Anal. Calcd. for $C_{14}H_{17}O_6Br$: C, 46.53; H, 4.70. Found: C, 46.47; H, 4.65.

The ethoxy acid was obtained in 50% yield by cautious hydrolysis of the ethoxy ester with alcoholic potassium hydroxide and was separated from the unsaturated acid which is also formed by taking advantage of the lack of solubility of the latter in cold chloroform.

When the unsaturated ethyl ester was treated with potassium hydroxide in the presence of methyl alcohol in the way described for the unsaturated methyl ester, a 69% yield of the methyl ester of the methoxy acid was formed; likewise the unsaturated methyl ester in the presence of ethyl alcohol gave an 80% yield of the ethyl ester of the ethoxy acid. In neither reaction was a second substance found; the poorer yields than were obtained when the reaction was carried out with an ester in the presence of the corresponding alcohol are accounted for by the formation, in both cases, of a considerable amount of yellow decomposition product.

Summary

5-Bromo-2,4-dimethoxybenzoylacrylic acid and its methyl ester are not isomerized or polymerized in the sunlight; the ethyl ester is stable to light in benzene solution but it is rapidly polymerized when exposed as a solid. Hydrolysis of the esters with sodium carbonate solution is extremely slow and incomplete; the methyl ester gives the unsaturated acid and a trace of α-hydroxy-5-bromo-2,4-dimethoxybenzoylpropionic acid on boiling for many hours with dilute hydrochloric acid. These esters react in methyl and ethyl alcohol solution in the presence of a few drops of potassium hydroxide solution to give α-alkoxyl addition products which are a result of 1:4 addition to one of the two conjugated systems of double linkages present in the esters.

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

THE RELATION OF THE STRUCTURE OF KETONES TO THEIR REACTIVITY AND AFFINITY IN ACETAL FORMATION

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The reaction of ketones with alcohols to form acetals analogous to the reaction of aldehydes with alcohols proceeds to so slight an extent, if at all, that the reaction is of no importance. In order to form the acetal of the ketones it is necessary to react the ketones with an ortho ester according to the equation $R_2C{=}O + HC(OR')_3 \rightleftharpoons R_2C(OR')_2 + HCO_2R'$. The reaction like that of aldehydes with alcohols is a reversible one and hence may be used for the evaluation of the relation of the structure of a ketone to the strength of the linkage between oxygen and carbon in the acetal.[1,2,3] To this end the extent of the reaction of eight ketones

[1] Adkins and Adams, THIS JOURNAL, **47**, 1377 (1925).

[2] Hartung and Adkins, *ibid.*, **49**, 2517 (1927).

[3] Street and Adkins, *ibid.*, **50**, 162 (1928).

with orthoformic ester has been determined. The ketones whose reactions have been investigated include five methyl ketones in which the second radical was methyl, ethyl, *n*-hexyl, phenyl or tertiary butyl, besides diethyl, diphenyl and propylphenyl ketones.

The reaction of the ketone with orthoformic ester did not proceed in a toluene or xylene solution containing hydrogen chloride, but proceeded smoothly in an alcoholic solution containing hydrogen chloride as a catalyst. It is apparently necessary to have a considerable proportion of alcohol in the solution, at least in some cases, for 0.1 mole of phenylpropyl ketone did not react with 0.12 mole of orthoformic ester in the presence of 4 cc. of ethanol but the reaction proceeded readily with 14 cc. of alcohol, the amount of hydrogen chloride being constant.

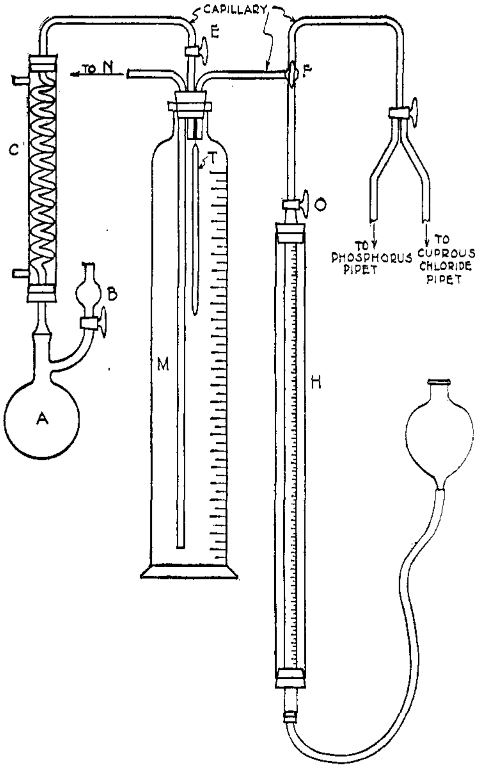

Fig. 1.—Apparatus for analysis for ethyl formate.

