Rearrangements of Dewar 4-Pyrimidinones and 4-Methoxy-2-azetidinones. Reactions through Azetidinyl and Acyl Cations

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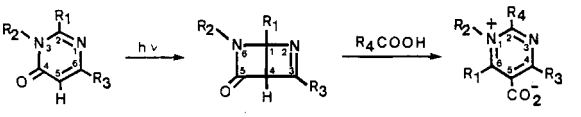
Irradiation of 2,3,6-trialkyl-4-pyrimidinones **1** and the thermal reactions of the Dewar 4-pyrimidinones **2** in aliphatic carboxylic acid solutions gave the corresponding tetraalkylpyrimidinium-5-carboxylates **3**. The structures of the betaines **3** were established by spectroscopic and chemical methods. The ^{13}C-labeling experiments indicated that the carboxy carbon atom of the carboxylic acid is incorporated in the 2 position of the pyrimidine moiety. The products **3** and results of the ^{13}C-labeling experiments can be explained in terms of an initial cleavage of the C(1)–N(2) bond of the Dewar isomers **2** by protonation of the imine nitrogen to give an azetidinyl cation, which rearranges to an acyl cation by the subsequent fission of the C(5)–N(6) bond. Thermolysis of the Dewar 4-pyrimidinones **2** gave the 4-alkylidene-2-azetidinones **20**, cyclobutenones **21**, and 4-pyrimidinones **1**, indicating cleavages of the C(1)–N(2), C(5)–N(6), and C(1)–C(4) bonds. The products (**20** and **21**) and fission of the bonds suggest a ketene intermediate, which is formed by rearrangement of the azetidinyl cation. The acetoacetates **24** were formed by transfer of the methoxy group to the amide carbonyl carbon in the thermolysis of the 4-methoxy-2-azetidinones **10** and by rearrangement of the 4-methoxy-3-(aminoalkylidene)-2-azetidinones **11** in the presence of acids. The mechanism and intermediates of the intramolecular migration of the methoxy group are discussed.

In previous publications[1] we have reported that 4-pyrimidinones undergo a wide variety of photochemical reactions in protic solvents. The photochemical intermediates are the highly reactive Dewar 4-pyrimidinones **2**, which have recently been isolated as the crystalline compounds.[1f] In the course of these studies, we encountered a zwitterionic product that resulted from an unusual photochemical rearrangement of 2,3,6-trialkyl-4-pyrimidinones **1** in acetic acid.[1e] In this paper we now report the complete experimental details of this study and additional observations concerning intermediates and mechanism of the rearrangement. Furthermore, to elucidate this rearrangement, the thermolysis of **2** and 4-methoxy-2-azetidinones **10** and reactions of 3-(aminoalkylidene)-4-methoxy-2-azetidinones **11** with acetic acid in benzene solution were carried out.

Photochemistry of 4-Pyrimidinones 1a–g and Reactions of Dewar 4-Pyrimidinones 2a and 2h in Aliphatic Carboxylic Acid Solutions. When an acetic acid solution of 2,3,6-trimethyl-4-pyrimidinone (**1a**) [λ_{max} (CH_3COOH) 269 nm (ϵ 3910)] was irradiated at 25 °C with a 100-W high-pressure mercury lamp through quartz under an argon atmosphere, crystalline compound **3a** was obtained in a yield of 69% (based on the consumed **1a**). Analogous photolysis of **1b–g** in acetic acid–acetonitrile solution and of **1a** in acetonitrile solution containing either propanoic acid or cyclohexanecarboxylic acid gave the corresponding products (**3b–g**, **3m**, and **3n**) in 40–84% yields, respectively (Scheme I).

When the Dewar 4-pyrimidinone **2a** was treated in acetic acid–acetonitrile solution at 0 °C, **3a** was obtained in a yield of 54%. Similarly, the reactions of the Dewar 4-pyrimidinone **2h** with acetic acid, formic acid, propanoic acid, 2-methylpropanoic acid, and 3,3-dimethylbutanoic acid in protic and aprotic solvents at 20 °C gave the corresponding products **3h–l** and 4-pyrimidinones **1h**, suggesting that the Dewar 4-pyrimidinones[2] **2** are one of the intermediates in the photoreaction (Scheme I). The yields of the products are listed in Tables I and II. The spectral data of **3a–h** and **3m** are shown in Table III (supplementary material).

Scheme I



1a–h 2a–h 3a–n

	R_1	R_2	R_3	R_4
a	CH_3	CH_3	CH_3	H
b	C_2H_5	CH_3	CH_3	CH_3
c	CH_3	CH_3	C_2H_5	C_2H_5
d	Ph	CH_3	CH_3	$(CH_3)_2CH$
e	CH_3	CH_3	Ph	$(CH_3)_3CCH_2$
f	CH_3	Ph	CH_3	c-C_6H_{11}
g	$-(CH_2)_4-$		CH_3	
h	CH_3	CH_3	t-Bu	

Irradiation of **1a** or **1h** in acetonitrile containing 2,2-dimethylpropanoic acid at 0 °C did not give the corresponding product **3**. The reaction of the Dewar isomer **2h** with 2,2-dimethylpropanoic acid in benzene solution at 20 °C gave **1h** (10%) and polymeric products. The steric effects of alkyl groups will be discussed further below.

The products **3** had the decomposition points above 180 °C and were soluble in protic solvents, such as methanol, water, and acetic acid, but were insoluble in aprotic solvents. The solubilities suggested ionic or zwitterionic compounds. The mass spectrum of **3a** showed a small molecular ion (M^+), a large ($M^+ - CO_2$), and CO_2^+ peaks. In the IR spectrum, the β-lactam carbonyl band of **2** is absent and new carbonyl frequencies appeared at 1615

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(1) (a) Hirokami, S.; Hirai, Y.; Nagata, M.; Yamazaki, T.; Date, T. *J. Org. Chem.* **1979**, *44*, 2083. (b) Hirai, Y.; Yamazaki, T.; Hirokami, S.; Nagata, M. *Tetrahedron Lett.* **1980**, *21*, 3067. (c) Hirokami, S.; Takahashi, T.; Nagata, M.; Hirai, Y.; Yamazaki, T. *J. Org. Chem.* **1981**, *46*, 1769. (d) Takahashi, T.; Hirokami, S.; Kato, K.; Nagata, M.; Yamazaki, T. *Ibid.* **1983**, *48*, 2914. (e) Hirokami, S.; Takahashi, T.; Nagata, M.; Yamazaki, T. *Tetrahedron Lett.* **1983**, *24*, 5237. (f) Hirokami, S.; Takahashi, T.; Kurosawa, K.; Nagata, M.; Yamazaki, T. *J. Org. Chem.* **1985**, *50*, 166. (g) Takahashi, T.; Hirokami, S.; Nagata, M.; Yamazaki, T. *Tetrahedron Lett.* **1985**, *26*, 3247.

(2) The Dewar isomers **2b–e** and **2g** were observed spectroscopically and were trapped by methanol. However, the Dewar 4-pyrimidinone **2f** could not be observed in methanol and acetonitrile at −20 to −30 °C. The Dewar isomer **2f** may be unstable and reverts to the starting **1f**.

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Table I. Yields of Betaines 3 Formed in the Photochemical Reactions of 4-Pyrimidinones 1 in Carboxylic Acid Solutions

starting material	solvent	carboxylic acid	product compd	substituents R_1	R_2	R_3	R_4	yield,[a] %
1a	CH_3COOH	CH_3COOH	3a	CH_3	CH_3	CH_3	CH_3	69
1b	CH_3CN	CH_3COOH	3b	C_2H_5	CH_3	CH_3	CH_3	84
1c	CH_3CN	CH_3COOH	3c	CH_3	CH_3	C_2H_5	CH_3	55
1d	CH_3CN	CH_3COOH	3d	Ph	CH_3	CH_3	CH_3	62
1e	CH_3CN	CH_3COOH	3e	CH_3	CH_3	Ph	CH_3	74
1f	CH_3CN	CH_3COOH	3f	CH_3	Ph	CH_3	CH_3	79
1g	CH_3CN	CH_3COOH	3g	$-(CH_2)_4-$		CH_3	CH_3	57
1a	CH_3CN	C_2H_5COOH	3m	CH_3	CH_3	CH_3	C_2H_5	40
1a	CH_3CN	c-$C_6H_{11}COOH$	3n	CH_3	CH_3	CH_3	c-C_6H_{11}	43

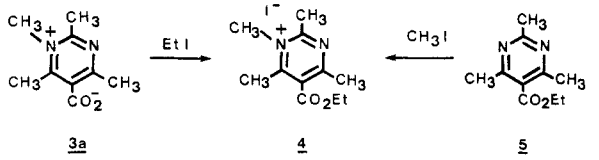
[a] The yields were corrected for the recovered 4-pyrimidinones.

Table II. Yields of the Products Formed in the Reactions of Dewar 4-Pyrimidinones 2 with Carboxylic Acids in Protic and Aprotic Solvents

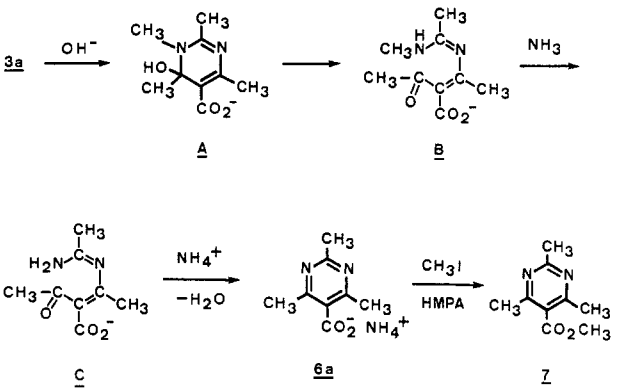
starting material	solvent	carboxylic acid	products compd	substituents R_1	R_2	R_3	R_4	yield,[a] %	compd	yield,[a] %
2a	CH_3CN	CH_3COOH	3a	CH_3	CH_3	CH_3	CH_3	54	1a	n.d.[b]
2h	C_6H_6	HCOOH	3i	CH_3	CH_3	*t*-Bu	H	40	1h	10
2h	C_6H_6	CH_3COOH	3h	CH_3	CH_3	*t*-Bu	CH_3	76	1h	0
2h	C_6H_6	C_2H_5COOH	3j	CH_3	CH_3	*t*-Bu	C_2H_5	66	1h	3
2h	C_6H_6	$(CH_3)_2CHCOOH$	3k	CH_3	CH_3	*t*-Bu	$(CH_3)_2CH$	70	1h	7
2h	C_6H_6	$(CH_3)_3CCH_2COOH$	3l	CH_3	CH_3	*t*-Bu	$(CH_3)_3CCH_2$	41	1h	14
2h	CH_3COOH	CH_3COOH	3h	CH_3	CH_3	*t*-Bu	CH_3	74	1h	10
2h	CH_3CN	CH_3COOH	3h	CH_3	CH_3	*t*-Bu	CH_3	64	1h	5
2h	$CHCl_3$	CH_3COOH	3h	CH_3	CH_3	*t*-Bu	CH_3	59	1h	5
2h	C_6H_6	$(CH_3)_3CCOOH$	c						1h	10

[a] The yields were determined by the HPLC analysis except for those of **3a** and **3i**. [b] Not determined. [c] The corresponding betaine was not formed.

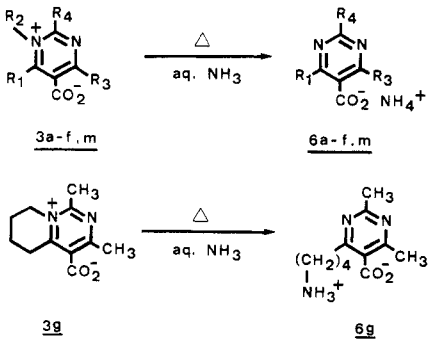
Scheme II



Scheme III



Scheme IV



cm^{-1} and 1600 cm^{-1}, indicating the formation of a conjugated carboxylate. The ^1H NMR spectrum showed the N-methyl signal shifted to lower field (δ 4.14), suggesting the presence of a quaternary N-methyl group. The UV spectrum (MeOH) at 276 nm (ϵ 4360) and 230 nm (sh, ϵ 5320) was similar to that of **1a**. From these data, the compound **3a** was assigned to 1,2,4,6-tetramethylpyrimidinium-5-carboxylate.

To confirm the structure of **3a** by synthesis, it was converted to the ethyl ester **4** with iodoethane at 70 °C. The product **4** was identical (spectra) with a sample prepared by alkylation of pyrimidine **5**[3] with methyl iodide (Scheme II).

Treatment of **3a** in an aqueous ammonia solution (25%) at 20 °C for 38 h gave ammonium pyrimidine-5-carboxylate **6a** (93%). The structure of **6a** was deduced from spectral data and was confirmed by conversion to the methyl ester **7**,[4] which was also obtained from **5** by an alkoxy exchange reaction. The reaction of **3a** with ammonia in methanol under 10 atm of pressure at 25 °C gave inseparable products. The initial reaction of **3a** in aqueous ammonia solution is an addition of hydroxide anion to the 6 position to give hydroxypyrimidine A. The bond cleavage, subsequent replacement[5] of methylamine by ammonia, and ring closure give **6a** (Scheme III).

Similarly, the pyrimidines **6b–g** and **6m** were obtained in high yields when the betaines **6b–g** and **6m** were treated in aqueous ammonia solution at 15–20 °C for 1–3 days

(3) (a) Urban, R.; Schnider, O. *Helv. Chim. Acta* **1958**, *41*, 1806. (b) It would be worthwhile to state here that this alkylation required 9 weeks for completion.

(4) Shaw, J. E.; Kunerth, D. C. *J. Org. Chem.* **1974**, *39*, 1968.

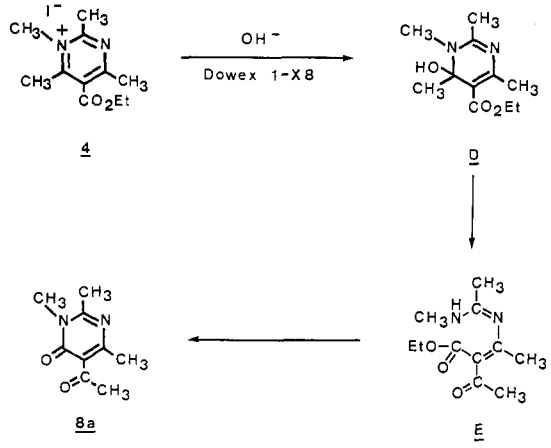
(5) Reynaud, P.; Brion, J.-D.; Menard, G. *Bull. Soc. Chim. Fr.* **1978**, 449.

Table IV. Yields of Ammonium Pyrimidine-5-carboxylates 6 Formed in the Reactions of the Betaines 3 in Aqueous Ammonia Solution[a]

starting material	product compd	substituent R_1	R_3	R_4	yield, %
3a	**6a**	CH_3	CH_3	CH_3	93
3b	**6b**	Et	CH_3	CH_3	96
3c	**6c = 6b**	CH_3	Et	CH_3	97
3d	**6d**	Ph	CH_3	CH_3	87
3e	**6e = 6d**	CH_3	Ph	CH_3	98
3f	**6f = 6a**	CH_3	CH_3	CH_3	98
3g	**6g**	$(CH_2)_4{}^+NH_3$	CH_3	CH_3	97
3m	**6m**	CH_3	CH_3	Et	85

[a] The reactions of betaines **3** were conducted in 25% aqueous ammonia solution at room temperature.

