Filtration, drying, and crystallization afforded the colorless crystals. A comparison of the observed melting points with the corresponding literature values is given below.

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl azide (**1a**), mp 125.5–127.5° (lit.[12] mp 129°).

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl azide (**1b**), mp 95–96° (lit.[13] mp 96°).

Hepta-*O*-acetyl-β-D-maltosyl azide (**1c**), mp 94–96° (lit.[14] mp 91°).

Hepta-*O*-acetyl-β-D-cellobiosyl azide (**1d**), mp 180–181° (lit.[6] mp 182–182.5°).

Preparation of 1-Ethylthio-2-phenylacetylene (**2d**).—The compound **2d** was prepared by treating phenylbromoacetylene[15] with sodium hydride and ethyl mercaptan in dry DMF according to the general procedure of Brandsma, *et al.*[16] The product was characterized: bp 92–96° (1.5 mm); refractive index, $n^{25}D$ 1.6075 (lit.[16] $n^{25}D$ 1.6133); and nmr τ 2.73 (m, 5, Ar H), 7.33 (q, 2, SCH_2), 8.68 (t, 3, SCH_2CH_3).

Addition of Glycosyl Azides 1a–d to Ynamines 2a–b.—A solution of the glycosyl azide (4.6 mmol) and ynamine (7 mmol) in dry THF (10 ml) was heated under reflux. When tlc of the reaction mixture showed the disappearance of the spot due to the azide, the solvent and the excess ynamine were removed by evaporation under reduced pressure. The triazoles **2a**, **3c**, and **3d** were obtained by simple crystallization of the residue. On the other hand, triazoles **3b**, **3f**, and **3g** were obtained by dry column chromatography over silica gel using a fraction collector. A mixture of chloroform and acetone (9:1) was used for elution of the products from the column. The properties are recorded in Table II. The ir spectra were also consistent with the structures proposed.

Addition of 1a–d to Ethoxyacetylene (**2c**).—A solution of the glycosyl azide (4.6 mmol) and ethoxyacetylene (7 mmol) in dry THF (10 ml) was heated in a sealed tube at 60–70° for 12 days. After that the solvent and excess ethoxyacetylene were removed by evaporation *in vacuo*. Dry column chromatography of the resulting black residue, as described above, afforded the corresponding triazole (Table II).

Addition of 1d to 1-Ethylthio-2-phenylacetylene (**2d**).—A solution of **1d** (4.6 mmol) and **2d** (7 mmol) in THF (10 ml) was heated in a sealed tube at 130–140° for 5 days. Column chromatography, as described above, of the resulting black gum afforded the crystalline triazole **4c** in low yield (Table II). The reactions of **2d** with the azides **1a–c** failed to give any isolable products.

Registry No.—**3a**, 29751-37-9; **3b**, 29751-38-0; **3c**, 29751-39-1; **3d**, 29751-40-4; **3e**, 29751-41-5; **3f**, 29751-42-6; **3g**, 29751-43-7; **3h**, 29751-44-8; **3i**, 29751-45-9; **3j**, 29751-46-0; **3k**, 29751-47-1; **4a**, 29751-48-2; **4b**, 29751-49-3; **4c**, 29751-50-6.

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(12) A. Bertho, *Chem. Ber.*, **63**, 836 (1930).
(13) A. Bertho and J. Maier, *Justus Liebigs Ann. Chem.*, **498**, 50 (1932).
(14) A. Bertho, *ibid.*, **562**, 229 (1949).
(15) S. Miller, G. Ziegler, and R. Wieleseck, *Org. Syn.*, **45**, 86 (1965).
(16) L. Brandsma, H. E. Wijers, and C. Jonker, *Recl. Trav. Chim. Pays-Bas*, **83**, 208 (1964).

