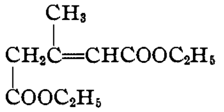
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Use of Methylallyl Chloride in the Synthesis of Compounds with Conjugate Unsaturation

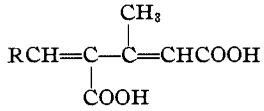
BY CHARLES D. HURD AND JOHN LEO ABERNETHY

Satisfactory methods of synthesis of systems containing conjugate unsaturation are not numerous and this lack of good methods is still more noticeable when a branched chain skeleton of the isoprene type is to be incorporated in the synthesis. Condensation of β-methylglutaconic ester



$$\underset{COOC_2H_5}{CH_2}\overset{CH_3}{C}=CHCOOC_2H_5$$

with an aldehyde so as to form a substituted isoprenedicarboxylic acid

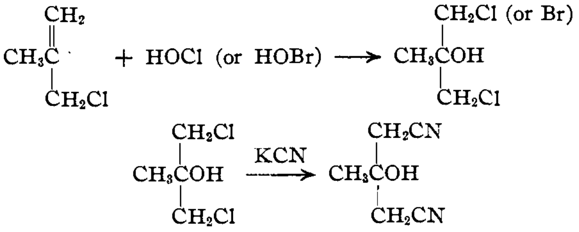


$$RCH=\underset{COOH}{C}-\overset{CH_3}{C}=CHCOOH$$

suggested itself as a feasible approach to this problem.

Ethyl β-methylglutaconate is not new but previous syntheses[1] of it have been tedious and have given very low yields. The present paper describes a convenient new synthesis of it starting with methylallyl chloride.

The first step is conversion of methylallyl chloride to its chlorohydrin or bromohydrin, following which there is reaction with potassium cyanide.

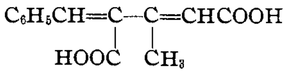


$$CH_3\underset{CH_2Cl}{\overset{CH_2}{\overset{\|}{C}}} + HOCl\text{ (or HOBr)} \longrightarrow CH_3\underset{CH_2Cl}{\overset{CH_2Cl\text{ (or Br)}}{C}}OH$$

$$CH_3\underset{CH_2Cl}{\overset{CH_2Cl}{C}}OH \xrightarrow{KCN} CH_3\underset{CH_2CN}{\overset{CH_2CN}{C}}OH$$

The 1,3-dicyano-2-methyl-2-propanol was a viscous oil which was changed at once to the hydroxy ester, $CH_3\underset{OH}{C}(CH_2COOC_2H_5)_2$, by alcoholysis. Distillation of the latter in the presence of a crystal of iodine caused dehydration to the desired ethyl β-methylglutaconate.

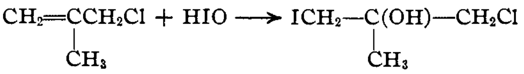
Condensation of the latter with benzaldehyde in the presence of alcoholic potash yielded potassium α-benzal-β-methylglutaconate from which α-benzal-β-methylglutaconic acid



$$C_6H_5CH=\underset{HOOC}{C}-\underset{CH_3}{C}=CHCOOH$$

was readily prepared. By use of β-cyclocitral in place of benzaldehyde this opens up a new route to the carotenoids and Vitamin A.

Since both the chlorohydrin and bromohydrin of methylallyl chloride were prepared the iodohydrin was synthesized also to complete the list. It was made by adding iodine to a mixture of methylallyl chloride, ether, water, and mercuric oxide.



$$CH_2=\underset{CH_3}{C}CH_2Cl + HIO \longrightarrow ICH_2-\underset{CH_3}{C}(OH)-CH_2Cl$$

All three halohydrins were liquids.

Experimental Part

1,3-Dichloro-2-methyl-2-propanol.—A generous supply of methylallyl chloride was furnished us for this work by Shell Development Company. It was redistilled before use, the fraction boiling at 73–74° being taken.

Hypochlorous acid was made by passing chlorine into a cold mixture of 25 g. of mercuric chloride, 180 g. of sodium hydroxide, 1800 g. of ice and water according to directions of Coleman and Johnstone.[2] After the precipitate of mercuric oxide just disappeared 600 cc. of cold 1.5 *N* nitric acid was stirred in slowly. To this solution 135 g. (1.5 moles) of methylallyl chloride (b. p. 73–74°) was added during fifteen minutes while the temperature was kept below 5°. Then the mixture was given vigorous mechanical shaking for ninety minutes. The two layers were separated and the aqueous layer twice extracted with 500-cc. portions of ether. After drying with sodium sulfate and removal of the ether the product was fractionated under reduced pressure. About 52 cc. was collected below 71° (23 mm.), then 71 g. of the desired dichloromethylpropanol was collected at 72–73° (23 mm.). This is a 30% yield. Also, there was 23 g. which boiled between 74–80° (23 mm.).

Anal. Calcd. for $C_4H_8Cl_2O$: Cl, 49.5. Found: Cl. 50.1.

1-Chloro-3-bromo-2-methyl-2-propanol.—A solution of 320 g. of bromine (2 moles) dissolved in water containing 140 g. of potassium bromide was added dropwise during four hours to a mixture of 190 g. (2.1 moles) of freshly distilled methylallyl chloride (b. p. 73–74°) in one liter of water. Vigorous stirring was maintained throughout

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[1] Feist, *Ann.*, **345**, 89 (1906); Bland and Thorpe, *J. Chem. Soc.*, **101**, 865, 1557 (1912); Jordan and Thorpe, *ibid.*, **107**, 388 (1918).

