Nucleophilic Attack on the 2,5-Bis(perfluoroalkyl)-1,3,4-oxadiazoles. II. Synthesis of Perfluoroalkyl-Substituted 1,2,4,5-Tetrazines, 1,2-Dihydro-1,2,4,5-tetrazines, and 4-Amino-1,2,4,4H-triazoles[1]

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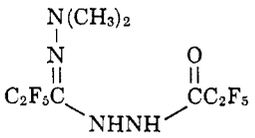
2,5-Bis(perfluoroalkyl)-1,3,4-oxadiazoles were attacked readily by hydrazine with opening of the ring and formation of the acyclic N^2-(α-hydrazonoperfluoroalkyl)perfluoroacylhydrazides, $R_FC(=NNH_2)NHNHC(=O)R_F$. Concurrent dehydration and oxidation of these intermediates produced the corresponding 3,6-bis(perfluoroalkyl)-1,2,4,5-tetrazines; ring closure without oxidation produced the corresponding 3,5-bis(perfluoroalkyl)-4-amino-1,2,4,4H triazoles. The 3,6-bis(perfluoroalkyl)-1,2,4,5-tetrazines were reduced to 3,6-bis(perfluoroalkyl)-1,2-dihydro-1,2,4,5-tetrazines, which could be isomerized to 4-amino-1,2,4,4-triazoles. Deamination of the 3,5-bis(perfluoroalkyl)-4-amino-1,2,4,4H-triazoles resulted in the formation of 3,5-bis(perfluoroalkyl)-1,2,4-triazoles.

The previous paper[1] described the attack of ammonia and methylamine on the 2,5-bis(perfluoroalkyl)-1,3,4-oxadiazoles[2] in which ring opening occurred to form the acyclic N^2-perfluoroacylperfluoroalkylhydrazidines. Dehydration of these compounds reclosed the ring to form 3,5-bis(perfluoroalkyl)-1,2,4-triazoles.

This paper describes a similar ring-opening attack on the 2,5-bis(perfluoroalkyl)-1,3,4-oxadiazoles by hydrazine, with subsequent ring closure of the acyclic intermediates.

Reaction of hydrazine with 2,5-bis(perfluoroalkyl)-1,3,4-oxadiazoles (I) in the absence of a solvent was vigorous, exothermic, and resulted in a wide variety of products not easily separated. Moderation of the reaction was obtained by using alcohol as a solvent and lowering the reaction temperature to 0°. Under these conditions, good yields of N^2-(α-hydrazonoperfluoroalkyl)perfluoroacylhydrazides (II) were isolated (Scheme I).

The structure of the N^2-(α-hydrazonoperfluoroalkyl)perfluoroacylhydrazides was confirmed by infrared absorption analyses. The following maxima were observed: 2.95–2.99 (N–H stretch), 3.30–3.42 (N–H associated), 5.78–5.82 (C=O stretch), 5.99–6.05 (C=N stretch), 6.19–6.25 (NH_2 deformation), and 6.60–6.69 μ (N–H deformation). Assignment of the N–H deformation bands (as distinguished from the C=N stretching absorption) was made on the basis of the spectrum of a deuterated sample of N^2-(α-hydrazonoperfluoropropyl)perfluoropropionhydrazide. This material showed maxima assigned to N–D (stretch) at 4.10 μ, N–D (associated) at 4.45 μ, and an absence of absorption at 6.20 and 6.60 μ, where N–H deformation absorption appeared in the nondeuterated analog. The infrared spectrum of N^2-(α-dimethylhydrazonoperfluoropropyl)perfluoropropionhydrazide (VI) was examined also and showed no absorption in

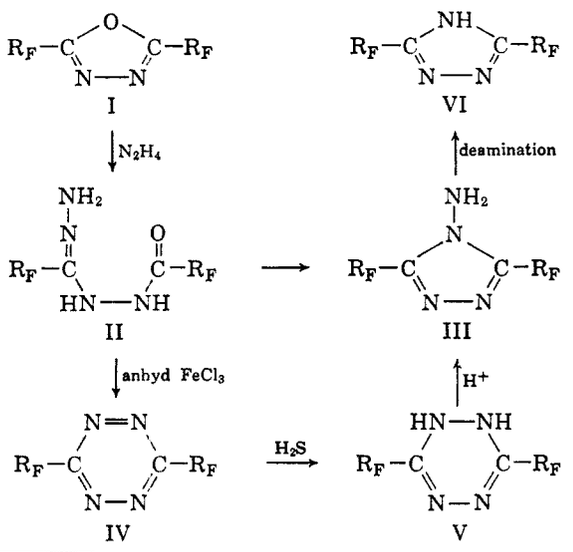


VI

the 6.20-μ N–H deformation region but did show the C=N stretching absorption at 6.06 μ. F^{19} nmr studies of II showed that the two perfluoroalkyl groups were in different environments, and the empirical formula of this compound was verified by elemental analysis.