2′,3′-Carbonates of 8-Hydroxypurine Nucleosides

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The synthesis of modified nucleosides has recently attracted a great deal of attention. Much of this effort has been directed toward nucleosides possessing an oxygen,[1–4] a sulfur,[4–6] or a nitrogen[7–8] bridge between the purine or pyrimidine ring and the sugar ring, in addition to the *N*-glycoside bond. Very successful syntheses of pyrimidine 2,2′-*O*-anhydronucleosides, particularly 2,2′-*O*-anhydrouridines[2] have been developed. However, published methods for obtaining purine 8,2′-*O*-anhydronucleosides are much less efficient[4,9,10] involving many steps and very low yields.

It has been shown[11] that uridine 2′,3′-carbonate can be converted in high yield to *O*²,2′-anhydrouridine by heating in dimethylformamide (DMF) in the presence of a base catalyst such as sodium bicarbonate. It occurred to us that the 2′,3′-carbonates of 8-hydroxyadenosine (**1a**) and 8-hydroxyguanosine (**1b**) might closely resemble uridine 2′,3′-carbonate and might therefore be easily converted to the corresponding 8,2′-*O*-anhydronucleosides. This report discusses the synthesis of compounds **1a** and **1b** and attempts to convert them to the anhydronucleosides.

Syntheses of 8-Hydroxypurine Nucleosides.—Syntheses of both 8-hydroxyadenosine and 8-hydroxyguanosine have been reported.[9,12,13] Our approach (Scheme I) to the 8-hydroxynucleosides was similar to that used by Holmes and Robins[12] to obtain 8-hydroxadenosine. The purine nucleoside **2** was first acetylated[14] to **3** and then brominated[15,16] to yield the 8-bromotriacetyl derivative **4**. Treatment with sodium acetate in refluxing acetic anhydride yielded, after work-up, the 8-hydroxytetraacetyl derivative **5**. Hydrolysis of the acetyl groups gave the 8-hydroxy nucleosides **6**.

The scheme worked smoothly for adenosine resulting in an overall yield of 41% for the conversion to 8-hydroxyadenosine. With guanosine the conversion of **4** to **5** was 53%. However, a 28% yield of 8-bromotetraacetylguanosine (**7**) was obtained and this was converted in 55% yield to **5**. Thus a good yield of **5** could be obtained by recycling the recovered 8-bromotetraacetylguanosine.

Conversion of the 8-hydroxypurine nucleosides **6** to their 2′,3′-carbonates was readily accomplished[2] by heating the nucleoside in DMF at 150° for 30 min with diphenyl carbonate in the presence of a catalyst (sodium bicarbonate). For comparison we first subjected guanosine and adenosine to these conditions and obtained guanosine 2′,3′-carbonate (**8**) and the previously reported[2] adenosine 2′,3′-carbonate (**9**) in 77 and 75% yields, respectively. 8-Hydroxyadenosine 2′,3′-carbonate (**1a**) and 8-hydroxyguanosine 2′,3′-car-

(1) J. J. Fox and I. Wempen, *Tetrahedron Lett.*, 643 (1965).
(2) A. Hampton and A. W. Nichol, *Biochemistry*, **5**, 2076 (1966).
(3) D. Lipkin, C. Cori, and M. Sano, *Tetrahedron Lett.*, 5993 (1968).
(4) M. Ikehara, *Accounts Chem. Res.*, **2**, 47 (1969).
(5) E. J. Reist, A. Benitez, and L. Goodman, *J. Org. Chem.*, **29**, 554 (1964).
(6) I. Wempen and J. J. Fox, *ibid.*, **34**, 1020 (1969).
(7) I. L. Doerr, R. J. Cushley, and J. J. Fox, *ibid.*, **33**, 1592 (1968).
(8) I. L. Doerr and J. J. Fox, *J. Amer. Chem. Soc.*, **89**, 1760 (1967).
(9) M. Ikehara, H. Tada, and M. Kaneko, *Tetrahedron*, **24**, 3489 (1969); *J. Amer. Chem. Soc.*, **88**, 3165 (1966).
(10) M. Ikehara and K. Muneyama, *J. Org. Chem.*, **32**, 3039 (1967).
(11) K. K. Ogilvie and D. Iwacha, *Can. J. Chem.*, **47**, 495 (1969).
(12) R. E. Holmes and R. K. Robbins, *J. Amer. Chem. Soc.*, **87**, 1772 (1965).
(13) M. Ikehara, H. Tada, and Muneyama, *Chem. Pharm. Bull (Tokyo)*, **13**, 1140 (1965).
(14) M. Ikehara, *ibid.*, **8**, 367 (1968).
(15) R. E. Holmes and R. K. Robins, *J. Amer. Chem. Soc.*, **86**, 1242 (1964).
(16) J. F. Gerster, B. C. Hinshaw, R. K. Robins, and L. B. Townsend, *J. Org. Chem.*, **33**, 1070 (1968).

