[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Stereochemistry of the Diels–Alder Reaction. I. 4,4,4-Trifluorocrotonic Acid as Dienophile[1]

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trans-4,4,4-Trifluorocrotonic acid is the sole product resulting from the dehydration and subsequent ester interchange of ethyl 3-hydroxy-4,4,4-trifluorobutyrate. *trans*-4,4,4-Trifluorocrotonic acid gives a 2:1 mixture of *exo* (II):*endo* (I) products with cyclopentadiene. Hydration of the mixture in 85% sulfuric acid gives a lactone III and a hydroxy acid V. Bromination of mixed I and II in bicarbonate solution at 0° gives a bromolactone VIII, a bromohydroxy acid X or XI, and a tricyclene product XII. Bromination in chloroform gave a dibromoacid XV and a bromolactone VIII. *trans*-4,4,4-Trifluorocrotonic acid reacts stereospecifically with furan to produce the *endo* adduct XVI, as shown by bromination in acidic or basic media to give lactone XVIII. The effect of the trifluoromethyl group in these reactions is discussed.

Discussion

Original reports of the stereospecificity of the Diels–Alder reaction[2] and the general rules for predicting its course are well known. That the *cis* addition may be modified to give mixed *endo* and *exo* products under specific conditions has been demonstrated by studies of several systems.[3,4]

In the case of furan, it was assumed[5] that the unshared electrons of the oxygen atom are comparable to olefinic unsaturation and thus effect steric control of the Diels–Alder synthesis. This investigation is concerned with the stereospecificity of the Diels–Alder reaction wherein the dienophile contains both olefinic and unshared electron systems. The results of a study of *trans*-4,4,4-trifluorocrotonic acid in the Diels–Alder reaction with cyclopentadiene and furan are presented herein.

The initial preparation of the 4,4,4-trifluorocrotonic acid[6] was repeated and it has been found that only the *trans* acid results from the dehydration and subsequent ester interchange of the ethyl 3-hydroxy-4,4,4-trifluorobutyrate. The infrared spectrum of the acid shows a strong *trans* —CH=CH— absorption at 10.3 μ (970 cm.$^{-1}$).[7]

Cyclopentadiene and *trans*-4,4,4-trifluorocrotonic acid react quantitatively to form a mixture of the *endo*, I, and *exo*, II, adducts. The mixture was uneffected by treatment under the usual hydration conditions, *i.e.*, 50% sulfuric acid,[8] but on treatment with 85% sulfuric acid at 25° for six hours, the mixed I and II was converted to a lactone III, and a hydroxy acid V. As noted in Fig. 1, III could have resulted from either I or II, and V could have resulted only from II. The type of rearrangement which would lead from II by way of a carbonium ion to VI and hence through VII to III has been reported.[8,9]

When the mixed I and II was treated with bromine in an aqueous sodium bicarbonate solution at 0°, there were obtained a bromolactone VIII, a bromohydroxy acid X or XI, and a bromotricyclene XII. Compound VIII is obtained from I; X or XI from II, and XII from the bromonium ion from II (Fig. 2). The structure of the bromolactone VIII was proved by saponification with sodium hydroxide; an epoxyacid IX resulted which could not be formed from the bromolactone XIII, derived from II through rearrangement. The infrared spectrum of XII is similar to that reported for nortricyclene[10] with bands at 12.3 to 12.5 μ (800–813 cm.$^{-1}$) specific for the parent hydrocarbon (Fig. 3). If XII was formed by the loss of carbon dioxide to form a carbanion, it could have arisen from either I or II. However, since the reaction was run at 0° in aqueous bicarbonate solution, this appears unreasonable. It is, therefore, suggested that a synchronous mechanism is involved; as carbon dioxide is lost from C_2 the carbonium ion at C_6 will simultaneously attack from the rear; on this basis XII is formed solely from II. If the intermediate carbonium ion is blocked by the hydroxyl ion, cyclization cannot occur and the hydroxy acid X will result.[11] The molar ratio of VIII:X or XI:XII was approximately 1:1:1. The ratio of I to II was therefore 1:2.

