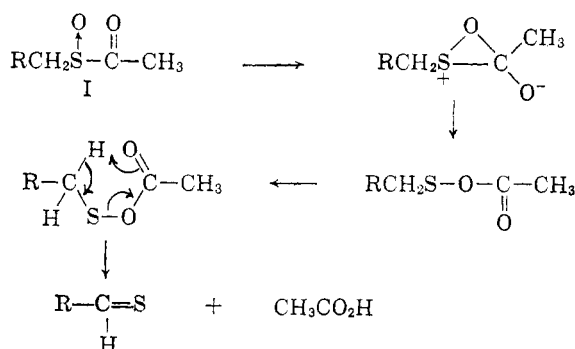sulfenic acid,[11] a class of compounds of known facile oxidizability. The intermediate acyl sulfoxide, I, could rearrange by an intramolecular path:


The thioaldehyde, RCHS, could be the source of

(11) N. Kharasch, S. J. Potempa, and H. L. Wehrmeister, *Chem. Rev.* **39**, 269 (1946).

the small amount of carboxylic acid, RCO_2H, that is formed.

All attempts to detect intermediate stages of oxidation failed. The oxidation of the thiolacetate was carried out with only one-third of the required hydrogen peroxide. Only one-third of the expected sulfonic acid was formed along with unchanged starting material; no intermediates could be detected by ultraviolet and infrared analysis.

Surprisingly, the reaction between sulfonic acids and diazomethane to give methyl sulfonates is not reported in the literature:

$$RSO_2OH + CH_2N_2 \xrightarrow[0°]{\text{Diethyl ether}} RSO_2OCH_3 + N_2$$
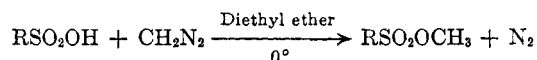
The reaction is rapid, smooth, and gives high yields of methyl esters. Some polymethylene is produced in a competing reaction but this byproduct can be conveniently separated by column chromatography, along with traces of unchanged sulfonic acid.

Preparation and Reactions of Perfluoroalkylthioimidates. Alkyl Perfluoroalkyldithiocarboxylates and Perfluoroalkylorthothiocarboxylates[1]

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Several perfluoroalkylnitriles reacted under pressure with methyl and ethyl mercaptans in the presence of anhydrous potassium carbonate as catalyst to give the corresponding perfluoroalkylthioimidates in high yields. Hydrochlorides of the thioimidates were converted to the esters of dithiocarboxylic acids by reaction with hydrogen sulfide and to orthothioesters by mercaptolysis under pressure. Mechanism of the dithioester formation is discussed. Spectra of the compounds prepared are listed and discussed.

This paper presents the initial results of a research program designed to examine the chemical behavior of a number of fluorocarbon derivatives with sulfur-containing functional groups, with particular interest in establishing the effect of the fluorocarbon group on the reactivity and nature of the carbon-sulfur single and double linkages in terms of general electron-distribution theory. Although a number of studies have reported the properties of the perfluoroalkyl sulfides and the perfluoroalkyl mercaptans, much less information is available regarding the thiocarbonyl group attached to a perfluoroalkyl group, with the exception of brief descriptions of the thioamides,[2] the thioesters,[3,4] and, in more detail, the recently reported

thioketones.[5] No derivatives of the perfluoroalkyl dithiocarboxylic acids or the perfluoroalkylthioimidates have been reported.

The reaction of perfluoroalkylnitriles with mercaptans was selected as the starting point for this work, both for the useful intermediate compounds that would be formed and for the opportunity this reaction presented to verify the generalizations made by Schaeffer and Peters[6] concerning the effect of basic catalysts and α-substituents on the reactivity of alkylnitriles.

Perfluoroalkylnitriles were allowed to react with alkyl mercaptans in sealed tubes in the presence of a very small amount of anhydrous potassium carbonate as a heterogeneous catalyst to give the corresponding perfluoroalkyl thioimidates in high yields. No reaction was observed in the absence of

(1) This work was supported by a research grant, Cy 5083.SSS. from the National Institutes of Health, Public Health Service.

(2) W. L. Reilly and H. C. Brown, *J. Am. Chem. Soc.*, **78**, 6032 (1956).

(3) M. Hauptschein, C. S. Stokes, and E. A. Nodiff, *ibid.*, **74**, 4005 (1952).

(5) K. E. Rapp *et al.*, *ibid.*, **72**, 3642 (1950).

(5) (a) E. G. Howard and W. J. Middleton, U.S. Patent 2,970,173, January 31, 1961; (b) W. J. Middleton, E. G. Howard, and W. H. Sharkey, *J. Am. Chem. Soc.*, **83**, 2589 (1961).

(6) F. C. Schaeffer and G. H. Peters, *J. Org. Chem.*, **26**, 412 (1961) and references therein.

