

hydrolysis, as recorded in Table XIII, was unimolecular; the final rotation of $+64.2^\circ$, calculated as the glycoside, is equivalent to $+68.7^\circ$, expressed as the anhydrous sugar.

Anal. Calcd. for $C_8H_{16}O_7$: C, 42.84; H, 7.19; OCH_3 , 13.84. Found: C, 42.80; H, 7.26; OCH_3 , 13.90.

Pentaacetyl- β -methyl-D-manno-D-gala-heptofuranoside.—The crystalline furanoside was acetylated at 0° with pyridine and acetic anhydride and the product isolated as a sirup by the customary procedure. The new acetate was crystallized at 25° from ether by dilution with petroleum ether, and recrystallized from these solvents to a constant rotation of -43.5° in chloroform (*c*, 2). The pentaacetyl- β -methyl-D-manno-D-gala-heptofuranoside was obtained as prisms melting at 78° , and in a 72% yield.

Anal. Calcd. for $C_{18}H_{28}O_{12}$: C, 49.74; H, 6.03; OCH_3 , 7.14; acetyl, 11.52 cc. 0.1 *N* NaOH per 100 mg. Found: C, 49.70; H, 6.07; OCH_3 , 7.18; acetyl, 11.54 cc.

Conversion to aldehyde-D-Manno-D-gala-heptose Hexaacetate.—The open-chain compound was obtained by treating the acetylated glycofuranoside (see preceding paragraph) with a 4% solution of sulfuric acid in a 70-30 mixture of acetic anhydride and acetic acid. The rotation of this solution changed to a final value of -33.0° within fifteen minutes. The acetate was separated as small, square prisms by pouring the solution into ice and water, and was purified as described previously.¹³ The yield of aldehyde-

¹³ Montgomery and Hudson, *This Journal*, **56**, 2463 (1934).

D-manno-D-gala-heptose hexaacetate, rotating -34.1° in chloroform (*c*, 2) and melting at 146° , was 94% of the theoretical.

Summary

1. D-Manno-D-gala-heptose has been prepared by applying a modification of the cyanohydrin synthesis to mannose. Evidence has been presented to indicate the existence of two distinct α -modifications of initial $[\alpha]^{20}_D +124^\circ$ and $+144^\circ$, respectively. Two β -modifications also are reported.

2. The acetochloro- and acetobromo- derivatives, the α - and β -methyl-D-manno-D-gala-heptopyranosides and their acetates, and the β -methyl-D-manno-D-gala-heptofuranoside and its acetate have been described.

3. A comparison of the molecular rotations of D-manno-D-gala-heptose and its derivatives with the molecular rotations of the configurationally related D-galactose and its derivatives shows agreement between some compounds and disagreement between others.

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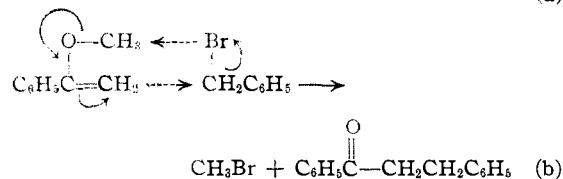
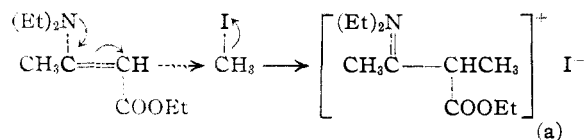
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Ketene Acetals. VII.¹ The Reaction of Ketene Diethylacetal with Various Halogen Compounds and Acids

BY S. M. McELVAIN AND D. KUNDIGER²

In previous papers³ of this series the unusual hetero-enoid structure of ketene diethylacetal has been discussed, and many of its reactions interpreted on the basis of the polarization that is characteristic of this type of structure. In the continuation of the study of the chemical properties of this compound, it seemed desirable to investigate the course of its reaction with a variety of organic halides. Two interesting cases of reaction between aliphatic hetero-enoid systems and alkyl halides have been reported in the literature: (a) the carbon alkylation of ethyl β -diethylamino-crotonate⁴ with methyl iodide, and (b) the condensation of α -methoxystyrene with such halides as benzyl bromide with the formation of an ω -al-

kylated acetophenone.⁵ These reactions may be illustrated as follows:



The work with ketene acetal which is now reported shows some interesting variations of the simple type of carbon alkylation that is illustrated above. In the case of butyl bromide, the least reactive of the halides that were used, the reaction did follow the above pattern with the formation of ethyl caproate and ethyl bromide

⁵ Mortenson and Spielman, *ibid.*, **62**, 1609 (1940).

