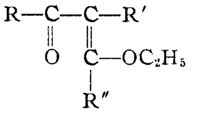
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Condensation of Ethyl Triethoxyacetate with Some Active Methylene Compounds

BY REUBEN G. JONES

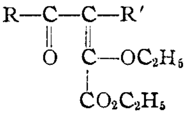
Triethyl α-ethoxy-γ-ketoaconitate, diethyl β-acetyl-α-ethoxy-γ-ketoglutaconate, diethyl α-ethoxy-β-trifluoroacetylfumarate, diethyl α-acetyl-β-ethoxyfumarate and ethyl β,β-diacetyl-α-ethoxyacrylate have been synthesized by heating together ethyl triethoxyacetate, acetic anhydride and the appropriate β-ketoester or β-diketone.

α-Ethoxymethylene-carbonyl compounds like I are useful intermediates for the synthesis of pyridines,[1] quinolines,[2] pyrimidines,[3] pyrazoles[4] and other aromatic heterocycles. However, relatively few compounds of type I are known, and for this reason it has been of interest to investigate the preparation of new members of this class. A preceding paper from this Laboratory described the synthesis of several new examples of type I by the condensation of ethyl orthoformate with certain compounds containing activity methylene groups.[5] This was an extension of the original Claisen synthesis of ethoxymethylene compounds using orthoformic esters.[1,6] The present study is concerned with the condensations of an ortho ester of oxalic acid, ethyl triethoxyacetate,[7] with several active methylene compounds in the presence of acetic anhydride. These reactions have led to the preparation of compounds II, III, IV, V and VI.



I

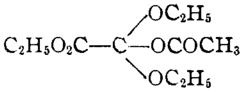
$$\begin{array}{l} R-C-C-R' \\ \;\;\;\;\| \;\;\;\, \| \\ \;\;\;\;O \;\;\, C-OC_2H_5 \\ \;\;\;\;\;\;\;\;\;\;\; | \\ \;\;\;\;\;\;\;\;\;\;\; R'' \end{array}$$



$$\begin{array}{l} R-C-C-R' \\ \;\;\;\;\| \;\;\;\, \| \\ \;\;\;\;O \;\;\, C-OC_2H_5 \\ \;\;\;\;\;\;\;\;\;\;\; | \\ \;\;\;\;\;\;\;\;\;\;\; CO_2C_2H_5 \end{array}$$

II, R = R′ = $-CO_2C_2H_5$
III, R = $-CO_2C_2H_5$, R′ = $-COCH_3$
IV, R = $-CF_3$, R′ = $-CO_2C_2H_5$
V, R = $-CH_3$, R′ = $-CO_2C_2H_5$
VI, R = R′ = $-COCH_3$

Consistently satisfactory yields (55–65%) of triethyl α-ethoxy-γ-ketoaconitate (II)[8] have been obtained by heating together equimolecular quantities of ethyl triethoxyacetate and ethyl oxalacetate in the presence of acetic anhydride. The other products of the reaction were ethyl oxalate, ethyl acetate and acetic acid. It is probable that the mechanism of this reaction is similar to that of the reaction of ethyl orthoformate, ethyl oxalacetate and acetic anhydride.[5] Thus the initial step may be the formation of diethoxycarbethoxymethyl acetate, VII, by reaction of ethyl triethoxyacetate with acetic anhydride.[9] The compound VII may then undergo two competing reactions, (1) condensation with ethyl oxalacetate followed by loss of ethanol to yield II, and (2) thermal decomposition to form ethyl oxalate and ethyl acetate. Other interpretations of this reaction are possible, however, and it is planned to discuss these in a subsequent communication.



VII

Diethyl β-acetyl-α-ethoxy-γ-ketoglutaconate (III)[8] was obtained in 57% yield by heating together ethyl triethoxyacetate, ethyl acetopyruvate and acetic anhydride. A somewhat lower yield (34%) of diethyl α-ethoxy-β-trifluoroacetylfumarate (IV)[8] resulted from the reaction of ethyl triethoxyacetate with ethyl trifluoroacetoacetate and acetic anhydride. Still smaller yields (12–15%) of diethyl α-acetyl-β-ethoxyfumarate (V)[8] and ethyl β,β-diacetyl-α-ethoxyacrylate (VI)[8] were obtained from the reactions of ethyl triethoxyacetate and acetic anhydride with ethyl acetoacetate and acetylacetone, respectively.

Acknowledgment.—The author is grateful to W. L. Brown, H. L. Hunter and W. J. Schenck for the microanalyses reported here and to K. C. McLaughlin for valuable assistance.