Table I

Perfluoroalkylthioimidates, Dithiocarboxylates, and Orthothioesters

Compound	B.p.	d^{25}	n^{25}	$\lambda_{max}{}^a$	log ϵ_{max}
$CF_3C(NH)SC_2H_5$	37.5–38.0/56 mm.	1.238	1.4072	242	3.73
$C_2F_5C(NH)SCH_3$	43.5/78 mm.	1.421	1.3811	242	3.72
$C_3H_7C(NH)SCH_3$	55/79 mm.	1.496	1.3669	244	3.76
$C_3F_7C(NH)SC_2H_5$	45/27 mm.	1.413	1.3713	246	3.79
$CH_3S(NH)C(CF_2)_3C(NH)SCH_3{}^b$	...	...	...	231	4.04
$CF_3CSSC_2H_5$	62/54 mm.	1.301	1.4593	494	1.23
				322	4.08
$C_2F_5CSSCH_3$	51–52/50 mm.	1.455	1.4435	497	1.28
				321	4.08
$C_3H_7CSSCH_3$	62–63/46 mm.	1.530	1.4200	498	1.34
				322	4.08
$C_3F_7CSSC_2H_5$	71–72/37 mm.	1.459	1.4225	505	1.37
				325	4.08
$C_2F_5C(SCH_3)_3$	86/0.7 mm.	1.360	1.4630	234	...
$C_3F_7C(SCH_3)_3$	111/0.7 mm.	1.483	1.4528	235	3.08
$C_3F_7C(SC_2H_5)_3$	100/0.7 mm.	1.346	1.4530	237	3.08

^{a} All measurements in cyclohexane. ^{b} Solid, decomposes at 125°.

the catalyst, even with an increase in temperature to 100°.

An attempt to extend this reaction to aryl mercaptans was unsuccessful; thiophenol and perfluorobutyronitrile in the presence of potassium carbonate reacted exothermally, but the resulting solid product decomposed on removal of the excess nitrile at −20°.

Alkyl perfluoroalkylimidates apparently do not form under similar conditions of basic catalysis. Perfluorobutyronitrile and methyl alcohol were recovered unchanged from an attempted reaction. The instability of methyl perfluorobutyrimidate may be attributed to the difficulty in operation of a mesomeric electron displacement as indicated in I and II. As a result of the strong inductive effect of the perfluoroalkyl groups (which tends to reverse
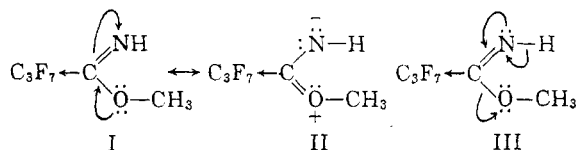
the usual polarity of the carbon-nitrogen double bond) and also the high electronegativity of the oxygen atom, an electronic displacement as indicated in III is promoted and is responsible for the collapse of the imidate group.

Anhydrous potassium carbonate proved to be a quite useful catalyst for the reaction between perfluoroalkylnitriles and mercaptans. Its action was moderate, compared to that of a strongly basic homogeneous catalyst such as trimethylamine, yet

IV
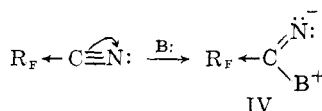
effective in concentrations of 0.003–0.004 mole percent. Activation of the perfluoroalkylnitriles by a basic catalyst can be pictured by assuming that the nitrile, acting as a Lewis acid, is engaged in

complex formation with the base to give a strongly nucleophilic, proton-seeking intermediate, IV, from which the catalyst is diplaced in the next step of the reaction. Formation of solid complexes of this type, the existence of which was assumed by Woodburn and Pins,[7] has been observed in this laboratory between perfluoroalkylnitriles and aliphatic tertiary amines.

The monofunctional alkyl perfluoroalkylthioimidates were colorless liquids with pleasant odors and were relatively stable at room temperature. In solution in methyl alcohol, the thioimidates underwent decomposition which could be followed by changes in the ultraviolet absorption spectra. The hydrochlorides of the perfluoroalkylthioimidates were quite stable, in marked contrast to the reported instability of the hydrochlorides of trichloroacetimidates. Physical properties of the alkyl perfluoroalkylthioimidates are shown in Table I.

Synthesis of alkyldithiocarboxylates previous to 1955 was carried out using the free, basic thioimidates with dry hydrogen sulfide. Sakurada[8] reported the synthesis of many aromatic dithioesters and thionesters by this method. Houben and Zivadinovitsch[9] succeeded in preparing esters of dithioformic acid; other aliphatic thioimidates failed, however, to follow the desired route, thioamides being formed instead.[10] The results of many experiments made it evident that "the reaction of imidates with hydrogen sulfide parallels their hydrolysis in that formimidates and aromatic imidates form esters, whereas aliphatic imidates form amides.[11]" In 1955 Marvel et al.[12] modified

(7) H. M. Woodburn and L. N. Pins, J. Org. Chem., **16**, 1389 (1951).

