Fumaronitrile.—The purified product was obtained by the dehydration of fumaramide with phosphorus pentoxide.[6]

Santomerse D.—The product of Monsanto Chemical Co. was used.

Benzoyl Peroxide.—The Lucidol Corp. product was used as received.

Mass Copolymerizations.—A total of 100 g. of the styrene–fumaronitrile mixture was placed in a 4-oz. French square bottle. The concentrations of monomer used are given in Table I. Air above the monomers was displaced with nitrogen and a metal cap screwed tightly in place. Copolymerizations were carried out in an air oven regulated at 79 ± 1°. Polymerization was allowed to continue until a slight increase in viscosity was observed. The solution was then poured into 3000 ml. of stirred denatured ethanol (2B) at room temperature and the bottle was rinsed with ethanol. The mixture was boiled to complete coagulation and filtered. The copolymer was washed with two fresh 1500-ml. portions of ethanol. The copolymer was then dried in an evaporating dish for 24 hours at 60° in a circulating air oven. Duplicate micro-Dumas analyses were made on the copolymer samples. Analytical data and conversions are given in Table I.

Solution Copolymerizations.—Appropriate monomer mixtures (100 g.) with equal weights of dioxane were charged to 8 oz. French square bottles. These mixtures were allowed to polymerize and the copolymer was isolated in the same way as described for mass copolymerizations.

Emulsion Copolymerizations.—A master batch of emulsifier solution was prepared by dissolving 200 g. of Santomerse D in 1800 ml. of distilled water. All emulsion polymerizations utilized 300 g. of this emulsifier solution and 150 g. of total monomer. Emulsifier solution was added to a stirred 1-liter, three-necked, round-bottomed flask and appropriate weights of styrene and fumaronitrile were added. The reaction mixture was stirred for 1.5 hours at room temperature and then heated to 60° over a 30-minute period. Polymerization was continued until a low conversion was obtained. Conversions during reaction were approximated by estimating turbidity when 5 ml. of emulsion was added to 200 ml. of ethanol. The entire reaction mixture was then poured into 3000 ml. of stirred ethanol and this mixture was boiled to coagulate the product. The polymer which usually was obtained as a fine white powder was filtered on a Buchner funnel, boiled with 1500 ml. of fresh ethanol and refiltered. This operation was repeated. In some cases there was a tendency for polymer particles to stick together after the first boiling operation. Such products were recomminuted by mixing in a Waring Blendor with fresh alcohol prior to filtration. The resulting white powder was then purified by the above procedure. The copolymer was dried at 60° in a circulating air oven for 24 hours. Conversions corrected for residue in the polymerization flask and for samples withdrawn during the polymerization were determined gravimetrically.

Heat distortion points were determined by the A.S.T.M. method (ASTMD648-41T) employing an air-bath. Molded specimens (0.5″ × 0.5″ × 5.0″) were placed in the heat distortion apparatus and the temperature gradually raised from room temperature at the rate of 0.5° per minute until a deflection of 10 mils was obtained.

(6) deWolfe and van de Straete, *Bull. soc. chim. Belg.*, **44**, 288 (1935).

Summary

The monomer reactivity of styrene–fumaronitrile mixtures in mass, solution, and emulsion was determined. The similarity of monomer reactivity in the three systems is regarded as further proof of a non-aqueous locus of emulsion polymerization. The copolymerization of α-methylstyrene and fumaronitrile was studied and the predicted monomer reactivity ratios confirmed. A theory accounting for the direct proportionality of heat distortion point and fumaronitrile content of styrene copolymers is proposed.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

The Effect of Fluorine Substitution on Medicinal Agents. III.[1] Synthesis of 2-Trifluoromethyl-1,4-naphthoquinone

BY ARTHUR F. HELIN,[2] AUGUST SVEINBJORNSSON[3] AND CALVIN A. VANDERWERF

The results obtained in the earlier studies in this series on the physiological and pharmacological properties of fluorine analogs of known medicinals have been of sufficient interest to warrant the extension of this program to include the fluorine derivatives of certain vitamins and compounds with vitamin-like activity. As a step toward this end, the synthesis of 2-trifluoromethyl-1,4-naphthoquinone, a trifluoro derivative of menadione of particular interest as a possible vitamin K antagonist,[4] has been carried out.

