2,4-dinitrophenylhydrazone, m. p. 59°, and into ethyl methyl ketone the semicarbazone of which melted at 136°.[17]

β-Ethoxypropylphenylcarbinol has not been previously described. It has the following constants: b. p., 82.5° (1 mm.); n^{21}_D 1.4995; d^{20}_4 0.994; M_D, found, 56.8; M_D, calcd., 52.0; mol. wt., cryoscopic in benzene 202, cryoscopic in camphor 198; mol. wt. calcd., 194; % hydroxyl, found, 8.76, 8.75[18]; calcd., 8.76. The Baeyer and iodoform tests are negative. We are unable to explain the anomaly in molecular refractivity except on the basis that this product is in all probability a mixture of two racemic forms.

β-Ethoxybutyrophenone was thought to be present in the reaction mixture resulting from limited hydrogenation of O-ethylbenzoylacetone over nickel. Nine fractions boiling 94–110° (1 mm.) were collected from a 3-plate distillation. The first six of these, 94–100°, showed a gradual drop in refractive index, n^{20}_D 1.5137–1.5075 and represented 64% of the weight of starting material. The last two fractions n^{20}_D 1.5645 represented 11% recovery of crude starting material. Fraction number three gave negative tests with bromine and with permanganate, and the presence of an aryl ketone in approximately 50% concentration was demonstrated by the polarograph, $\pi = -1.68$. Assuming the mixture to be pure alcohol and ketone the Grignard machine analysis indicated 56% of alcohol of molecular weight 195 and 44% ketone of molecular weight 194. The calculated molecular weights of the expected ketone and alcohol, V and VI, are 194 and 196, respectively.

Butyrophenone, n^{20}_D 1.5127, showed a polarographic wave in lithium chloride solution at −1.68 volts (empirical). It gave a semicarbazone, m. p. 189–190°, and a 2,4-dinitrophenylhydrazone, m. p. 190°, in agreement with the literature.[17]

Ethyl β-ethoxybutyrate, n^{20}_D 1.4076; d^{20}_4 0.925; M_D found, 42.6, calcd., 42.4; had the correct boiling point at 745 mm., 173°.[19]

Summary

1. Compounds which are open-chain vinylogs of esters are too much like esters to be reduced by aluminum alkoxides. They, however, are not sufficiently ester-like to undergo alkoxyl exchange with these reagents.

2. When the alkoxyl group is in a vinylogous position to both a keto-carbonyl and a carbethoxyl, it undergoes hydrogenolysis over nickel under very mild conditions. When the alkoxyl is vinylogous to only a keto-carbonyl it is more resistant to hydrogenolysis and the nature of the hydrogenation products may be controlled by selection of catalysts. The carbethoxyl group does not labilize such groups sufficiently to allow of hydrogenolysis prior to hydrogenation of the ethylenic linkage.

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[17] Huntress and Mulliken, "Identification of Pure Organic Compounds," Order I, John Wiley and Sons, Inc., New York, N. Y., 1941.

[18] Adkins, Frank and Bloom, THIS JOURNAL, 63, 554 (1941).

[19] Purdie and Marshall, *J. Chem. Soc.*, 59, 478 (1891).

EVANSTON, ILL. RECEIVED OCTOBER 28, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

The Acetylation of Certain Unsymmetrical Aliphatic Ketones with Acetic Anhydride in the Presence of Boron Trifluoride[1,2]

BY CHARLES R. HAUSER AND JOE T. ADAMS

The acetylation of ketones with acetic anhydride in the presence of boron trifluoride to form 1,3-diketones has been carried out previously apparently only with ketones such as acetone,[3,4] diethyl ketone[3] or acetophenone,[3,5] each of which can yield but a single monoacetyl derivative. The purpose of this investigation has been to determine the products of acetylation, in the presence of boron trifluoride, of certain unsymmetrical aliphatic ketones each of which might form two different monoacetyl derivatives. Three types of unsymmetrical ketones have been studied, types I, II and III, represented below, with which it is possible to form, respectively, the methyl and methylene derivatives, the methyl and methinyl derivatives, and the methylene and methinyl derivatives, thus

