[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MAINE]

Decarboxylation of α-Substituted Glycidic Acids

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Two previously unreported glycidic esters, ethyl α-*n*-butyl-α,β-epoxycyclohexylidene acetate and ethyl α-*n*-hexyl-α,β-epoxycyclohexylidene acetate have been prepared. Upon hydrolysis and decarboxylation they yielded the expected ketones, 1-cyclohexyl-1-pentanone and 1-cyclohexyl-1-heptanone. Small amounts of unidentified oxidizable materials were also formed which caused the pyrolysis products to give positive aldehyde color reactions.

Glycidic acids containing α-methyl or ethyl groups yield ketones on decarboxylation. One would expect other α-substituted glycidic acids to react similarly. However, Darzens[3] reported that aldehydes were obtained from the decarboxylation of several substituted glycidic acids containing α-*n*-decyl groups. It was stated that the pyrolysis products gave positive aldehyde color reactions and that a migration of the decyl group must have taken place during the decarboxylation, such that tertiary aldehydes were formed. Thus, upon pyrolysis, α-*n*-decyl-α,β-epoxycyclohexylidene acetic acid gave 1-decylcyclohexane-1-carboxaldehyde instead of 1-cyclohexyl-1-undecanone.

It was of interest to determine whether aldehydes or ketones would result on decarboxylation of glycidic acids containing α-substituents intermediate between *n*-decyl and ethyl. Accordingly, the previously unreported glycidic esters, ethyl α-*n*-butyl-α,β-epoxycyclohexylidene acetate and ethyl α-*n*-hexyl-α,β-epoxycyclohexylidene acetate were prepared and hydrolyzed to the corresponding acids. Upon decarboxylation, both acids yielded products that decolorized permanganate solution, reduced Tollens reagent, and gave positive Schiff tests. It has been shown by alternate syntheses, however, that the principal products of decarboxylation were the expected ketones, 1-cyclohexyl-1-pentanone and 1-cyclohexyl-1-heptanone. The positive aldehyde color reactions must be attributed to small amounts (10% or less) of unidentified by-products.

The glycidic esters were prepared by the condensation of cyclohexanone with ethyl α-bromocaproate and ethyl α-bromocaprylate, respectively. Freshly prepared sodium ethoxide was used as the condensing agent. It has been found that a period of heating after the initial reaction period is essential to ensure a yield of the glycidic ester. When this period of heating was omitted, the reaction product gave a positive halogen test and gave a mixture of products after hydrolysis and decarboxylation.

The glycidic esters were hydrolyzed with alcoholic potassium hydroxide, and the crude acids were decarboxylated without purification by heating them at reduced or atmospheric pressure until decarboxylation was complete. The resultant products were then fractionated under reduced pressure.

To verify the structures of the pyrolysis products, the following ketones were synthesized by alternate methods. Using a modification of a procedure by Nenitzescu and Cioranescu,[4] 1-cyclohexyl-1-pentanone was prepared by the acylation of cyclohexene with valeryl chloride in the presence of aluminum chloride and cyclohexane. While 1-cyclohexyl-1-heptanone was prepared by the condensation of di-*n*-hexylcadmium and cyclohexane carboxyl chloride, following a procedure given by Cason.[5] In both cases, the predicted ketone gave a 2,4-dinitrophenylhydrazone having the same melting point as the similar derivative of the pyrolsis product. Mixed melting points were also the same.

Further work in this field is being continued by Mr. Morris.

Experimental

Preparation of Intermediates.—The α-bromo esters were prepared by the Hell–Volhard–Zelinsky reaction and purified by fractionation through a 10-in. Widmer column. Technical grade cyclohexanone was redistilled before use. All reagents were carefully dried over calcium chloride. The sodium ethoxide, just before use, was heated for one hour on an oil-bath at 180–190° while under a reduced pressure of 5 mm. in order to remove as much alcohol as possible.

