methylene chloride, with nitromethane, and finally with ether. Concentration of the combined filtrate and washings to 100 mL on a rotary evaporator led to precipitation of 3.28 g (73% recovery) of unreacted starting material (**16**). About 800 mL of ether was then added to the filtrate to precipitate a brown solid, which was washed with benzene and ether. One recrystallization of this material from acetonitrile–ether gave 0.17 g (3% yield) of crude product, mp 156–157 °C. Further recrystallization gave pure 1-methyl-3,6-dibromo-2,5-diphenyl-1,4-dithiinium tetrafluoroborate (**17**): mp 161–163 °C; NMR (CD_3CN) δ 7.62 (m, 10, Ar H), 3.30 (s, 3, CH_3); UV λ_{max} 282 nm (log ϵ 4.11).

Anal. Calcd for $C_{17}H_{13}S_2Br_2BF_4$: C, 38.67; H, 2.48; S, 12.14. Found: C, 38.47; H, 2.61; S, 12.40.

Registry No. **2**, 17250-79-2; **4**, 17278-23-8; **5**, 6317-72-2; **8**, 72525-34-9; **12**, 72525-35-0; **13**, 72525-37-2; **14**, 72525-38-3; **15**, 72525-40-7; **16**, 6317-71-1; **17**, 72525-42-9; silver tetrafluoroborate, 14104-20-2; methyl iodide, 74-88-4.

Acid-Catalyzed Rearrangement of α-Aminoalkylidene-β-alkoxy β-Lactams

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Hydrolysis of six nonfused 4-methoxy β-lactams (**1–6**) on alumina gave the corresponding enamino ketone derivatives (**11–16**), whereas the fused β-alkoxy β-lactams (**7** and **8**) afforded the alkyl 2-piperidylideneacetoacetates **17** and **18**, respectively. The structures of the products (**11**, **17**, and **18**) were confirmed by synthesis. Treatment of the fused β-methoxy β-lactam **7** in ethanol solution containing water (11%) and a catalytic amount of acetic acid (1%) leads to a mixture of two products, **17** and enamino ketone derivative **21**. Similarly, treatment of the fused β-ethoxy β-lactam **8** in an acidic methanol solution containing water (11%) afforded **18** and **21**. Under similar conditions the fused β-alkoxy β-lactams **9** and **10** also gave the corresponding alkyl 2-(2-hexahydroazepinylidene)acetoacetate (**19** and **20**), enamino ketone derivative **22**, and 3-acetyl-β-alkoxy β-lactams (**23** and **24**), respectively. Furthermore, hydrolysis of **24** in a similar acidic solution gave the enol-type product **25**. Hydrolysis of fused CD_3O β-lactam **7a** and fused $CH_3{}^{18}O$ β-lactam **7b** on alumina gave methyl-d_3 2-piperidylideneacetoacetate (**17a**) and methyl 2-piperidylideneacetoacetate-*carboxy*-^{18}O (**17b**), respectively. These observations suggest that an intramolecular migration of the alkoxy group to the amide carbonyl carbon is responsible for the formation of the products (**17–20**).

Irradiation of 2,3,6-trialkyl-4-pyrimidinone derivatives in alcoholic solution gives α-aminoalkylidene-β-alkoxy β-lactams (**1–10**).[1b] The structure of the fused β-lactam **7** was unambiguously established by the X-ray analysis. The structures and properties of these β-lactams in solution were also studied in detail.

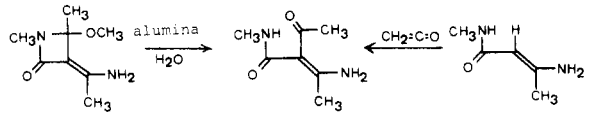
During the course of the investigation, we found that when the fused β-lactam **7** or **8** was eluted from a column of alumina with benzene, products **17** and **18** (about 90% yield), respectively,[1a] were obtained. The structures of these products were assigned by spectral data and confirmed by synthesis. However, the structure was inconsistent with those of compounds expected from the hydrolysis of the corresponding acyclic β-lactams.[2]

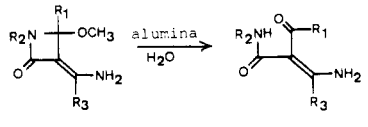
These β-lactams are of interest since these are model compounds related to the penicillin and cephalosporin antibiotics, and the hydrolysis of these β-lactams may provide important information about the stability of the β-lactams.

With this prospect in mind, we have now undertaken the hydrolysis of the β-alkoxy β-lactam under various experimental conditions.

Hydrolysis of α-Aminoalkylidene-β-alkoxy β-Lactams 1–6 on Alumina. The nonfused β-lactam **1** was not stable to alumina chromatography. The only product isolated from **1** on alumina was **11**, obtained in 34% yield.

Scheme I





compd	R_1	R_2	R_3
2, 12	CH_3	CH_2CH_3	CH_3
3, 13	CH_3	$CH_2CH_2CH_3$	CH_3
4, 14	CH_3	$CH_2C_6H_5$	CH_3
5, 15	CH_2CH_3	CH_3	CH_3
6, 16	CH_3	CH_3	CH_2CH_3

The ^1H NMR spectrum showed a doublet at δ 2.72 (J = 4.5 Hz, 3 H) and a quartet at 7.82 (J = 4.5 Hz, 1 H) which could be assigned to the secondary *N*-methyl group. The ^1H NMR spectrum also exhibited signals at δ 7.60 (br s, 1 H) and 10.14 (br s, 1 H) which, when considered in terms of the stretching bands at 3330, 3200, and 3100 cm^{-1}, indicated a primary amino group. The ^1H NMR spectrum (δ 10.14) showed that one of the hydrogen atoms in the primary amino group is bonded by an intramolecular hydrogen bond. The IR bands at 1640 and 1610 cm^{-1} sug-

(1) (a) T. Yamazaki, M. Nagata, S. Hirokami, Y. Hirai, and T. Date, *Heterocycles*, **9**, 505 (1978); (b) S. Hirokami, Y. Hirai, M. Nagata, T. Yamazaki, and T. Date, *J. Org. Chem.*, **44**, 2083 (1979).

(2) R. J. Stoodley, *Tetrahedron*, **31**, 2321 (1975).

