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SYNTHESIS OF ADENINE 8,2'-CYCLONUCLEOSIDES USING DIPHENYL CARBONATE

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Synthesis of a number of purine 8-cyclonucleosides via arylsulfonyl intermediates was reported (1). Recently, Ogilvie and Slotin (2) showed that cyclic carbonate of 8-bromoadenosine could be cyclized to 8,2'-anhydro-8-mercapto-9-β-D-arabinofuranosyladenine (IIIa). However, they failed (3) to obtain 8,2'-O-cyclonucleoside (IIIb) from cyclocarbonate of 8-oxyadenosine (IIb). In this paper we describe a versatile method for the synthesis of 8,2'-cyclonucleosides having S-(IIIa) and O-anhydro bonds (IIIb) from 8-mercapto-(Ia) and 8-oxyadenosine (Ib) using diphenyl carbonate as cyclizing reagent.

8-Mercaptoadenosine (4) (Ia) (400 mg, 1.33 mmole) was heated at 150° for 30 min in DMF (1.5 ml) with diphenyl carbonate (5) (370 mg, 1.73 mmole) and sodium bicarbonate (15 mg). Resulting cyclonucleoside (IIIa) was easily obtained by precipitation in ether and recrystallization from methanol. Yield was 285 mg (79%). This sample (m.p. 238-240°; UV: $\lambda_{max}^{H^+}$ 278.5 nm, λ_{max}^{H2O} 277 nm, $\lambda_{max}^{OH^-}$ 278 nm; NMR (60 mHz, TMS internal standard): 8.01 ppm (S,H-2), 6.43 ppm (d,H-1'); PPC (6): Rf(A) 0.10, Rf(B) 0.56, Rf(C) 0.52) was completely identical with an authentic specimen of 8,2'-S-cycloadenosine (7). The present method is far more convenient than that described by Ogilvie (2) especially for large scale synthesis.

8-Oxyadenosine (7) (Ib) (283 mg, 1 mmole) was analogously treated in DMF (2 ml) with diphenyl carbonate (320 mg, 1.5 mmole) and sodium bicarbonate (6 mg). Heating of the mixture at 150-155° for 1 hr and precipitation as described above, followed by treatment with NH_3-methanol overnight, gave cyclonucleosides as white powder. Purification of this material by Dowex 1x2 (bicarbonate form) column chromatography gave 750 OD_{257} units of cyclonucleosides. Recrystallization from water gave two compounds, 8,2'-O-cyclonucleoside (IIIb) (yield 2.5%) and 8,5'-anhydro-8-oxy-9-β-D-ribofuranosyladenine (8) (IV) in a ratio of 7:1. Compound IIIb (UV: $\lambda_{max}^{H^+}$ 260.5 nm, 280 (sh), λ_{max}^{H2O} 258 nm, $\lambda_{max}^{OH^-}$ 259 nm; PPC: Rf(C) 0.46, Rf(D) 0.47, Rf(E) 0.15) and IV (UV: $\lambda_{max}^{H^+}$ 261 nm, λ_{max}^{H2O} 262, $\lambda_{max}^{OH^-}$ 261;

PPC: Rf(C) 0.44, Rf(D) 0.47, Rf(E) 0.17; Paper electrophoresis in borate buffer: R_{Ad} 1.0) were identical with authentic samples, respectively. Occurrence of IV may be explained by a migration of carbonate to 5'-position or from the dinucleoside 5',5'-carbonate as previously reported by Hampton (4).

Thus, it was confirmed that 8,2'-O- as well as -S-cyclonucleoside could be synthesized from 8-substituted adenosines by the cyclocarbonate method.

References

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6. PPC stands for paper partition chromatography and solvent used were as follows: A, sat. $(NH_4)_2SO_4$-IspOH-H_2O, 79:19:2; B, n-ButOH-AcOH-H_2O, 5:2:3; C, IspOH-conc. NH_3-H_2O, 7:1:2; D, H_2O adjusted to pH 10 with NH_3, E, n-ButOH-H_2O, 86:14.
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