(1) Paper VI of this series, Walters and McElvain, *This Journal*, **62**, 1482 (1940).

(2) Wisconsin Alumni Research Foundation Research Assistant, 1938-1941.

(3) McElvain, *et al.*, *This Journal*, **62**, 964, 1251 (1940).

(4) Robinson, *J. Chem. Soc.*, **109**, 1038 (1910); Lauer and Jones, *This Journal*, **59**, 332 (1937).

converted into ethyl acetate and the ethyl ester of the acid used (reaction (1)). When the reactants were mixed in the reverse order, *i. e.*, the acetal added to the ether solution of the acid, the reaction followed (1) mainly with the yield of VIII dropping in each case to less than 10% of the theoretical. The lower yields of VIII from the halogen acids are difficult to understand. The behavior of hydrofluoric acid is particularly striking since it does not appear to react with ketene acetal (*cf.* footnote *a*, Table I). No explanation can be offered for the marked difference in the yields of VIII that are produced by hydrochloric and hydrobromic acids.

The behavior of the phenols is interesting. The less acidic ones, phenol and bromophenol ($10^{10}K_a = 0.32 - 1.55$ at 25°), show no tendency to add 1,4 to two molecules of ketene acetal and produce VIII. However, the more acidic tribromophenol and trichlorophenol ($10^5 K_a$ approximately 0.1) give quite high yields of VIII. It would seem, therefore, from these results that there is a threshold of acidity that must be reached before an acid will add 1,4 across two molecules of ketene acetal.

Experimental

Reactions of Alkyl and Alkenyl Bromides with Ketene Acetal

(a) *n*-Butyl Bromide.—A mixture of 62 g. (0.45 mole) of *n*-butyl bromide and 26.7 g. (0.23 mole) of ketene acetal divided between two sealed tubes was heated at 250° for seventy-two hours. After cooling to -80° , the tubes were opened; there was considerable pressure (ethylene) in the tubes. Fractionation of the contents gave: (a) 4.8 g. (20%) of ethyl bromide, b. p. $37-40^\circ$, (b) 14.8 g. (79%) of ethyl acetate, b. p. $77-83^\circ$, (c) 53.3 g. of butyl bromide, b. p. $96-102^\circ$, and (d) 4.2 g. (13%) of ethyl caproate, b. p. $106-110^\circ$ (105 mm.) which on redistillation boiled at $164-167^\circ$ and contained 31.1% ethoxyl (calcd. 31.2%).

(b) Allyl Bromide.—A mixture of 29 g. (0.24 mole) of allyl bromide and 28 g. (0.24 mole) of ketene acetal was heated in a sealed tube at 190° for five hours. Subsequent fractionation through a 15 cm. modified Widmer column gave: (a) 12.1 g. (46%) of ethyl bromide, b. p. $36-40^\circ$, (b) 19.3 g. of a mixture of allyl bromide and ethyl acetate, b. p. $67-75^\circ$, (c) 3.2 g. of a mixture of allylacetic ester and ethyl orthoacetate, b. p. $80-87^\circ$ (97 mm.), and (d) 7.3 g. of a mixture of diallylacetic ester and the orthoester (V), b. p. $120-123^\circ$ (92 mm.). From the 9 g. of residual tar fractions material could be distilled at 1 mm. that had ethoxyl values as high as 64%, a value which approached the ethoxyl content (76%) of ketene acetal polymers. On the basis of density measurement, fraction (b) was found to contain 7.5 g. of ethyl acetate and 11.7 g. of allyl bromide. On the basis of its ethoxyl content (42.7%), fraction (c) contained about 13% of ethyl orthoacetate, which was

removed by shaking an ether solution of (c) with 10% aqueous hydrochloric acid for twenty minutes. After washing the ether layer with 10% aqueous sodium bicarbonate and water, and drying, the ethyl allylacetate, after removal of the ether boiled at $140-142^\circ$ and contained 35.4% ethoxyl (calcd. 35.2%). Saponification of this ester gave allylacetic acid, b. p. $185-187^\circ$.⁹

The ethoxyl content of fraction (d) was 33.8%, which indicated that it contained the orthoester V (R is allyl). This was shown to be the case when the ester obtained from a treatment similar to that described above for allylacetic ester, boiled at $183-186^\circ$,¹⁰ and had an ethoxyl content of 27.3% (calcd. for ethyl diallylacetate, 26.8%). The saponification equivalent of the purified ester was 167 (calcd. 168). Saponification of 4.8 g. of fraction (d) gave 2.8 g. (70%) of diallylacetic acid,¹¹ b. p. $218-223^\circ$.

