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α,α-Difluoroglutaric Acid

By A. L. Barney and T. L. Cairns

An unusual hydrolytic ring scission has been observed in studies of the highly fluorinated cyclobutane derivatives described in recent publications from this Laboratory.[1,2] These cyclobutane compounds are obtained by the 1:1 addition of either tetrafluoroethylene or chlorotrifluoroethylene to unsaturated compounds generally.

Although 2,2,3,3-tetrafluorocyclobutanecarboxylic acid was readily isolated from the nitric acid oxidation of the corresponding 1-vinyl compound or from the acid hydrolysis of the corresponding nitrile[1] (II), only a water-soluble dibasic acid, identified as α,α-difluoroglutaric acid (III), has been obtained from the alkaline hydrolysis of 2,2,3,3-tetrafluorocyclobutanecarbonitrile (II). The same dibasic acid was isolated from hydrolysates of 2-chloro-2,3,3-trifluorocyclobutanecarbonitrile (I) and was more readily obtained by heating a mixture of acrylonitrile, chlorotrifluoroethylene and water. The transformations involved in these reactions and the structure of the dibasic acid are indicated in Fig. 1. This series of reactions coincidentally proves the structure of the acrylonitrile/chlorotrifluoroethylene reaction product to be that indicated (I), and not the isomeric 3-chloro-2,2,3-trifluorocyclobutanecarbonitrile.

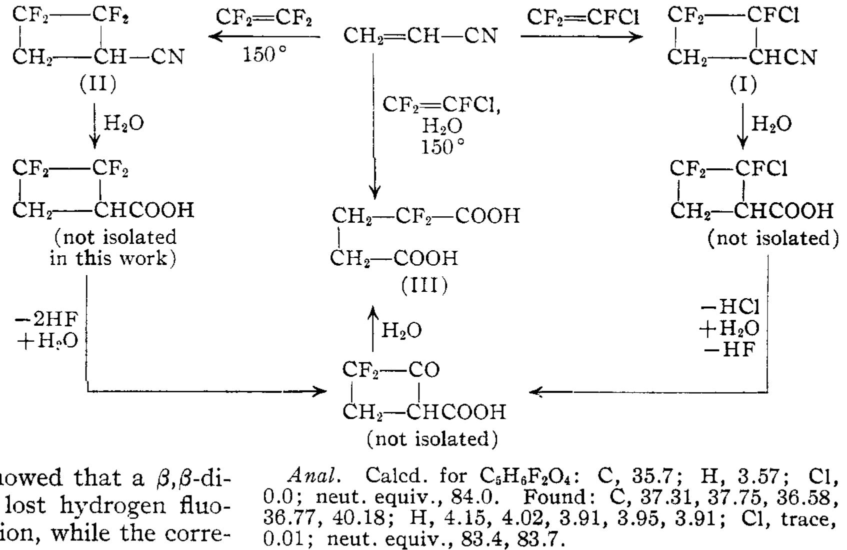
Analyses of the acid (III) and derivatives are in agreement with values calculated for the structures postulated. Qualitative tests for unsaturation were negative. Assignment of the position of the fluorine atoms is based on their stability toward aqueous alkali. Henne and Zimmerscheid[3] showed that a β,β-difluorocarboxylic acid readily lost hydrogen fluoride in aqueous alkaline solution, while the corresponding α,α-difluoro acid was relatively stable.

Also shown in Fig. 1 is a plausible mechanism for the observed ring scission involving normal hydrolysis of the nitrile to a carboxylic acid, hydrolytic loss of the halogen atoms from the beta-carbon atom, and "acid" splitting of the resulting keto acid.

Experimental Details

1. **Preparation of α,α-Difluoroglutaric Acid.**—One hundred grams of acrylonitrile, 100 ml. of distilled water, 1 g. of hydroquinone and 50 g. of chlorotrifluoroethylene were heated for eight hours at 150° and autogenous pressure in a vigorously shaken, silver-lined pressure vessel. The reactor was cooled to room temperature, unreacted chlorotrifluoroethylene vented, and the resulting two-phase liquid product steam distilled. The organic portion of the distillate was separated from the aqueous layer, the latter was extracted once with about 25 ml. of ether, and the extract combined with the organic layer. After drying and removal of solvent, 68 ml. of acrylonitrile was recovered by distillation. There was no more than a trace of higher boiling product. The non-volatile aqueous solution from the steam distillation, already acid to litmus, was further acidified with dilute hydrochloric acid and extracted eight times with 50-ml. portions of ether. The combined ether extracts were dried over sodium sulfate and evaporated to dryness. Thirty-nine grams of crude acid, m. p. 62–78°, was obtained. The material was very soluble in oxygenated solvents such as ether, ethanol, acetone, ethyl acetate and water, and in chloroform, but only slightly soluble in hydrocarbon solvents. A sample was crystallized from hot toluene (about 20 ml. per gram), which gave an excellent separation from dark colored impurities in the crude. The recrystallized product melted at 103–105°.

