groine (bp 60–100 °C) to give 88.4 g of amine: mp 75.5–79.5 °C. Mass spectrum, *m/e* (relative intensity): 328 (<1), which corresponds to the molecular ion for **9**; 283 (7) and 281 (5), which correspond to the molecular ion for **8**; 241 (12), 239 (67), and 237 (100), which correspond to the molecular ion for **10**. Anal. Calcd for 62.9% **10**, 28.6% **8**, and 8.5% **9**: C, 58.24; H, 3.69; Br, 8.09; Cl, 24.15. Found: C, 57.83; H, 3.49; Br, 8.08; Cl, 24.15.

Registry No.—**2**, 68014-50-6; **3**, 19020-41-8; **4**, 68014-51-7; **5**, 68014-52-8; **6**, 68014-53-9; **7**, 68014-54-0; **8**, 13676-98-7; **9**, 68014-55-1; **10**, 6962-04-5; *N*-phenyl-4′-chloroacetanilide, 68014-56-2; 4-chlorodiphenylamine, 1205-71-6; *N*-phenyl-*o*-toluidine, 1205-39-6; *N*-phenyl-2,6-xylidine, 4058-04-2; di-*o*-tolylamine, 617-00-5; *N*-(*o*-tolyl)-2,6-xylidine, 68014-57-3; *N*-phenyl-2,4,6-trimethylaniline, 23592-67-8; *N*-(*o*-tolyl)-2,4,6-trimethylaniline, 39267-45-3; 4′-chloroacetanilide, 539-03-7; bromobenzene, 108-86-1; *o*-acetotoluidide, 120-66-1; 2′,6′-acetoxylidide, 2198-53-0; *o*-bromotoluene, 95-46-5; acetanilide, 103-84-4; 2-bromomesitylene, 576-83-0; *N*-(2,6-dimethylphenyl)-2,4,6-trimethylaniline, 68014-58-4; 1-bromo-4-chlorobenzene, 106-39-8.

References and Notes

(1) Abstracted in part from the M.S. Theses of J. R. Butler, North Carolina State University, 1977, and H. S. Freeman, North Carolina State University, 1978.
(2) I. Goldberg, *Ber. Dtsch. Chem. Ges.*, **40**, 4541 (1907).
(3) (a) H. Wieland and A. Wecker, *Ber. Dtsch. Chem. Ges.*, **55**, 1804 (1922); (b) T. L. Davis and A. A. Ashdown, *J. Am. Chem. Soc.*, **46**, 1051 (1924); (c) P. E. Weston and H. Adkins, *ibid.*, **50**, 859 (1928); (d) A. B. Sen and A. K. Sen Gupta, *J. Indian Chem. Soc.*, **34**, 413 (1957); (e) J. Hebký, O. Rádek, and J. Kejha, *Collect. Czech. Chem. Commun.*, **24**, 3988 (1959); (f) J. Hebký, J. Kejha, and M. Karásek, *ibid.*, **26**, 1559 (1961); (g) E. A. Nodiff, S. Lipschutz, P. N. Craig, and M. Gordon, *J. Org. Chem.*, **25**, 60 (1960); (h) T. Thu-Cuc, N. P. Buu-Hoi, and N. D. Xuong, *J. Heterocycl. Chem.*, **1**, 28 (1964).
(4) J. W. Schulenberg and S. Archer, *Org. React.*, **14**, 1 (1965).
(5) A. W. Chapman and C. H. Perrott, *J. Chem. Soc.*, 2462 (1930).
(6) S. P. Massie and P. K. Kadaba, *J. Org. Chem.*, **21**, 347 (1956).
(7) Monsanto Chemical Co., British Patent 989 257, April 14, 1965; *Chem. Abstr.*, **63**, 14755h (1965).
(8) M. S. Newman and W. H. Powell, *J. Org. Chem.*, **26**, 812 (1961).
(9) C. Izard-Verchère and C. Viel, *Bull. Soc. Chim. Fr.*, 2122 (1971).
(10) R. J. Sundberg and K. B. Sloan, *J. Org. Chem.*, **38**, 2052 (1973).

