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Reduction of Acylguanidines to Alklyguanidines with Lithium Aluminum Hydride

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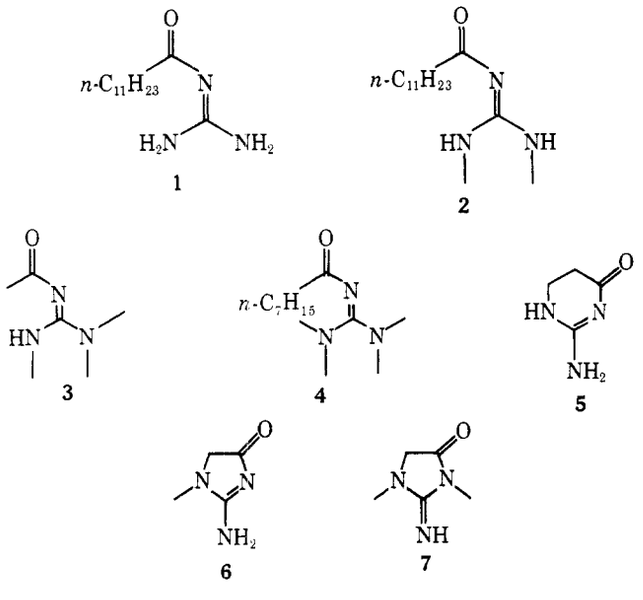
Six acylguanidines bearing different alkylation patterns, namely dodecanoylguanidine (1), *N*-dodecanoyl-*N'*,*N''*-dimethylguanidine (2), *N*-acetyl-*N'*,*N'*,*N''*-trimethylguanidine (3), β-alacreatinine (5), creatinine (6), and methylcreatinine (7), have been reduced to the corresponding alkylguanidines with lithium aluminum hydride in yields ranging from 51 to 62%. A seventh reduction substrate, *N*-octanoyl-*N'*,*N'*,*N''*,*N''*-tetramethylguanidine (4), gave only nonguanidine reduction products resulting from cleavage of the guanidine moiety, including *N*-(dimethylaminomethyl)octanamide (25). Syntheses of the various substrates are described and reaction mechanisms and general synthetic utility are discussed.

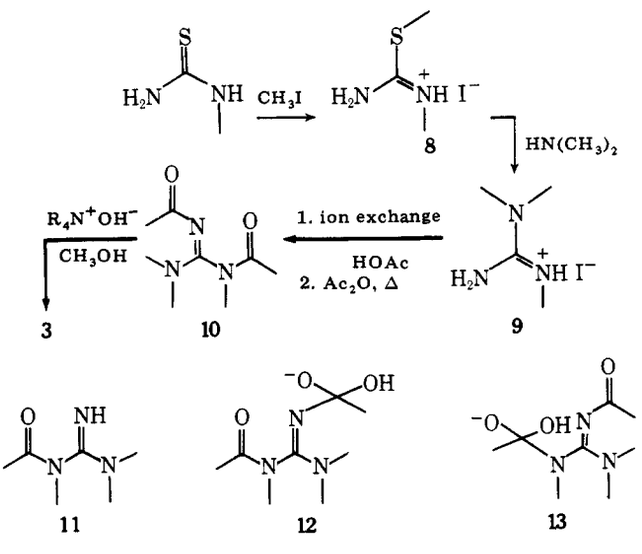
Although a literature search revealed no examples of reduction of an acylguanidine with lithium aluminum hydride ($LiAlH_4$), a statement[1] that the guanidine group is inert to $LiAlH_4$ suggested to us that the reduction of an acylguanidine to an alkylguanidine might be possible. The utility of such a conversion is illustrated by the occurrence of the alkylguanidine moiety in a wide variety of biological systems and the presence of the guanidine group in antihypertensive drugs such as clonidine[2] and guanethidine.[3]

Results and Discussion

Preparation of Reduction Substrates. The acylguanidines **1–7**, selected because they represent a broad range of substitution patterns, were in most cases easily prepared. Compounds **1**[4] and **2** were prepared by acylating the appropriate guanidine free base with methyl dodecanoate following the general procedure for acylating guanidines with esters.[5] To acylate the *sym*-tetramethylguanidine and prepare substrate **4**, the acid chloride was required. Compounds **1**, **2**, and **4** displayed the spectral properties expected for such acylguanidines.[6]

Considerable difficulty was encountered in the preparation of *N*-acetyl-*N'*,*N'*,*N''*-trimethylguanidine (**3**), the major problem being the selective conversion of **10** to **3**. The preparation of **9** proceeded according to conventional methods,[7,8] and then **9** hydriodide was converted by ion exchange to the acetate to obtain increased solubility in acetic anhydride.

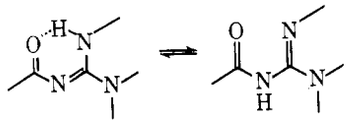




Peracetylation of the trimethylguanidine by heating with acetic anhydride gave the diacetylguanidine **10** in excellent yield. Initial attempts to convert **10** to the monoacetylguanidine **3** were based on a procedure for converting diacetylguanidine to monoacetylguanidine via ethanolysis.[9] With **10**, however, solvolysis required reflux for 3 days and a complex mixture of products was obtained.

In a second approach to the monodeacetylation of **10** to **3**, we employed a quaternary ammonium hydroxide resin for both practical and theoretical reasons. The practical advantage of the resin over metal hydroxides arises from the relative ease of product isolation. Alkaline cleavage was chosen over acid, since hydroxide attack on **10** should give **3** rather than **11**, as the unconjugated tetrahedral intermediate **12** is of higher energy than **13**. Furthermore, **13** proceeds to a resonance stabilized anion which **12** does not.

Having thus rationalized that hydrolysis of diacetylguanidine **10** should result in the acyliminoguanidine **3** rather than the acylaminoguanidine **11**, we were surprised to find that the product from hydroxide cleavage of **10** showed λ_{max} 209 nm, consistent with an acylaminoguanidine,[6] i.e., structure **11**. This discrepancy between the predicted and observed UV absorption was resolved, however, when it was found that **3** gave a bathochromic shift of 35 nm (to λ_{max} 247 nm) by changing the solvent from ethanol to dioxane. Similar solvent changes with **1** and **2** gave bathochromic shifts of only 5 nm, implying that **3** exhibits unusual properties and may even exist as the more polar deconjugated tautomer **3b** in protic solvents.



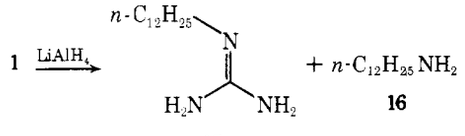
3a **3b**

Changing to an aprotic solvent would then favor the intramolecularly hydrogen-bonded tautomer **3a**. Experiments on the reduction product of **3** (discussed later) further substantiate our structure assignment.

β-Alacreatinine (**5**) hydrochloride was obtained from β-guanidinopropionic acid (**14**) which, in turn, was prepared from β-alanine and, finally, methylcreatinine [1,3-dimethyl-2-imino-4-imidazolidinone, (**7**)] was obtained by methylation of creatinine (**6**) with dimethyl sulfate.[10] This methylation of **6** gives a good yield, and the incorrect structure (CH_3 on exo nitrogen) assigned to methylcreatinine in ref 10 was subsequently corrected to structure **7**.[11]

Reductions. Since the reduction of each substrate had some unique features, we will consider them separately before discussing the more general aspects of the reaction. One common problem, however, was the tendency of the alkylguanidine products to be overreduced and form amines. Good yields required controlled reaction times, and these varied individually from 4 to 36 h.

