and *l*-*o*-chlorophenylsuccinic acids, *d*-cyclohexylsuccinic acid; β-anilide-α-acid and anil of *d*- and *l*-methyl-, *d*-cyclohexyl-, *d*-phenyl-, *d*-anisyl- and *d*-*o*-chlorophenylsuccinic acid; anil of *dl*-*o*-chlorophenylsuccinic acid; β-amide-α-acid of *d*-phenyl-, *d*-anisyl-, *dl*- and *d*-*o*-chlorophenylsuccinic acids; β-N-methylamide-α-acid of *d*-phenyl-, *d*-anisyl- and *d*-*o*-chlorophenylsuccinic acids; anhydrides of *d*-cyclohexyl-, *d*- and *l*-anisyl-, *dl*-, *d*- and *l*-*o*-chlorophenylsuccinic acids; imide of *dl*-N-methyl-*o*-chlorophenylsuccinic acid.

3. *d*-Phenyl-, *d*-*o*-chlorophenyl- and *d*-cyclohexylsuccinic acids have been proven to have the same configuration.

4. Several cases of unusual effects of solvents on rotatory power and of spontaneous racemization have been pointed out.

AMES, IOWA RECEIVED JULY 1, 1940

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DUKE UNIVERSITY]

Condensations. XIII. The Alkylation of Ethyl Isobutyrate and of Certain other Esters by Means of Sodium Triphenylmethyl and Alkyl Halides

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

Esters of diphenylacetic acid have been alkylated by converting them into their sodium enolates by means of sodium triphenylmethyl,[1] sodium amide,[2] potassium amide,[3] or potassium ethoxide[4] and treating the enolates with certain alkyl halides. Scheibler and Schmidt[5] have reported that ethyl acetate (or ethyl phenylacetate) reacts with potassium to give the potassium enolate which reacts with ethyl bromide to give ethyl butyrate; however, the yield of this product was very low, and there is some doubt whether the intermediate potassium enolate of the ester was obtained as claimed by these workers.[6]

This paper describes the successful alkylation of ethyl isobutyrate and of ethyl methylethylacetate. These esters are converted into their sodium enolates by means of sodium triphenylmethyl and the enolates treated with alkyl halides. In this way ethyl isobutyrate has been alkylated with benzyl chloride and with ethyl and methyl iodides, while ethyl methylethylacetate has been alkylated with *n*-propyl iodide. With one exception the yields obtained were approximately 60% of the theoretical amount. The alkylation of ethyl isobutyrate may be illustrated by the following equations in which RX represents an alkyl halide

$$\mathrm{H{-}C(CH_3)_2CO_2C_2H_5 + (C_6H_5)_3CNa \rightleftharpoons Na[C(CH_3)_2CO_2C_2H_5] + (C_6H_5)_3CH}$$

$$\mathrm{RX + Na[C(CH_3)_2CO_2C_2H_5] \longrightarrow R{-}C(CH_3)_2CO_2C_2H_5 + NaX}$$

This type of reaction serves as a direct and convenient method for the synthesis of tri-substituted acetic acid esters or of the corresponding acids, which may be obtained readily from the esters by hydrolysis. The alkylation of esters of the type of ethyl methylethylacetate may be of value for the synthesis of optically active acids or their esters.

The method of alkylation described above appears to be entirely satisfactory only with disubstituted esters. The ethylation of ethyl isovalerate gave only a fair yield (22%) of the corresponding alkylated ester, while an attempt to benzylate ethyl acetate was unsuccessful, apparently because of the relatively rapid rate at which this ester undergoes self-condensation.[7]

Experimental[8]

Alkylation of Ethyl Isobutyrate with (a) Ethyl Iodide.—To an ether solution of sodium triphenylmethyl[9] containing 0.18 mole of the base was added 21 g. (0.18 mole) of ethyl isobutyrate (Eastman Kodak Co.). The mixture was shaken, and at the end of nine minutes 28.3 g. (0.18 mole) of ethyl iodide (Eastman) was added. The reaction vessel was shaken, stoppered, and allowed to stand overnight. The mixture was acidified with 3 cc. of glacial acetic acid and extracted with a small amount of 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 the ether distilled off up to 50°. The residue was vacuum-

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[1] Schlenk, Hillemann and Rodloff, *Ann.*, **487**, 147 (1931).

