[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DUKE UNIVERSITY]

Condensations Brought about by Bases. VIII. The Conversion of Ethyl Benzoyldimethylacetate to Ethyl Benzoate and Ethyl Isobutyryl-isobutyrate in the Presence of Sodium Ethoxide and Triphenylmethane. The Reversibility of the Claisen Type of Condensation[1]

BY CHARLES R. HAUSER AND BOYD E. HUDSON, JR.

Recently[2] it was shown that ethyl isobutyrate condenses with ethyl benzoate in the presence of sodium triphenylmethyl to form ethyl benzoyldimethylacetate, but in order to obtain this product it was necessary to stop the reaction by acidification within a short time (thirty minutes). When the reaction mixture was allowed to stand for several days before acidification no ethyl benzoyldimethylacetate could be isolated. This indicated that ethyl benzoyldimethylacetate, although first formed by the condensation of ethyl isobutyrate with ethyl benzoate, was cleaved later by the sodium ethoxide and triphenylmethane which were produced during the reaction. This has now been definitely established.

It has been found that ethyl benzoyldimethylacetate (synthesized from the enolate of ethyl isobutyrate and benzoyl chloride[3]) on standing in ether solution with sodium ethoxide and triphenylmethane at room temperature decomposes completely within five days. On working up the reaction mixture after this time, none of the original ethyl benzoyldimethylacetate could be isolated; instead ethyl benzoate and ethyl isobutyryl-isobutyrate were obtained.

The condensation of ethyl isobutyrate with ethyl benzoate, in the presence of sodium triphenylmethyl, to form ethyl benzoyldimethylacetate, as well as the cleavage of the latter and the condensation of ethyl isobutyrate with itself, may be represented by the following equations.

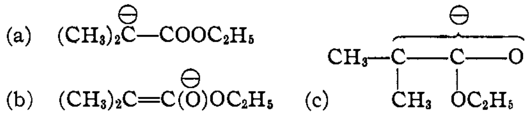
$$\text{(I)}\quad H{-}C(CH_3)_2COOC_2H_5 + (C_6H_5)_3CNa \rightleftarrows Na[C(CH_3)_2COOC_2H_5] + (C_6H_5)_3CH$$

$$\text{(II)}\quad \underset{\text{Component A}}{C_6H_5COOC_2H_5} + \underset{\text{Component B}}{Na[C(CH_3)_2COOC_2H_5]} \rightleftarrows C_6H_5C(ONa)(OC_2H_5)C(CH_3)_2COOC_2H_5 \rightleftarrows C_6H_5COC(CH_3)_2COOC_2H_5 + NaOC_2H_5$$

$$\text{(III)}\quad \underset{\text{Component A}}{H{-}C(CH_3)_2COOC_2H_5} + \underset{\text{Component B}}{Na[C(CH_3)_2COOC_2H_5]} \rightleftarrows H{-}C(CH_3)_2C(ONa)(OC_2H_5)C(CH_3)_2COOC_2H_5 \rightleftarrows H{-}C(CH_3)_2COC(CH_3)_2COOC_2H_5 + NaOC_2H_5$$

These reactions are regarded as essentially ionic.[4] The ethyl isobutyrate is converted into its sodium derivative (enolate) by means of sodium triphenylmethyl as represented by equation (I). The anion of the sodium enolate is undoubtedly a resonance structure, its two resonance forms being represented by (IV) (a) and (b); the mesomeric form of the anion may be represented by (c).

(IV)



$$\text{(a)}\quad (CH_3)_2\overset{\ominus}{C}{-}COOC_2H_5 \qquad \text{(b)}\quad (CH_3)_2C{=}C(\overset{\ominus}{O})OC_2H_5$$

The condensations represented by equations (II) and (III) may be considered to involve the addition of the enolate anion to the carbon atoms of the carbonyl groups of the esters, ethyl benzoate and ethyl isobutyrate, to form intermediate anions with the charge on the oxygen atoms; the intermediate anions release ethoxide ion giving the β-keto esters.