(8) Y. Sakurada, Mem. Coll. Sci., Univ. Kyoto, **10**, 79 (1926); Chem. Abstr., **21**, 3609 (1927).

(9) J. Houben and R. Zivadinovitsch, Ber., **69**, 2354 (1936).

(10) S. A. Karjala and S. M. McElvain, J. Am. Chem. Soc., **55**, 2966 (1933).

(11) J. B. Jepson, V. D. Lawton, and A. Lawton, J. Chem. Soc. (London), 1795 (1955).

(12) C. S. Marvel, P. de Radzitsky, and J. J. Brader, J. Am. Chem. Soc., **77**, 5997 (1955).

Sakurada's procedure by subjecting the hydro-chlorides of several aliphatic thioimidates to a reaction with dry hydrogen sulfide in pyridine solution at 0°. The yields of aliphatic dithiocarboxylic acid esters in this medium were high. Recent attempts, however, to extend this procedure to the synthesis of carboxymethyl esters of dithioacids, which are important as thioacylating agents for aminoacids, gave less than satisfactory results.[13] In some cases the yield of undesired thioamides was 90%.

We have found alternative conditions for Sakurada's procedure in which the hydrochlorides of alkyl perfluoroalkylthioimidates reacted directly in ether solution with dry hydrogen sulfide under pressure. The dithioesters were obtained in high yields in a two-step process, which is an essential feature of the modification of this reaction.
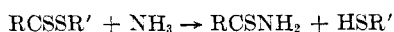
The hydrochloride of an alkyl perfluoroalkyl-thioimidate was preformed by condensing dry hydrogen chloride (20–50% excess) into a pressure tube containing an ethyl ether solution of the thioimidate and allowing the sealed tube to warm up to room temperature. The tube was shaken well to provide a better dispersion of the precipitated hydrochloride, immersed again in liquid nitrogen and then opened, under exclusion of air and moisture, in order to condense in the tube an excess of dry hydrogen sulfide. On resealing the tube and warming it to room temperature, a smooth reaction occurred accompanied by change in color of the tube contents. The ammonium chloride produced in the reaction averaged 84–86% of the theoretical amount.

$$R_FC\underset{SR}{\overset{NH \cdot HCl}{\lessgtr}} + H_2S \longrightarrow R_FC\underset{SR}{\overset{S}{\lessgtr}} + NH_4Cl$$
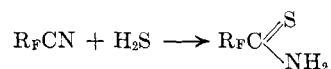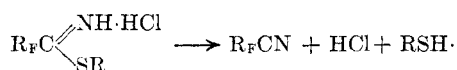
$$(84\text{–}86\%)$$
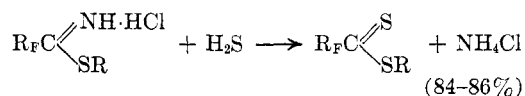
The alkyl perfluoroalkyldithioesters are deep-red liquids, stable in air, and may be distilled at atmospheric pressure without decomposition. They give a positive test for the C=S group with alcoholic silver nitrate. Physical properties of these compounds are listed in Table I.

The infrared spectra of the distilled perfluoroalkyl dithioesters indicated the presence of a nitrogen-containing impurity which was not removed by careful fractional distillation. Chromatographic separation in an alumina-packed column showed that the impurity was the corresponding perfluoroalkylthioamide.

The presence of the thioamide in this reaction product cannot be explained on the basis of the side reaction observed by Marvel[12] in which the dithioester underwent ammonolysis

$$RCSSR' + NH_3 \rightarrow RCSNH_2 + HSR'$$

nor by the sequence of reactions

$$R_FC\underset{SR}{\overset{NH \cdot HCl}{\lessgtr}} \longrightarrow R_FCN + HCl + RSH \cdot$$

$$R_FCN + H_2S \longrightarrow R_FC\underset{NH_2}{\overset{S}{\lessgtr}}$$

for there is no free ammonia present nor do the perfluoroalkylnitriles react with hydrogen sulfide in an acidic medium. There is also no evidence for the so-called "Pinner cleavage":

