

## Synthesis of 8,2'-Cyclopurinenucleosides (I)

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Received June 22, 1972

Cyclonucleosides are important analogues of natural nucleosides. They are characterized by having, in addition to the *N*-glycoside linkage, a covalent linkage either directly or *via* bridging atoms between the 2', 3', or 5' carbons of the sugar and a carbon or nitrogen atom (other than the nitrogen of the glycoside bond) of the purine or pyrimidine ring. Chemical conversion of cyclonucleosides has led to the synthesis of numerous modified nucleosides including arabinocytidine and cordycepin (2-4). Cyclonucleosides have even been detected as intermediates in proposed prebiotic syntheses (5-6) and have been used as intermediates in the chemical synthesis of nucleotides (7-9).

This report describes a general method for the synthesis of 8,2'-cyclopurinenucleosides. The thio- and aminocyclonucleosides of all the common purine nucleosides are described (Figure 1). While this report was in preparation the synthesis of one of the compounds described herein was reported by Ikehara using this same method (10).

The procedure (Figure 1) involves the conversion of an 8-thio- or 8-aminopurinenucleoside (I) into the 8,2'-thio or 8,2'-aminocyclonucleoside (II) using diphenyl carbonate in dimethylformamide. The reaction undoubtedly involves conversion of I to the 2',3'-cyclic carbonate derivative with subsequent displacement of the carbonate by the 8-thio or 8-amino group (11).

Using this method, we have obtained the 8,2'-thio and 8,2'-aminocyclonucleosides of adenosine, guanosine, and inosine (Table I). Except for the adenosine derivatives, the yields for the 8,2'-thiocyclonucleosides were much higher than for the 8,2'-aminocyclonucleosides. Ikehara reported (10) the synthesis of 8,2'-*O*-cycloadenosine from 8-oxyadenosine in 2.5% yield. We have not been able to obtain any 8,2'-*O*-cyclopurinenucleoside by this procedure (12).

The 8,2'-thioanhydronucleosides, IIa, IIc, and IIe were further characterized by Raney Nickel reduction to their respective 2'-deoxyribonucleosides, 2'-deoxyadenosine, 2'-deoxyguanosine, and 2'-deoxyinosine. The adenosine cyclonucleosides (IIa and IIb) were deaminated by adenosine deaminase (13) to yield respectively the inosine cyclonucleosides IIe and IIIf.

This report represents a convenient general procedure for the synthesis of 8,2'-cyclopurinenucleosides. The 8,2'-thio- and 8,2'-aminocyclonucleosides of all the common purine nucleosides have been prepared by this procedure.

## EXPERIMENTAL

Paper chromatography was carried out on Whatman 3MM paper by the descending technique. Thick-layer chromatography was carried out on glass plates (20 x 20 cm) coated with a 2mm

