Nucleophilic Attack on the 2,5-Bis(perfluoroalkyl)-1,3,4-oxadiazoles. I. Synthesis of 3,5-Bis(perfluoroalkyl)-1,2,4-triazoles and 4-Methyl-1,2,4,4*H*-triazoles[1]

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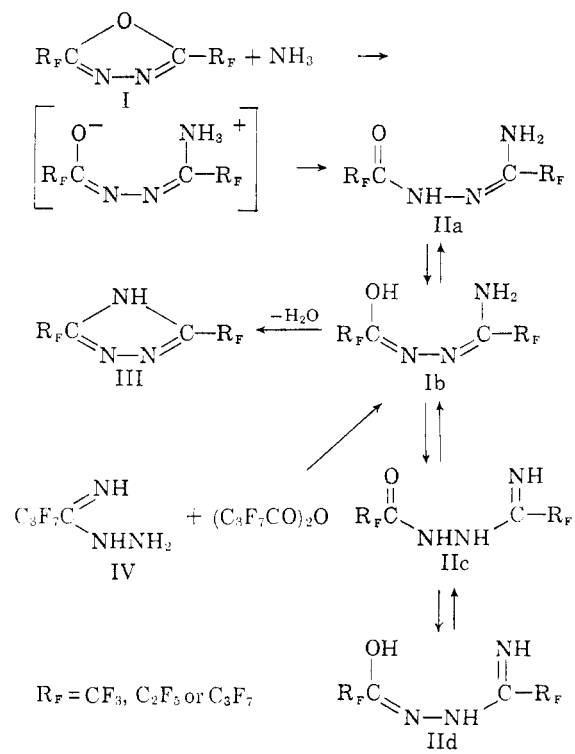
2,5-Bis(perfluoroalkyl)-1,3,4-oxadiazoles were easily attacked by ammonia or methylamine with opening of the ring and formation of the acyclic 1-(perfluoroacylimidoyl)-2-(perfluoroacyl)hydrazine, $R_FC(:NH)NHNHC(:O)R_F$ or 1,2-bis(*N*-methylperfluoroacylimidoyl)hydrazine, $R_FC(:NCH_3)NHNHC(:NCH_3)R_F$; dehydration or deammination of these intermediates produced the corresponding 3,5-bis(perfluoroalkyl)-1,2,4-triazole or the 3,5-bis(perfluoroalkyl)-4-methyl-1,2,4,4*H*-triazole. The 3,5-bis(perfluoroalkyl)-1,2,4-triazoles are strong acids with pK_a values of 2.7–3.1 (in water–dioxane).

A previous paper[2] described the preparation of the 2,5-bis(perfluoroalkyl)-1,3,4-oxadiazoles and mentioned the ease of attack by nucleophilic reagents on this perfluoroalkyl-substituted heterocycle. This paper describes the attack by ammonia and methylamine and shows, by isolation of intermediate products, the probable mechanism of the reaction.

Meyer[3] reported that treatment of 2,5-dimethyl-1,3,4-oxadiazole with alcoholic methylamine at 110° produced 3,4,5-trimethyl-1,2,4,4*H*-triazole; no intermediate product was recorded. Replacement of —O— by —NH— in certain other heterocycles has been shown, for example, Bordner's[4] preparation of pyrroles from furan, but the mechanism has not been clearly shown.

In the 2,5-bis(perfluoroalkyl)-1,3,4-oxadiazoles, the strongly inductive perfluoroalkyl groups enhanced the ease of nucleophilic attack at the ring carbon atoms and the reaction with ammonia or methylamine proceeded readily at room temperature.

The reaction of ammonia with a 2,5-bis(perfluoroalkyl)-1,3,4-oxadiazole, I, apparently began with the nucleophilic attack of ammonia on a ring carbon to give an intermediate compound with ring opening; immediate proton shifts then gave the tautomeric forms IIa, b, c, d of 1-(perfluoroacylimidoyl)-2-(perfluoroacyl)hydrazine.[5] Dehydration of II formed the 3,5-bis(perfluoroalkyl)-1,2,4 triazole III. The structure of II was confirmed by the synthesis of an identical sample by acylation of perfluorobutyrhydrazidine[6] (IV) with perfluorobutyric anhydride.



