[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DUKE UNIVERSITY]

Condensations Brought about by Bases. X.[1] The Michael Type of Condensation with Certain Esters and α,β-Unsaturated Keto Compounds[2,3]

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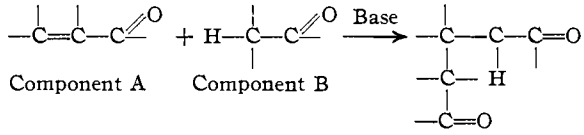
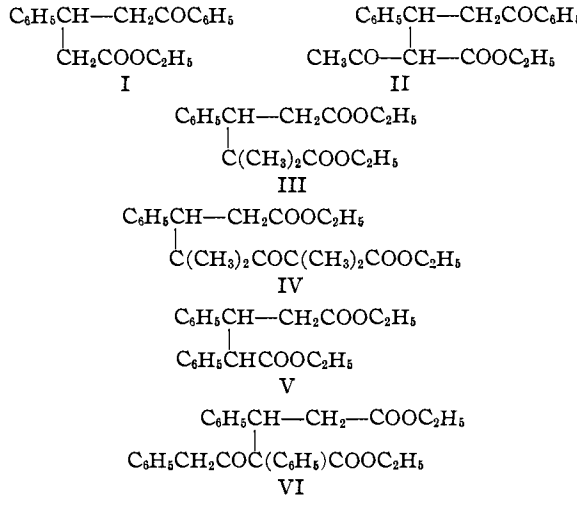
The Michael type of condensation may be represented as an addition reaction between a compound containing an enolizable hydrogen (component B) and an α,β-unsaturated keto compound (component A), thus



In the present investigation a study has been made of the possibility of using certain simple aliphatic esters as component B in the Michael type of condensation. Since esters are capable of undergoing self-condensation (Claisen type) in the presence of bases, the procedure followed has been to treat a mixture of the ester and α,β-unsaturated keto compound with a base. It was a matter of considerable interest to determine which type of condensation, the Michael or Claisen, would predominate under these conditions.

It has been found that when a mixture of ethyl acetate and benzalacetophenone is added to sodium triphenylmethyl in ether solution, compound II is obtained. None of the direct Michael condensation product (compound I) was found. Obviously, compound II is the Michael condensation product of acetoacetic ester and benzalacetophenone. The formation of compound II from ethyl acetate is to be explained on the basis that the ester first underwent self-condensation to form acetoacetic ester which then condensed with the benzalacetophenone; that is, a Claisen condensation occurred first, followed by a Michael condensation. It is of interest to note that compound II was obtained in good yield (60%) even though the reaction mixture of ethyl acetate, benzalacetophenone and sodium triphenylmethyl was acidified after standing at room temperature for only six minutes. Previously it has been shown that in the presence of this very strong base, ethyl acetate undergoes self-condensation very rapidly, giving at room temperature a good yield of acetoacetic ester within three minutes.[4]



In contrast to the reaction of ethyl acetate (with benzalacetophenone), when a mixture of ethyl isobutyrate and ethyl cinnamate is treated either with sodium triphenylmethyl or with sodium ethoxide, the direct Michael condensation product (compound III) is obtained. Apparently none of compound IV, which would be the Michael condensation product of ethyl isobutyrylisobutyrate (the self-condensation product of ethyl isobutyrate) and ethyl cinnamate, is formed with either base. This is not surprising since with sodium ethoxide the self-condensation of ethyl isobutyrate does not take place under any conditions,[5] and even with the stronger base, sodium triphenylmethyl, the self-condensation of ethyl isobutyrate takes place only at a relatively slow rate.[6]

Similar to the result reported previously with ethyl phenylacetate and α,β-unsaturated keto compounds in the presence of sodium ethoxide,[7]

(1) For paper IX of this series see, THIS JOURNAL, **62**, 393 (1940).

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

(3) This paper was presented before the Division of Organic Chemistry at the Boston meeting of the American Chemical Society, September, 1939.

(4) Hudson, Dick and Hauser, THIS JOURNAL, **60**, 1961 (1938).

(5) See McElvain, *ibid.*, **51**, 3124 (1929).

(6) Although ethyl isobutyrate undergoes self-condensation when allowed to stand with sodium triphenylmethyl for several hours, the reaction apparently does not take place to an appreciable extent within ten minutes, since a good yield of ethyl benzoyldimethylacetate is obtained when the reaction mixture is treated with benzoyl chloride after this time. See Hauser and Renfrow, *ibid.*, **59**, 1823 (1937), and ref. 4.

