(1958); (b) C. Schöpf, H. Arm, and H. Krimm, *Chem. Ber.*, **84**, 690 (1951); (c) however, the monomer **12** (R = H) has been isolated as a salt: G. Adam, *Chem. Ber.*, **101**, 1 (1968).
(16) We had expected this reduction to proceed more readily, since under these conditions the related *N*-benzoyl-*N'*-*n*-butylbispidine gave 83% of the respective *N*-benzyl derivative.[9]
(17) (a) J. Skolik, M. Wiewiórowski, and P. J. Krueger, *J. Mol. Struct.*, **5**, 461 (1970); (b) T. E. Borowiak, N. G. Bokii, and Y. T. Struchkov, *Zh. Strukt. Khim.*, **14**, 387 (1973); *Chem. Abstr.*, **79**, 24503y (1973).
(18) P. Scheiber and K. Nádor, *Acta Chim. Acad. Sci. Hung.*, **84**, 193 (1975).

Syntheses and Spectral Properties of Substituted Imidazolidones and Imidazolines

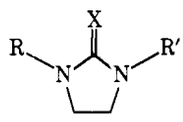
Harold Kohn,* Melanie J. Cravey, Janice H. Arceneaux, Rodney L. Cravey, and M. R. Willcott, III*

Department of Chemistry, University of Houston, Houston, Texas 77004

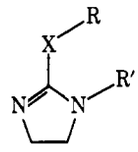
Received August 6, 1976

A series of substituted imidazolidones and imidazolines were synthesized as potential model compounds for the coenzyme, biotin. The syntheses and mass, infrared, ^{1}H NMR, and ^{13}C NMR spectral properties for these substrates are described. The ^{1}H NMR spectra for the acetyl substituted imidazolidones and imidazolidinethiones exhibited a characteristic downfield shift for the acetyl methyl proton (ca. δ 2.50 and 2.80, respectively). Surprisingly, the ^{1}H NMR spectra for the acyl substituted thioimidazolines consistently showed a singlet for the ethylene unit rather than the expected AA'BB' pattern. Verification of this unusual accidental equivalence in the ^{1}H NMR spectra was accomplished by the use of ^{13}C NMR. The ^{13}C NMR spectra for these compounds exhibited two distinct resonances which were attributed to the different ring carbon atoms.

Substituted imidazolidones (**1**) and imidazolines (**2**) are compounds of considerable current interest both as model

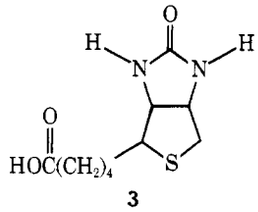


1 (X = O, S)



2 (X = O, S)

substrates for biological processes[1-7] and as chemotherapeutic agents.[8-10] As part of a current project dealing with the mechanism of biotin catalysis,[1] we synthesized a series of imidazolidones (**1**) and imidazolines (**2**) as model substrates. Compounds of types **1** and **2** possess many of the unique structural features found in biotin (**3**).[11]

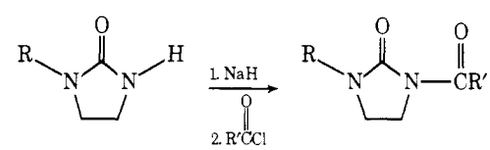


3

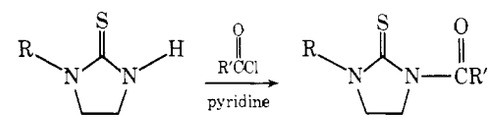
Many of the simple members of these classes of compounds have not been prepared. In this paper, we report the syntheses and characterization of these substrates, as well as a comparison of their properties to those of previously reported congeners.[12,13] Although the acyl substituted thioimidazolines prepared gave satisfactory elemental analyses, mass, and infrared spectral data, the surprising simplicity of their ^{1}H NMR necessitated a ^{13}C NMR study of these compounds. We also examined the ^{13}C NMR spectra of their counterparts, the substituted imidazolidones. The importance of ^{13}C NMR in clarifying the structural assignment of these heterocyclic molecules is outlined. In a subsequent paper, the chemistry of some of these compounds will be described.[14]

Synthesis. Tables I and II list the substrates we have prepared and pertinent infrared and ^{1}H NMR data. The majority of these substrates are new. They were prepared by a variety of synthetic routes. All new compounds gave the appropriate parent peak in the mass spectrum and satisfactory elemental analysis or high-resolution mass spectral characterization. Most of the compounds reported herein were crystalline,[15] with only the dialkyl substituted imidazolines generally being liquids.

Two general synthetic methods were adopted for the preparation of the new acyl-substituted imidazolidones and imidazolidinethiones. The imidazolidones (**9, 10, 12,** and **13**) were synthesized by the prior formation of the corresponding imidazolidone anion, followed by the addition of the acylating



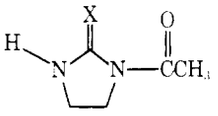
agent. By comparison, in the sulfur series (**16, 18, 19, 20, 21,** and **22**), the acylating agent was introduced to a solution containing both the imidazolidinethione and pyridine. Although the method of choice for the preparation of the substituted imidazolidones was the initial formation of the anion, these substrates could be prepared in lower yields by a method analogous to that used for the imidazolidinethiones. The re-



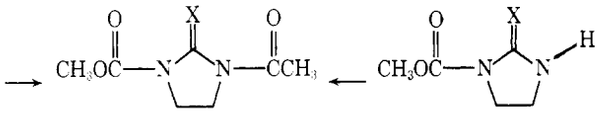
duced reactivity observed in the oxygen series appears to stem from the decreased nucleophilicity of the imidazolidone's ring carbonyl group as compared to the thione group in the imidazolidinethiones.[16] In an experiment to verify this reactivity pattern, procedures comparable to those employed in the syntheses of **18** and **21** (CH_2Cl_2, reflux) were adopted for the preparation of **8** and **12.** Even though the reaction times were doubled in the imidazolidone series, considerably lower yields were observed for these reactions.[14]

The molecular structure assigned by us for each of these acyl substrates was the N,N'-disubstituted products rather than the isomeric N,O- or N,S-substituted imidazolines.

Support for this assignment stems from a variety of sources, the foremost being (1) literature precedent,[1,4,12,13,17] (2) the correlation of spectral absorptions with structure, (3) the synthesis and characterization of alternate isomers (cf. **8** vs. **27**, **9** vs. **28**, **18** vs. **32**, and **19** vs. **37**), and (4) the subsequent derivatization of some of these substrates.[1,14] Additional chemical support for N,N′ disubstitution pattern stems from the syntheses of **12** and **21**. In these cases, the diacylated compounds (**12** and **21**) could be easily prepared from the corresponding *N*-acetyl (**5** and **15**) or the *N*-carbomethoxy (**6** and **16**) derivatives.