Fig. 1.



Anal. Calcd. for $C_5H_6F_2O_4$: C, 35.7; H, 3.57; Cl, 0.0; neut. equiv., 84.0. Found: C, 37.31, 37.75, 36.58, 36.77, 40.18; H, 4.15, 4.02, 3.91, 3.95, 3.91; Cl, trace, 0.01; neut. equiv., 83.4, 83.7.

The erratic carbon analyses are believed to result from incomplete removal of hydrogen fluoride from the combustion train.

For further identification, the acid was converted to its ethyl ester in the usual manner using *p*-toluenesulfonic acid as an esterification catalyst and benzene as an entraining agent. From 9 g. of crude acid, 6 g. of diethyl ester, b. p. 127–128° (28 mm.) was obtained. Mechanical losses were primarily responsible for the relatively low yield.

Anal. Calcd. for $C_9H_{14}F_2O_4$: C, 48.2; H, 6.25; F, 17.0; sapon. equiv., 112. Found: C, 48.93, 48.86; H, 6.33, 6.39; F, 18.4, 18.2; sapon. equiv., 111, 111.

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[1] D. D. Coffman, P. L. Barrick, R. D. Cramer and M. S. Raasch, This Journal, **71**, 490 (1949).

[2] P. L. Barrick, U. S. Patent 2,462,345, February 22, 1949.

[3] Henne and Zimmerscheid, This Journal, **69**, 281 (1947).

2. **Preparation of α,α-Difluoroglutaric Acid by Hydrolysis of 2-Chloro-2,3,3-trifluorocyclobutanecarbonitrile.**—A mixture of 10 g. of 2-chloro-2,3,3-trifluorocyclobutanecarbonitrile (I), b. p. 164°, prepared by heating chlorotrifluoroethylene, acrylonitrile and a polymerization inhibitor for eight hours at 150° and autogenous pressure according to the general procedure of Barrick,[2] was heated with 50 ml. of concd. hydrochloric acid under reflux on a steam-bath overnight. Two liquid layers, both miscible with sodium hydroxide solution, were present at the end of this time. After being taken up in alkali the combined solutions were reacidified, but only a small amount of acid-insoluble material separated. The mixture was extracted five times with 50-ml. portions of ether, and the combined extracts were dried over sodium sulfate. After evaporation of the ether about 4 g. of crystals, m. p. 85–94°, was obtained. Recrystallization from hot toluene gave 2 g. of the dibasic acid previously described, identified by its melting point alone and in admixture with the sample described previously.

A mixture of 10 g. of the 2-chloro-2,3,3-trifluorocyclobutanecarbonitrile (I) with 50 g. of 20% aqueous sodium hydroxide solution darkened immediately with the liberation of ammonia and with a temperature rise from 25° to vigorous reflux. A dark solid formed. After standing overnight, the alkaline solution was filtered to remove the solid and the filtrate acidified with hydrochloric acid. The dark acid solution was extracted with five 50-ml. portions of ether, the extract dried, and the solvent removed. From the residual dark oil upon recrystallization from toluene, the same dibasic acid, identified by melting point alone and in admixture with a known sample, was obtained in low yield.

3. **Preparation of α,α-Difluoroglutaric Acid by Hydrolysis of 2,2,3,3-Tetrafluorocyclobutanecarbonitrile.**—Alkaline hydrolysis of 2,2,3,3-tetrafluorocyclobutanecarbonitrile (II), prepared by the method described in the literature,[1] with an equal weight of 25% sodium hydroxide solution for eight hours at reflux gave an isolated yield of recrystallized dibasic acid of about 30%. The purified product melted at 103–105° alone or in admixture with the acid from 2-chloro-2,3,3-trifluorocyclobutanecarbonitrile and showed agreement with the calculated values for fluorine content and neutral equivalent.