(7) (a) Borsche, *Ber.*, **42**, 4497 (1909); (b) Connor and Andrews, THIS JOURNAL, **56**, 2713 (1934).

it has been found that in the presence of sodium triphenylmethyl, ethyl phenylacetate condenses with ethyl cinnamate to give the direct Michael condensation product (compound V). Apparently compound VI, which would have resulted if the Claisen condensation occurred first followed by the Michael condensation, was not formed.

The mechanism of these condensations very probably involves the reaction of the ester with the base to form the ester enolate, which then condenses either with unchanged ester to give the Claisen condensation product (as occurs in the reaction with ethyl acetate) or with the α,β-unsaturated keto compound to give the Michael condensation product (as occurs in the reaction with ethyl isobutyrate or ethyl phenylacetate). The Claisen condensation has been represented previously by ionic equations.[8] The Michael type of condensation of ethyl isobutyrate with ethyl cinnamate may be illustrated by the following ionic equations in which Na^+B^- represents sodium ethoxide or sodium triphenylmethyl.

$$H{-}C(CH_3)_2COOC_2H_5 + Na^+B^- \rightleftharpoons [C(CH_3)_2COOC_2H_5]^- Na^+ + BH$$

$$C_6H_5CH{=}CHCOOC_2H_5 + [C(CH_3)_2COOC_2H_5]^-Na^+ \rightleftharpoons$$

$$\left[\begin{array}{l} C_6H_5CH{-}CHCOOC_2H_5 \\ \quad\quad | \\ \quad\quad C(CH_3)_2COOC_2H_5 \end{array}\right]^- Na^+ \xrightarrow{+\ \text{Acid}} \text{Compound III}$$

The fact that ethyl isobutyrate condenses with ethyl cinnamate in the presence of sodium ethoxide, together with the result of Brown and Eberly[9] showing that ethyl isobutyrate slowly undergoes hydrogen exchange in the presence of deuteroalcohol and sodium ethoxide, indicates that this ester is enolized, at least to a small extent, by this base. Therefore, the failure of ethyl isobutyrate to undergo self-condensation (Claisen type) in the presence of sodium ethoxide is not to be attributed to a lack of enolization of this ester, although the relatively weakly acidic character of the ester may be one of the factors involved.[10]

Experimental[11]

Preparation and Purification of Materials.—The best grades of Eastman Kodak Co. chemicals were used (benzalacetophenone without purification). The ethyl esters, except the cinnamate (it was only dried and distilled), were washed with 10% sodium carbonate solution and with water, and then dried with Drierite. Fractionally distilled, the acetate boiled at 76.9–77.0°, the isobutyrate at 110–111°, and the phenylacetate at 120–124° at 17 mm.

Ethyl isobutyrylisobutyrate prepared from ethyl isobutyrate and isobutyryl chloride[12] distilled at 95–97° at 18 mm. Sodium triphenylmethyl was prepared from triphenylchloromethane and 1% sodium amalgam.[13] Sodium ethoxide[5] was prepared from freshly cut sodium and absolute ethanol,[14] the excess alcohol being distilled off *in vacuo* and the residue dried at 150° at 20 mm. for one hour in nitrogen.

Reaction of Benzalacetophenone and Ethyl Acetate.—A solution of benzalacetophenone (20.8 g.) and ethyl acetate (8.8 g.) in 150 cc. of dry ether was added, with shaking during five minutes, to a solution of 0.1 mole of sodium triphenylmethyl in 800 cc. of ether. Shaking was continued for one minute. After the color had changed from red to orange-yellow, 10 cc. of glacial acetic acid was added and the precipitate was dissolved with a minimum amount of water. The ether layer was washed with 10% sodium carbonate solution, dried with Drierite and concentrated to about 100 cc. After standing for several days in the refrigerator, small amounts of a white solid precipitated. The filtrate from this, after another day of standing, yielded an additional crop of crystals, as did a further day of standing. The combined solids, after recrystallization from alcohol, weighed 17.6 g. (66% yield). This compound, ethyl α-acetyl-β-phenyl-γ-benzoylbutyrate (II) (m. p. 167–168°), was also prepared from acetoacetic ester and benzalacetophenone.[7b] A mixed melting point of the two samples showed no depression.