The reaction of methylamine with 2,5-bis(perfluoroalkyl)-1,3,4-oxadiazoles at room temperature or at the reflux temperature of methylamine produced only the symmetrical 1,2-bis(N-methylperfluoroacylimidoyl)hydrazine (VI). No product of structure V, resulting from the reaction of one molecule of methylamine, was isolated. Since a similar replacement of the carbonyl oxygen does not occur with ammonia, the greater nucleophilicity of methylamine must promote the further attack on the C=O group. Deamination of VI by heating produced 3,5-bis(perfluoroalkyl)-4-methyl-1,2,4,4*H*-triazole (VII).

Additional evidence of the ease with which methylamine attacked and replaced the carbonyl

(1) This work was supported by a Grant-in-Aid from the General Chemical Division, Allied Chemical Corp.

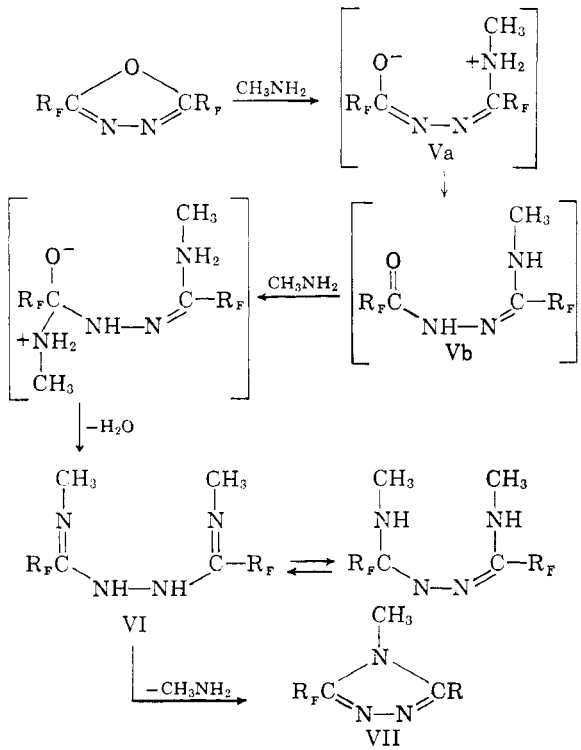
(2) H. C. Brown, M. T. Cheng, L. J. Parcell, and D. Philipovich, *J. Org. Chem.*, **26**, 4407 (1961).

(3) R. Meyer, German Patent 574,944 (April 21, 1933); *Chem. Abstr.*, **27**, 4541 (1933).

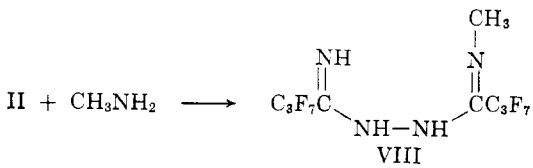
(4) C. A. Bordner, U. S. Patent 2,600,689 (June 10, 1952); *Chem. Abstr.*, **47**, 4373 (1953).

(5) The nomenclature employed obviously refers to structure IIc, although the infrared data indicate IIa to be the more probable form in the solid state; consideration of the ammonia and methylamine products as hydrazine derivatives makes the nomenclature somewhat more consistent.

(6) H. C. Brown and D. Pilipovich, *J. Am. Chem. Soc.*, **82**, 4700 (1960).

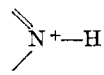


oxygen was gained by treatment of II with methylamine; this reaction produced 1-(perfluorobutyrimidoyl) - 2 - (N - methylperfluorobutyrimidoyl)hydrazine (VIII).



The infrared absorption spectra of the 1-(perfluoroacylimidoyl)-2-(perfluoroacyl)hydrazines (II) showed maxima at 2.80, 2.95, and 3.10 μ (N—H stretching), at 5.85 μ (C=O stretching) and 6.05, 6.15, and 6.50 μ (C=N stretching and possibly N—H deformation); 1,2-bis(N-methylperfluoroacylimidoyl)hydrazine (VI) showed weak N—H stretching absorption at 3.35–3.60 μ, a rather broad band at 6.30 μ (C=N) and no absorption in the C=O region. The reaction product of II with methylamine, 1-(perfluorobutyrimidoyl)-2-(N-methylperfluorobutyrimidoyl)hydrazine, VIII, gave two maxima for N—H stretching at 2.80 and 2.95 μ, characteristic C—H stretching at 3.30–3.50 μ, and absorption at 6.02 (sh.), 6.15, 6.23, and 6.40 μ, assigned to C=N stretching and N—H deformation; no C=O absorption was found in the spectrum of VIII.

