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Mono- and Difluorobutenedioic Acids

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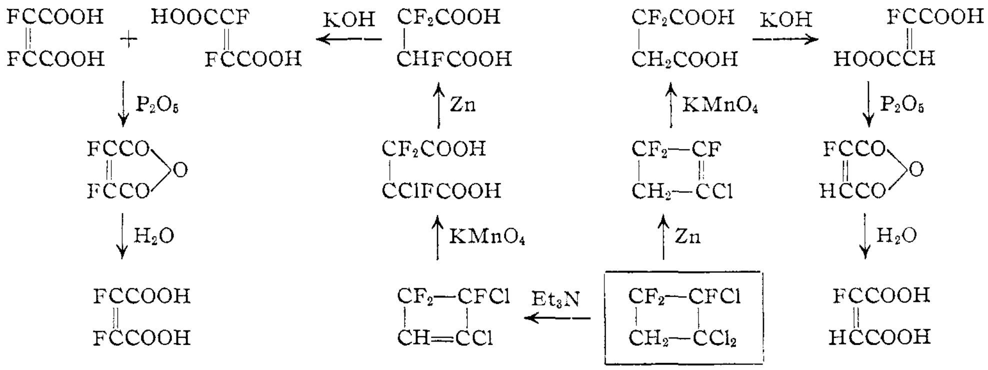
All four mono- and difluorobutenedioic acids, the anhydrides of the *cis* forms, 2,2-difluorosuccinic acid, trifluorosuccinic acid and chlorotrifluorosuccinic acid have been synthesized starting with 1,1,2-trichloro-2,3,3-trifluorocyclobutane, the adduct of chlorotrifluoroethylene and vinylidene chloride.

Although maleic and fumaric acids are versatile chemicals, useful in copolymerizations and organic syntheses, their fluoro derivatives have not been reported except for a reference by Martius[1] to a test of fluorofumaric acid as an inhibitor of the tricarboxylic acid cycle. Martius said the compound was obtained from W. Theilacker, but the procedure for synthesizing it seems not to have been published. The present paper describes the synthesis of all four mono- and difluorobutenedioic acids, and the anhydrides of the *cis* forms, from a single starting compound, and illustrates the synthetic possibilities of fluorocyclobutanes as intermediates.

The starting material employed was 1,1,2-trichloro-2,3,3-trifluorocyclobutane, prepared by the thermal addition of chlorotrifluoroethylene and 1,1-dichloroethylene. This cyclobutane was transformed into the mono- and difluorobutenedioic acids, as well as the new fluoro acids, 2,2-difluorosuccinic acid, chlorotrifluorosuccinic acid and trifluorosuccinic acid, by the sequence of reactions shown in Chart I.

CHART I



Use of a fluorocyclobutane to prepare a fluorinated succinic acid was first made by Henne and Zimmerschied,[2] who synthesized tetrafluorosuccinic acid. 2,3-Dichloro-2,3-difluorosuccinic acid[3] has been prepared similarly.

Unlike dichloromaleic anhydride, difluoromaleic anhydride copolymerizes readily with styrene; and unlike maleic anhydride, the copolymer is not restricted to a 1:1 ratio. Difluoromaleic anhydride is pyrolyzed to fluoropropiolyl fluoride[4] at 650° while monofluoromaleic anhydride is converted to fluoroacetylene.[5] Various derivatives of the fluorinated butenedioic acids and succinic acids are described in the Experimental section.

Experimental

1,1,2-Trichloro-2,3,3-trifluorocyclobutane.—A 1-liter, stainless-steel reactor was charged with 350 g. (3.6 moles) of vinylidene chloride, 1 g. of hydroquinone and 300 g. (2.6 moles) of chlorotrifluoroethylene and heated at 180° for 10 hours. The product was filtered from polymer and distilled to give 266 g. (48% yield) of 1,1,2-trichloro-2,3,3-trifluorocyclobutane, b.p. 120–121°, n^{25}_D 1.4139.

Anal. Calcd. for $C_4H_2Cl_3F_3$: C, 22.51; H, 0.95; Cl, 49.85. Found: C, 22.61; H, 1.09; Cl, 49.32.