When equimolar quantities of ethyl isobutyrate, ethyl benzoate and sodium triphenylmethyl are used, reaction (II) at first predominates over reaction (III). This is the case even though the ethyl isobutyrate and the sodium triphenylmethyl are allowed to react for a few minutes before adding the ethyl benzoate. After a time, however, reaction (III) becomes predominant, reaction (II) being reversed completely. This illustrates the reversibility of the Claisen type of condensation.[5]

The fact that reaction (II) at first predominates was anticipated on the basis that not only is the carbonyl group of ethyl benzoate probably more reactive than that of ethyl isobutyrate, but the

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

[2] Renfrow and Hauser, THIS JOURNAL, **60**, 463 (1938).

[3] Hauser and Renfrow, "Organic Syntheses," Vol. XIX, John Wiley and Sons, New York, N. Y., 1939, p. 43. See also Hudson, Dick and Hauser, THIS JOURNAL, **60**, 1961 (1938).

[4] See (a) Hauser and Renfrow, *ibid.*, **59**, 1823 (1937); (b) Hauser, *ibid.*, **60**, 1957 (1938).

[5] In this connection see Dieckmann, *Ber.*, **33**, 2670 (1900); *ibid.*, **41**, 1260 (1908); see also Arndt and Loewe, *ibid.*, **71**, 1636 (1938).

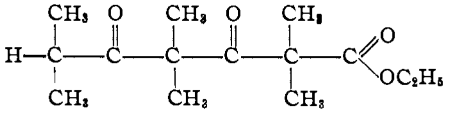
concentration of the latter, which may serve as component A, is much lower than that of ethyl benzoate; this is so because most of the ethyl isobutyrate is soon converted by the sodium triphenylmethyl into its enolate which is incapable of serving as component A.

The reason why ethyl benzoyldimethylacetate, in the presence of sodium ethoxide and triphenylmethane, is converted completely into ethyl benzoate and ethyl isobutyryl-isobutyrate is not entirely clear, but this change appears to be connected with the capacity for enolization of the latter and its existence in the reaction mixture in the form of its enolate. The formation of this enolate from the reactants used may be illustrated thus

$$\text{(V)}\quad 2\mathrm{C_6H_5COC(CH_3)_2COOC_2H_5} + \mathrm{NaOC_2H_5} \xrightarrow{\mathrm{(C_6H_5)_3CH}} 2\mathrm{C_6H_5COOC_2H_5} + \mathrm{Na[C(CH_3)_2COC(CH_3)_2COOC_2H_5]}$$

The formation of ethyl isobutyryl-isobutyrate from ethyl benzoyldimethylacetate presumably involves the cleavage of the latter and the condensation of two isobutyrate residues as represented in (III). The reversal of equation (II) gives the enolate of ethyl isobutyrate but apparently the only way the free ester, required for reaction (III), could be formed from ethyl benzoyldimethylacetate is by the reaction of the enolate of ethyl isobutyrate (formed by the reversal of II) with the proton donor, triphenylmethane (the reverse of reaction I). This gives the strong base sodium triphenylmethyl, which readily can convert the ethyl isobutyryl-isobutyrate as it is formed in reaction (III) into its enolate.

Experimental evidence has been obtained that at least most of the ethyl isobutyryl-isobutyrate, produced by the action of sodium ethoxide on ethyl benzoyldimethylacetate in the presence of triphenylmethane, is in the form of its enolate. The evidence has been obtained as follows. The reaction mixture of ethyl benzoyldimethylacetate, sodium ethoxide and triphenylmethane, after standing five days (during which time the cleavage is complete) was treated with isobutyryl chloride. On working up the resulting mixture, there was obtained, in addition to ethyl benzoate and ethyl isobutyryl-isobutyrate, a 32% yield of the compound represented by formula (VI).