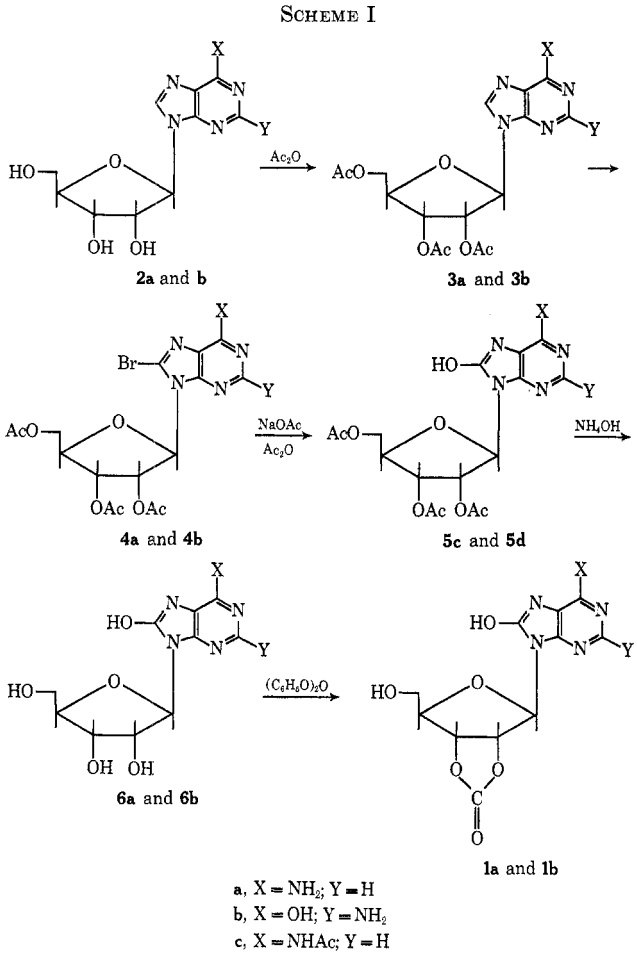
TABLE I

Compd no.	Yield, %	Mp, °C	Formula	Calcd, % C	H	N	Br	Found, % C	H	N	Br
1a	76	151 dec	$C_{11}H_{11}N_5O_6$	42.72	3.59			42.40	3.84		
1b	62	240 dec	$C_{11}H_{11}N_5O_7 \cdot 0.5H_2O$	39.53	3.62	20.95		39.92	3.54	20.08	
5c	80	110–112	$C_{18}H_{21}N_5O_9$	47.89	4.69	15.52		47.43	4.62	15.12	
5d	53	131–134	$C_{18}H_{21}N_5O_{10} \cdot 0.5H_2O$	45.38	4.65	14.70		45.23	4.44	14.62	
6a	94	210 dec	$C_{10}H_{13}N_5O_5$	42.40	4.63	24.73		42.31	4.68	24.64	
6b	83	180 dec	$C_{10}H_{13}N_5O_6 \cdot H_2O$	39.53	3.62	20.95		39.92	3.54	20.08	
7	28	101–104	$C_{18}H_{20}BrN_5O_9$	40.77	3.80	13.21	15.07	40.92	3.82	13.17	14.70
8	77	246 dec	$C_{11}H_{11}N_5O_6 \cdot 0.5H_2O$	41.51	3.80	22.01		42.25	4.31	21.66	

