Identification of the Condensation Products of 1,2- and 1,3-Amino Alcohols with Keto Esters by NMR Spectroscopy, Mass Spectrometry and X-Ray Crystallography Studies. Open or Ring Forms?

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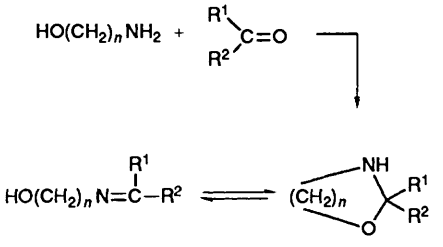
The structure of fifteen products of the condensation of 1,2- and 1,3-amino alcohols with different keto esters has been studied in the solid state, in non-polar solution and in the gas phase by X-ray crystallography, nuclear magnetic resonance spectroscopy and mass spectrometry. The 1,3-keto esters gave rise to open-chain products stabilized by a conjugated double-bond system formed through a hydrogen-atom rearrangement from the expected Schiff base. In the gas phase, the ring form was also observed. 1,4- and 1,5-keto esters gave 1,3-oxazolidines and tetrahydro-1,3-oxazines as primary products, which were easily converted into bicyclic lactams. The mass spectral fragmentations of the compounds are discussed in detail.

Substituted 1,3-oxazolidines and perhydro-1,3-oxazines are compounds with potential biological and pharmacological activity on their own or as a part of more complicated molecules.[1,2] They are also important in synthesis. In particular, 1,3-oxazolidines are used as chiral auxiliaries in asymmetric synthesis[3] and in resolution of chiral aldehydes.[4]

The conventional method[2,5] of synthesizing 1,3-oxazolidines and perhydro-1,3-oxazines is the condensation of primary 1,2- or 1,3-amino alcohols with aldehydes and ketones. Different products are formed depending on the substitution of the amino alcohol and the nature of the aldehyde and ketone. In addition to heterocycles, open-chain Schiff bases and dynamic tautomeric mixtures of both forms (Scheme 1) are found.[6] In non-



Scheme 1

polar solvents the condensation products of amino alcohols with a primary amino group mostly exist as a tautomeric equilibrium mixture, but a secondary amino group can lead only to ring compounds.[7] The situation in the gas phase appears to be similar to that in non-polar solvents.[8]

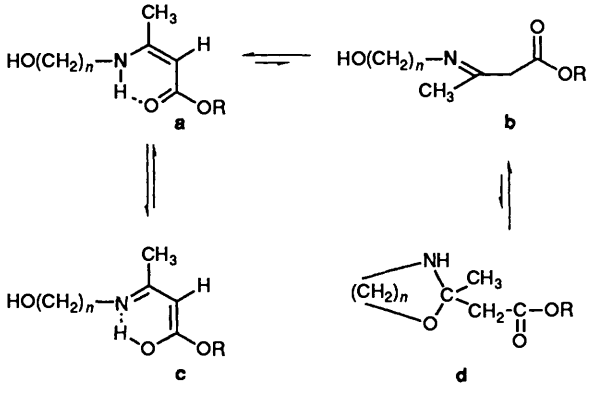
Meyers *et al.*[9] report that bicyclic lactams are formed in the reaction of γ-keto acids with *l*-valinol. These lactams have been used successfully as intermediates in the asymmetric synthesis of chiral quaternary-carbon compounds.[9,10]

In this paper we examine in detail the gas-phase, solution and solid-state structural properties of the condensation products formed in the reaction of 1,2- and 1,3-amino alcohols with 1,3-, 1,4- and 1,5-keto esters. Mass spectrometry, ^1H and ^{13}C NMR spectroscopy, and in some cases also COSY, NOESY and ^1H–^{13}C correlated NMR, and single crystal X-ray analysis have been used to verify the structures. Because the mass spectrometric behaviour of this type of compound is not well known, the detailed fragmentation patterns were also determined using metastable-ion analysis and exact mass measurement. The collision-induced dissociation (CID) technique[11] was used to compare some of the ion structures; most of the structures indicated are speculative, however, and merely meant as an aid to the visualization of the fragmentation processes.

Results and Discussion

The compounds studied were prepared from the 1,2- or 1,3-amino alcohols and keto esters by azeotropic removal of water with dichloromethane or toluene; the expected products were 1,3-oxazolidines and tetrahydro-1,3-oxazines or the related Schiff bases (Scheme 1).

1,3-Keto esters yielded crystalline solids (**1**–**4**) possessing an open chain structure (Scheme 2). According to the NMR results



Compound	*n*	R
1	2	CH_3
2	2	CH_2CH_3
3	3	CH_3
4	3	CH_2CH_3

Scheme 2

(Tables 1 and 2), no ring form (**d**) was present. The structure of the open-chain form was not, however, that of the expected imine **b**. In the ^{13}C NMR spectra C-2 gave rise to a doublet, which indicated the presence of a CH group in this position as in structures **a** and/or **b**, both of which are stabilized by a

conjugated double bond system and an intramolecular hydrogen bond between NH and C=O groups. The $^3J_{CH}$ coupling from the methyl carbon to the double bond hydrogen likewise indicated that these two groups were *cis*-orientated.[12] Structure **a** was clearly predominant, since the chemical shift of C-1 indicated that it was a carbonyl rather than ethylenic carbon. The chemical shifts of C-2 and C-3 were quite unusual, however, clearly suggesting rapid equilibrium between different open-chain structures.

The results of the X-ray analysis of compound **1** in the solid state completely paralleled the results in the liquid phase, showing the existence of the open-chain structure as presented in Fig. 1. The observed N(4)···O(2) distance of 2.754 Å indicated an intramolecular hydrogen bond between these atoms, and the participating proton could be bound to either N(4) or O(2). Fourier difference maps showed it to belong, in fact, to N(4), supporting structure **a** in Scheme 2. The bond lengths and angles in the hydrogen-bonded, six-membered ring (Table 3) nevertheless showed delocalized π bonding. By contrast, the O(3)···N(4) intramolecular distance of 2.925 Å was not a hydrogen-bond interaction since there was no proton in this direction, but O(3) was hydrogen-bonded to O(2) in the neighbouring molecule [O(3)···O(2) 2.847, O(3)–H 0.93 and H···O(2) 1.970 Å].

