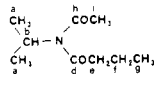
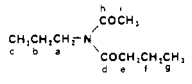
IR spectrum (neat) showed characteristic absorptions at 3000 (OH), 1700 (C=O), and 2120 (C—D) cm^{-1}.

***N*-Isopropyl-*N*-acetylbutyramide (14).** Samples of **14** have been synthesized by an independent route as reported:[17] ^1H NMR (CCl_4) 0.94 (t, 7 Hz, H_g), 1.37 (d, 7 Hz, H_a), 1.63 (sextet, 6.5 Hz, H_f), 2.24 (s, H_i), 2.59 (t, 6.5 Hz, H_e), 4.21 (septet, 7 Hz, H_b); ^{13}C NMR ($DCCl_3$) 13.6 (C_g), 18.4 (C_f), 20.4 (C_a), 26.5 (C_i), 39.8 (C_e), 49.1 (C_b), 172.4 (C_h), 175.9 (C_d).



***N*-*n*-Propyl-N-acetylbutyramide (15).** Butyryl chloride (22 g, 0.2 mol) was added to 25 g (0.2 mol) of *N*-*n*-propylacetamide in the presence of 15.5 mL (0.2 mol) of anhydrous pyridine. After 5 h of reflux, the cold reaction mixture was treated with water and extracted with ether. After removal of the solvent from the dried organic layer, **15** was purified by column chromatography (silica gel, Merck 60, 0.063-0.2). The yield was 55 mmol (27%). The product gave correct elemental and mass spectral analyses. Futher characterization is based on its IR absorption (neat) at 1690 (C=O) and both ^1H NMR and ^{13}C NMR spectra: ^1H NMR (CCl_4) 0.9 and 0.92 (t, 6.5 Hz, H_c and H_g), 1.2-2.0 (m, H_b and H_f), 2.3 (s, H_i), 2.63 (t, 7 Hz, H_e), 3.61 (t, 7.5 Hz, H_a); ^{13}C NMR ($DCCl_3$) 11.3 (C_c), 13.7 (C_g), 18.3 (C_f), 22.6 (C_b), 26.4 (C_i), 39.5 (C_e), 46.0 (C_a), 172.4 (C_h), 175.9 (C_d).



Electrolysis. General. The electrolyses were performed in a closed 300-mL Tacussel reactor system equipped with a thermostated (25 °C) double-wall water jacket and a magnetic stirrer. The chamber of the Pt anode was separated from the cathode by an alumina crucible and equipped with a gas carrier system. The anodic potential was kept constant at 2 V relative to the calomel electrode (potentiostat, Tacussel Model PRT 40-1X). The current used in the electrolysis was determined by means of an in-line integrator placed in the cathodic circuit.

Electrolyses were performed on 300-L solutions of 30–50 mmol of butyric acid in the presence of 30 mol% potassium hydroxide in wet acetonitrile (3% (v/v) water). Gaseous products were swept from the anode chamber by a weak current of nitrogen. After passage through a $CaCl_2$/Ascarit tower, they were collected in a trap system cooled with liquid air. Redistilled samples were used for mass spectrometry and NMR analysis, the latter being condensed into CCl_4 and then sealed. The relative composition of the gaseous mixture was determined by ^1H NMR integration. Absolute yields are based on the material balance.

Acetonitrile was removed from the liquid phase of the reaction mixture by vacuum distillation. The products were then dissolved in methylene chloride and treated with 5% aqueous sodium bicarbonate solution to eliminate any remaining butyric acid. After the organic layer was dried over $MgSO_4$ and the solvent was removed, the products were purified by chromatography. Either column chroamtography on silica gel (Merck 60, 0.063-0.2) or preparative TLC on silica gel (Merck 60) was used. Unelectrolyzed butyric acid was recovered from the aqueous phase by acidification and exhaustive extraction with CH_2Cl_2.

The identification of all products is based on comparison of their chromatographic, mass spectrometric, and NMR spectroscopic features with authentic samples.

Electrolysis of Butyric Acid. Butyric acid (4.4 g, 50 mmol) was electrolyzed according to the general procedure given above. Starting material (25%) was recovered unchanged. The current used integrated to 8900 C; i.e., 2.5 electrons per molecule were consumed. The products and their yields after purification are compiled in Table I. In addition, a small quantity of *n*-propyl butyrate (<2%) was isolated from this run.

The ^1H NMR spectrum of the gaseous products is shown in Figure 1a. The ^1H NMR, ^{13}C NMR, and mass spectra of **14** and **15** (not separated from each other) are in full agreement with those of the authentic samples.

Electrolysis of 2,2-Dideuteriobutyric Acid. The labeled acid (2.9 g, 32 mmol) was electrolyzed as indicated in the general procedure above. Starting material (12%) was recovered when 4750 C had passed through the cell. This amounts to a pickup of 1.82 electrons per molecule.

The relative deuterium distribution in the products was determined from the computer-integrated ^2H-(^1H) FT NMR spectra and is compiled in Table I (see also Figure 1b and 2). The line intensities, isotope shift effects, and off-resonance multiplicities in the ^{13}C NMR spectra of **14d** and **15d** are in agreement with the deuterium distribution shown in Table I. However, quantitative information based on the ^{13}C NMR spectra, as reported in a preliminary note, is clearly less reliable than the direct ^2H NMR spectroscopic analysis presented here.

Registry No. 6, 461-55-2; **10**, 74-98-6; **11**, 110-54-3; **12**, 115-07-1; **13**, 75-19-4; **14**, 21855-95-8; **15**, 74432-12-5; 2,2-dideuteriobutyric acid, 19136-92-6; benzyl propionate, 122-63-4; 1,1-dideuteriopropanol, 40422-04-6; 1,1-dideuterio-*n*-propyl bromide, 40422-05-7; butyryl chloride, 141-75-3; *N*-*n*-propylacetamide, 5331-48-6; 2,2-dideuteriobutyrate ion, 58978-98-6.

Syntheses and Stereochemistry of Amidoximes

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The configuration and tautomeric structure of a variety of amidoximes have been examined. The compounds studied were simple acyclic amidoximes possessing alkyl substituents and cyclic amidoximes including thiomorpholines, piperazines, imidazolidines, and 2-iminothiazolidines. The syntheses of these novel amidoximes are described along with NMR determinations of the stereochemistry of the oxime moiety. Factors determining the configuration and tautomeric structure of amidoximes are also discussed.

Configuration (*E* vs. *Z* isomers), conformation, and tautomerism are important characteristics associated with amidoximes. Although amidoximes have been known since the late 1800's, a review by Eloy and Lenaers[1] in 1962 only briefly mentioned the tautomeric question and did not address the configuration and/or conformation problems. Considerable work has been done since 1960 in determining these properties for simple amidoximes such as benzamidoximes,[2-7] formamidoxime,[2-8] and *N*,*N*-di-

(1) F. Eloy and R. Lenaers, *Chem. Rev.*, **62**, 155 (1962).

(2) O. Exner and N. Motekov, *Collect. Czech. Chem. Commun.*, **43**, 2740 (1978).

(3) O. Exner, *Collect. Czech. Chem. Commun.*, **30**, 652 (1965).

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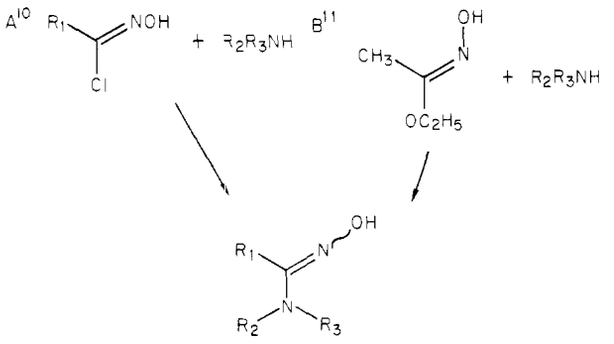
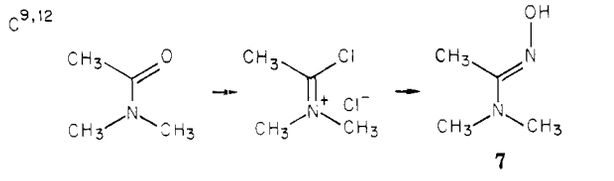
Scheme I



	method	R_1	R_2	R_3
1	B	CH_3	CH_3	H
2	B	CH_3	n-C_4H_9	H
3	A	$(CH_3)_2CH$	n-C_3H_7	H
4	B	CH_3	$CH_2CH_2OCH_2CH_2$	
5	B	CH_3	$-(CH_2)_4-$	
6	B	CH_3	$-(CH_2)_5-$	



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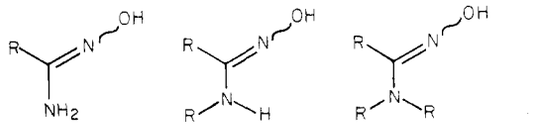
methylacetamidoxime.[9] These studies indicate that there is a major configurational difference between unsubstituted amidoximes (I) or their *N*-alkyl analogues (II) and the *N*,*N*-dialkyl derivatives (III).



