The ether solutions were combined and dried with Drierite and then distilled. Twelve grams of a mixture of pentafluoro- and trifluoroacetoacetic esters was obtained boiling at 130–133°. The presence of the trifluoroacetoacetic ester was shown by the formation of a copper chelate, m.p. 188–189°[4] and by hydrolysis to trifluoroacetone which gave a 2,4-dinitrophenylhydrazone, m.p. 139°.[4]

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DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, INDIANA

1,3,3,3-Tetrafluoropropylene Oxide

BY E. T. McBEE, O. R. PIERCE AND H. W. KILBOURNE[1]

RECEIVED MARCH 30, 1953

It was of interest to prepare an epoxide containing a fluorine atom substituted on a bridge carbon atom for a study of the orientation effect of fluorine in epoxide ring opening. Only two fluorine-containing propylene oxides have been previously reported[2] and no compound having fluorine substituted directly on the epoxide ring has been described.

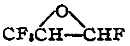
The synthesis of the desired epoxide was based on bromotetrafluoroacetone. It was found that this material could be obtained directly in excellent yield by treating ethyl α,γ,γ,γ-tetrafluoroacetoacetate[3] with a mixture of sulfuric acid and bromine at moderate temperatures. The bromotetrafluoroacetone obtained was reduced with lithium aluminum hydride at 0° in an excess of the ketone to produce 3-bromo-1,1,1,3-tetrafluoro-2-propanol in 80% yield. Dehydrobromination of the alcohol was accomplished by reaction with hot 50% sodium hydroxide and 1,3,3,3-tetrafluoropropylene oxide was obtained in 96% yield.

It was first thought that bromination probably occurred during the decarboxylation reaction in accordance with the postulates of other researchers.[4] However, it was found that use of excess bromine produced 3,3-dibromo-1,1,1,3-tetrafluoroacetone in high yield. This would indicate that the introduction of the first bromine atom took place before decarboxylation since any further bromination of the ketone formed would be extremely difficult under these conditions.[5] In support of this postulate, ethyl α-bromo-α,γ,γ,γ-tetrafluoroacetoacetate was prepared and found to undergo ready hydrolysis and decarboxylation yielding the monobromoketone. If this reaction was conducted in the presence of bromine, the principal product was the dibromoketone.

The properties of the compounds prepared are given in Table I.

TABLE I

NEW COMPOUNDS

Formula	B.p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
$CF_3COCHFBr$	65	17.20	17.01	0.48	0.60
$CF_3COCFBr_2$	81	12.50	12.81	0.00	0.10
$CF_3CHOHCHFBr$	124	17.10	17.12	1.43	1.54
 $CF_3\overset{O}{CH-CHF}$	37	27.70	27.78	1.53	1.89
$CF_3COCFBrCO_2C_2H_5$	51 at 15 mm.	25.60	25.90	1.78	1.81

Experimental

3-Bromo-1,1,1,3-tetrafluoroacetone.—A solution of 40% sulfuric acid (200 ml.) was prepared in a 500-ml., round bottomed flask which was equipped with a reflux condenser, a sealed stirrer and an addition funnel. Ethyl α,γ,γ,γ-tetrafluoroacetoacetate (86 g.) was added to the aqueous acid and the mixture was heated to 80–90°. While the mixture was being stirred vigorously, bromine (75 g.) was added dropwise and at such a rate that only a light red color was maintained in the solution. After all the bromine had been added, the mixture was heated and stirred for an additional two hours. The cooled mixture was diluted with 100 ml. of water and extracted with ether. The ether solution was dried with Drierite and then distilled. When the pot temperature reached 50°, the distillation was stopped and the residue was cooled in an ice bath. An equal volume of concd. sulfuric acid was added to the flask and the contents were mixed. Distillation was then continued and 87 g. (95%) of ketone was obtained. The material had an unpleasant odor similar to that of 3-bromo-1,1,1-trifluoroacetone.[2b]

3,3-Dibromo-1,1,1,3-tetrafluoroacetone.—A solution of 40% sulfuric acid (100 ml.) was prepared in the reaction flask. Ethyl α,γ,γ,γ-tetrafluoroacetoacetate (20 g.) was added to the flask and the mixture was heated to 90°. Bromine (30 g.) was added to the hydrolysis mixture over a period of 30 minutes. The bromine concentration in the reaction flask was high at all times as shown by the dark red color in the flask. An additional two hours of heating and stirring was required to remove all the bromine color from the solution. The aqueous mixture was cooled and extracted with ether. The ether solution was dried with Drierite and then distilled until the pot temperature reached 50°. The residue was mixed with an equal volume of concd. sulfuric acid and distillation was continued. The monobromo compound (4 g.) was obtained boiling at 65–67°, the temperature then rose to 81° and 23 g. (80%) of the dibromoketone was obtained.

