

Summary

1. α -Ergosterol, prepared by the catalytic reduction of ergosterol acetate in acetic acid solution with platinum oxide (Adams') as a catalyst, contains small amounts of allo- α -ergosterol.

2. Ergosterol chloroacetate was found to be very largely α -ergosterol chloroacetate with smaller amounts of the chloroacetates of β -ergosterol and of allo- α -ergosterol.

3. Ergosterol reacts with chloroacetyl chloride to form, in small amount, an addition product, $C_{31}H_{49}O_3Cl_2$.

4. Ergosterol chloroacetate forms neither a bromide nor a peroxide nor does it react with potassium permanganate. Upon reduction evidence of some degree of isomerization is found in the increased yield of the reduction product, allo- α -ergosterol.

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THE PREPARATION OF DIMETHYLACETOACETIC ESTER AND OF $\Delta^3,2,2$ -DIMETHYLBUTENOL-1

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A considerable quantity of $\Delta^3,2,2$ -dimethylbutenol-1 was desired in order to study its behavior over oxide catalysts.¹ It appeared that this compound could be most easily prepared from acetoacetic ester through the following series of compounds: (1) monomethylacetoacetic ester, (2) dimethylacetoacetic ester, (3) 3-hydroxy-2,2-dimethylbutyric ester, (4) $\Delta^3,2,2$ -dimethylbutyric ester, (5) $\Delta^3,2,2$ -dimethylbutenol-1.

There does not seem to be available in the literature adequate directions for the methylation of acetoacetic ester, although the two derivatives have been prepared in a more or less pure state by a number of investigators.² The method of preparation described below has been developed.

Ethyl 2-Methylacetoacetate.—Thirty-nine and eight-tenths grams (1.73 moles) of sodium was very finely powdered in xylene so that it was like sand. After decanting the xylene, the sodium was washed with two 75-ml. portions of dry toluene (Note 1). The sodium was then covered with one liter of dry toluene, and the flask fitted with a reflux condenser, immersed in an ice-bath, and allowed to cool for fifteen minutes, after which 218.3 g. (1.68 moles) of ethyl acetoacetate (Note 2) was added down the condenser during the course of ten to fifteen minutes (Note 3) while the flask was vigorously shaken and kept in the ice-bath. The top of the condenser was now fitted with a calcium chloride tube and, after an additional ten minutes' cooling, was allowed to stand at room

¹ Adkins and Folkers, *THIS JOURNAL*, **53**, 1095 (1931).

² Frankland and Duppa, *Ann.*, **138**, 328 (1860); Conrad and Limpach, *ibid.*, **192**, 153 (1878); Michael, *Ber.*, **38**, 2083 (1905); Clark, *THIS JOURNAL*, **33**, 527 (1911).

temperature for seven to ten hours, with an occasional vigorous shaking during the first hour. The reflux condenser was then temporarily removed, a long-stem funnel pushed down into the semi-solid salt, and 253 g. (1.78 moles) of methyl iodide added. After standing overnight, the flask was heated on the steam-bath for four to six hours with an occasional vigorous shaking. The sodium iodide settled out completely at the end of this time. The sodium iodide was then filtered off with suction through a 20-cm. Büchner funnel (Note 4). The filter cake was pressed with a cork and sucked as dry as possible. The filtrate was then fractionated through a 25-cm. Widmer column. The toluene was conveniently fractionated at about 250 mm. pressure, or at atmospheric pressure with the use of a heater around the column. The yield of ethyl 2-methylacetoacetate was 170 g. (70–71%) (Note 5), boiling at 75–76° at 15 mm.