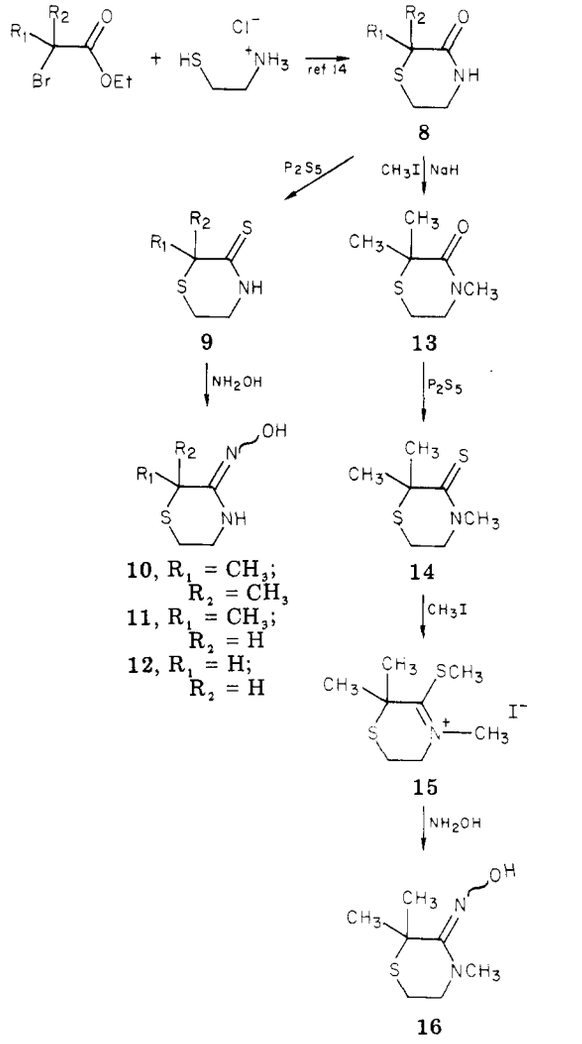
I II III

The factors governing the configuration of amidoximes have been derived from compounds with limited structural variation. As part of a pesticide discovery project, we have prepared a wide variety of novel amidoximes that have allowed us to test the generality of the rules governing the configuration of benzamidoximes and to expand those rules to include more complex amidoximes. This paper deals with the effects of major structural changes, substituents, methods of synthesis, and workup on the configuration of acyclic and cyclic amidoximes with a brief mention of an unusual tautomeric form.

Synthesis

The acyclic amidoximes were prepared by one of three standard reactions listed in Scheme I. Reaction B required temperatures >80 °C with the amine in large excess. In contrast, reaction A could be done at lower temperatures (0–25 °C) with an equimolar reactant ratio. Reaction A was not used when $R_1 = CH_3$ because of the instability of acetohydroxamoyl chloride.[13]

Scheme II



10, $R_1 = CH_3$; $R_2 = CH_3$
11, $R_1 = CH_3$; $R_2 = H$
12, $R_1 = H$; $R_2 = H$

Four novel classes of five- and six-membered cyclic amidoximes were prepared in this study: (1) 3-oximinothiomorpholines, (2) 2-oximinopiperazines, (3) 4-oximinoimidazolidines, and (4) 2-imino-4-oximinothiazolidines.

The oximinothiomorpholines were prepared as described in Scheme II.

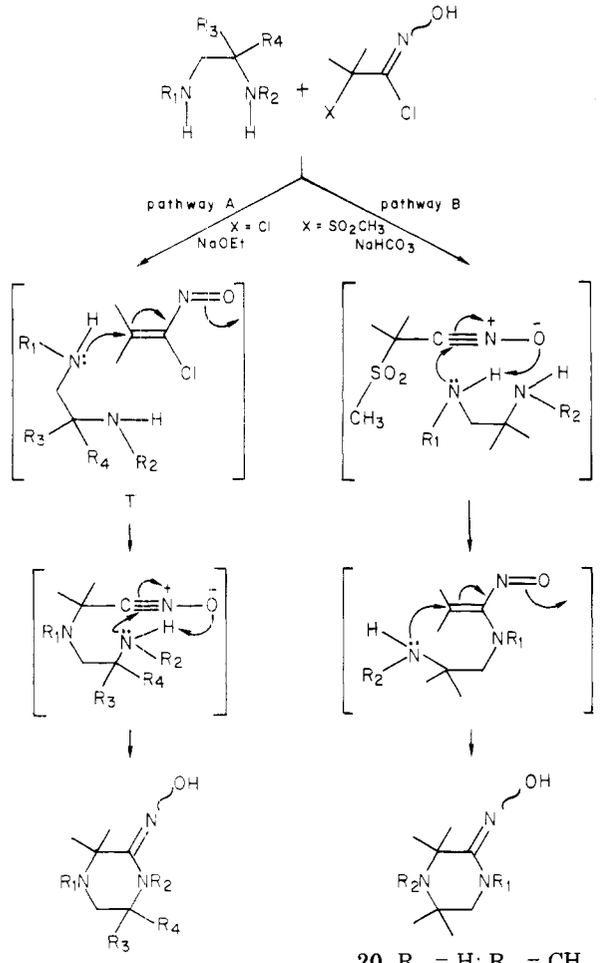
Treatment of **14** with hydroxylamine gave no reaction. Therefore, intermediate **15** was prepared which could be converted to **16** by reaction with hydroxylamine.

The 2-oximinopiperazines were prepared by reacting a substituted ethylenediamine with hydroxamoyl chloride as outlined in Scheme III.

When X = Cl (pathway A) 2-chloro-2-methylpropanehydroxamoyl chloride loses hydrogen chloride, preferentially via a 1,4-elimination,[15] to form the nitroso olefin which reacts with the amine in a "Michael-like" fashion. This mechanism would favor the more nucleophilic and/or less sterically hindered nitrogen reacting at the β-position, thus giving compounds **17**–**19**. The NMR shifts of the *N*-methyl signals are consistent with these products. The presence of the disubstituted free amine (**17** and **19**) is also

(4) O. Exner, V. Jehlička, A. Dondoni, and A. Boicelle, *J. Chem. Soc., Perkin Trans. 2*, 567 (1974).
(5) C. Venkatesh, R. Srivastava, and I. Brinn, *J. Chem. Soc., Perkin Trans. 2*, 873 (1979).
(6) K. Dignam and A. Hegarty, *J. Chem. Soc., Chem. Commun.*, 862 (1976).
(7) J. Mollin and F. Kašpárek, *Collect. Czech. Chem. Commun.*, **26**, 1882 (1961).
(8) D. Hall, *Acta Crystallogr.*, **18**, 955 (1965).
(9) D. Bright, H. Plessius, and J. de Boer, *J. Chem. Soc., Perkin Trans. 2*, 2106 (1973).
(10) A. Werner and C. Bloch, *Ber. Dtsch. Chem. Ges.*, **32**, 1975 (1899).
(11) W. Lossen, *Justus Liebigs Ann. Chem.*, **252**, 214 (1889).
(12) Ciba Geigy Corp., German Offen. 2 132 598, 1972.
(13) A. Brandi, F. DeSarto, and A. Guarna, *J. Chem. Soc., Perkin Trans. 1*, 1827 (1976).
(14) H. Lehr, S. Karlan, and M. W. Goldberg, *J. Med. Chem.*, **6**, 136 (1963).
(15) A. Dornow, H. D. Jordan, *Ber. Dtsch. Chem. Ges.*, **94**, 76 (1961).

