

tected the 17 $\alpha$ -hydroxy groups of the 21-acetates of 11-desoxycortisol and cortisone to prevent attack of the side chain by the reagent, no precautions were taken to protect the 11 $\beta$ - and 17 $\alpha$ -hydroxyls in the present study. The reaction was carried out in a similar manner to that described by Sondheimer, *et al.*,<sup>7</sup> for testosterone acetate. A major reaction product (I) (produced in *ca.* 10% yield on the basis of ultraviolet spectrophotometry) was isolated, following paper chromatography, in crystalline form. The compound was more polar than cortisol 21-acetate in the toluene-propylene glycol system, reduced the blue-tetrazolium reagent and had an adsorption maximum at 242  $m\mu$ . Infrared analysis<sup>8</sup> showed a doublet in the double bond region which suggested a 1,4-diene-3-one system.<sup>9</sup> The spectrum of I in sulfuric acid had the strongest absorption maxima at 235 and 360  $m\mu$  two hours after dissolving the steroid in acid. The corresponding strongest bands for 17 $\beta$ -hydroxy-1,4-androstadiene-3-one have been reported by Bernstein and Lenhard<sup>10</sup> to be located at 232  $m\mu$  (infection) and 327  $m\mu$  (maximum).

The isolated reaction product I was identified conclusively with a sample of authentic 21-acetoxy-11 $\beta$ ,17 $\alpha$ -dihydroxy-1,4-pregnadiene-3,20-dione that became available to us through the courtesy of the Schering Corporation. When compound I was tested by the thymolytic test<sup>11</sup> it was found to have *ca.* four times the activity of cortisol 21-acetate. 11 $\beta$ ,17 $\alpha$ ,21-Trihydroxy-1,4-pregnadiene-3,20-dione recently was discovered to have three to four times the activity of cortisol in the eosinopenic response.<sup>12</sup>

When the reaction of cortisol 21-acetate was carried out at 108–110° for 3.5 hours no I was isolated. A complex mixture was produced which upon chromatography on alumina, silica gel and on paper separated into several fractions which resisted crystallization.

Clarke, *et al.*,<sup>13</sup> recently have described the reaction of progesterone, testosterone and desoxycorticosterone acetates with lead tetraacetate in which under mild conditions 21-acetoxy-1,4-pregnadiene-3,20-dione and 17 $\beta$ -acetoxy-1,4-androstadiene-3-one were isolated in *ca.* 8% yields.

#### Experimental

Cortisol 21-acetate (200 mg.) was dissolved by heating in glacial acetic acid (3 cc.) and lead tetraacetate (300 mg.) was added. The mixture was heated in an oil-bath at 100° for 1 hour and then poured on ice, neutralized with NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extract was washed with 0.1 N NaOH, H<sub>2</sub>O, and evaporated under reduced pressure. The residue was chromatographed on 10 paper strips (15 cm. wide) in the toluene-propylene glycol system for 10 hours. The blue-tetrazolium reducing zone, more polar

(7) F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez and G. Rosenkrantz, *THIS JOURNAL*, **75**, 4712 (1953).

(8) The infrared spectra were determined by the Perkin-Elmer 12C spectrometer on solid films deposited on NaCl plates.

(9) H. Rosenkrantz, "The Analysis of Steroids by Infrared Spectrometry. Methods in Biochemical Analysis," Ed. D. Glick, Interscience Publishers, Inc., New York, N. Y., Vol. II, 1955, pp. 1–56.

(10) S. Bernstein and R. H. Lenhard, *J. Org. Chem.*, **18**, 1146 (1953).

(11) R. I. Dorfman, *Rec. Progr. Hor. Res.*, **8**, 87 (1953).

(12) H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. L. Perlman and M. M. Pechet, *Science*, **121**, 176 (1955).

(13) R. L. Clarke, K. Dobriner, A. Mooradian and C. M. Martini, *THIS JOURNAL*, **77**, 661 (1955).

than cortisol 21-acetate, was eluted with methanol, the propylene glycol evaporated *in vacuo* (0.2 mm.) at 35° and the eluate crystallized from ethanol after removal of acetone-insoluble material; prisms, m.p. (uncor.) 230–233°;  $\lambda_{max}$  (methanol) 242  $m\mu$ ; infrared analysis: 3420 (–OH), 1736 and 1720 (C-21 acetate and C-20 carbonyls showing the C-20 carbonyl and C-21 acetate interaction), 1655 (C-3 conjugated carbonyl), 1615 (infection) and 1595 (double bond region doublet), and 1229  $cm^{-1}$  (acetate).