Synthesis of Perfluoroalkyladamantanes[1]

Robert E. Moore* and Gary L. Driscoll

Applied Research Department, Chemicals Division, Suntech Group, Marcus Hook, Pennsylvania 19061

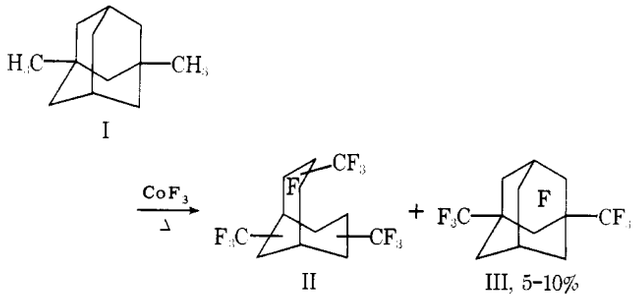
Received March 21, 1978

Fluorination of alkyladamantanes over CoF_3 leads to complex products with only a small amount (5–10%) of the desired perfluoroadamantane. Partial fluorination of the individual alkyladamantane substrate, however, prior to exhaustive fluorination over CoF_3 stabilizes the adamantane ring structure and allows the synthesis of perfluoroalkyladamantanes in good yield. The physical and spectral properties of three perfluoroalkyladamantanes are reported.

Because of the current interest in fluorocarbons as synthetic blood candidates[2a-d] and because of our previous work in adamantane chemistry[3a-d] we sought to synthesize perfluoroalkyladamantanes. This paper reports on the synthesis of perfluoro-1-methyl-, 1,3-dimethyl-, and 1,3,5,7-tetramethyladamantane.

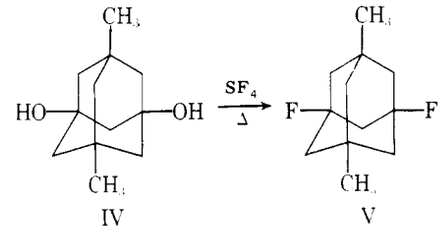
Results and Discussion

Fluorination of 1,3-dimethyladamantane over CoF_3 gives products containing two more fluorines than expected (*m/e* 562 vs. 524) had the starting adamantane structure remained intact. Subsequent isolation and analytical tests identified these as ring-opened products. Repeated preparative chromatography separations did finally result in the isolation of a small quantity of perfluoro-1,3-dimethyladamantane (III) (perfluorinated ring systems are indicated by an F).



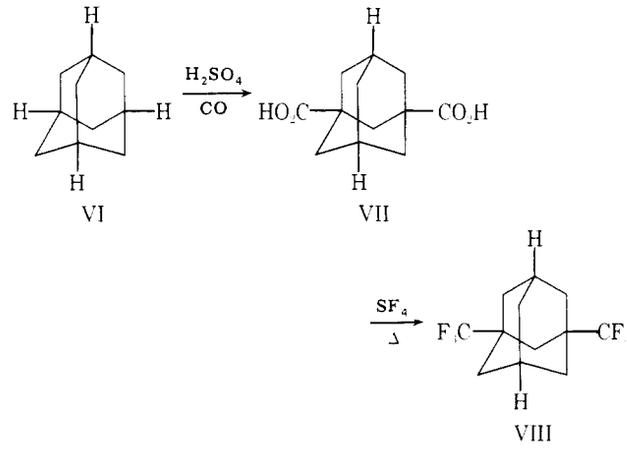
In view of the above, attempts were then made to improve the yield by incorporating fluorine into the molecule prior to exhaustive fluorination over CoF_3. Reaction of SF_4 with 1,3-dihydroxy-5,7-dimethyladamantane[4a,b] gave 1,3-difluoro-5,7-dimethyladamantane in 95% yield.