TABLE II

Compd no.	R_f (tlc) THF	EtOH	R_f (paper chromatography) A	B	C	D	Uv spectral data Solvent	λ_{max}, nm (ϵ)
1a	0.87	0.65		0.85	0.83	0.79	95% EtOH	266 (10,300), 257 (10,200)
1b	0.45	0.59		0.75	0.63	0.59	95% EtOH	247.5 (11,400), 295.5 (8,700)
5c	0.88	0.66		0.91	0.89	0.89	95% EtOH	288 (12,300), 219.5 (24,700)
5d	0.70	0.49	0.73				95% EtOH	303 (8,300), 265.5 (15,500)
6a	0.29	0.62	0.44	0.65	0.56	0.65	H_2O	270 (15,800), 260 (13,700) sh
6b		0.48	0.23	0.64	0.63	0.51	H_3O	294 (7,500), 247 (9,000).
7	0.69	0.54	0.78				95% EtOH	286 (13,300), 263 (7,450), 259 (17,380)
8	0.16	0.47		0.75			95% EtOH	273 (8,700), 254.5 (11,100)

SCHEME I



bonate (**1b**) were similarly obtained in 76 and 62% from **6a** and **6b**, respectively.

Several conditions were investigated in attempting to convert **1a** and **1b** to the 8,2′-*O*-anhydronucleosides. These included heating **1** in DMF at 150° for 30 min using sodium bicarbonate, sodium benzoate, or potassium *tert*-butoxide as catalysts. In another attempt potassium *tert*-butoxide in *tert*-butyl alcohol at 80° for 30 min was tried. In all cases only unreacted starting material and the 8-hydroxynucleosides **6** (resulting from hydrolysis of the cyclic carbonate) were obtained. No anhydronucleoside was detected in any of the reactions. It therefore appears that the 8-hydroxy function of purine nucleosides is not completely analogous to the 2-hydroxy function of uridine, at least with respect to interaction with the 2′ position. The incorporation of the 8-bromo- and 8-hydroxynucleosides into oligonucleotides will be reported at a later date.

Experimental Section

Methods and Materials.—Descending paper chromatography was carried out using Whatman 3MM paper. The solvent systems employed were solvent A, isopropyl alcohol–concentrated ammonium hydroxide–water (7:1:2); solvent B, 0.5 *M* ammonium acetate–ethanol (3:7, adjusted to pH 3.5 with acetic acid); solvent C, 5% ammonium bicarbonate in water; solvent D, ethanol–water (7:3). The solvents were prepared on a volume basis. Thin layer chromatography was carried out employing the ascending technique in closed jars which were not coated with absorbent paper. All thin layer chromatography was run on Eastman chromagram sheets 6060, silica gel with fluorescent indicator, on strips 10 cm × 2 cm. Thick layer chromatography was carried out on glass plates (20 cm × 20 cm) coated with a 2-mm-thick layer of silica gel DSF-5 (Mondray Chemicals Ltd.). Nucleosides and their derivatives were detected on paper chromatograms, thin and thick layer sheets, using an ultraviolet source (Mineralite, output ~254 mμ).

Infrared spectra were obtained on a Perkin-Elmer 337 recording instrument using KBr disks for sample preparation. Ultraviolet spectra were obtained on a Perkin-Elmer 450 instrument. Melting points were determined on a Fisher-Johns melting point apparatus and are reported uncorrected. Elemental analyses were performed by Micro-Tech laboratories, Skokie, Ill. Samples submitted to them were prepared by crystallization, lyophilization, or precipitation from tetrahydrofuran with hexane followed by heating in a drying apparatus over P_2O_5.