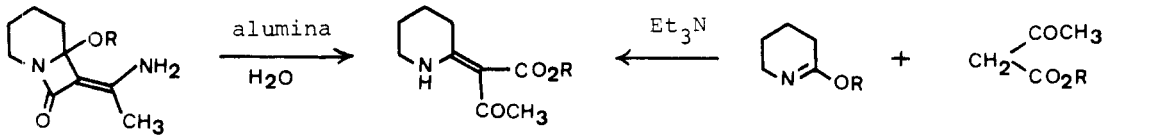
0022-3263/80/1945-0936$01.00/0

Table I. UV, IR, and ^{1}H NMR Spectral Data for Products 11-16

compd	UV, nm (MeOH) (ε)	IR, cm^{-1} (KBr)	^{1}H NMR,[a,b] δ (Me$_2$SO-d_6) NH-R	^{1}H NMR,[a,b] δ (Me$_2$SO-d_6) NH$_2$
11	302 (13 700) 240 (2100)	3330, 3200, 3100, 1640, 1610	R = CH$_3$ 2.72 (d, J = 4.5, 3 H) 7.82 (q, J = 4.5, 1 H; NH)	 7.60 (br s, 1 H) 10.14 (br s, 1 H)
12	302 (14 100) 240 (2000)	3330, 3150, 1640, 1610	R = CH$_3$CH$_2$ 1.05 (t, J = 6.9, 3 H) 3.10 (quin, J = 6.9, 2 H) 7.90 (t, J = 6.9, 1 H; NH)	 7.58 (br s, 1 H) 10.10 (br s, 1 H)
13	302 (13 100) 240 (2000)	3330, 3280, 3120, 1635, 1615	R = CH$_3$CH$_2$CH$_2$ 0.90 (t, J = 6.0, 3 H) 1.48 (sext, J = 6.0, 2 H) 3.08 (q, J = 6.0, 2 H) 7.92 (t, J = 6.0, 1 H; NH)	 7.58 (br s, 1 H) 10.12 (br s, 1 H)
14	302 (13 700) 240 (2600)	3330, 3160, 1630, 1620	R = C$_6$H$_5$CH$_2$ 4.32 (d, J = 6.0, 2 H) 7.28 (s, 5 H) 8.33 (t, J = 6.0, 1 H; NH)	 7.50 (br s, 1 H) 10.16 (br s, 1 H)
15	302 (13 900) 240 (1800)	3340, 3250, 3100, 1640	R = CH$_3$ 2.67 (d, J = 4.5, 3 H) 7.79 (q, J = 4.5, 1 H; NH)	 7.52 (br s, 1 H) 10.12 (br s, 1 H)
16	302 (13 800) 240 (2300)	3330, 3200, 1635, 1610	R = CH$_3$ 2.66 (d, J = 4.5, 3 H) 7.80 (q, J = 4.5, 1 H; NH)	 7.48 (br s, 1 H) 10.16 (br s, 1 H)

[a] Coupling constants in hertz. [b] The abbreviations s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), and sext (sextet) refer to the multiplicity of the absorption in ^{1}H NMR spectrum.

Scheme II



7, R = CH$_3$
8, R = CH$_2$CH$_3$

17, R = CH$_3$
18, R = CH$_2$CH$_3$

27a, R = CH$_3$
27b, R = CH$_2$CH$_3$

28a, R = CH$_3$
28b, R = CH$_2$CH$_3$

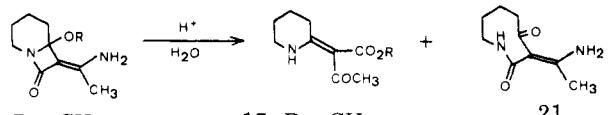
gested a conjugated carbonyl group. From these data, the structure was assigned as β-amino-α-acetyl-*N*-methylcrotonamide (**11**). Confirmation of **11** by synthesis was achieved by the reaction of β-amino-*N*-methylcrotonamide with ketene[3] (see Scheme I). Analogous hydrolysis of **2–6** on alumina led to the formation of **12–16**, respectively, in 36–64% yield (see Scheme I). The structures of these compounds were assigned from their spectra in comparison with those for **11** (see Table I).

The nonfused β-lactams (**1** and **4**) gave no separable product in acidic methanol solution (11% water and 1% acetic acid). In basic methanol solution (11% water and 1% triethylamine) **4** was relatively stable, and the starting material was recovered in nearly quantitative yield after 7 days.

Hydrolysis of Fused α-Aminoethylidene-β-alkoxy β-Lactams 7–10. Hydrolysis of **7** and **8** by column chromatography on alumina gave a crystalline compound, **17**, in 86% yield and an oily compound, **18**, in 90% yield, respectively.

In the ^{1}H NMR spectrum of **17**, the methoxy signal was shifted to lower field (δ 3.27 in **7**, δ 3.75 in **17**; solvent $CDCl_3$). The IR spectrum of **17** showed the disappearance of a primary amino group in **7** and the formation of new conjugated carbonyl groups at 1700 and 1600 cm^{-1}, indicating the presence of an ester carbonyl group and an unsaturated carbonyl moiety. The UV spectrum of **17** at 304 nm (ε 13 900) and 248 nm (ε 6700) was similar to that of **11**. The ^{1}H NMR spectrum of **17** showed a secondary amino group at δ 12.93 (br s, 1 H), thus suggesting the presence of an enamino ketone moiety. The spectral data on **18** were analogous to those of **17** (see Table II).

Scheme III



7, R = CH$_3$
8, R = CH$_2$CH$_3$

17, R = CH$_3$
18, R = CH$_2$CH$_3$

21

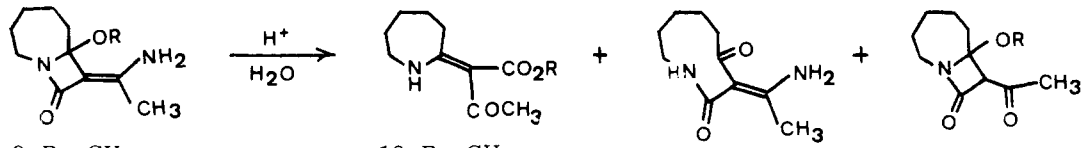
From these data, the structure of **17** was assigned to methyl 2-(2-piperidylidene)acetoacetate. The spectral data also showed that **18** was ethyl 2-(2-piperidylidene)acetoacetate. To confirm the structures, **17** and **18** were synthesized by condensation of 2,3,4,5-tetrahydro-6-methoxypyridine with methyl acetoacetate and of 2,3,4,5-tetrahydro-6-ethoxypyridine with ethyl acetoacetate, in the presence of triethylamine.[4] The synthesized compounds were found to be identical (spectra) with the samples obtained from the hydrolysis of **7** and **8** on alumina (see Scheme II).