Subsequent fluorination of V over CoF_3 gave the same



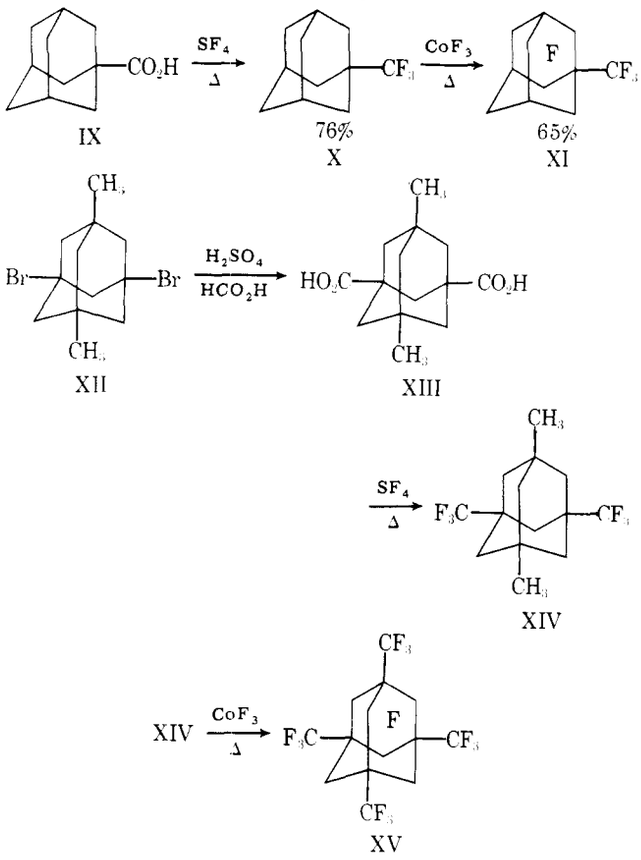
products (II and III) in the same proportion as obtained from fluorination of 1,3-dimethyladamantane. This contrasts sharply with the successful results obtained by Lagow[1] from the direct fluorination of 1,3-difluoro-5,7-dimethyladamantane with fluorine.

Adamantanes containing trifluoromethyl groups were prepared in a manner analogous to earlier work done with benzene-containing trifluoromethyl groups.[5] The following



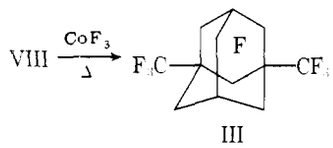
0022-3263/78/1943-4978$01.00/0

Scheme I



reaction scheme was used to prepare 1,3-bis(trifluoromethyl)adamantane (VIII).[6,7]

Fluorination of VIII over CoF_3 led to a 60% yield of perfluoro-1,3-dimethyladamantane (III). The following similar reactions (Scheme I) led to perfluoro-1-methyladamantane (XI) and perfluoro 1,3,5,7-tetramethyladamantane (XV). The biological results obtained from using these compounds as synthetic blood candidates will be reported separately.



Experimental Section

Vapor phase chromatographic analyses were carried out using a 1/8 in. × 20 ft SE-30 (15%) on Chromosorb P column in a thermal conductivity equipped Hewlett Packard Model 5750, and a Perkin-Elmer Model 900 equipped with a flame ionization detector containing a 300 ft Kel-F (3% hexadecane) capillary column.

Preparative chromatography was accomplished over a 0.5 in. × 42 ft column packed with 15% SE-30 on 30/60 Chromosorb P contained in a Hewlett Packard Model 775 equipped with a thermal conductivity detector.

Infrared data were collected on a Perkin-Elmer Model 337 grating spectrophotometer. Mass spectra were obtained from a GC–mass spectrometer combination (Perkin-Elmer Model 900 GC–Hitachi RMU-6 mass spectrometer) operating at 70 eV. Proton NMR were run on a Varian T-60 and ^{19}F NMR on an XL-100 at 94.1 MHz. Elemental analyses were by Schwartzkopf Microanalytical Laboratory.

Perfluorinations were carried out over a horizontal stirred bed of 3500 g of Cobalt trifluoride contained in a 3.5 ft × 3 in. i.d. Monel reactor stirred by a series of paddles connected to a central shaft. The reactor had four separate heating zones allowing thermal graduations. The compound to be perfluorinated was charged into a preheater by means of a Harvard Infusion syringe pump. The preheater was maintained at a temperature sufficiently high to vaporize the compound prior to entering the reactor.

In almost all cases, the material to be fluorinated was passed through the reactor twice. The first pass was made with the reactor temperatures somewhat above the reported boiling points of the material being charged. As fluorination takes place, the boiling point of the product increases until 50% of the hydrogens have been replaced; further fluorination causes a decrease in the boiling point of the product. Thus the first pass was generally made at a moderate charge rate with the reactor thermally graduated from just above the boiling point of the charge material at the entrance to approximately 50 °C above its boiling point at the exit. The second pass was made at considerably higher temperatures (approximately 100 °C greater across the reactor) to complete the perfluorination.