The first substrate, dodecanoylguanidine (**1**), chosen for its solubility in THF, was reduced smoothly to dodecylguanidine (**15**), accompanied by dodecylamine (**16**). Reaction monitoring



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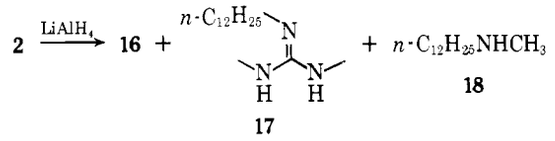
by GC on OV-225 was sufficient to set an approximate reaction time which was then verified by three reductions; 33 ± 5 h represents the optimum time under the conditions reported. An attempt at shortening this reaction time by heating to reflux in THF produced a drastic increase in amine formation; therefore, all subsequent reductions were conducted at 23 °C. Attempts to minimize the formation of amine by using only a slight excess of $LiAlH_4$ and longer reaction times led to lower yields. Although the acetate salt is the most convenient form for isolation, the sulfate was superior for characterization.

To determine whether amine **16** was formed by reduction of guanidine **15** or by conjugate addition of H^- to **1**, **15** was treated with $LiAlH_4$. The amount of amine **16** formation (15% by GC) in this reduction suggested that all or most of the amine **16** formed in the reduction of **1** comes from subsequent reduction of **15**; the best yield of **15**, 60%, was accompanied by 15% of **16**.

Reduction of *N*-dodecanoyl-*N'*,*N''*-dimethylguanidine (**2**) to the trialkylguanidine **17** also proceeded in good yield and could be monitored by TLC with good resolution of **2**, dodecylamine (**16**), and *N*-dodecyl-*N'*,*N''*-dimethylguanidine (**17**). The ratio of **16** to **18** (about 2:1) would be expected from a

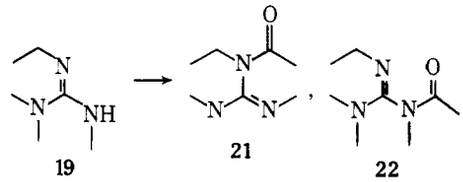


17 **18**

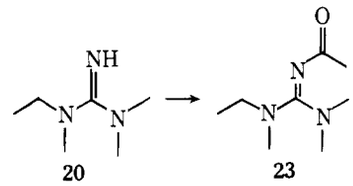
purely random breakup of the intermediate aluminum complex followed by reduction of the resulting metalated amidine. Although **17**·HI has been reported,[12] we found **17** was more conveniently characterized as its tosylate.

N-Acetyl-*N'*,*N'*,*N''*-trimethylguanidine (**3**) was reduced rapidly to *N*-ethyl-*N'*,*N'*,*N''*-trimethylguanidine (**19**). Since we sought further evidence for the structure of **3**, two experiments were undertaken to confirm the structure of **19**. The first was derivatization of **19**; the second was a CIMS fragmentation study.

The competing structure for the monodeacetylation product of **10** would be **11**, in which the remaining acetyl group is on a methylated nitrogen, rather than **3**, in which the acetylated nitrogen bears no methyl. If **10** cleaves to **3** and is reduced to **19**, then acetylation should give **21** and/or **22**, both



19 **21** **22**



20 **23**

of which are tetraalkylacylaminoguanidines (nonconjugated). If **10** cleaves to **11**, which is then reduced to **20**, acetylation of **20** would give a tetraalkylacyliminoguanidine **23** (conjugated). It was found that acetylation of **19** gave a compound whose NMR and UV are consistent only with structure **22** (Table I), a nonconjugated derivative. Molecular models of **21** and **22** show extreme crowding in the coplanar conformation. Structure **22** appears slightly less crowded and is probably formed preferentially for steric reasons.

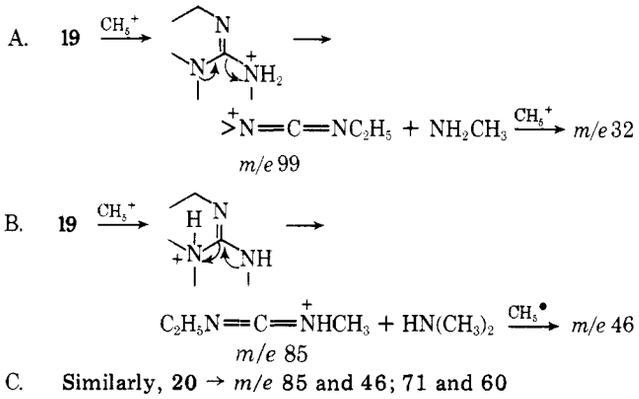
As further evidence, the assigned structure of **19** was supported by its fragmentation in the CIMS. To maximize the fragmentation, CH_4 reagent gas was used, since this gives the high-energy protonating species, CH_5^+.[13] The possible fragmentation patterns for **19** and **20** are shown in Scheme I. The fragments *m/e* 85 and 46 are predicted for both **19** and **20**, and both were observed. In addition, both *m/e* 99 and 32 were observed and *m/e* 71 and 60 were not, clearly demonstrating

Table I. Spectral (UV and NMR) Characterization of Acetyltetraalkylguanidines

Compd	UV absorption, λ_{max} (ϵ) in ethanol (OH^-)	NMR absorption δ, in CCl_4
N-Acetyl-*N'*-ethyl-*N,N''*-trimethylguanidine (**22**)	225 nm (8000)	1.09 (t, CH_2CH_3) 3.05 (q, CH_2CH_3) 1.83 (s, $CH_3C{=}O$) 2.82 (s, $2NCH_3$) 2.86 (s, $AcNCH_3$)
N'-Acetyl-*N,N,N'',N''*-tetramethylguanidine[a]	238 nm (15 100)	1.90 (s, $CH_3C{=}O$) 2.80 (s, $4NCH_3$)
N-Acetyl-*N,N',N'',N''*-tetramethylguanidine[a]	225 nm (8950)	1.85 (s, $CH_3C{=}O$) 2.80 (s, $3NCH_3$) 2.85 (s, $AcNCH_3$)

[a] Data from ref 6.

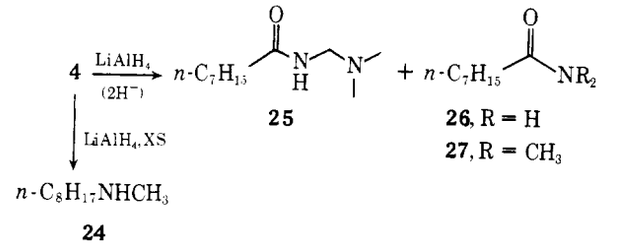
Scheme I. CIMS Fragmentation of *N*-Ethyl-*N',N',N''*-trimethylguanidine (19)



C. Similarly, **20** → *m/e* 85 and 46; 71 and 60

the presence of **19** and the absence of **20.** By establishing the structure of **19,** we have also established the structure of **3.**

In anticipation of a rapid reduction, octanoyl-*N,N'*-tetramethylguanidine (**4**) was treated with excess $LiAlH_4$ for 1 h in ether to produce *N*-methyloctylamine (**24**) in 60% yield. A stoichiometric reduction ($2H^-$, 0.5 mol of $LiAlH_4$/mol of acylguanidine) was then carried out with the hope of arresting the reduction of **4** at the guanidine stage. Instead of a guanidine, the reaction product consisted of a mixture of compounds **25, 26,** and **27.** A third reduction was performed using less $LiAlH_4$ ($1.3H^-$, 0.33 mol of $LiAlH_4$/mol of acylguanidine) in the hope of isolating an acylamidine. Instead, the same three products were obtained as in the previous reduction; only the relative yields had changed (see Table II).