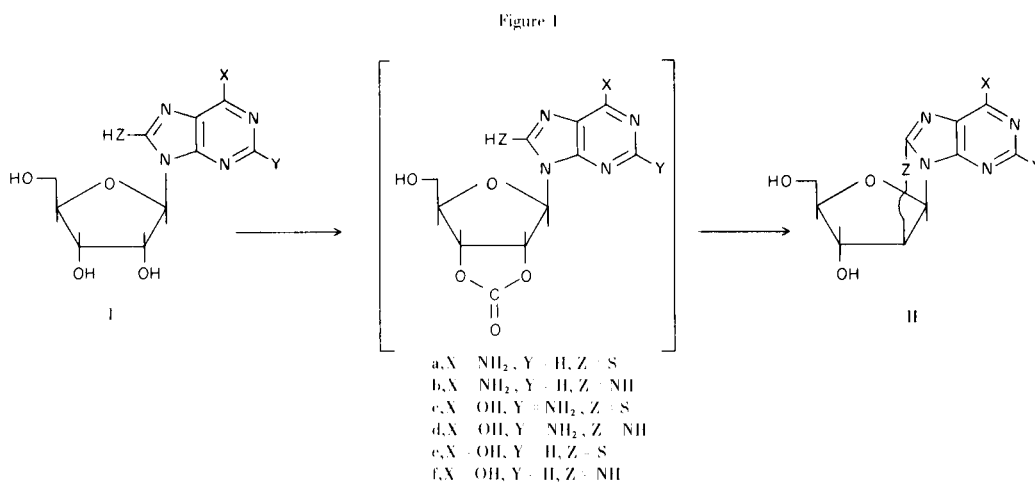


TABLE I

Compound	Yield %	M.p., °C	Properties of Cyclonucleosides				H <sub>2</sub> O λ max (ε) (d)	Reference
			Parent (a) Peak	R <sub>f</sub> EtOH (b)	(c) R <sub>f</sub> A	(c) R <sub>f</sub> B		
IIa	75	159-162	497	0.66	0.46	0.30	276.5 (17,000) 222 (19,100)	14
IIb	85	dec. >260	552	0.48	0.44	0.30	273 (15,100)	15
IIc	70	dec. >256	585	0.43	0.23	0.22	268 (16,630) sh 283 (13,590)	14
IId	20	dec. >203	640	0.27	0.16	0.11	258 (15,050), sh 290 (10,100)	
IIe	85	dec. >217	498	0.58	0.34	0.28	265 (10,080)	14
IIf	31	dec. >210	553	0.49	0.25	0.13	263 (12,800)	

(a) Silyl derivative, spectra recorded on a Hitachi RMU-6D mass spectrometer. (b) Thin layer chromatography on Eastman Chromagram Sheets 6060. (c) Paper chromatography on Whatman 3MM paper; solvent A, isopropyl alcohol - concentrated ammonium hydroxide-water (7:1:2); solvent B, 1-butanol-ethanol-water (4:1:5, organic phase used). (d) Spectra recorded on a Cary 14 spectrophotometer.

thick layer of silica gel DSF-5 (Mondray Chemicals Ltd.). Nucleosides and their derivatives were detected on paper chromatograms, thin- and thick-layer plates, using an ultraviolet source (Mineralite output 254 nm).

#### General Procedure for the Synthesis of Compounds IIa-f.

The chemistry is illustrated by the synthesis of 8,2'-thioanhydroguanosine (IIc). 8-Thioguanosine (Ic, 1 g., 3.2 mmoles), diphenyl carbonate (1.36 g., 6.4 mmoles) and sodium bicarbonate (10 mg.) were heated at 150° for 30 minutes in DMF-pyridine (20 ml., 9:1). The solution was cooled to room temperature and diluted with an equal volume of ammonium hydroxide and the solution was allowed to stand overnight. The solution was applied to Whatman 3MM paper developed in Solvent A, (see Table I), and the product (R<sub>f</sub><sup>A</sup>0.23) was eluted with water. On concentration of the aqueous solution, the product 8,2'-thioanhydroguanosine crystallized out, m.p. dec., >256° (655 mg., 70%, IIc, see Table I).

This procedure was used for all the conversions except that pyridine was used only in the guanosine conversions. All the other compounds were sufficiently soluble in DMF such that addition of pyridine was not necessary to effect solution.

All compounds obtained by this procedure were compared directly with authentic material prepared according to the literature (Table I). The previously unreported compounds IId and IIf were analyzed by high resolution mass spectrometry as follows:

*Anal.* Calcd. for IId + 5 TMS (C<sub>25</sub>H<sub>52</sub>O<sub>4</sub>N<sub>6</sub>Si<sub>5</sub>): 640.2896. Found: 640.2879.

*Anal.* Calcd. for IIf + 4 TMS (C<sub>22</sub>H<sub>43</sub>O<sub>4</sub>N<sub>5</sub>Si<sub>4</sub>): 553.2392. Found: 553.2406.

#### Acknowledgement.

We wish to acknowledge support from the National Research Council of Canada.

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