S_2$: C, 35.29, H, 4.84. Found: C, 35.00; H, 4.84. A mass spectrum showed peaks at 343 and 332, corresponding to m/e – OCH_3 and m/e – $CH_2{=}C{=}O$. R_f 0.55 spot: amorphous solid, 670 mg, methyl 4-*O*-acetyl-2,3,6-tri-*O*-mesyl-α-D-glucopyranoside (3, R^3 = Ac), containing some (~10%) compound 5 (an impurity in the starting material). R_f 0.37 spot: crystalline, 740 mg, mp 130–131 °C, methyl 3,4-anhydro-2,6-di-*O*-mesyl-α-D-allopyranoside (18). Anal. Calcd for $C_9H_{16}O_9S_2$: C, 32.52; H, 4.85. Found: C, 32.8; H, 4.9. A mass spectrum showed a peak at 301, corresponding to m/e – OCH_3.

A mixture of 18 (164 mg), dioxane (3 mL), water (1.5 mL), and 1 N sodium hydroxide (1 mL) was allowed to stand 5 days, and the brown solution was neutralized. When this solution was diluted with water (5 mL), crystalline material separated from the solution; it was removed by filtration. This crystalline material was slightly impure starting compound 18: mp 128–131 °C; 38.2 mg. The filtrate was extracted with three 10-mL portions of dichloromethane. After drying, the extracts were evaporated to a syrup, which was dissolved in dichloromethane (5 mL), and pyridine (1 mL) and acetic anhydride (0.5 mL) were added. After the mixture had been allowed to stand overnight, methanol (1 mL) was added to destroy excess anhydride. Three days later, the mixture was evaporated to a syrup. The evaporation was repeated two times with toluene (5 mL) to remove pyridine. The syrup was placed on a dry column (1.5 × 16 cm) and developed with toluene–ethyl acetate (50 mL/25 mL, 50 mL/50 mL, 50 mL/100 mL). Progressive elution from the column gave the following: 19, crystalline, 5.3 mg, mp 98–99 °C; 18, crystalline, 35.2 mg, mp 130–131 °C.

Reaction of 4 and Derived Products. A mixture of 4 (4.6 g), ethanol (200 mL), and 1 N sodium hydroxide (40 mL) was stirred until the solution was homogenous (~3 h) and then allowed to stand overnight. TLC (toluene–ethyl acetate, 1:2 v/v) showed two spots: R_f 0.39, 0.28. After neutralization and evaporation the mixture, a semisolid was covered with water (125 mL) and ethyl acetate (50 mL) and transferred to a separatory funnel. An additional four 50-mL portions of ethyl acetate were used to extract the aqueous portion. The combined extracts were dried and evaporated to an amorphous solid. Dry column chromatography (3.5 × 43 cm) and development with toluene–ethyl acetate (300 mL/600 mL, 200 mL/700 mL) and ethyl acetate–methanol (450 mL/50 mL) gave two spots progressively. R_f 0.39 spot: solid, recrystallized from acetone–ethanol (1:1 v/v, ~0.2 g/mL), 1.75 g, mp 137–139 °C, methyl 2,3,4-tri-*O*-mesyl-α-D-glucopyranoside (4, R^4 = H). Anal. Calcd for $C_{10}H_{20}O_{12}S_3$: C, 28.03; H, 4.70; S, 22.45. Found: C, 28.12; H, 4.67; S, 22.27. R_f 0.28 spot: solid, recrystallized from acetone (3 mL), 2.82 mg, mp 140–141 °C, methyl 2,3-anhydro-4-*O*-mesyl-α-D-allopyranoside[5] (20).

Reaction of 5 and Derived Products. A mixture of 5 (1.0 g), dioxane (30 mL), and 0.2 N sodium hydroxide (30 mL) was heated to 50 ± 1 °C for 7.5 h, cooled, and neutralized. After evaporation of the dark brown mixture to a small volume, it was covered with water (100 mL) and extracted with ten 10-mL portions of dichloromethane. TLC (toluene–ethyl acetate, 1:2 v/v) revealed three spots: R_f 0.55, 0.43, 0.31. Evaporation of the combined extracts, followed by dry-column chromatography (2.6 × 46 cm) with development by toluene–ethyl acetate (300 mL/300 mL, 150 mL/300 mL) gave the following: R_f 0.55 spot, solid, recrystallized from ethanol–acetone, 317 mg, mp 145–146 °C, unaltered 5; R_f 0.43 spot, solid, recrystallized from ethanol–acetone, 113 mg, mp 133–135 °C, 6; R_f 0.31 spot, syrup, 40 mg. Although this latter spot appeared homogenous, on reaction with benzoyl chloride in pyridine at least four different spots were revealed by TLC, and it was not investigated further.

Acknowledgment is made to Clara E. Johnson for microchemical analyses, Larry W. Tjarks for NMR data, and R. Plattner for mass spectral data.

Registry No. 1, 76947-05-2; 2, 61252-79-7; 3 (R^3 = Ac; R^1, R^2, R^3 = Ms), 76947-06-3; 3 (R^3 = H; R^1, R^2, R^3 = Ms), 61252-77-5; 4 (R^4 = H; R^1, R^2, R^3 = Ms), 76947-07-4; 4 (R^4 = Bz; R^1, R^2, R^3 = Ms), 76947-08-5; 5, 6160-89-0; 6, 26922-78-1; 7, 76947-09-6; 8, 70941-23-0; 9 (R = Bz), 76947-10-9; 10, 76947-11-0; 11, 76947-12-1; 12, 76947-13-2; 13, 76947-14-3; 14, 5540-31-8; 15, 10226-98-9; 16, 23262-47-7; 17, 70941-14-9; 18, 76947-15-4; 19 (R = Ac), 76947-16-5; 20, 70941-22-9; methyl 2-*O*-benzoyl-3-*O*-mesyl-α-D-glucopyranoside–pyridine complex, 70941-30-9.

Acylation of Dibasic Compounds Containing Amino Amidine and Aminoguanidine Functions

Peter L. Barker, Paul L. Gendler, and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

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The site of acylation in difunctional compounds containing an amine and either an amidine or guanidine can be determined from the ultraviolet absorption spectrum of the acylated product. If the amidine or guanidine has been acylated, the product possesses a chromophore that is pH dependent, whereas if an amide was formed, the chromophore is independent of pH.

There exists a modest class of compounds (1–8, Chart I) whose characteristic functional groups are combinations of amides, amidines, and guanidines.[1-6] These amido amidines and guanidines possess a remarkable spectrum

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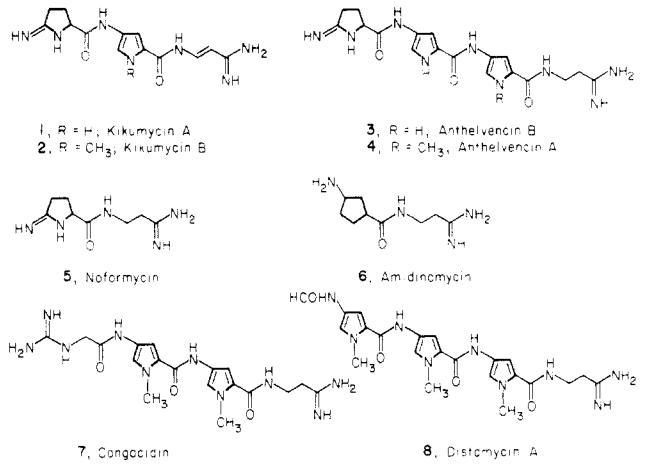
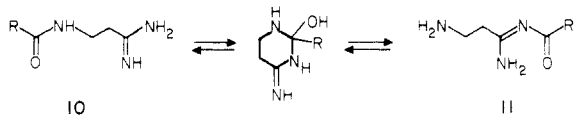
Chart I



of biological properties, including antibacterial, antifungal, anthelmintic, antitumor, and antiviral activity. The structures of several of these and related compounds have been proved by synthesis.[4,5,7-14] However, a potential problem arises both in the isolation and synthesis of these natural products. This involves the site of acylation in the dibasic intermediates and the structural integrity of the acylated products.

Discussion

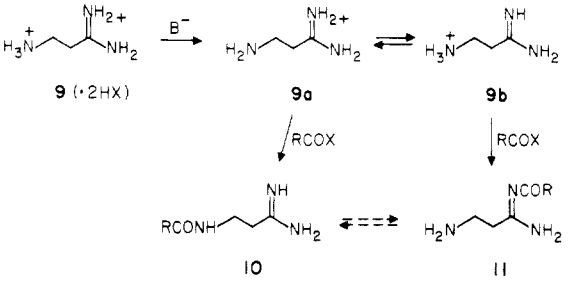
3-Aminopropionamidine (**9**),[15] may be considered as a model since it contains functionality common to the majority of these natural products. Acylation of such a bifunctional molecule can occur on the amine to give an amidoamidine (**10**) or on the amidine to give an amino



acylamidine (**11**). The following questions arise: how can these isomers be differentiated, and how can their integrity and possible interconversion be established?

Independent of the method of preparation, equilibration between **10** and **11** is possible via acyl migration; thus the entire series of natural products could have structures related to **11** and not **10**. Such transformations could easily occur during the manipulations necessary for isolation which require exposure to acidic or alkaline conditions and ion-exchange or other chromatography.[2,3,16-19] A description of just such an intramolecular acyl migration has recently appeared.[20]

Scheme I. Acylation of β-Aminopropionamidine



With regard to synthesis, the acylation of dibasic compound **9** could take place at either of the two sites to give amide **10** or acylamidine **11** (Scheme I). To favor acylation of the amine, we considered the use of **9** as its disalt and treatment with 100 mol % of a suitable base on the basis of the related pK_a's of the two groups: amine (9) and amidine (11–12).[21] This assumption could be misleading because although the concentration of **9b** is only 10^{-2} or 10^{-3} that of **9a**, a nonprotonated amidine (**9b**) reacts with acylating agents at a rate of 10^4 that of amines (**9a**).[21] This isomer dichotomy was considered in the structure determination of amidinomycin (**6**), but the isomeric amino acylamidine analogous to **11** was rejected on the basis of a pK_a argument.[1] The observed pK_a's of amidinomycin (9.6, >12) fit structure **6** and not the isomeric amino acylamidine.

Thus we sought to develop an analytical method to distinguish acylamidine and acylguanidines in the presence of several other functional groups such as amides, amines, amidines, and guanidines. This has been accomplished by preparing several compounds of this type of unambiguous structures. Comparison of their properties has led to a method for clearly delineating the various *N*-acyl derivatives.

Results

Acylamidines are not a well-known class of compound in spite of the fact that they were first prepared over 100 years ago,[21] while acylguanidines are understood to a much greater extent.[22,23] The only acylamidines reported that have been prepared by acylating an existing amidine are substituted benzoylbenzamidines;[24] one dialkylacylamidine has been prepared in an entirely different manner,[25] by the reaction of acetamide, acetonitrile, and tri-*n*-propylborane, followed by HCl in ether.

