appearance and decomposition point resulted. Furthermore, cross-seeding of supersaturated solutions of the two samples induced crystallization in each case and thus it can be assumed that VI and VII are esters derived from the same acid.

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46. Found: C, 59.13; H, 4.72.

1-Carbomethoxy-6,7,8,9-tetrahydro-4-quinolizone (IX).—A mixture containing 2.0 g. of 1-carbomethoxy-4-quinolizone, 50 mg. of prereduced Adams catalyst, 50 ml. of alcohol and 5 ml. of concentrated hydrochloric acid was subjected to hydrogenation at room temperature and under atmospheric pressure of hydrogen. Hydrogen uptake stopped after two molar equivalents of hydrogen had been absorbed (about four hours). After removal of the catalyst and solvent, the residue was taken up in warm water and neutralized with potassium carbonate. The solution, on cooling, deposited clusters of crystals which after recrystallization from water yielded 1.6 g. (79%) of white needles, m.p. 139–140°.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.93; H, 6.63; N, 6.82.

1-Carbomethoxy-4-quinolizidone (X).—A mixture of 1.00 g. of IX and 50 mg. of prereduced Adams catalyst in 50 ml. of ethanol was subjected to hydrogenation at room temperature under atmospheric pressure of hydrogen. Two molar equivalents of hydrogen were absorbed in the course of several hours. After removal of the catalyst and solvent, the residue was sublimed yielding 1.00 g. (98%) of white crystals, m.p. 70–71°.

Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.53; H, 8.11. Found: C, 62.78; H, 8.54.

3-Carbomethoxy-4-quinolizidone.—As further evidence that the structure assigned to X was correct, we prepared a sample of 3-carbomethoxy-4-quinolizidone for comparison. This was accomplished by dissolving a sample (2.0 g.) of 3-carbethoxy-4-quinolizidone[16] in methanolic hydrogen chloride and allowing the solution to stand for four days. After removal of the solvent, the residue was neutralized with aqueous sodium carbonate solution and the organic material was extracted with ether. The ether was removed and the residue was subjected to a molecular-type distillation by heating at 100° under 3 mm. pressure. A colorless oil resulted which could not be induced to crystallize by seeding it with X.

Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.53; H, 8.11. Found: C, 62.21; H, 8.39.

1-Hydroxymethylquinolizidine (XII).—The reduction of 1-carbomethoxy-4-quinolizidone to 1-carbomethoxyquinolizidine (XI) was carried out by the procedure of Galinovsky and Stern.[19] A mixture of 500 mg. of X, 200 mg. of Adams catalyst and 2 ml. of concentrated hydrochloric acid in 25 ml. of water was subjected to hydrogenation at room temperature and under atmospheric pressure of hydrogen. At the end of 72 hours, two molar equivalents of hydrogen had been absorbed. The catalyst was removed; the solution was neutralized with potassium carbonate, extracted with ether and dried over Drierite. After removal of the ether, the residual oil was distilled in a molecular-still type apparatus by heating at 100° under 3 mm. pressure. The resulting colorless oil, although slightly impure as indicated by analysis (*Anal.* Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71. Found: C, 65.75; H, 9.67.), was employed directly in the next step.

A solution of 150 mg. of XI in 20 ml. of anhydrous ether was added dropwise with stirring to 50 ml. of a 0.05 *M* ethereal solution of lithium aluminum hydride. The reaction mixture was boiled under reflux for four hours, and the excess reagent was then decomposed by addition of moist ether. Sufficient dilute hydrochloric acid was then added to dissolve the precipitated alumina and the aqueous layer was separated and added with cooling to an excess of a 35% solution of potassium hydroxide. The basic solution was extracted with ether, the ethereal solution was dried, and the ether was removed. Sublimation of the residue gave 60 mg. of a colorless oil which quickly formed thick crystals, m.p. 54–57°. After recrystallization from pentane there resulted white crystals, m.p. 57–58° (lit.,[9] 59°).

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.31. Found: C, 70.29; H, 11.49.

