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SYNTHESIS OF 4′-METHOXYADENOSINE AND RELATED COMPOUNDS*†

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ABSTRACT

Addition of iodine and methanol to N^6,N^6-dibenzoyl-9-(2,3-*O*-carbonyl-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (**4**) selectively gives N^6,N^6-dibenzoyl-2′,3′-*O*-carbonyl-5′-deoxy-5′-iodo-4′-methoxyadenosine (**5**). Compound **5** can be converted into 4′-methoxyadenosine *via* hydrolysis of the carbonate followed by benzoylation, displacement of the 5′-iodo function by benzoate ion, and hydrolysis with ammonia. Configurational assignments are based upon comparisons of ^{1}H- and ^{13}C-n.m.r. spectra with those of previously characterised analogues in the uracil series and by borate electrophoresis. Intermediates in the above scheme have also been converted into 5′-amino-5′-deoxy-4′-methoxyadenosine, 4′-methoxy-5′-*O*-sulfamoyladenosine, and ethyl 4′-methoxyadenosine-5′-carboxylate, each of which is a 4′-methoxy analogue of biologically active derivatives of adenosine.

INTRODUCTION

Previous work from this Laboratory has led to the development of synthetic routes to several types of 4′-substituted nucleosides. We have described the preparation of 4′-methoxyuridine[2], 4′-fluoro derivatives of purine[3] and pyrimidine[4] nucleosides, and 4′-hydroxymethyl derivatives of purine and pyrimidine nucleosides[1,5]. In addition, some 4′-azidonucleosides have also been prepared[6], and the general subject of 4′-substituted nucleosides has been reviewed[7]. Certain nucleosides containing functionalised carbon substituents at C-4′ have also been the subject of investigation in other laboratories[8].

With respect to the introduction of such electronegative substituents as methoxyl, fluorine, and azide, we have developed the general approach of addition of suitable reagents (*e.g.*, iodine and methanol, iodine fluoride, and iodine azide) to appropriately substituted 4′,5′-unsaturated nucleosides. A similar approach to 5′-bromo-5′-deoxy-4′-methoxynucleosides has also been described by Sasaki *et al.*[9], but, on the basis of

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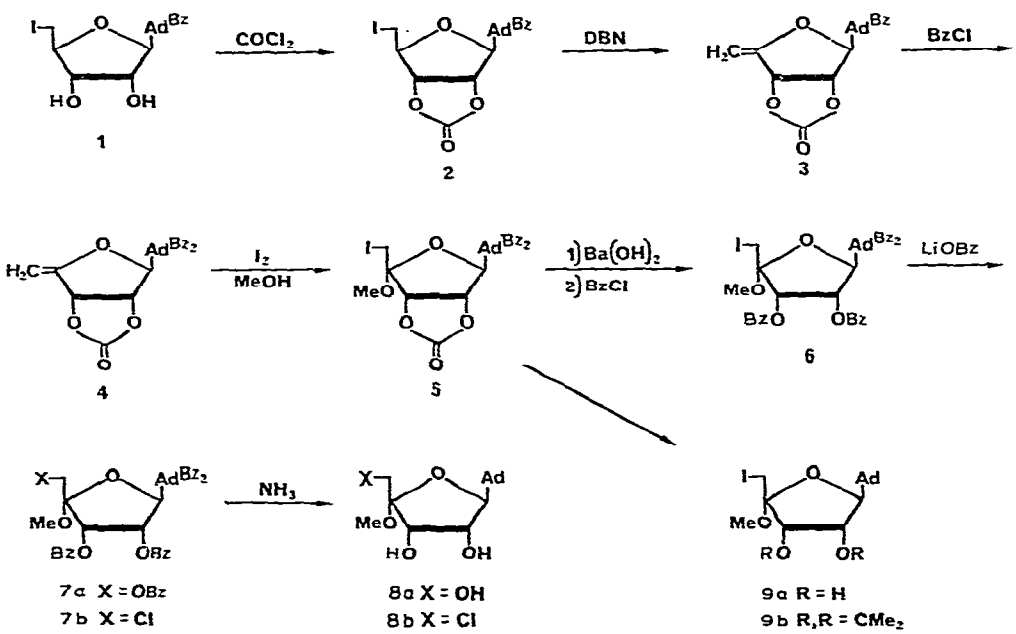
the results of our earlier work[2,3], we have concluded that the products[9] had the α-L-lyxofuranosyl rather than the desired β-D-ribofuranosyl configurations.

We now detail our work on the synthesis of 4′-methoxyadenosine (**8a**) and several of its C-5′-modified analogues.

DISCUSSION

In view of the known acid-lability of 4′-methoxynucleosides, the readily available N^6-benzoyl-1-(5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranosyl)-adenine[3] was not considered to be a suitable starting-material, since removal of the isopropylidene group from the final product would be accompanied by decomposition. The use of simple 2′,3′-di-*O*-acyl derivatives was also deemed inappropriate, since we have previously observed the formation of 3′,4′-orthoesters during the reaction of 1-(2,3-di-*O*-acetyl-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)uracil with iodine and methanol[2]. Accordingly, we considered N^6,N^6-dibenzoyl-9-(2,3-*O*-carbonyl-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (**4**) to be a suitable key-intermediate, since ultimate removal of protecting groups by base could be used and intramolecular participation of a 3′-*O*-acyl function with cationic intermediates derived from the 4′,5′-olefin would also be precluded. The selection of the N^6,N^6-dibenzoyl derivative was based upon our earlier observations on the efficient inhibition of formation of N^3,5′-cycloadenosine derivatives in the presence of good C-5′-leaving groups[3,10].

