were conducted with linoleic and linolenic acids autoxidized at 20° to a peroxide content of about 7-8% or methyl elaidate autoxidized at 35° to a peroxide content of 18%. With linoleic acid and methyl elaidate, a fourfold increase in peroxide content was achieved; with linolenic acid, the increase was twofold.

PHILADELPHIA 18, PENNA.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Reactions of Orthoesters with Active Methylene Compounds

BY REUBEN G. JONES

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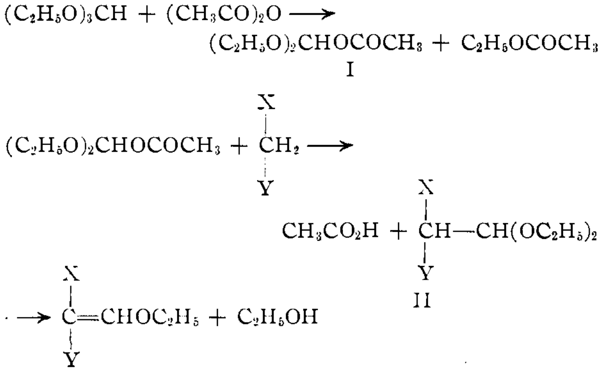
Ethyl orthoformate was found to react directly with a number of active methylene compounds in the absence of acetic anhydride to give the corresponding ethoxymethylene derivatives and ethanol. In the reaction with ethyl cyanoacetate, the presence of a little sulfuric acid decreased the yield, while the presence of a little sodium methylate appeared to increase the yield of ethyl ethoxymethylenecyanoacetate. Ethyl triethoxyacetate reacted with ethyl oxalacetate in the absence of acetic anhydride to give triethyl α-ethoxy-γ-ketoaconitate. The possible mechanism of the reaction is commented upon briefly.

Ethyl orthoformate in the presence of acetic anhydride reacts with a variety of compounds containing active methylene groups such as acetoacetic ester, acetylacetone, malononitrile, etc., to form the ethoxymethylene derivatives (III).[1] Post and Erickson[2] and more recently, Fuson, Parham and Reed[3] have presented good evidence that this reaction involves first a condensation of ethyl orthoformate with acetic anhydride to form diethoxymethyl acetate (I). This compound then alkylates the active methylene carbon to give the acetal (II), from which a mole of alcohol is finally eliminated to yield III.



$$(C_2H_5O)_3CH + (CH_3CO)_2O \longrightarrow \underset{\text{I}}{(C_2H_5O)_2CHOCOCH_3} + C_2H_5OCOCH_3$$

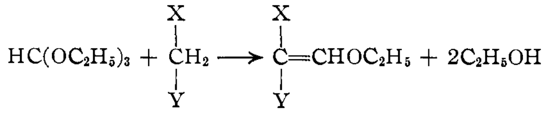
$$(C_2H_5O)_2CHOCOCH_3 + \overset{X}{\underset{Y}{CH_2}} \longrightarrow CH_3CO_2H + \underset{\text{II}}{\overset{X}{\underset{Y}{C}}H\text{—}CH(OC_2H_5)_2}$$

$$\longrightarrow \overset{X}{\underset{Y}{C}}\text{=}CHOC_2H_5 + C_2H_5OH$$

III X and Y = CO_2R, $COCH_3$, CN, etc.

That this may not be the only mechanism by which ortho esters can react with active methylene compounds, has become evident from a number of observations in this Laboratory and elsewhere.[4]

The purpose of this paper is to report that ethyl orthoformate will undergo reaction with a number of active methylene compounds *in the absence of acetic anhydride* to give the ethoxymethylene derivatives (III). The two reactants are simply heated together at about 140° for several hours. This reaction can be represented by the equation



$$HC(OC_2H_5)_3 + \overset{X}{\underset{Y}{CH_2}} \longrightarrow \overset{X}{\underset{Y}{C}}\text{=}CHOC_2H_5 + 2C_2H_5OH$$

III

Thus, when ethyl acetoacetate and ethyl orthoformate were heated at 140–150° for eight hours, an 18% yield of ethyl ethoxymethyleneacetoacetate[5] was isolated. The only other product, aside from the unchanged starting materials, was ethanol. In a like manner, ethyl orthoformate and ethyl cyanoacetate underwent reaction on heating at 140° for several hours to give ethanol and ethyl ethoxymethylenecyanoacetate[6] (20% yield). Ethyl oxalacetate and ethyl orthoformate gave a 30% yield of ethyl ethoxymethyleneoxalacetate.[1] Malononitrile and ethyl orthoformate gave a 66% yield of ethoxymethylenemalononitrile.[7] In this latter condensation an interesting side reaction took place. In addition to ethanol, large quantities of diethyl ether and ethyl formate were obtained, and only a little unchanged ethyl orthoformate was recovered. It is surprising that malononitrile can cause this decomposition of ethyl orthoformate into ether and ethyl formate, although it is well known that such strongly acidic substances as hydrogen chloride[8] and boron trifluoride[9] can do so. Diethyl malonate failed to react with ethyl orthoformate even after prolonged heating at 150°.

