been shown to be correct. A new compound *o*-(2,4-dihydroxy-3-chlorobenzoyl)-benzoic acid has been synthesized and characterized.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE GEORGIA SCHOOL OF TECHNOLOGY]

The Use of Sodium Methoxide in the Claisen Reaction

BY E. EARL ROYALS

Freri has reported[1] that the condensation of diethyl oxalate with acetone or acetophenone by means of sodium methoxide in absolute methanol gives the methyl ester of the corresponding acylpyruvate in excellent yield and that the reaction requires less care than the condensation using sodium ethoxide. In the present investigation the corresponding reactions have been carried out with four other methyl ketones. The results are summarized in Table I.

TABLE I

PREPARATION OF METHYL ACYLPYRUVATES

Acyl substituent	Yield, %	B. p., °C.	mm.	$n^{25}D$ [b]	Equivalent wt. Calcd.	Found	
Aceto-	69.7	93–97[a]	9–12		72.06	71.75	71.65
Propiono-	42.1	90–95	4	1.4722–1.4751	79.10	79.30	79.75
Butyro-	51.5	110–112	7–8	1.4725–1.4750	86.10	87.07	87.24[c]
Isovalero-	84.0	103	4	1.4719–1.4729	93.10	95.02	95.07[c]
Pivalo-	74.5	112–113	11	1.4720	93.10	92.55	92.97

[a] This product melted at 61.5–62.5° after a single crystallization from benzene. Reported (ref. 1) m. p. 63°. [b] The variations in refractive index represent variations in individual samples. [c] It is possible, as was suggested by the Referee, that these high values may indicate contamination of the methyl ester with some of the ethyl ester.

It is assumed that, in common with other base-catalyzed condensations,[2] the present reactions involve the methyl rather than the methylene group of the ketone to form methyl acylpyruvates having the structure $RCOCH_2COCO_2CH_3$. On boiling with dilute aqueous sodium hydroxide, these acylpyruvates were found to be cleaved quantitatively according to the equation

$$RCOCH_2COCO_2CH_3 + 2NaOH \longrightarrow RCOCH_3 + (CO_2Na)_2 + CH_3OH$$

The equivalent weights given in the final column of Table I were calculated on the basis of this reaction.

Experimental

Materials.—Diethyl oxalate, prepared by a standard procedure, was distilled through a modified Widmer column under reduced pressure and used without further purification. C. P. grade acetone was dried for one week over calcium chloride and distilled through a modified Widmer column. A middle cut of accepted boiling point and refractive index was taken for use. The other ketones used were Eastman Kodak Co. practical grade products purified as described for acetone. Methanol was dried just prior to use by the method of Lund and Bjerrum.[3]

Condensation Procedure.—One-half gram atom of sodium was cut into thin strips and dissolved in 150 cc. of absolute methanol contained in a 500-cc., three-necked flask fitted with a reflux condenser, a dropping funnel and a modified Hershberg stirrer.[4] The reaction flask was protected from atmospheric moisture by drying tubes filled with absorbent cotton previously dried at 100°.[5] The solution was cooled to room temperature. The reaction vessel was immersed in a basin of tap water, the stirrer was started and a mixture of one-half mole each of diethyl oxalate and the required ketone was run in from the dropping funnel during one hour. Stirring was continued for four to six hours. The reaction mixture was allowed to stand overnight at room temperature. It was then cooled in an ice-bath, and an ice-cold solution of 15 g. of concd. sulfuric acid in 100 cc. of water was rapidly run in from the dropping funnel. The mixture was stirred for five to ten minutes, then poured into 500 cc. of water. The liberated methyl acylpyruvate was extracted with three 50-cc. portions of benzene. The benzene extracts were combined and washed with two 50-cc. portions of water. The benzene was removed by distillation at atmospheric pressure, and the residue was distilled under reduced pressure from an ordinary Claisen flask. The crude product was collected over a somewhat wider range than that recorded in Table I and was redistilled from a modified Claisen flask.[6]

A modification of the above procedure was necessary in the condensation of acetone with diethyl oxalate because of the unusually heavy precipitation of the sodium salt of methyl acetopyruvate during the reaction. In this case, 300 cc. of methanol was used as solvent for a run of the size described above. After reaction was complete, the precipitated sodium salt of the product was filtered from the reaction mixture and sucked dry on the filter. It was then returned to the reaction flask and worked up as described above. The product was distilled under reduced pressure from a modified Claisen flask fitted with an air condenser.

The last four compounds listed in Table I were colorless to light yellow oils; the yields and physical properties recorded are for products redistilled as described above. Methyl acetopyruvate was solid at room temperature. Crystallization of this compound was difficult because of its tendency to oil out of solution. It could, however, be crystallized from benzene with considerable loss due to its solubility in this medium. The yield reported in Table I is for the uncrystallized compound, while the analytical data were determined on a crystallized sample.

(1) Freri, *Gazz. chim. ital.*, **68**, 616 (1938).

(2) See Tracy and Elderfield, *J. Org. Chem.*, **6**, 70 (1941); see also Hauser and Adams, THIS JOURNAL, **66**, 345 (1944).

(3) Lund and Bjerrum, *Ber.*, **64**, 210 (1931).

(4) Hershberg, *Ind. Eng. Chem., Anal. Ed.*, **8**, 313 (1936).

(5) Adkins and Rainey, "Organic Syntheses," Vol. 20, 1940, p. 9.