The most interesting features of the infrared spectra of the bis(perfluoroalkyl)triazoles, III, (in the solid state) were a strong, broad band at 3.20–3.50 μ and a weak, broad band at 5.50–5.70 μ. Otting,[7] following similar assignments made by Witkop[8] and Potts,[9] interpreted these absorptions as being due to intermolecular association in which the hydrogen atom of the imino group protonates an unsaturated nitrogen of an adjacent molecule, the two charged molecules being stabilized by resonance. The band at 3.20–3.50 μ is an ammonium-type absorption and the maxima at 5.50–5.70 μ the so-called immonium band due to the structural element



Substitution of a methyl group for hydrogen, as in the 3,5-bis(perfluoroalkyl)-4-methyl-1,2,4,4*H*-triazoles (VII) eliminated these two broad bands from the infrared spectra.

Assignment of C=N stretching absorption bands in the perfluoroalkylsubstituted triazoles cannot be made with certainty with the information presently available concerning this class of substituted heterocycles. 3,5-Bis(perfluoropropyl)-1,2,4-triazole showed weak absorption at 6.70 μ and strong absorption at 6.93 μ, with no absorption between 6.0 and 6.5 μ. Substitution of a methyl group for the N-hydrogen in this compound results in the same two bands with their intensity reversed. If these represent C=N stretching, they appear at an unusually long wave length.

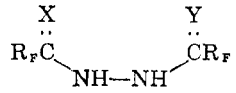
The n.m.r. spectra confirmed the structure shown for 1-(perfluorobutyrimidoyl)-2-(perfluorobutyryl)-hydrazine (II); two triplets were found at 2.93 and 3.19 p.p.m., (CF_3) and two quartets at 38.9 and 42.1 p.p.m., (CF_2)$_2$, indicating unsymmetrical placement of the perfluoroalkyl groups. In addition, two types of hydrogen were indicated for II. 3,5 - Bis(perfluoropropyl) - 1,2,4 - triazole (III) exhibited only one triplet at 3.4 p.p.m. (CF_3), one quartet at 35.8 p.p.m. (CF_2), and only one kind of hydrogen. This structure was therefore apparently symmetrical.

The 3,5 - bis(perfluoroalkyl) - *s* - triazoles were readily soluble in polar solvents and only slightly soluble in nonpolar solvents. The introduction of methyl group into 4-position lowers the melting point considerably and increases the solubility in nonpolar solvents. The 3,5-bis(perfluoroalkyl)-1,2,4-triazoles were not oxidized by acidic potassium permanganate or hydrolyzed by water or concentrated sulfuric acid. These compounds were quite stable to high temperatures; all of the original sample was recovered when a quantity of 3,5-bis(perfluoropropyl)-1,2,4-triazole was heated in a previously evacuated tube at 200–350° (with a 25° rise in temperature each hour) and held at 350° for three hours.

(7) W. Otting, *Chem. Ber.*, **89**, 2887 (1956).
(8) B. Witkop, J. B. Patrick, and H. M. Kissman, *Chem. Ber.*, **85**, 949 (1952).
(9) K. T. Potts, *J. Chem. Soc.*, 3461 (1954).

