ethanol the material melted at 268–269°. The analytical data obtained does not fit any expected by-product. Found: C, 58.7; H, 7.12; N, 6.14.

**6-Dimethylamino-4-*p*-chlorophenyl-4-phenyl-3-heptanol.**—Seventeen grams (0.04 mole) of (I) as the hydrobromide salt was converted to the base with alkali, taken into ether and the solution dried carefully. The solution was added to an ether solution of 2 g. (0.05 mole) of lithium aluminum hydride in 500 ml. of ether. The mixture was refluxed sixteen hours and cooled in an ice-bath. The excess lithium aluminum hydride was destroyed through the cautious addition of 200 ml. of 10% sodium hydroxide dropwise to the stirred reaction mixture. The ether layer was separated and the water layer extracted with 500 ml. of ether. The combined ether solutions were dried over potassium carbonate and concentrated. The residual oil solidified and was recrystallized from ligroin (b. p. 60–71°). The yield was 13.6 g. of product melting at 136–138°. *Anal.* Calcd. for $C_{21}H_{28}ClNO$: C, 72.89; H, 8.17. Found: C, 73.00; H, 8.05.

**3-Acetoxy-6-dimethylamino-4-*p*-chlorophenyl-4-phenylheptane Hydrochloride.**—Three grams of the 6-dimethylamino-4-*p*-chlorophenyl-4-phenyl-3-heptanol was dissolved in 50 ml. of ethyl acetate and refluxed with 2 ml. of acetyl chloride for one hour. The solution was cooled and the solid which separated filtered and recrystallized from ethyl acetate. After three recrystallizations, 2.5 g. of crystals melting at 230–231° was obtained. *Anal.* Calcd. for $C_{23}H_{30}ClNO_2 \cdot HCl$: C, 65.08; H, 7.36. Found: C, 65.03; H, 7.37.

**2-Chloroethyl 6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexyl-carbonate Hydrochloride.**—A mixture of 5 g. (0.0161 mole) of 6-dimethylamino-4,4-diphenyl-5-methyl-3-hexanol, 3 g. (0.021 mole) of 2-chloroethyl chloroformate and 50 ml. of ethyl acetate was boiled under reflux for one hour and then cooled. The salt which separated was collected by filtration and recrystallized twice from isopropyl alcohol to obtain 4.5 g. of colorless crystals, m. p. 188–189°; *cf.* Table I.

## Summary

The preparation of some halogen containing esters related to methadone is reported. The synthesis of methadone and isomethadone with a chlorine substituent on one benzene ring is presented.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

# Ketene Acetals. XXI. The Dealcoholation of Orthoesters. Dimethylketene Dimethylacetal

BY S. M. MCELVAIN AND JAMES T. VENERABLE[1]

Of all the methods now available for the preparation of ketene acetals, the direct dealcoholation of an orthoester would appear to be the most promising from the standpoint of general applicability. However, this method has had quite limited success. Such an orthoester as I, in which R is the negative cyano or carbethoxy group, may be pyrolyzed smoothly in the presence of a trace of acid catalyst to the corresponding ketene acetal (II),[2] but when the less negative phenyl group is the $\alpha$-substituent, a considerable amount (20–33%) of the normal ester is formed concurrently with the ketene acetal.[3] The normal ester appears to be formed, when R is phenyl and R′ is ethyl, by the loss of ethylene from the ketene acetal (II) at the temperature of pyrolysis; in the case of the methyl orthophenylacetate a complex sequence of reactions has been postulated to account for its pyrolysis to methyl phenylacetate.[3] The pyrolysis of such an orthoester as ethyl orthoacetate yields only the normal ester as the initially formed ketene acetal is further pyrolyzed to ethyl acetate and ethylene at the higher temperature required for the dealcoholation of the orthoester.[4]

$$\underset{\text{I}}{RCH_2C(OR')_3} \longrightarrow \underset{\text{II}}{RCH{=}C(OR')_2} + R'OH$$

The preparation of tetraethoxyethylene (V) from pentaethoxyethane (III) involved a novel method of dealcoholation of an orthoester, *viz.*, the removal of the elements of alcohol at ordinary temperatures by means of a strong base,[5] sodium ethyl. This dealcoholation was thought to involve an acid–base reaction in which the ethyl anion removed the single proton from the $\alpha$-carbon of the orthoester (III) to form the anion (IV) which then passed into the ketene acetal (V) by the expulsion of an ethoxyl anion. However, other reactions were involved in the action of sodium ethyl on III; the yield of V was only 39% while the yields of ethane and sodium ethoxide were 160 and 235%, respectively, on the basis of the reaction

$$\underset{\text{III}}{(C_2H_5O)_2CHC(OC_2H_5)_3} + \overset{+}{Na}C_2\overset{-}{H}_5 \longrightarrow$$
$$C_2H_6 + \underset{\text{IV}}{(C_2H_5O)_2\overset{-}{C}{-}C(OC_2H_5)_3Na^+} \longrightarrow$$
$$\underset{\text{V}}{(C_2H_5O)_2C{=}C(OC_2H_5)_2} + NaOC_2H_5$$

It is apparent that the sodium ethyl removed hydrogens from the ethoxyl groups, as well as the single one on the $\alpha$-carbon of the orthoester III, to produce the amount of ethane that is formed in this reaction; also the high yield of sodium ethoxide indicates still another mode of reaction. Nevertheless, this reasonably successful low temperature dealcoholation of III in-

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[1] Wisconsin Alumni Research Foundation Research Assistant, 1946–1949.

[2] McElvain and Schroeder, THIS JOURNAL, **71**, 47 (1949).

[3] McElvain and Stevens, *ibid.*, **68**, 1917 (1946).

[4] McElvain, Anthes and Shapiro, *ibid.*, **64**, 2525 (1942).

[5] McElvain and Clarke, *ibid.*, **69**, 2661 (1947).

dicated the desirability of an investigation of the action of strong bases on other orthoesters. Also, the necessity of a trace of acid catalyst in the pyrolysis of such an orthoester as I (R is CN or $COOC_2H_5$) suggested a study of the effect of an aprotic acid, such as aluminum methoxide, on the pyrolysis of an orthoester. The present paper is a report of these studies.

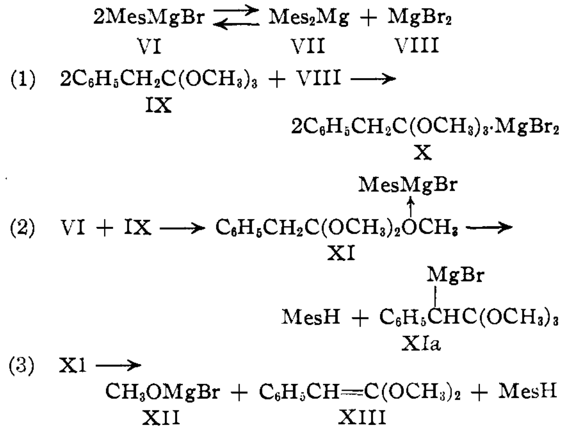
**The Reaction of Strong Bases with Orthoesters.**—The action of sodium ethyl on a series of orthoesters was first investigated. The results are summarized in Table I and briefly discussed in the Experimental section. It is sufficient to state here that this base showed no promise as a general reagent for the dealcoholation of orthoesters; only methyl orthophenylacetate (IX) was converted to the ketene acetal in any yield that could be detected. The behavior of the purely aliphatic orthoesters indicated that this base preferentially attacked the alkoxyl groups to give excessive yields of ethane and high boiling products of low alkoxy content; in each case a considerable amount of unchanged orthoester was recovered from the reaction, even when an excess of sodium ethyl was present.

