triethylamine (0.51 ml.) were added to chloroform (8 ml.). The resulting suspension was stirred at room temperature for 15 min. and then allowed to stand at room temperature without further stirring for 16 hr. Chloroform was removed *in vacuo* and ether (50 ml.) was added to the residue. The mixture was allowed to stand at room temperature for 3 hr. The solid product was filtered and washed successively with ether (40 ml.) and water (13 ml.). It then was dissolved in glacial acetic acid (6 ml.) and water (35 ml.) was added in small portions while the solution was heated to about 60°. The solution was allowed to cool gradually to room temperature during which time the product began to crystallize. The mixture was allowed to stand at 5° for 6 days. The product was filtered and washed with water (20 ml.); wt. 0.50 g., m.p. 115.5–116.5°, $[\alpha]^{21}D$ −44.0° (*c* 1, tetrahydrofuran).

Anal. Found: C, 56.6; H, 6.56; N, 8.29.

Ethyl N-Acetyl-S-benzyl-DL-cysteinylglycinate.—This compound was prepared from *p*-nitrophenyl N-acetyl-S-benzyl-DL-cysteinate and ethyl glycinate hydrochloride by the procedure described for the preparation of ethyl N-acetyl-S-benzyl-L-cysteinylglycinate from the L *p*-nitrophenyl ester and ethyl glycinate hydrochloride. The reaction was carried out on the same scale and the product was purified by exactly the same procedure; wt. 0.48 g., m.p. 86.5–87.5°, $[\alpha]^{21}D$ 0° (*c* 1, tetrahydrofuran).

Anal. Calcd. for $C_{16}H_{22}O_4N_2S$: C, 56.8; H, 6.55; N, 8.28. Found: C, 56.9; H, 6.57; N, 8.26.

Methyl N-Acetyl-S-benzyl-L-cysteinyl-L-tyrosinate. Method A.—Methyl S-benzyl-N-carbobenzoxy-L-cysteinyl-L-tyrosinate[21] (1.57 g.) was dissolved in 4 *N* hydrogen bromide in glacial acetic acid (8 ml.). The solution was allowed to stand at room temperature for 20 min. and then anhydrous ether (240 ml.) was added. The decarbobenzoxylation product settled out as a viscous oil on the sides of the reaction vessel. Ether was removed by decantation. The product was washed with two 25-ml. portions of ether, the ether again being removed by decantation. The oily product was dissolved in water (50 ml.). Potassium bicarbonate (3.8 g.) was added and the resulting suspension was extracted four times with 30-ml. portions of ethyl acetate. The ethyl acetate extracts were combined, dried over anhydrous magnesium sulfate, and filtered. *p*-Nitrophenyl acetate[20] (0.54 g.) was added to the filtrate. The resulting solution was concentrated *in vacuo* to a volume of about 5 ml. and the concentrated solution was allowed to stand at room temperature for 3 days. Ethyl acetate was removed *in vacuo*. The residue was dissolved in glacial acetic acid (10 ml.) and then water (50 ml.) was added in an unsuccessful attempt to crystallize the product. The oily suspension was extracted five times with 25-ml. portions of ethyl acetate. The ethyl acetate extracts were combined, dried over anhydrous magnesium sulfate, and filtered. Ethyl acetate and acetic acid were removed *in vacuo* from the filtrate. The oily residue was dissolved in ethyl acetate (10 ml.) and hexane (20 ml.) was added. The crystalline product was filtered; wt. 0.50 g., m.p. 130–135°. It was recrystallized twice from glacial acetic acid (5 ml.) and water (20 ml.); wt. 0.26 g., m.p. 138.5–141.5°, $[\alpha]^{21}D$ −20.0° (*c* 1, tetrahydrofuran).

Anal. Calcd. for $C_{22}H_{26}O_5N_2S$: C, 61.4; H, 6.09; N, 6.51. Found: C, 61.5; H, 6.13; N, 6.47.

Method B.—*p*-Nitrophenyl N-acetyl-S-benzyl-L-cysteinate (1.12 g.) and methyl L-tyrosinate[22] (0.64 g.) were dissolved in tetrahydrofuran (34 ml.). The solution was allowed to stand at room temperature for 3 days. Tetrahydrofuran was removed *in vacuo* and the residue was dissolved in glacial acetic acid (10 ml.). Water (50 ml.) was added in small portions while the solution was heated to about 60°. The solution was allowed to cool gradually to room temperature during which time the product began to crystallize. The mixture was stored at 5° for 16 hr. The product was filtered and washed with water (25 ml.); wt. 1.18 g. It was recrystallized from ethyl acetate (20 ml.) and hexane (40 ml.), wt. 1.05 g., m.p. 141.5–142.5°, $[\alpha]^{20}D$ −20.0° (*c* 1, tetrahydrofuran).

Anal. Found: C, 61.4; H, 6.25; N, 6.46.