The conversion of the readily available N^6-benzoyl-5′-deoxy-5′-iodoadenosine[11] (**1**) into the 2′,3′-cyclic carbonate **2** was readily accomplished in 69% yield *via*



reaction with phosgene in pyridine at −35°. Generation of the conformationally restraining, five-membered ring was accompanied by a characteristic reduction of the value of $J_{1',2'}$ from 6 to 1.5 Hz in the ^{1}H-n.m.r. spectrum and by the expected downfield shifts of the signals for H-2′,3′. Treatment of **2** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in pyridine at room temperature readily gave the crystalline 4′,5′-olefin **3** (77%). The ^{1}H-n.m.r. spectrum of **3** showed the characteristic pattern for H-5′,5′ as two doublets of doublets at δ 4.81 and 4.68 (J_{gem} 3, $J_{3',5'}$ 1 Hz)[10,11]. Treatment of **3** with benzoyl chloride in pyridine readily gave **4**. For larger-scale work, it was more convenient to reverse the sequence of the first two steps, by converting **1** into N^6-benzoyl-1-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine[10] and subsequently, without purification of intermediates, treating with phosgene and with benzoyl chloride to give **4** (54% overall yield).

The reaction of **4** with 4 mol.equiv. of iodine in methanol at room temperature in the presence of lead carbonate gave the 5′-deoxy-5′-iodo-4′-methoxy adduct **5** (94%) that crystallised readily, and it was apparent that only a single diastereomer had been formed. A similar situation has been encountered in the uridine series[2], where the product was convincingly characterised as having the β-D-*ribo* configuration. Although the ^{1}H- and ^{13}C-n.m.r. spectra of **5** and those of several subsequent products (*e.g.*, **8a**, **9a**, **9b**) are more similar to those of comparably substituted 5′-deoxy-5′-iodo-4′-methoxy-β-D-ribofuranosylnucleosides than to those of the α-L-lyxofuranosyl isomers, the absence of a second diasteromer makes rigorous configurational assignment difficult. However, borate electrophoresis (see below) of **8a** provided compelling evidence for the *ribo* configuration of **5**. Attempts to confirm the *ribo* configuration by generation of an N^3,5′-cyclonucleoside from appropriate derivatives such as **9a** or **9b**, or by acid-catalysed C-4′-epimerisation as was demonstrated in the uridine series[2], led only to decomposition.

Preliminary attempts to displace the 5′-iodo substituent from **5** with benzoate anion caused partial loss of the carbonate group. The carbonate group was therefore removed by treatment of **5** with barium hydroxide in aqueous methanol for 15 min at room temperature. Partial *N*-debenzoylation also occurred, and hence the crude product was treated with benzoyl chloride in pyridine, generating crystalline N^6,N^6,$O^{2'}$,$O^{3'}$-tetrabenzoyl-5′-deoxy-5′-iodo-4′-methoxyadenosine (**6**). For larger-scale purposes, it was convenient to combine the three steps leading from **4** to **6** without purification of intermediates, and in this way an overall yield of 91.5% of chromatographically homogeneous **6** could be obtained and then crystallised. Care was necessary during the benzoylation step, in order to avoid the formation of a trace of the chromatographically indistinguishable 5′-chloro analogue of **6**.

Based upon our earlier work in the uridine series[2], **6** was treated with an excess of lithium benzoate in dimethyl sulfoxide at 120° for 70 h. The resulting, crude N^6,N^6,$O^{2'}$,$O^{3'}$,$O^{5'}$-pentabenzoyl-4′-methoxyadenosine (**7a**) (in which a trace of the corresponding 5′-chloro-5′-deoxy derivative, **7b**, could now be detected by t.l.c.) was debenzoylated by treatment with methanolic ammonia at 37° for 18 h. Chromatography then yielded 82% of pure 4′-methoxyadenosine (**8a**). Once again (see below),

^{1}H- and ^{13}C-n.m.r. spectroscopy confirmed the presence of a single isomer related to 4′-methoxyuridine rather than its α-L-lyxofuranosyl isomer. This conclusion was substantiated by the behaviour of **8a** upon borate electrophoresis[12] at pH 6.0. Lyxofuranosyl nucleosides have mobilities[12] 1.3–1.7 times those of the corresponding ribofuranosyl isomers, due to the formation of a 2′,3′,5′-tridentate complex. In the 4′-methoxyuridine series, this ratio is even larger (~3), which can largely be explained by some retardation of 4′-methoxyuridine relative to uridine (4′-MeOUr/Ur = 0.5–0.6), presumably due to steric inhibition of borate-complex formation by MeO-4′. In 1-(4-methoxy-α-L-lyxofuranosyl)uracil, MeO-4′ does not affect formation of the tridentate complex. In the adenosine series, the single MeO-4′ isomer had a mobility (M_{Ad}) of 0.77 relative to that of adenosine (*cf.* M_{Ad} 1.33 for 9-α-L-lyxofuranosyladenine), strongly supporting the β-D-ribofuranosyl structure of **8a**.