The product was removed from the reactor through traced lines into a series of traps varying in temperature from 0 to −78 °C which are designed not only to remove product but also HF and other gaseous products. A 3 to 4 h nitrogen purge was required to remove all product from the reactor. This reactor is ideal for preparing small experimental samples and is also capable of preparing up to 300 g of fluorocarbon per run.

Regeneration of Cobalt Trifluoride. After the reactor had been purged sufficiently with nitrogen to remove the products of fluorination, the reactor temperature was adjusted to 250 °C in all four zones with the shaft rotating at 5–7 rpm. The valving system was changed to open the fluorine line into the reactor. The rate of fluorine addition was monitored by a fluorine regulator and flowmeter. The reaction of fluorine with CoF_2 is essentially quantitative and highly exothermic. The course of the regeneration was easily followed by observing the progression of the exotherm from zone 1 through zone 4 of the reactor.

Perfluorotrimethylbicyclo[3.3.1]nonane (II). The product resulting from the fluorination of 1,3-dimethyladamantane (I) over CoF_3 was a mixture of materials, the majority of which had an *m/e* of 562 rather than an *m/e* of 524. ^{19}F NMR showed these materials to be an isomeric mixture of trimethylbicyclo[3.3.1]nonanes (II).

The same results were obtained when 1,3-difluoro-5,7-dimethyladamantane (V) was fluorinated in the same manner.

1,3-Difluoro-5,7-dimethyladamantane (V). 1,3-Dihydroxy-5,7-dimethyladamantane (IV) (39 g; 0.2 mol) was placed in a stainless steel reactor and excess (~75 g) SF_4 added to the cooled reactor. The mixture was heated to 125 °C for 4 h, cooled, and allowed to stand overnight. Excess SF_4 was bled from the reactor and the contents poured into water. Chloroform was added and the organic layer extracted several times with water and sodium carbonate solution. The product was isolated by collecting the fraction which distilled at 45–47 °C at 0.5 mm Hg. The molar yield of V was 96% (38 g), a clear, colorless liquid.

The mass spectrum run at 9 eV displayed a parent peak at *m/e* 200 and a large parent-methyl peak at *m/e* 185. Anal. Calcd for $C_{12}H_{18}F_2$: C, 72.00; H, 9.00; F, 19.00. Found: C, 72.23; H, 9.05; F, 18.92.

The ^1H NMR spectrum in CCl_4 consisted of peaks at 2.0, 2.2, 3.1 (triplet), and 3.9 (triplet) ppm with respect to $SiMe_4$ with integration in a ratio of 6:2:8:2, respectively.

1-(Trifluoromethyl)adamantane (X). Adamantane carboxylic acid (IX) (Aldrich) (36 g; 0.2 mol) was placed in a dry ice cooled stainless steel reactor to which excess SF_4 (ca. 100 g) was added. The reaction mixture was heated to 150 °C for about 18 h. After excess SF_4 was vented, the contents of the reactor was poured into water. Chloroform was added and the organic layer extracted three times each with water and sodium carbonate solution. The mixture was distilled collecting the fraction boiling at 45 °C at 0.3 mm Hg. The molar yield was 31 g (76%). Analysis by combined gas–liquid chromatography–mass spectrometry showed a small parent peak at *m/e* 204 and a large parent-fluorine peak at *m/e* 185. Anal. Calcd for $C_{11}H_{15}F_3$ (X): C, 64.71; H, 7.35; F, 27.94. Found: C, 64.80; H, 7.00; F, 28.20.

Perfluoro-1-methyladamantane (XI). Fluorination of 1-(trifluoromethyl)adamantane (X) over CoF_3 gave perfluoro-1-methyladamantane (XI) in 65% yield (mp 123–125 °C). Identification was made by mass spectrometry and ^{19}F NMR. The mass spectrum had a small parent peak at *m/e* 474 and a large parent-fluorine peak at *m/e* 455. The ^{19}F NMR spectrum consisted of peaks at −12.0, +43.1, +53.2, and +151.8 ppm with respect to Freon 113 in the ratio of 1:2:2:1. Anal. Calcd for $C_{11}F_{18}$: C, 27.85; F, 72.15. Found: C, 27.34; F, 72.31.