Ethyl α-*n*-Butyl-α,β-epoxycyclohexylidene Acetate.—A 2-l. 3-necked flask was equipped with gas inlet and outlet tubes, a mercury-sealed stirrer, and a 12-in. length of large diameter rubber tubing which had been attached to a 125-ml. erlenmeyer flask. The system was swept dry with a stream of nitrogen, and kept under a blanket of nitrogen throughout the reaction. Into the flask was added a solution of 157 g. (1.6 moles) of cyclohexanone, 300 ml. of absolute ether and 223 g. (1 mole) of ethyl α-bromocaproate. While the flask was cooled in an ice–salt bath, 109 g. (1.6 moles) of freshly prepared sodium ethoxide was added from the erlenmeyer flask to the vigorously stirred solution over a period of 1.5 hours. The reaction mixture was then packed in ice and stirred under nitrogen for 18 hours. The ether was slowly removed on a steam-bath, and the residue was heated for 1.5 hours. After cooling, a solution of 10 ml. of acetic acid in 200 ml. of ice-water was added, and the resulting product was extracted with 500 ml. of ether. The ether solution was washed twice with 100-ml. portions of water, and successively with 100-ml. portions of saturated sodium bicarbonate solution, water and saturated sodium chloride solution. It was then dried over anhydrous sodium sulfate, and the ether was removed on a steam-bath, leaving a red-brown, viscous oil. Vacuum distillation of the oil gave approximately 130 g. of a material having a boiling point range of 100–132° (3 mm.). Fractionation, using a Todd precise fractionating assembly which was operated at a reflux ratio of 5:1, gave 110 g. (46% yield) of a colorless, rather viscous liquid boiling at 160° (18 mm.) (126° at 2 mm.), with the following constants: $n^{20}D$ 1.4606, d^{t}_{4} 20°, 0.9907, 25°, 0.9862; 30°, 0.9825; 35°, 0.9787; 40°, 0.9747.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 69.97; H, 10.07; sapon. equiv., 241; *MR*, 66.52. Found: C, 70.33; H, 9.69; sapon. equiv., 243 ± 3; *MR*, 66.46.

When the sodium bicarbonate wash was acidified with

(1) Shell Oil Company, Wood River, Illinois.

(2) From the thesis submitted by H. H. Morris in partial fulfillment of the requirements of the degree of Master of Science in Chemistry, June, 1952.

(3) G. Darzens, *Compt. rend.*, **195**, 884 (1932).

(4) C. D. Nenitzescu and E. Cioranescu, *Ber.*, **69**, 1820 (1936).

(5) J. Cason, THIS JOURNAL, **68**, 2078 (1946).

hydrochloric acid, an oil separated which appeared to be the glycidic acid.

Ethyl α-n-Hexyl-α,β-epoxycyclohexylidene Acetate.—This ester was prepared in the manner described above, using 251.2 g. (1.0 mole) of ethyl α-bromo-n-caprylate, 157 g. (1.6 moles) of cyclohexanone and 109 g. (1.6 moles) of freshly prepared sodium ethoxide. The viscous, colorless product was obtained in 43–48% yield by fractionation through the Todd column mentioned above. The physical constants are: b.p. 151° (2 mm.); $n^{20}D$ 1.4619; d^t_4 20°, 0.9741; 25°, 0.9699; 30°, 0.9659; 35°, 0.9620; 40°, 0.9581.

Anal. Calcd. for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52; *MR*, 75.62. Found: C, 71.72; H, 10.33; *MR*, 75.72.

When the sodium bicarbonate wash was acidified, an amorphous yellow solid precipitated. This compound was dissolved in ether and later could not be induced to crystallize. It appeared to be the glycidic acid, since on distillation it decarboxylated to yield a product with the same physical constants as the product from the hydrolysis and decarboxylation of the glycidic ester.

Effect of Heat in the Preparation of Ethyl α-n-Butyl-α,β-epoxycyclohexylidene Acetate.—The effect of heating the product after the initial 18-hour reaction period is shown below.

TABLE I

Conditions	Beilstein Test	B.p. °C.	B.p. Mm.	Refractive index
Run 1, No heat	Positive	153	13	$n^{20}D$ 1.4705
Run 2, 50°, 0.5 hr.	Positive	112	1	$n^{21}D$ 1.4605
Run 3, 100°, 1.5 hr.	Negative	126	2	$n^{20}D$ 1.4606

The products from the first two runs showed signs of decomposition during distillation, although colorless cuts were obtained. The material from run 2 gave positive halogen tests even though it was repeatedly washed and distilled. All products could be saponified, but only the product from run 3 gave a saponification equivalent corresponding to the glycidic ester, ethyl n-butyl-α,β-epoxycyclohexylidene acetate. Only the acid from run 3 gave identifiable products on decarboxylation and distillation.