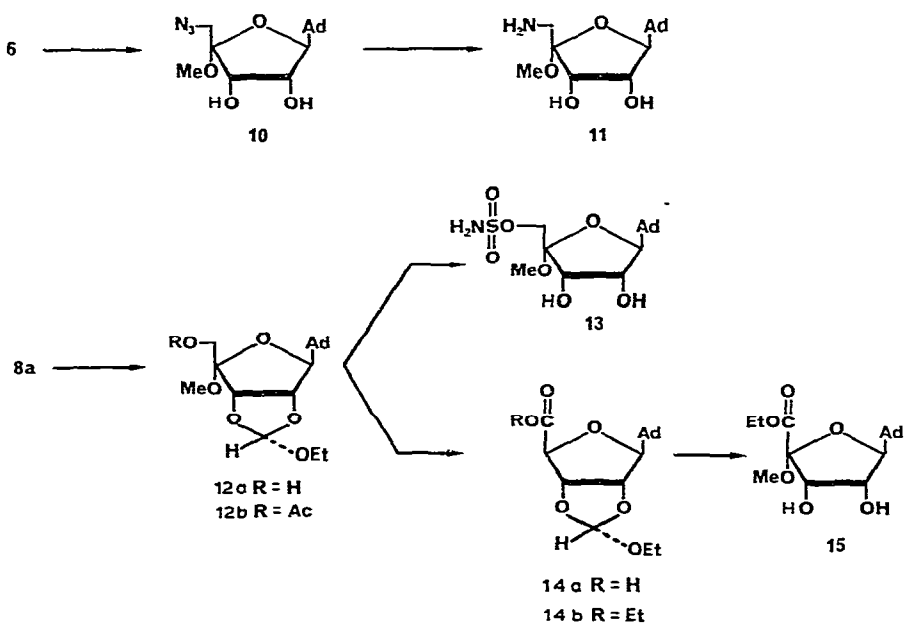
If a temperature close to 0° was not maintained during the benzoylation step in the preparation of **6**, a minor impurity with a t.l.c. mobility just greater than that of **8a** could be detected in the crude product. This impurity, which was abundant when hexamethylphosphoramide was used during the benzoate displacement (**6**→**7a**), was isolated crystalline by preparative t.l.c. and identified as 5′-chloro-5′-deoxy-4′-methoxyadenosine (**8b**). Compound **8b** was presumably formed by displacement of I-5′ in **5** by chloride ion generated during benzoylation. Compounds such as **5** do not usually undergo nucleophilic displacements under less than forcing conditions, and hence the formation of **8b** is surprising. It is possible that the formation of **8b**, at least in part, takes place during the benzoate displacement reaction. Care must therefore be taken to extract all residual chloride ion from the crude **6** prior to benzoylation.

Several derivatives closely related to 4′-methoxyadenosine were also synthesised. One such compound was 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylidene-4′-methoxyadenosine (**9b**), which provided an additional reference-point for configurational assignment through comparison with the previously described 5′-bromo analogues[3] and with the corresponding uridine derivatives[2]. The pentabenzoate **6** was debenzoylated with methanolic ammonia and the resulting, crude 5′-deoxy-5′-iodo-4′-methoxyadenosine (**9a**) was converted into crystalline **9b** (57% overall yield).

In addition to the previously established selectivity for formation of *ribo* adducts during the addition[2] of iodine and methanol to the uracil equivalent of **4** and the results of borate-electrophoresis experiments (see above), substantial support for the *ribo* configuration in the products of the present study is provided by ^{1}H- and ^{13}C-n.m.r. data. Since only single isomers are available in the adenosine series, it is necessary to compare signals for certain atoms with those in the uridine series that showed significant differences in the β-D-*ribo* and α-L-*lyxo* series. A summary of the most pertinent comparisons follows. For **9a** in aqueous acetone, the ^{13}C-n.m.r. signal for C-4′ appeared at 105.07 p.p.m., whereas those for C-4′ in the β-D-*ribo* and α-L-*lyxo* epimers in the uracil series were at 104.42 and 109.72 p.p.m., respectively[2]. Similarly, the signal for C-5′ of **9a** appeared at 5.27 p.p.m., whereas those[2] for the β-D-*ribo* and α-L-*lyxo* uracil analogues were at 4.68 and 1.17 p.p.m. In the ^{1}H-n.m.r. spectrum of **9a**, H-1′ resonated at δ 6.73 ($J_{1',2'}$ 4 Hz) in pyridine-d_5 [*cf.* δ 6.63

($J_{1',2'}$ 3.5 Hz) and 7.09 ($J_{1',2'}$ 7.5 Hz) for the β-D-*ribo* and α-L-*lyxo* uracil analogues, respectively]. For **9b**, C-4′ and C-5′ resonated at 106.62 and 6.26 p.p.m. (*cf.* 106.27 and 111.64 p.p.m. and 5.95 and 0.52 p.p.m., respectively[2], for the β-D-*ribo* and α-L-*lyxo* isomers in the uracil series). Finally, the signals for C-1′, C-2′, and C-5′ in **8a** occurred at 90.63 (*cf. ribo* U analogue, 90.85; *lyxo* U, 89.11 p.p.m.[2]), 72.22 (*cf. ribo* U, 72.89; *lyxo* U, 74.44 p.p.m.[2]), and 62.67 p.p.m. (*cf. ribo* U, 59.62; *lyxo* U, 56.92 p.p.m.[2]). Similarly, the signals for H-1′, H-3′, and H-5′ for **8a** occurred at δ 6.74 ($J_{1',2'}$ 5 Hz) [*cf. ribo* U analogue, δ 6.77 ($J_{1',2'}$ 3.5 Hz); *lyxo* U, 7.10 ($J_{1',2'}$ 7 Hz)[2]], 5.19 ($J_{2',3'}$ 6 Hz) [*cf. ribo* U, δ 5.05 ($J_{2',3'}$ 8 Hz); *lyxo* U, 4.74 ($J_{2',3'}$ 4 Hz)[2]], and 4.06, 4.26 (J_{gem} 11 Hz) [*cf. ribo* U, δ 4.08, 4.25 (*J* 11 Hz); *lyxo* U, 4.18, 4.58 (*J* 12 Hz)[2]]. All of the above data are in much closer agreement with the proposed β-D-*ribo* rather than the epimeric α-L-*lyxo* configuration. It should be noted, however, that the signal for C-3′ of **8a** at 74.71 p.p.m. is closer to that (74.44 p.p.m.) of 1-(4-methoxy-α-L-lyxofuranosyl)uracil than to that (70.36 p.p.m.) of 4′-methoxyuridine, whereas the signal for H-2′ at δ 5.43 is also more akin to that (δ 5.04) of the *lyxo* U analogue than that (δ 4.85) of its *ribo* counterpart. These exceptions are, however, far outweighed by the other comparisons listed above that support the β-D-ribofuranosyl assignments.