Recently Winternitz, Mousseron and Rouzier[12] described a method suitable for the determination of the percentage of *exo* and *endo* isomers. The mixed adduct I and II, under comparable conditions, gave a 33% yield of crude bromolactone VIII, and a 66% yield of crude dibromoacid XV. The compound XV was debrominated with zinc dust to give the *exo* adduct II; hence XV was derived from

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[1] Grateful acknowledgment is made to the Westinghouse Electric Corporation for their support of this work. Presented before the XIV International Congress of Pure and Applied Chemistry, July, 1955, Zurich, Switzerland.

[2] K. Adler and G. Stein, *Angew. Chem.*, **50**, 510 (1937).

[3] (a) R. B. Woodward and H. Baer, THIS JOURNAL, **66**, 645 (1944); (b) K. Alder and R. Rühemann, *Ann.*, **566**, 1 (1950); (c) K. Alder and W. Trimborn, *ibid.*, **566**, 58 (1950); (d) D. Craig, THIS JOURNAL, **73**, 4889 (1951).

[4] J. A. Berson and R. Swidler, *ibid.*, **75**, 1721 (1953), and subsequent papers.

[5] K. Alder and E. Windemuth, *Ber.*, **71**, 1939 (1938).

[6] E. T. McBee, O. R. Pierce and D. D. Smith, THIS JOURNAL, **76**, 3722 (1954).

[7] (a) R. G. Sinclair, *et al.*, *ibid.*, **74**, 2578 (1952); (b) N. K. Freeman, *ibid.*, **75**, 1859 (1953).

[8] K. Alder and G. Stein, *Ann.*, **514**, 1, 197 (1934).

[9] (a) O. Aschan, *Ber.*, **61**, 38 (1928); (b) K. Alder, F. W. Chambers and W. Trimborn, *Ann.*, **566**, 27 (1950); (c) R. C. Woodward and H. Baer, THIS JOURNAL, **70**, 1161 (1948).

[10] J. D. Roberts, *et al.*, *ibid.*, **72**, 3116 (1950).

[11] Subsequent to the completion of this work C. D. Ver Nooy and C. S. Rondestvedt, Jr., *ibid.*, **77**, 3583 (1955). reported that bromolactonization of cyclopentadiene–*trans*-cinnamic acid adducts was an inapplicable method for determining *endo-exo* adduct ratios because of the conversion of part of the *exo* adduct to neutral bromonortricyclenes. Discussion is included in the above reference of mechanisms for the tricyclene structure. In an additional article C. S. Rondestvedt, Jr., and C. D. Ver Nooy, *ibid.*, **77**, 4878 (1955), describe the use of an analytical method for determining iodolactonization *endo–exo* ratios which method was not used in this work.

[12] F. Winternitz, M. Mousseron and G. Rouzier, *Bull. soc. chim. France*, 170 (1955).

