Amidine **7** may be formed by [1,3] rearrangement of an ethyl group from nitrogen to carbon in the initially formed **5**. Actually, heating of **5b** in diethylamine at 200 °C gave a 28% yield of **7b** (run 3 in Table III). Other 1,1-diaminoethylenes **5c** and **5i** also gave the corresponding rearrangement products **7c** and **7i** under the same reaction condition (runs 5 and 11). These ethyl migrations proceeded smoothly in diethylamine but not in triethylamine. However, in the presence of a catalytic amount of DTBP, the *N*-ethyl or *N*-*n*-propyl group of **5** migrated to give the corresponding butyr- or hexanamidine derivative in triethylamine (runs 6 and 12). The *N*-methyl group in **5** did not migrate to give the corresponding propionamidine derivatives in any cases, but the demethylation products **8** or **9** were formed.

Thermal [1,3] alkyl rearrangement may occur either by a sigmatropic shift following a suprafacial path with inversion at the migrating center or by a radical dissociation–recombination path.[6] The accelerating effect of DTBP, mentioned above, seems to suggest that the transformation of **5** to **7** proceeds via radical intermediates. From the present results, however, we cannot conclude it. 1-Allylphenylamino-1-methylphenylaminoethylene (**5f**) was converted into *N,N'*-diphenyl-*N*-methyl-4-pentenamidine (**7f**) in a high yield by heating without the aid of DTBP (run 9 in Table III).

Experimental Section

All boiling points are uncorrected. NMR spectra were recorded using a JEOL Model JNM-MH-100 spectrometer employing Me_4Si as internal standard. IR spectra were taken on a JASCO Model IRA-2 spectrometer. GLC analyses were performed on a JEOL Model JGC-1100 FID chromatograph. Fractional distillation was accomplished by a Büchi Model GKR-50 Kugelrohr distillation apparatus. All solvents were distilled in a nitrogen atmosphere just prior to use and the reactions were carried out under nitrogen atmosphere.

N,N,N',N'-Tetrasubstituted 1,1-Diaminoethylenes (5). A mixture of 10 mmol of silylynamine [*N*-methyl-*N*-(trimethylsilylethynyl)aniline (**1**), *N*-ethyl-*N*-(trimethylsilylethynyl)aniline (**2**), or *N,N*-diethyl(trimethylsilylethynyl)amine (**3**)],[5] 30 mmol of secondary amine, and 10 mg (0.53 mol %) of *N*-methylaniline hydrobromide was heated with stirring at 150 °C for 1–10 h. The reaction mixture was distilled under reduced pressure to give the corresponding **5**.

The yields and characterizing data are summarized in Tables I and II.

Thermal Reaction of 5. A solution of 7 mmol of **5** in 2 mL of amine (diethylamine, triethylamine, diisopropylamine, or piperidine) was heated with 100 mg (10 mol %) of DTBP (or without DTBP) in a sealed tube at 200 °C for 24 h. The reaction mixtures were analyzed by GLC using a 3 mm × 1 m stainless steel column filled with 10% silicone SE-30, and the yields were determined by the internal standard method. Samples of the products were isolated by fractional distillation of the reaction mixtures. The yields and characterizing data are shown in Tables III and IV.

***N*-Methyl-*N*-phenyl-*N'*-ethylbutyramidine (7b).** To a chilled suspension of PCl_5 (5.6 g, 27 mmol) in dry chloroform (30 mL) was added dropwise *N*-ethylbutyramide (2.6 g, 23 mmol) and stirring was continued for 15 min. Then a solution of *N*-methylaniline (2.42 g, 23 mmol) in chloroform (5 mL) was added and the mixture was stirred for 2 h at room temperature and an additional 2 h at reflux. After the addition of water (50 mL) to the reaction mixture, the aqueous layer was separated and made alkaline with NaOH solution and then extracted with ether. The ethereal extract was dried, concentrated, and distilled to give 1.60 g (35%) of **7b**, bp 120–122 °C (20 mm).

Acknowledgment. The authors are grateful to the Shin-Etsu Chemical Industry Co., Ltd., for a generous gift of chlorosilanes. We also wish to thank Dr. T. Konaka, Shionogi Research Laboratory, for helpful discussions.

Registry No.—*N*-Ethylbutyramide, 13091-16-2.

References and Notes

(1) S. M. McElvain and B. E. Tate, *J. Am. Chem. Soc.*, **67**, 202 (1945).
(2) H. Baganz and L. Domaschke, *Chem. Ber.*, **95**, 2095 (1962).
(3) H. Weingarten and W. A. White, *J. Org. Chem.*, **31**, 2874 (1966).
(4) C. Jutz and H. Amschler, *Chem. Ber.*, **96**, 2100 (1963).
(5) For the preparation of silylynamines, see Y. Sato, Y. Kobayashi, M. Sugiura, and H. Shirai, *J. Org. Chem.*, **43**, 199 (1978).
(6) C. W. Spangler, *Chem. Rev.*, **76**, 187 (1976).
(7) L. Hunter and J. A. Marriott, *J. Chem. Soc.*, 777 (1941).
(9) J. v. Braun, F. Jostes, and A. Heymons, *Ber.*, **60**, 92 (1927).

