Thermally Catalyzed and Noncatalyzed [2 + 2] Cycloadditions between Ketene Acetals and Carbonyl Compounds. A Simple Route to 2,2-Dialkoxyoxetanes

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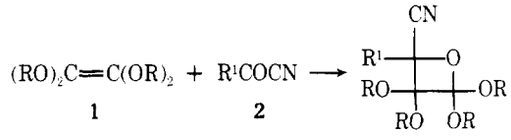
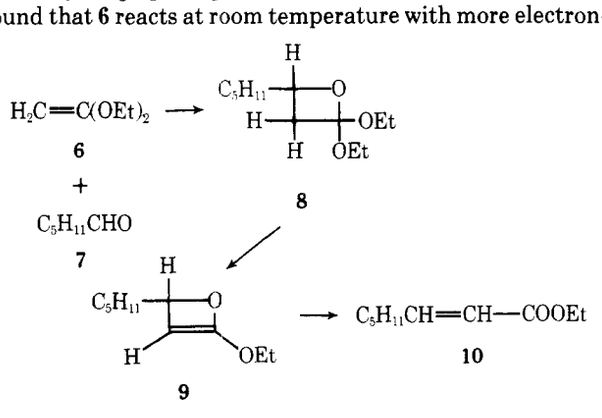
The known thermal cycloaddition between ketene acetals and electron-poor carbonyl compounds can be extended to all sorts of aldehydes and ketones by application of zinc chloride as a catalyst. In general the reactions proceed at room temperature. Only with dialkoxyethene the expected product cannot be isolated owing to thermal instability. Some examples of the reactivity of the 2,2-dimethoxyoxetanes, thus obtained, toward nucleophiles are given.

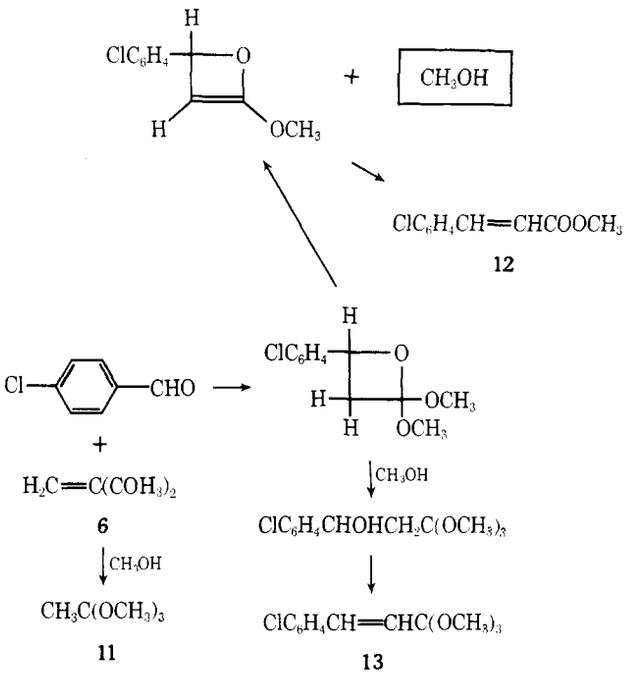
It is known that oxetanes arise photochemically from many types of olefins and carbonyl compounds.[1] However, the regiospecificity of these reactions, at least for enol ethers and ketene acetals, is low. Irradiation of a mixture of an aldehyde or ketone and a ketene acetal yields a mixture of a 2,2- and a 3,3-dialkoxyoxetane. In general, the 2,2-dialkoxy compound cannot simply be isolated from the reaction mixture, since the 3,3-disubstitution product is usually the main product.[2,3]

In a recent paper[4] we reported that [2 + 2] cycloadditions between tetraalkoxyethenes (**1**) and sufficiently electron-poor carbonyl compounds (e.g., acyl cyanides **2**) provide a simple method for the preparation of distinct tetraalkoxyoxetanes (**3**). In view of the varied, synthetic applications of ortho esters such oxetanes are potentially useful compounds. Relief of strain in reactions with nucleophiles will enhance the reactivity of their ortho ester function. The usefulness of compounds **3** is, however, limited as a consequence of the additional alkoxy groups on C_3 and the cyano group (or other electron-withdrawing substituent) on C_4. Therefore, we investigated if the oxetane formation via cycloadditions could be extended to less substituted ketene acetals (**4**) and less activated carbonyl compounds (**5**).