1-Cyclohexyl-1-pentanone. (a) From the Hydrolysis of Ethyl α-n-Butyl-α,β-epoxycyclohexylidene Acetate and Decarboxylation of the Resultant Glycidic Acid.—To a solution of 7 g. of KOH in 100 ml. of water and 60 ml. of 95% ethanol was added 23.5 g. of ethyl α-n-butyl-α,β-epoxycyclohexylidene acetate, and the mixture was refluxed for four hours. After cooling, the reaction mixture was poured into a slurry of ice and concd. HCl, whereupon a yellow, agglutinous solid separated. The mixture was extracted with three 50-ml. portions of ether. These portions were combined and washed once with 150 ml. of water and once with 50 ml. of saturated NaCl solution. After drying over anhydrous Na_2SO_4, the ether was removed on a steam-bath, leaving 15.3 g. of the crude glycidic acid.

A 15.1-g. sample of the crude acid was placed in a flask equipped with a 10-inch Vigreux column and heated at 3 mm. pressure. On heating, vigorous ebullition took place, and a white fog was observed throughout the system. However, no liquid distilled. After evidence of decarboxylation had ceased (two to three hours), the temperature was raised, and the decarboxylation product was allowed to distil slowly, yielding 5.6 g. of a crude ketone and 4.0 g. of higher boiling material. The higher boiling fraction on redistillation at atmospheric pressure gave an additional gram of the ketone. On fractionation, using a 10-in. Vigreux column, 4.5 g. (38% yield) of product boiling at 85–86° (3 mm.) was obtained. The physical constants are $n^{20}D$ 1.4556; d^t_4 20°, 0.894; 25°, 0.889; 30°, 0.886; 35°, 0.882; 40°, 0.879.

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.52; H, 11.98; *MR*, 50.83. Found: C, 78.62; H, 11.89; *MR*, 51.12.

The compound formed a 2,4-dinitrophenylhydrazone (bright orange clusters) which melted at 70–71° after three recrystallizations from ethanol.

Anal. Calcd. for $C_{17}H_{24}N_4O_4$: N, 16.08. Found: N, 15.94.

The compound formed a semicarbazone melting at 161° after three recrystallizations from 50% ethanol.

Mixed melting points with the corresponding derivatives of the ketone prepared by method (b) below showed no depression.

Although the decarboxylation product was principally 1-cyclohexyl-1-pentanone, it gave a positive Schiff test, reduced Tollens reagent, and decolorized dilute permanganate solution. When it was treated with saturated permanganate at room temperature, however, only a small portion of the product was oxidized (less than 10%). The residue gave a 2,4-dinitrophenylhydrazone which melted at 70–71° after two recrystallizations from ethanol. The trace of oxidized product was not isolated.

(b) From the Acylation of Cyclohexene with Valeryl Chloride.—This alternate synthesis is an adaptation of the procedure developed by Nenitzescu and Cioranescu.[4]

One mole (82.1 g.) of cyclohexene, 1.84 moles (154 g.) of cyclohexane and one mole (120.5 g.) of valeryl chloride were placed in a 1-liter, 3-necked flask equipped with a stirrer, a condenser with an attached gas absorption tube, and a large diameter rubber tube connected to a 125-ml. erlenmeyer flask in which was placed 2 moles (276 g.) of anhydrous aluminum chloride. The mixture was cooled to 0° by means of an ice–salt bath, and the $AlCl_3$ was added slowly, in small portions. After the addition was completed, the temperature was slowly raised to 70° and held at this temperature until the evolution of HCl ceased (2–3 hours). The cooled mixture was then poured slowly, with stirring, into a beaker containing 600 g. of ice and 200 cc. of concentrated hydrochloric acid. The organic layer was separated and dissolved in ether. This solution was washed successively with water, 10% sodium carbonate, and again with water. It was then dried over anhydrous sodium sulfate. The ether was removed on a steam-bath, and the residue was fractionated through a 10-in. Vigreux column at reduced pressure. The product boiling at 98–104° (3 mm.) (42 g., 25% yield) gave a 2,4-dinitrophenylhydrazone melting at 70.5° after three recrystallizations from ethanol and a semicarbazone melting at 161° after three recrystallizations from 50% ethanol. As mentioned previously, mixed melting points with the corresponding derivatives of the compound prepared by method (a) showed no depression.