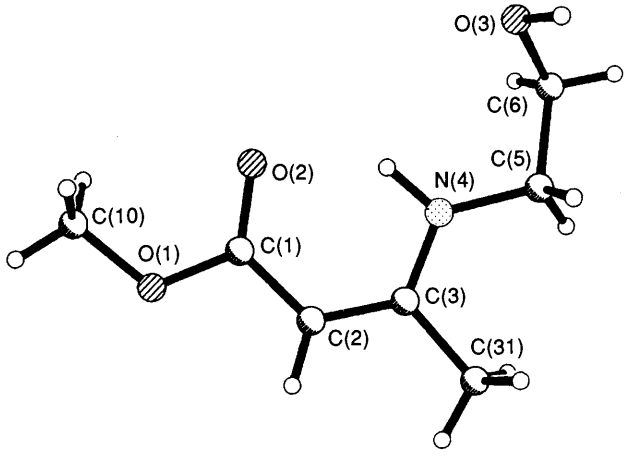


Fig. 1 Molecular structure of compound **1**

The gas-phase structures of compounds **1–4** differed slightly from those observed in solution and in the solid state. Although the 70 eV mass spectra, presented in Fig. 2 and Table 4, were best rationalized in terms of the predominance of the open-chain forms, certain features in the spectra indicated that, to some extent, the ring form was also present in the gas phase.

The main fragmentation routes for compound **2** are presented in Scheme 3. The most important pathway, which most reasonably proceeds from the open-chain forms, started with the loss of $CH_3O^\bullet$ through an α-cleavage reaction with respect to the nitrogen atom. This was followed by the elimination of ethanol through a hydrogen-atom rearrangement leading to the formation of the $[C_5H_6NO]^+$ ion at *m/z* 96 (base peak). These fragmentations as well as the elimination of $C_2H_5O^\bullet$ from the molecular ion were completely absent from the spectrum of compound **5** (Fig. 2) where the formation of the open-chain form is prohibited by an *N*-methyl substituent.

The ions at *m/z* 96 also formed the base peak of the spectra of compounds **1**, **3** and **4**. In these three compounds, as well as in compound **2**, this ion had a similar structure or mixture of structures as can be seen from the CID spectra in Table 5. Slight differences existed in the spectra of the tetrahydrooxazines **3** and **4** compared with those of the oxazolidines **1** and **2** most probably because, for compounds **3** and **4**, the *m/z* 96 ions were formed *via* three different routes in contrast with only one route for compounds **1** and **2**. The main route was the same as for compounds **1** and **2**, however. The decompositions of the $[C_5H_6NO]^+$ ions at *m/z* 96 (Table 5) are best explained if the ions are considered to be formed from all the open-chain forms **a–c**. Without extensive rearrangements the *m/z* 55 ion could most easily have originated from forms **b** or **d**, whereas the loss of 28 and 29 mass units leading to the formation of the *m/z* 68 and 67 ions are best associated with form **a**. The formation of the *m/z* 55 ion was the only process that gave rise to metastable transition, and since this is the lowest-energy fragmentation pathway it must originate in form **b**, which, lacking conjugation,

Table 1 ^{1}H chemical shifts for compounds **1–4**

$HOCH_2CH_2CH_2NH–C(CH_3)=CHC(O)OCH_2CH_3$
a b

Compound	1	2	3	4
NH	8.65 br s	8.68 br s	8.54 br s	8.56 br s
OH	2.59 br s	2.16 br s	2.17 br s	2.08 br s
OCH_2	3.73 t	3.74 t	3.72 t	3.72 t
OCH_2CH_2	—	—	1.79 m	1.79 m
NCH_2	3.36 t + d	3.36 t + d	3.34 t + d	3.33 t + d
CH_3	1.93 s	1.94 s	1.92 s	1.91 s
=CH	4.47 s	4.48 s	4.43 s	4.42 s
a	3.60 s	4.07 q	3.59 s	4.05 s
b	—	1.24 t	—	1.22 t

Table 3 Bond lengths/Å and angles/° for $C_7H_{13}NO_3$ (**1**)

O(1)–C(1)	1.353(7)	C(1)–O(1)–C(10)	116.5(4)
O(1)–C(10)	1.450(8)	C(3)–N(4)–C(5)	125.1(6)
O(2)–C(1)	1.236(7)	O(1)–C(1)–O(2)	122.1(6)
O(3)–C(6)	1.417(8)	O(1)–C(1)–C(2)	112.6(5)
N(4)–C(3)	1.337(7)	O(2)–C(1)–C(2)	125.3(6)
N(4)–C(5)	1.459(8)	C(1)–C(2)–C(3)	124.3(5)
C(1)–C(2)	1.421(10)	N(4)–C(3)–C(2)	122.6(6)
C(2)–C(3)	1.385(9)	N(4)–C(3)–C(31)	118.2(6)
C(3)–C(31)	1.491(10)	C(2)–C(3)–C(31)	119.2(5)
C(5)–C(6)	1.503(9)	N(4)–C(5)–C(6)	110.5(6)
		O(3)–C(6)–C(5)	112.6(6)

Table 2 ^{13}C Chemical shifts for compounds **1–4**

$HOCH_2CH_2CH_2NH–C(CH_3)=CHC(O)OCH_2CH_3$
a b

	δ_C (ppm relative to Me_4Si)								
Compd.	C=O	C=*C*H	*C*=CH	NCH_2	OCH_2CH_2	$HOCH_2$	CH_3	a	b
1	170.93 s	82.25 d	162.12 s	45.02 t	—	61.79 t	19.44 q	49.88 q	—
2	170.64 s	82.64 d	161.99 s	45.02 t	—	61.77 t	19.44 q	58.31 t	14.46 q
3	170.85 s	81.41 d	162.18 s	39.57 t	32.74 t	59.30 t	19.09 q	49.72 q	—
4	170.44 s	81.67 d	161.99 s	39.44 t	32.67 t	59.06 t	18.96 q	58.01 t	14.27 q

