I am indebted to Prof. P. W. Bridgman for subjecting the samples to pressure, and to Mrs. Elizabeth Shapleigh for technical assistance.

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An Improved Synthesis of Perfluoroaldehydes[1]

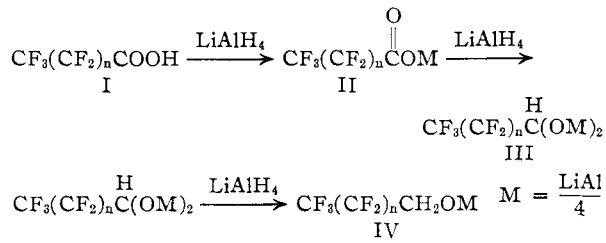
BY MILTON BRAID, HYMAN ISERSON AND FRANCIS E. LAWLOR

RECEIVED FEBRUARY 6, 1954

Published methods for the preparation of perfluoroaldehydes by reduction of the corresponding acid chloride,[2] or nitrile[3] and the oxidative nitration of 1,1,1-trifluoropropane[4] are inconvenient and give low yields of the desired aldehydes. The reduction of the corresponding perfluoro acid with lithium aluminum hydride,[2b] while more direct and convenient since it does not require the preparation of intermediates or catalysts, does not give a good yield of the perfluoroaldehyde. A substantial amount of the corresponding 1,1-dihydroperfluoro alcohol is also obtained by this reduction.

Greatly improved yields of perfluoroaldehydes have been obtained in this laboratory by the reduction of the appropriate perfluoro acids with lithium aluminum hydride by employing an inverse addition of the hydride to the acids.[5] The reductions were carried out at low temperature (−5 to 0°) using a 1:2 *M* ratio of hydride to acid and relatively concentrated ethereal solutions of the reactants. Only small quantities of the corresponding 1,1-dihydroperfluoro alcohols are obtained by this method. The liberation of the free aldehyde from its hydrate, the product of the reduction reaction, was most advantageously accomplished by adding it to a preheated mixture of phosphoric anhydride and concentrated sulfuric acid rather than either reagent alone. The dehydration medium did not thicken and the aldehyde was isolated without prolonged refluxing which leads to polymerization. Trifluoroacetic, pentafluoropropionic and heptafluorobutyric acids have been reduced by this method to give the corresponding perfluoroaldehydes in 77.5, 60 and 64% yield, respectively.

If the lithium aluminum–acid complex II is less easily reduced than the acid I, it will undergo little further attack in the absence of excess reducing agent (present in the normal order of addition) while any unreacted acid is present. When the transformation of the acid to complex II has been completed, the addition of more reducing agent will yield the aldehyde precursor III. The presence of an excess of hydride would favor further attack on III to give the alcohol precursor IV at the expense of the aldehyde. Thus the inverse order of addition favors the formation of the aldehyde.



A similar explanation has been reported[6] for the reduction of lactones to hydroxyaldehydes by lithium aluminum hydride using the inverse addition procedure.

Experimental

A solution of one mole of the perfluoro acid in 1 l. of anhydrous ether was cooled to −5° (brine-bath) in a 3-l. flask fitted with addition funnel, stirrer and condenser. The system was flushed with nitrogen while cooling. A slurry of 21.5 g. of lithium aluminum hydride in 750 ml. of anhydrous ether was added slowly with continuous stirring at −5° to 0° during 1.5 hours. Stirring was continued at −5° for one hour.

The reaction mixture was hydrolyzed with 40 ml. of water followed by 80 ml. of concentrated sulfuric acid in 200 ml. of water. The ether was decanted, and the solids remaining in the flask were dissolved in 300 ml. of water. The aqueous solution was extracted with ether, and the extracts were combined with the main ether portion and fractionally distilled to remove the solvent and alcohol leaving as a residue the crude aldehyde hydrate.

The crude aldehyde hydrate was dropped slowly into a vigorously stirred mixture of phosphorus pentoxide and concentrated sulfuric acid heated to 85–90°. The free aldehyde was collected in a suitably cooled receiver.

