Synthesis of DL-S-Trifluoromethylhomocysteine (Trifluoromethylmethionine)

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The successful use of compounds such as 6-mercaptopurine in the treatment of cancer has given impetus to the search for other antimetabolites. The preparation of analogs of methionine offers promise because of the general metabolic significance of the parent compound. The role of methionine as a methyl donor suggests that substitution of the trifluoromethyl group for the essential methyl unit might be of particular value. Such an analog, in addition to being a possible antimetabolite, conceivably might serve as an intermediate in the biosynthesis of other compounds of physiological interest.

Haszeldine[2] has reported the synthesis of mercuric trifluoromethylmercaptide in small quantities from the reaction of mercury with bis(trifluoromethyl) disulfide. In the present work, however, adequate quantities of the mercaptide were obtained more readily from mercuric fluoride and carbon disulfide by the method of Muetterties.[3] This product was conveniently converted to the mercaptan in essentially quantitative yield by treatment with a dioxane solution of hydrogen chloride.

Initial attempts to add trifluoromethyl mercaptan to acrolein in the presence of cupric acetate gave low yields, apparently due to a competing polymerization which produced an adduct of one molecule of the mercaptan to three of the aldehyde. By the reverse addition of acrolein to the mercaptan, the side reaction was minimized and 61% yields of the desired β-trifluoromethylmercaptopropionaldehyde were obtained. The competing polymerization reaction is not unique, for Gilbert and Donleavy[4] have reported analogous adducts of one molecule of water to several molecules of acrolein in the base-catalyzed hydration of the aldehyde. Although in the present work the type of catalyst and the highly acidic nature of the trifluoromethyl mercaptan are conducive to ionic reaction, it is interesting to note that in the addition of simple mercaptans to unsaturated esters,[5] the polymerization reaction becomes predominant only under free radical conditions and ionic catalysis gives almost exclusively simple addition.

The β-trifluoromethylmercaptopropionaldehyde was smoothly converted to *S*-trifluoromethylhomocysteine by the method of Tishler, Giella, and Pierson.[6] An over-all yield of 11% was obtained, based on the mercaptan used.

The *S*-trifluoromethylhomocysteine will be tested physiologically by Dr. Arnold Welch of the Department of Pharmacology, Yale University School of Medicine.

EXPERIMENTAL

Mercuric trifluoromethyl mercaptide.[3] A mixture of 50.0 g. (0.66 mole) of carbon disulfide and 140 g. (0.59 mole) of technical mercuric fluoride (Harshaw Chemical Co.) was heated to 150° for 6 hr. in a pressure vessel and then extracted with 200 ml. of ether. The ether extract, after filtration, was evaporated to give 61.4 g. (0.15 mole) of crude mercuric trifluoromethylmercaptide. The crude mercaptide (used without purification in the present work) when allowed to stand, formed white crystals, m.p. 37.5–39° (lit.[3] m.p. 37–38°), together with a very small quantity of dark supernatant liquid.

Trifluoromethyl mercaptan. Hydrogen chloride was passed into anhydrous dioxane and the resultant solution weighed to determine the acid content (24%). To 30.0 g. (0.075 mole) of crude mercuric trifluoromethyl mercaptide, cooled with ice, was added 22.8 g. (0.15 mole hydrogen chloride content) of the dioxane–hydrogen chloride mixture. An exothermic reaction resulted, accompanied by a copious precipitation of mercuric chloride. The trifluoromethyl mercaptan was quite soluble in dioxane and no product was collected in an attached trap, cooled with Dry Ice, during the addition. After diluting with 15 ml. of anhydrous dioxane and refluxing for 2 hr., however, 14.3 g. (0.14 mole, 94% yield) of the mercaptan condensed in the trap. A quantitative yield was obtained using an excess of hydrogen chloride, but in the present work a stoichiometric quantity was employed to avoid the presence of hydrogen chloride, as a contaminant, in the product.

The mercaptan has been previously prepared in small quantity by Haszeldine and Kidd,[2] using hydrogen chloride gas, instead of the dioxane solution. The method herein described is more readily carried out in common laboratory equipment upon a macro scale.