8-Hydroxy-*N*,2′,3′,5′-tetraacetylpurine Nucleosides (5c and 5d).—The 8-bromo-2′,3′,5′-tri-*O*-acetyl nucleoside[15,16] was refluxed in acetic anhydride for 1.5 hr with a tenfold excess of sodium acetate. The solution was cooled to room temperature, diluted with ethanol, and stored overnight at room temperature. The solvents were removed at reduced pressure and the residue was extracted with chloroform. The chloroform solution was filtered, dried over sodium sulfate, concentrated to a small volume, and applied to thick layer plates. The plates were developed in ether (adenosine) or ethyl acetate (guanosine) and

the product bands were eluted from the silica gel with tetrahydrofuran. In the case of **5d**, a 28% yield of 8-bromo-*N*-2′,3′,5′-tetraacetylguanosine (**7**) was also obtained. Compound **7** could be converted to **5d** in 55% yield using the above procedure. Results and properties are listed in Tables I and II.

8-Hydroxyadenosine (6a) and 8-Hydroxyguanosine (6b).—Compound **5** was dissolved in a mixture of pyridine and ammonium hydroxide (1:3, 20 ml/mmol) and the solution was stirred at room temperature for 3 to 7 days. The solvents were removed at reduced pressure and the product was crystallized from water (Tables I and II).

8-Hydroxypurine 2′,3′-Carbonates (1a and 1b).—Compound **6** (1 mmol), diphenyl carbonate (1.3 mmol), and sodium bicarbonate (6 mg) were heated in dimethylformamide (6 ml) at 150° for 30 min. The products were separated by thick layer chromatography using THF for the adenosine derivative and chloroform–ethanol (7:3) for the guanosine derivative (Tables I and II).

Purine 2′,3′-Carbonates (8 and 9).—Compounds **8** and **9** were prepared from guanosine and adenosine respectively in the same manner as **1** above. The products were isolated by thick layer chromatography using THF. Compound **8** crystallized from ethanol (Tables I and II).

Attempted Synthesis of 8,2′-*O*-Anhydronucleosides.—Several attempts were made to convert **1a** and **1b** to their respective 8,2′-*O*-anhydro derivatives. Both compounds were subjected to each of the following sets of conditions: (A) nucleoside, sodium bicarbonate, and dimethylformamide at 150° for 30 min; (B) nucleoside, sodium benzoate, and dimethylformamide at 150° for 30 min; (C) nucleoside, potassium *tert*-butoxide, and dimethylformamide at 150° for 30 min; (D) nucleoside, potassium *tert*-butoxide, and *tert*-butyl alcohol at 80° for 30 min. In all cases 10 mg of either **1a** or **1b** was used, the volume of solvent was 0.5 ml, and 1 mg of the base catalyst was used. Products were identified by paper chromatography. In all cases only unreacted starting material and **6** were detected. No other nucleoside material was detected in any of these experiments.

Registry No.—**1a**, 29851-53-4; **1b**, 29851-54-5; **5c**, 29851-55-6; **5d**, 29851-56-7; **6a**, 29851-57-8; **6b**, 29851-58-9; **7**, 29851-59-0; **8**, 29842-76-0.

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Synthesis of 19-Hydroxy-19a-methyl-5-ene Steroids *via* the 6β,19-Epoxy Derivatives