Scheme V



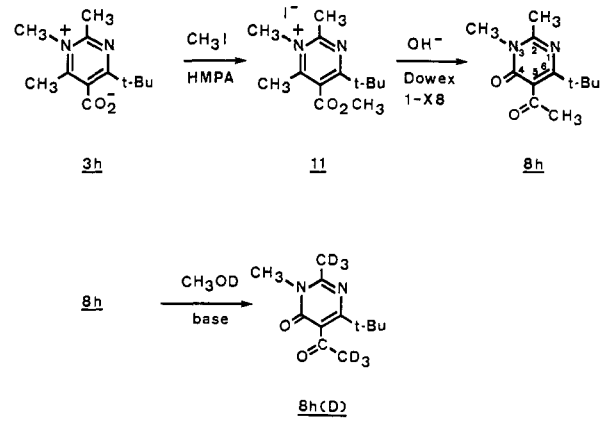
(Scheme IV). The yields and spectral data of the products **6a–g** and **6m** are shown in Tables IV and V. The pyrimidines **6a** and **6f** were the same compound. Thus, **3f** is 1-phenyl-2,4,6-trimethylpyrimidinium-5-carboxylate. Each pair of the pyrimidines **6b** and **6c** and **6d** and **6e** were the same compounds.

In the ^1H NMR spectrum of **6m**, the chemical shifts of the two methyl groups appeared at δ 2.54 (s, 2 × 3 H). The chemical shift equivalence of the two methyl groups indicated that **6m** has a symmetry of C_{2v}. The two methyl groups are located on the 4 and 6 positions and the ethyl group derived from propanoic acid is located on the 2 position. The position of the substituent R_4 is assigned to the 2 position of the betaines **3**.

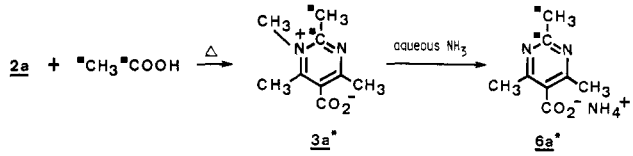
Another informative reaction was observed when an aqueous solution of the pyrimidinium iodide **4** was passed through a column[6] of Dowex 1-X8 in the hydroxide form. The crystalline product **8a**, obtained in 73% yield, was assigned as 5-acetyl-2,3,6-trimethyl-4-pyrimidinone by spectral data and was confirmed by comparison with those of an authentic sample[7] (Scheme V). A plausible mechanism involves addition of hydroxide anion to the 6 position of **4**. The formed 4-hydroxypyrimidine D undergoes a cleavage of the N(3)–C(4) bond of the pyrimidine to give an amidine intermediate (E). The secondary amine nitrogen attacks the ester carbonyl carbon with concomitant elimination of alcohol to give the 5-acetyl-4-pyrimidinone **8a**. The methyl group at the 6 position of **4** is converted into the acetyl methyl group at the 5 position of **8a** (Scheme V).

(6) Kosower, E. M.; Patton, J. W. *J. Org. Chem.* **1961**, *26*, 1318.
(7) Kato, T.; Yamanaka, H.; Kawamata, J.; Shimomura, H. *Chem. Pharm. Bull.* **1969**, *17*, 1889.

Scheme VI



Scheme VIII



Esterification[4] of the carboxylate of the betaine **3h** with iodomethane was carried out in HMPA containing water for 5 h at room temperature to give pyrimidinium iodide **11**. Since **11** could not be separated from the solvent, the solution was passed over a column of Dowex 1-X8 in the hydroxide form. Crystalline compound **8h**, which was not **11**, was obtained in 69%. Analysis, molecular ion, and the spectral data indicated that the compound was either 5-acetyl-6-*tert*-butyl-2,3-dimethyl-4-pyrimidinone (**8h**) or the 5-pivaloyl-2,3,6-trimethyl isomer. The decisive information for structure **8h** was obtained from the fragment ion peak at *m/e* 43 (C_2H_3O; exact mass, *m/e* 43.0176, calcd 43.0184) assigned as an acetyl cation. No peak at *m/e* 85 corresponding to a pivaloyl cation was observed. To confirm the assignment, the deuterium-labeled compound **8h(D)** was prepared in methanol-*d* containing a catalytic amount of *tert*-butylamine at room temperature. The ^1H NMR analysis of **8h(D)** indicated that the two methyl groups were deuterated in 98 atom % D. The compound **8h(D)** exhibited the fragment ion peak at *m/e* 46 corresponding to a trideuterioacetyl cation (CD_3CO^+) (Scheme VI).

Further confirmation of the positional assignments of the substituents (R_1 and R_3) was achieved by analyses of the mass fragment ion peaks of the betaines (**3d**, **3e**, and **3f**). The mass spectra of **3d–f** are summarized in Table VI (supplementary material). The assignments were established by comparison with those of **3a** and deuterated **3a(D)**. The fragmentation sequence is shown in Scheme VII (supplementary material).

One mechanistic question left unanswered in regard to the reaction of the Dewar isomers **2** with the carboxylic acids is whether the carboxylate functionality is formed by conversion of the amide carbonyl of **2** to the carboxyl group (process A) or by addition of the carboxyl group of the carboxylic acid to the 4 position of the Dewar isomers **2** with concomitant cleavage of the C(1)–C(2) bond of the carboxylic acid (process B). The question could be solved by the reaction of **2a** with acetic acid-*1,2*-^{13}C. The former mechanism would predict the two ^{13}C atoms to be found in the 2 position of **3a** as the ring carbon atom and 2-methyl carbon, while the latter mechanism would predict the ^{13}C atoms to be found in the 2-methyl and 5-carboxyl group of **3a**.

Table V. Spectroscopic Data for Ammonium Pyrimidine-5-carboxylates 6

compd	condtn[a] of compd	UV,[b] λ_{max}, nm (ϵ)	IR (ν_{CO}),[c] cm^{-1}	^1H NMR,[d] δ		
				6-R_1 (4-R_1)	4-R_3 (6-R_3)	2-R_4
6a	A	261 (4230)	1585	2.53 (s)	2.53 (s)	2.60 (s)
		237 (5030)	1565	(CH_3)	(CH_3)	(CH_3)
6b′	B	262 (4480)	1720	1.29 (t)	2.51 (s)	2.62 (s)
		223 (sh, 4930)	1705	2.81 (q)		
				(Et)[e]	(CH_3)	(CH_3)
6d	A	281 (4960)	1575	7.5 (m)	2.60 (s)	2.70 (s)
		244 (sh, 4490)	1550	8.0 (m)		
				(Ph)	(CH_3)	(CH_3)
6g	C	263 (4380)	1625	1.8 (m)	2.53 (s)	2.62 (s)
				3.0 (m)		
				(4 × CH_2)	(CH_3)	(CH_3)
6m	A	260 (4250)	1545	2.54 (s)	2.54 (s)	1.31 (t)
		225 (sh, 5370)				2.86 (q)
				(CH_3)	(CH_3)	(Et)[e]

[a] A, ammonium salt; B, carboxylic acid; C, inner salt. [b] Methanol. [c] KBr. [d] CD_3OD. [e] The coupling constants were J = 7.5 Hz.

Table VII. ^{13}C Chemical Shifts and Coupling Constants of Betaine 3a* and Pyrimidine 6a*

chemical shift, δ[a]			
3a*		**6a***	
signal	assignment	signal	assignment
19.0 (br)[b]	6-CH_3	21.9 (q)	4-CH_3 and 6-CH_3
23.7 (q)	4-CH_3	25.0 (dq)[c]	2-CH_3
24.1 (dq)[c]	2-CH_3	133.4 (s)	C-5
40.4 (q)	1-CH_3	163.6 (s)	C-4 and C-6
136.5 (s)	C-5	166.2 (d)[c]	C-2
159.0 (s)	C-4	175.3 (s)	C-5′
162.4 (d)[c]	C-2		
169.3 (s)	C-6 or C-5′		
170.3 (s)	C-6 or C-5′		

coupling constants, Hz		
	3a*	**6a***
$^1J_{^{13}C(2')-H}$[d]	132	129
$^1J_{^{13}C(2)-^{13}C(2')}$[c]	57.8 ± 0.4	59.4 ± 0.4
$^2J_{^{13}C(2)-^{13}C(2')-H}$[d]	7.1	6.9

[a] Chemical shifts are given in δ units from internal tetramethylsilane and measured in CD_3OD. [b] The broadening of methyl signal is due to the H/D exchange. [c] The coupling constants were measured by the proton noise-decoupled ^{13}C NMR spectra. [d] The coupling constants were measured by the ^1H NMR spectra.

The ^{13}C-labeled betaine **3a*** was prepared by the reaction of **2a** with acetic acid-*1,2-*^{13}C [24 mol %; 1-^{13}C (92.4 atom %) and 2-^{13}C (91 atom %)]. Treatment of **3a*** in aqueous ammonia solution gave the ^{13}C-labeled **6a*** (Scheme VIII).

The ^1H and proton-noise-decoupled ^{13}C NMR spectra[8] showed the ^1H–^{13}C, ^1H–^{13}C–^{13}C, and ^{13}C–^{13}C couplings between the 2-methyl and C(2) (see Table VII). The presence of the couplings ruled out the mechanism involving the fission of the C(1)–C(2) bond of acetic acid. The ^{13}C chemical shifts and coupling constant ^1J[^{13}C-(Me)–H] of the pyrimidine-5-carboxylate **6a*** are similar to those of 2,4,6-trimethylpyrimidine.[9] The ^{13}C–^{13}C coupling constant values of **3a*** and **6a*** are larger than that of ethane [$^1J(^{13}C–^{13}C)$ = 34.6 Hz] and are approximately the same as those of acetic acid [$^1J(^{13}C–^{13}C)$ = 56.7 Hz][10] and acetonitrile [$^1J(^{13}C–^{13}C)$ = 56.5 Hz].[13] The larger coupling constant value may be due to the presence of the adjacent electronegative atoms that are known to increase the ^{13}C–^{13}C coupling constant.[11]

The mass spectrometric measurements of the ^{13}C-labeled and unlabeled compounds are listed in Tables VIII and IX. The spectral data confirmed incorporation of the two ^{13}C atoms in the molecular (M^+) and fragment ($M^+ - CO_2$) ions. Both fractions of the ^{13}C atoms of **3a*** and **6a*** were 23 ± 1 mol % estimated by the ^1H NMR and mass spectra.

Thus, we can rule out the mechanism in which the C-(1)–C(2) bond of the carboxylic acid is cleaved and the carboxyl group adds to the Dewar isomer **2** (process B). We can also eliminate the mechanism in which N-alkyl and N-aryl groups of the Dewar isomers **2** migrate to other ring atoms because these groups remain attached to the same nitrogen atom during the reaction. Furthermore, to approach the reaction mechanism, we assume that the alkyl and aryl groups at the 1 and 3 positions of the Dewar isomers **2** act as positional labels for the ring atoms of the betaines **3**.

On the basis of the results and assumptions, the pyrimidine ring atoms and carboxy carbon atom of **3** were assigned to those of **2** and carboxy carbon atom of the carboxylic acid. The pathways to these rearrangement products **3** from the Dewar isomers **2** require the cleavage of the C(1)–N(2) and C(5)–N(6) bonds of **2** and bond formation of the carboxy carbon atom among the N(1) and N(6) atoms. Both of the bond cleavage may be heterolytic fission, which leads to the formation of ionic intermediates.

A number of aliphatic carboxylic acids of the primary and secondary alkyl groups reacted with the Dewar isomers **2** to give the corresponding betaines **3**. However, the corresponding betaine **3** was not formed by the reaction of **2h** with pivalic acid. The substitution of the *tert*-butyl group for the methyl group of acetic acid has a significant effect on the rate of reaction. The initial reaction of **2h** with the carboxylic acids may be nucleophilic attack by the imine nitrogen to the carboxy carbon atom or would be protonation on the imine nitrogen. The former mechanism would predict that the relative rate constants depend markedly upon the structure of alkyl group,[12] while the latter mechanism would not lead to marked reduction

(8) The protons of the 6-methyl group were observed as a small broadened signal due to the H/D exchange in CD_3OD after 5–6 h at room temperature. After 17 h, the relative intensities of the 2-methyl, 4-methyl, and 6-methyl to that of the 1-methyl in ^1H NMR spectrum were 65%, 75%, and 25%, respectively.

(9) (a) Riand, J.; Chenone, M. T.; Lumbroso-Bader, N. *Tetrahedron Lett.* **1974**, 3123. (b) Riand, J.; Chenone, M. T.; Lumbroso-Bader, N. *J. Am. Chem. Soc.* **1977**, *99*, 6838.

(10) Maciel, G. E.; McIver, J. W., Jr.; Ostlund, N. S.; Pople, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 11.

(11) Levy, G. C.; Lichter, R. L.; Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance Spectroscopy*, 2nd ed.; Wiley: New York; 1980; pp 68–77.

(12) Streitwieser, A., Jr.; Heathcock, C. H. *Introduction to Organic Chemistry*, 2nd ed.; Macmillan Publishing Co., Inc: New York, 1981; pp 161–163.

(13) Hirai, Y.; Hirokami, S.; Nagata, M.; Morita, M.; Yamazaki, T. *J. Org. Chem.* **1980**, *45*, 936.

Table VIII. Mass Spectrometric Data for ^{13}C-Labeled and Unlabeled Betaines 3a* and 3a

compd	relative intensity[a]											
	molecular ion (M^+), m/e					fragment ion ($M^+ - CO_2$), m/e					CO_2^+, m/e	
	183	182	181	180	179	139	138	137	136	135	45	44
3a	0	0.9	6.0	27.0	3.6	1.5	7.6	21.7	100	5.8	3.1	62.7
		(0.2)	(0.1)	(0.6)	(0.3)	(0.2)	(0.5)	(0.4)		(0.6)	(1.6)	(2.9)
3a*	1.3	8.4	5.9	31.1	2.5	3.6	32.0	18.0	100	6.3	3.0	59.2
	(0.1)	(0.4)	(0.3)	(2.1)	(0.1)	(0.6)	(0.8)	(0.7)		(0.6)	(0.7)	(1.8)

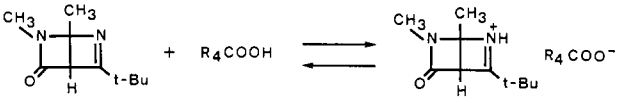
[a] Standard deviation in parentheses.

Table IX. Mass Spectrometric Data for ^{13}C-Labeled and Unlabeled Ammonium Trimethylpyrimidine-5-carboxylates 5a and 5a*

	relative intensity,[a] molecular ion (M^+) – NH_3			
	169	168	167	166
6a	0	0.9	11.2	100
		(0.3)	(0.3)	
6a*	3.6	26.3	20.0	100
	(1.0)	(0.9)	(3.2)	

[a] Standard deviation in parentheses.

Scheme IX



2h 9h

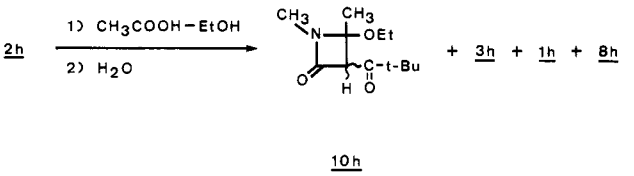
of the rate constants and the observed steric effect of 2,2-dimethylpropanoic acid may be due to a nucleophilic attack on the carboxy carbon in a subsequent reaction.

The relative rate measurements may provide decisive information about the reaction mechanism. With this prospect in mind, we examined the competitive reactions of two carboxylic acids with **2h** in benzene solution at 20 °C. The relative rates were determined by the ratios of the respective yields of the betaines formed by the reaction of **2h** with two aliphatic carboxylic acids **A** (acetic acid or propanoic acid) and **B** (propanoic acid, 2-methylpropanoic acid, 2,2-dimethylpropanoic acid, or 3,3-dimethylbutanoic acid) as a function of molar fraction of **A**. The yields of the betaines and mean values of the relative rate constants of the carboxylic acids are listed in Tables X and XI (supplementary material).