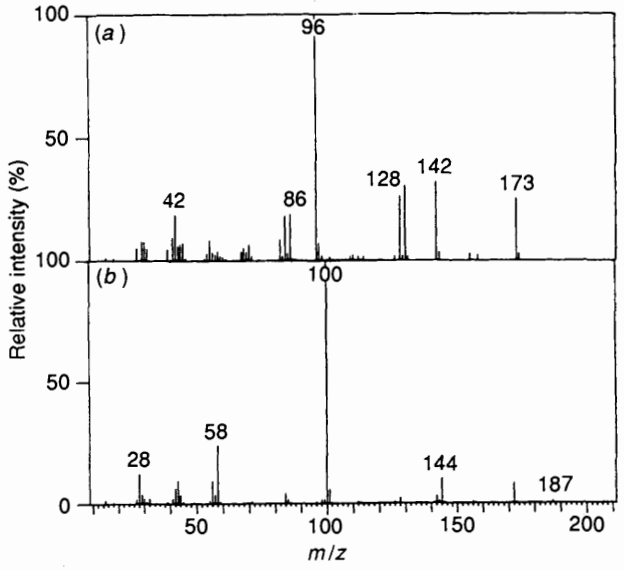
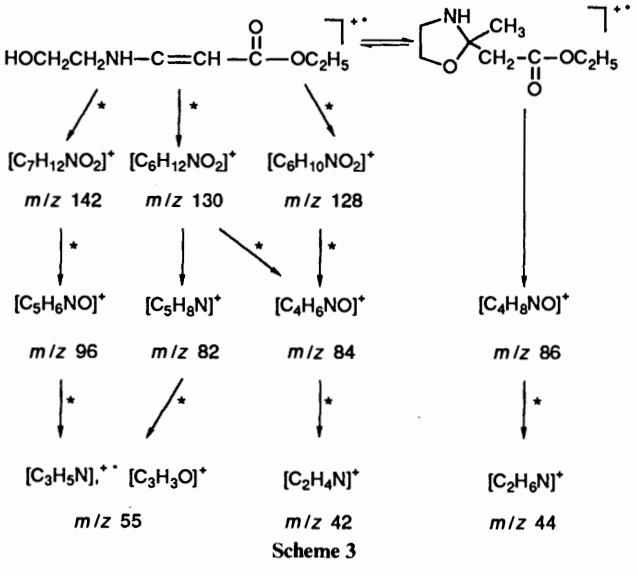


Fig. 2 70 eV mass spectrum of (*a*) ethyl 6-hydroxy-3-methyl-4-azahex-2-enoate (**2**) and (*b*) ethyl 2,3-dimethyl-1,3-oxazolidin-2-ylacetate (**5**)



Scheme 3

is the most unstable structure of the open-form structures. It should be remembered, however, that the collision-induced dissociation process itself can cause isomerization.

The existence of the $[C_4H_8NO]^+$ and $[C_5H_{10}NO]^+$ ion peaks at *m/z* 86 and 100 in the mass spectra of 1,3-oxazolidines (**1**, **2**) and tetrahydro-1,3-oxazines (**3**, **4**), respectively, strongly indicated the presence of the ring form in the gas phase. The elimination of the larger substituent at position 2 in the ring would be very favourable as can be seen by comparison with the spectrum of compound **5** (Fig. 2) and other related compounds.[13] The formation of the *m/z* 86 and 100 ions would also be possible from structure **b**, although according to the elemental principles of mass spectral fragmentations not very likely. The absence of the *m/z* 86 ions from the CID spectra of the molecular ions of compounds **1** and **2** showed that their mother ions were completely decomposed in the ion source, in accordance with the low stability of the ring forms towards electron ionization (*cf.* the spectra of ring compounds in Table 4).

The gas-phase structures of compounds **1**–**4** were also examined under ND_3 chemical ionization in order to determine the number of active hydrogen atoms in the molecules.[14] In all the spectra observed, the $[M + D + 3]^+$ ion gave rise to the base peak, showing the presence of three active hydrogens and thus indicating structures **a** or **c** or both. Small $[M + D + 1]^+$ and $[M + D + 2]^+$ ion peaks also existed, showing that the ring form **d** cannot be excluded. Some hydrogen-atom scrambling must have taken place because peaks originating in the exchange of 4–6 hydrogens were present. However, the dominance of the $[M + D + 3]^+$ ions was unquestioned.

Both ethyl 4-oxopentanoate and methyl 5-oxoheptanoate gave product mixtures in condensation with 2-aminoethanol when dichloromethane was used as solvent (Table 6). Gas chromatography showed that 1,3-oxazolidine formed first, and

Table 4 70 eV mass spectra of the compounds synthesized. Peaks with relative intensities greater than 5% of the intensity of the base peak are included unless not due to a molecular ion. The spectra are uncorrected for isotopic contributions.

