then evaporated yielding colorless needles (150 mg.), m.p. 219–220°.

Anal. Calcd. for $C_{18}H_{16}O_5IBr$: C, 41.64; H, 3.11; Halogen, 39.84. Found: C, 41.74; H, 3.04; Halogen, 39.72.

Its structure was confirmed as *8-bromo-3'-iodo-5,7,4'-trimethoxyflavanone* by conversion to *bromochalcone* (X), which was identical with that obtained from condensation of 2-hydroxy-3-bromo-4,6-dimethoxyacetophenone[4] (XII) with 3-iodo-4-methoxybenzaldehyde, yellow needles, m.p. 224–225°.

Anal. Calcd. for $C_{18}H_{16}O_5IBr$: C, 41.64; H, 3.11; Halogen, 39.84. Found: C, 41.52; H, 3.14; Halogen, 39.70.

By oxidation with selenium dioxide, the bromochalcone (X) was converted into the corresponding *8-bromoflavone* (XI), colorless needles, m.p. 257–258°.

Anal. Calcd. for $C_{18}H_{14}O_5IBr$: C, 41.80; H, 2.73; Halogen, 40.00. Found: C, 41.70; H, 2.94; Halogen, 39.70.

This product was identical with *8-bromo-3'-iodo-5,7,4'-trimethoxyflavone* (XI) obtained from the chalcone (V) by bromination, yielding the *tribromochalcone* (XIII), m.p. 190–191°.

Anal. Calcd. for $C_{18}H_{16}O_5IBr_3$: C, 31.84; H, 2.38; Halogen, 54.00. Found: C, 31.64; H, 2.44; Halogen, 53.50.

After heating above the melting point, it gave yellow needles (XIV). This compound melted at 275.°

Anal. Calcd. for $C_{17}H_{12}O_5IBr$: C, 40.58; H, 2.40; Halogen, 41.11. Found: C, 40.10; H, 2.74; Halogen, 41.00.

Methylation of this compound (XIV) in acetone with dimethyl sulfate and sodium hydroxide in the usual manner yielded the flavone (XI).

Acknowledgment. The authors wish to express their appreciation to Professor Simon H. Wender of the University of Oklahoma for kindly reading this manuscript, to Professor T. S. Wheeler of Dublin for valuable discussions, to Professor Y. Sebe of Japan and President S. L. Chien of this University for interest and encouragement, to Mr. T. Ueng and Mr. S. T. Choong for experimental assistance. Financial support by the Asia Foundation and the National Council on Science Development is also gratefully acknowledged.

TAIPEI, TAIWAN (FORMOSA)

---

[4] J. A. Donnelly, *Tetrahedron Letters*, 19, 1 (1959).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

Diels-Alder Syntheses of 2,6-Dimethylcyclohexanecarboxylic Acids

THOMAS L. JACOBS, DONALD M. FENTON,[1] AND RUSSELL REED[1]

Received July 17, 1961

Racemic 2,6-dimethylcyclohexanecarboxylic acid is obtained in 50% over-all yield from the Diels-Alder reaction of 1,3-pentadiene and diethyl ethylidenemalonate followed by saponification of the adduct, hydrogenation, and decarboxylation. The reaction of 1,3-pentadiene with crotonic acid or ethyl crotonate yields mixtures of isomers.

2,6-Dimethylcyclohexanecarboxylic acid can exist in two meso-forms (*cis* and *trans*) and in a racemic modification resolvable into enantiomers. The meso forms are readily available,[2] but the racemic modification was obtained in only poor yield by reduction of 2,6-dimethylbenzoic acid with sodium in boiling isoamyl alcohol.[2,3] The racemic form was needed for studies of steric hindrance and an improved synthesis was therefore sought.

The Diels-Alder reaction offers an attractive route for the synthesis of 2,6-dimethylcyclohexanecarboxylic acids. It was reported[4] that 1,3-pentadiene and diethyl ethylidenemalonate gave diethyl 2,6-dimethyl-3-cyclohexene-1,1-dicarboxylate (I) in good yield. I was saponified and decarboxylated to yield a 2,6-dimethyl-3-cyclohexenecarboxylic acid (IV). The structure of IV was shown by selenium dehydrogenation to *m*-xylene which was oxidized to isophthalic acid, but the stereochemistry of IV was not established.