A typical procedure for an experiment was as follows. One-tenth of a mole (7.35 cc.) of acetone was run from a standard buret into a Pyrex test-tube (25 × 3.5 cm.). Twenty cubic centimeters or 0.1268 of a mole of orthoformic ester was added, followed by 11.65 cc. of absolute alcohol. A sampling device similar to that described by Child[4] was connected to the test-tube and the test-tube placed in a thermostat at 25°. After allowing the contents of the tube to come to the temperature of the thermostat, 1 cc. of alcohol containing 0.0136 g. of hydrogen chloride was added through the sampling device and thoroughly mixed with the contents of the tube by several times drawing the liquid up into the sampling device and allowing it to run back into the test-tube. After 48 to 60 hours a 5cc. sample was withdrawn and analyzed for ethyl formate. The time interval was chosen after it had been ascertained by experiment that the reaction had gone to completion in that time.

The retrograde reactions were run upon the diethyl acetals of acetone, acetophenone, diethyl ketone and methyl-*n*-hexyl ketone. Again, acetone diethyl acetal is given as typical. One-tenth of a mole of the diethyl acetal of acetone was put into a Pyrex test-tube, 0.1 mole of ethyl formate was added, together with sufficient alcohol to make the volume of the reaction mixture the same as that in the synthetic reaction. The test-tube was placed in a thermostat and, when the contents had reached 25°, 1 cc. of ab-

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[4] Child and Adkins, This Journal, 45, 3020 (1923).

solute alcohol containing 0.0136 g. of hydrogen chloride was added through the sampling device. After standing 48–60 hours a 5cc. sample was withdrawn and analyzed.

The method for the determination of ethyl formate was developed by making use of Geuther's observation that sodium ethoxide catalyzes the decomposition of the ester into carbon monoxide and alcohol.[5] An apparatus, a diagram of which is shown in Fig. 1, was developed in which ethyl formate was decomposed by sodium ethoxide and the evolved gas collected and analyzed for carbon monoxide. Such an analysis was conducted in the following manner.

One-half of a gram of sodium ethoxide was placed in the 50cc. flask (A) connected to a 20cm. spiral condenser (C) by a rubber stopper sealed in with collodion. The sample was run into the side-arm bulb (B) from which it was allowed to run into the flask through a stopcock. Ice water was placed about the flask in order to absorb the heat generated at the beginning of the reaction; otherwise the temperature in the flask would rise so rapidly that some of the ethyl formate would volatilize and condense on the cooler portions of the flask and condenser before reacting with the sodium ethoxide. Two cc. of dry toluene was poured down the sides of the side arm and bulb to wash down any of the ester which might be adhering to the sides of the glass. The evolved gas passed up through the condenser and replaced the saturated salt solution in the graduated container (M), the replaced liquid passing into a second graduated container (N). The level of the liquid in (N) was maintained slightly lower than that of the liquid in (M), so that no back pressure would be set up. After five minutes the ice-bath was replaced by a paraffin oil-bath which was gradually heated until it attained a temperature of 110–115° and this temperature was maintained for about one hour. All of the gas in the flask, condenser coils and connecting capillary tubing was forced into (M) by passing a saturated salt solution into the system through the side arm (B). The three-way stopcock (E) was closed and the container (N) was adjusted so that the level of the solution in it was the same as that in (M). The volume of gas in (M) was recorded and the temperature of the gas was obtained from the thermometer (T) which was immersed in it. The barometric pressure was recorded. A thorough mixing of the gas in (M) was accomplished by drawing a portion of it into the volumetric buret (H) and then passing it back into (M) eight or ten times until, finally, a 100cc. portion was confined in (H) by closing the three-way stopcock (F). This aliquot was analyzed for carbon monoxide, after removing the oxygen over phosphorus. The carbon monoxide was absorbed in acid cuprous chloride. The time required to decompose the ethyl formate and analyze the resulting gas was from one and three-quarters to two hours.