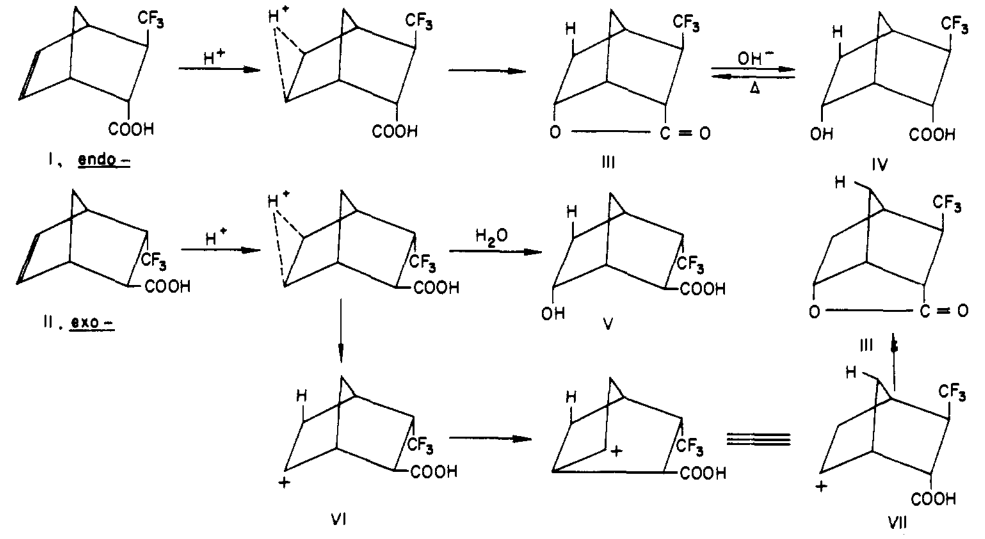

Fig. 1.

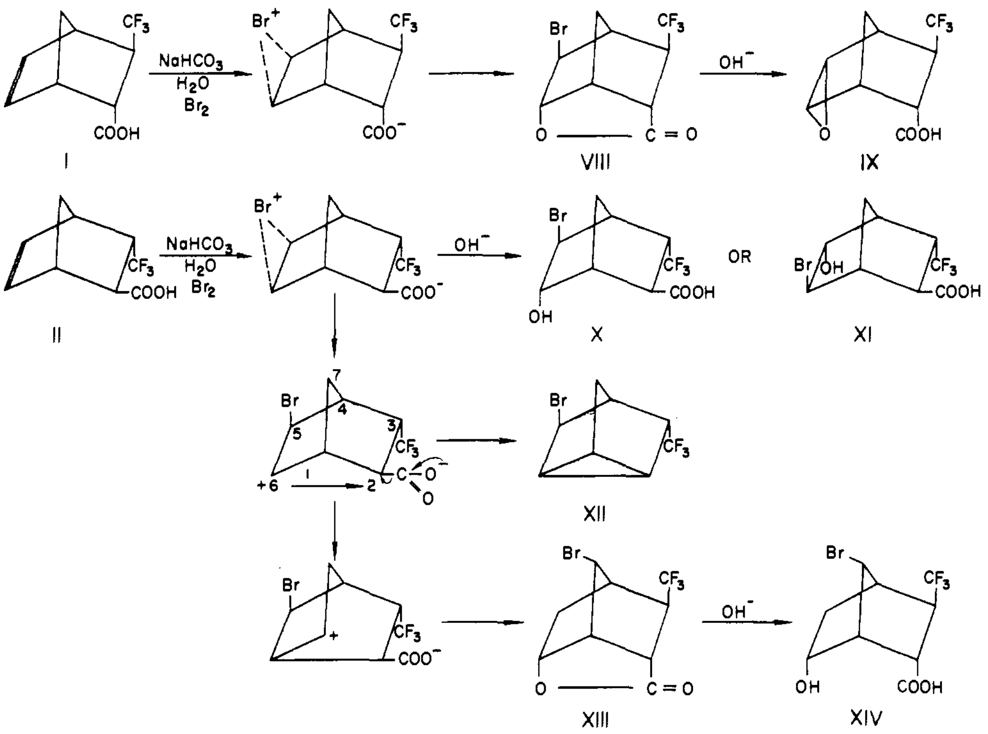

Fig. 2.

II. The *exo* configuration of this debrominated product was shown by bromination to the original dibromoacid XV.[13] If it were the *endo* adduct I, the bromolactone VIII would have been obtained. Therefore, the ratio of I to II in the mixed adduct was 1:2 is substantiated.

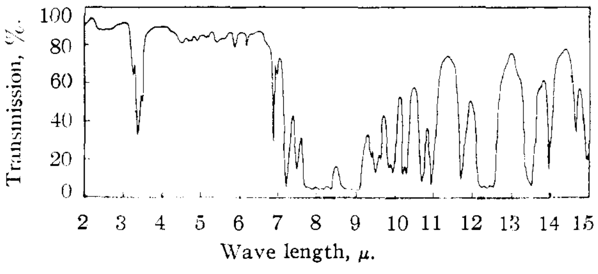

Fig. 3.—Infrared absorption spectrum of 5-bromo-3-trifluoromethylnortricyclene (X) (prism, NaCl; phase, liquid; thickness, 0.05 mm.).