The yields of ethoxymethylene compounds are considerably lower when no acetic anhydride is used in the reactions. At first thought this may seem to indicate that an equilibrium is established so that the reaction proceeds only part way, but if acetic anhydride is added the equilibrium is shifted by removal of the alcohol with formation of ethyl acetate, and the reaction goes to completion

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(1) For leading references see R. G. Jones, THIS JOURNAL, **73**, 3684 (1951).

(2) H. W. Post and E. R. Erickson, *J. Org. Chem.*, **2**, 260 (1937).

(3) R. C. Fuson, W. E. Parham and L. J. Reed, *ibid.*, **11**, 194 (1946).

(4) J. Pascual Vila and M. Ballester, *Anales real soc. fis. y quim.*, **45B**, 87 (1949) [*C. A.*, **44**, 3884 (1950)], have found that ethyl orthoacetate reacts directly with malononitrile to yield methylethoxymethylenemalononitrile.

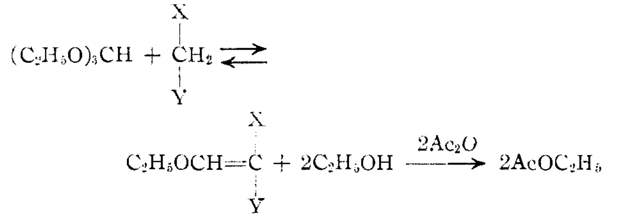
(5) L. Claisen, *Ann.*, **297**, 1 (1897).

(6) M. E. G. de Bellemont, *Bull. soc. chim.*, **25**, 18 (1901).

(7) T. Passalacqua, *Gazz. chim. ital.*, **43**, II, 566 (1913) [*C. A.*, **8**, 1273 (1914)].

(8) W. Lippert, *Ann.*, **276**, 177 (1893).

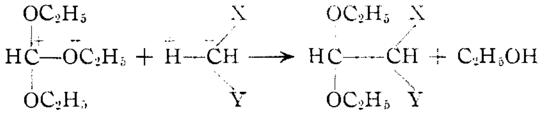
(9) J. McKenna and F. Sowa, THIS JOURNAL, **60**, 124 (1938).



$$(C_2H_5O)_3CH + \underset{\displaystyle Y}{\overset{\displaystyle X}{CH_2}} \rightleftarrows C_2H_5OCH{=}\underset{\displaystyle Y}{\overset{\displaystyle X}{C}} + 2C_2H_5OH \xrightarrow{2Ac_2O} 2AcOC_2H_5$$

This essentially is the mechanism first proposed by Claisen.[5] Such a mechanism, however, is not in accordance with the facts, for the reactions are *not* reversible as pictured above, at least under the conditions of the experiment. Thus, when a mixture of ethyl ethoxymethyleneacetoacetate and ethanol was heated under reflux for eight hours, no trace of ethyl orthoformate or ethyl acetoacetate could be isolated, but the starting materials were quantitatively recovered.

Most probably the condensation of orthoformate with an active methylene carbon operates through an ionic mechanism. The ortho ester undoubtedly is capable of becoming polarized,[10] especially under the influence of an active (acidic) methylene compound.



Therefore, it might be expected that the reaction rate would be influenced by either a strong acid or a strong base. In order to test the catalytic effect of acid and base, some preliminary experiments were carried out on the ethyl orthoformate–ethyl cyanoacetate reaction. In each of three flasks was placed an equal molar mixture of ethyl orthoformate and ethyl cyanoacetate. To the first was added no catalyst, to the second was added a small quantity of sulfuric acid, and to the third was added a small quantity of sodium methoxide. The three were heated in the same bath for the same length of time, and then each mixture was fractionally distilled. The experiment was repeated several times with fairly consistent results. On the basis of the equation

$$(C_2H_5O)_3CH + CNCH_2CO_2C_2H_5 \longrightarrow \underset{\text{V}}{C_2H_5OCH{=}C(CN)CO_2C_2H_5} + 2C_2H_5OH$$