**Acknowledgment.**—The technical assistance of Miss Arline M. Tillotson is gratefully acknowledged. Thanks also are due to Mr. Paul Skogstrom for recording the infrared and ultraviolet spectra.

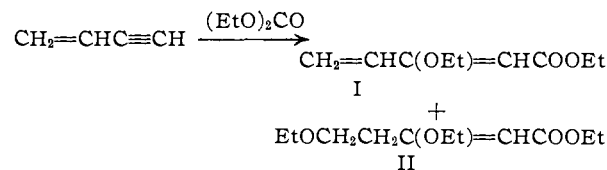
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### Synthesis and Reactions of Ethyl 3-Ethoxy-2,4-pentadienoate

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RECEIVED APRIL 19, 1955

A new polymerizable monomer, ethyl 3-ethoxy-2,4-pentadienoate (I) has been obtained from the reaction of vinylacetylene with ethyl carbonate in the presence of sodium ethoxide.<sup>1</sup>



Ethyl 3,5-diethoxy-2-pentenoate (II), the other product of this reaction, apparently results from the 1,6-addition of ethanol to compound I followed by rearrangement of the double bond so that it is conjugated with the ester group. This 1,6-addition is in contrast to the 1,4-addition reported for ethanol and ethyl 3-ethoxy-4-methyl-2,4-pentadienoate to give ethyl 3,3-diethoxy-4-methyl-4-pentenoate.<sup>2</sup>

The structure of ethyl 3-ethoxy-2,4-pentadienoate (I) is based on the following evidence. Carboethoxylation can take place only at the hydrogen-bearing acetylenic carbon atom.<sup>2</sup> A conjugated diene carbonyl system is indicated by the ultraviolet and infrared spectra and by formation of a Diels-Alder adduct with maleic anhydride. The  $\beta$ -position of the ethoxy group is shown by acidic hydrolysis to a  $\beta$ -keto ester which forms a copper chelate.

The designation of compound II as ethyl 3,5-diethoxy-2-pentenoate is based on the following reactions. Elimination of ethanol by action of sodium bisulfate gives compound I.  $\beta$ -Ethoxyethyl methyl ketone is obtained by hydrolysis and decarboxylation. Hydrogenation of compound II followed by saponification yields a diethoxy acid, presumably 3,5-diethoxypentanoic acid, which was shown to have its two ethoxy groups attached to different carbon atoms by its resistance to acidic

(1) W. J. Croxall and H. J. Schneider, *THIS JOURNAL*, **71**, 1257 (1949), describe the base-catalyzed reactions of alkyl carbonates with acetylene.

(2) W. J. Croxall and M. F. Fegley, *ibid.*, **71**, 1261 (1949).

hydrolysis. Finally the infrared and ultraviolet spectra indicate the presence of a double bond conjugated with a carbonyl group and the absence of terminal unsaturation.

Ethyl 3-ethoxy-2,4-pentadienoate polymerizes spontaneously on standing at room temperature and it can be polymerized readily or copolymerized in solution or in emulsion systems using azo, peroxide or oxidation-reduction catalysts. These polymers can be hydrolyzed to polymeric  $\beta$ -keto esters capable of chelate formation with copper.

Dimethylamine reacts with ethyl 3-ethoxy-2,4-pentadienoate to form an adduct. This product has been designated as ethyl 5-dimethylamino-3-ethoxy-2-pentenoate based on the nature of its preparation and the similarity of its infrared spectrum to that of ethyl 3,5-diethoxy-2-pentenoate.