In view of the modest antiviral activities of certain 5′-amino-5′-deoxynucleosides[13], it was of interest to prepare 5′-amino-5′-deoxy-4′-methoxyadenosine (**11**). Reaction of **6** with sodium azide in dimethyl sulfoxide at 110° for 24 h gave (t.l.c.) a fairly clean product, which, without purification, was debenzoylated with methanolic ammonia to give crystalline 5′-azido-5′-deoxy-4′-methoxyadenosine (**10**, 77%). Hydrogenation of **10** gave **11**, which showed the expected 2.5-p.p.m. upfield-shift



of the signals for H-5',5' relative to those for **10**. An acceptable elemental analysis for free **11** could not be obtained, and it was characterised as its crystalline 5'-*N*-dinitrophenyl derivative.

The 4'-methoxy analogues (**13** and **15**) of the nucleoside antibiotic nucleocidin[3,14] and of the cardiovascular agent ethyl adenosine-5'-carboxylate[15] were also synthesised *via* the very acid-labile 2',3'-*O*-ethoxymethylidene intermediates[16]. Treatment of **8a** with ethyl orthoformate and *p*-toluenesulfonic acid in *N*,*N*-dimethylformamide readily gave 2',3'-*O*-ethoxymethylidene-4'-methoxyadenosine (**12a**). Chromatography on silica gel gave the pure *exo*-H isomer (**12a**, 57%). In addition, a 23% yield of the *endo*-H isomer was also obtained. The configurations of the orthoester functionality were assigned by the downfield position (δ 6.18) of the H atom in the *endo* isomer relative to that in its *exo* counterpart (δ 6.07), on the assumption that the rules developed for benzylidene derivatives[17] can be extrapolated to the ethoxymethylidene case[16]. The 5'-acetate (**12b**) of **12a** showed the expected 0.4-p.p.m. downfield-shift of the signals for H-5',5'. The 2',3'-*O*-(1-methoxyethylidene) analogue of **12a** was also prepared, but only in modest yield (19%).

The 4'-methoxy analogue of nucleocidin (**13**) was synthesised as follows. Treatment of **12a** with hexabutyldistannoxane in benzene gave the 5'-tributylstannyl ether, which was not purified but directly converted into the 5'-*O*-sulfamoyl derivative by reaction with sulfamoyl chloride. This method was previously shown to be superior to direct, base-catalysed sulfamoylation[18] during synthesis of nucleocidin[3]. The 2',3'-orthoester was then cleaved by sequential treatment with 1% formic acid and methanolic ammonia. Chromatography of the product gave 4'-methoxy-5'-*O*-sulfamoyladenosine (**13**, 60%).

For the preparation of ethyl 4'-methoxyadenosine-5'-carboxylate (**15**), HO-5' of **12a** was oxidised with alkaline potassium permanganate[19]. The silver salt of the resulting 5'-carboxylic acid **14a** was treated with ethyl iodide to generate the ethyl ester **14b** (30% yield from **12a**). Treatment with 0.5% formic acid at room temperature then removed the ethoxymethylidene group, and the resulting ethyl 4'-methoxyadenosine-5'-carboxylate (**15**) was isolated by chromatography.

In collaboration with Shionogi Research Laboratories (Osaka, Japan), compounds **8a**, **10**, **11**, and **13** were found to be essentially inactive *in vitro* against a spectrum of bacteria, fungi, and viruses, and *in vivo* against L-1210 leukemia and *Ehrlich ascites* carcinoma in mice. Also, **8a**, **10**, and **11** were non-cytotoxic towards He La cells in culture, but the nucleocidin analogue **13** was highly cytotoxic and exhibited an ED_{50} value of 0.15 μg/mL. In view of the pronounced antimicrobial activity of nucleocidin[3,20] and of 5'-*O*-sulfamoyladenosine[21], the lack of such activities by **13** in the presence of its rather potent cytotoxicity towards mammalian cells is surprising. Because of this cytotoxicity, the antiviral test of **13** was difficult to assess, but appeared to be negative.

Since adenosine and various derivatives are potent inhibitors of adenosine 5'-diphosphate and collagen-induced, platelet aggregation[22], 4'-methoxyadenosine was tested for this activity. Using a turbidometric method[23], it was found that, with

4.4×10^{-5}M adenosine 5′-diphosphate, 50% inhibition of the aggregation of platelet-rich plasma was achieved using either adenosine or 4′-methoxyadenosine (**8a**) at $\sim 10^{-5}$M. At lower concentrations (5×10^{-6}M) of inhibitor, adenosine appeared to be somewhat more active than **8a**, whereas, at higher concentrations (10^{-4}M), **8a** was considerably more active. Adenosine and **8a** each showed 85–90% inhibition of collagen-induced aggregation at 3.7×10^{-4}M.

In view of the established cardiovascular effects of ethyl adenosine-5′-carboxylate and related derivatives[15], we have examined the actions of **10** and **15** upon i.v.-administration to dogs. Neither **10** (50–1000 μg/kg) nor **15** (10–100 μg/kg) led to any alteration of coronary blood-flow or other cardiovascular parameters.

Thus, the introduction of a 4′-methoxyl group into the adenosine nucleus leads to rather varied modifications of biological responses. Incorporation of this functionality into other types of nucleosides will be reported elsewhere.

EXPERIMENTAL

General methods. — T.l.c. was performed on silica gel HF (Analtech Corp.) and preparative t.l.c. on 0.75-mm layers of silica gel GF (Merck). Merck silica gel (0.05–0.22 mm) was used for column chromatography. ^{1}H-N.m.r. spectra (Table I) were recorded with a Varian HA-100 instrument and ^{13}C-n.m.r. spectra with a Bruker-90 spectrometer operating at 22.63 MHz. Both are recorded in p.p.m. downfield of an internal standard of Me_4Si. Melting points were obtained on a hot-stage microscope and are corrected.