$$\underset{\text{Type I}}{\mathrm{CH_3COCH_2R}} \xrightarrow[\mathrm{BF_3}]{\mathrm{Ac_2O}} \underset{\text{Methyl deriv.}}{\mathrm{CH_3COCH_2COCH_2R}} + \underset{\text{Methylene deriv.}}{\mathrm{CH_3COCHRCOCH_3}}$$

$$\underset{\text{Type II}}{\mathrm{CH_3COCHR_2}} \xrightarrow[\mathrm{BF_3}]{\mathrm{Ac_2O}} \underset{\text{Methyl deriv.}}{\mathrm{CH_3COCH_2COCHR_2}} + \underset{\text{Methinyl deriv.}}{\mathrm{CH_3COCR_2COCH_3}}$$

$$\underset{\text{Type III}}{\mathrm{RCH_2COCHR_2}} \xrightarrow[\mathrm{BF_3}]{\mathrm{Ac_2O}} \underset{\text{Methylene deriv.}}{\mathrm{CH_3COCHRCOCHR_2}} + \underset{\text{Methinyl deriv.}}{\mathrm{CH_3COCR_2COCH_2R}}$$

Seven ketones have been acetylated, five of type I, methyl ethyl, methyl *n*-propyl, methyl isobutyl, methyl *n*-amyl and methyl *n*-hexyl ketones, and one each of types II and III, methyl isopropyl ketone and 2-methylcyclohexanone,[6] respectively. The yields of acetylation products isolated from these ketones were 28–59%, the

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[1] Paper XXIII of series on "Condensations;" for paper XXII, see THIS JOURNAL, 66, 309 (1944).

[2] This investigation was supported in part by a grant from the Duke University Research Council.

[3] Meerwein and Vossen, *J. prakt. Chem.*, 141, 149 (1934).

[4] "Organic Syntheses," Vol. 20, 6 (1940).

[5] Breslow and Hauser, THIS JOURNAL, 62, 2385 (1940).

[6] Although this ketone has a cyclic, instead of the linear structure represented by the general formula above, it should react as a typical type III ketone.

highest yields being obtained from methy *n*-amyl and methyl *n*-hexyl ketones. Considerable amounts (15–25%) of the ketones were generally recovered and relatively little high boiling material was obtained. The only other product found was acetylacetone resulting from the self-condensation of the acetic anhydride as described previously.[3]

The acetylation products obtained from each of the ketones (except methyl ethyl ketone) were found to consist of a mixture of the two possible acetyl derivatives shown in the general equations represented above. A reasonably good separation of the isomeric 1,3-diketones has been realized by extracting ether solutions of the acetylation products with alkali, in which the methyl derivatives are relatively much more soluble than are the methylene derivatives, while the methinyl derivatives are insoluble in alkali. Essentially complete extraction of the methyl derivatives was indicated when the alkaline extracts no longer gave the red enol test (characteristic of the methyl derivatives),[7] but instead gave the purple enol test (characteristic of the methylene derivatives),[7] or gave no enol test (characteristic of isopropylacetylacetone[8] and the methinyl derivatives). Complete extraction of the methylene derivative of 2-methylcyclohexanone was indicated when the alkaline extract no longer gave the purple enol test. The methyl and methylene derivatives of ketones of type I were recovered with relatively little loss so that a fairly reliable estimate of the proportions in which these derivatives were present in the original acetylation products could be made. Alkali extractions of acetylation products from the ketones of types II and III, however, produced some cleavage apparently involving mainly the methinyl derivative. The proportions of the acetyl derivatives of methyl isopropyl ketone (type II) has been obtained by treating the original acetylation product with copper acetate, only the methyl derivative yielding a copper salt. This method has not been applicable to the acetylation product from 2-methylcyclohexanone (type III), since the copper salt of the methylene derivative could not be crystallized.

In Table I are given the relative percentages of the two isomeric acetyl derivatives comprising the original acetylation products. These values are probably reproducible within ±3% for the derivatives of the methyl *n*-alkyl ketones, within ±5% for the derivatives of methyl isobutyl ketone, and within ±10% for the derivatives of methyl isopropyl ketone and 2-methylcyclohexanone. Since the first alkaline extract of the acetylation product from methyl ethyl ketone gave the purple enol test we have concluded that this product consists essentially only of the methylene derivative.

