9-(β-D-Arabinofuranosyl)adenine 3′,5′-Cyclic Phosphate (1)

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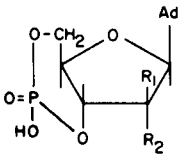
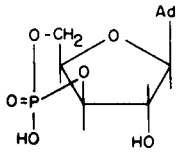
Sir:

The action of many hormones is mediated by the 3′,5′-cyclic phosphate (I) (2) of adenosine. Other adenine nucleosides such as the β-D-xylofuranoside and the β-D-arabinofuranoside have antitumor activity (3,4) probably as their 5′-phosphates. We are therefore interested in the biological properties of their cyclic phosphates. The xyloside gave a 3′,5′-cyclic phosphate (IV) (5); the arabinoside, a 2′,5′-cyclic phosphate (V) (5,6) on direct cyclization of their 5′-phosphates. In (IV) and (V) the phosphorylated secondary hydroxy group was on the *same* side of the plane of the furanose ring as adenine rather than the *opposite* side. In order to prepare a 3′,5′-cyclic phosphate of an adenine nucleoside more closely related to I, we have synthesized 9-(β-D-arabinofuranosyl)adenine 3′,5′-cyclic phosphate (II). It is the first example of a nucleoside cyclic phosphate from an unnatural sugar with the same phosphate ester stereochemistry as (I).

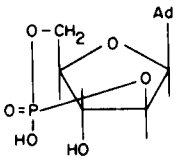
Let Ad = adenine and Q = $CH_2C_6H_5$



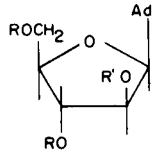
(I) R_1 = H, R_2 = OH
(II) R_1 = OH, R_2 = H
(III) R_1 = OQ, R_2 = H



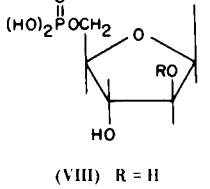
(IV)



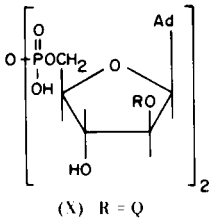
(V)



(VI) R = H, R′ = Q
(VII) R = R′ = H



(VIII) R = H
(IX) R = Q



(X) R = Q

Since the direct cyclization of (VIII) afforded (V), it was necessary to block the 2′-hydroxyl as in (IX) before attempting cyclization. To obtain (IX), 2-*O*-benzyl-3,5-di-*O*-*p*-nitrobenzoyl-α- -arabinofuranosyl chloride (7) and 6-benzamidopurine were condensed by Fletcher's procedure (8) in hot 1,2-dichlorethane for several days to afford 6-benzamido-9-(2-*O*-benzyl-3,5-di-*O*-*p*-nitrobenzoyl-β-D-arabinofuranosyl)-9*H*-purine (9). Deacylation in hot methanolic sodium methoxide gave (VI), whose β-configuration was established by CD and catalytic hydrogenolysis to (VII). Using the direct phosphorylation method of Yoshikawa, Kato and Takenishi (10), (VI) was treated with phosphoryl chloride in cold trimethyl phosphate to give (IX), easily isolated by precipitation from acidic solution.

Dicyclohexylcarbodi-imide (4-5 equivalents) in hot pyridine effected the cyclization of (IX) to (III) in high yields by the procedure of Smith *et al.* (11). Compound (III) was a monobasic acid different and distinguishable from the pyrophosphate (X) that was obtained under different conditions (12) from (IX). Hydrogenolysis of the soluble *N*-morpholino-*N*′,*N*″-dicyclohexylcarboxamidine salt of (III) at 1 atmosphere of hydrogen with palladium black in aqueous ethanol gave the salt of (II). Crystallization and acidification afforded the 3′,5′-cyclic phosphate (II). Like (V), (II) was more stable than the 5′-phosphate (VIII) in 1*N* hydrochloric acid at 50°.

The nmr spectrum of (II) was different from that of (V). In (V) and other compounds where the phosphorus atom can be in close proximity to the adenine, specific deshielding of the H-8 proton by the phosphorus atom (13,14) was shown by the downfield shift of the H-8 signal relative to that of H-2 [see tabulation of $\Delta\delta = (\delta H\text{-}8 - \delta H\text{-}2)$ below]. No specific deshielding of H-8 occurred in (I), (II), and (III) where the phosphorus atom is attached to a secondary hydroxyl on the opposite side of the furanose ring from adenine; this is reflected in the much smaller values of $\Delta\delta$ for (I), (II), and (III) than for the other compounds. This provided additional confirmation for the structure of (II).

Biological studies with (II) are in progress.

Nmr Data

Compound	$\Delta\delta$ (a), Hz	Compound	$\Delta\delta$ (a), Hz
I	6	V	33
II	11	VIII	33
III	8	IX	28
IV	19	X	24

(a) $\Delta\delta = \delta_{H-8} - \delta_{H-2}$ as measured in 2.5% sodium deuteroxide in deuterium oxide at 100 Hz with a Varian HA-100 instrument using TMS (external) as reference.

REFERENCES

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