Perfluoroalkyl Derivatives with Functional Groups Containing Divalent Sulfur. II. Synthesis and Reactions of Perfluoroalkylthiohydrazides[1]

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Perfluoroalkylthiohydrazides, $R_FC(S)NHNR_1R_2$, were synthesized by conversion of the corresponding perfluoroalkylhydrazidine, $R_FC(=NH)NHNR_1R_2$, by hydrogen sulfide. The scope of the reaction was shown by examples in which the N^2 substituent was hydrogen, an aromatic ring, an electron-releasing group, or an electron-attracting group; limitations of the method are also discussed. Syntheses of the intermediate hydrazidines are described. A variety of bis(α-hydrazonoperfluoroalkyl) disulfides, $[R_FC(=NNR_1R_2)S-]_2$, where R_1 and R_2 are H, C_6H_5, or CH_3 and R_F is a perfluoroalkyl group, were prepared by oxidation of the perfluoroalkylthiohydrazides. Bis(α-hydrazonoheptafluorobutyl) disulfide appears to be the first stable example of a disulfide produced by oxidation of an N^2-unsubstituted thiohydrazide. Additional reactions of perfluorothiobutyrhydrazide described include the formation of 2,5-bis(perfluoropropyl)-1,3,4-thiadiazole, the synthesis of the S-methyl derivative of the thiohydrazide and its conversion to methyl 1,1-dihydroheptafluorosulfide, and synthesis of 5-perfluoropropyl-1,2,3,4-thiatriazole.

This paper describes the continuation of research on methods of synthesis of fluorocarbon derivatives containing the $-C(=S)X$ grouping, and comparison of their chemical and physical properties in relation to hydrocarbon derivatives with the same functional group. The previous paper[1c] described the perfluoroalkylthioimidates and perfluoroalkylthiocarboxylates and indicated significant changes in the nature of the $-C(=S)X$ structure produced by the presence of a perfluoroalkyl group attached to the carbon atom. Extension of this area of study to the perfluoroalkylthiohydrazides (where $X = NHNR_1R_2$) has provided further examples of the effects of the substituent group X on the C=S moiety.

Thiohydrazides derived from alkyl or aryl hydrocarbons have received relatively little attention in the chemical literature. In general, only the reactions of alkyl- or aryl-substituted hydrazines and dithiocarboxylic acid derivatives such as the lower alkyl esters,[2] hydrazinium salts,[3,4] the alkali metal salts,[5] and the carboxymethyl esters[6] have been used for their preparation. Phenylhydrazine was reported to react with aliphatic thiono esters to give the corresponding phenyl-substituted thiohydrazides.[2] A review of the more recent literature[7] shows that only one example of an aliphatic nitrogen-unsubstituted thiohydrazide, *t*-butylthiohydrazide, has been prepared. The functional group of this compound appears to owe its stability to steric factors. Undesired side reactions frequently interfere when this general method of preparation is applied to the synthesis of N-unsubstituted thiohydrazides. Reduction of the dithio acids occurs when they are subjected to the action of an alkyl- or aryl-substituted hydrazine and the corresponding hydrazone is formed (the Wuyts reaction[5,8]); another side reaction is a condensation (bimolecular, involving 2 molecules of thiohydrazide) leading to the formation of the respective thiadiazoles, dihydrotetrazines, or N-aminotriazoles.[5,9] The latter reaction often proceeds so readily that the unsubstituted aliphatic thiohydrazides and some aromatic thiohydrazides cannot be isolated at all.

Jensen and Pedersen[7] discussed five other potential methods for synthesis of the thiohydrazides which they tried with little success. One of these was an attempted conversion of acethydrazidine to thioacethydrazide with hydrogen sulfide.

Although the reported attempted reaction of acethydrazidine with hydrogen sulfide was unsuccessful, replacement of an imino group is a classical method for synthesis of the C=S group and has been shown to be effective in the synthesis of thioamides, dithio esters, thiono esters, and substituted thioamides. The present work describes the application of this type of reaction to the perfluoroalkyl hydrazidines and its development as a method of synthesis for the perfluoroalkylthiohydrazides.

Several of the intermediate hydrazidines whose reactions with hydrogen sulfide are discussed in this work have been reported previously by Brown and Pilipovich.[10] In the present work the necessary additional procedures were developed for adding phenylhydrazine and benzenesulfonylhydrazide to perfluoroalkylnitriles to produce the corresponding hydrazidines. Phenylhydrazine reacted quantitatively with perfluoroalkylnitriles in methyl alcohol at room temperature in an exothermic reaction; the use of ether as a solvent required heating of the reaction mixture to 50°. A temperature of about 100° was necessary to complete the reaction if no solvent were used.

Addition of benzenesulfonylhydrazide to perfluoroalkylnitriles was extremely slow in ether, even at 100°, but proceeded rapidly to completion at 40–50° in a 1:1 mixture of ether and methyl alcohol.

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(2) Y. Sakurada, *Bull. Soc. Chem. Japan*, **2**, 307 (1927); *Chem. Abstr.*, **22**, 764 (1928).

(3) K. A. Jensen and C. L. Jensen, *Acta Chem. Scand.*, **6**, 957 (1952).

(4) Danish Patent 79776 (1955); *Chem. Abstr.*, **50**, 8730*g* (1956).

(5) H. B. Koenig, W. Siefken, and H. A. Offe, *Chem. Ber.*, **87**, 825 (1954).

(6) B. Holmberg, *Arkiv Kemi, Mineral Geol.*, **17A**, 23 (1943); B. Holmberg, *Arkiv Kemi*, **9**, 47 (1956).

(7) K. A. Jensen, *Acta Chem. Scand.*, **15**, 1067 (1961); K. A. Jensen and C. Pedersen, *ibid.*, **15**, 1097 (1961); K. A. Jense, H. R. Baccaro, O. Buchardt, G. E. Olsen, C. Pedersen, and J. Toft, *ibid.*, **15**, 1109 (1961).

(8) H. Wuyts and H. Lacourt, *Bull. soc. chim. Belges*, **42**, 1 (1933); H. Wuyts and L. C. Kuang, *ibid.*, **42**, 153 (1933).

(9) K. A. Jensen and C. Pedersen, *Acta Chem. Scand.*, **15**, 1124 (1961).

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

The synthesis of these additional perfluoroalkylhydrazidines made available not only the N-unsubstituted examples (I) but also hydrazidines in which the N^2 substituent was aromatic (V), strongly electron withdrawing (VII), or markedly electron releasing (III).

$$\underset{\text{I}}{R_FC(NH_2)=NNH_2} + H_2S \longrightarrow \underset{\text{II, } R_F = CF_3 \text{ or } C_3F_7}{R_FC(SNH_4)=NNH_2}$$

$$\underset{\text{III}}{R_FC(NH_2)=NN(CH_3)_2} \xrightarrow[HCl]{H_2S} \underset{\text{IV, } R_F = CF_3,\ C_2F_5, \text{ or } C_3F_7}{R_FC(=S)NHN(CH_3)_2}$$

$$\underset{\text{V}}{R_FC(NH_2)=NNHC_6H_5} \xrightarrow[HCl]{H_2S} \underset{\text{VI, } R_F = CF_3,\ C_2F_5}{R_FC(=S)NHNHC_6H_5}$$

$$\underset{\text{VII}}{R_FC(NH_2)=NNHSO_2C_6H_5} + H_2S \longrightarrow \underset{\text{VIII, } R_F = CF_3,\ C_2F_5, \text{ or } C_3F_7}{R_FC(SNH_4)=NNHSO_2C_6H_5}$$

The reaction of each of these perfluoroalkylhydrazidines with hydrogen sulfide at pressures of several atmospheres led to the formation of the corresponding perfluoroalkylthiohydrazides or their ammonium salts in good yields. A careful selection of the reaction conditions, however, was necessary in each particular case to avoid other reactions due either to solvolytic or reductive action of hydrogen sulfide.