(VI) 

$$\mathrm{H{-}\underset{CH_3}{\overset{CH_3}{C}}{-}\overset{O}{\overset{\|}{C}}{-}\underset{CH_3}{\overset{CH_3}{C}}{-}\overset{O}{\overset{\|}{C}}{-}\underset{CH_3}{\overset{CH_3}{C}}{-}C{\overset{\displaystyle /\!\!/O}{\underset{\displaystyle \backslash OC_2H_5}{}}}}$$

Presumably, compound (VI) could have resulted only if the ethyl isobutyryl-isobutyrate were in the form of its enolate,[6] since the free β-keto ester does not condense with acid chlorides. Previously,[6] a yield of 46% of compound (VI) has been obtained from the enolate of pure ethyl isobutyryl-isobutyrate and isobutyryl chloride. Judging from this yield of compound (VI), it would appear that most of the ethyl isobutyryl-isobutyrate obtained from ethyl benzoyldimethylacetate (in the presence of sodium ethoxide and triphenylmethane) was in the form of its enolate. The passage from ethyl benzoyldimethylacetate (which is incapable of enolizing) to the enolate anion of ethyl isobutyryl-isobutyrate, which is a resonance structure, might furnish a driving force for the reaction.[7]

That the proton donor, triphenylmethane, is necessary for the conversion of ethyl benzoyldimethylacetate to ethyl benzoate and ethyl isobutyryl-isobutyrate is shown by the fact that the former ester may be recovered unchanged after standing for five days with sodium ethoxide in ether. Stronger proton donors, such as water or alcohol, cause ethyl benzoyldimethylacetate to be cleaved into acids or esters.[8]

In connection with the results presented above it is of interest to consider the reaction of sodium ethoxide with certain other β-keto esters. Dieckmann[5] reported that ethyl α,α-diethylacetoacetate with sodium ethoxide gave the acetyl derivative of this β-keto ester. We have obtained similar results with ethyl α,α-dimethylacetoacetate (VII). In the presence of sodium ethoxide, compound (VII) gave a good yield of ethyl isobutyrate, a fair yield of ethyl γ-acetyl-α,α-dimethylacetoacetate (VIII), and some ethyl acetate; also, some unchanged compound (VII) was recovered.

$$\mathrm{CH_3COC(CH_3)_2COOC_2H_5}$$
(VII)

$$\mathrm{CH_3COCH_2COC(CH_3)_2COOC_2H_5}$$
(VIII)

It is assumed that compound (VII), in the presence of sodium ethoxide, is cleaved to form ethyl

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[6] Similar evidence has been obtained that the ethyl isobutyryl-isobutyrate, produced by the self-condensation of ethyl isobutyrate by means of sodium triphenylmethyl, is in the form of its sodium enolate. See Hudson and Hauser, THIS JOURNAL, **61**, 3567 (1939).

[7] The over-all reaction may depend upon the relative acidities (including the "activities" of the carbonyl groups) and basicities of the starting materials and of the products formed.

[8] In the presence of sodium ethoxide and alcohol, β-keto esters undergo "ester cleavage" giving two moles of ester (see ref. 5). Ethyl benzoyldimethylacetate in the presence of aqueous sodium hydroxide probably forms sodium benzoate and ethyl isobutyrate, the latter undergoing hydrolysis giving sodium isobutyrate.

acetate and the sodium enolate of ethyl isobutyrate. The latter, which is a strong base, immediately enolizes unchanged ethyl α,α-dimethylacetoacetate (VII). The enolate thus produced condenses with the ethyl acetate formed by the cleavage of (VII) giving compound (VIII) which is converted into its enolate by sodium ethoxide.

It is of interest to note that no appreciable amount of ethyl acetoacetate, which might have resulted by the self-condensation of the ethyl acetate, was obtained from the reaction. This is in agreement with theoretical considerations. One should expect that the enolate of ethyl isobutyrate, practically as rapidly as it is formed, should enolize unchanged ethyl α,α-dimethylacetoacetate (VII) rather than the ethyl acetate. The keto ester is not only the stronger acid but it is present in higher concentration than ethyl acetate, since the equilibrium of the cleavage reaction is probably far on the side of the unchanged β-keto-ester.

Finally, it should be noted that the original keto-ester, ethyl α,α-dimethylacetoacetate (VII), is not enolized appreciably by sodium ethoxide, whereas the final keto-ester, ethyl γ-acetyl-α,-α-dimethylacetoacetate (VIII), is enolized by this base.