N^6-*Benzoyl-2′,3′-O-carbonyl-5′-deoxy-5′-iodoadenosine* (**2**). — A 12.5% solution of phosgene in benzene (1.2 mL, 1.5 mmol) was stirred with a solution of **1** (481 mg, 1 mmol) in pyridine (10 mL) at −35° for 30 min and then concentrated, and the residue was partitioned between chloroform and water. The organic phase was dried ($MgSO_4$) and concentrated, and the foamy residue was chromatographed on a column of silica gel (45 g) with chloroform–acetone (7:3), to give **2** (351 mg, 69%), m.p. 210–215° (dec.) (from ethanol), $[\alpha]_D^{25}$ −40.5° (*c* 1, chloroform), λ_{max}^{MeOH} 279 nm (ε 21,800).

Anal. Calc. for $C_{18}H_{14}IN_5O_5$ (507.23): C, 42.62; H, 2.78; N, 13.81. Found: C, 42.85; H, 2.79; N, 13.66.

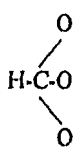
N^6-*Benzoyl-9-(2,3-O-carbonyl-5-deoxy-β-*D-erythro-*pent-4-enofuranosyl)adenine* (**3**). — 1,5-Diazabicyclo[4.3.0]non-5-ene (90 mg, 0.75 mmol) was added to a solution of **2** (253 mg, 0.5 mmol) in pyridine (5 mL), and the mixture was kept at 20° for 3 h and then concentrated. Toluene (4 × 5 mL) was distilled from the residue, which was then eluted from a column of silica gel (30 g) with chloroform–acetone (7:3), to give **3** (147 mg, 77%), m.p. 217–218° (from ethanol), $[\alpha]_D^{25}$ +143° (*c* 1.7, chloroform), λ_{max}^{MeOH} 279 nm (ε 20,900).

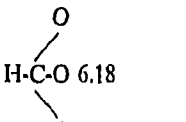
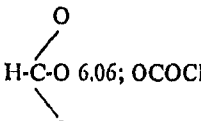
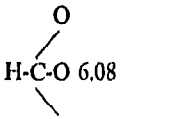
Anal. Calc. for $C_{18}H_{13}N_5O_5$ (379.33): C, 56.99; H, 3.45; N, 18.46. Found: C, 56.85; H, 3.48; N, 18.34.

N^6,N^6-*Dibenzoyl-9-(2,3-O-carbonyl-5-deoxy-β-*D-erythro-*pent-4-enofuranosyl)-*

TABLE I

^{1}H-N.M.R. DATA

Compound (solvent)[a]	*H-1'*	*H-2'* ($J_{1',2'}$)	*H-3'* ($J_{2',3'}$)	*H-5'a* ($J_{4',5'a}$)	*H-5'b* ($J_{4',5'b}$)	($J_{5'a,5'b}$)	*OMe*	*H-2*	*H-8*	*Others*
2 (c)	6.35	6.09 (1.5)	5.64 (7.0)	3.29 (9.0)	3.15 (6.0)	(11.0)	—	8.17	8.72	H-4' 4.74; $J_{3',4'}$ 3.0 Hz
4 (c)	6.47	6.04 (0.0)	5.87 (7.0)	4.81[e]	4.68[e]	(3.0)	—	8.15	8.58	
5 (c)	6.24	5.61 (2.0)	5.46 (8.0)	3.53	3.37	(12.0)	3.41	8.16	8.61	
6 (c)	6.38	6.09 (3.0)	6.24 (7.0)	3.74	3.60	(11.0)	3.51	8.31	8.70	
8a (p)	6.74	5.35 (5.0)	5.19 (6.0)	4.26	4.06	(11.0)	3.61	8.57	8.63	
8b (p)	6.68	5.38 (5.0)	5.16 (6.0)	4.27	4.09	(12.0)	3.53	8.52	8.62	
9a (p)	6.73	5.43 (4.0)	5.17 (6.0)	3.98	3.82	(11.0)	3.53	8.67	8.90	
9b (p)	6.66	5.59 (1.5)	5.50 (6.0)	3.80	—	—	3.43	8.49	8.64	$C(CH_3)_2$ 1.40 and 1.71
10 (p)	6.66	5.29 (3.0)	5.18 (6.5)	5.78	—	—	3.53	8.52	8.62	
11 (p)	6.68	5.29 (3.0)	5.18 (6.5)	3.25	—	—	3.49	8.60	8.62	
12a (c)	6.40	5.31 (5.0)	5.15 (7.0)	4.02	3.67	(11.0)	3.50	7.86	8.28	 6.07

12a (*endo*-H) (c)	6.03	5.21 (3.5)	5.43 (6.0)	4.02	3.76	(11.5)	3.46	7.84	8.26	 H-C-O 6.18
12b (c)	6.31	5.71 (4.0)	5.04 (7.5)	4.38	—	—	3.44	7.86	8.31	 H-C-O 6.06; $OCOCH_3$ 2.07
(c)[b]	6.02	5.26 (4.0)	5.42 (7.0)	4.09	3.73	(11.5)	3.50	7.86	8.30	CH_3-C-OCH_3 3.27; CH_3O-C-CH_3 1.78
13 (d)	6.10	4.79 (5.0)	4.46 (5.5)	4.19	—	—	3.39	8.15	8.33	
14b (c)	6.43	5.53 (2.5)	5.40 (7.0)	—	—	—	3.46	7.96	8.26	 H-C-O 6.08
15 (p)	6.90	5.72[d]	5.72[d]	—	—	—	3.58	8.61	8.74	CH_3 1.10; CH_2 4.20, *J* 7 Hz

[a]Solvent: c, $CDCl_3$; p, pyridine-d_5, d, $(CD_3)_2SO$. [b]4'-Methoxy-2',3'-*O*-(1-methoxyethylidene)adenosine. [c]$J_{3',5'a} = J_{3',5'b} = 1$ Hz. [d]Virtual coupling between H-1', H-2', and H-3'.