One mole of trifluoroacetic acid, after being subjected to the described reduction procedure, gave 21 g. of trifluoroethanol, crude, b.p. 68–85° and 110 g. of the crude aldehydrol. A 50-g. portion of the crude aldehydrol was dehydrated in a mixture of 21.6 g. of phosphorus pentoxide and 83 ml. of 96.7% sulfuric acid. There was obtained 34.5 g. of trifluoroacetaldehyde, representing a 77.5% overall yield. The aldehyde gave a 2,4-dinitrophenylhydrazone, m.p. 149°, and a hydrate, m.p. 69–70°.[2b]

Similarly treated, perfluoropropionic acid gave a 60% yield of perfluoropropionaldehyde, b.p. 1–2°, and perfluorobutyric acid gave a 64% yield of perfluorobutyraldehyde, b.p. 29°.

The physical constants observed for the aldehydes or their derivatives are in agreement with previous literature values.[2b]

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Synthesis of 8-C^{14} and of S^{35}-6-Mercaptopurine

BY GERTRUDE B. ELION AND GEORGE H. HITCHINGS

RECEIVED MARCH 10, 1954

The marked biological activities of 6-mercaptopurine[1–5] made the study of its metabolism in various species of considerable interest. For this reason

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it was necessary to prepare radioactively-labeled 6-mercaptopurine for tracer studies. In order to follow the fate of both the purine moiety and of the mercapto group, both the 8-C^{14}- and the 6-S^{35}-labeled compounds were required. The original synthesis of 6-mercaptopurine[6] from hypoxanthine was not considered satisfactory for small quantities of material if the most economical use was to be made of the C^{14}-formate. In the present method, the labeled formate is introduced in the last step.

The method consists of the synthesis of 4,5-diamino-6-mercaptopyrimidine from 4-amino-6-chloro-5-nitropyrimidine[7] followed by formylation and ring closure of the sodium salt of the 5-formyl derivative. For the synthesis of S^{35}-6-mercaptopurine, the reaction of 6-chloropurine with potassium hydrosulfide was employed.

4,5-Diamino-6-mercaptopyrimidine.—A suspension of 15 g. of 4-amino-6-chloro-5-nitropyrimidine[7] in 435 ml. of *N* potassium hydrosulfide solution was heated on the steam-bath for two hours with the intermittent passage of a stream of hydrogen sulfide through the mixture. The solution was cooled, resaturated with hydrogen sulfide and allowed to stand at room temperature overnight. Pale yellow needles separated, were collected by filtration and washed with a small amount of water. The crude precipitate (9 g.) was recrystallized from 350 ml. of water and gave 7.2 g. (60% yield) of colorless 4,5-diamino-6-mercaptopyrimidine after filtration and drying in a vacuum desiccator. An additional 1.2 g. of product was recovered by acidification of the reaction mixture filtrate, removal of the sulfur precipitate, and evaporation of the filtrate to 100 ml. Ultraviolet absorption spectrum: at *p*H 1, λ_{max} 240,305 mμ (E_m 16,100, 17,900); at *p*H 11, λ_{max} 240,309 mμ (E_m 17,100, 15,400).

Anal. Calcd. for $C_4H_6N_4S$: C, 33.8; H, 4.2; N, 39.4. Found: C, 34.1; H, 4.2; N, 39.7.

8-C^{14}-6-Mercaptopurine.—An aqueous solution of C^{14}-sodium formate containing 0.1915 millimole, with an activity of 0.608 millicurie, in 0.574 ml. was evaporated to dryness under reduced pressure at 60° in a flask of 30-ml. capacity. To the residue was added 0.5 g. (3.5 millimoles) of finely powdered 4,5-diamino-6-mercaptopyrimidine and 2.2 ml. of 90% formic acid containing 0.18 millicurie of C^{14}-formic acid. The mixture was heated at 85° for 4.5 hours in the same distillation apparatus used previously for the removal of water. The formic acid was then removed at 50° under reduced pressure and this distillate was stored for reuse. The residue was freed of traces of formic acid by the addition of 3-ml. portions of water three times and the removal of each portion by distillation under reduced pressure.