When the fused β-methoxy β-lactam **7** was treated in an acidic ethanol solution (11% water and 1% acetic acid), the ethoxy product **18** was not formed. Instead, two products, **17** and **21**, were obtained in 67% and 24% yield, respectively. Similarly, the fused β-ethoxy β-lactam **8** in an acidic methanol solution (11% water and 1% acetic acid) gave two products, **18** in 61% and **21** in 26% yield. No product containing a methoxy group, such as **17**, was detected (see Scheme III).

(3) T. Kato, H. Yamanaka, J. Kawamoto, and H. Shimoura, *Chem. Pharm. Bull.*, 17, 1889 (1969).

(4) T. Oishi, M. Nagai, T. Onuma, H. Moriyama, K. Tsutae, M. Ochiai, and Y. Ban, *Chem. Pharm. Bull.*, 17, 2306 (1969).

Scheme IV



9, R = CH_3
10, R = CH_2CH_3

19, R = CH_3
20, R = CH_2CH_3

22

23, R = CH_3
24, R = CH_2CH_3

Table II. UV, IR, and ^1H NMR Spectral Data for Products 17-20

compd	UV, nm (MeOH) (ϵ)	IR, cm^{-1}	^1H NMR, δ ($CDCl_3$)[b] OR	NH
17	304 (13 900)	1700, 1600 (KBr)	R = CH_3	
	248 (6700)		3.73 (s, 3 H)	12.93 (br s, 1 H)
18[a]	300 (15 300)	1695, 1605 (neat)	R = CH_3CH_2	
	248 (7500)		1.33 (t, J = 7.6, 3 H)	12.93 (br s, 1 H)
			4.23 (q, J = 7.6, 2 H)	
19	309 (15 500)	1700, 1590 (neat)	R = CH_3	
	251 (5300)		3.78 (s, 3 H)	12.44 (br s, 1 H)
20	310 (17 700)	1700, 1590 (Nujol)	R = CH_3CH_2	
	249 (5600)		1.35 (t, J = 7.5, 3 H)	12.47 (br s, 1 H)
			4.27 (q, J = 7.5, 2 H)	

[a] Reference 4. [b] Coupling constants in hertz.

Table III. UV, IR, and ^1H NMR Spectral Data for Products 21, 22, and 25

compd	UV, nm (MeOH) (ϵ)	IR, cm^{-1} (KBr)	^1H NMR, δ[a]
21	300 (13 800)	3350, 3260, 3130, 1600	7.47 (t, J = 7.5, 1 H; NH)
	244 (3700)		7.73 (br s, 1 H; NH)
			10.17 (br s, 1 H; NH)
22	304 (12 200)	3340, 3170, 1630, 1610	7.20-7.70 (br, 2 H; 2 NH)
	244 (1700)		9.95 (br, s, 1 H; NH)
25	283 (10 500)	3200, 1660, 1595	5.93-6.67 (br s, 1 H; NH)
			16.17 (s, 1 H; OH)

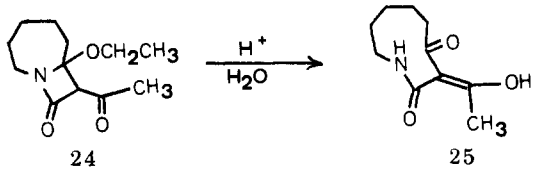
[a] Coupling constants in hertz. Solvents: Me_2SO-d_6 for 21 and 22, $CDCl_3$ for 25.

Table IV. ^{13}C NMR Spectral Data for Products 21 and 22

21		22	
signals[a]	assignment	signals[a]	assignment
25.1 (t)	CH_2-5	26.2 (t)	CH_2-6
27.9 (q)	CH_3	26.7 (t)	CH_2-5
29.4 (t)	CH_2-6	27.4 (q)	CH_3
32.2 (t)	CH_2-4	29.8 (t)	CH_2-7
42.0 (t)	CH_2-7	31.9 (t)	CH_2-4
102.7 (s)	C-2	44.3 (t)	CH_2-8
165.5 (s)	C-1'	105.0 (s)	C-2
172.2 (s)	C-1	163.3 (s)	C-1'
193.9 (s)	C-3	173.0 (s)	C-1
		192.2 (s)	C-3

[a] Chemical shifts are given in δ units from internal tetramethylsilane and measured in Me_2SO-d_6.

Scheme V



24 25

The structure of **21** was clear from its spectra. The IR spectrum showed the amine and carbonyl groups, and the UV spectrum was similar to that of **11**, indicating the presence of an enamino ketone moiety. The ^1H NMR spectrum showed a triplet at δ 2.25 (J = 6.8 Hz, 2 H) which could be assigned to a methylene group attached to the carbonyl group. Additionally, in the ^1H NMR spectrum of **21**, the signal of an amino group appeared as a triplet at δ 7.47 (J = 7.5 Hz, 1 H), indicating that the amino group was attached to another methylene group (see Table III). Further confirmation of the structure came from ^{13}C NMR spectra which clearly showed the presence of four methylene groups, one carbonyl group, and an amide carbonyl group (see Table IV).

The analogous reaction of the fused β-methoxy β-lactam **9** in acidic ethanol solution (11% water and 1% acetic acid) gave **19** in 15%, **22** in 37%, and **23** in 21% yield. Likewise, the fused β-ethoxy β-lactam **10** in the acidic methanol solution (11% water and 1% acetic acid) gave **20** in 10%, **22** in 39%, and **24** in 13% yield (see Scheme IV).

The structures of **19**, **20**, and **22** were deduced by comparison of their spectra with those of **17**, **18**, and **21**, respectively (see Tables II, III, IV). In the IR spectrum of **23**, the primary amine band of the β-lactam **9** disappeared and new carbonyl bands appeared at 1765 and 1705 cm^{-1}. A striking change was the decrease in the absorption coefficient (ϵ 1270 at 309 nm; **23**) in the UV spectrum compared with that of **9** (ϵ 22 400 at 273 nm),[1b] indicating that the amino group in **9** was hydrolyzed. Furthermore, the spectral data on **24** were similar to those of **23**. From these data, the β-lactam structures **23** and **24** were assigned. The ^1H NMR spectra for **23** and **24** indicated that both products were a mixture of two stereoisomers (see Table V). Both ratios of stereoisomers, **23A**:**23B** and **24A**:**24B**, were about 5:2. The corresponding stereoisomers may be the trans and cis isomers defined by the relationship of the alkoxy group to the methine proton at C(9). The stereochemistry of the isomers could not be assigned from the spectral data.

