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Nucleosides. IV. Synthesis of 5-Substituted-2'-deoxy-6-azauridines

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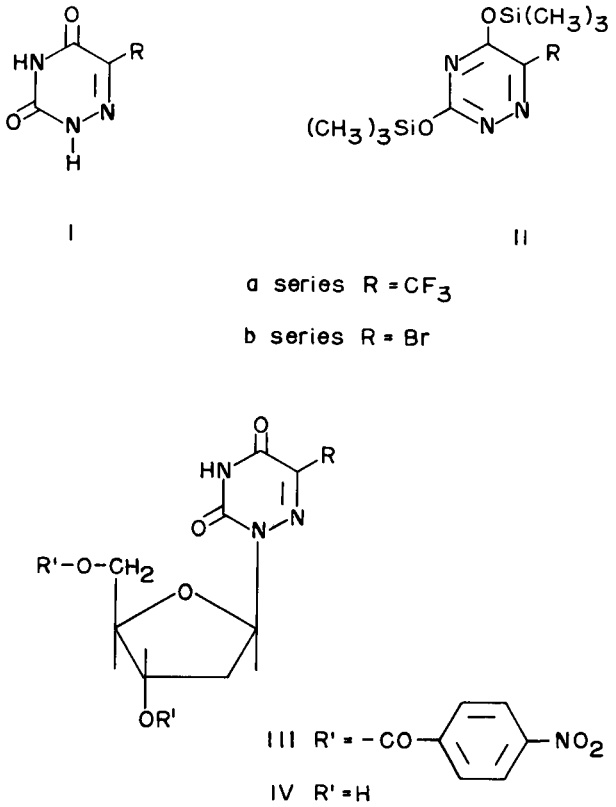
Sir:

In the search for antiviral chemotherapeutic agents several thymidine antimetabolites, such as 5-iodo (1), 5-bromo (2), 5-trifluoromethyl (3) and 5-methylamino-2'-deoxyuridine (4) have been found to have inhibitory activity against herpes simplex and several other DNA viruses (2). The clinical efficacy of 5-iodo-2'-deoxyuridine (Idoxuridine) has been well demonstrated (5); some of the undesirable side-effects observed, such as photophobia, cornea toxicity and loss of activity, have been attributed to the facile dehalogenation *in vivo* and the cleavage product 5-iodouracil (6). Of course, the potential mutagenic effect due to the incorporation of idoxuridine into host DNA remains a major concern in its wider applications.

As part of our continued study of antiviral agents, we have become interested in the 6-aza analogs of these thymidine antimetabolites, particularly on the basis of the following observations (7). The *p*Ka's of the pyrimidine nucleosides are generally decreased by the introduction of the electronegative 6-aza group, a trend in accordance with the lower *p*Ka values commonly associated with the antiviral thymidine analogs. 6-Azauridine is resistant to the enzymatic cleavage by pyrimidine nucleoside phosphorylase. Its phosphorylated derivative is incorporated into bacterial RNA to a minor extent but apparently not utilized by mammalian cells. Furthermore, moderate antiviral activities of 6-azauridine have been found *in vitro* and *in vivo*. Recently the 6-aza analog of thymidine has been described as an inhibitor of thymidine synthetase. It is incorporated into DNA by *S. faecalis*, but the mutagenic effect was considered of minor significance only (7a, 8). Therefore, it would seem desirable to investigate the biological properties of various 5-substituted 6-aza-2'-deoxyuridines. In this communication, the chemical syntheses of two members of the series, 2'-deoxy-5-trifluoromethyl-6-azauridine[2-(2'-deoxy-β-D-ribofuranosyl)-6-trifluoromethyl-*as*-triazine-3, 5(2*H*, 4*H*)-dione] (IVa) and 2'-deoxy-5-bromo-6-azauridine [2-(2'-deoxy-β-D-ribofuranosyl)-6-bromo-*as*-triazine-3, 5(2*H*, 4*H*)-dione] (IVb), are described.

The chemical syntheses of 2'-deoxy-6-azauridine and 6-azathymidine have been reported (9). The method employed by these workers required the use of a blocking group (diphenylmethyl) on the 3-position of the 6-azauracil moiety to ensure the attachment of the sugar portion at the 1-position. In our present report we have used a modification of the method of Nishimura *et al.* (10), which involves the reaction of the bis-(trimethylsilyl) ether derivative of the 6-azauracil moiety (II) with a glycosyl halide. This method apparently gives a preponderance of the β-anomer of the 1-substituted-6-azauracil; none of the unwanted isomers have been isolated thus far.