The relative rate constants of four carboxylic acids to acetic acid were in the range of about 0.4 to 0.7. No appreciable reduction in the rate constants was observed. Then, the initial step of the reaction is transfer of proton from the carboxylic acid to the imine nitrogen to give an iminium ion **9h** (Scheme IX).

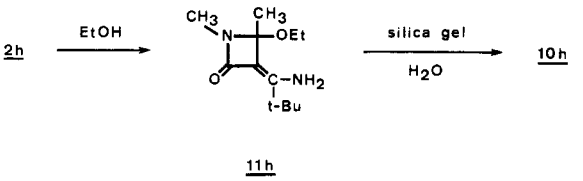
The iminium ion **9h** formed by protonation of **2h** may undergo either cleavage of the C(1)–N(2) bond to give an azetidinyl cation or fission of the C(5)–N(6) bond to form an acyl cation. To distinguish between these two mechanisms, we attempted to trap ionic intermediates with a nucleophile.

Scheme X



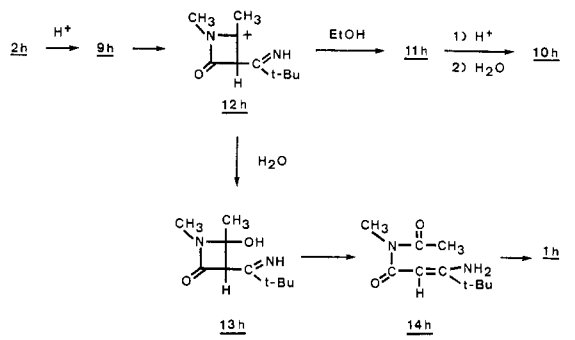
10h

Scheme XI



11h

Scheme XII



When the Dewar isomer **2h** was treated in benzene solution containing acetic acid and ethanol at 23 °C, the betaine **3h**, 4-pyrimidinone **1h**, 5-acetyl-4-pyrimidinone **8h**, and 4-ethoxy-2-azetidinone **10h** were isolated (Scheme X).

The structure of **10h** was assigned by spectral data and was confirmed by synthesis from the (*E*)-4-ethoxy-2-azetidinone **11h** which was prepared by solvolysis[1a] of the Dewar isomer **2h** in ethanol (Scheme XI).

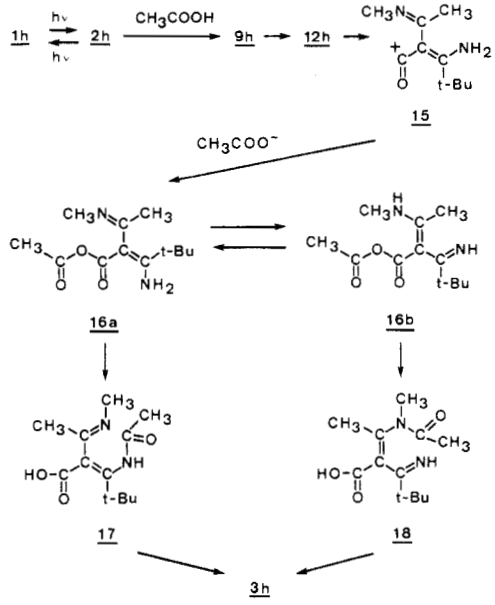
The precursor of **10h** is **11h** or a tautomer of **11h**. The yields of the products (**1h**, **3h**, **8h**, and **10h**) under a variety of conditions are shown in Table XII. The yield of **3h** decreased when ethanol was added. The yields of **9h**, **1h**, and **8h** were roughly constant in the range of 0.14–0.57 M of ethanol. The direct reaction of **2h** with ethanol could be ignored because of a very slow reaction in benzene solution. The formation of **10h** leads to the conclusion that

Table XII. Reaction of Dewar 4-Pyrimidinone 2h in Benzene Solution in the Presence of Acetic Acid and Ethanol[a]

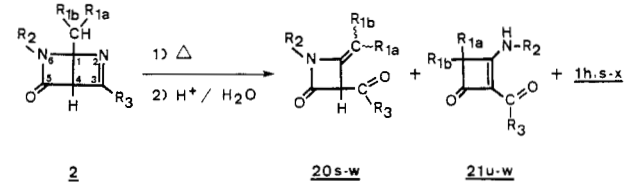
solvent (C_6H_6) (mL)	Dewar **2h** (M)	acetic acid (M)	ethanol (M)	yields of products (%)			
				3h	**10h**	**1h**	**8h**
5.00	0.0518	2.92	0	81	0	13	0
10.0	0.0126	0	1.56	0	*b*	0	0
25.0	0.0117	2.77	0.137	46	21	4	2
25.0	0.0117	2.62	0.286	41	16	3	3
25.0	0.0117	2.33	0.571	41	19	4	6

[a] Experimental conditions: temperature 23 °C; reaction time 1 h. [b] The yield of the 2-azetidinone **10h** was much less than 1%.

Scheme XIII



Scheme XIV



	R_{1a}	R_{1b}	R_2	R_3
a	H	H	CH_3	CH_3
h	H	H	CH_3	t-Bu
r	H	Ph	CH_3	CH_3
s	H	CH_3	CH_3	t-Bu
t	CH_3	CH_3	CH_3	t-Bu
u	H	Ph	CH_3	t-Bu
v	H	p-CH_3-Ph	CH_3	t-Bu
w	H	p-CH_3O-Ph	CH_3	t-Bu
x	H	$-(CH_2)_3-$		t-Bu

added ethanol captures an ionic intermediate, presumably an azetidinyl cation (Scheme XII). The protonation of **2h** by acetic acid gives the iminium cation **9h**, which undergoes the cleavage of the C(1)–N(2) bond to give an azetidinyl cation **12h**. Addition of ethanol to the cation **12h** gives **11h**. Subsequent hydrolysis of **11h** affords **10h**.

The 4-pyrimidinone **1h** was formed in the reaction of **2h** with carboxylic acid in protic and aprotic solvents. The yield of **1h** varied with experimental conditions. The contribution of the thermal isomerization of **2h** to **1h** in benzene at room temperature is negligible due to a very slow reaction.[14] The Dewar isomers reverted to the corresponding 4-pyrimidinones in aqueous solution.[1g] Then, we presume that **12h** is a precursor of **1h**. A plausible mechanism for the formation of **1h** is shown in Scheme XII. Addition of water to **12h** gives a 4-hydroxy-2-azetidinone **13h**. The cleavage of the C(3)–C(4) bond of **13h** leads to the formation of a ring-opened adduct **14h** and the subsequent ring closure gives **1h**.

The reaction of **2h** with acetic acid in benzene containing ethanol gave **8h**. Attempts to elucidate the mechanism were unsuccessful.[15]

The mechanism for the photochemical reaction of 4-pyrimidinone **1h** in acetic acid solution is shown in Scheme XIII. Photoexcitation of **1h** produces a singlet excited molecule that leads to the formation of the Dewar isomer **2h**. The protonation takes place on the imine nitrogen to give iminium ion **9h**, which rearranges to azetidinyl cation **12h**. The ring opening of the cation **12h** gives acyl cation **15**, followed by the addition of acetoxy anion, to yield mixed anhydride **16a**, which may be in the equilibrium with isomeric anhydride **16b**. Intramolecular acylation of the primary amine gives amide **17** and subsequent ring closure leads to the formation of the betaine **3h**. A similar intramolecular acetylation of the secondary amine **16b** forms amide **18** and subsequent reactions also give the betaine **3h**. The two mechanisms cannot be distinguished in the present case because both lead to the same product.

Table XVII. Yields of Products Formed by Thermolysis[a] of Dewar 4-Pyrimidinones 2

	product yield, %		
starting compd	4-pyrimidinone **1**	2-azetidinone **20**	c-butenone **21**
2h	73	0	0
2s	23	56	0
2t	17	68	0
2u	13	59	25
2v	7	64	29
2w	13	42	22
2x	45	0	0

[a] The reactions were conducted at 35–40 °C.

When 2,2-dimethylpropanoic acid reacts with **2h**, the rate of the intramolecular acylation may be drastically slowed down by the structural effects, and the alternative side reactions that do not give the corresponding betaine begin to compete.

Finally, it should be noted that irradiation of 2,3-dimethyl-4-pyrimidinone **1p** and 3,6-dimethyl-4-pyrimidinone **1q** in acetic acid–acetonitrile solution at 0 °C did not give the corresponding betaines and afforded only polymeric products. Presumably, the location of hydrogen at the 1 or 3 position of the Dewar 4-pyrimidinone reduces the stability of the intermediates and the side reactions tend to dominate.

Thermal Rearrangements of Dewar 4-Pyrimidinones 2. Thermolysis[16] of the Dewar 4-pyrimidinone **2u** in the presence of a small amount of benzene to melt the crystals at 40 °C for 52 h gave the 2-azetidinone **20u** (59%), cyclobuten-1-one **21u** (25%), and 4-pyrimidinone **1u** (13%) after separation of the products by column chromatography on silica gel (Scheme XIV).

Similarly, the thermal reactions of the Dewar 4-pyrimidinones **2s**, **2t**, **2v**, and **2w** in the absence of solvent at 35–40 °C for 24–48 h gave the corresponding 2-azetidinones **20s**, **20t**, **20v**, and **20w**, cyclobuten-1-ones **21v** and **21w**, and 4-pyrimidinones **1s**, **1t**, **1v**, and **1w**. The configuration about the double bond of **20** was not defined by the spectral data. The analogous reactions of the Dewar 4-pyrimidinones **2h** and **2x** at 40 °C for 97–110 h gave the respective 4-pyrimidinones **1h** and **1x**. The results are shown in Scheme XIV. The yields of the products are summarized in Table XVII. The spectral data of **20** and

(14) The rate of the thermal isomerization of **2h** to **1h** in benzene at room temperature was about 10^{-7} s^{-1}.

(15) The acetylation of 4-pyrimidinone **1h**, Dewar isomer **2h**, and 2-azetidinone **11h(a)** by acetic anhydride was carried out in benzene solution at room temperature. From **1h**, the starting material **1h** was recovered quantitatively. Treatment of **11h(a)** with acetic anhydride gave the 2-azetidinone **10h(a)** (46%) and recovered **11h(a)** (54%). From **2h**, **1h** (13%) and **3h** (68%) were obtained.

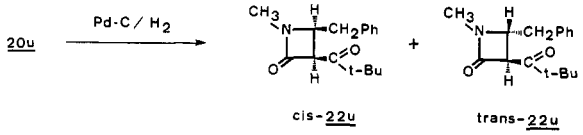
(16) The ^1H NMR spectrum of the reaction mixture before separation showed the formation of the imine 2-azetidinone which could not be isolated by crystallization and column chromatography.

Table XXI. ^{13}C NMR Spectral Data[a] for 4-Benzylidene-2-azetidinone 20u and Cyclobutenones 21u and 23u

20u		21u		23u	
signals	assignment	signals	assignment	signals	assignment
26.0 (q)	*t*-BuCH$_3$	25.2 (q)	*t*-BuCH$_3$	28.0 (q)	*t*-BuCH$_3$
28.0 (q)	NCH$_3$	32.2 (q)	NCH$_3$	29.8 (q)	NCH$_3$
44.5 (s)	*t*-BuC	41.9 (s)	*t*-BuC	36.3 (s)	*t*-BuC
63.5 (d)	3-C	63.5 (d)	4-C	90.4 (d)	4-C
100.2 (d)	4'-C	115.5 (s)	2-C	96.4 (s)	2-C
126.2 (d)	ArC	127.2 (d)	ArC	127.7 (d)	ArC
126.4 (d)	ArC	127.9 (d)	ArC	129.3 (d)	ArC
128.5 (d)	ArC	129.2 (d)	ArC	130.9 (d)	ArC
134.8 (s)	ArC	134.0 (s)	ArC	132.9 (s)	ArC
136.5 (s)	4-C	175.2 (s)	3-C or 1-CO	155.5 (s)	3-C
163.1 (s)	amide CO	176.9 (s)	3-C or 1-CO	163.3 (s)	1-CO
204.9 (s)	acyl CO	201.3 (s)	acyl CO	172.3 (s)	acyl CO

[a] Chemical shifts are given in δ units from internal tetramethylsilane and are measured in $CDCl_3$.

Scheme XV



cis-22u trans-22u

21 are shown in Tables XVIII–XX (supplementary material).

When the Dewar isomer **2u** was heated in benzene solution at 40 °C for 180 h, the ^1H NMR spectrum showed the formation of **1u** (28%) and imine 2-azetidinone (24%) and unreacted **2u** (48%), indicating decrease of the rate of reaction in the nonpolar solvent. This suggests that the reaction involves ionic intermediates.

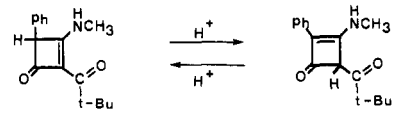
Thermal reactions of **2a** and **2r** gave dark brown tarry materials at 35 °C. The methyl group at the 3 position of the Dewar isomers **2** does not stabilize the imine moiety.

The structure of **20u** was deduced from spectra. The ^1H NMR spectrum of **20u** showed disappearance of the methylene group in **2u** and formation of a vinyl proton at δ 5.87 (s, 1 H), indicating the presence of a benzylidene moiety. The IR spectrum exhibited two carbonyl frequencies at 1805 cm^{-1} and 1695 cm^{-1} and a double-bond stretching frequency at 1680 cm^{-1}, suggesting the presence of a β-lactam carbonyl, an aliphatic ketone, and an enamine double bond. The ^{13}C NMR spectrum of **20u** showed one *tert*-butyl methyl, one N-methyl, one methine, one quaternary, two olefinic, two carbonyl, and four aromatic carbon signals (Table XXI). From these spectral data and comparison with those of the reported 4-alkylidene-2-azetidinones,[17] the structure of **20u** is assigned as *N*-methyl-4-benzylidene-3-pivaloyl-2-azetidinone.

Compound **20u** was reduced by catalytic hydrogenation on 5% Pd/C in methanol to give a mixture of *cis*-2-azetidinone **22u** (63%) and *trans*-**22u** (37%) (Scheme XV). The stereochemistry of the isomers was determined by the ^1H NMR spectra.[18] Chromatography on alumina completely converted the cis and trans mixture to the trans isomer.

The cyclobutenone structures of **21u–w** are based on comparison of spectral data with those of reported cyclobutenone derivatives.[19] The products **21u–w** showed a carbonyl frequency in the IR spectra at 1760–1745 cm^{-1}, an olefinic frequency at 1610–1600 cm^{-1}, and a conjugated carbonyl frequency at 1640–1630 cm^{-1}. The ^1H and ^{13}C NMR spectra of **21u** exhibited the presence of methine and enamine moieties. Another information of the cyclobutenone structure was obtained from mass spectra of **21u–w**. In the mass spectra of **21u–w**, the prominent fragment ions were (M$^+$ – CO – CH$_3$), (M$^+$ – *t*-Bu), (M$^+$ – CO – C$_4$H$_8$), (M$^+$ – 2CO – *t*-Bu), (M$^+$ – 2CO – *t*-Bu – C), and *t*-Bu. The spectra of **21u** and **21w** indicated the respective ketene peaks at *m/e* 118 ($C_6H_5CH{=}C{=}O$) and 148 ($CH_3OC_6H_4CH{=}C{=}O$) which assign the positions of the substituent groups of **21u–w**.

Scheme XVI



21u 23u

A single-crystal X-ray diffraction study of **21v** was carried out to confirm this structure. The cyclobutenone structure and positions of the substituents were revealed by crystallography.