Although the production of **25, 26,** and **27** in the second and third reductions was unexpected, the data substantiating these results is clear. Initially, the CIMS indicated only the presence of **25, 26,** and **27** plus two other ions, *m/e* 156 and 127, which turned out to be fragments of **25.**

NMR data supplied the first clues to the structure of **25,** notably, the coupling of the NH proton to the NCH_2N methylene, which was erased by exchanging the NH proton for deuterium. Two examples of acylaminals such as **25** have been reported,[14,15] both of which were prepared by condensation of formaldehyde, a primary amide, and a secondary amine. Using this approach, an authentic sample of **25** was prepared for comparison with the reduction product, thus establishing its structure.

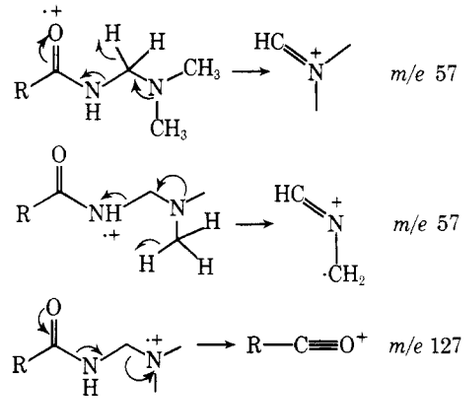
Table II. Distribution of Products from the Reduction of *N*-Octanoyl-*N',N',N'',N''*-tetramethylguanidine (4) with Varying Amounts of Lithium Aluminum Hydride

	Amount of lithium aluminum hydride		
Product	Excess	2 equiv[a]	1.3 equiv[b]
24[c]	60%		
25[d]		58%	9%
26[d]		10%	11%
27[d]		18%	69%

[a] $2H^-$ or 0.5 mol of $LiAlH_4$/mol of **4.** [b] $1.3H^-$ or 0.33 mol of $LiAlH_4$/mol of **4.** [c] Isolated yield. [d] Yields from GC and NMR integration; tertiary mixture was distilled, but components were not separated.

Since the reduction products from the limited $LiAlH_4$ reductions of **4** could be distilled without any change in the NMR or CIMS, the mixtures were analyzed by GC/MS and high-resolution mass spectrometry (both with electron impact sources). The first and second GC peaks eluted had parent ions of *m/e* 171 and 143, respectively, as well as all the fragments predicted by structures **26** and **27,** including McLafferty rearrangements (giving the base peaks) and α cleavage.[16] The third GC peak gave a weak parent (*m/e* 200) and the two other ions, *m/e* 127 and 57 (base), which can be explained by the following fragmentations (Scheme II). Authentic **25** and

Scheme II

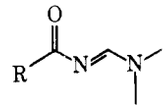


26 gave GC/MS retention times and fragmentation patterns which correspond to the second and third GC/MS peaks from the reduction mixtures. Finally, all the molecular formulas for the three parent ions and their electron impact MS fragments were obtained from a computerized high-resolution scan over the entire mass range of a reduction mixture (see Experimental Section).

Although the reduction of **4** to **24** and **25** can be easily explained, the formation of **26** and **27** is more difficult to rationalize. The formation of **24** and **25** probably arises from conjugate addition, followed by elimination of metalated dimethylamide ion, to give the intermediate acylamidine **28.** This species is probably extremely labile to reduction, since as little as 1.3 equiv of hydride/mol of **4** failed to show any evidence of **28.** In the presence of excess $LiAlH_4$, **28** can undergo conjugate addition of hydride, elimination of dimethylamide ion, further conjugate addition to the *N*-methylamide, and finally, reduction to amine **24.** With 2 equiv of H^-, this process stops at the acylaminal (**25**) stage, and with 1.3 equiv of H^- the reduction rate is slow enough that di-

methylamide ion attacks either **4** or **28** to produce **27.** The primary amide **26** probably arises from **25,** undergoing a reverse Mannich during the isolation.

Reduction of the three cyclic substrates, **5, 6,** and **7,** to the corresponding guanidines, **29, 30,** and **31,** was complicated by



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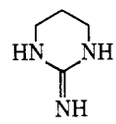

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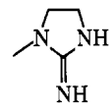

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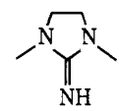
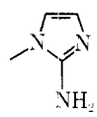


31

occlusion of nearly half of the product in the metal salts formed during isolation. To overcome this problem, two general methods were developed which allow separation of the highly water soluble guanidines from metal salts. The physical purification method (method B) relies on precipitation of Al^{3+} and Na^+ ions, followed by removal of Li^+ via ion-exchange chromatography. Method B, when applied to the isolation of **29,** increased the yield to 53% from 28% obtained using conventional methods.

The derivatization method (method A) employs a digestion of the mixed salts in aqueous alkali, followed by acylation with excess benzyloxycarbonyl chloride. Excess acid chloride is then destroyed by adding glycine before extraction of the guanidine derivative with CH_2Cl_2. The extract is then combined with the filtrate from the reduction and the combined material is subjected to hydrogenolysis. This isolation scheme greatly increased yields of both **30** and **31.** The reason for including the filtrate in the hydrogenation is that reduction of **6** with $LiAlH_4$ produces a mixture of the guanidine **30** and the imidazole **32.** Similarly, **7** produces both **31** and **33.** After



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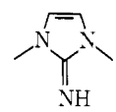

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finding that **32** could be converted to **30** by catalytic hydrogenation, it became obvious that the hydrogenation step served a dual purpose, i.e., removal of the benzyloxycarbonyl group and the reduction of the 2-aminoimidazoles to 2-iminoimidazolidines.

Summary

A critical point to consider in the $LiAlH_4$ reduction of acylguanidines is the electron density on the metalated acylguanidine in the reduction medium. This electron density depends primarily on the number of NH protons which are replaced by Al (with hydrogen evolution) and will have an effect on both the rate and the stoichiometry. Quantitation of the hydrogen evolved in the reaction of $LiAlH_4$ with both **1** and **6** clearly indicated that all available NH protons are removed under reduction conditions. The hydrogen evolution is somewhat slower with **5,** but this is probably due to formation of a precipitate, presumably a polyaluminate.

Two factors emerge, then, which suggest an approximate reaction time. Compounds **1, 5,** and **6** are reduced at relatively slow rates; **1** is slow because it has a formal −4 charge, and **6** and **7** are slow because they both give precipitates. Reduction of **4** is very fast (homogeneous and no NH protons) and the reductions of **2, 3,** and **7** are moderately rapid (homogeneous with one or two NH protons). In addition to the proper reaction time, the use of THF, room temperature, excess $LiAlH_4$, and extraction of the metal salts during isolation all favor increased yields.