adenine (**4**). — A solution of **1** (2.4 g, 5 mmol) and 1,5-diazabicyclo[4.3.0]non-5-ene (1.86 mL, 15 mmol) in pyridine (150 mL) was stirred in the dark for 24 h at room temperature and then at 37° for 6 h. The solution was cooled to −40°, stirred with a 12.5% solution of phosgene in benzene (8 mL, 10 mmol) for 18 h at room temperature, and then concentrated *in vacuo*. A chloroform solution of the residue was washed with water, dried ($MgSO_4$), and concentrated. Pyridine and xylene were evaporated three times from the syrupy residue, which was then treated with benzoyl chloride (2.8 mL, 25 mmol) in pyridine (150 mL) in the dark for 48 h at room temperature. After evaporation of the solvent *in vacuo*, a chloroform solution of the residue was washed with water, dried ($MgSO_4$), and concentrated, and the residue was chromatographed on a column of silica gel with chloroform–acetone (9:1), to give **4** (1.3 g, 54%). An analytical sample from ethanol–hexane had m.p. 214.5–215.5°, $[\alpha]_D^{25}$ +86.5° (*c* 0.99, chloroform), λ_{max}^{MeOH} 272 nm (ε 19,200) and 251 (24,900).

Anal. Calc. for $C_{25}H_{17}N_5O_6$ (483.44): C, 62.11; H, 3.55; N, 14.49. Found: C, 62.16; H, 3.46; N, 14.72.

N^6,N^6-*Dibenzoyl-2',3'-O-carbonyl-5'-deoxy-5'-iodo-4'-methoxyadenosine* (**5**). — A solution of iodine (508 mg, 2 mmol) in methanol (60 mL) was added with vigorous stirring in the dark to a solution of **4** (242 mg, 0.5 mmol) in methanol (20 mL) in the presence of lead carbonate (550 mg, 2 mmol). After 1 h at room temperature, the mixture was filtered and concentrated, and a solution of the residue in chloroform was washed with aqueous 10% sodium thiosulfate and water, dried ($MgSO_4$), and concentrated. The residue was chromatographed on a column of silica gel (30 g) with ethyl acetate–chloroform (4:1), to give **5** (301 mg, 94%), m.p. 141.5–143.5° (from ethanol–hexane), $[\alpha]_D^{25}$ −73° (*c* 0.5, chloroform), λ_{max}^{MeOH} 272 nm (ε 19,300) and 250 (25,200).

Anal. Calc. for $C_{26}H_{20}IN_5O_7$ (641.38): C, 48.69; H, 3.14; N, 10.92. Found: C, 48.61; H, 3.13; N, 10.66.

N^6,N^6,$O^{2'}$,$O^{3'}$-*Tetrabenzoyl-5'-deoxy-5'-iodo-4'-methoxyadenosine* (**6**). — A solution of iodine (9.6 g, 37.8 mmol) in methanol (375 mL) was added during 4 h at room temperature to a stirred solution of **4** (6.99 g, 14.5 mmol) in methanol (150 mL) in the presence of finely powdered lead carbonate (16.5 g, 60 mmol). After a further 12 h, the mixture was worked up as described for **5**, and a methanol solution (600 mL) of the crude product (without chromatography) was stirred with 0.2M barium hydroxide (75 mL, 15 mmol). After 15 min, the mixture was neutralised with carbon dioxide and filtered through Celite. The solids were thoroughly washed with hot methanol, and the combined filtrates were concentrated *in vacuo*. Pyridine was evaporated from the residue and a solution of the final residue in pyridine (150 mL) at 0° was then gradually treated with benzoyl chloride (16.5 mL, 150 mmol). After 48 h at room temperature, the mixture was cooled in ice, and methanol (30 mL) was gradually added. The solvents were then evaporated and toluene (200 mL) was evaporated twice from the residue, a solution of which in chloroform was washed with water, dried ($MgSO_4$), and concentrated to dryness. The residue was chromatographed on a column of silica gel (200 g), using a gradient of ethyl acetate (0 to 5%)

in chloroform, to give **6** (10.9 g, 91.5%). Crystallisation from ethanol gave material with m.p. 114.5–116.5°, $[\alpha]_D^{25}$ −109° (*c* 1, chloroform), λ_{max}^{MeOH} 274 nm (ε 19,200) and 230 (42,800).

Anal. Calc. for $C_{39}H_{30}IN_5O_8$ (823.60): C, 56.88; H, 3.67; N, 8.50. Found: C, 57.04; H, 3.75; N, 8.48.

4′-Methoxyadenosine (**8a**). — A solution of **6** (8.24 g, 10 mmol) and lithium benzoate (12.8 g, 100 mmol) in dimethyl sulfoxide (550 mL) was heated at 115–120° for 70 h and then concentrated to dryness *in vacuo* at 80°. A solution of the residue in chloroform was washed twice with water, dried, and concentrated to a foam that was treated with saturated, methanolic ammonia at 37° for 18 h. The mixture was concentrated *in vacuo* and the residue was chromatographed on a column of silica gel (300 g) with chloroform–methanol (4:1), to give **8a** (2.43 g, 82%) as a white foam with $[\alpha]_D^{25}$ −80° (*c* 1, methanol), λ_{max}^{MeOH} 259 nm (ε 13,300). ^{13}C-N.m.r. (acetone-d_6–D_2O): 50.71 (OMe), 62.67 (C-5′), 72.23 (C-2′), 74.71 (C-3′), 90.63 (C-1′), 108.03 (C-4′), 120.39 (C-5), 141.32 (C-8), 149.87 (C-4), 153.67 (C-2), and 157.08 p.p.m. (C-6).

Anal. Calc. for $C_{11}H_{15}N_5O_5$ (297.27): C, 44.44; H, 5.09; N, 23.56. Found: C, 44.63; H, 5.26; N, 23.30.

5′-Chloro-5′-deoxy-4′-methoxyadenosine (**8b**). — If the benzoylation leading to **6** was not maintained at 0°, **8a** was contaminated by some of the 5′-chloro analogue, **8b**. A sample of **8b** was obtained by preparative t.l.c., using multiple developments with chloroform–methanol (9:1), and then crystallised from methanol; it had m.p. 209–210°, λ_{max}^{MeOH} 259 nm (ε 13,000).