Treatment of **21u** in acidic methanol solution gave a mixture of **21u** (39%) and **23u** (61%). Analysis and molecular ion of the isolated **23u** indicated an isomer of **21u**. The structure of **23u** is based on the spectral data. Two carbonyl groups in the IR spectrum (KBr) showed broad absorptions at 1665 cm^{-1} and 1640 cm^{-1}, which are not normal absorptions of the conjugated ketones. The methine carbon signal in the ^{13}C NMR spectrum (Table XXI) appeared at δ 90.4, thus indicating the presence of a β-diketone moiety. From these data, the structure of **23u** was assigned as 3-(methylamino)-2-phenyl-4-pivaloyl-2-cyclobutenone (Scheme XVI).

The reaction mechanism of the thermolysis of the Dewar 4-pyrimidinones is discussed together with that of the thermolysis of the 4-methoxy-2-azetidinones **10**.

Thermal Rearrangements of 4-Methoxy-2-azetidinones 10. Thermolysis of **10h(a)** in a melt at 121 °C for 5 h gave the crystalline **24h** (80%). Similar reactions of **10u** and **10x** led to the formation of **24u** (71%) and **24x** (62%), respectively. The spectral data of **24x** were analogous to those of methyl 2-(2-piperidylidene)acetoacetate,[13] which was formed by rearrangement of the fused 4-methoxy-2-azetidinone **11g** on alumina or in an acidic ethanol solution. Then, the product **24x** was assigned as 2-(piperidylidene)trimethylacetoacetate and was identified by comparison with an authentic sample prepared by condensation of 2,3,4,5-tetrahydro-6-methoxypyridine with methyl trimethylacetoacetate.

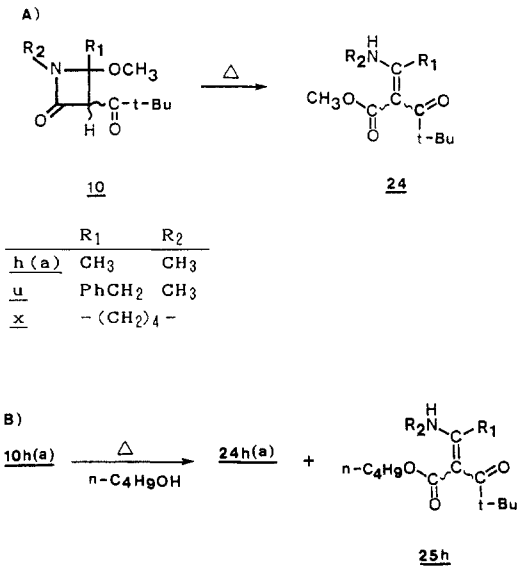
Considering possible pathways to these thermolysis products, the structures of **24** require the cleavage of the N(1)–C(2) and C(4)–OCH$_3$ bonds and the bond formation of the methoxy group with the lactam carbonyl carbon atom. The ester functionality in **24** may be formed by either intramolecular migration of the methoxy group to the amide carbonyl carbon by ionic cleavage of the C(4)–OCH$_3$ bond (ionic mechanism) or cleavage of the C(4)–OCH$_3$ bond in the ether functionality to give the ketene and methanol, which lead to the formation of **24** (ketene mechanism).

(17) Bachi, M. D.; Goldberg, O.; Gross, A.; Vaya, J. *J. Org. Chem.* **1980**, *45*, 1481.

(18) (a) Kagan, H. B.; Basselier, J. J.; Luche, J. L. *Tetrahedron Lett.* **1964**, 941. (b) Barrow, K. D.; Stopswood, T. M. *Ibid.* **1965**, 3325.

(19) (a) Wasserman, H. H.; Dehmlow, E. *Tetrahedron Lett.* **1962**, 1031. (b) Fishbein, P. L.; Moore, H. W. *J. Org. Chem.* **1985**, *50*, 3226.

Scheme XVII



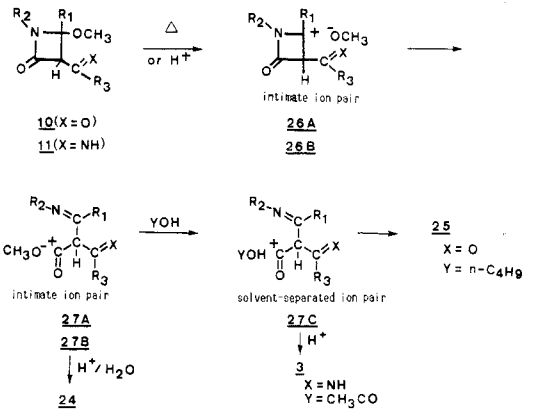
To distinguish clearly between the ionic mechanism and ketene mechanism, we undertook the thermolysis of **10h(a)** in xylene and *n*-butyl alcohol. When the thermal reaction of **10h(a)** was carried out in xylene, the yield of **24h** was reduced to 7% and the starting material (86%) was recovered. The drastic decrease of the rate of reaction in the nonpolar solvent suggests the reaction involving an ionic intermediate. Thermolysis of **10h(a)** in the presence of *n*-butyl alcohol gave **24h** (50–64%) and the crystalline compound **25h** (7–15%). The structure of **25h** was assigned as *n*-butyl trimethylacetoacetate from spectral data (Scheme XVII). No methoxy–*n*-butoxy exchange reactions was observed in the thermal reactions of **10h(a)** and **24h** in *n*-butyl alcohol at 121 °C, indicating that **25h** is formed by the reaction of *n*-butyl alcohol with a transient intermediate. The formation of the methyl trimethylacetoacetate **24h** as a major product in *n*-butyl alcohol solution rules out the ketene mechanism.[20] The intermediate of the methoxy transfer reaction is a closely associated ion pair of an acyl cation and methoxy anion.

The thermolysis of **10h** involves an intimate ion pair in which the counterions are in very close association with no solvent molecules between them. The intimate ion pair **26A** of the methoxy anion and azetidinyl cation is formed by a heterolytic fission of the C(4)–OCH_3 bond. The azetidinyl cation rearranges to an acyl cation. The formed acyl cation is an intimate ion pair **27A**. The methoxy anion returns to the acyl cation to give the ester **24**. Conversion of the intimate ion pair **27A** to a solvent-separated ion pair **27C** occurs by insertion of solvent molecules between the acyl cation and methoxy anion. Nucleophilic attack by *n*-butyl alcohol results in the formation of **25** (Scheme XVIII).

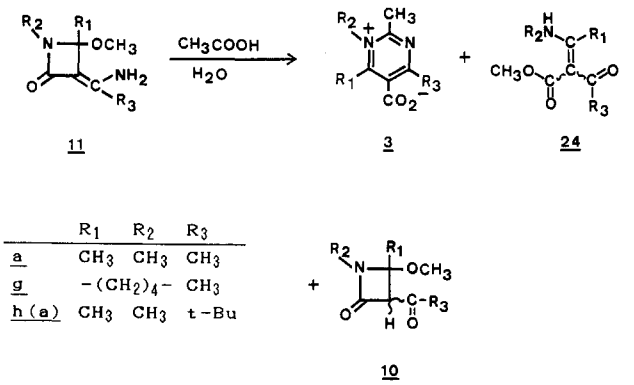
In a previous paper,[13] we reported the formation of the acetoacetates **24** from the fused 2-azetidinones **11** by an intramolecular migration of the alkoxy group to the amide carbonyl carbon in the presence of acids. We reinvestigated the rearrangement reactions of the 4-methoxy-2-azetidinones [**11a**, **11g**, and **11h(a)**] in acetic acid–benzene solution. Treatment of **11g** gave the betaine **3g** (48%) and

(20) The ratio of the measured rates of methanol and *n*-butyl alcohol with phenylketene was 1:0.38 at 0 °C. This result may indicate that the rates of primary alcohols with phenylketene are of the same order of the magnitude. The half-life time of **10h(a)** in *n*-butyl alcohol at 121 °C was about 1 h. From these data, the reaction of the assumed ketene intermediate with methanol could be ignored.

Scheme XVIII



Scheme XIX

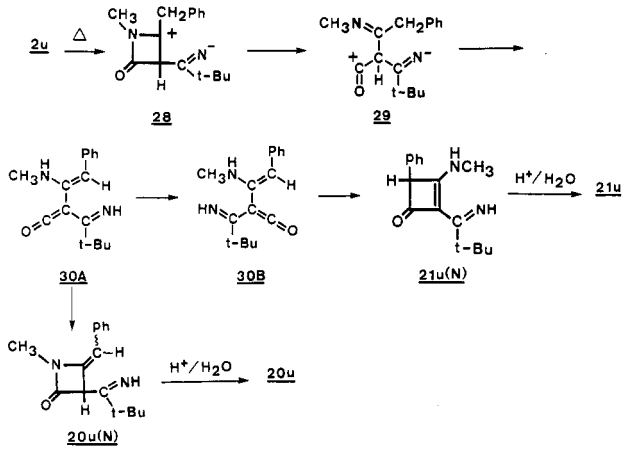


methyl acetoacetate **24g** (52%). Similarly, **11a** led to the formation of **3a** (37%) and **24a** (6%). The structure of **24a** was determined by the spectral data. The 2-azetidinone **11h(a)** gave **3h** (63%) and **10h(a)** (34%) (Scheme XIX). The intermediates of these reactions are similar to those of the thermal reactions of **10**. The products result from competition among the hydrolysis of the amino group, internal return of the methoxy group to the acyl cation, and nucleophilic attack to the acyl cation by an acetoxy anion.

We must revise our earlier intramolecular migration mechanism[13] and now conclude that the intermediates of these reactions are the azetidinyl and acyl cations, which are closely associated with the methoxy anion. Protonation on the enamine nitrogen of **11** leads to the formation of intimate ion pairs (**26B** and **27B**). The reactions are analogous to those of **10** (Scheme XVIII). The betaines **3** are formed from a solvent-separated ion pair **27C**. The formation of this ion pair competes with combination of the intimate ion pair **27B** (Scheme XVIII).

The rearrangement of the Dewar 4-pyrimidinones **2** to the 2-azetidinones **20** and cyclobutenones **21** could be explained by similar ionic intermediates assumed in the thermal reactions of the 4-methoxy-2-azetidinones **10** and **11**. The formation of **20u** and **21u** from **2u** may proceed by an initial cleavage of the C(1)–N(2) bond to give zwitterionic intermediate **28**. Subsequent ring opening leads to acylic dipolar intermediate **29**. The intermediate **29** undergoes conversion to ketene intermediate **30A** by hydrogen transfer and tautomerization. An intramolecular reaction of the secondary amine with the ketene moiety results in the formation of the imine 2-azetidinone **20u(N)**. Hydrolysis of the imine moiety on silica gel gives **20u**. Bond rotation of **30A** to intermediate **30B** and intramolecular [2 + 2] cycloaddition of the ketene moiety to the carbon–carbon double bond[21] of **30B** lead to the formation

Scheme XX



of the imine cyclobutenone **21u(N)**. The subsequent hydrolysis of **21u(N)** on silica gel gives **21u** (Scheme XX).

The thermal reactions of the Dewar isomers **2h–x** gave the corresponding 4-pyrimidinones **1h–x**. Thermal disrotatory cleavage of the central bond of the Dewar isomers **2** is symmetry-forbidden.[22] A plausible mechanism that rationalizes the formation of the 4-pyrimidinones **1** is intramolecular combination of the carbocation with the imino anion and concomitant ring opening of the C(3)–C(4) bond.

In summary, the diverse rearrangement products (**3**, **20**, **21**, and **24**) appear to arise through the azetidinyl and acyl cations from the Dewar isomers **2** and 4-methoxy-2-azetidinones **10** and **11**.

Experimental Section

Melting points were measured with a Yanako melting point apparatus and were uncorrected. The spectroscopic measurements were carried out with the following instruments: IR, JASCO A-102; UV, Hitachi Model 200–10; mass spectra (MS), JEOL OISG-2 at 70 eV; NMR (^{1}H and ^{13}C), Varian EM-390 and Varian XL-200. Chemical shifts were reported in parts per million on the δ scale relative to a Me_4Si internal standard. Elemental combustion analyses were performed by the Microanalytical Laboratory of this university. High-pressure liquid chromatography (HPLC) was performed on a Waters Analytical HPLC equipped with an M-45 pumping system, M-U6K injector, and M-440 UV spectrometer, using a reverse-phase micro Bondapak C_{18} (3.9 × 300) column. Isolation of the Dewar 4-pyrimidinones was carried out on a column (150 × 2.5 cm) made from a slurry of Sephadex LH-20 (ca. 180 g of dry gel) swelled in chloroform. The chromatographic isolations were accomplished by a medium pressure liquid chromatography (MPLC), using a column (25 × 2.5 cm) packed with Fuji-Davison silica gel BW-300 (200–400 mesh). Products isolated by MPLC were detected by an Oyo-Bunko UVILOG-5IIIA absorbance monitor at wavelength 280 nm. The column chromatography was conducted by utilizing Merck 70–230-mesh neutral alumina (activity II–III) and Wakogel C-200 (silica gel; 100–200 mesh).

Materials. Propionamidine,[23] isobutylamidine,[23] phenylacetamidine,[23] (4-methylphenyl)acetamidine, and (4-methoxyphenyl)acetamidine were prepared from the corresponding nitriles by a slight modification of the Pinner method.

(4-Methylphenyl)acetamidine hydrochloride: mp 152–154 °C (MeOH–ether). Anal. $C_9H_{13}N_2Cl$ (C, H, N).

(4-Methoxyphenyl)acetamidine hydrochloride: mp 129–131 °C (MeOH–ether). Anal. $C_9H_{13}N_2OCl$ (C, H, N).

2-Benzyl-6-methyl-4(3*H*)-pyrimidinone, 6-*tert*-butyl-2-ethyl-4(3*H*)-pyrimidinone, 6-*tert*-butyl-2-isopropyl-4(3*H*)-pyrimidinone, 6-*tert*-butyl-2-(4-methylbenzyl)-4(3*H*)-pyrimidinone, and 6-*tert*-butyl-2-(4-methoxybenzyl)-4(3*H*)-pyrimidinone were synthesized from the amidine hydrochlorides[22,24] and β-keto esters[25] as described in the literature.[26]

2-Benzyl-6-methyl-4(3*H*)-pyrimidinone: mp 174–176 °C (MeOH); MS, *m/e* 200 (M^+). Anal. $C_{12}H_{12}N_2O$ (C, H, N).

6-*tert*-Butyl-2-ethyl-4(3*H*)-pyrimidinone: mp 79–82 °C (ether–pentane); MS, *m/e* 180 (M^+); exact mass calcd for $C_{10}H_{16}N_2O$, *m/e* 180.1262, found *m/e* 180.1233.

6-*tert*-Butyl-2-isopropyl-4(3*H*)-pyrimidinone: mp 114–116 °C (ether–pentane); MS, *m/e* 194 (M^+). Anal. $C_{11}H_{18}N_2O$ (C, H, N).

6-*tert*-Butyl-2-(4-methylbenzyl)-4(3*H*)-pyrimidinone: mp 125–127 °C (ether); MS, *m/e* 256 (M^+). Anal. $C_{16}H_{20}N_2O$ (C, H, N).

6-*tert*-Butyl-2-(4-methoxybenzyl)-4(3*H*)-pyrimidinone: mp 134–136 °C (EtOH–hexane); MS, *m/e* 272 (M^+). Anal. $C_{16}H_{20}N_2O_2$ (C, H, N).

