Novel Synthesis of 3-Deaza-adenosine

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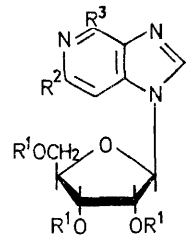
Summary A new and general route for the synthesis of 4-substituted 1-(β-D-ribofuranosyl)imidazo[4,5-*c*]pyridines has been established and is illustrated by the preparation of 3-deaza-adenosine.

THE nitrogen atom at position three of adenosine has been postulated to function as a binding site in several biochemical reactions.[1] The previous syntheses[2] of 3-deaza-adenosine (IV) have been achieved in low yields which precluded chemotherapeutic and biological investigations. The principal disadvantage of these syntheses[2] is the lack of reactivity towards nucleophilic displacement of the 4-chloro-group of 4-chloro-1-(β-D-ribofuranosyl)imidazo-[4,5-*c*]pyridine.

We therefore synthesized a nucleoside with an electron-withdrawing group at C-6 thus decreasing the electron density at C-4 and providing a concomitant increase in the reactivity of the 4-chloro-group towards nucleophilic displacement. We report here a novel synthesis of 3-deaza-adenosine.

The silylation of 4,6-dichloroimidazo[4,5-*c*]pyridine[3] with bistrimethylsilylacetamide in acetonitrile at room tempera-

ture gave a syrup which was presumed to be a monotrimethylsilyl derivative. The condensation of this derivative with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide[4] in the presence of a catalytic amount of sodium iodide at



(I) R^1 = Bz, R^2 = R^3 = Cl
(II) R^1 = H, R^2 = R^3 = Cl
(III) R^1 = H, R^2 = Cl, R^3 = NH_2
(IV) R^1 = R^2 = H, R^3 = NH_2

85° for 45 min gave a white crystalline solid (49%) which was tentatively assigned†‡ the structure (I) (m.p. 145—146°). Treatment of a methanolic solution of (I) with sodium methoxide gave (II) in 95% yield (m.p. 202—203°). Treatment of (II) with liquid ammonia at 110° for 30 h in a steel reaction vessel gave a solid which was recrystallized from water (93% yield) and tentatively assigned the structure (III) (m.p. 101—103°). The ^{1}H n.m.r. spectrum of (III) indicated the presence of only one amino-group which was as expected since the introduction of one electron-donating group should deactivate the second chloro-group towards nucleophilic displacement. To prove the initial site of nucleophilic displacement, catalytic hydrogenation (20% Pd–C) of (III) was done in water containing an equivalent amount of sodium hydroxide. The filtrate was concentrated to a small volume and the solid product recrystallized from water to give a 73% yield of (IV), m.p. 229—231°. A comparison of the u.v. spectra and the specific rotation of (IV) with the reported[2] values established the site of glycosidation as N-1, the anomeric configuration as β, and the initial site of nucleophilic displacement as C-4 for this series of nucleosides. This method provides a new and general route for the synthesis of various 4-substituted 1-(β-D-ribofuranosyl)imidazo[4,5-*c*]pyridines.

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† Satisfactory analytical data (C, H, N) were obtained for all new compounds. They were also shown to be homogeneous by t.l.c.

‡ Another nucleoside was obtained in very low yield from this reaction but was not characterized.

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