In the preparation of 2,2-dialkoxyoxetanes via thermal cycloadditions, instability of the desired product under the reaction conditions has to be considered when hydrogen atoms are present on C_3. McElvain isolated[5] the α,β-unsaturated ester (**10**) from the reaction between 1,1-diethoxyethene (**6**) and hexanal (**7**) at 150 °C, and ascribed the result to elimination of ethanol from an initially formed oxetane (**8**), followed by ring opening of the second intermediate (**9**). We found that **6** reacts at room temperature with more electron-poor carbonyl compounds (chloral, benzoyl cyanide, *p*-chlorobenzaldehyde). The reaction mixtures were rather complex. The presence of large amounts of methyl orthoacetate (**11**) among the products indicated that even under the mild reaction conditions alcohol had been eliminated at some stage. Careful workup in the experiment with *p*-chlorobenzaldehyde yielded methyl *p*-chlorocinnamate (**12**) (mp 74–76 °C, lit.[6]





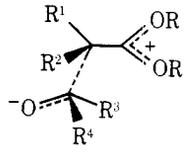
72–73 °C) and the corresponding ortho ester (**13**) (*m/e* 244, 242, M^+ and 213, 211 $M^+ - OCH_3$; NMR δ 7.30, s, 4 H; 6.82 and 5.87, d, AB pattern, J = 15 Hz; 3.22, s, 9 H) which can be explained by the following scheme. Thus it seems that the thermal stability of 2,2-dialkoxyoxetanes having two hydrogen atoms on C_3 is too low for isolation under normal conditions.[7] [It may, however, be possible that with 1,1-dialkoxyethenes oxetanes are not formed at all (see under mechanistic aspects).]

2,2-Dialkoxyoxetanes having only one hydrogen atom on C_3 were obtained from reactions between 1,1-dimethoxypropene and several strongly electrophilic carbonyl compounds at room temperature. The products appeared to be stable up to 80 °C so that they could be purified by distillation. By performance of the reactions in an NMR tube, rough estimates of relative reaction rates could be made by determination of the time of half change ($t_{1/2}$) for the reactants (Table I). The reactions show a moderate solvent effect. Apparently the rate of the cycloadditions strongly depends on the electron-withdrawing ability of the groups at the carbonyl func-

tion. The influence of steric effects is more apparent on variations in the ketene acetal. 1,1-Dimethoxyisobutene is much less reactive toward benzoyl cyanide than 1,1-dimethoxypropene (Table II).

An interesting observation was made with reactions between *p*-chlorobenzaldehyde and 1,1-dimethoxypropene. Whereas freshly distilled aldehyde showed hardly any reaction, older, partly oxidized samples reacted much better, yielding beside polymeric products the expected oxetane. The results were ascribed to acid catalysis since a similar acceleration was found on addition of slight amounts of a proton acid (*p*-toluenesulfonic acid) or a Lewis acid (BF_3, $AlCl_3$, $TiCl_4$, $ZnCl_2$). Best results, viz., high conversion rates at moderate temperatures without serious polymerization of the ketene acetal, were obtained with 0.5–1% $ZnCl_2$. The use of this catalyst gives the preparation of 2,2-dialkoxyoxetanes via thermal cycloadditions a much wider scope. Even simple aldehydes and ketones without electron-withdrawing groups can be converted in this way at room temperature (see Experimental Section, Table III). Unsymmetrical carbonyl compounds yield always a mixture of diastereomeric products in reactions with 1,1-dimethoxypropene.

