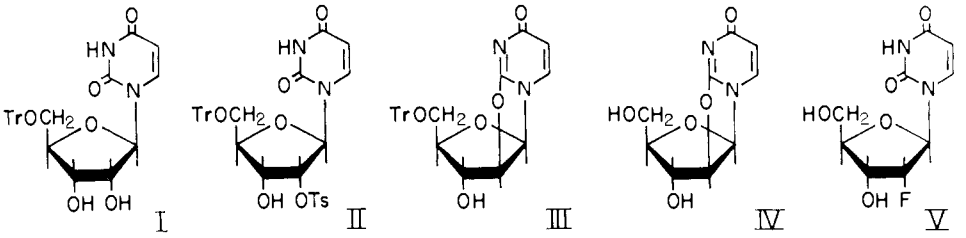
NUCLEOSIDES. XIV. SYNTHESIS OF 2′-DEOXY-2′-FLUOROURIDINE[1]

Sir:

We wish to report the synthesis of the potential anti-metabolite or antitumor agent 2′-deoxy-2′-fluorouridine (V), an analog of the nucleosides of deoxyribonucleic acid. Brown, *et al.*,[2] showed that reaction of 2,2′-anhydro-1-(β-D-arabinofuranosyl)-uracil (IV) with aqueous acid results in cleavage of the 2,2′-anhydro bond by addition of the elements of water, the OH^- ion adding to C2 of the pyrimidine. A nucleoside with the 2′-OH in the "up" or arabino configuration results. We have found that under anhydrous conditions hydrogen halides cleave the 2,2′-anhydro bond with a nucleophilic attack by halide at C2′ to yield 2′-halogeno derivatives. In addition to the 2′-fluoro nucleoside, 2′-chloro- and 2′-bromo-2′-deoxyuridines have been prepared by this method. Synthesis of a derivative of 2′-deoxy-2′-iodouridine has been reported.[3]



Compound IV was prepared by a more direct route than that previously described.[2] 5′-O-Trityluridine (I)[4] was treated with *p*-toluenesulfonyl chloride in pyridine to give the 2′-O-tosyl derivative (II), m.p. 174–175°, in 48% yield. (*Anal.* Calcd. for $C_{35}H_{32}N_2O_8S$: C, 65.61; H, 5.04; N, 4.37; S, 5.00. Found: C, 65.75; H, 5.29; N, 4.32; S, 4.88). Cyclization occurred upon heating II with sodium benzoate in acetamide at 100–110° to give the 2,2′-anhydro-5′-O-trityl nucleoside (III), m.p. 207–209° (dec.), $[\alpha]^{26}D$ −19° (methanol), in 55% yield. (*Anal.* Calcd. for $C_{28}H_{24}N_2O_5$: C, 71.77; H, 5.16; N, 5.98. Found: C, 71.32; H, 5.12; N, 6.42.) Removal of the trityl group in ethereal HCl gave IV in 70–80% yield.[5] IV was found to be identical with an authentic sample of 2,2′-anhydro-1-(β-D-arabinofuranosyl)-uracil[2] kindly supplied by Dr. D. M. Brown of Cambridge University.

2′-Deoxy-2′-fluorouridine (V) was formed by the action of anhydrous hydrogen fluoride on IV in dioxane at 100–110° for 18 hours. The crude product was purified by passage through a Celite column (ethyl acetate, methanol, water, *n*-heptane (10:6:5:3).[6] The desired compound was collected after five holdback volumes of the mobile phase (upper layer) had passed through the column. Crystallization from ethanol gave colorless needles, m.p. 150–151°, $[\alpha]^{20}D$ +52° (water), in 40–50% yield. (*Anal.* Calcd. for $C_9H_{11}N_2O_5F$: C, 43.90; H, 4.50; N, 11.38; F, 7.72. Found: C, 44.11; H, 4.73; N, 11.95; F, 8.02.)

Compound V was converted back to the 2,2′-anhydro derivative (IV) in 59% yield by heating V with sodium *tert*-butoxide in dimethylformamide.[7] Although this result offers strong evidence for the 2′-position and ribo ("down") configuration of the fluorine (IV resulting from nucleophilic displacement of fluorine by the 2-carbonyl of the pyrimidine) it does not exclude the unlikely possibility of 2,2′-anhydro bond formation by 2-carbonyl attack on C2′ of a 2′,3′-ribo ("down") epoxide.[8,9,10] Such an epoxide could have resulted from elimination of either a 2′- or 3′-"up" fluorine by anionic attack of the *trans* vicinal hydroxyl. Proof for the position *and* configuration of fluorine was obtained by the elimination of possible 2′,3′-epoxide formation. The 3′,5′-di-O-trityl derivative of V was prepared and converted to the di-O-trityl-2,2′-anhydro nucleoside by the action of sodium *tert*-butoxide in dimethylformamide. After acid hydrolysis (removal of the trityl groups and 2,2′-anhydro bond cleavage) the resulting solution was subjected to paper electrophoretic separation in borate buffers of pH 6[10] and 9.[11] The fact that both 1-β-D-arabinofuranosyluracil and the 2,2′-anhydro nucleoside (IV) (because of incomplete hydrolysis) were present in large amount in the hydrolysate[12] constitutes proof that compound V is, in fact, 2′-deoxy-2′-fluorouridine.