Attention then was turned to the action of other bases on methyl orthophenylacetate (IX). Sodium triphenylmethyl did not react with the orthoester in ether solution; in fact 74% of the ester could be recovered by distillation from this base. Sodium naphthalene reacted readily and exothermically with the orthoester but it was not possible to separate the naphthalene formed from the other reaction products. Sodium allylbenzene, lithium butyl and isopropyl-, *t*-butyl- and mesitylmagnesium bromides gave varying yields of the ketene acetal. Of these bases mesitylmagnesium bromide was chosen for more extensive study both for its ease of manipulation and because it completely destroyed the orthoester, which is quite difficult to separate from the ketene acetal.

When methyl orthophenylacetate (IX) was added to an equivalent of mesitylmagnesium bromide in ether solution, a small quantity of a viscous oil immediately separated; the nature of this product (X) is discussed below. After about two hours of refluxing, this oil disappeared and the precipitation of a white solid began. The separation of this precipitate was accompanied by a decrease in the basicity of the supernatant solution. The precipitation of the solid and the concurrent loss of basicity were complete after nine hours. Separation and distillation of the ether solution gave mesitylene (86%), the ketene acetal (XIII) (52%) and some higher boiling material. The precipitate was shown to be methoxymagnesium bromide (XII) by determination of methanol, bromide ion and titratable basicity after hydrolysis.

When the solution of mesitylmagnesium bromide was added to the orthoester, a large quantity of the viscous oil precipitated, but there was no concurrent decrease in the basicity of the supernatant ether solution. Separation and hydrolysis of the oil showed it to be a complex (X) composed of two moles of the orthoester with one mole of magnesium bromide.

These observations lead to the conclusion that mesitylmagnesium bromide (VI) and its equilibrium products, dimesitylmagnesium (VII) and magnesium bromide (VIII) may react with methyl orthophenylacetate (IX) in two ways, depending on the relative concentration of the reactants: (a) in the presence of an excess of the orthoester (addition of Grignard reagent) the insoluble complex (X) separates (reaction (1)) to remove most of the orthoester but none of the basicity from the solution, and (b) in the presence of an excess of the Grignard reagent (addition of the orthoester) an ether-soluble orthoester Grignard compound (XI) is formed (reaction 2). This complex may decompose directly into methoxymagnesium bromide (XII), the ketene acetal (XIII) and mesitylene (reaction 3), or it may first pass through the intermediate XIa. It would seem, however, that very little, if any, XIa is produced in view of the fact that no propane is liberated directly when IX is treated with isopropylmagnesium bromide (see Experimental). Intermolecular loss of XII and mesitylene from two or more molecules of XI would account for the higher boiling and non-distillable reaction products and the consequent lower yield of the ketene acetal (XIII) relative to that of mesitylene.



$$\underset{\text{VI}}{2\text{MesMgBr}} \rightleftarrows \underset{\text{VII}}{\text{Mes}_2\text{Mg}} + \underset{\text{VIII}}{\text{MgBr}_2}$$

$$(1)\quad \underset{\text{IX}}{2C_6H_5CH_2C(OCH_3)_3} + \text{VIII} \longrightarrow \underset{\text{X}}{2C_6H_5CH_2C(OCH_3)_3\cdot MgBr_2}$$

$$(2)\quad \text{VI} + \text{IX} \longrightarrow \underset{\text{XI}}{C_6H_5CH_2C(OCH_3)_2\overset{\text{MesMgBr}\uparrow}{O}CH_3} \longrightarrow \text{MesH} + \underset{\text{XIa}}{C_6H_5\overset{\text{MgBr}}{\overset{|}{C}}HC(OCH_3)_3}$$

$$(3)\quad \text{XI} \longrightarrow \underset{\text{XII}}{CH_3OMgBr} + \underset{\text{XIII}}{C_6H_5CH{=}C(OCH_3)_2} + \text{MesH}$$

The phenylketene dimethylacetal (XIII) prepared by this procedure has a purity comparable to that of the product obtained from the dehydrohalogenation of $\alpha$-bromophenylacetaldehyde dimethylacetal.[6] Both of these products are of much higher purity than the ketene acetal obtained by the pyrolysis of methyl orthophenylacetate.[3]

The reaction of mesitylmagnesium bromide with methyl orthopropionate, $CH_3CH_2C(OCH_3)_3$, followed a course similar to that of IX, except that about thirteen hours at the temperature of

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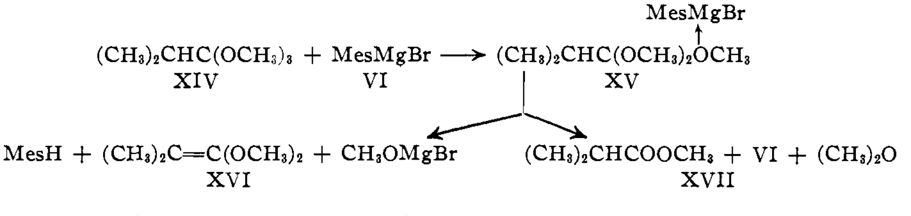
[6] McElvain and Curry, This Journal, **70**, 3782 (1948).

refluxing ether were required to reduce the basicity of the ether solution to 6% of its original value. Methylketene dimethylacetal (54%) and mesitylene (85%) were the main reaction products; none of the orthoester was recovered.

In view of the successful dealcoholations of these orthoesters with mesitylmagnesium bromide, it seemed of particular interest to extend this study to methyl orthoisobutyrate (XIV). This orthoester resists bromination[7] and consequently cannot be converted to dimethylketene dimethylacetal (XVI) *via* the $\alpha$-bromo-orthoester.[8] When methyl orthoisobutyrate was allowed to react with mesitylmagnesium bromide as described above, approximately one hundred hours were required to reduce the basicity of the solution to 20% of its initial value; only 40% of the expected mesitylene together with considerable higher boiling material was obtained from the reaction mixture.

However, if the ether were removed from the reactants immediately after the addition of the orthoester to the Grignard solution and the remaining residue warmed, there occurred a vigorous exothermic reaction, which caused distillation of liquid from the reaction flask. After further heating to remove remaining volatile material, the distillate, on careful fractionation, yielded methyl isobutyrate (28%), dimethylketene dimethylacetal (XVI) (16%), methyl orthoisobutyrate (6%) and mesitylene (65%).

The behavior of methyl orthoisobutyrate with mesitylmagnesium bromide indicates that these compounds form a relatively stable complex, such as XV, which decomposes slowly and incompletely at the temperature of refluxing ether, but quite rapidly at higher temperatures. The presence of the large amount of normal ester (XVII) among the products of the latter decomposition indicates that that principal course of disintegration of the complex (XV) produces this ester; however, none of the products, dimethyl ether or methyl bromide, that might be expected to be formed simultaneously were detected. It seems likely that considerably more methyl isobutyrate than was isolated from this reaction was actually formed, and that it was the main source of the high yield of mesitylene through its ability to undergo an acetoacetic ester condensation with mesitylmagnesium bromide.[9]



$$\underset{\text{XIV}}{(CH_3)_2CHC(OCH_3)_3} + \underset{\text{VI}}{MesMgBr} \longrightarrow \underset{\text{XV}}{(CH_3)_2CHC(OCH_3)_2\overset{\overset{MesMgBr}{\uparrow}}{O}CH_3}$$

$$MesH + \underset{\text{XVI}}{(CH_3)_2C{=}C(OCH_3)_2} + CH_3OMgBr \qquad \underset{\text{XVII}}{(CH_3)_2CHCOOCH_3} + VI + (CH_3)_2O$$

Dimethylketene dimethylacetal as obtained from this reaction is a colorless liquid, b. p. 103–105°, which rapidly absorbs bromine (neither XIV nor XVII shows any reaction with this reagent), but reacts quite slowly with methanol in the presence of acid to yield the orthoester XIV.

In the postulated coördination compounds XI and XV the Grignard reagent is functioning as an *acid* (*cf.* the action of aluminum methoxide below) rather than as a base. This type of behavior is indicated also by the fact that methyl orthoisobutyrate (XIV) may be distilled unchanged from lithium butyl, which reacts with methyl orthophenylacetate (IX) to give good yields of the ketene acetal (XIII) and butane. Thus it appears that XIV is too weak an acid to react with lithium butyl and that the lithium of this base is unable to coördinate with a methoxyl oxygen as does the magnesium of the Grignard reagent in XV.