In setting out to synthesize compounds of type **10** and **11**, we chose first to prepare the isolated amide, amidine, and acylamidine functions in order to examine their properties without influence from any mixed functionality. Guanidines and acylguanidines were included in this study because they constitute an obvious extension of amidines

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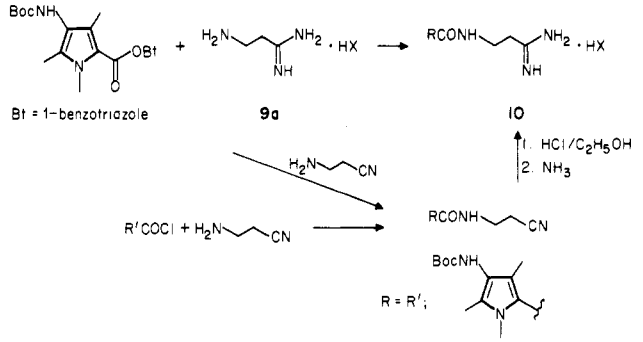
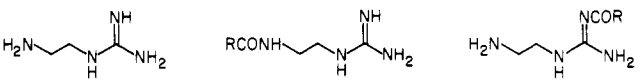
Scheme II. Regiospecific Formation of Amidoamidines



and because an amidoguanidine appears in congocidin (**7**). As monobasic model nitrogen compounds we selected ethylamine, ethylguanidine, propionamidine and benzamidine; as acyl groups we chose acetyl, propionyl and octadecanoyl (typical alkyl), benzoyl and *o*-toluoyl (typical aromatic), formyl (atypical, but of specific importance[10]), and some pyrroyl derivatives, since pyrrole is common to several of the natural products. In general, the free base of the model was prepared and treated with various acylating agents: for amidine and guanidine, an ester was usually sufficient, save that no formylamidine could be prepared by this method; for amine, an acid chloride or an active ester was employed.

As dibasic models we chose 3-aminopropionamidine (**9**) and (2-aminoethyl)guanidine (**12**). Specific monoacyl



12 **13** **14**

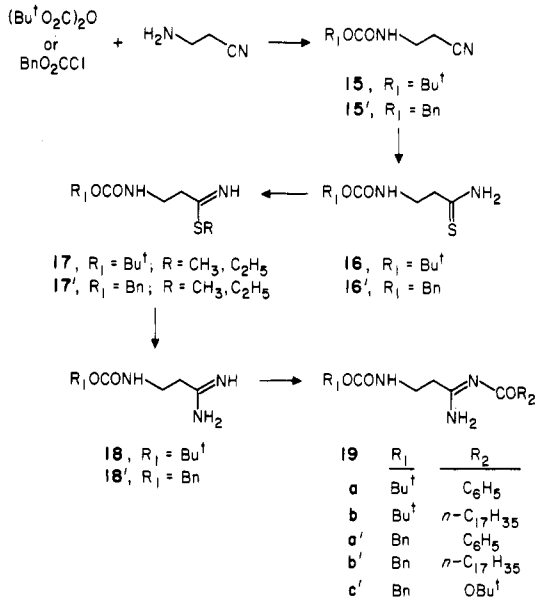
derivatives of these compounds to give an amido amidine (**10**) or an amino acylamidine (**11**), and the corresponding amidoguanidine (**13**) and amino acylguanidine (**14**) were obtained by unambiguous syntheses.

The acyl derivatives of the monobasic model compounds were prepared and then fully characterized, especially in regard to spectrophotometric properties in the hope of developing a pattern that would distinguish these functions from each other as well as from nonacylated amidines and guanidines. The substituted amides were either known compounds or were prepared by known methods. Similarly, the model amidines and guanidines were known compounds and were acylated in a straightforward manner as described in the Experimental Section.

Synthesis of the regiospecific monoacylated dibasic compounds was more challenging. First, preparation of the amido amidines **10** was carried out by acylation of 3-aminopropionitrile followed by conversion of the nitrile to an amidine via a Pinner synthesis. In some cases 3-aminopropionamidine (**9**) could be selectively acylated on the amine to give the amido amidine (Scheme II). The selectivity in these cases was subsequently proven spectroscopically. For those compounds (amido nitriles) which could not withstand the conditions of the Pinner amidine synthesis and could not be made by selective acylation of **9**, a new alternative approach was developed. This will be discussed below.

The amino acylamidines **11** proved to be more difficult to prepare than the isomeric amido amidines. Direct acylation of free base **9** should in principle acylate the amidine since it is both more basic and more nucleophilic than the amine. However, such an attempt failed to give the desired product. We then turned to making compound **10** where RCO is a removable protecting group and then acylating the amidine followed by liberating the amine.

Scheme III. Regiospecific Formation of Amino Acylamidines



This approach called for a protecting group that would withstand the conditions of the Pinner amidine synthesis and yet be removable under conditions mild enough not to destroy the sensitive acylamidine moiety. 3-(Toluenesulfonylamino)propionamidine,[15] an intermediate in the synthesis of **9**, was acylated on the amidine, and two unsuccessful attempts to cleave the tosyl group were made. Electrolysis[26] failed to remove the tosyl group, and treatment with sodium in liquid ammonia not only removed the tosyl but concomitantly displaced acylamine and gave the amino amidine **9**.

Therefore a new approach (Scheme III) to converting nitrile to amidine was begun, one which would not interfere with an easily removable amine protecting group. Since thioamides are easily alkylated on sulfur and the alkylthio group subsequently displaced by an amine with facility to give an amidine, 3-[(*tert*-butoxycarbonyl)amino]propionitrile (**15**) was prepared and treated with hydrogen sulfide and diethylamine to give such a thioamide (**16**).[27] Treatment of thioamide **16** with triethyloxonium fluoroborate or methyl iodide gave the *S*-alkylthioimidate **17** which, with ammonium bromide in refluxing 2-propanol, was converted to 3-[(*tert*-butoxycarbonyl)amino]propionamidine hydrobromide (**18**). Anion-exchange chromatography of the amidine hydrobromide gave the free base of amidine **18** which was variously acylated. Cleavage of the *tert*-butylcarbamate of **19** by acid gave the amino acylamidines **11** as the dihydrochloride salts.

The isomeric sets of amidoguanidines and amino acylguanidines also proved troublesome to obtain. As with the corresponding amidines, their unambiguous acylation called for juggling protecting groups and deprotecting methods. Our approach to both sets of guanidine compounds called for a monoprotected ethylenediamine which could be elaborated at the free amine end. Thus ethylenediamine was monocarbobenzyloxylated,[28] and this product (**20a**) was treated with a variety of guanidinating reagents.[29-31] All of these reagents, however, had their

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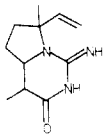
Table I. IR and ^{13}C NMR Absorptions of Amides, Amidines, Acylamidines, and Acylguanidines

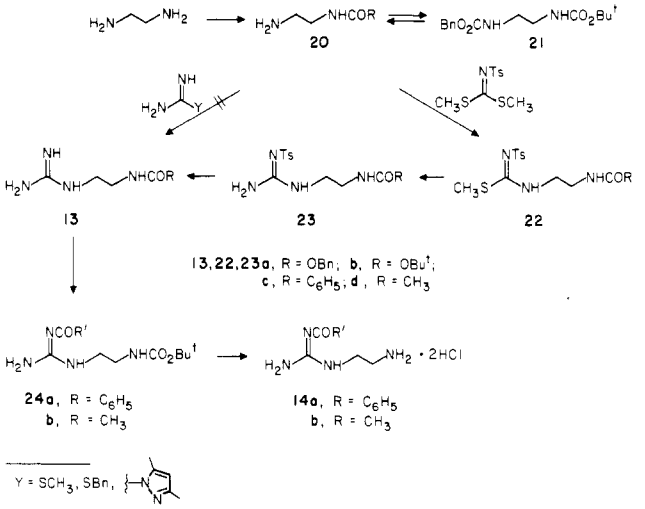
compd	IR,[a] μm	^{13}C NMR,[c] δ
N-ethyl-*o*-toluamide	6.12	170.1[d]
N-ethylacetamide	6.05[b]	170.6[d]
N-ethylformamide	6.03[b]	161.8 (164.8)[d]
acetamidine hydrochloride	5.91, 6.02	168.2, 18.2
propionamidine hydrochloride	5.95, 6.66	172.6, 25.3, 11.3[e]
propionamide	6.15[b]	168.3, 28.6, 11.2[e]
benzamidine hydrochloride	5.90, 5.99	166.3, 134.2, 129.1, 127.4, 127.2
benzoylbenzamidine	6.25, 6.41[b]	179.3, 166.6, 138.3, 135.0, 131.9, 131.4, 129.3, 128.3, 128.1, 127.7, 127.6[f]
benzoylbenzamidine hydrochloride	5.93, 6.25, 6.54	170.9, 166.3, 135.6, 135.1, 130.4, 129.6, 129.2, 128.9, 127.6, 126.5
acetylbenzamidine hydrochloride	5.78, 6.25, 6.51	176.1, 165.7, 135.2, 130.0, 129.5, 128.9, 128.4, 24.3
benzoylacetamidine hydrochloride		174.9, 164.4, 134.6, 129.8, 128.8, 25.1[e]
benzoylpropionamidine hydrochloride	5.89	
N-(*n*-octadecanoyl)propionamidine hydrochloride		178.9, 173.8, 37.5, 31.9, 29.7, 29.4, 29.0, 26.7, 24.2, 22.7, 14.0, 12.3[d]
β-aminopropionamide dihydrobromide (**9**)		166.6, 36.4, 30.1
β-(*o*-toluoylamino)propionamidine hydrochloride		173.0, 168.8, 135.4, 134.9, 130.9, 130.5, 126.9, 125.9, 36.5, 32.6, 18.9
5-[[(β-amidinoethyl)amino]carbonyl]-3-formamino-1,2,4-trimethylpyrrole (**25**)	5.91, 6.02, 6.16	169.0, 164.7, 164.4, 130.8, 121.5, 119.1, 114.3, 36.4, 32.6, 31.8, 8.8, 8.6
β-(benzoylamino)propionamidine hydrochloride (**10**)		169.9, 166.9, 133.8, 131.4, 130.8, 128.9, 127.2, 126.6, 36.4, 32.0
β-amino-*N*-benzoylpropionamide		173.3, 168.7, 133.7, 132.1, 129.6, 128.9, 128.1, 127.5, 34.7, 34.0
		179.6, 158.3, 142.3, 115.9, 64.9, 62.9, 42.1, 40.5, 29.7, 20.4, 11.3

[a] In KBr pellets unless otherwise specified. [b] As a thin film. [c] In D_2O unless otherwise specified. [d] In $CDCl_3$. [e] In Me_2SO-d_6. [f] In acetone-d_6. [g] From ref 23.

shortcomings (hydrolysis, incomplete reaction), and all failed to produce a clean guanidine (**13a**). Similarly, treatment of **20a** with cyanamide failed, giving no reaction. As an alternative approach, **20a** was treated with dimethyl [(*p*-toluenesulfonyl)imino]dithiocarbonate,[32] producing the crystalline *N*-tosylisothiourea **22a**, which was converted to the *N*-tosylguanidine **23a** on treatment with ammonia and silver nitrate.[33] We found it critical to treat the dithiocarbonate reagent first with a substituted amine (**20a**) and then the product of that reaction with ammonia; reversal of the order of substitution, giving an intermediate unsubstituted *N*-tosylisothiourea, failed to produce the tosylguanidine **23a**.