Classically, conversion of a carboxyl group to an alkylguanidine requires preparation of an amide, reduction to an amine, and reaction with a reagent such as *S*-methylisothiourea.[7] The same conversion may now be accomplished more directly by preparing and reducing the appropriate acylguanidine. From another point of view, the sequence of acylation and reduction allows the selective alkylation of an already existing guanidine, a manipulation with no previous parallel.

Experimental Section[17]

Dodecanoylguanidine (1). Methyl laurate (26.0 g, 122 mmol)[18] and ethanol (50 mL, absolute) were mixed with guanidine free base (7.3 g, 124 mmol, freshly prepared by ion exchange)[5] and allowed to stand (23 °C, under dry N_2) for 12.5 h. Evaporation of the ethanol, addition of ether (30 mL, anhydrous) and chilling gave a cake of crystals to which was added hexane (150 mL, reagent), and the flask was stoppered and shaken vigorously. The mixture was then chilled, filtered, and dried to give 20.0 g (68%) of crude product, mp 101–104 °C (lit.[4] mp 80–82 °C). This crude material was crystallized from acetone to produce 14.1 g (48%) of colorless crystals: mp 110–111 °C; UV λ_{max} (0.01 N NaOH, C_2H_5OH) 232 nm (ϵ 16 000), λ_{max} (dioxane) 237 nm; NMR ($CDCl_3$) δ 6.10 (4 H, s, NH), 2.0–2.4 (2 H, m, $COCH_2$), 0.7–1.9 (21 H, m, aliphatic CH); CIMS *m/e* (relative intensity) 242 (MH^+, 100), 200 (56), 83 (2), 60 (4).

Anal. Calcd for $C_{13}H_{27}N_3O$: C, 64.7; H, 11.3; N, 17.4. Found: C, 64.7; H, 10.9; N, 17.3.

***N*-Dodecanoyl-*N',N''*-dimethylguanidine (2).** *N,N'*-Dimethylguanidine hydrobromide[19] (6.45 g, 38.4 mmol) was converted to the free base by ion exchange[5] under N_2 before adding methyl laurate (10.5 mL, 42.7 mmol). The reaction mixture was left at room temperature for 26 h, at which time UV and TLC showed that it was predominantly acylguanidine. A column of neutral alumina (300 g, activity IV, 100–200 mesh, BioRad) was prepared in hexane, and the reaction mixture was washed onto it with five 10-mL portions of hexane. Separation of three components was monitored by TLC (silica gel, acetone). The first component (ester) eluted from the column with 500 mL of 3:1 hexane/benzene, an intermediate fraction of 300 mL of acetone followed, and the third fraction (375 mL of acetone) removed all of the product. Evaporation of this third fraction gave 6.5 g of oil which was dried under vacuum over P_2O_5, yielding 5.2 g (50%) of slowly deliquescing crystals: mp 38 °C; UV λ_{max} (0.01 N NaOH, C_2H_5OH) 237 nm (ϵ 15 300), λ_{max} (dioxane) 242 nm; NMR (CCl_4) δ 2.84 (6 H, s, NCH_3), 2.0–2.3 (2 H, m, $COCH_2$), 0.7–1.8 (21 H, m, aliphatic CH).

Anal. Calcd for $C_{15}H_{31}N_3O$: C, 66.9; H, 11.6; N, 15.6. Found: C, 66.8; H, 11.5; N, 15.3.

***N,N,N'*-Trimethylguanidine (9) Acetate.** A quaternary ammonium cation-exchange resin (36 mL, 44 mequiv OH^- form, 20–50 mesh, BioRad) was converted to the acetate form by soaking with two portions of aqueous acetic acid (60 mL, 1 N). A column was then prepared and washed with 100 mL of H_2O. *N,N,N'*-Trimethylguanidine (**9**) hydriodide[7,8] (5.00 g, 21.8 mmol) was dissolved in 10 mL of H_2O and applied to the column. Elution with 150 mL of H_2O followed by evaporation gave 4.64 g of hygroscopic oil, which on drying at 23 °C (0.05 mm) for 12 h gave 3.48 g (99%) of deliquescent crystals, used without purification for the next step.

***N,N'*-Diacetyl-*N,N'',N''*-Trimethylguanidine (10).** *N,N,N'*-Trimethylguanidine (**9**) acetate (1.98 g, 12.3 mmol) was stirred with acetic anhydride (50 mL) under N_2 at 100 °C for 40 min. Excess acetic anhydride was then evaporated, finally at 60 °C (1 mm) for 30 min to remove the last traces of anhydride, producing 2.26 g of crude oil. This material was distilled through a short Vigreux column to give 2.13 g (95%) of colorless oil: bp 120–125 °C (0.025 mm); UV λ_{max} (C_2H_5OH) 205 nm (ϵ 5750), 257 (14 400); NMR (CCl_4) δ 3.01 (6 H, s, $N(CH_3)_2$), 2.91 (3 H, s, NCH_3), 2.04 (3 H, s, $COCH_3$), 1.99 (3H, s, $COCH_3$).

Anal. Calcd for $C_8H_{15}N_3O_2$: C, 51.9; H, 8.2; N, 22.7. Found: C, 51.7; H, 8.0; N, 22.5.

***N*-Acetyl-*N',N',N''*-trimethylguanidine (3).** *N,N'*-Diacetyl-*N,N'',N''*-trimethylguanidine (**10**) (6.00 g, 32.4 mmol) was mixed with 50 mL of methanol and quaternary ammonium ion-exchange resin (60 mL, 84 mequiv, BioRad AG1-X8 hydroxide form, 20–50 mesh, washed with 4 × 100 mL of methanol) and allowed to stand at room temperature. After 20 h, the reaction was diluted with 500 mL of methanol and stirred for 10 min, the methanol was decanted, the resin was washed again with 150 mL of methanol, and the combined methanol extracts were evaporated. The resulting oil was azeotropically dried (evaporate 100 mL of CCl_4; 100 mL of 1:1 benzene/CH_2Cl_2) and mixed with benzene (7.0 mL) and CH_2Cl_2 (1.0 mL). After chilling (0 °C, 3 days), layering with petroleum ether (20 mL), and chilling again (0 °C, 4 days), the monoacetic product crystallized. The liquid

phase was decanted, the crystals were rinsed with hexane (30 mL), and the solid was dried to give 3.50 g (75%) of crude deliquescent solid, which was then azetropically dried with CH_2Cl_2 (100 mL), redissolved in 100 mL of CH_2Cl_2, and stored at 0 °C. Filtration, evaporation, and drying under vacuum over P_2O_5 gave 1.66 g (69%) of deliquescent partial hydrate: mp 99–107 °C; UV λ_{max} (0.01 N NaOH, C_2H_5OH) 209 nm (ϵ 14 000), λ_{max} (dioxane) 247 nm; NMR (CCl_4) δ 2.95 (6 H, s, $N(CH_3)_2$), 2.67 (3 H, s, NCH_3), 1.87 (3 H, s, $COCH_3$); CIMS *m/e* (rel intensity), 144 (MH^+, 100), 102 (1).

Anal. Calcd for $C_6H_{13}N_3O \cdot H_2O$: C, 48.8; H, 9.2; N, 28.5. Found: C, 48.5; H, 9.1; N, 28.5.