**Dealcoholations with Aluminum Methoxide.**—The catalytic effect of hydrogen-acids on the pyrolytic dealcoholation of orthoesters[2] indicates that aprotic acids, which have the same coördination ability but carry no anions to promote the acidolysis of the O-alkyl bond, might prove effective dealcoholation catalysts, particularly when used in molecularly equivalent amounts. As earlier work[10] had shown that boron trifluoride-ammonia catalyzed the decomposition of orthoesters to the corresponding normal esters and ethers, the less active aluminum methoxide was selected as the aprotic acid for the present work.

When methyl orthophenylacetate (IX) was heated with an equivalent of aluminum methoxide, 82% of the expected methanol was evolved rapidly at 210°; distillation of the remaining material gave a 92% yield of phenylketene dimethylacetal (XIII), which was comparable in purity to that obtained with mesitylmagnesium bromide (reactions 2 and 3). None of the normal ester or unchanged orthoester was obtained. This smooth and practically complete dealcoholation is in marked contrast to the direct pyrolysis of this orthoester,[3] which required heating above 250° to produce any dealcoholation, yielded only 40–50% of the expected alcohol, and produced a considerable amount (33%) of the normal ester together with a relatively impure phenylketene dimethylacetal.[6]

Methyl orthoisobutyrate distils unchanged (b. p. 134°) when mixed with aluminum methoxide and heated. For this reason it was necessary to pass the vapors of this orthoester through preheated aluminum methoxide to effect the dealcoholation. A reaction temperature of 290–300° was necessary to

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(7) Robert E. Kent, Ph.D. Thesis, University of Wisconsin, 1944.

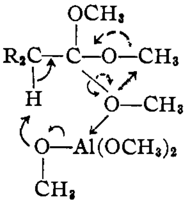
(8) Walters and McElvain, THIS JOURNAL, **62**, 1482 (1940).

(9) Spielman and Schmidt, *ibid.*, **59**, 2009 (1937).

(10) McElvain and Stevens, *ibid.*, **69**, 2663 (1947).

produce any reaction and under these conditions there was considerable decomposition of the orthoester to methyl isobutyrate and dimethyl ether. The yield of dimethylketene dimethylacetal (XVI) amounted to only 8.6%. Methyl orthopropionate was dealcoholated by aluminum methoxide at 240–245°; the corresponding ketene acetal was produced in 15% yield and 54% of the orthoester was recovered unchanged.

The dealcoholation of an orthoester with aluminum methoxide doubtless involves the coördination of this aprotic acid with an oxygen of the orthoester as in XVIII, which is similar to postulated intermediate XV. Decomposition of this complex by route (↷) would yield the ketene acetal and methanol and by route (↷) the normal ester and dimethyl ether. The relatively high activity of the α-hydrogen of methyl orthophenylacetate (IX) produces exclusive decomposition *via* (↷), while with methyl orthoisobutyrate the lower reactivity of the α-hydrogen causes the decomposition to proceed mainly *via* (↷). Of course, the complex XVIII might first break into $Al(OCH_3)_4^-$ and the carbonium ion, $RR'CH\overset{+}{C}(OCH_3)_2$, which then could lose a proton or a methyl cation to yield the products that are isolated.


XVIII

It is an interesting fact that the substitution of aluminum oxide for aluminum methoxide in the dealcoholation of methyl orthophenylacetate (IX) gave only a 31% of the ketene acetal (XIII); the main reaction products were dimethyl ether and methyl phenylacetate (54%). The difference in behavior of these two aprotic acids may well be due to the ability of the aluminum oxide to coördinate simultaneously with two oxygens of the orthoester to produce a complex more disposed to eliminate dimethyl ether than methanol.

## Experimental

**Orthoesters.**—(a) **Methyl orthophenylacetate** was prepared free of methyl phenylacetate by the following procedure: A mixture of 92.5 g. (0.5 mole) of methyl phenyliminoacetate hydrochloride[3] and 100 ml. of absolute methanol was shaken; the salt dissolved rapidly and endothermally. Ammonium chloride began to precipitate almost immediately. After two days, 50 ml. of dry ether was added and the mixture filtered. The ammonium chloride that was separated amounted to 24 g. (90%). After making the solution basic to phenolphthalein with sodium methoxide, the solvents were removed from the filtrate at room temperature under diminished pressure. The filtrate then was cooled in a Dry Ice–acetone mixture and filtered to remove 5.4 g. (8%) of phenylacetamide. The filtrate was distilled under reduced pressure to give 57 g. (58%) of impure methyl orthophenylacetate, b. p. 78–91° (0.5 mm.); methoxyl content 42.4% (calcd. 47.4%). From the methoxyl content it was estimated that the orthoester was contaminated with approximately 19% of methyl phenylacetate. The mixture of esters was added to a flask containing 5 g. (0.2 mole) of sodium hydride and 15 ml. of low boiling ligroin and the resultant mixture refluxed over a hot-plate for five hours. The solution then was decanted and distilled under reduced pressure. The fraction of methyl orthophenylacetate collected at 72–76° (0.5 mm.) had a methoxyl content of 46.2%; $n^{25}D$ 1.4948. The yield amounted to 45 g. (46% from the iminoester hydrochloride).

(b) **Methyl Orthoisobutyrate.**[7]—A 1-liter erlenmeyer flask was fitted with rubber stopper containing an inlet tube extending almost to the bottom of the flask and an outlet tube reaching just through the stopper and protected against moisture with a calcium chloride tube. In the flask was placed a mixture of 138 g. (2 moles) of dry isobutyronitrile, 90 ml. (2.2 moles) of anhydrous methanol, and 750 ml. of anhydrous ether (it was found necessary to add the ether at this point rather than after crystallization of the iminoester hydrochloride to prevent the reaction from solidifying into a hard cake), the flask cooled in an ice-bath and a stream of dry hydrogen chloride gas passed into the reaction mixture until 78 g. (2.2 moles) had been absorbed. The stoppered reaction flask was cooled in the ice-bath for an additional hour, then allowed to crystallize for forty-eight hours in the refrigerator. The mass of crystals was filtered with suction, the solid thoroughly triturated with absolute ether and then dried for forty-eight hours in a vacuum desiccator over solid sodium hydroxide. A small additional crop of crystals was obtained on further cooling of the mother liquors to give a total yield of glistening white flakes amounting to 270 g. (99%). If the **methyl iminoisobutyrate hydrochloride** at this point gave an acid test with moistened congo red paper, it was triturated again with absolute ether and dried in the vacuum desiccator.

*Anal.* Calcd. for $C_5H_{12}ClNO$: Cl, 25.8. Found: Cl, 26.1.

In a 3-liter 3-necked flask fitted with a Hershberg stirrer and spiral reflux condenser protected by a calcium chloride tube, was placed 137 g. (1 mole) of methyl iminoisobutyrate hydrochloride and 365 ml. (9 moles) of anhydrous methanol. The mixture was stirred until the salt was dissolved and then 1850 ml. of anhydrous ether added. Ammonium chloride began to precipitate as a fine suspension. The ether–alcohol mixture was stirred and refluxed gently for eighteen hours from an oil-bath at 45°, then cooled in ice and filtered through a large fluted filter paper to remove the precipitated ammonium chloride, which amounted to 33 g. (61%). The ethereal solution was made alkaline to litmus with sodium methoxide and then distilled through a 20-cm. modified Widmer column. After removing the solvent, the product was distilled, leaving a residue of isobutyramide in the distilling flask amounting to 30 g. (35%); recrystallization from ethyl acetate–ligroin (60–68°) gave glistening plates, m. p. 127–129°. The higher cuts, boiling at 130–136°, were treated with 5 g. of sodium hydride to form a non-distillable salt with the isobutyramide that had sublimed during the distillation and then refractionated to give 63 g. (43%) of **methyl orthoisobutyrate**, a colorless liquid with a pungent, camphor-like odor, b. p. 135–136°, $d^{25}_4$ 0.9253, $n^{25}D$ 1.4003.