Experimental

Ethyl Triethoxyacetate.[7]—A mixture of 500 g. of ethyl oxalate and 735 g. of phosphorus pentachloride was heated in an oil-bath at 100–110° for 10 to 15 hours with occasional stirring. The resulting liquid was distilled under reduced pressure. After the large forerun of phosphorus oxychloride, a mid-fraction was collected up to 75° (12 mm.), and then the main fraction of ethyl dichloroethoxyacetate was collected between 75 and 82° (12 mm.). The forerun and tailings were redistilled to yield an additional quantity of the desired compound, total 535 g. Some unreacted phosphorus pentachloride distilled over and was collected with the product. It was best separated by cooling the distillate to 0° and decanting or filtering. During the distillation it is essential to maintain a pressure of at least 15 mm. or lower. Distillation at pressures much higher than 15 mm. results in almost complete decomposition of the ethyl dichloroethoxyacetate to ethyl chloride and ethoxalyl chloride.[7]

The conversion of ethyl dichloroethoxyacetate to ethyl triethoxyacetate by reaction with sodium ethylate according to the directions of Anschutz[7] was not very satisfactory. Therefore, a method suggested by Blaise and Maire[10] was used. Since the French authors gave no details, the procedure is described here.

In a flask provided with a stirrer, reflux condenser and dropping funnel was placed 310 g. (1.54 moles) of ethyl dichloroethoxyacetate, 160 g. (3.5 moles) of absolute ethanol and 500 ml. of anhydrous ether. With stirring 280 g. (3.5 moles) of dry pyridine was added from the dropping funnel during one hour. The solution refluxed gently and pyridine hydrochloride gradually separated. After standing for several hours the mixture was filtered. The pyridine hydrochloride was washed with about 300 ml. of dry ether, and the filtrate was heated on the steam-bath. After the

---

(1) Claisen, *Ann.*, **297**, 16 (1897).

(2) Price and Roberts, THIS JOURNAL, **68**, 1204 (1946).

(3) Wheeler and Johns, *Am. Chem. J.*, **40**, 233 (1908); Bergmann and Johnson, *Ber.*, **66**, 1492 (1933).

(4) Claisen, *Ann.*, **295**, 301 (1897).

(5) Jones, THIS JOURNAL, **73**, 3684 (1951).

(6) Claisen, *Ber.*, **26**, 2729 (1893).

(7) Anschutz, *Ann.*, **254**, 1 (1889).

(8) The structure of this compound follows not only from the method of preparation and the analysis but also from the structures of certain pyridine and pyrazole derivatives prepared from it which will be reported subsequently.

(9) For the formation of diethoxymethyl acetate from ethyl orthoformate and acetic anhydride, see Post and Erickson, *J. Org. Chem.*, **2**, 260 (1937).

(10) Blaise and Maire, *Ann. chim. phys.*, [8] **15**, 564 (1908) [*C. A.*, **3**, 907 (1909)].

ether had been distilled, heating was continued for one-half hour. The cooled liquid was washed with two 300-ml. portions of cold 3 *N* sulfuric acid solution then with sodium bicarbonate solution, and, together with 300 ml. of ether used to extract the aqueous washes, it was dried with magnesium sulfate and distilled under reduced pressure. Rather careful fractionation was required to separate ethyl oxalate which was present as an impurity. The ethyl triethoxyacetate was collected at 84–86° (6 mm.) or 90–92° (8 mm.). The yield was 260 g. (77%).

Triethyl α-Ethoxy-γ-ketoaconitate (II).—In a one-liter round-bottom flask carrying a short Vigreux column and a condenser for distillation was placed 188 g. (1.0 mole) of ethyl oxalacetate (b.p. 96–97° at 2 mm.), 220 g. (1.0 mole) of ethyl triethoxyacetate and 225 g. (2.2 moles) of acetic anhydride. The flask was placed in a wax-bath at 140° and heated for six hours. Volatile products of the reaction were allowed to distil and were collected. The residual liquid was distilled under a pressure of about 10 mm. in the bath at 140° until nothing more came over. Finally the remaining liquid was distilled under greatly reduced pressure. At first some decomposition took place, then a forerun was collected between 130 and 165°. The triethyl α-ethoxy-γ-ketoaconitate distilled at about 165–170° (1 mm.) with some superheating near the end of the distillation. The yield, after redistilling the forerun was 208 g. (66%), and the yields in five similar experiments ranged from 55 to 66%. The product was a viscous, colorless liquid that turned a little yellow on standing; b.p. 166–168° (1 mm.), 154–156° (0.3 mm.); $n^{25}\text{D}$ 1.4697; $d^{25}{}_{25}$ 1.1556.

Anal. Calcd. for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 52.90; H, 6.40.

All of the lower boiling products and foreruns in the above experiment were carefully collected and fractionated, and the following compounds were isolated: ethyl acetate, 134 g. (1.56 moles); acetic acid, 94 g. (1.56 moles); acetic anhydride, 40 g. (0.39 mole); ethyl oxalate, 42 g. (0.29 mole); ethyl oxalacetate, 45 g. (0.24 mole). High-boiling residues after distillation of the triethyl α-ethoxy-γ-ketoaconitate weighed 30 g.