1-Cyclohexyl-1-heptanone. (a) From the Hydrolysis of Ethyl α-n-Hexyl-α,β-epoxycyclohexylidene Acetate and Decarboxylation of the Resultant Glycidic Acid.—Using the same procedure as for the hydrolysis of ethyl n-butyl epoxycyclohexylidene acetate, 51 g. of ethyl α-n-hexyl-α,β-epoxycyclohexylidene acetate was hydrolyzed to give 37 g. of the crude glycidic acid.

A 34-g. sample of the crude acid was placed in a flask equipped with a 10-in. Vigreux column and heated under atmospheric pressure until evidence of decarboxylation had ceased. It was then fractionated under reduced pressure using a 10-in. Widmer column. The yield was 16.4 g. (61%). The product had the following physical constants: b.p. 109–110° (1 mm.); $n^{20}D$ 1.4560; d^t_4 20°, 0.8878; 25°, 0.8827; 30°, 0.8790; 35°, 0.8750; 40°, 0.8716.

Anal. Calcd. for $C_{13}H_{24}O$: C, 79.52; H, 12.33; *MR*, 60.07. Found: C, 79.54; H, 12.25; *MR*, 60.56.

The material gave a 2,4-dinitrophenylhydrazone melting at 64° after three recrystallizations from ethanol.

Anal. Calcd. for $C_{29}H_{28}N_4O_4$: N, 14.88. Found: N, 14.41.

A mixed melting point of this derivative and the 2,4-dinitrophenylhydrazone of the ketone prepared by method (b) below showed no depression.

The decarboxylation product gave a positive Schiff test and reduced Tollens reagent. It formed a bisulfite addition product and decolorized dilute permanganate solution.

To determine the extent of the by-product, the material was subjected to the following oxidation. A suspension of 10 g. of the purified decarboxylation product from α-n-hexyl-α,β-epoxycyclohexylideneacetic acid in 100 ml. of water was stirred vigorously with 400 ml. of saturated $KMnO_4$ solution for one hour. The mixture was then acidified with dilute H_2SO_4 and treated with saturated $NaHSO_3$ solution until no color remained. This mixture was extracted three times with ether. The extracts were combined and washed twice with water, three times with 10% NaOH, once more with water, and dried over anhydrous Na_2SO_4. Removal of the ether left a residue of unoxidized material weighing 8.8 g. This product gave a 2,4-dinitrophenylhydrazone melting at 63° after two recrystallizations from ethanol. The NaOH washes were combined, acidified and extracted with ether. Upon evaporation of the ether, 0.9 g. of a wax-like substance was obtained. This product was not identified.

(b) **From the Condensation of Di-*n*-hexylcadmium and Cyclohexanecarboxyl Chloride.**—This alternate synthesis is a modification of a procedure reported by Cason.[5]

To the Grignard reagent prepared from 82.5 g. (0.5 mole) of *n*-hexyl bromide and 12.2 g. (0.5 mole) of magnesium was added, over a 5-minute period, 45.9 g. (0.25 mole) of $CdCl_2$ and the mixture was stirred under reflux for one hour. The ether was removed by distillation, and 100 ml. of benzene was added. Another 15 ml. of distillate was removed, and 200 ml. of benzene was added. The stirred solution was heated to boiling, and 73.3 g. (0.5 mole) of cyclohexanecarboxyl chloride was added as fast as the exothermic reaction would permit (5–10 minutes). The mixture was stirred for one hour and poured into a slurry of ice and dilute H_2SO_4. The benzene and water layers were separated, and the water layer was extracted three times with benzene. The benzene portions were combined and the product was washed successively with water, saturated Na_2CO_3 solution, water and saturated NaCl solution. It was then dried by filtration through anhydrous Na_2SO_4. Distillation through a 10-in. Vigreux column gave 26 g. of material boiling 110–116° at 3 mm. A 2,4-dinitrophenylhydrazone from the material melted at 63.5° after two recrystallizations from ethanol. As mentioned before, a mixed melting point of this derivative and the 2,4-dinitrophenylhydrazone of the ketone prepared by method (a) showed no depression.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Synthesis of Higher Aliphatic α,ω-Dicarboxylic Acids[1]

