Preliminary communication

Novel access to 2′-deoxyuridine, and reactive intermediates to pyrimidine nucleosides★

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Relatively few procedures[1] are available for the synthesis of 2′-deoxyuridine and related nucleosides. Those based on nucleoside interconversion resulting in the ultimate placement at C-2′ of a reducible function, such as a halogen atom[2-5], are among the more practical routes to 2′-deoxyuridine. We report herein a novel synthesis of various 2′-bromo-2′-deoxyuridine derivatives, which serve as valuable precursors to 2′-deoxyuridine and its selectively substituted derivatives. Several of the easily accessible intermediates are the starting points for a variety of important reactions in nucleoside chemistry.

Reaction of 2′,3′-*O*-benzylideneuridine[6] (**1**) (see Scheme 1) with 2.2 molar equivalents of *N*-bromosuccinimide (NBS) in a mixture of 1,1,2,2-tetrachloroethane and carbon tetrachloride[7] afforded a 56% yield† of 3′-*O*-benzoyl-2′,5-dibromo-2′-deoxyuridine (**3**), m.p. 212–214°. Catalytic hydrogenation (20% Pd–C) afforded 80–85% of 3′-*O*-benzoyl-2′-deoxyuridine (**5**), m.p. 225–226.5°, which, on debenzoylation with methanolic ammonia gave crystalline 2′-deoxyuridine, m.p. 158–161° (80% yield). The procedure is adaptable to a direct synthesis of the latter compound without isolation of intermediates. The configuration at C-2′ in **3** was ascertained by partial hydrogenation in the presence of 6% Pd–C to 3′-*O*-benzoyl-2′-bromo-2′-deoxyuridine (**4**), m.p. 179–181° (94% yield), and controlled debenzoylation to give the known 2′-bromo-2′-deoxyuridine[3,8]. Reaction of the 5′-*O*-acetyl derivative **2** with NBS afforded crystalline 2,2′-anhydro-[1-(5-*O*-acetyl-3-*O*-benzoyl-β-D-arabinofuranosyl)-5-bromouracil] (**6**), m.p. 220–220.5° (50% yield)†, which was transformed into the known[9,10] 2,2′-anhydro-(1-β-D-arabinofuranosyluracil), m.p. 235–238° (dec.) by sequential hydrogenation and de-esterification, via crystalline intermediates. Reaction of the

★Reactions of *O*-benzylidene sugars with *N*-bromosuccinimide. Part. V. For previous papers in this series, see Ref. 7.
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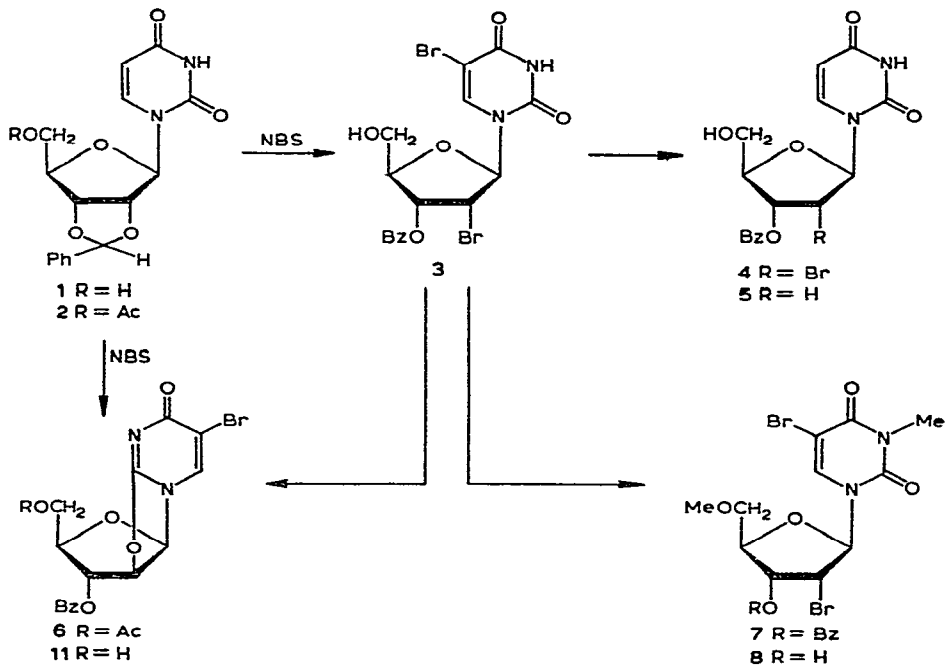
†The mother liquors of these preparations contained additional product which could be recovered by chromatography on silicic acid.