(6) Noyes and Skinner, THIS JOURNAL, **39**, 2718 (1917).

Equivalent weights were determined by heating an accurately weighed sample of the methyl acylpyruvate, about 0.5 g., under reflux with a small excess of 0.25 *N* sodium hydroxide for four to six hours. The excess of base was then back titrated with standard hydrochloric acid.

Summary

Five aliphatic methyl ketones have been condensed with diethyl oxalate by means of sodium methoxide in absolute methanol to give methyl acylpyruvates in consistently good yields. This modification of the Claisen reaction is superior to the usual procedure in that good yields of acylpyruvates may be obtained with less care.

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[CONTRIBUTION NO. 553 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Determination of Linoleic Acid in Cholesteryl Linoleate[1]

BY JACQUELINE S. FRONT AND B. F. DAUBERT

In a study of methods for the quantitative determination of linoleic acid in small volumes of blood, we have had occasion to prepare the linoleic acid ester of cholesterol in a high degree of purity. The ester was prepared by a slight modification of the method of Page and Rudy[2] and also by direct esterification of cholesterol with linoleyl chloride in quinoline–chloroform solution.

It was anticipated that if cholesteryl linoleate could be directly isomerized in alkaline ethylene glycol solution and the absorption spectra measured on the isomerized product according to the method of Mitchell, Kraybill and Zscheile,[3] an additional and perhaps a more satisfactory method of ascertaining its purity would result. The assumption that the ester could be directly isomerized was based upon the fact that natural fats,[3] synthetic glycerides[4] and potassium linoleate are directly isomerizable, and the linoleic acid content determined from subsequent spectral absorption data on the isomerized products.

It has been determined experimentally in this investigation, however, that it is not possible to isomerize cholesteryl linoleate directly in alkaline ethylene glycol or glycerol solution, precisely according to the method of Mitchell, *et al.*[3] Cholesteryl linoleate is not soluble in ethylene glycol or glycerol. Consequently, when the mixture of alkaline glycol or glycerol is heated with the cholesteryl linoleate at 180° for thirty minutes in an oil-bath, the ester fuses and rises to the surface. Partial hydrolysis of the ester does occur under these conditions as may be observed from the data in Table I. The average $E^{1\%}_{1\,cm.}$ value of 46 from six isomerizations of cholesteryl linoleate in alkaline ethylene glycol definitely indicates that although partial hydrolysis occurred, it represents only 12.3% of the theoretical $E^{1\%}_{1\,cm.}$ value of 374. This value is based on an experimentally determined $E^{1\%}_{1\,cm.}$ of 867 for linoleic acid. The bulk of the ester was recovered unhydrolyzed. Mechanical agitation of the mixture during the heating did not affect materially the magnitude of the hydrolysis.

The apparent failure of the ester to saponify completely when subjected to the above conditions seems to indicate that isomerization did not occur for one or both of two reasons. First, because of the insolubility of the ester in the solvent, and, second, because saponification was inhibited under the almost anhydrous conditions of heating. If the latter reasoning is correct, then saponification of the ester seems to be necessary before isomerization of the linoleic acid can occur.

Preliminary efforts to find a material suitable as a solvent for both potassium hydroxide and cholesteryl linoleate in order to test the hypothesis that saponification must be preliminary to isomerization have not been successful. Therefore, a modification of the procedure of Mitchell, *et al.*, has been used to determine the linoleic acid in cholesteryl linoleate, to thus serve as a method for the determination of the purity of the ester.

Experimental

Cholesteryl Linoleate.—The ester was prepared from cholesterol (m.p. 148°) and linoleyl chloride according to the method of Page and Rudy[2] with the following modification: after reaction, the cooled liquid ester was dissolved in 300 ml. of ethyl ether and the solution washed with 5% potassium carbonate and water. The ether was removed from the dried and filtered liquid under nitrogen and the liquid residue dissolved in small volume of ether. Sufficient ethyl alcohol was then added to impart slight turbidity to the solution. Crystallization of the ester occurred on cooling overnight at 0 to 5°. Recrystallization several times from the same mixture of solvents yielded a product melting sharply at 42.5° (Page and Rudy, 42.0°).

The ester was also prepared by the following method. Cholesterol (5 g.) was dissolved in a mixture of chloroform (20 ml.) and quinoline (5 g.) and to this solution there was added linoleyl chloride (3.9 g.). The mixture was refluxed on a steam-bath for three hours and after cooling was dissolved in ethyl ether (300 ml.). The ether solution was transferred to a separatory funnel and washed successively with 30-ml. portions of 0.5 *N* sulfuric acid, 5% potassium carbonate solution and water. After drying over anhydrous sodium sulfate, the solution was treated in the same manner as above. The melting point of the crystallized product is 42.0–42.5°; mol. wt.,[5] 465 (calcd.

(1) The generous financial assistance of the Buhl Foundation and Nutrition Foundation, Inc., is gratefully acknowledged.

(2) Page and Rudy, *Biochem. Z.*, **220**, 304 (1930).

(3) Mitchell, Kraybill and Zscheile, *Ind. Eng. Chem., Anal. Ed.*, **15**, 1 (1943).

(4) Baldwin and Daubert, *Oil & Soap*, **22**, 180 (1945).

(5) Hanson and Bowman, *Ind. Eng. Chem., Anal. Ed.*, **11**, 440 (1939).