The presence of ethyl alcohol was found by Geuther to inhibit the decomposition of ethyl formate. This difficulty was overcome by adding a small piece of sodium, in slight excess of the amount necessary to react with all the alcohol formed. The presence of toluene and orthoformic ester did not affect the amount of carbon monoxide evolved. It was found that the amount of sodium ethoxide used to decompose ethyl formate did not influence the amount of carbon monoxide evolved, in most experiments 0.5 g. of sodium ethoxide being used. The analysis of nineteen samples of known and varying ethyl formate content showed that the amount of carbon monoxide formed was 64.6% ± 1.5% of that required by the equation given by Geuther, $HCO_2C_2H_5 \rightleftarrows CO + C_2H_5OH$. The course of this reaction will be considered later; suffice it for the present

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[5] Geuther, *Chem. Cent.*, 39, 632 (1868).

to say that apparently approximately three molecules of the ester yield two molecules of carbon monoxide. Not a trace of carbon dioxide was detected when over three liters of the evolved gas was passed through a solution of barium hydroxide.

The ratio of carbon monoxide to ethyl formate was found to vary slightly, depending on the amount and kind of ketone present in the reaction mixture. Presumably this discrepancy is due to the condensation of ethyl formate with the ketone according to the Claisen reaction. A concentration of 0.0125 mole of acetone in the reaction so affected the decomposition that only 33.8% of ethyl formate was accounted for. If the concentration was decreased to 0.00085 mole of acetone, which was about that in the samples analyzed in the equilibrium-point determinations, the amount of carbon monoxide formed was 66.6% of the ethyl formate known to be present. This conversion factor was used in calculating the percentage conversion of ketone to acetal. The conversion factors for the other ketones used were obtained by analyses of four or more samples in which the concentration of ketone was approximately that in the samples of equilibrium mixtures analyzed. These factors ±1.5% were: acetophenone 62.5%; diethyl ketone 63.4%; phenylpropyl ketone 65.2%; methylethyl ketone 66.0%; methylhexyl ketone 65.6%; methyl-*tert.*-butyl ketone 59.4% and benzophenone 66.8%.

TABLE I

SUMMARY OF DATA ON PERCENTAGE CONVERSION OF VARIOUS KETONES INTO ACETALS BY ORTHOFORMIC ESTER

Ketone	Per cent. conversion Retrograde	Per cent. conversion Synthetic	Ketone	Per cent. conversion Retrograde	Per cent. conversion Synthetic
$CH_3C{=}OCH_3$	92.62	89.87	$CH_3C{=}OC_6H_5$	67.45	66.87
$CH_3C{=}OC_2H_5$	...	87.73	$C_3H_7C{=}OC_6H_5$	...	64.25
$C_2H_5C{=}OC_2H_5$	86.16	87.49	$C_6H_5C{=}OC_6H_5$	...	31.55
$CH_3C{=}OC_6H_{13}$	85.82	84.91	*tert.*-$C_4H_9C{=}OCH_3$	...	12.48

A summary of the percentage of ethyl orthoformate found as ethyl formate is shown in the table for the synthesis of the acetal of eight ketones and for the retrograde reaction on four of the acetals. An inspection of the values given in the table shows that replacement of one or both of the methyl groups in acetone with higher straight-chain alkyl radicals results in a slight lowering of the percentage conversion to the acetal. A hexyl group has a rather marked effect. The substitution of a phenyl group for a methyl group in acetone lowers the percentage conversion by over 20%, while a second phenyl group causes a further lowering of over 30%. The negative effect of the higher as contrasted with the lower alkyl groups is again shown by the fact that the percentage conversion of phenylpropyl ketone is lower than that of phenylmethyl ketone.

The similarity of the tertiary alkyl radicals to the aryl radicals has been previously noted,[6] but it is surprising to find that methyl tertiary butyl ketone shows a lower conversion than methylphenyl ketone and even lower than diphenyl ketone. The number of ketones for which data are now available is too small to justify any attempt at a theoretical treatment of the subject.[7]

Preparation and Purification of Reagents

Orthoformic Ester was prepared in the usual way.[8]

Fourteen preparations each involving the use of 250 g. of sodium and 400 g. of chloroform averaged 375 g. of orthoformic ester boiling at 144–146° at 740 mm. after two fractionations. The 5250 g. of ester so obtained was reduced to 2500 g. by three fractionations through a 20cm. Vigreux column, the product boiling at 145–146° under atmospheric pressure and at 45–46° under 15 mm. This product was further fractionated just before use. The pure ester as used in this work had a density of d_{25}^{25} = 0.9385. The density given in the critical tables[9] is 0.8964.

