to a preparative TLC plate (system B), the band corresponding to **5** was removed, and 19.8 mg of solids was eluted with ethanol. By UV analysis (UV max 244 nm, 0.1 N HCl) this contained 9.7 mg (21% yield) of **5**:[20,21] mass spectrum m/e 118 (M^+).

Conversion of 10 to *N*-Formyldiaminomaleonitrile (9). In methanol (50 mL) were dissolved **10** (6.3 mg, 0.0467 mmol) and *p*-toluenesulfonic acid monohydrate (8.82 mg, 0.047 mmol). A portion of this solution was diluted further with methanol, and the UV spectrum showed a broader peak with a maximum at 310 nm. After 20–30 min a portion of the original 50-mL solution was diluted and showed a sharp maximum at 289 nm (ϵ 12900) compared to 289 nm (ϵ 12200) for authentic **9**.[13] In a more concentrated (1 mL) methanolic solution **10** (~6 mg) is wholly converted as observed by TLC (solvent A) in ≤1 h to **9** under the influence of equimolar *p*-TsOH·H_2O.

Stability of 10 to NH_3 in EtOH. Compound **10** (9.8 mg) was dissolved in 10% NH_3 in ethanol (1.5 mL). After 40 min at ambient temperature no change was observed by TLC (solvent mixture A).

Stability of 10 to $Et_3N/CH_3OH/H_2O$. Compound **10** (9.5 mg, 0.0705 mmol) was dissolved in 2 mL of 1:1:1 Et_3N (~4.8 mmol)–H_2O–CH_3OH and stirred at 25 °C. Over 30 min two new materials were detected by TLC (solvent mixture B) at R_f 0.15 and 0.25, but nothing corresponding to **8** or **11** was observed. No attempt was made to isolate the products which proved stable over 18 h after NH_4OH (1 mL) was added to the solution.

Stability of 10 to Pyridine and Et_3N. Compound **10** (9.6 mg, 0.0711 mmol) was dissolved in pyridine (1 mL) and samples for TLC were withdrawn. No change in the TLC was observed for up to 3 h. Triethylamine (1.5 mL) was added and no change was observed by TLC after 30 min at ambient temperature.

Stability of 10 to Morpholine and Diethylamine. Compound **10** (10 mg, 0.074 mmol) was dissolved in a mixture of water (1 mL) and ethanol (0.5 mL) and after 2 h no change was noted by TLC. Morpholine (29.6 mg, 0.34 mmol) was added and stirred for 4 h without any change. Diethylamine (1 mL, 0.71 g, 9.7 mmol) was added with immediate darkening and conversion of **10** to material at the origin by TLC (system B).

Registry No. **2**, 1187-42-4; **4**, 73-24-5; **5**, 1122-28-7; **8**, 5098-11-3; **9**, 53144-01-7; **10**, 71749-37-6; **10** *p*-toluenesulfonate salt, 71749-38-7; **11**, 7269-66-1; **11**·2HCl, 71749-39-8; hydrocyanic acid, 74-90-8; ammonium cyanide, 12211-52-8; formamidine acetate, 40730-94-7.

(20) D. Woodward, U.S. Patent 2534331 (1950).
(21) H. Wakamatsu, Y. Yamada, T. Saito, I. Kumashiro, and T. Takenishi, *J. Org. Chem.*, **31**, 2035 (1966).

Bicyclic Guanidino Ketones

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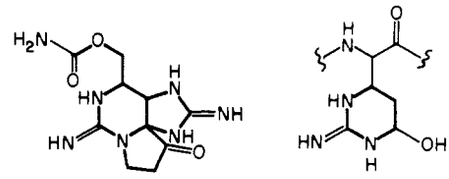
Syntheses of bicyclic [3.3.1] guanidino ketones are described by methods that permit the preparation of compounds substituted at the endo- and exocyclic nitrogen as well as at C-4. The primary synthetic method involved the synthesis of substituted and protected 3-aminopiperidones and their subsequent cyclization with *S,S*-dimethyl *N*-(*p*-toluenesulfonyl)dithiocarbonimidate to the substituted and protected bicyclic guanidino ketones. The ketones, blocked as the ethylene ketals, were deblocked by transketalization with cyclohexanone while the guanidine, blocked by tosylation, was deblocked by liquid HF.

Recent reported examples of natural products containing the guanidino functionality as part of a ring system include the puffer fish poison tetrodotoxin,[1] the paralytic shellfish poison saxitoxin (**1**),[2-4] the peptide antibiotics capreomycin,[5] viomycin (**2**),[6] and tuberactinomycin,[7] the antifungal agent stendomycin,[8] and the alkaloids of *Alchornea jovanensis* (**3**).[9] Since the available methods for the preparation of functionalized cyclic guanidines are limited, it was of interest to develop such methods and to prepare a series of functionalized cyclic guanidines in order to study



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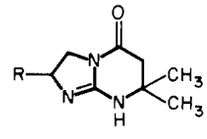

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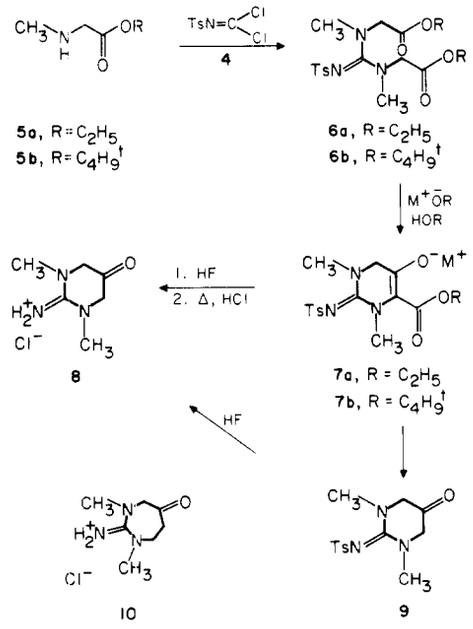
their chemistry and to examine their biological activity. We present at this time the synthesis of a number of bicyclic [3.3.1] guanidino ketones.

The first compound sought was the monocyclic guanidino ketone 1,3-dimethyl-2-imino-5-oxohexahydropyrimidine hydrochloride (**8**) (Scheme I), and its preparation was attempted by using the ethyl ester of sarcosine (**5a**). Good yields of diester **6a** and the cyclic salt **7a** were obtained, but deblocking and decarboethoxylation gave only a poor yield of **8**. An alternative procedure, whereby

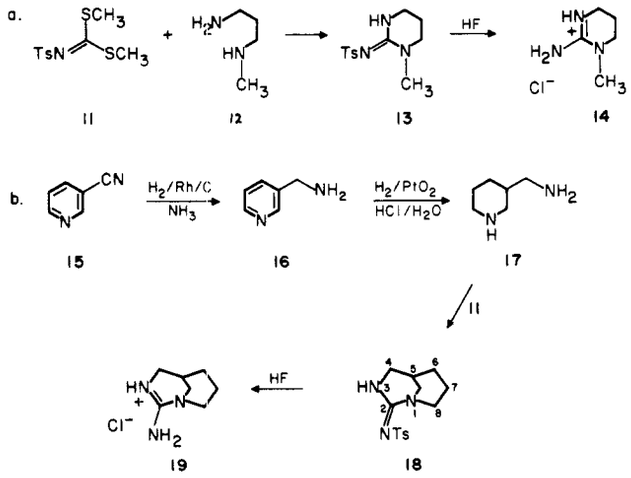
(1) A. Furusaki, Y. Tomiie, and I. Nitta, *Bull. Chem. Soc. Jpn.*, **43**, 3332 (1970).
(2) J. Wong and H. Rapoport, *J. Am. Chem. Soc.*, **93**, 7344 (1971).
(3) J. Bordner, W. E. Thiessen, H. A. Bates, and H. Rapoport, *J. Am. Chem. Soc.*, **97**, 6008 (1975).
(4) E. J. Schantz, V. E. Ghazarossian, H. K. Schnoes F. M. Strong, J. P. Springer, J. O. Pezzanite, and J. Clardy, *J. Am. Chem. Soc.*, **97**, 1238 (1975).
(5) S. Nomoto, T. Teshima, T. Wakamiya, and T. Shiba, *Tetrahedron*, **34**, 921 (1978).
(6) B. W. Bycroft, *J. Chem. Soc., Chem. Commun.*, 660 (1972).
(7) H. Yoshioka, T. Aoki, H. Goko, K. Natkatsu, T. Noda, H. Sakakibara, T. Take, A. Nagata, J. Abe, T. Wakamiya, T. Shiba, and T. Kaneko, *Tetrahedron Lett.*, **23**, 2043 (1971).
(8) M. Bodansky, J. Izdebski, and I. Muramatsu, *J. Am. Chem. Soc.*, **91**, 2351 (1969).
(9) N. K. Hart, S. R. Johns, J. A. Lamberton, and R. I. Willing, *Aust. J. Chem.*, **23**, 1679 (1970).

0022-3263/79/1944-4536$01.00/0

Scheme I



Scheme II



the ethyl ester of **7a** was first hydrolyzed and decarboxylated to give **9**, was rejected due to the low yield and instability of **9**. Replacement of the ethyl ester with the *tert*-butyl ester, however, gave a clean and high-yield synthesis of **8**. The attempted preparation of larger ring analogues for **8**, for example **10**, failed in the cyclization step due to the elimination of acrylate.