The proportions of the two isomeric acyl derivatives produced from at least the ketones of type I are evidently independent of the anhydride used, since, in an investigation now in progress on the acylation of ketones with higher anhydrides, it has been found that methyl ethyl, methyl isobutyl and methyl *n*-amyl ketones with propionic and butyric anhydrides yield essentially the same proportions of the corresponding methyl and methylene derivatives as those given in Table I for the acetylation products.

TABLE I

THE RELATIVE PERCENTAGES OF THE TWO ISOMERIC ACETYL DERIVATIVES COMPRISING THE ACETYLATION PRODUCTS OF KETONES

Ketone acetylated	% Methyl derivative	% Methylene derivative	% Methiny derivative
Methyl ethyl	0	100	
Methyl *n*-propyl	10	90	
Methyl isobutyl	55[a]	45	
Methyl *n*-amyl	10	90	
Methyl *n*-hexyl	10	90	
Methyl isopropyl	32[b]		68
2-Methylcyclohexanone		50	50

[a] This is the average of the values found by the alkali extraction method and by the preparation of the copper salt directly from the original acetylation product. [b] This is the value obtained by the preparation of the copper salt directly from the original acetylation product.

It can be seen from Table I that the methyl *n*-alkyl ketones of type I yield largely the methylene derivatives with only small amounts (or none) of the methyl derivatives, whereas methyl isobutyl ketone, which has a branched chain, yields a little more of the methyl than methylene derivative. Methyl isopropyl ketone (type II) yields mainly the methinyl derivative, but also a considerable amount of the methyl derivative, while 2-methylcyclohexanone (type III) yields the methylene and methinyl derivatives apparently in about equal amounts. Thus, in the presence of boron trifluoride, ketones are capable of being acylated at the α-methyl, α-methylene or α-methinyl groups at which the α-carbon atom holds, respectively, three, two and one hydrogen atoms.

Although the α-hydrogen of a ketone is involved in the acylation, it would appear that the number of hydrogens present on the β-carbon atom in the ketones of type I, $CH_3CO{-}\underset{\alpha}{CH_2}{-}\underset{\beta}{C}\langle$, determines the relative proportions of the methyl and methylene derivatives that result, the proportion of the methylene derivative decreasing and that of the methyl derivative increasing as the number of β-hydrogens is decreased.[9] Thus, methyl ethyl ketone, which has three β-hydrogens yields apparently only the methylene derivative; methyl *n*-propyl, methyl *n*-amyl or methyl *n*-hexyl ke-

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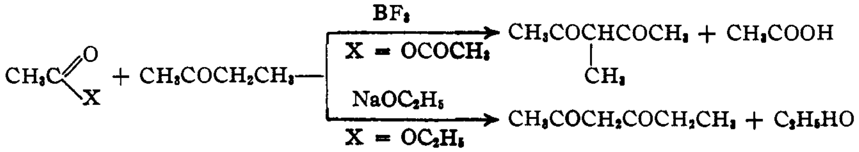
(7) See Morgan, Drew and Porter, *Ber.*, **58**, 333 (1925).

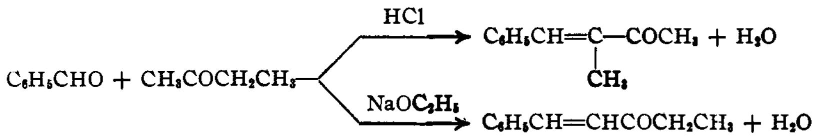
(8) Morgan and Thomason, *J. Chem. Soc.*, **125**, 754 (1924).

(9) On the basis that these acylations are dependent on the conversion of the ketone into its enol form by the acidic mechanism (which may be regarded as a special case of the elimination reaction), these results may be explained by the application of the theory of Baker and Nathan that CH-bond electrons may participate in tautomeric electron displacements. For the application of this theory to the elimination reaction see Hughes and Ingold, *Trans. Faraday Soc.*, **37**, 675 (1941).

tone, which has two β-hydrogens yields 90% of the methylene and 10% of the methyl derivative; while methyl isobutyl ketone, which has only one β-hydrogen, yields 45% of the methylene and 55% of the methyl derivative. An attempt to acetylate methyl neopentyl ketone, which has no β-hydrogens, failed.