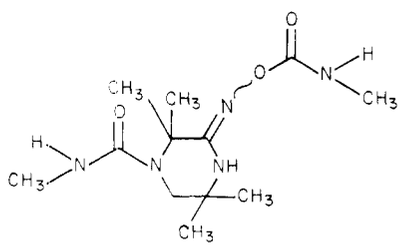
Scheme III



17, R_1 = H; R_2 = CH_3; R_3 = H; R_4 = H
18, R_1 = CH_3; R_2 = CH_3; R_3 = H; R_4 = H
19, R_1 = H; R_2 = H; R_3 = CH_3; R_4 = CH_3

20, R_1 = H; R_2 = CH_3

confirmed by its facile reaction with methyl isocyanate (MIC), a reaction that does not occur with the nonnucleophilic nitrogen of an amidoxime. The relative NMR shifts of **19** to its diadduct **19a** also support the assignments as given (for NMR data, see Table II).

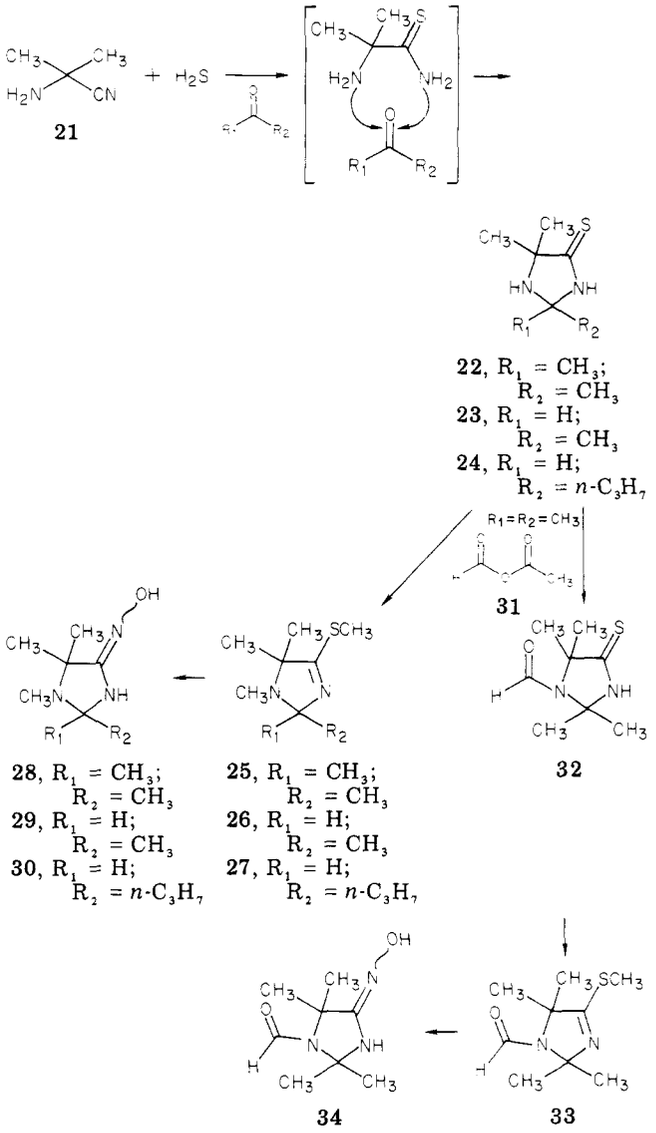


19a

When X = SO_2CH_3 (pathway B, Scheme III), the direction of addition was altered according to the mechanism as diagramed in Scheme III. This allowed the preparation of the β-*N*-methylpiperazine oxime (**20**), unavailable through pathway A. The NMR shifts are consistent with **17** and **18**. Also, **20** reacts with only 1 equiv of MIC.

The yield of oximes prepared in Scheme III ranged from 6% to 44%. These low yields were attributed in part to the hygroscopic nature of the oxime. The corresponding carbamates proved to be much easier to manipulate and purify.

Scheme IV



22, R_1 = CH_3; R_2 = CH_3
23, R_1 = H; R_2 = CH_3
24, R_1 = H; R_2 = *n*-C_3H_7

28, R_1 = CH_3; R_2 = CH_3
29, R_1 = H; R_2 = CH_3
30, R_1 = H; R_2 = *n*-C_3H_7

25, R_1 = CH_3; R_2 = CH_3
26, R_1 = H; R_2 = CH_3
27, R_1 = H; R_2 = *n*-C_3H_7

The oximinoimidazolidines were prepared as outlined in Scheme IV.

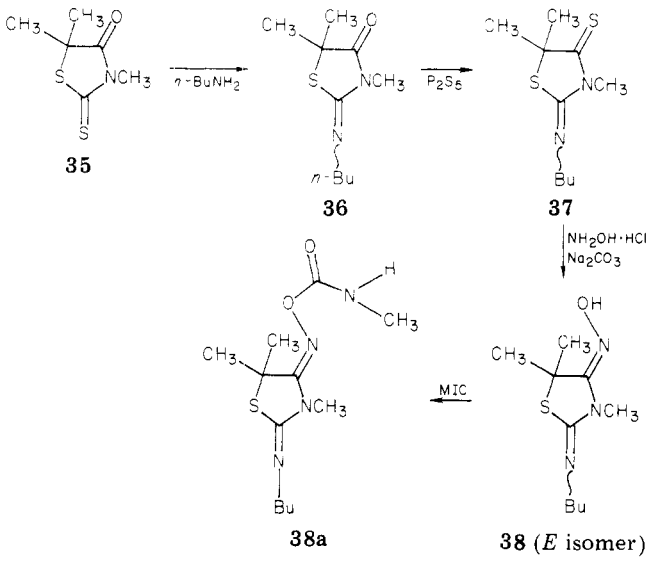
The thioamide **22** was prepared according to the procedure described by Gatewood and Johnson.[16] Compounds **23** and **24** were easily prepared from the appropriate aldehydes. The thioamides were converted to the oxime via standard procedures.

The oximino-2-iminothiazolidines were prepared by two independent syntheses (Scheme V and Scheme VI).

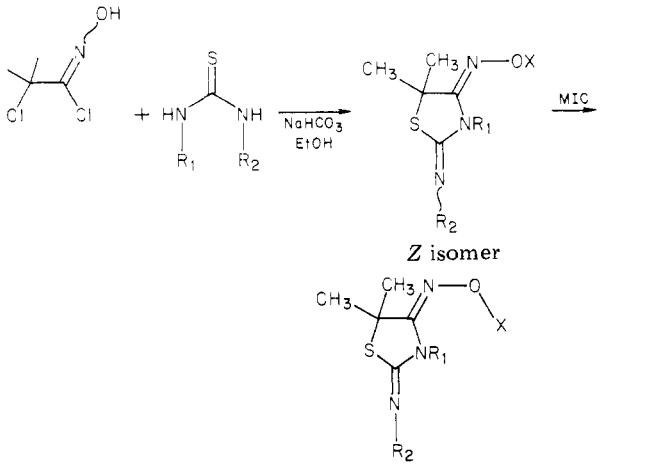
The sequence shown in Scheme V was reported in a 1975 patent by Imperial Chemical Industries.[17] The importance of the base in the preparation of **38** is of some interest. When **37** was treated with hydroxylamine hydrochloride, pyridine, and ethanol, the thioamide oxime **42** (Scheme VII) was obtained in 36% yield. This unexpected result can be explained by comparing the base strength of the imino nitrogen to that of the added base, i.e., pyridine. If the imino nitrogen of **37** were the stronger "base" relative to pyridine, it would be preferentially protonated by the HCl. Such protonation could cause this nitrogen function to be a more facile leaving group than is the thiocarbonyl moiety, resulting in the formation of **42**. By using a slightly stronger base, e.g., sodium bicarbonate, we obtained a

(16) E. Gatewood and T. B. Johnson, *J. Am. Chem. Soc.*, **50**, 1427 (1928).
(17) Imperial Chemical Industries, U.S. Patent 3 904 759, 1975.

Scheme V



Scheme VI



39, $R_1 = n\text{-}C_4H_9$; $R_2 = CH_3$; X = H
40, $R_1 = CH_3$; $R_2 = n\text{-}C_4H_9$; X = H
41, $R_1 = CH_3$; $R_2 = CH_3$; X = H
39a, $R_1 = n\text{-}C_4H_9$; $R_2 = CH_3$; X = $CONHCH_3$
40a, $R_1 = CH_3$; $R_2 = n\text{-}C_4H_9$; X = $CONHCH_3$
41a, $R_1 = CH_3$; $R_2 = CH_3$; X = $CONHCH_3$

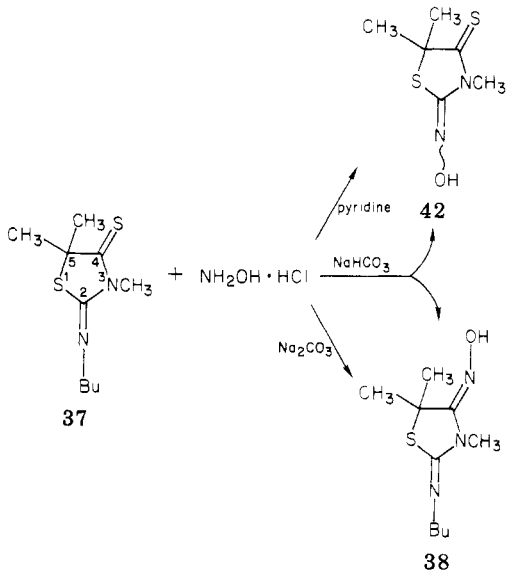
mixture of **42** and **38**, and, finally, sodium carbonate gave only the desired oxime **38**.