Attempts to cyclize II to the dihydrotetrazine (V) with a variety of dehydrating reagents resulted in the formation of a small yield of 3,5-bis(perfluoroalkyl)-4-amino-1,2,4,4H-triazole (III) and many other products difficult to separate. Good yields of III were obtained from II by refluxing in glacial acetic acid. The infrared spectrum of III showed the distinctive asymmetrical and symmetrical stretching absorption maxima of the NH_2 group at 2.95–3.09 μ; NH_2 deformation appeared at 6.04–6.08 μ. The assignment of the deformation frequency was substantiated by comparison of these spectra with the spectra of deuterated samples of 3,5-bis(perfluoroethyl)-4-amino-1,2,4,4H-triazole and 3,5-bis(perfluoropropyl)-4-amino-1,2,4,4H-triazole; N–D stretching occurred at 3.93–4.17 μ and no absorption was found in the previously assigned N–H deformation region. 3,5-Bis(perfluoroalkyl)-4-amino-1,2,4,4H-triazoles showed two maxima (at 6.50 and 6.75 μ) assigned to C=N stretching in ac-

SCHEME I



(1) This investigation was supported in part by Public Health Service Research Grant No. CA-05083 from the National Cancer Institute, in part by a Grant-in-Aid from the General Chemical Division, Allied Chemical Corp., and in part by U. S. Air Force, Aeronautical Systems Division, Contract AF 33(615)1368. Previous paper in this series: H. C. Brown and M. T. Cheng, *J. Org. Chem.*, **27**, 3240 (1962).

(2) H. C. Brown, M. T. Cheng, L. J. Parcell, and D. Pilipovich, *J. Org. Chem.*, **26**, 4407 (1961).

cordance with previous assignments[1] made for 3,5-bis(perfluoromethyl)-4-methyl-1,2,4,4H-triazole.

The far-ultraviolet spectrum of 3,5-bis(perfluoroethyl)-4-amino-1,2,4,4H-triazole showed a maximum at 195.5 mμ (log ϵ_{max} 3.85) (in acetonitrile). The NH_2 auxochrome is responsible for a bathochromic shift, since 3,5-bis(perfluoropropyl)-1,2,4-triazole absorbs at λ_{max} 185 mμ (log ϵ_{max} 3.74) (in acetonitrile). A bathochromic shift of 10 mμ is also observed for the anion of 3,5-bis(perfluoropropyl)-1,2,4-triazole prepared by adding aqueous NaOH to the acetonitrile solution of the triazole. It was expected that the amino group with its free pair of electrons would exhibit an electron-donating effect upon the triazole ring. Though a quantitative determination of the effect of the auxochrome cannot be made with the present data, one can state qualitatively that the amino group has much the same effect as the anion of the triazole.

Further proof of the structure of the 3,5-bis(perfluoromethyl)-4-amino-1,2,4,4H-triazole and 3,5-bis(perfluoropropyl)-4-amino-1,2,4,4H-triazole was obtained by deamination with nitrous acid, which gave 3,5-bis(perfluoroalkyl)-1,2,4-triazole.[1] Similar replacements of NH_2 by hydrogen have been reported for N-amino compounds[3] and probably proceed by the loss of nitrous oxide, as is found in similar reactions of N,N-disubstituted hydrazines.[4]

The 3,5-bis(perfluoroalkyl)-4-amino-1,2,4,4H-triazoles were acylated to give the corresponding 3,5-bis(perfluoroalkyl)-4-acylamino-1,2,4,4H-triazoles, reconfirming the presence of the NH_2 group by the characteristic spectra of the products, since the NH_2 deformation band at 6.04–6.08 μ disappeared from the spectra of the acylated products.

