Transacetalation of Methyl 9,9-Dimethoxynonanoate

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The stability of acetals, especially cyclic acetals, in the presence of alkaline and neutral reagents is well known.[2,3] This stability makes possible the reactions of other functional groups in compounds containing carbonyl groups protected in the acetal form. Although considerably fewer in number, selective reactions of the acetal group in a polyfunctional compound also are recorded. For example, selective hydrolysis[4,5] and transacetalation to form acyclic[6] as well as cyclic[7,8] acetals in compounds also containing an ester group have been described. The ease with which 1,2- and 1,3-diols form cyclic acetals and their stability in general have been noted.[9,10] However, we have reported a special case of transacetalation of cyclic acetals in the presence of an ester group: the cross linking of poly(ester acetals) and poly(amide acetals) with certain metal oxides and salts.[11-13]

Selective transacetalation to form acyclic acetals with acidic catalysts has been noted only for certain β,β-dialkoxypropionate and β-alkoxyacrylate derivatives.[6] Since alkoxide catalysts cause both transacetalation and transesterification, β-alkoxy esters cannot be considered representative members of a homologous series of ω-dialkoxy esters. We therefore report our findings on selective alcoholysis with acidic and alkaline catalysts of a more representative homolog, methyl 9,9-dimethoxynonanoate (I), and discuss the kinetics of the reaction in a quantitative sense. We also describe the cleavage of I to form enol ethers.

Alcoholysis of the acetal group of I was carried out in the presence of potassium acid sulfate catalyst, 100% excess of alcohol, and a slow stream of nitrogen to aid removal of methanol. A study of time and temperature effects was carried out with 1-hexanol (Table I). A 95% conversion to methyl 9,9-(1-hexoxy)nonanoate (III) was obtained in 4 hr. at 75° with none of the hexyl ester (IV) *or of the mixed acetal* (II) detected by gas-liquid chromatography (g.l.c.) at any point during this period. Higher reaction temperatures and longer heating periods resulted in the formation of increasing amounts of IV. Similar conversions were obtained with other alcohols, including butyl, 2-ethylhexyl, and *n*-octadecyl alcohols, ethylene glycol, glycerol, and 2-methoxyethanol. Ester formation was more significant with ethyl and allyl alcohols.

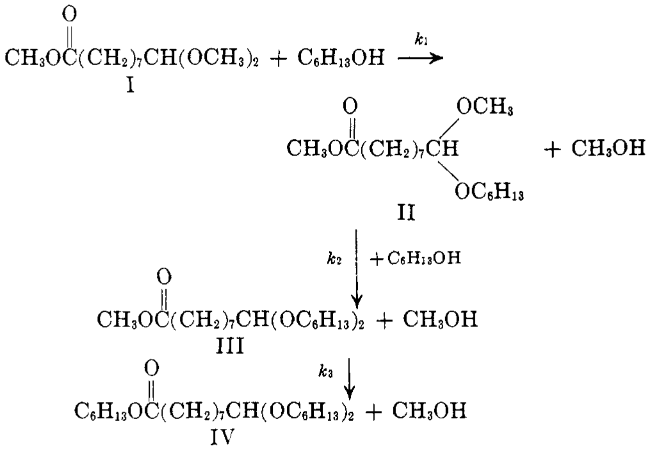
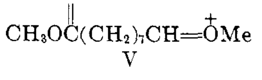


TABLE I

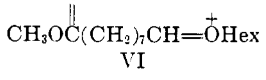
EFFECT OF REACTION CONDITIONS ON ACETAL ALCOHOLYSIS

Reaction temp., °C.	Reaction time, 4 hr.		Reaction time, 7 hr.	
	Total conversion, %	Ester acetal IV, %	Total conversion, %	Ester acetal IV, %
50	82.5	0.0	87.0	0.0
75	95.0	0.0	95.6	0.8
85	94.5	2.9	97.0	3.5
115	88.0	4.4	92.5	18.0
155	92.0	21.2	92.5	33.0

The absence of a detectable quantity of the mixed acetal II leads to the conclusion that $k_2 > k_1$. A semiquantitative value for the ratio $K = k_2/k_1$ may be calculated from the equations developed for series first-order reactions.[14] Thus, at $K = 30$, for 75% completion of the reaction, the concentration of II should be about 0.9%; 2.6% at 25% completion. Assuming the limit of detection of the gas chromatograph to be about 1%, then K must be at least 30. This difference in reaction rates is in qualitative accord with the findings of Juvet and Chiu,[15] who studied the methanolysis of the diethyl acetal of acetaldehyde. On the basis of several rate determinations, they concluded that alcoholysis rate depends on the remaining alkoxy group rather than on the leaving or attacking group. Thus, inductive stabilization by the *n*-hexyl group makes VI (and the transition states leading to it from II and from it to III) more stable than V (and its corresponding transition states).