Ketones.—Acetone was fractionated from a commercial product and purified as by Conant and Kirner;[10] b. p. 56.2–56.7° (740 mm.); $d_{25}^{25} = 0.7964$.

Methylethyl ketone, diethyl ketone, methyl-*n*-hexyl ketone, acetophenone and phenylpropyl ketone were supplied by the Eastman Kodak Co. Each ketone was dried over anhydrous potassium carbonate and then distilled from a Claisen flask carrying a Vigreux distilling column 20 cm. in length. The products used had the following constants: methylethyl ketone, b. p. 79–81° (760 mm.), $d_{25}^{25} = 0.8072$; diethyl ketone, b. p. 101–102° (corr.), sp. gr. 0.8156 (25/25); methyl-*n*-hexyl ketone, b. p. 173–175° (760 mm.), $d_{25}^{25} = 0.8360$; acetophenone, b. p. 200–202° (760 mm.), $d_{25}^{25} = 1.030$; and phenylpropyl ketone, b. p. 228–229.5° (760 mm.), $d_{25}^{25} = 0.9967$.

Benzophenone was an Eastman Kodak Co. product which had a melting point of 47.5–48°. Methyl-*tert.*-butyl ketone was prepared from pinacol by the pinacoline rearrangement as described in "Organic Syntheses."[11] The boiling point of this product was 103–105° (uncorr.) and its specific gravity was 0.7250 (25/25).

Ethyl formate was obtained from the Eastman Kodak Co., and after standing over anhydrous potassium carbonate was freshly distilled before using. The boiling point of this reagent was 54° and its specific gravity was 0.9250 (25/25).

Acetals.—The diethyl acetal of acetone was prepared by a method described by

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[6] Conant and Sloan, THIS JOURNAL, **48**, 1743 (1926); Adkins and Adams, *ibid.*, **47**, 1368 (1925).

[7] Without further experimental work it does not seem advisable to use these determinations on the amount of ethyl formate formed, for the calculation of the equilibrium constant for the reaction of the orthoformic ester with the ketones, because in some cases it is possible that small amounts of the ethyl formate reacted with ketone according to the Claisen reaction and were therefore not found in the analytical determination. It is anticipated that further work will be done on the extent of the Claisen reaction under the conditions used in this work so that the values given in this paper may be more quantitatively interpreted.

[8] Adkins and McElvain, "Practice of Organic Chemistry," McGraw-Hill Book Co., New York, **1925**, p. 80.

[9] "International Critical Tables," Vol. I, p. 215.

[10] Conant and Kirner, THIS JOURNAL, **46**, 245 (1924).

[11] "Organic Syntheses," John Wiley and Sons, Inc., New York, **1925**, Vol. V, p. 91.

Claisen,[12] with the exception that 0.0136 g. of dry hydrogen chloride was used as a catalyst in place of 1 g. of ammonium chloride; b. p. (15 mm.) 24–25.5°; d^{25}_{25} = 0.8714.

Diethyl acetal of acetophenone was prepared by the method described by Claisen,[13] with the exception that 0.0136 g. of dry hydrogen chloride was used as a catalyst instead of 0.15 cc. of aqueous hydrochloric acid; b. p. (12 mm.) 110–112°; d^{25}_{25} = 1.0012.

The other diethyl acetals synthesized were prepared in the same manner as was that of acetophenone and possessed the following constants: diethyl acetal of diethyl ketone, b. p. (15 mm.) 51–53°, d^{25}_{25} = 0.8810; diethyl acetal of methylethyl ketone, b. p. (16 mm.) 40–41°, d^{25}_{25} = 0.8787; diethyl acetal of methyl-*n*-hexyl ketone, b. p. (16 mm.) 101–103°, d^{25}_{25} = 0.8798; and diethyl acetal of phenylpropyl ketone, b. p. (15 mm.) 118–120°, d^{25}_{25} = 0.9406.

The preparation of methyl-*n*-hexyl acetal and phenylpropyl acetal are not described in the literature.

Anal. Calcd. for $(CH_3)(C_6H_{13})C(OC_2H_5)_2$: C, 71.28; H, 12.87. Found: 71.48, 13.11.

Anal. Calcd. for $(C_3H_7)(C_6H_5)C(OC_2H_5)_2$: C, 75.67; H, 9.90. Found: 75.90, 10.12.