We have repeated this diene synthesis and converted the adduct to 2,6-dimethylcyclohexanecarboxylic acid by two routes: (a) saponification, hydrogenation, decarboxylation (I → II → III → V) and (b) saponification, decarboxylation, hydrogenation (I → II → IV → V). Although mixtures of isomers were present, the main product, racemic 2,6-dimethylcyclohexanecarboxylic acid, was easily isolated. An over-all yield of about 50% was obtained by either route (a) or (b). This synthetic method is the best now available for the racemic isomer. The melting point obtained, 83.0–83.5°, is higher than that of the best sample of racemic acid synthesized by Noyes' method (80.8–81.3°); a mixture of samples prepared by the two methods melted between the temperatures indicated.

Pure racemic acid gives melting point depressions with either of the pure meso isomers. Binary melting point diagrams were obtained for racemic acid with each meso isomer. Neither compound nor solid solution formation was observed. Racemic and meso *cis* isomers form a eutectic mixture at 54% *dl*, m.p. 52–52.4°; racemic and meso *trans* isomers form a eutectic mixture at 40% *dl*, m.p. 77.5–78°.

---

[1] Most of the material for this paper is taken from the Ph.D. thesis of Donald M. Fenton, U.C.L.A., 1958. The rest is from the Ph.D. thesis of Russell Reed, U.C.L.A., 1950.

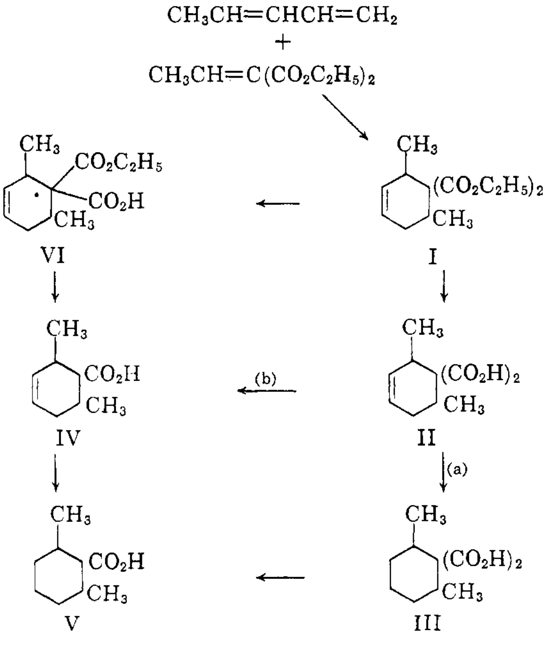
[2] T. L. Jacobs, R. Reed, and E. Pecovska, *J. Am. Chem. Soc.*, 73, 4505 (1951).

[3] W. A. Noyes, *Am. Chem. J.*, 20, 789 (1898); R. W. Hufferd and W. A. Noyes, *J. Am. Chem. Soc.*, 43, 925 (1921).

[4] B. A. Arbuzov and E. G. Kataev, *Zhur. Obshchei Khim.*, 20, 68 (1950).

It is not possible to determine from the data on hand the stereoisomeric composition of the mixture of 2,6-dimethylcyclohexanecarboxylic acid isomers formed in this synthesis. Quite possibly the original adduct or its hydrogenation product could be separated by vapor phase chromatography methods (not available when this work was done) and the course of the decarboxylation of the *cis* diacid then followed. It is believed that at least small amounts of one or both of the meso isomers were present in the crude 2,6-dimethylcyclohexanecarboxylic acid since lower melting samples gave analytical results in agreement with the composition of pure acid. However, these results may have been due to the presence of 2,3-dimethylcyclohexanecarboxylic acids. The ease with which pure racemic acid was obtained by a single recrystallization suggests that these crude preparations contained relatively little of other isomers.

Attempts were made to separate other isomers by selective saponification of the diester mixture or selective esterification of diacids, but these were unsuccessful. A monoacid-monoester was isolated but saponification, decarboxylation, and hydrogenation gave mixtures of isomers from which only racemic acid could be isolated. These mixtures all melted below the melting point of racemic-meso *trans* eutectic; their melting points were raised by admixture with pure racemic acid.