After purification, 2.75 g. (9%) of allylacetic ester and 6.2 g. (31%) of diallylacetic ester were obtained from this reaction.

(c) Benzyl Bromide.—A mixture of 17 g. (0.1 mole) of benzyl bromide and 11.6 g. (0.1 mole) of ketene acetal was placed in a 50 ml. flask, fitted with a 6-inch Vigreux column attached to a receiver protected by a drying tube and immersed in dry-ice, and heated at $120-125^\circ$ for three hours. A mixture of ethyl bromide and ethyl acetate began to distil immediately, and 10.1 g. of this mixture was collected over the three hour reaction period. On refractionation this mixture yielded 7.3 g. (71%) of ethyl bromide, b. p. $37-40^\circ$, and 2.1 g. (24%) of ethyl acetate, b. p. $72-78^\circ$. Fractionation of the products remaining in the reaction flask gave: (a) 4.6 g. (27%) of benzyl bromide, b. p. $96-97^\circ$ (30 mm.), (b) 2.1 g. (14%) of ethyl hydrocinnamate,¹² b. p. $131-134^\circ$ (21 mm.), (c) 0.4 g. of a mixture of ethyl hydrocinnamate and the orthoester V (R is benzyl) that boiled at $100-105^\circ$ (1.0 mm.), (d) 0.4 g. of an intermediate fraction, (e) 7.2 g. (46%) of ethyl dibenzylacetate, b. p. $145-149^\circ$ (0.4 mm.), and (f) 2.4 g. of tar residue. After redistillation, fraction (b) showed a saponification equivalent of 177 (calcd. 178 for ethyl hydrocinnamate) and yielded hydrocinnamic acid,¹³ m. p. $48-49^\circ$, that was identical with an authentic specimen. After redistillation of fraction (e) at $174-175^\circ$ (2 mm.), it contained 17.7% ethoxyl (calcd. for ethyl dibenzylacetate¹⁴ 16.9%) and had a saponification equivalent of 262 (calcd. 268). Saponification gave dibenzylacetic acid¹⁴ (88%), m. p. $82-89^\circ$, which on recrystallization from petroleum ether (b. p. $60-68^\circ$) melted at $88-89^\circ$, had a neutral equivalent of 237 (calcd. 240) and was identical with an authentic specimen.

When two equivalents of ketene acetal to one of benzyl bromide were used, fractions (c) and (d) increased and considerable ethyl orthoacetate (26%) was obtained. On the basis of its ethoxyl content (39.9%), fraction (c) from the experiment using this ratio of reactants was an equimolecular mixture of ethyl hydrocinnamate and the ortho-ester V (R is benzyl) and fraction (d), the ethoxyl content of which

(8) Zeidler, *Ann.*, **187**, 39 (1877).

(9) Fittig and Messerschmidt, *ibid.*, **208**, 92 (1881).

(10) Auwers and Moosbrugger, *ibid.*, **387**, 198 (1912).

(11) Conrad and Bischoff, *ibid.*, **204**, 173 (1880).

(12) Erlenmeyer, *ibid.*, **237**, 334 (1886).

(13) "Organic Syntheses," Coll. Vol. I, 304 (1932).

(14) Fittig and Christ, *Ann.*, **268**, 123 (1892); Dolique, *Ann. chim.*, **16**, 445 (1931).

was 47.8%, contained about 25% of ethyl hydrocinnamate and about 75% of the ortho-ester V. This ortho ester was converted to the normal ester of the correct ethoxyl content by the procedure described above for the purification of allylacetic ester. The total yield of the normal ester amounted to 29%.