$CH_3O\overset{O}{\overset{\|}{C}}(CH_2)_7CH{=}\overset{+}{O}Me$

V


$CH_3O\overset{O}{\overset{\|}{C}}(CH_2)_7CH{=}\overset{+}{O}Hex$

VI

However, Juvet and Chiu found that conversion of the mixed acetal to the diethyl acetal occurred at a rate

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[1] One of the laboratories of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. Article not copyrighted.

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only 1.6 times faster than the conversion of the dimethyl to the mixed acetal. The larger ratio of 30 for the corresponding two steps as described herein may be due to the greater steric effect of the hexyl group as compared to ethyl. The steric effect would cause the methyl hexyl acetal II to be less stable than the methyl ethyl acetal of acetaldehyde relative to their respective carbonium ions VI and CH_3CHOEt^+.

Our results are also in qualitative accord with those of Salomaa,[16] who found a ratio of *ca.* 6 for the rate constants in acid-catalyzed hydrolysis of $EtOCH_2OEt$ compared to $MeOCH_2OMe$, and with Jansson's,[17] who found ratios ranging from 5 up to 9 for the rate constants in acid-catalyzed hydrolysis of $CH_3CH(OEt)_2$ compared to $CH_3CH(OMe)(OEt)$.

Alcoholysis of the ester group was carried out in the presence of sodium methoxide with *n*-butyl and 2-ethylhexyl alcohols, ethylene glycol, glycerol, and 2-methoxyethanol. Heating at about 100° for up to 10 hr. was required to obtain yields comparable to those obtained in transacetalation. No evidence for transacetalation with the alkaline catalysts showed by g.l.c., in contrast to the results reported for β,β-dialkoxypropionates.[6]

Analogous to the cracking reaction that simple acetals undergo,[18] I underwent a cracking reaction to form the enol ether (VII). The cracking reaction was carried out

$$CH_3OCH{=}CH(CH_2)_6COOCH_3$$

VII

in the liquid phase with heating in the presence of potassium acid sulfate. Cracking at 150° was quite pronounced, and crude yields of 80–90% were obtained in 8 hr. Under the same heating conditions but in the absence of catalyst or acidic substance, no significant cracking occurred.

The apparently homogeneous cracked product VII contained two components by g.l.c. analysis. These components are believed to be the *cis* and *trans* isomers. Evidence for this conclusion was obtained from the infrared spectrum, by ozonation, and by re-formation of the dimethyl acetal. Infrared analysis of both I and VII indicated several changes. Bands at 1130, 1055, and 950 cm.$^{-1}$ in the spectrum of I no longer appeared in the spectrum of VII, and new bands at 1667, 1266, 1115, 1025, and 934 cm.$^{-1}$ appeared for VII. The band at 934 cm.$^{-1}$ is attributed to the *trans* configuration, the shift from the normal 965 cm.$^{-1}$ resulting from the presence of the ether group.[19] This assignment of structure is in agreement with an absorption at 930 cm.$^{-1}$ for certain *trans* alkenyl ethers as reported by Warner and Lands.[19b] Position of the double bond was established by ozonizing VII and oxidatively decomposing the ozonolysis products by the method of Ackman, *et al.*[20] G.l.c. analysis of the product methyl esters showed the presence of the expected C_8 diester and the complete absence of the C_7 diester, which would have resulted if the double bond had shifted to give a positional isomer. The enol ether VII added methanol rapidly and quantitatively at room temperature in the presence of hydrochloric acid to re-form I[21]; it was also hydrogenated to give methyl 9-methoxynonanoate in good yields.

The cyclic acetal from ethylene glycol was considerably more stable and not subject to cracking under the conditions used. The infrared spectrum before and after treatment, under conditions known to produce enol ethers from dialkyl acetals, showed no enol ethers present. This stability was useful in the preparation of high-boiling ester derivatives, which otherwise would crack at the elevated temperatures necessary for distillation.