Acknowledgment.—This work was supported in part by a grant (H-1675) from the National Heart Institute, U.S. Public Health Service. The author is indebted to Dr. Vincent du Vigneaud for helpful suggestions and encouragement and to Mr. Joseph Albert for carrying out the microanalyses.

(21) This compound was prepared by the *p*-nitrophenyl ester method following a procedure reported earlier from this laboratory (ref. 1). In the reported procedure the crude dipeptide methyl ester was saponified and the resulting free acid was purified. In the present work the crude ester was purified by recrystallization from methanol and water, m.p. 110–112°, $[\alpha]^{20}D$ −27.6° (*c* 2.1, dimethylformamide), $[\alpha]^{19}D$ −20.8° (*c* 2, 95% ethanol). The methyl ester prepared by the dicyclohexylcarbodiimide method (ref. 1) when recrystallized from methanol and water melted at 109–110° and possessed a rotation of −27.5° in dimethylformamide (M. Bodanszky, unpublished). This same dipeptide ester synthesized by the azide method has been reported to melt at 110–111° and to possess an optical rotation of −30.5° in 95% ethanol [H. S. Bachelard and V. M. Trikojus, *J. Chem. Soc.*, 4541 (1958)]. Since the observed rotation in 95% ethanol was not in agreement with the reported value, the dipeptide ester was synthesized in this laboratory by the azide method and also by the mixed anhydride method [J. R. Vaughan, Jr., and J. A. Eichler, *J. Am. Chem. Soc.*, **75**, 5556 (1953)]. It was not possible by either of these procedures to obtain material with a rotation significantly different from −20.8° in 95% ethanol, the value found for the product prepared by the *p*-nitrophenyl ester method.

(22) E. Fischer, *Ber.*, **41**, 850 (1908).

Partially Fluorinated Aliphatic Compounds by Reductive Desulfurization of Substituted Thiophene

S. PORTNOY AND H. GISSER

Pitman-Dunn Laboratories,
U.S. Army Ordnance Corps,
Frankford Arsenal, Philadelphia, Pennsylvania

Received March 9, 1962

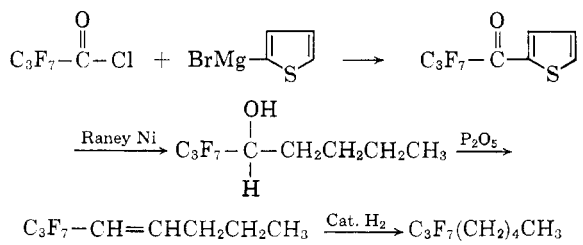
The reductive desulfurization of substituted thiophenes has been proposed as a synthetic route for the preparation of long-chain acids, ketones, alcohols, and hydrocarbons.[1] The preparation of a straight-chain saturated hydrocarbon was accomplished by the condensation of thiophene and an acid in the presence of phosphorus pentoxide, Clemmensen reduction of the resulting ketone, and finally, desulfurization with Raney nickel. Lengthening of the chain can be accomplished by further reaction in the 5-position of thiophene. Various branched-chain compounds can be prepared by the use of suitably β-substituted thiophenes.

The purpose of our investigation was to determine whether this synthetic technique could be utilized for the preparation of partially fluorinated

(1) H. Wynberg and A. Logothetis, *J. Am. Chem. Soc.*, **78**, 1958 (1956).

compounds and thus provide a method for preparation of heat-stable fluids. As described previously,[2] the preparation of 2-heptafluorobutyrylthiophene was achieved by a reverse Grignard technique. The attempted condensation of heptafluorobutyric acid and thiophene in the presence of phosphorus pentoxide, resulted only in the conversion of the fluorinated acid to the acid anhydride. Other methods were equally unsuccessful.

Reduction of 2-heptafluorobutyrylthiophene was unsuccessful *via* a Clemmensen or a Wolff-Kishner reaction using in the latter either 85% hydrazine hydrate or semicarbazide hydrochloride. Reductive desulfurization with Raney nickel resulted in the isolation of the alcohol 1,1,1,2,2,3,3-heptafluoro-4-octanol. The partially fluorinated olefin and hydrocarbon were then prepared as shown by the following over-all scheme.



In the reductive desulfurization reaction, a small amount of 1,1,1,2,2,3,3-heptafluoro-4-octanone was also isolated. Attempted reduction of this ketone by the Clemmensen or Wolff-Kishner reactions was unsuccessful. However, the ketone was easily converted in high yield to the alcohol by treatment with lithium aluminum hydride.

Experimental[3]

2-Heptafluorobutyrylthiophene.—An ether solution of 1 mole of thiophene magnesium bromide was added slowly to an ether solution of 1.2 moles of heptafluorobutyryl chloride and worked up in a manner previously described.[2] Distillation gave a 32% yield, b.p. 91.5–92.1° at 32 mm., $n^{20}D$ 1.43186.

Anal. Calcd. for $C_8H_3OF_7S$: C, 34.29; H, 1.08; F, 47.47. Found: C, 34.13; H, 1.25; F, 46.85.

