Transnucleosidation: Adenine Analogue of the Nucleoside Skeleton of the Polyoxins

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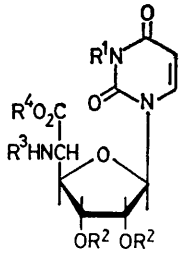
Summary An adenine analogue of the nucleoside skeleton of the antibiotic polyoxins has been prepared from the natural pyrimidine nucleoside by an improved transglycosylation reaction.

WE have reported recently[1] an efficient transglycosylation reaction which led to the successful synthesis of an adenine analogue of octosyl acid, a naturally occurring pyrimidine nucleoside having a 3,7-anhydro-octofuranose uronic acid sugar skeleton. Here we report an extension of this reaction to prepare an adenine analogue of the pyrimidine nucleoside unit of the antibiotic polyoxins, which contain the labile 5-amino-5-deoxy-D-allofuranose uronic acid unit.[2] The synthesis of this pyrimidine nucleoside has been reported;[3] however, the adenine analogue has not been synthesized.

Because of difficulty encountered in thiation of the polyoxin nucleoside,† transglycosylation was performed with the 3-benzoyluracil derivative instead of the N^4-acetylcytosine derivative.[1] Uracil polyoxin C (**1**), prepared

† There are four naturally occurring modifications in the pyrimidine base of this nucleoside, *i.e.*, uracil, thymine, 5-hydroxymethyluracil, and 5-carboxyuracil. Nucleosides were designated as uracil polyoxin C, thymine polyoxin C, polyoxin C, and polyoxin C acid, respectively (ref. 2).

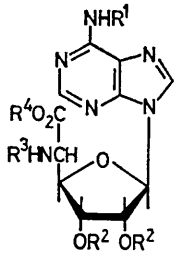
by bisulphite-catalysed decarboxylation of polyoxin C acid,[4] was esterified in methanolic hydrogen chloride to give the hydrochloride of the methyl ester (**2**), m.p. 199—202 °C (decomp.), ν (KBr) 1745 cm^{-1} (C=O). Treatment of (**2**) with benzyloxycarbonyl chloride and $NaHCO_3$ afforded crystalline (**3**), m.p. 196—197 °C. Acetylation of (**3**) followed by treatment with benzoyl chloride and pyridine afforded the 2′,3′-di-*O*-acetyl derivative (**4**) as a syrup, λ_{max} (EtOH) 252 nm (ε, 18,600).



	R¹	R²	R³	R⁴
(**1**)	H	H	H	H
(**2**)	H	H	H	Me
(**3**)	H	H	$PhCH_2OCO$	Me
(**4**)	PhCO	Ac	$PhCH_2OCO$	Me

To an acetonitrile solution of (**4**) (1·6 mmol) was added a solution of N^6-benzoyl-N^6,9-bis(trimethylsilyl)adenine[5] (2·37 mmol) in dichloroethane, followed by addition of trimethylsilyl trifluoromethanesulphonate[6] (1·6 mmol) in dichloroethane. The solution was refluxed for 15 h. After work-up with cold $CHCl_3$–5% $NaHCO_3$ followed by purification by silicic acid t.l.c., two products were obtained as colourless syrups together with the starting material (**4**) (280 mg). The major product (140 mg) was assigned the structure (**5**), λ_{max} (EtOH) 234 and 279·5 nm (ε, 12,900 and 18,200), δ ($CDCl_3$) 2·06 and 2·10 (3H each, s, $MeCO_2$), 3·76 (3H, s, CO_2Me), 4·55 (1H, t, 4′-H), 4·84 (1H, q, 5′-H), 5·07 (2H, s, $PhCH_2$), 5·81 (2H, m, 2′- and 3′-H), 6·13 (1H, d, 1′-H), 6·41 (1H, d, C-5′-NH), 7·28 (5H, s, $PhCH_2OCO$), 7·3—7·6 and 7·9—8·0 (5H, m, PhCO), and 8·08, and 8·74 (1H each, s, 2- and 8-H); $J_{1',2'} = 4{\cdot}4$, $J_{3',4'} = J_{4',5'} = 4{\cdot}2$, and $J_{5'NH} = 7{\cdot}3$ Hz. The minor product (25 mg), λ_{max} (EtOH) 228, 279·5 nm (ε, 18,200, 15,700) was considered to be the corresponding $N^{5'}$-benzoyl derivative (**6**), δ 5·29 (1H, q, 5′-H, 6·16 (1H, d, 1′-H), and 7·2—8·1 (11H, m, PhCO and 2- or 8-H). The 3-benzoyl group of (**4**) is apparently a benzoyl donor in this transacylation.

Compound (**5**) was hydrogenated over palladium black in EtOH containing a drop of AcOH, followed by hydrolysis in 0·5 N NaOH–MeOH (1 : 1) at 57 °C for 1 h. After purification by cellulose chromatography, the free nucleoside (**7**) was obtained as colourless needles in 50% yield, m.p. 257—260 °C (decomp.). λ_{max} (H_2O) 260 nm (ε, 13,900), λ_{max} (0·1 N HCl) 257 nm (ε, 14,200), λ_{max} (0·1 N NaOH) 260 nm (ε, 14,600); $[\theta]_{264}$ — 4160 (H_2O). δ (1 N ND_4OD) 6·30 (1H, d, 1′-H), and 8·47 and 8·63 (1H each, s, 2- and 8-H), $J_{1',2'} = 6{\cdot}0$ Hz. (**7**) was further characterized by mass spectrometry of its trimethylsilyl derivative.[7] The major peaks are characteristic of adenyl[8] and polyoxin sugar[9] units; *M* (pentasilyl derivatives) *m/e* 670; *M* — CH_3, 655, M — CO_2SiMe_3, 553; base + $C_2H_3OSiMe_3$, 322; base + 2H, 208; 208 — CH_4, 192; $SiMe_3$, 73. Bond cleavage between C-4′ and C-5′ yields ions at *m/e* 452 and 218,[9] and the abundant peak at *m/e* 332 arises from a characteristic polyoxin sugar fragment[10] which contains C-3′,4′,5′ and their substituents.



	R¹	R²	R³	R⁴
(**5**)	PhCO	Ac	$PhCH_2OCO$	Me
(**6**)	PhCO	PhCO	Ac	Me
(**7**)	H	H	H	H

The anomeric configuration of (**7**) is tentatively assigned as β, since it showed a weak negative Cotton effect at 264 nm as seen in β-D-adenosine. In addition, an α-anomer is not obtained when this reaction is applied to the usual uridine or cytidine derivatives. Apparently, the '*trans* rule' (participation of 2′-acetoxy group) is dominant in this reaction.

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