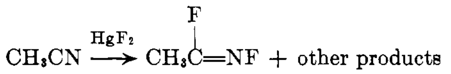

$$CH_3CN \xrightarrow{HgF_2} CH_3\overset{F}{\overset{|}{C}}{=}NF + \text{other products}$$

Experimental

Dichloromalononitrile and N-1,1-Trichlorocyanoacetimidoyl Chloride.—A solution of 33.0 g. of malononitrile (0.5 mole) and 500 ml. of water was added to a 1-l. flask equipped with stirrer, thermometer, Dry Ice–acetone reflux condenser, inlet tube, and external ice–water cooling bath. Chlorine gas (118.3 g., 1.67 moles) was introduced slowly with stirring over a period of 4 hr., taking care to keep the temperature at or below 5°. The cooling bath was removed and the stirring was continued another 3 hr., during which time the upper portion of the flask was heated gently with warm air in order to decompose the solid chlorine hydrate. The reaction mixture was then separated. The upper aqueous phase was evaporated to 3.2 g. of white solid, identified as ammonium chloride by infrared spectrum. It gave positive tests for ammonia and chloride ion. The lower, organic phase was fractionated. At atmospheric pressure, 46.9 g. of dichloromalononitrile was collected at 86–93°, with an additional 3.0 g. at 41° when the pressure was reduced to 105 mm. The total yield amounted to 74.0% based on malononitrile. Continuation of the distillation at 45 mm. yielded 8.9 g. (8.5% of theory) of N-1,1-trichlorocyanoacetimidoyl chloride boiling at 93–97°. Redistillation at 45 mm. furnished pure material at 97°.

Anal. Calcd. for $C_3Cl_4N_2$: C, 17.50; H, 0.00; Cl, 68.89; N, 13.61; mol. wt., 205.9. Found: C, 17.23; H, 0.05; Cl, 68.90; N, 13.95; mol. wt., 226.9 (ebulioscopic in carbon tetrachloride).

Both dichloromalononitrile and N-1,1-trichlorocyanoacetimidoyl chloride are lachrymatory and extremely irritating.

Dichlorocyanoacetamide.—The operations in the above procedure were carried out with the following changes: 150 ml. of water and 150 ml. of chloroform were used. After reaction, the aqueous phase yielded 8.2 g. of ammonium chloride upon evaporation. The organic phase yielded 5.7 g. of white solid (III) when diluted with 200 ml. of hexane. Evaporation of the filtrate at room temperature yielded only a small amount of oily solid. After recrystallization of III from ethanol–water, it melted at 90–93°.

Anal. Calcd. for $C_3H_2Cl_2N_2O$: C, 23.55; H, 1.32; Cl, 46.36; N, 18.31. Found: C, 23.90; H, 1.58; Cl, 46.39; N, 18.36.

Reaction with Sodium Iodide.—A weighed sample (0.2–0.3 g.) of dichloromalononitrile or N-1,1-trichlorocyanoacetimidoyl chloride was added to 10 ml. of a 20% solution of sodium iodide in acetone. After about 10 min. the mixture was filtered through a weighed fine-fritted funnel. The filter cake was washed thoroughly with acetone until all of the iodine was removed. The funnel was then dried at 110° and reweighed to determine sodium chloride. The acetone filtrate was diluted with water and titrated with 0.1 *N* sodium thiosulfate to a starch end point to determine iodine.

Conversion of Dichloromalononitrile to N-1,1-Trichlorocyanoacetimidoyl Chloride.—Five grams of dichloromalononitrile was treated with 2.6 g. of chlorine at room temperature in an apparatus which allowed reflux of chlorine. After the reaction had proceeded for about 2 hr., the mixture was allowed to stand overnight to permit evaporation of unused chlorine. Based on the infrared spectrum of the product mixture, the reaction had converted 40% of I into II. No other constituents were evident from the spectrum.

Conversion of N-1,1-Trichlorocyanoacetimidoyl Chloride to Dichloromalononitrile.—A solution of 2.0 g. of pure N-1,1-trichlorocyanoacetimidoyl chloride (II) in 10 ml. of dimethylformamide was added dropwise to a stirred mixture of 2.0 g. of zinc powder in 10 ml. of sulfolane, which was used as a moderator for the reaction. The reaction flask was kept at 50° with a water bath, and a reduced pressure of 20 mm. was maintained throughout the reaction. The effluent from the flask was fed through a cold trap at −78°. The contents of the trap (0.31 g.) consisted of nearly pure dichloromalononitrile, as shown by infrared spectral comparison.

Acknowledgment.—The authors express their gratitude to Dr. R. A. Henry for his helpful suggestions and encouragement.