Although the N^2-(α-hydrazonoperfluoroalkyl)perfluoroacylhydrazides (II) were not cyclized to the 1,2-dihydrotetrazines in good yield, cyclization with concurrent dehydration and oxidation by reaction with anhydrous ferric chloride at elevated temperatures gave 3,5-bis(perfluoroalkyl)-1,2,4,5-tetrazines (IV), as deep red liquids. Carboni and Lindsey[5] reported the preparation of 3,5-bis(polyfluoroalkyl)-1,2,4,5-tetrazines produced by the reaction of fluoro olefins with hydrazine. Their method, however, produced compounds which had one hydrogen atom on the carbon α to the ring; the present work furnished the first example of *sym*-tetrazines with completely fluorinated alkyl substituents, as well as a new method for the preparation of 1,2,4,5-tetrazines.

3,6-Bis(perfluoropropyl)-1,2,4,5-tetrazine exhibited an absorption maximum at 7.15 μ, with no other significant peaks in the region 2.5–7.15 μ; other symmetrically perfluoroalkyl-substituted tetrazines had comparable spectra. 3-Perfluoromethyl-6-perfluoropropyl-1,2,4,5-tetrazine showed maxima at 6.85 (weak) and 7.09 μ (strong), as might be expected with dissimilar substituents in the conjugated ring structure. These maxima are therefore assigned to ring stretching; diphenyl-*s*-tetrazine[6] also shows characteristic strong absorption at 7.14 μ, which does not appear to be due to C–H absorption alone.

3,6-Bis(perfluoroalkyl)-1,2-dihydro-1,2,4,5-tetrazines[7] (V) were prepared by the reduction of the 3,6-bis(perfluoroalkyl)-1,2,4,5-tetrazines by hydrogen sulfide. This conversion was carried out at room temperature by sealing the tetrazine in a glass tube with a large excess of hydrogen sulfide; the resulting dihydrotetrazine could be oxidized to the original tetrazine by concentrated nitric acid.

Isomerization of 3,5-bis(perfluoropropyl)-1,2-dihydro-1,2,4,5-tetrazine to 3,5-bis(perfluoropropyl)-4-amino-1,2,4,4H-triazole (III) was accomplished by refluxing a slurry of the dihydrotetrazine in a mixture of ethyl alcohol and concentrated hydrochloric acid.[8]

Experimental Section

2,5-Bis(perfluoroethyl)-1,3,4-oxadiazole and 2,5-Bis(perfluoropropyl)-1,3,4-oxadiazole.—These two compounds were prepared by the method previously described,[2] with the added modification of bringing the reaction temperature of the bis(perfluoroacyl)hydrazine–phosphorus pentoxide mixture rapidly to 350° and maintaining this temperature for 4 hr. After this heating period, no additional 2,5-bis(perfluoroalkyl)-1,3,4-oxadiazole passed to the collection trap.

2-Perfluoromethyl-5-perfluoropropyl-1,3,4-oxadiazole.—Silver 5-perfluoropropyltetrazole,[7] 16.0 g (0.063 mole), was dried by heating for 3 hr at 70° under vacuum and then packed lightly in a 25 × 250 mm Pyrex tube with two inlets and one outlet. Dry nitrogen was passed through the tube as the temperature was raised to 150°. Perfluoroacetyl chloride was admitted at a rate of 0.067 g/min until a total of 12.0 g (9.1 × 10^{-2} mole) had been used. The crude oxadiazole, 17.2 g, was collected in a Dry Ice cooled trap, washed with dilute sodium bicarbonate solution, dried, and fractionated to give 15.0 g (78%) of 2-perfluoromethyl-5-perfluoropropyl-1,3,4-oxadiazole, bp 95.8°, n^{25} 1.2980.

N^2-(α-Hydrazonoperfluoropropyl)perfluoropropionhydrazide.—Hydrazine (95+%), 25.6 g (0.8 mole), was dissolved in 25 ml of ethyl alcohol (95%) and placed in a 100-ml flask equipped with a stirrer and cooled by an ice bath. 2,5-Bis(perfluoroethyl)-1,3,4-oxadiazole, 31.0 g (0.101 mole), was added slowly over a 15-min period with stirring; the reaction mixture was allowed to stand for 0.5 hr, and 100 ml of water was added to the solution. Adjustment of the acidity of the solution to pH 6.0 with dilute hydrochloric acid precipitated the product, which was recrystallized from an acetonitrile–water solution to give 32.0 g (93%) of N^2-(α-hydrazonoperfluoropropyl)perfluoropropionhydrazide, mp 177° dec, $\lambda_{max}^{i\text{-PrOH}}$ 265 mμ (log ϵ_{max} 4.07).