#### Experimental

**Reaction of Vinylacetylene with Ethyl Carbonate.**—Vinylacetylene (51 g., 0.98 m.) was added dropwise from a Dry Ice-cooled dropping funnel or bubbled in as a gas with vigorous stirring to a mixture of alcohol-free sodium ethoxide (25.8 g., 0.38 mole) in ethyl carbonate (360 g., 3.05 moles) at 80° so that the pressure never exceeded 5 lb./sq. in. (gage). After the addition, the temperature was maintained at 70–80° for 8 hours. The solution was then cooled, neutralized with acetic acid (22 ml.) in water (90 ml.), and extracted with ether. The combined extracts were dried over magnesium sulfate. Hydroquinone (0.1 g.) was added and ethyl carbonate (246 g.) was distilled from the solution. Distillation of the residue gave a forerun, 35.5 g., b.p. 92–116° (3 mm.), and a second fraction which proved to be ethyl 3,5-diethoxy-2-pentenoate (II), 29.6 g., b.p. 73–76° (0.2 mm.).

*Anal.* Calcd. for fraction II,  $C_{11}H_{20}O_4$ : C, 61.08; H, 9.32; sapn. equiv., 216. Found: C, 60.98; H, 9.61; sapn. equiv., 218.

Two absorption bands near 6  $\mu$  in the infrared spectrum of this compound indicate a double bond conjugated with a carbonyl group. No absorption bands for a terminal olefinic group are present. Strong absorption at 230  $m\mu$  in the ultraviolet ( $\epsilon_{max}$  12960 in *n*-heptane) is also evidence for an  $\alpha,\beta$ -unsaturated carbonyl system.

The forerun, a mixture of compounds I and II, was converted solely to ethyl 3-ethoxy-2,4-pentadienoate (I) by elimination of ethanol from compound II. A mixture of the forerun (35.5 g.), hydroquinone (0.1 g.) and sodium bisulfate (0.2 g.) in toluene (92 ml.) was distilled at 75–110°. The residual oil then was distilled quickly under 3 mm. pressure and then redistilled to give pure ethyl 3-ethoxy-2,4-pentadienoate (26.2 g.), b.p. 79–80.5° (2.8 mm.),  $n_D^{25}$  1.4819. When this same procedure was used with pure ethyl 3,5-diethoxy-2-pentenoate, a 62% yield of the pentadienoate was obtained. On standing at room temperature this diene ester polymerizes to a clear colorless gel. Polymerization can be prevented either by adding hydroquinone or by storage in Dry Ice.

*Anal.* Calcd. for compound I,  $C_9H_{14}O_4$ : C, 63.51; H, 8.29; sapn. equiv., 170. Found: C, 63.26; H, 8.47; sapn. equiv., 169.

The ultraviolet and infrared spectra of ethyl 3-ethoxy-2,4-pentadienoate indicate a conjugated diene carbonyl system. Bands at 10.65 and 10.0  $\mu$  for terminal unsaturation are present and 3 bands near 6  $\mu$  and strong absorption in the ultraviolet at 260  $m\mu$  ( $\epsilon_{max}$  14700 in *n*-heptane) indicate a carbonyl group in conjugation with a 1,3-diene.

**Maleic Anhydride Adduct of Ethyl 3-Ethoxy-2,4-pentadienoate.**—Maleic anhydride (7 g.), hydroquinone (0.1 g.) and a polymerization inhibitor,  $\alpha,\alpha$ -diphenyl- $\beta$ -picrylhydrazyl (0.1 g.), were dissolved in chlorobenzene (20 ml.) and heated to reflux. The diene ester (12 g.) in chlorobenzene (10 ml.) was added to the refluxing mixture. After refluxing for 22 hours the mixture was poured into petroleum ether (250 ml.). The petroleum ether was decanted from a black oil which was distilled to give a clear yellow oil (6.5 g., 34% yield), b.p. 170–190° (0.7 mm.). This distillate crys-

tallized on standing overnight. After four recrystallizations from 1:1 toluene-ether mixture the product separated as white needles, m.p. 74.6–75.5°.

*Anal.* Calcd. for  $C_{13}H_{16}O_6$ : C, 58.20; H, 6.01; sapn. equiv., 89.4. Found: C, 58.12; H, 6.64; sapn. equiv., 93.