Ketene Acetals. I. A New Synthesis of Ketene Acetals and Ortho Esters[1]

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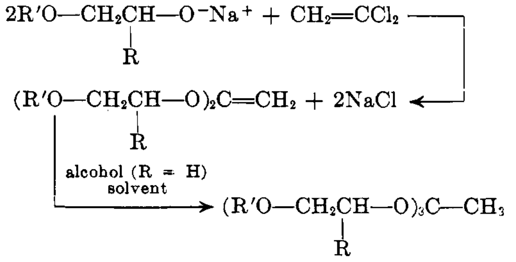
We have found that ketene acetal and ortho ester derivatives of β-alkoxy alcohols may be synthesized by a simple one-step process which involves the slow addition of vinylidene chloride to a sodium β-alkoxy alcoholate, dissolved or suspended in a solvent. This process results in an exothermic reaction which yields either the ketene acetal or ortho ester derivative of the alcohol, with the concomitant precipitation of solid sodium chloride. The resultant product depends on the solvent conditions used, and the steric nature of the β-alkoxy alcohol.



$$2R'O{-}CH_2\underset{R}{\underset{|}{C}}H{-}O^-Na^+ + CH_2{=}CCl_2 \longrightarrow (R'O{-}CH_2\underset{R}{\underset{|}{C}}H{-}O)_2C{=}CH_2 + 2NaCl$$

$$(R'O{-}CH_2\underset{R}{\underset{|}{C}}H{-}O)_2C{=}CH_2 \xrightarrow[\text{solvent}]{\text{alcohol (R = H)}} (R'O{-}CH_2\underset{R}{\underset{|}{C}}H{-}O)_3C{-}CH_3$$

When tetrahydrofurfuryl alcohol was used in this synthesis as both the reactant and solvent, the ortho acetate (IX) was obtained in a 53.4% yield. However, when diethylene glycol dimethyl ether was used as the solvent, the ketene acetal (II) was obtained in a 48.3% yield.

Using 2-ethoxyethanol (Cellosolve solvent), or diethylene glycol monomethyl ether (Methyl Carbitol solvent), as both the reactant and solvent, only the corresponding ortho acetates (VII and VIII) were isolated in yields of 56.6 and 40.5%, respectively. However, when 1-methoxypropanol-2 (Ucar solvent LM) was used as both the reactant and solvent, the ketene acetal derivative (I) was obtained in a 46.8% yield, thus demonstrating the steric effect of the α-methyl group ($R = CH_3$).

Attempts to prepare ketene acetals or ortho esters from simple alcohols, such as methanol, ethanol, 1-butanol, and 2-butanol in this process, resulted in failure as neither the exotherm nor salt precipitation was observed.

The methyl ketene acetal derivative (III) of 1-methoxypropanol-2 was obtained in an 8.3% yield when 1,1-dichloropropene-1 was used in the place of vinylidene chloride. Similarly, using 1,1,2-trichloroethylene and tetrahydrofurfuryl alcohol, the chloroortho ester (X) was obtained in a 13.6% yield. A tabulation of ketene acetals and ortho esters made by this synthesis, together with their analyses and physical properties, is found in Table I.

The assignment of structures was based on the elemental analyses, ebullioscopic molecular weight deter-

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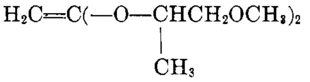
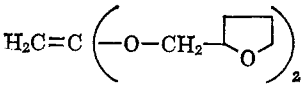
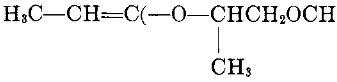
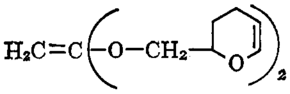
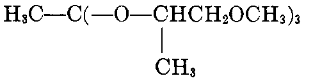
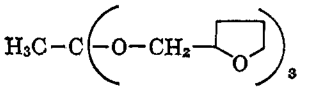
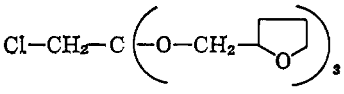
[1] Presented in part at the 146th National Meeting of the American Chemical Society, Denver, Colo., Jan., 1964.