[2] Ramart, *Bull. soc. chim.*, **4**, 35, 196 (1924); *Compt. rend.*, **178**, 396 (1924); Ramart and Amagat, *Ann. chim.*, **10**, 8, 273 (1927).

[3] Staudinger and Meyer, *Helv. Chim. Acta*, **5**, 670 (1922).

[4] See ref. 3, p. 669.

[5] Scheibler and Schmidt, *Ber.*, **58**, 1191 (1925).

[6] In this connection see ref. 1, p. 135.

[7] See Hudson, Dick and Hauser, THIS JOURNAL, **60**, 1960 (1938).

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

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

distilled, collecting up to 150° at 15 mm. The distillate was redistilled at atmospheric pressure through a six-inch (15-cm.) Widmer column. Fifteen grams or 58% of the theoretical amount of ethyl α,α-dimethylbutyrate, boiling at 140–142°, was obtained. This boiling point is in agreement with that reported[10] in the literature. A portion of the ester was converted into the amide by treating 2 g. of the former with the equivalent amount of sodium amide in 25 cc. of liquid ammonia. The ammonia was allowed to evaporate and 50 cc. of ether containing 5% of acetic acid was added to the residue. The mixture was extracted with water and washed with 10% sodium carbonate solution. The resulting ether solution was evaporated and the crystalline residue was recrystallized from a minimum of ligroin (90–120°). The purified material melted at 101–102°, in agreement with the melting point reported in the literature for α,α-dimethylbutyramide.[11]

(b) **With Benzyl Chloride.**—Eleven and one-half grams (0.10 mole) of ethyl isobutyrate (Eastman) was alkylated with 12.6 g. (0.10 mole) of benzyl chloride (Eastman) as in the previous experiment, using an ether solution containing 0.10 mole of sodium triphenylmethyl. Vacuum fractionation through a five-inch (13-cm.) Vigreux column gave 8.5 g., or 42% of the theoretical amount, of ethyl α,α-dimethylhydrocinnamate boiling at 130–131° at 15 mm. The ester was redistilled and a small mid-fraction taken out for analysis.[12] Calcd. for $C_{13}H_{18}O_2$: C, 75.7; H, 7.8. Found: C, 75.7; H, 8.0.

Four grams of the ester was hydrolyzed by boiling with 50 cc. of 20% sodium hydroxide solution for fifteen hours. The hydrolysis mixture was acidified with excess hydrochloric acid and allowed to stand overnight in the refrigerator. The crude acid, after filtering off and drying, melted at 54–56°. The acid was recrystallized by dissolving it in a minimum of ligroin (90–120°) at about 40° and cooling the solution in an ice-bath. The crystals were filtered off and dried. The recrystallized acid melted at 58° in agreement with the melting point reported in the literature for α,α-dimethylhydrocinnamic acid.[13]

(c) **With Methyl Iodide.**—An ether solution of 0.20 mole of sodium triphenylmethyl,[9] contained in the bottle in which it was prepared, was cooled thoroughly in an ice-bath. The glass stopper was removed while a tube delivering dry nitrogen was held near the mouth of the bottle, and 20.6 g. (nine-tenths of the equivalent amount, 0.18 mole) of ethyl isobutyrate (Eastman) was added. The bottle was stoppered and shaken. After five minutes, 33.5 g. (0.22 mole) of methyl iodide (Eastman) was added and the bottle was stoppered, shaken, and allowed to stand for six hours. The reaction mixture was extracted with water. The ether layer was separated from the mercury and water, and dried with anhydrous sodium sulfate followed by "Drierite." The ether solution was filtered and the ether distilled off through a twenty-inch (51-cm.) Vigreux column. The residue was distilled on a metal bath at 200 mm., collecting up to a bath temperature of 225°. The distillate was redistilled through a twelve-inch (31-cm.) Widmer column, collecting up to 116°. The residue was set aside and the distillate again distilled up to 116°. The two residues were combined and distilled from a small flask equipped with a five-inch (13-cm.) Vigreux column. Thirteen grams of ethyl trimethylacetate, 55% of the theoretical amount based on the quantity of ethyl isobutyrate used, boiling at 116–118°, was obtained. The temperature rose rapidly to 116°, indicating the absence of an appreciable amount of ethyl isobutyrate (b. p. 111–112°). The boiling point of 116–118° agrees with that obtained for a sample of ethyl trimethylacetate synthesized from trimethylacetic acid; the boiling point recorded in the literature[14] for ethyl trimethylacetate is 118.5°.