For the preparation of bicyclic guanidine **19** (Scheme IIb) a two-step hydrogenation of 3-cyanopyridine **15** was found to be convenient, as its reduction in the presence of Rh/C became prohibitively slow once **16** had been formed. The diamine **17** was sufficiently pure to be used directly in the preparation of bicyclic tosylguanidine **18** by condensation with *S,S*-dimethyl *N*-tosyldithiocarbonimidate (**11**).[10] From **18**, the free guanidine **19** was prepared in high yield by deblocking with anhydrous HF. For comparison purposes, the monocyclic *N*-alkylguanidine **14** was prepared in a straightforward manner as shown in Scheme IIa.

For the synthesis of the first bicyclic guanidino ketone, we began with the cyclic β-keto ester **20**, prepared by using a known procedure,[11] which was converted to ketal **21**

(10) R. Gompper and W. Hagele, *Chem. Ber.*, **99**, 2885 (1966).
(11) J. D. Baty, G. Jones, and C. Moore, *J. Chem. Soc. C*, 2645 (1967).

Scheme III

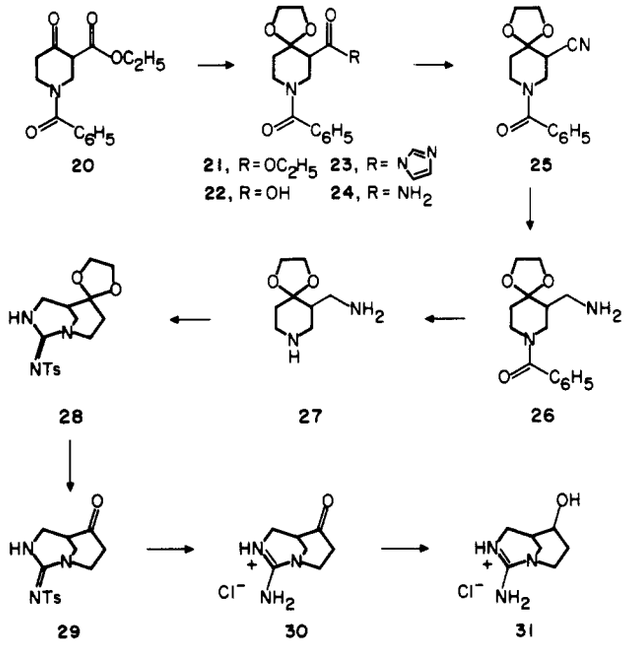


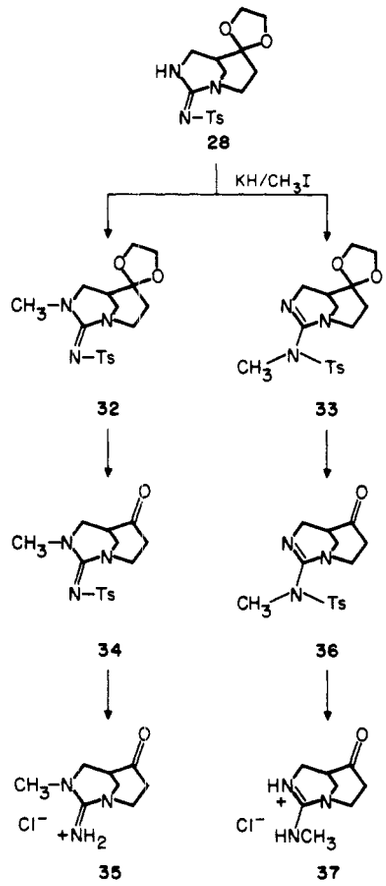
Table I. Methylation of 6,6-Ethylenedioxy-2-(*p*-toluenesulfonimido)-1,3-diazabicyclo[3.3.1]nonane (28)

solvent	base	% endo, 32	% exo, 33
Me_2SO	NaH	25	0.3
DMF	NaH	45	3
benzene	NaH	60	40
dioxane	NaH	67	33
diglyme	NaH	80	20
diglyme	KH	87	13
diglyme	MeLi	47	53
xylene	MeLi	45	55

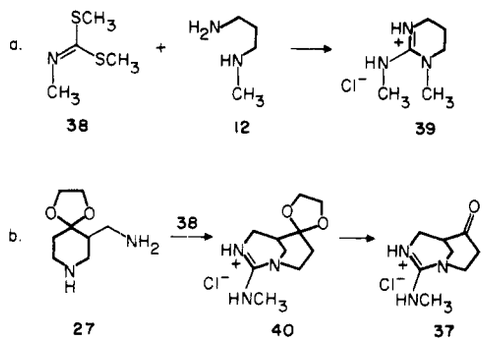
(Scheme III). Preparation of amide **24** was first attempted by direct ammonolysis of the ethyl ester **21**; however, all conditions attempted (aqueous ammonia,[12] $CH_3OH/NH_3/CH_3ONa$,[13] and liquid NH_3 at 180 °C)[14] failed. After hydrolysis of ester **21**, the imidazolide **23** was prepared[15] from the acid **22**, which in turn gave a quantitative yield of the desired amide **24**. Nitrile **25** was prepared by dehydration with *p*-toluenesulfonyl chloride[16] and reduced to amine **26** which was used directly to prepare diamine **27**. The cyclization of 3-(aminomethyl)-4-piperidone ethylene ketal **27** gave a good yield of the bicyclic tosylguanidino ketal **28**. Hydrolysis of the ketal in **28** with aqueous acid in dioxane gave only low yields of ketone **29** and considerable polymer. Similarly, initial removal of the tosyl group with HF gave the bicyclic guanidino ketal, but this ketal required 6 N HCl at reflux for 24 h for hydrolysis and also gave much polymer. However, transketalization of **28** with cyclohexanone was found to give a good yield of ketone **29**, and this was followed by straightforward detosylation of **29** with HF to give the desired bicyclic guanidino ketone **30** in good yield. Catalytic reduction of **30** gave the alcohol **31** as a mixture of epimers.

(12) M. Gordon, J. G. Miller, and A. R. Day, *J. Am. Chem. Soc.*, **71**, 1245 (1949).
(13) E. L. Allred and M. D. Hurwitz, *J. Org. Chem.*, **30**, 2376 (1965).
(14) E. T. Roe, J. T. Scanlan, and D. Swern, *J. Am. Chem. Soc.*, **71**, 2215 (1949).
(15) H. A. Staab, *Angew. Chem., Int. Ed. Engl.*, 1, 351 (1962).
(16) C. R. Stephens, E. J. Bianco, and F. J. Pilgrim, *J. Am. Chem. Soc.*, **77**, 1701 (1955).

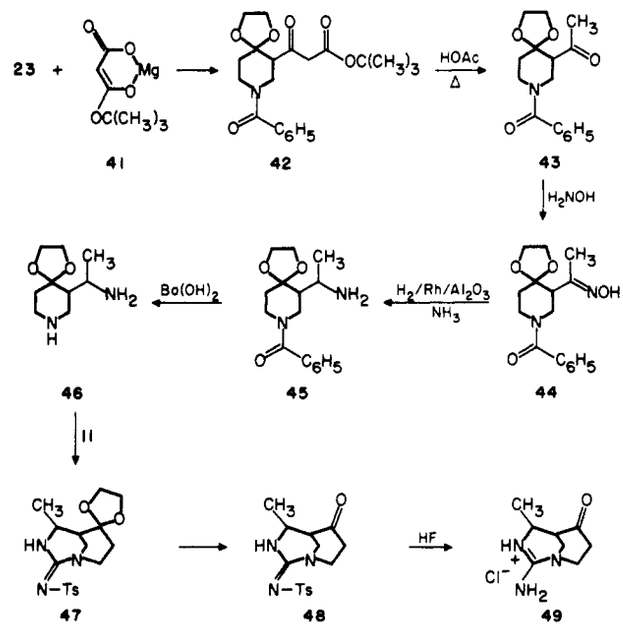
Scheme IV



Scheme V



Scheme VI



The methylation of bicyclic guanidino ketal **28** (Scheme IV) gave both endocyclic methylated product **32** and exocyclic methylated product **33** in ratios dependent upon the reaction conditions. Since two alternative methods were avaliable (see Schemes V and VII) for the ultimate preparation of exocyclic methylated bicyclic guanidino ketone **37**, a high ratio of endocyclic isomer **32** to exocyclic isomer **33** was desired at this stage. The effect on this ratio of different solvents and bases is shown in Table I. Thus the endo isomer **32** was favored in polar solvents with potassium as the cation, while the exo isomer was favored in nonpolar solvents with lithium as cation. Both Me_2SO and DMF gave excellent endo/exo ratios but also gave large amounts of side products. The very high thermal stability of **32** and **33** permitted examination of the reaction mixtures by GC at 275 °C, and complete separation of the exo and endo isomers **32** and **33** was effected readily by column chromatography.