Experimental

2,5-Diacetamidobenzotrifluoride.—Exactly 19 g. (0.77 mole) of 2-nitro-5-acetamidobenzotrifluoride,[5] purified by recrystallization from benzene, dilute ethanol and dilute acetic acid, was dissolved in 50 ml. of acetic anhydride and shaken with hydrogen under a pressure of about 3 atmospheres in the presence of platinum oxide catalyst, while heat was applied by means of an infrared lamp. Absorption of hydrogen was complete in 2 hours. The cooled solution was filtered, diluted with 100 ml. of water and cooled in an ice-bath. Colorless crystals (14 g., 70%) of **2,5-diacetamidobenzotrifluoride**, m.p. 184–187°, separated slowly. After recrystallization from ethanol, the product melted at 188.4–189.1°.

Anal. Calcd. for $C_{11}H_{11}O_2N_2F_3$: N, 11.3. Found: N, 11.1.

Trifluoromethylbenzoquinone.—A 50-g. (0.19 mole) portion of 2,5-diacetamidobenzotrifluoride was heated with a solution of 255 ml. of concentrated sulfuric acid in 770 ml. of water until all of the solid had dissolved, indicating that hydrolysis was complete. The hot solution was decolorized by filtration with charcoal. It was placed in an ice-bath, 750 ml. of benzene was added and the resulting heterogeneous system was cooled to 8°. A solution of 68 g. (0.26 mole) of sodium dichromate dihydrate in 125 ml. of water was added with vigorous stirring at such a rate that the temperature did not rise above 10°. The mixture was stirred for 2 hours in the cold. The benzene layer was then

(1) For the second paper in this series, see Lindenstruth, Fellman and VanderWerf, THIS JOURNAL, **72**, 1886 (1950). The authors are indebted to the Office of Naval Research for a grant which made this and continuing investigations possible.

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(4) For a report on the effectiveness of monofluorophenylalanines and tyrosines as competitive inhibitors for their parent amino acids, see Mitchell and Niemann, THIS JOURNAL **69**, 1232 (1947).

(5) Obtained, along with small amounts of 2-nitro-3-acetamidobenzotrifluoride and of 2,3,4,6-tetranitro-5-acetamidobenzotrifluoride, m.p. 191.2–192.2°, by nitration of 3-acetamidobenzotrifluoride with fuming nitric acid (sp. gr. 1.5) in concd. sulfuric acid. The 3-acetamidobenzotrifluoride was prepared by nitration of benzotrifluoride, followed by catalytic reduction of the 3-nitro compound and acetylation of the resulting amine.

separated, dried over anhydrous sodium sulfate and concentrated to about 40 ml. by distillation of the benzene under reduced pressure provided by the water-pump. Approximately 100 ml. of Skellysolve C was added and the solution was chilled in a Dry Ice–chloroform-bath. Reddish-orange crystals of trifluoromethylbenzoquinone separated, together with colorless crystals of benzene. The benzene crystals dissolved upon slight warming and the trifluoromethylbenzoquinone was removed by filtration. By addition of another 100 ml. of Skellysolve C to the filtrate and cooling as before, a second crop of crystals was obtained. The total weight of the **trifluoromethylbenzoquinone**, m.p. 48–52°, was 12 g. (35%). After one recrystallization from alcohol, the product was a dull yellow color and melted at 51.2–54.0°.

Anal. Calcd. for $C_7H_3O_2F_3$: C, 47.7; H, 1.8. Found: C, 47.8; H, 2.0.

2-Trifluoromethyl-1,4-naphthoquinone.—This compound was prepared by the general method of Fieser[6] for the preparation of substituted naphthoquinones from substituted benzoquinones. A solution of 12 g. (0.068 mole) of trifluoromethylbenzoquinone in 35 ml. of acetic acid was placed in a pressure flask and cooled in ice-water. A 4.3-g. (0.08 mole) portion of butadiene which had been condensed out of a tank into a graduated cylinder surrounded by Dry Ice was added. The flask was then stoppered tightly and immersed in running water for 40 hours. The solution was filtered with acetic acid-washed charcoal. The product, 2-trifluoromethyl-5,8,9,10-tetrahydro-1,4-naphthoquinone, was not isolated, but instead the acetic acid solution was placed in a 200-ml. three-necked flask equipped with a Hershberg stirrer and thermometer, warmed to 50° and treated with a solution of 27.3 g. (0.092 mole) of sodium dichromate dihydrate and 1.4 ml. of concentrated sulfuric acid in 17 ml. of water.