1,4-Dichloro-3,3,4-trifluorocyclobutene.—To 555 g. (2.6 moles) of 1,1,2-trichloro-2,3,3-trifluorocyclobutane in 850 ml. of ether was added with stirring 400 ml. (2.9 moles) of triethylamine. After the mixture had stood for 20 hours, it was stirred with 1200 ml. of water and 75 ml. of hydrochloric acid. The ether layer was washed with water, dried and distilled to give 400 g. (87% yield) of 1,4-dichloro-3,3,4-trifluorocyclobutene, b.p. 91–92°, n^{25}_D 1.3942.

Anal. Calcd. for $C_4HCl_2F_3$: Cl, 40.07. Found: Cl, 39.96.

Chlorotrifluorosuccinic Acid.—To 4 liters of water, 153 g. (2.3 moles) of potassium hydroxide and 718 g. (4.6 moles) of potassium permanganate in a 5-liter, 3-necked flask was added with stirring 410 g. (2.3 moles) of 1,4-dichloro-3,3,4-trifluorocyclobutene at 15–20° during 2.5 hours. After the mixture had been stirred for 10 hours longer at 25°, it was filtered from manganese dioxide which was washed with water. The volume of the filtrate was reduced to 1500 ml. and 295 ml. of concd. sulfuric acid was added. The solution was extracted with ether, the extract was dried briefly with magnesium sulfate, and the ether was evaporated off. The chlorotrifluorosuccinic acid thus obtained was taken up in methylene chloride. Part of the product crystallized out and was filtered off and washed with methylene chloride. By judiciously adding water to the filtrate, more crystalline product was obtained. A total of 409 g. (85% yield) of very hygroscopic crystals was obtained. After being dried over phosphorus pentoxide, the compound melted at 55°.

Anal. Calcd. for $C_4H_2ClF_3O_4$: Cl, 17.17. Found: Cl, 16.77.

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(1) C. Martius, *Ann.*, **561**, 231 (1949).

(2) A. L. Henne and W. J. Zimmerschied, THIS JOURNAL, **69**, 281 (1947).

(3) R. N. Haszeldine and J. E. Osborne, *J. Chem. Soc.*, 3880 (1955).

(4) W. J. Middleton, U. S. Patent 2,831,835 (April 22, 1958).

(5) W. J. Middleton, U. S. Patent 2,857,366 (October 21, 1958).

A portion was converted to the dipotassium salt which was recrystallized from ethyl alcohol–water.

Anal. Calcd. for $C_4ClF_3K_2O_4$: Cl, 12.54. Found: Cl, 12.52.

Chlorotrifluorosuccinic Anhydride.—Chlorotrifluorosuccinic acid (62 g., 0.3 mole) and 120 g. (0.84 mole) of phosphorus pentoxide were heated in a simple still to give 46 g. (81% yield) of chlorotrifluorosuccinic anhydride. This was distilled through a packed column at 78°; $n^{25}D$ 1.3661.

Dimethyl and Diethyl Chlorotrifluorosuccinates.—A mixture of 35 g. of chlorotrifluorosuccinic anhydride, 50 ml. of methanol and 5 ml. of concd. sulfuric acid was refluxed for 16 hours. From it was obtained 27.5 g. (61% yield) of dimethyl chlorotrifluorosuccinate, b.p. 192–194°, $n^{25}D$ 1.3908.

The diethyl ester was made by azeotropic removal of water with benzene, using *p*-toluenesulfonic acid as catalyst; b.p. 70–74° (2–3 mm.), 219° (760 mm.); $n^{25}D$ 1.3945.

Chlorotrifluorosuccinamide.—Diethyl chlorotrifluorosuccinate (36 g.) was added dropwise to 135 ml. of concentrated, aqueous ammonia with stirring at 0°. After 1.5 hours, 23 g. (83% yield) of chlorotrifluorosuccinamide was filtered off; m.p. 250° after recrystallization from water.