the yield of V from the reaction mixture containing no catalyst was about 22%, and the yield of ethanol was 26%. From the mixture containing sulfuric acid, the yield of V was about 15%, and the yield of ethanol was 18%. From the mixture containing sodium methoxide, the yield of V was about 25% and the yield of ethanol 40%. The reaction containing sodium methoxide was not as clean-cut as the other two in that a relatively large quantity of non-volatile, resinous material was formed. This probably accounts for the large discrepancy between the yields of V and ethanol in this case. Although the differences are not great they appear to be significant, and the indications are that the presence of strong acid definitely retards the reaction while the presence of strong base probably has a slight promoting effect.

The ortho ester reaction with active methylene compounds is not confined to orthoformates. Ethyl triethoxyacetate was found to undergo reaction with ethyl oxalacetate in the absence of acetic anhydride to give triethyl α-ethoxy-γ-ketoaconitate[11] in 20% yield. This, in addition to the first example (orthoacetate with malononitrile) reported by Pascual Vila and Ballester,[4] may indicate that the reaction is fairly general.

Experimental

Reaction of Ethyl Orthoformate with Ethyl Acetoacetate.—Ethyl orthoformate 52 g. (0.35 mole) and ethyl acetoacetate, 32 g. (0.25 mole) were heated together under reflux for eight hours. Distillation of the resulting mixture gave 0.5 g. of liquid, b.p. 55–75°; 4.5 g. of ethanol, b.p. 75–80°; 1.0 g. of liquid, b.p. 80–140°; 60 g. of liquid which was apparently a mixture of ethyl orthoformate and ethyl acetoacetate, b.p. 50–90° (15 mm.); 4 g. of liquid, b.p. 90–140° (15 mm.) and 9.5 g. of ethyl ethoxymethyleneacetoacetate, b.p. 140–145° (14 mm.). After redistillation there was obtained 8.0 g. (18% yield) of pure ethyl ethoxymethyleneacetoacetate. It was characterized by conversion to the copper salt, m.p. 154–155° (lit.[5] 156°). The melting point was not depressed when mixed with the copper salt prepared from an authentic sample of ethyl ethoxymethyleneacetoacetate.[5]

Reaction of Ethyl Orthoformate with Malononitrile.—A mixture of 34 g. (0.50 mole) of malononitrile and 111 g. (0.75 mole) of ethyl orthoformate was heated in an oil-bath at 140° under reflux for four hours. The resulting dark liquid was fractionally distilled first at atmospheric pressure, later under reduced pressure, using a small packed column, and the following fractions were obtained: 28 g., b.p. 35–55°, identified as a mixture of diethyl ether and ethyl formate; 4 g., b.p. 55–75°; 29 g., b.p. 75–80°, identified as ethanol; 1 g., b.p. 80–140°; 20 g., b.p. 140–145°, identified as ethyl orthoformate; 10 g., b.p. 95–105° (10 mm.), identified as malononitrile; and 40 g., b.p. 140–145° (10 mm.), m.p. 67°, which was ethoxymethylenemalononitrile.[7] Five grams of black residue remained in the distilling flask. In this experiment the yield of ethoxymethylenemalononitrile was 66%, or, on the basis of unrecovered malononitrile, 93%.

In another experiment similar to the above the mixture was heated at 140° under reflux for four hours and then for an additional two hours during which time the volatile constituents were allowed to distil. There was obtained 51 g. of ethyl ether and ethyl formate, b.p. 35–55°; 32 g. of ethanol, b.p. 75–80°; 2 g. of ethyl orthoformate, b.p. 130–150°; 9.5 g. of malononitrile, b.p. 75–80° (3 mm.) and 40 g. of ethoxymethylenemalononitrile.

When a mixture of 34 g. of malononitrile, 111 g. of ethyl orthoformate and 125 g. of acetic anhydride was heated on the steam-bath for four hours then in a bath at 140° for two hours during which time the volatile products were allowed to distil, there was obtained 60.0 g. (98.5% yield) of ethoxymethylenemalononitrile; b.p. 140–145° (10 mm.).

Reactions of Ethyl Orthoformate with Ethyl Cyanoacetate.—A mixture of 56.5 g. (0.50 mole) of ethyl cyanoacetate and 74.0 g. (0.50 mole) of ethyl orthoformate was heated under reflux in a bath at 140° for eight hours. The liquid was carefully fractionated and the following products with yields (average of two experiments) were obtained: ethanol, 12 g. (b.p. 75–80°); ethyl orthoformate, 47.5 g. (b.p. 140–147°); ethyl cyanoacetate, 39 g. (b.p. 78–83° at 4 mm.); ethyl ethoxymethylenecyanoacetate,[6] 19 g., b.p. 150–155° (5 mm.), m.p. 51–53°, non-volatile residue 4 g.