*Anal.* Calcd. for $C_7H_{16}O_3$: C, 56.72; H, 10.88; $CH_3O$, 62.8. Found: C, 57.01; H, 10.47; $CH_3O$, 61.2.

(c) **Ethyl orthoisobutyrate** was prepared by procedure (b) using ethyl instead of methyl alcohol. It is of interest to note that ethyl iminoisobutyrate hydrochloride, as obtained from the interaction of isobutyronitrile, ethyl alcohol and hydrogen chloride, failed to crystallize when kept in a refrigerator; however, crystallization began after one day at room temperature. The properties of this orthoester as well as those of methyl and ethyl orthoacetates have been reported previously.[11]

(d) **Methyl Orthobenzoate.**[7,12]—A solution of sodium methoxide, prepared by dissolving 75 g. (3.25 atoms) of

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[11] McElvain and Nelson, This Journal, **64**, 1825 (1942).

[12] Post, "Chemistry of Aliphatic Orthoesters," Reinhold Publ. Corp., New York, N. Y., 1943, pp. 26 and 103, reports of preparation of this compound by Hill (unpublished results) in 51% yield by the Tschitschibabin reaction between phenylmagnesium bromide and methyl orthocarbonate. Since no constants are quoted in this description and because better yields are given by the present method, the preparation of methyl orthobenzoate is given in detail.

sodium in 1 liter of dry methanol, contained in a 3-liter 3-necked flask fitted with dropping funnel, Hershberg stirrer, and reflux condenser, was cooled to 0° in an ice-salt freezing mixture. To this cooled and stirred solution was added dropwise 195 g. (1 mole) of benzotrichloride. After the addition was complete, the reaction was stirred one hour, then allowed to stand overnight and come to room temperature, after which time it was refluxed for four hours. The reaction mixture then was cooled in ice to precipitate sodium chloride, which was removed by filtration and washed with a small portion of dry methanol. After distilling most of the methanol from the filtrate, the solution was again cooled and filtered to remove additional sodium chloride; the total yield of this salt was 166 g. (95%).

After removing the remaining alcohol from the filtrate, the residual liquid was distilled through a 20-cm. modified Widmer column and the distillate, b. p. 110–114° (25 mm.), heated for sixty hours with a solution of 6 g. of sodium in 75 ml. of dry methanol to remove the 4% chlorine (Stepanov) which it was found to contain. Distillation of the resulting halogen-free product gave 157 g. (86%) of methyl orthobenzoate, a colorless, oily liquid, b. p. 114–115° (25 mm.), $d^{25}_4$ 1.0637, $n^{25}_D$ 1.4858.

*Anal.* Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.94; H, 7.44.

**Sodium Ethyl.**—This compound was prepared by the method of Whitmore and Zook.[13] The following procedure includes the modifications and precautions that were found necessary or desirable in the present work. A mixture of 4.6 g. (0.2 atom) of sodium sand and 50 ml. of dry, olefin-free ligroin (b. p. 35–40°) was placed in a 500-ml. flask fitted with a stirrer, a dropping funnel, and a condenser closed with a calcium chloride tube. An atmosphere of nitrogen was maintained in the apparatus. A mixture of 39 g. (0.15 mole) of mercury diethyl[14] in 100 ml. of ligroin was added through the dropping funnel over a period of twenty minutes. Reaction began almost immediately at room temperature as evidenced by a change in the appearance of the sodium sand and a slight warming of the reaction flask. In some runs it was necessary to gently warm the reaction flask with a water-bath to initiate the reaction. The reaction mixture was held at room temperature by means of a water-bath. After the addition of the mercury diethyl was complete, stirring was continued for two hours, at the end of which time the solid material at the bottom of the flask had a waxy, grey to gold appearance. The solid sodium ethyl was washed *five times* with fresh solvent; this step was necessary prior to its use with orthoesters in order to remove the excess mercury diethyl,[15] which co-distils with the products of the reactions of orthoesters and sodium ethyl.

The yield of sodium ethyl may be calculated from the amount of mercury formed in the reaction

$$2Na + HgEt_2 \rightleftharpoons 2NaEt + Hg$$

The sodium amalgam formed from the liberated mercury and some of the sodium was decomposed by refluxing in dilute sulfuric acid. The mercury thus obtained from such a preparation as described above amounted to 15.28 g. (0.076 mole). The yield of sodium ethyl based on the amount of sodium originally put into the reaction was therefore 76%. This method of estimating the yield of sodium ethyl could be used after this base had been allowed to react with the various orthoesters as described below. The average yield of sodium ethyl as determined from the weight of mercury remaining from ten such runs was 77%.

**Reaction of Sodium Ethyl with Orthoesters.**—The procedures followed for the determination of the course of the reaction of sodium ethyl with two orthoesters (a) methyl orthophenylacetate, which yields the corresponding ketene acetal, and (b) methyl orthoisobutyrate, a typical aliphatic orthoester that is not converted to a ketene acetal, are given below. The results obtained with these and other orthoesters are summarized in Table I.

(a) **Methyl Orthophenylacetate** (Run 2, Table I).—Sodium ethyl was prepared as described above from 4.8 g. (0.208 atom) of sodium sand in 25 ml. of dry, olefin-free ligroin and 40 g. (0.154 mole) of mercury diethyl contained in a 300-ml. flask fitted with a dropping funnel, stirrer, and a reflux condenser, the top of which was connected to a gas collector. A ligroin solution of 15 g. (0.077 mole) of methyl orthophenylacetate was added over a period of fifteen minutes. Ethane was evolved immediately but this evolution was never vigorous and ceased soon after the orthoester addition was complete. The solution became wine red in color. After thirty minutes the ligroin solution was decanted from the insoluble material. The latter was washed twice with 25-ml. portions of solvent, and the washings were added to the original ligroin solution. The combined ligroin solutions were then distilled to give 10.6 g. of a mixture of methyl orthophenylacetate and phenylketene dimethylacetal, b. p. 76–78° (0.4 mm.). A negligible amount of residue remained in the distilling flask. The refractive index, $n^{25}_D$ 1.5413, of this mixture indicated that it was composed of 74% ketene acetal, $n^{25}_D$ 1.5576, and 26% orthoester, $n^{25}_D$ 1.4948, showing that the amount of ketene acetal produced in the reaction was 62% of the theoretical. Treatment of this mixture of ketene acetal and orthoester with methanol in an acid-washed flask converted it to the pure orthoester, b. p. 86–89° (0.5 mm.); $n^{25}_D$ 1.4950.

The ethane evolved during the reaction amounted to 1120 ml., which reduced to standard conditions amounted to 0.044 mole (57%).

The solid reaction residue from which the ligroin solution was decanted was covered with toluene and water added to decompose any unreacted sodium ethyl and sodium compounds that might be present. The amount of methanol formed by this treatment (presumably from sodium methoxide) was determined in the following manner. The toluene and water layers were decanted from the sodium amalgam and distilled until all of the toluene with some of the water had been removed. The water layer in the distillate was saturated with potassium carbonate and extracted several times with toluene. The combined portions of toluene were diluted to 100 ml., and a 5-ml. aliquot of this solution was added to 3 g. of 3,5-dinitrobenzoyl chloride. The methyl 3,5-dinitrobenzoate that resulted weighed 1.07 g., m. p. 106–107°. This amount of ester indicated that 0.098 mole of methanol had been present in the toluene solution.

The sodium amalgam was hydrolyzed by boiling in dilute hydrochloric acid to give 16.44 g. (0.082 mole) of mercury. This amount of mercury showed that 0.164 mole of sodium ethyl had been present for reaction with the methyl orthophenylacetate.