Mechanistic Aspects. According to a recent frontier orbital treatment of [2 + 2] cycloadditions[9] two limiting geometries, symbolized as $1_s^D + 1_s^A$ and $2_s^D + 1_s^A$, can be considered for the addend approach in reactions between an electron-donating and an electron-accepting compound. The transition state of the respective pathways can be visualized as in the formulas **14** and **15**. The solvent effects [$t_{1/2}$ $(CDCl_3)/t_{1/2}$ (cyclohexane) ca. 0.01] as well as the strong electronic influences of the residues (R_3, R_4) at the carbonyl group are in agreement with such polar transition states. The observed acid catalysis can be ascribed to activation of the carbonyl group by protonation or complexation with a Lewis acid. The complete regiospecificity of cycloadditions with unsymmetrically substituted donor compounds (1,1-dimethoxypropene and -isobutene) points to the $1_s^D + 1_s^A$ approach (via **14**) which leads to a favorable charge separation in these cases. It may be expected that in reactions between donors and acceptors having different R residues ($R^1 \neq R^2$, $R^3 \neq R^4$) via **14** the isomer ratio of the product will not be very sensitive to steric factors. This was found to be true. The cycloadditions between 1,1-dimethoxypropene and several carbonyl compounds gave, in general, isomer ratios between 0.35 and 0.65. Only in one case (biacetyl) a lower value (0.15) was found (Table III). Cycloadditions of tetramethoxyethene via **14** should be expected to be slower than corresponding reactions of 1,1-dimethoxyisobutene as a consequence of the destabilizing effect of the β-methoxy groups (R_1 and R_2) on the positive charge. The reactivity of tetramethoxyethene is, however, much higher (Table II). Probably highly symmetrical donor compounds react via the three-center transition state[10] (**15**) in which the positive charge is delocalized over both sides of the olefin.



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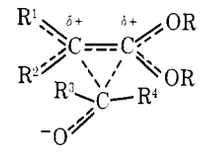

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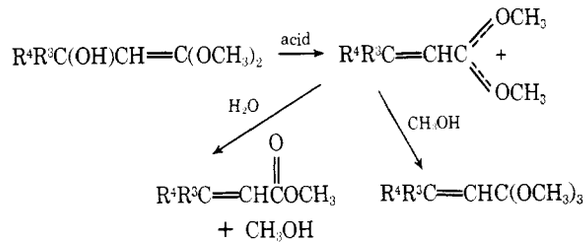
The transition state with the strongest dipolar character (**14**) should be expected for $R^1 = R^2 = H$. In this case proton shift may be faster than ring closure, delivering $R^4R^3C(OH)$-$CH{=}C(OR)_2$. Another explanation for the products of the reaction of 1,1-dimethoxyethene with carbonyl compounds could therefore be:

Table I. $t_{1/2}$ Values for Cycloadditions between 1,1-Dimethoxypropene and Various Carbonyl Compounds (Both Concentrations 0.25 mol L^{-1}) at 25 °C

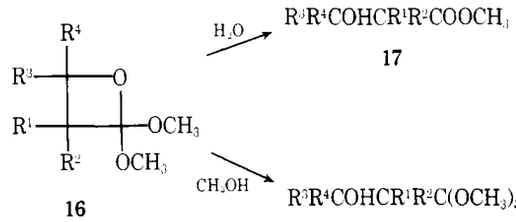
Registry no.	Carbonyl compd	$t_{1/2}$ ($CDCl_3$), min	$t_{1/2}$ (cyclohexane)
75-87-6	CCl_3CHO	<1	50 min
631-57-2	CH_3COCN	~1	
613-90-1	C_6H_5COCN	40	75 h
431-03-8	$CH_3COCOCH_3$	No reaction	
104-88-1	p-ClC_6H_4CHO	No reaction	



We are investigating more systematically the influence of R^1 and R^2 on the character of the transition state in several [2 + 2] cycloadditions and will report on it in another paper.

Reactivity of the Oxetanes. All oxetanes synthesized appeared to be stable at room temperature, even in the presence of 1 mol % $ZnCl_2$. The composition of isomer mixtures obtained from 1,1-dimethoxypropene did not vary under these conditions. In the absence of acids most of the products did not decompose below ca. 80 °C. At higher temperature, the reverse reaction, accompanied by change in the isomer ratio, was observed by following the reactions with NMR. In only one case (the oxetane from chloral and dimethoxypropene) could a pure isomer (probably the trans compound) be obtained in this way. In other cases elimination of alcohol leading to a complex reaction mixture was a serious side reaction on heating oxetanes having hydrogen on C_3.