Compd.	*m/z* (relative intensity)
1	$M^{+\cdot}$ 159 (29), 129 (5), 128 (56), 116 (32), 97 (8), 96 (100), 86 (13), 84 (16), 82 (11), 70 (5), 69 (5), 68 (8), 67 (6), 59 (5), 56 (6), 55 (17), 45 (13), 43 (9), 42 (27), 41 (15), 39 (9), 30 (11), 29 (5), 27 (5), 15 (5)
3	174 (7), $M^{+\cdot}$ 173 (48), 156 (9), 142 (56), 130 (7), 129 (94), 128 (13), 124 (10), 112 (7), 110 (28), 100 (16), 98 (16), 97 (17), 96 (100), 84 (24), 83 (6), 82 (17), 74 (16), 71 (20), 70 (35), 69 (18), 68 (27), 67 (12), 59 (17), 57 (7), 56 (27), 55 (24), 54 (12), 45 (9), 44 (9), 43 (16), 42 (62), 41 (41), 39 (19), 31 (27), 30 (19), 29 (13), 27 (12), 15 (10)
4	188 (8), $M^{+\cdot}$ 187 (53), 172 (5), 170 (8), 156 (15), 144 (8), 143 (86), 142 (70), 140 (11), 139 (9), 124 (11), 115 (9), 114 (8), 112 (6), 110 (28), 100 (25), 98 (10), 97 (16), 96 (100), 88 (6), 84 (36), 82 (15), 72 (7), 71 (76), 70 (41), 69 (16), 68 (19), 67 (10), 60 (5), 59 (10), 58 (6), 57 (11), 56 (26), 55 (19), 54 (10), 45 (6), 44 (9), 43 (14), 42 (63), 41 (41), 40 (6), 39 (17), 31 (35), 30 (29), 29 (30), 27 (21), 15 (6)
7	$M^{+\cdot}$ 155 (2), 141 (8), 140 (100), 127 (5), 112 (6), 99 (10), 97 (5), 86 (24), 85 (10), 70 (8), 69 (8), 55 (32), 44 (71), 43 (13), 42 (15), 41 (13), 39 (7), 27 (7)
9	$M^{+\cdot}$ 201 (<1), 186 (7), 171 (6), 158 (6), 156 (38), 129 (8), 128 (50), 112 (10), 110 (13), 101 (8), 100 (100), 99 (6), 98 (27), 96 (5), 85 (10), 84 (51), 83 (5), 82 (28), 72 (11), 70 (13), 68 (6), 59 (70), 58 (6), 57 (6), 56 (12), 55 (23), 54 (8), 44 (7), 43 (10), 42 (88), 41 (27), 39 (6), 31 (38), 30 (17), 29 (19), 28 (18), 27 (13)
10	$M^{+\cdot}$ 201 (–), 186 (10), 156 (18), 112 (6), 101 (7), 100 (100), 98 (6), 58 (38), 56 (6), 43 (9), 42 (5), 29 (5)
11	$M^{+\cdot}$ 155 (3), 141 (9), 140 (100), 125 (17), 112 (28), 110 (8), 99 (8), 98 (9), 97 (21), 84 (11), 82 (7), 69 (9), 58 (14), 56 (40), 55 (15), 43 (14), 42 (14), 41 (15), 30 (7), 27 (8)
12	$M^{+\cdot}$ 169 (<1), 155 (9), 154 (100), 126 (20), 113 (5), 111 (12), 100 (6), 99 (9), 98 (24), 83 (20), 70 (6), 58 (17), 56 (9), 55 (25), 43 (18), 42 (20), 41 (16), 39 (6), 30 (12), 27 (8)
13	$M^{+\cdot}$ 187 (<1), 172 (5), 157 (5), 156 (38), 140 (7), 128 (7), 114 (10), 112 (5), 101 (34), 98 (6), 96 (19), 87 (7), 86 (100), 85 (5), 84 (13), 82 (7), 71 (8), 70 (23), 68 (6), 59 (5), 58 (16), 57 (6), 56 (8), 55 (22), 45 (25), 44 (45), 43 (14), 42 (44), 41 (15), 39 (6), 30 (8), 27 (7), 15 (5)
14	$M^{+\cdot}$ 201 (<1), 186 (6). 170 (24), 157 (11), 156 (8), 142 (18), 129 (5), 128 (25), 126 (6), 115 (42), 112 (5), 100 (64), 98 (26), 96 (32), 85 (21), 84 (48), 82 (9), 74 (6), 72 (12), 71 (100), 70 (21), 69 (6), 68 (10), 59 (64), 58 (9), 57 (10), 56 (10), 55 (24), 54 (6), 43 (10), 42 (88), 41 (37), 39 (8), 31 (38), 29 (8), 28 (12), 27 (9), 15 (9)
15	$M^{+\cdot}$ 201 (–), 186 (14), 170 (13), 112 (13), 101 (8), 100 (100), 59 (5), 58 (30), 56 (5), 55 (18), 44 (6), 43 (8), 42 (6)

Table 5 The CID spectra of the *m/z* 96 ions generated from compounds **1**–**4**. Intensities are normalized to a total fragment-ion abundance of 100. The data are not corrected for metastable peaks

m/z	**1**	**2**	**3**	**4**
26	—	—	—	1.8
27	—	1.6	1.4	0.8
28	—	—	1.7	1.8
29	—	—	—	2.9
30	—	—	2.4	2.8
38	2.0	3.0	1.7	2.0
39	10.4	10.7	8.8	8.4
40	3.8	3.7	3.1	2.2
41	5.5	5.8	6.1	7.0
42	2.5	3.1	4.4	5.9
43	—	—	1.6	2.2
52	5.2	5.3	3.3	3.3
53	3.9	3.6	4.0	2.1
54	3.7	3.6	3.8	3.8
55	22.7	20.4	15.8	13.7
56	5.0	5.1	4.8	3.8
66	—	0.5	—	—
67	22.8	23.0	15.1	14.1
68	10.3	10.8	7.7	7.3
69	2.0	1.8	6.6	7.2
80	—	—	1.6	1.0
81	—	—	3.4	2.3
94	—	—	3.7	3.8

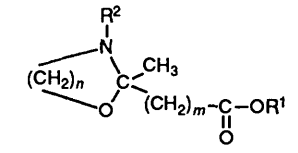
Table 6 Product distribution (%) in the condensation reaction of 2-aminoethanol with ethyl 4-oxopentanoate in different solvents as a function of time

Solvent	*T*/°C	Product	*t*/h 2	4	6	24
CH_2Cl_2	40	**6**	1.3	1.7	2.2	11.1
		8	98.7	98.3	97.8	88.9
CH_2Cl_2 + *p*-TsOH	40	**6**	1.4	2.8	6.3	15.4
		8	98.6	97.2	93.7	84.6
C_6H_6	80	**6**	15.2	37.6	47.8	100
		8	84.8	62.4	52.2	—
$C_6H_5CH_3$	110	**6**	55.0	86.2	96.4	100
		8	45.0	13.8	3.6	—
C_2H_5OH	25	**6**	12.3	39.0	57.9	100
		8	87.7	61.0	42.1	—

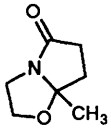
Table 7 ^{1}H Chemical shifts for compounds **6**, **7**, **11** and **12**

Signal	Compound **6**	**7**	**11**	**12**
OCH_2	3.85	3.99	3.98	3.96/3.77
NCH_2	3.92/3.09	4.07/3.05	3.98/3.33	4.65/2.90
OCH_2CH_2	—	1.74/1.46	—	1.85/1.50
$COCH_2$	2.11	2.05	2.35	2.35
CCH_2	2.64/2.41	2.45/2.36	2.07/1.58	1.85
CCH_2CH_2	—	—	1.87/1.73	1.80/1.65
CH_3	1.35	1.54	1.33	1.55

[a] CH_3 signals were singlets; all other signals were complicated multiplets.