$$RC\underset{SR'}{\overset{NH \cdot HCl}{\lessgtr}} \longrightarrow RC\underset{NH_2}{\overset{S}{\lessgtr}} + R'Cl$$
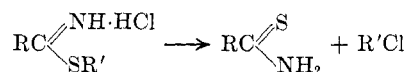
It was observed that the free, basic perfluoroalkylthioimidate reacted rapidly with hydrogen sulfide in ethyl ether to give the corresponding thioamide exclusively; high yields of the dithioesters were obtained only if the hydrochloride of the thioimidate were prepared and an excess of hydrogen chloride maintained before admission of hydrogen sulfide to the reaction tube. The following mechanism, involving an initial equilibrium between the thioimidate hydrochloride and the free base, is therefore proposed to account for the formation of both the dithioester and thioamide in a strongly acidic medium:
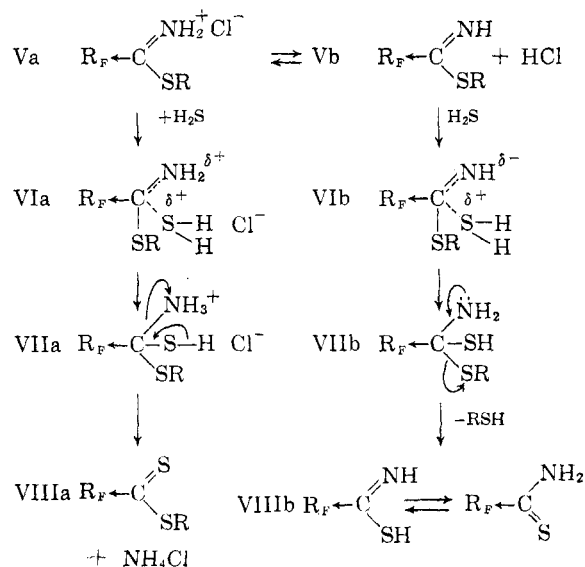
In order to break the strong double bond between the nitrogen atom and the strongly electron-seeking carbon atom to which a perfluoroalkyl group is attached, a positive charge must be placed on nitrogen to induce an electron flow away from the carbon (Va). With the approach of the nucleophile, there will be a sharing of partial positive charges on the sites of both donors (N and S atoms) as in VIa, which will rearrange to a transition state VIIa. The latter will collapse through an elimination process at the weakened C—N bond (a positive charge on the nitrogen atom persists through the reaction), since there is much greater electron pressure toward the carbon atoms from each of the sulfur atoms than from the positively charged nitrogen. The NH₄⁺

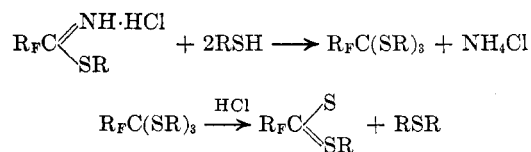(13) K. A. Jensen and C. Pederson, Acta Chem. Scand., 15, 1087 (1961).

TABLE II

COMPARATIVE ELECTRONIC SPECTRA OF ALKYL- AND PERFLUOROALKYLDITHIOCARBOXYLATES

Compound	λ_{max},[a] mμ	log ϵ_{max}	Compound	λ_{max},[b] mμ	log ϵ_{max}
$CF_3C(:S)SC_2H_5$	494	1.23	$CH_3C(:S)SC_2H_5$[c]	460	1.26
	322	4.08		306	4.08
$C_2F_5C(:S)SCH_3$	497	1.28	$C_2H_5C(:S)SCH_3$	(350)	
	321	4.08		305	3.45

[a] In cyclohexane.   [b] In hydrocarbon or ether.   [c] M. J. Janssen, *Rec. trav. chim.*, **79**, 464 (1960).

group departs to give ammonium chloride and the perfluoroalkyldithioester is formed.

A nucleophilic attack by hydrogen sulfide on the free basic thioimidate (Vb–VIIIb) results in the formation of the thioamide.

Perfluoroalkylorthothioesters were prepared by mercaptolysis of the corresponding perfluoroalkylthioimidate hydrochlorides under pressure at elevated temperatures. Formation of the corresponding dithioesters as by-products was observed in each case and could be accounted for by a subsequent reaction of the orthothioester with hydrogen chloride.

$$R_FC\overset{NH \cdot HCl}{\underset{SR}{\big<}} + 2RSH \longrightarrow R_FC(SR)_3 + NH_4Cl$$

$$R_FC(SR)_3 \overset{HCl}{\longrightarrow} R_FC\overset{S}{\underset{SR}{\big<}} + RSR$$

Even at the elevated temperature, there was no formation of the corresponding thioamide which might result from Pinner's splitting of the starting thioimidate hydrochloride.

Perfluoroalkylorthothioesters are colorless oily liquids with an odor resembling turpentine. They are stable in nonpolar organic solvents but are attacked by alcoholic silver nitrate solution. Physical properties of these compounds are shown in Table I.

Perfluoroalkylthioimidates show strong absorption in the ultraviolet region (Table I) which can be attributed to the —C(:NH)SR grouping. Although other examples of the imido group do not necessarily show absorption maxima in the ultraviolet region[14] the perfluoroalkylthioimidates can exhibit p-π conjugation[15,16] between the p-electrons of the sulfur and the π-electrons of the C=N and thus undergo electronic transition at energies in the region studied.

A comparison of the electronic spectra of the perfluoroalkyldithiocarboxylates with their hydrocarbon analogs is interesting. Both have similarly intense bands in the ultraviolet region, log ϵ_{max} for the ethyl esters being identical, but the wavelengths of the absorption maxima differ markedly. The fluorine-containing compounds show a bathochromic shift of 16 mμ from the corresponding

maximum of the hydrocarbon analog. An even more pronounced shift is shown in the visible region between the deep-red perfluoroalkyl derivatives and the yellow-orange hydrocarbon compounds.