5, X = O
15, X = S

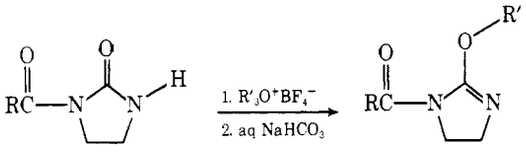


12, X = O
21, X = S

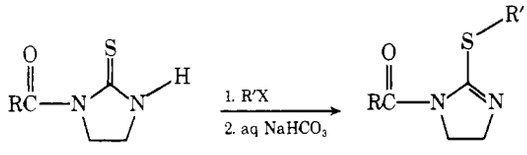
6, X = O
16, X = S

Although no mechanistic studies were conducted, analogy with previous work suggests two likely possibilities.[4,12,13,17] One involves the initial formation of the oxygen or sulfur bound imidazoline, followed by a Chapman-type rearrangement[16,18-22] to the N,N′-disubstituted product, while the other involves direct acylation of one of the ring nitrogen atoms of the imidazolidone or imidazolidinethione. Of these two mechanisms, the former has enjoyed the widest support.[16,18-22]

The *O*-alkyl-*N*-acylimidazolines (**27**, **28**, and **29**) were prepared by the addition of either trimethyloxonium[23] or triethyloxonium fluoroborate[24] (Meerwein salts) to a solution containing the starting acyl imidazolidone. When less reactive alkylating agents, alkyl halides, were used in place of the Meerwein salts, only the starting acyl imidazolidones were recovered ($CHCl_3$, 40 °C, 5 days).[14]

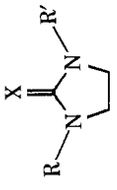


Syntheses of the corresponding substituted thioimidazolines were generally accomplished by one of two methods. Unlike the preparation of the acyl imidazolines, the acyl imidazolidinethiones readily underwent direct S-alkylation with the alkyl halides, to give the desired products (**32**, **37**, **38**, and **43**). These results are in accord with the reactivity pattern



previously observed for these substrates.[16] Alternatively, these compounds (**34**, **35**, **39**, **40**, **41**, **42**, and **43**) were prepared by the introduction of the alkylating agent to a solution containing both the starting substrate and triethylamine. In the cases where both methods were utilized, the second method gave slightly higher yields.[1,14,25] Comparison of the experimental yields for the S-alkylation of *N*-acetylimidazoli-

Table I. Summary of Selected Physical and Spectral Properties of the Substituted Imidazolidones

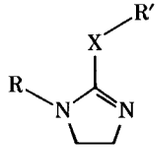


No.	X	R	R′	Bp,[a] °C	Mp,[a] °C	IR data[b]			¹H NMR data[c]			
						X=C	O=NCR	Other	NCH_3,	$-CH_2CH_2-$,	O=$-CCH_3$,	O=$-COCH_3$
4	O	H	CH_3[d]		114–115			1690, 1510	2.75	3.40		
5	O	H	O=CCH_3[e]		176–180	1750	1645			3.25–4.14	2.50	
6	O	H	O=$COCH_3$[f]		179–180		1750	1640		3.23–4.07		3.80
7	O	CH_3	CH_3[g]	106–108 (17 mm)		1710[h]			2.75	3.25		
8	O	CH_3	O=CCH_3[i]		78–81	1730	1670		2.80	3.20–3.95	2.40	
9	O	CH_3	O=$COCH_3$		56–59	1720	1760	1805	2.81	3.20–3.95		3.80
10	O	CH_3	O=$COCH_2CH_3$	128 (0.30 mm)		1720	1760	1800	2.82	3.20–4.00		
11	O	O=CCH_3	O=CCH_3[i]		126–127	1750, 1760[i]	1700, 1710[i]			3.80	2.52	
12	O	O=CCH_3	O=$COCH_3$		143–145	1715	1695, 1750			3.82	2.48	3.85
13	O	O=$COCH_3$	O=$COCH_3$		233–239	1785	1760			3.85		3.95
14	S	H	CH_3[j]		131.5–132	1510, 1520			3.12	3.52–3.77		
15	S	H	O=CCH_3[i]		165–167	1530	1650			3.38–4.41	2.85	
16	S	H	O=$COCH_3$[k]		156–158		1750	1675		3.37–4.32		3.82
17	S	CH_3	CH_3[l]		108–110	1510			3.13	3.60		

18	S	CH_3	$O{=}CCH_3$	81–82	1520	1665		3.22	3.40–4.25	2.80		
19	S	CH_3	$O{=}COCH_3$	111–112.5	1515	1745		3.17	3.44–4.23		3.82	
20	S	$O{=}CCH_3$	$O{=}CCH_3$[i]	87–89	1470	1685			3.95	2.77		
21	S	$O{=}CCH_3$	$O{=}COCH_3$	95–97		1690, 1760	1710		4.05	2.84	3.87	
22	S	$O{=}COCH_3$	$O{=}COCH_3$	198–199.5		1735, 1765			3.97		3.80	

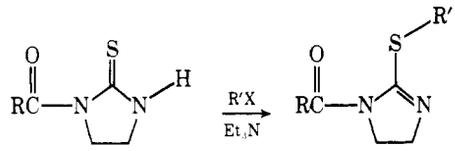
[a] Boiling and melting points are uncorrected. [b] Infrared peak position recorded in cm^{-1} vs. the 1601-cm^{-1} band in polystyrene and were taken in KBr disks unless otherwise noted. [c] ^1H NMR chemical shift value (δ) recorded vs. Me_4Si in $CDCl_3$. [d] Reference 40. [e] Reference 17. [f] Reference 4. [g] A. B. A. Jansen and P. J. Stokes, *J. Chem. Soc.*, 4909 (1962). [h] Infrared taken in $CHCl_3$ in matching cells. [i] Reference 12. [j] Reference 41. [k] Reference 1. [l] L. Maier, *Helv. Chim. Acta*, **53**, 1417 (1970).

Table II. Summary of Selected Physical and Spectral Properties of the Substituted Imidazolines



						IR data[b]			^1H NMR data[c]					
No.	X	R	R′	Bp,[a] °C	Mp,[a] °C			Other	NCH_3	$-CH_2CH_2-$			$-XCH_3$	$-XCH_2-$
23	O	H	CH_3[d]		86–87	1625		1601		3.59			3.81	
24	O	H	CH_2CH_3[d]		50–51	1635				3.62				4.24 (q, J = 7.0)
25	O	CH_3	CH_3	127–128		1640[e]		1505	2.65	3.07–3.70			3.80	
26	O	CH_3	CH_2CH_3	71 (25 mm)		1635[f]			2.63	3.20–3.72				4.20 (q, J = 7.5)
27	O	$O{=}CCH_3$	CH_3		39–42	1645	1680			3.42–4.12	2.28		3.93	
28	O	$O{=}COCH_3$	CH_3		79–82	1650	1740			3.63–4.10		3.77	3.95	
29	O	$O{=}COCH_3$	CH_2CH_3		67–70	1655	1760			3.40–4.08		3.76		4.33 (q, J = 7.0)
30	S	H	CH_3[d]		102–107	1560				3.24–4.17			2.49	
31	S	CH_3	CH_3	31 (0.15 mm)		1590[e]			2.75	3.08–3.94			2.49	
32	S	$O{=}CCH_3$	CH_3		112–113.5	1580	1670			3.97	2.18		2.40	
33	S	$O{=}CCH_3$	CH_2CH_3		56.5–58.5	1580	1670			3.92	2.18			2.87 (q, J = 7.5)
34	S	$O{=}CCH_3$	$CH_2CH{=}CH_2$	130 (0.2 mm)		1590[e]	1680			3.98	2.20			3.55–3.75 (m)
35	S	$O{=}CCH_3$	$CH_2Ph(p\text{-}F)$		138–139	1585	1670			3.92	2.18			4.20
36	S	$O{=}CCH_3$	$CH_2C(=O)Ph$[g]		149–149.5	1575	1670	1670		3.90	2.18			4.48
37	S	$O{=}COCH_3$	CH_3		103.5–105.5	1585	1715			3.88		3.77	2.40	
38	S	$O{=}COCH_3$	CH_2CH_3		71–73.5	1590	1710			3.84		3.73		2.97 (q, J = 7.5)
39	S	$O{=}COCH_3$	$CH_2CH{=}CH_2$	97–98 (0.19 mm)	32–33.5	1585[e]	1715			3.90		3.80		3.55–3.82 (m)
40	S	$O{=}COCH_3$	$CH_2C(=O)CH_3$		73–75	1585	1705	1705		3.82		3.75		3.79
41	S	$O{=}COCH_3$	$CH_2COOCH_2CH_3$		66–67	1600	1710	1755		3.91		3.83		3.83
42	S	$O{=}COCH_3$	$CH_2Ph(p\text{-}F)$		101.5–102	1585	1725			3.85		3.71		4.15
43	S	$O{=}COCH_3$	$CH_2C(=O)Ph$[h]		153.5–155.5	1580	1715	1670		3.87		3.78		4.54

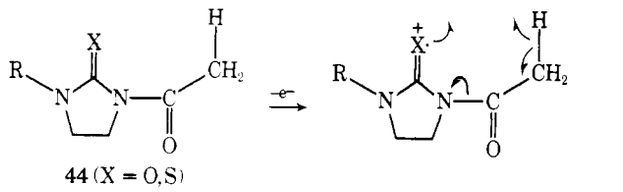
[a] Boiling and melting points are uncorrected. [b] Infrared peak positions recorded in cm^{-1} vs. the 1601-cm^{-1} band in polystyrene, and were taken in KBr disks unless otherwise noted. [c] ^1H NMR chemical shift value (δ) recorded vs. Me_4Si in $CDCl_3$. [d] G. I. Poos, J. Kleis, and C. K. Cain, *J. Org. Chem.*, **24**, 645 (1959). [e] Infrared taken neat on NaCl plates. [f] Infrared taken in CCl_4 in matching cells. [g] Reference 25. [h] Reference 1.



