Reduction of α- and β-Ketoesters

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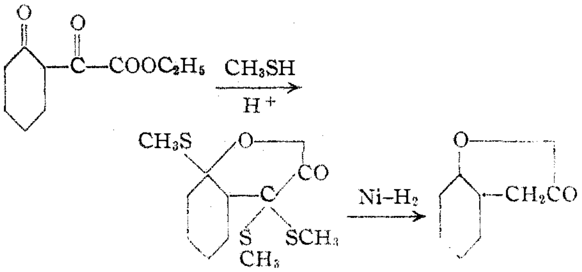
The reduction of α-keto- and β-ketoesters to the corresponding desoxy esters by the Clemmensen[2,3] or the Wolff–Kishner[4,5] methods has not proved to be a general applicability. We have studied the reduction of such esters by the thioacetal hydrogenolysis method of Wolfrom and Karabinos,[6] and found that reduction can be effected in good over-all yield. Ethyl acetoacetate, 2-carbethoxycyclohexanone, 2-methyl-2-carbethoxycyclohexanone, ethyl benzoylacetate and methyl benzoylformate were converted into ethyl butyrate (74%), ethyl cyclohexanecarboxylate (75%), ethyl 1-methylcyclohexanecarboxylate (70%), ethyl hydrocinnamate (77%) and methylphenylacetate (79%), respectively, in the yields indicated.

The reduction of ethyl cyclohexanoneglyoxylate, an α,γ-diketoester, yielded a mixture of the stereoisomeric lactones of 2-cyclohexanol-1-acetic acid[7] in 78% yield. Although the intermediate thioacetal was not isolated in this experiment, the formation of this lactone may be explained as indicated below.



Experimental

The procedure described below is typical. Each experiment was repeated and the yield reported represents the average of two fairly close checking runs. Because of the small scale of these experiments, it is likely that larger yields were actually obtained so that the yields reported are a minimum. The yields are based on over-all conversion of ketoester to desoxyester.

Ethyl Butyrate from Ethyl Acetoacetate (Single Experiment).—Five grams of anhydrous zinc chloride was placed in a 28-mm. Pyrex tube which was then heated. The zinc chloride was fused under vacuum and the tube was rotated so that the lower three inches were coated with zinc chloride when it had cooled. After adding 10 g. of ethyl acetoacetate, 3 g. of anhydrous sodium sulfate and 100 g. of methyl mercaptan the tube was sealed and shaken at room temperature until the zinc chloride had dissolved. After standing overnight at room temperature (25–30°) the tube was cooled and opened. The excess methyl mercaptan was recovered by distillation and the residue taken up in ice water and ether. The ether layer and washings were combined, washed with cold 10% sodium hydroxide, water, and saturated sodium chloride solution. After drying over anhydrous sodium sulfate the ether was removed to yield 17 g. of crude thioacetal. This was taken up in alcohol and added to a suspension of 280 g. of freshly prepared Raney nickel[8] in a total of 500 cc. of alcohol. After refluxing for about twelve hours the catalyst was removed and the filtrate concentrated. The catalyst was washed well with benzene and these washings used to extract the desired ester from the diluted alcoholic residue. In the case of ethyl butyrate careful fractionation was needed to obtain 6.2 g. (70%) of the ester free from solvent as a colorless liquid, b. p. 118–121°, $n^{22}\mathrm{D}$ 1.400.[9] Butyramide, m. p. and mixed m. p. 113–114°, was obtained from this ester.

Reduction of 2-Carbethoxycyclohexanone.—The mercaptole was prepared in the previously described manner, using 10 g. (0.06 mole) of 2-carbethoxycyclohexanone, 5 g. of zinc chloride, 3 g. of anhydrous sodium sulfate, and 100 cc. of methyl mercaptan. An oil, 16 g., was obtained.

The desulfurization was carried out with 150 g. of Raney nickel, to yield 7.1 g. (0.045 mole, 75%) of ethyl hexahydrobenzoate, b. p. 82–83° at 12 mm., $n^{25}\mathrm{D}$ 1.466.[10] The amide melted at 185–186° alone and mixed with an authentic sample.[11]

Preparation of 2-Methyl-2-carbethoxycyclohexanone.—To a well-stirred suspension of 8 g. (0.3 mole) of sodium hydride in 400 ml. of dry benzene was added dropwise 50 g. (0.3 mole) of 2-carbethoxycyclohexanone. After one-half hour 43 g. (0.3 mole) of methyl iodide was added and the mixture was refluxed until the vapor temperature reached 80° (1 hour). A further 5 g. of methyl iodide was added and the heating continued for four hours. This treatment afforded 50 g. (90%) of a product, b. p. 96–100° at 4 mm., $n^{26}\mathrm{D}$ 1.4491, which gave a negative ferric chloride test.[12]