The identity of XII with *d,l*-lupinine was demonstrated by the agreement in melting point of the following derivatives with those recorded for *d,l*-lupinine: picrolonate, m.p. 203–204° (lit.,[9] 203°); picrate, m.p. 124–125° (lit.,[9] 127°); and methiodide, m.p. 298–301° (dec.) (lit.,[9] 303° (dec.)).

[19] F. Galinovsky and E. Stern, *Ber.*, **76**, 1034 (1943).

ROCHESTER, NEW YORK RECEIVED MARCH 2, 1951

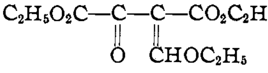
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Synthesis of Ethyl Ethoxymethyleneoxalacetate and Related Compounds

BY REUBEN G. JONES

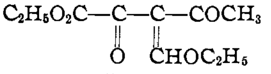
The condensation of ethyl oxalacetate with ethyl orthoformate in the presence of acetic anhydride has been found to take place readily to yield ethyl ethoxymethyleneoxalacetate. Ethyl ethoxymethyleneacetylpyruvate and ethyl ethoxymethylenetrifluoroacetoacetate have been prepared similarly by reactions of ethyl orthoformate with ethyl acetylpyruvate and ethyl trifluoroacetoacetate, respectively. Some observations have been made on the mechanism of these reactions. Ethyl aminomethyleneoxalacetate and ethyl hydroxymethyleneoxalacetate have been synthesized.

Ethyl ethoxymethyleneoxalacetate (I) was envisioned as a desirable intermediate for the synthesis of certain pyridine and other heterocyclic nitrogen compounds. This compound, I, has been prepared in excellent yields by the condensation of ethyl oxalacetate with ethyl orthoformate and acetic anhydride. Optimum conditions have been determined for carrying out the condensation and some observations have been made on the mechanism of the reaction. In addition, the condensations of ethyl orthoformate and acetic anhydride with ethyl acetylpyruvate and with ethyl trifluoroacetoacetate have been carried out to yield ethyl ethoxymethyleneacetylpyruvate II and ethyl ethoxymethylenetrifluoroacetoacetate III, respectively.



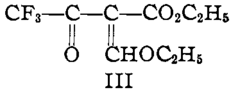
$$C_2H_5O_2C—\underset{\displaystyle O}{\underset{\|}{C}}—\underset{\displaystyle CHOC_2H_5}{\underset{\|}{C}}—CO_2C_2H_5$$

I



$$C_2H_5O_2C—\underset{\displaystyle O}{\underset{\|}{C}}—\underset{\displaystyle CHOC_2H_5}{\underset{\|}{C}}—COCH_3$$

II



$$CF_3—\underset{\displaystyle O}{\underset{\|}{C}}—\underset{\displaystyle CHOC_2H_5}{\underset{\|}{C}}—CO_2C_2H_5$$

III

The reaction of ethyl orthoformate and acetic anhydride with active methylene compounds was first reported by Claisen who prepared ethyl ethoxymethyleneacetoacetate,[1] ethoxymethyleneacetylacetone,[1] and ethoxymethylenemalonic ester.[1] In the latter preparation zinc chloride was used as catalyst.[1,2] Other investigators have reported condensations of ethyl orthoformate and acetic anhydride with ethyl acetonedicarboxylate,[3]

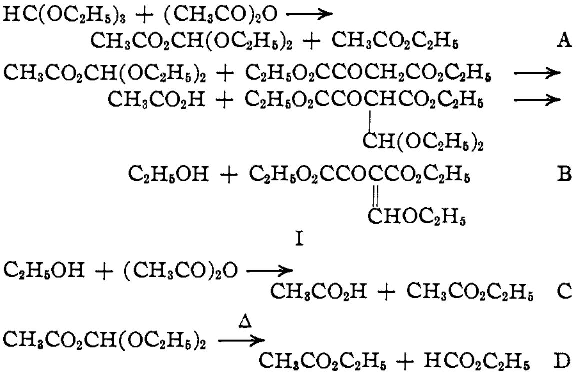
[1] Claisen, *Ber.*, **26**, 2729 (1893); *Ann.*, **297**, 1 (1897).

[2] Wheeler and Johns, *Am. Chem. J.*, **40**, 237 (1908).