TABLE I

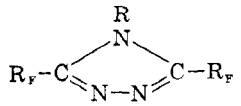
PERFLUOROACYLIMIDOYL–PERFLUOROACYL SUBSTITUTED HYDRAZINES



R_F	X	Y	M.p., °C.	Calcd., % C	H	F	N	Found, % C	H	F	N
CF_3	NH	O	147.0–147.5	21.52	1.34	51.12	18.83	21.76	1.14	50.77	18.60
C_2F_5	NH	O	156.0–156.5	22.29	0.93	58.82	13.00	22.48	0.98	59.12	12.87
C_2F_7	NH	O	148–149	22.69	0.71	62.88	9.93	22.65	0.95	61.98	9.95
CF_3	NCH_3	NCH_3	99.0–99.5	...	...	...	22.40	...	...	...	21.95
C_2F_5	NCH_3	NCH_3	94.5–95.0	27.43	2.28	...	16.00	27.31	2.50	...	16.00
C_3F_7	NCH_3	NCH_3	105.0–105.8	...	...	...	12.45	...	...	...	12.30
C_3F_7	NH	NCH_3	122.0–122.5	...	...	...	12.84	...	...	...	13.00

TABLE II

3,5-BIS(PERFLUOROALKYL)-1,2,4-TRIAZOLES



R_F	R	M.p., °C.	Calcd., % C	H	F	N	Mol. Wt.	Found, % C	H	F	N	Mol.[a] wt.
CF_3	H	76–77	23.41	0.48	55.60	20.48	205	23.30	0.66	55.57	20.35	197
C_2F_5	H	104.0–104.5	23.60	0.33	62.29	13.77	305	23.81	0.35	62.57	13.57	304
C_3F_7	H	110–111	23.70	0.25	65.68	10.37	405	23.56	0.48	65.32	10.31	395
CF_3	CH_3	199.5–200 (b.p.)[b]	27.39	1.37	52.05	19.17		27.11	1.50	51.88	19.00	
C_2F_5	CH	49.5–50.0	26.33	0.94	59.56	13.17		26.63	0.87	59.30	13.00	
C_3F_7	CH	47.5–48.0	25.77	0.71	63.48	10.02		26.01	1.01	63.46	10.03	

[a] By titration in dioxane–water solution. [b] d^{25} 1.631, n^{25} 1.3647.

Each of the 3,5-bis(perfluoroalkyl)-1,2,4-triazoles prepared was an unusually strong acid; titration with sodium hydroxide in a dioxane–water solution gave pK_a values ranging from 2.72 to 3.10. In contrast, the 3,5-bis(alkyl)-*s*-triazoles are amphoteric in nature. The strong acidity of the perfluoroalkyl-substituted compounds must be attributed to the extreme electron deficiency of the aromatic ring caused by the electron-attracting properties of the perfluoroalkyl groups.

Experimental[10]

1-(Perfluorobutyrimidoyl)-2-(perfluorobutyryl)hydrazine. Method A.—2,5-Bis(perfluoropropyl)-1,3,4-oxadizoale,[2] 20.0 g. (0.049 mole), was placed in a heavy-walled glass tube previously constricted for sealing. The reaction tube was cooled in liquid nitrogen and pumped free of air; 1.5 g. (0.088 mole) of dry ammonia was condensed in the tube, which was then sealed and warmed slowly to room temperature. White solid product formed within 2 hr. The tube was opened, excess ammonia pumped off and 21.0 g. of crude product removed. Recrystallization from ethyl alcohol gave 19.3 g. (93%) of white crystalline 1-(perfluorobutyrimidoyl)-2-(perfluorobutyryl)hydrazine, m.p. 148–149°.

Method B.—Perfluorobutyrhydrazidine,[6] 1.5 g. (0.0066 mole), and 5 ml. of perfluorobutyric acid were placed in a round-bottom flask, the flask cooled in an ice bath, and 8.2 g. (0.02 mole) of perfluorobutyric anhydride added slowly. The solid product was filtered from the cold reaction mixture and recrystallized from ethyl alcohol to give a quantitative yield of 1-(perfluorobutyrimidoyl)-2-(perfluorobutyryl)-hydrazine, identical with the product from method A.

1-(Perfluoropropionimidoyl)-2-(perfluoropropionyl)hydrazine and 1-(Perfluoroacetimidoyl)-2-(perfluoroacetyl)-hydrazine.—The two compounds were prepared by method A shown for 1-(perfluorobutyrimidoyl)-2-(perfluorobutyryl)-hydrazine and were obtained in 95 and 75% yields, respectively.