Luttringhaus and Cleve[17] came to the conclusion that the C=S group manifests a strong chromophoric character if the double bond is but little polarized. The presence of the perfluoroalkyl group in the dithioesters reported here reduces the opportunity for polarization of C=S by its strong inductive effect. The overlap between the $2p$-orbital of the carbon atom and the $3p$-orbital of sulfur is strengthened and the delocalization of the π-electrons is enhanced; the latter effect is responsible for the bathochromic shift.

Tabulation of the colors of a series of compounds containing the C=S group shows the progressive change in the nature of this structure as visible light absorption goes to higher frequencies: CF_3C(:S)CF_3, deep blue[5]; R_FC(:S)SR, deep red; RC-(:S)SR′, yellow-orange[12]; R_FC(:S)NH_2, pale yellow[2]; C_3F_7C(:S)NHNH$_2$, white (colorless).[18]

In the infrared region, perfluoroalkylthioimidates show absorption for N—H stretching at 2.87–2.97 μ, for C—H stretching at 3.30 μ and for C=N stretching at 6.20 μ. Careful examination of the spectra of the perfluoroalkyl thioimidates and dithiocarboxylates did not allow a definite assignment for C=S stretching. According to Bellamy,[19] who recently gave revised assignments for this group, C=S in this type of compound should appear at wave lengths shorter than 8.5 μ, at which the thiocarbonyl group of an alkyl dithiocarboxylate absorbs. Examination of the region between 7.0 and 8.5 μ in the spectra of perfluoroalkyl derivatives, however, is frequently inconclusive because of the strong absorption of C—F in this area.

Experimental

Ethyl Heptafluorobutyrthioimidate.—Into an evacuated heavy-walled Pyrex glass tube of 70–80 ml. capacity, previously constricted for sealing, and containing 35 ml. of ethyl mercaptan and 0.03 g. of anhydrous potassium carbonate, was condensed 35 g. of perfluorobutyronitrile. The tube was sealed, allowed to warm to room temperature, and left standing until a strongly exothermic reaction was completed, then heated at 100° for 2 hr. After cooling to 0°, the tube was opened, excess ethyl mercaptan removed, and the remaining product distilled from a 50-ml. flask under

(14) For example, R_FC(:NH)N(CH$_3$)C(:NH)R_F or R_FC(:NH)-NH$_2$ do not show absorption maxima in the region 220–340 mμ; R_FC(:NH)NR$_2$ does show a maximum (unpublished results from this laboratory).

(15) K. Bowden, E. A. Braude, and E. R. H. Jones, *J. Chem. Soc.*, 948 (1946).

(16) K. Bowden and E. A. Braude, *ibid.*, 1068 (1952).

(17) A. Luttringhaus and W. Cleve, *Ann.*, **575**, 112 (1951).

(18) R. Pater, unpublished results.

(19) L. J. Bellamy and P. G. Rogasch, *J. Chem. Soc.* (London), 2218 (1960).

reduced pressure to give about 42 g. (91% yield) of pure ethyl heptafluorobutyrthioimidate, b.p. 45° at 27 mm. Redistillation of a sample stored for 2 months showed no deterioration of the material.

Anal. Calcd. for $C_6H_6F_7NS$: C, 28.0; H, 2.32; N, 5.45; S, 12.45; F, 51.75. Found: C, 28.24; H, 2.26; N, 5.23; S, 12.49; F, 52.03.

Methyl Heptafluorobutyrthioimidate.—This reaction was carried out in a manner similar to that described above. Perfluorobutyronitrile (35 g.), 0.03 g. of anhydrous potassium carbonate, and 35 ml. of methyl mercaptan yielded 39 g. (90% yield) of pure methyl heptafluorobutyrthioimidate, b.p. 55° at 79 mm.

Anal. Calcd. for $C_5H_4F_4NS$: C, 24.7; H, 1.65; N, 5.76; S, 13.17; F, 54.7. Found: C, 24.90; H, 1.48; N, 5.72; S, 13.08; F, 54.82.

Methyl Pentafluoropropionthioimidate.—Pentafluoropropionitrile, 25 g., was allowed to react with methyl mercaptan, 30 ml., in the presence of 0.02 g. of anhydrous potassium carbonate in a sealed tube to give 31 g. (94% yield) of a crude product. Fractional distillation under reduced pressure in a 40 cm. glass helices-packed column yielded pure methyl pentafluoropropionthioimidate, b.p. 43.0–43.5° at 78 mm.

Anal. Calcd. for $C_4H_4F_5NS$: C, 24.84; H, 2.08; N, 7.26; S, 16.58 F, 49.22. Found: C, 24.99; H, 2.22; N, 7.00; S, 16.67; F, 49.22.