Esterification of the diacid with diazomethane gave either a mono- or a diester depending upon the relative proportions of acid and diazomethane. Only the diester was isolated when esterification was carried out with diazoethane or with ethanol and sulfuric acid.

Diethyl ester I was also hydrogenated to a saturated diester which had different physical properties from those reported[5] for a diethyl 2,6-dimethylcyclohexane-1,1-dicarboxylate prepared by a Perkin reaction.

The Diels-Alder reaction of 1,3-pentadiene with crotonic acid, ethyl crotonate, crotononitrile, or crotonaldehyde offers alternative syntheses for 2,6-dimethylcyclohexanecarboxylic acid, but in practice these appear to be less useful. It was reported[6] that the reaction with crotonic acid gave an acid, m.p. 86–87°, which yielded a 2,6-dimethylcyclohexanecarboxylic acid, *A*, m.p. 77–78°, on hydrogenation. Meek later reported[7] that careful fractional crystallization of *A* gave pure samples of both racemic and meso *trans* acids which gave no melting point depressions when mixed with authentic samples which we supplied. He also condensed methyl crotonate and 1,3-pentadiene to yield an ester, b.p. 184–186°/630 mm., which was saponified to an acid, m.p. 70–74°. Recrystallization produced material, m.p. 91.5–93°, which gave no melting point depression with adducts from crotonic acid and 1,3-pentadiene.

We have allowed 1,3-pentadiene and crotonic acid to react under less vigorous conditions and obtained a 26% yield of an acidic product, m.p. 85.5–87° (which agrees with the m.p. reported by Meek). Hydrogenation gave a high yield of material, m.p. 73–78°, which showed no melting point depression with pure racemic acid. However, we did not succeed in isolating the racemic acid from our product; instead a 12% yield of meso *cis* acid, m.p. 103–104°, was the only pure compound obtained. Two experiments were also carried out with *cis*-crotonic acid and 1,3-pentadiene, but the main product was an acidic gum possibly a copolymer of the reactants. Reaction of ethyl crotonate and 1,3-pentadiene gave an ester readily saponified to an acid, m.p. 83–85°. This acid gave a melting point depression when mixed with 2,6-dimethyl-3-cyclohexenecarboxylic acid obtained from the ethylidenemalonate reaction, but no depression in a mixture with the acid from crotonic acid and 1,3-pentadiene.

Mention should also be made of the product reported[8] from crotonaldehyde and 1,3-pentadiene. The aldehyde was shown to be 2,6-dimethyl-3-cyclohexenecarboxaldehyde and was oxidized to an acid, m.p. 66–67°. This may correspond to the 2,6-dimethyl-3-cyclohexenecarboxylic acid, m.p. 68.5–69°, which we obtained from the ethylidenemalonate reaction. The over-all yield was 23%. Evi-

---

(5) E. van Heyningen, *J. Am. Chem. Soc.*, 76, 2241 (1954).

(6) J. S. Meek, R. T. Merrow, B. T. Poon, E. W. Lane, and S. J. Cristol, Abstracts Papers, Division of Organic Chemistry, of the American Chemical Society, Atlantic City, N. J., Sept. 1949, p. 18M.

(7) J. S. Meek, private communication.

(8) H. L. Holmes, K. Alcock, D. G. Demianiw, J. W. Robinson, C. E. S. Rooney, and F. A. Sundberg, *Can. J. Research*, **26B**, **248** **(1948)**.

dence has been presented that the aldehyde is a single isomer.[9]

A number of years ago in our laboratory[10] an attempt was made to prepare 2,6-dimethylcyclohexanecarboxylic acids by hydrogenation and oxidation of the adduct from crotonaldehyde and 1,3-pentadiene. The adduct had about the same boiling point (76–78°/17 mm.) as reported by others,[8,9] but the saturated acid obtained was clearly a mixture of isomers. Fractional crystallization gave a very low yield of pure meso *trans*-2,6-dimethylcyclohexanecarboxylic acid, m.p. 103.4–103.6°.