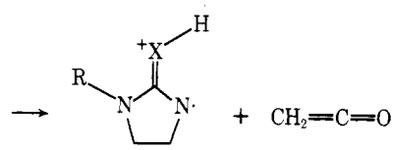
dinethione vs. that for the corresponding *N*-carbomethoxyimidazolidinethione with a variety of alkylating agents also showed that consistently higher yields were obtained for the *N*-carbomethoxy derivatives. Despite efforts to increase the conversion in the former series of compounds by increasing the reaction times, reaction temperatures, and the ratio of alkylating agent to starting material, only moderate yields were observed.[14] This reactivity pattern appears to be a reflection of the enhanced nucleophilicity of the thione group in the *N*-carbomethoxyimidazolidinethiones vs. the thione group in the *N*-acetyl compounds.

Mass Spectral Data. Each substituted acyl imidazolidone and imidazoline gave a discernible parent peak in the mass spectrum (ionization voltage 70 eV). Two distinct modes of cleavage emerge upon examination of the fragmentation patterns for these compounds.

A significant feature in the breakdown patterns for the *N*-acetyl substituted imidazolidones (**44**, X = O) (compound **12**) and imidazolidinethiones (**44**, X = S) (compounds **18**, **20**, and **21**) was the P − 42 peak. Similarly the *N*-carbomethoxy substituted imidazolidones (**46**, X = O) (compounds **9** and **13**) and imidazolidinethiones (**46**, X = S) (compounds **16**, **19**, **21**, and **22**) gave a characteristic P − 58 fragment. Both of these

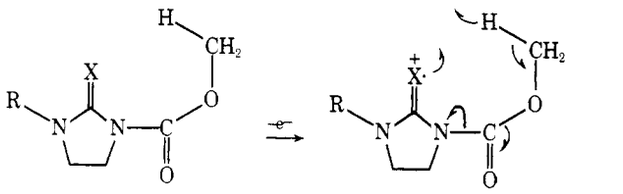


44 (X = O,S)

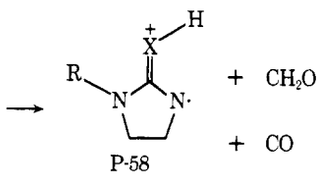


P-42

45



46 (X = O,S)

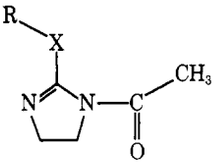


P-58

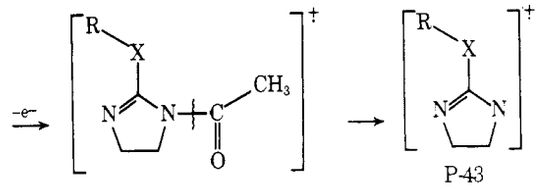
47

peaks can be rationalized in terms of a McLafferty type rearrangement[26,27] of the starting molecular ion to give **45** and **47**, respectively.

This pattern was not observed in the *N*-acyl substituted imidazolines and thioimidazolines. Instead the *N*-acetyl derivatives (**48**) (compounds **27**, **32–35**) gave a diagnostic peak at P − 43, while the *N*-carbomethoxy substrates (**50**) (compounds **28**, **29**, **37–39**) gave rise to a peak at P − 59. Cleavage of the bond adjacent to the ring with loss of O=CCH_3 and O=$COCH_3$, respectively, accounts for these peaks.[26,27]

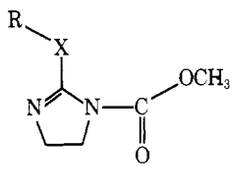


48 (X = O,S)

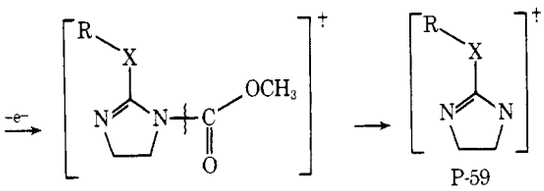


P-43

49



50 (X = O,S)



P-59

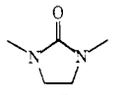
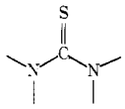
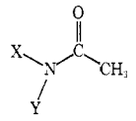
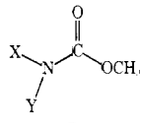
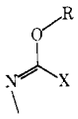
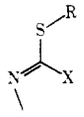
51

The composite set of mass spectral data for all newly prepared acyl substituted imidazolidones and imidazolines reveals that exceptions do exist to these generalizations. The mass spectral data provide helpful but not conclusive evidence for structure.

Infrared Spectral Data. The infrared group frequencies which have been reported for thioureas, ureas, and cyclic derivatives are sketchy.[28,29] Furthermore, the examples which have been cited do not reveal an invariant set of frequencies. We have constructed the following table (Table III) to summarize the literature values found in Bellamy,[28,29] Nakanishi,[30] and our work. We also note the number of cases observed in our study for each structural type. Even though a substantial number of examples agree with expectation, we have recorded enough exceptions that we feel these frequencies are not unique diagnostic tools. For example, **4** and **6** do not exhibit the expected urea carbonyl band at ca. 1720 cm^{-1},[30] but instead show enolic absorptions at 1690 and 1640 cm^{-1}, respectively. Compounds **9** and **10** exhibit extra strong absorptions in the carbonyl region at 1805 and 1800 cm^{-1}, respectively. Compound **16** is characterized by a 1675-cm^{-1} band, a feature for which we have no explanation. Finally, we could not confidently find the three sets of bands abscribed to thioureas.[29] In most cases the high-frequency absorption was easily observed, but every assignment of the lower frequency bands we attempted to make was ambiguous.

Our experience with the interpretation of the infrared spectra of these 40 compounds leads us to the following generalizations. The cyclic imine band characteristic of compounds in Table II exhibits a reliable infrared absorption at 1655–1600 cm^{-1} (X = O) and 1605–1560 cm^{-1} (X = S), and is useful in structure elucidation. In contrast, the ring carbonyl and thione frequencies for the substituted imidazolidones and

Table III. Summary of Selected Infrared Group Frequencies

Functional group	Lit. values, cm^{-1}	Obsd values, cm^{-1}	No. of observations
	1720[a]	1750–1712	7
	1570–1395[b] 1420–1260 1140– 940	1530–1470	6
	1650[a,c]	1710–1645	14
	1740–1690[a] 1736–1700[c]	1765–1705	18
	1665[b]	1655–1600	7
	1611[b]	1605–1560	14

[a] Reference 30. [b] Reference 29. [c] Reference 28.

imidazolidinethiones are much less reliable and do not provide a conclusive demonstration of the absence or presence of these functional groups.