1,3-Bis(trifluoromethyl)adamantane (VIII). Adamantane (VI) (Aldrich) (100 g; 0.74 mol) was placed in a stirred pressure reactor with 250 mL of 96% sulfuric acid and 250 mL of 20% fuming sulfuric acid. The reaction was heated to 95 °C for 6 h after adding 600 psig of carbon monoxide. The resulting mixture was poured over 4 L of flaked ice. The crude product was isolated by filtration and thoroughly

washed with water. The crude 1,3-adamantanedicarboxylic acid (VII) was stirred four times with 1 L of boiling chloroform. This removes monocarboxylic acid and some unknown impurities. The resulting white diacid was dried in air at room temperature for 3 days.

The diacid mp 280–281 °C (25 g; 0.11 mol) was placed in a stainless steel reactor and excess SF_4 (85 g) was added at low temperature. After the addition was completed the mixture was heated to 150 °C for 20 h, the excess SF_4 vented, and the mixture poured into water. Carbon tetrachloride was added and the mixture was distilled, the product being collected at 70–75 °C at 10 mm Hg. Three combined runs were distilled on a 45-plate spinning-band column. The product was collected at 71 °C at 10 mm Hg. The yield after the first distillation was (22.5 g) 74% of theory.

The mass spectrum run at 9 eV showed a parent peak at *m/e* 272 and a large parent-fluorine peak at *m/e* 253. Anal. Calcd for $C_{12}H_{14}F_6$: C, 52.94; H, 5.14; F, 41.91. Found: C, 52.81; H, 5.49; F, 42.05.

Perfluoro-1,3-dimethyladamantane (III). Fluorination of 1,3-bis(trifluoromethyl)adamantane (VIII) over CoF_3 gave perfluoro-1,3-dimethyladamantane (III) (mp 67–68 °C) in 60% yield. The product was isolated by preparative chromatography and identified by mass spectrometry and ^{19}F NMR.

The mass spectrum run at 70 eV had a parent peak at *m/e* 524 and a very large parent-fluorine peak at *m/e* 505. Other major fragmentation masses were observed at *m/e* 455, 417, 367, 355, 317, 305, and 267. Anal. Calcd for $C_{12}F_{20}$: C, 27.48; F, 72.51. Found: C, 26.95; F, 72.78.

The ^{19}F NMR spectrum in CD_2Cl_2 consisted of peaks at −20.72, +23.02, +35.42, +44.63, and +142.13 ppm with respect to an external trifluoroacetic acid reference, with integration in a ratio of 6:2:8:2:2, respectively. The infrared spectrum consisted of bands at 1330 (m), 1310 (s), 1250 (w), 1180 (m), 1160 (w), 1115 (m), 970 (s), 890 (m), 820 (w), 745 (w), 690 (w), and 625 (w) cm^{-1}.

1,3-Bis(trifluoromethyl)-5,7-dimethyladamantane (XIV). 1,3-Dibromo-5,7-dimethyladamantane (XII) (32.3 g; 0.1 mol) was slowly added to sulfuric acid (100 mL of 95% sulfuric acid and 100 mL of 20% fuming sulfuric acid) cooled to about 10 °C in an ice bath. Formic acid, 98% (10 g; small excess), was slowly added to the well-stirred mixture. Near completion, extensive foaming was observed in the mixture. The mixture was poured over ca. 4 L of flaked ice. The resulting white solid was recovered by filtration. Extensive washing with cold water was necessary to remove the sulfuric acid. The white solid was dried in air at room temperature for 1 week.

The resulting 1,3-dicarboxy-5,7-dimethyladamantane (XIII), mp 270 °C, was placed in a cooled stainless steel reactor and 25% excess sulfur tetrafluoride added. After addition, the mixture was heated to 150 °C (ca. 850 psig) for 18 h. The cooled reactor was slowly vented to atmospheric pressure and the contents poured into water and washed once with sodium carbonate solution and two further times with water. The product was then distilled, collecting the fraction boiling at 80–83 °C at 0.5 mm Hg. The isolation yield (27.6 g) was 92% of theory. The product which solidified upon cooling melted at 57–59 °C. Anal. Calcd for $C_{14}H_{18}F_6$: C, 56.00; H, 6.00; F, 38.00. Found: C, 55.73; H, 6.22; F, 37.60. The mass spectrum run at 9 eV showed a parent peak at *m/e* 300, a large parent-methyl peak at *m/e* 285, and a parent-CF_3 peak at *m/e* 231. The proton NMR run in CCl_4 consisted of peaks at 3.4, 2.9, 2.4, and 2.0 ppm with respect to $SiMe_4$ in the following ratio: 2:8:2:6.