Experimental

Methyl 9,9-Dimethoxynonanoate (I).—A mixture consisting of methyl azelaaldehydate[22] (233.5 g., 1.25 moles), 500 ml. of methanol, 250 ml. of 2,2-dimethoxypropane, and 5 ml. of 5% methanolic hydrogen chloride was refluxed for 4 hr. The dimethoxypropane served as a water scavenger for the acetalation reaction similar to its use in the preparation of methyl esters.[23] To the product solution was added about 500 ml. of methylene chloride, and the solution was washed with water several times until the aqueous wash became neutral. Each water wash was backwashed with methylene chloride. This solution was distilled to remove methylene chloride, and the residue was distilled under reduced pressure through a 1 × 6 in. glass helices-packed column. There was recovered 271.8 g. (1.17 moles, 93.4% yield) of product distilling at 78–80° at 0.13 mm., $n^{30}D$ 1.4294. G.l.c. analyses did not indicate any detectable impurities.

Effect of Temperature and Reaction Time upon Selectivity of Acetal Alcoholysis.—Ester acetal I (15.0 g., 0.065 mole), *n*-hexyl alcohol (26.15 g., 0.260 mole), and potassium hydrogen sulfate (0.1 g.) were heated at a predetermined temperature for 12 hr. The removal of methanol was assured by using a steam-heated condenser between the reaction flask and the take-off head. Samples were withdrawn every 0.5 hr. for the first 3 hr., every hour for the next 4 hr., and at the end of the heating period. For samples, 2 ml. were taken up in methylene chloride and washed three times with water. The methylene chloride layer was dried over anhydrous sodium sulfate. After filtering off the sodium sulfate and removing solvent, g.l.c. analysis was carried out on each sample. An F and M Model 500 temperature programmed gas chromatograph with a 2-ft. silicone gum rubber column was used. Compositions obtained from g.l.c. analysis were plotted for each reaction temperature. Information taken from the composition curves are summarized in Table I. Conversions of 95% are obtained in 4 hr. at 75° with no ester acetal IV detected. None of the mixed acetal II was found, even with the starting material I still present in the mixture.

In a preparative run at 75° for 4 hr., there was obtained a 95% yield of crude methyl 9,9-(di-1-hexoxynonanoate). Distillation gave a pure product boiling at 115–116° (0.03 mm.), $n^{30}D$ 1.4440, $d^{20}{}_{20}$ 0.9046.

Anal. Calcd. for $C_{22}H_{44}O_4$; C, 71.25; H, 11.95. Found: C, 71.04; H, 11.79.

Cracking Procedure.—The acetal ester I (69.12 g., 0.298 mole) and potassium acid sulfate (0.20 g.) were heated in a three-necked round-bottom flask fitted with a capillary inlet for nitrogen, a thermometer, and a distillation head. Heating was carried out at 135–150° under reduced pressure for 7 hr. The product was taken up in methylene chloride and washed several times with water. After drying over anhydrous sodium sulfate, the solution was filtered and the solvent was stripped. Flash-distilled, the product left a polymeric residue of 23.3% based on starting material. The distillate contained 70.3% cracked product; the remainder was starting material and a trace of

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dimethyl azelate. The distillate was redistilled on a spinning band Podbielniak column without further condensation. The main fraction boiled at 107–109° (4.5 mm.), n^{30}D 1.4434, and contained 98.6% cracked product.

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 66.05; H, 10.08; hydroxylamine value, 200.2 g./equiv. Found: C, 66.14, H, 10.06; hydroxylamine value, 205.0 g./equiv.

G.l.c. analyses of the mixture during the cracking step showed two new peaks, believed to be the isomeric-substituted enol ether VII. Attempts to separate the isomers by fractional distillation were unsuccessful although *cis*- and *trans*-methyl propenyl ether have been successfully separated by this means.[24]

Methyl 9-Methoxynonanoate.—The enol ether VII (11.50 g. of 90.6% cracked products) was dissolved in 100 ml. of diethyl ether. Hydrogenation over 0.2 g. of platinum oxide was carried out at ambient temperature and 40 p.s.i. in a Parr low-pressure hydrogenation apparatus. The product was distilled through a spinning band Podbielniak column. The main fraction boiled from 109–110° (5.5 mm.), n^{30}D 1.4282. The purity was 98% calculated from g.l.c. data.

Anal. Calcd. for $C_{11}H_{22}O_3$: C, 65.30; H, 10.90; sapon. equiv., 202.3. Found: C, 65.15; H, 10.87; sapon equiv., 201.3.