Magnetic Resonance Data. ^{1}H NMR. We routinely recorded ^{1}H NMR spectra of all the compounds in this study, in order to characterize the structure unambiguously. Unfortunately, this expectation was not realized. The chemical shift for the protons of the substituted imidazolidones and imidazolidinethiones are recorded in Table I. The *N*-methyl, the *N*-carbomethoxymethyl, and the ring ethylene protons all exhibited chemical shifts in regions previously assigned.[31,32] The ethylene pattern was an AA'BB' spin system for the asymmetric substituted compounds and was an A_4 singlet for the symmetric substituted compounds. In three instances (compounds **4, 12,** and **21**) the near equivalence of the substitution on the two nitrogens gave rise to accidental equivalence of the ring ethylene protons.

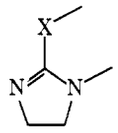
The consistent appearance of the *N*-acetyl methyl group at ca. δ 2.50 in the substituted imidazolidones and ca. δ 2.80 in the sulfur analogues was at lower field than we anticipated.[31,32] Greenhalgh and Weinberger[13] have noted downfield shifts in a related series of compounds, and have explained the observations in terms of anisotropy and of selective population of a particular conformer. Whatever the cause, we note that the *N*-acetyl imidazolidones exhibit a diagonistic peak at δ 2.40–2.52, and the *N*-acetyl imidazolidinethiones at δ 2.75–2.85.[33]

The chemical shifts of N-substituted imidazolines and thioimidazolines can be identified by correlation charts.[31,32] Indeed the *N*-methyl, *N*-carbomethoxymethyl, and even the *N*-acetyl methyl resonances occur at the expected values.

The chemical shifts of the ethylene protons agree well with previous correlation charts.[31,32] As expected, the oxygenated compounds of Table II exhibited the AA'BB' spectra that are required by their symmetry. Thus we were astonished by the simple single absorption for the ring ethylene protons that was invariably observed for the *N*-acetyl- and *N*-carbomethoxythioimidazolines. The highly asymmetric substitution patterns for these compounds cannot be easily reconciled with accidental degenerate $-CH_2CH_2-$ resonances. The use of a variety of solvents ($CDCl_3$, CD_3CN, $C_6H_5NO_2$) did not lift the degeneracy. In one case (compound **37**) the effect of benzene-d_6 caused the singlet to become a perceptibly more complicated pattern [δ 3.25–3.53 (m, 4 H)]. Varying the temperature of the NMR sample of compound **37** between −40 and 30 °C did not lift the degeneracy.

Our inability to alter the $-CH_2CH_2-$ singlet resonance in these classes of compounds (12 substrates) led us to consider alternative structures and/or kinetic processes which interconvert alternative structures, as well as to question the correctness of the topological description of this whole class of compounds. ^{13}C NMR, however, provides an immediate indication of whether the ^{1}H spectra require a special explanation.

^{13}C NMR. Examination of the proton decoupled ^{13}C NMR spectrum[35] of six of the *N*-acyl substituted thioimadozolines (**32, 36–38, 40,** and **43**) of Table II gave the expected number of signals for carbons bound to hydrogens. In a few cases the low intensity of the quaternary carbons precluded the confident assignment of these atoms. The key observation is the consistent appearance of two resonances in the indicated shift range, separated by ca. 6 ppm for the two carbons in the ring ethylene bridge. The identity of these two carbons was assured



53.8- 47.0-
54.5 48.6

by observing triplets, J = 144 and 142 Hz, for the resonances at δ 48.1 and 53.8 in the proton coupled spectra of compound **32.** Additionally, triplets, J = 150 and 145 Hz, occurred at δ 47.9 and 54.2 in the spectrum of compound **43.** Using these chemical shifts as references we made consistent assignments to the ethylene resonances in the remaining compounds. Under ordinary ^{13}C NMR conditions, there is no convenient observation to assign the two resonances separately, so we assign them as a set. The values recorded for the carbons of the ethylene bridge may be reversed, but the pattern of shifts makes the paired assignment certain. The consistent appearance of two ^{13}C NMR signals for the ethylene bridge verifies the structure and assures that the ^{1}H NMR results from accidental equivalence. The remaining resonances were assigned from proton coupling constants, correlation charts,[36–39] and internal consistency.

Model compounds have been reported by Jackman and Jen.[36] Their ^{13}C NMR assignments accord well with ours with a single exception. We suggest that the resonances recorded as C-4 and C-6 in their Table VIII should be reversed.

The ^{13}C NMR spectra[35] of eight of the imidazolidones (**4, 9, 13, 16–19,** and **22**) which appear in Table I were recorded. In those cases where the substituents at the two nitrogen atoms differed, two resonances for the ring ethylene carbons were noted. The assignments were made as before. We find nothing unusual in these shifts and present them without comment.

In extensions of this work, we have relied extensively upon the assignments of the chemical shift values observed in this study to provide positive identification of other analogues. The complete data set and two histograms which summarize all of the ^{13}C NMR data appear in the microfilm edition of this journal.

Experimental Section

General. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on Perkin-Elmer Model 700 and 237B spectrometers and calibrated against the 1601-cm^{-1} band of polystyrene. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Varian Associates Model T-60 and EM-390 instruments. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were determined on Bruker Models HFX-90 and WH-90, JEOL Model FX60H, and Varian Associates Models CFT-20 and XL-100-15 spectrometers. The XL-100 was equipped with a Nicolet Technology Corp. TT-100 data system.

Chemical shifts are expressed in parts per million relative to Me_4Si, and coupling constants (J values) in hertz. Spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Mass spectral (MS) data were obtained at an ionizing voltage of 70 eV on a Hitachi Perkin-Elmer Model RMU-6H mass spectrometer. High-resolution mass spectra were performed by Dr. James Hudson at the Department of Chemistry, Rice University, on a CEC21-110B double focusing magnetic sector spectrometer at 70 eV. Exact masses were determined by peak matching. Elemental analyses were obtained at Spang Microanalytical Laboratories, Ann Arbor, Mich.

The solvents and reactants were of the best commercial grade available and were used without further purification unless noted. When dry solvents were required, CH_2Cl_2 was distilled from P_2O_5, benzene was distilled and then stored over sodium, dimethylformamide was stored over sodium sulfate and then distilled from CaH_2, and anhydrous ether was stored over sodium metal. All reactions were run under nitrogen, and all glassware dried before use.

Materials. All previously reported substrates were synthesized by their literature procedures unless otherwise indicated. The physical and spectral properties observed for these compounds were generally in good agreement with the reported values.

***N*-Carbomethoxy-*N'*-methylimidazolidone (9).** NaH (50% mineral oil dispersion) (2.75 g, 0.05 mol) was washed with benzene (3 × 50 ml) and then an additional 50 ml of benzene was added. A benzene solution (250 ml) of **4**[40] (4.00 g, 0.04 mol) was slowly added (5 h), followed by 4.4 ml (0.05 mol) of methyl chloroformate. The solution was stirred for 18 h at room temperature, filtered, and evaporated in vacuo. Fractional recrystallization from Et_2O gave 3.93 g (62%) of the desired product: selected ^{13}C NMR ($CDCl_3$) 40.6, 43.2 ppm (CH_2CH_2); MS *m/e* (rel %) 158 (100), 138 (13), 113 (17), 100 (36), 99 (33), 98 (35), 70 (39).

Anal. Calcd for $C_6H_{10}N_2O_3$: C, 45.56; H, 6.37; N, 17.71. Found: C, 45.68; H, 6.27; N, 17.69.

***N*-Carboethoxy-*N'*-methylimidazolidone (10).** The preceding reaction was repeated using 1.44 g (0.03 mol) of NaH (50% mineral oil dispersion), 2.00 g (0.02 mol) of **4**,[40] and 2.9 ml (0.03 mol) of ethyl chloroformate. Distillation gave 4.58 g (67%) of a white semisolid: MS *m/e* (rel %) 172 (42), 128 (12), 99 (100), 70 (21), 56 (24).