Attempts to cleave the tosyl group in preference to the benzylcarbamate from **23a** failed. Electrolysis[26] of **23a** gave no tosyl removal, and sodium in liquid ammonia removed both tosyl and benzoxycarbonyl groups. A protecting group other than benzoxycarbonyl was needed; therefore, **20a** was acylated with di-*tert*-butyl dicarbonate to **21**, and the (benzyloxy)carbonyl group was removed by hydrogenolysis to give (*tert*-butoxycarbonyl)ethylenediamine (**20b**). Repeating the tosylguanidine forming sequence with **20b** gave **23b**. Similarly prepared were amides **23c** and **23d**. Sodium/liquid ammonia treatment of these compounds cleaved the tosyl group but left the amide (or carbamate) intact. Compounds **13c** and **13d** were the ultimate amidoguanidine products; **13b** was acylated on the guanidine and the Boc group was cleaved from **24** to give the isomeric compounds **14**. This completed the preparation of **13** and **14**; the various sequences are shown in Scheme IV.

Scheme IV. Regiospecific Formation of Amidoguanidines and Amino Acylguanidines



With these compounds in hand we examined their spectral properties in an effort to differentiate the isomeric sets of compounds. ^1H and ^{13}C NMR, IR, UV, and mass spectra were all investigated. ^1H NMR and mass spectra were inconclusive. IR and, surprisingly, ^{13}C NMR spectroscopy were also inconclusive and suffered the same drawback; namely, the resolution between the characteristic absorptions of the various functionalities was insufficient (Table I). For instance, in the IR spectrum various amidine hydrochlorides appear at 5.91–5.99 μm, while amides absorb at 6.03–6.12 μm. The IR spectrum of **25**[34] shows three signals in the carbonyl region at 5.91, 6.02, and 6.16 μm, and only tentative assignments can be made. In

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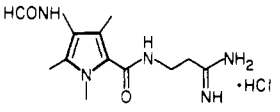
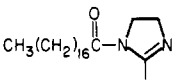
(31) Bannard, R. A. B.; Casselman, A. A.; Cockburn, W. F.; Brown, G. M. *Can. J. Chem.* **1958**, *36*, 1541.
(32) Gompper, R.; Hagele, W. *Chem. Ber.* **1966**, *99*, 2885.
(33) Ferris, A. F.; Schutz, B. A. *J. Org. Chem.* **1963**, *28*, 71.
(34) Gendler, P.; Rapoport, H. *J. Med. Chem.* **1981**, *24*, 33.

the ^{13}C NMR spectra, amidine hydrochlorides appear at 168.2–172.6 ppm and amides at 161.8–170.6 ppm, and **25**



25



26

shows three signals at δ 169.0, 164.7, and 164.4, again making assignment tenuous. A carbonyl group is not sensitive enough to structural changes to produce an easily distinguished, unmistakeable change when present as an acylamidine or acylguanidine as opposed to an amide, amidine, or guanidine.[35,36]

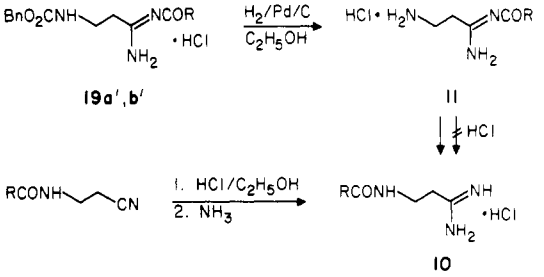
The UV absorption spectrum is ideal since none of the accompanying groups which interfere in the IR or ^{13}C NMR spectra have a significant chromophore. Examination of the data (Table II) reveals that simple acylamidines and acylguanidines show approximately a 20-nm bathochromic shift on going from an acidic to basic solution, that there is no great change in extinction coefficient (of protonated and deprotonated form), and that the extinction coefficient is of the same order of magnitude (~15 000) as the extinction coefficients found in the aromatic rings of the model systems examined. This behavior is mimicked in the difunctional amino acylamidines and amino acylguanidines.

One acylamidine (**26**) that cannot form the preferred acylimine tautomer was synthesized; its UV spectrum (Table II) reveals no 20-nm pH shift but only a shift of 7 nm. It is also much more readily hydrolyzed than the other acylamidines which exist in the acylimino form. This UV and hydrolytic behavior is reminiscent of acyl(amino)guanidines[22] which have λ_{max} at shorter wavelength than their imino counterparts. Thus the UV/pH profile is specific for acyl(imino)amidines and acyl(imino)guanidines and provides a simple and sensitive analysis for their presence. Recently[37] an exhaustive ^{13}C NMR, ^{15}N NMR, and CNDO/2 study reached the same conclusion on these structural and tautomeric questions.

A type of structural feature that also showed a UV/pH profile which might interfere with this analysis is that of β-aminopyrrole. It shows a similar shift in the UV from acid to base (Table II); however, none of the β-(acylamino)pyrroles that we prepared, whether carbamates or amides, show any such behavior. Congocidin (**7**), on the other hand, a β-(acylamino)pyrrole (acylated with a guanidinoacetic acid residue) does shown an unexpected modest (9 nm) shift. The pH dependence in the UV spectrum for a β-aminopyrrole is not surprising since the nitrogen lone pair, upon protonation, is lost for conjugation with the aromatic ring, but protonation on congocidin should have no effect on its UV spectrum. Kikumycins A and B (**1** and **2**) also exhibit a UV/pH shift (23 nm). Examining the structure of the eastern side chain of these compounds reveals that there is an amide conjugated by a double bond to the terminal amidine. In other words, this group is a vinylogous acylguanidine, and its UV/pH behavior is that of an acylguanidine.

We have found two examples of acylamidine compounds in which the carbonyl carbon is substituted not by aliphatic or aromatic groups but by a heteroatom. Compound **19c′** (Scheme III) has an alkoxycarbonylamidine and shows

Scheme V. Acyl Transfer in Amino Acylamidines



UV/pH behavior characteristic of the isolated acylamidine. Similarly, a cytosine dimer (**27**)[38] which is an example of an amino acylamidine behaves as a typical acylamidine (Table III).

Acyl Transfer

In considering the integrity of the amido amidine moiety (**10**) purported to be the structure of the various natural products (**3–8**), several points can be made. There is no doubt that these are the structures isolated from natural sources since they (**5–8**) have been synthesized and they are stable to the conditions used in the isolation. Our model compounds related to **10** and **11** all show different and reversible UV/pH profiles. Thus there is no acyl transfer occurring during that time. The UV/pH profile analysis is complete in less than 5 min at room temperature in ethanol solution. During isolation, the compounds **1–8** have been subjected to much longer exposure to hydrolytic conditions; that they survive is testimony to their stability, although there are undoubtedly hydrolytic losses during isolation. Compounds derived from the isomeric acylamidine structure, or its hydrolysis products, have not been isolated; thus these natural products were not originally present as acylamidines. Furthermore, when compound **10a** (R = C_6H_5) was treated with excess triethylamine in ethanol, there was no evidence of acyl transfer to **11a** even after 5 days.

The first indication that acyl transfer might be occurring from amino acylamidine **11** to amido amidine **10** was found in our early attempts to prepare compounds **11**. At that time (benzyloxy)carbonyl-protected amino acylamidines (**19′**, Scheme III) were prepared as the immediate precursors to **11**. Catalytic hydrogenolysis of **19′** hydrochloride (Scheme V) in ethanol to remove the benzyl carbamate should have given the hydrochlorides of amino acylamidines **11**, but the UV spectra of the products did not show the characteristic acylamidine behavior. Because acylamidines readily hydrolyze to imides, moisture in the ethanol was suspect as the cause of slow hydrolysis of the product during the long (12–18 h) exposure to hydrogenolytic conditions. However, preparation of an authentic imide showed that such an imide had a UV absorption distinct from both acylamidine and our isolated product. Elemental analysis of the isolated product was consistent with the desired hydrochlorides of amino acylamidine **11** or its isomeric amido amidine counterpart **10**. On the basis of this information coupled with the UV behavior, it was concluded that upon cleavage of the benzyl carbamate the initial product (**11**) had undergone acyl transfer. Further support for this conclusion came with the observation that when hydrogenolysis of the (benzyloxycarbonyl)amino acylamidine **19b′** was carried out with the addition of excess anhydrous HCl, the amine upon deprotection was protonated and isolated as the amino acylamidine salt,

(35) Levy, G. C.; Nelson, G. L. In "Carbon-13 NMR for Organic Chemists"; Wiley: New York, 1972; p 120.
(36) Bellamy, L. J. "The Infrared Spectra of Complex Molecules", 3rd ed.; Wiley: New York, 1975; Vol. 1.
(37) Smith, R. L.; Cochran, D. W.; Gund, P.; Cragoe, E. J., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 191.
(38) Taguchi, H.; Hahn, B.-S.; Wang, S. Y. *J. Org. Chem.* **1977**, *42*, 4127.