The 2,4-dinitrophenylhydrazone, recrystallized from an alcohol–water mixture, melted at 90.2–90.8°.

1,1,1,2,2,3,3-Heptafluoro-4-octanol.—2-Heptafluorobutyrylthiophene (25 g., 0.09 mole), 250 g. Raney nickel,[4] and 900 ml. of 95% alcohol were stirred and refluxed for 16 hr. The alcohol was decanted and the nickel was washed with alcohol and ether. The solvents were distilled off, the remaining liquid dried overnight over anhydrous sodium sulfate and filtered. Fractionation gave 1,1,1,2,2,3,3-heptafluoro-4-octanol (9.5 g., 41%), b.p. 148.1–148.6°, $n^{25}D$ 1.34445.

Anal. Calcd. for $C_8H_{11}OF_7$: C, 37.51; H, 4.33; F, 51.92. Found: C, 38.31; H, 4.64; F, 52.65.

There was also isolated a small amount of 1,1,1,2,2,3,3-heptafluoro-4-octanone (1.0 g., 4%), b.p. 119.7–121.3°, $n^{25}D$ 1.326, semicarbazone 92.4–95.3°. These values correspond to that found in the literature.[5]

1,1,1,2,2,3,3-Heptafluoro-4-octene.—Phosphorus pentoxide (56.8 g., 0.4 mole) was placed in a 500-ml. flask and to this was added 1,1,1,2,2,3,3-heptafluoro-4-octanol (102.5 g., 0.4 mole). The mixture was distilled and the material from 59–124° collected. The distillate was washed with 5% sodium bicarbonate until slightly alkaline and then washed twice with distilled water. The combined washings were extracted once with ether. The ether-distillate solution was dried overnight over anhydrous sodium sulfate, filtered, and stripped of solvent. Fractionation through a 3-in. column with 1/8-in. helices gave 1,1,1,2,2,3,3-heptafluoro-4-octene (25.4 g., 27%), b.p. 105.3–106.2°, $n^{25}D$ 1.32980. Infrared spectra (max. at 5.98 μ) confirmed the olefin.

Anal. Calcd. for $C_8H_9F_7$: C, 40.34; H, 3.81; F, 55.85. Found: C, 40.52; H, 3.86; F, 55.39.

1,1,1,2,2,3,3-Heptafluoroöctane.—In a Parr hydrogenation apparatus was placed 1,1,1,2,2,3,3-heptafluoro-4-octene (16.8 g., 0.7 mole), 60 ml. of dry ether, and 90 mg. of platinum oxide catalyst.[6] After 26 hr. of hydrogenation, the solution was filtered, stripped of ether, and fractionated through a 3-in. column containing 1/8-in. helices. This gave 1,1,1,2,2,3,3-heptafluoro öctane (13.3 g., 79%), b.p. 108.8–109.6° at 751 mm., $n^{25}D$ 1.3226. Infrared spectra showed the absence of the double bond.

Anal. Calcd. for $C_8H_{11}F_7$: C, 40.01; H, 4.62; F, 55.38. Found: C, 40.48; H, 4.63; F, 55.41.

(2) S. Portnoy and H. Gisser, *J. Org. Chem.*, **22**, 1752 (1957).

(3) All temperature readings are uncorrected. The analyses were carried out by Wyanel Laboratories, Philadelphia, Pa. and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(4) R. Mozingo, "Organic Synthesis," Coll. Vol. III, E. C. Horning ed., J. Wiley and Sons, Inc., New York, 1955, p. 181.

(5) K. T. Dishart and R. Levine, *J. Am. Chem. Soc.*, **78**, 2268 (1956).

(6) R. Adams, V. Voorhees, and R. L. Shriner, "Organic Synthesis," Coll. Vol. I, H. Gilman, ed., J. Wiley and Sons, Inc., New York, 1941, p. 463.

Potential Inhibitors of Cancerous Growth. I. Synthesis of Cyclic Nitrogen Mustard Phosphamide Ester Derivatives of D-Ribose

W. J. SERFONTEIN AND J. H. JORDAAN

Department of Organic Chemistry, University of Pretoria, Pretoria, South Africa

March 12, 1962

Arnold and co-workers[1] have shown that certain cyclic amide esters of phosphorylated nitrogen mustard have outstanding properties as anticancer agents. As a result compound IV (Cytoxan) has found successful clinical application in the treatment of certain cancers in various countries. It has been claimed[2] that IV acts as an inactive "transport form" which is reactivated in cancerous tissue by enzymic cleavage and removal of the electron-attracting phosphate group, thereby liberating free nitrogen mustard *in situ*. The same authors have also shown that a three carbon unit particularly as an aminopropane group as in (IV) in the heterocyclic ring system greatly enhances the clinical usefulness of the compounds.

(1) H. Arnold, F. Bourseaux, and N. Brock, *Arzneimittel-Forsch.*, **11**, 143 (1961).

(2) H. Arnold and F. Bourseaux, *Angew. Chem.*, **70**, 539 (1958).