TABLE I

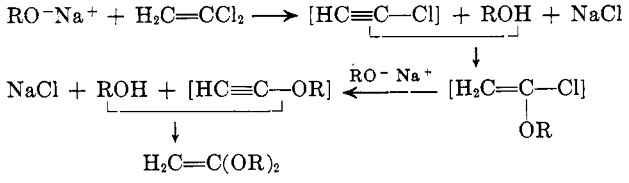
NEW KETENE ACETALS AND ORTHO ESTERS

Compd. no.	Structure	Solvent[a]	Yield, %	B.p., °C. (mm.)	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Formula	Mol. wt. Calcd.	Mol. wt. Found
I	 $H_2C{=}C(-O-\underset{\textstyle CH_3}{\underset{\mid}{C}}HCH_2OCH_3)_2$	A	46.8	58–59 (3.0)	58.9	9.9	58.8	10.1	$C_{10}H_{20}O_4$	204	214
II		D	48.3	109–110 (2.0)	63.1	8.8	62.9	8.9	$C_{12}H_{20}O_4$	228	223
III	 $H_3C-CH{=}C(-O-\underset{\textstyle CH_3}{\underset{\mid}{C}}HCH_2OCH_3)_2$	A	8.3	81–83 (0.1)	60.6	10.1	60.4	9.9	$C_{11}H_{22}O_4$	218	205
IV	$H_2C{=}C(-O-CH_2CH_2OCH_3)_2$	D	51.4	78–80 (2.0)	54.5	9.16	54.5	9.05	$C_8H_{16}O_4$	176	178
V		D	28.4	149–150 (2.4)	66.7	7.94	66.5	8.05	$C_{14}H_{20}O_4$	252	236
VI	 $H_3C-C(-O-\underset{\textstyle CH_3}{\underset{\mid}{C}}HCH_2OCH_3)_3$	B	74.0	78–80 (0.3)	57.1	10.3	56.9	10.3	$C_{14}H_{30}O_6$	294	290
VII	$H_3C-C(-O-CH_2CH_2OCH_2CH_3)_3$	A	56.6	98–100 (0.5)	57.1	10.3	57.2	10.3	$C_{14}H_{30}O_6$	294	281
VIII	$H_3C-C[-O-(CH_2CH_2O)_2-CH_3]_3$	A	40.5	170–172 (0.5)	53.5	9.5	53.1	9.5	$C_{17}H_{36}O_9$	384	376
IX		A	53.4	151–154 (0.5)	61.9	9.1	62.3	9.3	$C_{14}H_{24}O_6$	330	326
X		A	13.6	145–160 (1.5)	56.0 Cl, 9.8	8.0	55.8 Cl, 9.6	8.2	$C_{17}H_{29}ClO_6$	364	321

[a] A = corresponding alcohol; B = product of I with the corresponding alcohol; D = diethylene glycol dimethyl ether.

minations, and infrared and n.m.r. spectra. The ketene acetals all showed a very strong (sharp) infrared absorption band at about 1640 cm.$^{-1}$, which is characteristic of the ketene acetal structure.[2] The n.m.r. spectrum of ketene di(2-methoxyethyl)acetal (IV) lends very strong support for the assignment of the ketene acetal structure (Fig. 1).

Acid-catalyzed hydrolysis of the orthoacetate derivative (VII) of 2-ethoxyethanol (Cellosolve solvent) gave the expected products, as shown by a vapor phase chromatographic analysis of the product mixture. The postulated mechanism for this reaction is illustrated by the following scheme.



One mole of sodium alcoholate dehydrochlorinates the vinylidene chloride to yield 1 mole of chloroacetylene, alcohol, and sodium chloride. The alcohol and chloroacetylene then react to form an intermediate, 1-chloro-1-alkoxyethene, which in turn dehydrochlorinates with an additional mole of sodium alcoholate to yield 1 mole of alkoxyacetylene, alcohol, and sodium chloride. Reaction of the alkoxyacetylene with the alcohol results in the formation of the observed ketene acetal product. At this point the ketene acetal may react with an alcohol solvent to yield an ortho ester.

The reaction mechanism outlined above is similar to a mechanism recently published by Flynn, Badiger, and Truce[3] in which sodium *t*-butylmercaptide reacts with vinylidene chloride to give a mixture of 1,2-bis(*t*-butylmercapto)ethenes. The versatility and mechanism of this novel reaction are currently under active study and additional work will be reported in subsequent publications.

Experimental

The ketene acetals of Table I were all synthesized by essentially the same procedure. This was also true of the ortho esters, with one exception which is fully described below. The following will therefore serve as a general description for the synthesis of either a ketene acetal, or an ortho ester.