***N*-Octanoyl-*N',N',N'',N''*-tetramethylguanidine (4).** Octanoyl chloride (3.25 g, 20 mmol, freshly distilled, bp 194–196 °C) and *N,N,N',N'*-tetramethylguanidine (5.00 g, 43.5 mmol) were each dissolved in ethyl ether (50 mL each, anhydrous). To the guanidine solution, chilled in an ice bath, was slowly added the octanoyl chloride solution with stirring. A vigorous reaction ensued, precipitating the HCl salt of tetramethylguanidine (3.4 g, 22 mmol), which was removed by filtration, and the filtrate was evaporated. The oily residue was dissolved in 50 mL of CCl_4, washed twice with aqueous NaOH (20 mL each, pH 13), dried over K_2CO_3, filtered, and distilled to produce 4.30 g (89%) of colorless oil: bp 126–134 °C (0.05 mm, Kugelrohr): UV λ_{max} (0.01 N NaOH, C_2H_5OH) 239 nm (ϵ 14 700); NMR (CCl_4) δ 2.77 (12 H, s, NCH_3), 1.9–2.4 (2 H, m, $COCH_2$), 0.7–1.9 (13 H, m, aliphatic CH).

Anal. Calcd for $C_{13}H_{27}N_3O$: C, 64.7; H, 11.3; N, 17.4. Found: C, 64.6; H, 11.0; N, 17.6.

β-Alacreatinine [2-Amino-4-oxo-1,4,5,6-tetrahydropyrimidine (5)] Hydrochloride. β-Guanidinopropionic acid (**14**)[20] was cyclized with concentrated HCl as described,[21] producing 43% of **5**: mp 272–275 °C (lit.[21] mp 268–271 °C); UV λ_{max} (0.01 N NaOH, C_2H_5OH) 237 nm (ϵ 13 000) [lit.[6] UV 237 mm (13 100)]; NMR (D_2O) δ 3.80 (2 H, t, J = 7 Hz), 2.83 (2 H, t, J = 7 Hz).

Methylcreatinine [1,3-Dimethyl-2-imino-4-imidazolidinone (7)] Hydrogen Sulfate. Creatinine [2-amino-1-methyl-4-oxo-4,5-dihydroimidazole (**6**)] was methylated with dimethyl sulfate as described[10] to produce 89% of the hydrogen sulfate (**7**):[11] mp 118 °C (lit.[10] mp 118 °C); CIMS *m/e* 128 (MH^+), parent ion only.

General Procedure for Reduction of Acylguanidines. A 2.35 M homogeneous solution of $LiAlH_4$ in THF was prepared and assayed by the method described.[22] THF was distilled from $LiAlH_4$ under N_2 directly into a graduated cylinder with an outer ground glass top. This cylinder also had a side arm near the top fitted with a rubber septum for N_2 purging. After distillation, the ground joint was sealed with a second septum, and subsequent solvent transfers were made via a stainless steel cannula and positive N_2 pressure. THF thus prepared could be stored several weeks by sealing the punctured septa with unpunctured inverted septa. For reduction, starting material and a magnetic stir bar were added to a three-neck flask under N_2, the flask was fitted with a thermometer and a rubber septum, and dry THF was added by cannula. The system was cooled to −65 °C, the $LiAlH_4$ solution was added by syringe with stirring, and the temperature was maintained at −60 °C for 20 min, then at 0 °C for 30 min, and finally at 23 °C for the appropriate reaction time. Isolation of products proceeded by chilling, followed by addition of H_2O and aqueous NaOH as described.[23] After filtering off the metal salts, small amounts of H_2O and CO_2(s) were added to the THF filtrate to protect the products as carbonate salts.

Isolation of Guanidines. Method A.[24] In a typical reduction of **6** (1.00 g, 8.85 mmol), all of the metal salts from the hydrolyzed reduction mixture were dissolved immediately in cold H_2O (12 mL, pH to 14)[25] contained in a glass-stoppered 100-mL flask, and aqueous NaOH (15 mL, 2 N, 0 °C) and benzyloxycarbonyl chloride (4 mL, 24 mmol, 0 °C) were added alternately in five portions over a period of 25 min with shaking and chilling after each addition of acid chloride. The mixture was then treated with CH_2Cl_2 (30 mL, 0 °C) and aqueous glycine (3.0 g in 20 mL, pH to 14, 0 °C), and the resulting two-phase system was stirred for 30 min at 0 °C, whereupon a second portion of CH_2Cl_2 (50 mL) was added. The organic phase was separated, the aqueous layer was extracted a second time (40 mL of CH_2Cl_2), and the combined extracts were washed with H_2O to pH 7. After drying with K_2CO_3, the CH_2Cl_2 extracts were combined with the THF filtrate from the reduction for subsequent evaporation and hydrogenolysis[26] (see reduction of **6** with excess hydride).

Method B.[24] In a typical reduction of **5** to **29**, a portion of the metal salts from the hydrolyzed reduction mixture (containing a maximum of 1.17 mmol of **29**) was dissolved in HCl (24 mL, 4 M). After chilling and neutralizing with 12 M NaOH to pH 7, the $Al(OH)_3$ was removed by centrifugation at 7700*g* (0 °C, 15 min). The supernatant was decanted, the $Al(OH)_3$ pellet was washed with 30 mL of H_2O, the $Al(OH)_3$ was spun down a second time, and the combined H_2O solutions were concentrated to 25–30 mL. Addition of 100 mL of isopropyl alcohol produced precipitation (mostly NaCl), and this mixture was heated to boiling followed by filtration and evaporation of the filtrate to dryness. The resulting solid residue was again suspended in 100 mL of hot isopropyl alcohol; filtration and evaporation to dryness gave 370 mg of a mixture of LiCl and **29**·HCl. A cation-exchange column was then prepared (12-mL bed, BioRad AG 50W-8X, hydrogen form, 200–400 mesh) and washed with HCl (500 mL, 1 M) and H_2O. The mixture of LiCl and **29**·HCl was washed onto the column with H_2O, washing until the eluent returns to the pH of distilled H_2O. Lithium was eluted first with HCl (~100 mL, 0.3 M); the guanidine was also eluted with HCl (~200 mL, increasing strength from 1 to 10 M). Evaporation to dryness, crystallization (isopropyl alcohol/ether), and drying over P_2O_5 produced 55 mg of **29**·HCl, mp 153 °C.

Dodecylguanidine (15) Acetate. Dodecanoylguanidine (**1**) (1.0 g, 4.15 mmol) was reduced with $LiAlH_4$ (53 mmol) in 120 mL of THF for 33 h. After decomposition (H_2O, NaOH) and filtration, the THF solution was acidified with 1 mL of acetic acid and chilled. Filtration produced 330 mg (60%) of acetate salt: mp 133–134 °C; CIMS *m/e* (rel intensity) 228 (MH^+, 100), 211 (5), 186 (1).

Anal. Calcd for $C_{15}H_{33}N_3O_2$: C, 62.7; H, 11.6; N, 14.6. Found: C, 62.9; H, 11.3; N, 14.8.

The filtrate (THF solution) was evaporated to an oil and the residue was suspended in hexane and filtered to yield 70 mg (15%) of crude salt. This material was primarily dodecylamine acetate: GC retention time (96 °C), 11 min 50 s (identical with authentic sample); CIMS *m/e* (rel intensity), 242 (8), 228 (4), 200 (2), 186 (100).