The one-step procedure outlined in Scheme VI gives a 1:1 mixture of **39** and **40** in a 47% yield. This mixture was treated with methyl isocyanate to prepare the carbamates **39a** and **40a** which could be separated by chromatography. The following NMR data were used in distinguishing **39a** from **40a**. Since the position of the butyl and methyl moieties of **38a** are unequivocally assigned on the basis of the synthetic route, the NMR shifts of **38a** were used in the shift assignments in **39a** and **40a**. The differences in the *gem*-dimethyl (δ 1.90) and *N*-methyl (δ 3.20) shift of **38a** in comparison with those found with **40a** (δ 1.70 and 3.66, respectively) may be explained by assigning the *Z* configuration to **40a** and the *E* configuration to **38a**. The carbamate **41a** was prepared via Scheme VI, and its NMR shifts agree with those of **40a** and **39a**.

Discussion

Numerous techniques have been used to determine the configuration, conformation, and tautomeric structure of amidoximes in the solid state and in solution. These include X-ray,[8,9] dipole moment,[2-4] IR,[7] NMR[4,18,19] and

Scheme VII

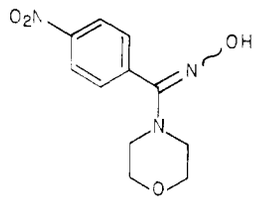


melting point[20] techniques and cyclization reactions.[20] Since we were not concerned with conformation studies[2-7] and the tautomer structure has been determined to be in favor of the oximino form,[21] our investigations were directed to (*E* vs. *Z*) configurational determinations. NMR provided the optimum analytical technique due to both speed and simplicity. Where both isomers were present, the NMR signals could be identified by relative shifts on the basis of the deshielding effect of the hydroxy moiety. When only one isomer was present, assignments by NMR are tenuous but were made on the basis of trends within a series or by using NMR shifts of analogues.

The exploration of amidoximes was initiated by studying a series of mono- and dialkyl acyclic amidoximes (see Scheme I).

Amidoxime **3** prepared via method A was isolated as a single isomer. This was assigned the "*Z*" configuration on the basis of the bulk at R_1, the presence of the NH moiety (R_3 = H), and literature precedent which suggests that hydroxamoyl chlorides react through a nitrile oxide intermediate which favors formation of the "*Z*" isomer.[18] Method C also gave a single isomer (**7**), previously identified as having the "*E*" configuration.[9] The configuration of oximes obtained from method B of Scheme I (**1**, **2**, **4**–**6**) was influenced by substituents, reaction time, and workup procedure. When **1** was prepared under conditions involving a 24-h reflux period, a mixture of *E* and *Z* isomers ($E \gg Z$) was isolated. When the mixture was refluxed for 2.5 days, only the *E* isomer was detected. In the case of **2**, a 1:3 mixture of *E* and *Z* isomers was isolated even after a reflux period of 3 days. In the preparation of **4**, we noticed an isomerization analogous to that reported by Dignam,[6] who, in 1976, reported the first isolation, characterization, and interconversion of the *Z* and *E* isomers, utilizing morpholino-*p*-nitrobenzamidoxime (**43**). When excess morpholine was reacted with ethyl *N*-hydroxyacetamidate, the crude product was found to be a mixture of isomers ($E > Z$). Heat or chromatography on silica gel

(18) (a) K. Dignam, A. Hegarty, and P. Quain, *J. Chem. Soc., Perkin Trans. 2*, 1457 (1977); (b) K. Dignam, A. Hegarty, and P. Quain, *J. Org. Chem.*, **43**, 388 (1978).
(19) G. Elitropi, E. Panto, and S. Tricerri, *J. Heterocycl. Chem.*, **16**, 1545 (1979).
(20) J. Barassin, J. Armand, and H. Lumbroso, *Bull. Soc. Chim. Fr.*, 3409 (1969).
(21) C. Bell, C. Namburg, and L. Baurer, *J. Org. Chem.*, **29**, 2873 (1964).



43

caused complete isomerization of the *Z* isomer to the more stable *E* isomer (see Scheme VIII).

If the mixture of isomeric oximes was immediately treated with methyl isocyanate, however, a thermally stable mixture of *E* and *Z* carbamates **4a** was obtained from which the *E* isomer was selectively precipitated, leaving a solution considerably enriched in the *Z* isomer. In the cases of **5** and **6**, a single isomer was obtained to which the "*E*" configuration was assigned.

Table I lists a series of oximinothiomorpholines and carbamates studied in this program, with their respective configurational assignments.

The "*Z*" configuration of **10** was assigned by comparing its *gem*-dimethyl shift (δ 1.50) with those of **9** (*E* δ 1.67, *Z* δ 1.43). The "*E*" configuration of **12** is a logical conclusion based on the trend established by oxime **11**, and the assignment is reinforced by its NMR spectrum. In 5% Me_2SO-d_6 the methylene protons α to the oxime are represented by a sharp singlet. On addition of D_2O this singlet changes to a multiplet, indicating possible interaction between the hydroxyl proton with the adjacent methylene. Such perturbation could arise as a result of the "*E*" configuration.

The thiomorpholine series demonstrates the importance of the *gem*-dimethyl substituents (**10** vs. **11** and **12**) and the effect of the second nitrogen substituent (**10** vs. **16**).

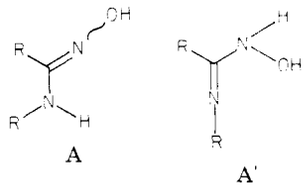
The steric interactions demonstrated by the thiomorpholines extended to the piperazine oximes. Table I lists the configurational assignments of the oximinopiperazine and carbamate derivatives.

Comparison of **17** to **19** or **18** to **20** again shows the effect of a disubstituted α-nitrogen, previously seen in the thiomorpholine series. A more subtle effect is that seen in comparing **17** and **18**. The oxime moiety is so sensitive to steric interactions from α substituents that the buttressing effect, through the α,α-*gem*-dimethyls of a methyl group on the β-nitrogen, is expressed in the oxime configuration.

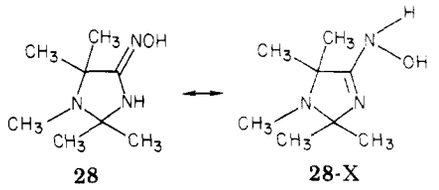
It should be mentioned at this time that the oxime *E*/*Z* ratios listed in Tables I and II were determined on the crude product mixtures. This ratio is stable to longer reaction times, heat, and chromatography on silica gel. The *E*/*Z* ratio of the carbamate for a given pair differs from that of the corresponding oxime. This may be attributed to steric interactions affecting either the rate of reactivity of the oxime isomers or the equilibrium of the final carbamate. In every case the ratio is shifted toward the "*E*" isomer, implying more steric interactions from the α-nitrogen position than from the α-carbon substituents. This interaction is easily seen by using molecular models if one assumes planarity within the amidoxime moiety.

Previously we mentioned that the tautomer structure of amidoximes has been decided in favor of the oximino form A.[21] In the imidazolidine series, we found a case where the hydroxylamino form A′ could be isolated.

Although only a single configurational isomer was isolated in the cases of the imidazolidine oximes,[22] an unexpected tautomerization of compound **28** was discovered. Along with the expected oximino form **28** (1680 cm^{-1}), we obtained the hydroxylamine **28**-X (1605 cm^{-1}; see ref 23),



A A′



28 **28**-X

in a 3:1 ratio, respectively. If pure **28**-X was heated (90 °C) in Me_2SO-d_6, a thermally stable 50:50 equilibrium mixture of **28** and **28**-X was obtained. This tautomerization may result from the strain of the imidazolidine ring and/or the steric interactions of the five methyl groups. The former seems less likely since the tetrasubstituted derivatives **29**, **30**, and **34** did not exhibit similar tautomerism. Therefore, this phenomenon may be associated with the steric interactions of pentaalkyl-substituted imidazolidines.