[3] Errera, *Ber.*, **31**, 1682 (1898).

ethyl cyanoacetate,[4] malononitrile,[5] and ethyl benzoylacetate.[6] Aside from these early studies, little work appears to have been done with reactions of this type.

The optimum conditions for the preparation of I were determined by varying the ratios of reactants, the temperature and the time of the reactions (see Experimental). In some experiments all of the reaction products were carefully collected and separated. For example, when 0.7 mole of ethyl oxalacetate, 1.2 moles of ethyl orthoformate and 1.8 moles of acetic anhydride were heated at 120–140° for two to three hours there was obtained approximately 0.3 mole of ethyl formate, 2.4 moles of ethyl acetate, 1.3 moles of acetic acid and 0.62 mole of I. If it is assumed that the initial condensation is between ethyl orthoformate and acetic anhydride to yield ethyl acetate and diethoxymethyl acetate[7] (equation A), the products can be accounted for by the accompanying series of reactions.



$$\mathrm{HC(OC_2H_5)_3 + (CH_3CO)_2O \longrightarrow CH_3CO_2CH(OC_2H_5)_2 + CH_3CO_2C_2H_5} \quad \mathrm{A}$$

$$\mathrm{CH_3CO_2CH(OC_2H_5)_2 + C_2H_5O_2CCOCH_2CO_2C_2H_5 \longrightarrow CH_3CO_2H + C_2H_5O_2CCO\underset{\displaystyle CH(OC_2H_5)_2}{\underset{|}{C}}HCO_2C_2H_5 \longrightarrow C_2H_5OH + C_2H_5O_2CCO\underset{\displaystyle \underset{\text{I}}{CHOC_2H_5}}{\underset{\|}{C}}CO_2C_2H_5} \quad \mathrm{B}$$

$$\mathrm{C_2H_5OH + (CH_3CO)_2O \longrightarrow CH_3CO_2H + CH_3CO_2C_2H_5} \quad \mathrm{C}$$

$$\mathrm{CH_3CO_2CH(OC_2H_5)_2 \xrightarrow{\Delta} CH_3CO_2C_2H_5 + HCO_2C_2H_5} \quad \mathrm{D}$$

Based on the quantities of reactants used and the yield of I obtained, the expected yield of ethyl formate from thermal decomposition of diethoxymethyl acetate (reaction D) is 0.5 mole. The expected total yield of ethyl acetate from reaction A, C and D is 2.4 moles, and the expected yield of acetic acid from reactions B and C is 1.4 moles. In this experiment the initially formed diethoxymethyl acetate appears to enter into two competing reactions, B and D. Eighty-five to ninety per cent. yields of I were obtained consistently when, in accordance with the above equations, the number of moles of acetic anhydride used was at least equal to or greater than the combined number of moles of ethyl orthoformate and ethyl oxalacetate.

A noteworthy feature of the reactions of the present study was the rapidity with which they appeared to reach completion. When the volatile products were allowed to distil from the mixture, the reaction involving ethyl oxalacetate was largely complete within one to two hours at 120–140°. This is in contrast with the 13-hour heating period recommended in the preparation of ethyl ethoxymethylenemalonate.[8]

Ethyl ethoxymethyleneoxalacetate, I, reacted normally with ammonia under anhydrous conditions to yield ethyl aminomethyleneoxalacetate.

The copper salt of ethyl hydroxymethyleneoxalacetate, formed in almost quantitative yields by the reaction of ethyl ethoxymethyleneoxalacetate with aqueous cupric chloride or acetate, was unusually stable toward acids. It was almost unaffected by 6 *N* hydrochloric acid or even 12 *N* sulfuric acid. Vigorous shaking with a mixture of 12 *N* hydrochloric acid and ether liberated ethyl hydroxymethyleneoxalacetate which was obtained, after distillation in vacuum, as a stable, colorless liquid.

