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°.

Acknowledgment.—The authors wish to express their thanks to the Westinghouse Electric Corporation for the financial support of this work.

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Reactivity of 5-Bromoisocytosine with Some Amines

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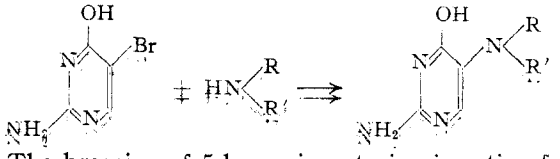
RECEIVED APRIL 30, 1953

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.

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The Preparation of Free Hydroxylamine and Deutero-hydroxylamine

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RECEIVED APRIL 10, 1953

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

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

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