Condensation of Ethyl Isobutyrate with Ethyl Cinnamate. (a) With Sodium Ethoxide.—Preliminary experiments indicated that excess ethyl isobutyrate was desirable and that too long heating gave considerable very high boiling material and tar. In two experiments in which the reaction mixture was heated for three hours and six hours the yields of desired condensation product were 13 and 10%, respectively. The following experiment gave the best results.

To 0.2 mole of dry, pulverized sodium ethoxide was added a mixture of 35.2 g. (0.2 mole) of ethyl cinnamate and 46.4 g. (0.4 mole) of ethyl isobutyrate. The mixture was contained in a round-bottomed flask attached to a reflux condenser fitted with a soda-lime drying tube. The mixture was heated for one hour and forty-five minutes on an oil-bath kept at 125–135°. The ethyl isobutyrate refluxed slowly. The mixture, which had developed a red-brown color, was cooled quickly to room temperature and then poured onto 150 g. of crushed ice containing 20 cc. of glacial acetic acid. Sufficient water was added to dissolve the precipitate (leaving an insoluble oil), and the mixture extracted with ether. The ethereal layer was separated and washed with 10% sodium carbonate solution followed by water until neutral, and dried over Drierite. The dry ether solution was transferred to a flask equipped with a 15-cm. Widmer column. Most of the ether was distilled

(8) See Hauser, THIS JOURNAL, **60**, 1957 (1938).

(9) Brown and Eberly, *ibid.*, **62**, 113 (1940).

(10) The Claisen condensation of esters may depend on rate or equilibrium factors; for a discussion of the steps involved see especially ref. 8.

(11) All melting points and boiling points are corrected.

(12) Hauser and Renfrow, THIS JOURNAL, **59**, 1826 (1937).

(13) Renfrow and Hauser, "Organic Syntheses," Vol. XIX, John Wiley and Sons, Inc., New York, N. Y., 1939, p. 83.

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

off on a water-bath. The residue was then distilled up to 120° at atmospheric pressure. Approximately 15 g. of ethyl isobutyrate (b. p. 107–111°) was recovered. The residue was transferred to a Claisen flask and distilled *in vacuo*. A small fraction (0.6 g.), presumably containing unchanged ethyl cinnamate, was obtained boiling at 140–169° at 10 mm. A large fraction (34.3 g.) of pale yellow oil was obtained boiling at 169–189° at 10 mm. After redistilling once through a Vigreux column, 29.2 g. of colorless oil was obtained boiling at 174–175° at 8 mm. The oil was identified as diethyl α,α-dimethyl-β-phenylglutarate (III) by analysis, molecular weight, and by hydrolysis to the corresponding acid. The yield of crude product was 59%, and of purified ester 50% of the theoretical amount based on the ethyl cinnamate used.

Anal.[15] Calcd. for $C_{17}H_{24}O_4$: C, 69.86; H, 8.22; mol. wt., 292. Found: C, 69.93; H, 8.42; mol. wt., 305.

The ester was hydrolyzed by refluxing 2 g. of it with 80 cc. of 5% potassium hydroxide solution for twelve hours, after which time it had completely dissolved. The liquid was filtered free of a small amount of inorganic material, and when cool acidified with 10 cc. of concentrated hydrochloric acid and chilled in the refrigerator. The precipitated acid was filtered by suction and recrystallized twice from water; yield, 1.90 g. (95% of the theoretical amount). The acid softened at 165° and melted at 171–172°. Its neutral equivalent corresponded to that of α,α-dimethyl-β-phenylglutaric acid; the value found was 117 (calcd. 118).

(b) With Sodium Triphenylmethyl.—To a solution of 0.2 mole of sodium triphenylmethyl in 1500 cc. of dry ether was added at room temperature (25°) a mixture of 35.2 g. (0.2 mole) of ethyl cinnamate and 23.2 g. (0.2 mole) of ethyl isobutyrate. The mixture was added in a quick dropwise fashion, with occasional gentle shaking, during the course of five minutes. It was noticed that the blood-red color of the condensing agent became less intense after the first few additions, and when the last portion had been added, the color of the mixture was pale brown. The mixture was allowed to stand under nitrogen for twelve hours at room temperature, during which time a white flocculent precipitate had formed. Twenty cc. of glacial acetic acid was added, whereupon the color changed to yellow and a voluminous white precipitate appeared. Cold water was added until two homogeneous layers were obtained. The ether solution was washed with 10% sodium carbonate solution until it reacted basic to litmus paper, and dried over Drierite. The solution was distilled from a water-bath through a short Widmer column until most of the ether was removed. The residue was then fractionated at atmospheric pressure in order to recover unreacted ethyl isobutyrate (2.65 g., b. p. 100–110°). The residue was then cooled to room temperature and dissolved in 100 cc. of absolute alcohol. The solution was chilled overnight in a refrigerator. The precipitate (18 g.) of triphenylmethane (m. p. 94°) was filtered off and washed with cold alcohol. The ethyl alcohol was removed from the filtrate by means of a water pump, and the residue distilled under reduced pressure. No ethyl isobutyrylisobutyrate (Claisen product, b. p. 95° at 18 mm.) was obtained. The following fractions were collected: (a) 144–163° at 12 mm., 5.80 g. (ethyl cinnamate); (b) 163–180° at 8 mm., 13.10 g. (main portion boiling at 172–176° at 8 mm.); (c) 155–170° at 1 mm. 28.05 g. (considerable triphenylmethane crystallizing out in the receiver).