2,3,6-Trimethyl-4(3*H*)-pyrimidinone (**1a**),[1a] 2-ethyl-3,6-dimethyl-4(3*H*)-pyrimidinone (**1b**),[1a] 6-ethyl-2,3-dimethyl-4(3*H*)-pyrimidinone (**1c**),[1a] 3,6-dimethyl-2-phenyl-4(3*H*)-pyrimidinone (**1d**),[1d] 2,3-dimethyl-6-phenyl-4(3*H*)-pyrimidinone (**1e**),[1d] 2,6-dimethyl-3-phenyl-4(3*H*)-pyrimidinone (**1f**),[1d] 6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**1g**),[1a] 6-*tert*-butyl-2,3-dimethyl-4(3*H*)-pyrimidinone (**1h**),[1f] 2,3-dimethyl-4(3*H*)-pyrimidinone (**1p**),[1d] 3,6-dimethyl-4(3*H*)-pyrimidinone (**1q**),[1d] 2-benzyl-3,6-dimethyl-4(3*H*)-pyrimidinone (**1r**), 6-*tert*-butyl-2-ethyl-3-methyl-4(3*H*)-pyrimidinone (**1s**), 6-*tert*-butyl-2-isopropyl-3-methyl-4(3*H*)-pyrimidinone (**1t**), 2-benzyl-6-*tert*-butyl-3-methyl-4(3*H*)-pyrimidinone (**1u**),[1f] 6-*tert*-butyl-3-methyl-2-(4-methylbenzyl)-4(3*H*)-pyrimidinone (**1v**), and 6-*tert*-butyl-2-(4-methoxybenzyl)-3-methyl-4(3*H*)-pyrimidinone (**1w**) were prepared from iodomethane and the corresponding 4(3*H*)-pyrimidinones[1f] in ethanol containing base at 80 °C.

2-*tert*-Butyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**1x**) was synthesized by condensation of 2-amino-3,4,5,6-tetrahydropyridine hydrochloride with ethyl trimethylacetoacetate.[1f]

The compounds **1r**, **1s**, **1t**, **1v**, and **1w** showed λ_{max} (MeOH) 275 ■ 1 nm (ϵ 5000–7000) and 224 ± 1 nm (ϵ 5000–12800).

For **1r**: oil; IR (neat) 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3 H), 3.40 (s, 3 H), 4.17 (s, 2 H), 6.28 (s, 1 H), 7.13–7.60 (m, 5 H); MS, *m/e* 214 (M^+); exact mass calcd for $C_{13}H_{14}N_2O$, *m/e* 214.1105, found *m/e* 214.1101.

For **1s**: mp 41–43 °C (pentane); IR (KBr) 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 9 H), 1.33 (t, *J* = 7.0 Hz, 3 H), 2.75 (q, *J* = 7.0 Hz, 2 H), 3.52 (s, 3 H), 6.33 (s, 1 H); MS, *m/e* 197 (M^+). Anal. $C_{11}H_{18}N_2O$ (C, H, N).

For **1t**: mp 65–66 °C (pentane); IR (KBr) 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 9 H), 1.30 (d, *J* = 6.7 Hz, 6 H), 3.13 (sept, *J* = 6.7 Hz, 1 H), 3.56 (s, 3 H), 6.30 (s, 1 H); MS, *m/e* 208 (M^+). Anal. $C_{12}H_{20}N_2O$ (C, H, N).

For **1v**: mp 77–79 °C (ether); IR (KBr) 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 9 H), 2.33 (s, 3 H), 3.43 (s, 3 H), 4.10 (s, 2 H), 6.35 (s, 1 H), 7.15 (s, 4 H); MS, *m/e* 270 (M^+). Anal. $C_{17}H_{22}N_2O$ (C, H, N).

For **1w**: mp 93–94 °C (ether); IR (KBr) 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9 H), 3.43 (s, 3 H), 3.82 (s, 3 H), 4.08 (s, 2 H), 6.37 (s, 1 H), 6.88 (d, *J* = 9.0 Hz, 2 H), 7.18 (d, *J* = 9.0 Hz, 2 H); MS, *m/e* 286 (M^+). Anal. $C_{17}H_{22}N_2O_2$ (C, H, N).

General Procedures for Preparation of Dewar 4-Pyrimidinones 2. The 4-pyrimidinone (2.3–1.2 g) was dissolved in 280 mL of liquid NH_3–ether in a reaction cell at about −45 °C. The solution was irradiated under an argon atmosphere with a 100-W high-pressure mercury lamp. The reaction progress was routinely followed by ^{1}H NMR. After irradiation, the solvent was evaporated under vacuum and the reaction mixture was chro-

(21) (a) Marko, I.; Ronsmans, B.; Hesbain-Frisque, A.-M.; Dumas, S.; Ghosez, L.; Ernst, B.; Greuter, H. *J. Am. Chem. Soc.* **1985**, *107*, 2192. (b) Snider, B. B.; Hui, R. A. H. F.; Kulkarni, Y. S. *Ibid.* **1985**, *107*, 2194. (c) Snider, B. B.; Hui, R. A. H. F. *J. Org. Chem.* **1985**, *50*, 5167 and references cited therein.

(22) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim/Bergstr., West Germany, 1970.

(23) Fanta, P. E.; Hedman, E. A. *J. Am. Chem. Soc.* **1956**, *78*, 1434.

(24) Schaefer, F. C.; Krapcho, A. P. *J. Org. Chem.* **1962**, *27*, 1255.

(25) (a) Ingilis, J. K. H.; Roberts, K. C. *Organic Syntheses*, 2nd ed.; Wiley: New York, 1941; Collect. Vol. I, p 235. (b) Ger. Pat. 2412784, 1975; *Chem. Abstr.* **1976**, *84*, 43341p.

(26) Snyder, H. R.; Foster, H. M. *J. Am. Chem. Soc.* **1954**, *76*, 118.

matographed on Sephadex LH-20 with chloroform–hexane (4:1 v/v; each fraction 10 mL) as an eluant.[1f]

The preparations of the Dewar 4-pyrimidinones **2a**, **2h**, **2u**, and **2x** are described in the previous paper.[1f]

1-Benzyl-3,6-dimethyl-5-oxo-2,6-diazabicyclo[2.2.0]hex-2-ene (2r). From 2.307 g (10.78 mmol) of **1r**, a mixture of **2r** (26%) and **1r** (74%) was obtained after 5 h of irradiation. The reaction mixture was divided into two portions (ca. 1.1 g and 1.2 g) and each portion was chromatographed to give 0.128 g (6%) of **2r** as a pale yellow oil. The starting material **1r** (0.613 g, 27%) and a mixture (1.399 g, 61%) of **1r** and **2r** were recovered. The compound **2r** changed to dark yellow after 1 h and polymerized after 10–20 h at 25 °C.

For **2r**: MS, *m/e* (relative intensity) 214 (M^+, 24), 213 (19), 173 (22), 131 (26), 91 (31), 82 (100).

3-*tert*-Butyl-1-ethyl-6-methyl-5-oxo-2,6-diazabicyclo-[2.2.0]hex-2-ene (2s). From 2.015 g (10.39 mmol) of **1s**, a mixture of **2s** (29%) and **1s** (71%) was obtained after 5.5 h of irradiation. The reaction mixture was divided into two portions (ca. 1.1 g and 0.9 g) and each portion was chromatographed to give 0.325 g (16%) of **2s** as a colorless oil and a mixture (1.489 g, 74%) of **1s** and **2s**.

For **2s**: MS, *m/e* (relative intensity) 195 (4), 194 (M^+, 5), 193 (5), 111 (70), 82 (100), 70 (78), 42 (53), 41 (34); exact mass calcd for $C_{11}H_{18}N_2O$, *m/e* 194.1418, found *m/e* 194.1401.

3-*tert*-Butyl-1-isopropyl-6-methyl-5-oxo-2,6-diazabicyclo[2.2.0]hex-2-ene (2t). From 2.055 g (9.88 mmol) of **1t**, a mixture of **2t** (29%) and **1t** (71%) was obtained after 5 h of irradiation. Column chromatography of the reaction mixture gave 0.170 g (8%) of **2t** as a colorless oil and a mixture (1.869 g, 91%) of **1e** and **2t**.

For **2t**: MS, *m/e* (relative intensity) 209 (20), 208 (M^+, 3), 207 (3), 125 (27), 110 (21), 97 (33), 84 (26), 82 (100), 42 (50), 41 (31); exact mass calcd for $C_{12}H_{20}N_2O$, *m/e* 208.1575, found *m/e* 208.1540.

3-*tert*-Butyl-6-methyl-1-(4-methylbenzyl)-5-oxo-2,6-diazabicyclo[2.2.0]hex-2-ene (2v). From 1.687 g (6.25 mmol) of **1v**, a mixture of **2v** (24%) and **1v** (76%) was obtained after 4 h of irradiation. The reaction mixture was divided into two portions (ca. 0.6 g and 1.1 g) and each portion was chromatographed to give 0.135 g (8%) of crystalline **2v**. A mixture (1.408 g, 83%) of **1v** and **2v** was obtained. Recrystallization of **2v** from pentane–CCl_4 gave colorless fine needles: mp 85–86 °C; MS, *m/e* (relative intensity) 270 (M^+, 40), 269 (26), 255 (34), 187 (20), 145 (32), 130 (20), 105 (52), 82 (100). Anal. $C_{17}H_{22}N_2O$ (C, H, N).

3-*tert*-Butyl-1-(4-methoxybenzyl)-6-methyl-5-oxo-2,6-diazabicyclo[2.2.0]hex-2-ene (2w). From 1.163 g (4.07 mmol) of **1w**, a mixture of **2w** (16%) and **1w** (85%) was obtained after 2 h of irradiation. When the irradiated solution was cooled to −70 °C for 1 h, the crude crystals of **1w** (0.871 g, 75%) were separated and collected by filtration. After evaporation of the solvent of the mother liquor, the oily residue was chromatographed. Fractions 1 and 2 were a mixture (0.036 g, 3.1%) of **2w** (91%) and **1w** (9%). Fraction 3 was a mixture (0.040 g, 3.4%) of **2w** (62%) and **1w** (38%). Fractions 4 and 5 were a mixture (0.099 g, 8.5%) of **2h** (38%) and **1h** (62%). Fractions 6–10 were a mixture (0.135 g, 11.6%) of **2w** (27%) and **1w** (73%). Evaporation of the solvent from the fractions (1 and 2) gave crude **2w** as a colorless oil: MS, *m/e* (relative intensity) 286 (M^+, 10), 285 (4), 203 (13), 121 (28), 82 (100).

Further purification of the crude **2w** was unsuccessful by column chromatography.

The IR and ^1H NMR spectra of the Dewar isomers **2** are shown in Tables XV and XVI (supplementary material).

General Procedures for the Irradiation of 4-Pyrimidinones in Carboxylic Acid Solutions and for the Isolation of the Photoproducts. The 4-pyrimidinone **1** (0.6–3.1 g) was dissolved in carboxylic acid or carboxylic acid–acetonitrile solution. The solution was irradiated under an argon atmosphere with a 100-W high-pressure mercury lamp for 3–9 h. The reaction progress was routinely followed by ^1H NMR spectra. After irradiation, the solvent was evaporated and the products were isolated by crystallization and/or by column chromatography on alumina (30–100 g).

1,2,4,6-Tetramethylpyrimidinium-5-carboxylate (3a). From 3.150 g (22.8 mmol) of **1a** in 230 mL of acetic acid, 1.284 g (7.13 mmol) of **3a** was obtained after 7 h of irradiation at 25 °C. The starting material **1a** (1.728 g, 55%) was recovered. Recrystallization of **3a** from methanol–ether gave colorless leaflets: mp 223–225 °C dec; MS, *m/e* (relative intensity) 180 (M^+, 18), 136 ($M^+ - CO_2$, 100), 94 (49), 56 (31), 55 (71), 54 (39), 44 (61); exact mass calcd for $C_9H_{12}N_2O_2$, *m/e* 180.0898, found *m/e* 180.0866.

1-Methyl-2,4,6-tris(trideuteriomethyl)pyrimidinium-5-carboxylate [3a(D)]. The betaine **1a** (53 mg, 0.294 mmol) was dissolved in 7.02 g of CH_3OD (99 atom % D; Merck) and was allowed to stand for 90 h at 30 °C. Evaporation of the solvent gave crystalline solid **3a(D)** (55 mg, 99%), which was used without further purification: mp 222–228 °C dec; MS, *m/e* 189 (M^+, 14), 188 (8), 187 (5), 186 (3), 185 (2), 145 ($M^+ - CO_2$, 67), 144 (69), 101 (16), 100 (28), 99 (31), 59 (53), 58 (68), 57 (96), 56 (52), 55 (14), 54 (11), 44 (100). The ^1H NMR spectrum in CD_3OD showed that D atoms were incorporated in the 2-methyl (100 atom % D), 4-methyl (85 atom % D), and 6-methyl (100 atom % D) groups.

6-Ethyl-1,2,4-trimethylpyrimidinium-5-carboxylate (3b). From 1.809 g (11.9 mmol) of **1b** in 250 mL of acetic acid–acetonitrile (8:17) solution, 1.064 g (5.48 mmol) of **3b** was obtained after 7 h of irradiation at −2 °C. The starting material **1b** (0.813 g, 45%) was recovered. Recrystallization of **3b** from ethanol–ether gave a pale yellow powder: mp 229–231 °C dec; MS, *m/e* (relative intensity) 194 (M^+, 3), 193 ($M^+ - 1$, 3), 150 ($M^+ - CO_2$, 94), 149 (100), 81 (45), 68 (26), 56 (17), 44 (63).

4-Ethyl-1,2,6-trimethylpyrimidinium-5-carboxylate (3c). From 0.635 g (4.18 mmol) of **1c** in 250 mL of acetic acid–acetonitrile (8:17) solution, 0.287 g (1.48 mmol) of **3c** was obtained after 3 h of irradiation at 0 °C. The starting material **1c** (0.228 g, 36%) was recovered. Recrystallization of **3c** from methanol–benzene–ether gave pale yellow powders: mp 226–227 °C dec; MS, *m/e* (relative intensity) 194 (M^+, 10), 150 ($M^+ - CO_2$, 100), 94 (55), 56 (52), 55 (55), 44 (61); exact mass calcd for $C_{10}H_{14}N_2O_2$, *m/e* 194.1054, found *m/e* 194.1075.

6-Phenyl-1,2,4-trimethylpyrimidinium-5-carboxylate (3d). From 1.604 g (8.01 mmol) of **1d** in 250 mL of acetic acid–acetonitrile (8:17) solution, 0.518 g (2.14 mmol) of **3d** was obtained after 5 h of irradiation at −9 °C. The starting material **1d** (0.910 g, 57%) was recovered. Recrystallization of **3d** from methanol–benzene–ether gave a white powder: mp 204–206 °C dec; MS, *m/e* (relative intensity) 198 ($M^+ - CO_2$, 100), 197 (45), 118 (94), 77 (33), 44 (54); exact mass calcd for $C_{13}H_{14}N_2$ ($M^+ - CO_2$), *m/e* 198.1158, found *m/e* 198.1156.

4-Phenyl-1,2,6-trimethylpyrimidinium-5-carboxylate (3e). From 1.360 g (6.80 mmol) of **1e** in 250 mL of acetic acid–acetonitrile (8:17) solution, 0.434 g (1.79 mL) of **4e** was obtained after 2.3 h of irradiation at 0 °C. The starting material **1e** (0.877 g, 65%) was recovered. Recrystallization of **3e** from methanol–ether gave colorless needles: mp 194 °C dec; MS, *m/e* (relative intensity) 198 ($M^+ - CO_2$, 100), 156 (100), 55 (60), 44 (52).