Sodium bicarbonate in aqueous solution reacted rapidly with ethyl ethoxymethyleneoxalacetate (I), to hydrolyze the ether linkage and form the sodium salt of ethyl hydroxymethyleneoxalacetate. This sodium salt was surprisingly stable in water solution, even in the presence of excess sodium bicarbonate. It underwent no decomposition when solutions were allowed to stand at room temperature for as long as 24 hours. Ethyl hydroxymethyleneoxalacetate was readily isolated by acidifying solutions of the sodium salt with hydrochloric or sulfuric acid and extracting with ether.

The reactions of ethyl orthoformate and acetic anhydride with ethyl acetylpyruvate and with ethyl trifluoroacetoacetate appeared to take place in the same way as with ethyl oxalacetate. In one experiment with ethyl trifluoroacetoacetate all of the reaction products were collected. Fractionation again yielded ethyl formate, ethyl acetate and acetic acid in addition to III.

Experimental

Ethyl Ethoxymethyleneoxalacetate.—A number of experiments on the reaction of ethyl oxalacetate with ethyl orthoformate and acetic anhydride were carried out under various conditions of time and temperature, and using various ratios of reactants. These experiments are summarized in Table I. The general procedure is illustrated in the following typical example, under which conditions the highest yields of the desired ethyl ethoxymethyleneoxalacetate were obtained:

TABLE I

REACTIONS OF ETHYL OXALACETATE WITH ETHYL ORTHOFORMATE AND ACETIC ANHYDRIDE

Reactants, moles			Ethyl ethoxymethyleneoxalacetate, yield, %	Reaction conditions
Ethyl oxalacetate	Ethyl orthoformate	Acetic anhydride		
1	2	2	87	1 hr., 120°; 1.5 hr., 140°
1	1	1	53	1 hr., 120°; 1.5 hr., 140°
1	2	1	72	1 hr., 120°; 1.5 hr., 140°
1	1	2	52	6 hr., 150°
1	1.1	2.2	59, 62	6 hr., 150°
1	1.5	3	81, 81	1 hr., 120°; 1 hr., 140°
1	1.7	2.5	88, 88	1 hr., 120°; 1 hr., 140°
1	1.8	3.6	51	3 hr., 140°; 3 hr., 160°; 3 hr., 180°
1	1.75	2.85	90, 90	1 hr., 120°; 1 hr., 130°; 1 hr., 140°

A one-liter flask was provided with a short, upright condenser containing in the jacket hot water which was not cir-

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[4] De Bollemont, *Bull. soc. chim.*, **25**, 18, 28 (1901).

[5] Passalacqua, *Gazz. chim. ital.*, **43**, II 566 (1913); [*C. A.*, **8**, 1273 (1914)].

[6] Weis and Woidich, *Monatsh.*, **47**, 427 (1926).

[7] Diethoxymethyl acetate has been shown to result from the reaction of ethyl orthoformate with acetic anhydride. It has been shown to react with ethyl acetoacetate to yield ethyl ethoxymethyleneacetoacetate; see Post and Erickson, *J. Org. Chem.*, **2**, 260 (1937). It also reacts with malonic ester to yield first diethoxymethylmalonic ester which, on further heating is converted to ethoxymethylenemalonic ester; see ref. (8).

[8] Fuson, Parham and Reed, *J. Org. Chem.*, **11**, 194 (1946); see also Parham and Reed, "Org. Syntheses," Vol. 28, p. 60.

culating. In the flask was placed 188 g. (1.0 mole) of ethyl oxalacetate, 260 g. (1.75 moles) of ethyl orthoformate and 290 g. (2.84 moles) of pure acetic anhydride. A few "boiling chips" were added and the flask was immersed in a wax-bath at 120°. After one hour the temperature of the bath was raised to 140° where it was held for an additional two hours. The volatile products of the reaction were allowed to distil out through the upright condenser. After the heating period the mixture was cooled somewhat and then distilled in vacuum. A forerun of lower boiling products distilled first. The ethyl ethoxymethyleneoxalacetate came over at 163–165° (2 mm.); 155–160° (1 mm.); 145–147° (0.2 mm.). There was some superheating near the end of the distillation, and the temperature sometimes went up to 175–185°, but the distillate was almost pure ethyl ethoxymethyleneoxalacetate. A little amber residue remained in the flask. The yield was 220 g. (90%). The product was an almost colorless, viscous liquid. It turned slightly yellow after standing for several days, but no noticeable decomposition had taken place after standing at room temperature for several months. A middle fraction was taken for analysis; b.p. 146° (0.2 mm.); n^{25}_{D} 1.4782; d^{25}_{25} 1.1375.