Two grams of the ester was converted into the amide by treatment with a slight excess of sodium amide, essentially as described in (a). After standing for thirty minutes the reaction mixture was neutralized by the addition of a few grams of ammonium chloride. The ammonia was allowed to evaporate and the residue was shaken with ether and a small amount of water. The ether layer was separated and the solvent evaporated on a water-bath. The amide after recrystallization once from ligroin (90–120°) and twice from water, melted at 152–153°. Melting points of 153–154°[15] and 155–156°[11] have been reported for trimethylacetamide.

Alkylation of Ethyl Methylethylacetate with Propyl Iodide.—Methylethylacetyl chloride, b. p. 115–116°,[16] was prepared in 40% yield from methylethylacetic acid[17] and phosphorus trichloride. Fifty grams of the acid chloride was refluxed two hours with 50 cc. of absolute alcohol and the reaction mixture diluted with ether, washed with sodium carbonate solution and dried. Distillation of the ether and fractionation of the residue through a twelve-inch (31-cm.) Widmer column gave 45 g. or 83% of the theoretical amount of ethyl methylethylacetate boiling at 132°.[18]

Twenty-three and one-half grams (0.18 mole) of ethyl methylethylacetate was added to an ether solution of sodium triphenylmethyl[9] containing 0.18 mole of base. The mixture was shaken and after five minutes 30.7 g. (0.18 mole) of *n*-propyl iodide (Eastman) was added. The reaction vessel was stoppered, shaken, and allowed to stand overnight. The reaction mixture was extracted with 200 cc. of water and dried with anhydrous sodium sulfate followed by "Drierite." Ether was distilled off and the residue distilled up to 150° at atmospheric pressure. The pressure was then reduced and the distillation continued up to 130° at 30 mm. Fractionation of the distillate through a six-inch Widmer column gave 19 g. or 61% of the theoretical amount of ethyl methylethylpropylacetate boiling at 180–185° at atmospheric pressure. The product was redistilled through a five-inch Vigreux column and boiled constantly at 81° at 20 mm. A small mid-fraction was taken out for analysis.[19]

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.8; H, 11.7. Found: C, 70.2; H, 11.7.

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(10) Bouveault and Blanc, *Bull. soc. chim.*, [3] **31**, 749 (1904).

(11) Haller and Bauer, *Compt. rend.*, **148**, 129 (1909).

(12) Microanalysis by R. L. Peck.

(13) Haller and Bauer, *Compt. rend.*, **149**, 9 (1909).

(14) Butlerow, *Ann.*, **173**, 372 (1874).

(15) Franchimont and Klobbie, *Rec. trav. chim.*, **6**, 238 (1887).

(16) Rupe, *Ann.*, **369**, 338 (1909).

(17) Gilman and Parker, "Organic Syntheses," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1925, p. 75.

(18) A boiling point of 133.5° is reported by Pagenstecher, *Ann.*, **195**, 120 (1879).

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

Two grams of the ester was converted into the amide by treatment with sodium amide as described above in (c). Evaporation of the ether left an oily residue which failed to crystallize. The residue was heated to boiling in a short test-tube and approximately one-half of it distilled off. The remaining material solidified on cooling and melted at 43-44°. Methylethylpropylacetamide has been reported to melt at 46°[20] and at 42-43°.[21]