Anal. Calcd. for $C_4H_4ClF_3NO_2$: N, 13.69. Found: N, 13.82.

Chlorotrifluorosuccinimide.—Chlorotrifluorosuccinamide (40.9 g., 0.2 mole) and 20.6 g. (0.2 mole) of 95% sulfuric acid were heated at 200° under 12 mm. pressure. The distillate (18.7 g.) was redistilled to give 14.6 g. (39% yield) of the imide, b.p. 48° (2 mm.), $n^{25}D$ 1.4333. The imide was also made by heating 0.1 mole of the diamide with 0.3 mole of phosphorus pentoxide under reduced pressure.

Anal. Calcd. for $C_4HF_3ClNO_2$: C, 25.63; H, 0.53; N, 7.46. Found: C, 25.72; H, 0.84; N, 7.48.

Trifluorosuccinic Acid Dioxanate.—Zinc dust (121 g., 1.76 moles) was added in portions to a stirred solution of 332 g. (1.6 moles) of chlorotrifluorosuccinic acid in 700 ml. of dioxane. The temperature was kept at 40–50° with cooling. After 3 hours a small amount of heat was still being given off, and the mixture was allowed to stir for 15 hours more. The thick mixture was decanted from unreacted zinc and most of the dioxane was removed under reduced pressure. The residue was dissolved in water and a solution of 103 ml. (1.85 moles) of concd. sulfuric acid in 200 ml. of water was added. The solution was extracted with ether and the extract was dried with magnesium sulfate. Evaporation of the ether left a crystalline residue. This was stirred with methylene chloride to give 236 g. (68% yield) of trifluorosuccinic acid associated with one-half mole of dioxane. An additional 40 g. (11%) of the dioxanate was obtained by evaporating the filtrate, dissolving the residue in dioxane, and treating it with additional zinc. After recrystallizing the hygroscopic dioxanate from a mixture of ether and chloroform, it melted at 95–96°.

Anal. Calcd. for $(C_4H_3F_3O_4)_2 \cdot C_4H_8O_2$: C, 33.35; H, 3.26; F, 26.37. Found: C, 33.18; H, 3.26; F, 25.77.

Tetrafluorosuccinic acid forms a 1:1 complex with dioxane.[6]

Trifluorosuccinic Acid.—To a solution of 63 g. (0.29 mole) of trifluorosuccinic acid dioxanate in 250 ml. of ether was added 55 ml. (0.60 mole) of aniline. The dianilinium salt (94 g., 90% yield) was filtered off and recrystallized from ethyl alcohol–water in 75% return; m.p. 181–186° dec. A solution of the salt in 100 ml. of water and 35 ml. of hydrochloric acid was extracted with ether. Evaporation of the dried ether solution left 31 g. of trifluorosuccinic acid which was recrystallized from trifluoroacetic acid–benzene to give 26 g. (83% return), m.p. 111–112°.

Anal. Calcd. for $C_4H_3F_3O_4$: C, 27.92; H, 1.76; F, 33.13. Found: C, 28.08; H, 1.90; F, 34.51.

Trifluorosuccinic Anhydride.—Trifluorosuccinic acid was converted to its anhydride by heating with phosphorus pentoxide. The anhydride distilled at 122–124°.

Trifluorosuccinamide.—From 2.6 g. of diethyl trifluorosuccinate, b.p. 75–76° (2 mm.), and 22 ml. of cold, concentrated aqueous ammonia, after stirring for one hour, there was obtained 1.8 g. (78% yield) of trifluorosuccinamide, m.p. 195–197° from water.

Anal. Calcd. for $C_4H_5F_3O_2N_2$: N, 16.48; F, 33.54. Found: N, 16.91; F, 32.92.

Trifluorosuccinanilic Acid.—Trifluorosuccinic anhydride was treated with a molar equivalent of aniline in ether and the product was filtered off, washed with dilute hydrochloric acid and recrystallized from water. The anilide melted at 111–113° and presumably has the structure $HOOCCF_2CHFCONHC_6H_5$.