Ethyl Trifluoroacethioimidate.—Trifluoroacetonitrile, 25 g., was allowed to react in a sealed tube with ethyl mercaptan, 30 ml., in the presence of 0.02 g. of anhydrous potassium carbonate. A strongly exothermic reaction took place, the temperature of the tube rising to 75°. The tube was then allowed to cool down to room temperature and opened at 0°. The crude product was distilled and a fraction boiling between 35–42.5° at 56 mm. was collected in an ice-cooled receiver. Subsequent fractionation separated pure ethyl trifluoroacethioimidate, b.p. 37.5–38.0° at 56 mm. The yield was 70%.

Anal. Calcd. for $C_4H_6F_3NS$: C, 30.60; H, 3.82; N, 8.92; S, 20.36; F, 36.31. Found: C, 30.70; H, 3.83; N, 8.88; S, 20.26; F, 36.30.

Dimethyl Perfluoroglutarthioimidate.—Into an evacuated heavy-walled Pyrex glass tube of about 40-ml. capacity, previously constricted for sealing, was placed 0.02 g. of anhydrous potassium carbonate. After the tube was connected to a vacuum system and cooled in liquid nitrogen, 15 g. of perfluoroglutaronitrile and about 25 ml. of methyl mercaptan were allowed to condense in the tube. The tube was warmed to room temperature and left until an exothermic reaction was completed, then opened after cooling down to 0°. Excess methyl mercaptan was removed at low temperature under reduced pressure. A mixture consisting of a liquid material and a colorless solid, which crystallized in large bars, was found in the tube. The solid was filtered and washed, first with toluene and then with carbon tetrachloride. White crystals, 7 g. (30% yield), of dimethyl perfluoroglutarthioimidate were collected and further purified by a high-vacuum sublimation at 0.05 mm. This product decomposed on heating at 125°.

Anal. Calcd. for $C_7H_8F_6N_2S_2$: C, 28.19; H, 2.70; N, 9.40; S, 21.46 F, 38.25. Found: C, 28.32; H, 2.89; N, 9.50; S, 21.37; F, 38.32.

Ethyl Trifluorodithioacetate.—Ethyl trifluoroacethioimidate, 10 g., was dissolved in 50 ml. of dry ethyl ether and placed in a heavy-walled Pyrex glass tube (approximate volume, 70–80 ml.) which was drawn in the upper part to form a double constriction. The tube was connected to a calibrated vacuum system and then immersed in liquid nitrogen. Dry hydrogen chloride, 2.9 g., was condensed in the tube and the tube was sealed at the first constriction. It was warmed to room temperature and shaken while the reaction proceeded. After a good dispersion of the salt was effected, the tube was immersed again in liquid nitrogen, connected to the vacuum system, and dry hydrogen sulfide,

5 g., was condensed in the tube. After the tube was resealed, it was warmed to room temperature and shaken well during the course of the reaction, then allowed to stand overnight. The reaction tube was opened at 0°; the precipitated ammonium chloride was filtered off and washed with ether. The filtrate and washing ether were combined, the ether was evaporated under reduced pressure, and the residue, 9.1 g., was distilled under reduced pressure. The distilled sample of impure ester was dissolved in petroleum ether and was further purified by passage through a chromatographic column packed with alumina, using petroleum ether as the eluent for the ester. Pure ethyl perfluorodithioacetate, 8.5 g. (73% yield), was recovered on removing the petroleum ether and redistilling the product which boiled at 62° at 54 mm., 135° at 760 mm. Like all of the perfluoroalkyl dithioesters, this compound is extremely volatile and lachrymatory in the vapor state.

The thioamide formed as a by-product was recovered on washing the alumina column with ethyl ether.

Anal. Calcd. for $C_4H_5F_3S_2$: C, 27.60; H, 2.90; S, 36.78 F, 32.75. Found: C, 27.31; H, 3.08; S, 36.84; F, 33.01.

Methyl Pentafluorodithiopropionate.—The reaction was carried out as described above for ethyl trifluorodithioacetate; 10 g. of methyl pentafluoropropionthioimidate was allowed to react in ethyl ether, 50 ml., with 3.0 g. of dry hydrogen chloride and subsequently with 6 g. of dry hydrogen sulfide to give 8.0 g. (78% yield) of pure methyl perfluorodithiopropionate, b.p. 51–52° at 50 mm.

Anal. Calcd. for $C_4H_3F_5S_2$: C, 22.84; H, 1.43; S, 30.48; F, 45.20. Found: C, 22.70; H, 1.69; S, 30.92; F, 45.23.

Methyl Heptafluorodithiobutyrate.—Methyl heptafluorobutyrthioimidate, 10 g., reacted in 50 ml. of dry ether with 3.0 g. of dry hydrogen chloride and subsequently with 6 g. of dry hydrogen sulfide. There was obtained 2.4 g. of an ether-insoluble solid (largely ammonium chloride) and 9.4 g. (90% yield) of crude, distilled methyl heptafluorodithiobutyrate. The product, purified in an alumina-packed chromatographic column, boiled at 62° at 46 mm.