Dodecylguanidine (15) Sulfate. In a separate reduction of **1**, the guanidine product **15** was isolated as a carbonate salt: mp 91–95 °C dec; CIMS *m/e* (rel intensity) 228 (MH^+, 100), 211 (4), 186 (1). The carbonate salt was treated with 1 equiv of H_2SO_4 to give the sulfate: mp 250–260 °C dec, mmp with authentic **15** sulfate[27] was undepressed; IR (KBr) 3480, 3160, 2920, 2880, 1630, 1470, 1380, 1120, 1060, 980, 720, 620 cm^{-1}, identical with IR obtained from authentic sample.

Reduction of Dodecylguanidine (15) Sulfate. **15** sulfate (500 mg, 1.81 mmol) was treated with $LiAlH_4$ (26 mmol) in THF (50 mL) for 21 h. Isolation gave dodecylamine in 15% yield.

***N,N'*-Dimethyl-*N''*-dodecylguanidine (17) Tosylate.** *N*-Dodecanoyl-*N',N''*-dimethylguanidine (**2**) (1.00 g, 3.71 mmol) was reduced with $LiAlH_4$ (24 mmol) in 100 mL of THF for 8 h. After workup, the THF filtrate was treated with H_2O (0.5 mL, 28 mmol) and CO_2 (s, ~1 g). Chilling (0 °C, 12 h) produced a crude carbonate, mp 96–110 °C dec. This material was converted to 985 mg (62%) of tosylate: mp 85–87 °C; NMR (HBr salt in $CDCl_3$) δ 3.4 (2 H, m, NCH_2), 3.0 (6 H, s, $2NCH_3$), 0.7–1.8 (23 H, m); CIMS *m/e* (rel intensity) 256 (MH^+, 100), 225 (8), 186 (2), 71 (3), 32 (10).

Anal. Calcd for $C_{22}H_{41}N_3O_3S$: C, 61.8; H, 9.7; N, 9.8. Found: C, 62.1; H, 9.5; N, 9.9.

***N*-Ethyl-*N',N',N''*-trimethylguanidine (19) *p*-Bromobenzenesulfonate.** *N*-Acetyl-*N',N',N''*-trimethylguanidine (**3**) (593 mg, 4.02 mmol, ¼ hydrate) was reduced with $LiAlH_4$ (13.2 mmol) in 30 mL of THF for 4 h. After workup, a carbonate, prepared by the method used for compound **17**, was isolated and melted at 73–75 °C dec. The carbonate was treated with *p*-bromobenzene sulfonic acid to give 870 mg (59%) of salt: mp 97–98 °C from ethanol/ether; NMR (D_2O) δ 7.73 (4 H, q, ArH), 3.28 (2 H, q, NCH_2CH_3, J = 7 Hz), 2.96 [6 H, s, $N(CH_3)_2$], 2.90 (3 H, s, NCH_3), 1.20 (3 H, t, NCH_2CH_3, J = 7 Hz); CIMS (NaOH added) *m/e* (rel intensity) 130 (MH^+, 100), 99 (3), 85 (12).

Anal. Calcd for $C_{12}H_{20}BrN_3O_3S$: C, 39.4; H, 5.5; N, 11.5; Br, 21.8. Found: C, 39.4; H, 5.5; N, 11.5; Br, 21.9.

A sample of pure **19** *p*-bromobenzenesulfonate was converted to the free base (ion exchange)[5] and then to the carbonate: CIMS (CH_4 reactant) *m/e* (rel intensity) 130 (MH^+, 100), 99 (9), 85 (16), 46 (6), 32 (1).

Acetylation of *N*-Ethyl-*N',N',N''*-trimethylguanidine (19). Purified **19** carbonate (200 mg, ~1.2 mmol) was mixed with 30 mL of acetic anhydride and heated for 6 h (100 °C, N_2). Evaporation and distillation of the resulting oil (45 °, 0.05 mm, Kugelrohr) gave product with the following spectra: UV λ_{max} (0.01 N NaOH, C_2H_5OH) 225 nm (ϵ 8000); NMR (CCl_4) δ 3.05 (2 H, q, NCH_2CH_3, J = 7 Hz), 2.86 (3 H, s, NCH_3), 2.82 [6 H, s, $N(CH_3)_2$], 1.83 (3 H, s, $COCH_3$), 1.09 (3 H, t, NCH_2CH_3, J = 7 Hz).

Reduction of Octanoyl-*N,N'*-tetramethylguanidine (4) with excess $LiAlH_4$. **4** (2.4 g, 10 mmol) was reduced with $LiAlH_4$ (26.3 mmol) for 1 h using 50 mL of Et_2O instead of THF. After workup, the Et_2O filtrate was evaporated to give *N*-methyloctylamine, which was converted to 2.25 g (60%) of *N*-methyloctylamine picrate: mp 96–98

°C (lit.[28] mp 98–98.5 °C); NMR (CCl_4) δ 2.4–2.7 (2 H, m, NCH_2), 2.33 (3 H, s, NCH_3), 0.7–1.7 (15 H, m, aliphatic CH); CIMS *m/e* (rel intensity) 144 (100), 130 (5).

Reduction of 4 using 2 equiv of Hydride per Mole of Acylguanidine. 4 (1.48 g, 6.12 mmol) was reduced with $LiAlH_4$ (3.12 mmol) at 0 °C for 4 h and then at 23 °C for 1 h. After workup, the resulting oil was distilled to yield 983 mg of a hygroscopic mixture: bp 110–115 °C (0.4 mm, Kugelrohr); NMR (CCl_4) δ 8.00 (1 H, t, $CONHCH_2N$, J = 6 Hz), 3.92 (2 H, d, $CONHCH_2N$, J = 6 Hz), 2.92 and 3.04 (equivalent singlets, dimethyloctanamide), 2.20 [m, $NCN(CH_3)_2$ and CH_2CO], 0.70–1.90 (m, aliphatic CH); CIMS *m/e* (rel intensity) 201 (100), 172 (15), 156 (25), 144 (30), 127 (1), rel intensities of 172 and 144 varied with time and temperature. The NMR sample was shaken with D_2O and the signal at δ 8.00 disappeared, while the previous doublet at δ 3.92 became a singlet at δ 3.92 (2 H).

The distilled product was found to contain three components by GC, identified as octanamide (**26**), *N,N*-dimethyloctanamide (**27**), and *N*-(dimethylaminomethyl)octanamide (**25**) by low-resolution GC/MS (ei). The empirical formulas were obtained from the mixture with a scanning high-resolution MS: first GC peak, *m/e* (rel intensity, molecular formula, Δmmu) 171 (3, $C_{10}H_{21}NO$, 0.3), 87 (100, C_4H_9NO, 0.3), 72 (40, C_3H_6NO, 2.8); second peak, 143 (1, $C_8H_{17}NO$, 0.0), 59 (100, C_2H_5NO, 2.7), 44 (21, CH_2NO, 0.4); third peak, 200 (1, $C_{11}H_{24}N_2O$, 0.4), 127 (40, $C_8H_{15}O$, 0.6), 57 (100, C_3H_7N, 3.6).[29] The mole fractions (from corrected GC and NMR integration) of each component were as follows: **26**, 0.12; **27**, 0.21; **25**, 0.67. Based on the 983 mg of distilled mixture, the yields were 10, 18, and 58%, respectively.