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A general synthetic procedure has been developed for the preparation of higher α,ω-dicarboxylic acids. The method involves the reaction between half ester acid chlorides of certain lower α,ω-dicarboxylic acids and the cadmium reagents formed from α,ω-dibromoalkanes to yield long chain diketodiesters. The final product is obtained by saponification of the diketodiester and subsequent reduction of both carbonyl groups. The acids from C_{14} through C_{22} have been prepared.

The aliphatic α,ω-dicarboxylic acids having more than ten carbon atoms are not readily accessible. In general, three synthetic methods have been employed for their preparation.

The first two methods require the use of an α,ω-dibromoalkane which can be prepared by the reduction of the corresponding α,ω-dicarboxylic acid ester to the diol followed by treatment with hydrogen bromide. Further treatment of the α,ω-dibromoalkane with potassium cyanide followed by hydrolysis leads to an α,ω-dicarboxylic acid having two more carbon atoms than the parent compound[2]; treatment, instead, with diethyl sodiomalonate and subsequent saponification and decarboxylation leads to an α,ω-dicarboxylic acid having four more carbon atoms than the parent compound.[3,4] These methods can be repeated again and again to build chains of considerable length. However, such processes are tedious and inefficient.

The third general method, known as the Crum Brown–Walker reaction, is the electrolytic coupling between two molecules of a half ester metal salt of an α,ω-dicarboxylic acid with the elimination of two molecules of carbon dioxide.[5,6] Usually only acids containing an even number of carbon atoms can be prepared in this way.

Recently, a fourth method has been disclosed which utilizes the condensation between 2,6-dimethoxyphenyllithium and α,ω-dibromoalkanes followed by demethylation, treatment with sodium amalgam to open the ring and reduction of the carbonyl groups to give α,ω-dicarboxylic acids in low over-all yield.[7]

This paper describes a new method for preparing higher aliphatic α,ω-dicarboxylic acids containing from fourteen to twenty-two carbon atoms.

The most effective method found involved the reaction between an α,ω-alkylene cadmium compound and a half ester acid chloride to yield a diketodiester. Subsequent saponification and reduction of the carbonyl groups of the diketodicarboxylic acid by means of the Wolff–Kishner reaction yielded the α,ω-dicarboxylic acid.

$$[\text{-Cd}(CH_2)_m\text{-}] + 2\text{ROOC}(CH_2)_n\text{COCl} \xrightarrow{\text{benzene}} \text{ROOC}(CH_2)_n\text{CO}(CH_2)_m\text{CO}(CH_2)_n\text{COOR}$$

This approach is an extension of the reaction between dialkyl cadmium compounds and half ester acid chlorides.[8]

For most practical purposes terminal bifunctional aliphatic compounds are limited to those having ten or less carbon atoms. Granting this restriction any single coupling reaction involving two molecules would be limited to the preparation of compounds having a maximum of twenty carbon atoms. In addition, single coupling usually leads to the formation of compounds with an even number of carbon atoms.

By achieving a simultaneous two-way coupling with three molecules (A + B + A → ABA), a method became available for the preparation of higher homologs through to the C_{30} compound inclusive.

Work done on the preparation of di-Grignard reagents by earlier investigators[3,9–11] indicated that

(1) Taken from the thesis of A. Kreuchunas, submitted in partial fulfillment of the requirements for the Ph.D. Degree at the Massachusetts Institute of Technology, June, 1950.

(2) P. Chuit and J. Hausser, *Helv. Chim. Acta*, **12**, 850 (1929).

(3) P. Chuit, *ibid.*, **9**, 264 (1926).

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(8) J. Cason, *Chem. Revs.*, **40**, 15 (1947).

(9) S. Hilpert and G. Gruttner, *Ber.*, **47**, 177 (1914).

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(11) R. Brown and W. E. Jones, *J. Chem. Soc.*, 781 (1946).