The oxetanes (**16**) react easily with water and alcohols, giving β-hydroxy esters (**17**) and ortho esters (**18**), respectively.



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They may be valuable starting compounds for the preparation of β-hydroxy and β-keto esters and of α,β-unsaturated esters (when $R^1 = H$). Further applications will be reported in a subsequent paper.

Experimental Section

Since most of the oxetanes are easily hydrolyzed in contact with moisture elemental analyses have only been made for the more stable oxetanes. Therefore, complete purity of all products is not fully guaranteed. From the spectral data, used for structure assignments, it could be concluded, however, that the purity of all preparations is more than 95%.

Infrared spectra were measured with a Perkin-Elmer spectrophotometer, Model 257. Proton magnetic resonance spectra were traced with a Varian T-60 NMR spectrometer, using solutions in deuteriochloroform unless otherwise indicated. Chemical shifts are reported as δ values relative to tetramethylsilane as an internal standard. Mass spectra were obtained with a double focusing Varian Associates SM1-B mass spectrometer.

Table II. $t_{1/2}$ Values for Cycloadditions between Benzoyl Cyanide and Various Ketene Acetals

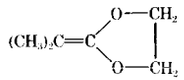
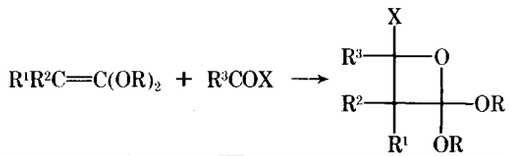
Registry no.	Ketene acetal	Temp, °C	Solvent	Concn	$t_{1/2}$
5634-52-6	$CH_3CH{=}C(OCH_3)_2$	25	$CDCl_3$	Both 0.25 mol L^{-1}	40 min
5634-54-8	$(CH_3)_2C{=}C(OCH_3)_2$	120	None	Acetal in twofold excess	48 h
4351-16-0		25	$CDCl_3$	Both 0.25 mol L^{-1}	200 min[a]
1069-12-1	$(CH_3O)_2C{=}C(OCH_3)_2$	100	None	Acetal in twofold excess	7 h

Table III. Preparation, Yield, Physical Constants, and Spectral Data for Oxetanes from the Reaction



Ketene acetal	Carbonyl compd	Reaction time, h	Yield, %	Isomer ratio[a]	Purification method	Bp, °C (mm)	Mp, °C	IR[b] ν_{C-O}, cm^{-1}	NMR, δ ppm
$CH_3CH{=}C(OCH_3)_2$	C_6H_5CHO[f]	1	75	0.35	*a*	78 (0.2)		952 926	7.20 and 7.25 (s, 5 H), 5.27 and 4.65 (d, 1 H, J = 7 Hz), 2.75 (m, 1 H), 1.20 and 0.60 (d, 3 H, J = 7 Hz) (cis–trans mixture)
	p-$NO_2C_6H_4CHO$[g]	1	85	0.55	*c*		Oil	950–970	8.70 and 7.50 (AB, 4 H), 5.40 and 4.80 (d, 1 H, J = 7 Hz), 2.75 (m, 1 H), 1.25 and 0.62 (d, 3 H, J = 7 Hz) (cis–trans mixture)
	CCl_3CHO	1[c]	75	0.65	*a*	64 (0.5)		975 950	4.16 (d, 1 H, J = 6 Hz), 3.06 (m, 1 H), 1.06 (d, 3 H, J = 7 Hz) (trans isomer)
	C_6H_5COCN	1	80	0.35	*c*		Oil	975 955	7.35 (m, 5 H), 1.45 and 0.75 (d, 3 H, J = 8 Hz) the methine signal is hidden under the methoxy absorptions (cis–trans mixture)
	CH_3COCN	1[c]	75	0.60	*a*	45–50 (0.3)		970 945	2.87 (m, 1 H), 1.62 and 1.53 (s, 3 H), 1.25 and 1.10 (d, 3 H, J = 7 Hz) (cis–trans mixture)
	$CH_3COCOCH_3$	1	70	0.15	*a*	48 (0.5)		952	2.85 (m, 1 H), 2.25 (s, 3 H), 1.40 and 1.30 (s, 3 H), 1.10 and 0.90 (d, 3 H, J = 7 Hz) (cis–trans mixture)
	$(CH_3)_2CHCHO$[h]	1	60		*b*	68 (15)		928 916	2.53 (m, 1 H), 1.73 (m, 1 H), 1.15–0.75 (complex pattern, 9 H). A methine signal is hidden under the methoxy absorptions (cis–trans mixture)
	CH_3COCH_3[i]	2	25[d]		*b*	54 (15)		956	2.58 (q, 1 H), 1.31 (s, 3 H), 1.23 (s, 3 H), 0.96 (d, 3 H, J = 7 Hz)
$(CH_3)_2C{=}C(OCH_3)_2$	$(CH_3)_2CHCHO$	48	70		*a*	78 (15)		995–965 Several absorptions	(in CCl_4) 3.25 (d, 1 H), 1.75 (m, 1 H), 1.16 (s, 3 H), 1.10 (s, 3 H), 0.83 (d, 3 H, J = 9 Hz), 0.72 (d, 3 H, J = 9 Hz)