Anal. Calcd for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.03; N, 16.27. Found: C, 48.90; H, 7.04; N, 15.81.

***N*-Acetyl-*N'*-carbomethoxyimidazolidone (12). Method A.** This compound was synthesized in 55% yield (1.02 g) from 0.62 g (0.013 mol) of NaH (50% mineral oil dispersion), 1.28 g (0.01 mol) of **5**,[17] and 1.0 ml (0.013 mol) of methyl chloroformate using the method described for the preparation of **9**. Reprecipitation of the white solid from chloroform–hexanes gave the purified product: MS *m/e* (rel %) 186 (26), 158 (40), 144 (38), 88 (100), 59 (26), 56 (26).

Anal. Calcd for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.42; N, 15.05. Found: C, 45.12; H, 5.32; N, 15.10.

***N*-Acetyl-*N'*-carbomethoxyimidazolidone (12). Method B.** Acetyl chloride (0.4 ml, 0.007 mol) was added to a stirred CH_2Cl_2 suspension (25 ml) of **6**[4] (0.72 g, 0.005 mol) and pyridine (0.4 ml, 0.005 mol). The mixture was refluxed for 48 h. The resulting solution was washed with H_2O (2 × 30 ml), dried (Na_2SO_4), and evaporated in vacuo. Reprecipitation of the white solid from chloroform–hexanes gave purified product, yield 0.37 g (40%).

***N,N'*-Dicarbomethoxyimidazolidone (13).** NaH (50% mineral oil dispersion) (4.80 g, 0.1 mol) was washed with DMF (3 × 75 ml) and an additional 20 ml of DMF was added. Imidazolidone (2.15 g, 0.025 mol) in DMF (50 ml) was then slowly added (5 h), followed by 7.0 ml (0.1 mol) of methyl chloroformate. The reaction was exothermic, and the mixture was allowed to stir at room temperature for 18 h. The mixture was filtered and the filtrate evaporated in vacuo. The yellow-brown residue was taken up in H_2O (50 ml) and continuously extracted (48 h) with CH_2Cl_2. The CH_2Cl_2 was dried (Na_2SO_4) and evaporated in vacuo. The yellow-white solid was chromatographed on a neutral alumina column (15 × 2.3 cm) using $CHCl_3$ as the eluent. The first eluted material was the desired product. The title compound was further purified by reprecipitation from chloroform–hexanes: yield 1.28 g (25%); selected ^{13}C NMR ($CDCl_3$) 39.9 ppm (CH_2CH_2); MS *m/e* (rel %) 202 (29), 158 (100), 144 (37), 113 (17).

Anal. Calcd for $C_7H_{10}N_2O_5$: C, 41.59; H, 4.99; N, 13.86. Found: C, 41.27; H, 4.85; N, 14.09.

***N*-Acetyl-*N'*-methylimidazolidinethione (18).** To a stirred CH_2Cl_2 solution (100 ml) containing **14**[41] (4.64 g, 0.04 mol) and pyridine (3.16 g, 0.04 mol), acetyl chloride (2.8 ml, 0.04 mol) was slowly added. The solution was refluxed overnight and then washed with H_2O (2 × 60 ml), dried (Na_2SO_4), and evaporated in vacuo. Purification of the desired compound was accomplished by reprecipitation from carbon tetrachloride–hexanes: yield 4.35 g (69%); selected ^{13}C NMR ($CDCl_3$) 44.3, 47.5 ppm (CH_2CH_2); MS *m/e* (rel %) 158 (100), 116 (50), 115 (27), 72 (14).

Anal. Calcd for $C_6H_{10}N_2OS$: C, 45.54; H, 6.37; N, 17.71. Found: C, 45.61; H, 6.40; N, 17.76.

***N*-Carbomethoxy-*N'*-methylimidazolidinethione (19).** The preceding reaction was repeated using 4.64 g (0.04 mol) of **14**,[41] 6.32 g (0.08 mol) of pyridine, and 60.0 ml (0.78 mol) of methyl chloroformate. The exothermic reaction was kept under control (moderate CH_2Cl_2 reflux) by adjusting the rate of addition of methyl chloroformate. Recrystallization from CCl_4 afforded 3.75 g (54%) of the desired product: selected ^{13}C NMR ($CDCl_3$) 44.5, 48.5 ppm (CH_2CH_2); MS *m/e* (rel %) 174 (100), 116 (48), 115 (24), 72 (32).

Anal. Calcd for $C_6H_{10}N_2O_2S$: C, 41.36; H, 5.79; N, 16.08. Found: C, 41.34; H, 5.66; N, 16.08.

***N*-Acetyl-*N'*-carbomethoxyimidazolidinethione (21). Method A.** Using the method described for the preparation of **18**, **21** was synthesized from 4.00 g (0.025 mol) of **16**,[1] 1.98 g (0.025 mol) of pyridine, and 2.5 ml (0.035 mol) of acetyl chloride. Purification of **21** was accomplished by reprecipitation from chloroform–hexanes: yield 4.11 g (81%); MS *m/e* (rel %) 202 (66), 160 (100), 144 (87), 102 (95), 88 (35), 74 (34), 72 (66).

Anal. Calcd for $C_7H_{10}N_2O_3S$: C, 41.57; H, 4.98; N, 13.85. Found: C, 41.68; H, 4.97; N, 13.82.

***N*-Acetyl-*N'*-carbomethoxyimidazolidinethione (21). Method B.** Using the method described for the preparation of **18**, **21** was synthesized from 0.86 g (0.006 mol) of **15**,[12] 0.95 g (0.012 mol) of pyridine, and 7.2 ml (0.093 mol) of methyl chloroformate. The exothermic reaction was kept under control (moderate CH_2Cl_2 reflux) by adjusting the rate of addition of methyl chloroformate. The solution was refluxed for 72 h. Purification of **21** was accomplished by reprecipitation from chloroform–hexanes; yield 0.75 g (60%).

***N,N'*-Dicarbomethoxyimidazolidinethione (22).** Compound **22** was synthesized in 33% yield (1.45 g) from 2.04 g (0.02 mol) of imidazolidinethione, 4.74 g (0.06 mol) of pyridine, and 23.3 ml (0.30 mol) of methyl chloroformate using the method described for the preparation of **18**. The exothermic reaction was kept under control (moderate CH_2Cl_2 reflux) by adjusting the rate of addition of methyl chloroformate. Reprecipitation from chloroform–hexanes gave purified **22**: selected ^{13}C NMR ($CDCl_3$) 44.7 ppm (CH_2CH_2); MS *m/e* (rel %) 218 (100), 160 (66), 102 (23), 88 (52), 72 (69).

Anal. Calcd for $C_7H_{10}N_2O_4S$: C, 38.52; H, 4.62; N, 12.84. Found: C, 38.70; H, 4.68; N, 12.84.

***N*-Methyl-2-methoxyimidazoline (25).** A methanolic solution (20 ml) containing *N*-methyl-2-methylthioimidazolinium hydriodide[41] (5.10 g, 0.02 mol) was added to 20 ml of a freshly prepared 2.5 N NaOMe–MeOH (0.05 mol) solution. The solution was refluxed for 24 h and filtered and then 20 ml of H_2O added. The solution was continuously extracted with CH_2Cl_2 for 18 h, and the organic layer dried (Na_2SO_4) and evaporated in vacuo. Bulb-to-bulb distillation at 55 °C (0.45 mm) gave 0.78 g (34%) of the desired compound, a clear liquid: MS *m/e* (rel %) 114 (56), 113 (42), 99 (35), 84 (12), 71 (26), 56 (100); mol wt 114.0791 (calcd for $C_5H_{10}N_2O$, 114.0793).