The fact that the methylene derivative is the main product with methyl *n*-alkyl ketones and acetic anhydride in the presence of the acidic reagent, boron trifluoride, is in contrast to the formation of only[10] the methyl derivative with these ketones and ethyl acetate in the presence of a base, which has been the more common method of acylation of ketones. A similar relationship exists for the aldol reaction between at least methyl ethyl ketone and benzaldehyde,[11] which yields chiefly the methylene derivative in the presence of hydrogen chloride, but the methyl derivative in the presence of sodium hydroxide.





The fact that the methinyl derivative is the main product with methyl isopropyl ketone and acetic anhydride in the presence of boron trifluoride is also in contrast to the formation of only the methyl derivative with this ketone and ethyl acetate in the presence of a base.[12] The contrast is not as great with methyl isobutyl ketone,[13] however, which yields a little more of the methyl than methylene derivative in the presence of boron trifluoride and only the methyl derivative in the presence of a base.[12]

The two different courses of the acylation or aldol reaction with methyl ethyl ketone in the presence of acidic and basic reagents are paralleled by the halogenations of this ketone, which, in the presence of chlorine and hydrochloric acid, yields mainly the methylene chloro derivative,[14] 3-chloro-2-butanone, but which, in the presence of alkali, undergoes the well-known haloform reaction involving the halogenation of the methyl hydrogens. Since the formation of the enol of the ketone is generally considered to be prerequisite for the halogenation,[15] it would appear that the formation of the enol form of the ketone is also prerequisite for the acylation and aldol reactions.

Thus, these carbon–carbon condensations effected by acidic reagents may involve the activation not only of the electron-accepting component,[16] the anhydride or aldehyde, but also of the electron-donating component,[16] the ketone. The activation of the anhydride or aldehyde consists in the coördination of the acidic reagent with the carbonyl oxygen thereby making the carbonyl carbon a stronger electron-acceptor. The activation of the ketone (which, in most cases, is probably the more weakly activated of the two) consists in the coördination of the acidic reagent with its carbonyl oxygen thereby facilitating the conversion of the ketone into the enol form, which presumably is a stronger electron donor. A base, however, can activate only the ketone; of course the base used as condensing agent may attack the carbonyl carbon of the anhydride or aldehyde but this should consist in a deactivation, rather than an activation, since the electron-accepting capacity of the carbonyl carbon would thereby be destroyed. It should be pointed out also, that although the Friedel–Crafts type of acylation of benzene with an anhydride is somewhat analogous to the acylation of a ketone in the presence of an acidic reagent, probably only the anhydride is activated in the former reaction.

Certain of the acetylations described in this paper are of value for the synthesis of 1,3-diketones. The use of these and other acylations in syntheses will be discussed in a later paper.

Experimental[17]

Acetylation.—One mole of acetic anhydride and one-half mole of the ketone were placed in a three-neck flask equipped with an inlet tube (1 cm. above the surface of the liquid), a mercury-sealed stirrer and a calcium chloride tube. The mixture was cooled in an ice-bath and stirred. Boron trifluoride was passed in at such a rate that the mixture was saturated (as indicated by the copious evolution of white fumes) within two to three hours. After the mixture was saturated, the boron trifluoride was passed in for fifteen to twenty minutes longer, and the reaction mixture

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[10] See Hurd and Kelso, THIS JOURNAL, **62**, 2184 (1940).

[11] Harries and Muller, *Ber.*, **35**, 966 (1902).

[12] See Sprague, Beckham and Adkins, THIS JOURNAL, **56**, 2666 (1934).

[13] A study is in progress in this Laboratory to determine the products of reaction of benzaldehyde with such ketones as methyl isobutyl and methyl neopentyl ketones in the presence of an acidic reagent.

[14] Kling [*Bull. soc. chim.*, [3] **33**, 325 (1905)] found that on monochlorination in slightly acid medium, methyl ethyl ketone yields about 80% of the methylene chloro derivative and 20% of the methyl chloro derivative, 1-chloro-2-butanone. In this Laboratory Mr. R. Levine has found that in strong acid medium, the percentage of the methylene chloro derivative is even greater. Also, a preliminary experiment by Levine has indicated that, similar to the acylation in the presence of boron trifluoride, methyl isobutyl ketone yields on chlorination in strongly acid medium at least as much of the methyl chloro derivative as the methylene chloro derivative.

[15] See Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, pp. 231–233.

[16] See Hauser and Breslow, THIS JOURNAL, **62**, 2389 (1940).