In the preparation of cyclic guanidine **39** and bicyclic guanidino ketal **40** (Scheme V), we found that the reaction of *S,S*-dimethyl *N*-methyldithiocarbonimidate[17] (**38**) with amines does not proceed in the absence of an acid catalyst. Aqueous HCl worked well, but anhydrous HCl in THF eliminated the small amount of side product found when H_2O was present. Hydrolysis of ketal **40** to ketone **37** proceeded with greater facility than the analogous reaction for the deblocking of **30**, giving much less decomposition and a better yield under less strenuous reaction conditions.

In the preparation of the carbon-methyl analogue **49** (Scheme VI), the imidazolide method,[18] as modified,[19] was used to give the β-keto ester **42**. Hydrolysis and decarboxylation with hot glacial acetic acid transformed β-keto ester **42** to methyl ketone **43** which was converted to oxime **44**. Its hydrogenation gave a good yield of amine **45** although a long induction period was sometimes found prior to inception of reduction. Hydrolysis gave diamine **46** from which the bicyclic guanidines **47**, **48** and **49** were prepared in good yield by using methods already described above.

An alternative approach to the desired compounds, which involves the reduction of substituted pyrimidines, is outlined in Scheme VII. Ketalization of β-keto ester **53** gave the desired ketal **54** but also a significant amount of the ethylene glycol ester through transesterification. The catalytic reduction of **54** required the presence of 100 mol % of HCl; less HCl gave equivalently less reduction, and greater amounts of HCl gave benzylic hydrogenolysis of the ketal. Reduction of the ester in ketal **55** with lithium aluminum hydride gave a lower yield of alcohol **56** and involved a more difficult isolation than its reduction with diborane. Preparation of chloride[20] **57** and its cyclization to **33** were straightforward and proceeded in good yields.

The pK_a's of the guanidinium salts **8**, **14**, **19**, **30**, **31**, **35**, **37**, and **49** were determined in duplicate by using standard procedures,[21] and values are given in Table II. All the bicyclic guanidinium salts with an oxygen function at C-6 (**30**, **31**, **35**, **37**, **49**) have pK_a's in the range 10.5–11.8. These values are reasonably close to, but slightly lower than, the nonoxygenated analogue **19** with pK_a 12.0, indicating a

(17) M. Delephine, *Bull. Soc. Chim. Fr.*, **27**, 58 (1902).
(18) G. Bram and M. Vilkas, *Bull. Soc. Chim. Fr.*, 945 (1964).
(19) R. Pappo, P. Collins, and C. Jung, *Ann. N.Y. Acad. Sci.*, **180**, 64 (1971).
(20) J. Hooz and S. H. Gilani, *Can. J. Chem.*, **46**, 86 (1968).
(21) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases", Wiley, New York, 1962, p 31.

Scheme VII

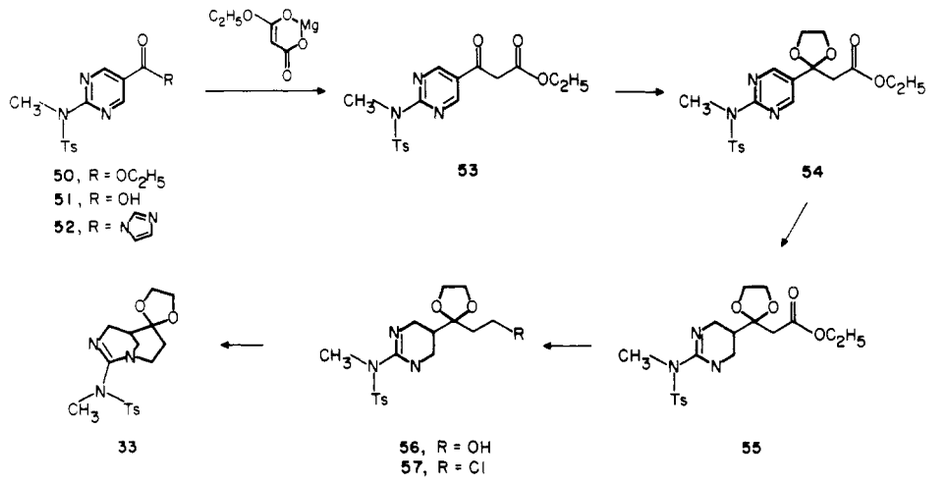


Table II. The pK_a's of Various Cyclic Guanidines, Determined on the Hydrochloride Salts

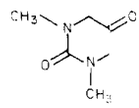
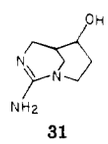
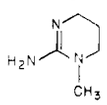
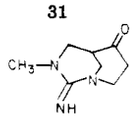
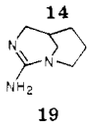
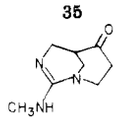
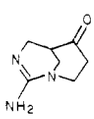
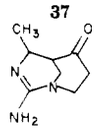
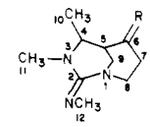
compd	pK_a	compd	pK_a
 8	9.7	 31	11.4
 14	12.4	 35	11.8
 19	12.0	 37	10.5
 30	10.8	 49	11.0

Table III. ^{13}C NMR Spectral Assignments (δ Values) in D_2O of Various Bicyclic Guanidines as the Hydrochloride Salts



assignment	compd 19	30[a]	35	37[b]
6 (R = O)			212.5	
2	165.3	163.7	164.0	162.2
6 (R = $C(OH)_2$)		94.6	94.8	95.0
9	55.7	52.5	52.7	52.5
8	50.0	46.8	47.0	47.0
5	29.1	38.0	37.8	38.0
7	21.2	36.5	34.6	34.5
10				
4	46.7	44.0	40.8	
11			50.7	
12				42.5
6 (R = H_2)	27.4			

[a] Additional absorptions at δ 52.0, 44.3, 42.0, 39.0, and 34.0. [b] Additional absorption at δ 28.5.

distinct but minor base-weakening effect for the distant oxygen. Fusion into the bicyclic system lowers the pK_a by about half a unit as compared to the nonbridged compound **14**. This decrease is probably ascribable to slight departure for complete planarity in the resonating guanidium ion in the bicyclo[3.3.1] structures. More striking is the marked decrease in basicity (2.7 pK units) caused by the carbonyl group at C-5 in the comparison of monocyclic guanidine **8** and its deoxo analogue **14**.

The ^{13}C NMR spectral data are shown in Table III. There appears to be a relationship between the increased multiplicity of peaks for a given compound in its ^{13}C spectrum and a lowering of the pK_a for the compound in question. This can possibly be explained by an equilibrium between the ketone form of a given cyclic guanidine and its corresponding ketone hydrate.

Experimental Section

^1H NMR spectra were obtained with a Varian T-60 spectrometer and were taken in $CDCl_3$ unless otherwise noted. IR spectra were recorded on KBr pellets, and UV absorptions were measured in ethanol. Ion-exchange chromatography was on AG50W-X4, 100–200 mesh resin unless otherwise noted. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Thin-layer chromatography was done on Eastman Chromagram sheets (no. 6060). Vapor-phase chromatography was done on a Hewlett-Packard Model 402 GC using a 5-ft glass column with 3% OV-17 on Aeropack 30 (100–200 mesh). Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley, and agreed with calculated values within 0.4%. All solvents were freshly distilled from the appropriate drying agent. Solutions were dried over $MgSO_4$ and were removed in vacuo by using a Berkeley rotary evaporator.

2-(*p*-Toluenesulfonyl)-1,3-dimethyl-1,3-bis[(*tert*-butoxycarbonyl)methyl]guanidine (6b). To a stirred solution of dichloro-*N*-(*p*-toluenesulfonyl)carbonimidate (**4**; 19.0 g, 75 mmol)[22] in 70 mL of acetonitrile at 0 °C was added in 15 min a solution of *tert*-butyl sarcosinate (**5b**; 21.7 g, 150 mmol) and triethylamine (20.8 g, 200 mmol) in 100 mL of acetonitrile. The solution was stirred for 30 min at 0 °C, allowed to warm to room temperature overnight, and evaporated, and the residue was dissolved in 500 mL of chloroform and washed with 5% aqueous acetic acid (3 × 300 mL) and saturated $NaHCO_3$ (3 × 300 mL). Drying, solvent removal, and chromatography of the residue using 800 g of silica with benzene/acetone (10/1) as eluent gave 28.2 g (80%) of yellow crystals, pure by TLC (R_f 0.59, $CHCl_3$). The small amount of yellow impurity can be removed by recrystallization from ether (100 mL/28 g of crystals) to give 19.0 g (55%) of pure white crystals: mp 123–125 °C; NMR δ 1.47 (s, 18 H, *t*-C_4H_9), 2.38 (s, 3 H, $ArCH_3$), 3.05 (s, 6 H, NCH_3), 4.08 (s, 4 H, CH_2), 7.30 (d, 2

(22) R. Neidlein and W. Haussmann, *Tetrahedron Lett.*, 1753 (1965).

H, J = 8 Hz, Ar), 7.72 (d, 2 H, J = 8 Hz, Ar). Anal. Calcd for $C_{22}H_{35}N_3O_6S$: C, 56.3; H, 7.5; N, 9.0. Found: C, 56.0; H, 7.7; N, 9.1.