To the residue was added 3.5 ml. of *N* sodium hydroxide and the mixture was evaporated carefully to dryness at 50° under reduced pressure. The residue was heated gradually to 220° in an oil-bath and the temperature maintained at 220 to 240° for one hour. During this time water was evolved and the melt turned dark orange. After cooling, the residue was dissolved in 70 ml. of water, filtered, acidified with acetic acid to *p*H 5, heated to boiling and filtered hot to remove an amorphous red precipitate. The filtrate was chilled for 24 hours and the yellow crystalline precipitate collected, washed with water and dried in a vacuum desiccator. The yield was 0.38 g. (64%) of 6-mercaptopurine hydrate with an activity of 21.5 microcuries/millimole. Its ultraviolet absorption spectrum was identical with that of analytically pure 6-mercaptopurine.[6]

S^{35}-6-Mercaptopurine.—To 2.5 g. (16.2 millimoles) of powdered 6-chloropurine in a glass bomb was added 1.9 ml. of a solution containing 0.91 mg. per ml. of S^{35}-barium sulfide (with a total radioactivity of 30 millicuries) in 0.188 *N* barium hydroxide, 10 ml. of water and 18 ml. of 2 *N* potassium hydrosulfide solution. The glass tube was sealed and heated in a boiling water-bath for seven hours. A yellow granular precipitate formed. After chilling, the tube was opened and 18 ml. of 2 *N* sodium hydroxide was added. The clear solution was treated with 2 g. of sodium sulfate to precipitate the barium ion. After filtration, the combined filtrates and washings were placed in a 500-ml. flask connected to a series of three vessels containing 25 ml. each of 0.5 *M* cadmium chloride solution and a gas-drying cylinder containing sodium hydroxide pellets. Thirty-seven ml. of 2 *N* hydrochloric acid was run slowly into the flask below the surface of the liquid. A light yellow precipitate began to form immediately. The hydrogen sulfide was driven over by a stream of carbon dioxide for three hours and collected as cadmium sulfide. The gas issuing from the final sodium hydroxide trap was not radioactive. The reaction mixture was filtered and the precipitate washed with water and dried in a vacuum desiccator. The yield was 2.28 g. (83%) with a radioactivity of 595 microcuries/millimole. The ultraviolet absorption spectrum was identical with that of an authentic specimen.

To the filtrate from this first precipitate was added 1 g. of non-radioactive 6-mercaptopurine hydrate dissolved in 4 ml. of 2 *N* sodium hydroxide. The solution was reacidified with 2 *N* hydrochloric acid and the yellow crystalline precipitate collected (0.87 g. with a radioactivity of 110 microcuries/millimole).

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Evidence for the Existence of 1-Amino-2-methyl-2-propanol in the Phospholipids of Neurospora

BY GEORGE L. ELLMAN[1] AND HERSCHEL K. MITCHELL

RECEIVED MARCH 24, 1954

This investigation, on the lipids of *Neurospora crassa*, provides evidence that the phospholipid fraction contains choline, serine, ethanolamine and, in addition, the base 1-amino-2-methyl-2-propanol. Several other amines were also found to be present in very small concentrations and these have not been identified. That the phospholipid fractions from several animal tissues contain unidentified bases has been observed previously.[2]

It has been found advantageous to prepare dinitrophenyl (DNP) derivatives of crude cephalins obtained by solvent fractionation prior to hydrolysis. The yellow derivatives can then be separated as such by chromatography or the derivatives of the bases can be separated by chromatography after hydrolysis of the cephalins. Details on the latter procedure only are presented here but the former has promise as a method for studying the various components of cephalin fractions. Although considerable quantities of DNP-serine and DNP-ethanolamine were obtained from the Neurospora cephalins only a very small amount of the crystalline derivative that corresponds to that of 1-amino-2-methyl-2-propanol was isolated. Identification of the substance has therefore been dependent on the chromatographic methods, oxidation with periodate and permanganate[3] and melting temperatures.

Experimental

Extraction and Purification of Neurospora Phospholipid.—Wild type *Neurospora crassa* (strain 5256A) was grown in 40-liter carboys for 6–7 days on Fries medium[4] containing 2% sucrose. The mycelia were extracted in batches in the following way: they were collected, pressed as dry as pos-

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