C_6H_5CHO	4	80	*b*	78 (0.05)		990–950 Several absorptions	(in CCl_4) 7.20 (s, 5 H), 4.83 (s, 1 H), 1.33 (s, 3 H), 0.73 (s, 3 H)
C_6H_5COCN	4	85	*c*		44–46	990–950 Several absorptions	7.37 (s, 5 H), 1.57 (s, 3 H), 0.79 (s, 3 H)
$(CH_3O)_2C{=}C(OCH_3)_2$ $(CH_3)_2CHCHO$	36	65	*a*	52 (0.1)		982 950	(in CCl_4) 3.60 (d, 1 H, J = 9 Hz), 1.93 (m, 1 H), 0.93 (d, 3 H)
C_6H_5CHO	2	75	*a*	104 (0.1)		960 940	(in CCl_4) 7.33 (m, 5 H), 4.83 (s, 1 H), 3.43 (s, 6 H), 3.38 (s, 3 H), 3.30 (s, 3 H)
C_6H_5COCN[e]	1	90	*c*		50	990 958	(in CCl_4) 7.35 (m, 5 H), 5.25 (s, 1 H), 3.55 (s, 6 H), 3.45 (s, 3 H), 3.00 (s, 3 H)
CH_3COCN	2[c]	60	*b*	95 (0.05)		955	3.96 (m, 4 H), 1.57 (s, 3 H), 1.40 (s,
CCl_3CHO	1[c]	60	*b*	90 (0.2)		950	3 H), 1.17 (s, 3 H)
						925	4.40 (s, 1 H), 4.08 (m, 4 H), 1.42 (s, 6 H)
C_6H_5COCN	24	70	*c*		92–95	945	7.40 (s, 5 H), 4.13 (m, 4 H), 1.60 (s,
						918	3 H), 0.80 (s, 3 H)
$p\text{-}NO_2C_6H_4CHO$	24	75	*c*		Oil		8.16–7.43 (AB, 4 H), 5.03 (s, 1 H), 4.10 (m, 4 H), 1.45 (s, 3 H), 0.73 (s, 3 H)

[a] Determined from NMR spectra of the reaction mixture after concentration at room temperature. For all compounds having R^3 = aryl the methyl protons (R^1) of the minor product were at higher field. This shielding effect indicates that the larger groups (R^1 and R^3) are in cis position. [b] Oxetanes have C–O stretch vibrations in the range 995–925 cm^{-1}. See ref 1 and 3 and F. Nerdel, D. Frank, H.J. Lengert, and P. Weyerstahl, *Chem. Ber.*, **101**, 1850 (1968). In the table all vibrations in this region are given. [c] No catalyst was used. Therefore, removal of $ZnCl_2$ could be omitted in the isolation procedure. [d] The reaction leads to an equilibrium. Higher yields are obtained when the acetal is used in larger excess. [e] See ref 1. [f] Registry no., 100-52-7. [g] Registry no., 555-16-8. [h] Registry no., 78-84-2. [i] Registry no., 67-64-1.