3-Bromo-1,1,1,3-tetrafluoroisopropyl Alcohol.—Anhydrous ether (500 ml.) and lithium aluminum hydride (3.8 g.) were mixed in a 1000-ml., 3-necked flask which was equipped with a reflux condenser, a sealed stirrer, and an addition funnel. The flask was immersed in an ice-bath and a solution of 3-bromo-1,1,1,3-tetrafluoroacetone (41 g.) in anhydrous ether (80 ml.) was added dropwise over a period of 8 hours. The reaction was stirred at 0° for an additional 6 hours and then permitted to stand at room temperature for 8 hours. Absolute ethanol (3 ml.) was added to decompose any unreacted lithium aluminum hydride and the mixture was then poured over a mixture of concd. sulfuric acid (50 g.) and crushed ice (500 g.). The ether solution was separated and the aqueous solution was extracted with ether. The ether solution was dried with Drierite and then distilled. Phosphorus pentoxide (2 g.) was added to the mixture and distillation was continued. The bromoketone (4 g.) was recovered boiling at 60–70° and 33.5 g. (91%) of 3-bromo-1,1,1,3-tetrafluoroisopropyl alcohol was obtained.

1,3,3,3-Tetrafluoropropylene Oxide.—A solution of water (50 g.) and sodium hydroxide (50 g.) was prepared in a 300-ml., 3 necked flask. The reaction flask was equipped with a sealed stirrer, an addition funnel and a side arm distilling head. The side arm of the distilling head was connected to an ice-cooled trap followed by a Dry Ice-cooled trap. A thermometer was inserted through the distilling head into the aqueous sodium hydroxide so that the temperature of the reaction mixture could be checked at all times.

The reaction mixture was heated to 95–100° and 3-bromo-1,1,1,3-tetrafluoroisopropyl alcohol (21 g.) was added dropwise over a period of 3 hours. The bromohydrin was added

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[1] Abstracted, in part, from the doctoral thesis of H. W. Kilbourne, Purdue University.

[2] (a) E. Gryskiewiscz-Trochimowski, A. Sporzynski and J. Wnuk, *Rec. trav. chim.*, **66**, 413 (1947); (b) E. T. McBee and T. M. Burton, THIS JOURNAL, **74**, 3022 (1952).

[3] E. T. McBee, O. R. Pierce, H. W. Kilbourne and E. R. Wilson, *ibid.*, **75**, 3152 (1953).

[4] L. P. Hammett, "Physical Organic Chemistry," First Ed., McGraw-Hill Book Co., Inc., New York, N. Y., p. 362.

[5] E. T. McBee and T. M. Burton, THIS JOURNAL, **74**, 3902 (1952).

slowly due to the tendency for the mixture to froth. The epoxide was condensed in the ice-cooled trap and no material was condensed in the Dry Ice-cooled trap. The epoxide was then cooled in Dry Ice, the water which had been carried over from the aqueous solution was frozen out, the epoxide was decanted, dried and rectified. The yield was 12.5 g. (96%).

Ethyl α-Bromo-α,γ,γ,γ-tetrafluoroacetoacetate.—Ethyl α,γ,γ,γ-tetrafluoroacetoacetate (42 g.) was dissolved in carbon tetrachloride (150 ml.) and the mixture was heated to 70°. Bromine (40 g.) was added dropwise over a period of 12 hours and the mixture was then stirred and heated for an additional 12 hours. The carbon tetrachloride and a small amount of bromine was distilled out of the mixture, and the pressure was reduced to 15 mm., and distillation was continued. Ethyl α-bromo-α,γ,γ,γ-tetrafluoroacetoacetate (50 g., 72%) was obtained boiling at 51–52° at 15 mm.

Hydrolysis of Ethyl α-Bromo-α,γ,γ,γ-tetrafluoroacetoacetate.—A mixture of ethyl α-bromo-α,γ,γ,γ-tetrafluoroacetoacetate (14 g.) and 50% sulfuric acid (100 ml.) was refluxed for 6 hours. The aqueous solution was then cooled and extracted with ether. The ether extract was dried with sodium sulfate and distilled. When the pot temperature reached 50°, the residue was mixed with 50 ml. of concd. sulfuric acid and distillation was continued. 3-Bromo-1,1,1,3-tetrafluoroacetone (9 g., 90%) was obtained boiling at 65–66°.

Hydrolysis and Bromination of Ethyl α-Bromo-α,γ,γ,γ-tetrafluoroacetoacetate.—The ester (28 g.) and 50% sulfuric acid (150 ml.) were mixed in a 500-ml., 3-necked flask which was equipped with a reflux condenser, a sealed stirrer and an addition funnel. The mixture was heated to 90° and bromine (16 g.) was added dropwise. Heating and stirring was continued for an additional two hours and then the aqueous solution was cooled and extracted with ether. The ether extract was dried with anhydrous sodium sulfate and distilled. After distillation of the ether, the residue was mixed with concd. sulfuric acid (50 ml.) and distillation was continued. 3,3-Dibromo-1,1,1,3-tetrafluoroacetone (25 g., 83%) was obtained boiling at 81–82°.