**Methyl Orthoisobutyrate** (Run 3, Table I).—Sodium ethyl was prepared as described above from 9.2 g. (0.40 mole) of sodium sand and 78 g. (0.30 mole) of mercury diethyl in a 250-ml. flask fitted with a dropping funnel, stirrer, and a reflux condenser closed with a calcium chloride tube. A mixture of 30 g. (0.20 mole) of methyl orthoisobutyrate in 60 ml. of dry, olefin-free ligroin (b. p. 63–66°) was placed in the dropping funnel. The end of the condenser was connected to a gas collector through the drying tube and a Dry Ice-acetone cold trap. The orthoester was added with stirring over a period of thirty minutes. Reaction was immediate as evidenced by the rapid evolution of heat and gas. However, the temperature of the reaction mixture was easily controlled by placing the flask in an ice-bath whenever necessary. Stirring was continued for fifteen minutes after the addition of the orthoester was complete. The gas collected during the reaction amounted to 3485 ml. of ethane (0.133 mole at standard conditions); this gas had a carbon to hydrogen ratio of 0.251 (calcd. for ethane, 0.250).

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[13] Whitmore and Zook, THIS JOURNAL, **64**, 1783 (1942).

[14] Gilman and Brown, *ibid.*, **52**, 3314 (1930).

[15] Caution: Mercury diethyl is extremely poisonous. Great care should be taken not to inhale the vapor of this compound. All solutions containing it should be carefully decontaminated before they are discarded. Mercury diethyl is easily destroyed by treatment with bromine. Apparatus can be decontaminated by washing with bromine water.

The reaction mixture was centrifuged and the supernatant liquid decanted. The residue then was washed with a 25-ml. portion of solvent and the washing was added to the original ligroin solution. Distillation of this solution gave 14.6 g. of crude methyl orthoisobutyrate, b. p. 126–133°; $n^{25}D$ 1.4013. The 20.6 g. of residue remaining in the distilling flask reacted vigorously with water. The oil that separated was extracted with benzene and distilled into four fractions: (a) 1.4 g., b. p. 60–115° (15 mm.), $n^{25}D$ 1.4529; (b) 1.2 g., b. p. 115–126° (15 mm.), $n^{25}D$ 1.4878; (c) 0.9 g., b. p. 126–150° (15 mm.), $n^{25}D$ 1.4950; and (d) 0.9 g., b. p. 115–160° (0.5 mm.), $n^{25}D$ 1.5070. The distillation residue amounted to 1.3 g. Each of these fractions gave positive tests for unsaturation with bromine (with no evolution of hydrogen bromide) and potassium permanganate. An 0.0844-g. sample of fraction (b) decolorized 2.875 ml. of a 0.0146 *N* solution of bromine in carbon tetrachloride; assuming four double bonds per molecule, this titration gave a calculated molecular weight of 251. A combustion analysis showed fraction (b) to contain 77.6% carbon, 10.4% hydrogen, indicating an empirical formula of $C_{17}H_{28}O_2$, the molecular weight (264) of which compares with that obtained from the bromine titration.

The sodium amalgam remaining from the reaction of sodium ethyl with the orthoester was decomposed with dilute hydrochloric acid. The liberated mercury weighed 28.12 g. (0.14 atom), indicating that 0.28 mole of sodium ethyl had been available for reaction with the orthoester.

Table I

Reaction of Sodium Ethyl with Orthoesters, $R—C(OR')_3$

| Run | R is | R' is | NaEt/ Ortho-ester, moles | Yield, %[a] | $C_2H_6$ (%)[b] | Yield, ketene acetal, % | Recov. ortho-ester, % |
|---|---|---|---|---|---|---|---|
| 1 | $C_6H_5CH_2$ | $CH_3$ | 1 | 52 | ( 76) | 48 | 32 |
| 2 | $C_6H_5CH_2$ | $CH_3$ | 2 | 57 | ( 77) | 62 | 26 |
| 3 | $(CH_3)_2CH$ | $CH_3$ | 1.4 | 67 | (134) | 0 | 50 |
| 4 | $(CH_3)_2CH$ | $C_2H_5$ | 1 | 65 | (186) | 0 | 65 |
| 5 | $CH_3$ | $CH_3$ | 1 | 40 | ( 60) | 0 | 33 |
| 6 | $CH_3$ | $C_2H_5$ | 1 | 44 | (157) | 0 | 72 |
| 7 | $C_6H_5$ | $CH_3$ | 1 | 80 | (190) | .. | 58[c] |

[a] Based on orthoester put into the reaction. [b] Based on orthoester not recovered from the reaction. [c] Approximately one-third of this recovered orthoester came from the hydrolysis of ligroin-insoluble reaction products, indicating that the aromatic nucleus of the orthoester had reacted with the sodium ethyl to form a sodium trimethoxymethylphenyl and ethane.

The purely aliphatic orthoesters listed in Table I (runs 3–6) show a generally similar behavior toward sodium ethyl. Methyl orthoacetate appears to be the least reactive; however, the others, particularly the ethyl esters, give such high yields of ethane without any concurrent formation of ketene acetals as to indicate that the reagent attacks the alkoxyl groups rather than the $\alpha$-hydrogen of these orthoesters. In addition to this type of behavior, methyl orthobenzoate (run 7) which was selected because of the absence of an $\alpha$-hydrogen in its structure, shows reaction with the hydrogen of the aromatic nucleus (*cf.* footnote *c*, Table I). The behavior of these orthoesters makes even more significant the fact that the $\alpha$-hydrogen of methyl orthophenylacetate (runs 1 and 2) has a sufficiently enhanced reactivity to compete successfully with the methoxyl and phenyl substituents for the sodium ethyl and yield the ketene acetal.

**Reaction of Methyl Orthophenylacetate with Strong Bases.** (a) **Sodium Triphenylmethyl.**—The blood-red ether solution of this base prepared from 60 g. (0.22 mole) of triphenylchloromethane[16] remained unchanged when treated with 35 g. (0.18 mole) of methyl orthophenylacetate and the resulting solution refluxed for four hours. Distillation of the reaction mixture gave a 74% recovery of the orthoester; none of the ketene acetal could be detected (bromine in carbon tetrachloride).

(b) **Sodium Naphthalene.**—A solution of this base, prepared from 28 g. of naphthalene and 6 g. of sodium in 200 ml. of ethylene glycol dimethyl ether,[17] gave an exothermic reaction and a precipitate when treated with 39 g. of the orthoester. However, the presence of naphthalene among the reaction products made their separation impossible.

(c) **Sodium Allylbenzene.**—To a benzene solution of this base prepared from 26 g. (0.225 mole) of allylbenzene[18] was added 39 g. (0.2 mole) of methyl orthophenylacetate, and the mixture heated on a steam-bath for two hours. The precipitate which appeared was separated by decanting the benzene solution. Distillation of the decanted solution gave 12.5 g. (53%) of propenylbenzene, b. p. 175°, $n^{25}D$ 1.5474, and 18.5 g. (56%) of phenylketene dimethylacetal, b. p. 79–81° (0.2 mm.); $n^{25}D$ 1.5576; methoxyl content 34.6% (calcd. 37.5%). The non-distillable residue weighed 4.5 g.

(d) **Isopropylmagnesium Bromide.**—An ether solution of this Grignard reagent prepared from 25.2 g. (0.2 mole) of isopropyl bromide and 5 g. (0.21 atom) of magnesium turnings was filtered into a 500-ml. flask fitted with a dropping funnel, stirrer, and a condenser closed with a gas collector. An ether solution containing 28.4 g. (0.145 mole) of methyl orthophenylacetate was added with stirring. A precipitate began to form after fifteen minutes but no propane was evolved. After the reaction mixture was refluxed for eight hours, an aliquot of the supernatant liquid was titrated and found to contain no basicity. The precipitate was collected on a filter and found to weigh 40 g. The filtrate was distilled. A mixture of phenylketene dimethylacetal and methyl orthophenylacetate, amounting to 6.5 g., was collected between 70–80° (0.4 mm.); $n^{25}D$ 1.5334. The ketene acetal contained in this distillate as calculated from the refractive index amounted to a 14.2% yield. A small quantity (1 g.) of resin remained in the distilling flask.