In contrast to the mixed *endo-exo* adducts with cyclopentadiene, *trans*-4,4,4-trifluorocrotonic acid reacts with furan to give an 89% yield of the *endo* adduct XVI (Fig. 4). Bromination of XVI in an aqueous sodium bicarbonate solution gave a 95% yield of a lactone XVIII; the same product was ob-

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(13) At the suggestion of the Referee we note here that *pure* I was never isolated from our mixed I and II and that the *pure* II obtained by debromination of XV gave only an 85% yield of the dibrominated product, XV. This latter experimental figure is based on recrystallized product and it should be noted that a quantitative bromination was indeed initially effected.

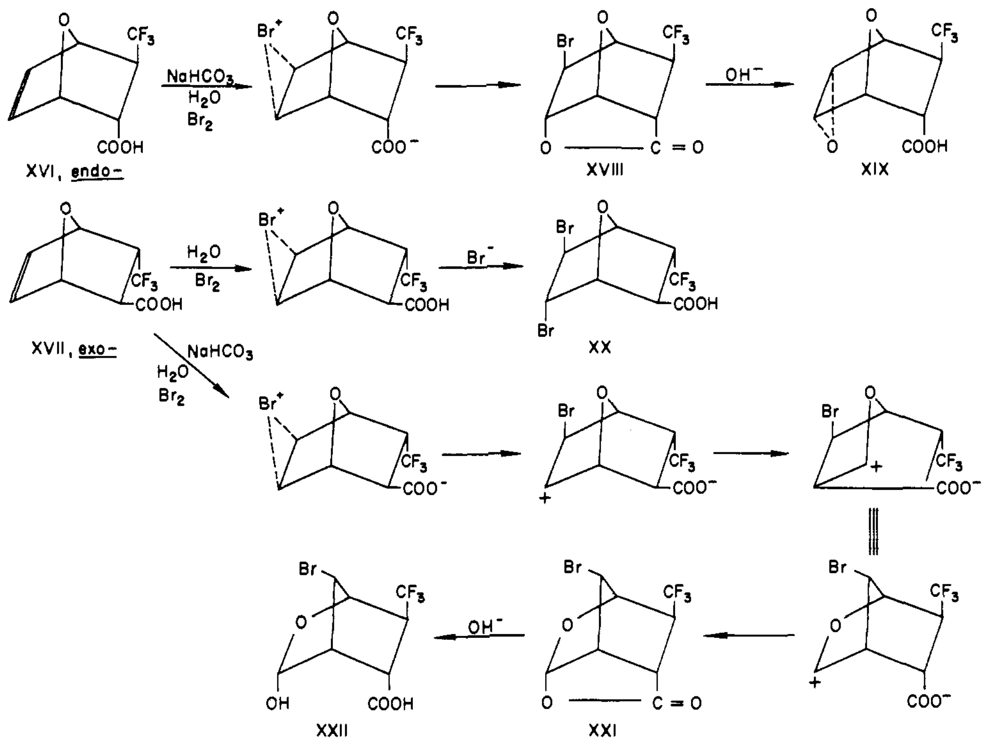

Fig. 4.

tained in 82% yield using an acidic medium. Although a lactone XXI could be obtained from the *exo*-form XVII in a basic medium by a rearrangement,[14] it would be expected that in an acidic medium an acid, XX would be the product.[4,14] XVI does not form a dibromo derivative XX.

Since XVIII is obtained under both sets of bromination conditions, XVI is assumed to be only the *endo* product. Further confirmation of this is the fact that saponification of XVIII gave an epoxy acid XIX. If the bromolactone had been derived from the *exo* form, then a hydroxy acid XXII would have been isolated instead of the epoxy acid XIX.