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Synthesis of 5-Substituted Derivatives of 3-Acetamido-1-methyl-2,4-dioxopyrrolidine[1]

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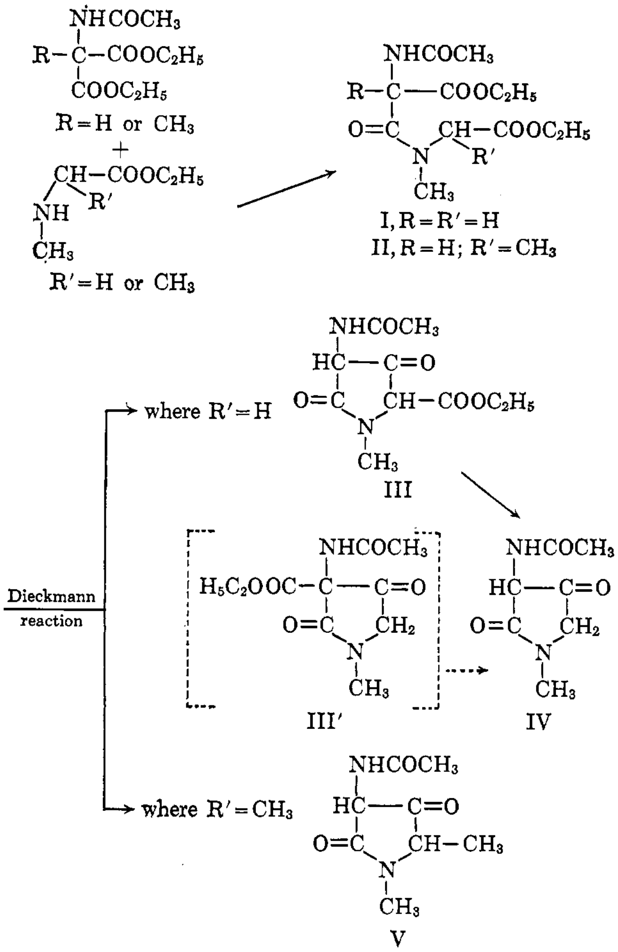
The structures of thiolutin and aureothricin, both yellow crystalline sulfur-containing antibiotics, were elucidated by Celmer and Solmons,[2] respectively, as 3-acetamido and 3-propionamido derivatives of 3-amino-5-methylpyrrolin-4-oxo[4,3-*d*]-1,2-dithiol (Ic). It is of interest that they are the first recognized examples of microbiologically active unsaturated lactams.

As part of investigation on the synthesis of thiolutin, the Dieckmann reaction of some N-(α-acetamido-α-ethoxycarbonylacetyl)-N-methylamino acid ethyl esters (I, $R = R' = H$; II, $R = H$, $R' = CH_3$) was carried out.

First, N-(α-acetamido-α-ethoxycarbonylacetyl)-N-methyl derivatives of glycine and alanine ethyl esters (I and II) were prepared from the corresponding amino acid esters and diethyl acetamidomalonates. Some 5-substituted 3-acetamido-1-methyl-2,4-dioxopyrrolidines (III, IV, and V) were prepared by the Dieckmann cyclization of the above ester derivatives. The product of this Dieckmann reaction of N-(α-acetamido-α-ethoxycarbonylacetyl)-N-methylglycine ethyl ester (I) was found to be 3-acetamido-5-ethoxycarbonyl-1-methyl-2,4-dioxopyrrolidine (III) and not 3-acetamido-3-ethoxycarbonyl-1-methyl-2,4-dioxopyrrolidine (III′), which is also a possibility. In this connection, compound III was found to be a useful intermediate for the preparation of α-amino-α'-methylamino-β-hydroxyglutaric acid. These 2,4-dioxopyrrolidines form a tautomeric system and derivatives of both ketonic and enolic tautomers were also prepared.

The sequence of reactions leading to 5-substituted derivatives of 3-acetamido-1-methyl-2,4-dioxopyrrolidine is shown in Scheme I.

Scheme I



The starting materials, N-methylamino acid esters, were prepared *via* the α-methylamino derivatives of acetonitrile from formaldehyde or of propionitrile from acetaldehyde. In the case of the N-methylalanine ethyl ester, isolation of the intermediate, α-methylaminopropionitrile, was necessary in order to reduce the by-product formation to a minimum during esterification of the nitrile.

The condensation of N-methylamino acid ethyl esters and diethyl acetamidomalonates was effected in xylene at a refluxing temperature by the dropwise addition of the ester into the boiling xylene solution of the acetamidomalonate so as to avoid the formation of diketopiperazines by self-condensation. Completion of the reaction required more than 24 hr. of heating. The

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(1) Part of this paper was read at the 11th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1958.

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