The mixture was heated to 65° over a hot-plate and maintained at 65–70°. After about 20 minutes, the temperature suddenly began to rise and cooling was provided by means of an ice-bath. The mixture was maintained at 65–70° for another half hour, then poured onto a mixture of 70 g. of ice and 70 g. of water. The yellow solid which appeared was filtered, washed with water and dried to yield 4.0 g. (26%) of **2-trifluoromethyl-1,4-naphthoquinone**, m.p. 73.0–83.5°. After two recrystallizations from ethanol, the product melted at 104.3–105.0°.

Anal. Calcd. for $C_{11}H_5O_2F_3$: C, 58.4; H, 2.2. Found: C, 58.7; H, 2.2.

2-Trifluoromethyl-5,8,9,10-tetrahydro-1,4-naphthohydroquinone.—An acetic acid solution of 2-trifluoromethyl-5,8,9,10-tetrahydro-1,4-naphthoquinone, prepared as described above from 3.0 g. (0.017 mole) of trifluoromethylbenzoquinone, was heated on a steam-bath for 20 minutes, and to the hot solution there was added a solution of 2.8 ml. of concentrated hydrochloric acid and 0.42 g. of stannous chloride in 14 ml. of water. The solution was allowed to stand 12 hours at room temperature and was then chilled in ice. After several hours, light-colored crystals which appeared to be a mixture of several products separated. The only pure compound which could be isolated from the mixture was **2-trifluoromethyl-5,8,9,10-tetrahydro-1,4-naphthohydroquinone**, m.p. 176.8–177.0°, obtained in 2.5% yield (0.1 g.) after repeated recrystallization from ethanol.

Anal. Calcd. for $C_{11}H_{11}O_2F_3$: C, 56.9; H, 4.8. Found: C, 57.0, 56.9; H, 5.0, 4.9.

(6) Fieser, THIS JOURNAL, **70**, 3165 (1948).

Discussion

The general method for the synthesis of 2-trifluoromethyl-1,4-naphthoquinone described proved the most successful of several variations explored. Attempts to obtain the product directly by treatment of 1,4-naphthoquinone with the peroxide of trifluoroacetic acid according to the method for alkylating naphthoquinones developed by Fieser and Oxford[7] were thwarted by our failure to obtain the required di-(trifluoroacetyl) peroxide by the general procedure of Gambarjan.[8]

Attempted direct oxidation of 3-aminobenzotrifluoride to trifluoromethylbenzoquinone gave only tarry products. A second proposed route for the preparation of the benzoquinone by oxidation of 2-nitroso-5-hydroxybenzotrifluoride could not be tried because the latter compound was not obtained upon attempted nitrosation of *m*-trifluoromethylphenol. An alternative route for the preparation of trifluoromethylbenzoquinone which was approximately as successful as that used involved reduction of 2-nitro-5-acetamidobenzotrifluoride by means of stannous chloride and hydrochloric acid, with simultaneous hydrolysis of the acetamido group, to yield 2,5-diaminobenzotrifluoride dihydrochloride. This product was converted into the dihydrosulfate which was oxidized with dichromate to the benzoquinone.

Pharmacological testing of 2-trifluoromethyl-1,4-naphthoquinone is in progress.

Summary

The successful synthesis of 2-trifluoromethyl-1,4-naphthoquinone, a trifluoro derivative of menadione, is described. Variations of the general synthetic method were attempted and are discussed.

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(7) Fieser and Oxford, *ibid.*, **64**, 2060 (1942).

(8) Gambarjan, *Ber.*, **42**, 4010 (1909). A study of the preparation of this and certain other halogenated acetyl peroxides by the improved method of Fieser, *et al.* [Fieser, Leffler and co-workers, THIS JOURNAL, **70**, 3178 (1948)] is in progress.