Hydrolysis of **24** was carried out in acidic methanol solution (11% water and 1% acetic acid). The only product isolated was **25**, obtained in 29% yield (see Scheme V). No product corresponding to **18** or **20** was obtained.

The structure of **25** was determined from its spectra. The ^1H NMR spectrum showed no ethoxy group, but ex-

Table V. UV, IR, and ^{1}H NMR Spectral Data for Products 23 and 24

compd	UV, nm (MeOH) (ε)	IR, cm^{-1} (Nujol)	^{1}H NMR, δ ($CDCl_3$)[b] isomer A	isomer B
23[a]	309 (1270)	1765	3.33 (s, OCH_3)	3.26 (s, OCH_3)
	258 (1060)	1705	4.07 (s, CH)	3.77 (s, CH)
24[a]	311 (1140)	1762	1.29 (t, J = 7.5; OCH_2CH_3)	1.28 (t, J = 7.5; OCH_2CH_3)
	260 (1030)	1710	3.63 (q, J = 7.5; OCH_2CH_3)	3.61 (q, J = 7.5; OCH_2CH_3)
			4.10 (s, CH)	3.81 (s, CH)

[a] Products 23 and 24 were a mixture of stereoisomers (isomer A and isomer B). The isomers (A and B) were present in a ratio of 5:2 estimated by the integration of the peak areas of the methine protons. [b] Coupling constants in hertz.

Table XI. Mass Spectrum of ^{18}O-Labeled and Unlabeled Fused Methoxy β-Lactams (7b and 7)

	relative intensity (standard deviation in parentheses)										
	molecular ion (M^+), m/e			fragment ion, m/e			fragment ion, m/e				
compd	198	197	196	183	182	181	167	166	165	164	163
fused methoxy β-lactam 7	1.5 (0.3)	16 (0.6)	100	4.3 (0.6)	40 (3)	350 (10)	19 (1)	32 (1)	270 (9)	44 (2)	20 (3)
fused methoxy-^{18}O β-lactam 7b[a]	7.6 (0.4)	14 (0.7)	100	25 (3)	42 (3)	351 (24)	21 (1)	34 (2)	285 (15)	51 (4)	24 (2)

[a] Fused methoxy-(^{18}O) β-lactam **7b** was photochemically prepared from the fused 4-pyrimidinone[1b] in ^{18}O-labeled methanol (^{18}O; 5.3 atom %).

Table XII. Mass Spectrum of ^{18}O-Labeled and Unlabeled Methyl 2-(2-Piperidylidene)acetoacetate (17b and 17)

	relative intensity (standard deviation in parentheses)										
	molecular ion (M^+), m/e			fragment ion, m/e			fragment ion, m/e				
compd	199	198	197	184	183	182	168	167	166	165	164
methyl acetoacetate 17	1.4 (0.2)	13 (0.5)	100	2.0 (0.2)	14 (0.5)	133 (5)	5.5 (0.3)	5.8 (0.4)	50 (1)	57 (1)	12 (1)
^{18}O-labeled methyl acetoacetate 17[a]	7.4 (0.4)	13 (0.5)	100	10 (0.6)	15 (0.9)	134 (4)	6.8 (0.9)	6.7 (0.8)	55 (6)	65 (5)	16 (2)

[a] ^{18}O-Labeled methyl acetatoacetate **17b** was prepared by the hydrolysis of the fused methoxy-^{18}O **7b** on alumina.

hibited a broad signal at δ 5.93–6.67 (br, 1 H) assigned to a secondary amino group and a sharp singlet at δ 16.17 due to an enol-type proton. The IR spectrum showed the presence of a hydroxyl group and/or an amino group at 3200 cm^{-1}. The IR bands at 1660 and 1595 cm^{-1} suggested a conjugated carbonyl group (see Table III). This permitted us to assign the structure **25**.

Hydrolysis of **7** in basic methanol solution (11% water and 1% triethylamine) was carried out at room temperature. After 35 days, the product **17** was isolated in 14% yield and the starting material was recovered in 83% yield. This shows that the fused β-lactam **7** is relatively stable in basic solution and the reaction is extremely slow.

Mechanistic Consideration. In the hydrolysis of the β-lactams **1–10**, the following reactions are observed: (i) formation of an ester group for the fused β-lactams **7–10**, (ii) cleavage of the N(1)–C(4) bond of nonfused β-lactams **1–6** and cleavage of the bridgehead N–C bond of the fused β-lactams **7–10**, and (iii) hydrolysis of the primary amino group in the enamine moiety of the fused β-lactams **9–10**. However, each of the β-lactams (**1–10**) which we studied reacted very differently. Initially we considered plausible mechanisms which rationalize formation of the products **17** and **21** from **7** in acidic solution.

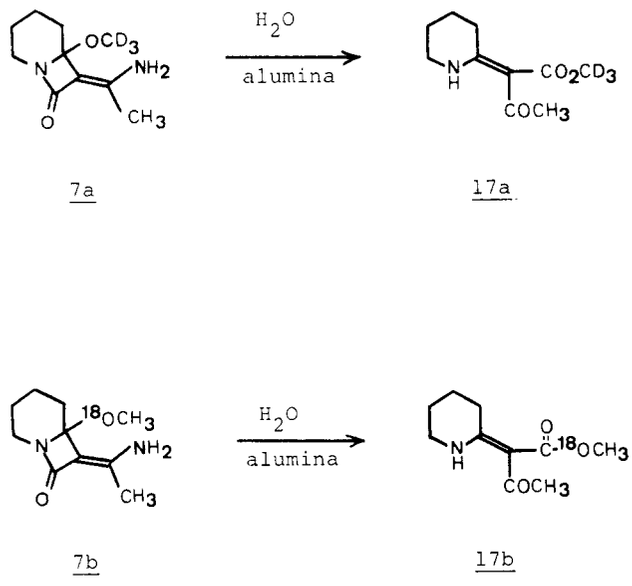
The formation of **21** can be explained by postulating a hemiacetal intermediate formed by cleavage of the bridgehead N–C bond of the β-lactam **7**. The mechanistic question concerns the nature of the pathway from the β-lactam **7** to the acetoacetate **17**. A fused acetyl β-lactam formed by hydrolysis of the amino group could be ruled out as an intermediate since no product corresponding to the acetoacetate was obtained for **24**. If a hemiacetal intermediate is assumed for **17**, the ester functionality in **17** may then be formed by either intramolecular migration of the methoxy group to the amide carbonyl carbon or intramolecular methyl transfer from the methoxy group to the amide carbonyl oxygen.