Reaction of Acyl Halides with Ketene Acetal: (a) **Acetyl Chloride.**—In a 250-ml. round-bottom three-necked flask fitted with a mercury-sealed stirrer and a dropping-funnel with drying tube, was placed 47 g. (0.60 mole) of freshly distilled acetyl chloride. This halide was heated at 50–55°, while 63.8 g. (0.55 mole) of ketene acetal was added with stirring over a period of one and one-half hours. After another half hour, 26.4 g. of liquid collected in the cold traps. Fractionation of the reaction mixture through a 15 cm. modified Widmer column at atmospheric pressure gave: (a) 4.9 g. in the cold trap, (b) 5.3 g. of acetyl chloride, (c) 32.2 g. (0.37 mole) of ethyl acetate, b. p. 70–77°; then at 8 mm. the following fractions distilled: (d) 3.1 g. (0.02 mole) of acetoacetic ester, b. p. 68–74°, (e) 9.5 of O-ethylacetoacetic ester (VIII), b. p. 78–84°, (f) 3.3 g. of an intermediate, and finally (g) 12.1 g. of O-acetylacetoacetic ester (VI), b. p. 87–88° (8 mm.); d_{25}^{25} , 1.0587; n_D^{20} , 1.4426. Preparation of VI by Claisen's method¹⁶ gave a product, b. p. 87–88° (8 mm.); d_{25}^{25} , 1.0583; n_D^{20} , 1.4423. About 87% of fraction (e) redistilled at 80–82° (8 mm.). Successive recrystallizations (freezings) of fraction (e), which contained 49.0% ethoxyl, finally gave a product, m. p. 29–31°, with an ethoxyl value of 56.63% (calcd. 56.95% for VIII).¹⁵ The yield of VI and VIII, respectively, amounted to 30 and 26% of the theoretical. The 8.2 g. of the higher boiling reaction residue did not distill into any clear cut fractions. Refractionations of the material in the cold trap and fractions (a) and (b) gave 21.1 g. (0.33 mole) of ethyl chloride and 13.7 g. (0.18 mole) of acetyl chloride. Fraction (g) did not form a copper salt. When 3.3 g. of (g) and 3.3 g. of VI prepared from acetoacetic ester were converted¹⁶ to ethyl diacetoacetate and this latter compound converted to its copper salt, there were obtained 2.0 and 2.1 g. samples, respectively, of this copper salt, each of which melted at 149–150°,¹⁷ and gave no depression as a mixture.

Reverse addition of the reactants to that described above gave the same products and in practically the same yields.

When to 47 g. (0.6 mole) of acetyl chloride, 23.2 g. (0.2 mole) of ketene acetal was added over a period of three quarters of an hour at 50°, fractionation of the product returned most of the excess acetyl chloride and yielded 8.9 g. (52%) of the O-acetylacetoacetic ester (VI).

Acetylation of Acetoacetic Ester in the Presence of Ketene Acetal.—A mixture of 19.5 g. (0.15 mole) of acetoacetic ester and 11.8 g. (0.15 mole) of acetyl chloride was stirred at 80–90° while 17.4 g. (0.15 mole) of ketene acetal was added over a period of three quarters of an hour. After another half hour at 90°, fractionation of the liquid in the trap and the reaction mixture gave: (a) 9.2 g. (0.14 mole) of ethyl chloride, b. p. 12–14°, (b) 10.6 g. (0.12 mole) of ethyl acetate, b. p. 72–77°, (c) 6.0 g. (31% recovery) of acetoacetic ester, b. p. 70–73° (13 mm.).

(d) 14.2 g. (79%) of a mixture of O-acetylacetoacetic ester (VI) and ethyl diacetoacetate, b. p. 92–96° (13 mm.), and (e) 3.0 g. of a non-distillable residue. From fraction (d) the copper salt of ethyl diacetoacetate could be precipitated at once. Extractions of an ethereal solution of fraction (d) with 10% sodium hydroxide solution resulted in the separation of (d) into 4.1 g. of VI and 8.8 g. of ethyl diacetoacetate. Such extraction was shown to convert 33% of a pure sample of VI to the C-acetyl compound.