The N-unsubstituted thiohydrazides II could be obtained only by carrying out the reaction in liquid hydrogen sulfide in which the ammonium salts formed in the course of the reaction were insoluble. Yields of the CF_3 and C_3F_7 thiohydrazides were good; the amounts of the corresponding thioamides formed as a result of solvolytic action of hydrogen sulfide were negligible.

The ammonium salt of trifluorothioacethydrazide was hygroscopic, water soluble, and less stable than the corresponding heptafluorothiobutyrhydrazide salt. Unlike the ammonium salt of heptafluorothiobutyrhydrazide, it was insoluble in ether. At atmospheric pressure and at room temperature the ammonium salt of trifluorothioacethydrazide decomposed slowly with evolution of ammonia and hydrogen sulfide.

Free trifluorothioacethydrazide was recovered from an aqueous solution of the ammonium salt, after acidification with 10% hydrochloric acid, as a yellow liquid which decomposed on standing with the deposition of sulfur. For the purpose of identification and characterization, the ammonium salt of trifluorothioacethydrazide was allowed to react with methyl iodide in a methyl alcohol–ether solvent mixture to give a stable, liquid, S-methyl derivative.

The structure of S-methyltrifluorothioacetisohydrazide is supported by the ultraviolet spectrum of the compound [λ_{max} 241 mμ (ϵ 4800) in isooctane] which shows no absorption above 241 mμ. A high-intensity absorption maximum would appear around 270–280 mμ if N-methylation occurred and if the methylated product possessed a thiocarbonyl group. The appearance of a maximum at 241 mμ is understandable in view of the fact that the type of chromophore present in S-methyltrifluorothioacetisohydrazide is similar to that encountered in perfluoroalkylthioimidates,[1c] which absorb at 242–246 mμ.

The ammonium salt of heptafluorothiobutyrhydrazide was a white, extremely hygroscopic solid which could be purified by sublimation (65–70°) at 0.1-mm. pressure. This compound decomposed slowly at room temperature and rapidly at 75–80° at atmospheric pressure. The salt dissolved in water and also in ether; the latter circumstance may well explain the complete failure of an attempt to obtain this compound in a reaction carried out in anhydrous ether in which the following solvolytic reaction to produce perfluorothiobutyramide took place almost exclusively.

$$C_3F_7C(NH_2)=NNH_2 \xrightarrow[Et_2O]{H_2S} C_3F_7C(=S)NH_2 + N_2H_4\cdot H_2S$$

Free heptafluorothiobutyrhydrazide was recovered from an aqueous solution of the ammonium salt by treatment with 15% hydrochloric acid; it was a low-melting white solid which was stable at room temperature for a few days. Heptafluorothiobutyrhydrazide formed a yellow, strongly hygroscopic hydrochloride with gaseous hydrogen chloride. It dissolved easily in concentrated hydrochloric acid solutions and in dilute aqueous alkalies.

Preparation of the N,N-dimethyl-substituted perfluoroalkylthiohydrazides IV was carried out by allowing the hydrochloride salts of the perfluoroalkylhydrazidines to react with hydrogen sulfide under pressure at 100° in the absence of a solvent. Perfluoroalkylthiohydrazides of this type also were prepared, more conveniently, by allowing the hydrazidine hydrochloride to react with hydrogen sulfide in a methyl alcohol–ether solvent mixture. Neither solvolysis nor reduction accompanied these reactions.

N,N-Dimethylperfluoroalkylthiohydrazides were relatively stable in air. They dissolved readily in dilute aqueous alkalies but were soluble in only concentrated hydrochloric acid solutions, from which they precipitated on dilution. This solubility is in marked contrast to the solubility shown by the hydrocarbon thiohydrazides, which are said to dissolve also in dilute solutions of strong acids.

N-Phenyl-substituted perfluoroalkylhydrazidines V did not react with hydrogen sulfide in sealed tubes at room temperature. When the temperature of the reaction mixture was raised to 70°, a reduction, accompanied by sulfur precipitation, took place and led to the formation of the corresponding 1,1-dihydroperfluoroalkylmercaptans as final products. When 1 molar equiv. of hydrogen chloride was added to a methyl alcohol or ether–methyl alcohol solution of an N-phenyl-substituted perfluoroalkylhydrazidine (in order to remove ammonia as it was formed in the course of the reaction), the reaction with hydrogen sulfide under pressure resulted in the formation of the corresponding thioamide only.

Moderate yields of N-phenyl-substituted perfluoroalkylthiohydrazides could be obtained if a suspension of the hydrazidine hydrochloride in dry ether were allowed to react with hydrogen sulfide in a sealed tube at 100°. For N-phenyl trifluoroacethydrazidine hydrochloride with hydrogen sulfide under these conditions, however, the yield of trifluorothioacetamide as a by-product was about 50%. Hydrogen chloride, if used in a nonpolar solvent and if present in a small excess over the theoretical amount, appeared to prevent the reduction reaction and to suppress the thioamide

formation to a considerable degree. An additional side reaction occurring in this system was oxidation of the phenyl-substituted thiohydrazides in the acidic medium by small amounts of oxygen present in the sealed tubes.

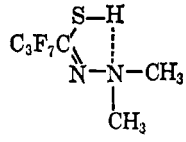
N-Phenyl-substituted perfluoroalkylthiohydrazides were quite unstable in air and for this reason were characterized in their oxidized forms as the corresponding hydrazonodisulfide. One example, however, N^2-phenylpentafluorothiopropionhydrazide, was isolated in the pure form as a low-melting solid and was shown to be colorless.

N^2-Benzenesulfonyl-substituted perfluoroalkylhydrazidines (VII) reacted readily with hydrogen sulfide at room temperature. Reactions involving the CF_3 and C_2F_5 homologs were carried out in ether as a solvent with a large excess of hydrogen sulfide; the C_3F_7 compound was converted to the corresponding thiohydrazide in liquid hydrogen sulfide. In each case an ammonium salt of the N^2-benzenesulfonyl-substituted thiohydrazide precipitated from the reaction mixture in good yield and was recovered as a white, nonhygroscopic solid which was stable at room temperature over a period of 2–4 weeks. The ammonium salt formed concentrated aqueous solutions from which the free thiohydrazide precipitated upon acidification with dilute hydrochloric acid.

The formation of relatively stable ammonium salts by certain types of perfluoroalkylthiohydrazides can be attributed to the strong acidifying influence of the perfluoroalkyl group upon the N^1 hydrogen atom of the thiohydrazides. Thiohydrazides of the perfluoroalkyl series thus seem to be much stronger acids and much weaker bases than their hydrocarbon analogs.

Heptafluorothiobutyrhydrazide showed strong infrared absorption in the region of 3.0–3.5 μ, assigned to N–H stretching. There is also a strong band at 7.2 μ which may possibly be assigned to a "thioureide" grouping, >NC=S. Although there is little information concerning the infrared spectra of hydrocarbon thiohydrazides available in the literature, Lieber[11] mentioned that aryl nitrogen-unsubstituted thiohydrazides exhibit bands characteristic of the >NC=S grouping at 6.47–6.99 and 7.55–7.69 μ.