To distinguish clearly between the methoxy migration mechanism and the methyl transfer mechanism, we undertook an experiment with methoxy-^{18}O-labeled fused β-lactam . The former mechanism would predict the isotope oxygen (^{18}O) to be found in the ester group, while the latter mechanism would lead to loss of ^{18}O as H_2O regardless of any intermediate postulated in the reaction mechanism.

Deuterium-labeled fused methoxy β-lactam was prepared and hydrolyzed on alumina as a model experiment for the ^{18}O-labeled compounds. Irradiation of the fused 4-pyrimidinone[1b] in methanol-d_4 gave a fused CD_3O methoxy-d_3 β-lactam **7a** after treatment with methanol for D/H exchange of the primary amino group. Fused methoxy-d_3 β-lactam was hydrolyzed on alumina to give trideuteriomethyl acetoacetate **17a** in a yield of 97%. The D-labeled compounds, **7a** and **17a**, were used for assignment of the mass fragment ion peaks of **7** and **17**. The fragment ions of **7**, m/e 181 and 165, are assigned to ($M^+ - CH_3$) formed by elimination of CH_3 from the methoxy group and ($M^+ - CH_3O$), respectively. Likewise, the fragment ion peaks of **17**, m/e 182, 166, and 165, are assigned to ($M^+ - CH_3$) formed by elimination of CH_3 from the acetyl group, ($M^+ - CH_3O$), and ($M^+ - CH_4O$), respectively.

Fused ^{18}O-labeled β-lactam **7b** was photochemically prepared from the fused 4-pyrimidinone[1b] in ^{18}O-labeled methanol (^{18}O; 5.3 atom %). Hydrolysis of the fused ^{18}O-labeled β-lactam **7b** on alumina gave ^{18}O-labeled acetoacetate **17b** in a yield of 87%. Both fractions of ^{18}O-labeled compounds in **7b** and **17b** were (0.050 ± 0.003) estimated

Scheme VI



by the molecular ion peak height of the ^{18}O-labeled and unlabeled compounds listed in Tables XI and XII. This shows that ^{18}O atoms are quantitatively incorporated in the product **17** within experimental error. The position of ^{18}O in **7b** and **17b** could be deduced by comparing the relative intensity difference of molecular and fragment ions between the respective ^{18}O-labeled and unlabeled compounds listed in Tables XI and XII. The results indicate clearly that both the ^{18}O atoms in **7b** and **17b** are incorporated in the molecular (M^+) and fragment ($M^+ - CH_3$) ions but are not in the fragment ($M^+ - CH_3O$) ions; that is, ^{18}O atoms are incorporated in the methoxy group (see Scheme VI).

Thus, we can rule out the internal methyl transfer mechanism for the explanation of acetoacetate formation. The formation of products is shown in Scheme VII.

Hydrolysis of **7** gives a hemiacetal intermediate, A, which would lead to the formation of a cyclic oxonium ion intermediate, B. The intermediate A also affords **21** by elimination of the methoxy group. The intermediate B which arises in this way undergoes a 1,3-methoxy shift to give intermediate C. Subsequent ring closure and hydrolysis of the amino group in the enamine moiety gives the product **17**.

The same reaction mechanism can be applied to **8** since the hydrolysis of **8** gave the corresponding products approximately in the same yields as from **7**. These experimental results suggest that the reactivities of these β-lactams do not vary with substitution of the alkoxy group.

The formation of **19** and **22** from **9** and of **20** and **22** from **10** can be similarly rationalized. However, the hydrolyses of **9** and **10** gave the additional products **23** and **24**, respectively. The difference in the reactivity of **9** and **10** from that of **7** and **8** should be due to the additional methylene unit in the ring. This effect suggests that the rate of bridgehead N–C bond cleavage by hydrolysis is reduced and the hydrolytic reaction of the amine group in the enamine moiety is competitive.

Formation of the products **11–18** on alumina from the nonfused and fused β-lactams **1–8** suggests the presence of the hemiacetal intermediate. The plausible mechanism for the formation of **11** from **1** is shown in Scheme VIII.

Hydrolysis of **1** gives an intermediate, D, which affords the product **11** by the elimination of the methoxy group. The formation of **12–16** from **2–6**, respectively, could also be explained by a mechanism analogous to Scheme VIII.

Finally, in Scheme V, we show the formation of **25** from **24** in acidic solution. This suggests that β-lactams having an alkoxy group at the position β to the carbonyl group can undergo reaction of the N(1)–C(4) or bridgehead N–C bond cleavage to form products **11–25** via a hemiacetal intermediate under the experimental conditions used.

Experimental Section[5]

Materials. The β-lactams were photochemically prepared as described in the literature.[1b]

General Procedures for Hydrolysis of β-Lactams 1–10 and the Isolation of Products. The respective β-lactam (250–300 mg), dissolved in about 3 mL of methanol, was adsorbed on alumina (15 g, column chromatographic alumina) which had been treated with benzene saturated with water. After 48–160 h, the product and the remainder of the starting material were obtained from column chromatography using methanol as an eluent. The solvent was removed by rotary evaporation. The products were isolated by column chromatography on alumina. Hydrolyses of the fused β-lactams **7–10** were also carried out in 10 mL of acidic solution at room temperature (15–20 °C). Reaction progress was routinely followed by thin-layer chromatography. After 60–90 h, the solution was neutralized by addition of sodium bicarbonate. The reaction mixture was extracted thoroughly with $CHCl_3$. The products were isolated by crystallization and column chromatography.