***N*-Methyl-2-ethoxyimidazoline (26).** The preceding reaction was repeated using an ethanolic solution (50 ml) containing 5.10 g (0.02 mol) of *N*-methyl-2-methylthioimidazolinium hydriodide[41] and 20 ml (0.05 mol) of 2.5 N NaOEt–EtOH solution. Distillation gave 1.64 g (64%) of the desired compound, a clear liquid: selected ^{13}C NMR ($CDCl_3$) 48.9, 53.6 ppm (CH_2CH_2); MS *m/e* (rel %) 128 (100), 114 (12), 99 (71), 87 (25).

Anal. Calcd for $C_6H_{12}N_2O$: C, 56.22; H, 9.44; N, 21.86. Found: C, 56.25; H, 9.51; N, 21.84.

***N*-Acetyl-2-methoxyimidazoline (27).** To 0.64 g (0.005 mol) of **5**,[17] 1.11 g (0.0075 mol) of trimethyloxonium fluoroborate[23] in CH_3NO_2 (7 ml) was slowly added. The solution was heated at 35 °C for 18 h, and then Et_2O (20 ml) added causing the separation of an oil. The supernatant layer was decanted off, and the remaining oil dried

in vacuo. CH_2Cl_2 (10 ml) was then added, and the mixture neutralized with aqueous 5% $NaHCO_3$ (10 ml). The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The desired product was further purified by sublimation (40 °C, 0.1 mm) to yield 0.81 g (29%) of white crystals; MS *m/e* (rel %) 142 (2), 113 (39), 99 (36), 56 (100).

Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.55; H, 7.15; N, 19.57.

***N*-Carbomethoxy-2-methoxyimidazoline (28).** The preceding reaction was repeated using 1.44 g (0.01 mol) of **6**[4] and 2.96 g (0.02 mol) of trimethyloxonium fluoroborate.[23] After the addition of aqueous 5% $NaHCO_3$ (20 ml) the CH_2Cl_2–H_2O mixture was continuously extracted (48 h) with CH_2Cl_2. The organic layer was then dried (Na_2SO_4) and evaporated in vacuo, and the title compound further purified by two successive sublimations (30 °C, 0.05 mm) to give 0.36 g (11%) of white crystals: selected ^{13}C NMR ($CDCl_3$) 47.6, 47.7 ppm (CH_2CH_2); MS *m/e* (rel %) 158 (80), 143 (10), 127 (15), 99 (19), 71 (43), 56 (100).

Anal. Calcd for $C_6H_{10}N_2O_3$: C, 45.56; H, 6.37; N, 17.71. Found: C, 45.58; H, 6.44; N, 17.57.

***N*-Carbomethoxy-2-ethoxyimidazoline (29).** To 0.72 g (0.005 mol) of **6**,[4] 1.90 g (0.01 mol) of triethyloxonium fluoroborate[24] in CH_2Cl_2 (50 ml) was slowly added. The solution was refluxed for 18 h, then washed with aqueous 5% $NaHCO_3$ (2 × 20 ml) and H_2O (20 ml). The CH_2Cl_2 solution was dried (Na_2SO_4) and evaporated in vacuo. The desired compound was purified by sublimation (35 °C, 0.05 mm) to yield 0.48 g (78%) of white crystals: MS *m/e* (rel %) 172 (44), 144 (72), 143 (26), 113 (39), 88 (100).

Anal. Calcd for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.03; N, 16.27. Found: C, 48.74; H, 7.10; N, 16.27.

***N*-Acetyl-2-methylthioimidazoline (32).** The preceding reaction was repeated using 5.76 g (0.04 mol) of **15**[12] and 5.0 ml (0.08 mol) of MeI. The reaction solution was refluxed for 72 h, during which time the *N*-acetyl-2-methylthioimidazolinium hydriodide salt precipitated out. The salt was collected and then neutralized using the procedure described above. Purification was accomplished by reprecipitation from carbon tetrachloride–hexanes: yield 2.43 g (38%); selected ^{13}C NMR ($CDCl_3$) 48.1 (t, $J_{^{13}C-H}$ = 144 Hz), 53.8 ppm (t, $J_{^{13}C-H}$ = 142 Hz) (CH_2CH_2); MS *m/e* (rel %) 158 (47), 143 (98), 116 (82), 115 (56), 87 (100), 72 (47).

Anal. Calcd for $C_6H_{10}N_2OS$: C, 45.54; H, 6.37; N, 17.71. Found: C, 45.55; H, 6.28; N, 17.59.

***N*-Acetyl-2-ethylthioimidazoline (33).** Using the method described for the preparation of **29, 33** was synthesized from 1.44 g (0.01 mol) of **15**[12] and 2.09 g (0.011 mol) of triethyloxonium fluoroborate.[24] The reaction mixture was allowed to stand at room temperature overnight. The desired compound was purified by reprecipitation from chloroform–hexanes: yield 1.51 g (88%); MS *m/e* (rel %) 172 (17), 157 (7), 144 (72), 143 (29), 129 (33), 102 (100), 101 (19), 97 (48), 72 (41), 70 (33).

Anal. Calcd for $C_7H_{12}N_2OS$: C, 48.81; H, 7.02; N, 16.27. Found: C, 48.63; H, 6.93; N, 16.13.

***N*-Carbomethoxy-2-methylthioimidazoline (37).** Compound **37** was synthesized in 61% yield (5.32 g) from 8.00 g (0.05 mol) of **16**[1] and 6.3 ml (0.10 mol) of MeI using the method described for the preparation of **29.** The reaction mixture was refluxed for 72 h. The desired product was purified by reprecipitation from carbon tetrachloride–hexanes: NMR ($CDCl_3$) δ 2.40 (s, 3 H), 3.77 (s, 3 H), 3.88 (s, 4 H) (the three peaks remained singlets at −40 °C); (CD_3CN) δ 2.32 (s, 3 H), 3.68 (s, 3 H), 3.80 (s, 4 H); ($C_6H_5NO_2$) δ 2.43 (s, 3 H), 3.84 (s, 7 H); (C_6D_6) δ 2.32 (s, 3 H), 3.25–3.53 (m, 4 H), 3.42 (s, 3 H); selected ^{13}C NMR ($CDCl_3$) 47.7, 54.1 ppm (CH_2CH_2); MS *m/e* (rel %) 174 (100), 115 (66), 87 (47), 72 (64).

Anal. Calcd for $C_6H_{10}N_2O_2S$: C, 41.36; H, 5.79; N, 16.08. Found: C, 41.33; H, 5.76; N, 16.10.

***N*-Carbomethoxy-2-ethylthioimidazoline (38).** Using the method described for the preparation of **29, 38** was synthesized from 4.80 g (0.03 mol) of **16**[1] and 4.8 ml (0.06 mol) of EtI. The reaction was refluxed for 72 h. The product was purified by sublimation (55 °C, 1.0 mm) to yield 3.24 g (57%) of product: selected ^{13}C NMR ($CDCl_3$) 47.0, 53.9 ppm (CH_2CH_2); MS *m/e* (rel %) 188 (17), 160 (100), 155 (30), 129 (43), 102 (42), 72 (57), 70 (43), 59 (30).

Anal. Calcd for $C_7H_{12}N_2O_2S$: C, 44.66; H, 6.43; N, 14.88. Found: C, 44.45; H, 6.26; N, 14.79.

***N*-Methyl-2-methylthioimidazoline (31).** *N*-Methyl-2-methylthioimidazolinium hydriodide[41] (3.00 g, 0.012 mol) was dissolved in 50 ml of an aqueous 1 N NaOH (0.05 mol) solution and immediately extracted with CH_2Cl_2 (5 × 20 ml). The organic layer was dried (Na_2SO_4), evaporated in vacuo, and distilled to give a clear liquid, yield 0.63 g (40%): MS *m/e* (rel %) 130 (100), 105 (28), 100 (18), 87 (77), 72 (97), 56 (70); mol wt 130.0562 (calcd for $C_5H_{10}N_2S$, 130.0565).