Compound	*n*	*m*	R^1	R^2
5	2	1	CH_2CH_3	CH_3
8	2	2	CH_2CH_3	H
9	3	2	CH_2CH_3	H
10	2	2	CH_2CH_3	CH_3
13	2	3	CH_3	H
14	3	3	CH_3	H
15	2	3	CH_3	CH_3



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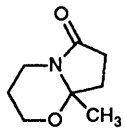

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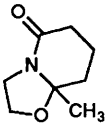

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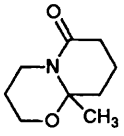

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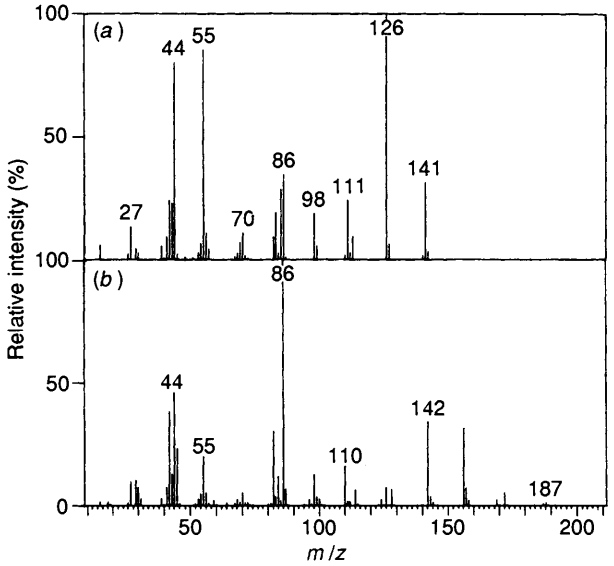


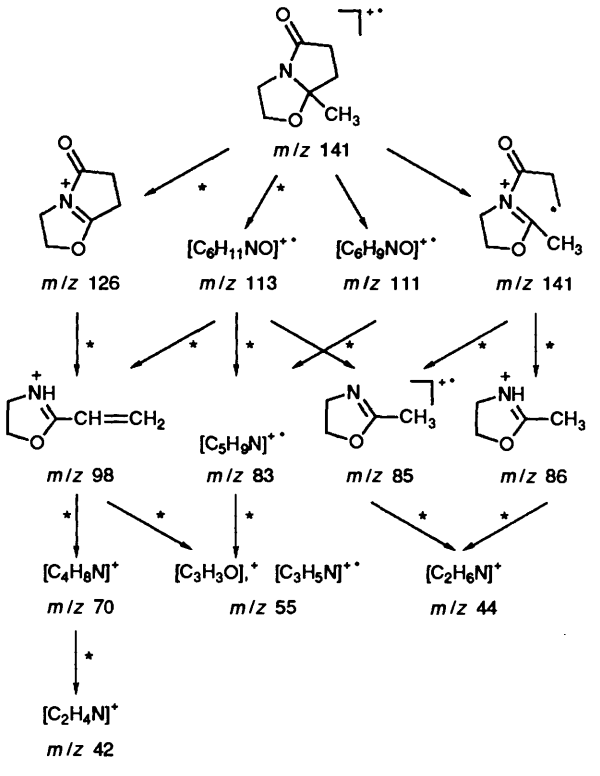
Fig. 3 70 eV mass spectrum of (*a*) 5-methyl-4-oxa-1-azabicyclo[3.3.0]octan-8-one (**6**) and (*b*) ethyl 2-methyl-1,3-oxazolidin-2-ylpropanoate (**8**)

with time and higher temperature decomposed to a compound with a bicyclic lactam structure. In ethanol, which is capable of participating in the nucleophilic substitution reaction involved in the oxazolidine-ring formation,[15] the formation of the lactam structure occurred at room temperature, as can be seen from the results in Table 6. 3-Aminopropan-1-ol behaved analogously to 2-aminoethanol, whereas 2-methylaminoethanol gave rise only to 1,3-oxazolidines (**10** and **15**).

Bicyclic lactam structures (compounds **6**, **7**, **11** and **12**), first identified by mass spectrometry were verified by ^{1}H and ^{13}C NMR spectroscopy. The chemical shifts are reported in Tables

Table 8 ^{13}C Chemical shifts for compounds **6**, **7**, **11** and **12**

Signals	Compound			
	6	**7**	**11**	**12**
C=O	178.44	173.16	167.16	168.57
O–C–N	99.32	89.70	91.52	86.07
OCH_2	65.35	60.77	61.63	60.01
NCH_2	41.13	35.00	40.96	34.50
OCH_2CH_2	—	24.58	—	25.30
$COCH_2$	32.36	33.40	29.61	32.31
$C\text{-}CH_2$	32.51	28.80	33.53	37.20
CCH_2CH_2	—	—	16.59	16.47
CH_3	23.61	19.82	22.08	20.70



Scheme 4

7 and 8. Because the proton spectra were moderately complicated, COSY and ^1H–^{13}C-correlated spectra were also run to allow exact assignment of the equatorial and axial protons on every hydrogen-bearing carbon. Especially noteworthy was the unusually large difference in the chemical shifts of the equatorial and axial protons on the carbon next to the nitrogen atom (Table 7). This, however, is in accordance with the results observed by Böhlmann and Schumann[16] for some bicyclic nitrogen heterocycles. Coupling constants were not calculated because the extensive computer simulation that was needed was not available.

The 70 eV mass spectra of compounds **6**, **7**, **11** and **12** (Fig. 3 and Table 4) were also completely in accordance with the bicyclic lactam structure, as can be seen in Scheme 4 where the most important fragmentation routes for compound **6** are presented. As expected, the nitrogen atom most affected the fragmentation behaviour. The routes leading to the most abundant fragment ions started with an α-cleavage reaction with respect to the nitrogen atom, usually followed by a hydrogen-atom rearrangement to the nitrogen resulting in C–N bond cleavage. In principle, 1,3-oxazolidine (**6**, **7**) and tetrahydro-1,3-oxazine (**11**, **12**) derivatives behaved similarly, the major difference being in the decomposition of the $[M - CH_3]^+$ ions. Whereas the ions generated from compounds **6** and **7** lost CO, as presented in Scheme 4, the ions from compounds **11** and **12** eliminated C_2H_4 as a consequence of a retro-Diels–Alder reaction made possible by the double bond formed through the α-cleavage reaction, now in the six-membered tetrahydro-1,3-oxazine ring.