1,3-Dimethyl-2-(*p*-toluenesulfonimido)-4-(*tert*-butoxycarbonyl)-5-oxohexahydropyrimidine Potassium Salt (7b). To a stirred solution of potassium *tert*-butoxide (1.83 g, 16 mmol) in benzene (400 mL, distilled from NaH) and *tert*-butyl alcohol (200 mL, distilled from CaH_2) in a nitrogen atmosphere was added di-*tert*-butyl ester **6b** (7.19 g, 15.5 mmol) during a 15-min period. After a total of 1 h at room temperature the pale yellow solution was evaporated, leaving 5.70 g of residue: NMR (D_2O) δ 1.57 (s, 9 H, t-C_4H_9), 2.32 (s, 3 H, $ArCH_3$), 2.88 (s, 3 H, NCH_3 next to enol), 3.25 (s, 3 H, NCH_3), 3.68 (s, 2 H, CH_2), 7.50 and 7.80 (dd, 4 H, J = 8 Hz, Ar).

1,3-Dimethyl-2-imino-5-oxohexahydropyrimidine Hydrochloride (8). To crude ester **7b** (5.05 g, 11.7 mmol) was added HF (60–70 mL, distilled from CoF_2).[23] The resulting red solution was left at room temperature for 6 h, after which the HF was evaporated, and the residue was partitioned between water (100 mL) and methylene chloride (100 mL) to remove the *p*-toluenesulfonyl fluoride formed. The aqueous solution was made 4 N with concentrated HCl and refluxed in a nitrogen atmosphere for 16 h followed by decolorizing the solution with carbon, evaporating the solvent, and passing the residue through 50 mL of a cation-exchange column. Collecting 25-mL fractions and eluting first with water (250 mL) and then with 3.0 N HCl gave 0.70 g of yellow material in fractions 14 and 15 and 1.6 g (80%) of product in fractions 16, 17, and 18: NMR (D_2O) δ 3.05 (s, 5 H, NCH_3, hydrate), 3.10 (s, 1 H, NCH_3, ketone), 3.40 (s, 3.5 H, CH_2, hydrate), 4.00 (s, 0.5 H, CH_2, ketone); mass spectrum, m/e 141, (M^+ – HCl). Anal. Calcd for $C_6H_{12}N_3OCl \cdot H_2O$: C, 36.8; H, 7.2; N, 21.5. Found: C, 37.2; H, 7.1; N, 21.7.

1-Methyl-2-(*p*-toluenesulfonimido)hexahydropyrimidine (13). A solution of **11** (6.88 g, 25 mmol) and *N*-methyl-1,3-diaminopropane (**12**; 2.20 g, 25 mmol) in 200 mL of absolute ethanol was stirred and refluxed under a nitrogen sweep. The liberated methyl mercaptan was monitored by bubbling the emerging stream through $AgNO_3/CH_3CN$. After 6 h, no further precipitation occurred, and the reaction mixture was cooled and evaporated and the residue crystallized from 100 mL of benzene and 100 mL of cyclohexane to give 5.33 g (68%) of crystals, mp 123–126.5 °C. A second crystallization gave 4.25 g (54%) of material: mp 123.5–125.5 °C; NMR δ 6.95 and 7.32 (dd, Ar), 7.15 (br s, NH), 2.30 (s, $ArCH_3$), 2.85 (s, NCH_3), 3.10 (t, $HNCH_2$ and CH_3NCH_2), 1.80 (pentet, $CH_2CH_2CH_2$). Anal. Calcd for $C_{12}H_{17}N_3O_2S$: C, 53.9; H, 6.4; N, 15.7. Found: C, 54.0; H, 6.4; N, 15.7.

1-Methyl-2-imino-1,4,5,6-tetrahydropyrimidine Hydrochloride (14). The procedure followed in the preparation of **8**, omitting the reflux in HCl, was used to detosylate **13** (1.07 g, 4 mmol) by using 18 mL of HF; 0.29 g (90.3%) of detosylated product was recovered: TLC (73/10/12 *n*-BuOH/HOAc/H_2O) R_f 0.55; NMR (D_2O) δ 1.95 (pentet, J = 6 Hz, 2 H, $CH_2CH_2CH_2$), 3.05 (s, 3 H, CH_3), 3.30 (t, J = 6.5 Hz, 2 H, NCH_2), 3.42 (t, J = 6.5 Hz, 2 H, NCH_2).

3-(Aminomethyl)piperidine (17). A solution of 3-cyanopyridine (20.8 g, 0.2 mol) in concentrated aqueous ammonia (250 mL) containing 5% Rh/C (10 g) was hydrogenated at 40 psi for 12 h. After the solvent was filtered and evaporated, the crude material (22 g) was dissolved in 250 mL of water containing 2.2 equiv of HCl. The solution was then hydrogenated at 40 psi for 6 h in the presence of 1 g of PtO_2. Filtration followed by evaporation of the solvent gave the crude dihydrochloride, which was mixed with 50% aqueous NaOH and extracted with ether. After the extract was dried and solvent removed, there remained 21 g (93%) of pure **17** as a pale yellow liquid: NMR δ 1.90 (s, 2 H, NH_2), 1.0–2.2 (m, 5 H, $NCH_2CH_2CH_2CH$ and NH), 2.2–3.4 (m, 6 H, 3 NCH_2); TLC (pyr/CH_3OH, 1/1) R_f 0.5.

2-(*p*-Toluenesulfonimido)-1,3-diazobicyclo[3.3.1]nonanone (18). To a solution of diamine **17** (1.14 g, 0.01 mol) in 100 mL of absolute ethanol was added **11** (2.75 g, 10 mmol).[10] The solution was refluxed, and the liberated methanethiol was swept out with nitrogen and trapped in 0.05 M $AgNO_3$ in CH_3CN. The precipitated $AgSCH_3$ was filtered and weighed periodically in order to monitor the reaction. The solution was evaporated after 10 h, and the residue was chromatographed on silica (100 g), eluting with 13% acetone in benzene. Crystallization from boiling toluene gave 1.26 g (43.2%) of **18**: mp 161.5–163 °C; NMR δ 2.35 (s, 3 H, CH_3), 7.10–7.85 (q, 4 H, Ar), 8.10 (br s, 1 H, NH). Anal. Calcd for $C_{14}H_{19}N_3O_2S$: C, 57.3; H, 6.5; N, 14.3. Found: C, 57.4; H, 6.5; N, 14.3.

2-Amino-1,3-diazabicyclo[3.3.1]non-2-ene Hydrochloride (19). By use of liquid HF as described for **8** and **14**, **18** (0.41 g, 1.4 mmol) was detosylated with 10 mL of HF for 2 h at room temperature. After the liquid HF was evaporated, the residue was dissolved in 30 mL of H_2O and extracted with CH_2Cl_2 (4 × 10 mL) to give 68 mg (28%) of tosyl fluoride. The aqueous solution was eluted through 50 mL of ion-exchange resin with 100 mL of H_2O, and then the product was eluted with 300 mL of 4 N HCl. Evaporation of the solvent gave 238 mg (97%) of product: mp 217–220 °C; TLC (*n*-BuOH/HOAc/H_2O, 73/10/17) R_f 0.60; NMR (D_2O) δ 1.70 (m, 4 H, $CHCH_2CH_2$), 2.35 (br s, 1 H, CH), 3.10–3.70 (m, 6 H, 3 NCH_2). Anal. Calcd for $C_7H_{14}N_3Cl$: C, 47.9; H, 8.0; N, 23.9. Found: C, 47.9; H, 8.0; N, 23.9.

1-Benzoyl-3-(ethoxycarbonyl)-4,4-ethylenedioxypiperidine (21). Water was azeotropically removed from a solution of **20** (22.6 g, 82 mmol), ethylene glycol (70.4 g, 1.13 mol), *p*-toluenesulfonic acid monohydrate (0.43 g, 2.3 mmol), and benzene (300 mL). Distillation was continued for 10 h, after which time the benzene solution was washed with saturated $NaHCO_3$ (3 × 200 mL) and water (2 × 100 mL). Drying and evaporating the benzene left a residue which was chromatographed on 550 g of silica gel, with 1% acetone in benzene as eluant. The eluant was collected in 75-mL portions, and after 38 fractions, the eluant was changed to 5% acetone in benzene. Combined fractions 56–116, after removal of solvent, left 15.5 g (61%) of a pale yellow oil: TLC (acetone/benzene, 3/22), R_f 0.52; NMR δ 1.24 (t, J = 7 Hz, 3 H, CH_3), 2.75 (t, J = 5 Hz, 1 H, CH), 3.98 (s, 4 H, OCH_2CH_2O), 4.16 (t, J = 7 Hz, 2 H, CH_2CH_3); IR (film) 1740 (ester), 1640 cm^{-1} (amide). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.9; H, 6.6; N, 4.4. Found: C, 64.1; H, 6.6; N, 4.3.

1-Benzoyl-3-carboxy-4,4-ethylenedioxypiperidine (22). A solution of ester **21** (17.58 g, 50 mmol) in 100 mL of ethanol was mixed with $LiOH \cdot H_2O$ (2.1 g, 50 mmol) in 100 mL H_2O and left at room temperature for 24 h. The reaction solution was washed with CH_2Cl_2 (3 × 100 mL), evaporated to dryness, azeotroped three times with absolute ethanol, and finally dried at 100 °C under high vacuum, giving 15.1 g (98%) of dry lithium salt: NMR (D_2O) δ 1.85 (m, 2 H, CH_2CO), 2.65 (m, 1 H, $CHCO_2^-$), 3.70 (m, 4 H, 2 NCH_2), 4.10 (s, 4 H, OCH_2CH_2O), 7.50 (s, 5 H, Ar).