***N*-Acetyl-2-allylthioimidazoline (34).** To a stirred CH_2Cl_2 solution containing **15**[12] (2.88 g, 0.02 mol) and Et_3N (8.08 g, 0.08 mol), 7.0 ml (0.08 mol) of allyl bromide was slowly added. The solution was gently refluxed for 330 h, then consecutively washed with aqueous 5% $NaHCO_3$ (2 × 50 ml) and H_2O (50 ml) and dried (Na_2SO_4). The CH_2Cl_2 layer was evaporated in vacuo, leaving an approximate 50:50 ratio of starting material to product. The mixture was triturated with hexanes (100 ml) and then filtered. The remaining residue was placed in a Soxhlet extractor and extracted with hexanes. The hexanes layer was filtered, combined with the initial hexanes layer, and evaporated in vacuo to give 1.66 g (45%) of the desired compound. The product was further purified by distillation: MS *m/e* (rel %) 184 (37), 182 (36), 169 (41), 141 (100), 70 (35).

Anal. Calcd for $C_8H_{12}N_2OS$: C, 52.14; H, 6.57; N, 15.21. Found: C, 52.19; H, 6.56; N, 15.23.

***N*-Acetyl-2-*p*-fluorobenzylthioimidazoline (35).** The preceding reaction was repeated using 2.88 g (0.02 mol) of **15**,[12] 8.08 g (0.08 mol) of Et_3N, and 9.0 ml (0.075 mol) of 4-fluorobenzyl chloride. The residue was triturated with hexanes (100 ml) and then the remaining solid was recrystallized from hot hexanes: yield 2.52 g (50%); MS *m/e* (rel %) 252 (100), 210 (61), 209 (50), 177 (22), 144 (61), 70 (21).

Anal. Calcd for $C_{12}H_{13}FN_2OS$: C, 57.12; H, 5.19; N, 11.10. Found: C, 57.01; H, 5.23; N, 11.18.

***N*-Carbomethoxy-2-allylthioimidazoline (39).** Using the method described for the preparation of **34, 39** was synthesized from 3.20 g (0.02 mol) of **16**,[1] 4.04 g (0.04 mol) of Et_3N, and 3.5 ml (0.04 mol) of allyl bromide. The solution was refluxed for 168 h. The remaining oil was distilled to yield 3.00 g (75%) of **39:** MS *m/e* (rel %) 200 (59), 185 (100), 141 (19), 72 (56).

Anal. Calcd for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04; N, 13.99. Found: C, 47.92; H, 6.16; N, 14.01.

2-(1′-Carbomethoxy-2′-imidazoline-2′-thiyl)ethyl Acetate (41). Compound **41** was synthesized in 22% yield (2.15 g) from 6.40 g (0.04 mol) of **16**,[1] 8.08 g (0.08 mol) of Et_3N, and 5.3 ml (0.048 mol) of ethyl chloroacetate using the method described for the preparation of **34.** The solution was refluxed for 72 h. Recrystallization of the remaining oil with hexanes (1000 ml) gave purified **41:** MS *m/e* (rel %) 246 (63), 201 (46), 173 (54), 160 (100), 113 (24), 102 (43), 72 (96), 70 (73), 59 (63), 56 (59).

Anal. Calcd for $C_9H_{14}N_2O_4S$: C, 43.89; H, 5.73; N, 11.38. Found: C, 43.98; H, 5.64; N, 11.41.

***N*-Carbomethoxy-2-*p*-fluorobenzylthioimidazoline (42).** Using the method described for the preparation of **34, 42** was synthesized from 3.20 g (0.02 mol) of **16**,[1] 4.04 g (0.04 mol) of Et_3N, and 4.5 ml (0.0375 mol) of 4-fluorobenzyl chloride. The solution was gently refluxed for 72 h. The crude product was recrystallized from hot hexane: yield 3.75 g (70%); MS *m/e* (rel %) 268 (100), 235 (14), 180 (10), 63 (25).

Anal. Calcd for $C_{12}H_{13}FN_2O_2S$: C, 53.72; H, 4.88; N, 10.44. Found: C, 53.81; H, 4.79; N, 10.44.

1-(1′-Carbomethoxy-2′-imidazoline-2′-thiyl)-2-propanone (40). To a stirred CH_2Cl_2 solution (250 ml) containing **16**[1] (4.96 g, 0.031 mol) and Et_3N (6.57 g, 0.065 mol), 4.8 ml of distilled chloroacetone (0.06 mol) was added all at once. The solution was allowed to stand at room temperature for 72 h, and then washed with aqueous 5% $NaHCO_3$ (2 × 100 ml) and H_2O (100 ml), and dried (Na_2SO_4). An additional 100 ml of CH_2Cl_2 was added to the organic layer and the whole solution was diluted to 1000 ml with hexanes. The solution was then concentrated in vacuo to 200 ml, causing a red-brown oil to rapidly drop out of solution. The oil was separated and the remaining solution was refrigerated overnight, resulting in the precipitation of 2.45 g (37%) of the desired product. A sample for elemental anaylsis was prepared by sublimation (60 °C, 0.2 mm): selected ^{13}C NMR ($CDCl_3$) 47.8 (t, $J_{^{13}C-H}$ = 155 Hz), 54.0 ppm (t, $J_{^{13}C-H}$ = 140 Hz) (CH_2CH_2); MS *m/e* (rel %) 216 (29), 201 (98), 199 (100), 115 (54), 72 (63), 70 (48).

Anal. Calcd for $C_8H_{12}N_2O_3S$: C, 44.43; H, 5.59; N, 12.96. Found: C, 44.41; H, 5.60; N, 13.00.

Acknowledgment. We would like to thank the National Institutes of Health (H.K.) and the Robert A. Welch Foundation (H.K., M.R.W.) for their support of our work. We also express our appreciation to Drs. Ralph H. Obenauf, JEOL; Chris Tanzer, Bruker; C. A. Reilley, Shell Research & Development, Houston, Texas; and Roger Knapp, Baylor College of Medicine, for assistance in obtaining ^{13}C NMR spectra.

Registry No.—**4,** 694-32-6; **5,** 5391-39-9; **6,** 41730-78-3; **7,** 80-73-9; **8,** 61076-68-4; **9,** 61076-69-5; **10,** 61076-70-8; **11,** 5391-40-2; **12,**

61076-71-9; **13**, 26407-92-1; **14**, 13431-10-2; **15**, 5391-52-6; **16**, 59863-98-8; **17**, 13461-16-0; **18**, 60546-76-1; **19**, 60546-78-3; **20**, 5391-53-7; **21**, 61076-72-0; **22**, 61076-73-1; **23**, 28118-54-9; **24**, 61076-74-2; **25**, 61076-75-3; **26**, 61076-76-4; **27**, 61076-77-5; **28**, 61076-78-6; **29**, 61076-79-7; **30**, 20112-79-2; **31**, 52839-23-3; **32**, 60546-75-0; **33**, 61076-80-0; **34**, 61076-81-1; **35**, 61076-82-2; **36**, 60498-94-4; **37**, 60546-77-2; **38**, 61076-83-3; **39**, 61076-84-4; **40**, 61076-85-5; **41**, 61076-86-6; **42**, 61076-87-7; **43**, 59863-93-3; methyl chloroformate, 79-22-1; ethyl chloroformate, 541-41-3; acetyl chloride, 75-36-5; imidazolidone, 120-93-4; imidazolidinethione, 96-45-7; *N*-methyl-2-methylthioimidazolinium HI, 61076-89-9; *N*-acetyl-2-methylthioimidazolinium HI, 61076-88-8; MeI, 74-88-4; allyl bromide, 106-95-6; 4-fluorobenzyl chloride, 352-11-4; ethyl chloroacetate, 105-39-5; chloroacetone, 78-95-5; *N*-methylethylenediamine, 109-81-9; ethyl carbonate, 105-58-8.