The precipitate from the reaction was placed in dry benzene and refluxed for three hours in an attempt to break up any complex of the Grignard reagent and the orthoester. No change was observed so the mixture was decomposed with dilute hydrochloric acid. The methyl phenylacetate which separated was dried and distilled; the fraction collected between 100–105° (12 mm.); $n^{25}D$ 1.5067, weighed 7.8 g. (36%).

When a similar run was made at a higher temperature with benzene as the reaction medium the orthoester was transformed into methyl phenylacetate and no ketene acetal was formed.

(e) ***t*-Butylmagnesium Bromide.**—A solution of 0.065 mole of this Grignard reagent in a mixture of 100 ml. of ether and 200 ml. of benzene was treated with 12.7 g. (0.065 mole) of a benzene solution of the orthoester. After four hours of refluxing the reaction mixture was allowed to cool to room temperature, and the precipitate that had formed was separated by decanting the supernatant liquid. The benzene solution was distilled to give 9.0 g. of a mixture of methyl orthophenylacetate and phenylketene dimethylacetal, b. p. 60–65° (0.3 mm.) $n^{25}D$ 1.5341. The ketene acetal present in this mixture (calculated from the refractive index) represented a yield of 46%.

(f) **Lithium Butyl.**—An ether solution of this base was prepared[19] from 3 g. (0.432 atom) of lithium and 23.4 g. (0.171 mole) of *n*-butyl bromide. The reaction mixture was filtered by decantation through a tube plugged with glass wool into a 500-ml. flask fitted with a dropping funnel, stirrer, and a condenser closed with a cold trap protected with a calcium chloride tube. An ether solution containing 17.2 g. (0.088 mole) of methyl orthophenylacetate was added with stirring over a period of fifteen

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[16] Renfrow and Hauser, "Org. Syntheses," Coll. Vol. II, 607 (1943).

[17] Scott, Walker and Hansley, This Journal, **58**, 2442 (1936).

[18] Levy and Cope, *ibid.*, **56**, 2121 (1934).

[19] Gilman, *et al.*, *ibid.*, **71**, 1499 (1949).

minutes. The reaction mixture slowly became deep orange in color and a precipitate formed. After sixteen hours, 0.56 g. of butane had collected in the cold trap. The reaction mixture was refluxed for three hours, at the end of which time, an additional 3.49 g. of butane (total yield 79%) was found in the cold trap. The reaction mixture was centrifuged and the supernatant ether solution was distilled to give 9.94 g. of a mixture of methyl phenylacetate and phenylketene dimethylacetal, b. p. 75-77° (0.6 mm.), $n^{25}D$ 1.5485. The methoxyl content and refractive index of this mixture indicated that it contained 1.8 g. (13.6%) of the normal ester and 8.14 g. (56.4%) of the ketene acetal.

Reaction of **Mesitylmagnesium Bromide with Orthoesters.** (a) **Methyl Orthophenylacetate.**—Mesitylmagnesium bromide was prepared from a mixture of 10 g. (0.412 mole) of magnesium turnings and 68 g. (0.34 mole) of bromomesitylene in 100 ml. of dry ether under strictly anhydrous conditions. A crystal of iodine and ten drops of ethyl bromide were used to initiate the reaction. The mixture was refluxed for five hours and then diluted with anhydrous ether to a total volume of 350 ml. Titration of a 2-ml. aliquot with 0.1 $N$ hydrochloric acid against methyl orange indicated the presence of 0.272 mole of basicity.

A volume containing 0.234 mole of the Grignard reagent was pipetted into a 500-ml. flask fitted with a stirrer and a condenser closed with a calcium chloride tube. A nitrogen atmosphere was maintained in the apparatus. An ether solution containing 40.0 g. (0.204 mole) of methyl orthophenylacetate was added to the Grignard solution. After fifteen minutes a viscous brown oil separated from the solution. The reaction mixture was stirred and warmed to reflux. The basicity of the solution was determined periodically by titrating 2-ml. aliquots of the supernatant liquid. A white solid began to form after two hours, and thereafter the original oily precipitate gradually disappeared. After nine hours the basicity of the solution remained constant at 7% of the original value, and the entire precipitate was a solid.

The reaction mixture was centrifuged and the supernatant liquid decanted. The precipitate was washed three times with 25-ml. portions of ligroin (b. p. 67°) and dried; it weighed 39.6 g. The solvents were removed from the combined ether solution and washings by distillation. A further quantity (2.5 g.) of precipitate was separated by decantation after the ether had been removed. Distillation of the remainder of the solution under diminished pressure gave 21.2 g. (86%) of mesitylene, b. p. 65-67° (20 mm.); 21.6 g. of crude phenylketene dimethylacetal, b. p. 74-92° (1.2 mm.); 0.8 g. of a higher boiling material, b. p. 125-175° (0.5 mm.), $n^{25}D$ 1.5470, methoxyl content 9.6%; and 3.0 g. of a non-distillable residue. The ketene acetal fraction was redistilled to give 2.7 g. (8.8%) of methyl phenylacetate and 17.4 g. (52%) of phenylketene dimethylacetal, b. p. 76-80° (0.4 mm.), $n^{25}D$ 1.5576,[20] methoxyl content 36.4% (calcd. 37.5%).

The precipitate from the reaction was hydrolyzed with dilute sulfuric acid. The oil that separated was taken up in ether, dried, and distilled under vacuum to give 4.5 g. of methyl phenylacetate, b. p. 55-64° (0.8 mm.), and 4.8 g. of a non-distillable residue. The methanol in the water solution remaining after the extraction of the oil was determined[21] and 0.195 mole found to be present; Volhard analysis showed 0.220 mole of bromide ion to be present.

In runs in which the refluxing of the original reaction mixture was omitted the basicity of the supernatant liquid did not decrease appreciably and the slow precipitation of a white solid was not observed. Some of the solid did form during the distillation of the ether. The yields of mesitylene in such cases ranged from 65 to 85% and those of the ketene acetal from 20 to 35%.

In runs in which the Grignard solution was added to the orthoester, there was an immediate precipitation of large amounts of the viscous oil. When this oil was separated and hydrolyzed with standard acid, it was found to contain practically no basicity, *one* equivalent of methyl phenylacetate, *one* equivalent of bromide ion and *two* equivalents of methanol.[21] This indicates that the initial precipitate is a complex of one magnesium bromide with two molecules of the orthoester and that this complex is hydrolyzed to the normal ester and methanol when treated with dilute acid. Distillation of the separated ether solution gave approximately 40% yield of mesitylene, but only a 6% yield of the ketene acetal.

(b) **Methyl Orthopropionate.**—An ethereal solution of mesitylmagnesium bromide containing 0.227 mole of basicity was pipetted into a 500-ml. flask under a nitrogen atmosphere. A solution of 27.8 g. (0.207 mole) of methyl orthopropionate in 50 ml. of ether was added with stirring to the Grignard solution over a period of twenty-five minutes. The resulting ether solution then was warmed to reflux over a hot-plate. After a few minutes it became turbid, and a small amount of a thick oil collected on the walls of the flask. After thirteen hours of refluxing and stirring a large amount of solid had precipitated and only 6.5% of the original basicity remained in solution. The reaction mixture was centrifuged and the supernatant liquid decanted. The residue, after washing with two 25-ml. portions of ether and drying, weighed 35.8 g. The combined ether solution and washings were distilled to give 11.3 g. (54%) of methylketene dimethylacetal,[22] b. p. 98-102°, $n^{25}D$ 1.4093; 57.3% methoxyl (calcd. 60.7%), 21.1 g. (85%) of mesitylene, b. p. 158-160°, and 3.7 g. of non-distillable residue.