Anal. Calc. for $C_{11}H_{14}ClN_5O_4$ (315.17): C, 41.85; H, 4.47; N, 22.18. Found: C, 41.70; H, 4.65; N, 22.35.

5′-Deoxy-5′-iodo-4′-methoxyadenosine (**9a**). — Aqueous 0.2M barium hydroxide (55 mL, 11 mmol) was added to a stirred solution of **5** (6.15 g, 9.6 mmol) in methanol (400 mL). After 5 min at room temperature, the solution was neutralised with carbon dioxide and filtered through Celite. The solids were washed with hot methanol, and the combined filtrates were concentrated, to give crude **9a** (5.3 g) containing some of the N^6-benzoyl derivative. A portion was treated with charcoal and crystallised from ethanol, to give 9a, m.p. 180–182°, $[\alpha]_D^{25}$ −63° (*c* 1, pyridine), λ_{max}^{MeOH} 259 nm (ε 15,800). ^{13}C-N.m.r. (acetone-d_6–D_2O): 5.27 (C-5′), 49.61 (OMe), 73.80 and 74.06 (C-2′,3′), 89.99 (C-1′), 105.07 (C-4′), 141.42 (C-8), and 153.77 p.p.m. (C-2).

Anal. Calc. for $C_{11}H_{14}IN_5O_4$ (407.16): C, 32.45; H, 3.46; N, 17.20. Found: C, 32.41; H, 3.59; N, 17.38.

5′-Deoxy-5′-iodo-2′,3′-O-isopropylidene-4′-methoxyadenosine (**9b**). — A solution of **5** (461 mg, 1 mmol) in half-saturated, methanolic ammonia (25 mL) was kept at 37° for 16 h and then concentrated to dryness. The resulting, crude **9a** was treated for 30 min at room temperature with acetone (11 mL) and 2,2-dimethoxypropane (1.1 mL) containing anhydrous *p*-toluenesulfonic acid (1.8 g) and then added to cold, saturated, aqueous sodium hydrogencarbonate (20 mL). This mixture was extracted into chloroform, the extract was washed with water, dried ($MgSO_4$), and concentrated, and the residue was chromatographed on a column of silica gel

(20 g) with chloroform–methanol (9:1), to give **9b** (256 mg, 57%), m.p. 201.5–202.5° (from ethanol), $[\alpha]_D^{25}$ −78° (*c* 1, pyridine), λ_{max}^{MeOH} 259 nm (ε 15,600). ^{13}C-N.m.r. (acetone-d_6, MeOH-d_4): 6.26 (C-5′), 26.18, 26.51 (C*Me*$_2$), 49.78 (MeO), 85.11, 85.35 (C-2′,3′), 88.83 (C-1′), 106.62 (C-4′), 141.31 (*C*Me$_2$), 141.31 (C-8), and 154.20 p.p.m. (C-2).

Anal. Calc. for $C_{14}H_{18}IN_5O_4$ (447.23): C, 37.60; H, 4.06; N, 15.66. Found: C, 37.56; H, 4.12; N, 15.54.

5′-Azido-5′-deoxy-4′-methoxyadenosine (**10**). — A solution of **6** (644 mg, 0.78 mmol) and sodium azide (644 mg) in dimethyl sulfoxide (50 mL) was heated in the dark at 110° for 24 h and then concentrated *in vacuo* at 80°. The residue was treated with saturated, methanolic ammonia at 100° for 1.5 h in a sealed tube and then concentrated to dryness, and the residue was partitioned between water and ethyl acetate. The aqueous phase was concentrated *in vacuo* and the residue was chromatographed on a column of silica gel (60 g) with chloroform–methanol (9:1), to give **10** (193 mg, 77%), m.p. 217.5–219.5° (from ethanol).

Anal. Calc. for $C_{11}H_{14}N_8O_4$ (322.28): C, 40.99; H, 4.38; N, 34.77. Found: C, 40.83; H, 4.20; N, 34.67.

5′-Amino-5′-deoxy-4′-methoxyadenosine (**11**). — A solution of **10** (101 mg, 0.3 mmol) in ethanol (50 mL) was stirred in an atmosphere of hydrogen in the presence of 10% Pd/C for 1 h and then filtered through Celite. Concentration of the filtrate left **11** (100 mg), for which an acceptable elemental analysis could not be obtained. It was therefore treated with a small excess of 1-fluoro-2,4-dinitrobenzene and sodium hydrogencarbonate in ethanol for 5 min. A solution of the yellow precipitate in chloroform was filtered and concentrated, and the residue was crystallised from ethanol, to give the $N^{5'}$-dinitrophenyl derivative of **11** as a hydrate, m.p. 151° (dec.), $[\alpha]_D^{25}$ −45° (*c* 1, pyridine), λ_{max}^{MeOH} 348 nm (ε 16,200) and 269 (22,200).

Anal. Calc. for $C_{17}H_{18}N_8O_8 \cdot H_2O$ (480.39): C, 42.50; H, 4.20; N, 23.32. Found: C, 42.75; H, 4.28; N, 23.37.

2′,3′-O-Ethoxymethylidene-4′-methoxyadenosine (**12a**). — A mixture of **8a** (3.2 g, 10.8 mmol), anhydrous *p*-toluenesulfonic acid (2.38 g, 11.9 mmol), ethyl orthoformate (129 mL), and *N*,*N*-dimethylformamide (60 mL) was stirred at room temperature for 30 min, made alkaline with concentrated ammonium hydroxide, and concentrated to dryness. The residue was partitioned between chloroform and water, the organic phase was concentrated, and the residue was treated with aqueous 0.5% formic acid and ethanol (1:1, 230 mL) for 40 min. The solution was made alkaline with ammonium hydroxide and concentrated, and the residue was chromatographed on a column of silica gel (250 g) with chloroform–methanol (19:1), to give, first, the *exo*-H isomer **12a** (2.2 g, 57%), m.p. 214.5–216° (from ethanol), $[\alpha]_D^{25}$ −117° (*c* 0.5, chloroform), λ_{max}^{MeOH} 259 nm (ε 14,900).