β-Amino-α-acetyl-*N*-methylcrotonamide (11). A. From Hydrolysis of *N*-Methyl-3-(aminoethylidene)-4-methoxy-4-methyl-2-azetidinone (1) on Alumina. The β-lactam **1** (300 mg) was adsorbed on alumina for 48 h. Removal of the solvent gave an oily mixture which, on column chromatography, afforded 90 mg (33%) of **11** and 8 mg (3%) of the starting material. Recrystallization of **11** from ether–methanol gave colorless prisms, mp 146–148 °C. The conversion yield of **11** was 34%.

B. By Synthesis.[3] To a solution of β-amino-*N*-methylcrotonamide (3.0 g) in 60 mL of acetone at 0 °C was added dropwise with stirring a slight excess of ketene in 40 mL of acetone. After 0.5 h, the solvent and excess ketene were evaporated at 0 °C under reduced pressure to give an oily residue. The residue was chromatographed on alumina with benzene to give 2.0 g (49%) of β-acetylamino-α-acetyl-*N*-methylcrotonamide, mp 176–177 °C.[3] Further elution with benzene containing 3% methanol gave 0.22 g (5%) of β-amino-α-acetyl-*N*-methylcrotonamide which was found to be identical (spectra) with **11** obtained from hydrolysis of **1** on alumina.

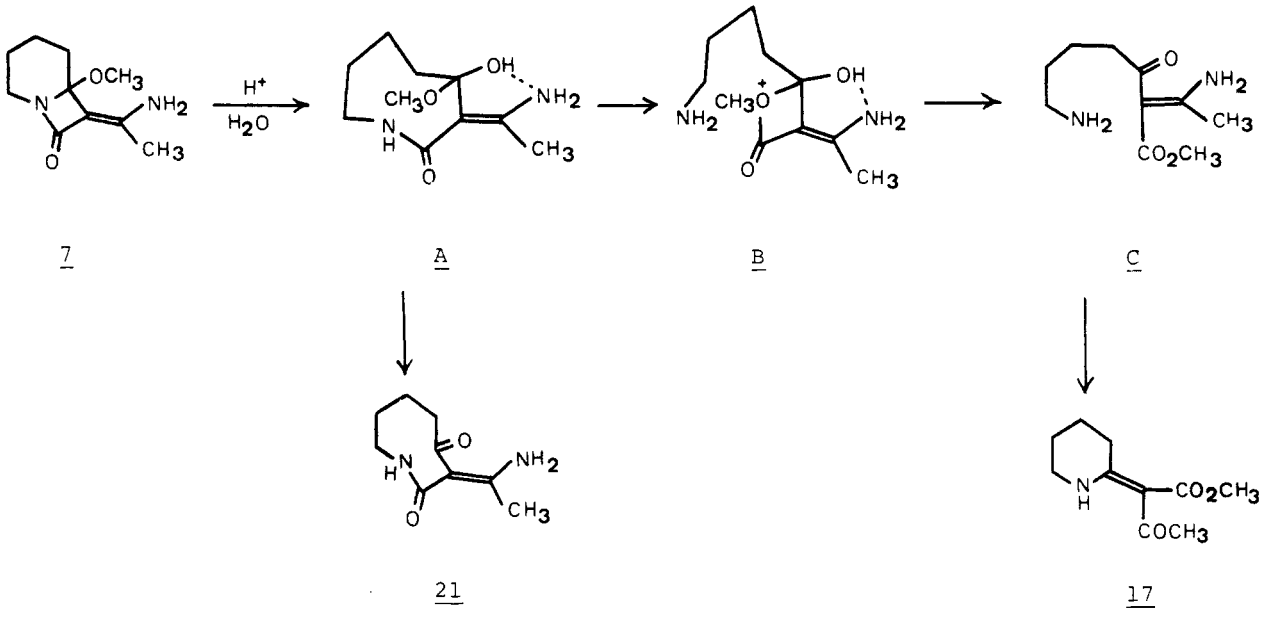
β-Amino-α-acetyl-*N*-ethylcrotonamide (12). From Hydrolysis of *N*-Ethyl-3-(aminoethylidene)-4-methoxy-4-methyl-2-azetidinone (2) on Alumina. The β-lactam **2** (300 mg) was adsorbed on alumina for 68 h. Removal of the solvent gave an oily mixture which, on column chromatography, gave 100 mg (36%) of **12**. Recrystallization of **12** from ether–methanol gave colorless prisms, mp 124–126 °C.

β-Amino-α-acetyl-*N*-propylcrotonamide (13). From Hydrolysis of *N*-Propyl-3-(aminoethylidene)-4-methoxy-4-methyl-2-azetidinone (3) on Alumina. The β-lactam **3** (300 mg) was adsorbed on alumina for 48 h. Removal of the solvent gave an oily mixture which, on column chromatography, gave 150 mg (54%) of **13**. Recrystallization of **13** from ether–methanol gave colorless prisms, mp 111–113 °C.

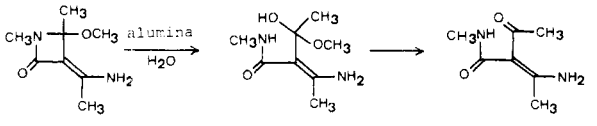
β-Amino-α-acetyl-*N*-benzylcrotonamide (14). From Hydrolysis of *N*-Benzyl-3-(aminoethylidene)-4-methoxy-4-methyl-2-azetidinone (4) on Alumina. The β-lactam **4** (250 mg) was adsorbed on alumina for 95 h. Removal of the solvent gave an oily mixture which, on column chromatography, gave 150 mg (64%) of **14**. Recrystallization of **14** from ether–methanol gave colorless prisms, mp 172–173 °C.

(5) Melting points were measured with a Yanako micromelting-point apparatus and are uncorrected. Hitachi 215 grating infrared and Hitachi Model 200-01 spectrophotometers were used, respectively, to determine IR and UV spectra. Mass spectra were measured with JEOL-OISG-2 and JEOL-JMS-D 200 mass spectrometers. The ^1H NMR and ^{13}C NMR spectra were measured with Me_4Si as an internal standard on Varian EM-390 90-MHz and Hitachi R-900 FT spectrometers, respectively. Column chromatography was performed on alumina (activity II–III, Merck).

Scheme VII



Scheme VIII



N-Methyl-2-(aminoethylidene)-3-oxovaleramide (15). From Hydrolysis of N-Methyl-3-(aminoethylidene)-4-methoxy-4-ethyl-2-azetidinone (5) on Alumina. The β-lactam **5** (300 mg) was adsorbed on alumina for 95 h. Removal of the solvent gave an oily mixture which, on column chromatography, gave 145 mg (52%) of **15**. Recrystallization of **15** from ether–methanol gave colorless prisms, mp 145–146 °C.