Table II. UV Absorption Spectra and pH Profiles of Amines, Amides, Amidines, Guanidines, Acylamidines, and Acylguanidines in Acid and Base

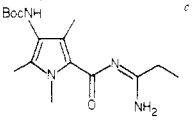
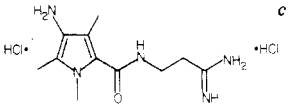
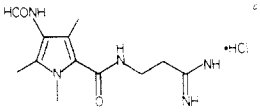
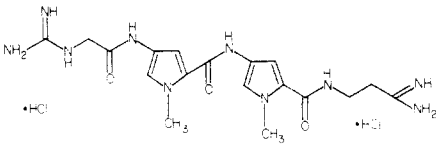
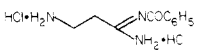
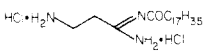
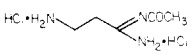
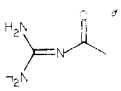
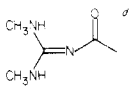
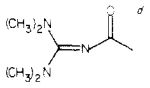
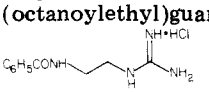
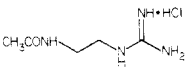
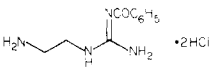
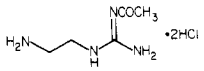
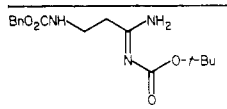
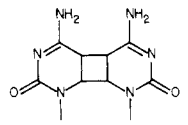
compd	UV (C_2H_5OH), λ_{max} nm (rel A)		
	plain	added base[a]	added acid[b]
N-ethyl-*o*-toluamide	266 (0.09), sh 220 (0.99)	265 sh (0.36)	266 (0.10), 220 sh (1.00)
benzamidine hydrochloride	270 (0.066), 230 (1.00)	end absorption	
N-benzoylbenzamidine	294 sh (0.59), 281 (0.70), 251 (0.58)	294 sh (0.71), 282 (0.83), 247 (0.61)	255 (1.00)
N-acetylbenzamidine hydrochloride	262 (0.95), 245 sh (0.87)	261 (0.91), 245 sh (0.88)	243 (1.00)
N-benzoylacetamidine hydrochloride	247 (0.86) (ϵ 15 690)	260 (1.00)	279 sh (0.12), 247 (0.90)
N-benzoylpropionamidine hydrochloride	247.5 (0.90) (ϵ 15 750)	268 (1.00)	248 (0.94)
N-(*n*-octadecanoyl)-propionamidine hydrochloride	245 (0.11), 215 (1.00) (ϵ 9370)	245 (0.97)	216 (0.95)
	322 (0.95) (ϵ 18 510), 245 (0.34)	322 (1.00), 254 (0.40)	327 (0.87), 287 sh (0.29), 217 (0.59)
2-methyl-1-(*n*-octadecanoyl)-2-imidazoline	234 (0.983)	233 (1.00)	240 (0.76)
N-acetylbenzamide	268 sh (0.08), 235 (1.00)	262 (0.47)	268 sh (0.05), 227 (0.71)
β-(*p*-toluoylamino)-propionamidine hydrochloride	269 (0.05), 215 sh (1.00)	269 (0.12)	269 sh (0.048), 215 sh (0.99)
β-(benzoylamino)-propionamidine hydrochloride	270 sh (0.09), 225 (1.00)	270 sh (0.09), 225 (1.00)	270 sh (0.09), 225 (1.00)
β-(stearoylamino)-propionamidine hydrochloride	end absorption		
	287 (0.74), 265 sh (0.64)	284 (0.84), 265 sh (0.76)	268 (1.00)
	275 (0.98)	273 (1.00)	275.5 (0.97)
		305 (unstable)	296 (1.00), 236 (0.96)
	249 (ϵ 9600)	269	249
	end absorption	244	end absorption
	end absorption	245	end absorption
		231	end absorption
		235	end absorption
		238	end absorption
(benzoylethyl)guanidine	261 (1.00)	261 (ϵ 18 000)	240 (1.00)
(acetylethyl)guanidine hydrochloride	234 (0.55)	234 (1.00) (ϵ 17 500)	end absorption
(octanoylethyl)guanidine	233 (1.00)	233	end absorption
	225 (1.00)	225	225
	end absorption	end absorption	end absorption
	257 (0.95), 235 sh	261 (ϵ 20 560) (1.00)	240 (0.1)

Table II (*Continued*)

compd	UV (C_2H_5OH), λ_{max} nm (rel A) plain	added base[a]	added acid[b]
	end absorption	233 (ϵ 6850)	end absorption

[a] With several drops of 3.7 M NaOH added. [b] Acidified by dropwise addition of concentrated HCl. [c] From ref 34. [d] From ref 22.

Table III. UV/pH Profile of Acylamidines with Acyl Group Not Bonded to Carbon

compd	heteroatom group	UV absorption, nm ^-OH	UV absorption, nm H^+
 19c′	OR	230	<210
 27	NR_2	243	219

11·2HCl, unable as such to undergo acyl transfer in the strongly acidic medium (Scheme V).

Fully characterized 11 (R = OBz), prepared as its dihydrochloride salt via the Boc-protected amine, was dissolved in absolute ethanol and, with UV monitoring, was found to undergo acyl transfer to 10 (R = OBz) over several days. Thus even the slight amount of amine salt which dissociated in solution to the free amine underwent irreversible acyl migration. Such facile arrangement supports the conclusion that the natural products 1–8 do not exist in vivo as the amino acylamidines.

Acyl transfer was not observed in the analogous amino acylguanidines 14. However, since such a rearrangement would involve an unfavorable seven-membered-ring intermediate, this is not surprising. Possible acyl transfer involving a carbamate was also examined since an acylamidine in which the acyl group is a removable protecting group would be of synthetic interest. Compound 18′ [(benzyloxy)carbonyl-protected amine] was acylated with di-*tert*-butyl dicarbonate, giving a Cbz-amino-Boc-amidine, **19c′**. Selective hydrogenolytic removal of the (benzyloxy)carbonyl group gave the Boc amidine without any indication of acyl transfer to the Boc amine. This is a useful intermediate since amide formation and then Boc removal would give the amidopropionamidine moiety found in natural products 3–8. These new Boc- and Cbz-protected amidines as well as the principle of acyl transfer are now being applied in the synthesis of compounds 1–8 and their analogues.

Experimental Section

Unless otherwise indicated all melting points are uncorrected; microanalyses were performed by the Analytical Laboratory, Department of Chemistry, University of California at Berkeley. IR spectra were taken on a Perkin-Elmer 337; ^1H NMR spectra were taken on a Varian T-60 in $CDCl_3$ unless otherwise stated with Me_4Si as an internal standard (coupling constants (J) are given in hertz throughout); ^{13}C NMR spectra were taken on a TT-23 with dioxane (aqueous) or Me_4Si as internal standards. UV spectra were taken on a Varian Cary 14 spectrophotometer in 95% C_2H_5OH followed by addition of 3.7 M NaOH and then concentrated HCl; mass spectra were obtained on an AEI MS12 with a 1N COS data system. Organic solvent solutions were dried over Na_2SO_4 prior to evaporation in a Berkeley Rotovap.

Acylamidines. General Procedures. Method A. For those amidines whose free base was easily obtained by treating the hydrochloride with a concentrated KOH solution and extracting with CH_2Cl_2, the free base and a phenyl ester of the desired acyl group were combined under N_2, either neat or in CH_2Cl_2, and stored at room temperature. The best yields for heat-sensitive products were obtained by adding 200 mol % of amidine to the phenyl ester, both in CH_2Cl_2, at room temperature. The solvent, if any, was removed after sufficient time for reaction (usually a few hours), and the residue was dissolved in acetone and filtered. Concentrated HCl was added and the solution set aside until the salt precipitated; this can be immediate or take almost a week.

Method B. The free base of the amidine was obtained from the corresponding salt by ion-exchange chromatography on a column of Dowex AG-21 (OH^- form) and combined with phenyl ester of the desired acyl group in $CHCl_3$ and a slight excess of *N,N,N′N′*-tetramethylguanidine. After a sufficient reaction time the solution was washed several times with water and once with brine. Drying and concentrating left the crude acylamidine which was either recrystallized or converted to the hydrochloride salt as in method A.

Acylguanidines were prepared by the general procedure B above.

Benzoylbenzamidine was prepared as directed[24] on a 10-mmol scale. The product was 1.59 g (98.7% yield) of a crude oil which slowly crystallized: mp 95–96 °C (from hexane); TLC R_f ($CHCl_3/Al_2O_3$) 0.48, R_f (50% acetone/$CHCl_3$/silica) 0.84; ^1H NMR (acetone-d_6) δ 8.29 (m, 5 H), 7.49 (m, 7 H); mass spectrum, m/e (relative intensity) 224 (7), 223 (5), 103 (100), 77 (72). Anal. Calcd for $C_{14}H_{12}N_2O$: C, 75.0; H, 5.4; N, 12.5. Found: C, 74.7; H, 5.5; N, 12.6. **Hydrochloride salt**: mp 182–185 °C; mass spectrum, m/e (relative intensity) 224 (5), 223 (3), 103 (66), 91 (73), 36 (100).

Acetylbenzamidine hydrochloride was prepared as above in 80% yield: mp 188 °C; TLC R_f (50% acetone/$CHCl_3$/silica) 0.79, R_f ($CHCl_3$/alumina) 0.40; ^1H NMR (D_2O) δ 7.81 (m, 5 H), 2.48 (s, 3 H); mass spectrum, m/e (relative intensity) 162 (6), 121 (3), 103 (100). Anal. Calcd for $C_9H_{10}N_2O$·HCl: C, 54.4; H, 5.6; N, 14.1. Found: C, 54.6; H, 5.6; N, 14.1.

Benzoylacetamidine Hydrochloride. Phenyl benzoate (2.18 g, 11 mmol) and acetamidine hydrochloride (945 mg, 10 mmol) were dissolved in 5 mL of DMF to which was added TEA (1.01 g, 1.39 mL, 10 mmol). The solution was stirred at room temperature for 3 days, after which the DMF was evaporated, and the residue was treated with 6 mL of acetone and stirred for 2 h. The mixture was filtered, and the precipitate was washed with acetone, dried (1.25 g), dissolved in water, heated, and cooled slowly to give 467 mg (28.9%) of acetylbenzamide. The acetone filtrate and washings were treated with concentrated HCl (0.92 mL, 11 mmol) and refrigerated for several days, depositing 140 mg of needles: mass spectrum, m/e (relative intensity) 162 (27), 161 (23), 105 (100), 77 (100). Anal. Calcd for $C_9H_{10}N_2O$·HCl: C, 54.4; H, 5.6; N, 14.1. Found: C, 54.4; H, 5.6; N, 14.1.

Benzoylpropionamidine hydrochloride was prepared as above from phenyl benzoate and propionamidine: 30% yield; mp 173–175 °C; TLC R_f ($CHCl_3/Al_2O_3$) 0.27; mass spectrum, m/e (relative intensity) 176 (35), 121 (39), 105 (98), 103 (34), 99 (41), 77 (100), 54 (51), 51 (82), 36 (33). Anal. Calcd for $C_{10}H_{12}N_2O$·HCl: C, 56.5; H, 6.2; N, 13.2. Found: C, 56.6; H, 6.1; N, 12.8.

***N*-[3-[(*tert*-Butoxycarbonyl)amino]-1,2,4-trimethyl-5-pyrroyl]propionamidine.** To propionamidine (108 mg, 1.50 mmol) in 1 mL of CH_2Cl_2 cooled in an ice bath was slowly added over 1 h the hydroxybenztriazolide of 3-[(*tert*-butoxycarbonyl)-

amino]-5-carboxy-1,2,4-trimethylpyrrole[34] (356 mg, 0.925 mmol) dissolved in 2 mL of CH_2Cl_2. The mixture was stirred at room temperature overnight and poured into $CHCl_3/H_2O$, followed by separation of the organic phase which was washed twice with H_2O, dried, and evaporated to give 272 mg (92%) of product: mp 140–148 °C (from methylcyclohexane); NMR δ 5.73 s (br, 1 H), 3.83 (s, 3 H), 2.32 (s), 2.32 (q, J = 7.5), 2.13 (s, 8 H total), 1.90 (s, 9 H), 1.23 (t, J = 7.5, 3 H), 0.87 (s, br, 2 H); mass spectrum, m/e (relative intensity) 322 (1), 167 (65), 57 (100). Anal. Calcd for $C_{16}H_{26}N_4O_3$: C, 59.6; H, 8.1; N, 17.4. Found: C, 59.6; H, 8.1; N, 17.0.