1-Phenyl-2,4,6-trimethylpyrimidinium-5-carboxylate (3f). From 1.313 g (6.56 mmol) of **1f** in 250 mL of acetic acid–acetonitrile (8:17) solution, 0.382 g (1.58 mmol) of **3f** was obtained after 4 h of irradiation at −10 °C. The starting material **1f** (0.913 g, 70%) was recovered. Recrystallization from methanol–ethyl acetate–ether gave pale brown leaflets: mp 176–178 °C dec; MS, *m/e* (relative intensity) 242 (M^+, 4), 241 (3), 198 ($M^+ - CO_2$, 68), 197 (100), 183 (31), 93 (97), 77 (63), 66 (41), 51 (33), 44 (95).

1,3-Dimethyl-5,6,7,8-tetrahydropyrido[1,2-*c*]pyrimidinium-4-carboxylate (3g). From 1.529 g (9.32 mmol) of **1g** in 230 mL of acetic acid–acetonitrile (7:16) solution, 0.510 g (2.48 mmol) of **3g** was obtained after 6.5 h of irradiation at 0 °C. The starting material **1g** (0.818 g, 53%) was recovered. Recrystallization of **3g** from methanol–ethyl acetate gave a pale gray powder: mp > 300 °C; MS, *m/e* (relative intensity) 206 (M^+, 25), 205 (28), 162 ($M^+ - CO_2$, 69), 161 (100), 44 (35).

2-Ethyl-1,4,6-trimethylpyrimidinium-5-carboxylate (3m). From 1.504 g (10.9 mmol) of **1a** in 230 mL of propanoic acid–acetonitrile (1:46) solution, 0.428 g (2.20 mmol) of **3m** was obtained after 7 h of irradiation at −18 °C. The starting material **1a** (0.743 g, 49%) was recovered. Recrystallization of **3m** from ethanol–ether gave colorless needles: mp 217–220 °C dec; MS, *m/e* (relative intensity) 194 (M^+, 38), 193 (18), 179 (48), 150 ($M^+ - CO_2$, 83), 149 (66), 135 (100), 44 (83).

2-Cyclohexyl-1,4,6-trimethylpyrimidinium-5-carboxylate (3n). From 1.536 g (11.2 mmol) of **1a** in 250 mL of cyclohexanecarboxylic acid–acetonitrile (1:50) solution, 0.485 g (1.96

mmol) of **3n** was obtained after 6 h of irradiation at −2 °C. The starting material **1a** (0.903 g, 59%) was recovered. Recrystallization of **3n** from ethanol–benzene–hexane gave a white powder: mp 249–250 °C; MS, *m/e* (relative intensity) 248 (M^+, 4), 204 ($M^+ - CO_2$, 61), 189 (100), 161 (44), 149 (51), 122 (47), 44 (46).

The yields of the betaines **3a–g** and **3m,n** are listed in Table I.

Reaction of 2a with Acetic Acid. From 2.083 g (15.1 mmol) of **1a**, a mixture of **2a** (33%) and **1a** (67%) was obtained after 8 h of irradiation. The reaction mixture was dissolved in 300 mL of acetic acid–acetonitrile (1:99) solution at 20 °C. The solution was allowed to stand for 63 h at 0 °C. After evaporation of the solvent, the residue was chromatographed on alumina (80 g) to give starting material **1a** (1.284 g, 62%) and betaine **3a** (0.488 g, 2.71 mmol).

4-*tert*-Butyl-1,6-dimethylpyrimidinium-5-carboxylate (3i). The Dewar 4-pyrimidinone **2h** (0.291 g, 1.62 mmol) was dissolved in 15 mL of benzene containing 0.797 g (17.3 mmol) of formic acid. The solution was stirred for 0.3 h at 10–15 °C. After removal of the solvent, methanol and ether were added to an oily residue. When the solution was cooled, crude crystals of **3i** (0.133 g, 40%) were separated and collected by filtration. Recrystallization from methanol–ether gave colorless prisms: mp 212–214 °C dec; MS, *m/e* (relative intensity) 165 (25), 164 ($M^+ - CO_2$, 100), 163 (20), 149 (66), 122 (53), 108 (38), 93 (14), 44 (70).

The 4-pyrimidinone **1h** (30 mg, 10%) was isolated by column chromatography of the filtrate on alumina (40 g) with benzene–ethyl acetate (4:1).

Reactions of 2h with Carboxylic Acids. The yields of the products formed in the reaction of **2h** with acetic acid, propanoic acid, isobutanoic acid, 2,2-dimethylpropanoic acid, and 3,3-dimethylbutanoic acid were measured by HPLC with water–acetonitrile–methanol (80:15:5) as the mobile phase at a flow rate of 2.0 mL/min. The 4-pyrimidinones **1f** and **1h** were used as the internal standards. The authentic samples for HPLC analyses were prepared by the reactions of **2h** (0.33–0.47 mmol) with carboxylic acids (3.44–4.28 mmol) in 10 mL of benzene or chloroform at room temperature.

The yields of the products **1a**, **1h**, **3a**, and **3h–l** are listed in Table II.

Reactions of 2h with Two Carboxylic Acids in Benzene Solution. A benzene solution (2.0–2.1 mL) of **2h** (0.0153–0.0160 M) and a solution of two carboxylic acids (0–1.8 M) were mixed and stirred at 20 °C for 2 h. The solvent and excess acids were evaporated and the residue was dissolved in 2 mL of acetic acid.

The yields of the products are listed in Table X (supplementary material).

4-*tert*-Butyl-1,2,6-trimethylpyrimidinium-5-carboxylate (3h): mp 194–195 °C dec (MeOH–ether); MS, *m/e* (relative intensity) 222 (M^+, 0.8), 178 ($M^+ - CO_2$, 100), 163 (55), 136 (40), 122 (50), 56 (89), 44 (56).

4-*tert*-Butyl-1,6-dimethyl-2-ethylpyrimidinium-5-carboxylate (3j): mp 189–190 °C dec (MeOH–ether); MS, *m/e* (relative intensity) 236 (M^+, 0.2), 235 (0.6), 192 ($M^+ - CO_2$, 55), 191 (29), 177 (100), 70 (31), 44 (39).

4-*tert*-Butyl-1,6-dimethyl-2-isopropylpyrimidinium-5-carboxylate (3k): mp 184–185 °C dec (MeOH–ether); MS, *m/e* (relative intensity) 250 (M^+, 0.3), 249 (1.2), 206 ($M^+ - CO_2$, 32), 191 (100), 44 (33).

4-*tert*-Butyl-1,6-dimethyl-2-(2,2-dimethylpropyl)pyrimidinium-5-carboxylate (3l): mp 192 °C dec (MeOH); MS, *m/e* (relative intensity) 278 (M^+, 0.2), 277 (0.4), 234 ($M^+ - CO_2$, 31), 219 (100), 178 (66), 44 (37).

The infrared spectra (KBr) for all compounds **3a–n** showed two peaks at ~1620 and ~1600 cm^{-1}. The ^1H NMR and UV spectra of the betaines **3a–n** were shown in Table III (supplementary material). All crystalline betaines **3a–n** contained water of crystallization. The analytical data of the betaines **3a–n** are listed in Table XIII (supplementary material).

General Procedures for the Reactions of Betaines 3 in Aqueous Ammonia Solution and for the Isolation of the Products. The betaines **3** (0.120–1.35 mmol) were dissolved in 5–20 mL of 25% aqueous ammonia solution (aqueous NH_3) at 15–20 °C. The solution was allowed to stand for 0.7–3 days. After evaporation of the solvent, the products were isolated by crystallization. The yields of the products are listed in Table IV.

Ammonium 2,4,6-Trimethylpyrimidine-5-carboxylate (6a = 6f). From 0.217 g (1.21 mmol) of **3a** in aqueous NH_3, 0.206 g (1.13 mmol) of **6a** was obtained. Recrystallization of **6a** from ethanol–benzene gave a white powder: mp 162–165 °C; MS, *m/e* 166 ($M^+ - NH_3$).

From 0.069 g (0.29 mmol) of **3f** in aqueous NH_3, 0.051 g (0.28 mmol) of **6f** (= **6a**) was obtained.

5-Carboxy-2,4-dimethyl-6-ethylpyrimidine (6b′ = 6c′). From 0.166 g (0.857 mmol) of **3b** in aqueous NH_3, 0.162 g (0.822 mmol) of ammonium 2,4-dimethyl-6-ethylpyrimidine-5-carboxylate (**6b**) was obtained. Recrystallization of **6b** from methanol–ethyl acetate–ether gave the carboxylic acid **6b′** as colorless needles: mp 172–174 °C; MS, *m/e* 180 (M^+).

From 0.092 g (0.474 mmol) of **3c** in aqueous NH_3, 0.0905 g (0.459 mmol) of **6b** (= **6c**) was obtained. Recrystallization gave **6c′** (= **6b′**).

Ammonium 2,4-Dimethyl-6-phenylpyrimidine-5-carboxylate (6d = 6e). From 0.143 g (0.589 mmol) of **3d** in aqueous NH_3, 0.126 g (0.514 mmol) of **6d** was obtained. Recrystallization of **6d** from methanol–ethyl acetate–ether gave colorless needles: mp 225–226 °C; MS, *m/e* 228 ($M^+ - NH_3$).

From 0.0290 g (0.120 mmol) of **3e** in aqueous NH_3, 0.029 g (0.118 mmol) of **6e** (= **6d**) was obtained.

4-(4-Ammoniobutyl)-2,6-dimethylpyrimidine-5-carboxylate (6g). From 0.282 g (1.35 mmol) of **3g** in aqueous NH_3, 0.292 g (1.31 mmol) of **6g** was obtained. Recrystallization of **6g** from methanol–ethyl acetate–pentane gave pale brown plates: mp 261–262 °C; MS, *m/e* (relative intensity) 223 (M^+, 2), 179 (40), 166 (64), 122 (43), 42 (33), 30 (100).

Ammonium 4,6-Dimethyl-2-ethylpyrimidine-5-carboxylate (6m). From 0.0886 g (0.456 mmol) of **3m** in aqueous NH_3, 0.0764 g (0.0388 mmol) of **6m** was obtained. Recrystallization of **6m** from methanol–ethyl acetate–benzene–hexane gave colorless needles: mp 148–149 °C; MS, *m/e* 180 ($M^+ - NH_3$).

The ^1H NMR, UV, and IR spectra of the pyrimidines (**6a**, **6b′**, **6d**, **6g**, and **6m**) are shown in Table V and the analytical data of these compounds are listed in Table XIV (supplementary material).

5-(Ethoxycarbonyl)-1,2,4,6-tetramethylpyrimidinium Iodide (4). A. By Synthesis. A solution of 5-(ethoxycarbonyl)-2,4,6-trimethylpyrimidine[8a] (**5**) (4.0 g, 20.6 mmol) and iodomethane (10 g) in 20 mL of ether was refluxed for 64 days. During the reaction, iodomethane (2 g) and ether (4 mL) were added to the solution every 2 days. The solid that had precipitated was filtered and recrystallized from acetone–ether to give 1.60 g (23%) of **4** as yellow needles: mp 116–118 °C; MS, *m/e* (relative intensity) 208 ($M^+ - HI$, 24), 194 (49), 179 (37), 156 (71), 149 (99), 142 (59), 29 (100); IR ($CHCl_3$) 1740, 1610 cm^{-1}; UV (MeOH) λ_{max} 261 nm (ϵ 5330), 219 (ϵ 18800); ^1H NMR ($CDCl_3$) δ 1.45 (t, J = 7 Hz, 3 H, CH_3CH_2), 2.76 (s, 3 H, 4-CH_3), 2.94 (s, 3 H, 6-CH_3), 3.18 (s, 3 H, 2-CH_3), 4.41 (s, 3 H, N^+CH_3), 4.55 (q, J = 7 Hz, 2 H, CH_3CH_2). Anal. $C_{11}H_{17}N_2O_2I$ (C, H, N).

B. From the Reaction of 3a with Iodoethane. A solution of **3a** (0.203 g, 1.13 mmol) and iodoethane (1.58 g, 10.1 mmol) in 10 mL of methanol was refluxed for 3 h. After evaporation of the solvent and excess iodoethane, the residue was extracted with chloroform. Removal of the solvent under reduced pressure gave crude crystals (0.049 g). Recrystallization of this product from acetone–ether gave 0.037 g (10%) of the pyrimidinium iodide **4** as yellow needles. The compound was found to be identical (spectra) with that synthesized from **5**.

5-(Methoxycarbonyl)-2,3,6-trimethylpyrimidine (7). Ammonium 2,3,6-trimethylpyrimidine-5-carboxylate (**6a**) (0.184 g, 1.00 mmol) was dissolved in 10 mL of hexamethylphosphoric triamide (HMPA) containing 1.1 mL of 1% aqueous potassium hydroxide and iodomethane (0.80 g, 5.6 mmol).[4] The solution was allowed to stand for 2 h at 20 °C. After evaporation of excess iodomethane, the residue was dissolved in 40 mL of water. The reaction mixture was extracted with ether (4 × 50 mL). Evaporation of the solvent gave 0.864 g of an oily residue, which was chromatographed on alumina (100 g) with benzene–ethyl acetate (3:1) as an eluant to give 0.144 g (0.800 mmol, 80%) of crystalline **7**. Recrystallization of **7** from pentane–ether gave colorless needles: mp 56–58 °C; MS, *m/e* 180 (M^+); IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.53 (s, 6 H, 4- and 6-CH_3), 2.70 (s, 3 H, 2-CH_3), 3.98 (s, 3 H, OCH_3). Anal. $C_9H_{12}N_2O_2$ (C, H, N).

The compound **7** was found to be identical (spectra) with that synthesized from 5-(ethoxycarbonyl)-2,4,6-trimethylpyrimidine (**5**) (oil) in methanol containing base.

5-Acetyl-2,3,6-trimethyl-4-pyrimidinone (8a). A solution of 0.307 g (0.914 mmol) of 5-(ethoxycarbonyl)-1,2,4,6-tetramethylpyrimidinium iodide (**4**) in 10 mL of water was passed through a column (2 × 12 cm) of Dowex 1-X8[6] in the hydroxide form. The column was eluted with 50 mL of water. After evaporation of the solvent, a white crystalline compound (0.151 g) was obtained. The crude product was chromatographed on alumina (30 g) with ethyl acetate–benzene (1:9) as an eluant to give 0.120 g (0.667 mmol, 73%) of **8a** (mp 93–94 °C; lit.[7] mp 89–90.5 °C). The spectral data of the compound were found to be identical with those of an authentic sample.

5-Acetyl-6-*tert*-butyl-2,3-dimethyl-4-pyrimidinone (8h). The betaine **3h** (0.347 g, 1.56 mmol) was added to 10 mL of HMPA containing water (1.5 mL) and iodomethane (1.2 g, 8.5 mmol). The solution was stirred for 5 h at 29 °C. The crystalline **3h** gradually dissolved and color of the solution changed to dark brown. After evaporation of excess iodomethane, the residue was dissolved in 90 mL of water. The solution was passed through a column (2 × 12 cm) of Dowex 1-X8 in the hydroxide form and was eluted with an additional 100 mL of water. The reaction mixture was extracted with ether (4 × 200 mL). After evaporation of the solvent, the residue was chromatographed on alumina (177 g) with benzene–ethyl acetate (2:1) to give 0.239 g (1.08 mmol, 69%) of **8h**. Recrystallization of **8h** from benzene–pentane gave colorless needles: mp 88–90 °C; MS, *m/e* 222 (M^+, 8), 207 (100), 179 (22), 150 (21), 81 (14), 56 (100), 43 (24); IR ($CHCl_3$) 1700 cm^{-1} (CO), 1643 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 1.28 (s, 9 H, *t*-Bu), 2.53 (s, 3 H, CH_3), 2.57 (s, 3 H, CH_3), 3.52 (s, 3 H, NCH_3); UV (MeOH) λ_{max} 283 nm (ϵ 4990). Anal. $C_{12}H_{18}N_2O_2$ (C, H, N).