On the basis of these preliminary results, it is reasonable to state that in the Diels–Alder reaction, the trifluoromethyl group in *trans*-4,4,4-trifluorocrotonic acid exerts a considerable *endo* directing effect on reaction with cyclopentadiene, it being about twice as influential as the carboxyl group. The stereospecificity of the reaction with furan indicates that the trifluoromethyl group and the heterocyclic oxygen atom exert parallel directive forces as shown by nearly quantitative formation of the *endo* adduct.

Experimental[15,16]

3-Trifluoromethylbicyclo[2,2,1]-5-heptene-2-carboxylic Acid (I and II).—*trans*-4,4,4-Trifluorocrotonic acid[6] (28 g., 0.2 mole) was treated with cyclopentadiene (13.2 g., 0.2 mole) in a flask fitted with a Dry Ice condenser. After an initial vigorous evolution of heat, the reaction mixture was allowed to stand for 6 hr. at 25°. The semi-solid reaction mixture was distilled to give a viscous liquid, b.p. 104–105° (2.5 mm.), which solidified on standing, m.p. 60–70°. The yield of this reaction was quantitative. As is shown below, this material is a mixture of *endo*- (I) and *exo*-adducts (II) and will be referred to as "mixed I and II."

Anal. Calcd. for $C_9H_9F_3O_2$: C, 52.43; H, 4.37; F, 27.67. Found: C, 52.36; H, 4.65; F, 27.18.

Hydration of Mixed I and II.—A mixture of 18 g. (0.087 mole) of I and II and 210 ml. of 85% sulfuric acid was stirred at room temperature for 5–6 hr. The resulting brown solution was diluted with a mixture of 250 ml. of water and 250 g. of ice and continuously extracted with ether for 2 days. The ether extract was washed with two 100-ml. portions of 10% sodium carbonate solution and dried over anhydrous magnesium sulfate. The ether was removed and the residue was distilled to give 5 g. (28%) of lactone III, b.p. 97° (1.8 mm.), n^{25}D 1.4378.

Anal. Calcd. for $C_9H_9F_3O_2$ (III): C, 52.43; H, 4.37; F, 27.67. Found: C, 52.57; H, 4.34; F, 27.61.

The sodium carbonate solution was acidified with 10% sulfuric acid and extracted with ether. After drying over anhydrous magnesium sulfate the ether extract was distilled. Nine and a half grams (49%) of a white solid resulted; recrystallization from ether–petroleum ether (35–37) mixture gave the hydroxy acid V, m.p. 164–168°.

Anal. Calcd. for $C_9H_{11}F_3O_3$ (V): C, 48.21; H, 4.91; F, 25.44. Found: C, 48.49; H, 5.03; F, 25.76.

Hydroxy Acid IV.—When the lactone III was saponified with a 2% sodium hydroxide solution, a hydroxy acid IV resulted, m.p. 94–95°. This hydroxy acid slowly reverted to the lactone III on standing or heating.

Anal. Calcd. for $C_9H_{11}F_3O_3$ (IV): C, 48.21; H, 4.91; F, 25.44. Found: C, 48.01; H, 4.99; F, 25.82.

Bromination of Mixed I and II. A. In Sodium Bicarbonate Solution.—Ten grams (0.048 mole) of the mixed I and II was dissolved in a solution containing 6.1 g. (0.072 mole) of sodium bicarbonate in 100 ml. of water. The solution was cooled in an ice-bath, and bromine was added dropwise with constant stirring until a faint yellow color persisted. The resulting solution was extracted with ether. The extracts were combined, washed with a saturated sodium sulfite solution and dried over anhydrous magnesium sulfate. Upon distillation, 2.5 g. (14.4%) of tricyclic compound XII, b.p. 52–53° (10 mm.) or 75–76° (20 mm.), n^{20}D 1.4610 and 3.5 g. (17%) of lactone VIII (b.p. 120–124° (1.8 mm.)), were obtained. VIII solidified on standing and was recrystallized from hexane; m.p. 70–72°.