The preparation of dimethylmethylenedioxolane (lit. in ref 7), 1,1-dimethoxyethene,[11] and tetramethoxyethene[12] was done as described in the literature.

1,1-Dimethoxypropene. 3,3-Dimethoxypropene (0.25 mol) is dissolved in dry ether (50 mL) and the solution is dropped into a solution of potassium amide (0.1 mol) in liquid ammonia at −40 °C. The mixture is left for 2 h at this temperature. Ammonia is then evaporated, and the residue is diluted with dry ether (75 mL). Unreacted potassium amide is filtered off on a glass filter, and carefully destroyed with a 20% solution of *tert*-butyl alcohol in hexane. The filtrate is distilled with a Vigreux column (50 × 1.2 cm), bp 99 °C (lit.[13] 98–102 °C), yield 65%. The corresponding diethyl acetal can be obtained in a similar way, bp 134 °C [lit.[14] 134–137 °C (740 mm)].

1,1-Dimethoxyisobutene. The same procedure is followed with a reaction time of 48 h, bp 108–110 °C (lit.[14] 107–109 °C). The corresponding diethoxy compound has bp 68 °C (55 mm) [lit.[14] 139–140 °C (740 mm)].

General Procedure for the Preparation of 2,2-Dimethoxyoxetanes. A 40% solution of a carbonyl compound in acetonitrile is mixed with 1.1 equiv of a ketene acetal and 0.5–1% $ZnCl_2$. The mixture is left at room temperature for the time indicated in Table III. The solvent and the excess of ketene acetal are then evaporated at reduced pressure (below 40 °C). In order to eliminate the catalyst, pentane and a slight amount of triethylamine are added until the oxetane has been dissolved. Zinc chloride is left undissolved and can be filtered off. The filtrate is evaporated leaving the oxetane.

For further purification sufficiently volatile products are distilled in the presence of a slight amount of potassium *tert*-butanolate either with a Vigreux column (30 × 1 cm) (method a) or in a ball tube (method b). Oxetanes which cannot be distilled are purified by repeated washings with pentane (10 mol per 0.05 mol) at 0 °C (method c). Yields, physical constants and spectral data of the products are given in Table III. In the mass spectrometer the molecular ions of oxetanes undergo fragmentations by loss of dialkyl carbonate and ketene acetal fragments. M^+ peaks are generally weak. Sometimes $M^+ + 1$ peaks were observed.

Anal. Calcd for 2,2-dimethoxy-3,3-dimethyl-4-phenyloxetane, $C_{13}H_{18}O_3$: C, 70.24; H, 8.16; Found: C, 70.16; H, 8.26. Calcd for 2,2,3,3-tetramethoxy-4-phenyloxetane, $C_{13}H_{18}O_5$: C, 61.41; H, 7.14. Found: C, 61.06; H, 7.31.

Methyl Esters of β-Hydroxycarboxylic Acids by Hydrolysis of 2,2-Dimethoxyoxethanes. Two equivalents of water and a pinpoint of *p*-toluenesulfonic acid are added to a 20% solution of an oxetane in acetonitrile. The mixture is left at room temperature for 1 h. Acetonitrile is evaporated, and ether is added to the residue. The ethereal solution is dried over sodium sulfate, the solvent evaporated, and the residual oil distilled. The following esters were obtained in this way.

Methyl 3-hydroxy-2-methyl-3-phenylpropionate, $C_6H_5CHOHCH(CH_3)COOCH_3$: yield 90%; bp 92–98 °C (0.5 mm); *m/e* 194 (M^+), 163 ($M - OCH_3$), 107 [$M - CH(CH_3)COOCH_3$]; NMR: ($CDCl_3$) δ 7.17 (s, 5 H), 4.58 (d, 1 H, J = 9 Hz), 3.58 (s, 3 H), 2.63 (m, 1 H), 1.05 and 0.87 (d, 3 H, J = 8 Hz) (mixture of diastereomers).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.84; H, 7.35.