Preparation of 6-*tert*-Butyl-5-(trideuterioacetyl)-2-(trideuteriomethyl)-3-methyl-4-pyrimidinone [8h(D)]. A solution of **8h** (35 mg, 0.16 mmol) in 10.0 mL of CH_3OD (99 atom % D; Merck) containing 0.10 mL of *tert*-butylamine was allowed to stand for 96 h under an argon atmosphere at 30 °C. Evaporation of the solvent gave crystalline solid **8h(D)** (37 mg, 101%). Recrystallization of **8h(D)** in benzene–pentane gave colorless needles: mp 88–89 °C; MS, *m/e* 228 (M^+, 5), 213 (30), 210 (71), 185 (14), 153 (17), 81 (13), 59 (100), 58 (36), 46 (21).

The ^1H NMR spectrum in $CDCl_3$ indicated that the D atoms were incorporated in the 2-methyl (98 atom % D) and 5-acetylmethyl (98 atom % D) groups.

2-([^{13}C]Methyl)-1,4,6-trimethyl[2-^{13}C]pyrimidinium-5-carboxylate (3a*). A solution containing 2.243 g (16.3 mmol) of **1a** in 230 mL of acetonitrile was irradiated under an argon atmosphere at −18 °C for 8 h. The ^1H NMR analysis showed that the solution contained **1a** (72%) and **2a** (28%). An acetonitrile solution (20 mL) containing 0.503 g (8.11 mmol) of acetic acid-*1,2-*^{13}*C* [*1-*^{13}*C* (92.4 atom %) and *2-*^{13}*C* (91 atom %): The British Oxygen CO. Ltd.] and 1.707 g (28.45 mmol) of acetic acid was added to the irradiated solution at −20 °C and the solution was stirred at 0 °C for 14 h. After evaporation of the solvent under reduced pressure, the residue was chromatographed on alumina (80 g) with benzene–ethyl acetate (2:1) to give the starting **1a** (1.638 g, 73%). Further elution with chloroform–methanol (94:6) gave 0.471 g (2.62 mmol) of **3a***. The conversion yield of **3a*** was 57% of **2a**. Recrystallization of **3a*** from methanol–benzene–chloroform gave colorless fine needles: mp 225–229 °C dec. The mass spectrum and NMR spectra (^1H and ^{13}C) confirmed that the two ^{13}C atoms were incorporated in the C(2) and 2-CH_3. The fraction of the ^{13}C-labeled compound in **3a*** was 23% by ^1H NMR spectrum (calculated value 24%).

Ammonium 2-([^{13}C]Methyl)-4,6-dimethyl[2-^{13}C]pyrimidine-5-carboxylate (6a*). The ^{13}C-labeled betaine **3a*** (48 mg, 0.26 mmol) was dissolved in 5 mL of 25% aqueous ammonia solution and was allowed to stand at 20 °C for 45 h. Evaporation of the solvent gave the crystalline **6a*** (48 mg, 98%). Recrystallization of **6a*** from methanol–ethyl acetate gave a white powder: mp 155–165 °C. The mass spectrum and NMR spectra (^1H and ^{13}C) confirmed that the two ^{13}C atoms were incorporated in the C(2) and 2-CH_3. The fraction of the ^{13}C-labeled compound in **6a*** was 24% by ^1H NMR spectroscopy (calculated value 24%).

The ^1H and ^{13}C NMR spectra and mass spectra of **3a*** and **6a*** are shown in Tables VII, VIII, and IX.

General Procedures for the Reaction of the Dewar 4-Pyrimidinone 2h in Benzene Solution Containing Acetic Acid and Enthanol. The reactions of **2h** with acetic acid in the presence of ethanol were carried out in benzene at 20–23 °C for 1 h. The isolated and identified products were the betaine **3h**, 4-pyrimidinone **1h**, 2-azetidinone **10h**, and 5-acetyl-4-pyrimidinone **8h**. The fractions of **1h**, **8h**, and **10h** for routine runs were determined by the ^1H NMR spectra after separation of **3h**. The experimental conditions and yields of the products were listed in Table XII.

General Procedures for Thermolysis of the Dewar 4-Pyrimidinones 2. The Dewar 4-pyrimidinones **2** in a 25 mL round-bottomed flask were heated under an argon atmosphere in the absence of solvent or in the presence of small amount of anhydrous benzene at 35–40 °C for 24–110 h. The products were isolated by MPLC on silica gel with benzene–ethyl acetate (9:1–1:1) as the mobile phase.

Thermolysis of 2h. The Dewar isomer **2h** (100 mg, 0.556 mmol) was heated without solvent at 40 ± 1 °C for 110 h. The MPLC separation gave the 4-pyrimidinone **1h** (73 mg, 73%) and unidentified products (18 mg, 18 w/w %).

Thermolysis of 2s. The Dewar isomer **2s** (166 mg, 0.856 mmol) was heated without solvent at 35 ± 1 °C for 24 h. The MPLC separation gave the 4-pyrimidinone **1s** (39 mg, 23%), *N*-methyl-4-ethylidene-3-pivaloyl-2-azetidinone (**20s**) (93 mg, 56%) as a colorless oil and unidentified products (26 mg, 16 w/w %). The ^1H NMR spectrum indicated that **20s** was a mixture of two geometrical isomers. The ratio of the major isomer **20s(A)** and minor isomer **20s(B)** was 85:15.

For **20s**: MS, *m/e* (relative intensity) 195 (M^+, 93), 138 (75), 110 (78), 82 (64), 81 (61), 69 (72), 57 (100), 41 (100); exact mass calcd for $C_{11}H_{17}NO_2$, *m/e* 195.1258, found *m/e* 195.1253.

Thermolysis of 2t. The Dewar isomer **2t** (70 mg, 0.34 mmol) was heated without solvent at 40 ± 1 °C for 46 h. The MPLC separation gave the 4-pyrimidinone **1t** (12 mg, 17%) and *N*-methyl-4-isopropylidene-3-pivaloyl-2-azetidinone (**20t**) (48 mg, 68%) as a crystalline solid. Recrystallization of **20t** from pentane gave colorless needles: mp 57–58 °C; MS, *m/e* (relative intensity) 209 (M^+, 27), 194 (11), 152 (12), 124 (22), 83 (23), 57 (100), 41 (35). Anal. $C_{12}H_{19}NO_2$ (C, H, N).

Thermolysis of 2u. A viscous liquid containing the Dewar isomer **2u** (279 mg, 1.09 mmol) and benzene (392 mg) was heated at 40 ± 1 °C for 52 h. The MPLC separation gave the 4-pyrimidinone **1u** (37 mg, 13%), *N*-methyl-4-benzylidene-3-pivaloyl-2-azetidinone (**20u**) (165 mg, 59%) as a crystalline compound, and 3-(*N*-methylamino)-4-phenyl-2-pivaloyl-2-cyclobuten-1-one (**21u**) (71 mg, 25%) as a white solid.

Recrystallization of **20u** from benzene–pentane gave colorless prisms: mp 111–112 °C; MS, *m/e* (relative intensity) 257 (m^+, 98), 131 (80), 116 (40), 85 (65), 83 (100), 57 (99), 41 (43). Anal. $C_{16}H_{19}NO_2$ (C, H, N).

Recrystallization of **21u** from carbon tetrachloride–pentane gave colorless prisms: mp 147–149 °C; MS, *m/e* (relative intensity) 257 (M^+, 100), 214 (57), 200 (29), 173 (33), 144 (24), 132 (24), 118 (4), 57 (57). Anal. $C_{16}H_{19}NO_2$ (C, H, N).

Thermolysis of 2u in Benzene Solution. A solution of **2u** (85 mg) in 10 mL of benzene was heated at 40 ± 1 °C for 180 h. The ^1H NMR spectrum indicated that the reaction mixture contained the unreacted Dewar isomer **2u** (48%), 4-pyrimidinone **1f** (28%), and imine 2-azetidinone (24%). The reaction was completed by heating the solution at 80 °C for 3 h. After evaporation of the solvent, the products were isolated by MPLC to give the 2-azetidinone **20u** (37 mg, 43%), 4-pyrimidinone **1u** (33 mg, 39%), cyclobutenone **21u** (7 mg, 8%), and unidentified compounds (6 mg, 7 w/w %).

Thermolysis of 2v. An oily mixture of the Dewar isomer **2v** (95 mg, 0.27 mmol) and 4-pyrimidinone **1v** (22 mg) was heated without solvent at 40 ± 1 °C for 43 h. The MPLC separation gave the 4-pyrimidinone **1v** (27 mg), *N*-methyl-4-(4-methylbenzylidene)-3-pivaloyl-2-azetidinone (**20v**) (47 mg, 64%) as an oily solid, and 3-(*N*-methylamino)-4-(4-methylphenyl)-2-pivaloyl-2-cyclobuten-1-one (**21v**) (21 mg, 29%) as a white solid. The yield of **1v** from **2v** was 7%.

Recrystallization of **20v** from ether–pentane gave colorless prisms: mp 115–117 °C; MS, *m/e* (relative intensity) 271 (M^+, 60), 145 (40), 57 (100). Anal. $C_{17}H_{21}NO_2$ (C, H, N).

Recrystallization of **21v** from carbon tetrachloride–pentane gave colorless prisms: mp 153–155 °C; MS, *m/e* (relative intensity) 271 (M^+, 100), 228 (66), 214 (31), 187 (69), 158 (27), 146 (26), 57 (58). Anal. $C_{17}H_{21}NO_2$ (C, H, N).

Thermolysis of 2w. An oily mixture of the Dewar isomer **2w** (54 mg, 0.19 mmol) and 4-pyrimidinone **1w** (18 mg) was heated without solvent at 40 ± 1 °C for 48 h. The MPLC separation gave **1w** (25 mg), *N*-methyl-4-(4-methoxybenzylidene)-3-pivaloyl-2-azetidinone (**20w**) (23 mg, 42%) as a white solid, and 4-(4-methoxyphenyl)-3-(*N*-methylamino)-2-pivaloyl-2-cyclobuten-1-one (**21w**) (12 mg, 22%) as a colorless oil. The yield of **1w** from **2w** was 13%.

Recrystallization of **20w** from benzene–pentane gave colorless fine needles: mp 132–132.5 °C; MS, *m/e* (relative intensity) 287 (M^+, 100), 161 (52), 146 (54), 145 (42), 57 (100). Anal. $C_{17}H_{21}NO_3$ (C, H, N).

Crystallization of **21w** from carbon tetrachloride–pentane gave colorless fine prisms: mp 157–159 °C; MS, *m/e* (relative intensity) 287 (M^+, 100), 244 (13), 230 (16), 203 (34), 174 (16), 162 (11), 148 (5), 57 (45). Anal. $C_{17}H_{21}NO_3$ (C, H, N).

Thermolysis of 2x. A viscous liquid containing the Dewar isomer **2x** (84 mg, 0.41 mmol) and benzene (183 mg) was heated at 40 ± 1 °C for 97 h. The MPLC separation gave **1x** (38 mg, 45%) and polymeric compounds (22 mg, 26 w/w %).

The yields of the products **1**, **20**, and **21** are summarized in Table XVII. The ^{13}C NMR spectra for **20u**, **21u**, and **23u** are shown in Table XXI. The spectral data (^1H NMR, IR, and UV) for the 2-azetidinones **20** and cyclobutenones **21** were shown in Tables XVIII–XX (supplementary material). The assignment of the fragment ions of **21u–w** by the exact mass spectra are summarized in Tables XXVI–XXVIII (supplementary material).

***N*-Methyl-4-benzyl-3-pivaloyl-2-azetidinone (22u).** A mixture of the 2-azetidinone **20u** (71 mg, 0.28 mmol) dissolved in 20 mL of methanol and 5% palladium carbon (73 mg) was stirred under a hydrogen atmosphere at 20 °C for 3 h. The mixture was filtered and the filtrate was washed with methanol. Evaporation of the solvent under vacuum left an oil (82 mg) that was a mixture of *cis*-**22u** (63%) and *trans*-**22u** (37%) assigned by the ^1H NMR spectrum. The mixture was chromatographed on alumina (60 g) with benzene–ethyl acetate (9:1) as an eluant to give *trans*-**22u** (71 mg, 99%) as crystals and the cis isomer was not obtained. Recrystallization of *trans*-**22u** from benzene–pentane gave colorless needles: mp 117–119 °C; IR (KBr) 1750 cm^{-1} (CO), 1695 cm^{-1} (CO); UV (MeOH) λ_{max} 290 nm (ϵ 40), 258 nm (ϵ 196); MS, *m/e* (relative intensity) 259 (M^+, 3), 168 (37), 145 (97), 127 (31), 91 (37), 57 (100); ^1H NMR ($CDCl_3$) δ 1.05 (s, 9 H, *t*-Bu), 2.72 (d.d, *J* = 13.8 and 8.4 Hz, 1 H, HC-*H*), 2.80 (d, *J* = 0.8 Hz, 3 H, NCH_3), 3.16 (dd, *J* = 13.8 Hz and 5.9 Hz, 1 H, HC-*H*), 4.15 (ddd, *J* = 8.4 Hz, 5.9 Hz, and 2.2 Hz, 1 H, 4-CH), 4.37 (dq, *J* = 2.2 Hz and 0.8 Hz, 1 H, 3-CH), 7.10–7.50 (m, 5 H, C_6H_5). Anal. $C_{16}H_{21}NO_2$ (C, H, N). The ^1H NMR ($CDCl_3$) spectrum of *cis*-**22u**: δ 0.97 (s, 9 H, *t*-Bu), 2.70 (s, 3 H, NCH_3), 3.10 (d, *J* = 7.5 Hz, 2 H, CH_2), 4.06 (dt, *J* = 7.5 Hz and 5.2 Hz, 1 H, 4-CH), 4.55 (d, *J* = 5.2 Hz, 1 H, 3-CH), 7.10–7.50 (m, 5 H, C_6H_5).

Isomerization of Cyclobutenone 21u in Acidic Solution. The cyclobutenone **21u** (23.0 mg, 0.089 mmol) was dissolved in 1.0 mL of methanol containing water (0.10 mL) and trifluoroacetic acid (0.050 mL). The solution was allowed to stand for 90 h at 28 °C. After evaporation of the solvent, the oily residue was chromatographed on silica gel (52 g) with benzene–ethyl acetate (9:1–1:1). Fraction 1 (9.0 mg, 39%), eluted with benzene–ethyl acetate (4:1), was **21u**. Fraction 2 (14.0 mg, 61%), eluted with benzene–ethyl acetate (2:1), was 3-(*N*-methylamino)-2-phenyl-4-pivaloyl-2-cyclobuten-1-one (**23u**) as a white solid.

Recrystallization of **23u** from acetone–hexane gave fine needles: mp 171–173 °C; IR (KBr) 3320 cm^{-1} (NH), 1665 cm^{-1} (CO), 1640 cm^{-1} (CO); UV (MeOH) λ_{max} 310 nm (ϵ 10 200), 222 nm (ϵ 28 100); MS, *m/e* (relative intensity) 257 (M^+, 84), 229 (45), 214 (29), 200 (100), 144 (73); ^1H NMR ($CDCl_3$) δ 1.33 (s, 9 H, *t*-Bu), 2.86 (d, *J* = 5.1 Hz, 3 H, NCH_3), 4.73 (br, 1 H, NH), 5.92 (s, 1 H, CH), 7.3–7.5 (m, 5 H, C_6H_5). Anal. $C_{16}H_{19}NO_2$ (C, H, N).

General Procedures for Preparation of 4-Alkoxy-2-azetidinones 11.[1c] The Dewar 4-pyrimidinones **2** were converted to the 4-alkoxy-2-azetidinones **11** in methanol or ethanol solution at 0–22 °C. After evaporation of the solvent, the products **11** were separated by crystallization or by column chromatography on Sephadex LH-20 (280 g of dry gel) eluted with acetone.