[17] Analyses are by Dr. T. S. Ma, Microchemical Laboratory, Department of Chemistry, University of Chicago, Chicago, Illinois. Boiling points and melting points are uncorrected.

then poured into a solution of 130 g. of sodium acetate in one liter of water. The mixture was steam distilled[18] until the distillate no longer gave an enol test with ferric chloride. The steam distillate was cooled and practically all of the acetic acid present was neutralized by adding dilute sodium hydroxide solution until the mixture just turned litmus red. The slightly acidic mixture was extracted with ether and, after drying over sodium sulfate, the solvent distilled. The residue was fractioned *in vacuo* and the acetylation products of the ketones were collected. The forerun generally contained acetylacetone.

Alkali Extraction Method.—The two isomeric acetyl derivatives of the ketones comprising the acetylation products were separated in the following manner. Samples (10–20 g.) of the acetylation products were dissolved in 100 cc. of ether and the solutions were extracted with 100-cc. portions of cold 1% aqueous sodium hydroxide until two successive alkaline extracts (after acidification) gave, respectively, the red and the purple enol tests, the red and no enol test, or the purple and no enol test. Generally several extractions were required. The ether solutions were then distilled, while the combined alkaline extracts were acidified, extracted with ether and the solvent distilled. The methylene and methinyl derivatives were recovered essentially pure but the recovered methyl derivatives generally contained a little of the methylene derivative; however, the pure copper salt of the methyl derivative was readily obtained. The 1,3-diketones were identified by boiling points, analyses (of the single or mixture of isomeric 1,3-diketones) and by their enol tests and copper salts (which are blue with methyl derivatives and gray with methylene derivatives)[7] or by the failure to give enol tests or copper salts.

With Methyl Ethyl Ketone.—The acetylation yielded 18 g. (32%) of product, b. p. 77–79° at 30 mm., evidently consisting of only methyl acetylacetone. The first alkaline extract (using 1% or 0.5% alkali) gave the purple enol test and gray copper salt, which gave no sharp melting or decomposition point. The isomeric propionylacetone (which is more soluble in alkali) gives the red enol test and blue copper salt, m. p. 197–198.[19] A similar alkaline extraction of the forerun (6 g., b. p. 73–76° at 30 mm.), obtained on fractionation of the acetylation product, gave only acetylacetone, isolated as its blue copper salt, which decomposes above 230°.[20]

With Methyl *n*-Propyl Ketone.—The acetylation yielded 22 g. (34%) of product, b. p. 78–81° at 20 mm. *Anal.* Calcd. for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.58; H, 9.27. The alkali extraction method showed that this acetylation product consisted of 10% *n*-butyrylacetone (giving the red enol test, isolated as its blue copper salt, m. p. 164–165°[21]) and 90% (by difference) of ethyl acetylacetone, b. p. 80–81° at 20 mm., which gave the purple enol test and gray copper salt, m. p. 209–211°.[22]

With Methyl Isobutyl Ketone.—The acetylation yielded 29 g. (41%) of product, b. p. 79–81° at 20 mm. *Anal.* Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.41; H, 9.50. The alkali extraction method showed that this product consisted of 60% of isovalerylacetone (b. p. 78–79° at 20 mm., giving the red enol test and blue copper salt, m. p. 154–155°[21]) and 40% of isopropyl acetylacetone (b. p. 183–185° at 750 mm. *Anal.* Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.92; H, 10.07), which gave no enol test or copper salt.

A sample of the original acetylation product gave the copper salt of isovalerylacetone in a yield which corresponded to 50% of the 1,3-diketone.

With Methyl *n*-Amyl Ketone.—The acetylation yielded 46 g. (59%) of product, b. p. 104–106° at 20 mm. This product was not extracted with alkali; instead, the experiment was repeated and the total ether extract was subjected directly to the alkali extraction method. In this manner, the acetylation product was found to consist of 10% of *n*-hexoylacetone (b. p. 102–103° at 20 mm., giving the red enol test and blue copper salt, m. p. 137–138°[23]) and 90% of *n*-butyl acetylacetone (b. p. 105–106° at 20 mm.) which gave the purple enol test and gray copper salt, m. p. 185–186°.