Reduction of 2-Methyl-2-carbethoxycyclohexanone.—The mercaptole was prepared using 10 g. (0.055 mole) of 2-methyl-2-carbethoxycyclohexanone, 5 g. of zinc chloride, 3 g. of anhydrous sodium sulfate and 100 cc. of methyl mercaptan. The product obtained was an oil weighing 10.5 g. The desulfurization was carried out using 150 g. of Raney nickel to yield 6.5 g. (0.038 mole, 78%) of 1-methyl-1-carbethoxycyclohexane, b. p. 82–83° at 12 mm., $n^{28}\mathrm{D}$ 1.4430.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.6; H, 10.6. Found: C, 70.7; H, 10.7.

Reduction of Ethyl Cyclohexanoneglyoxylate.—The mercaptole was prepared using 10 g. (0.55 mole) of ethyl cyclohexanoneglyoxylate, 5 g. of zinc chloride, 3 g. of anhydrous sodium sulfate, and 100 cc. of methyl mercaptan. A crude oil, 13 g. was obtained. The desulfurization was accomplished with 200 g. of Raney nickel and 500 cc. of alcohol to yield 6 g. (0.043 mole, 78%) of a mixture of the isomeric cyclohexanolacetic acid lactones,[7] b. p. 119–122° at 6–7 mm., $n^{20}\mathrm{D}$ 1.4773, d^{20}_{20} 1.0896.

Reduction of Methyl Benzoylformate.—The mercaptole was prepared using 10 g. (0.061 mole) of methyl benzoylformate, 5 g. of zinc chloride, 3 g. of anhydrous sodium sulfate and 100 cc. of methyl mercaptan. A crude oil, 18 g., was obtained. The desulfurization was accomplished with 150 g. of Raney nickel and 500 cc. of alcohol, to yield 7.2 g. (79%) of methyl phenylacetate, b. p. 102–105° at 10 mm., $n^{20}\mathrm{D}$ 1.500[13] melting point and mixed melting point of the amide, 154.5–156°.

Reduction of Ethyl Benzoylacetate.—The mercaptole was prepared in the usual manner, using 10 g. (0.052 mole) of ethyl benzoylacetate, 5 g. of zinc chloride, 3 g. of anhydrous sodium sulfate and 100 cc. of methyl mercaptan. A crude oil, 14.5 g., was obtained. The desulfurization

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[1] Taken from the Ph.D. thesis of H. M. W. August, 1949.

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[7] M. S. Newman and C. A. VanderWerf, *ibid.*, **67**, 233 (1945).

[8] R. Mozingo, *Org. Syn.*, **21**, 15 (1941).

[9] J. Mathews and K. Faville, *J. Phys. Chem.*, **22**, 6 (1918).

[10] A. Wahl and A. Mayer, *Bull. soc. chim.*, [4] **3**, 959 (1908).

[11] W. Markownikoff, *Ber.*, **25**, 3355 (1892).

[12] Compare N. Chattergee and H. Roy, *J. Ind. Chem. Soc.*, **20**, 329 (1943).

[13] N. A. Prileshajev, *J. Russ. Phys.-Chem. Soc.*, **42**, 1416 (1910).

was accomplished with 200 g. of Raney nickel and 500 cc. of alcohol, to yield 7.2 g. (0.05 mole, 77%) of ethyl hydrocinnamate, b. p. 113–115° at 10 mm., $n^{20}D$ 1.487, amide m. p. 99–100°.[14,15]

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The Relation between Steric Hindrance and Ionization Constant of Certain Acids

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In a number of cases aliphatic and alicyclic carboxylic acids which are sterically hindered, as indicated by a very low rate of esterification under ordinary Fischer esterification conditions, have been found to be weaker than unhindered acids of the same molecular weight and type. In the few instances in which the ionization constants of hindered alicyclic or aliphatic acids have been determined the acids have been tertiary acids, *i. e.*, the carboxyl group was attached to a tertiary carbon atom. These were found to be about one K_a unit weaker than unhindered acids of the same type[2,3] One such acid, campholic, may be separated from the isomeric unhindered isocampholic acid by taking advantage of the fact that campholic acid may be liberated from its sodium salt solution by carbonic acid and so has been considered to be a much weaker acid.[4]

Since highly hindered acids in which the carboxyl group is attached to a secondary carbon are now available in *cis*- and *trans*-2,2,6-trimethylcyclohexanecarboxylic acids it seemed worthwhile to determine, in a single series of measurements, the ionization constants of a number of unhindered, hindered tertiary and the two hindered secondary acids mentioned, all of the acids, except benzoic, being alicyclic in nature.