Anal. Calcd for $C_6H_4F_{10}N_4O$: C, 21.31; H, 1.20; N, 16.57. Found: C, 21.48; H, 1.11; N, 16.73.

N^2-(α-Hydrazonoperfluorobutyl)perfluorobutyrhydrazide.—This compound was prepared from 3,5-bis(perfluoropropyl)-1,3,4-oxadiazole by the procedure shown in the preceding preparation and was obtained in 91% yield: mp 171° dec, $\lambda_{max}^{i\text{-PrOH}}$ 272 mμ (log ϵ_{max} 4.05).

Anal. Calcd for $C_8H_4F_{14}N_4O$: C, 21.93; H, 0.92; F, 60.73; N, 12.79. Found: C, 22.20; H, 1.11; F, 60.45; N, 12.71.

N^2-(α-Hydrazonoperfluoroethyl)perfluorobutyrhydrazide.—The procedure described above for N^2-(α-hydrazonoperfluoropropyl)perfluoropropionhydrazide was used to prepare this compound from 2-perfluoropropyl-5-perfluoromethyl-1,3,4-oxadiazole. N^2-(α-Hydrazonoperfluoroethyl)perfluorobutyrhydrazide was obtained in 81% yield: mp 154° dec, $\lambda_{max}^{i\text{-PrOH}}$ 263 mμ (log ϵ_{max} 4.02).

Anal. Calcd for $C_6H_4F_{10}N_4O$: C, 21.31; H, 1.20; N, 16.57. Found: C, 21.19; H, 1.38; N, 16.57.

(3) E. Hoggarth, *J. Chem. Soc.*, 4811 (1952); E. Lieber, *et al.*, *J. Org. Chem.*, **18**, 218 (1953); A. W. Lutz, *ibid.*, **29**, 1174 (1964).

(4) T. W. J. Taylor and W. Baher, "Sidgwicks Organic Chemistry of Nitrogen," Clarendon Press, Oxford, 1937, p. 380.

(5) R. A. Carboni and R. V. Lindsey, Jr., *J. Am. Chem. Soc.*, **80**, 5793 (1958).

(6) A sample of 3,6-diphenyl-1,2,4,5-tetrazine was made available by Dr. Merle A. Battiste of the Department of Chemistry, University of Florida.

(7) The first example of a 3,6-bis(perfluoroalkyl)-1,2-dihydro-1,2,4,5-tetrazine was isolated in small yield from the pyrolysis of 5-perfluoroalkyltetrazoles in this laboratory by R. J. Kassal (Ph.D. Dissertation, University of Florida, Dec. 1963).

(8) A. Pinner, *Ber.*, **26**, 2126 (1893).

3,5-Bis(perfluoroethyl)-4-amino-1,2,4,4H-triazole.—N^2-(α-Hydrazonoperfluoropropyl)perfluoropropionhydrazide, 2.10 g (6.2×10^{-3} mole), was refluxed for 3 hr with 7 ml of glacial acetic acid. Upon cooling and diluting the solution with 15 ml of water, crystalline (plates) 3,5-bis(perfluoroethyl)-4-amino-1,2,4,4H-triazole precipitated: mp 96.0–96.5° (after recrystallization from toluene), yield 1.80 g (86%).

Anal. Calcd for $C_6H_4F_{10}N_4$: C, 22.51; H, 0.63; N, 17.51. Found: C, 22.27; H, 0.80; N, 17.52.

3-Perfluoromethyl-5-perfluoropropyl-4-amino-1,2,4,4H-triazole.—N^2-(α-Hydrazonoperfluoroethyl)perfluorobutyrhydrazide, 0.494 g (1.46×10^{-3} mole), was refluxed for 1.5 hr in a solution of 8 ml of glacial acetic acid and 10 ml of concentrated hydrochloric acid. The solution was cooled to room temperature and 15 ml of water was added. Product was extracted from the solution with 30 ml of ethyl ether in successive small portions; the total ether extract was washed with dilute sodium bicarbonate and dried over anhydrous calcium sulfate. Removal of the ether under reduced pressure and recrystallization of the solid from toluene gave 0.068 g (15%) of white, crystalline 3-perfluoromethyl-5-perfluoropropyl-4-amino-1,2,4,4H-triazole, mp 90.0–90.5°.