The above experiment was repeated except that 1 g. of concentrated sulfuric acid was added to the mixture at the beginning of the reaction. The products with yields (average of two experiments) were: ethyl formate, 3.3 g. (b.p. 53–55°); ethanol, 8.5 g. (b.p. 75–80°); ethyl orthoformate, 46 g. (b.p. 140–147°); ethyl cyanoacetate, 48 g. (b.p. 83–88° at 6 mm.); ethyl ethoxymethylenecyanoacetate, 12.8 g. (m.p. 51–53°); residue, 2 g.

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(10) Evidence of this is found in the facile ortho ester interchange reactions reported by H. W. Post and E. R. Erickson, THIS JOURNAL, **55**, 3851 (1933).

(11) R. G. Jones, *ibid.*, **73**, 5168 (1951).

The experiment was again repeated except that 1.0 g. of sodium methoxide was added to the mixture instead of the sulfuric acid. The products and yields (average of four experiments) were: ethanol, 18.3 g.; ethyl orthoformate, 40.9 g.; ethyl cyanoacetate, 27.2 g.; ethyl ethoxymethylenecyanoacetate, 20.1 g.; residue, 14 g.

Reaction of Ethyl Orthoformate with Ethyl Oxalacetate.—A mixture of 65 g. (0.44 mole) of pure, freshly distilled ethyl orthoformate and 47 g. (0.25 mole) of ethyl oxalacetate was heated in an oil-bath at 140° under reflux for eight hours. The liquid was distilled under reduced pressure and collected in two fractions. The first fraction b.p. up to 90° (10 mm.) was collected in a cold trap, and the second was taken up to 200° (2 mm.). A higher boiling residue, 20 g., remained in the flask. The first fraction was distilled through a packed column to give the following: 0.5 g., b.p. 55–75°; 18 g., b.p. 75–80°, identified as ethanol; 0.5 g., b.p. 80–142°; and 35 g., b.p. 142–144° identified as ethyl orthoformate. The higher boiling fraction was again distilled through a Vigreux column and 14 g. of liquid, b.p. 95–100° (2 mm.), was obtained which was thought to be ethyl oxalacetate. Following this, 17 g. (29% yield) of ethyl ethoxymethyleneoxalacetate[1] was obtained, b.p. 150–155° (0.7 mm.). This was characterized by conversion to the copper salt, m.p. 230–231° (uncor.). The meltin point was unchanged when mixed with the copper salt prepared from an authentic sample of ethyl ethoxymethyleneoxalacetate.[1]

In a duplicate experiment 22.5 g. (0.12 mole) of ethyl oxalacetate and 22.5 g. (0.15 mole) of ethyl orthoformate were heated together at 140° for two hours. The yield of ethyl ethoxymethyleneoxalacetate was 9.5 g. (32.5%).

Ethyl Orthoformate and Diethyl Malonate.—A mixture of 0.5 mole of ethyl orthoformate and 0.5 mole of diethyl malonate was heated under reflux for eight hours. There was no evidence that any reaction took place. Reaction also failed to take place in similar experiments in which 1 g. of sulfuric acid or 1 g. of sodium methoxide was added to the mixture. In each case the starting materials were recovered almost quantitatively by fractional distillation.

When mixtures of 0.25 mole of diethyl ethoxymethylenemalonate and 1.25 mole of absolute ethanol were heated either alone or in the presence of 1 g. of sulfuric acid or 1 g. of sodium methoxide under reflux for eight hours no reaction took place. The starting materials were recovered quantitatively.

Heating Ethyl Orthoformate with Ethyl β-Acetoxycrotonate.—A mixture of 74 g. (0.5 mole) of ethyl orthoformate and 86 g. (0.5 mole) of ethyl β-acetoxycrotonate[12] was heated under reflux for three hours. The liquid became colored pale yellow but no reaction appeared to take place. After careful fractionation through a packed column there was obtained 72 g. (97%) of unchanged ethyl orthoformate, b.p. 138–145° and 80 g. (93%) of unchanged ethyl β-acetoxycrotonate, b.p. 80–88° (8 mm.).