β-Trifluoromethylmercaptopropionaldehyde. To a mixture of 45.5 g. (0.543 mole) of trifluoromethyl mercaptan and 0.3 g. of cupric acetate in 700 ml. of chloroform was added 36.6 g. (0.651 mole) of acrolein. After the addition was complete, stirring was continued for 2 hr. The chloroform and excess acrolein were removed at room temperature, under reduced pressure. The residue was distilled at 20 mm. pressure to give 38.7 g. of β-trifluoromethylmercaptopropionaldehyde (b.p. 44–48°). Additional product (13.4 g.) was recovered by fractionation of the chloroform distillate through a helices-packed column and vacuum distillation of the residue thus obtained. The total yield was 52.1 g. (61%). The procedure just described was found necessary, because the β-trifluoromethylmercaptopropionaldehyde undergoes appreciable decomposition if heated for an extended period of time. A portion of the aldehyde was fractionated through a multiplate column to give an analytical sample, b.p. 46.5° at 20 mm., n_D^{23} 1.4120, d_4^{25} 1.3713.

Anal. Calcd. for $C_4H_5F_3OS$: C, 30.4; H, 3.18 F, 36.1. Found: C, 31.01; H, 3.60 F, 35.7.

(1) From the thesis submitted by Robert G. Taborsky to the Graduate School of Western Reserve University in partial fulfillment of the requirements for the doctor's degree.

(2) R. N. Haszeldine and J. M. Kidd, *J. Chem. Soc.*, 3219 (1953).

(3) E. L. Muetterties, U. S. Patent 2,729,663, Example V.

(4) E. E. Gilbert and J. J. Donleavy, *J. Am. Chem. Soc.*, 60, 1911 (1938).

(5) M. S. Kharasch and C. F. Fuchs, *J. Org. Chem.*, 13, 97 (1948).

(6) M. Tishler, M. Giella, and E. Pierson, *J. Am. Chem. Soc.*, 70, 1450 (1948).

In a preliminary experiment, the mercaptan was added to the acrolein. From this reaction, in addition to the desired product, a fraction, b.p. 112° at 1 mm. ($n_D^{25.5}$ 1.4490) was obtained, which corresponded roughly in analysis to the addition product of one mole of the mercaptan to three moles of acrolein.

Anal. Calcd. for $C_{10}H_{13}F_3O_3S$: C, 44.5; H, 4.73; S, 11.8. Found: C, 43.56; H, 5.65; S, 10.26.

5-(β-Trifluoromethylmercaptoethyl)hydantoin. A mixture of 20.0 g. (0.127 mole) of β-trifluoromethylmercaptopropionaldehyde, 90.5 g. (0.79 mole) of finely powdered ammonium carbonate, 10.6 g. (0.40 mole) of sodium cyanide, 270 ml. of ethanol, and 270 ml. of water was stirred and heated to 50–55° for 16 hr. The mixture was concentrated to about 200 ml. at room temperature under reduced pressure, made slightly acid with concentrated hydrochloric acid, and heated to 90° for 5 min. to cyclize any of the hydantoic acid which might be present. After cooling the mixture to 0° overnight, the yellow crystals which deposited were removed by filtration. After drying, the compound was recrystallized from boiling chloroform to give 8.7 g., (30.0% yield) of 5-(β-trifluoromethylmercaptoethyl)hydantoin, m.p. 128–128.5°.

Anal. Calcd. for $C_6H_7F_3O_2N_2S$: C, 31.60; H, 3.09; F, 25.0. Found: C, 31.76; H, 3.19; F, 25.7.

S-Trifluoromethylhomocysteine. A solution of 17.0 g. (0.074 mole) of 5(β-trifluoromethylmercaptoethyl)hydantoin, 68.0 ml. of water, and 7.5 g. (0 19 mole) of sodium hydroxide were refluxed for 6 hr An additional 3.7 g (0.09 mole) of sodium hydroxide was then added and refluxing continued for 18 hr. The solution was cooled and neutralized with concentrated hydrochloric acid to a *p*H of 6. Cooling to 0° for 1 hr. produced a cream colored solid which was washed twice with water and twice with acetone, dried, and extracted with 560 ml. of boiling methanol. Cooling the methanol solution to 0° overnight gave 4.4 g. of *S*-trifluoromethylhomocysteine, m.p. 229° dec. Reduction of the volume of the methanol mother liquor and cooling produced an additional 4.5 g. of product. The total (8.9 g.) represented a 60% yield. Recrystallization from methanol gave an analytical sample, m.p. 230° with decomposition

Anal. Calcd. for $C_5H_8F_3O_2NS$: C, 29.60; H, 3.97; N, 6.94; F, 28.2. Found: C, 29.65; H, 3.95; N, 6.52; F, 26.6.