Anal. Calcd for $C_6H_2F_{10}N_4$: C, 22.51; H, 0.63; N, 17.51. Found: C, 22.35; H, 0.77; N, 17.56.

3,6-Bis(perfluoropropyl)-1,2,4,5-tetrazine.—N^2-(α-Hydrazonoperfluorobutyl)perfluorobutyrhydrazide, 30.0 g (6.8×10^{-2} mole) and 100 g (0.64 mole) of anhydrous ferric chloride were mixed intimately in a 200-ml flask which was swept by dry nitrogen (10 cc/min) into two Dry Ice cooled traps arranged in series. The reaction mixture was heated at 75° for 12 hr, at 90° for 6 hr, and at 125° for 4 hr. During this time crude product, 7.5 ml, passed into the traps. Fractionation at atmospheric pressure gave 10.0 g (35%) of deep red 3,6-bis(perfluoropropyl)-1,2,4,5-tetrazine: bp 150°; d^{25} 1.709; n^{25} 1.3301; $\lambda_{max}^{isooctane}$ 525 mμ (log ϵ_{max} 2.72), 252 mμ (log ϵ_{max} 3.22).

Anal. Calcd for $C_8F_{14}N_4$: C, 22.98; F, 63.62; N, 13.40. Found: C, 22.93; F, 63.83; N, 13.07.

3-Perfluoromethyl-6-perfluoropropyl-1,2,4,5-tetrazine.—N^2-(α-Hydrazonoperfluoroethyl)perfluorobutyrhydrazide, 60.0 g (0.177 mole), was allowed to react in 12.0-g portions with 75 g of anhydrous ferric chloride for each portion, in the manner described above for the preparation of 3,6-bis(perfluoropropyl)-1,2,4,5-tetrazine. The temperature of the reaction mixture was kept at 45° for 12 hr. Higher temperatures than 45° caused extensive decomposition. The total crude liquid product, 8 ml, was distilled to yield 1.0 g of trifluoroacetic acid, 2.4 g of 2-perfluoromethyl-5-perfluoropropyl-1,3,4-oxadiazole, and 4.3 g of the desired tetrazine. Infrared analysis showed the tetrazine still to be contaminated. Final purification by vapor phase chromatography (Silicone SE-30 on Chromosorb P, 85°, He flow 110 cc/min in a 3/8 in. × 20 ft column) gave pure 3-perfluoromethyl-6-perfluoropropyl-1,2,4,5-tetrazine, 4.0 g (7.1%), as a deep red liquid: bp 123°; d^{25} 1.685; n^{25} 1.3409; $\lambda_{max}^{isooctane}$ 533 mμ (log ϵ_{max} 2.70), 252 mμ (log ϵ_{max} 3.23).

Anal. Calcd for $C_6F_{10}N_4$: C, 22.65; N, 17.62; F, 59.73. Found: C, 22.57; N, 18.09; F, 59.87.

3-Perfluoromethyl-6-perfluoropropyl-1,2-dihydro-1,2,4,5-tetrazine.—3-Perfluoromethyl-6-perfluoropropyl-1,2,4,5-tetrazine, 0.10 g (3.14×10^{-4} mole), was condensed in a heavy-wall glass tube previously constricted for sealing. Hydrogen sulfide, 1.0 g (2.7×10^{-2} mole), was condensed in the tube, which was then sealed and allowed to warm to room temperature. After 4 hr the red color of the tetrazine had disappeared. The tube was opened, excess hydrogen sulfide was removed, and the remaining yellow solid was dissolved in toluene in order to remove sulfur by filtration. Crystallization of the solid from the toluene solution gave 0.09 g (90%) of pale yellow 3-perfluoromethyl-6-perfluoropropyl-1,2-dihydro-1,2,4,5-tetrazine, mp 98.0–98.5°, $\lambda_{max}^{i\text{-PrOH}}$ 227 mμ (log ϵ_{max} 3.61).

Anal. Calcd for $C_6H_2F_{10}N_4$: C, 22.51; H, 0.63; N, 17.51. Found: C, 21.81; H, 0.85; N, 17.28.

3,6-Bis(perfluoropropyl)-1,2-dihydro-1,2,4,5-tetrazine.—This compound was prepared by the method described above for 3-perfluoromethyl-6-perfluoropropyl-1,2-dihydro-1,2,4,5-tetrazine. Reduction of 3,5-bis(perfluoropropyl)-1,2,4,5-tetrazine by hydrogen sulfide in this manner gave 3,5-bis(perfluoropropyl)-1,2-dihydro-1,2,4,5-tetrazine, mp 117.5–118.0°, in 80% yield: $\lambda_{max}^{i\text{-PrOH}}$ 232 mμ (log ϵ_{max} 3.54).

