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SYNTHESIS OF 9-β-D-ARABINOFURANOSYLADENINE-3',5'-CYCLIC PHOSPHATE FROM ADENOSINE-3',5'-CYCLIC PHOSPHATE

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Synthesis of 9-β-D-arabinofuranosyladenine from 8,2'-anhydro-8-oxy-9-β-D-arabinofuranosyladenine has been reported (1). We report that the same method can be applied to the synthesis of biologically active (2,3) 9-β-D-arabinofuranosyladenine-3',5'-cyclic phosphate (I).

8-Bromoadenosine-3',5'-cyclic phosphate (II) (100 mmoles) [obtained from the bromination of 3',5'-cyclic AMP by the method of Holmes and Robins (4,5)] was treated with p-toluene sulfonyl chloride (400 mmoles) in aqueous dioxane in the presence of sodium hydroxide (250 mmoles). After 4 hours (room temp.) the reaction mixture was poured over ice-water to obtain 8-bromo-2'-O-tosyladenosine-3',5'-cyclic phosphate (III) as a white precipitate (yield 94%). Compound III showed a strong band at $1179^{cm^{-1}}$ in its IR-spectrum indicating a tosyl group and its ultraviolet absorption (λ_{max}^{pH1} 264 mμ, λ_{max}^{pH11} 266 mμ) showed that only the sugar moiety of the cyclic phosphate had been tosylated. Compound III (40 mmoles) was refluxed with sodium acetate and acetic anhydride in acetic acid (6) for 3.75 hours at 125° to provide 6-N-acetyl-8-oxy-2'-O-tosyladenosine-3',5'-cyclic phosphate (IV) (yield 85%, λ_{max}^{pH1} 289 mμ, λ_{max}^{pH11} 268 and 308 mμ). Compound IV was deacetylated with methanolic ammonia (90 hour, room temp.) to obtain 8-oxy-2'-O-tosyladenosine-3',5'-cyclic phosphate (V) (yield 90%, λ_{max}^{pH1} 265 and 288.5 mμ, λ_{max}^{pH11} 283 and 273^{sh} mμ). Compound V (33.1 mmoles) was heated in a bomb with methanolic ammonia (200 ml) at 75° for 9 hours. The reaction products were evaporated and the residue was dissolved in aqueous ethanol and acidified (pH2) to obtain crystalline 8,2'-anhydro-8-oxy-9-β-D-arabinofuranosyladenine-3',5'-cyclic phosphate (VI) in 47% yield. Compound VI was characterized by elemental analysis ($C_{10}H_{10}N_5O_6P$ requires C, 36.71; H, 3.08; N, 21.40%. Found: C, 36.85; H, 3.13 and N, 21.22%), ultraviolet

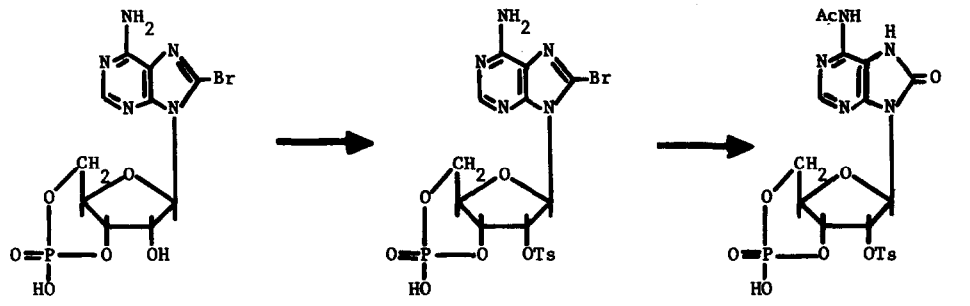
absorption properties (λ_{max}^{pH1} 259 and 286^{sh} mμ, λ_{max}^{pH11} 257 mμ) and PMR spectrum (the anomeric proton appeared as a doublet centered at δ6.5 indicating an arabinose configuration of the 2'-anhydro-linkage. The 2'-proton was a triplet located at δ5.95).

Compound VI (23.3 mmoles) was suspended in DMF and liquid H_2S in a bomb and maintained at 110° for 20 hours. The cooled product was filtered, washed with ethanol, ether and recrystallized from aqueous ethanol to provide 8-mercapto-9-β-D-arabinofuranosyladenine-3',5'-cyclic phosphate (VII) in 61.2% yield. Analysis: $C_{10}H_{12}N_5O_6PS.H_2O$ required C, 31.60; H, 3.72; N, 18.46%. Found: C, 31.44; H, 3.48 and N, 18.34%. Ultraviolet absorption (λ_{max}^{pH1} 244 and 308 mμ, λ_{max}^{pH11} 294 mμ) was characteristic of 8-mercaptoadenosine. PMR in D_2O showed the anomeric proton as a doublet centered at δ7.0.

Compound VII (8 mmoles) was desulfurized with Raney Nickel catalyst and crystallized from water (pH2) to obtain compound I in over 80% yield. Analysis: $C_{10}H_{12}N_5O_6P$ requires C, 36.48; H, 3.67; N, 21.09%. Found: C, 36.20; H, 3.52 and N, 21.27%. Ultraviolet absorption: λ_{max}^{pH1} 256 mμ (ε 15,200), λ_{max}^{pH11} 258 mμ (ε 15,400). Compound I in electrophoretic behaviour like other intermediates (compounds II-VII) moved like adenosine-3',5'-cyclic phosphate.

The PMR spectrum of I showed no significant shift of its 8-proton, relative to that of 2-proton as described by Lee, et al., (7) for the 2',5'-cyclic phosphate of 9-β-D-arabinofuranosyladenine confirming the retention of the 3',5'-cyclic phosphate structure throughout the synthesis. The anomeric proton was a doublet located at δ6.1.

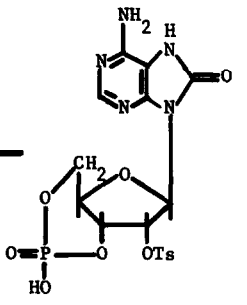
The synthesis of (I) is superior to that described in literature (7) for its simplicity and high yields and provides a variety of interesting analogs of adenosine-3',5'-cyclic phosphate.



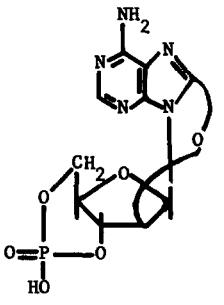
(II)

(III)

(IV)



(V)



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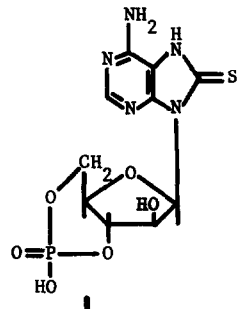

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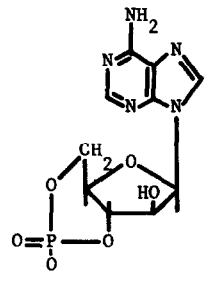

(I)

Ac = acetyl

Ts = p. toluene sulfonyl

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