(b) **Benzoyl Chloride.**—The dropwise addition of 42 g. (0.3 mole) of benzoyl chloride to 34.8 g. (0.3 mole) of ketene acetal with stirring in an apparatus similar to that described above caused sufficient evolution of heat to raise the temperature of the mixture to 90°. When the temperature declined, the mixture was heated at 90° for one hour and finally at 110° for one hour. During this time, 18 g. of liquid collected in the cold trap. The reaction residue was cooled successively to 0, –15, and –40°, and each crop of crystals obtained filtered off by suction. The total of 21.8 g. (59%) of ethyl O-benzoyl-benzoylacetate (IX) that was obtained was then triturated with 25 ml. of absolute ether for ten minutes, filtered, and recrystallized twice from 40 ml. portions of absolute ethanol, and finally dried in a vacuum desiccator. The 14.9 g. of IX so obtained melted at 84–85°.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 72.95; H, 5.45; OC_2H_5 , 15.2. Found: C, 72.75; H, 5.54; OC_2H_5 , 15.3.

When saponified in 4% alcoholic alkali IX gave a 73% yield of acetophenone. Hydrolysis of IX in 50% aqueous potassium hydroxide yielded benzoic acid and acetic acids in approximately a 2:1 ratio.

Fractionation of the liquid in the cold trap and the 34.3 g. of filtrate from which IX had crystallized gave: (a) 18.0 g. (93%) of ethyl chloride, (b) 8.1 g. of ethyl acetate, (c) a number of intermediate fractions from which 8.8 g. (20%) of ethyl benzoate was obtained, and finally (d) 2.2 g. (3%) of benzoylacetic ester, b. p. 120–125° (1 mm.). The 10 g. of remaining residue could not be satisfactorily distilled.

Ethyl o-Benzoyl-benzoylacetate (IX) from Ethyl Benzoylacetate.—To a mixture of 15.8 g. (0.2 mole) of dry pyridine and 19.2 g. (0.1 mole) of benzoylacetic ester, 21 g. (0.15 mole) of benzoyl chloride was added dropwise with stirring over a period of half an hour. The heat of reaction kept the mixture at about 60°. After stirring for two hours, the precipitated pyridine hydrochloride was filtered off with suction and washed with ether. On cooling to 0°, the filtrate deposited IX, which, when filtered off and dried, weighed 10.4 g. The filtrate was then diluted with ether and extracted with three 20-ml. portions of 10% aqueous sodium hydroxide which had been cooled to 0°, washed with water, then extracted with two 20-ml. portions of 30% sulfuric acid, and finally washed with a saturated sodium bicarbonate solution and water. The dried ether layer, after distillation of the ether, gave 14.1 g. of IX. Recrystallization from absolute ethanol and then from petroleum ether (b. p. 60–68°) gave ethyl O-benzoylbenzoylacetate that melted at 84–85° and was identical with the product obtained above from the reaction of benzoyl chloride with ketene acetal. The total yield of IX from cooling the reaction filtrate and from the ethereal solution after the various extractions amounted to 24.5 g. (83%).

(15) Friedrich, *Ann.*, **219**, 333 (1883).

(16) Claisen, *Ber.*, **33**, 3780 (1900).

(17) James, *Ann.*, **226**, 212 (1884).

(c) **Benzenesulfonyl Chloride.**—A mixture of 17.4 g. (0.15 mole) of ketene acetal and 26.5 g. (0.15 mole) of benzenesulfonyl chloride was heated for two hours at 125°. Fractionation of the reaction mixture yielded 2.8 g. (21%) of ethyl acetate, 15.1 g. (57%) of unchanged benzenesulfonyl chloride and 6.9 g. (25%) of ethyl benzenesulfonate, b. p. 145–149° (10 mm.). Experiments in which the ratio of ketene acetal to benzenesulfonyl chloride was increased gave higher yields of the ethyl benzenesulfonate and correspondingly lower recovery of unreacted benzenesulfonyl chloride. In one case in which 58 g. (0.5 mole) of ketene acetal and 8.9 g. (0.05 mole) of benzenesulfonyl chloride were used, none of the sulfonyl chloride was recovered, and the yields of ethyl acetate and ethyl benzenesulfonate were 86 and 80%, respectively; also an 8% yield of ethyl O-ethylacetoacetate (VIII) and a 28% yield of ethyl orthoacetate were obtained.