On the basis of Alder's *ortho* rule[11] one would expect 1,3-pentadiene to react with dienophiles, such as crotonic acid, to give almost exclusively 2,6-dimethylcyclohexene derivatives rather than 2,3-dimethyl compounds. One would also expect on the basis of *cis* addition that the carboxyl or similar group would be *trans* to the methyl which originates from the dienophile because the *trans* forms of crotonic acid, ethyl crotonate, and crotonaldehyde were used except as mentioned. It is interesting that with respect to the remaining stereochemical choice (either *cis* or *trans* orientation of the carboxyl and the methyl which originates from the diene) the reaction appears to be far less specific. Further discussion of this point must await more exact determination of the products in these reactions. It will also be necessary to know whether there is kinetic or thermodynamic control of products. It should be mentioned that fairly pure *trans*- 1,3-pentadiene was used in the reactions; only this isomer has been observed to undergo the Diels-Alder reaction.[12]

Of the two adducts that might be formed from diethyl ethylidenemalonate and 1,3-pentadiene (assuming exclusive formation of 2,6-dimethyl cyclohexene derivatives) it is interesting that the one having methyl groups *cis* and hence permitting both to be equatorial is the minor constituent. The major product has the 2- and 6-methyl groups *trans*. In this isomer one methyl and one carboethoxyl must be axial. One would not expect this to be the more stable isomer.

EXPERIMENTAL

All melting points were taken with total immersion Anschutz thermometers.

Diethyl 2,6-dimethyl-3-cyclohexene-1,1-dicarboxylate (I). 1,3-Pentadiene was prepared by vapor phase dehydration of 3-penten-2-ol over alumina[13]; n_D^{25} 1.4266 indicates almost pure *trans* product. A mixture of 25 g. (0.37 mole) of diene, 75 g. (0.47 mole) of diethyl ethylidenemalonate,[14] and a few mg. of trinitrobenzene was heated in a hydrogenation bomb at 180–200° for 14 hr. The product was distilled through a center rod column to give 64 g. (68%) of a liquid b.p. 136–138°/11 mm., n_D^{25} 1.4595; reported[4] 74%, b.p. 136–138°/11 mm., n_D^{20} 1.4619 for a product prepared by heating at 170–175° for 13 hr. in a sealed glass tube. We obtained lower yields at 170°. A lower yield was obtained when commercial 1,3-pentadiene was used (mixture of *cis* and *trans*) with enough *trans* present to give the same molecular ratio to dienophile, because more polymer was formed and product separation was more difficult.

2,6-Dimethyl-3-cyclohexene-1,1-dicarboxylic acid (II). Saponification of 2.6 g. (0.01 mole) of I with 8 g. of potassium hydroxide in 40 ml. of alcohol (refluxed 40 hr.) gave 1.7 g. (85%) of II after alcohol was removed and the solution acidified to *p*H 6. II was insoluble in petroleum ether. The m.p. was around 200° but depended on the rate of heating of the bath. Reported[4]: 42% yield, m.p. 188°.

Partial hydrolysis of I. To 100 g. (1.78 moles) of potassium hydroxide dissolved in 600 ml. of 95% alcohol was added 100 g. (0.394 mole) of I. The yellow solution was refluxed for 1 hr., 700 ml. of water was added, and the reaction mixture was extracted with chloroform. The water layer was acidified and extracted with ether. The ether layer was concentrated to give 60 g. of a yellow precipitate which was stirred with 500 ml. of petroleum ether and filtered. The remaining precipitate was recrystallized from ethyl acetate to give a 40–55% yield of II.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.60; H, 7.12. Found: C, 60.85; H, 7.41.

The filtrate from the petroleum ether extraction was concentrated to give a yellow solid which was likewise recrystallized from ethyl acetate to give colorless 2,6-dimethylcyclohex-3-ene-1-carboethoxy-1-carboxylic acid (VI), m.p. 98–99°, in 10–20% yield.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.68; H, 8.02. Found: C, 63.43; H, 8.13.

Hydrogenation of II in methanol in a Parr apparatus at 40–30 p.s.i. pressure over Adams' catalyst gave almost quantitative yields of III, m.p. 180–228°, depending on rate of heating.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 60.00; H, 8.04. Found: C, 60.09; H, 8.02.

Decarboxylation of II. Heat was applied to 10 g. of II in a distillation apparatus until decarboxylation and distillation had ceased. The 2,6-dimethyl-3-cyclohexenecarboxylic acids IV crystallized in the receiver, and were recrystallized from formic acid, m.p. 68.5–69°, yielding 6.9 g. (89%). Crude IV melted as low as 45°. Reported[4] yield, 70%; m.p. 55–56°.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.09; H, 9.15. Found: C, 69.87; H, 8.95.