(c) **Methyl Orthoisobutyrate. Dimethylketene Dimethylacetal.**—When this orthoester was used instead of methyl orthopropionate in the preceding experiment, it was found that one hundred hours of refluxing of the ethereal reaction mixture was required to reduce the basicity of the solution to approximately 20% of its initial value. After decantation from the precipitated solid, the ether solution was distilled to yield a small amount (*ca.* 15%) of a mixture of the ketene acetal and orthoester, b. p. 105-108°, mesitylene (40%) and a higher boiling material which amounted to 22% of the weight of the orthoester originally used in the reaction. Because of the time required for this incomplete reaction, the procedure was discarded in favor of the following more expeditious method.

The Grignard reagent prepared from 14.6 g. (0.6 mole) of magnesium turnings and 84.4 g. (0.422 mole) of mesityl bromide in ether was pipetted into a 500-ml. distilling flask. After 50 g. (0.337 mole) of methyl orthoisobutyrate had been added, the ether solvent was removed by distillation. As the last portion of the ether was distilling, a new receiver closed with a large cold trap was attached to the apparatus. Shortly thereafter, a vigorous exothermic reaction occurred, accompanied by a rapid distillation of a liquid material. A fresh receiver was substituted after the reaction had subsided and the remainder of the reaction mixture was heated gently under reduced pressure. The combined distillates obtained were fractionated from a

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[20] McElvain and Curry (ref. 6) report $n^{25}D$ 1.5620 for this ketene acetal.

[21] The following procedure was used: a mixture of a 10-ml. aliquot of a 0.1 $N$ standard potassium dichromate solution and a 5-ml. aliquot of concentrated sulfuric acid was placed in a 200-ml. glass-stoppered bottle. A 5-ml. aliquot of the solution to be analyzed was then added, the bottle firmly stoppered, and the mixture heated on a steam-bath. After thirty minutes the solution was washed out into a flask, 1 g. of potassium iodide was added, and the iodine that was liberated was titrated with 0.1 $N$ standard sodium thiosulfate solution. Water solutions containing known amounts of alcohol were oxidized and titrated in this manner and the volumes of sodium thiosulfate solution required for the titrations were plotted against the moles of methanol present. The graph that resulted was then used for the analyses of solutions containing unknown amounts of methanol. This microanalysis may be used for very dilute solutions of methanol or ethanol in water. The presence of other oxidizable organic materials in the solution interferes with the analysis.

[22] A sample of this ketene acetal, prepared by William E. Davie in this Laboratory from methyl ortho-α-bromopropionate by the procedure of Walters and McElvain (THIS JOURNAL, **62**, 1482 (1940)), had the following properties: b. p. 98-100°, $n^{25}D$ 1.4110. This work will be reported later.

small modified Claisen flask into the following fractions: (a) 19.2 g. of unsaturated material,[23] b. p. 85–136°; (b) 11.1 g. of a mixture of methyl orthoisobutyrate and mesitylene, b. p. 41–61° (21 mm.), $n^{25}\text{D}$ 1.4693; (c) 18.0 g. of mesitylene, b. p. 61–67° (21 mm.); and (d) 6.0 g. of an unidentified oil, b. p. 72–80° (21 mm.). The fraction (a) was refractionated through an 18-plate Fenske column to give 9.6 g. (28%) of methyl isobutyrate, b. p. 91–94°, $n^{25}\text{D}$ 1.3811, and 6.1 g. (15.6%) of dimethylketene dimethylacetal, b. p. 103–105°; $n^{25}\text{D}$ 1.4046.

*Anal.* Calcd. for $C_6H_{12}O_2$: C, 62.03; H, 10.41; $CH_3O$, 53.4. Found: C, 62.07; H, 10.54; $CH_3O$, 49.7.

Fraction (b) contained 3.1 g. (6.2%) of unchanged methyl orthoisobutyrate and 8.0 g. of mesitylene (calculated from the refractive index). The total yield of mesitylene was 26.0 g. (64.5%).

When a thermometer whose tip previously had been dipped into concentrated hydrochloric acid was placed in a mixture of 5.4 g. of dimethylketene dimethylacetal, b. p. 103–105°, and 3 ml. of dry methanol, the temperature of the mixture rose 11°. The material was refluxed for one hour and allowed to stand for several days. It then was made alkaline with a few grains of sodium hydride and distilled to give 1.1 g. of a mixture of methyl isobutyrate and methyl orthoisobutyrate; b. p. 85–115°; $n^{25}\text{D}$ 1.3913 and 3.5 g. of methyl orthoisobutyrate, b. p. 115–127°; $n^{25}\text{D}$ 1.3982. Neither of these fractions showed any unsaturation with bromine. When a mixture of the ketene acetal and methanol was distilled immediately after mixing and treatment with acid, the unsaturated acetal was recovered unchanged.

When 15 g. (0.1 mole) of methyl orthoisobutyrate was treated with lithium butyl prepared from 3.0 g. (0.432 atom) of lithium wire and 23.4 g. (0.171 mole) of *n*-butyl bromide,[19] there was no evidence of reaction. After refluxing for six hours, the reaction mixture was distilled to yield 12.3 g. (82%) of unchanged orthoester. No ketene acetal was detected and no butane collected in a cold trap attached to apparatus.

**Aluminum methoxide** was prepared by the following procedure adapted from that used for aluminum isopropoxide.[24] Absolute methanol, 300 ml. (7.5 moles), was added to a mixture of 27 g. (1.0 mole) of aluminum turnings and 0.5 g. of mercuric chloride. Reaction began immediately and was continued for six hours with stirring and refluxing. External cooling was unnecessary. Most of the aluminum dissolved. The excess methanol was removed by distillation, and the final traces were removed by heating to 200° (10 mm.). The aluminum methoxide prepared in this way is a fine, grey, infusible powder.

**Dealcoholation of Orthoesters with Aluminum Methoxide.** (a) **Methyl Orthophenylacetate.**—A mixture of 15.3 g. (0.128 mole) of aluminum methoxide and 25.5 g. (0.130 mole) of methyl orthophenylacetate was heated in a distilling flask. Methanol began to distill from the mixture when the temperature reached 210°. Heating was continued until the distillation of methanol ceased (twenty minutes); 3.4 g. (81.5%) of methanol, b. p. 58–62°, $n^{25}\text{D}$ 1.3294, was obtained. After the reaction mixture had partially cooled, colorless phenylketene dimethylacetal was distilled from the aluminum methoxide under reduced pressure. The yield was 19.7 g. (92%), b. p. 75–82° (1.5 mm.) 124–126° (14 mm.); $n^{25}\text{D}$ 1.5575; 36.0% methoxyl (calcd. 37.8%).

When a mixture of 25 g. (0.128 mole) of methyl orthophenylacetate and 13 g. (0.13 mole) of alumina pellets[25] was heated in a distillation apparatus attached to a cold trap, dealcoholation occurred in the range of 175–210°. The collected methanol amounted to 2.3 g. (56%); 2.3 g. of dimethyl ether (identified as the boron fluoride complex, b. p. 125–128°) collected in the cold trap. Distillation of the remaining material from the alumina under diminished pressure gave a mixture of methyl phenylacetate (54%) and phenylketene acetal (31%).

(b) **Methyl Orthoisobutyrate.**—A 30-cm. distilling head with a 12-cm. Vigreux section in the lower portion was wrapped with a layer of asbestos and a heating coil from the side arm to the glass joint that connected to a 100-ml. flask; the wrapped portion then was surrounded by a glass jacket. A plug of glass wool was placed at the top of the Vigreux section and the remainder of the head was filled with aluminum methoxide powder to just below the exit to the side arm. Then a thermometer was inserted into the head of the column so that it extended into the column of aluminum methoxide. The head was set into the 100-ml. flask and the side arm connected to a water-cooled condenser, a receiver and finally a cold trap.

With the aluminum methoxide heated to 290–300°, 30 g. of methyl orthoisobutyrate was distilled through the head. The distillate that collected in the receiver was redistilled from a small Claisen flask to give methanol, an unsaturated fraction boiling from 90 to 132°, and unchanged orthoester. The last fraction was recycled and the distillate was again separated into the three fractions. This procedure was repeated with an additional 30 g. of orthoester. The unchanged orthoester fractions from the two runs were combined and recycled. It was found that the aluminum methoxide lost approximately half its weight after two passes and, consequently, it was replaced after every two cycles.