3,4-Bis(perfluoropropyl)-1,2,4-triazole.—1-(Perfluorobutyrimidoyl)-2-(perfluorobutyryl)hydrazine, 5.0 g. (0.0118 mole) and an equal weight of phosphorus pentoxide were placed in an 8 in. test tube with a side arm near the top to which a drying tube was attached. A water-cooled cold-finger condenser was fitted in the tube and the tube contents were heated at 60–70° for 12 hr. The temperature was then raised to 150° over a period of 2 hr. and 3.5 g. (73%) of white solid, 3,5-bis(perfluoropropyl)-1,2,4-triazole, m.p. 110–111°, collected on the cold finger.

3,5-Bis(perfluoroethyl)-1,2,4-triazole and 3,5-Bis(perfluoromethyl)-1,2,4-triazole.—These two compounds were prepared by the method described for 3,5-bis(perfluoropropyl)-1,2,4-triazole. 3,5-Bis(perfluoroethyl)-1,2,4-triazole was obtained in 80% yield, m.p. 104.0–104.5°; 3,5-bis(perfluoromethyl)-1,2,4-triazole was obtained in 70% yield, m.p. 76–77°.

1,2-Bis(N-methyl perfluorobutyrimidoyl)hydrazine.—2,5-Bis(perfluoropropyl)-1,3,4-oxadiazole, 6.55 g. (0.0161 mole), was placed in a heavy-walled glass tube, previously constricted for sealing, of 60-ml. capacity. The tube was cooled in liquid nitrogen and pumped free of air. Methylamine, 2.9 g. (0.093 mole), was condensed in the tube, the tube sealed and slowly warmed to room temperature and held at this temperature for 4 hr. The reaction tube was then opened, excess methylamine (0.061 mole—indicating

(10) N.m.r. spectra were obtained on a Varian high resolution spectrometer Model V-4300-2 operating at 56.4 Mc. (F) and 60 Mc. (H) with trifluoroacetic acid as an external standard. Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside, New York.

reaction of the oxadiazole with two moles of methylamine) pumped off and 7.00 g. (95%) of 1,2-bis(N-methylperfluorobutyrimidoyl)hydrazine removed. After recrystallization from toluene, the product melted at 105.0–105.8°.

This product also was prepared in 93% yield by allowing 2,5-bis(perfluoropropyl)-1,2,4-oxadiazole to react with refluxing methylamine for 2 hr.

1,2-Bis(N-methylperfluoropropionimidoyl)hydrazine and 1,2-Bis(N-methylperfluoroacetimidoyl)hydrazine.—These two compounds were prepared by either method described for 1,2-bis(N-methylperfluorobutyrimidoyl)hydrazine. 1,2-Bis(N-methylperfluoropropionimidoyl)hydrazine was obtained in quantitative yield, m.p. 94.5–95.0°, as was 1,2-bis(N-methylperfluoroacetimidoyl)hydrazine, m.p. 99.0–99.5°.

3,5-Bis(perfluoropropyl)-4-methyl-1,2,4,4*H*-triazole.—1,2-Bis-(N-methylperfluorobutyrimidoyl)hydrazine, 3.0 g. (0.0066 mole), was placed in an 8-in. test tube, equipped with side arm and drying tube, and mixed with 3.0 g. of phosphorus pentoxide. A water-cooled cold-finger condenser was fitted in the reaction tube and the reaction mixture heated at 80–85° for 4 hr. A white, flaky solid, 3,5-bis-(perfluoropropyl)-4-methyl-1,2,4,4*H*-triazole, 2.4 g. (88%), m.p. 47.5–48.0°, was deposited on the condenser and sides of the reaction tube.

3,5-Bis(perfluoroethyl)-4-methyl-1,2,4,4*H*-triazole and 3,5-Bis(perfluoromethyl)-4-methyl-1,2,4,4*H*-triazole.—These two compounds were prepared by the procedure described for 3,5-bis(perfluoropropyl)-4-methyl-1,2,4,4*H*-triazole. 3,5-Bis(perfluoroethyl)-4-methyl-1,2,4,4*H*-triazole was obtained in 94% yield, m.p. 49.5–50.0°. 3,5-Bis(perfluoromethyl)-4-methyl-1,2,4,4*H*-triazole was distilled from the reaction mixture as a liquid (93% yield), b.p. 199.5–200°; d^{25} 1.613; n^{25} 1.3647.