Ketene Di(2-methoxyethyl) Acetal (IV).—To a solution of 2-methoxyethanol (Methyl Cellosolve solvent, 304 g., 4.00 moles) in diethylene glycol dimethyl ether (500 g.), was added metallic sodium (92.0 g., 4.00 g.-atoms) at a temperature of 100–130°, and under a nitrogen atmosphere. When solution of the sodium was complete, 1,1-dichloroethene (vinylidene chloride, 243 g., 2.51 moles) was slowly added dropwise to the above mixture at 130° with rapid stirring and under a nitrogen atmosphere. The temperature of the reaction mixture increased from 130 to 170° during the addition of the vinylidene chloride, with the concomitant precipitation of solid sodium chloride. The reaction mixture was then vacuum filtered to give a brown filtrate and tan solid sodium chloride. The solid was washed several times with anhydrous ether and oven-dried overnight to give 225 g. (96% based on the sodium) of sodium chloride.

The ether washings and brown filtrate were combined and vacuum distilled to yield, as the higher boiling product fraction, 181 g. (1.03 moles, 51.4%, b.p. 78–80° at 2.0 mm.) of ketene di(2-methoxyethyl) acetal.

Anal. Calcd. for $C_8H_{16}O_4$: C, 54.5; H, 9.16; mol. wt., 176. Found: C, 54.5; H, 9.05; mol. wt., 178 (Menzies–Wright in benzene).

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(2) S. M. McElvain and R. E. Starn, Jr., *J. Am. Chem. Soc.*, **77**, 4571 (1955).

(3) J. Flynn, Jr., V. V. Badiger, and W. E. Truce, *J. Org. Chem.*, **28**, 2298 (1963).

The infrared spectrum showed a very strong C=C absorption band at 1640 cm.$^{-1}$. The n.m.r. spectrum (Fig. 1) showed a typical A_2B_2 splitting for the —CH$_2$— protons at a midpoint of τ 6.39 (8), —O—CH$_3$ protons at 6.76 (6), and =CH$_2$ protons at 7.00 (2). This spectrum was run on a Varian A-60 high resolution n.m.r. spectrometer, at a frequency of 60 Mc./sec., using Si(CH$_3$)$_4$ as the internal standard and at a 30% concentration in CCl$_4$. The numbers represent τ-values as defined by Jackman.[4] Values in parentheses indicate the ratio of the integrated areas under the peaks, and are in complete agreement with the ketene acetal structure.

Ketene Di(1-methoxy-2-propyl) Acetal (I).—To 1-methoxy-2-propanol (Ucar solvent LM, 1000 g., 11.1 moles), under a nitrogen atmosphere, was added metallic sodium (100 g., 4.35 g.-atoms) to form a solution of the sodium alcoholate in the alcohol. Vinylidene chloride (300 g., 3.10 moles) was slowly added to the above solution at an initial temperature of 90°, with rapid stirring and under a nitrogen atmosphere. During the addition of the vinylidene chloride, the temperature of the reaction mixture increased from 90 to 140°, with the concomitant precipitation of solid sodium chloride. The reaction mixture was then filtered to yield a tan-colored filtrate and solid sodium chloride. The solid was washed several times with anhydrous ether and oven-dried overnight to give 235 g. (92.5% yield based on the sodium) of sodium chloride. The liquid filtrate was vacuum distilled to yield 206 g. (1.01 moles, 46.6%, b.p. 58–59° at 3.0 mm.) of ketene di(1-methoxy-2-propyl) acetal as the higher boiling product fraction; infrared spectrum: $\nu_{C=C}$ 1650 cm.$^{-1}$ (very strong).

Anal. Calcd. for $C_{10}H_{20}O_4$: C, 58.9; H, 9.9; mol. wt., 204. Found: C, 58.8; H, 10.1; mol. wt., 214 (Menzies–Wright in benzene).

Tri(2-ethoxyethyl) Orthoacetate (VII).—To 2-ethoxyethanol (Cellosolve solvent, 1000 g., 11.1 moles), under a nitrogen atmosphere, was added metallic sodium (100 g., 4.35 moles) to form a solution of the sodium alcoholate in the alcohol. Vinylidene chloride (250 g., 2.58 moles) was slowly added to the above solution at an initial temperature of 100°, with rapid stirring and under a nitrogen atmosphere. During the addition of the vinylidene chloride, the temperature of the reaction mixture increased from 100 to 160°, with the concomitant precipitation of solid sodium chloride. Filtration of this reaction mixture gave a total of 230 g. (after ether washing and drying, 91% based on the sodium) of sodium chloride. Vacuum distillation of the liquid filtrate gave tri(2-ethoxyethyl) orthoacetate (362 g., 1.23 moles, 56.6%, b.p. 98–100° at 0.5 mm.) as the higher boiling product fraction; infrared spectrum: the —OH, C=O, and C=CH$_2$ absorptions were completely absent.

Anal. Calcd. for $C_{14}H_{30}O_6$: C, 57.1; H, 10.3; mol. wt., 294. Found: C, 57.2; H, 10.3; mol. wt., 281 (Menzies–Wright in benzene).