Supplementary Material Available. The complete experimental procedures employed for the preparation of all new compounds, the physical and spectral properties observed for all compounds, as well as two histograms summarizing extensive ^{13}C NMR data for the compounds reported herein (18 pages). Ordering information is given on any current masthead page.

References and Notes

(1) H. Kohn, *J. Am. Chem. Soc.*, **98**, 3690 (1976).
(2) R. F. Pratt and T. C. Bruice, *J. Am. Chem. Soc.*, **94**, 2823 (1972); R. F. Pratt and T. C. Bruice, *Biochemistry*, **10**, 3178 (1971).
(3) M. Caplow and M. Yager, *J. Am. Chem. Soc.*, **89**, 4513 (1967); M. Caplow, *ibid.*, **87**, 5774 (1965).
(4) H. J. Schaeffer and P. S. Bhargava, *J. Pharm. Sci.*, **51**, 1116 (1962); **53**, 137 (1964).
(5) J. Knappe and F. Lynen, *Colloq. Ges. Physiol. Chem.*, **74**, 265 (1963).
(6) J. Knappe, *Int. Congr. Biochem., Proc., 6th*, **32**, 355 (1965).
(7) Y. Akasaki and A. Ohno, *J. Am. Chem. Soc.*, **96**, 1957 (1974).
(8) For reviews, see (a) W. T. Comer and A. W. Gomoll, "Medicinal Chemistry", Part II, 3d ed, A. Burger, Ed., Wiley-Interscience, New York, N.Y., 1970, Chapter 39, p 1019; (b) J. N. Delgado and E. I. Isaacson, ibid., Chapter 52, p 1386; (c) A. Krentzberger, *Prog. Drug Res.*, **11**, 356 (1968).
(9) H. Kohn, B. A. Kohn, M. L. Steenberg, and J. P. Buckley, *J. Med. Chem.*, **20**, 158 (1977).
(10) J. L. Marx, *Science*, **191**, 57 (1976).
(11) (a) J. Moss and M. D. Lane, *Adv. Enzymol.*, **35**, 321 (1971); (b) J. Knappe, *Annu. Rev. Biochem.*, **39**, 757 (1970); (c) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms", Vol. II, W. A. Benjamin, New York, N.Y., 1966, Chapter 11; see also these references for a review of the earlier literature.
(12) J. G. Roberts, *J. Chem. Soc.*, 176 (1964).
(13) R. Greenhalgh and M. A. Weinberger, *Can. J. Chem.*, **43**, 3340 (1965).
(14) H. Kohn, J. H. Arceneaux, and M. J. Cravey, unpublished results.
(15) Unlike their parent compounds, the substitution of sulfur for the oxygen at the central carbonyl position of the acyl substituted imidazolidones did not always raise the melting point of the substrate.[16] Most of the newly prepared acyl substituted thioimidazolines, however, did melt higher than their imidazoline counterparts.
(16) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds", Vol. 1, W. A. Benjamin, New York, N.Y., 1965, Chapter 6, p 233.
(17) H. K. Hall and A. K. Schneider, *J. Am. Chem. Soc.*, **80**, 6409 (1958).
(18) J. W. Schulenberg and S. Archer, *Org. React.*, **14**, 1 (1965), and references cited therein.
(19) C. G. McCarty, "The Chemistry of the Carbon-Nitrogen Double Bond", S. Patai, Ed., Interscience, New York, N.Y., 1970, Chapter 9, p 363, and references cited therein.
(20) A. F. Hegarty and T. C. Bruice, *J. Am. Chem. Soc.*, **92**, 6561, 6568, 6575 (1970); A. F. Hegarty, R. F. Pratt, T. Giudici, and T. C. Bruice, *ibid.*, **93**, 1428 (1971); T. C. Bruice and A. F. Hegarty, *Proc. Natl. Acad. Sci. U.S.A.*, **65**, 805 (1970).
(21) A. E. Dixon and J. Taylor, *J. Chem. Soc.*, **117**, 720 (1920).
(22) D. Y. Curtin and L. L. Miller, *Tetrahedron Lett.*, 1869 (1965).
(23) H. Meerwein, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 1096.
(24) Reference 23, p 1080.
(25) C. J. Sharpe, R. S. Shadbolt, A. Ashford, and J. W. Ross, *J. Med. Chem.*, **14**, 977 (1971).
(26) F. W. McLafferty, "Interpretation of Mass Spectra", 2d ed, W. A. Benjamin, New York, N.Y., 1973, Chapter 4, p 40.
(27) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day, San Francisco, Calif., 1967, Chapters 4, 9, 15.
(28) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules", Wiley, New York, N.Y., 1958; see also this reference for a review of the earlier literature.
(29) L. J. Bellamy, "Advances in Infra-red Group Frequencies", Methuen, London, 1968, and references cited therein.
(30) K. Nakanishi, "Infra-red Absorption Spectroscopy", Holden-Day, San Francisco, Calif., 1969.
(31) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2d ed, Pergamon Press, Elmsford, N.Y., 1969; see in particular Part 3, p 159.
(32) N. F. Chamberlain and J. J. R. Reed, "The Analytical Chemistry of Sulfur and Its Compounds", Part 3, J. H. Karchmer, Ed., Wiley-Interscience, New York, N.Y., 1971, p 287.
(33) This unusual resonance has already been used to advantage in examining the thermal rearrangement of *N*-acetyl-2-allythioimidazoline (**34**) to the isomeric *N*-acetyl-*N'*-allylimidazolidinethione. In this case the acetyl resonances appeared at δ 2.20 and 2.81, respectively.[34]
(34) H. Kohn and J. H. Arceneaux, unpublished results.
(35) These spectra were obtained using a variety of spectrometers as noted in Figures 1 and 2. It is gratifying that the reproducibility from spectrometer to spectrometer was within the experimental error of the measurements.
(36) L. M. Jackman and T. Jen, *J. Am. Chem. Soc.*, **97**, 2811 (1975).
(37) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, and references cited therein.
(38) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, and references cited therein.
(39) H. O. Kalinowski and H. Kessler, *Angew. Chem., Int. Ed. Engl.*, **13**, 90 (1974).
(40) J. G. Frick, B. A. Kottis, and J. D. Reid, *Text. Res. J.*, **29**, 314 (1959).
(41) A. F. McKay and M. E. Kreling, *J. Org. Chem.*, **22**, 1581 (1957).

A Short Synthesis of Aromatic Analogues of the Aranotins

David L. Coffen,* David A. Katonak, Nels R. Nelson, and Fred D. Sancilio

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received September 17, 1976

Various pyrazino[1,2-*a*:4,5'-*a'*]diindoles have been synthesized corresponding in structure to the diketopiperazine type dimers of indole- and indoline-2-carboxylic acids. 7,14-Dihydroxy-6*H*,13*H*-pyrazino[1,2-*a*:4,5-*a'*]diindole-6,13-dione reacted with sulfur monochloride and pyridine to give epidithio and epitrithio derivatives. These are aromatic analogues of the aranotins. The structure of the epitrithio derivative was verified by single-crystal x-ray crystallography. The space group is $P_{2_1}P_{2_1}P_{2_1}$ with pertinent cell data as follows: a = 9.199 (4), b = 13.846 (4), c = 13.248 (3) Å, and Z = 4.

The aranotins are a small group of sulfur-bridged diketopiperazines produced by the fungal species *Arachniotus aureus* and *Aspergillus terreus*.[1] The compounds have elicited attention from chemotherapists because of their antiviral activity which is observed in both in vivo and in vitro testing.[2]

Aranotin (**1**) and acetylaranotin (**2**, also known as LL-S88$_{(1)}$) are naturally occurring members of the group. Compounds **3** and **4** are partially synthetic members obtained by chemical modifications of acetylaranotin.[3] Since the dihydrooxepin rings may not be crucial to the biological activity of this series,[4] a synthesis of some aromatic analogues was initiated and led