5-Carboxy-6-azauracil (11) was treated with sulfur tetrafluoride in hydrogen fluoride to afford 82% of 5-trifluoromethyl-6-azauracil (Ia) (12), m.p. 161-162°; λ max (*p*H 1): 262.5 mμ, (ε, 5,800); λ max (*p*H 13): 292 mμ, (ε, 7,000). Calcd. for $C_4H_2F_3N_3O_2$: C, 26.53; H, 1.11; F, 31.47; N, 23.21. Found: C, 26.46; H, 1.14; F, 31.7; N, 23.08. Treatment of Ia with trimethylsilyl chloride and hexa-

methyldisilazane (13) yielded *ca.* 100% of 6-trifluoromethyl-3,5-bis-trimethylsilyloxy-*as*-triazine (IIa). Compound IIa was heated with 2-deoxy-3,5-di-*O*-*p*-nitrobenzoyl-D-ribofuranosyl chloride (14) to yield the crystalline blocked nucleoside (IIIa), yield 51%, m.p. 209-211°. Calcd. for $C_{23}H_{16}F_3N_5O_{11}$: C, 46.40; H, 2.71; F, 9.57; N, 11.76. Found: C, 46.37; H, 2.64; F, 9.6; N, 11.61. Deblocking of IIIa was achieved by heating in a methanolic di-isopropylamine solution to yield 29% of 2-(2'-deoxy-β-D-ribofuranosyl)-6-trifluoromethyl-*as*-triazine-3,5(2*H*,4*H*)-dione, IVa, m.p. 152-154°. $[\alpha]_D^{25}$ -36.2 (C 1.0, H_2O). λ max (0.1 *N* HCl): 268 mμ (ε, 5,880) λ max (*p*H 11): 263 mμ (ε, 5,610). The optical rotatory dispersion curve in methanol showed a negative cotton effect, with extrema at 288 mμ, [Φ] -6,400 (tr.) and 238 mμ, [Φ] 11,800 (pk.). Calcd. for $C_9H_{10}F_3N_3O_5$: C, 36.37; H, 3.39; F, 19.18; N, 14.14. Found: C, 36.67; H, 3.54; F, 18.73; N, 14.09. In a similar series of transformations, starting with 5-bromo-6-azauracil (Ib) (15), the following compounds were obtained: 6-bromo-3,5-bis-(trimethylsilyloxy)-*as*-triazine (IIb), yield 100%, m.p. *ca.* 50°; 2-(2'-deoxy-3',5'-di-*O*-*p*-nitrobenzoyl-β-D-ribofuranosyl)-6-bromo-*as*-triazine-3,5(2*H*,4*H*)-dione (IIIb), yield 86%, m.p. 131-132°, Calcd. for $C_{22}H_{16}BrN_5O_{11}$: C, 43.58; H, 2.66; Br, 13.18; N, 11.55. Found: C, 43.45; H, 2.49; Br, 12.84; N, 11.86. 2-(2'-Deoxy-β-D-ribofuranosyl)-6-bromo-*as*-triazine-3,5(2*H*,4*H*)-dione (IVb), yield 65%, m.p. 214-215°, $[\alpha]_D^{25}$ -23.2° (C 0.8, H_2O), λ max (*p*H 1): 279 mμ (ε, 6,440); λ max (*p*H 13): 267 mμ (ε, 5,760); Calcd. for $C_8H_{10}BrN_3O_5$: C, 31.18; H, 3.27; Br, 25.94; N, 13.64. Found: C, 31.71; H, 3.25; Br, 25.53; N, 13.80. o.r.d. curve (MeOH): [Φ] (295 mμ) -5200 (tr.), [Φ] (230 mμ) 10,600 (pk.). The assignment of structure to compounds IVa and IVb is based on the following considerations: The hypsochromic shift of the absorption maximum in the alkaline ultraviolet spectrum of IV is typical of 1-substituted-6-azauracils (16). If IV were a 3-(2'-deoxyribosyl)-6-azauracil, a very substantial bathochromic shift would be expected in the alkaline spectrum (16). The negative cotton effect shown by IV is indicative of the β-configuration of the sugar portion, since it has been reported (9,17) that 6-azapyrimidine nucleosides follow Hudson's iso-rotation rule. Furthermore, H_1 appears in the n.m.r. spectrum of IVa in acetone as a triplet at τ 3.48, *J* 6 c.p.s., and in the spectrum of IVb in pyridine as a triplet at τ 2.95, *J* 6 c.p.s. Such triplets are typical of β-2'-deoxyribosides; the α-anomer would be expected to show a quartet in this region (18). Thus far, none of the α-anomers of III or IV have been isolated from reaction mixtures, although the search for these compounds is continuing. The use of IVb as an intermediate for the preparation of other 5-substituted-2'-deoxy-6-azauridines is being investigated.

The evaluation of thymidine analogs IVa and IVb in various biological systems is still in progress. So far, both compounds show no cytotoxicity in KB cell culture at 100 γ/ml. (19). There is no evidence of phosphorylation of analog IVa upon incubation with whole Ehrlich ascites cells (20,21).

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