Catalyst.—The catalyst used was made up as described by Adkins and Adams,[1] so that a concentration of 0.0136 g. of hydrogen chloride per cubic centimeter of ethyl alcohol was obtained.

Sodium Ethoxide.—Fifty grams of sodium was added to 150 cc. of absolute alcohol in a flask of 500cc. capacity. The flask was connected to a reflux condenser to the top of which was attached a calcium chloride tube. As soon as all of the sodium had reacted, the alcohol was distilled off from an oil-bath in an atmosphere of dry hydrogen. The hydrogen was dried by passing it through concentrated sulfuric acid. The temperature of the sodium ethoxide in the flask was maintained at 180–200° for at least an hour. A pure white product was obtained which turned slightly yellow after a week's time.

Summary

A method has been developed for the quantitative estimation of ethyl formate in the presence of alcohol, orthoformic ester, a ketone and its acetal, which consists in partially converting ethyl formate into carbon monoxide using sodium ethoxide as a catalyst. The percentage of ethyl formate converted into carbon monoxide varied somewhat with the amount and kind of ketone present.

The method of analysis for ethyl formate has been used to determine the extent of the reaction of orthoformic ester with eight ketones: dimethyl, methylethyl, diethyl, methyl-*n*-hexyl, methylphenyl, phenylpropyl, diphenyl and methyl-*tert.*-butyl ketones. Certain conclusions have been drawn with respect to the relation of the structure of a ketone to the affinity manifested in acetal formation.

The reaction of orthoformic ester with ketones does not proceed in a xylene or toluene solution. The true catalyst would then appear to be a compound of alcohol and hydrogen chloride. Acetophenone reacts much more rapidly than does acetone.

[12] Claisen, *Ber.*, **40**, 3908 (1907).

[13] Ref. 12, p. 3913.

The diethyl acetals of methyl-*n*-hexyl and phenylpropyl ketones were prepared and analyzed for the first time.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF GEORGETOWN (KENTUCKY) COLLEGE]

ALKYL AMINO-ETHANOL AND PROPANOLS[1]

BY J. STANTON PIERCE

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Many naturally occurring compounds of therapeutic importance contain the grouping alkyl-N-C-C-O or alkyl-N-C-C-C-O. Among these compounds are cocaine, quinine, strychnine, hydrastine, hyoscine, atropine and adrenaline. Also, many synthetic medicinals, as procaine, stovaine, alypine, apothesin, butyn and homatropine contain one of these groups.

Since the linkages referred to above are prevalent in so many compounds of marked physiological action, a good method for the preparation of simple substances containing these groupings should be of considerable value in the synthesis of more complex compounds, as those mentioned above. A large number of alkyl amino-ethanols have been prepared by Matthes[2] by the action of ethylene oxide on the monoalkyl amines, but there was usually obtained as by-product the corresponding alkyl dihydroxyethylamine. The latter compounds were difficult to separate from the desired product. A similar method was used by Knorr and Matthes[3] and Knorr and Schmidt.[4] Knorr[5] also condensed aqueous methylamine with ethylene chlorohydrin to form methylamino-ethanol.

This paper deals with the preparation of alkyl amino-ethanol and alkyl aminopropanols by the method used by Otto[6] and Adams and Segur[7] for aryl amino-ethanols and Pierce with Adams[8] for aryl-aminopropanols. By this method there are no by-products of tertiary amines and in most cases the yield of pure product is fair.

Discussion of Results

The condensation of the alkyl amines with β-chloro-ethylchloroformate and with γ-chloropropylchloroformate took place readily, as was the case

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[1] The author wishes to express his thanks to Professor Roger Adams, of the University of Illinois, for his valuable suggestions at the outset of this work. Also, acknowledgment is made to the Chemical Department of the University of South Dakota, at which place part of this work was done.

[2] Matthes, *Ann.*, **315**, 104 (1901).

[3] Knorr and Matthes, *Ber.*, **31**, 1069 (1898).

[4] Knorr and Schmidt, *Ber.*, **31**, 1073 (1898).

[5] Knorr, *Ber.*, **22**, 2088 (1889).

[6] Otto, *J. prakt. Chem.*, [2] **44**, 15 (1890).

[7] Adams and Segur, THIS JOURNAL, **45**, 785 (1923).

[8] Pierce with Adams, *ibid.*, **45**, 790 (1923).