***N*-Methyl-3-(1-amino-2,2-dimethylpropylidene)-4-ethoxy-4-methyl-2-azetidinone (11h).** The 4-pyrimidinone **1h** (2.097 g) was dissolved in 280 mL of ethanol and the solution was irradiated under an argon atmosphere with a 100-W high-pressure mercury lamp for 4.5 h at −13 °C. The ^1H NMR analysis showed that the solution contained 69% of **1h** and 31% of **2h**. The irradiated solution was allowed to stand for 14 days at 18–22 °C. After removal of the solvent, the reaction mixture was chromatographed on Sephadex LH-20. The pure **11h** (0.442 g, 17%) was obtained as a colorless oil: exact mass calcd for $C_{12}H_{22}N_2O_2$, *m/e* 226.1680, found *m/e* 226.1683.

The starting material **1h** (1.090 g, 52%) and a mixture (0.739 g, 33%) of **1h** (72%) and **11h** (28%) were recovered.

***N*-Methyl-3-(1-amino-2,2-dimethylpropylidene)-4-benzyl-4-methoxy-2-azetidinone (11u).** The Dewar 4-pyrimidinone **2u** (0.278 g, 1.09 mmol) was dissolved in 200 mL of methanol. The solution was allowed to stand for 8 days at 0 °C. After evaporation of the solvent, crude crystals of (*E*)-**11u** (0.304 g, 97%) were separated. Recrystallization of (*E*)-**11u** from benzene–pentane gave colorless needles: mp 146–148 °C. Anal. $C_{17}H_{24}N_2O_2$ (C, H, N).

7-(1-Amino-2,2-dimethylpropylidene)-6-methoxy-8-oxo-1-azabicyclo[4.2.0]octane (11x). The Dewar 4-pyrimidinone **2x** (0.111 g, 0.539 mmol) was dissolved in 10.0 mL of methanol. The solution was allowed to stand for 30 h at 0 °C. After evaporation of the solvent, crude crystals of (*E*)-**11x** (0.119g, 93%) were obtained. Recrystallization of (*E*)-**11x** from benzene–pentane gave colorless needles: mp 106–107 °C. Anal. $C_{13}H_{22}N_2O_2$ (C, H, N).

The 2-azetidinones **11h**, **11u**, and **11x** showed λ_{max} (MeOH) 277 ± 3 nm (ϵ 20 000). The infrared spectra (KBr) in each case showed three peaks of 3490–3230 cm^{-1} (NH_2) and two at 1715–1695 cm^{-1} (CO) and 1645–1625 cm^{-1} (C=C).

The ^1H NMR spectral data and the equilibrium ratios of *E* and *Z* isomers of the 2-azetidinones **11h**, **11h(a)**, **11u**, and **11x** are shown in Table XXII (supplementary material).

General Procedures for Preparation of 4-Methoxy-2-azetidinones 10. The 4-methoxy-2-azetidinones **11** were adsorbed on silica gel (10–70 g) at 20–30 °C for 13–40 h. Elution with chloroform–benzene (1:1) or benzene–ethyl acetate (10:1–1:1) gave **10**.

Reaction of 11h. From the 2-azetidinone **11h** (0.442 g), 0.406 g (91%) of *N*-methyl-4-ethoxy-4-methyl-3-pivaloyl-2-azetidinone (**10h**) was obtained as an oily solid. Recrystallization of **10h** from *n*-pentane–ether gave colorless prisms: mp 52–54 °C; IR ($CHCl_3$) 1765 cm^{-1} (CO), 1695 cm^{-1} (CO); UV (MeOH) λ_{max} 293 nm (ϵ 47); MS, *m/e* 227 (M^+, 0.23), 170 (35), 113 (75), 85 (51), 57 (100). Anal. $C_{12}H_{21}NO_3$ (C, H, N).

Reaction of 11h(a). From *N*-methyl-3-(1-amino-2,2-dimethylpropylidene)-4-methoxy-4-methyl-2-azetidinone (**11h(a)**)[1f] (409 mg, 1.93 mmol), 377 mg (92%) of *N*-methyl-4-methoxy-4-methyl-3-pivaloyl-2-azetidinone (**10h(a)**) was obtained as an oily solid. Recrystallization from ether–pentane gave colorless prisms: mp 65–67 °C; IR (KBr) 1770, 1695 cm^{-1} (CO); UV (MeOH) λ_{max} 294 nm (ϵ 35); MS *m/e* (relative intensity) 214 (1.0), 213 (M^+, 0.11), 156 (93), 100 (41), 99 (100), 88 (100), 82 (54), 57 (99), 56 (84), 42 (64). Anal. $C_{11}H_{19}NO_3$ (C, H, N).

The ^1H NMR spectrum of the filtrate (80 mg) indicated the presence of two stereoisomers. The fractions of the major **10h(a)** (identical with the crystalline compound) and minor **10h(a)** were 81% and 19%. The ratio of the original major and minor **10h(a)** was 96:4.

Reaction of 11u. From the 4-methoxy-2-azetidinone **11u** (500 mg, 1.74 mmol), a mixture (456 mg, 91%) of two stereoisomers of *N*-methyl-4-benzyl-4-methoxy-3-pivaloyl-2-azetidinone (**10u**) was obtained. The ^1H NMR analysis indicated that the ratio of the major and minor compounds was 81:19. When benzene was added to the mixture, crude crystals (294 mg, 59%) were separated and collected by filtration. Recrystallization from benzene gave the major **10u** as colorless prisms: mp 118–121 °C; IR (KBr) 1765, 1700 cm^{-1} (CO); UV (MeOH) λ_{max} 265 nm (sh, ϵ 171), 259 nm (ϵ 217), 254 nm (sh, ϵ 183); MS, *m/e* (relative intensity) 289 (M^+, 3), 198 (100), 175 (68), 163 (75), 91 (75), 82 (48), 57 (100), 41 (46). Anal. $C_{17}H_{23}NO_3$ (C, H, N).

Isolation of the minor **10u** by chromatography on silica gel was unsuccessful.

Reaction of 11x. From the 4-methoxy-2-azetidinone **11x** (54 mg, 0.23 mmol), crude crystals (51 mg, 93%) of 6-methoxy-8-oxo-7-pivaloyl-1-azabicyclo[4.2.0]octane (**10x**) were obtained. Recrystallization of **10x** from carbon tetrachloride–pentane gave colorless prisms: mp 95–97.5 °C; IR (KBr) 1765, 1695 cm^{-1} (CO); UV (MeOH) λ_{max} 293 nm (ϵ 45); MS, *m/e* (relative intensity) 239 (M^+, 1.2), 208 (11), 207 (9), 182 (73), 124 (100), 114 (27), 82 (32), 57 (62), 41 (67). Anal. $C_{13}H_{21}NO_3$ (C, H, N).

The compounds **10h**, **10h(a)**, **10u**, and **10x** were single isomers and the stereochemistry of these compounds could not be determined by the spectral data. The ^1H NMR spectral data of the 2-azetidinones **10h**, **10h(a)**, **10u**, and **10x** are shown in Table XXIII (supplementary material).

General Procedures for Reactions of 3-(Aminoalkylidene)-2-azetidinones 11 with Acetic Acid and for Isolation of the Products. The reactions of the 2-azetidinones **11** were carried out in benzene–acetic acid solution at 22 °C for 4–16 h. After evaporation of the solvent, the reaction mixture was chromatographed on alumina and silica gel.

Reaction of 11a[1a] with Acetic Acid in Benzene. From *N*-methyl-3-(aminoethylidene)-4-methoxy-4-methyl-2-azetidinone (**11a**) (106 mg, 0.624 mmol) in benzene (20.0 mL)–acetic acid (1.00 mL) solution for 4 h, 6.0 mg (0.035 mmol, 6%) of methyl 2-(*N*-methylaminoethylidene)acetoacetate (**24a**) as an oily solid and 42 mg (0.23 mmol, 37%) of the betaine **3a** were obtained.

Crystallization of **24a** in benzene–pentane gave colorless prisms: mp 72.0–72.5 °C; MS, *m/e* (relative intensity), 171 (M^+, 50), 156 (80), 140 (25), 124 (22), 98 (38), 56 (100), 43 (28). Anal. $C_8H_{13}NO_3$ (C, H, N).

Reaction of 11g[1a] with Acetic Acid in Benzene. From 7-(aminoethylidene)-6-methoxy-8-oxo-1-azabicyclo[4.2.0]octane (**11g**) (100 mg, 0.510 mmol) in benzene (40.0 mL)–acetic acid (1.00 mL) solution, 52 mg (0.26 mmol, 52%) of **24g** as an oily solid and 50 mg (0.24 mmol, 48%) of the betaine **3g** were obtained. The spectral data of the compound **24g** were found to be identical with those of methyl 2-(2-piperidylidene)acetoacetate.[13]

Reaction of 11h(a) with Acetic Acid in Benzene. From the 4-methoxy-2-azetidinone **11h(a)** (117 mg, 0.552 mmol) in benzene (20.0 mL)–acetic acid (1.00 mL) solution, 77 mg (0.35 mmol, 63%) of the betaine **3h** and 40 mg (0.19 mmol, 34%) of the 2-azetidinone **10h(a)** were obtained.

General Procedure for Thermolysis of 4-Methoxy-2-azetidinones 10. In a Pyrex tube, the crystalline **10** or solution of **10** was degassed under vacuum or by repeated freeze–pump–thaw cycles, and the tube was sealed and placed in an oil bath at 121 ± 1 °C. After 5 h, the tube was removed, cooled, and opened. After removal of the unreacted material and solvent, the reaction mixture was chromatographed on silica gel eluted with benzene–ethyl acetate (9:1–2:1).

A. Thermolysis of 4-Methoxy-2-azetidinone [10h(a)]. The crystalline **10h(a)** (71 mg, 0.33 mmol) was heated without solvent. The MPLC separation gave methyl 2-(*N*-methylaminoethylidene)trimethylacetoacetate (**24h**) (57 mg, 80%) as a white solid. Recrystallization of **24h** from *n*-pentane gave colorless fine plates: mp 65–67 °C; MS, *m/e* (relative intensity) 213 (M^+, 1.3), 156 (100), 56 (100). Anal. $C_{11}H_{19}NO_3$ (C, H, N).

B. Thermolysis of 10h(a) in Xylene. The 4-methoxy-2-azetidinone **10h(a)** (72 mg, 0.34 mmol) in xylene mixture (0.38 g, 0.44 mmol) was heated. The MPLC separation gave **24h** (5.3 mg, 7%) and unreacted **10h(a)** (62 mg, 86%).

C. Thermolysis of 10h(a) in *n*-Butyl Alcohol. a. The 4-methoxy-2-azetidinone **10h(a)** (72 mg, 0.34 mmol) in *n*-butyl alcohol (0.49 g, 6.63 mmol) was heated. The MPLC separation gave *n*-butyl 2-(*N*-methylaminoethylidene)trimethylacetoacetate (**25h**) (13 mg, 15%) as a white solid. Further elution gave **24h** (36 mg, 50%).

Recrystallization of **25h** from *n*-pentane gave colorless fine needles: mp 73–76 °C; MS, *m/e* (relative intensity) 255 (M^+, 2.9), 198 (100), 142 (71), 57 (38). Anal. $C_{14}H_{25}NO_3$ (C, H, N).

b. A solution of **10h(a)** (111 mg, 0.521 mmol) in *n*-butyl alcohol (0.055 g, 0.74 mmol) was heated. The MPLC separation gave **25h** (9 mg, 7%) and **24h** (71 mg, 64%).

Thermolysis of 4-Methoxy-2-azetidinone 10u. The crystalline **10u** (63 mg, 0.22 mmol) was heated without solvent. The MPLC separation gave methyl 2-[1-(*N*-methylamino)-2-phenylethylidene]trimethylacetoacetate (**24u**) (45 mg, 71%) as a crystalline solid. Recrystallization of **24u** from *n*-pentane gave colorless fine needles: mp 64.5–65.5 °C; MS, *m/e* (relative intensity) 289 (M^+, 2.6), 232 (100), 200 (19), 132 (19), 91 (26). Anal. $C_{17}H_{23}NO_3$ (C, H, N).

Thermolysis of 4-Methoxy-2-azetidinone 10x. A. The crystalline **10x** (61 mg, 0.26 mmol) was heated without solvent. The MPLC separation gave methyl 2-(2-piperidylidene)trimethylacetoacetate (**24x**) (38 mg, 62%) as a colorless oil, which was solidified in a refrigerator. Recrystallization of **24x** from *n*-pentane gave colorless prisms: mp 37–39 °C; MS, *m/e* (relative intensity) 239 (M^+, 1.9), 182 (100), 82 (31). Anal. $C_{13}H_{21}NO_3$ (C, H, N).

B. By Synthesis.[27] A solution of 0.69 g of 2,3,4,5-tetrahydro-6-methoxypyridine, 1.12 g of methyl trimethylacetoacetate, and 1.24 g of *N,N*-diisopropylethylamine was degassed in a Pyrex tube by repeated freeze–pump–thaw cycles, and the tube was sealed and heated at 110 °C for 90 h. Removal of the unreacted materials under reduced pressure gave a light brown oil, which was chromatographed on silica gel (78 g). Elution with benzene–ethyl acetate (9:1) afforded an oily solid. Recrystallization of the solid from *n*-pentane gave 57 mg (4%) of methyl 2-(2-piperidylidene)trimethylacetoacetate as colorless prisms. This compound was found to be identical (spectra) with those of **24x** obtained from the thermolysis of **10x**.

The spectral data of ^1H NMR, IR, and UV of the acetoacetates **24** are shown in Tables XXIV and XXV (supplementary material).

Crystal Data for the Cyclobutenone 21v: $C_{17}H_{21}NO_2$, M = 271.2; monoclinic; space group $P2_1/n$ (from systematic absence); a = 13.512 (2) Å, b = 12.541 (2) Å, c = 9.659 (2) Å, β = 108.49 (2)°; U = 1558.1 (4) Å;[3] D_x = 1.16 g cm^{-3}; Z = 4; Mo Kα (λ = 0.7107 Å).

Intensity Data Collection. A single crystal of **21v** suitable for X-ray diffraction study was grown from a solution of hexane–acetone. A column (0.2 × 0.2 × 0.8 mm) was used for data collection. Unit-cell dimensions were found by a least-squares fit to the observed value of θ–2θ scans for 46 strong reflections measured on a diffractometer Rigaku AFC-5 using graphite monochromated Mo Kα radiation. Of the 2453 independent reflections, 2093 [$F_o \geq 2\sigma(F_o)$] were used in the structure solution and refinement. The structure was solved by direct methods using the MULTAN78 programs and refined by full matrix least-squares technique on F. Hydrogen atoms were located by difference synthesis. Final least-squares refinement with anisotropic temperature factors for the non-hydrogen atoms and isotropic temperature factors for the hydrogen atoms lowered the unweighted R value of 0.079. The weighted R_w was 0.089. Deterioration of the intensities was not observed during the course of data collection. No absorption corrections was made.

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Supplementary Material Available: Tables of analytical data of the starting materials and products, tables of the spectral data (^1H NMR, MS, IR, and UV) of the compounds **2**, **3**, **10**, **11**, **20**, **21**, and **24**, scheme of mass fragment sequence of **3d–f**, the results of competitive reactions of **2h** with two aliphatic carboxylic acids, structure drawing with atomic numbering scheme of the compound **21v**, and tables of atomic coordinates, thermal parameters, bond lengths, and bond angles for **21v** (28 pages). Ordering information is given on any current masthead page.

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