The Synthesis of Bicyclic Nucleosides Related to Uridine, 4-(β-D-Ribofuranosyl)thiazolo[5,4-*d*]pyrimidines

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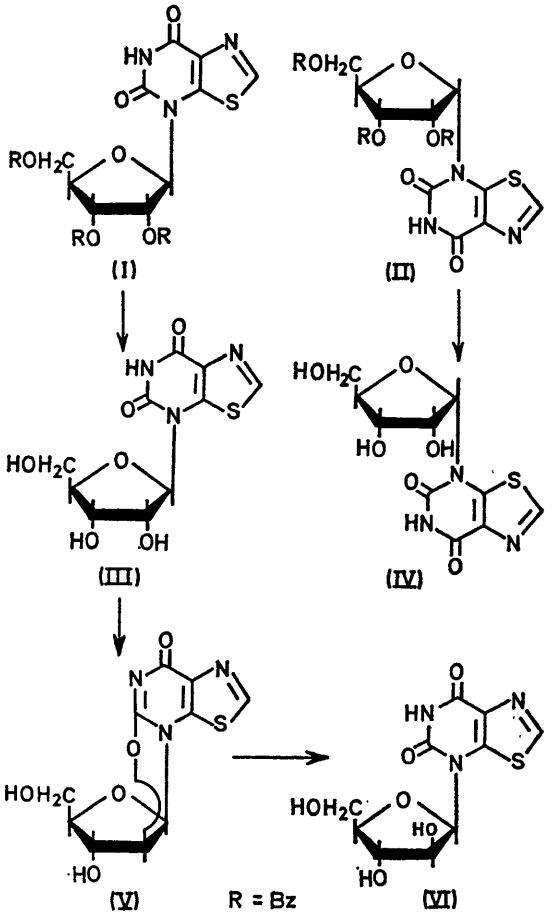
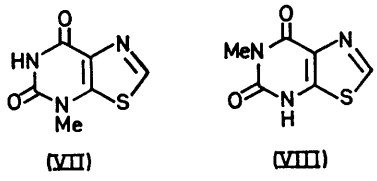
Summary The silyl alkylation procedure has furnished the first thiazolo[5,4-*d*]pyrimidine nucleoside (both α and β anomers isolated and characterized), and the site of alkylation has been established by a comparison of the u.v. spectra of the nucleoside and model *N*-methyl compounds.

THE isolation[1] and characterization[2] of uric acid riboside from beef blood as 9-D-ribofuranosyluric acid was followed by a reinvestigation which revised the structure to 3-D-ribofuranosyluric acid.[3] Several other 3-glycosylpurines have been prepared[4,5] *in vitro* by pyrimidine phosphorylases



and these purine nucleosides resemble the pyrimidine nucleoside uridine much closer than they do any naturally occurring purine nucleosides. This has created considerable interest in the synthesis of other 3-glycosylpurines[6] and certain closely related derivatives. We now report the synthesis of the first thiazolo[5,4-*d*]pyrimidine nucleoside, 4-(β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (I) which has the same juxtaposition between the ribosyl moiety and the two keto-groups (5 and 7) as the naturally occurring nucleoside uridine.

The silylation of thiazolo[5,4-*d*]pyrimidine-5,7-dione[7] was accomplished with an excess of hexamethyldisilazane and a catalytic amount of ammonium sulphate. The silyl derivative (a syrup) was mixed with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide[8] in dry dimethylformamide and the mixture stirred at room temperature for three days. Addition of the solution to methanol containing a small amount of NH_4OH yielded crystalline nucleoside (I) (m.p. 231—233°).† Silica gel column chromatography of the filtrate yielded an additional quantity of (I) and another nucleoside (II) which was isolated as a foam. The u.v. spectra observed for (I) and (II) were identical with the yield of (I) being 31% while that of (II) was 14%. The only major difference observed in the ^1H n.m.r. spectra of (I) and (II) was the chemical shift difference for the peak assigned to the anomeric proton. Removal of the blocking groups from the carbohydrate moiety without ring opening of the thiazole ring was accomplished with methanolic ammonia (saturated with ammonia at −5°) at room temperature to give (III) (m.p. 203—205°, cloudy melt) and (IV) (slow decomp. >170°). The ^1H n.m.r. spectrum of (III) showed a singlet at δ 8·95 (2-H) and a doublet at 6·11 (1-H) with $J_{1',2'}$ 6·0 Hz while that of (IV) showed a singlet at 8·83 (2-H) and a doublet at 6·17 (1'H) with $J_{1',2'}$ 2·8 Hz.



The site of ribosidation was established by a comparison of the u.v. spectral data (Table) of the unprotected nucleosides (III and IV) with that observed for 4-methylthiazolo-[5,4-*d*]pyrimidine-5,7-dione (VII) and 6-methylthiazolo-[5,4-*d*]pyrimidine-5,7-dione (VIII). The model compounds (VII) and (VIII) were prepared by routes analogous to previously reported methods.[9] On the basis of these data we tentatively assigned the structures of (I)—(IV) as the α and β anomers of 4-(D-ribofuranosyl)thiazolo[5,4-*d*]-pyrimidine-5,7-dione with (II) and (IV), having the lowest field chemical shift for the anomeric proton, as the *cis*-nucleosides (α).

† Correct C, H, and N analyses were obtained for all compounds reported, except (V).

TABLE

Compound	pH 1 λ_{max}	pH 1 ϵ_{max}	pH 11 λ_{max}	pH 11 ϵ_{max}
(III)	257	9040	264	10,050
(IV)	256·5	8280	265	10,230
(VII)	261	9800	266	10,400
(VIII)	257	9150	282	10,940
(VI)	258·5	8260	265	8500

That (I) and (II) were an anomeric pair was firmly established by the sodium periodate cleavage and sodium borohydride reduction procedure[10] using the unprotected nucleosides (III) and (IV) which gave products of equal and opposite optical rotation ($[\alpha]_D^{27}$ +73·5 and −75·0, respectively). The coupling constants observed in the ^{1}H n.m.r. spectra for the anomeric proton of the two nucleosides were larger than 1·0 Hz and precluded using ^{1}H n.m.r.[11] for the assignment of anomeric configuration. However, the the reaction of (III) with diphenyl carbonate in dimethylformamide at 150°[12] gave the 5,2′-anhydronucleoside (V) which was then converted into 4-(β-D-arabinofuranosyl)-thiazolo[5,4-*d*]pyrimidine-5,7-dione (VI) on exposure to 1 N-sodium hydroxide for 30 min followed by neutralization with dilute hydrochloric acid. The ^{1}H n.m.r. spectrum of (VI) revealed a broad singlet at δ 11·7 (N–H), a sharp singlet at 8·81 (2-H), and a doublet ($J_{1',2'}$ 3·0 Hz) at 6·15. This provided strong evidence that (III) was the β-anomer, and further corroboration for the structural assignment of (VI) was obtained by heating (VI) on a steam bath for 2 h in 2N-hydrochloric acid. Paper chromatography of the reaction mixture showed the carbohydrate to be D-arabinose. This also established that the anomeric configuration of (II) and (IV) was α.

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