***N*-*n*-Octadecanoylpropionamidine Hydrochloride.** The acylamidine, obtained in quantitative yield by the general procedure above, was dissolved in 5/1 acetone/$CHCl_3$ (6 mL/450 mg) from which the HCl salt was precipitated. The crude salt was dissolved in $CHCl_3$, and an insoluble material was allowed to settle out. Addition of hexane formed crystals: mp 130–132 °C; ^1H NMR δ 2.90 (m, 1 H), 1.48 (t), 1.30 (m, 33 H), 0.88 (t, 3 H); TLC R_f ($CHCl_3/Al_2O_3$) 0.68; mass spectrum, m/e (relative intensity) 338 (2), 114 (85), 99 (55), 72 (100), 59 (100), 55 (99), 43 (100), 41 (100), 36 (99). Anal. Calcd for $C_{21}H_{42}N_2O$·HCl: C, 67.2; H, 11.6; N, 7.5. Found: C, 67.1; H, 11.6; N, 7.7.

Attempts to recrystalize the HCl salt from ethanol gave the corresponding imide: mp 96–98 °C; mass spectrum, m/e (relative intensity) 339 (1), 115 (57), 74 (54), 43 (100). Anal. Calcd for $C_{21}H_{41}NO_2$: C, 74.3; H, 12.2; N, 4.1. Found: C, 74.0; H, 11.9; N, 4.4.

Propionamidine Hydrochloride. A solution of 27.54 g (0.5 mol) of propionitrile in 23 mL of anhydrous methanol and 190 mL of anhydrous ether was immersed in an ice bath, and hydrogen chloride was bubbled through the stirred mixture. After 1 h the reaction mixture was cooled at −15 °C for 96 h, after which it was evaporated to dryness. The resulting crystalline imidate hydrochloride was dried at room temperature, dissolved in 300 mL of 20% ammonia in ethanol, stirred at room temperature for 24 h, treated with 200 mL of anhydrous ether, and evaporated to approximately 75 mL. An additional 600 mL of ether was added, and after 24 h of cooling at −10 °C, the product was collected, washed with ether (2 × 100 mL), and dried: yield 34.6 g (64%); mp 128–130 °C; mass spectrum, m/e (relative intensity) 72 (22), 71 (27), 44 (68), 43 (100), 36 (69); ^1H NMR (Me_2SO-d_6) δ 5.65 (s, 3.5 H), 2.08 (dq, J = 7, 2 H), 1.08 (dt, J = 7, 3 H).

2-Methyl-2-imidazoline was prepared as reported.[39]

2-Methyl-1-*n*-octadecanoyl-2-imidazoline (26). A solution of 2-methyl-2-imidazoline (188 mg, 2.24 mmol) and phenyl octadecanoate (385 mg, 1.07 mmol) in 10 mL of CH_2Cl_2 was stirred overnight after which the CH_2Cl_2 was washed with H_2O, saturated Na_2CO_3, and H_2O and dried and the solvent evaporated. The residue was dissolved in benzene and filtered, and evaporation gave 128 mg of product: mp 48–49 °C (from hexane); NMR δ 3.75 (s, 4 H), 2.33 (s), 2.18 (m, 5 H total), 1.22 (s, 30 H), 0.83 (m, 3 H); mass spectrum, m/e (relative intensity) 350 (1), 84 (100), 55 (71), 43 (78); UV λ_{max} (relative A) 234 (0.98), 233 (OH^-, 1.00), 240 (H^+, 0.76), H^+ after 15 min, 240 (0.73), 40 min, 240 (0.64), 13 h, 235 (0.23).

***N*-Ethylformamide**: ^1H NMR δ 8.13 (s, 0.88 H), 7.97 (br s, 0.12 H), 6.69 (br s, 1 H), 3.33 (dq, J = 7, 2 H), 1.17 (dt, J = 7, 3 H), mass spectrum, m/e (relative intensity) 73 (100), 58 (55), 46 (13), 44 (65), 42 (88).

***N*-Ethylacetamide**: ^1H NMR δ 7.02 (br s, 1 H), 3.33 (q), 3.23 (q, J = 7, 2 H total), 1.98 (s, 3 H), 1.14 (t, J = 7, 3 H).

***N*-Ethyl-*o*-toluamide** was prepared as directed:[40] ^1H NMR δ 7.18 (s, 4 H), 6.17 (br s, 1 H), 3.42, 3.32 (dq, J = 7, 2 H total), 2.37 (s, 3 H), 1.17 (t, J = 7, 3 H); mass spectrum, m/e (relative intensity) 163 (38), 119 (100), 91 (71), 30 (67).

Ethylguanidine sulfate was prepared as directed:[41] mp 243–248 °C (lit.[41] mp 245–250 °C); NMR (D_2O) δ 3.0 (q, J = 7.5, 2 H), 0.98 (t, J = 7.5, 3 H).

***N*-Acetyl-*N'*-ethylguanidine hydrochloride** was prepared by general procedure B from *N*-ethylguanidine sulfate and isolated as the hydrochloride: mp 161–162 °C; NMR (D_2O) δ 3.2 (q, 2 H), 2.1 (s, 3 H), 1.1 (t, 3 H). Anal. Calcd for $C_5H_{11}N_3O$·HCl: C, 36.3; H, 7.3; N, 25.4. Found: C, 36.4; H, 7.3; N, 25.4.

***N*-Benzoyl-*N'*-ethylguanidine** was prepared by general procedure B and recrystallized from benzene: mp 95–97 °C; NMR ($CDCl_3/Me_2SO$-d_6) δ 7.9 (m, 2 H), 7.2 (m, 3 H), 3.2 (q, J = 7, 2 H), 1.2 (t, J = 7, 3 H). Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.8; H, 6.9; N, 22.0. Found: C, 62.9; H, 6.9; N, 22.1.

3-[[(Benzyloxy)carbonyl]amino]propionitrile (15′). A solution of 22.31 g (174 mmol) of 3-aminopropionitrile fumarate in 200 mL of water was adjusted to pH 10 with sodium hydroxide, a solution of 26.2 mL (174 mmol) of 95% benzyl chloroformate in 50 mL of ether was added, and the two-phase mixture was stirred vigorously for 4 h, with addition of dilute NaOH as needed to maintain pH 10. An additional 200 mL of ether was added, the ether layer was removed, and the aqueous phase was again washed with 200 mL of ether, after which the combined ether layers were washed with water (100 mL) and saturated NaCl solution (100 mL). Drying and evaporation left 35.0 g (172 mmol) of product which was recrystallized from benzene/hexane in nearly quantitative recovery: mp 65–67 °C; IR ($CHCl_3$) 2300 (nitrile), 1730 (C=O) cm^{-1}; NMR δ 7.4 (s, 5 H), 5.3 (br s, 1 H), 5.2 (s, 2 H), 3.4 (q, J = 6, 2 H), 2.6 (t, J = 6, 2 H).

3-[[(Benzyloxy)carbonyl]amino]propiothioamide (16′). Into a stirred solution of 22 g (108 mmol) of 3-[[(benzyloxy)carbonyl]amino]propionitrile (15′) and 12 mL of diethylamine (108 mmol) in 108 mL of DMF maintained at 55 °C was bubbled hydrogen sulfide at a moderate rate over 3.5 h. The deep blue-green solution was poured into 600 g of ice, water was added to bring the total volume to 1 L, and the aqueous DMF solution was allowed to stand until the ice had completely melted and a copious precipitate had formed. The precipitate was collected by suction filtration, washed with water, and dissolved in chloroform. Residual water was separated from the chloroform solution, and the organic phase was dried and evaporated to give 20 g (84 mmol, 78% yield) of thioamide 16′: mp 106–108 °C (from benzene/hexane); TLC (10% $CH_3OH/CHCl_3$) R_f 0.48 (16′), 0.30 (15′); NMR δ 7.4 (s, 5 H), 7.4 (br s, 2 H), 5.4 (br s, 1 H), 5.1 (s, 2 H), 3.6 (q, J = 6, 2 H), 2.8 (t, J = 6, 2 H); IR ($CHCl_3$) 1730 (C=O), 1620 (C=S) cm^{-1}.

***S*-Ethyl-3-[[(benzyloxy)carbonyl]amino]propiothioimidate (17′).** To 407 mg (1.71 mmol) of thioamide 16′ dissolved in 20 mL of methylene chloride was added 357 mg (1.88 mmol) of triethyloxonium tetrafluoroborate. The solution was stirred under N_2 for 12 h, after which time a new spot had appeared on TLC (10% MeOH/$CHCl_3$, R_f 0.60). At this time 148 mg (1.07 mmol) of potassium carbonate in 0.15 mL of water was added, the mixture was stirred for 5 min and then filtered, and the filtrate was diluted to 100 mL with methylene chloride and washed with water. Drying and evaporation left 266 mg (1.0 mmol, 59% yield) of 17′: NMR δ 8.4 (br s, 1 H), 7.4 (s, 5 H), 5.5 (br s, 1 H), 5.1 (s, 2 H), 3.5 (q, J = 6, 2 H), 2.8 (t, J = 7, 2 H), 2.6 (t, J = 6, 2 H), 1.3 (t, J = 7, 3 H).

3-[[(Benzyloxy)carbonyl]amino]propionamidine (18′). Thioimidate 17′ (3.68 g, 14.6 mmol) and ammonium bromide (1.72, 17.6 mmol) in 50 mL of 2-propanol were heated at reflux for 24 h. The 2-propanol was then evaporated, and the residue was triturated with hot ether, leaving a residue of oily 3-[[(benzyloxy)carbonyl]amino]propionamidine hydrobromide and ammonium bromide. Applying this residue to a Dowex 21K anion-exchange column (OH^- form) and evaporating the ethanol eluant left 3.06 g (13.9 mmol, 95% yield) of amidine 18′: mp 99–102 °C (from benzene/hexane); NMR δ 7.3 (s, 5 H), 5.3 (br s, 3 H), 5.1 (s, 2 H), 3.4 (t, J = 6, 2 H), 2.3 (t, J = 6, 2 H).