Methyl 3-hydroxy-2,2-dimethyl-3-phenylpropionate, $C_6H_5CHOHC(CH_3)_2COOCH_3$: yield 80%; bp 96 °C (0.3 mm); mp 69.5–70.5 °C; *m/e* 208 (M^+), 177 ($M - OCH_3$); 107 [$M - C(CH_3)_2COOCH_3$]; NMR ($CDCl_3$) δ 7.16 (s, 5 H), 4.77 (s, 1 H), 3.60 (s, 3 H), 3.20 (s, 1 H), 1.07 (s, 3 H), 1.00 (s, 3 H).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.66; H, 7.74. Found: C, 69.21; H, 7.92.

Registry No.—3,3-Dimethoxypropene, 6044-68-4; (*R*,R**)-methyl 3-hydroxy-2-methyl-3-phenylpropionate, 14366-89-3; (*R*,S**)-methyl 3-hydroxy-2-methyl-3-phenylpropionate, 17226-79-8; methyl 3-hydroxy-2,2-dimethyl-3-phenylpropionate, 35022-33-4; *cis*-2,2-dimethoxyl-3-methyl-4-phenyloxetane, 62841-79-6; *trans*-2,2-dimethoxy-3-methyl-4-phenyloxetane, 62841-80-9; *cis*-2,2-dimethoxy-3-methyl-4-*p*-nitrophenyloxetane, 62841-81-0; *trans*-2,2-dimethoxy-3-methyl-4-*p*-nitrophenyloxetane, 62841-82-1; *trans*-2,2-dimethoxy-3-methyl-4-trichloromethyloxetane, 62841-83-2; *cis*-2,2-dimethoxy-3-methyl-4-cyano-4-phenyloxetane, 62841-84-3; *trans*-2,2-dimethoxy-3-methyl-4-cyano-4-phenyloxetane, 62841-85-4; *cis*-2,2-dimethoxy-3,4-dimethyl-4-cyanooxetane, 62841-86-5; *trans*-2,2-dimethoxy-3,4-dimethyl-4-cyanooxetane, 62841-87-6; *cis*-2,2-dimethoxy-3,4-dimethyl-4-acetyloxetane, 62841-88-7; *trans*-2,2-dimethoxy-3,4-dimethyl-4-acetyloxetane, 62841-89-8; *cis*-2,2-dimethoxy-3-methyl-4-isopropyloxetane, 62841-90-1; *trans*-2,2-dimethoxy-3-methyl-4-isopropyloxetane, 62841-91-2;

2,2-dimethoxy-3,4,4-trimethyloxetane, 62841-92-3; 2,2-dimethoxy-3,3-dimethyl-4-isopropyloxetane, 62841-93-4, 2,2-dimethoxy-3,3-dimethyl-4-phenyloxetane, 62841-94-5; 2,2-dimethoxy-3,3-dimethyl-4-cyano-4-phenyloxetane, 62841-95-6; 2,2,3,3-tetramethoxy-4-isopropyloxetane, 62841-96-7; 2,2,3,3-tetramethoxy-4-phenyloxetane, 62841-97-8; 2,2,3,3-tetramethoxy-4-cyano-4-phenyloxetane, 60299-87-8; 2,3,3-trimethyl-2-cyano-1,5,8-trioxaspiro[3.4]octane, 62841-98-9; 3,3-dimethyl-2-trichloromethyl-1,5,8-trioxaspiro[3,4]octane, 62841-99-0; 2-cyano-2-phenyl-3,3-dimethyl-1,5,8-trioxaspiro[3.4]octane, 62842-00-6; 2-*p*-nitrophenyl-3,3-dimethyl-1,5,8-trioxaspiro[3,4]octane, 62842-01-7; 1,1-diethoxypropene, 21504-43-8; 3,3-diethoxypropene, 3054-95-3.