Apparatus and Method

Several of the acids are not sufficiently soluble in water to permit its use as solvent in this series of measurements which were to be made under as nearly identical conditions as possible. It was found that a 25% solution of dioxane in water can be used as solvent with all of the acids. Peroxides were removed from Eastman Kodak Co. dioxane by distillation from powdered iron and ferrous sulfate. The distillate gave no iodide test for peroxides and was redistilled as the binary azeotrope before each series of determinations and then diluted to 25% with carbon dioxide-free water.

It was decided to use the method of Kumler[5] using glass electrodes for the *p*H determinations after preliminary experiments indicated that the hydrogen electrode was not satisfactory in the dioxane solution used. To avoid electrical interferences in the glass electrode measurements, water from a thermostat operating at 25.0 ± 0.1° was circulated through a quart vacuum bottle in which the titration vessel consisting of a large Pyrex test-tube was suspended. The Beckman external glass electrode–saturated calomel electrode system and a glass capillary were hung in the large test-tube. Stirring was effected by hydrogen gas bubbled through the capillary.

It was found that erratic results were obtained in the *p*H measurements on standard buffers as well as in K_a value determinations on pure benzoic acid using Kumler's formula unless certain precautions were taken in conditioning the glass electrodes.

Dioxane solution was used to rinse the electrodes between titrations of different samples of the same acid. On completion of readings on any one acid the electrodes were rinsed with distilled water and allowed to remain in water for at least an hour before use with a different acid.

Three samples, weighed on a semi-micro balance to 0.01 mg., were placed in titration vessels and 70 ml. of 25% dioxane–water solution added to each. The vessels were heated in a water-bath to dissolve the samples and allowed to cool to room temperature. Before use the electrodes were rinsed with the dioxane solution, placed in the titration cell and left in contact with the solution for 15 minutes before any measurements were taken. After this waiting period the exact volume of sodium hydroxide solution required for 0.333 neutralization of the acid was added from a micro buret and the *p*H determined after stopping the hydrogen stream through the capillary. Similar readings were obtained after 0.500 and 0.666 equivalent of sodium hydroxide had been added. The three samples yielded then data for nine K_a values for each acid. In the typical case of cyclohexanecarboxylic acid these values were 0.182, 0.182, 0.175; 0.173, 0.181, 0.167; and 0.162, 0.178, 0.167 $\times 10^{-5}$. The K_a values listed in Table I represent averages of the three averages obtained from such data.

Table I

Acid	M. p., °C.	$K_a \times 10^{-5}$
Benzoic	121–122	1.17
Cyclohexanecarboxylic	30[a]	0.174
Cyclopentanecarboxylic	b. p. 215–216[b]	.126
1-Isopropylcyclohexanecarboxylic	103–104[c]	.0362
1,2,2-Trimethylcyclopentanecarboxylic	191–192[d]	.0348
1,2,2,3-Tetramethylcyclopentanecarboxylic	106–107[e]	.0353
"*trans*"-2,2,6-Trimethylcyclohexanecarboxylic	82–83[f]	.106
"*cis*"-2,2,6-Trimethylcyclohexanecarboxylic	73–74[g]	.0241

[a] Prepared *via* Grignard reaction; b. p. 230–233°. [b] Prepared by Ney, This Journal, **65**, 770 (1943); refractionated. [c] Prepared by Shive, *ibid.*, **63**, 2979 (1941); recrystallized. [d] Isolated from petroleum and purified by Hancock, *ibid.*, **61**, 2448 (1939); recrystallized. [e] Prepared by alkali fusion of camphor by Stallings, Ph.D. Thesis, University of Texas, 1949. [f] Isolated from petroleum and purified by Horeczy, This Journal, **64**, 385 (1942); recrystallized. [g] Prepared by Shive, *ibid.*, **64**, 385 (1942); recrystallized.

The unexpectedly large differences between K_a values of the second and third acids and the very large difference between the "*cis*" and "*trans*" acids are far outside of experimental error and remain unexplained. They may indicate that glass electrode *p*H measurements in dioxane–water solutions even though reproducible, should not

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[1] Presented in partial fulfillment of requirements for the degree of Master of Arts, the University of Texas, 1949.

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