The 2-iminothiazolidines illustrate the importance of the method of preparation in determining the final oxime configuration. The difference in configuration of **38** and **40** is attributed to two completely different mechanisms of formation combined with a slow rate of isomerization of the resulting amidoximes. Experiments have demonstrated that the *N*,*N*-dimethyl analogue **41** may be thermally isomerized to the "*E*" isomer. Compound **40** (Scheme VI) is the kinetic product formed from the nitrile oxide intermediate. Gozlan et al.[24] explained this stereoselectivity by a reaction analogous to a 1,3-dipolar addition (Scheme IX).

Conclusion

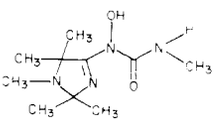
A factor that repeatedly proved to be important to the configuration and tautomeric structure in our studies was the steric interactions of the α-carbon, the α-nitrogen, and even the substituents in the β-position. Although this is analogous to the benzamidoxime cases, we do feel the importance of the α-carbon substituents has not been fully appreciated. The other prevalent factor, especially in the N,N-disubstituted amidoximes, is the method of preparation and subsequent workup.

Experimental Section

General Methods. All melting points are uncorrected. IR spectra were taken on a Perkin-Elmer Model 137 spectrometer. NMR spectra were obtained on either a Varian A-60 or a Varian EM-360 at 60 MHZ with $(CH_3)_4Si$ as an internal standard. C, H, and N elemental analyses were performed by the Technical

(22) By analogy to previous cases, we assume the imidazolidine oximes are the "*Z*" configuration.

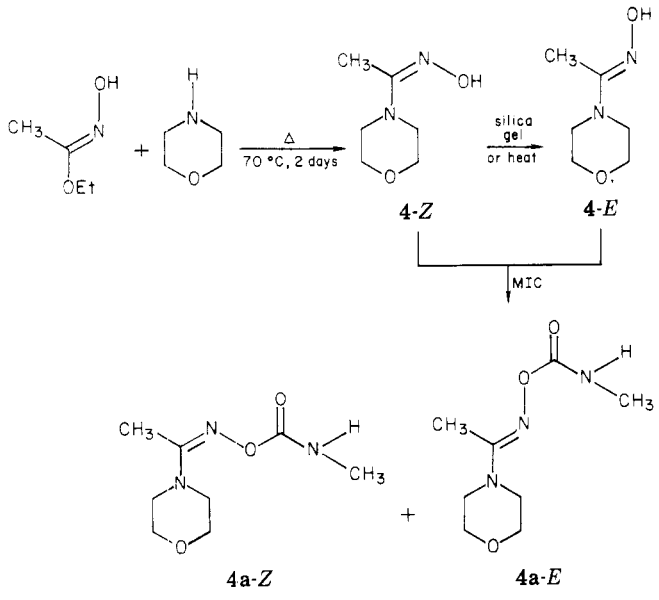
(23) Treatment of **28**-X with MIC gave the *N*-hydroxyurea compound i with correct NMR and IR, mp 161–162 °C.



i

(24) H. Gozlan, R. Michelot, C. Riche, and R. Rips, *Tetrahedron*, **33**, 2535 (1977).

Scheme VIII



Scheme IX

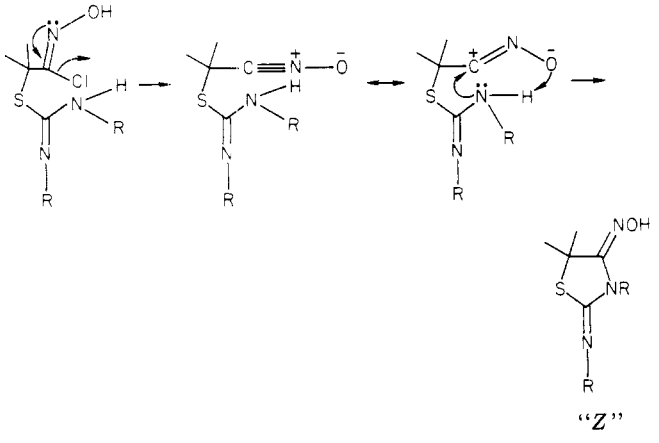


Table I

	oxime		carbamate	
compd	*Z*	*E*	*Z*	*E*
10	100	0	100	0
16	80	20	66	33
11	<10	>90	0	100
12	0	100	0	100
17	35	65	0	100
18	50	50	20	80
19	100	0	100	0
20	100	0	100	0

Center Analytical Group; S elemental analyses were performed by Schwarzkopf Microanalytical Laboratory.

Method A. *N*-*n*-Propyl-2-methylpropionamide Oxime (3). A 11.69-g (86.2 mmol) quantity of 2-methylpropanehydroxamoyl chloride was dissolved in 300 mL of ethyl ether and cooled to 0 °C. To this was added dropwise 11.23 g (190 mmol) of *n*-propylamine. Following the addition, the reaction mixture was allowed to warm to 25 °C and stir overnight. Filtration and concentration in vacuo gave 13.1 g (96%) of **3**.

Method B. General Procedure. Scheme I, Compounds 1, 2, 4–6. A sample of ethyl *N*-hydroxyacetimidate[25] was dissolved in a large excess of amine. The mixture was heated to 80–90 °C until TLC showed no starting acetimidate (1–3 days). The excess amine was removed in vacuo and the crude amidoxime isolated and purified when necessary.

(25) Tridom Chemical, Inc. (see ethyl acethydroxamate).

Method D. General Procedure. Scheme II, Compounds 10–12. A 1.00-g (6.90 mmol) quantity of 2,2-dimethyl-3-oxothiomorpholine (**8**,[13] $R_1 = R_2 = CH_3$) was dissolved in 12 mL of dry dioxane. To this solution was added 1.53 g (7.0 mmol) of phosphorus pentasulfide. The reaction was placed under a nitrogen atmosphere and stirred at 25 °C for 2 days. The reaction mixture was poured into ca. 100 mL of ice–water and filtered through glass wool, and the milky aqueous solution was extracted with ether (3 × 50 mL). The combined ether fractions were washed with water (100 mL), dried (Na_2SO_4), and concentrated in vacuo to give 1.10 g (99%) of 2,2-dimethyl-3-thioxothiomorpholine (**9**, $R_1 = R_2 = CH_3$).

A 1.10-g (6.82 mmol) sample of crude 2,2-dimethyl-3-thioxothiomorpholine (**9**) was dissolved in 30 mL of methanol, and added to this solution in one portion were 591 mg (8.50 mmol) of hydroxylamine hydrochloride and 714 mg (8.50 mmol) of sodium bicarbonate. The mixture was refluxed under nitrogen for 15 h before being cooled in an ice bath, filtered, and concentrated in vacuo to give a solid residue. This residue was extracted with ether (5 × 50 mL), and the combined ether layers were concentrated to ca. 50 mL and allowed to cool. The precipitate was collected, giving 610 mg (55% from **8**; $R_1 = R_2 = CH_3$) of 2,2-dimethyl-3-oximidothiomorpholine (**10**).

***N*-Methyl-2,2-dimethylthiomorpholinone (13).** To a suspension of 3.8 g (0.77 mol) of 50% sodium hydride oil dispersion in 175 mL of dimethylformamide stirred at room temperature was added rapidly a solution of 10.0 g (0.07 mol) of 2,2-dimethylthiomorpholinone in a minimum amount of dimethylformamide. The reaction mixture was stirred at room temperature for 30 min, and then 12 g (0.084 mol) of methyl iodide was added slowly, after which the mixture was allowed to stir at room temperature overnight. The reaction mixture was then filtered and stripped in vacuo. The solid residue was extracted with three 200-mL portions of diethyl ether. The combined ether extracts were washed with cold brine, dried ($MgSO_4$), and evaporated. The residual oil was distilled to give 8.0 g (73%) of the title compound as a colorless oil: bp 60 °C (0.15 mm); NMR ($CDCl_3$) δ 3.8–3.6 (m, 2, N–CH_2), 3.0–2.8 (m, 2, SCH_2), 2.90 (s, 3, NCH_3), 1.47 (s, 6, *gem*-dimethyl).