Experimental[9]

The Reaction of Ethyl Benzoyldimethylacetate with Sodium Ethoxide in the Presence of Triphenylmethane.—A solution of sodium triphenylmethyl was prepared as described previously[10,11] from 63 g. of triphenylchloromethane (m. p. 112–113°), 1500 cc. of dry ether (dried with sodium), and 2000 g. of 1% sodium amalgam. The average concentration of the base in solutions prepared from recrystallized[12] triphenylchloromethane has been found to be about 0.13 mole per liter. Approximately 1150 cc. of this solution was delivered by means of a nitrogen siphon to a previously calibrated 2-liter Pyrex glass-stoppered bottle filled with dry nitrogen. By means of a bent tube, an atmosphere of dry nitrogen was maintained in the bottle while the solution was neutralized with absolute alcohol[13] from a siphon-filled buret. The red color of the sodium triphenylmethyl became lighter as the alcohol was added, and finally, on the addition of a single drop of alcohol, there was a definite color change from orange to light yellow. This was considered to be the equivalence point of the neutralization. To this suspension of sodium ethoxide in an ether solution of triphenylmethane was added 33 g. (0.15 mole) of ethyl benzoyldimethylacetate (b. p. 146–148°) prepared from the enolate of ethyl isobutyrate and benzoyl chloride.[8] The stopper was lubricated with a little "Lubriseal," inserted immediately, and clamped in place. The mixture was allowed to stand for two weeks at room temperature with occasional shaking. At the end of that time, the stopper was removed and the mixture poured with vigorous shaking into 25 cc. of glacial acetic acid. The resulting mixture was extracted once with water and twice with 300-cc. portions of 10% sodium carbonate solution. The ether solution was dried with anhydrous sodium sulfate followed by "Drierite." The solution was filtered and the ether distilled off until the volume of the residue was approximately 75 cc. The residue was chilled overnight in the refrigerator and the supernatant solution decanted from the crystallized triphenylmethane, the latter being washed with a little ether and the washings added to the solution. After a final removal of ether by distillation at atmospheric pressure, the remaining liquid was vacuum-distilled, collecting up to 180° at 18 mm., at which point triphenylmethane began coming over. The distillate was redistilled and yielded 18 g. of material, presumably a mixture of ethyl benzoate and ethyl isobutyryl-isobutyrate, boiling at 96–116° at 18 mm. No ethyl benzoyldimethylacetate could be recovered. The fraction obtained was hydrolyzed by refluxing with 200 cc. of 8% potassium hydroxide; at the end of five hours, 8 g. additional alkali was added and refluxing continued three hours longer. The resulting mixture was cooled and extracted with four 50-cc. portions of ether. The combined ether extract was washed with a small quantity of water and dried with anhydrous sodium sulfate. The ether was distilled off. The residue yielded, on distillation at atmospheric pressure, 0.5 g. of di-isopropyl ketone boiling at 123–126°, which is the boiling point recorded previously[14] for this ketone. An additional 0.5 g. of the ketone boiling a few degrees above and below this range was obtained. The semicarbazone of the ketone melted at 159–160° in agreement with the melting point reported by Hauser and Renfrow.[4a] The alkaline solution, after the ether extraction, was boiled to remove dissolved ether. When cool, it was acidified with excess hydrochloric acid and chilled in the refrigerator. The precipitated benzoic acid was filtered by suction and air-dried; yield, 9.0 g., m. p. 118–120°. After one recrystallization from water, the melting point was 121–122° and was not lowered by the addition of an authentic specimen of benzoic acid.

A similar experiment was carried out using 10 g. (0.045 mole) of ethyl benzoyldimethylacetate and the corresponding amount of neutralized sodium triphenylmethyl solution. The reaction mixture was allowed to stand only five days and on working up yielded a fraction boiling at 91–111° at 15 mm. and weighing 6.0 g. There was no evidence of unchanged ethyl benzoyldimethylacetate.

Treatment of the Reaction Mixture of Ethyl Benzoyldimethylacetate, Sodium Ethoxide, and Triphenylmethane with Isobutyryl Chloride.—A suspension of sodium ethoxide in an ether solution of triphenylmethane was prepared as described above by neutralizing 1050 cc. of sodium triphenylmethyl solution (containing about 0.14 mole of base) with alcohol. To this suspension was added 30 g.