References and Notes

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A Novel Acylative Degradation of Uric Acid. Carbon-13 Nuclear Magnetic Resonance Studies of Uric Acid and Its Degradation Products

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Treatment of uric acid (1) with boiling isobutyric anhydride causes cleavage and rearrangement of the pyrimidine and imidazole rings to give a new heterocyclic derivative, 2-(1-methylethyl)-4-(1-hydroxy-2-methylpropylidene)aminoimidazole-5-carboxylic acid 5,1′-lactone (2). The structures of the lactone and related derivatives have been elucidated by infrared spectroscopy, ^1H and ^{13}C NMR, and mass spectrometry. Experiments with uric acids labeled with carbon-14 at either C-2, C-6, or C-8 confirmed that C-2 and C-8 were eliminated during the cleavage process. Uric acid, its 1,3-$^{15}N_2$ labeled derivative, and a series of degradation products and related model compounds have been studied by ^{13}C NMR spectroscopy, and the carbon-13 chemical shifts and coupling constants correlated with molecular structure.

In the course of a study of uric acid (1) to find volatile derivatives for chemical analysis of 1 in serum by isotope dilution mass spectrometry, we have examined its reactions with a series of aliphatic acylating agents, including acetic, propionic, *n*-butyric, and isobutyric acid anhydrides. Considerable work on the acetylation of uric acid has been described previously, notably conversion of 1 into 8-methylxanthine (3) by prolonged treatment (80 h) of 1 with a boiling mixture of acetic anhydride and pyridine.[1-4] However, there has been little or no work on the reaction of higher boiling, aliphatic acid anhydrides with 1.

Whereas reactions of 1 with boiling propionic or *n*-butyric anhydrides in the presence of pyridine, as observed in this laboratory, generally follow the path described earlier for acetic anhydride (e.g., conversion of 1 to 3),[1-4] treatment of 1 with boiling isobutyric anhydride either alone or in the presence of a tertiary amine (e.g., pyridine) gave surprising results. Reactions of 1 with a variety of oxidants[5] lead to either cleavage of the pyrimidine ring (e.g., with alkaline permanganate) to give allantoin, or degradation of the imidazole ring (e.g., with nitric acid) to produce alloxan, or cleavage of both rings (e.g., with permanganate in acetic acid) to give acyclic oxaluric acid. The structures and carbon-13 nuclear magnetic resonance (^{13}C NMR) data of some of the degradation products of 1 are shown in Table I.

We report here a novel acylative degradation that involves simultaneous cleavage and rearrangement of the pyrimidine and imidazole rings in 1, with the formation of a new heterocyclic ring system. When mixtures of uric acid with isobutyric anhydride or isobutyric anhydride and pyridine were boiled under reflux for 8–24 h and 3–4 h, respectively, concentration followed by trituration of the resulting residues with ethyl acetate yielded 32–36% of a colorless crystalline material, mp 211–212 °C, that has proved to be 2-(1-methylethyl)-4-(1-hydroxy-2-methylpropylidene)aminoimidazole-5-carboxylic acid 5,1′-lactone (2).

Results and Discussion

Spectroscopic Evidence for the Structure of 2. The infrared spectrum of 2 displayed a strong absorption at 1772 cm^{-1} that suggested the possibility of an ester or lactone group derived from an unsaturated alcohol. The ^{13}C NMR spectra of 2 (see Figure 1) and its proton NMR spectra revealed that two, chemically nonequivalent isopropyl groups had been introduced.[6] The presence of a nonacylated NH group in the structure of 2 was indicated by its proton NMR spectra in pyridine-d_5 and dry methyl-d_6 sulfoxide solutions, each of which displayed a broad, one-proton signal at low field that was displaced to higher field on addition of deuterium oxide to the solution. The chemical shift of this signal was found to be highly variable, in agreement with its assignment as an NH proton. The proton-decoupled ^{13}C NMR spectra (Figure 1a and 1b) of 2 display only five carbon resonances other than those of the isopropyl groups, which indicates that two carbon atoms have been eliminated from the reactants.

The apparent molecular ion in the electron impact (EI)