The ND_3 chemical ionization spectra also verified the lactam structure by showing that no active hydrogen atoms were present in the molecules. Unlike compounds **1**–**4**, with the bicyclic lactams no hydrogen atom scrambling took place; only $[M + 2]^+$ ions were observed.

The expected ring compounds **8**–**10** and **13**–**15** were identified only by mass spectrometry. The spectra of the *N*-methyl-substituted compounds **10** and **15** were simple and easy to rationalize (Table 4). As with compound **5**, and typically for this kind of 1,3-heterocycle, the loss of the largest substituent from position 2 totally dominated the fragmentations.[13,17]

With compounds **8**, **9**, **13** and **14**, the results indicate some kind of ring–chain tautomeric equilibrium (Scheme 1), at least in the gas phase. In addition to the elimination of the larger substituent from position 2, the loss of the ester group, $CH_3O^•$ or $C_2H_5O^•$, was favourable, and in the case of the oxazines (**9**, **14**) also the elimination of $C_2H_4O^•$ from the ring. These are all features that point to 1,3-oxazolidine and tetrahydro-1,3-oxazine structures.[13,17] Some fragmentations are, however, hard to explain without invoking the presence of the open-form Schiff base, *e.g.* the formation of an abundant $[M - CH_3O]^+$ ion in the case of compound **8**.

Because compounds **8**–**10** and **13**–**15** gave rise to tiny molecular ion peaks or no molecular ion peaks at all, their molecular weights were checked by chemical ionization using methane as the reagent gas. All showed an intense $[M + H]^+$ ion peak at the expected mass number.

It has, on many occasions, been suggested that thermal and mass spectrometric decompositions of organic compounds might resemble each other.[18] With compounds **8**, **9**, **13** and **14** this most certainly was not the case. Although in solution they decomposed easily to bicyclic lactams, there was little or no indication of lactam formation in the mass spectrometer, under either electron impact or chemical ionization conditions. Whereas all the bicyclic lactams gave rise to very intense $[M - CH_3]^+$ ion peaks, the corresponding peaks in the spectra of compounds **8**, **9**, **13** and **14** were small or totally absent. This is surprising since with 1,3-dioxolanes formed from 4-oxopentanoates, relative lactone formation is quite favourable, although in this case the bicyclic structure generally decomposes further to a single-ring lactone.[19] Under chemical ionization, both 4-oxopentanoate derivatives and 5-oxohexanoate derivatives readily give rise to lactone formation.[20]

Conclusions

The structure of the condensation products of keto esters with primary amino alcohols depends on the structure of the keto ester and also to some extent on reaction conditions.

1,3-Keto esters give open-chain products stabilized by a conjugated double-bond system, although a rapid tautomeric equilibrium between different open-chain forms exists in solution and the solid state. In the gas phase, the ring form also participates in the equilibrium.

1,4- and 1,5-keto esters formed 1,3-*O*,*N*-heterocyclic compounds which readily lost alcohol from the sidechain forming stable bicyclic lactams. Although this lactam formation was extremely favourable in solution, little or no lactam was formed in the gas phase.

Experimental

Melting points were determined with a Büchi melting-point

Table 9 Crystal data and details of the crystallographic analysis of $C_7H_{13}NO_3$ (1)

M_r	159.21
Space group	$Pca2_1$
a/Å	22.163(7)
b/Å	4.602(2)
c/Å	8.384(5)
Z	4
Crystal dimensions/mm	0.30 × 0.35 × 0.35
D_c/g cm^{-3}	1.24
F(000)	344
Radiation	Mo-Kα
μ/cm^{-1}	0.90
Scan range/°	$4.0 < 2\theta < 50.0$
Scan type	ω
Number of unique data	811
Number $F_{obs} > 3\sigma(F)$	502
Residual density:	
Maximum (e cm^{23})	0.2
Minimum (e cm^{-3})	0.2
R	0.054
R′	0.045
g	0.0005
Goodness of fit	1.14

Table 10 Non-hydrogen atomic co-ordinates (× 10^4) for $C_7H_{13}NO_3$ (1)

O(1)	6971(2)	4290(10)	5000
O(2)	6086(2)	1827(8)	4940(7)
O(3)	4609(2)	−2381(10)	2779(7)
N(4)	5894(2)	−1373(10)	2212(8)
C(1)	6564(3)	2533(15)	4285(9)
C(2)	6756(2)	1581(13)	2755(10)
C(3)	6427(2)	−260(14)	1779(8)
C(5)	5514(3)	−3208(13)	1208(9)
C(6)	5009(3)	−4509(16)	2171(9)
C(10)	6792(3)	5571(15)	6507(9)
C(31)	6665(3)	−993(15)	165(10)

apparatus and are uncorrected. Gas chromatographic analysis was carried out with a Carlo Erba Fractovap 4160 gas chromatograph. A chemically bonded SE-52 fused-silica capillary column was used throughout. The temperature program was started at 60 °C followed after one minute by a rise of 10 °C min^{-1} to 170 °C. Elemental analyses were obtained with a Carlo Erba CHN-S/O analyser 1106.

NMR Spectroscopy.—The spectra were recorded with a Bruker AC-250 ASPECT 3000 system using a 5 mm $^1H/^{13}C$ dual probe. All experimental observations were made for $CDCl_3$ solutions. For ^1H measurements 20 mg and for ^{13}C measurements 70 mg of sample were added to 0.5 cm^3 of deuteriated solvent with tetramethylsilane as an internal reference. The number of data points in the ^1H experiment was 32 kW, and in the ^{13}C experiment 64 kW. Decoupled ^{13}C NMR spectra were measured using the composite pulse sequence (Waltz decoupling). COSY and NOESY spectra were acquired as 256*512 matrices with zero filling to 512*512 points and ^1H–^{13}C correlated as 128*4096 with zero filling.

Mass Spectrometry.—The mass spectra were recorded on a JEOL JMS-D300 mass spectrometer equipped with a combined electron impact/chemical ionization source and coupled with a Carlo Erba Fractovap 4160 gas chromatograph. The system was controlled by a JEOL JMA-2000H data system. The source conditions were: temperature 170 °C, electron energy 70 eV, accelerating voltage 3 kV and ionization current 300 μA unless stated otherwise. Samples were introduced through a direct inlet system and/or gas chromatograph. When both inlet systems were used no discernible differences were observed in the spectra. Accurate mass measurements were determined at resolution 5000 using the data system. Fragmentation pathways were verified with metastable-ion transitions and/or CID spectra using linked scans at constant B/E. For ion-structural studies helium was led into the first field-free region so that transmission of the main beam was 33%. To ensure identical experimental conditions, spectra of all ions with the same mass value but generated from different compounds were recorded one after another without adjustment of the instrumental parameters.