2′-Chloro-2′-deoxyuridine, m.p. 207–212° (dec.), $[\alpha]^{26}D$ +18° (water), was obtained in 70–80% yield by the action of anhydrous hydrogen chloride on IV in dioxane. (*Anal.* Calcd. for $C_9H_{11}N_2O_5Cl$: C, 41.15; H, 4.21; N, 10.66; Cl, 13.50. Found: C, 41.34; H, 4.46; N, 10.42; Cl, 13.50). The

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, Public Health Service (Grant No. 3190).

(2) D. M. Brown, A. Todd and S. Varadarajan, *J. Chem. Soc.*, 2388 (1956).

(3) 5′-O-Acetyl-2′-deoxy-2′-iodouridine was prepared by D. M. Brown, D. B. Parihar, C. B. Reese and A. Todd (*J. Chem. Soc.*, 3035 (1958)) from 5′-O-acetyl-2′-O-tosyluridine and sodium iodide in acetonylacetone *via* a 2,2′-anhydro intermediate.

(4) P. A. Levene and S. Tipson, *J. Biol. Chem.*, **104**, 385 (1934).

(5) This synthesis utilizes in essence the procedure of N. Yung, J. H. Burchenal, R. Fecher, R. Duschinsky and J. J. Fox (*J. Am. Chem. Soc.*, **83**, 4060 (1961)) for preparing 2,2′-anhydro-1-(β-D-arabinofuranosyl)-5-fluorouracil.

(6) It was subsequently possible to obtain crystalline product without recourse to a column. The amorphous glass was dissolved in a minimum amount of warm absolute ethanol and seeded with a crystal of V. After two days at room temperature the product was collected.

(7) R. Letters and A. M. Michelson, *J. Chem. Soc.*, 1410 (1961).

(8) D. M. Brown, D. P. Parihar, A. Todd and S. Varadarajan, *ibid.*, 3028 (1958).

(9) E. J. Reist, J. H. Osiecki, L. Goodman and B. R. Baker, *J. Am. Chem. Soc.*, **83**, 2208 (1961).

(10) J. F. Codington, R. Fecher and J. J. Fox, *ibid.*, **82**, 2794 (1960).

(11) M. P. Gordon, O. M. Intrieri and G. B. Brown, *ibid.*, **80**, 5156 (1958).

(12) A complete separation of all four 1-β-D-aldopentofuranosyluracil isomers, as well as IV and V, can be made by use of the two buffer systems.

2′-bromo analog, m.p. 186–190° (dec.), $[\alpha]^{26}D$ +15° (water), was prepared in 46% yield by the reaction of IV with anhydrous hydrogen bromide in trifluoroacetic acid. (*Anal.* Calcd. for $C_9H_{11}N_2O_5Br$: C, 35.19; H, 3.61; N, 9.12; Br, 26.02. Found: C, 35.28; H, 3.45; N, 9.50; Br, 26.68.)

It is probable that this synthesis of 2′-halogeno nucleosides from 2,2′-anhydro derivatives can be extended to halogeno nucleosides of other bases. Inasmuch as the requisite intermediates have been prepared in this laboratory, the method is being applied to the thymidine series.

Acknowledgment.—We wish to express our sincere thanks to Dr. George B. Brown for his helpful suggestions and continued interest.

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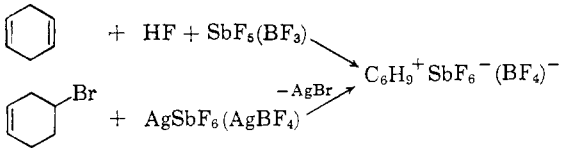
NON-CLASSICAL CYCLOHEXENYL CARBONIUM ION

Sir:

Protonation of cyclohexadiene-1,4 with HF + BF_3 or HF + SbF_5 (either by the acids or by *in situ* treatment with $AgBF_4$ + HCl or $AgSbF_6$ + HCl) gave in liquid SO_2 at −30° deep brown to red colored homogeneous solutions. After distilling off the solvent in a vacuum line system, solid tetrafluoroborate and hexafluoroantimonate complexes of the composition $C_6H_9BF_4$ and $C_6H_9SbF_6$, respectively, were obtained. In the strong acid media side reactions, leading to coupling and polymeric products, also take place and purification of the complexes represented difficulty.