Reaction of Acids and Phenols with Ketene Acetal.—In a 250-ml. round-bottom three-necked flask immersed in a water bath at 25° and fitted with a 15-cm. Vigreux column, an efficient mercury-sealed stirrer, and a dropping funnel with drying tube, was placed 46.4 g. (0.4 mole) of ketene acetal. The Vigreux column was attached to a condenser set for downward distillation and fitted to a receiver with drying tube. A 1.6 *N* solution of 0.2 mole of the acid or phenol in absolute ether was added dropwise with stirring over a period of one and three-quarters of an hour. When the volume of liquid in the flask reached 120 ml., the cooling bath was replaced by an oil-bath, and the ether distilled off at a rate approximating the rate of addition of the ether solution of the acid. Fractionation of the remaining reaction product was then carried out with a modified Widmer column. Ethyl acetate, the ethyl ester of the acid used, and ethyl orthoacetate were first distilled, and then the ethyl O-ethylacetoacetate (VIII) in the amounts shown in Table I was collected. If the reactants were mixed in the reverse order, the yields of VIII were always less than 10%.

In the case of phenol the main reaction product was diethyl phenylorthoacetate (68%), if the reaction mixture was fractionated under at least 14 mm. of pressure. Distillation at atmospheric pressure yielded phenetole and phenyl acetate, decomposition products of this mixed ortho-ester. Diethyl phenyl-ortho-acetate boils at 103–104° (14 mm.); n_D^{25} 1.4783; d_4^{25} 0.9904.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 68.54; H, 8.63; C_2H_5O , 42.9. Found: C, 68.14; H, 8.52; C_2H_5O , 42.7.

In the case of *p*-bromophenol the main reaction product was *p*-bromophenetole, b. p. 60–69° (1 mm.). The yield of material boiling over this range amounted to 95% of the theoretical. Refractionation of this material gave an 81% yield of *p*-bromophenetole that boiled at 104–105° (11 mm.) or 228–230° at atmospheric pressure.¹⁸

(18) Cf. Birosel, *THIS JOURNAL*, **53**, 1409 (1931).

With tribromophenol there was obtained a 26% yield of O-ethylacetoacetic ester (VIII). Also tribromophenetole,¹⁹ b. p. 119–123° (2 mm.), m. p. 69–70° after recrystallization from petroleum ether, was obtained in 98% yield.

In the case of trichlorophenol a 21% yield of ethyl O-ethylacetoacetate (VIII) and an 89% yield of trichlorophenetole, b. p. 81–83° (2 mm.) and m. p. 44–45,²⁰ after recrystallization from petroleum ether, were obtained. In addition to these products a 6% yield of trichlorophenylacetate that boiled at 110–115° (2 mm.) and at 258–263° at atmospheric pressure²¹ was isolated.

Summary

The reaction of ketene diethylacetal with a variety of organic halides has been studied. *n*-Butyl bromide adds to a small extent to the acetal to produce ethyl caproate. The more reactive allyl and benzyl bromides add much more readily and to a greater extent to form the mono- and di-substituted acetic esters, RCH_2COOEt and $R_2CHCOOEt$ (R is allyl and benzyl).

Acetyl chloride and benzoyl chloride each yield the corresponding O-acyl derivative of the acylacetic ester, $RC(OCOR)=CHCOOEt$. Accompanying this product in the case of acetyl chloride is ethyl O-ethylacetoacetate, $CH_3C(OEt)=CHCOOEt$, which, it is believed, results from the 1,4 addition of hydrogen chloride across two molecules of ketene acetal.

Benzenesulfonyl chloride does not react with ketene acetal as do the other acyl halides, but instead causes it to polymerize and is then converted to ethyl benzenesulfonate by the alcohol eliminated from the polymer.

A study of the action of a variety of acids on ketene acetal has shown that those acids and phenols the $K_a \times 10^6$ of which is 1 or more produce ethyl O-ethylacetoacetate when added to an excess of ketene acetal. Weaker acids, such as phenol and *p*-bromophenol, do not show this type of reaction but simply add to a single molecule of ketene acetal to produce a mixed ortho-ester, $CH_3C(OEt)_2OR$, or decomposition products thereof.

MADISON, WISCONSIN

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(19) Torrey and Hunter, *Ber.*, **40**, 4334 (1907).

(20) Hunter, Olson and Daniels, *THIS JOURNAL*, **38**, 1762 (1916).

(21) Fischer, *Ann. Spl.*, **7**, 185 (1870).