***N*-(*tert*-Butoxycarbonyl)-3-[[(benzyloxy)carbonyl]amino]propionamidine (19c′).** To 868 mg (4.94 mmol) of amidine 18′ was added 1.19 g (5.44 mmol) of di-*tert*-butyl dicarbonate in 10 mL of acetone, and the solution was stirred 12 h. The acetone was evaporated, and the residue was dissolved in $CHCl_3$ and washed with water. Drying of the organic phase and evaporation left 1.12 g (3.67 mmol, 77% yield) of 19c′: mp 66–69 °C (from benzene/hexane); NMR δ 7.0–7.8 (br, 2 H), 7.4 (s, 5 H), 5.5 (br t, J = 7, 1 H), 5.1 (s, 2 H), 3.5 (q, J = 7, 2 H), 2.4 (t, J = 7, 2 H), 1.5 (s, 9 H).

3-[(*tert*-Butoxycarbonyl)amino]propionitrile (15). 3-Aminopropionitrile fumarate (19.5 g, 152 mmol) was dissolved in 200 mL of water, the pH was adjusted to 10 with NaOH, 30.1 g (138 mmol) of di-*tert*-butyl dicarbonate in 100 mL of ether was

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added, and the mixture was stirred vigorously for 12 h. The ether phase was separated, the water phase was extracted with ether (2 × 200 mL), and the combined ether fractions were washed with water and saturated aqueous NaCl, and then dried. Evaporation left a crude oil which solidified; trituration of the solid with hexane left 21.3 g (125 mmol, 91% yield) of **15**: mp 40–42 °C; NMR δ 5.4 (br s, 1 H), 3.4 (q, J = 6, 2 H), 2.6 (t, J = 6, 2 H), 1.5 (s, 9 H).

3-[(*tert*-Butoxycarbonyl)amino]propiothioamide (16). Nitrile **15** (21.3 g, 125 mmol) was combined with 14 mL (125 mmol) of diethylamine in 125 mL of DMF. Addition of H_2S and isolation, carried out as for **15'**, gave 21.6 g (106 mmol, 85% yield) of **16**: mp 106–110 °C (from benzene/hexane); NMR δ 7.7 (br s, 2 H), 5.2 (br s, 1 H), 3.5 (q, J = 6, 2 H), 2.8 (t, J = 6, 2 H), 2.4 (s, 9 H).

***S*-Methyl-3-[(*tert*-butoxycarbonyl)amino]propiothioimidate Hydroiodide (17).** To 10.38 g (50.8 mmol) of thioamide **16** was added 16 mL (254 mmol) of methyl iodide, and the mixture was heated to reflux. The thioamide slowly (2 min) went into solution, and after about 5 min a solid rapidly precipitated, forming a solid cake. This cake was broken up, 25 mL of methylene chloride was added, the heterogeneous mixture was further stirred, heated for 12 h, and then cooled, and the solid was collected and washed with methylene chloride, yielding 15.6 g (45.1 mmol, 89% yield) of **17**: mp 120–123 °C dec; NMR δ 9.3 (br s, 2 H), 5.4 (br s, 1 H), 3.6 (t, J = 6, 2 H), 3.2 (t, J = 6, 2 H), 2.9 (s, 3 H), 1.4 (s, 9 H).

3-[(*tert*-Butoxycarbonyl)amino]propionamidine (18). A solution of 8.56 g (24.8 mmol) of thioimidate **17** in 150 mL of 2-propanol was warmed while ammonia was bubbled through for 30 min and then refluxed for 12 h. The reaction mixture was evaporated, and the residue, dissolved in absolute ethanol, was applied to a Dowex 21K anion-exchange column (OH^- form). Evaporation of the ethanol eluant left 4.45 g (23.8 mmol, 96% yield) of amidine **18**: NMR δ 5.4 (br s, 3 H), 3.3 (t, J = 6.5, 2 H), 2.3 (t, J = 6.5, 2 H), 1.4 (s, 9 H).

***N*-Benzoyl-3-[(*tert*-butoxycarbonyl)amino]propionamidine (19a)** was prepared from **18** and phenyl benzoate by procedure B and recrystallized from benzene/hexane: mp 156–158 °C; NMR δ 8.2 (m, 2 H), 7.4 (m, 4 H), 5.4 (br t, 1 H), 3.5 (q, J = 6, 2 H), 2.5 (t, J = 6, 2 H), 1.4 (s, 9 H).

3-Amino-*N*-benzoylpropionamidine Dihydrochloride (11, R = C_6H_5). Into a solution of **19a** in ethyl acetate was bubbled HCl with stirring and cooling for 5 min. The reaction mixture was then evaporated, the residue was triturated with ether, and the white solid was collected by filtration. Recrystallization from 2-propanol/ether gave **11** (R = C_6H_5), mp 184–186 °C dec. Anal. Calcd for $C_{10}H_{13}N_3O$·2HCl: C, 45.5; H, 5.7; N, 15.9. Found: C, 45.4; H, 5.9; N, 15.6.

***N*-Stearoyl-3-[(*tert*-butoxycarbonyl)amino]propionamidine (19b)** was prepared from **18** and phenyl stearate by procedure B and recrystallized from hexane: mp 59–61 °C; NMR δ 7.0–8.0 (br s, 2 H), 5.4 (t, J = 5, 1 H), 3.4 (pseudo q, J = 6, 2 H), 2.4 (t, J = 6), and 2.35 (t, 4 H total), 1.5 (s, 9 H), 1.2–1.4 (s, 30 H), 0.95 (t, J = 5, 3 H).

3-Amino-*N*-stearoylpropionamidine dihydrochloride (11, R = *n*-$C_{17}H_{35}$) was prepared from **19b** by the procedure used for **11** (R = C_6H_5): mp 203–209 °C dec; NMR (Me_2SO-d_6) δ 7.0–8.4 (br s, 1.5 H), 3.2–4.2 (br s), 3.0 (br s), 2.5 (m), 1.3 (s, 30 H), 0.95 (t, J = 5, 3 H). Anal. Calcd for $C_{21}H_{43}N_3O$·2HCl: C, 59.1; H, 10.6; N, 9.8. Found: C, 59.1; H, 10.3; N, 9.1.

Attempts to recrystallize **11b** from 2-propanol led to hydrolysis of the acylamidine to the imide: mp 153–156 °C; UV λ_{max} <210 nm, OH^-, unchanged.

***N*-Stearoyl-3-[[(benzyloxy)carbonyl]amino]propionamidine (19b')** was prepared from **18'** and phenyl stearate by procedure B and recrystalized from benzene/hexane: mp 98–101 °C; UV λ_{max} 245, 210 (H^+); NMR δ 7.5 (br s, 2 H), 7.3 (s, 5 H), 5.6 (br s, 1 H), 5.1 (s, 2 H), 3.4 (q, J = 6, 2 H), 2.4 (t, J = 6, 2 H), 2.3 (t, J = 6, 2 H), 1.1–1.8 (30 H), 1.8 (t, J = 6, 2 H). The hydrochloride of the acylamidine was prepared by dissolving the compound in acetone and adding a slight access of concentrated hydrochloric acid. After the mixture had been allowed to stand for several hours, the white precipitate was collected by suction filtration; mp 70–80 °C.

3-(Stearoylamino)propionamidine Hydrochloride (10, R = *n*-$C_{17}H_{35}$). Protected amine **19b'** was dissolved in absolute ethanol and shaken with hydrogen over 10% of 10% Pd/C. After 12 h, the catalyst was removed and the filtrate evaporated to dryness. Recrystallization of the residue from ethanol/ether gave **10b**: mp 110–112 °C; NMR ($CDCl_3$/Me_2SO-d_6) δ 8.6 (br s, 4 H), 3.5 (q, 2 H), 2.8 (t, 2 H), 2.2 (t, 2 H), 1.5 (m, 2 H), 1.2 (br s, 28 H), 0.8 (t, 3 H). Anal. Calcd for $C_{21}H_{43}N_3O$·HCl: C, 64.7; H, 11.4; N, 10.8. Found: C, 64.5; H, 11.1; N, 11.0.

3-Amino-*N*-stearoylpropionamidine dihydrochloride (11, R = *n*-$C_{17}H_{35}$) was prepared exactly as for **10** (R = *n*-$C_{17}H_{35}$) except excess anhydrous HCl was added to the solution prior to hydrogenolysis. Evaporation left crude **11b** which was recrystallized from EtOH/Et_2O and was identical with that prepared via the Boc amine **19b**.

3-(Benzoylamino)propionitrile. To 3.2 g (25 mmol) of 3-aminopropionitrile fumarate were added 5.8 mL (7.03 g, 50 mmol) of benzoyl chloride and 100 mL of H_2O, and the pH was adjusted to 10. The two-phase mixture was stirred vigorously for 1 h with periodic addition of NaOH to keep the pH at 10. The pH was then adjusted to 7 with dilute HCl, and the mixture was extracted with chloroform. The chloroform was evaporated, methanol was added to the residue, and it was allowed to stand for 1 h to destroy any residual benzoyl chloride. Evaporation gave 3.85 g of 3-(benzoylamino)propionitrile: mp 88–90 °C; NMR ($CDCl_3$) δ 7.8 (m, 2 H), 7.4 (m, 4 H), 3.6 (q, J = 6, 2 H), 2.7 (t, J = 6, 2 H).

3-(Benzoylamino)propionamidine Hydrochloride (10, R = C_6H_5). 3-(Benzoylamino)propionitrile (2 g) was dissolved in 150 mL of MeOH/Et_2O (1/1), and the mixture was saturated with anhydrous HCl with ice-bath cooling. After being allowed to stand for 18 h, the solution was filtered, and the filtrate was evaporated. Resolution of the residue in anhydrous methanol, saturation with anhydrous ammonia with ice-bath cooling, and standing for 24 h followed by evaporation gave **10a**: mp 178–181 °C (from ethanol/ether); NMR (D_2O) δ 7.6 (m, 5 H), 3.6 (t, J = 7, 2 H), 2.6 (t, J = 7, 2 H). Anal. Calcd for $C_{10}H_{13}N_3O$·HCl: C, 52.8; H, 6.2; N, 18.5. Found: C, 52.8; H, 6.2; N, 18.6.

***N*-[(Benzyloxy)carbonyl]ethylenediamine (20a)** was prepared as reported for *N*-[(benzyloxy)carbonyl]piperazine[28] and isolated in 54% yield as a slightly yellow oil, which solidified on prolonged standing: NMR δ 7.3 (s, 5 H), 5.9–6.2 (br s, 1 H), 5.1 (s, 2 H), 3.2 (q, J = 5, 2 H), 2.8 (t, J = 5, 2 H), 2.3 (br s, 2 H). The hydrochloride was obtained by adding 110 mol % of concentrated HCl to an acetone solution of the amine. Upon evaporation and recrystallization from acetone, **20a**·HCl was obtained; mp 158–159 °C. Anal. Calcd for $C_{10}H_{14}N_2O_2$·HCl: C, 52.1; H, 6.6; N, 12.1. Found: C, 52.1; H, 6.4; N, 12.0.