An aqueous solution (15 mL) of the lithium salt of **22** (3.35 g, 10.6 mmol) was adjusted to pH 4.0 with 1.0 N HCl, resulting in a precipitate which was filtered, washed with water (3 × 5 mL), and dried: 2.45 g (83%); mp 185–191 °C; NMR δ 1.20–2.30 (m, 2 H, CH_2 next to ketal), 2.70 (t, 1 H, J = 5.5 Hz, methine), 3.3–4.0 (m, 4 H, 2 NCH_2), 4.0 (s, 4 H, OCH_2CH_2O), 7.30 (s, 5 H, Ar), 9.15 (s, 1 H, COOH). Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.6; H, 5.9; N, 4.8. Found: C, 61.9; H, 5.9; N, 4.9.

1-Benzoyl-3-(imidazolylcarbonyl)-4,4-ethylenedioxypiperidine (23). To a mixture of 250 mL of THF and acid **22** (48.0 g, 165 mmol) was added carbonyldiimidazole (32.1 g, 198 mmol).[15] After 10 min, the resulting mixture was cooled to 0 °C and filtered, and the precipitate was washed with cold THF (2 × 25 mL) and crystallized from dioxane to give 57 g (100%) of imidazolide **23**: mp 182–183 °C; TLC (ethyl acetate) R_f 0.18; NMR δ 1.90 (m, 2 H, CH_2 adjacent to ketal), 3.2–4.1 (m, 9 H, all except Ar and imidazolyl protons), 7.40 (s, 5 H, Ar), 7.05, 7.50, 8.20 (3 s, 3 H, imidazolyl protons). Anal. Calcd for $C_{18}H_{19}N_3O_4$: C, 63.3; H, 5.6; N, 12.3. Found: C, 63.4; H, 5.7; N, 12.4.

1-Benzoyl-3-carbamoyl-4,4-ethylenedioxypiperidine (24). A solution of imidazolide **23** (253 mg, 0.74 mmol) in 5 mL of chloroform was saturated with NH_3 at room temperature. After 17 h the chloroform was evaporated, and the residue was heated at 100 °C (0.1 mm) to remove imidazole. There remained 215 mg (101%) of pure amide: mp 182–182 °C; NMR δ 1.90 (m, 2 H, NCH_2CH_2), 2.70 (m, 1 H, $CHCONH_2$), 3.20–3.9 (m, 4 H, 2 NCH_2), 4.0 (s, 4 H, OCH_2CH_2O), 5.7 and 6.2 (s, 2 H, NH_2), 7.34 (s, 5 H, ArCO). Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.1; H, 6.3; N,

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9.7. Found: C, 62.3; H, 6.0; N, 9.7.

1-Benzoyl-3-cyano-4,4-ethylenedioxypiperidine (25). A solution of amide **24** (0.70 g, 2.40 mmol) in 25 mL of pyridine was treated with tosyl chloride (685 mg, 3.60 mmol).[16] After 3 h at room temperature, the pyridine was evaporated, and the residue was dissolved in $CHCl_3$ and washed with H_2O. After the solution was dried and the solvent removed, the residue was chromatographed on 100 g of silica with $CHCl_3$ as eluant to give 0.59 g (91%) of product: mp 115–117 °C; NMR δ 1.80 (m, 2 H, NCH_2CH_2), 2.87 (dd, 1 H, CHCN), 3.65 (t, J = 6 Hz, 2 H, NCH_2CH_2), 3.75 (d, J = 8 Hz, 2 H, CH_2CHCN), 4.05 (s, 4 H, OCH_2CH_2O), 7.40 (s, 5 H, Ar); TLC ($CHCl_3$) R_f 0.78. Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.2; H, 5.9; N, 10.3. Found: C, 65.9; H, 6.0; N, 10.3.

1-Benzoyl-3-(aminomethyl)-4,4-ethylenedioxypiperidine (26). A solution of nitrile **25** (0.60 g, 2.20 mmol) and ammonia (0.65 g, 37 mmol) in 100 mL of absolute ethanol was hydrogenated at 40 psi of H_2 over 0.5 g of 5% Rh/Al_2O_3.[24,25] After 12 h, a further 0.9 g of catalyst was added, and the hydrogenation was continued for 12 h. After the mixture was filtered and the filtrate evaporated, there was 0.60 g (97%) of **26**: TLC (CH_3OH/H_2O, 23/2) R_f 0.50; NMR δ 1.65 (m, 4 H, NCH_2CH_2, H_2NCH_2), 3.50 (m, 3 H, $CHNCH_2$), 3.95 (s, 4 H, OCH_2CH_2O), 6.40 (s, 5 H, Ar).

3-(Aminomethyl)-4,4-ethylenedioxypiperidine (27). A solution of **26** (590 mg, 2.0 mmol) and $Ba(OH)_2$ (0.75 g, 4.1 mmol) in 20 mL of H_2O was refluxed for 3 h, and the resulting solution was extracted continuously for 12 h with $CHCl_3$. The crude extract was chromatographed by using 50 g of silica and concentrated NH_3/CH_3OH (1/9) as eluant (7-mL fractions) and gave 0.279 g (76%) of **27** in fractions 6–20: NMR δ 1.70 (m, 3 H, NCH_2CH_2, NCH_2CH), 4.00 (s, 4 H, OCH_2CH_2O).

6,6-Ethylenedioxy-2-(*p*-toluenesulfonimido)-1,3-diazabicyclo[3.3.1]nonane (28). A solution of diamine **27** (279 mg, 1.02 mmol) and **11** (450 mL, 1.62 mmol) in 30 mL of absolute ethanol was refluxed for 40 h. Removal of the solvent gave crude product which was chromatographed (125 g of silica; benzene/acetone, 9/1; 19-mL fractions) and gave 371 mg (65%) of **28** in fractions 103–125: mp 159–160 °C; NMR δ (s, 3 H, $ArCH_3$), 3.90 (s, 4 H, OCH_2CH_2O), 7.18–7.88 (4 H, Ar), 8.10 (s, 1 H, NH). Anal. Calcd for $C_{16}H_{21}N_3O_4S$: C, 54.7; H, 6.0; N, 12.0. Found: C, 55.0; H, 6.0; N, 11.7.

2-(*p*-Toluenesulfonimido)-1,3-diazabicyclo[3.3.1]nonan-6-one (29). A solution of ketal **28** (9.70 g, 277 mmol) in cyclohexanone (170 g, 1.7 mol) containing *p*-toluenesulfonic acid monohydrate (1.0 g, 5.5 mmol) was heated at 90 °C for 15 h. The cyclohexanone was evaporated, and the residue was chromatographed (800 g of silica; benzene/acetone, 2/1) to give recovered ketal (4.0 g, 35%) and ketone **29** (5.2 g, 60%): pure by TLC (benzene/acetone, 2/1) R_f 0.31; mp 156–157 °C; NMR δ 1.5–2.5 (m, 3 H, CH_2COCH), 2.41 (s, 3 H, $ArCH_3$), 2.70–4.4 (m, 6 H, 3 NCH_2), 7.35 and 7.70 (dd, 4 H, Ar), 8.1 (br s, 1 H, NH); IR 1700 cm^{-1}. Anal. Calcd for $C_{14}H_{17}N_3O_3S$: C, 54.7; H, 5.6; N, 13.7. Found: C, 54.9; H, 5.5; N, 13.8.

2-Amino-1,3-diazabicyclo[3.3.1]non-2-en-6-one Hydrochloride (30). To the tosyl ketone **29** (4.7 g, 153 mmol) was added anhydrous HF (40 mL, distilled from CoF_3), and the tosyl cleavage reaction was performed as previously described. After 3 h, the HF was evaporated, and the residue was partitioned between water and methylene chloride. The thoroughly washed water layer was applied to 150 g of an ion-exchange column which was washed with H_2O until the eluant was no longer acidic (250 mL of H_2O), and then the detosylated product **30** was eluted with 3 N HCl in fractions 26–40 (25-mL fractions). After evaporation of the aqueous acid, the residue of **30** (2.3 g, 80%) remained as a pale orange glass: NMR (D_2O, pH 2.0) δ 1.8 (m, 1 H, one proton of $COCH_2$), 3.20 (m, 2 H, NCH_2), 3.50 (m, 4 H, 2 NCH_2); IR 1700 cm^{-1}. Anal. Calcd for $C_7H_{12}N_3OCl$: C, 44.3; H, 6.4. Found: C, 43.8; H, 6.5.

2-Amino-1,3-diazabicyclo[3.3.1]non-2-en-6-ol Hydrochloride (31). A solution of ketone **30** (0.375 g, 20 mmol) in 150 mL of water containing 5% Pd/C (175 mg) was hydrogenated at 40 psi of H_2 for 4 h. Removing the catalyst and evaporating the solvent gave alcohol **31** (380 mg, 101%): NMR (H_2O) δ 0.9–2.1 (m, 2 H, CH_2CHOH), 2.5 (br s, 1 H, CHCHOH), 3.1 (s, 2 H, NCH_2), 3.4 (s, 2 H, NCH_2).