Ethyl 2,2-Dimethylacetoacetate.—The sodium salt of ethyl 2-methylacetoacetate was prepared as above using 35.6 g. (1.55 moles) of sodium, 216 g. (1.50 moles) of ethyl 2-methylacetoacetate and one liter of dry toluene. After adding 227 g. (1.6 moles) of methyl iodide and allowing to stand overnight, the flask was heated for fourteen hours on the steam-bath with a vigorous shaking every other hour. Because the closeness of the boiling points of the mono- and dimethylacetoacetic esters makes fractionation impossible, the di-substituted ester was purified by treatment with more sodium and methyl iodide to react with the mono-substituted ester (Note 6). To carry out this purification the sodium iodide was next filtered, and the filtrate distilled through a 25-cm. Widmer column until approximately 350 ml. of distillate had been collected and the temperature of the vapor was 109–110°. This distillate was chiefly toluene, with a little water and the greater portion of the lower-boiling by-products. Then, assuming the presence of 1.1 moles of substituted acetoacetic ester (75% of the original 1.5 moles), 10% of which is the monomethyl derivative, the distillation residue was added to this calculated amount of powdered sodium (2.5 g.). The flask was fitted under a reflux condenser, and after standing from four to five hours, 7 ml. of methyl iodide added. After standing overnight and a half hour's heating on the steam-bath, the reaction was complete. The sodium iodide was then filtered off and the toluene and ester fractionated through a Widmer column. The yield of ethyl 2,2-dimethylacetoacetate was 128 g. (54% of the theoretical amount based on ethyl 2-methylacetoacetate) and boiled at 72–73° at 14 mm.

Notes.—1. Due to the closeness of the boiling points of xylene and the mono- and dimethyl substituted acetoacetic esters, the fractionation of the product is facilitated by washing out all of the xylene. Absolute ethanol may be used in the preparation of the monomethyl substituted ester (70% yields) as the solvent; however, the high solubility of sodium iodide in alcohol makes its removal very difficult. Benzene may be used as the solvent to prepare the monomethyl substituted ester in 70–80% yields and the dimethyl substituted ester in 50–60% yields (without purification); however, the use of ordinary benzene (or toluene) containing thiophene introduces sulfur-containing compounds into the product, which make it impractical to reduce the ester over a nickel catalyst. Mallinckrodt's c. p. quality toluene was distilled, until the distillate was no longer turbid, before using as the solvent.

2. Ethyl acetoacetate, b. p. 70° (16 mm.) from the U. S. Industrial Alcohol Company was redistilled before using.

3. No difficulty was encountered in agitating the bulky sodium salt, if the ester was added quite rapidly and the solution kept well cooled. If the ester was added more slowly, the salt became too solid for thorough mixing before all of the ester could be added. The sodium salt prepared in this manner had a bluish-white color.

4. The finely divided sodium iodide precipitate was easily filtered if a 25-cm. filter paper was used in a 20-cm. funnel, the edge of the paper being held to the side of the funnel with gummed paper.

5. By cutting the fractionation of the toluene solution at 71–72° at 14 mm., 78% yields of crude ethyl 2-methylacetoacetate may be obtained, and used directly for the preparation of the dimethyl substituted ester in 50% yields.

6. This method of purification gave a product which showed a slight test for enol with ferric chloride, indicating the presence of some monomethyl substituted ester.

Ethyl 2,2-dimethyl-3-hydroxybutyrate, b. p. 94–95° (21 mm.), was obtained in 88–93% yields by the reduction with a nickel catalyst of ethyl 2,2-dimethylacetoacetate.³

Ethyl $\Delta^3,2,2$ -dimethylbutyrate, b. p. 139–141°, was obtained in 74–80% yields by the dehydration of ethyl 2,2-dimethyl-3-hydroxybutyrate with phosphorus pentoxide.⁴

$\Delta^3,2,2$ -Dimethylbutenol-1.—Courtot⁵ stated that he reduced ethyl $\Delta^3,2,2$ -dimethylbutyrate with sodium and ethanol by the method of Bouveault and Blanc but gives no further information on the preparation. At least three modifications of the procedure of Bouveault and Blanc have been proposed as advantageous for the reduction of various esters to the corresponding alcohols through the use of sodium and ethanol. Levene and Allen⁶ used a hydrocarbon (toluene) as a reaction medium, and added the ester slowly to the sodium completing the reaction in one hour. Adams and Marvel⁷ did not use a hydrocarbon solvent and added the sodium as rapidly as possible (one hour) to the ester. Ford and Marvel⁸ used a hydrocarbon as a reaction medium and added the ester very rapidly (two to five minutes) to the sodium.