1-(Perfluorobutyrimidoyl)-2-(N-methylperfluorobutyrimidoyl)hydrazine.—1-(Perfluorobutyrimidoyl)-2-(perfluorobutyryl)hydrazine (1.65 g., 0.0039 mole) was placed in a 50-ml. round-bottom flask equipped with a Dry Ice reflux condenser and 10 ml. of ethyl alcohol added. The reaction solution was frozen in liquid nitrogen, the flask pumped free of air, and excess methylamine condensed in the flask. The mixture was allowed to warm to the reflux temperature of methylamine and refluxed for 3 hr. at atmospheric pressure. Unchanged methylamine was removed under reduced pressure to give a white solid product. Recrystallization from toluene yielded 1.50 g. (90%) of 1-(perfluorobutyrimidoyl)-2-(N-methylperfluorobutyrimidoyl)hydrazine, m.p. 122.0–122.5°. Heating this product with an equal weight of phosphorus pentoxide at 150° for 2 hr. resulted in deamination and produced 3,5-bis(perfluoropropyl)-1,2,4-triazole in 80% yield.

Determination of pK_a of the Triazoles.—3,5-Bis(perfluoromethyl)-1,2,4-triazole, 0.0162 g., was dissolved in a mixture of 4 ml. of water (freshly distilled, free of carbon dioxide) and 4 ml. of dioxane (free of peroxides and acid). The solution was titrated with 0.0100 *N* sodium hydroxide and the pH determined by the potentiometric method. The change in pH was very rapid near the end point, and the curve had the characteristic shape of a strong acid–strong base titration. The pK_a value of 3.0 was taken from the curve at the point where one half of the triazole had been neutralized (where pH = pK_a). The molecular weight found by titration was 197; the calculated value is 205.

Titrations of 3,5 bis(perfluoroethyl)-1,2,4-triazole and 3,5-bis(perfluoropropyl)-1,2,4-triazole were carried out by the same procedure. The pK_a values of these two compounds were 2.72 and 3.10, respectively. Molecular weights found by titration were 304 (calcd. 305) and 395 (calcd. 405).

Acknowledgment.—The authors are indebted to Dr. Wallace S. Brey of the University of Florida for the n.m.r. measurements and interpretations.

1,2,4-Triazoles. VI.[1] The Synthesis of Some *s*-Triazolo[4,3-*a*]pyrazines

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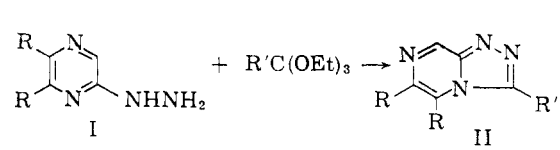
A series of *s*-triazolo[4,3-*a*]pyrazines has been synthesized by ring closure of 2-hydrazinopyrazines with ortho esters, a method superior to that of acidic cyclodehydration. The structures of several interesting by-products obtained in these reactions are discussed.

Of the two possible ring systems formed by the fusion of an *s*-triazole nucleus with a pyrazine nucleus, only one is known and that in the form of its benzo derivative, *s*-triazolo[4,3-*a*]quinoxaline.[3] This communication describes the preparation of the parent ring system itself, *s*-triazolo-[4,3-*a*]pyrazine, and several alkyl and aryl substituted members of this system.

The most efficient method of synthesis of the *s*-triazolo[4,3-*a*]pyrazine ring system (II) was found to be the ring closure of 2-hydrazinopyrazines (I) with ortho esters, a method analogous to the cyclization of 2-hydrazino derivatives of the pyridazine, pyrimidine, and quinoxaline ring systems to the corresponding fused *s*-triazole derivatives with these reagents.[3,4]



I II

The hitherto unknown 2-hydrazinopyrazines were readily prepared in good yield from the cor-

(1) Part V, K. T. Potts and T. H. Crawford, *J. Org. Chem.*, **27**, 2631 (1962).

(2) Department of Chemistry, University of Louisville.

(3) Den-itsu Shiho and S. Tagami, *J. Am. Chem. Soc.*, **82**, 4044 (1960).

(4) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. van Allan, *J. Org. Chem.*, **24**, 787, 793 (1959).