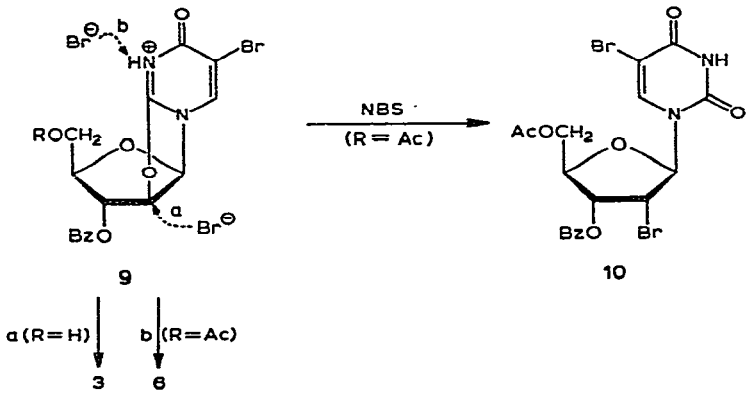


3-*N*,*O*-dimethyl analog of **1** with NBS afforded 3′-*O*-benzoyl-2′,5-dibromo-2′-deoxy-3-*N*-methyl-5′-*O*-methyluridine (**7**), m.p. 164–166° in 65% yield★, which was subjected to a variety of selective transformations (partial and total hydrogenation; de-esterification to **8**, via crystalline derivatives). A definitive configurational assignment to these products was possible by the controlled methylation (NaH, MeI, $HCONMe_2$) of **3** to give **7**. For **7**, a higher-melting, crystalline form★★ could also be obtained, m.p. 183–185°.

In previous papers[7], detailed studies of the mechanism of ring-opening reactions of *O*-benzylidene acetals with NBS have been reported, with the conclusion that the reaction proceeds via benzoxonium ions. The intermediacy of 2′,3′-benzoxonium ions in the case of nucleosides[11] presents some intriguing mechanistic possibilities and important synthetic implications, as nucleophilic attack can occur by the external nucleophile, namely, bromide ion, or by an intramolecular process involving the C–2 carbonyl function[11,12]. The stereoselectivity observed in the reaction of **1** and its derivatives with NBS can be explained satisfactorily by invoking benzoxonium-ion formation, followed by intramolecular participation to yield the protonated 2,2′-anhydro intermediate **9** (see Scheme 2). In the case of **1** and its methylated analog, this intermediate undergoes stereoselective attack by bromide ion to give the observed product. With **2**, proton abstraction is favored, to yield the 2,2′-anhydride. The validity of these arguments was ascertained by the following transformations. Treatment of **3** with acetamide and sodium benzoate at [13] 105° gave the corresponding 2,2′-anhydride **11**, m.p. 208–211°, in 67% yield.

★The mother liquors of these preparations contained additional product which could be recovered by chromatography on silicic acid.

★★The lower-melting form could be transformed into the higher-melting form by recrystallization with nucleation by the latter.



Acetylation of **11** afforded a product identical with **6**, thus establishing the configurational relation between the two series. Treatment of **11** with one equivalent of methanesulfonic acid to effect protonation[14] of the uracil ring, followed by reaction with NBS, gave compound **3** in 95% yield. Similarly, protonation of **6** followed by reaction with NBS afforded the crystalline 5′-*O*-acetyl derivative **10**, m.p. 199–202°, in 90% yield, also obtained from **3** by acetylation. In the absence of the acid, negligible reaction of **6** with NBS took place. These sequences unambiguously establish the site of bromination and the stereochemical identities and interrelationships of the products.

It is evident that the successful application of the ring-opening reaction of *O*-benzylidene acetals with NBS to afford easily accessible nucleoside derivatives provides a preparative route to selectively substituted halo- and deoxy-nucleosides from which a variety of preparatively significant transformations can be effected★.

ACKNOWLEDGMENTS

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★All compounds gave acceptable analyses, and afforded i.r., n.m.r., and mass spectra that were in accord with their structures. Melting points are uncorrected.

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ANNOUNCEMENT

The International Union of Pure and Applied Chemistry has issued Information Bulletin No. 7 (September 1970) entitled "Tentative Rules for Carbohydrate Nomenclature, Part 1". Copies may be obtained from Dr. R. J. M. Ratcliffe, Assistant Secretary IUPAC, Bank Court Chambers, 2–3 Round Way, Cowley Centre, Oxford OX4 3YF, England.

Comments on these proposals should be sent, within eight months of publication of this Bulletin, to Professor P. E. Verkade, Ary Schefferstraat 217, 's-Gravenhage, The Netherlands.