Copper Salt of Ethyl Dioxalacetate.—A few drops of triethyl α-ethoxy-γ-ketoaconitate were shaken with a saturated aqueous solution of copper acetate and allowed to stand several hours. The resulting blue, crystalline precipitate was collected, washed with water and taken up in ethyl acetate in which it was highly soluble. The filtered ethyl acetate solution was diluted with petroleum ether which caused precipitation of the copper compound as a bright blue crystalline powder. It was recrystallized from a benzene–petroleum ether mixture; m.p. 174–175°.

Anal. Calcd. for $C_{24}H_{30}O_{16}Cu$: C, 45.17; H, 4.75; Cu, 9.96. Found: C, 45.15; H, 4.74; Cu, 9.95.

Diethyl β-Acetyl-α-ethoxy-γ-ketoglutaconate (III).—A mixture of 79 g. (0.50 mole) of ethyl acetopyruvate, 121 g. (0.55 mole) of ethyl triethoxyacetate and 125 g. (1.2 moles) of acetic anhydride was heated in a wax-bath first at 120° for two hours and then at 140° for six hours. Volatile products were allowed to distil out of the mixture. The residual liquid was distilled under reduced pressure. At first considerable decomposition took place, and then distillate was collected from 130 to 190° (2 mm.). A very little brown residue remained in the flask. The product was redistilled to yield 82 g. (57%) of nearly colorless viscous liquid; b.p. 155–158° (1 mm.); 145° (0.5 mm.); $n^{25}\text{D}$ 1.4775; $d^{25}{}_{25}$ 1.1477. The compound darkened after standing.

Anal. Calcd. for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.35; H, 6.46.

Diethyl α-Ethoxy-β-trifluoroacetylfumarate (IV).—A mixture of 52 g. (0.28 mole) of ethyl trifluoroacetoacetate,[11] 88 g. (0.40 mole) of ethyl triethoxyacetate and 80 g. (0.8 mole) of acetic anhydride was heated in a wax-bath at 125° for two hours, and then at 140° for seven hours. The volatile products were allowed to distil out through a short air condenser. Fractionation of the residual liquid yielded 30 g. (34%) of ethyl α-ethoxy-β-trifluoroacetylfumarate; b.p. 141–142° (14 mm.); $n^{25}\text{D}$ 1.4263; $d^{25}{}_{25}$ 1.244.

Anal. Calcd. for $C_{12}H_{15}F_3O_6$: C, 46.16; H, 4.84. Found: C, 46.27; H, 5.19.

Diethyl α-Acetyl-β-ethoxyfumarate (V).—A mixture of 33 g. (0.25 mole) of ethyl acetoacetate, 56 g. (0.25 mole) of ethyl triethoxyacetate and 60 g. (0.59 mole) of acetic anhydride was heated at 140° for 48 hours and then distilled under reduced pressure to yield 9.0 g. (14%)[12] of diethyl α-acetyl-β-ethoxyfumarate; b.p. 149–150° (8 mm.), 110–115° (0.3 mm.); $n^{25}\text{D}$ 1.4650; $d^{25}{}_{25}$ 1.104.

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.80; H, 7.02. Found: C, 55.69; H, 7.12.

Copper Salt of Diethyl α-Acetyl-β-hydroxyfumarate.—The blue copper salt obtained by shaking a few drops of the above ethoxy compound with aqueous cupric acetate solution was recrystallized from ethyl acetate–petroleum ether mixture; m.p. 187–188°.

Anal. Calcd. for $C_{20}H_{26}O_{12}Cu$: C, 46.01; H, 5.02; Cu, 12.18. Found: C, 46.02; H, 4.95; Cu, 12.08.

Ethyl β,β-Diacetyl-α-ethoxyacrylate (VI).—A mixture of 25 g. (0.25 mole) of acetylacetone, 56 g. (0.25 mole) of ethyl triethoxyacetate and 60 g. (0.59 mole) of acetic anhydride was heated at 140° for 24 hours and then distilled under reduced pressure. The fraction distilling at 85–140° (7 mm.), was redistilled to yield 8.5 g. (15%) of ethyl β,β-diacetyl-α-ethoxyacrylate; b.p. 135–136° (7 mm.), 105–110° (0.3 mm.); $n^{25}\text{D}$ 1.4730; $d^{25}{}_{25}$ 1.096.

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 58.03; H, 7.47.

INDIANAPOLIS, INDIANA RECEIVED APRIL 21, 1951

---

[11] Swarts, *Bull. sci. acad. roy. Belg.*, [5] **12**, 692 (1926) [*C. A.*, **21** 2120 (1927)].

[12] The yield in a duplicate experiment was 12%.