Alkylation of Ethyl Isovalerate with Ethyl Iodide.—To an ether solution of sodium triphenylmethyl[9] containing 0.205 mole of the base was added with shaking 26.6 g. (0.205 mole) of ethyl isovalerate (Eastman). After two minutes, 32.0 g. (0.205 mole) of ethyl iodide (b. p. 72°) was added. The reaction vessel was stoppered, shaken and allowed to stand overnight. The reaction mixture was worked up as in the preceding experiment. The material remaining after the removal of ether was vacuum-distilled up to 150° at 15 mm. After two or three fractionations at atmospheric pressure through a twelve-inch Widmer column, the following fractions were obtained from the distillate: (1) up to 132°, 2.5 g., (2) 132-140°, 4.0 g., (3) 140-150°, 3.5 g., (4) 150-163°, 3.6 g., (5) 163-166°, 5.9 g. Vacuum distillation of the residue from the fractionation yielded 2.3 g. of material boiling at 118-122° at 15 mm. Fraction (2), boiling at 132-140°, probably consisted largely of recovered ethyl isovalerate (b. p. 135°); most of this fraction came over at 134-138°. The boiling point of fraction (5), 163-166°, is in agreement with the boiling point reported in the literature[22] for ethyl α-ethylisovalerate. The yield of this ester, 5.9 g., was 22% of the theoretical amount. A portion of the ester was converted into the amide by the method described above in (c). After one recrystallization from ligroin (90-120°) the amide melted at 135-135.5° in agreement with the melting point reported in the literature for α-ethylisovaleramide.[22] The fraction boiling at 118-122° at 15 mm. was redistilled at 32 mm. and boiled at 129-132° in agreement with the boiling point reported in the literature[23] for ethyl isovalerylisovalerate. The redistilled material was hydrolyzed[24] to di-isobutyl ketone by refluxing three hours with 25 cc. of glacial acetic acid containing 10% sulfuric acid and 10% water by volume. The hydrolysis mixture was kept cold and made alkaline with sodium hydroxide, then extracted three times with ether. The ether was distilled off and the crude ketone (1.9 g.) converted directly into the semicarbazone. The latter melted at 121-122° in agreement with the melting point reported in the literature.[23]

Attempted Alkylation of Ethyl Acetate.—The addition of 16 g. (0.18 mole) of ethyl acetate to a rapidly stirred solution containing an equivalent quantity of sodium triphenylmethyl[9] was followed in ten seconds by the addition of 31 g. (0.18 mole) of benzyl chloride. After allowing the mixture to stand overnight and working up essentially as described above in (a), only 3 to 4 g. of material, boiling at 100-200° at 15 mm., which may have contained ethyl hydrocinnamate (b. p. approximately 150° at this pressure) was obtained. Twenty-five grams of lower boiling material, presumably largely ethyl acetoacetate, was obtained.

Summary

The di-substituted esters, ethyl isobutyrate and ethyl methylethylacetate, have been successfully alkylated by first converting the esters into their sodium enolates by means of sodium triphenylmethyl, and treating the enolates with alkyl halides. Treated in a similar manner, ethyl isovalerate gave a fair yield of the ethylated product, but ethyl acetate failed to give an appreciable amount of the alkylated ester.

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[20] Haller and Bauer, *Compt. rend.*, **148**, 130 (1909).

[21] Haller and Bauer, *Ann. chim.*, (9) **1**, 15 (1914).

[22] Crossley and LeSueur, *J. Chem. Soc.*, **77**, 94 (1900).

[23] Spielman and Schmidt, This Journal, **59**, 2010 (1937).

[24] The method of hydrolysis described here has been used successfully by the authors for the conversion of several β-keto esters to their corresponding ketones.

DURHAM, N. C.

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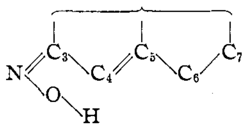
[A CONTRIBUTION FROM THE LABORATORY OF BIOLOGICAL CHEMISTRY, SCHOOL OF MEDICINE, UNIVERSITY OF BUFFALO]

Stereoisomeric Oximes of Cholestenone

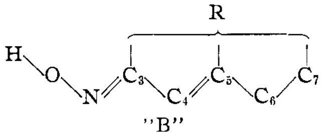
BY J. O. RALLS

Introduction

The isolation of the *syn* and *anti* oximes of an α, β unsaturated ketone was reported for the first time in 1931.[1] In 1938, the author suggested that some peculiarities observed during the reaction of cholestenoneoxime with iodine monobromide might be explained by means of the assumption that two stereoisomeric cholestenoneoximes existed, which, for want of better designations, were called "A" and "B."[2]



"A"



"B"

At that time, a product was described which had

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[1] Blatt and Stone, This Journal, **53**, 4135 (1931).

[2] Ralls, *ibid.*, **60**, 1748 (1938).