Anal. Calcd for $C_8H_2F_{14}N_4$: C. 22.87; H. 0.48; N. 13.34. Found: C. 22.90; H. 0.59; N. 13.99.

Isomerization of 3,6-Bis(perfluoropropyl)-1,2-dihydro-1,2,4,5-tetrazine.—3,6-Bis(perfluoropropyl)-1,2-dihydro-1,2,4,5-tetrazine, 0.12 g, was slurried in a mixture of 3 ml of ethyl alcohol and 5 ml of concentrated hydrochloric acid at room temperature and heated slowly to reflux. After 2 hr the yellow solution became colorless; on cooling the solution to room temperature, 0.08 g (75%) of 3,5-bis(perfluoropropyl)-4-amino-1,2,4,4H-triazole, mp 104.5–105.0°, was collected.

The infrared spectrum of this compound was identical with that of a sample of 3,5-bis(perfluoropropyl)-4-amino-1,2,4,4H-triazole prepared by the method described above for 3,5-bis(perfluoroethyl)-4-amino-1,2,4,4H-triazole; the melting point of a mixture showed no depression.

Anal. Calcd for $C_8H_2F_{14}N_4$: C, 22.87; H, 0.48; F, 63.32; N, 13.34. Found: C, 23.19; H, 0.57; F, 62.68; N, 13.94.

Acylation of 3,5-Bis(perfluoroethyl)-4-amino-1,2,4,4H-triazole.—3,5-Bis(perfluoroethyl)-4-amino-1,2,4,4H-triazole, 0.48 g (1.5×10^{-3} mole), was placed in a heavy-wall glass tube and the tube was pumped free of air. Acetyl chloride, 1.56 g (2.0×10^{-2} mole), was condensed in the tube, which was then sealed and heated at 110° for 12 hr. Removal of the excess acetyl chloride left a brown solid which was sublimed (0.05 mm, 125°) and recrystallized from toluene to give 0.31 g (57%) of white 3,5-bis(perfluoroethyl)-4-acetylamino-1,2,4,4H-triazole, mp 192.5–193.3°.

Anal. Calcd for $C_8H_4F_{10}N_4O$: C, 26.53; H, 1.12; N, 15.47. Found: C, 26.30; H, 1.03; N, 15.64.

Acylation of 3,5-Bis(perfluoropropyl)-4-amino-1,2,4,4H-triazole.—3,5-Bis(perfluoropropyl)-4-amino-1,2,4,4H-triazole was acylated using the procedure described in the previous preparation, with the exception that the mixture was heated at 150° for 24 hr, to give 3,5-bis(perfluoropropyl)-4-acetylamino-1,2,4,4H-triazole, mp 154.5–155.0°.

Anal. Calcd for $C_{10}H_4F_{14}N_4O$: C, 25.99; H, 0.81; N, 12.12. Found: C, 26.00; H, 1.10; N, 12.02.

Deamination of 3,5-Bis(perfluoroethyl)-4-amino-1,2,4,4H-triazole.—3,5-Bis(perfluoroethyl)-4-amino-1,2,4,4H-triazole, 0.10 g (3.1×10^{-4} mole), was dissolved in 4 ml of concentrated sulfuric acid, the solution was cooled to 10°, and a solution of 0.10 g (1.4×10^{-3} mole) of sodium nitrite in 3 ml of sulfuric acid was added. Gas was evolved rapidly; after 30 min the solution was poured over 10 g of ice. A white solid product separated and was recrystallized from toluene to give 0.060 g (65%) of 3,6-bis(perfluoroethyl)-1,2,4-triazole, mp 104°. Comparison of the infrared spectrum of this preparation with that of an authentic sample[1] and a mixture melting point of the two samples established the structure.

Deamination of 3,5-Bis(perfluoropropyl)-4-amino-1,2,4,4H-triazole.—This reaction was carried out by the procedure described in the previous preparation. Reaction of 3,5-bis(perfluoropropyl)-4-amino-1,2,4,4H-triazole gave 3,5-bis(perfluoropropyl)-1,2,4-triazole, mp 109–110° (lit.[1] mp 110–111°).