The infrared spectrum for N,N-dimethylheptafluorothiobutyrhydrazide showed the expected absorption at 3.3 μ for C–H stretching. Two strong absorption bands also appeared at 3.60 and 3.95 μ, which is a considerably longer wave length than the N–H stretching bands of the unsubstituted heptafluorothiobutyrhydrazide. The spectrum of this compound was run in carbon tetrachloride, and, upon increasing dilution of the carbon tetrachloride solution, the absorption maxima at 3.60 and 3.95 μ did not shift. This indicated a strong intramolecular hydrogen bonding and a contribution of S–H stretching. A molecular structure which seems to reflect most adequately the infrared data can be represented by the following formula



in which the hydrogen atom occupies an intermediate position between sulfur and nitrogen.

The N^2-benzenesulfonyl-substituted thiohydrazides showed an infrared band at 3.0–3.1 μ due to N–H stretching.

The ultraviolet absorption spectra of the perfluoroalkylthiohydrazides exhibited high-intensity absorption maxima in the region of 270–285 mμ as shown in Table I. The examination of this data indicates that hypsochromic shifts result from the substitution of hydrogen atoms at the N^2 atom by either the methyl or the benzene sulfonyl group.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA OF PERFLUOROALKYLTHIOHYDRAZIDES

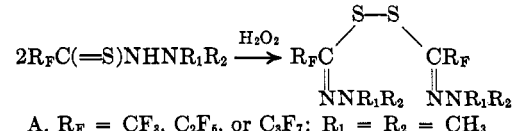
Compd.	λ_{max}, mμ	log ϵ_{max}
$C_3F_7C(S)NHNH_2$	284[a]	3.92
$CF_3C(S)NHN(CH_3)_2$	269.5[b]	3.96
$C_2F_5C(S)NHN(CH_3)_2$	276[c]	3.74
$C_3F_7C(S)NHN(CH_3)_2$	276[c]	3.88
$C_2F_5C(S)NHNHSO_2C_6H_5$	272.5, 267[d]	3.79, 3.79
$C_2F_5C(SNH_4)NNHSO_2C_6H_5$	283, 273[b]	3.97, 3.96
	272.5, 267[d]	3.98, 3.98
	281[e]	4.08

[a] In 0.4% isopropyl alcohol in isooctane. [b] In acetonitrile. [c] In isooctane. [d] In isopropyl alcohol. [e] In 0.5 *N* sodium hydroxide.

Comparison of the high-intensity bands shown by heptafluorothiobutyrhydrazide (λ_{max} 284 mμ) and its closest hydrocarbon analog, $C_6H_5CH_2C(S)NHNH_2$ (λ_{max} 266 mμ, in heptane[12]) indicates that the $\pi \rightarrow \pi^*$ transition is aided by electron-withdrawing substituents attached to the functional carbon atom of the thiohydrazide.

In the preparation of perfluoroalkylthiohydrazides, yellow-orange colorations were observed when these compounds were exposed to the air. N^2-Phenyl-substituted perfluoroalkylthiohydrazides, for example, underwent oxidation immediately on contact with air. N,N-Dimethylthiohydrazides with perfluoropropyl and perfluoroethyl groups showed discoloration when stored several weeks. As a preliminary experiment, it was possible to demonstrate that the product of air oxidation of N^2-phenylpentafluorothiopropionhydrazide was identical with the product obtained from an oxidation carried out in an aqueous methyl alcohol solution of hydrogen peroxide.

A variety of differently substituted perfluoroalkylthiohydrazides were oxidized, therefore, with hydrogen peroxide and with iodine. The reactions proceeded to yield bis(α-hydrazonoperfluoroalkyl) disulfides according to the following general equation.



A, $R_F = CF_3$, C_2F_5, or C_3F_7; $R_1 = R_2 = CH_3$
B, $R_F = CF_3$ or C_2F_5; $R_1 = H$; $R_2 = C_6H_5$
C, $R_F = C_3F_7$; $R_1 = R_2 = H$

Disulfides of this type were obtained by Wuyts[13] and Holmberg[14] on oxidizing several aromatic N^2-

(11) E. Lieber, C. N. R. Rao, and R. C. Orlowski, *Can. J. Chem.*, **41**, 926 (1963).

(12) J. Sandstroem and S. Sunner, *Acta Chem. Scand.*, **17**, 731 (1963).
(13) H. Wuyts and A. Lacourt, *Bull. soc. chim. Belges*, **48**, 193 (1939).
(14) B. Holmberg, *Arkiv Kemi*, **7**, 517 (1954).

substituted thiohydrazides. Holmberg[15] showed that the oxidation of many thiobenzhydrazones of simple aldehydes and sugars usually led to the formation of the corresponding substituted thiadiazoles, but in some instances substituted disulfides were obtained.

Oxidation by hydrogen peroxide required an excess of the oxidizing agent; the use of iodine as an oxidizing agent resulted in complete conversion of N,N-dimethyl-substituted perfluoroalkylthiohydrazides to the corresponding disulfides rapidly and required only equivalent amounts of iodine. This procedure has been reported to be of analytical value when applied to aromatic thiohydrazides.[13,14]

Perfluoroalkylthiohydrazides were oxidized with excess hydrogen peroxide in aqueous methyl alcohol solutions at temperatures ranging from 0–50° to give bis(α-hydrazonoperfluoroalkyl) disulfides in high yields. The compounds appeared to be stable when stored several months at room temperature but showed a marked susceptibility toward decomposition in the presence of basic impurities. All of the disulfides were colored.

Bis(α-hydrazonoheptafluorobutyl) disulfide deserves comment since no stable reaction product is reported in the literature from the oxidation of previously known N^2-unsubstituted thiohydrazides. The disulfide prepared from heptafluorothiobutyrhydrazide was stable at room temperature for about 2 months. When heated at 70° with dry hydrogen chloride in a sealed tube it underwent cyclization accompanied by release of sulfur and formation of the 1,3,4-thiadiazole ring. Treatment with concentrated sulfuric acid caused cyclization to occur at room temperature and at atmospheric pressure. On both cases the elimination of

$$C_3F_7C(=NNH_2)-S-S-C(=NNH_2)C_3F_7 \xrightarrow{HCl} \text{2,5-bis(heptafluoropropyl)-1,3,4-thiadiazole} + S + N_2H_4\cdot HCl$$

sulfur was rapid and there was no evidence that a perfluoroalkyl-substituted 1,2,4,5-dithiadiazine (an unknown ring structure) was formed as an intermediate. The bis(α-hydrazonoperfluoroalkyl) disulfides were insoluble in alkalies, indicating that they lack an acidic N^1 hydrogen atom.

The electronic absorption spectra of the bis(α-hydrazonoperfluoroalkyl) disulfides are shown in Table II. The infrared absorption spectra of bis[α-(N,N-dimethylhydrazono)heptafluorobutyl] disulfide showed no absorption maxima due to N–H stretching or deformation. A strong peak at 6.45 μ was assigned to C=N stretching. The infrared spectra of bis(α-hydrazonoheptafluorobutyl) disulfide showed a triplet at 2.85, 3.00, and 3.13 μ due to N–H stretching; absorption maxima at 6.28 and 6.55 were assigned to N–H deformation and C=N stretching vibrations. In the spectra of bis[α-(N-phenylhydrazono)pentafluoropropyl] disulfide there appears to be no band due to N–H stretching vibration below 3.35 μ.