Anal. Calcd. for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: 54.06; H, 6.63.

Another experiment was carried out just as described above in which 133 g. (0.70 mole) of ethyl oxalacetate, 180 g. (1.2 moles) of ethyl orthoformate and 185 g. (1.8 moles) of acetic anhydride were used. All of the volatile products of the reaction including the foreruns of the vacuum distillation were carefully collected and fractionated using a small packed column. The products and yields were as follows: ethyl formate, 20 g., b.p. 50–55°; mid-fraction, 7 g., b.p. 55–72°; ethyl acetate, 207 g., b.p. 72–75°; mid-fraction 7 g., b.p. 75–113°; acetic acid, 75.5 g., b.p. 113–117°; tailings 13 g., b.p. 117–135°. The yield of ethyl ethoxymethyleneoxalacetate was 150 g., b.p. 163–165° (2 mm.), and 8 g. of high boiling residue remained in the flask.

Ethyl Aminomethyleneoxalacetate.—A solution of 61 g. (0.25 mole) of ethyl ethoxymethyleneoxalacetate in 250 ml. of dry ether was cooled in an ice–salt-bath. To it was added rapidly, in one portion, 26 g. of 18% absolute alcoholic ammonia solution (0.27 mole of NH_3). The flask was stoppered and shaken, then allowed to stand for 20 hours. The mixture was filtered and the gelatinous precipitate was thoroughly washed with dry ether. Evaporation of the combined filtrates in vacuum on the steam-bath left a sirup which soon crystallized. The yield was 45–49 g. (84–91%); m.p. 65–66°. A sample was recrystallized from ether–petroleum ether; m.p. 68–69°.

Anal. Calcd. for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.42; H, 6.22; N, 6.44.

The compound was readily soluble in alcohol, ethyl acetate, moderately soluble in ether, insoluble in petroleum ether or water.

Copper Salt of Ethyl Hydroxymethyleneoxalacetate.—To a solution of 90 g. (0.5 mole) of cupric chloride dihydrate in 1 liter of cold water was added 100 g. (0.41 mole) of ethyl ethoxymethyleneoxalacetate. After the flask had been vigorously shaken for a few minutes, it was allowed to stand for about one hour. The resulting bright blue copper salt was collected on a filter, washed well with water and with petroleum ether and air-dried. The yield was 84–93 g. (83–92%). A sample for analysis was recrystallized from alcohol, and again from benzene; m.p. 232–233° dec., uncor.

Anal. Calcd. for $C_{18}H_{22}O_{12}Cu$: C, 43.77; H, 4.49; Cu, 12.87. Found: C, 43.45; H, 4.65; Cu, 12.67.

Ethyl Hydroxymethyleneoxalacetate.—The above copper salt, 84 g., was placed in a separatory funnel with 600 ml. of ether, and 200 ml. of ice-cold 12 *N* hydrochloric acid was added. The mixture was vigorously shaken until the solid had dissolved, and then the ether layer was separated and washed successively with 100 ml. of 6 *N* hydrochloric acid and two 100-ml. portions of water. The acid layer and the aqueous wash solutions were extracted two more times with 200-ml. portions of ether. After the combined ether extracts had been dried with magnesium sulfate the ether was removed and the residual liquid distilled in vacuum. It all distilled at 103–105° (2 mm.) as a colorless liquid; yield 60–66 g. (82–90%). A sample was redistilled, and the mid-fraction, b.p. 94–95° (1 mm.) was taken for analysis; n^{25}_{D} 1.4673; d^{25}_{25} 1.190.

Anal. Calcd. for $C_9H_{12}O_6$: C, 50.00; H, 5.60. Found: C, 49.91; H, 5.77.