Reduction of 4 Using 1.3 equiv of Hydride per Mole of Acylguanidine. 4 (3.05 g, 12.6 mmol) was treated with $LiAlH_4$ (4.3 mmol) in 100 mL of ether as in the previous reduction, except that the time at 23 °C was 2 h. Workup and distillation gave 1.90 g of oil: bp 108–114 °C (0.45 mm, Kugelrohr); CIMS *m/e* (rel intensity) 201 (15), 172 (100), 156 (2), 144 (21), rel intensity varied with time and temperature; NMR and GC/MS showed the same products as before in the following proportions: **26**, 0.12; **27**, 0.78; **25**, 0.10. These mole fractions correspond to yields of 11, 69, and 9%, respectively.

***N*-(Dimethylaminomethyl)octanamide (25).** Octanamide[30] (300 mg, 2.10 mmol), formaldehyde (2.5 mL, aqueous, 33.3 mmol), dimethylamine (1.45 g, 32.2 mmol), and 20 mL of *tert*-butyl alcohol were heated for 2 h in a pressure vessel on a steam bath. The reaction mixture was cooled and evaporated to a dark yellow oil; CCl_4 (3 × 40 mL) was evaporated from the oil to remove H_2O and other volatile materials. The residue was dissolved in petroleum ether (5.0 mL, reagent), the solution was cooled and then filtered, the filtrate was evaporated, and the residue was distilled to give 222 mg (53%) of colorless oil: bp 115–120 °C (0.40 mm, Kugelrohr); NMR (CCl_4) δ 8.00 (1 H, t, NH, J = 6 Hz), 3.92 (2 H, d, $NHCH_2N$, J = 6 Hz), 2.20 [8 H, m, RCH_2CO and $N(CH_3)_2$], 0.70–1.90 (13 H, m, aliphatic CH); CIMS *m/e* (rel intensity) 201 (MH^+, 100), 156 (30), 144 (5), 127 (2); high-resolution MS, calcd for $C_{11}H_{24}N_2O$, *m/e* 200.1889; found, 200.1892.

2-Iminohexahydropyrimidine (29) Hydrochloride. β-Alacreatinine (**5**) hydrochloride (614 mg, 4.11 mmol) was reduced with $LiAlH_4$ (35.0 mmol) in 130 mL of THF. After 36 h, the reaction was worked up, and the filtrate was acidified (concentrated HCl) and evaporated to dryness. Crystallization from isopropyl alcohol/ether gave 156 mg (28%) of **29** hydrochloride, mp 153 °C (lit.[31a] mp 127–129 °C of a hydrated sample). Treatment of the metal salts by method B gave an additional 139 mg (25%), producing a total yield of 53%: NMR (D_2O) δ 3.37 (4 H, t, J = 6 Hz), 1.95 (2 H, quintet, J = 6 Hz); CIMS *m/e* 100 (MH^+ only); picrate, mp 183–184 °C (lit.[31b] mp 185–186 °C).

Reduction of Creatinine (6). A. With 5 equiv of Hydride per Mole of Acylguanidine. Creatinine (**6**) (496 mg, 4.38 mmol) was treated with $LiAlH_4$ (5.5 mmol, 25% molar excess) in 100 mL of THF for 30 h at 23 °C. Addition of *p*-toluenesulfonic acid hydrate (1.0 g, 6 mmol) and evaporation gave an oil, which was dried and shaken with 30 mL of ether to give 125 mg (29%) of mixed guanidine (**30**) and imidazole (**32**) salts: NMR (D_2O) δ 3.53 (4 H, s, guanidine CH_2CH_2), 2.83 (3 H, s, guanidine CH_3), 3.39 (3 H, s, imidazole CH_3), 6.74 (2 H, q, imidazole ring), 37 mol % **30** and 63 mol % **32** (by integration); CIMS ($NaOCH_3$ added) *m/e* (rel intensity) 100 (50), 98 (100).

PdO (100 mg) and PtO_2 (10 mg) were powdered together and then mixed with 50 mL of CH_3OH and the mixture of **30** and **32** tosylate salts. Shaking with hydrogen (40 psi, 20 °C) for 17 h followed by filtration, evaporation, and crystallization (ethanol/ether) gave 117 mg of (**30**) *p*-toluenesulfonate: mp 170–171 °C; NMR (D_2O) δ 7.56 (4 H, q, ar-H), 3.53 (4 H, s, CH_2CH_2), 2.83 (3 H, s, NCH_3), 2.34 (3 H, s, ar-CH_3); CIMS ($NaOCH_3$ added) *m/e* 100 (MH^+ only).

Anal. Calcd for $C_{11}H_{17}N_3O_3S$: C, 48.7; H, 6.3; N, 15.5. Found: C, 48.9; H, 6.1; N, 15.2.

B. With Excess Hydride. Creatinine (**6**) (1.00 g, 8.85 mmol) was reduced with $LiAlH_4$ (52.6 mmol) in 100 mL of THF for 28 h. After workup, the filtrate was acidified with 1 mL of acetic acid and stored at 0 °C. The precipitate from the workup was extracted by method A, and the resulting CH_2Cl_2 extract was combined with the THF filtrate for evaporation. Hydrogenation as above using 600 mg of PdO and 60 mg of PtO_2 gave 1.3 g (54%) of 2-imino-1-methylimidazolidine (**30**) *p*-toluenesulfonate, mp 170–171 °C, identical with the product from the previous reduction.

Reduction of Methylcreatinine (7). Methylcreatinine[10,11] (257 mg, 2.02 mmol) was reduced with $LiAlH_4$ (3.6 mmol) in 50 mL of THF for 10 h. After workup, the filtrate was acidified with concentrated HCl and evaporated to give a crude product with the following spectra: NMR (D_2O) δ 3.46 (4 H, s, uganidine CH_2CH_2), 2.87 (6 H, s, quanidine NCH_3), 6.75 (2 H, m, imidazole ring), 3.20 (6 H, s, imidazole NCH_3), 20 mol % 1,3-dimethyl-2-iminoimidazolidine (**31**) and 80 mol % 1,3-dimethyl-2-iminodihydroimidazole (**33**) (by integration); CIMS ($NaOCH_3$ added) *m/e* (rel intensity) 114 (15), 112 (100).

1,3-Dimethyl-2-iminoimidazolidine (31) *p*-Toluenesulfonate. Methylcreatinine (**7**) hydrogen sulfate[10] (704 mg, 3.13 mmol) was reduced with $LiAlH_4$ (22 mmol) in 90 mL of THF for 5 h. The product (**31**) was isolated in exactly the same manner as the monomethyl compound (**30**). Crystallization from isopropyl alcohol/ether gave 456 mg (51%) of *p*-toluenesulfonate: mp 180–181 °C; NMR (D_2O) δ 7.56 (4 H, q, ArH), 3.46 (4 H, s, NCH_2CH_2N), 2.87 (6 H, s, NCH_3), 2.34 (3 H, s, $ArCH_3$); CIMS ($NaOCH_3$ added) *m/e* 114 (MH^+ only).