TABLE II

ELECTRONIC ABSORPTION SPECTRA OF BIS(α-HYDRAZONOPERFLUOROALKYL) DISULFIDES

Compd.	λ_{max}, mμ[a]	log ϵ_{max}
$[CF_2C(=NNHC_6H_5)S-]_2$	387, 285, 238	4.01, 4.18, 4.20
$[C_2F_5C(=NNHC_6H_5)S-]_2$	389, 291, 238	4.02, 4.20, 4.18
$\{CF_3C[=NN(CH_3)_2]S-\}_2$	307, 247, 232[b]	3.92, 4.00, 3.97
$\{C_3F_7C[=NN(CH_3)_2]S-\}_2$	300, 254, 233[b]	3.93, 4.04, 3.99
$[C_3F_7C(=NNH_2)S-]_2$	279, 254	3.74, 3.79

[a] In isooctane. [b] Inflection point.

The synthesis of heptafluorothiobutyrhydrazide provided an opportunity to investigate other reactions of this compound in addition to its oxidation with hydrogen peroxide. It was of interest to determine the influence of the perfluoroalkyl group on the ability of the thiohydrazide function to undergo a self-condensation reaction which might result in the formation of the corresponding thiadiazole or dihydrotetrazine. Reactions of this type are found to occur very readily in the preparation of many hydrocarbon thiohydrazides.[5,9]

Heptafluorothiobutyrhydrazide, however, decomposed on standing with the evolution of hydrogen sulfide and sulfur, formation of the latter being due to the Wuyts reduction.[5,8] It was therefore necessary to suppress the reduction of heptafluorothiobutyrhydrazide if it were to undergo a self-condensation to give a heterocyclic product. For this purpose a hydrochloride of the thiohydrazide was prepared in a sealed tube and heated at 131° until a vigorous reaction took place. This procedure gave 2,5-bis(heptafluoropropyl)-1,3,4-thiadiazole and was accompanied by very little sulfur precipitation. The same thiadiazole was pre-

$$2C_3F_7C(=S)NHNH_2\cdot HCl \xrightarrow{\Delta} \text{2,5-bis(heptafluoropropyl)-1,3,4-thiadiazole} + N_2H_4\cdot 2HCl + H_2S$$

viously obtained from bis(α-hydrazonoheptafluorobutyl) disulfide and hydrogen chloride as described above. For identification, the compound was also prepared by the method of Chambers and Coffman,[16] who synthesized the corresponding CF_3- and C_2F_5-substituted 1,3,4-thiadiazoles. Infrared spectra of the C_3F_7-thiadiazole prepared by these three different methods were identical.

Another reported general procedure for effecting the self-condensation of thiohydrazides to heterocyclic derivatives involves the reaction of an arylthiohydrazide with a base and methyl iodide; this gives the corresponding dihydrotetrazine.[9] No intermediate was reported in the description of this reaction. It may be presumed that methyl iodide acted as an alkylating agent and that the reaction occurred with the salt of the thiohydrazide. As a result, methylmercaptan, rather than hydrogen sulfide (which in a basic medium might cause the reduction) is eliminated in the course of the base-catalyzed condensation reaction.

A similar procedure was applied using the ammonium salt of heptafluorobutyrthiohydrazide with the exception that the reaction was carried out in ether rather than in a basic medium so that the alkylated product could be isolated. This reaction furnished the stable, colorless, liquid S-alkyl derivative of heptafluorobutyrthiohydrazide.

(15) (a) B. Holmberg, *Arkiv Kemi*, **4**, 33 (1952); (b) *ibid.*, **9**, 65 (1956).

(16) W. J. Chambers and D. D. Coffman, *J. Org. Chem.*, **26**, 4410 (1961).

$$C_3F_7C(SNH_4){=}NNH_2 + CH_3I \longrightarrow C_3F_7C(SCH_3){=}NNH_2 + NH_4I$$

The ultraviolet spectrum of methyl α-hydrazonoheptafluorobutyl sulfide is consistent with the S-methyl structure, which being similar to that of the perfluoroalkylthioimidates,[1c] would be expected to show an absorption maximum near 240 mμ. Spectral data on structurally related compounds possessing a thioimidate-type chromophore are listed in Table III.

TABLE III
ULTRAVIOLET ABSORPTION MAXIMA OF COMPOUNDS HAVING A THIOIMIDATE-TYPE CHROMOPHORE

Compd.	λ_{max}, mμ	log ϵ_{max}
$C_3F_7C(=NH)SCH_3$[a]	244	3.76
$C_3F_7C(=NNH_2)SCH_3$[b]	242	3.70
$CF_3C(=NNH_2)SCH_3$[b]	241	3.68

[a] In cyclohexane. [b] In isooctane.

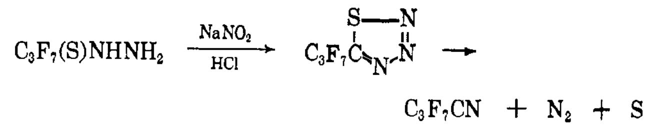
The infrared spectrum of methyl α-hydrazonoheptafluorobutyl sulfide indicates that the compound has an unsubstituted hydrazono group; there are three maxima assigned to N–H stretching absorption which are similar in appearance to those exhibited in the spectrum of bis(α-hydrazonoheptafluorobutyl) disulfide. Additional proof of structure was furnished by reaction in a sealed tube with hydrogen chloride to produce methyl 1,1-dihydroheptafluorobutyl sulfide.

$$C_3F_7C(SCH_3){=}NNH_2 \xrightarrow[HCl]{70°} C_3F_7CH_2SCH_3 + N_2$$

The S-methyl derivative of heptafluorothiobutyrhydrazide appeared to be quite stable and boiled at atmospheric pressure without the evolution of methyl mercaptan; formation of the heterocyclic 1,2-dihydro-1,2,4,5-tetrazine was not found.

Recent studies[11,17] have shown that reactions of arylthiohydrazides and nitrous acid give the corresponding 5-aryl-substituted 1,2,3,4-thiatriazoles rather than the isomeric thioazides. The infrared spectra of the products obtained showed no absorption around 4.66 μ; the azide group has a characteristic band in this region. Workers in this area described only one aliphatic thiatriazole, the very unstable 5-cyclohexyl-1,2,3,4-thiatriazole.

Reaction of heptafluorothiobutyrhydrazide with nitrous acid gave a clear oil of a pleasant aromatic odor. The purified compound decomposed slowly at room temperature to give heptafluorobutyronitrile, nitrogen, and sulfur. Its mode of decomposition thus corresponded to that reported for the aromatic thiatriazoles. The infrared spectra of the oil showed no azide band around 4.6 μ. In the region between 2.5 and 7.3 there is only one medium intensity absorption band and this occurs at 6.9 μ. This band may be assigned to a C=N stretching vibration in a five-membered ring and would be analogous to that found for the 2,5-bis(heptafluoropropyl)-1,3,4-thiadiazole (6.85 μ) and 3,5-bis(heptafluoropropyl)-1,2,4-triazole (6.93 μ).[18] On the basis of this evidence, the product



obtained from heptafluorothiobutyrhydrazide and nitrous acid was identified as 5-heptafluoropropyl-1,2,3,4-thiatriazole.