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(14) J. A. Berson and R. Swidler, THIS JOURNAL, **76**, 4060 (1954).

(15) All temperatures are uncorrected.

(16) Analyses were performed by Mrs. C. S. Yeh, Purdue University and by the Clark Microanalytical Laboratories.

Anal. Calcd. for $C_8H_8BrF_3$ (XII): C, 39.83; H, 3.32; Br, 33.20. Found: C, 40.10; H, 3.21; Br, 33.00.

Anal. Calcd. for $C_9H_8BrF_3O_2$ (VIII): C, 37.89; H, 2.81; Br, 28.07. Found: C, 37.85; H, 2.50; Br, 28.35.

When the aqueous reaction mixture was first treated with solid sodium sulfite, then acidified with concentrated hydrochloric acid, and the resulting acid solution extracted with ether, the ether extract dried and evaporated, a white solid (3 g., 13.8%) was obtained. This on recrystallization from water gave a pure hydroxy acid, X or XI, m.p. 176–178°.

Anal. Calcd. for $C_9H_{10}BrF_3O_2$: C, 35.64; H, 3.30; Br, 26.40. Found: C, 35.62; H, 3.33; Br, 26.60.

B. **In Chloroform Solution.**—The mixed adduct I and II (5 g., 0.024 mole) was dissolved in 150 ml. of chloroform and a solution of 4 g. (0.025 mole) of bromine in 30 ml. of chloroform was added slowly with constant stirring at 0°. After addition was complete, the resulting solution was allowed to stir for 8 hr. The solution was then washed with 100 ml. of 10% sodium carbonate solution and a few crystals of sodium sulfite were added to remove excess bromine. The washed chloroform solution was dried over anhydrous magnesium sulfate and evaporated to give 2.4 g. (33%) of crude VIII, m.p. 70–72°. The sodium carbonate solution was first acidified with 10% sulfuric acid and then extracted with ether. The ether extract was dried with anhydrous magnesium sulfate and evaporated to give a white solid (5.9 g., 66%). After recrystallization from cyclohexane, a pure dibromoacid XV was isolated, m.p. 162–163°.

Anal. Calcd. for $C_9H_9Br_2F_3O_2$ (XV): C, 29.51; H, 2.45; Br, 43.72. Found: C, 29.33; H, 2.29; F, 43.31.

Saponification of Bromolactone VIII.—A mixture of 2.9 g. (0.01 mole) of bromolactone VIII and 40 ml. of 2% aqueous sodium hydroxide was refluxed until the solution became homogeneous. After cooling, the resulting solution was washed with ether and acidified with 10% sulfuric acid. The acid solution was filtered and 1 g. (45%) of epoxyacid was obtained. This, on recrystallization from water, gave a pure 5,6-epoxy-3-trifluoromethylbicyclo[2,2,1]heptane-2-carboxylic acid (IX), m.p. (5.9 μ) for acid and no free OH (3.0 μ). A strong epoxy band was also present at 12.4 μ.[17]

Anal. Calcd. for $C_9H_9F_3O_2$ (IX): C, 48.65; H, 4.05; F, 25.68. Found: C, 48.34; H, 4.04; F, 26.44.

Debromination of Dibromoacid XV.—The dibromoacid IV (5.9 g., 0.016 mole), zinc dust (3.1 g., 0.048 mole) and absolute ethanol (30 ml.) were refluxed with stirring for 24 hr. The excess zinc dust was filtered, the filtrate diluted with twice its volume of water and acidified with 10% sulfuric acid. The solution was extracted with ether. Evaporation of the dried ether extract gave 2.7 g. (82%) of solid. Recrystallization from petroleum ether (60–70°) gave pure *exo* adduct II, m.p. 93.5–94°.

Anal. Calcd. for $C_9H_9F_3O_2$ (II): C, 52.43; H, 4.37; F, 27.67. Found: C, 52.07; H, 4.23; F, 27.41.