Crystallography.—Details of crystal parameters, data-collection parameters and refined data for compound **1** are summarized in Table 9. Intensity measurements were made on a Nicolet R3m diffractometer using graphite-monochromatized Mo-Kα radiation (ω scan mode with scan width 1.3° from $K\alpha_{1,2}$ and scan speed 2.93–29.3° min^{-1}). Monitoring of an intensity check reflection showed no crystal decay during the rapid data collection. The data set was corrected for Lorentz and polarization factors but not for absorption.

Structure Analysis and Refinement.—The crystal structure was determined by direct methods and subsequent Fourier synthesis using the SHELXTL program package.[21] Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed at calculated positions with fixed isotropic thermal parameters (C–H 0.96 Å and U 0.07 Å^2), except hydrogen atoms attached to C(2), N(4) and O(3) which were determined from difference Fourier maps but not refined. The values of R, R′ and the goodness of fit for the two alternative absolute structures were effectively the same. The final atomic co-ordinates are presented in Table 10.

Additional material available from the Cambridge Crystallographic Data Centre comprises H-atom co-ordinates and thermal parameters.*

Compounds.—Compounds were synthesized by refluxing equivalent amounts of the corresponding keto ester and amino alcohol in dichloromethane or toluene in a Dean–Stark apparatus. In the case of 2-methylaminoethanol, toluene-*p*-sulphonic acid was used as a catalyst. Solids were purified by crystallization from hexane and liquids by distillation. The purity of the compounds was checked by GLC. In the cases where the purification was not successful products were analysed only by GC–MS.

Methyl 6-hydroxy-3-methyl-4-azahex-2-enoate (**1**). 81%; m.p. 42–45 °C (Found: C, 52.75; H, 8.35; N, 8.98; $M^{+\bullet}$, 159.0898. Calc. for $C_7H_{13}NO_3$: C, 52.83; H, 8.18; N, 8.81; *M*, 159.0901).

Ethyl 6-hydroxy-3-methyl-4-azahex-2-enoate (**2**). 75%; m.p. 27 °C (lit.,[6a] 31–32 °C) (Found: C, 55.9, H, 8.95; N, 8.50; $M^{+\bullet}$ 173.1057. Calc. for $C_8H_{15}NO_3$: C, 55.49; H, 8.67; N, 8.09; *M*, 173.1051).

Methyl 7-hydroxy-3-methyl-4-azahept-2-enoate (**3**) 95% (Found: $M^{+\bullet}$ 173.1051. Calc. for $C_8H_{15}NO_3$: *M* 173.1051).

Ethyl 7-hydroxy-3-methyl-4-azahept-2-enoate (**4**) 93%; m.p. 39–41 °C (Found: $M^{+\bullet}$ 187.1220. Calc. for $C_9H_{17}NO_3$: *M*, 187.1209).

Ethyl 2,3-dimethyl-1,3-oxazolidin-2-ylacetate (**5**) (Found: $[M - CH_3]^+$, 172.0976. Calc. for $C_8H_{14}NO_3$: $M - CH_3$, 172.0974).

5-Methyl-4-oxa-1-azabicyclo[3.3.0]*octan-8-one* (**6**). B.p. 85–90 °C/5 Torr (Found: C, 54.55; H, 8.25; N, 9.7, $M^{+\bullet}$, 141.0759. Calc. for $C_7H_{11}NO_2$: C, 59.57; H, 7.80; N, 9.93; *M*, 141.0789).

* For details of the CCDC deposition scheme see 'Instructions for Authors' (1991), *J. Chem. Soc., Perkin Trans. 2*, Issue 1.

6-Methyl-5-oxa-1-azabicyclo[4.3.0]*nonan-9-one* (**7**). B.p. 100–107 °C/4 Torr (Found: C, 58.1; H, 9.25; N, 9.5; $[M - CH_3]^+$, 140.0715. Calc. for $C_8H_{13}NO_2$: C, 61.94; H, 8.39; N, 9.03; $M - CH_3^+$, 140.0711).

Ethyl 2-Methyl-1,3-oxazolidin-2-ylpropanoate (**8**). (Found: $[M - CH_3]^+$, 172.0974. Calc. for $C_8H_{14}NO_3$: $M - CH_3^+$, 172.0974).

Ethyl 2-Methyltetrahydro-1,3-oxazin-2-ylpropanoate (**9**). (Found: $[M - CH_3]^+$, 186.1168. Calc. for $C_9H_{16}NO_3$: $M - CH_3^+$, 186.1130).

Ethyl 2,3-Dimethyl-1,3-oxazolidin-2-ylpropanoate (**10**). (Found: $[M - CH_3]^+$, 186.1141. Calc. for $C_8H_{16}NO_3$: $M - CH_3^+$, 186.1130).

6-Methyl-7-oxa-1-azabicyclo[4.3.0]*nonan-2-one* (**11**). B.p. 114–116 °C/5 Torr (Found: C, 61.95; H, 8.65; N, 8.65; $[M - CH_3]^+$, 140.0707. Calc. for $C_8H_{13}NO_2$: C, 61.94; H, 8.39; N, 9.03; $M - CH_3^+$, 140.0711).

6-Methyl-5-oxa-1-azabicyclo[4.4.0]*decan-10-one* (**12**). B.p. 119–120 °C/4 Torr (Found: C, 63.05; H, 9.25; N, 7.96; $[M - CH_3]^+$, 154.0857. Calc. for $C_9H_{15}NO_2$: C, 63.86; H, 8.94; N, 8.28; $M - CH_3^+$, 154.0867).

Methyl 2-methyl-1,3-oxazolidin-2-ylbutanoate (**13**). (Found: $[M - CH_3]^+$, 172.0978. Calc. for $C_8H_{14}NO_3$: $M - CH_3^+$, 172.0974).

Methyl 2-methyltetrahydro-1,3-oxazin-2-ylbutanoate (**14**). (Found: $[M - CH_3]^+$, 186.1179. Calc. for $C_9H_{16}NO_3$: $M - CH_3^+$, 186.1130).