From fraction (c), after the addition of ethyl alcohol and chilling, triphenylmethane (8.80 g.) was removed. The alcohol was distilled off by means of a water pump, the residual oil combined with fraction (b), and the entire liquid fractionated using a 50-cc. flask fitted with a 15-cm. Vigreux column. The fractions collected were: (d) 167–169° at 6 mm., 5.70 g., containing ethyl cinnamate; (e) 169–171° at 6 mm., 13.80 g., diethyl α,α-dimethyl-β-phenylglutarate (III), 22% yield; (f) 178–188° at 6 mm., 6.55 g.

Fraction (e) was analyzed and the molecular weight determined.

Anal.[15] Calcd. for $C_{17}H_{24}O_4$: C, 69.86; H, 8.22; mol. wt., 292. Found: C, 71.84; H, 8.08; mol. wt., 302.

The high carbon content (2% higher than the calculated value) of fraction (e) was probably due to the presence of triphenylmethane. That this fraction consisted largely of the glutaric ester was shown by the fact that on hydrolysis with 5% potassium hydroxide solution the corresponding acid was obtained in high yield (85%). The melting point of the acid was 171.0–172.5° and neutral equivalent, 117.5 (calcd. for $C_{13}H_{16}O_4$: 118). A mixed melting point with the acid (m. p. 171–172°) prepared with the use of sodium ethoxide, as described above, was the same. A small amount (0.3 g.) of triphenylmethane was also isolated from the hydrolysis mixture.

Fraction (f) likewise was subjected to a similar hydrolysis for a period of twelve hours. α,α-Dimethyl-β-phenylglutaric acid melting at 171–172.5° was obtained; a mixed melting point with the acid obtained from fraction (e) was the same. The amount (4.8 g.) of this acid obtained from fraction (f) corresponded to 6.0 g. (or 10% of the theoretical amount) of the glutaric ester (compound III). The total yield of this ester was therefore 32% of the theoretical amount. None of the acid corresponding to the ester represented by compound IV was found in the hydrolysis products of fraction (f).

Reaction of Ethyl Cinnamate and Ethyl Phenylacetate.—To a solution of 0.2 mole of sodium triphenylmethyl in 1500 cc. of dry ether was added at room temperature (30°), during the course of six minutes, a mixture of 35.2 g. (0.2 mole) of ethyl cinnamate and 32.8 g. (0.2 mole) of ethyl phenylacetate. The color changed from red to brown. The mixture was shaken and allowed to stand for ten minutes longer. Twenty cc. of glacial acetic acid was then added, as well as water, the mixture shaken and the ether layer separated. The ether solution was washed with 10% sodium carbonate solution, followed by distilled water until neutral to litmus paper, and then dried over Drierite. As much ether as possible was distilled at atmospheric pressure from a boiling water-bath, the volume thus being reduced to about 110 cc. The liquid was chilled in the refrigerator for five hours. Some triphenylmethane had precipitated. The addition of cold ethyl alcohol (95%) precipitated more of this substance. The mixture was filtered, and the filtrate distilled under reduced pressure. Ethyl phenylacetate (12.4 g.) boiling at 120–135° at 17 mm. and ethyl cinnamate (8.4 g.) boiling at 135–178° at 17 mm. were

(15) Microanalysis by R. L. Peck.

recovered. The sirupy residue, pale reddish-brown in color, was transferred to a beaker, and placed in the refrigerator for one day. Since no solid appeared, the viscous mass was dissolved in warm 99% ethyl alcohol. The solution was allowed to cool slowly to room temperature, and then placed in the refrigerator. After three days a precipitate was present. This was filtered off and washed with cold alcohol; yield, 6.78 g. After two recrystallizations from 95% ethyl alcohol the product melted at 75.0–75.5°. This compound was presumably diethyl α,β-diphenylglutarate (compound V).