Bromination of Adduct II.—One gram (0.0048 mole) of adduct II was dissolved in 20 ml. of chloroform and cooled in an ice-bath. A solution of 1 g. (0.0062 mole) of bromine in 15 ml. of chloroform was added dropwise. After all the bromine solution was added, the mixture was stirred for 15 hr. The resulting solution was washed with 10% sodium carbonate and a few crystals of sodium sulfite added to remove the excess bromine. The chloroform solution was dried and distilled but no neutral product was isolated. The sodium carbonate solution was acidified and extracted with ether. The ether extract was dried and evaporated. One and a half grams (85%) of dibromoacid XV was obtained, m.p. 162–163°.

***endo*-7-Oxa-3-trifluoromethylbicyclo[2,2,1]-5-heptene-2-carboxylic Acid (XVI).**—*trans*-4,4,4-Trifluorocrotonic acid (3.5 g., 0.025 mole) and furan (3.09 g., 0.044 mole) was allowed to stand at room temperature for 6 days. The solid *trans*-4,4,4-trifluorocrotonic acid slowly disappeared and a crystalline material formed. The reaction mixture was treated with 5 ml. of carbon tetrachloride, and filtered to yield 4.6 g. (88.5%) of crude product. Recrystallization from a benzene–hexane mixture gave pure XVI, m.p. 104–106°.

Anal. Calcd. for $C_8H_7F_3O_3$ (XVI): C, 46.15; H, 3.37; F, 27.40. Found: C, 46.41; H, 3.44; F, 26.72.

Bromination of XVI. Method A. In Basic Medium.—One gram (0.0048 mole) of XVI was dissolved in a solution containing 2.7 g. (0.032 mole) of sodium bicarbonate in 34 ml. of water. The solution was cooled in an ice-bath and bromine was added dropwise with constant stirring until a faint color persisted. During that time XVIII (1.2 g.) gradually settled out. Separation by filtration and recrystallization from a benzene–petroleum ether (90–100°) mixture, gave a product, m.p. 137–139°. The aqueous solution was treated with solid sodium sulfite, acidified with concentrated hydrochloric acid and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and evaporated. An additional 0.1 g. of XVIII was obtained. The total yield of lactone XVIII was 1.3 g. or 95%.

Anal. Calcd. for $C_8H_6BrF_3O_3$ (XVIII): C, 33.46; H, 2.09; Br, 27.87. Found: C, 33.23; H, 2.09; Br, 27.55.

Method B in Acid Medium.—A suspension of 1.5 g. (0.0072 mole) of XVI and 50 ml. of water was cooled in an ice-bath and bromine was added dropwise with constant stirring until a yellow color persisted. The resulting solution was then filtered. The solid product (17 g., 82%) was recrystallized from water to give a product, m.p. 135–138°. The infrared spectrum showed that this product was identical with that of the lactone XVIII obtained in the above experiment.

Saponification of Bromolactone XVIII.—XVIII (1.2 g., 0.004 mole) was refluxed with 30 ml. of 2% aqueous sodium hydroxide until all solid dissolved. The resulting solution was extracted with ether and acidified with 10% sulfuric acid. The acid solution was extracted with ether and the ether solution was dried with anhydrous magnesium sulfate. XIX (0.5 g., 53%) was obtained upon evaporation of the solvent. It was purified by dissolution in ethyl acetate and reprecipitating with petroleum ether (60–70°) giving pure XIX, m.p. 188–190°. The infrared spectrum indicated the absence of a free hydroxy group; however, a strong carbonyl band for the acid (5.9 μ) and an epoxy band (12.4 μ) were present.

Anal. Calcd. for $C_8H_7F_3O_4$ (XIX): C, 42.86; H, 3.15; F, 25.45. Found: C, 43.06; H, 2.99; F, 25.27.

Absorption Spectra.—Infrared spectra were obtained on a Perkin-Elmer Model 21 Recording Infrared Spectrophotometer.

West Lafayette, Indiana

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[17] H. M. Randall, *et al.*, "Infrared Determination of Organic Structure," D. Van Nostrand Co., Inc., New York, N. Y., 1949.