**Acidic Hydrolysis of Ethyl 3-Ethoxy-2,4-pentadienoate.**—The diene ester (15 g.) and hydroquinone (0.2 g.) were dissolved in a mixture of dioxane (15 ml.) and distilled water (10 ml.) and heated to reflux. Concentrated hydrochloric acid (3 ml.) was added and the mixture was refluxed for 2 minutes. The reaction mixture was cooled immediately in an ice-bath and then extracted 3 times with ether (50 ml.). The ether extracts were dried over anhydrous magnesium sulfate and then evaporated on the steam-bath. The residue was distilled under reduced pressure and after removal of dioxane, 5.7 g. of a product, b.p. 31–45° (0.5–1 mm.), was obtained. On redistillation 2.5 g. (20%) of ethyl 3-oxo-4-pentenoate, b.p. 42–5° (3.5 mm.),  $n_D^{25}$  1.4848, was obtained.

*Anal.* Calcd. for  $C_7H_{10}O_3$ : C, 59.12; H, 7.10; sapn. equiv., 142. Found: C, 59.41; H, 7.21; sapn. equiv., 136.

The ultraviolet spectrum of this compound shows that the absorption band for acetoacetic ester is shifted 30  $m\mu$  toward longer wave lengths by the conjugated double bond. This compound polymerizes on standing at room temperature even in the presence of a small amount of hydroquinone. When the acidic hydrolysis of ethyl 3-ethoxy-2,4-pentadienoate was carried out using absolute ethanol in place of dioxane, ethyl 5-ethoxy-3-oxopentanoate, b.p. 95.5–96.5° (3.5 mm.),  $n_D^{25}$  1.4305, was obtained in 50% yield.

*Anal.* Calcd. for  $C_9H_{16}O_4$ : C, 57.43; H, 8.57; mol. wt., 188. Found: C, 58.03; H, 8.75; mol. wt. (ebullioscopic), 190; sapn. eq., 181.

The ultraviolet spectrum of this compound resembles that of acetoacetic ester very closely and shows no evidence for a terminal vinyl group. No polymerization occurred when this compound was distilled.

A solution of ethyl 5-ethoxy-3-oxopentanoate (0.5 g.) in methanol (1 ml.) was shaken with a hot aqueous saturated solution of cupric acetate monohydrate (0.27 g.) to give an oil which solidified to a pale green solid on cooling. Recrystallization from benzene-petroleum ether gave crystals, m.p. 113–114°.

*Anal.* Calcd. for  $C_{13}H_{20}O_5Cu$ : Cu, 14.51. Found: Cu, 14.56.

**3-Ethoxy-2,4-pentadienoic Acid.**—Ethyl 3-ethoxy-2,4-pentadienoate (15 g.) was refluxed with sodium hydroxide (12 g.) in water (30 ml.) containing hydroquinone (0.1 g.) for 3 hours. The solution was filtered from polymer. Acidification of the filtrate with hydrochloric acid gave a precipitate which was dissolved in ether and dried over magnesium sulfate. Evaporation of ether under reduced pressure left 5 g. of a colorless product, m.p. 118°. After recrystallization from petroleum ether the compound melted at 121–122°. This compound also could be recrystallized from water but considerable polymerization occurred under these conditions.

*Anal.* Calcd. for  $C_7H_{10}O_3$ : C, 59.14; H, 7.09. Found: C, 59.02; H, 7.09.

**Acidic Hydrolysis of Ethyl 3,5-Diethoxy-2-pentenoate.**—Hydrolysis of the diethoxy ester with dilute hydrochloric acid gave  $\beta$ -ethoxyethyl methyl ketone. The diethoxy ester (15.1 g.) was dissolved in a solution of water (7 ml.), hydrochloric acid (6 ml.) and ethanol (12 ml.). This solution was allowed to stand at room temperature for 91 hours, then refluxed for 30 minutes, cooled, neutralized with potassium carbonate, and extracted with ether. The combined ethereal extracts were dried over potassium carbonate. After removal of ether and alcohol, distillation under reduced pressure gave a product (4.6 g.) boiling at 78–80° (33 mm.). On redistillation  $\beta$ -ethoxyethyl methyl ketone, b.p. 57° (27 mm.),  $n_D^{25}$  1.4060, was obtained. This product gave a positive iodoform test and a negative test for aldehyde with Tollens reagent.

*Anal.* Calcd. for  $C_8H_{12}O_2$ : C, 62.03; H, 10.41. Found: C, 61.83; H, 11.00.