With Methyl *n*-Hexyl Ketone.—The acetylation yielded 45 g. (53%) of product, b. p. 112–113° at 15 mm. *Anal.* Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.12; H, 10.29. The alkali extraction method showed that this product consisted of 10% of *n*-heptoylacetone (giving the red enol test, isolated as its blue copper salt, m. p. 122–123°[24]) and 90% (by difference) of *n*-amyl acetylacetone (b. p. 112–113° at 15 mm.) which gave the purple enol test and gray copper salt, m. p. 177–178°.

With Methyl Isopropyl Ketone.—The acetylation yielded 18 g. (28%) of product, b. p. 73–76° at 20 mm. *Anal.* Calcd. for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.39; H, 9.18. On application of the alkali extraction method, using 5 g. of acetylation product, there was obtained 1 g. of isobutyrylacetone (giving the red enol test, and isolated as its blue copper salt, m. p. 170–171°[25]) and 1.4 g. of dimethylacetylacetone, b. p. 172–174° (*Anal.* Calcd. for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.57; H, 9.41), which gave no enol test or copper salt. In addition there was obtained a fraction (1 g.), b. p. 80–100°, which presumably was mainly methyl isopropyl ketone.

A sample of the original acetylation product gave the copper salt of isobutyrylacetone in a yield which corresponded to 32% of this 1,3-diketone.

With 2-Methylcyclohexanone.—The acetylation yielded 27 g. (35%) of product, b. p. 116–118° at 20 mm. *Anal.* Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.36; H, 9.19. On application of the alkali extraction method, using 10 g. of the acetylation product, there was obtained from the alkaline extracts 5 g. of material assumed to be 2-methyl-6-acetylcyclohexanone (giving the purple enol test and gray oily copper salt which could not be crystallized) and from the material insoluble in alkali, 1 g. of material (b. p. 168–183°) assumed to be mainly 2-methylcyclohexanone, and 2.5 g. of 2-methyl-2-acetylcyclohexanone (b. p. 190–222°, mostly at 220–222°). (*Anal.* Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.75; H, 9.08) which gave no enol test or copper salt.

Summary

The acetylation of certain unsymmetrical aliphatic ketones with acetic anhydride in the presence of boron trifluoride to form 1,3-diketones has been carried out, and the proportions of the two possible acetyl derivatives have been determined.

Methyl ethyl ketone yields apparently only the methylene derivative; methyl *n*-alkyl ketones yield 90% of the methylene derivative and 10% of the methyl derivative; while methyl isobutyl ketone yields 45% of the methylene derivative and 55% of the methyl derivative. Methyl isopropyl ketone yields 68% of the methinyl derivative and 32% of the methyl derivative, while 2-methylcyclohexanone yields the methylene and methinyl derivatives in about equal amounts.

These results are compared with acylations effected by bases. Correlations are made between

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[18] An alternate procedure was to extract the reaction mixture (after standing with the sodium acetate solution for a few hours) directly with ether, but apparently certain boron trifluoride complexes were not completely decomposed under these conditions and better yields of 1,3-diketones have been obtained by the steam distillation procedure.

[19] Griner, *Ann. Chim. Phys.*, [6] **26**, 362 (1892).

[20] Claisen, *Ann.*, **227**, 170 (1893).

[21] Morgan and Drew, *J. Chem. Soc.*, **125**, 731 (1924).

[22] Curtiss, *Am. Chem. J.*, **17**, 436 (1895).

[23] Morgan and Holmes, *J. Chem. Soc.*, **125**, 760 (1924).

[24] Claisen and Ehrhardt, *Ber.*, **22**, 1016 (1889).

[25] Conrad and Gast, *Ber.*, **31**, 1339 (1898).

acylations, aldolizations and halogenations in the presence of acidic and basic reagents. Certain aspects of the theory of the reactions are considered.

DURHAM, N. C. RECEIVED SEPTEMBER 10, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

The Preparation of β,β-Trehalose Octaacetate

BY CHESTER M. MCCLOSKEY,[1] RONALD E. PYLE AND GEORGE H. COLEMAN

In connection with work in this Laboratory on the chromatographic separation of the azoyl derivatives of sugars, it was necessary to prepare β,β-trehalose. Since procedures previously reported did not prove satisfactory for preparing moderate quantities of this compound, modification of one of these methods was undertaken.

Fischer and Delbrück,[2] who discovered β,β-trehalose octaacetate, prepared it by the action of silver carbonate and a small amount of water upon an ether solution of tetraacetyl-α-D-glucosyl bromide, in a yield of about 1%; they also obtained it from the action of phosphorus pentoxide on a chloroform solution of 2,3,4,6-tetraacetyl-β-D-glucose in a yield of 2%.