Anal. Calcd. for $C_{10}H_8F_3NO_3$: C, 48.58; H, 3.26; N, 5.67; F, 23.06. Found: C, 48.48; H, 3.49; N, 5.56; F, 23.43.

Difluorofumaric Acid.—A mixture of 10 ml. of water, 2.4 g. (0.06 mole) of sodium hydroxide and 3.44 g. (0.02 mole) of pure trifluorosuccinic acid was heated on a steam-bath for 15 hours. The mixture was cooled and 8 ml. of sulfuric acid in 5 ml. of water was added. It is necessary to use a high concentration of acid, otherwise the difluorobutenedioic acids cannot be extracted easily. The solution was extracted with ether and the ether solution was decolorized with carbon, dried and evaporated to give 3.02 g. (99% yield) of a mixture of difluorofumaric and difluoromaleic acids. Recrystallization of the mixed acids from 6 ml. of water gave 1.05 g. (34% yield) of difluorofumaric acid, m.p. 267°. After a second recrystallization it melted at 268–270°.

Anal. Calcd. for $C_4H_2F_2O_4$: C, 31.59; H, 1.33; F, 24.99. Found: C, 32.03; H, 1.61; F, 24.18.

Trifluorosuccinic acid dioxanate may be used instead of the pure acid.

Diethyl Difluoromaleate and Diethyl Difluorofumarate.—The dehydrofluorination mixture of difluoromaleic and difluorofumaric acids was esterified with ethyl alcohol to give diethyl difluoromaleate, b.p. 55–57° (1.1 mm.), $n^{25}D$ 1.4121, and diethyl difluorofumarate, b.p. 72–73° (1.1 mm.), $n^{25}D$ 1.4273. Both infrared and nuclear magnetic resonance indicated that the higher boiling fraction is the fumarate and the other the maleate. In contrast, diethyl maleate boils higher than diethyl fumarate.

Difluorofumaramide.—Concentrated aqueous ammonia (100 ml.) was added to 20.8 g. (0.1 mole) of diethyl difluorofumarate and the mixture was stirred for 24 hours. The crude, tan amide (12.6 g., 84% yield) was dissolved in 2 l. of hot water, decolorized, and 7 g. of white, crystalline amide was recovered by cooling the solution. The compound darkened at about 280° but did not melt.

Anal. Calcd. for $C_4H_4F_2N_2O_2$: C, 32.01; H, 2.67; F, 25.3; N, 18.66. Found: C, 32.24; H, 2.70; F, 25.42; N, 18.73.

Difluoromaleic Anhydride.—Mixed difluoromaleic and difluorofumaric acids (75 g., 0.49 mole) and 75 g. (0.52 mole) of phosphorus pentoxide were heated in a simple still. The difluoromaleic anhydride that came over was fractionated to give 58.5 g. (89% yield), b.p. 128°, m.p. 20°, $n^{25}D$ 1.4197.

Anal. Calcd. for $C_4F_2O_3$: C, 35.84; F, 28.36. Found: C, 35.63; F, 28.34.

Difluoromaleic Acid.—Difluoromaleic anhydride was hydrolyzed with an equivalent of water to difluoromaleic acid which was recrystallized from a mixture of acetone and benzene. The acid melted at 219–220°.

Anal. Calcd. for $C_4H_2F_2O_4$: C, 31.59; H, 1.33; F, 24.99. Found: C, 31.49; H, 1.68; F, 24.81.

Difluoromaleamic Acid.—A solution of 8 g. of difluoromaleic anhydride in 270 ml. of benzene was saturated with ammonia gas. The gummy solid that formed was separated, dissolved in 70 ml. of water, and decolorized with activated carbon. Dropwise addition of concentrated hydrochloric acid gave 3.8 g. (42% yield) of difluoromaleamic acid as white needles, m.p. 183–185°.

Anal. Calcd. for $C_4H_3F_2O_3N$: N, 9.27. Found: N, 9.33.