The combined methanol fractions amounted to 2.09 g. (16.7%); 4.1 g. of dimethyl ether collected in the cold trap. The combined middle fractions were again distilled to give 18.9 g. of unsaturated material, b. p. 94–131°, and 12.2 g. of unchanged orthoester.

The unsaturated material was fractionated through an 18-plate Fenske column into the following fractions: (a) 7.2 g. of methyl isobutyrate, b. p. 90–93°, $n^{25}\text{D}$ 1.3815; (b) 3.66 g. of dimethylketene dimethylacetal contaminated by methyl isobutyrate, b. p. 100–103°, $n^{25}\text{D}$ 1.4028; (c) 1.03 g. of dimethylketene dimethylacetal, b. p. 103–105°, $n^{25}\text{D}$ 1.4069; and (d) 10.70 g. of unchanged methyl orthoisobutyrate. The amount of the ketene acetal in fraction (b), as calculated from the refractive index, was 2.93 g., bringing the total yield of this product to 3.96 g. (8.6%). Two drops of fraction (b) decolorized 230 drops of a 0.05 *N* bromine in carbon tetrachloride solution, while 2 drops of fraction (c) decolorized 310 drops of this reagent.[13] The yield of methyl isobutyrate (7.93 g.) amounted to 20%, and the total orthoester recovered (22.7 g.) was 37.8% of that originally used.

(c) **Methyl Orthopropionate.**—This orthoester was distilled through a heated column of aluminum methoxide as described in (b) except that the methoxide was heated to 240–245° and the emerging vapors passed downward through a short vertical column of sodium hydride before they entered the water cooled condenser. There was considerable condensation of the vapors in the sodium hydride column and a vigorous reaction of the hydride with the methanol of the condensed liquid.

Fractionation of the condensate from a 15-g. run of the orthoester showed that 1.71 g. (15%) of methylketene dimethylacetal was produced and 8.13 g. (54%) of unchanged orthoester was recovered.

## Summary

The reaction of a variety of orthoesters with sodium ethyl has been studied. Only methyl orthophenylacetate was dealcoholated to the ketene acetal; purely aliphatic orthoesters appear to be attacked at their alkoxyl groups rather than at the $\alpha$-hydrogen by this base.

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[23] The unsaturation was measured in the following manner: 2 drops of the liquid to be tested was treated dropwise with a 0.05 *N* bromine solution in carbon tetrachloride. Two drops of this particular fraction decolorized 125 drops of the bromine solution. A similar amount of the pure ketene acetal decolorized 298 drops of the bromine solution.

[24] Wilds, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1944, Vol. II, p. 198.

[25] Prepared in this Laboratory by Spencer H. Watkins from aluminum hydroxide obtained by hydrolysis of aluminum isopropoxide.

The dealcoholation of methyl orthophenylacetate by a variety of strong bases is reported. Of these bases mesitylmagnesium bromide was selected as the most efficient for the preparation of the ketene acetal.

Methyl orthopropionate and methyl orthoisobutyrate have been dealcoholated by mesitylmagnesium bromide to the respective ketene acetals: methylketene dimethylacetal and dimethylketene dimethylacetal. The latter compound is the first dialkylketene acetal to be prepared.

The aprotic acid, aluminum methoxide, at 210° promotes a smooth and rapid dealcoholation of methyl orthophenylacetate to produce phenylketene dimethylacetal in 92% yield.

Methyl orthopropionate is partially (15%) dealcoholated by aluminum methoxide at 240–245°. Methyl orthoisobutyrate requires a reaction temperature of 290–300° for dealcoholation over aluminum methoxide, but only 8.6% yield of the dimethylketene dimethylacetal is produced; the principal reaction products are the normal ester, methyl isobutyrate, and dimethyl ether.

MADISON, WISCONSIN RECEIVED NOVEMBER 7, 1949

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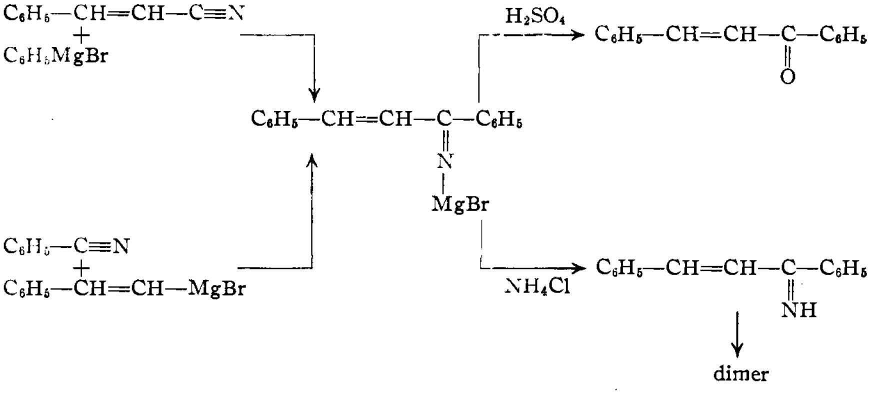
[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF TORONTO]

# The Grignard Reaction of Styryl Cyanide[1]

BY D. E. PIPER[2] AND GEORGE F WRIGHT

When the reaction mixture obtained by adding phenylmagnesium bromide to styryl cyanide is hydrolyzed with an ice-cold aqueous sulfuric acid solution, there is obtained[3] a 68% yield of benzalacetophenone. However when the reaction mixture is hydrolyzed with an ice-cold aqueous ammonium chloride solution little or no benzalacetophenone is formed but, instead, a 40% yield of a white crystalline compound melting at 183° and having the empirical formula $C_{15}H_{13}N$.[4] The present paper deals with the structure of this compound and its reactions.

Molecular weight determinations showed that the compound had the formula $C_{30}H_{26}N_2$, that is, double the formula of styryl phenyl ketimine, the ketimine corresponding to benzalacetophenone.



The fact that the compound is a dimer of styryl phenyl ketimine was demonstrated by its synthesis from styrylmagnesium bromide and benzonitrile. The aqueous ammonium chloride hydrolysis of this reaction mixture should produce styryl phenyl ketimine as did the former reaction.

The reactions of this dimer are best explained by structure I, 2,4,6-triphenyl-2,5-endo-(2′-phenylethylene)-2,3,4,5-tetrahydropyrimidine. A proposed mechanism for the formation of this compound from styryl phenyl ketimine is outlined.

Active hydrogen determinations using a half-mole excess of methylmagnesium iodide showed the presence of one active hydrogen per molecule. With a large excess of the Grignard reagent a total of 1.7 active hydrogens per molecule was indicated and at the same time a clear orange solution was formed instead of the white precipitate as in the previous case. This behavior is believed due to formation of a polymolecular complex in the presence of a large concentration of Grignard reagent. Determinations using lithium aluminum hydride showed the presence of 1.0 active hydrogen per molecule even when a large excess of the hydride was used. There was no indication of a Grignard absorbing group. Since the compound formed a mononitroso derivative when treated with very dilute nitrous acid in methanol, the active hydrogen is logically accounted for by a secondary amino group.

Although the compound could not be dehydrogenated by mild catalytic methods, there were obtained by heating with sulfur at 190° two fragments which were identified as styrene and 2,4,6-triphenylpyrimidine (II).[5] The compound when heated to about 300° in the absence of sulfur was found to decompose to three fragments which were

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(2) Holder of Imperial Oil Fellowship in Chemistry, 1946–1949.

(3) E. P. Kohler, *Am. Chem. J.*, **35**, 386 (1906).

(4) J. C. Bond and George F Wright, THIS JOURNAL, **72**, 1023 (1950).

(5) Asahina and Kuroda, *Ber.*, **47**, 1815 (1914).