[2] Coleman and Johnstone, "Organic Syntheses," Collective Vol. 1, John Wiley and Sons, New York, N. Y., 1932, p. 151.

and the addition was slow enough for the mixture to remain at room temperature. The bromohydrin layer was separated and the aqueous layer was extracted once with ether. The extract was added to the bromohydrin and the whole was dried over anhydrous sodium sulfate. The ether was removed and the colorless residue was distilled at 20 mm. Only 1.5 g. was collected up to 84°, then 365 g. of product distilled at 84–86°, most of it coming over at 84–85°; yield, 97.5%; n^{20}_{D} 1.5171, d^{20}_{20} 1.7578. Mr. H. E. Winberg assisted in this synthesis.

Anal. Calcd. for C_4H_8BrClO: total halogen, 0.01066 equiv. per g. Found: halogen, 0.0107, 0.0108.

1-Chloro-3-iodo-2-methyl-2-propanol.—Methylallyl chloride (45 g.) was diluted with 150 cc. of ether. To this solution was added 8 cc. of water and 55 g. of yellow mercuric oxide. The resulting mixture was stirred vigorously as 124 g. of iodine was added. This took thirty minutes and the resulting mixture was stirred for five hours longer. At the end of this time the solution was filtered to remove the solid suspended matter. Then it was shaken in a separatory funnel with sodium thiosulfate solution to remove the excess iodine. The ether layer was separated and dried over anhydrous magnesium sulfate. The ether was removed under reduced pressure and the iodohydrin was fractionated. About 18 g. of the iodohydrin was obtained at 101–103° and 18 mm. The product assumed an orange color on distillation, evidently due to slight decomposition. After clarification with thiosulfate and drying it was redistilled at 7 mm. but the orange colored distillate was obtained again. Its index of refraction, n^{20}_{D}, was 1.547.

Anal. Calcd. for C_4H_8ClIO: total halogen, 0.00853 equiv. per g. Found: halogen, 0.00861 equiv. per g.

1,3-Dicyano-2-methyl-2-propanol.—A 25-g. portion of 1,3-dichloro-2-methyl-2-propanol was added to 100 cc. of methyl alcohol in a round-bottom flask fitted with a reflux condenser and a dropping funnel. The solution was refluxed on a water-bath during the addition of 20 g. of potassium cyanide in 30 cc. of water. The potassium cyanide was added dropwise over a period of thirty minutes. Then the solution was refluxed for a period of forty-eight hours. A dark brown solution resulted. It was cooled and the solid material, potassium chloride and unreacted potassium cyanide, was removed by filtration. Then the methyl alcohol and water was removed under reduced pressure and the brown sludge was extracted with three 250-cc. portions of ether. The ether was removed on the steam-bath and the brown oil, the dicyano compound, was used directly in the next synthesis. Attempts to purify the nitrile by vacuum distillation led only to decomposition and polymerization.

Ethyl β-Methylglutaconate.—The brown oil mentioned above was dissolved in 300 cc. of absolute alcohol and it was then saturated with dry hydrogen chloride and allowed to stand at room temperature for ten hours. This was followed by refluxing for twelve hours. The resulting solution was allowed to cool, after which the ammonium salts were removed by filtration. The alcohol was removed under reduced pressure and the resulting brown oil was extracted with two 150-cc. portions of ether and the ethereal solution was dried over anhydrous sodium sulfate. Removal of the ether on the steam-bath was followed by distillation under reduced pressure, after first adding a crystal of iodine. About 9 cc. of ethyl β-methylglutaconate was obtained as a light yellow oil. It distilled at 129–133° at 18 mm. pressure (recorded value,[3] 131° at 19 mm.). Three cc. of an unidentified higher-boiling material was obtained at 133–152°, which solidified to a considerable extent on being cooled to room temperature. Tar remained in the flask.

When 15 cc. of concentrated sulfuric acid was used instead of dry hydrogen chloride the results were about the same except that there seemed to be somewhat more tarry material in the flask on distillation.

α-Benzal-β-methylglutaconic Acid.—A mixture of 5 g. of potassium hydroxide in 200 cc. of methyl alcohol was added to a mixture of 10 g. of ethyl β-methylglutaconate and 4.8 g. of benzaldehyde. Slight warming of the solution was noticed. It was allowed to stand for forty-eight hours, during which time the solution became a deep orange color.

The mixture was evaporated to 25 cc. under reduced pressure and the resulting brown solution was cooled by a freezing mixture. Crystals of potassium α-benzal-β-methylglutaconate were formed, which were filtered off, the solution further evaporated to obtain more crystals and the combined crystals were washed with 25 cc. of ether.

The light brown crystalline mass was acidified with an excess of dilute hydrochloric acid. The water was removed under reduced pressure on the steam-bath and the resulting material was extracted with three 50-cc. portions of acetone. On evaporation of the combined acetone solutions and recrystallization from acetone, about 3 g. of α-benzal-β-methylglutaconic acid was obtained. It softened at about 170° and turned brown and decomposed to a tarry substance at 175–200°.

Anal. Equiv. wt., calcd.: 116.05. Found: equiv. wt., 115.1, 114.5.

Summary

The three halohydrins of methylallyl chloride are described: 1,3-dichloro-2-methyl-2-propanol, 1-chloro-3-bromo-2-methyl-2-propanol, and 1-chloro-3-iodo-2-methyl-2-propanol. Conversion to 1,3-dicyano-2-methyl-2-propanol and alcoholysis of the latter provides a convenient synthesis of ethyl β-methylglutaconate.

Condensation of this ester with aldehydes yields substituted isoprenedicarboxylic acids. As a typical example, benzaldehyde yields α-benzal-β-methylglutaconic acid.

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[3] Auwers and Ottens, *Ber.*, **57**, 441 (1924).