Experimental Section

Heptafluorothiobutyrhydrazide and Its S-Methyl Derivative.—Freshly recrystallized heptafluorobutyrhydrazidine,[10] 10.0 g. (0.044 mole), and 6.8 g. (0.2 mole) of hydrogen sulfide were sealed in a previously evacuated 50-ml. heavy-wall glass tube. After standing at room temperature 13 hr., the reaction tube contained crystals of the ammonium salt of heptafluorobutyrthiohydrazide in the liquid hydrogen sulfide. Excess hydrogen sulfide was removed and pressure in the tube was reduced (<1.0 mm.) to remove small amounts of ammonium sulfide and heptafluorothiobutyramide formed in the reaction. The remaining solid product was dissolved in 75 ml. of ice-cold water to which 3 ml. of 28% aqueous ammonia solution had been added. Ice was added to the solution to maintain the temperature near 0° and the solution was filtered rapidly. The filtrate was cooled and acidified with ice-cold 15% hydrochloric acid solution. The free thiohydrazide was then extracted with ether, and the extract was washed with ice-cold water and dried with anhydrous calcium chloride. The solvent ether was removed under reduced pressure and the product distilled, b.p. 60–75° (0.1 mm.). The crude product, 8.5 g. (79%), was slightly yellow and was recrystallized twice from chloroform to give pure, white heptafluorothiobutyrhydrazide, m.p. 47°.

Heptafluorothiobutyrhydrazide was somewhat unstable in air; for identification, the ammonium salt, separated and purified by sublimation (65–70° at 0.1 mm., dec. pt. 80–84°), was used to prepare the S-methyl derivative, methyl α-hydrazonoheptafluorobutyl sulfide. The ammonium salt, 10.0 g. (0.038 mole), was dissolved in 30 ml. of anhydrous ether and treated with 15 g. of methyl iodide at room temperature. The reaction was exothermic and resulted in the precipitation of 5.5 g. of ammonium iodide; this solid was removed by filtration and the solvent was removed from the filtrate under reduced pressure. A yellow oil, 9.4 g., remained and was distilled to give a fraction boiling between 84–90° (25 mm.). Refractionation gave pure methyl α-hydrazonoheptafluorobutyl sulfide, 8.7 g. (86%), b.p. 87–88° (27 mm.), as a colorless oil.

Anal. Calcd. for $C_5H_5F_7N_2S$: C, 23.25; H, 1.95; F, 51.55; N, 10.85; S, 12.40. Found: C, 23.50; H, 1.96; F, 51.32; N, 11.00; S, 12.10.

Trifluorothioacethydrazide, Its S-Methyl Derivative and the Intermediate Hydrazidine.—Ethyl trifluorothioacetimidate,[1c] 8.2 g. (0.052 mole), was dissolved in 30 ml. of cold methyl alcohol and a solution of 2.0 g. of hydrazine in 12 ml. of methyl alcohol was added dropwise at 0°. The mixture was stirred at 0° for 1 hr. and then allowed to warm to room temperature and left standing overnight. The solvent and traces of moisture were removed under reduced pressure and the residual liquid was held at reduced pressure (0.1 mm.). Trifluoroacethydrazidine, 5.7 g. (87%), remained in the flask as a clear colorless liquid.

Trifluoroacethydrazidine, 5.0 g. (0.0394 mole), and hydrogen sulfide, 6.0 g., were placed in a previously evacuated tube at liquid nitrogen temperature. The reaction tube was sealed and allowed to warm slowly to room temperature. An exothermic reaction produced a white solid which separated from the excess liquid hydrogen sulfide. Volatile materials were removed under reduced pressure to leave the white, solid, water-soluble ammonium salt of trifluorothioacethydrazide.

The solid ammonium salt was suspended in 20 ml. of diethyl ether to which 5 ml. of methyl alcohol with 10 ml. of methyl iodide had been added. The mixture was shaken for 10 min. and filtered to remove ammonium iodide. Solvents were removed under reduced pressure to leave a light yellow liquid which distilled at 80–81° (31 mm.); 3.35 g. (55%) of the S-methyl derivative of trifluorothioacethydrazide was obtained as a colorless fraction. A second distillation (b.p. 75–76° at 23 mm.) yielded an analytically pure sample of the compound; ultraviolet spectrum (in isooctane), λ_{max} 241 mμ (ε 4800).

Anal. Calcd. for $C_2H_5F_3N_2S$: N, 17.71. Found: N, 17.52.

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N,N-Dimethyltrifluorothioacethydrazide.—N,N-Dimethyltrifluoroacethydrazidine,[10] 10 g. (0.065 mole), was dissolved in a mixture of 30 ml. of anhydrous ether and 20 ml. of methyl alcohol. The solution was placed in a heavy-wall glass tube and the tube was pumped free of air. Hydrogen sulfide, 7.0 g., and hydrogen chloride, 3.0 g., were condensed in the reaction tube which was sealed and heated at 50–70° until no additional precipitate appeared (2 hr.). Volatile material was removed under reduced pressure and the residual solid was washed with water, dried, and rewashed with carbon tetrachloride to leave 8.0 g. (79%) of crude N,N-dimethyltrifluorothioacethydrazide. The crude compound was recrystallized from methyl alcohol to give a pure product, m.p. 140–141°.

Anal. Calcd. for $C_4H_7F_3N_2S$: C, 27.90; H, 4.10; F, 33.14; N, 16.27; S, 18.60. Found: C, 27.64; H, 4.06; F, 32.93; N, 16.40; S, 18.46.

N,N-Dimethylpentafluorothiopropionhydrazide.—The reaction of N,N-dimethylpentafluoropropionhydrazidine,[10] 10 g., and hydrogen sulfide, 7.0 g., in the presence of hydrogen chloride, 2.5 g., was carried out in the mixture of solvents as outlined in the preceding procedure to give 8.7 g. (80%) of crude, yellow thiohydrazide. This product was recrystallized twice from carbon tetrachloride to give pure white N,N-dimethylpentafluorothiopropionhydrazide, m.p. 61–62°.

Anal. Calcd. for $C_5H_7F_5N_2S$: C, 27.03; H, 3.18; F, 42.75; N, 12.61; S, 14.43. Found: C, 26.79; H, 3.08; F, 42.88; N, 12.50; S, 14.33.

N,N-Dimethylheptafluorothiobutyrhydrazide.—N,N-Dimethylheptafluorobutyrhydrazidine,[10] 12.5 g. (0.049 mole), was allowed to react with 9.0 g. of hydrogen sulfide in the presence of 2.5 g. of hydrogen chloride and in a solvent mixture of 20 ml. of methyl alcohol and 20 ml. of diethyl ether. The reactants were held in a previously evacuated sealed tube at a 100° until the precipitation of ammonium chloride was complete. Volatile materials were removed from the tube to leave a residual oil which soon crystallized. This solid was washed with water and then dissolved in concentrated hydrochloric acid to give a yellow solution; the thiohydrazide was precipitated by adding ice-cold water, removed by filtration, and washed with additional cold water to yield 12 g. (90%) of crude, dry product. The product was recrystallized twice with carbon tetrachloride to give pure, white N,N-dimethylheptafluorothiobutyrhydrazide, m.p. 52–53°.

Anal. Calcd. for $C_6H_7F_7N_2S$: C, 26.47; H, 2.58; F, 48.88; N, 10.29. Found: C, 26.81; H, 2.99; F, 48.02; N, 10.05.