The acid-catalyzed hydrolysis of the above orthoacetate gave the expected products, as shown by a vapor phase chromatogram of the distilled product mixture.

Compound	Theor. wt. in product mixture, %	Obsd. v.p.c. area in mixture, %
2-Ethoxyethanol	57.7	60.8
2-Ethoxyethyl acetate	42.3	39.2

Tri(1-methoxy-2-propyl) Orthoacetate (VI).—Ketene di(1-methoxy-2-propyl) acetal (I, 51.0 g., 0.25 mole) and 1-methoxy-2-propanol (22.5 g., 0.25 mole) were placed in a stoppered 250-ml. erlenmeyer flask. Two drops of 85% phosphoric acid were then added to the above solution, whereupon the temperature of the contents rose from about 20 to over 70°. The tightly stoppered flask was then kept at room temperature overnight. Two small pellets of potassium hydroxide were added and the mixture was vacuum distilled to yield tri(1-methoxy-2-propyl) orthoacetate as the major product fraction (54 g., 0.184 mole, 74%, b.p. 78–80° at 0.25 mm.); infrared spectrum: the —OH, C=O, and C=CH$_2$ absorptions were completely absent.

Anal. Calcd. for $C_{14}H_{30}O_6$: C, 57.1; H, 10.3; mol. wt., 294. Found: C, 56.9; H, 10.3; mol. wt., 290 (Menzies–Wright in benzene).

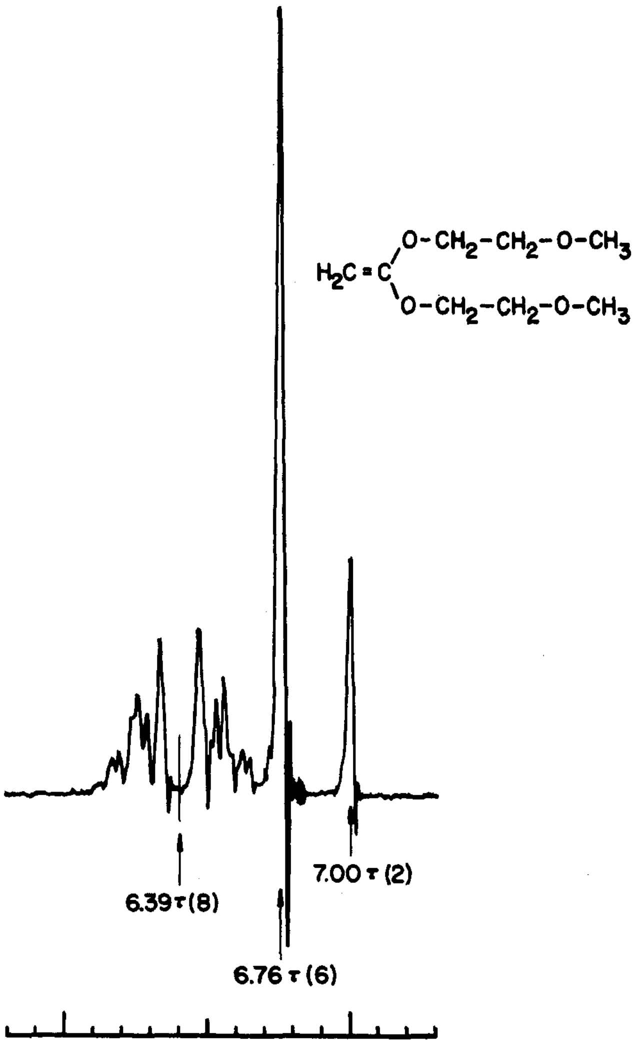

Fig. 1.—N.m.r. spectrum of ketene di(2-methoxyethyl) acetal (IV).

Acknowledgment.—It is a pleasure to acknowledge the laboratory assistance of L. J. Ford, and the analytical services of Johanna Holm, H. L. Thornburg, and R. A. Thursack.

The Synthesis of Certain 16α-Substituted Derivatives of the 3-Methyl Ethers of 16β-Cyanoestrone and 16β-Cyanoestradiol

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Received April 7, 1964

The possibility that modified estrogen-type compounds might be useful hypocholesterolemic agents has received considerable research attention in recent years.[1] In particular, mono- and disubstitution at the 16-position of estrone, estradiol, and their 3-etherified derivatives has been reported to give com-

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[4] S. L. M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959.

[1] See V. A. Drill and B. Riegel, *Recent Progr. Hormone Res.*, **14**, 50 (1958), for a brief resume of the rationale to this approach.