***N*-[(Benzyloxy)carbonyl]-*N'*-(*tert*-butoxycarbonyl)-ethylenediamine (21b).** In 250 mL of dry acetone were combined 5.03 g (25.9 mmol) of *N*-[(benzyloxy)carbonyl]ethylenediamine (**20a**) and 5.94 g (27.2 mmol) of di-*tert*-butyl dicarbonate. The solution was stirred at room temperature for 24 h and then refluxed for 1 h. The acetone was evaporated, and the residue was dissolved in chloroform which was washed with 5% HCl, saturated $NaHCO_3$, and saturated NaCl, dried, and evaporated, leaving a quantitative yield of **21b**: mp 123–124 °C; NMR δ 7.3 (s, 5 H), 7.2 (br s, 1 H), 5.3 (br s, 1 H), 5.1 (s, 2 H), 3.25 (m, 4 H), 1.45 (s, 9 H). Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.2; H, 7.5; N, 9.5. Found: C, 61.0; H, 7.6; N, 9.5.

***N*-Benzoyl-*N'*-[(benzyloxy)carbonyl]ethylenediamine (21c).** To 2.51 g (12.9 mmol) of *N*-[(benzyloxy)carbonyl]-ethylenediamine (**20a**) dissolved in 100 mL of ether and cooled with an ice bath was added triethylamine (1.86 mL, 13.5 mmol) followed by dropwise addition of 1.59 mL (13.5 mmol) of benzoyl chloride. Stirring was continued for several hours, after which the heterogeneous solution was filtered, and the filtrate was washed with 5% HCl (2 × 50 mL), saturated $NaHCO_3$ (2 × 50 mL), and saturated NaCl (1 × 50 mL) and then dried. Filtration and evaporation gave 3.37 g (11.3 mmol, 88% yield) of **21c**: NMR ($CDCl_3$) δ 7.8 (m, 2 H), 7.3 (m, 3 H), 7.2 (s, 5 H), 5.6 (br s, 1 H), 5.0 (s, 2 H), 3.4 (m, 4 H). Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.4; H, 6.1; N, 9.4. Found: C, 68.4; H, 6.0; N, 9.5.

***N*-(*tert*-Butoxycarbonyl)ethylenediamine (20b).** To a solution of 25.9 mmol of **21b** in 125 mL of absolute ethanol was added 3 g of 10% Pd/C, and the mixture was shaken under 40 psi of hydrogen for 48 h. The catalyst was removed and the filtrate evaporated, leaving oily **20b**: NMR δ 5.1 (br s, 2 H), 2.9–3.4 (br

s, 4 H), 1.4 (s, 9 H). Anal. Calcd for $C_7H_{16}N_2O_2$: C, 52.5; H, 10.1; N, 17.5. Found: C, 52.2; H, 10.0; N, 17.1.

N-Benzoylethylenediamine (20c). Crude **21c** (3.37 g, 11.3 mmol) was dissolved in 100 mL of absolute ethanol, 3 g of 10% Pd/C was added, and the mixture was shaken for 24 h under 60 psi of hydrogen. The catalyst was removed, the filtrate was evaporated, the residue was dissolved in $CHCl_3$ and extracted into 5% HCl, and the HCl was basified (K_2CO_3) and extracted with $CHCl_3$. Drying and evaporating the $CHCl_3$ left 740 mg (4.5 mmol) of oily **20c**: NMR δ 7.8 (m, 3 H, includes amide), 7.3 (m, 3 H), 3.45 (t, J = 6, 2 H), 3.2 (br s, 2 H), 2.8 (t, J = 6, 2 H). Anal. Calcd for $C_9H_{12}N_2O$: C, 65.8; H, 7.4; N, 17.1. Found: C, 65.9; H, 7.3; N, 17.0.

N-Acetylethylenediamine (20d) was prepared as reported[42] and distilled at 148 °C (13 mm): NMR ($CDCl_3$) δ 8.5 (t, J = 5, 1 H), 3.2 (q, J = 6, 2 H), 2.8 (t, J = 6, 2 H), 2.0 (s, 2 H), 1.95 (s, 2 H).

S-Methyl-N-[2-[(*tert*-butoxycarbonyl)amino]ethyl]-N′-tosylisothiourea (22b). In 150 mL of absolute ethanol were combined 13 mmol of crude **20b** and 3.25 g (11.8 mmol) of dimethyl (tosylimino)dithiocarbonate, and the mixture was refluxed for 24 h. The ethanol was evaporated, and the residue was dissolved in ether, washed three times with 5% HCl, $NaHCO_3$, and saturated NaCl, dried, and evaporated, leaving a quantitative yield of crude **22b**: NMR δ 7.85 (d, J = 8, 2 H), 7.3 (d, J = 8, 2 H), 4.9 (br s, 1 H), 2.39 (s, 3 H), 2.41 (s, 3 H), 1.5 (s, 9 H).

S-Methyl-N-[2-(benzoylamino)ethyl]-N′-tosylisothiourea (22c). A solution of **20c** and 1.125 g (4.5 mmol) of dimethyl (tosylimino)dithiocarbonate in 50 mL of absolute ethanol was refluxed for 48 h. The ethanol was then evaporated, and the crude residue was treated as in the preparation of **22b** and recrystallized from benzene/hexane, yielding 1.28 g (3.28 mmol, 73%) of **22c**: mp 54–56 °C; NMR δ 8.4 (br s, 1 H), 7.8 (m, 4 H, mixture of phenyl and tosyl absorption), 7.2 (m, 5 H, mixture of phenyl and tosyl), 3.6 (br s, 4 H), 2.4 (s, 3 H), 2.3 (s, 3 H).

S-Methyl-N-[2-(acetylamino)ethyl]-N′-tosylisothiourea (22d) was prepared by following the procedure for **22c** and chromatographed on a silica gel column (R_f with 10% MeOH/$CHCl_3$ was 0.40): NMR δ 8.2 (br s, 1 H), 7.5 (AB q, 4 H), 7.2 (br s, 1 H), 3.4 (m, 4 H), 2.3 (br s, 6 H), 1.8 (s, 3 H).

N-[2-[(*tert*-Butoxycarbonyl)amino]ethyl]-N′-tosylguanidine (23b). Into 150 mL of acetonitrile, saturated with anhydrous ammonia, were added 11.8 mmol of **22b** and 1.9 mL (13.6 mmol) of triethylamine. The solution was cooled with an ice bath, an acetonitrile solution of 2.31 g (13.6 mmol) of silver nitrate was added dropwise, and the solution was stirred overnight. The $AgSCH_3$ was filtered off, the acetonitrile was evaporated, and the residue was dissolved in ether, washed with 5% HCl, saturated $NaHCO_3$, and saturated NaCl, dried, and evaporated, leaving 4.22 g (11.65 mmol) of crude. Recrystallization from acetone/hexane gave 2.66 g (62% yield) of pure **23b**: mp 115–120 °C; NMR δ 7.75 (d, J = 8, 2 H), 7.25 (d, J = 8, 2 H), 6.7 (br s, 3 H), 5.35 (br s, 1 H), 3.3 (m, 4 H), 2.4 (s, 3 H), 1.4 (s, 9 H).

N-[2-(Benzoylamino)ethyl]-N′-tosylguanidine (23c). A solution of 1.28 g (3.28 mmol) of **22c** in 50 mL of acetonitrile was cooled (ice bath) and saturated with anhydrous ammonia. Triethylamine (0.5 mL, 3.61 mmol) was added followed by a dropwise addition over 10 min of a solution of 613 mg (3.61 mmol) of silver nitrate in 25 mL of acetonitrile. The ice bath was allowed to melt as the solution was stirred for 12 h. It was then filtered, the filtrate was evaporated, and the residue was redissolved in $CHCl_3$ and then washed with $NaHCO_3$ (2 × 50 mL) and saturated NaCl (50 mL). Drying and evaporation left 880 mg of product which was recrystallized from acetone/hexane to give 720 mg of **23c**: mp 155–157 °C; NMR δ 7.0–8.0 (m, 10 H), 6.6 (br s, 3 H), 3.4 (m, 4 H), 2.3 (s, 3 H). Anal. Calcd for $C_{17}H_{20}N_4O_3S$: C, 56.7; H, 5.6; N, 15.5. Found: C, 56.9; H, 5.6; N, 15.3.

N-[2-(Acetylamino)ethyl]-N′-tosylguanidine (23d) was prepared from **22d** by following the procedure used for **23c** and chromatographed on a column of silica gel. Recrystallization from benzene gave **23d** (very hygroscopic): mp 73–75 °C; NMR δ 7.4 (AB q, 4 H), 6.8 (br s, 3 H), 5.7 (br s, 1 H), 3.4 (m, 4 H), 2.3 (s, 3 H), 1.8 (s, 3 H). Anal. Calcd for $C_{12}H_{18}N_4O_3S{\cdot}0.5H_2O$: C, 46.9; H, 6.2; N, 18.2. Found: C, 46.9; H, 6.0; N, 17.9.

N-[2-[(*tert*-Butoxycarbonyl)amino]ethyl]guanidine (13b). To 867 mg (2.43 mmol) of N-[2-[(*tert*-butoxycarbonyl)amino]-ethyl]-N′-tosylguanidine (**23b**) dissolved in 150 mL of liquid ammonia were added small bits of sodium until a deep blue color persisted for about 1 min; 315 mg (13.7 mmol) of sodium was consumed, and 735 mg (13.7 mmol) of ammonium chloride was added to the solution. The ammonia was allowed to evaporate, the residue was dissolved in hot ethanol (150 mL), and the mixture was filtered hot to remove sodium chloride. The filtrate was then applied to a column of Dowex 21K ion-exchange resin (OH^- form) and eluted with ethanol. Evaporation of the ethanol left a residue of **13b**: NMR δ 7.4 (s, 4 H), 5.3 (br s, 1 H), 3.2 (b, 4 H), 1.5 (s, 9 H).

N-[2-(Benzoylamino)ethyl]guanidine hydrochloride (13c) was prepared from **23c** by following the procedure for **13b**. The free guanidine was dissolved in acetone, and concentrated HCl was added, precipitating the extremely hydroscopic guanidine hydrochloride: mp 215 °C dec; NMR (D_2O) δ 7.0–8.0 (m, 5 H), 3.4 (m, 4 H); FD mass spectrum, m/e 207 (MH^+).

N-[2-(Acetylamino)ethyl]guanidine hydrochloride (13d) was prepared from **23d** by following the procedure for **13b**. The free guanidine was dissolved in acetone, concentrated HCl was added, and the extremely hygroscopic guanidine hydrochloride precipitated: NMR (free guanidine in $CDCl_3$) δ 6.2 (br s, 1 H), 5.0 (br s, 4 H), 3.2 (m, 4 H), 2.0 (s, 3 H); FD mass spectrum, m/e 145 (MH^+).