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[9] All melting points and boiling points given are corrected.

[10] Renfrow and Hauser, "Organic Syntheses," Vol. XIX, John Wiley and Sons, Inc., New York, N. Y., 1939, p. 83.

[11] Hauser and Renfrow, This Journal, **59**, 1825 (1937).

[12] See ref. 10, p. 84, note 1.

[13] Prepared by the method of Lund and Bjerrum, *Ber.*, **64**, 210 (1931).

[14] See ref. (4a) p. 1826.

(0.136 mole) of ethyl benzoyldimethylacetate, the bottle being stoppered and allowed to stand five days at room temperature with occasional shaking. At the end of that time, the mixture was poured into a solution of 17.5 g. (0.16 mole) of isobutyryl chloride (Eastman Kodak Co.) in 500 cc. of dry ether vigorously agitated by a mechanical stirrer. After the mixture had stood an hour in a closed vessel, 3 cc. of glacial acetic acid was added and the mixture extracted with water. The resulting ether solution was washed with 10% sodium carbonate solution and dried with anhydrous sodium sulfate followed by "Drierite." The solution was filtered and most of the ether distilled off. The residue was chilled overnight in the refrigerator and the crystallized triphenylmethane filtered off and washed with a small quantity of ether, the washings being added to the filtrate. After the ether was removed by distillation at atmospheric pressure, the filtrate was distilled at 15 mm., a fraction boiling up to 50° and another boiling from 50–180° being collected. The low-boiling fraction (approximately 3 g.) consisted presumably of ethyl isobutyrate (probably formed from isobutyryl chloride and sodium ethoxide); on redistillation at atmospheric pressure it boiled at 110–120°. The higher boiling material was refractionated at 15 mm., the following fractions being obtained: (a) 95–115° at 15 mm., 17.8 g.; (b) 115–130° at 15 mm., 2 g.; (c) 130–140° at 15 mm., 5.5 g. (Most of this fraction distilled at 135–138°.)

Fraction (a) was shown to be a mixture of ethyl benzoate and ethyl isobutyryl-isobutyrate by hydrolysis as described in the preceding experiment. A yield of 5.5 g. of benzoic acid (m. p. 121–122°) and 1 g. of di-isopropyl ketone (b. p. 115–125°) was obtained. The latter was converted into its semicarbazone, which melted at 158–159°.

Fraction (c) undoubtedly consisted largely of ethyl 2,2,4,-4,6-pentamethyl-3,5-diketoheptanoate, which boils at 136–138° at 15 mm.[6] It was cyclized to hexamethylphloroglucinol, which was identified by the mixed melting point method.[6] The yield (5.5 g.) of the heptanoate obtained corresponds to 32% of the theoretical amount, based on the quantity of ethyl benzoyldimethylacetate used.

Preparation of Ethyl Benzoyldimethylacetate by the Oxidation of Ethyl β-Phenyl-β-hydroxypivalate.—Fifty grams of ethyl β-phenyl-β-hydroxypivalate[15] (m. p. 39–40°) was dissolved in 100 cc. of glacial acetic acid on a water-bath. The solution was maintained at 80–100° while 17.3 g. (a 15% excess over the equivalent quantity) of chromic anhydride was added in 0.5-g. portions. After each addition, the mixture was stirred until reaction was complete and no chromic anhydride remained on the bottom of the flask. When all the chromic anhydride had been added, the solution was heated on the water-bath an hour longer, at the end of which time it was poured into 500 cc. of water and shaken vigorously. The resulting mixture was extracted with three 100-cc. portions of ether. The combined ether extract was washed once with water and several times with 10% sodium carbonate solution, and was dried with anhydrous sodium sulfate followed by "Drierite." The solution was filtered and the ether was removed by distillation at atmospheric pressure. The residue was vacuum-distilled and the portion of ethyl benzoyldimethylacetate boiling at 146–148° at 15 mm. collected; yield, 36 g., 72% of the theoretical amount.