Decarboxylation of III. In a similar experiment III gave 2,6-dimethylcyclohexanecarboxylic acid (V) in 96% yield, m.p. 83–83.5°, after recrystallization from formic acid.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.20; H, 10.30. Found: C, 69.13; H, 10.05.

Hydrogenation of IV was carried out as for II. Crude V, m.p. 70–78°, was obtained in 98% yield. Recrystallization from formic acid gave pure V, m.p. 83–83.5°.

Hydrogenation of I was carried out as for II. The product was diethyl 2,6-dimethylcyclohexane-1,1-dicarboxylate, b.p. 129–133°/7–8 mm., n_D^{25} 1.4581.

Anal. Calcd. for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 65.59; H, 9.22.

Cyclization of diethyl 1-methyl-5-bromo-*n*-hexylmalonate was reported[5] to give a product with the same structure, b.p. 93–95°/0.8 mm., n_D^{25} 1.4510.

Preparation of V *from* VI. To 5.0 g. (0.022 mole) of VI was added an alcoholic potassium hydroxide solution. The mixture was refluxed for 4 hr., two thirds of the alcohol was removed, 100 ml. of water was added, and the mixture was acidified and extracted with ether. The ether concentrate was recrystallized from formic acid and was decarboxylated to give IV, m.p. 48.5–51.8°, which was hydrogenated to give V, m.p. 75.0–76.5°, 1.7 g. or 49%. Mixed melting

---

(9) J. C. Lunt and F. Sondheimer, *J. Chem. Soc.*, 2957 (1950).

(10) J. E. Hanson, Masters thesis, U.C.L.A., 1942.

(11) K. Alder and W. Vogt, *Ann.*, **571**, 157 (1951).

(12) D. Craig, *J. Am. Chem. Soc.*, **65**, 1006 (1943).

(13) M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky, and W. E. Vaughan, *J. Am. Chem. Soc.*, **59**, 831 (1937).

(14) W. S. Fones, *Org. Syntheses*, **32**, 54 (1952).

points with racemic, 2,6-dimethylcyclohexanecarboxylic acid all melted above 76.5°.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.20; H, 10.30. Found: C, 69.21; H, 10.40.

Also, VI was decarboxylated to give ethyl 2,6-dimethylcyclohex-3-ene-1-carboxylate, b.p. 65–68°/4.5 mm., n^{25}_D 1.4618.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.47; H, 9.96. Found: C, 72.37; H, 9.68.

This ester was saponified, and the acid produced was hydrogenated to give a saturated acid, m.p. 70–71°, which had the composition of V. A mixture with racemic 2,6-dimethylcyclohexanecarboxylic acid gave a higher melting point.

Esterification of II. Equimolar amounts of diazomethane and II in ether at room temperature for 2 hr. gave 79% methyl 2,6-dimethyl-3-cyclohexene-1-carboxylate-1-carboxylic acid, m.p. after recrystallization from formic acid, 145–145.5°.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.23; H, 7.60. Found: C, 62.03; H, 7.82.

Esterification with excess diazomethane gave diester, m.p. 72–73° after recrystallization.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.73; H, 8.02. Found: C, 63.79; H, 8.17.

2,6-Dimethyl-3-cyclohexene-1,1-dicarboxylic hydrazide. To 6.0 g. (0.024 mole) of I was added a solution of 2.0 g. (0.083 g.-atom) of sodium in 1.9 g. (0.059 mole) of 95% hydrazine and 50 ml. of anhydrous ethanol. The yellow solution was stirred and refluxed for 6 hr., then cooled in ice. A precipitate formed but dissolved when 100 ml. of water was added. A yellow oil separated and was taken up in petroleum ether. The petroleum ether solution was concentrated and 0.9 g. of I was recovered. The water solution was acidified cold and extracted with ether. The etheral extract was dried, the solvent was removed, and the residue recrystallized from ether. The crystals, m.p. 191–194°, gave a positive test for nitrogen; yield 56%.