The above experiment was repeated except that 2 ml. of boron trifluoride etherate was added. After fractionation of the liquid there was obtained 50 g. of distillate, b.p. 35–55°, which was identified as a mixture of ethyl ether and ethyl formate; 9 g. of ethyl orthoformate, b.p. 130–150°, and 75 g. (87%) of unchanged ethyl β-acetoxycrotonate, b.p. 86–88° (8 mm.).

This is evidence that ethyl β-acetoxycrotonate cannot be an intermediate in the reaction of ethyl acetoacetate with ethyl orthoformate and acetic anhydride to give ethyl ethoxymethyleneacetoacetate.

Reaction of Ethyl Triethoxyacetate with Ethyl Oxalacetate.—Fifty-five grams (0.25 mole) of ethyl triethoxyacetate and 47 g. (0.25 mole) of ethyl oxalacetate were heated together under reflux in an oil-bath at 140° for eight hours. Distillation of the reaction mixture gave 8.0 g. of ethanol, b.p. 76–80°; 2.0 g. of liquid, b.p. up to 85° (8 mm.); 65 g. of a mixture of unreacted ethyl oxalacetate and ethyl triethoxyacetate, b.p. 85–120° (8 mm.); and 18 g. of liquid, b.p. 170–185° (2 mm.). The latter, after redistillation, yielded 16 g. (20%) of ethyl α-ethoxy-γ-ketoaconitate,[11] b.p. 166–168° (1 mm.). This product was characterized by conversion of a sample to the copper salt of ethyl dioxalacetate, m.p. 172–173° (lit.[11] 174–175°). It was further characterized by reaction with hydrazine hydrochloride to yield triethyl 3,4,5-pyrazoletricarboxylate, m.p. 90–91°. When mixed with an authentic sample (see below) the melting point was also 90–91°.

Triethyl 3,4,5-Pyrazoletricarboxylate.—To a solution of 3 g. (0.03 mole) of hydrazine dihydrochloride in 20 ml. of water was added 7.9 g. (0.025 mole) of ethyl α-ethoxy-γ-ketoaconitate[11] followed by 25 ml. of ethanol. The mixture was shaken, and it became warm. After heating on the steam-bath for about 10 minutes the mixture was evaporated under vacuum to remove the alcohol. Water, 25 ml., was added, and the solution was extracted with two 50-ml. portions of ether. The ether solution was dried with magnesium sulfate and evaporated leaving a sirup which soon crystallized. The crude yield of triethyl 3,4,5-pyrazoletricarboxylate was 6.8 g. (95%) and after recrystallization from a benzene–petroleum ether mixture the yield was 5.0 g. (70%). A sample was again recrystallized from ether–petroleum ether, m.p. 90–91° (lit.[13] 91°).

Anal. Calcd. for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.86. Found: C, 50.59; H, 5.76; N, 10.41.

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[12] L. Claisen and E. Haase, *Ber.*, **33**, 1242 (1900).

[13] E. Buchner and C. Heide, *ibid.*, **34**, 345 (1901).

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

The Stereochemical Course of the Addition of Halogens to Cholesterol

BY J. B. ZIEGLER AND A. C. SHABICA

RECEIVED APRIL 7, 1952

Direct bromochlorination of the 5,6-double bond in cholesterol and a number of its derivatives, using the N-bromoacetamide–hydrogen chloride couple, has enabled the conclusive demonstration that the halogenation of steroids of this type proceeds through the non-Markownikoff attack of halide anion on an α-oriented cyclic intermediate of the halonium type. This confirms the conclusions reached by Barton.

In a recent paper Barton and Miller[1] clarified the nature of the mutarotation of ordinary, levorotatory cholesterol dibromide and certain of its derivatives which occurs in solution in certain solvents. They proved the ordinary cholesterol dibromide to be 5α,6β-dibromo-3β-cholestanol and the thermodynamically more stable dextrorotatory isomer to be 5β,6α-dibromo-3β-coprostanol.

These authors also proposed a mechanism for the formation and isomerization of ordinary cholesterol dibromide. They visualized the formation of this substance from cholesterol as proceeding through the intermediate 5,6β-bromonium ion, followed by Markownikoff attack by bromide anion to give the 5α,6β-dibromide. This may be designated as mechanism A (see Chart I) (Hal = Br). However, more recently,[2] following a suggestion of Fieser,[3] they have revised their views in favor of

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[1] D. H. R. Barton and E. Miller, THIS JOURNAL, **72**, 1066 (1950).

[2] D. H. R. Barton, E. Miller and H. T. Young, *J. Chem. Soc.*, 2598 (1951).

[3] L. F. Fieser, *Experientia*, **6**, 312 (1950).