Anal. Calcd. for $C_5H_6F_2O_4$: F, 22.6; neut. equiv., 84.0. Found: F, 23.9, 24.1; neut. equiv., 84.5, 84.5.

The dimethyl ester, b. p. 65° (12 mm.), was prepared in 70% yield from the free acid and methanol with *p*-toluenesulfonic acid as a catalyst.[4]

Anal. Calcd. for $C_7H_{10}F_2O_4$: F, 19.4; sapon. equiv., 98. Found: F, 19.2, 19.0; sapon. equiv., 95.2, 96.6.

4. **Preparation of N-Octyl α,α-Difluoroglutaramic Acid, Methyl Ester.**[4]—A mixture of 20 g. of dimethyl difluoroglutarate, 14.2 g. of *n*-octylamine and 35 g. of toluene was heated for four hours with slow distillation of 3.8 g. of methanol and toluene. The vapor temperature rose from 63° to 79.5°. Further heating at reflux for 3.5 hours, after the addition of 0.5 g. of triethylamine hydrochloride, failed to produce any reduction in the distillation temperature. The reaction mixture was cooled, washed with water, dilute hydrochloric acid, dilute sodium bicarbonate solution and with water until neutral. After drying over sodium sulfate and removal of the solvent, the residual waxy solid was distilled at 172–180° (3.7 mm.). Twenty-five and eight-tenths grams of distillate, which crystallized to form shiny plates, m. p. 38–39.5°, was obtained. Analyses indicated the amic ester structure rather than the imide.

Anal. Calcd. for $C_{13}H_{21}F_2NO_2$ (imide): N, 5.33; mol. wt., 261. Calcd. for $C_{14}H_{25}F_2NO_3$ (amide ester): N, 4.77; mol. wt., 293. Found: N, 4.93, 4.90; mol. wt. (ebullioscopic in benzene), 289, 300.

Summary

A novel cleavage of a cyclobutane ring has been observed in the hydrolysis of tetrafluoro- and chlorotrifluorocyclobutanecarbonitriles to α,α-difluoroglutaric acid.

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(4) We are indebted to Dr. N. E. Searle and Mr. H. E. Cupery of this laboratory for the details of these experiments.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Studies on the Mechanism of Chugaev and Acetate Thermal Decompositions. II. *cis*- and *trans*-2-Methyl-1-tetralol

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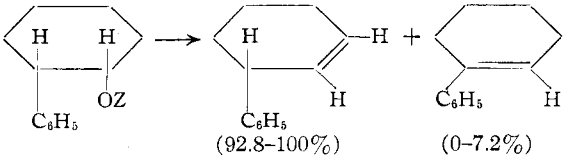
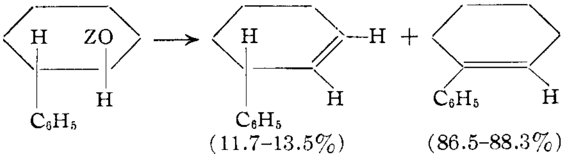
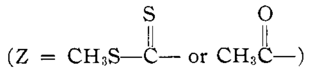
In an earlier communication[2] it was shown that Chugaev and acetate thermal decompositions of *cis*-2-phenylcyclohexanol lead predominantly to 3-phenylcyclohexene (Equation 1), whereas similar decompositions of the corresponding derivatives of the *trans*-alcohol lead principally to 1-phenylcyclohexene (Equation 2). This work supports the conclusion reached by other investigators[3] that in contrast to most elimination reactions, which appear to involve elements *trans* to each other, the Chugaev reaction proceeds with the preferential elimination of a *cis* hydrogen atom. Furthermore, it supports the suggestion that transitory six-membered rings are formed during Chugaev[3,4] and acetate[5] decompositions (Equation 3).



(1)



(2)



$$(Z = CH_3S\overset{\overset{\displaystyle S}{\|}}{C}— \text{ or } CH_3\overset{\overset{\displaystyle O}{\|}}{C}—)$$

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(1) Colgate-Palmolive-Peet Company, Jersey City, New Jersey.

(2) Alexander and Mudrak, THIS JOURNAL, **72**, 1810 (1950).

(3) Hückel, Tappe and Legutke, *Ann.*, **543**, 191 (1940).

(4) Stevens and Richmond, THIS JOURNAL, **63**, 3132 (1941).

(5) Hurd and Blunck, *ibid.*, **60**, 2421 (1938).