6,6-Ethylenedioxy-2-(*p*-toluenesulfonimido)-3-methyl-1,3-diazabicyclo[3.3.1]nonane (32). To a solution of **28** (10.5 g, 30 mmol) in diglyme (250 mL, distilled from $LiAlH_4$) at 0 °C was added potassium hydride (1.32 g, 33 mmol). After 5 min, the vigorous H_2 evolution had stopped, and methyl iodide was added to the mixture in one portion (4.2 mL, 9.55 g, 68 mmol). The resulting solution was evaporated, and the residue was purified by chromatography (800 g of silica; benzene/acetone, 2/1). Collecting 25-mL fractions gave **32** (7.6 g, 70%) in fractions 43–85 and **33** (2.2 g, 22%) in fractions 25–42. The *endo*-methyl product **32** had the following characteristics: mp 206–207 °C; TLC (benzene/acetone, 2/1) R_f 0.28; NMR δ 1.2–1.7 (m, 2 H, $COCH_2$), 2.2 (m, 1 H, methine), 2.38 (s, 3 H, $ArCH_3$), 3.0 (s, 3 H, NCH_3), 3.1 (br d, J = 6 Hz, 2 H, NCH_2CH_2), 3.35 (d, J = 4.5 Hz, 2 H, NCH_2CH), 3.95 (s, 4 H, OCH_2CH_2O), 3.5–4.6 (m, 2 H, NCH_2CH), 7.20 and 7.70 (2 d, J = 9 Hz, Ar). Anal. Calcd for $C_{17}H_{23}N_3O_4S$: C, 55.9; H, 6.4; N, 11.5. Found: C, 56.2; H, 6.3; N, 11.9.

2-(*p*-Toluenesulfonimido)-3-methyl-1,3-diazabicyclo-[3.3.1]nonan-6-one (34). A solution of ketal **32** (4.66 g, 128 mmol) in cyclohexanone (210 mL, 0.42 mol) containing *p*-toluenesulfonic acid monohydrate (800 mg, 4 mmol) was heated at 90 °C for 12 h. After evaporation of the solvent, chromatography (800 g of silica; benzene/acetone, 2/1; 25-mL fractions) gave a 65% yield of ketone **34** in fractions 85–157: mp 169–172 °C; TLC (benzene/acetone, 2/1) R_f 0.27; NMR δ 2.40 (s, 3 H, $ArCH_3$), 2.2–2.5 (m, 2 H, CH_2CO), 3.00 (s, 3 H, NCH_3), 3.3 (br s, 4 H, NCH_2CH_2 and NCH_2), 3.5–4.9 (m, 2 H, NCH_2CH), 7.35 and 7.80 (2 s, J = 9 Hz, 4 H, Ar); IR 1725 cm^{-1}. Anal. Calcd for $C_{15}H_{19}N_3O_3S$: C, 56.1; H, 6.0; N, 13.1. Found: C, 55.8; H, 5.9; N, 12.9.

2-Imino-3-methyl-1,3-diazabicyclo[3.3.1]nonan-6-one Hydrochloride (35). Tosyl ketone **34** (3.0 g, 9.35 mmol) was detosylated by using HF (40 mL) as previously described. The product was applied to an ion-exchange column and washed with H_2O (250 mL) until the washings were no longer acidic, and then it was eluted with 3 N HCl (25-mL fractions) and appeared in fractions 18–30. Evaporation of the HCl solution left detosylated ketone **35** as a crystalline solid (1.43 g, 75%): mp 268–275 °C dec; IR 1705 cm^{-1}; NMR (D_2O, pH 2.0) δ 1.74 (m, 1 H, one proton from CH_2C), 2.40 (m, 1 H, methine), 3.10 (s, 3 H, CH_3), 3.40–4.20 (m, 6 H, 3 NCH_2). Anal. Calcd for $C_8H_{14}N_3OCl$: C, 47.2; H, 6.9; N, 20.6. Found: C, 47.0; H, 6.9; N, 20.5.

1-Methyl-2-(methylamino)-1,4,5,6-tetrahydropyrimidine Hydrochloride (39). A solution of *N*-methyl-1,3-propanediamine (8.82 g, 0.1 mol), **38** (13.5 g, 0.1 mol),[17] 500 mL of absolute ethanol, and 0.1 mol of concentrated HCl was heated under reflux for 24 h. The ethanol was evaporated, leaving 16.45 g (101%) of crude **39**: NMR (D_2O) δ 1.95 (pentet, J = 5.8 Hz, 2 H, $CH_2CH_2CH_2$), 2.80 (s, 3 H, NCH_3), 2.95 (s, 3 H, NCH_3), 3.33 (2 t, 2 NCH_2).

6,6-Ethylenedioxy-2-(methylamino)-1,3-diazabicyclo-[3.3.1]non-2-ene (40). A solution of diamine **27** (1.72 g, 0.01 mol), **38** (1.35 g, 0.01 mol),[17] and 0.81 mL (0.01 mol) of concentrated HCl in 500 mL of absolute ethanol was refluxed for 72 h and then evaporated to give 2.40 g (97%) of crude product which was passed through 100 mL of AGI-X8 (50–100 mesh) in the hydroxide form to yield the free base. Chromatography on silica (2-propanol/concentrated NH_3, 20/1) gave 2.10 g (85%) of **40** as the free base: NMR δ 1.60 (m, 4 H), 2.70 (s, 3 H, NCH_3), 3.92 (s, 4 H, OCH_2CH_2O).

2-(Methylamino)-1,3-diazabicyclo[3.3.1]non-2-en-6-one Hydrochloride (37). A solution of ketal **40** (2.07 g, 9.05 mmol) and 250 mL of 6 N hydrochloric acid was refluxed (nitrogen atmosphere) for 48 h. At the end of this time, the solution was evaporated to 10 mL which was applied to 110 mL of cation-exchange resin (AG-50W-X8, 20–50 mesh) and eluted with 3.0 N HCl (collected in 25-mL fractions). Fractions 10–26 contained 1.10 g (60%) of **37**, identical with material prepared from **36** by detosylation: mp 216–218 °C; NMR (D_2O) δ 1.90 (m, 1 H, methine), 2.65 (m, 2 H, CH_2CO), 3105 (s, 3 H, NCH_3), 2.70 (m, 6 H, 3 NCH_2); IR 1700, 1660 cm^{-1}. Anal. Calcd for $C_8H_{14}N_3OCl$: C, 47.2; H, 6.9; N, 20.6. Found: C, 47.2; H, 6.9; N, 20.5.

1-Benzoyl-3-[1-oxo-2-(*tert*-butoxycarbonyl)ethyl]-4,4-ethylenedioxypiperidine (42). To a stirred solution of imidazolide **23** (3.41 g, 10 mmol) in 250 mL of THF was added the magnesium enolate of *tert*-butyl hydrogen malonate[18] [from 3.20

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Table IV. Titration of 30

mL added	pH	[BH]	[B]	[OH⁻]	[BH]/[B]	log [BH]/[B]	pK^a
0.00	3.55	0.0217	0.00				
0.10	9.71	0.0192	0.0025		7.69	0.885	10.60
0.20	10.22	0.0167	0.0050	0.00011	3.43	0.535	10.76
0.30	10.50	0.0142	0.0075	0.00021	1.97	0.290	10.79
0.40	10.72	0.0117	0.0100	0.00034	1.24	0.09	10.81
0.50	10.91	0.0092	0.0125	0.00054	0.81	−0.09	10.82
0.60	11.10	0.0066	0.0151	0.00099	0.49	−0.29	10.81
0.70	11.26	0.0042	0.0175	0.0015	0.33	−0.48	10.78
0.80	11.42	0.0017	0.0200	0.0020	0.21	−0.72	10.70

[a] pH + log [BH]/[B].

g (20 mmol) of *tert*-butyl hydrogen malonate and 13.3 mL (40 mmol) of CH_3MgBr in ether] in 500 mL of THF. Under a nitrogen atmosphere, the addition of the enolate was completed in 30 min, after which the resulting mixture was stirred overnight at room temperature. Saturated NH_4Cl was added (4.4 mL), the solution was filtered, the filtrate was dried, and the solvent was evaporated. The residue was dissolved in 200 mL of chloroform, washed with cold 5% aqueous HOAc, saturated aqueous $NaHCO_3$, and 10% aqueous Na_2CO_3, and then dried. Evaporation of the $CHCl_3$ and chromatography of the residue 100 g of silica; EtOAc/petroleum ether (30–60 °C), 2/1] gave 1.55 g (40%) of β-keto ester **42**: NMR δ 1.45 (s, 9 H, t-C_4H_9), 1.80 (m, 2 H, CH_2 adjacent to ketal), 3.10 (m, 1 H, methine), 3.45 (s, 2 H, OCH_2CO_2), 3.95 (s, 4 H, OCH_2CH_2O), 7.35 (s, 5 H, Ar). Anal. Calcd for $C_{21}H_{27}NO_6$: C, 64.8; H, 7.0; N, 3.6. Found: C, 64.7; H, 6.9; N, 3.8.