N-Methyl-2-acetyl-3-amino-2-pentenamide (16). From Hydrolysis of N-Methyl-3-(1-aminopropylidene)-4-methoxy-4-methyl-2-azetidinone (6) on Alumina. The β-lactam **6** (300 mg) was adsorbed on alumina for 48 h. Removal of the solvent gave an oily mixture which, on column chromatography, gave 125 mg (45%) of **16**. Recrystallization of **16** from ether–methanol gave colorless prisms, mp 147–149 °C.

Methyl 2-(2-Piperidylidene)acetoacetate (17). A. From Hydrolysis of 7-(Aminoethylidene)-6-methoxy-8-oxo-1-azabicyclo[4.2.0]octane (7) on Alumina. The fused β-lactam **7** (300 mg) was adsorbed on alumina for 65 h. Removal of solvent gave an oily mixture which, on column chromatography, gave 185 mg (61%) of **17** and 85 mg (28%) of the starting material **7**. Recrystallization of **17** from hexane–ether gave colorless needles, mp 49–50 °C. The conversion yield of **17** was 86%.

B. By Synthesis.[4] A mixture of 8.0 g of 2,3,4,5-tetrahydro-6-methoxypyridine, 8.7 g of methyl acetoacetate, and 10.0 g of triethylamine was heated in a sealed tube at 100 °C for 50 h. Removal of the unreacted materials under reduced pressure gave a brown oily residue, which was chromatographed on alumina. Elution with benzene afforded a pale yellow solid. Recrystallization of the solid from hexane–ether gave 6.52 g (47%) of methyl 2-(2-piperidylidene)acetoacetate as colorless needles, mp 49–50 °C. This material was found to be identical (spectra) with **17** obtained from hydrolysis of **7** on alumina.

Ethyl 2-(2-Piperidylidene)acetoacetate (18). A. From Hydrolysis of 7-(Aminoethylidene)-6-ethoxy-8-oxo-1-azabicyclo[4.2.0]octane (8) on Alumina. The fused β-lactam **8** (300 mg) was adsorbed on alumina for 160 h. Removal of the solvent gave an oily mixture which, on column chromatography, gave 270 mg (90%) of **18** as a pale yellow oil.

B. By Synthesis. Ethyl 2-piperidylideneacetoacetate **18** was synthesized by condensation of 2,3,4,5-tetrahydro-6-ethoxypyridine with ethyl acetoacetate in the presence of triethylamine as described in the literature.[4] This material was found to be identical (spectra) with **18** obtained from hydrolysis of **8** on alumina.

Hydrolysis of 7 in Acidic Solution. The fused β-lactam **7** (750 mg) was hydrolyzed in acidic ethanol solution (11% water and 1% acetic acid) at room temperature for 60 h. After neutralization of the solution, the reaction mixture was extracted with $CHCl_3$. The solvent was evaporated under reduced pressure and the residue was triturated with ether–ethanol (95:5) to give crystals. Recrystallization from ether–ethanol gave 130 mg (19%) of 2-(aminoethylidene)-3-oxo-7-heptane lactam **21** as colorless needles, mp 195–196 °C. Evaporation of the solvent from the liquid fraction under reduced pressure gave an oily residue. The residue was chromatographed on alumina (20 g) with benzene as eluent to give 505 mg (67%) of **17**. This compound (**17**) was identical with the sample obtained from hydrolysis of **7** on alumina. Further elution with benzene containing 5% methanol gave an additional 35 mg (5%) of **21**. The total amount of **21** was 165 mg. The yields of **17** and **21** were 67% and 24%, respectively.

Hydrolysis of 8 in Acidic Solution. The fused β-lactam **8** (700 mg) was hydrolyzed in acidic methanol solution (11% water and 1% acetic acid) at room temperature for 60 h. After neutralization of the solution, the reaction mixture was extracted with $CHCl_3$. The solvent was evaporated under reduced pressure and the residue was triturated with ether–methanol (95:5) to give crystals. Recrystallization from ether–methanol gave 160 mg (26%) of **21**. Evaporation of the solvent from the liquid fraction gave an oily residue. The residue was chromatographed on alumina (20 g) with benzene as eluent to give 427 mg (61%) of **18**. The compound **18** was identical (spectra) with the sample obtained from hydrolysis of **8** on alumina. Further elution with benzene–methanol (95:5) gave a trace amount of **21**. The yields of **18** and **21** were 61% and 26%, respectively.

Hydrolysis of 8-(Aminoethylidene)-7-methoxy-9-oxo-1-azabicyclo[5.2.0]nonane (9) in Acidic Solution. The fused β-lactam **9** (690 mg) was hydrolyzed in acidic ethanol solution (11% water and 1% acetic acid) at room temperature for 90 h. After neutralization of the solution, the reaction mixture was extracted with $CHCl_3$. After the solvent was removed under reduced pressure, ether–methanol (95:5) was added to the oily residue. Crude crystals separated on cooling and were collected by filtration. Recrystallization of the crude crystals from ether–methanol gave 227 mg (35%) of 2-(aminoethylidene)-3-oxo-8-octane lactam **22** as colorless needles, mp 169–170 °C. Evaporation of the solvent from the liquid fraction under reduced pressure gave an oily residue. The residue was chromatographed on alumina (30 g) with hexane–benzene (5:1) as eluent to give 100 mg (14%) of methyl 2-(2-hexahydroazepinylidene)acetoacetate (**19**) as a pale yellow oil. Further elution with benzene afforded 138 mg (20%) of 8-acetyl-7-methoxy-9-oxo-1-azabicyclo[5.2.0]-nonane (**23**) as a colorless oil and 38 mg (5.5%) of starting material **9**. The product **23** was shown to be a mixture of two stereoisomers

(23A and 23B) by ^1H NMR spectroscopy. The ratio of the isomers was approximately 5:2 (23A:23B), estimated from the peak heights of the methine protons. The conversion yields of 19, 22, and 23 were 15%, 37%, and 21%, respectively.