***N*-Methyl-2,2-dimethyl-3-thioxothiomorpholine (14).** See the procedure for the preparation of **9**. The title compound was prepared in 84% yield from **13**: bp 158–162 °C (9 mm); NMR ($CDCl_3$) δ 4.00–3.70 (m, 2, SCH_2CH_2N), 3.52 (s, 3, NCH_3), 3.15–2.80 (m, 2, SCH_2CH_2N), 1.80 (s, 6, *gem*-dimethyl); IR (neat) 1510, 1330, 1090 cm^{-1}.

Method E. *N*-Methyl-2,2-dimethyl-3-oximidothiomorpholine (16). A 2.56-g (14.6 mmol) quantity of *N*-methyl-2,2-dimethyl-3-thioxothiomorpholine (**14**) was allowed to stand overnight at 25 °C with 15.96 g (112 mmol) of methyl iodide. The solution solidified and was washed with ether (ca. 30 mL) and this was filtered to give 4.27 g (96%) of salt **15**, mp 107–109 dec. The salt was combined with 1.03 g (14.9 mmol) of hydroxylamine hydrochloride, 2.38 g (28.3 mmol) of sodium bicarbonate, and 100 mL of methanol. The mixture was refluxed for 24 h before another equivalent each of hydroxylamine hydrochloride and sodium bicarbonate were added. Refluxing was continued for an additional 24 h. The reaction mixture was cooled to 25 °C, filtered, and concentrated in vacuo to give 4.5 g of crude solid which was extracted with ether (3 × 100 mL). Concentration of the ether gave 1.78 g of solid which was chromatographed on a dry silica gel column (50 g of silica gel, 15% methanol–chloroform solvent). A 870-mg (34%) quantity of **16** was isolated.

Method F. 1-Methyl-3,3-dimethyl-2-oximidopiperazine (17). Into a dry, three-necked flask under a nitrogen atmosphere was placed 200 mL of dry ethanol followed by 1.61 g (70 mmol) of sodium. After the sodium had dissolved, the solution was cooled in an ice bath to ca. 5 °C before 5.18 g (70 mmol) of *N*-methylethylenediamine was added. After the mixture was stirred for 10 min, 10.92 g (70 mmol) of 2-chloro-2-methylpropanehydroxamoyl chloride[26] was added at a rate such that the temperature remained between 10 and 15 °C. Following the addition, the reaction mixture was stirred at 5 °C for 0.5 h before a solution of 50 mL of ethanol containing 1.61 g (70 mmol) of sodium was

(26) K. A. Oglobin et al., *J. Gen. Chem. USSR (Engl. Transl.)*, **34**, 1225 (1964).

Table II. Physical and Spectra Properties of Oximes and Carbamates[a]

oxime	carbamate	method (yield)	mp, °C	Z/E ratio[i]	NMR, δ
1		B[b] (75)	oil	0/100	($CDCl_3$) 9.40-9.00 (m, 1, NOH), 7.60-7.10 (m, 1, NH), 2.75 (d, 3, $NHCH_3$, J = 5 Hz), 1.97 (s, 3, CH_3)
2[c]		B (87)		70/30	(Me_2SO-d_6) 5.50-5.20 (br, 1, NH), 3.25-2.80 (m, 2, $NHCH_3$), 1.78 and 1.70 [2 s, 1/3 ratio, 3, 1.78 ("E" isomer) and 1.70 ("Z" isomer), CH_3], 1.50-1.10 (m, 4), 1.00-0.80 (m, 3, CH_3)
	2a[d]			70/30	*e*
3[d]		A (96)	78-81	100/0	(5% Me_2SO-d_6) 8.87 (s, 1, NOH), 4.90 (br t, 1, $NHCH_2$, J = 6 Hz), 3.25 (t, 2, $NHCH_2CH_2CH_3$, J = 7.5 Hz), 1.55-0.70 (m, 14, s at 1.12 and triplet at 0.85, J = 6 Hz)
4[c]		B	oil	0/100	(5% Me_2SO-d_6) 9.27 (br, 1, OH), 3.70-3.55 (m, 4, CH_2OCH_2), 3.10-2.85 (m, 4, CH_2-N-CH_2), 1.83 (s, 3, CH_3)
	4a[d]		128-130	0/100	*e*
5[d]		B (43)	112.5-113.5	0/100	(5% Me_2SO-d_6) 8.67 (s, 1, NOH), 3.25-3.00 (m, 4, CH_2-N-CH_2), 1.88 (s, 3 CH_3), 1.90-1.65 (m, 4, CH_2CH_2)
6[c]		B (45)	oil	0/100	(5% Me_2SO-d_6) 9.33-8.83 (br, 1 OH), 3.15-2.85 (m, 4, CH_2-N-CH_2), 1.82 (s, 3, CH_3), 1.60-1.40 (m, 6)
	6a[d]		97-100	0/100	*e*
10[c]		D (55)	135-137	100/0	(5% Me_2SO-d_6) 9.40 (s, 1, NOH), 5.80-5.60 (m, 1, NH), 3.50-3.20 (m, 2, SCH_2CH_2N), 2.95-2.70 (m, 2, SCH_2CH_2N), 1.50 (s, 6, *gem*-dimethyl)
	10a[d]		105.5-106.5	100/0	*e*
11[c]		D		<10/>90	(5% Me_2SO-d_6) 8.83 (br, 1, OH), 6.20-5.80 (m, 1, NH), 3.70 (q, 1, CH, J = 7 Hz), 3.50-3.20 (m, 2, SCH_2CH_2N), 3.00-2.70 (m, 2, NCH_2CH_2S), 1.29 (d, 3, CH_3, J = 7 Hz)
	11a[d]		95-99	0/100	*e*
12[c]		D (45)	121-124	0/100	(5% Me_2SO-d_6) 8.67 (br, NOH), 6.20-5.90 (m, 1, NH), 3.50-3.20 (m, 2, SCH_2CH_2N), 3.14 (s, 2, SCH_2C=NOH, s goes to m when D_2O is added), 2.90-2.65 (m, 2, SCH_2CH_2N)
	12a[d]		84.5-87	0/100	*e*
16[c]		E (34)	89-92	80/20	(5% Me_2SO-d_6) "Z isomer" 9.88 (s, 1, OH), 3.50-3.10 (m, 2, SCH_2CH_2N), 2.88 (s, 3, NCH_3), 2.70-2.30 (m, 2, SCH_2CH_2N), 1.43 (s, 6, *gem*-dimethyl); "E isomer" 2.61 (s, NCH_3), 1.67 (s, *gem*-dimethyl)
	16a			66/33	*e*
17[c]		F (23)		35/65	(5% Me_2SO-d_6) "E isomer" 8.83 (m, 1, NOH), 2.95-2.70 (m, 4, CH_2CH_2), 2.60 (s, 3, NCH_3), 1.37 (s, 6, *gem*-dimethyl); "Z isomer" 3.10 (s, NCH_3), 1.23 (s, *gem*-dimethyl)
	17a[d,f]		158.5-159.5	0/100	*e*
18[c]		G (9)	oil	50/50	(5% Me_2SO-d_6) "E isomer" 8.83 (m, 1, OH), 3.20-2.50 (m, 7, CH_2CH_2) and 2.61 (s of α-NCH_3), 2.33 (s, 3, β-NCH_3), 1.40 (s, 3, *gem*-dimethyl); "Z isomer" 3.07 (s, α-NCH_3), 1.22 (s, *gem*-dimethyl)
	18a		oil	20/80	*e*
19[c]		G (6)		100/0	(5% Me_2SO-d_6) 8.83 (br, 1, OH), 5.30-5.00 (br, 1, NH), 2.70-2.60 (m, 2, CH_2), 1.22 and 1.10 (2 s, 12, 2 *gem*-dimethyl)
	19a[d,f]		175 dec	100/0	(Me_2SO-d_6) 7.10-6.80 (br q, 1, NH), 6.60-6.50 (br, 1, NH), 6.50-6.10 (br q, 1, NH), 3.25-3.10 (m, 2, CH_2), 2.67 and 2.55 (2 d, 6, $NHCH_3$, J = 4.5 Hz), 1.70 (s, 6, *gem*-dimethyl α to carbamate), 1.20 (s, 6, *gem*-dimethyl)
20[c]		H (44)	oil	100/0	(5% Me_2SO-d_6) 5.70-5.50 (m, 1, NH), 3.20-2.40 (m, 4, NCH_2CH_2N), 2.23 (s, 3, NCH_3), 1.22 (s, 6, *gem*-dimethyl)
	20a[d]		oil	100/0	*e*
28[c]		D (16)	130-134	100/0	(5% Me_2SO-d_6) 8.47 (m, 1, OH), 6.60 (m, 1, NH), 2.20 (s, 3, NCH_3), 1.18 and 1.13 (2 s, 12, 2 *gem*-dimethyls)
	28a[d]		151-160 dec	100/0	*e*
28-X[d]		D (31)	98-100		(Me_2SO-d_6) 6.65-6.50 (m, 1, NH), 2.13 (s, 3, NCH_3), 1.33 and 1.17 (2 s, 12, 2 *gem*-dimethyls)
29[c]		D	98-100	100/0	(5% Me_2SO-d_6) 8.57 (br s, 1, OH), 6.60-6.40 (m, 1, NH), 3.78 (q, 1, CH, J = 6 Hz), 2.13 (s, 3, NCH_3), 1.13 (d, 3, $CHCH_3$, J = 6 Hz), 1.13 (s, 3, CH_3), 1.00 (s, 3, CH_3)
	29a[d]		82-84.5	100/0	*e*
30[d]		D	103-106	100/0	(5% Me_2SO-d_6) 8.57 (s, 1, NOH), 6.40-6.25 (m, 1, NH), 3.83-3.67 (m, 1, CH), 2.13 (s, 3, NCH_3), 1.70-0.70 (m, 13, methyl singlets at 1.12 and 0.98)
	30[a]		127-128.5		*e*
34		D (44)	217-218 dec	100/0	(5% Me_2SO-d_6) 8.93 (m, 1, OH), 8.38 (m, 1, CHO), 7.20-7.00 (m, 1, NH), 1.60-1.45 (m, 12)
38		J	oil	0/100	($CDCl_3$) 8.30-7.80 (m, NOH), 3.40-3.00 (m, 5, NCH_3 and $=NCH_2$), 2.00-1.20 (m, 10, *gem*-dimethyl s at 1.92), 1.10-0.75 (m, 3, $CH_2CH_2CH_2CH_3$)
	38a			0/100	*e*
39[g]					