Anal. Calcd. for $C_5H_3F_7S_2$: C, 23.04; H, 1.15; S, 24.62; F, 51.13. Found: C, 23.32; H, 1.33; S, 24.42; F, 51.02.

Ethyl Heptafluorodithiobutyrate.—Ethyl heptafluorobutyrthioimidate, 10 g., was allowed to react in ether (50 ml.) with 2.5 g. of dry hydrogen chloride and then with 4.0 g. of dry hydrogen sulfide in the manner previously described. Ammonium chloride, 1.80 g. (84% yield), and 8.7 g. of a crude, distilled dithiocarboxylate (80% yield) were recovered. Pure ethyl heptafluorodithiobutyrate boils at 71–72° at 37 mm.

Anal. Calcd. for $C_6H_5F_7S_2$: C, 26.28; H, 1.83; S, 23.34; F, 48.58. Found: C, 26.42; H, 1.95; S, 23.00; F, 48.43.

Triethyl Heptafluoroorthothiobutyrate.—A solution of 11.5 g. of ethyl heptafluorobutyrthioimidate in 50 ml. of ethyl mercaptan was prepared in a heavy-walled Pyrex glass tube (capacity approximately 70 ml.). After connecting the tube to a vacuum system, cooling it with liquid nitrogen, and evacuating the air, there was condensed in the tube 3 g. of dry hydrogen chloride. The tube was then sealed, warmed to room temperature and heated at 100° for 2 hr. The tube was opened at 0°, the precipitate (2.0 g. of ammonium chloride) filtered, and the solvent distilled to leave a liquid residue which was extracted with 25 ml. of ether. The ether solution was washed with water several times, when dried over anhydrous calcium sulfate. A liquid, 13.9 g., was obtained on removing the solvent. This product was fractionated under reduced pressure to yield a forerun of the dithioester and (at a lower pressure) triethyl heptafluoroorthothiobutyrate, 5 g., (30% yield) which distilled at 100° at 0.7 mm.

Anal. Calcd. for $C_{10}H_{15}F_7S_3$: C, 32.98; H, 4.12; S, 26.35; F, 36.55. Found: C, 33.02; H, 4.39; S, 26.14; F, 36.44.

Trimethyl Heptafluoroorthothiobutyrate.—Reaction involving 11.5 g. of ethyl heptafluorobutyrthioimidate with an excess of methyl mercaptan was carried out in accordance with the procedure described for the proceeding orthothioester. The yield of pure trimethyl heptafluoroorthothiobutyrate was 4 g. (27%), b.p. 111° at 0.7 mm.

Anal. Calcd. for $C_7H_9F_7S_3$: C, 26.06; H, 2.79; S, 29.81; F, 41.30. Found: C, 25.83; H, 3.05; S, 29.53; F, 41.17.

Trimethyl Pentafluoroorthothiopropionate.—Reaction of 6 g. of methyl pentafluoropropionthioimidate with methyl mercaptan under conditions described for the first compound of this series of orthothioesters gave 2 g. (25% yield) of pure trimethyl pentafluoroorthothiopropionate, b.p. 86° at 0.7 mm.

Anal. Calcd. for $C_6H_9F_5S_3$: C, 26.44; H, 3.30; S, 35.25; F, 34.92. Found: C, 26.69; H, 3.61; S, 35.44; F, 35.02.

Pyrido[2,3-d]pyrimidines from Malonaldehydes[1]

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The product from the condensation of 2,4-diamino-6-hydroxypyrimidine with nitromalonaldehyde has now been shown to be 2-amino-4-hydroxy-6-nitropyrido[2,3-d]pyrimidine (I). A number of analogs and derivatives have been prepared but various efforts to convert several of these to the folic acid analog failed.

Further investigation of the product formed readily by condensation of nitromalonaldehyde with 2,4-diamino-6-hydroxypyrimidine[2] has shown it to be 2-amino-4-hydroxy-6-nitropyrido[2,3-d]-pyrimidine (I). Evidence in support of this structure and the preparation and characterization of a number of related compounds is presented.

Experimental[3]

2-Amino-4-hydroxy-6-nitropyrido[2,3-d]pyrimidine (II).—A mixture of 12.6 g. of 2,4-diamino-6-hydroxypyrimidine (I)[4] and 15.7 g. of sodium nitromalonaldehyde monohydrate[5] in 100 ml. of 1% alkali was refluxed vigorously for 1 hr. On chilling to 5°, a voluminous mass of yellow needles separated, 18.4 g. (75%). Recrystallization from aqueous alkali gave samples of the sodium salt which tenaciously held from 0.5 to 2.5 moles of water.

Anal. Calcd. for $C_7H_4O_3N_5Na·^1/_2H_2O$: C, 35.30; H, 2.12; N, 29.41. Found: C, 35.78; H, 2.69; N, 30.33.