Anal. Calcd for $C_{12}H_{19}N_3O_3S$: C, 50.5; H, 6.7; N, 14.7. Found: C, 50.6; H, 6.7; N, 14.7.

Registry No.—**1**, 5634-27-5; **2**, 63493-47-0; **3**, 63493-48-1; **4**, 63493-49-2; **5**·HCl, 15231-28-4; **7**, 34293-22-6; **7** sulfate, 63493-50-5; **9** HI, 63493-51-6; **9** acetate, 63493-52-7; **10**, 63493-53-8; **14**, 353-09-3; **15** acetate, 2439-10-3; **15** carbonate, 63493-54-9; **15** sulfate, 41197-06-2; **17** carbonate, 63493-55-0; **17** tosylate, 63493-56-1; **19**, 63493-57-2; **19** *p*-bromobenzenesulfonate, 63493-58-3; **19** carbonate, 63493-59-4; **19** acetyl derivative, 63493-60-7; **22**, 63493-60-7; **25**, 63493-61-8; **26**, 629-01-6; **27**, 1118-92-9; **29**·HCl, 26893-39-0; **30** tosylate, 63493-62-9; **31** tosylate, 63493-64-1; **33**, 59581-72-5; methyl laurate, 111-82-0; guanidine, 113-00-8; *N,N'*-dimethylguanidine hydrobromide, 13314-44-8; *N,N'*-dimethylguanidine, 3324-71-8; octanoyl chloride, 111-64-8; *N*-methyloctylamine piorate, 63493-65-2; formaldehyde, 50-00-0; dimethylamine, 124-40-3; *N,N,N',N'*-tetramethylguanidine, 80-70-6.

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(17) Melting points are uncorrected and were determined on a Thomas-Hoover apparatus; boiling points are uncorrected. IR spectra were obtained with a Perkin-Elmer 337 grating infrared spectrophotometer. UV spectra were recorded either with a Cary Model 14 or 15 spectrophotometer. NMR spectra were determined either with a Varian A-60A or T60 instrument using Me_4Si (δ 0) as an internal standard in nonaqueous media and sodium 2,2-dimethyl-2-silapentane-5-sulfonate (δ 0) as an internal standard in D_2O. GC was performed on a Varian 2100 (FID) instrument with a 6 ft × 1/8 in. glass column packed with OV-225 (3% on Chromosorb W). Chemical ionization mass spectra (CIMS) were obtained with an AEI MS-902 instrument which had been modified for chemical ionization.[32] GC/MS (electron impact) were determined with an AEI MS-12 instrument. High-resolution mass spectra (ei) and microanalyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley, Calif. GC and CIMS work with nonvolatile guanidine salts was accomplished by adding a trace of $NaOCH_3$ just prior to analysis. Isobutane reactant was used for CIMS unless otherwise noted.

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Isolation and Characterization of Peroxyferolide, a Hydroperoxy Sesquiterpene Lactone from *Liriodendron tulipifera*

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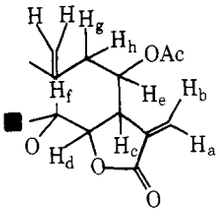
A naturally occurring germacranolide hydroperoxide, peroxyferolide, was assigned structure 1 from physical data, especially double-resonance ^1H NMR, and from chemical evidence. The allylic hydroperoxide function was supported by polarographic analysis, the preparation of anhydroderivative 3 under acetylation conditions, methylperoxyferolide (5) with methyl iodide and silver oxide, deoxyperoxyferolide (10) by mild reduction, and the presence of a characteristic absorption in the ^{13}C NMR. Formation of 1 from lipiferolide (2) by light-generated singlet oxygen confirmed the stereochemical assignments and established the configuration at the hydroperoxy-bearing carbon.

In screening ethanolic extracts of plants in a feeding test[2] for the larvae of the gypsy moth, *Lymantria dispar* L., it was found that the residue from the leaves of the tulip poplar, *Liriodendron tulipifera* L., showed antifeeding properties. On fractionating the crude extract a moderately active constituent,[3] peroxyferolide (1), was obtained and characterized to be the first naturally occurring germacranolide hydroperoxide[4] on the evidence reported herein. Previous work on this source had given lipiferolide (2) and epitulipinolide diepoxide (the 1,10-epoxide of 2) as the major sesquiterpene components.[5]

Peroxyferolide (1) was isolated by repeated column chromatography and crystallization from ethanol–chloroform. Elemental and chemical ionization mass spectral analyses established the molecular formula as $C_{17}H_{22}O_7$, and the infrared spectrum suggested hydroxyl, α,β'-unsaturated γ-lactone, ester, and olefinic functions. The ^1H NMR spectrum (Table I) showed a pair of one-proton doublets at 6.13 and 5.53 ppm split by 3.5 and 3.1 Hz, respectively, which are characteristic of α-methylene γ-lactones, and confirmed by preparation of a crystalline pyrazoline derivative that was too unstable for proper characterization. A three-proton singlet at 2.03 ppm supported an acetate as the ester function. The remainder of the molecule was assumed to be sesquiterpenoid.

Double-irradiation experiments clarified the arrangement of the substituents about the α,β'-unsaturated γ-lactone as shown in A, in which ■ designates a quaternary carbon. Irradiation of the doublet for H_a at 6.13 ppm caused the multiplet at 3.93 ppm to be simplified to a pair of triplets with J = 9.6, 3.1, and 3.1 Hz, and irradiation at 5.53 ppm (H_b) showed a similar collapse with coupling now 9.6, 3.5, and 3.1 Hz, thus locating H_c at 3.93 ppm. Saturation of this signal not only converted the H_a and H_b doublets to singlets but also changed



A

the one-proton triplet at 4.23 ppm to a doublet (J = 9.6 Hz) and the saw-tooth multiplet of eight-peaks at 5.95 ppm to a pair of doublets (J = 11.4 and 6.4 Hz). The lactonic proton H_d was assigned at 4.23 ppm, and H_e on the acetate-bearing carbon at 5.95 ppm in keeping with the chemical shifts observed for similar protons in other sesquiterpene lactones. Irradiation at 4.23 ppm collapsed the multiplet at 3.93 ppm (H_c) to a broadened quartet ($J \approx 3$ Hz) and the doublet at 2.98 ppm for H_f to a singlet. The pattern and chemical shift of H_f suggested it was adjacent to a quaternary carbon and most probably on a carbon with an epoxide oxygen (vide infra). Similar decoupling of H_e (5.95 ppm) caused the expected collapse of the H_c pattern at 3.93 ppm to a pair of triplets and of a one-proton (H_g) multiplet centered at 2.74 ppm; the A doublet (J = 17.2 Hz) of an AB quartet, further split into five peaks ($J \approx 2$ Hz) to a doublet split into four peaks. In addition, a change between 2.0 and 2.4 ppm was observed, but the region consists of overlapping peaks and was not clearly analyzable. Irradiation at ~2.2 ppm affected the large coupling for the pattern at 2.74 ppm and thus the hidden pattern corresponds to the second methylene proton H_h. Furthermore, the H_e multiplet at 5.95 ppm was changed to a pair of doublets and the one-proton broadened doublet at 5.33 ppm to a sharp doublet, as would be expected on elimination of allylic coupling. Finally, on irradiation of H_g (2.74 ppm), not only was