In 1932 Schlubach and Schetelig[3] prepared β,β-trehalose octaacetate by the condensation of tetraacetyl-α-D-glucosyl bromide and 2,3,4,6-tetraacetyl-β-D-glucose in a chloroform solution with silver carbonate, calcium chloride and iodine. The reduction value of the crude reaction mixture was determined by Bertrand's method and the condensation was calculated as 50%, based on the reduction value of pure tetraacetyl glucose. The yield of crystalline product was not given.

The procedure of Schlubach and Schetelig was repeated several times in this Laboratory. The best yield of crystalline β,β-trehalose octaacetate was not more than 4%. The conditions described by these authors were duplicated as nearly as possible. However, it may be that some necessary precaution was omitted, since the reaction product showed a reduction value corresponding to only 18.8% condensation.

This preparation has been modified to conform more closely to the technique used by Kreider and Evans[4] in the Koenigs and Knorr synthesis. By effecting condensation in the presence of Drierite as drying agent, a 10% yield of crystalline product, m. p. 180.5–181.5° cor., has been obtained. The reduction value of the crude reaction product indicated a condensation of approximately 30%. The non-crystalline residues from which no more product could be obtained, still contained two-thirds of the original condensation product as shown by reduction values. This problem is being investigated further.

The use of iodine has been found essential for satisfactory condensation. Excessive amounts of glucosyl bromide and elevated temperatures did not produce appreciably higher yields.

In a series of several runs the percentage yields calculated from the reducing values varied from 30–40%. The actual yield of crystalline product did not, however, in any case exceed 10.5%. In one run in which only 4.5 g. of iodine was used the percentage yield calculated from the reducing value was 30%. The yield of crystalline material was only 3.4%.

Experimental Part

2,3,4,6-Tetraacetyl-α-D-glucosyl Bromide.—This compound was prepared by the method of Karjala and Link[5] or Redemann and Niemann[6] from pentaacetylglucose or its glucose equivalent. The crude reaction mixture prepared by this method from 120 g. of glucose pentaacetate was poured with rapid stirring into 1.5 liters of ice-water. The precipitate, which solidified, was filtered off and ground in a mortar in order to break up the lumps. It was then returned to the filter funnel and washed thoroughly with ice-water and sucked as dry as possible. The precipitate without further drying was dissolved in 300 ml. of ether. The aqueous layer was separated and the ether layer cooled in a freezing mixture. The crystals which formed were filtered off and the filtrate which had partially evaporated during the filtration was cooled as before. In this manner several crops of crystals were obtained. The crystallization of the last portion was facilitated by the addition of a little ligroin to the ether. The crystals were air dried a short time and then in a vacuum desiccator over phosphorus pentoxide. The product can be kept indefinitely without decomposition. The yield of product melting at 87–88° (uncor.) was 121 g. (96%).

2,3,4,6-Tetraacetyl-β-D-glucose was prepared by a modification of the method of Georg.[7] A solution of 125 ml. of anhydrous acetone and 82.2 g. of tetraacetylglucosyl bromide was cooled to 0° in an ice-bath and 2.3 ml. of water added. To the cold solution 46.5 g. of silver carbonate was added in small portions, with thorough shaking or stirring, during a period of fifteen minutes. After about thirty minutes more shaking the mixture was warmed to 50–60° and filtered. The silver salts were washed with 65 ml. of dry acetone, removed from the funnel and warmed in a flask with 65 ml. more acetone, filtered and washed again on the funnel. The combined filtrates were concentrated under reduced pressure and at room temperature. When most of the solution was filled with crystals the concentration was stopped and the mixture warmed until solution was complete. To this acetone solution an equal volume of absolute ether and a similar volume of ligroin were added. The solution so obtained was cooled in a freezing mixture with gentle stirring. The crystals of tetraacetate soon formed and after ten minutes in the ice-bath to ensure complete crystallization were filtered and air-dried. The

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[1] Research Fellow of the Corn Products Refining Company.

[2] Fischer and Delbrück, *Ber.*, **42**, 2776 (1909).

[3] Schlubach and Schetelig, *Z. physiol. Chem.*, **213**, 83 (1932).

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