N-[2-[(*tert*-Butoxycarbonyl)amino]ethyl]-N′-benzoylguanidine (24a). Crude **13b** was acylated with phenyl benzoate by procedure B. Washing of the chloroform reaction mixture with water followed by drying and evaporation left acylguanidine **24a** which was recrystallized from benzene/hexane: mp 155–157 °C; NMR δ 8.2 (m, 2 H), 7.4 (m, 3 H), 6.8 (br s, 3 H), 5.5 (br s, 1 H), 3.3 (br m, 4 H), 1.4 (s, 9 H).

N-[2-[(*tert*-Butoxycarbonyl)amino]ethyl]-N′-acetylguanidine (24b) was prepared from **13b** and phenyl acetate by procedure B: NMR δ 8.2 (br s, 3 H), 7.2 (br s, 1 H), 3.2 (br s, 4 H), 2.0 (s, 3 H), 1.4 (s, 9 H).

N-Benzoyl-N′-(2-aminoethyl)guanidine Dihydrochloride (14a). Into a solution of 400 mg of **24a** in 150 mL of ethyl acetate, cooled with an ice bath, was bubbled HCl slowly for 30 min. The solution was then evaporated, and the residue was recrystallized from EtOH/Et_2O, giving **14a**: mp 203–205 °C; NMR ($CDCl_3$/Me_2SO-d_6) δ 9.6 (br m, 3 H), 8.3 (m, 2 H), 7.7 (m, 3 H), 3.8 (t, J = 6, 2 H), 3.4 (s, 2 to 3 H), 3.2 (t, J = 6, 2 H). Addition of D_2O led to the disappearance of the absorptions at δ 9.6 and 3.4. Anal. Calcd for $C_{10}H_{14}N_4O{\cdot}2HCl$: C, 43.0; H, 5.8; N, 20.1. Found: C, 42.7; H, 5.7; N, 19.9.

N-Acetyl-N′-(2-aminoethyl)guanidine Dihydrochloride (14b). Crude **24b** was dissolved in 100 mL of ethyl acetate, and the solution was saturated with anhydrous HCl with ice-bath cooling. The solvent was then evaporated, leaving a residue which was recrystallized from 2-propanol/ether: mp 217–218 °C dec; NMR (D_2O) δ 3.7 (t, J = 6, 2 H), 3.2 (t, J = 6, 2 H), 2.0 (s, 3 H). Anal. Calcd for $C_5H_{12}N_4O{\cdot}2HCl{\cdot}0.5H_2O$: C, 26.3; H, 6.7; N, 24.5. Found: C, 26.3; H, 6.3; N, 24.3.

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Registry No. 9·2HBr, 77152-88-6; **10**·HCl (R = $C_{17}H_{35}$), 77152-89-7; **10**·HCl (R = C_6H_5), 3965-98-8; **11**·2HCl (R = C_6H_5), 77152-90-0; **11**·2HCl (R = $C_{17}H_{35}$), 77152-91-1; **13b**, 77152-92-2; **13c**·HCl, 77152-93-3; **13d**·HCl, 77152-94-4; **14a**·2HCl, 77152-95-5; **14b**·2HCl, 77152-96-6; **15**, 53588-95-7; **15′**, 18877-96-8; **16**, 77152-97-7; **16′**, 77152-98-8; **17**·HI (R = Me), 77152-99-9; **17′** (R = Et), 77153-00-5; **18**, 77172-36-2; **18′**, 77153-01-6; **19a**, 77153-02-7; **19b**, 77172-37-3; **19b′**, 77153-03-8; **19b′**·HCl, 77153-04-9; **19c′**, 77172-38-4; **20a**, 72080-83-2; **20a**·HCl, 18807-71-1; **20b**, 57260-73-8; **20c**, 1009-17-2; **20d**, 1001-53-2; **21b**,

(42) Aspinall, S. R. *J. Am. Chem. Soc.* **1941**, *63*, 852.

77153-05-0; **21c**, 77153-06-1; **22b**, 77153-07-2; **22c**, 77153-08-3; **22d**, 77153-09-4; **23b**, 77153-10-7; **23c**, 77153-11-8; **23d**, 77153-12-9; **24a**, 77153-13-0; **24b**, 77153-14-1; **25**, 77153-15-2; **26**, 77153-16-3; **27**, 77209-98-4; *N*-ethyl-*o*-toluamide, 57056-81-2; *N*-ethylacetamide, 625-50-3; *N*-ethylformamide, 627-45-2; acetamidine HCl, 124-42-5; propionamidine HCl, 3599-89-1; propionamidine, 39800-84-5; benzamidine HCl, 1670-14-0; benzoylbenzamidine, 16776-73-1; benzoylbenzamidine HCl, 38063-74-0; acetylbenzamidine HCl, 38063-68-2; benzoylacetamidine HCl, 38063-70-6; benzoylpropionamidine HCl, 77153-17-4; *N*-octadecanoylpropionamidine HCl, 77153-18-5; β-(*o*-toluoylamino)propionamidine HCl, 77172-39-5; β-amino-*N*-benzoylpropionamide, 77153-19-6; *N*-acetylbenzamide, 1575-95-7; β-(*p*-toluoylamino)propionamidine HCl, 20482-62-6; *N*-octanoyl-*N'*-ethylguanidine, 77153-20-9; 3-amino-*N*-acetylpropionamidine 2HCl, 77153-21-0; *N*-[3-[(*tert*-butoxycarbonyl)amino]-1,2,4-trimethyl-5-pyrroyl]propionamidine, 77153-22-1; 3-[(*tert*-butoxycarbonyl)amino]-5-carboxy-1,2,4-trimethylpyrrole hydroxybenzotriazolide derivative, 77153-23-2; *N*-octadecanoylpropionimide, 77153-24-3; propionitrile, 107-12-0; 2-methyl-2-imidazoline, 534-26-9; *N*-acetyl-*N'*-ethylguanidine HCl, 77153-25-4; *N*-benzoyl-*N'*-ethylguanidine, 77153-26-5; 3-aminopropionitrile fumarate, 1119-28-4; 3-(benzoylamino)propionitrile, 1131-83-5; dimethyl (tosylimino)dithiocarbonate, 2651-15-2; 4-[[[(aminoiminomethyl)amino]acetyl]-amino]-*N*-[5-[[(3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-1*H*-pyrrol-3-yl]-1-methyl-1*H*-pyrrole-2-carboramide 2HCl, 18133-22-7; ethylguanidine sulfate, 57989-90-9.

Thiocarbonyl Transfer Reagent Chemistry. 3. Selective Displacements with Formaldehyde Hydrazones and Other Nucleophiles[1]

Charles Larsen*

Department of General and Organic Chemistry, University of Copenhagen, H. C. Orsted Institute, Copenhagen, Denmark DK2100

David N. Harpp

Department of Chemistry, McGill University, Montreal, Quebec, Canada H3A 2K6

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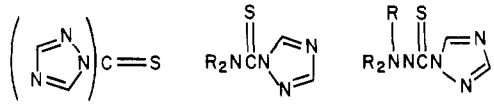
Formaldehyde hydrazones react with 1,1'-thiocarbonylbis(1,2,4-triazole) to effect C-thioacylation. The 1,2,4-triazole leaving group on these stable thioglyoxylic acid derivatives could in turn be displaced by hydrazones, sulfonohydrazides, thiosemicarbazides, and hydrazides.

As part of a study on the reaction of amines and hydrazines with thiocarbonyl transfer reagent **1** (giving **2** and **3**, respectively), we wished to examine the analogous re-



1 **2** **3**

action with other nucleophiles. We now report that formaldehyde hydrazones (**4**) react cleanly with **1** to effect C-thioacylation giving **5**. The yields of these stable, novel derivatives of thioglyoxylic acid (CHOCSOH, **6**) averaged nearly 80%. Clearly, **4** reacts through carbon via intermediate **7** to displace 1,2,4-triazole as indicated in Scheme I. The reaction is somewhat analogous to an enamine acylation.[2] We have, however, found no literature example of acylations of formaldehyde hydrazones.[4]

The triazolyl leaving group in **1** appears to possess a unique reactivity in that when **4b** and **4c** were combined with 1,1'-thiocarbonylbisimidazole **8**, no reaction took place.[5]

Attempts to extend this reaction to other aldehyde hydrazones (e.g., acetaldehyde *N,N*-dimethylhydrazone (**9**)) failed; only starting materials were isolated. It was our expectation that the acetaldehyde derivative **9** might react more slowly than **4b**, but at this time we have no explanation regarding the complete lack of reactivity with reagent **1**.

Table I. Preparation of Hydrazones of Thioglyoxalyl-1,2,4-triazoles 5[a]

compd	mp, °C	% yield	^{1}H NMR, δ
$(i\text{-}C_3H_7)_2NN{=}CH\text{-}CSTri$[b] (**5a**)	106-107	50	1.38 (d, 12 H, CH_3), 4.20 (sept, 2 H, CH), 8.02 (s, 1 H, triazole), 8.33 (s, 1 H, =CH), 9.27 (s, 1 H, triazole)
$(CH_3)_2NN{=}CHCSTri$ (**5b**)	134-135	96	3.40 (s, 6 H, CH_3), 8.13 (s, 1 H, triazole), 8.20 (s, 1 H, =CH), 9.33 (s, 1 H, triazole)
$(C_6H_5CH_2)_2NN{=}CH\text{-}CSTri$ (**5c**)	108-109	82	4.83 (s, 4 H, CH_2), 7.33 (m, 10 H, C_6H_5), 8.00 (s, 1 H, triazole), 8.33 (s, 1 H, =CH), 9.23 (s, 1 H, triazole)

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all compounds. [b] Tri = 1,2,4-triazoyl.

As expected from previous work,[5] **5a-c** (see Table I for physical data) are easily transformed by various amines and hydrazines to the corresponding thioamides and thiohydrazides (**10-13**, Table II). One reaction worthy of special note is that **5b** in its reaction with phenylhydrazine gives **14**. This product presumably arises by addition of a second molecule of phenylhydrazine to the C=N moiety followed by elimination of dimethylhydrazine. Finally, 1,2,4-triazole is displaced from **5b** and **5c** on treatment with

(1) For Part 2 in this series, see: Larsen, C.; Harpp, D. N. *J. Org. Chem.* **1980**, *45*, 3713.

(2) House, H. O. "Modern Synthetic Reactions"; Breslow, R., Ed.; W. A. Benjamin: Menlo Park, CA, 1972; pp 766-772. Reagent **1** has been shown to react with enamines.[3]

(3) Larsen, C., unpublished results.

(4) One report has appeared concerning the reaction of formaldehyde hydrazones with acetic anhydride; however, the reactions were complex, and acylation did not take place on carbon. Lamberton, J. A.; Nelson, E. R; Triffett, A. C. K. *Aust. J. Chem.* **1974**, *27*, 1521.

(5) Some of the special displacement reaction properties of reagent **1** have been published: Larsen, C.; Steliou, K.; Harpp, D. W. *J. Org. Chem.* **1978**, *43*, 337.

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