1-Benzoyl-3-acetyl-4,4-ethylenedioxypiperidine (43). A solution of β-keto ester **42** (67 mg, 0.2 mmol) in 50 mL of glacial acetic acid was heated at 100 °C for 14 h after which the acetic acid was evaporated, and the residue was chromatographed (100 g of silica; EtOAc/petroleum ether, 1/1) to give 37 mg (75%) of ketal ketone **43**: TLC (EtOAc/cyclohexane, 2/1) R_f 0.30; NMR δ 2.20 (s, 3 H, CH_3), 4.00 (s, 4 H, OCH_2CH_2O), 7.40 (s, 5 H, Ar). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.4; H, 6.6; N, 4.8. Found: C, 66.6; H, 6.7; N, 5.0.

1-Benzoyl-3-acetyl-4,4-ethylenedioxypiperidine Oxime (44). To a solution of ketal ketone **43** (24 mg, 0.08 mmol) in 3.5 mL of H_2O was added hydroxylamine hydrochloride (11.1 mg, 0.16 mmol) and NaOAc (22.0 mg). This solution was left overnight and then extracted with methylene chloride (2 × 5 mL) which, after being dried and evaporated, gave the oxime **44** (25 mg, 100%): TLC (chloroform/methanol, 100/1) R_f 0.62; NMR δ 1.90 (s, 3 H, CH_3), 3.90 (s, 4 H, OCH_2CH_2O), 2.60 (m, 1 H, methine), 7.35 (s, 5 H, Ar). Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 62.3; H, 6.5; N, 9.0. Found: C, 62.5; H, 6.6; N, 8.8.

1-Benzoyl-3-(1-aminoethyl)-4,4-ethylenedioxypiperidine (45). A solution of oxime **44** (21.5 g, 69 mmol) in 300 mL of methanol containing ammonia (8.3 g, 0.49 mol, anhydrous) and 5% Rh/Al_2O_3 (10.5 g)[24] was hydrogenated at 40 psi of H_2 for 10 h after which H_2 uptake ceased. Filtration and evaporation left 20.5 g of crude **45**: NMR δ 1.2 (br, 5 H, CH_3, NH_2), 1.8 (br, 3 H, CH_2C–CH), 3.2–4.2 (m, 4 H, 2 NCH_2), 4.0 (s, 4 H, OCH_2CH_2O), 7.25 (s, 5 H, Ar). This material was used without further purification.

3-(1-Aminoethyl)-4,4-ethylenedioxypiperidine (46). A mixture of **45** (20.5 g, 69 mmol), $Ba(OH)_2 \cdot H_2O$ (26 g, 0.137 mmol), and water (600 mL) was refluxed for 5 h and then continuously extracted with $CHCl_3$ overnight. Evaporation of the $CHCl_3$ gave pure diamine **46** (10.1 g, 78%) as a clear liquid: NMR δ 1.13 (d, J = 7 Hz, 3 H, CH_3), 1.95 (s, 2 H, NH_2), 2.25 (d, J = 3 Hz, 1 H, CHCHN), 2.5–3.7 (m, 5 H, NCH, 2 NCH_2), 4.0 (s, 4 H, OCH_2CH_2O). This material was used without further purification for the preparation of **47**.

2-(*p*-Toluenesulfonimido)-4-methyl-6,6-ethylenedioxy-1,3-diazabicyclo[3.3.1]nonane (47). A solution of diamine **46** (10.1 g, 54 mmol) and **11** (14.9 g, 54 mmol) in 4 L of absolute ethanol was refluxed overnight. After removal of the solvent, the crude material was purified by chromatography (benzene/acetone, 100/15) to give pure **47** (10.60 g, 54%): mp 143–147 °C; TLC (benzene/acetone, 85/15) R_f 0.35; NMR δ 1.20 (d, J = 7.0 Hz, 3 H, $CHCH_3$), 1.9 (br s, 1 H, $CHCH_2$), 2.35 (s, 3 H, $ArCH_3$), 3.0–3.8 (m, NCH, 2 NCH_2), 3.85 (s, 4 H, OCH_2CH_2O), 7.25 and 7.70 (d, J = 8.5 Hz, 4 H, Ar). Anal. Calcd for $C_{17}H_{23}N_3O_4S$: C, 55.9; H, 6.3; N, 11.5. Found: C, 56.1; H, 6.1; N, 11.4.

2-(*p*-Toluenesulfonimido)-4-methyl-1,3-diazabicyclo-[3.3.1]nonan-6-one (48). A solution of ketal **47** (10.0 g, 27 mmol) and 1.25 g of *p*-toluenesulfonic acid monohydrate in cyclohexanone (140 g, 1.41 mol) was heated at 95 °C for 36 h. The cyclohexanone then was evaporated, and the residue was chromatographed (800 g of silica; benzene/acetone, 4/1) to give recovered ketal **47** (1.70 g, 17%) and ketone **48** (6.4 g, 71%): mp 191–195 °C; IR 1700 cm^{-1}; TLC (benzene/acetone, 4/1) R_f 0.53; NMR δ 1.32 (d, J = 7.0 Hz, 3 H, $CHCH_3$), 2.40 (s, 3 H, $ArCH_3$), 2.60 (br s, 1 H, NCH), 1.40–2.60 (m, 3 H, CH_2CCH), 3.35 (m, 2 H, NCH_2CH_2), 2.90–4.30 (m, 3 H, NCH, NCH_2CH), 7.35 and 7.70 (d, J = 8.0 Hz, 4 H, Ar), 8.0 (s, 1 H, NH). Anal. Calcd for $C_{15}H_{19}N_3O_3S$: C, 56.1; H, 6.0; N, 13.1. Found: C, 56.0; H, 5.6; N, 12.9.

2-Amino-4-methyl-1,3-diazabicyclo[3.3.1]non-2-en-6-one Hydrochloride (49). A solution of tosyl ketone **48** (6.1 g, 19 mmol) in 80 mL of HF was detosylated and isolated as above. Ketone **49** was eluted with 3 N HCl (25-mL fractions) and was found in fractions 28–58 (3.80 g, 98%): IR 1705 cm^{-1}; NMR δ 1.30 (d, J = 7.0 Hz, 3 H, CH_3), 1.6–2.2 (br d, 1 H, one proton of CH_2CO), 2.60 (br s, 1 H, CHCO), 2.60–2.80 (br d, 1 H, one proton of CH_2CO), 3.4 (br s, 2 H, NCH_2), 3.65 (q, J = 7.0, 2 H, NCH_2). Anal. Calcd for $C_8H_{14}N_3OCl$: C, 47.2; H, 6.9; N, 20.6. Found: C, 47.1; H, 7.0; N, 20.4.

2-(*N*-Methyl-*p*-toluenesulfonamido)-5-carboxypyrimidine (51). To a solution of sodium hydroxide (1.28 g, 32 mmol) in 100 mL of dioxane/water (1/1) was added ester **50** (9.7 g, 29 mmol). The mixture was stirred at room temperature for 8 h, by which time a clear solution had formed, and then it was lyophilized, and the residue was redissolved in 250 mL of water, acidified with 3 mL of HCl, and extracted with ether. The ether was dried and evaporated to give 8.55 g (27.5 mmol, 96%) of acid **51**, recrystallized from ethanol, mp 241–242 °C dec. Anal. Calcd for $C_{13}H_{13}N_3O_3S$: C, 50.8; H, 4.3; N, 13.7. Found: C, 51.0; H, 4.3; N, 13.6.

2-(*N*-Methyl-*p*-toluenesulfonamido)-5-[1-oxo-2-(ethoxycarbonyl)ethyl]pyrimidine (53). To a stirred solution of *N*,*N*′-thionyldiimidazole in THF was added a THF solution of the pyrimidine acid **51** (6.8 g, 20.2 mmol) and the resulting solution immediately added to a THF suspension of the magnesium complex of ethyl hydrogen malonate (25 mmol).[18] The resulting mixture was heated to reflux for 0.5 h, stirred at room temperature for 2 h, and then poured into 10 mL of 15% sulfuric acid, and the layers were separated. The aqueous phase was extracted twice with 50-mL portions of ether, and the organic extracts were combined, washed with saturated sodium bicarbonate and saturated NaCl, dried, and evaporated to dryness, leaving an oil which was chromatographed (350 g of silica, chloroform) to give β-keto ester **53**: 7.54 g (20.0 mmol, 99% yield); bp 175 °C (0.03 mm). Anal. Calcd for $C_{17}H_{19}N_3O_5S$: C, 54.1; H, 5.1; N, 11.1. Found: C, 54.3; H, 5.2; N, 11.0.