Anal.[16] Calcd. for $C_{21}H_{24}O_4$: C, 74.12; H, 7.06. Found: C, 74.12; H, 6.89.

On hydrolysis with 5% aqueous potassium hydroxide (to which several cc. of ethyl alcohol was added) for eight hours the ester gave a good yield (90%) of the corresponding acid. Neutral equivalent of the acid, calcd. for $C_{17}H_{16}O_4$: 142. Found: 143. The crude acid melted at 192.5–197.5°. The melting points obtained after crystallization from various solvents were as follows: from a mixture of 10% ethanol and 90% water, 195.5–197.5°; from a mixture of 90% ligroin (90–120°) and 10% ethanol, 196.5–197.5°; from a small quantity of absolute ethanol, 207.5–218.5°, with considerable decomposition.

Borsche[7a] reported the melting point of the diethyl glutarate (prepared from ethyl phenylacetate and ethyl cinnamate in the presence of sodium ethoxide) as 92–93°; presumably this was a diastereoisomeric form of the ester obtained by us. The ester obtained by Borsche gave on hydrolysis an acid melting at 230–231°. Meerwein[17] prepared this acid by a different method and found that, by crystallization, several materials could be obtained; one melted at 203–204°, another at 215–224°, and still another at 230–231°.

(16) Microanalysis by Arlington Laboratories, Arlington, Va.

Summary

1. A study has been made of the possibility of using certain simple esters in the Michael type of condensation.

2. It has been found that when a mixture of ethyl acetate and benzalacetophenone is added to sodium triphenylmethyl in ether solution, the ester first undergoes self-condensation (Claisen type) to give acetoacetic ester which then condenses with the benzalacetophenone (Michael type).

3. Both ethyl isobutyrate and ethyl phenylacetate with ethyl cinnamate, on the other hand, give the direct Michael condensation. This reaction is effected either by sodium ethoxide or by sodium triphenylmethyl.

4. The mechanism of these condensations is discussed.

(17) Meerwein, *J. prakt. Chem.*, **97**, 274 (1918).

DURHAM, N. C. RECEIVED APRIL 10, 1940

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Preparation of Cholestanol Glucosides with All Four Possible Configurations of the Glucoside Link

BY R. P. LINSTEAD

The view has recently been advanced[1] that the capacity for glucoside formation of the characteristic steroid hydroxyl group (C_3) is profoundly affected by the stereochemical configuration. Miescher and Fischer[1] report that they were unable to prepare glucoside derivatives from *epi*-cholestanol, *epi*-coprostanol or from *epi*-androsterone, whereas isomeric steroids with the normal β-configuration at C_3 yielded glucosides in agreement with previous work.[2] From these results Miescher and Fischer have suggested that the capacity for glucoside formation runs parallel to the ability of steroids to form insoluble digitonides. They have also drawn certain inferences concerning the orientation of the C_3 hydroxyl group with respect to the angular methyl group at C_{10}. These have been criticized by Ruzicka.[3] In the writer's opinion these attempts to orientate the groups at C_3 with those at the neighboring bridgeheads by methods based on steric hindrance are of doubtful value in the present state of our knowledge.

Apart, however, from the debatable question of the interpretation of the facts, there were certain indications that the experimental results might be incorrect. First, among the heart poisons, isomeric glycosides are known with both normal and *epi*-configurations at C_3. Secondly, Dane and Brady[4] have prepared the glycoside of desoxycholic acid which has the *epi*-configuration at C_3. Miescher and Fischer have suggested that Dane and Brady's glucoside involved combination at C_{12} and not at C_3. Thirdly, there is no general

(1) Miescher and Fischer, *Helv. Chim. Acta*, **21**, 336 (1938).

(2) Salway, *J. Chem. Soc.*, **103**, 1026 (1913); MacCorquodale, Steenbock and Adkins, THIS JOURNAL, **52**, 2512 (1930); Lettré and Hagedorn, *Z. physiol. Chem.*, **242**, 210 (1936).

(3) Ruzicka, Furter and Goldberg, *Helv. Chim. Acta*, **21**, 498 (1938).

(4) Dane and Brady, *Z. physiol. Chem.*, **244**, 241 (1936).