Table II (*Continued*)

oxime	carbamate	method (yield)	mp, °C	*Z/E* ratio[i]	NMR, δ
	39a[d]	K (24)	99–102	100/0	($CDCl_3$) 6.45–6.10 (m, 1, NH), 3.66 (s, 3, NCH_3), 3.30–3.00 (m, 2, $=NCH_2$), 2.90 (d, 3, $NHCH_3$, J = 5 Hz), 2.00–1.20 (m, 10, *gem*-dimethyl s at 1.70), 1.10–0.80 (m, 3, $=NCH_2CH_2CH_2CH_3$)
40[h]					
	40a[d]	K (24)	94–97	100/0	($CDCl_3$) 6.50–6.10 (m, 1, NH), 4.40–4.10 (m, 2, NCH_2), 3.07 (s, 3, $=NCH_3$), 2.91 (d, 3, $NHCH_3$, J = 5 Hz), 1.70–1.20 (m, 10, *gem*-dimethyl s at 1.70), 1.10–0.80 (m, 3, $NCH_2CH_2CH_2CH_3$)
41[c]		K (27)		100/0	(5% Me_2SO-d_6) 10.38 (m, 1, OH), 3.50 (s, 3, NCH_3), 2.95 (s, 3, $=NCH_3$), 1.58 (s, 6, *gem*-dimethyl)
	41a[d]		88–90	100/0	($CDCl_3$) 6.50–6.10 (m, 1, NH), 3.68 (s, 3, NCH_3), 3.07 (s, 3, $=NCH_3$), 2.92 (d, 3, $NHCH_3$, J = 5 Hz), 1.70 (s, 6, *gem*-dimethyl)
42[d]		L (36)	137–140		($CDCl_3$) 3.57 (s, 3, NCH_3), 1.76 (s, 6, *gem*-dimethyl)

[a] Satisfactory IR data are reported in the supplementary material. [b] 40% aqueous methylamine used in reaction. [c] Analytical data obtained on the corresponding *N*-methyl carbamate. [d] Satisfactory analytical data (±0.4% for C, H, and N) are reported in the supplementary material. [e] NMR data consistent with the corresponding oxime are reported in the supplementary material. [f] The oxime reacted with 2 equiv of methyl isocyanate to give the *N*-methyl oxime carbamate *N*-methylurea derivative. [g] Not isolated, carbamoylated as a mixture with **40**. [h] Not isolated, carbamoylated as a mixture with **39**. [i] *Z/E* ratio of the crude product mixture for the oximes (except for compound **4**) and of the purified product for the carbamates.

added. The reaction mixture was then allowed to warm to 25 °C and stirred overnight. Filtration and concentration in vacuo gave 9.6 g of oil which was chromatographed by low-pressure LC to give 2.54 g (23%) of **17**.

Method G. *N,N'*-Dimethyl-3,3-dimethyl-2-oximidopiperazine (18). Into a 2-L flask equipped with a mechanical stirrer, a nitrogen inlet, and a dry ice–acetone bath were charged 1 L of methanol and 22.41 g (212 mmol) of sodium carbonate. At −78 °C, 11.26 mL (9.32 g, 106 mmol) of *sym*-dimethylethylenediamine was added. To this reaction mixture was added 15.0 g (96 mmol) of 2-chloro-2-methylpropanehydroxamoyl chloride, and the reaction was slowly allowed to warm to 25 °C (6 h). Filtration and concentration in vacuo gave a crude solid which was extracted with ether. Concentration of ether gave 12.4 g of reddish orange oil which was filtered through coarse silica gel and purified by low-pressure LC to give 1.47 g (9%) of product **18**.

Method H. 4-Methyl-3,3-dimethyl-2-oximidopiperazine (20). A 10.0-g (50.2 mmol) quantity of 2-methyl-2-(methylsulfonyl)propanehydroxamoyl chloride was dissolved in 120 mL of absolute ethanol. To this solution was added 3.86 g (52 mmol) of methylethylenediamine dropwise followed by 9.24 g (110 mmol) of sodium bicarbonate. The reaction mixture was stirred at 25 °C for 2 h followed by being refluxed for 20 h. After the mixture was cooled to 25 °C, filtered, and concentrated in vacuo, the residue was extracted with chloroform (2 × 50 mL), and the combined organic layers were washed with water (3 × 30 mL). The combined aqueous layers were back-washed with chloroform (30 mL), and the aqueous layer was concentrated in vacuo. The residue from the aqueous layer was dissolved in chloroform, and the solution was dried ($MgSO_4$), filtered, and concentrated in vacuo to give an oily residue which solidified on standing. The solid was extracted into hot diisopropyl ether. Cooling in a freezer gave 2.13 g of precipitate. Concentration and cooling of the mother liquor gave an additional 1.30 g (total yield 3.43 g (44%) of oxime **20**).

General Procedure. Scheme IV, Compounds 22–24. See ref 15. Spectral data are listed as follows.

2,2,5,5-Tetramethyl-4-thioxoimidazolidine (22): 93% yield; mp 153.5–154 °C; NMR ($CDCl_3$) δ 1.50–1.42 (m); IR (CH_2Cl_2) 3400, 3150, 1520, 1490, 1065 cm^{-1}.

2,5,5-Trimethyl-4-thioxoimidazolidine (23): 57% yield; mp 134–136 °C; NMR (Me_2SO-d_6) δ 4.62 (q, 1, CH, J = 7 Hz), 1.40–1.10 (m, 9, three methyls); IR (KBr) 3200, 3070, 1500, 1270, 1050 cm^{-1}.

5,5-Dimethyl-2-*n*-propyl-4-thioxoimidazolidine (24): NMR (Me_2SO-d_6) δ 10.5–9.0 (br, 1, CSNH), 4.60–4.30 (m, 1, CH), 3.70–3.10 (m, 1, NH), 1.70–0.60 (m, 13, methyl singlets at 1.22 and 1.10).

General Procedure. Scheme IV, Compounds 25–27. A 30.0-g (150 mmol) quantity of 2,2,5,5-tetramethyl-4-thioxoimidazolidine and 78.59 g (570 mmol) of potassium carbonate were dissolved in 1 L of acetone. To this solution was added 80.71 g (570 mmol) of methyl iodide, and the reaction was stirred overnight at 25 °C. Filtration and concentration gave a red liquid which was extracted with ether. Concentration of the ether and distillation of the residue gave 25.5 g (74%) of **25**.

1,2,2,5,5-Pentamethyl-4-(methylthio)-3-imidazoline (25): bp 48 °C (0.2 mm); NMR ($CDCl_3$) δ 2.33 (s, 3, NCH_3), 2.22 (s, 3, SCH_3), 1.20 (s, 6, *gem*-dimethyl), 1.10 (s, 6, *gem*-dimethyl); IR (neat) 1600, 1270, 1030 cm^{-1}.