Hydrolysis of 8-(Aminoethylidene)-7-ethoxy-9-oxo-1-azabicyclo[5.2.0]nonane (10) in Acidic Solution. The fused β-lactam 10 (1.00 g) was hydrolyzed in acidic methanol solution (11% water and 1% acetic acid) at room temperature for 80 h. After neutralization of the solution, the reaction mixture was extracted with $CHCl_3$. After the solvent was removed under reduced pressure, ether–methanol (95:5) was added to the oily residue. Crude crystals separated on cooling and were collected by filtration. Recrystallization of the crude crystals from ether–methanol gave 300 mg (34%) of 22. Evaporation of the solvent from the liquid fraction under reduced pressure gave an oily residue. The residue was chromatographed on alumina (30 g) with hexane–benzene (5:1) as eluent to give 86 mg (9%) of ethyl 2-(2-hexahydroazepinylidene)acetoacetate (20) as a pale yellow oil. Further elution with benzene afforded 117 mg (12%) of 8-acetyl-7-ethoxy-9-oxo-1-azabicyclo[5.2.0]nonane (24) as a colorless oil and 117 mg (12%) of starting material 10. The product 24 was a mixture of two stereoisomers (24A and 24B). The ratio of the isomers was approximately 5:2 (24A:24B). The conversion yields of 20, 22, and 24 were 10%, 39%, and 13%, respectively.

Hydrolysis of 24 in Acidic Solution. The fused β-lactam 24 (48 mg) was hydrolyzed in 2 mL of acidic methanol solution (11% water and 1% acetic acid) for 20 days. After evaporation of the solvent under reduced pressure, the reaction mixture was extracted with $CHCl_3$. The extract was washed with aqueous sodium bicarbonate solution, dried (Na_2SO_4), and evaporated to an oily residue. Crystallization from benzene–hexane gave 12.2 mg (29%) of 2-(hydroxyethylidene)-3-oxo-8-octane lactam 25. After evaporation of the solvent from the filtrate, the residue was chromatographed on alumina. No product was isolated.

Preparation of 7-(Aminoethylidene)-6-(trideuteriomethoxy)-8-oxo-1-azabicyclo[4.2.0]octane (7a). A solution containing 310 mg of the fused 4-pyrimidinone[1b] in 4 mL of methanol-d_4 (99.7 D atom %; Merck) was degassed with nitrogen for 10 min and irradiated with a low-pressure mercury lamp (30 W) for 38 h through a Corning 9-54 color filter. After irradiation, the solvent was removed by rotary evaporation. Methanol was added to the oily residue to exchange the deuterium of the amino group for hydrogen. After evaporation of methanol, ether was added. Crude crystals separated on cooling and were collected by filtration. Recrystallization from methanol–hexane gave 41 mg of 7a as colorless prisms. The starting material (246 mg) was recovered. The conversion yield was 54%. Mass spectrometric analysis confirmed that three deuterium atoms were incorporated in the methoxy group. The molecular ion m/e was 199.

Trideuteriomethyl 2-(2-Piperidylidene)acetoacetate (17a). From Hydrolysis of 7a on Alumina. The fused methyl-d_3 β-lactam 7a (40 mg) was adsorbed on alumina (10 g) for 68 h. Removal of the solvent gave 39 mg (97%) of 17a. Recrystallization of 17a from hexane gave colorless needles. ^1H NMR and mass spectrometric analysis of 17a confirmed that three deuterium atoms were incorporated in the methoxy group. The molecular ion m/e was 200.

Preparation of 7-(Aminoethylidene)-6-(methoxy-^{18}O)-8-oxo-1-azabicyclo[4.2.0]octane (7b). A solution containing 254 mg of the fused 4-pyrimidinone[1b] in 2.7 mL (2 g) of ^{18}O-labeled methanol (^{18}O, 5.3 atom %; The British Oxygen Co. Ltd.) was irradiated with a low-pressure mercury lamp through a Corning 9-54 color filter for 44 h. After irradiation, the solvent was removed by rotary evaporation. Ether was added to the oily residue. Crude crystals separated on cooling and were collected by filtration. Recrystallization from methanol–hexane gave 30 mg of 7b as colorless prisms. The starting material (200 mg) was recovered. The conversion yield was 62%. Mass spectrometric analysis confirmed that the ^{18}O atom was incorporated in the methoxy group (see Table XI). The fraction of ^{18}O-labeled compound in 7b was 0.050 ± 0.003.

Methyl 2-(2-Piperidylidene)acetoacetate-*carboxy*-^{18}O (17b). From hydrolysis of (7b) on Alumina. The fused methoxy-^{18}O β-lactam 7b (48 mg) was adsorbed on alumina (12 g) for 39 h. Removal of the solvent gave 42 mg (87%) of 17b. Recrystallization of 17b from hexane gave colorless needles. Mass spectrometric analysis confirmed that the ^{18}O atom was incorporated in the methoxy group (see Table XII). The fraction of ^{18}O-labeled compound in 17b was 0.050 ± 0.003.

Analytical data, molecular ion (mass spectrum), and the full ^1H NMR data are summarized in Tables VI–X (supplementary material).

Registry No. 1, 72611-06-4; 2, 72611-07-5; 3, 72611-08-6; 4, 72611-09-7; 5, 72611-10-0; 6, 72611-11-1; 7, 66849-14-7; 7a, 72611-12-2; 7b, 72611-13-3; 8, 66849-13-6; 9, 72611-14-4; 10, 72611-15-5; 11, 72611-16-6; 12, 72611-17-7; 13, 72611-18-8; 14, 72611-19-9; 15, 72611-20-2; 16, 72611-21-3; 17, 66849-15-8; 17a, 72611-22-4; 17b, 72611-23-5; 18, 25560-27-4; 19, 72611-24-6; 20, 72611-25-7; 21, 72611-26-8; 22, 72611-27-9; 23, isomer 1, 72611-28-0; 23, isomer 2, 72611-29-1; 24, isomer 1, 72611-30-4; 24, isomer 2, 72611-31-5; β-amino-*N*-methylcrotonamide, 24392-27-6; β-(acetylamino)-α-acetyl-*N*-methylcrotonamide, 24392-28-7; ketene, 463-51-4; 2,3,4,5-tetrahydro-6-methoxypyridine, 5693-62-9; methyl acetoacetate, 105-45-3.

Supplementary Material Available: Tables VI–X, analytical data, molecular ion (mass spectrum) data, and the full ^1H NMR data for compounds 11–25 (5 pages). Ordering information is given on any current masthead pages.