Anal. Calc. for $C_{14}H_{19}N_5O_6$ (353.34): C, 47.59; H, 5.42; N, 19.82. Found: C, 47.67; H, 5.45; N, 20.08.

Further elution gave the *endo*-H isomer of **12a** (0.89 g, 23%) as a homogeneous foam (t.l.c., n.m.r.).

Treatment of **12a** with acetic anhydride and pyridine for 30 min at room temperature gave the 5′-acetate **12b**, m.p. 136.5–137.5°, $[\alpha]_D^{25}$ −72° (*c* 0.5, chloroform), λ_{max}^{MeOH} 258 nm (ε 13,400).

Anal. Calc. for $C_{16}H_{21}N_5O_7$ (395.38): C, 48.60; H, 5.35; N, 17.71. Found: C, 48.22; H, 5.22; N, 17.81.

4′-Methoxy-2′,3′-O-(1-methoxyethylidene)adenosine. — A solution of **8a** (160 mg, 0.64 mmol), *p*-toluenesulfonic acid (180 mg, 0.96 mmol), methyl orthoacetate (1 mL), and *N*,*N*-dimethylformamide (0.5 mL) was stirred for 10 min, neutralised with conc. ammonium hydroxide, filtered, and concentrated. The residue was chromatographed on a column of silica gel (45 g) with chloroform–methanol (19:1), to give a single diastereomer (42 mg, 19%) of the title compound with m.p. 183.5–184.5° (from ethanol containing a trace of ammonium hydroxide), $[\alpha]_D^{25}$ −59° (*c* 0.5, chloroform), λ_{max}^{MeOH} 259 nm (ε 15,000).

Anal. Calc. for $C_{14}H_{19}N_5O_6$ (353.34): C, 47.59; H, 5.42; N, 19.82. Found: C, 47.59; H, 5.55; N, 19.86.

4′-Methoxy-5′-O-sulfamoyladenosine (**13**). — A solution of **12a** (706 mg, 2 mmol) and hexabutyldistannoxane (2.02 mL, 4 mmol) in benzene (75 mL) was heated under reflux with azeotropic removal of water for 1 h and then cooled to room temperature. A solution of sulfamoyl chloride (650 mg, 5.6 mmol) in 1,4-dioxane (2.5 mL) was added dropwise during 1 h followed by saturated, methanolic ammonia (5 mL), and the mixture was concentrated to dryness. The residue was triturated with hexane (40 mL), and the insoluble material was collected by centrifugation, dried, and dissolved in aqueous 1% formic acid (80 mL). After 24 h at room temperature, the solution was made basic with ammonium hydroxide and concentrated to dryness. The residue was washed with ether, and a solution in methanol was mixed with silica gel and concentrated to dryness. The residue was applied to the top of a column of silica gel (100 g) and eluted with a gradient of methanol (5→20%) in chloroform, to give **13** (456 mg, 60%) as an amorphous, white powder. An analytical sample, obtained by preparative t.l.c. with chloroform–methanol (4:1) followed by crystallisation from ethanol, had m.p. 192–193.5° (dec.), $[\alpha]_D^{25}$ −79° (*c* 0.5, pyridine), λ_{max}^{MeOH} 258 nm (ε 14,800).

Anal. Calc. for $C_{11}H_{16}N_6O_7S$ (376.30): C, 35.11; H, 4.29; N, 22.33. Found: C, 35.28; H, 4.28; N, 22.39.

Ethyl 2′,3′-O-ethoxymethylidene-4′-methoxyadenosine-5′-carboxylate (**14b**). — A solution of potassium permanganate (540 mg, 3.4 mmol) in water (21 mL) was added dropwise during 1.5 h to a solution of **12a** (302 mg, 0.85 mmol) in 0.04M potassium hydroxide (63 mL) at room temperature. After stirring for 3 days, the solution was cooled to 0° and 30% hydrogen peroxide (1.6 mL) was added. The mixture was filtered, concentrated to ~10 mL, and neutralised with 4M nitric acid. 3M Ammonium hydroxide (1 mL) and aqueous silver nitrate (550 mg in 4 mL) were added, and the resulting precipitate was collected by centrifugation, washed with water, and dried *in vacuo* at 56° overnight in the dark. A suspension of the resulting, off-white silver salt of **14a** (480 mg) in ethanol (15 mL) and ethyl iodide was heated

under reflux for 6 h, filtered through Celite, and concentrated to dryness. Chromatography of the resulting oil on a column of silica gel (45 g) with chloroform–methanol (19:1) gave **14b** (101 mg, 30%), m.p. 182.5–183.5° (from ethanol), $[\alpha]_D^{25}$ −46° (*c* 0.5, chloroform), λ_{max}^{MeOH} 259 nm (ε 15,500).

Anal. Calc. for $C_{16}H_{21}N_5O_7$ (395.37): C, 48.60; H, 5.35; N, 17.72. Found: C, 48.63; H, 5.44; N, 17.93.

Ethyl 4'-methoxyadenosine-5'-carboxylate (**15**). — A solution of **14b** (274 mg, 0.69 mmol) in 0.5% formic acid (300 mL) was stirred at room temperature for 20 h and then concentrated to dryness. Ethanol (2 × 50 mL) was distilled from the residue, which was then chromatographed on a column of silica gel (80 g) with chloroform–methanol (19:1), to give **15** (236 mg, 100%). Crystallisation from ethanol gave an analytical sample with m.p. 180–181°, $[\alpha]_D^{25}$ −51° (*c* 0.5, pyridine), λ_{max}^{MeOH} 258 nm (ε 14,700).

Anal. Calc. for $C_{13}H_{17}N_5O_6$ (339.31): C, 46.01; H, 5.05; N, 20.64. Found: C, 45.75; H, 5.23; N, 20.56.

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