Methyl 2,3-Dimethyl-1,3-oxazolidin-2-ylbutanoate (**15**). (Found: $[M - CH_3]^+$, 186.1138. Calc. for $C_9H_{16}NO_3$: $M - CH_3^+$, 186.1130).

References

1 See, for example, (*a*) E. Chalina, D. Dantchev, A. Georgiev and K. Mitova, *Arch. Pharm.*, 1986, **319**, 598; (*b*) J. A. Young-Harvey, I. D. Rae and I. H. Pitman, *Int. J. Pharm.*, 1986, **30**, 151; (*c*) S. E. Zayed, *Pakistan J. Sci. Ind. Res.*, 1987, **30**, 432; (*d*) A. Buur and H. Bundgaard, *Arch. Pharm. Chem. Sci. Ed.*, 1987, **15**, 76.

2 T. Kato, N. Katagiri and Y. Yamamoto, *Heterocycles*, 1980, **14**, 1333 and references therein.

3 See, for example, (*a*) F. Santiesteban, C. Grimaldo, R. Contreras and B. Wrackmeyer, *J. Chem. Soc., Chem. Commun.*, 1983, 1486; (*b*) H. Takahashi, Y. Chida, K. Higashiyama and H. Onishi, *Chem. Pharm. Bull.*, 1985, **33**, 4662; (*c*) A. I. Meyers and B. A. Lefker, *Tetrahedron*, 1987, **43**, 5663; (*d*) J. M. Takacs, M. A. Helle and L. Yang, *Tetrahedron Lett.*, 1989, **30**, 1777.

4 See, for example, (*a*) G. Just, C. Luthe and P. Potvin, *Tetrahedron Lett.*, 1982, **23**, 2285; (*b*) C. Agami and T. Rizk, *Tetrahedron*, 1985, **41**, 537; (*c*) C. Agami and F. Meynier, *J. Org. Chem.*, 1986, **51**, 73.

5 M. Sainsbury in *Rodd's Chemistry of Carbon Compounds*, Vol. IV, Part C, ed. M. F. Ansell, Elsevier, Amsterdam, 1986, pp. 337–343.

6 For leading reviews, see: (*a*) E. D. Bergmann, *Chem. Rev.*, 1953, **53**, 309; (*b*) P. R. Jones, *Chem. Rev.*, 1963, **63**, 461; (*c*) R. Valters and W. Flitsch, *Ring Chain Tautomerism*, Plenum, New York, 1985; (*d*) K. Pihlaja, *31st Int. Congress of Pure and Applied Chem.*, July 13–18, 1987, Sofia, Bulgaria, Invited Lectures, Section 6: Org. Chem., p. 173.

7 See, for example, (*a*) J. V. Paukstelis and L. L. Lambing, *Tetrahedron Lett.*, 1970, 299; (*b*) M. E. Alva Astudillo, N. C. J. Chokotho, T. C. Jarvis, C. D. Johnson, C. C. Lewis and P. D. McDonnell, *Tetrahedron*, 1985, **41**, 5919; (*c*) K. Aaljoki, *Dissertation*, University of Turku, Turku, 1986; (*d*) F. Fülöp, K. Pihlaja, J. Mattinen and G. Bernáth, *J. Org. Chem.*, 1987, **52**, 3821; (*e*) F. Fülöp, G. Bernáth, J. Mattinen and K. Pihlaja, *Tetrahedron*, 1989, **45**, 4317.

8 (*a*) M. E. Rennekamp, J. V. Paukstelis and R. G. Cooks, *Tetrahedron*, 1971, **27**, 4407; (*b*) P. Vainiotalo, S. Ronkanen, F. Fülöp and K. Pihlaja, *Tetrahedron*, 1990, **46**, 3683; (*c*) P. Vainiotalo, F. Fülöp and K. Pihlaja, *Org. Mass Spectrom.*, submitted.

9 A. I. Meyers, M. Harre and R. Garland, *J. Am. Chem. Soc.*, 1984, **106**, 1146.

10 A. I. Meyers and B. A. Lefker, *Tetrahedron*, 1987, **43**, 5663.

11 For leading reviews, see: (*a*) K. Levsen and H. Schwarz, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 509; (*b*) *Collision Spectroscopy*, ed. R. G. Cooks, Plenum Press, New York, 1978; (*c*) K. Levsen and H. Schwarz, *Mass Spectrom. Rev.*, 1983, **2**, 77; (*d*) *Tandem Mass Spectrometry*, ed. F. W. McLafferty, Wiley, New York, 1983.

12 U. Vogeli and W. von Philipsborn, *Org. Magn. Reson.*, 1975, **7**, 617.

13 P. Vainiotalo, T. Romppanen and P. J. Mälkönen, *Rapid Commun. Mass Spectrom.*, 1990, **4**, 77.

14 A. G. Harrison, *Chemical Ionization Mass Spectrometry*, CRC Press, Boca Raton, 1983.

15 (*a*) C. Agami, and T. Rizk, *J. Chem. Soc., Chem. Commun.*, 1983, 1485; (*b*) C. Agami and T. Rizk, *Tetrahedron*, 1985, **41**, 537.

16 F. Böhlmann and D. Schumann, *Tetrahedron Lett.*, 1965, 2435.

17 P. Vainiotalo, *Ann. Acad. Sci. Fenn., Seri. A2*, 1990, **227**, 105.

18 See, for example, (*a*) T. W. Bentley and R. A. W. Johnstone in *Physical Organic Chemistry*, ed. V. Gold, Academic Press, New York, 1970, vol. 8, pp. 236–241; (*b*) R. C. Dougherty, *Top. Curr. Chem.*, 1974, **45**, 93; (*c*) R. F. C. Brown, *Pyrolytic Methods in Organic Chemistry*, Academic Press, New York, 1980.

19 (*a*) J. R. Dias and C. Djerassi, *Org. Mass Spectrom.*, 1972, **6**, 385; (*b*) H. Bornowski, V. Feistkorn, H. Schwarz, K. Levsen and P. Schmith, *Z. Naturforsch., Teil. B*, 1977, **32**, 664.

20 P. Vainiotalo, *Adv. Mass Spectrom.*, 1989, **11A**, 618.

21 SHELXTL PLUS, Release 3.4, Nicolet Co., Madison, Wisconsin, 1988.

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