A more convenient method for preparing ethyl hydroxymethyleneoxalacetate was the hydrolysis of the ethoxy compound with sodium bicarbonate solution. To a solution of 50 g. of sodium bicarbonate in 250 ml. of water was added 122 g. (0.5 mole) of ethyl ethoxymethyleneoxalacetate, and the mixture was vigorously agitated. Carbon dioxide was evolved, and a clear water solution was formed. The solution was washed with 100 ml. of ether after which it was acidified with 100 ml. of concentrated hydrochloric acid and extracted with three 100-ml. portions of ether. The combined ether extracts were dried with magnesium sulfate, evaporated and the residual liquid distilled to yield 97 g. (90%) of ethyl hydroxymethyleneoxalacetate, b.p. 103–105° (2 mm.).

Ethyl Ethoxymethyleneacetylpyruvate.—A mixture of 79 g. (0.5 mole) of ethyl acetylpyruvate, 111 g. (0.75 mole) of ethyl orthoformate and 155 g. (1.5 mole) of pure acetic anhydride was heated in a wax-bath at 120° for 0.5 hour, 140° for 1 hour, and 150° for 2 hours. The volatile reaction products were allowed to distil off through a short upright air condenser. The residual product in the flask was distilled in vacuum, and after a forerun of lower boiling products, 85 g. of liquid came over at 150–160° (1 mm.). This was redistilled to yield 71 g. (66%)[9] of pale yellow liquid, b.p. 146–148° (0.5 mm.). There appeared to be slight decomposition during the distillation. The compound superheated very easily during distillation. If heat was applied too rapidly the boiling point went up to 160–170°. A middle fraction was taken for analysis; b.p. 147° (0.5 mm.); n^{25}_{D} 1.4885; d^{25}_{25} 1.130.

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.87; H, 7.15.

Copper Salt of Ethyl Hydroxymethyleneacetylpyruvate.—The blue crystalline salt obtained by shaking ethyl ethoxymethyleneacetylpyruvate with excess aqueous cupric acetate was dissolved in ethyl acetate in which it was highly soluble and precipitated by the addition of four volumes of petroleum ether. Recrystallization again from benzene containing a little ethyl acetate gave a bright blue crystalline powder which separated slowly; m.p. 190–191°.

Anal. Calcd. for $C_{16}H_{18}O_{10}Cu$: C, 44.29; H, 4.18; Cu, 14.65. Found: C, 44.51; H, 4.41; Cu, 14.35.

Ethyl Ethoxymethylenetrifluoroacetoacetate.—A mixture of 92 g. (0.50 mole) of ethyl trifluoroacetoacetate,[10] 110 g. (0.75 mole) of ethyl orthoformate and 155 g. (1.50 mole) of pure acetic anhydride was heated at 120° for two hours and at 140° for five hours. Volatile products distilled out through a short column and were collected. The liquid remaining in the flask was distilled in vacuum and after a forerun of lower boiling products there was obtained 78 g. (67% yield[11]) of ethyl ethoxymethylenetrifluoroacetoacetate as a colorless liquid which turned pale yellow on standing; b.p. 115–120° (10 mm.). A middle fraction was used for analysis; n^{25}_{D} 1.4262; d^{25}_{25} 1.239.

Anal. Calcd. for $C_9H_{11}F_3O_4$: C, 45.01; H, 4.62. Found: C, 45.27; H, 4.62.

The volatile products of the above reaction and foreruns of the distillation were collected and fractionated through a small packed column to yield the following fractions: ethyl formate, 15 g., b.p. 53–58°; mid-fraction, 7 g., b.p. 58–72°; ethyl acetate, 132 g., b.p. 72–80°; mid-fraction, 9 g., b.p. 80–110°; acetic acid, 56 g., b.p. 110–118°; fraction which appeared to consist of a mixture of acetic acid, ethyl trifluoroacetoacetate and acetic anhydride, 20 g., b.p. 118–135°; acetic anhydride, 25 g., b.p. 135–140°; mid-fraction, 8 g., b.p. 110–115° (10 mm.); residue 5 g.

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[9] The yield in a duplicate run was 60%.

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

[11] The yield from a duplicate run was 70%.