Anal. Calcd. for $C_{10}H_{14}O_2N_2$: C, 62.34; H, 7.27. Found: C, 62.06; H, 7.10.

Crotonic acid and trans-1,3-pentadiene. A solution of 8.6 g. (0.10 mole) of crotonic acid, 12.2 g. (0.18 mole) of 1,3-pentadiene, and a few crystals of hydroquinone were sealed under nitrogen in a heavy-walled Pyrex glass tube and heated at 180° for 2 hr. (Meek heated for 8 hr. at 200–230°). When cooled the tube contained a viscous oil that soon deposited crystals. Petroleum ether was added, and the solution soon deposited 8 g. of crystals. These were recrystallized from petroleum ether to give 4 g. (26%) of colorless crystals, m.p. 85.5–87°. These were hydrogenated in methanol over Adams' catalyst to a colorless solid, m.p. 73–78°, equivalent weight 155.8 (calcd. for $C_9H_{16}O_2$; 156.2). Several recrystallizations of the acid from 1.67 g. of adduct gave 0.20 g. of meso *trans*-2,6-dimethylcyclohexanecarboxylic acid, m.p. 103–104° (no m.p. depression in mixture with authentic meso *trans* acid).

Ethyl crotonate and trans-1,3-pentadiene. The procedure was like that used for ethylidenemalonic ester (12 hr., 170–180°). The product was fractionally distilled through a center rod column. Redistillation of a center cut, b.p. 85–86°/11 mm. (15 g.) gave several fractions; a portion with b.p. 87–88.5°/11 mm. was analyzed.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.47; H, 9.96. Found: C, 72.36; H, 10.21.

Yields were low because considerable polymerization occurred and because separation from other products was difficult.

Saponification of the ester and recrystallization of the acid from ethyl acetate gave an 83% yield of material, m.p. 83–85°.

LOS ANGELES, CALIF.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS, THE STATE UNIVERSITY]

Bicyclic Ortho Esters by Direct Esterification

RODERICK A. BARNES, GERALD DOYLE,[1] AND JOSEPH A. HOFFMAN[2]

Received August 17, 1961

The stronger organic acids, such as 3,5-dinitrobenzoic acid and di- and trichloroacetic acids, have been found to react directly with a 2-hydroxymethyl-2-methyl-1,3-propanediol to yield bicyclic ortho esters.

Ortho esters usually have been prepared from a nitrile which is converted first to the imino ester hydrochloride and this latter substance then is heated with an alcohol.[3] Bicyclic esters related to the present work have been previously prepared by an ester interchange involving a triol and a noncyclic ortho ester.[4,5]

The successful preparation of bicyclic phosphites and phosphates[6] from 2-hydroxymethyl-2-alkyl-1,3-propanediols led us to attempt similar preparations in the carbon series. The first approach, analogous to that used for the preparation of a phosphite, employed benzotrichloride, 2-hydroxymethyl-2-methyl-1,3-propanediol (I), and triethylamine. The only product isolated was tetrachlorodibenzyl (II). An attempt to promote SN1 reactions of benzotrichloride by using silver carbonate in the reaction mixture also failed and II was isolated again. Com-

---

[1] The major part of this work was taken from a thesis presented by Gerald Doyle for the B.S. degree, as a part of the Henry Rutgers Scholars program, May 1961.

[2] The first successful preparation of an ortho ester was described in a thesis presented by J. A. Hoffmann to the Graduate School for the Ph.D. degree, December 1958.

[3] S. M. McElvain and J. W. Nelson, *J. Am. Chem. Soc.*, **64**, 1825 (1942).

[4] E. Stetter and K. H. Steinacker, *Chem. Ber.*, **85**, 451 (1952), treated *cis*-phloroglucitol with ethyl γ,γ,γ-triethoxypropionate.

[5] W. E. Doering and L. K. Levy, *J. Am. Chem. Soc.*, **77**, 509 (1955), allowed 2-hydroxymethyl-2-methyl-1,3-propanediol to react with ethyl orthoformate.

[6] Our results with the phosphorus esters were generally similar to those which have been reported independently by J. G. Verkade and L. T. Reynolds, *J. Org. Chem.*, **25**, 663 (1960) and by W. S. Wadsworth and W. D. Emmons, Abstracts 138th Meeting, ACS, New York, p. 97P.