N-Phenyldifluoromaleamic Acid.—Addition of 7.1 g. (0.076 mole) of aniline in 100 ml. of ether to a solution of 10.2 g. (0.076 mole) of difluoromaleic anhydride in 200 ml. of ether followed by cooling in ice gave 17.3 g. (92% yield) of N-phenyldifluoromaleamic acid, m.p. 193–195°. After recrystallization from chlorobenzene it melted at 194–196°.

Anal. Calcd. for $C_{10}H_7F_2NO_3$: N, 6.16. Found: N, 6.17.

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(6) K. E. Rapp, J. T. Barr, R. L. Pruett, C. T. Bahner, J. D. Gibson and R. H. Lafferty, Jr., THIS JOURNAL, **74**, 752 (1952).

N-(*p*-Chlorophenyl)-difluoromaleamic acid was similarly prepared and recrystallized from chlorobenzene, m.p. 184–186°.

Anal. Calcd. for $C_{10}H_6F_2NO_3Cl$: N, 5.36; F, 14.54. Found: N, 5.51; F, 14.84.

N-(α-Naphthyl)-difluoromaleamic acid melted at 154–155.5° after recrystallization from dioxane–petroleum ether.

Anal. Calcd. for $C_{14}H_9F_2NO_3$: C, 60.65; H, 3.25; N, 5.06. Found: C, 60.54; H, 3.39; N, 5.07.

N-Phenyldifluoromaleimide.—A solution of 10 g. (0.044 mole) of N-phenyldifluoromaleamic acid in 200 ml. of hot chlorobenzene was stirred and heated with 10 g. (0.07 mole) of phosphorus pentoxide for 20 minutes. The reaction mixture was filtered and the gummy solid was extracted twice with chlorobenzene and then with boiling ether. The combined organic solutions were extracted with sodium bicarbonate solution and then evaporated to give 4.2 g. (46% yield) of N-phenyldifluoromaleimide, m.p. 88–89°. Recrystallization from petroleum ether did not alter the melting point.

Anal. Calcd. for $C_{10}H_5F_2NO_2$: N, 6.69; F, 18.17. Found: N, 6.75; F, 17.90.

N-(*p*-Chlorophenyl)-difluoromaleimide.—By means of the above procedure, this compound was obtained in 91% yield as bright yellow needles, m.p. 74–76°.

Anal. Calcd. for $C_{10}H_4ClF_2NO_2$: N, 5.74; Cl, 14.57. Found: N, 5.83; Cl, 13.92.

11,12-Difluoro-9,10-dihydro-9,10-ethanoanthracene-11,-12-dicarboxylic Anhydride.—Difluoromaleic anhydride (2.68 g., 0.02 mole) and 3.56 g. (0.02 mole) of anthracene were heated together for 10 minutes in a bath at 175°. The product was recrystallized from 1,1,2,2-tetrachloroethane to give 5.2 g. (83% yield) of the Diels–Alder adduct, m.p. 229–230°.

Anal. Calcd. for $C_{18}H_{10}F_2O_3$: C, 69.22; H, 3.23; F, 12.17. Found: C, 69.05; H, 3.17; F, 11.76.

Difluoromaleic Anhydride–Styrene Copolymer.—A solution of 6.7 g. (0.05 mole) of difluoromaleic anhydride, 5.2 g. (0.05 mole) of styrene and 0.05 g. of benzoyl peroxide in 30 ml. of xylene was heated under nitrogen at 100° for 16 hours. The polymer was isolated by pouring the solution into 400 ml. of petroleum ether and filtering; yield 4.6 g. The polymer was completely soluble in sodium hydroxide solution and softened at 178–183°. The inherent viscosity of a 0.5% solution in dimethylformamide at 25° was 0.37. *Anal.* Found: F, 10.04. This corresponds to a styrene/difluoromaleic anhydride molar ratio of 2.3/1.

1-Chloro-2,3,3-trifluorocyclobutene.—In a flask fitted with an efficient reflux condenser, sealed stirrer, and dropping funnel were placed 150 g. (2.2 moles) of 95% zinc dust and 300 ml. of absolute ethyl alcohol. To the refluxing mixture was added slowly 400 g. (1.87 moles) of 1,1,2-trichloro-2,3,3-trifluorocyclobutane and heating was continued for two hours. The mixture was cooled, diluted to 2 l. with water, and 10 ml. of hydrochloric acid was added. The organic layer was separated, dried over calcium chloride, and distilled to give 177 g. (66% yield) of 1-chloro-2,3,3-trifluorocyclobutene, b.p. 51.5–52°, $n^{25}D$ 1.3614.