N^2-Phenyltrifluorothioacethydrazide and the Intermediate Hydrazidine.—Freshly distilled phenylhydrazine, 5.41 g. (0.050 mole), 15 ml. of methyl alcohol, and 5.25 g. (0.055 mole) of trifluoroacetonitrile were placed in a previously evacuated 30-ml. heavy-wall glass tube. The tube was sealed and allowed to remain at room temperature for 24 hr. then opened after cooling to 0°. Methyl alcohol was removed under reduced pressure to leave crude N^2-phenyltrifluoroacethydrazidine, 10.2 g. (100%), which was recrystallized from carbon tetrachloride.

Freshly prepared N^2-phenyltrifluoroacethydrazine, 12.0 g. (0.059 mole), and 60 ml. of anhydrous ether were placed in an 80-ml. heavy-wall glass tube. Air was removed from the tube by allowing a small amount of ether to vaporize into the vacuum system and the tube was then cooled in liquid nitrogen. Dry hydrogen chloride, 2.25 g., and hydrogen sulfide, 10.0 g., were condensed in the tube which was then sealed and heated at 100° for 2 hr. The reaction tube was opened, hydrogen sulfide was allowed to escape, and the solids present were removed by filtration. The ether filtrate was washed with 15% aqueous hydrochloric acid and with water and dried over anhydrous calcium sulfate. Solvent was removed under reduced pressure and the residual dark red oil was held at reduced pressure (1.0 mm.) until the by-product trifluorothioacetamide was volatilized and removed. The remaining crude N^2-phenyltrifluorothioacethydrazide weighed 6.0 g. (46%). This product darkened rapidly in the air and could not be crystallized; it was oxidized with hydrogen peroxide to the corresponding disulfide which was fully characterized.

N^2-Phenylpentafluorothiopropionhydrazide and the Intermediate Hydrazidine.—Freshly distilled phenylhydrazine, 5.41 g. (0.05 mole), pentafluoropropionitrile, 8.0 g. (0.055 mole), and 15 ml. of methyl alcohol in a 30-ml. sealed tube at room temperature overnight gave a quantitative yield of N^2-phenylpentafluoropropionhydrazidine; recrystallization from carbon tetrachloride gave a product melting at 61°.

N^2-Phenylpentafluoropropionhydrazidine, 10 g. (0.0395 mole), 15 ml. of anhydrous ether, 2.2 g. (50% excess) of dry hydrogen chloride, and 10 g. of hydrogen sulfide were sealed in a 75-ml. heavy-wall glass tube and heated at 100° for 2 hr. The reaction mixture was removed from the tube and treated as described in the preceding preparation to yield 8.7 g. (81%) of crude yellow-orange N^2-phenylpentafluorothiopropionhydrazide. This solid product was recrystallized from N-hexane to give white crystals, m.p. 42°, which, on contact with air turned yellow-orange rapidly. The N^2-phenylpentafluorothiopropionhydrazide could also be separated from its oxidation product and purified by vacuum sublimation (40–50° at 0.1 mm.). This compound was also subsequently oxidized completely to the corresponding disulfide which was fully characterized.

N^2-Benzenesulfonyltrifluorothioacethydrazide and the Intermediate Hydrazidine.—Trifluoroacetonitrile, 7 g. (0.0735 mole), was allowed to react with benzenesulfonylhydrazide, 12.05 g. (0.07 mole), in a mixture of 20 ml. of ether and 20 ml. of methyl alcohol in a 60-ml. sealed glass tube at room temperature overnight. Crude N^2-benzenesulfonyltrifluoroacethydrazidine was obtained in quantitative yield after removal of the solvents under reduced pressure. This compound was recrystallized from 65% aqueous methanol to give a pure product melting at 162–164°.

The freshly crystallized N^2-benzenesulfonyltrifluoroacethydrazidine, 10 g. (0.0272 mole), was dissolved in a minimum amount of a 1:1 mixture of methyl alcohol and ether and sealed in a tube with 20 g. of hydrogen sulfide. After the reaction tube had been allowed to stand at room temperature for 48 hr., the product was recovered by allowing excess hydrogen sulfide to vaporize and filtering the remaining mixture. The solid collected from the filtration was ground to a powder, washed with a large amount of ether, and separated by filtration to give 7.2 g. (66%) of white, pure, ammonium salt of N^2-benzenesulfonyltrifluorothioacethydrazide, dec. pt. 138°.

Anal. Calcd. for $C_8H_{10}F_3N_3O_2S_2$: C, 31.89; H, 3.36; F, 18.93; N, 13.95; O, 10.63; S, 21.26. Found: C, 31.54; H, 3.43; F, 19.01; N, 14.00; S, 21.02.

The ammonium salt was dissolved in water and acidified with hydrochloric acid to precipitate free N^2-benzenesulfonyltrifluorothioacethydrazide which was separated by filtration, washed thoroughly with water, and dried. This compound could be recrystallized from *n*-butyl alcohol.

N^2-Benzenesulfonylpentafluorothiopropionhydrazide and the Intermediate Hydrazidine.—The reaction of benzenesulfonylhydrazide, 12.9 g. (0.075 mole), and pentafluoropropionitrile, 11.0 g. (0.076 mole), was carried out in a solvent mixture consisting of 15 ml. of ether and 20 ml. of methyl alcohol. The reactants were placed in a 50-ml. sealed glass tube, heated at 40–50° until the benzenesulfonylhydrazide went into solution, and allowed to stand at room temperature overnight. Solvent was removed under reduced pressure and the residual oil soon crystallized. The solid N^2-benzenesulfonylpentafluoropropionhydrazidine was washed with water, dried, and recrystallized from carbon tetrachloride to give a nearly quantitative yield of product melting at 99–100°.

Freshly prepared N^2-benzenesulfonylpentafluoropropionhydrazidine, 10 g. (0.024 mole), was placed in a heavy-wall glass tube and dissolved in 10 ml. of anhydrous ether. Hydrogen sulfide, 20 g., was condensed in the tube which was sealed and held at room temperature for 72 hr. Removal of the excess hydrogen sulfide yielded a solid product which was washed thoroughly with anhydrous ether to give 8.6 g. (79%) of pure, white ammonium salt of N^2-benzenesulfonylpentafluorothiopropionhydrazide, decomposing at 121° with strong gas evolution.

Anal. Calcd. for $C_9H_{10}F_5N_3O_2S_2$: C, 30.77; H, 2.88; F, 27.06; N, 11.96; S, 18.23. Found: C, 30.56; H, 2.94; F, 26.76; N, 12.10; S, 18.30.

The ammonium salt was dissolved in water and acidified with hydrochloric acid to precipitate free N^2-benzenesulfonylpentafluorothiopropionhydrazide which was separated by filtration, washed thoroughly with water, and dried. This compound was recrystallized from *n*-butyl alcohol to give a white solid having a decomposition point of 120°.

N^2-Benzenesulfonylheptafluorothiobutyrhydrazide and the Intermediate Hydrazidine.—N^2-Benzenesulfonylheptafluorobutyrhydrazidine was prepared in quantitative yield by allowing benzenesulfonylhydrazide, 13.0 g. (0.075 mole), to react with heptafluorobutyronitrile, 16.0 g. (0.082 mole), in a mixture of

30 ml. of methyl alcohol and 25 ml. of ether in a sealed tube at 60° for 1 hr. The product was recrystallized from carbon tetrachloride and melted at 106–107°.