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DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, INDIANA

Reactivity of 5-Bromoisocytosine with Some Amines

BY ARTHUR P. PHILLIPS

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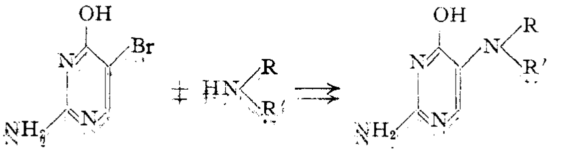
The reactivity of 5-bromouracil with amines permitted the preparation of a series of 5-substituted aminouracils for chemotherapeutic testing.[1] In order to obtain other 5-substituted aminopyrimidines bearing additional amino groups, the reactivity of 5-bromoisocytosine toward amines has now been examined.



The bromine of 5-bromoisocytosine is active for replacement reactions with amines but apparently less so than that of 5-bromouracil. Piperidine and morpholine reacted rapidly with 5-bromoisocytosine to give high yields of the 5-substituted amino derivatives. On the other hand, *n*-butylamine, ethylamine and methylbenzylamine either gave no reaction or no good product was isolated even when more strenuous reaction conditions were employed than were necessary to produce excellent yields with 5-bromouracil.

For example when a mixture of 0.1 mole of 5-bromouracil and 0.3 mole of *n*-butylamine was refluxed for three hours on a steam-bath a 90–100% yield of 5-*n*-butylaminouracil was obtained. But when 0.1 mole of 5-bromoisocytosine in 0.4 mole of *n*-butylamine was refluxed for 24 hours on the steam-bath a nearly quantitative recovery of unchanged 5-bromoisocytosine resulted.

Experimental

5-Piperidinoisocytosine.—A mixture of 19 g. (0.1 mole) of 5-bromoisocytosine and 25 cc. (21 g., 0.25 mole) of piperidine was refluxed in a metal-bath at 140–150° for four hours. The reaction mixture was washed out with 100 cc. of hot water and a little acetic acid was added bringing the *p*H to 8–8.5. After cooling, filtration gave 19 g. (100%) of white crystals. The product was purified by several reprecipitations from dilute hydrochloric acid solution by the addition of aqueous ammonia to *p*H 8 and then melted at 278–280°.

When 5-piperidinoisocytosine was treated with an excess of methanolic hydrogen chloride the dihydrochloride was formed. This salt was purified by several recrystallizations from methanol–ethyl acetate mixtures; m.p. 269–270° (dec.).

Anal. Calcd. for $C_9H_{16}Cl_2N_4O$: C, 40.4; H, 6.0. Found: C, 40.8; H, 5.8.

5-Morpholinoisocytosine.—A mixture of 19 g. (0.1 mole) of 5-bromoisocytosine and 25 cc. (22 g., 0.25 mole) of morpholine was refluxed in a metal-bath at 150–160° for four hours. The reaction product was taken up in about 80–90 cc. of hot water, the *p*H was adjusted to 6–7 with dilute acetic acid, and on cooling there was obtained 18 g. (90–95%) of white crystals. After recrystallization from hot water the product melted at 275–276° (dec.). The analytical sample was dried *in vacuo* at 120°.

Anal. Calcd. for $C_8H_{12}N_4O_2$: C, 48.9; H, 6.1. Found: C, 48.7; H, 6.1.

Attempted Reaction of *n*-Butylamine and 5-Bromoisocytosine.—A mixture of 19 g. (0.1 mole) of 5-bromoisocytosine and 35 cc. (25 g., 0.35 mole) of *n*-butylamine was refluxed on the steam-bath for 24 hours. The bulk of the *n*-butylamine was removed by evaporation. The residue was purified by reprecipitation from alkali solution by the addition of acid to *p*H 7–8. In this way 16–18 g. of solid was recovered which, upon purification both as the base and as the hydrochloride, was proved by analyses to be the original 5-bromoisocytosine. The recovery of unreacted bromo compound represents 85–95%.

Similar reactions were attempted with a number of other amines, ethylamine, methylbenzylamine, etc., but either the bromoisocytosine was recovered unchanged or no good product was readily isolable.

Acknowledgment.—The author is indebted to S. W. Blackman for the microanalyses included.

THE WELLCOME RESEARCH LABORATORIES
TUCKAHOE 7, NEW YORK

The Preparation of Free Hydroxylamine and Deutero-hydroxylamine

BY R. E. NIGHTINGALE AND E. L. WAGNER

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During a study of the infrared spectrum of crystalline hydroxylamine,[1] it was felt that additional information was needed which might be provided by deutero-hydroxylamine. It is well known that

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(1) A. P. Phillips, THIS JOURNAL, **73**, 1061 (1951).

(1) R. E. Nightingale and E. L. Wagner, submitted to *J. Chem. Phys.*