The methods of Adams and Marvel and of Ford and Marvel were compared for the reduction of the ethyl $\Delta^3,2,2$ -dimethylbutyrate, and it was found that the method of adding the ester rapidly to powdered sodium in a hydrocarbon medium (methylcyclohexane) was very much inferior to that of Adams and Marvel in that the yield of alcohol was only 25% and in that the corresponding acid was produced in large amounts, *i. e.*, 48%. The low yield of alcohol and the high yield of acid was not due to the quality of the reagents, because the same materials were used in the procedure described below.

The preferred method for carrying out the reduction was as follows. One hundred and thirteen grams (0.8 mole) of ethyl $\Delta^3,2,2$ -dimethylbutyrate and 927 ml. of absolute ethanol (dried once over lime and twice over magnesium methoxide) were placed in a three-necked, 5-liter flask, which was fitted with a rapid mechanical stirrer and a condenser 85 cm. in length and of 2.5 cm. bore. Through the other neck was added 110.5 g. (4.8 moles) of sodium in small pieces during the course of fifty minutes. At the end of this time only a few pin heads of sodium remained, which were dissolved after five minutes. A small flame was used toward the end of the addition to keep the solution hot enough so that the sodium remained melted. The color of the solution was now only light yellow. While still hot, the solution was poured into a 3-liter flask fitted with a 25-cm. Widmer column and 300 ml. of ethanol was distilled (oil-bath, 140–170°). Then 500 ml. of water (part of which was used to rinse out

³ Adkins, Connor and Cramer, *THIS JOURNAL*, **52**, 5195 (1930).

⁴ Courtot, *Bull. soc. chim.*, **35**, 111–113 (1906).

⁵ Courtot, *Ref.* 4, p. 121.

⁶ Levene and Allen, *J. Biol. Chem.*, **27**, 443 (1916).

⁷ Adams and Marvel, *THIS JOURNAL*, **42**, 315 (1920).

⁸ Ford and Marvel, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1930, Vol. X, p. 62.

the reaction flask) was cautiously added. The distillation was continued until the vapors were at 83.5° and 687 ml. of distillate was collected.

Since some $\Delta^3,2,2$ -dimethylbutenol-1 distilled over with this aqueous ethanol, it was recovered by adding 150 ml. of water to the 687 ml. of distillate and distilling this mixture through a 50-cm. Widmer column until the vapors were at 84° . The residue (about 150 ml.) was transferred to an ordinary 500-ml. distilling flask and distilled. Two 25-ml. portions of distillate were collected. Each of these was salted out with anhydrous potassium carbonate to give about 15 ml. (total) of ethanol and the unsaturated alcohol, which was added to the bulk of the alcohol before drying. The original distillation residue was steam distilled until about 300 ml. of distillate was collected. The alcohol layer was separated. The water layer was treated with potassium carbonate and distilled after removal of the alcohol layer. Twenty-five ml. distillates were collected and salted out until all the alcohol had been obtained. All the alcohol layers were combined and dried twice over anhydrous potassium carbonate. Ether was used as a solvent to prevent mechanical loss. The yield of $\Delta^3,2,2$ -dimethylbutenol-1, b. p. 128.5 – 131° , on fractionation through a 20-cm. Widmer column was 49.5 g. or 61.8% of the theoretical. The steam distillation residue, after removal of the alcohol, contained only very little non-volatile insoluble material. It was acidified with sulfuric acid and the $\Delta^3,2,2$ -dimethylbutyric acid was steam distilled. The entire distillate was just neutralized with a sodium hydroxide solution and evaporated to dryness. The yield of sodium $\Delta^3,2,2$ -dimethylbutyrate, dried to constant weight at 125° , was 8.6 g. or 7.9%.

Summary

Procedures are described for the preparation in good yields of dimethylacetoacetic ester from acetoacetic ester and for the reduction with sodium and ethanol of $\Delta^3,2,2$ -dimethylbutyric ester to $\Delta^3,2,2$ -dimethylbutenol-1. In the latter preparation the method of Adams and Marvel for the reduction of esters is shown to be very much superior to that which Ford and Marvel found to be advantageous in several such reductions.

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