Anal. Calcd for $C_9H_{18}N_2S$: C, 58.01; H, 9.74; N, 15.04. Found: C, 58.14; H, 9.33; N, 15.23.

1,2,5,5-Tetramethyl-4-(methylthio)-3-imidazoline (26): crude oil; NMR ($CDCl_3$) δ 4.25 (q, 1, CH, J = 7 Hz), 2.40 (s, 3, NCH_3), 2.27 (s, 3, SCH_3), 1.33 (d, 3, $CHCH_3$, J = 7 Hz), 1.20–1.03 (2 s, 6, *gem*-dimethyl); IR (CH_2Cl_2) 2960, 2930, 2790, 2650, 1590, 1450, 1025 cm^{-1}.

2-*n*-Propyl-1,5,5-trimethyl-4-(methylthio)-3-imidazoline (27): NMR ($CDCl_3$) δ 4.30–4.05 (m, 1, CH), 2.40 (s, 3, NCH_3), 2.25 (s, 3, SCH_3), 1.70–0.65 (m, 13, singlets at 1.20 and 1.03); IR (neat) 2960, 1590, 1455, 1035 cm^{-1}.

General Procedure. Scheme IV, Compounds 28–30. See method D for the preparation of **10**. Compounds **28** and **28-X** were prepared in 47% yield from **25** in a 1:3 ratio, respectively. They were separated by low-pressure LC.

1-Formyl-2,2,5,5-tetramethyl-4-thioxoimidazoline (32). A 20.0-mL (212 mmol) quantity of acetic anhydride was placed in a 100-mL flask. To this was added 8.23 mL (9.87 g, 189 mmol) of 88% formic acid. The clear solution was warmed to 50 °C for 2 h to prepare the anhydride **31** before being cooled in an ice bath. A 10.0-g (63 mmol) quantity of 2,2,4,4-tetramethyl-4-thioxoimidazoline (**22**) was added in small portions. The solid did not go into solution but did change consistency. After the mixture was stirred at 25 °C for 24 h, the insoluble white solid was collected by filtration and determined to be **32**: 86% yield; NMR (Me_2SO-d_6) δ 11.35–11.0 (m, 1, NH), 8.42 and 8.39 (2 s, 1, CHO isomers), 1.62–1.45 (m, 12); IR (KBr) 3450 (br), 3150, 1635, 1380, 1230, 1070 cm^{-1}.

1-Formyl-2,2,5,5-tetramethyl-4-(methylthio)-3-imidazoline (33) was prepared from **32** in 96% yield: mp 111–112 °C; NMR ($CDCl_3$) δ 8.54 and 8.48 (2 s, 1, CHO), 2.53 and 2.50 (2 s, 3, SCH_3), 1.70–1.55 (m, 12); IR ($CHCl_3$) 3000, 1660, 1365, 1180, 1045 cm^{-1}.

Anal. Calcd for $C_9H_{16}N_2OS$: C, 53.96; H, 8.05; N, 13.99. Found: C, 53.69; H, 8.03; N, 13.84.

Method J. Preparation of 3,5,5-Trimethyl-2-(*n*-butylimino)thiazolidine 4-Oxime (38). A 4.20-g (18.2 mmol) quantity of 3,5,5-trimethyl-2-(*n*-butylimino)thiazolidine-4-thione,[16] 1.90

g (27.3 mmol) of hydroxylamine hydrochloride, 3.78 g (27.3 mmol) of potassium carbonate and 60 mL of methanol were combined and refluxed overnight. TLC indicated the presence of starting material so another equivalent each of hydroxylamine hydrochloride and potassium carbonate were added, and the reaction mixture was again refluxed overnight. After the mixture was cooled to 25 °C and concentrated in vacuo, the residue was extracted with acetonitrile. Concentration gave 3.69 g of oil which was chromatographed on silica gel. A purple band was isolated and concentrated to give 620 mg of product **38**. (The sample may have decomposed on the column according to TLC.)

Method K. Scheme VI, Preparation of 39 and 40. A 5.0-g (32.0 mmol) quantity of 2-chlorohydroxamoyl chloride was dissolved in 100 mL of methanol and immediately cooled in an ice bath. To this solution was added 4.69 g (32.0 mmol) of *N*-methyl-*N'*-*n*-butylthiourea (addition time ca. 15 min). The reaction mixture was stirred at 0 °C for ca. 10 min before 5.38 g (64.1 mmol) of sodium bicarbonate was slowly added. The reaction was stirred overnight at 25 °C, filtered, and concentrated in vacuo. The residue was extracted with ethanol. Concentration of the ethanol solution gave a crude residue that was chromatographed on silica gel (gravity column) to give 3.5 g (48%) of a mixture of **39** and **40**. This mixture was treated with methyl isocyanate under standard conditions, and the resulting product was chromatographed on low-pressure LC to give **39a** and **40a** as pure compounds.

Method L. Preparation of 2-Oximido-4-thioxo-3,5,5-trimethylthiazolidine (42). A mixture of 3,5,5-trimethyl-2-(*n*-butylimino)thiazolidine-4-thione (500 mg, 2.17 mmol), hydroxylamine hydrochloride (470 mg, 6.72 mmol), pyridine (531 mg, 6.72 mmol), and ethanol (10 mL) was refluxed for 2.5 h. The reaction mixture was cooled to 25 °C and concentrated in vacuo to give a residue which was extracted with chloroform. Concentration of the chloroform gave an oil which was stirred in petroleum ether overnight. The ether was decanted off, the residue was dissolved in ethanol (2 mL), and water was added until the solution became cloudy. The precipitate was collected and dried to give 150 mg (36%) of **42**.

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Supplementary Material Available: Infrared, NMR, and analytical data (6 pages). Ordering information is given on any current masthead page.

Synthesis and Characterization of Stereoisomeric 11-Hydroxy-1,2,3,4,4a,5,6,11a-octahydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]-pyridines

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The four stereoisomeric 11-hydroxy-1,2,3,4,4a,5,6,11a-octahydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridines are prepared by reduction of 5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (**1**) either by catalytic reduction to give **3a** and **3b** or by sodium borohydride in boiling 2-propanol to give **3c** and **3d**. An intermediate borate complex, **6**, is proposed to account for reduction of the pyridine ring of **2** by sodium borohydride.

We have discovered an unprecedented total reduction of a pyridine ring to a piperidine derivative upon treatment of 5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (**1**)[2] with sodium borohydride. These results and the catalytic reduction of **1**, which together afford the four possible stereoisomeric amino alcohols, **3a–d**, are the subject of this report.

When **1** was treated with sodium borohydride in ethanol, an exothermic reaction to 40 °C occurred, and alcohol **2**[3] was isolated in 57% yield (Scheme I). Fractional crystallization of the mother liquor residue from **2** gave **3c**, a hexahydro derivative of **2** (13% yield). This was subsequently assigned trans, anti stereochemistry. When the reaction was repeated using a large excess of sodium borohydride in boiling 2-propanol for several hours, a 20% recrystallized yield of **3c** was obtained. Fractional crystallization of the mother liquor residue gave 3% of the trans, syn isomer, **3d**. The remaining product was **2**. Catalytic reduction of **1** or **2** in ethanol and hydrochloric acid[4] gave the two isomeric cis-ring-fused amino alcohols **3a** (55%) and **3b** (2.3%), which were isolated and separated by fractional crystallization.

Assignment of stereochemistry to the isomeric amino alcohols **3a–d** was readily accomplished from the 100-MHz ^{1}H NMR spectra by analysis of coupling constants and use of double-resonance techniques. The two isomers where H_{11} and H_{11a} are anti, **3b** and **3c**, show doublets for H_{11} at δ 4.88 (J = 8.5 Hz) and δ 4.82 (J = 9.0 Hz), respectively. Irradiation of H_{11} in **3c** simplifies the doublet of doublets (J = 9 Hz, J = 9 Hz) at δ 2.15 assigned to H_{11a} which is coupled to H_{11} and H_{4a}. Isomer **3c** was thus assigned trans, anti stereochemistry. The resonance signal for H_{11a} of **3b** could not be defined by the use of double-resonance or shift-reagent techniques.

Similarly, the isomers where H_{11} and H_{11a} are syn, **3a** and **3d**, have doublets for H_{11} at δ 4.98 (J = 2 Hz) and δ 4.61 (J = 2 Hz), respectively. For **3a**, irradiation of H_{11}

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