A 5.9-g. sample of this material was dissolved in 800 ml. of boiling 20% hydrochloric acid and filtered hot through glass wool. On cooling, green-tan needles separated, 3.6 g. (73%).

Anal. Calcd. for $C_7H_5O_3N_5$: C, 40.58; H, 2.43; N, 33.81. Found: C, 40.32; H, 2.56; N, 34.11.

The acetyl derivative of II was prepared by refluxing 0.21 g. of II in 20 ml. of acetic anhydride for 2.5 hr. On cooling, 0.17 g. of white crystals separated, which were recrystallized from ethanol, m.p. 320° dec.

Anal. Calcd. for $C_9H_7O_4N_5$: C, 43.38; H, 2.83; N, 28.11. Found: C, 43.72; H, 2.90; N, 28.47.

2,6-Diamino-4-hydroxypyrido[2,3-d]pyrimidine (III).—A mixture of 3.6 g. of II and 7.9 g. of stannous chloride was refluxed vigorously in 40 ml. of 20% hydrochloric acid for 45 min. The dark solution was diluted to 650 ml. and, at 60°, gaseous hydrogen sulfide was passed in for 1.5 hr.

After filtration the clear, green fluorescent filtrate was evaporated to 150 ml. and neutralized with excess solid sodium bicarbonate, precipitating 2.0 g. (65%) of orange-yellow solid, which was recrystallized from dilute sodium bicarbonate.

Anal. Calcd. for $C_7H_7ON_5$: C, 47.45; H, 3.69; N, 39.53. Found: C, 47.25; H. 4.15; N, 39.23.

The *diacetyl* derivative was prepared by refluxing 0.19 g. of III in 15 ml. of acetic anhydride for 20 hr. The resulting white solid was recrystallized from a large volume of water.

Anal. Calcd. for $C_{11}H_{13}O_3N_5$: C, 50.18; H, 4.98; N, 26.61. Found: C, 50.03; H, 4.58; N, 27.15.

The *6-N-formyl* derivative was prepared by boiling 1.0 g. of III in 20 ml. of 98% formic acid until it was concentrated to 5 ml. On dilution with 20 ml. of water, a pale yellow solid precipitated. It was purified by reprecipitation from formic acid solution.

Anal. Calcd. for $C_8H_7O_2N_5·^1/_2H_2O$: C, 44.86; H, 3.77; N, 33.46. Found: C, 44.81; H, 4.03; N, 33.29, 32.68.

2-Amino-4-hydroxy-6-(p-dimethylaminophenylazo)pyrido-[2,3-d]pyrimidine (IV).—A suspension of 0.48 g. of III in 15 ml. of 20% hydrochloric acid was prepared by chilling a hot solution to 3–5°. On adding 0.17 mg. of sodium nitrite in 5 ml. of water dropwise with cooling, the amine first dissolved and then the diazonium salt precipitated. A solution of 0.30 g. of dimethylaniline in 10 ml. of 1.5% hydrochloric acid and 25 ml. of 36% aqueous sodium acetate were added simultaneously to the diazonium salt suspension. After standing overnight, the deep red crystalline solid (0.48 g., 57%) was collected and recrystallized from dimethylformamide.

Anal. Calcd. for $C_{15}H_{15}ON_7$: C, 58.24; H, 4.89; N, 31.70. Found: C, 57.94; H, 5.23; N, 31.62.

2-Amino-4-hydroxypyrido[2,3-d]pyrimidine (V). A. By Deamination of III.—A diazonium salt suspension was prepared as above from 1.2 g. of III and 3.5 g. of sodium hypophosphite monohydrate in 30 ml. of cold water was added. The mixture was stirred for 1 hr. at 5° and 1 hr. at 25°. After filtration, the solution was diluted with 2 volumes of water and neutralized with excess sodium bicarbonate precipitating 0.91 g. (83%) of dark solid. It was purified by recrystallization from dilute aqueous sodium bicarbonate; the solutions fluoresced sky blue under ultraviolet light.

Anal. Calcd. for $C_7H_6ON_4·H_2O$: D, 46.67; H. 4.48; N, 31.10. Found: C, 47.38; H, 4.16; N, 31.70.

The water was not lost even on prolonged exposure at 110° (0.1 mm.). The same product was obtained from the diazonium salt in ethanol, although in poorer yield.

The *acetate* was prepared by refluxing 0.27 g. of V in 20 ml.

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(1) Abstracted largely from the Ph.D. dissertation of Raffaele Bernetti (1959).

(2) T. L. V. Ulbricht and C. C. Price, *J. Org. Chem.*, **22**, 235 (1957).

(3) Melting points are uncorrected; if none is given the compound did not melt below 300°. Analyses by Midwest Microlab and Galbraith.

(4) B. Roth, M. R. Hultquist, and J. M. Smith, *J. Am. Chem. Soc.*, **72**, 1915 (1950).

(5) P. E. Fanta, *Org. Syn.*, **32**, 95 (1952).