N^2-Benzenesulfonylheptafluorobutyrhydrazidine, 10 g. (0.0214 mole), and hydrogen sulfide, 20 g., were held in a sealed tube at room temperature for 48 hr. The solid recovered after removal of the excess hydrogen sulfide was washed with diethyl ether to give 8.3 g. (77%) of the ammonium salt of N^2-benzenesulfonylheptafluorothiobutyrhydrazide, decomposing at 114°. The ammonium salt was treated with hydrochloric acid as described in the preceding preparation to give free N^2-benzenesulfonylheptafluorothiobutyrhydrazide. This compound was the least stable of the N^2-benzenesulfonyl-substituted thiohydrazides.

Bis(α-hydrazonoheptafluorobutyl) Disulfide, $[C_3F_7C(=NNH_2)S-]_2$.—Freshly prepared heptafluorothiobutyrhydrazide, 16.0 g. (0.066 mole), was dissolved in 60 ml. of methyl alcohol and cooled to 0°. Into the stirred and cooled solution was dropped 15 g. of 30% hydrogen peroxide solution over a period of 10 min. The reaction mixture was stirred at 0–5° for 1 hr., then allowed to warm to room temperature for 2 hr. To the intensely yellow solution was added 150 ml. of ice–water to separate the product. The disulfide was extracted from the mixture with petroleum ether (b.p. 30–60°), and the extract washed with water and dried over calcium chloride. Removal of the solvent gave 14.2 g. (89%) of yellow bis(α-hydrazonoheptafluorobutyl) disulfide, recrystallized from *n*-hexane: m.p. 54–55°.

Anal. Calcd. for $C_8H_4F_{14}N_4S_2$: C, 19.75; H, 0.83; F, 54.73; N, 11.52; S, 13.17; mol. wt., 486. Found: C, 19.96; H, 1.05; F, 54.90; N, 11.22; S, 13.23; mol. wt. (cryoscopic in benzene), 502.

Bis[α-(N,N-dimethylhydrazono)trifluoroethyl] Disulfide, $\{CF_3C[=NN(CH_3)_2]S-\}_2$.—N,N-Dimethyltrifluorothioacethydrazide, 10.0 g. (0.058 mole), was dissolved in 70 ml. of methyl alcohol and oxidized with a 30% hydrogen peroxide solution (100% excess) at room temperature over a 3-hr. period. The crude disulfide was precipitated from the reaction mixture by adding 100 ml. of ice–water to the reaction solution, separated by filtration, and washed with ice-cold 50% aqueous methyl alcohol. The dried solid, 9.2 g. (92%), was recrystallized from aqueous methyl alcohol to give pure bis[α-(N,N-dimethylhydrazono)-trifluoroethyl] disulfide as yellow bars, m.p. 58–59°.

Anal. Calcd. for $C_8H_{12}F_6N_4S_2$: C, 28.07; H, 3.54; F, 33.33; N, 16.37; S, 18.71; mol. wt., 342. Found: C, 28.34; H, 3.45; F, 33.60; N, 16.17; S, 18.60; mol. wt. (cryoscopic in benzene), 325.

Bis[α-(N,N-dimethylhydrazono)heptafluorobutyl] Disulfide, $\{C_3F_7C[=NN(CH_3)_2]S-\}_2$.—N,N-Dimethylheptafluorothiobutyrhydrazide, 10 g. (0.037 mole), was dissolved in 50 ml. of methyl alcohol and oxidized by the addition of 100% excess of 30% hydrogen peroxide solution at 0° with stirring for 2 hr. The disulfide was separated by adding 100 ml. of ice-cold water to the yellow reaction solution; the crude product was extracted with petroleum ether and washed with water to remove methyl alcohol, and the petroleum ether solution was dried with anhydrous calcium sulfate. Removal of the solvent under reduced pressure gave 8.9 g. (89%) of yellow bis[α-(N,N-dimethylhydrazono)trifluoroethyl] disulfide which was purified by distillation, b.p. 120° (0.1 mm.).

Anal. Calcd. for $C_{12}H_{12}F_{14}N_4S_2$: C, 26.57; H, 2.23; F, 49.07; N, 10.33; S, 11.81. Found: C, 26.27; H, 2.24; F, 48.58; N, 10.40; S, 11.53.

Bis[α-(N-phenylhydrazono)trifluoroethyl] Disulfide $[CF_3C(=NNHC_6H_5)S-]_2$.—N^2-Phenyltrifluorothioacethydrazide, 6.0 g. (0.019 mole), was oxidized with 30% hydrogen peroxide solution (100% excess) in 30 ml. of methyl alcohol at room temperature for 1 hr. The solid disulfide was precipitated from the reaction solution by the addition of ice-cold water and was washed with ice-cold 70% aqueous methyl alcohol. The orange bis[α-(N-phenylhydrazono)trifluoroethyl] disulfide, 5.4 g. (90%), was recrystallized from aqueous methyl alcohol: m.p. 81°.

Anal. Calcd. for $C_{16}H_{12}F_6N_4S_2$: C, 43.80; H, 2.75; F, 26.03; N, 12.80; S, 14.61; mol. wt., 438. Found: C, 44.00; H, 2.38; F, 25.80; N, 12.74; S, 14.45; mol. wt. (cryoscopic in benzene), 413.

Bis[α-(N-phenylhydrazono)pentafluoropropyl] Disulfide, $[C_2F_5C(=NNHC_6H_5)S-]_2$.—Freshly prepared and recrystallized N^2-phenylpentafluorothiopropionhydrazide, 10.0 g. (0.037 mole), was oxidized with 30% hydrogen peroxide and purified as described in the preceding preparation. The orange bis[α-(N-phenylhydrazono)pentafluoropropyl] disulfide, 9.5 g. (95%), was recrystallized twice from aqueous methyl alcohol to give a pure product, m.p. 84°.

Anal. Calcd. for $C_{18}H_{12}F_{10}N_4S_2$: C, 40.15; H, 2.24; F, 35.31; N, 10.41; S, 11.89; mol. wt., 538. Found: C, 40.21; H, 2.10; F, 35.51; N, 10.27; S, 12.06; mol. wt. (cryoscopic in benzene), 497.

Methyl 1,1-Dihydroheptafluorobutyl Sulfide, $C_3F_7CH_2SCH_3$.—Freshly distilled methyl α-hydrazonoheptafluorobutyl sulfide, 5.0 g. (0.019 mole), and dry hydrogen chloride, 1.0 g., were heated in a sealed tube at 50–70° until a vigorous reaction took place. The tube was raised to 100° and kept at this temperature for an additional hour, then cooled to room temperature and opened. Excess hydrogen chloride was allowed to escape at −78°, the remaining reaction mixture was treated with water and the product was extracted with ether. The extract was dried and the ether was removed by distillation through a fractionation column at atmospheric pressure. The crude product was separated as a fraction (2.9 g., 65%), b.p. 100–106° at atmospheric pressure. Refractionation gave pure methyl 1,1-dihydroheptafluorobutyl sulfide, b.p. 101–103°.

Anal. Calcd. for $C_5H_5F_7S$: C, 26.08; H, 2.19; S, 13.91. Found: C, 25.98; H, 1.90; S, 14.02.