A *p*-nitrophenylhydrazone, golden needles, m.p. 92–95°, from aqueous methanol, was prepared. Admixture of this material with an authentic sample of the *p*-nitrophenyl-

hydrazone of  $\beta$ -ethoxyethyl methyl ketone, m.p. 93.5–96°, caused no depression in melting point.

$\beta$ -Ethoxyethyl methyl ketone also was obtained from ethyl 3,5-diethoxy-2-pentenoate by saponification to the acid followed by hydrolysis with dilute sulfuric acid.

**Hydrogenation of Ethyl 3,5-Diethoxy-2-pentenoate.**—The diethoxy ester was hydrogenated to a saturated ester, presumably ethyl 3,5-diethoxypentanoate, which was saponified to 3,5-diethoxypentanoic acid. This acid was unaffected by refluxing with hydrochloric acid. Therefore the ethoxy groups are not on the same carbon atom. The diethoxy ester (21.8 g.) in ethanol (50 ml.) was hydrogenated over Raney nickel (12 g.) at 80°/1500–2000 lb./sq. in. hydrogen for 4 hours. After filtration from catalyst and removal of alcohol, the residual oil was distilled to give a product (21.2 g., 96% yield), b.p. 73–74° (0.6 mm.),  $n_D^{25}$  1.4208.

*Anal.* Calcd. for  $C_{11}H_{22}O_4$ : C, 60.52; H, 10.16; sapon. equiv., 218. Found: C, 60.60; H, 10.20; sapon. equiv., 218.

The hydrogenation product (4.8 g., 0.022 mole) was refluxed with aqueous 25% sodium hydroxide (15 ml.) for 3 hours. Then the solution was acidified with hydrochloric acid and extracted with ether. The combined extracts were evaporated on the steam-bath and the residual oil was refluxed with hydrochloric acid (4 ml.) in water (6 ml.) for one hour. The mixture was extracted with ether and the combined extracts were dried over calcium sulfate. Evaporation left an oil which distilled at 99° (0.2 mm.),  $n_D^{25}$  1.4349. This distillate (2.7 g.) reacted vigorously with aqueous 5% sodium bicarbonate but not with 2,4-dinitrophenylhydrazine reagent.

*Anal.* Calcd. for 3,5-diethoxypentanoic acid,  $C_9H_{18}O_4$ : C, 56.82; H, 9.54; neut. equiv., 190; ethoxyl, 47.37. Found: C, 56.61; H, 9.39; neut. equiv., 188; ethoxyl, 47.10.

**Polymerization of Ethyl 3-Ethoxy-2,4-pentadienoate.**<sup>3</sup>—The diene ester (10 g.) was mixed with water (30 g.), potassium persulfate (0.2 g.), sodium bisulfate (0.05 g.), sodium lauryl sulfate (0.5 g.) and disodium phosphate (0.5 g.), and the mixture was heated at 50° for 10 hours in a pressure bottle mounted in a tumbler. The emulsion was coagulated by addition of alcohol and the polymer was collected by filtration. The colorless solid was washed with water and alcohol and then dried at 60° (0.5 mm.) to give 9 g. (90% yield) of polymer. The material melted at 90–125° and on cooling formed a hard brittle film. It had an inherent viscosity of 1.70 (0.1% solution in benzene at 25°) and a relative viscosity of 1.185.

Polymeric ethyl 3-ethoxy-2,4-pentadienoate (0.5 g.) was refluxed with methanol (4 ml.) and hydrochloric acid (0.24 ml.) for 5 minutes. The mixture was neutralized with ammonium hydroxide. The polymer was collected and then dissolved in boiling methanol (5 ml.). A solution of cupric acetate (0.3 g.) in the minimum amount of boiling water was added with vigorous shaking. The pale green solid which separated was insoluble in boiling water and did not soften as did the original polymer. This polymeric copper chelate did not melt below 205°. The analysis for copper indicated that about 23% of the  $\beta$ -keto ester groups had reacted.

*Anal.* Calcd. for  $C_{14}H_{18}O_6Cu$ : Cu, 18.38. Found: Cu, 4.3.

Polymeric ethyl 3-ethoxy-2,4-pentadienoate which had not been hydrolyzed with acid did not give a copper chelate with cupric acetate.