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16-Ketoyohimbane

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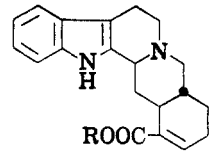
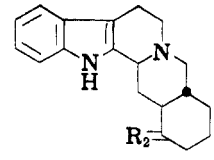
Because of its α,β-unsaturated ester grouping, apoyohimbine (I) should be convertible, by methods which transform a carboxyl group into an amino group, into 16-ketoyohimbane (III), a compound of interest in connection with stereochemical studies of the yohimbine alkaloids. An attempt to apply the Curtius reaction failed when apoyohimbine was recovered unchanged from treatment with hydrazine,[2] and apoyohimbic acid (II) was decomposed by thionyl chloride.

This transformation, however, was realized by means of the Schmidt reaction[3] on apoyohimbic acid, giving 16-ketoyohimbane in low yield. Evidence for the ketonic nature of the product was provided by the elementary analysis, a sharp carbonyl band in the infrared at 5.87 μ,[4] and the formation of an oxime.

The ketone could be reduced by the Huang-Minlon procedure to yohimbane[5,6] (IV), identical with the reduction product of 17-ketoyohimbane (yohimbone). Since the skeleton of yohimbine is in its most stable stereochemical configuration,[7–9] no isomerization takes place during this rather drastic reduction.



I. R = CH_3
II. R = H



III. R_2 = O
IV. R_2 = H_2

EXPERIMENTAL

16-Ketoyohimbane. Apoyohimbic acid hydrochloride[10] (6.7 g.) was dissolved in 30 ml. of concentrated sulfuric acid and stirred to drive off hydrogen chloride fumes. While stirring at room temperature, 40 ml. of a 0.6*N* chloroform solution of hydrazoic acid was added dropwise. Stirring was continued for 20 min., and 20 ml. more of the hydrazoic acid solution added. When gas evolution had ceased (about 30 min.), the mixture was poured into ice water, separated, and the aqueous layer filtered. The filtrate was made alkaline with ammonia, extracted with chloroform, and the extracts washed with saturated salt solution. Drying over sodium sulfate and evaporation left a tan solid which was recrystallized from ethanol. The yield was 1.1 g. (20%) of colorless needles; after two further recrystallizations from ethanol they melted at 283–285° (capillary inserted at 250°). Drying overnight at 100° *in vacuo* over P_2O_5 did not remove all the water of crystallization.

Anal. Calcd. for $C_{19}H_{22}N_2O \cdot {}^1/_2H_2O$: C, 75.21; H, 7.64; N, 9.23. Found: C, 74.88, 74.74; H, 8.03, 7.87; N, 9.00.

$[\alpha]_D^{21}$ −89° (*c*, 1.46 in pyridine).

An anhydrous sample could be prepared by two further recrystallizations from xylene, distilling half the xylene at each step to azeotrope the water. M.p. 274–276° dec.

(1) Taken in part from the B.A. thesis of Karl H. Muench, Princeton University, 1956.

(2) Compare the difficulty found in preparing the hydrazide and amide of yohimbine, by C. F. Huebner, R. Lucas, H. B. MacPhillamy, and H. A. Troxell, *J. Am. Chem. Soc.*, **77**, 469 (1955).

(3) H. Wolff, *Org. Reactions*, **III**, 1946.

(4) Yohimbone absorbs at the same frequency, somewhat shifted from the normal ketone position.

(5) J. Jost, *Helv. Chim. Acta*, **32**, 1297 (1949).

(6) B. Witkop and S. Goodwin, *J. Am. Chem. Soc.*, **75**, 3371 (1953).

(7) G. Stork, quoted in ref. 6.

(8) R. C. Cookson, *Chemistry & Industry*, **1953**, 337.

(9) M. M. Janot, R. Goutarel, A. Le Hir, M. Amin, and V. Prelog, *Bull. soc. chim. France*, 1085 (1952).

(10) G. Barger and E. Field, *J. Chem. Soc.*, **123**, 1038 (1923).