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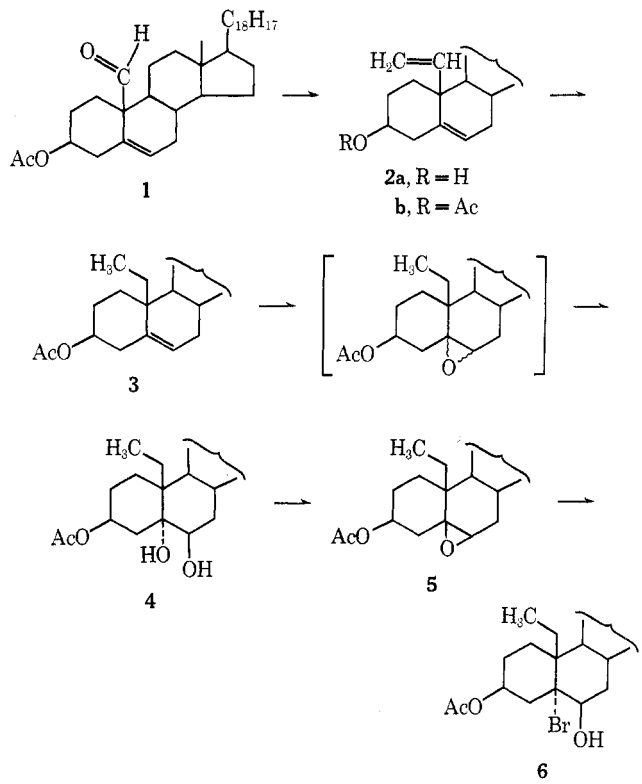
The reaction of methyllithium with steroidal 19-aldehydes has been reported by Caspi to give 19-hydroxy-19a-methyl-5-enes, and it has also been shown that only 19*R* alcohols are formed by this reaction.[2,3] The isomeric 19*S* alcohol was obtained by reduction of the 19a-methyl-19-oxo compound with lithium aluminium hydride.[4] We examined the reaction of lead tetraacetate with 3β-acetoxy-5α-bromo-6β-hydroxy-19a-methylcholestane to determine the stereochemistry of the formation of the ethers, 3β-acetoxy-5α-bromo-6β,19-epoxy-19a-methylcholestanes, and found that the resulting ethers could be reduced to the 19-hydroxy-19a-methyl-5-enes. This paper deals with the stereochemistry of the formation of the 6β,19-epoxides and the synthesis of 19-hydroxy-19a-methylcholest-5-enes from them.

The starting material **6** for the synthesis of the 6β,19-epoxides was prepared by the way summarized in Scheme I. The Wittig reaction on 3β-acetoxy-19-oxocholest-5-ene (**1**)[5] with methylene–triphenylphosphorane in ether gave the 19a-methylene derivative **2a** in good yield and its acetate **2b** was partially hydrogenated to the 19a-methyl-5-ene **3** with platinum catalyst in ethanol. The epoxidation of **3** with monoperphthalic acid gave a mixture of 5,6-epoxides, which consisted of 90% of α oxide and 10% of β isomer. The mixture of the epoxides was transformed into the 5α,6β-dihydroxy derivative **4** and then the diol was converted to the 5β,6β-epoxide **5** in the usual way.[6,7] Treatment of **5** with an equimolar amount of hydrobromic acid in acetic acid yielded the compound **6**.

SCHEME I



The 6β-hydroxy-19a-methyl compound **6** was treated with lead tetraacetate in cyclohexane in the presence of iodine, and the two main products, 45% of **7** and 20% of **8**, were obtained by column chromatography. Reduction of **7** and **8** with zinc in acetic acid afforded quantitatively the 19-hydroxy compounds, **9** and **10**, respectively. The results are summarized in Scheme II. The stereochemistry at C-19 of **7** and **8** was assigned in

(1) To whom all correspondences should be addressed.
(2) E. Caspi and J. Wicha, *Chem. Commun.*, 209 (1966).
(3) J. Wicha and E. Caspi, *J. Chem. Soc. C*, 1740 (1968).
(4) J. Wicha and E. Caspi, *ibid.*, 947 (1969).
(5) M. Akhtar and D. H. R. Barton, *J. Amer. Chem. Soc.*, **86**, 1528 (1964).
(6) M. Davis and V. Petrow, *J. Chem. Soc.*, 2536 (1949).
(7) C. W. Shoppee and R. Lake, *ibid.*, 4864 (1960).