2-(*N*-Methyl-*p*-toluenesulfonamido)-5-[1,1-ethylenedioxy-2-(ethoxycarbonyl)ethyl]pyrimidine (54). To a solution of β-keto ester **53** (0.6 g, 1.6 mmol) in 15 mL of benzene were added ethylene glycol (2.0 mL, 32 mmol) and *p*-toluenesulfonic acid hydrate (12 mg). The mixture was heated to reflux for 48 h, with 3A molecular sieves in a Soxhlet extractor to remove the water formed, cooled, washed with saturated sodium bicarbonate and saturated NaCl, dried, evaporated, and chromatographed (60 g of silica, chloroform). Four products were eluted in the following

order and amounts: β-keto ethyl ester, 0.05 g; ketal ethyl ester, 0.41 g; β-keto glycol ester, 0.02 g; ketal glycol ester, 0.18 g. The ketal esters were obtained in a 98% yield, based on consumed starting β-keto esters. Ketal ethyl ester **54**: IR ($CHCl_3$) 5.78, 6.28 μm; UV λ_{max} 237 nm (ε 23 600), 226 (24 300). Anal. Calcd for $C_{19}H_{23}N_3O_6S$: C, 54.2; H, 5.5; N, 10.0. Found: C, 54.3; H, 5.5; N, 10.1.

2-(*N*-Methyl-*p*-toluenesulfonamido)-5-[1,1-ethylenedioxy-2-(ethoxycarbonyl)ethyl]-1,4,5,6-tetrahydropyrimidine (55). To a solution of pyrimidine **54** (1.30 g, 3.1 mmol) in 20 mL of glacial acetic acid was added 6.2 mL of 0.5 M HCl in acetic acid. Platinum oxide (0.5 g) was added, and the mixture was shaken with hydrogen for 10 h, by which time the uptake of hydrogen had ceased. The catalyst was removed, the filtrate was evaporated, and the residual oil was dissolved in chloroform, washed with sodium bicarbonate and NaCl solutions, dried, concentrated to a small volume, and chromatographed (120 g of silica, 3% ethanol/chloroform) to give 1.04 g (2.4 mmol, 79% yield) of **55**: UV λ_{max} 228 nm (ε 17 100); mass spectrum *m/e* 361, 360 ($M^+ - 64$, 65). Anal. Calcd for $C_{19}H_{27}N_3O_6S$: C, 53.6; H, 6.4; N, 9.9. Found: C, 53.6; H, 6.2; N, 9.9.

2-(*N*-Methyl-*p*-toluenesulfonamido)-5-(1,1-ethylenedioxy-3-hydroxypropyl)-1,4,5,6-tetrahydropyrimidine (56). To a solution of THF containing ester **55** (130 mg, 0.3 mmol) was added 1.5 mL of 1 M B_2H_6 in THF, and the solution was stirred at room temperature for 8 h. The excess diborane and organoboron complexes were decomposed with methanol, the solution was concentrated, and the residue was chromatographed on alumina to give 88 mg (0.2 mmol, 73%) of alcohol **56**: mp 119.5–122.0 °C. Anal. Calcd for $C_{17}H_{25}N_3O_5S$: C, 53.3; H, 6.6; N, 11.0. Found: C, 53.0; H, 6.5; N, 10.8.

2-(*N*-Methyl-*p*-toluenesulfonamido)-5-(1,1-ethylenedioxy-3-chloropropyl)-1,4,5,6-tetrahydropyrimidine (57). A mixture composed of alcohol **56** (0.25 g, 0.65 mmol), triphenylphosphine (0.34 g, 1.3 mmol), and 5 mL of carbon tetrachloride (distilled from P_2O_5) was heated to reflux for 6 h.[20,26,27] The reaction mixture was evaporated to dryness, and the residue was dissolved in chloroform and chromatographed (50 g of silica, 3% ethanol/chloroform). Combination of the fractions containing only product gave 90 mg of **57** (0.22 mmol, 34% yield), with 35 mg of product contaminated with triphenylphosphine oxide. Short-path distillation of the eluted material gave **57** as an oil which slowly crystallized (125 mg, 47%), mp 150–158 °C. Anal. Calcd for $C_{17}H_{24}N_3O_4SCl$: C, 50.8; H, 6.0; N, 10.4. Found: C, 50.7; H, 6.1; N, 10.2.

2-(*N*-Methyl-*p*-toluenesulfonamido)-6,6-ethylenedioxy-1,3-diazabicyclo[3.3.1]non-2-ene (33). Tosylamido ketal chloride **57** (86 mg, 0.21 mmol) was dissolved in 10 mL of dry toluene, excess anhydrous potassium carbonate was added, and the mixture was heated at reflux for 48 h. The mixture was cooled and filtered, the filtrate was evaporated to dryness, and the residue was chromatographed on alumina (15 g, neutral, activity III, chloroform) to give 75 mg (94%) of **33**, identical with material prepared from **28** by methylation: mp 184–186 °C, after crystallization from hexane–benzene; NMR δ 1.42 (m, 2 H, $COCH_2$), 1.7 (m, 1 H, methine), 2.33 (s, 3 H, $ArCH_3$), 3.1 (s, 3 H, NCH_3), 2.6–3.6 (m, 4 H, NCH_2CH_2), 3.44 (d, 2 H, NCH_2CH), 3.82 (s, 4 H, OCH_2CH_2O), 7.13 and 7.68 (2 d, 4 H, Ar); IR 6.06 cm^{-1}; UV λ_{max} 226 nm; mass spectrum *m/e* 301, 300 ($M^+ - 64 - 65$), 278, 277. Anal. Calcd for $C_{17}H_{23}N_3O_4S$: C, 55.9; H, 6.3; N, 11.5. Found: C, 55.9; H, 6.1; N, 11.3.

pK_a Determination of Bicyclic Guanidino Ketones. The pK_a's were determined by using a Corning Digital 110 pH meter with a semimicro combination electrode with a triple-purpose glass membrane. Carbon dioxide free water was used to prepare CO_2-free potassium hydroxide (1.0 N) and to dissolve the guanidine hydrochlorides (approximately 100 mg). Titrations were conducted in a closed 100-mL vessel fitted with a rubber stopper which had ports for a buret, thermometer, nitrogen inlet and outlet, and electrode. The procedure as described[15] was used. Compound **30** will be used as an example; all were run in an identical manner. Compound **30** (164 mg, 0.865 mmol) was dissolved in 40 mL of water and then titrated. The results are shown in Table IV. Rows 3–9 give an average pK of 10.78 ± 0.08. The pK_a's for the other guanidines are listed in Table II.

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Registry No. **4**, 1886-67-5; **5b**, 5616-81-9; **6b**, 71766-73-9; **7b**, 71785-29-0; **8**, 71785-28-9; **11**, 2651-15-2; **12**, 6291-84-5; **13**, 71766-74-0; **14**, 71766-75-1; **17**, 23099-21-0; **17**·2HCl, 71766-76-2; **18**, 71766-77-3; **19**, 71766-78-4; **20**, 4451-86-9; **21**, 71785-32-5; **22**, 71766-79-5; **22**·Li, 71766-80-8; **23**, 71785-33-6; **24**, 71766-81-9; **25**, 71766-82-0; **26**, 71766-83-1; **27**, 71766-84-2; **28**, 71766-85-3; **29**, 71766-86-4; **30**, 71766-87-5; **31**, 71766-88-6; **32**, 71766-89-7; **33**, 71766-90-0; **34**, 71766-91-1; **35**, 71766-92-2; **37**, 71766-93-3; **38**, 18805-25-9; **39**, 71766-94-4; **40**, 71766-95-5; **42**, 71766-96-6; **43**, 71766-97-7; **44**, 71766-98-8; **45**, 71766-99-9; **46**, 71767-00-5; **47**, 71767-01-6; **48**, 71767-02-7; **49**, 71767-03-8; **50**, 38653-04-2; **51**, 71767-04-9; **53**, 71767-05-0; **54**, 71767-06-1; **55**, 71798-61-3; **56**, 71798-62-4; **57**, 71767-07-2; 2-methylsulfonimido-3,4-dimethyl-1,3-diazabicyclo-[3.3.1]nonan-6-one, 71767-08-3; 2-methylsulfonimido-3,4-dimethyl-1,3-diazabicyclo[3.3.1]nonan-6,6-diol, 71767-09-4; 2-methylsulfonimido-3,4-dimethyl-1,3-diazabicyclo[3.3.1]nonane, 71767-10-7; potassium *tert*-butoxide, 865-47-4; 3-cyanopyridine, 100-54-9; carbonyldiimidazole, 530-62-1; ethyl hydrogen malonate magnesium complex, 64679-38-5.

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Reactions of Ketenimines with Nitrones

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Dimethylketene-*N*-phenylimine reacts with benzylideneaniline *N*-oxides and cinnamylideneaniline *N*-oxide to give the corresponding 1:1 adducts, 1-(*o*-(benzylideneamino)phenyl)-1,1-dimethylacetanilides, which are easily hydrolyzed to 3,3-dimethyloxindole, whereas the reaction of the ketenimine with cyclic nitrones such as 1-pyrroline 1-oxides afforded 1:1 adducts, imidazolidinone and/or diazaspiro[4.4]nonanone derivatives. In the reaction of diphenylketene-*N*-phenylimine with cyclic nitrones, a perhydropyrrooxadiazinone or imidazolidinone is formed, depending on the nature of cyclic nitrones.

During the course of the study on the reaction of 1,2-diphenyl-1-azaspiro[2.2]pentane with benzylideneaniline *N*-oxide, we found that phenylketene-*N*-phenylimine, generated in situ from the azaspiropentane, reacted with the nitrone to give 2,3,4,5-tetrahydro-2,3,5-triphenyl-1*H*-benzo[*f*]-1,3-diazepin-4-one and its ring opening isomer,

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