Anal. Calcd. for $C_4H_2ClF_3$: Cl, 24.88. Found: Cl, 24.50.

2,2-Difluorosuccinic Acid.[7]—In a flask fitted with stirrer, thermometer and dropping funnel, and cooled by an ice-salt-bath were placed 4 l. of water, 160 g. (4.0 moles) of sodium hydroxide and 316 g. (2.0 moles) of potassium permanganate. 1-Chloro-2,3,3-trifluorocyclobutene (214 g., 1.5 moles) was added slowly at 15–20°. The reaction was complete in 3 hours. The manganese dioxide was filtered off, washed with water, and the filtrate was concentrated on a steam-bath. After addition of 170 ml. of concd. sulfuric acid, the filtrate was extracted with ether. After the ether solution had been dried with magnesium sulfate, it was evaporated to give 182 g. (79% yield) of 2,2-difluorosuccinic acid. The product was recrystallized from acetone–benzene in 88% return (2 crops) and melted at 154–155°.

Anal. Calcd. for $C_4H_4F_2O_4$: C, 31.17; H, 2.62; F, 24.66. Found: C, 30.90; H, 2.80; F, 24.68.

Diethyl 2,2-Difluorosuccinate.[7]—The acid was esterified with ethyl alcohol using sulfuric acid as catalyst. The ester boiled at 53–55° (1 mm.), 205–207° (749 mm.), $n^{25}D$ 1.3912.

Anal. Calcd. for $C_8H_{12}F_2O_4$: C, 45.71; H, 5.76; F, 18.08. Found: C, 46.10; H, 5.86; F, 18.54.

Fluorofumaric Acid.—To a solution of 97 g. (2.42 moles) of sodium hydroxide in 300 ml. of water were added 100 g. of ice and 125 g. (0.81 mole) of 2,2-difluorosuccinic acid. The solution was heated on a steam-bath for 16 hours, cooled, and 100 ml. of water and 205 ml. (2.44 moles) of hydrochloric acid were added. The solution was extracted with ether and the fluorofumaric acid obtained by evaporating the dried ether solution was recrystallized from acetone–benzene to give 83.5 g. (77% yield) in 3 crops, m.p. 236–237°. From the mother liquors 4 more grams of fluorofumaric acid plus 1 g. of sirup was obtained. Thus, little or no fluoromaleic acid is formed in the reaction.

Anal. Calcd. for $C_4H_3FO_4$: C, 35.83; H, 2.26; F, 14.17. Found: C, 36.40; H, 2.40; F, 14.04.

Fluoromaleic Anhydride.—Seventy grams (0.42 mole) of fluorofumaric acid and 45 g. (0.32 mole) of phosphorus pentoxide were heated in a simple still. The anhydride which came over (51.5 g.) was redistilled through a column to give 46 g. (76% yield) of fluoromaleic anhydride, b.p. 162°, $n^{25}D$ 1.4452.

Anal. Calcd. for C_4HFO_3: C, 41.37; H, 0.87; F, 16.37. Found: C, 41.39; H, 0.90; F, 16.32.

Fluoromaleic Acid.—Twenty-five grams (0.216 mole) of fluoromaleic anhydride and 3.9 ml. (0.216 mole) of water were mixed in a beaker. The fluoromaleic acid was recrystallized from acetone–benzene to give 22.6 g. (78% yield) in 3 crops, m.p. 128–129° in a capillary tube and 132–133° on a Fisher–Johns apparatus.

Anal. Calcd. for $C_4H_3FO_4$: C, 35.83; H, 2.26; F, 14.17. Found: C, 36.25; H, 2.43; F, 14.40.

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(7) M. S. Raasch, U. S. Patent 2,824,888 (February 25, 1958).