Perfluoro-1,3,5,7-tetramethyladamantane (XV). Fluorination of 1,3-bis(trifluoromethyl)-5,7-dimethyladamantane (XIV) over CoF_3 gave a mixture of products from which perfluoro-1,3,5,7-tetramethyladamantane crystallized on cooling, mp 128–129 °C.

The yield of XV was 10%. The remainder of the fluorinated material, liquid and composed of one major and several minor components on our $\frac{1}{8}$ in. × 20 ft SE-30 GC column, was not further characterized.

The difference in melting point for XV compared with the value (138 °C) reported by Lagow[1] is difficult to explain. The elemental analysis for XV is certainly consistent for a $C_{14}F_{24}$ compound. Then too, the infrared and ^{19}F NMR spectra of our two compounds are superimposable. There is some evidence,[1] however, that a small amount of impurity lowers the melting point substantially. Analysis of XV on a 300 ft Kel-f capillary column shows a small shoulder in addition to the single large peak. Anal. Calcd for $C_{14}F_{24}$: C, 26.92; F, 73.07. Found: C, 26.94; F, 73.09.

The mass spectrum of XV (at 70 eV) showed a large parent-fluorine peak at *m/e* 605. The ^{19}F NMR spectrum run in CCl_4 was very distinctive with peaks at −24.4 and +19.7 ppm with respect to trifluoroacetic acid in a 1:1 integration ratio.

Acknowledgment. The work upon which this publication is based was supported in part by contract No. 1-HB6-2927 with the National Heart Lung and Blood Institute, Department of Health, Education and Welfare, and by Suntech, Inc. We thank Mr. Ronald Bingeman for his invaluable assistance in purifying the subject compounds by preparative chromatography. The authors are also indebted to R. W. Warren for proton NMR interpretation and to Mr. Eugene F. White and Mr. David L. Kerr for performing much of the experimental work. The authors are especially indebted to Dr. Leland C. Clark, Jr., for being the driving force behind this work.

Registry No.—I, 702-79-4; II, 67711-54-0; III, 36481-20-6; IV, 10347-01-0; V, 60389-56-2; VI, 281-23-2; VII, 39269-10-8; VIII, 40556-46-5; IX, 828-51-3; X, 40556-44-3; XI, 60096-00-6; XII, 21912-23-2; XIII, 13928-68-2; XIV, 40556-52-3; XV, 67700-17-8; CoF_3, 10026-18-3; SF_4, 7783-60-0.

References and Notes

(1) This paper is a result of Suntech's fluorocarbon artificial blood program. Closely related work which grew out of a collaborative effort with R. J. Lagow as a Suntech Consultant appears in the next paper: R. J. Lagow, G. Robertson, and E. K. S. Liu, *J. Org. Chem.*, following paper in this issue.
(2) (a) L. C. Clark, Jr., F. Becatini, S. Kaplan, V. Obrock, D. Cohen, and C. Becker, *Science*, **181**, 681 (1973). (b) L. C. Clark, Jr., E. P. Wesseler, M. L. Miller, S. Kaplan, *Microvascular Res.*, **8**, 320 (1974). (c) R. Naito et al., *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **34**, 1478 (1975). (d) L. C. Clark, Jr., E. P. Wesseler, S. Kaplan, C. Emory, R. Moore, and D. Denson, *ACS Symp. Ser.*, **No. 28**, 135 (1976).
(3) (a) R. E. Moore, A. Schneider, and R. W. Warren, *Prepr., Div. Pet. Chem., Am. Chem. Soc.*, **15**, B43 (1970); (b) R. E. Moore, Kirk-Othmer Encylcopedia of Chemical Technology, Suppl., 2nd ed., 1971.
(4) (a) R. E. Moore, presented at Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1968; (b) R. E. Moore (Sun Oil Co.), U.S. Patent 3 383 423 (May 14, 1968).
(5) R. D. Fowler et al., *Ind. Eng. Chem.*, **39**, 292 (1947).
(6) A. A. Lamola (E. I. du Pont), U.S. Patent 3 250 805 (May 10, 1966).
(7) C. W. Tullock (E. I. du Pont), U.S. Patent 3 714 273 (Jan. 30, 1973).