Treatment of Ethyl Benzoyldimethylacetate with Sodium Ethoxide in the Absence of Proton Donors.—Fifteen grams (0.068 mole) of ethyl benzoyldimethylacetate, prepared by the oxidation of ethyl β-phenyl-β-hydroxypivalate, was dissolved in 500 cc. of dry ether and added to 4.65 g. (0.068 mole) of alcohol-free sodium ethoxide contained in a glass-stoppered flask. Several pieces of glass tubing 1 cm. long were dropped in the flask, and a glass stopper well lubricated with "Lubriseal" was inserted and clamped in place. The flask was shaken vigorously until all the caked sodium ethoxide was changed to a fine suspension. The reaction mixture was allowed to stand for five days with occasional shaking. At the end of that time, the mixture was poured with vigorous shaking into 5 cc. of glacial acetic acid, extracted with water, and washed twice with 10% sodium carbonate solution. The resulting ether solution was dried with anhydrous sodium sulfate followed by "Drierite." The solution was filtered and the ether distilled off. The residue was vacuum-distilled at 15 mm., yielding two fractions, 90–115° (2.3 g.) and 140–148° (9.8 g.). The lower boiling fraction was presumably a mixture of ethyl isobutyryl-isobutyrate and ethyl benzoate. The higher boiling fraction was shown to be ethyl benzoyldimethylacetate by conversion into its isoxazolone, which melted at 69–70° in agreement with the melting point reported in the literature.[16] The recovered ethyl benzoyldimethylacetate (9.8 g.) represents 65% of the initial quantity and 81% of the recovered products. These results indicate that ethyl benzoyldimethylacetate is essentially unaffected by sodium ethoxide in the absence of appreciable quantities of proton donors.

Reaction of Ethyl α,α-Dimethylacetoacetate with Sodium Ethoxide.—A solution of 50 g. (0.136 mole) of ethyl α,α-dimethylacetoacetate[17] (b. p. 75–76° at 15 mm.) in 1000 cc. of dry ether was added to 22 g. (0.32 mole) of alcohol-free sodium ethoxide contained in a glass stoppered flask. The flask was stoppered and allowed to stand three days with frequent shaking. At the end of that time, the mixture was acidified with 25 cc. of glacial acetic acid and extracted with water. The resulting ether solution was washed three times with 10% sodium carbonate solution and dried with anhydrous sodium sulfate. Ether was removed up to 40°. The remaining liquid was distilled through a short Widmer column up to 120°. Redistillation of the distillate and vacuum fractionation of the residue gave the following fractions:

(a)	60–80° at atm. press.	3.5 g.	ethyl acetate (b. p. 77°)
(b)	80–108° at atm. press.	1.5 g.	mid-fraction
(c)	108–112° at atm. press.	18.5 g.	ethyl isobutyrate (b. p. 111°)
(d)	up to 75° at 15 mm.	1.2 g.	mid-fraction
(e)	75–80° at 15 mm.	3.5 g.	unchanged ethyl α,α-dimethylacetoacetate
(f)	80–95° at 15 mm.	1.4 g.	mid-fraction
(g)	95–121° at 15 mm.	3.5 g.	largely ethyl γ-acetyl α,α-dimethylacetoacetate
(h)	121–123° at 15 mm.	5.3 g.	ethyl γ-acetyl α,α-dimethylacetoacetate

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(15) Blaise and Hermann, *Ann. chim. phys.*, [8] **23**, 532 (1911).

(16) See ref. 2, p. 464.

(17) Frankland and Duppa, *Ann.*, **138**, 328 (1866).

Ferric chloride tests with fractions (d) and (e) were negative, with fraction (f) faintly positive, and with fractions (g) and (h), strongly positive. Fraction (g) was shown to consist largely of ethyl γ-acetyl-α,α-dimethylacetoacetate by conversion (by means of concentrated ammonia) into the lactam of 2,2-dimethyl-3-keto-5-amino-4-hexenecarboxylic acid, melting at 139–140°; this is the melting point reported in the literature[18] for this lactam. Fraction (h) presumably consisted entirely of ethyl γ-acetyl-α,α-dimethylacetoacetate.