**Ethyl 5-Dimethylamino-3-ethoxy-2-pentenoate.**—The diene ester (26.2 g., 0.154 mole), anhydrous dimethylamine (7.3 g., 0.166 mole) and potassium carbonate (7.8 g.) were charged into a pressure bottle which was capped and placed in a rocker bath for 17 hours. After standing at room temperature for 6 more hours the bottle was opened and the contents were filtered from potassium carbonate which was washed with 2 10-ml. portions of ether. The combined filtrate and ether washings were distilled under reduced pressure leaving a residual oil which on distillation gave 24.5 g. (74% yield) of an amine adduct, b.p. 85.5–86° (1 mm.),  $n_D^{25}$  1.4609.

*Anal.* Calcd. for  $C_{11}H_{21}O_2N$ : C, 61.36; H, 9.83; N, 6.51; neut. equiv., 215. Found: C, 61.57; H, 9.96; N, 6.62; neut. equiv., 217.

(3) V. A. Engelhardt, U. S. Patent 2,647,106 (1953).

The infrared spectrum of this amino ester is very similar to that of ethyl 3,5-diethoxy-2-pentenoate, except for dimethylamino bands at 3.6 and 6.8  $\mu$ .

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## The Dissociation Constants of 7-Methyl- and 1,7-Dimethyluric Acid

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RECEIVED APRIL 14, 1955

In a recent paper<sup>1</sup> it was shown that in substituted uric acids ionization of the NH-groups occurs in the order 9 – 3 – 1. However, uric acid itself possesses only two dissociation constants, identified as  $pK_9$  and  $pK_3$ . As further support of this statement we now have measured the  $pK$  values of 7-methyluric acid, applying our spectrophotometric method,<sup>1</sup> and the results (see Fig. 1) confirm our observation that pre-occupation of the two oxygens in position 2 and 6 by charge distribution from  $N^3$  and  $N^9$  prevents ionization at  $N^1$ . Indeed, the constants obtained for 7-methyluric acid are very close to those for uric acid and its 1,7-dimethyl derivative, as shown in Table I. The latter compound has

TABLE I  
DISSOCIATION CONSTANTS OF URIC ACID, 7-METHYL- AND 1,7-DIMETHYLURIC ACID

	$pK_9$	$pK_3$
Uric acid	5.75	10.3
7-Methyluric acid	5.6	10.3
1,7-Dimethyluric acid	5.5	10.6

been studied systematically for the first time, and the curve representing  $\lambda_{max}$  as function of  $pH$  has been included in Fig. 1.

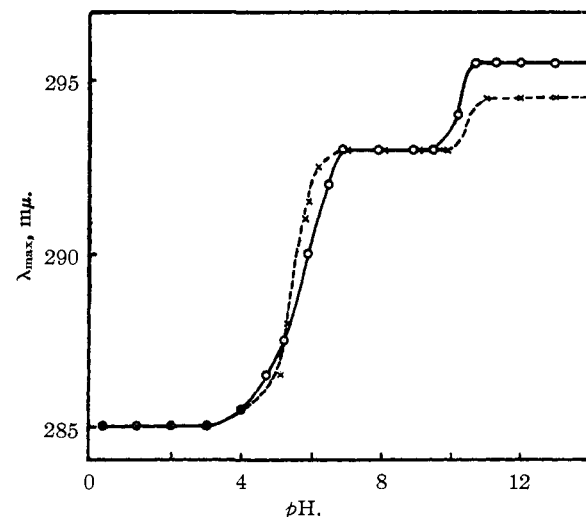


Fig. 1.—Long-wave absorption maxima as function of  $pH$ :  $\circ$ — $\circ$ —, 7-methyluric acid;  $\times$ — $\times$ —, 1,7-dimethyluric acid.

### Experimental

7-Methyluric acid was synthesized according to Fischer and Clemm<sup>2</sup> and Biltz and Damm.<sup>3</sup>

- (1) F. Bergmann and S. Dikstein, *THIS JOURNAL*, **77**, 691 (1955).
- (2) E. Fischer, *Ber.*, **30**, 561 (1897); E. Fischer and H. Clemm, *ibid.*, **30**, 3091 (1897).
- (3) H. Biltz and P. Damm, *ibid.*, **46**, 3670 (1913); H. Biltz, K. Marwitzky and M. Heyn, *Ann.*, **423**, 127 (1921).