The difficulty of the acid catalyzed side reactions was overcome when 3-cyclohexenyl bromide was treated in liquid SO_2 solution at −30° with anhydrous $AgBF_4$ and $AgSbF_6$. Quantitative silver halide elimination takes place and again colored solutions were obtained, with considerably less intense color, however, than in the case of protonation of cyclohexadiene-1,4. The precipitated



silver bromide was filtered and part of the solvent distilled off (all operations were carried out preferentially in a closed vacuum line system). Solid tetrafluoroborate (m.p. ~56° sealed tube) and hexafluoroantimonate (m.p. ~ 115° sealed tube) complexes were obtained with the composition corresponding to $C_6H_9BF_4$ (calcd.: C, 42.81; H, 5.36; F, 45.24. Found: C, 44.51; H, 6.17; F, 43.2) and $C_6H_9SbF_6$ (calcd.: C, 25.87; H, 2.84; F, 35.96. Found: C, 28.17; H, 3.13; F, 33.2). The complexes are light brown, highly sensitive compounds. Recrystallization from liquid SO_2 yielded only very lightly colored compounds, the pure salts being most probably colorless. The complexes must be rigorously protected from moisture and from oxygen. They dissolve to some extent in solvents such as nitromethane, sulfur dioxide and dioxane (in the latter, however, there is a fast observable color change and obvious reaction). The solutions are colored (brown to red in SO_2, blue in nitromethane and dioxane) but the color may arise from impurities still present.

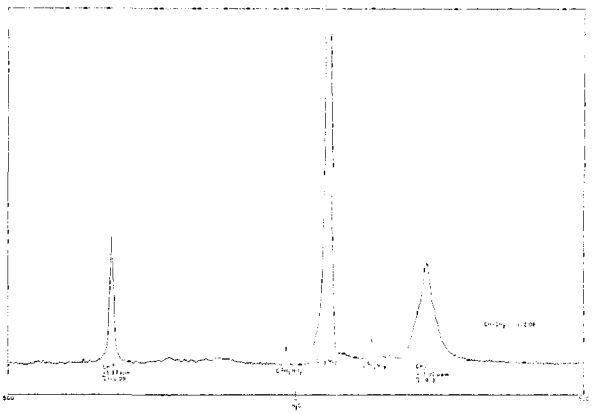


Fig. 1.—H^1 magnetic resonance of $C_6H_9^+$ SbF_6^- in CH_3NO_2 solution at 60 mc.

In considering the nature of the isolated complexes, we must assign them carbonium salt structures, $C_6H_9^+BF_4^-$ and $C_6H_9^+SbF_6^-$, as it is difficult to consider any covalent structure for BF_4 and SbF_6 complexes. The tetrafluoroborate and hexafluoroantimonate nature of the complexes was proved beside elementary analyses by the characteristic infrared bands and by n.m.r. proton and fluorine resonance investigations, giving proof of the symmetrical anions. (a) Infrared bands, $C_6H_9BF_4$: 3041 vw, 2927 vs, 2858 s, 1603 w, 1445 m, 1348 w, 1072 vs, br(BF_4^-), 1012 sh, 889 w, 840 w, 792 vw, 765 w, 720 m; $C_6H_9SbF_6$: 3012 vw, 2925 vs, 2865 s, 1601 w, 1430 m, 1260 w, 1150 m, 1070 w, 1015 w, 970 m, 890 w, 865 w, 795 w, 720 vs, 655 s (SbF_6^-) (spectra were obtained as Nujol–Fluorolube mixed mulls). (b) Ultraviolet absorption maxima, $C_6H_9SbF_6$: (in dioxane) λ_{max} mμ (E) 307 (234), 242 (1350), 250 (shoulder (1248). (The solvent is interfering with the complexes after a few minutes, thus fresh solutions must be used immediately and even so the data, as a result of solvent interference, are not considered entirely reliable). (c) Nuclear magnetic resonance: The proton resonance spectrum of $C_6H_9^+$ SbF_6^- (Fig. 1) in nitromethane solution at room temperature (60 Mc., water as external reference) indicates only two types of hydrogens. The corresponding tau values (using the correction factor of 5.21 p.p.m. for water–tetramethylsilane) are 9.13 and −0.09, respectively. The relative peak areas observed are 2.06:1. The fluorine resonance spectra of the compounds at 56.46 Mc. gave evidence only of the symmetrical anions BF_4^- and SbF_6^-.

The observed CH peak at so low field ($\tau = -0.09$, giving a negative value on the Tiers scale) indicates a positively charged "acidic" CH^+. The presence of only two types of protons, the position