Summary

1. In the presence of sodium ethoxide and triphenylmethane, ethyl benzoyldimethylacetate is converted completely into ethyl benzoate and ethyl isobutyryl-isobutyrate, the latter being converted into its enolate.

2. In the complete absence of proton donors, ethyl benzoyldimethylacetate is apparently stable toward sodium ethoxide.

3. In the presence of sodium ethoxide, α,α-dimethylacetoacetic ester is converted into γ-acetyl-α,α-dimethylacetoacetic ester and ethyl isobutyrate.

4. These results illustrate the reversibility of the Claisen type of condensation.

5. The mechanisms for these reactions are discussed.

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[18] See Conrad and Gast, *Ber.*, **31**, 1342 (1898).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Synthesis of Certain Oligosaccharide Acetates in the Mannose Series[1]

BY DELBERT D. REYNOLDS AND WM. LLOYD EVANS

In a recent publication, the authors[2] discussed certain improvements in the well-known Königs and Knorr reaction as it was applied to the synthesis of α- and β-gentiobiose octaacetates. Our present paper contains an account of the first successful use of this reaction in the synthesis of certain acetates in the mannose series of saccharides.

Several epimeric pairs of mono- and disaccharides have been prepared by other workers and the properties of these compounds have been studied carefully. As far as the authors are aware such an epimeric pair in the trisaccharide series has never been reported. Anticipating the interesting problems that would arise from such a synthesis, acetobromogentiobiose was condensed with β-*d*-mannose-1,2,3,4-tetraacetate, a reaction which gave rise to 6-β-gentiobiosido-β-*d*-mannose hendekaacetate. This new hendekaacetate and that of 6-β-gentiobiosido-β-*d*-glucose prepared by Helferich and co-workers[3] make available the first known epimeric pair of trisaccharides. An application of Hudson's isorotation rules has been made to these two compounds.

By another application of the improved Königs and Knorr reaction, 6-β-*d*-glucosido-α-*d*-mannose octaacetate was prepared by the condensation of acetobromoglucose with α-*d*-mannose-1,2,3,4-tetraacetate. This method of preparing this disaccharide is to be preferred to the oxidation of gentiobial by the procedure of Bergmann and Schotte[4] which was utilized previously in this Laboratory[5]; the new method involves fewer steps and gives higher yields.

During the progress of this work it became necessary to prepare ethyl gentiobioside heptaacetate, the synthesis of which is herein described, together with an application of the isorotation rules to its rotation.

Experimental Part

Purification of Reagents.—Chloroform was purified by the method described in an earlier paper.[2] The mannose was prepared according to the method of Levene.[6] Acetobromogentiobiose was prepared from gentiobiose octaacetate by the method of Brauns.[7]

6 - Trityl - β - *d* - mannose - 1,2,3,4 - tetraacetate.—The method of Helferich and Leete[8] was modified in such a way that the yield of 6-trityl-β-*d*-mannose-1,2,3,4-tetraacetate was doubled. One hundred grams of dry mannose and trityl chloride (161 g.) were added to anhydrous pyridine (500 cc.). The mixture was shaken in a thermostat at 50° until solution was complete (four hours). Without cooling, three hundred cc. of acetic anhydride was then

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[1] Abstracted from a Thesis presented by Delbert D. Reynolds to the Graduate School of The Ohio State University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] D. D. Reynolds and W. L. Evans, THIS JOURNAL, **60**, 2559 (1938).

[3] B. Helferich and R. Gootz, *Ber.*, **64**, 109 (1931); B. Helferich and W. Schaefer, *Ann.*, **450**, 236 (1926).

[4] M. Bergmann and H. Schotte, *Ber.* **54**, 440 (1921).

[5] H. J. Dauben and W. L. Evans, THIS JOURNAL, **60**, 886 (1938).

[6] P. A. Levene, *J. Biol. Chem.*, **108**, 419 (1935).

[7] D. H. Brauns, THIS JOURNAL, **49**, 3170 (1927).

[8] B. Helferich and J. Leete, *Ber.*, **62**, 1552 (1929).