5-Heptafluoropropyl-1,2,3,4-thiatriazole.—Into a stirred solution of 3.66 g. (0.015 mole) of heptafluorothiobutyrhydrazide in 20 ml. of methyl alcohol and 8 ml. of water acidified with 4.5 g. of 37% hydrochloric acid was dropped at 0° a solution of 1.28 g. of sodium nitrite in 7 ml. of water over a period of 15 min. The mixture was stirred vigorously at 0° for 30 min., then diluted with 20 ml. of ice-cold water to separate a clear slightly yellow oil which appeared to be relatively stable at 0°. The oil was extracted with ice-cold petroleum ether, and the ether extract was washed with water and dried with calcium chloride. Removal of the petroleum ether under reduced pressure left an oil which contained a little solid sulfur. The infrared spectra of this crude product showed, in addition to a band at 6.9 μ (assigned to the C=N of the perfluoroalkylthiatriazole ring) absorption in the regions of 2.5–3.0 and 6.0–6.5 μ due to impurities. To obtain purified thiatriazole, the oil was placed in a chromatographic column packed with neutral alumina wet with petroleum ether and eluted with anhydrous diethyl ether. The infrared spectra of the purified compound obtained after ether removal showed no absorption in the regions of 2.5–3.0 and 6.0–6.5 μ.

5-Heptafluoropropyl-1,2,3,4-thiatriazole decomposed at room temperature within 24 hr. to give heptafluorobutyronitrile, nitrogen, and sulfur. A very slow decomposition (gas evolution) occurred at 0°. Acids did not accelerate the decomposition of the thiatriazole. When a few drops of the thiatriazole in a test tube were heated, a violent decomposition occurred.

2,5-Bis(heptafluoropropyl)-1,3,4-thiadiazole. A. From 1,2-Bis(heptafluorobutyryl)hydrazine.[16]—1,2-Bis(heptafluorobutyryl)-hydrazine, 5 g., prepared from heptafluorobutyrylhydrazide and heptafluorobutyryl chloride, and phosphorus pentasulfide, 8 g., were heated at 220–250° under atmospheric pressure for 2 hr. The crude product, 2.6 g. (52%), was distilled from the reaction mixture at approximately 157° at atmospheric pressure. It was recrystallized from carbon tetrachloride to give pure, white, solid 2,5-bis(heptafluoropropyl)-1,3,4-thiadiazole, m.p. 30–31°, ultraviolet absorption maximum (in isopropyl alcohol) 213 mμ (ε 5200).

B. From Bis(α-hydrazonoheptafluorobutyl) Disulfide.—Bis(α-hydrazonoheptafluorobutyl) disulfide, 5 g., and dry hydrogen chloride, 2 g., were heated in a sealed tube at a 100° for 2 hr. The reaction tube was opened at −78°, excess hydrogen chloride was allowed to escape, and the residual mixture was transferred to a separatory funnel to which water and diethyl ether were added. The ether layer was separated, washed with water, and dried over anhydrous calcium sulfate. The ether solvent was removed under reduced pressure to give 3.6 g. (87%) of crude 2,5-bis(heptafluoropropyl)-1,3,4-thiadiazole which was recrystallized from carbon tetrachloride to give a pure product, m.p. 30–31°. Infrared spectrum of this material was identical with that of the product from the preceding preparation.

C. From Heptafluorothiobutyrhydrazide.—Heptafluorothiobutyrhydrazide, 2.5 g., and dry hydrogen chloride, 0.5 g., were sealed in a heavy-wall glass tube and heated at 100°. The intensely yellow, solid hydrochloride of the thiohydrazide re-

mained unchanged. The tube was then heated at 131° for 2 hr. until a reaction accompanied by formation of a liquid and discoloration of the material in the tube appeared complete. Excess hydrogen chloride and the hydrogen sulfide formed in the reaction were allowed to escape from the tube at −78°. The reaction mixture was then separated to give about 1.6 g. (74%) of crude product. Recrystallization from carbon tetrachloride gave pure 2,5-bis(heptafluoropropyl)-1,3,4-thiadiazole, m.p. 30–31°. Infrared spectrum of this material matched those of the two previous preparations.

α,α′-Diaminopimelic Acid Peptides. VIII.[1a] Synthesis of Symmetrical Peptides Containing *meso*-α,α′-Diaminopimelic Acid, D- or L-Alanine, and L-Glutamic Acid[1b,c]

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The synthesis of five tripeptides and three pentapeptides containing *meso*-α,α′-diaminopimelic acid, D- or L-alanine, and L-glutamic acid is described. In these peptides the *meso*-α,α′-diaminopimelic acid residue is symmetrically substituted: (a) at both carboxyl groups (peptides I, II, and III); (b) at both amino groups (peptides IV, V, and VI); and (c) at all four functions (peptides VII and VIII).

Natural peptides containing α,α′-diaminopimelic acid have been found in the peptide–amino sugar polymer forming the essential part of the cell wall of several bacteria and blue-green algae.[3,4]

Their amino acid composition and sequence have been especially well studied in the case of *Escherichia coli*[5] and *Aerobacter cloacae*.[6]

It was shown in the case of the cell wall peptides of these two gram-negative bacteria that the amino and carboxyl functions of *meso*-diaminopimelic acid were nonsymmetrically substituted, this amino acid being linked first to either the α- or the γ-carboxyl function of a D-glutamic acid residue, secondly to the amino function of a D-alanine residue, and thirdly probably also to the carboxyl function of another D-alanine residue.[7]

In order to determine exactly which functions of *meso*-α,α′-diaminopimelic acid are involved in these peptide bonds, it seemed to us particularly desirable to have synthetic model peptides of well-defined structure and configuration. We have recently worked out methods for the preparation of such model peptides. Some of our results have been presented in preliminary communications at the European Peptide Symposia.[8]

The present paper describes the synthesis of five tripeptides and of three pentapeptides. They all include *meso*-α,α′-diaminopimelic acid symmetrically substituted with D- or L-alanine or L-glutamic acid and they were used as model substrates in enzymatic assays with various peptidases.[9] Their structure and configuration are illustrated in Scheme I.

In these syntheses the benzyloxycarbonyl group was used as the protecting group of the amino functions, whereas methyl and benzyl esters were used as temporary protecting groups of the α- and γ-carboxyl functions. The formation of the peptide bond was performed either by the mixed anhydride[10] or by the dicyclohexylcarbodiimide method.[11] Coupling by the azide method gave unsatisfactory results.

Benzyloxycarbonyl groups and benzyl esters were removed by catalytic hydrogenolysis and the methyl esters by saponification in the usual way. In the preparation of pentapeptides III, VII, and VIII a stepwise condensing procedure starting with the C-terminal amino acid was used. The preparation of some of the intermediates used in these syntheses (as well as the preparation of α-L-glutamyl-D-alanine dibenzyl ester hydrochloride) has been reported elsewhere.[1a,12,13]

The rotatory values found for the antipodes of each pair of the enantiomorphic peptides I and II, IV and V, and VII and VIII, which were synthesized in many cases by different procedures, were of the same magnitude and of opposite sign, thus indicating that no appreciable racemization had occurred during their synthesis. Optical purity was of the utmost importance for some of these peptides since they were to be used as enzymatic substrates in the study of the stereospecificity of various peptidases.[9]

The main difficulties encountered in these syntheses were due to (a) the low solubilities of certain derivatives in organic solvent, (b) the formation, during the coupling reactions or during the removal of the protecting groups, of monosubstituted derivatives which

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