Preparation of the Enantiomeric Forms of 9-(5,6-Dideoxy-β-D-*ribo*-hex-5-enofuranosyl)adenine[1]

Leon M. Lerner

Department of Biochemistry, State University of New York, Downstate Medical Center, Brooklyn, New York 11203

Received November 17, 1977

D-Allose was converted to methyl 2,3:5,6-di-*O*-isopropylidene-β-D-allofuranoside, and this in turn was hydrolyzed in an acid solution to methyl 2,3-*O*-isopropylidene-β-D-allofuranoside. Treatment of the latter with methanesulfonyl chloride gave methyl 2,3-*O*-isopropylidene-5,6-bis(*O*-methanesulfonyl)-β-D-allofuranoside. The latter was treated with sodium iodide to afford methyl 2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranoside. The isopropylidene group was hydrolyzed, the hydroxyl groups were blocked with benzoyl groups, and the methoxyl group was replaced with an acetate by acetolysis. The sugar derivative, 1-*O*-acetyl-2,3-di-*O*-benzoyl-5,6-dideoxy-D-*ribo*-hex-5-enofuranose, was condensed with 6-benzamidochloromercuripurine by the titanium tetrachloride method, and the blocking groups were removed with sodium methoxide to afford the desired nucleoside, 9-(5,6-dideoxy-β-D-*ribo*-hex-5-enofuranosyl)adenine. As an aid to NMR clarification of the configuration at the anomeric carbon atom, the 2',3'-*O*-isopropylidene derivative was prepared. D-Talose was converted to methyl 2,3-*O*-isopropylidene-5,6-bis(*O*-methanesulfonyl)-α-D-talofuranoside in several steps without isolation of the intermediates. Sodium iodide treatment of the 5,6-bis(*O*-methanesulfonate) gave methyl 2,3-*O*-isopropylidene-β-L-*ribo*-hex-5-enofuranoside, which was used to prepare 9-(5,6-dideoxy-β-L-*ribo*-hex-5-enofuranosyl)adenine by the same pathway as used to prepare the D form.

This laboratory has been engaged in a study of the chemistry and biological effects of exocyclic unsaturation of nucleosides. In addition to the 4',5' unsaturation found in decoyinine (angustmycin A) type of analogues,[2,3] this laboratory has reported the preparation of several 5',6'-unsaturated hexofuranosyl nucleosides.[4,5] Weak biological activity,

0022-3263/78/1943-2469$01.00/0

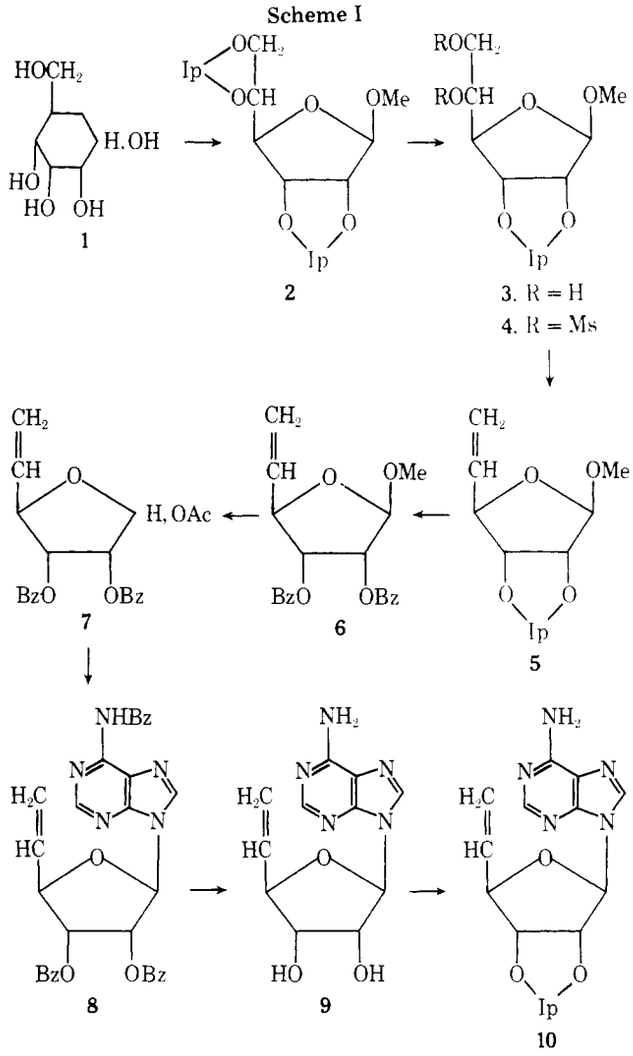
either antibacterial or antileukemic (L 1210 in culture), has been noted[5] and the two new compounds reported[5] at that time appear to have borderline activity.[6] It also seemed of interest to compare the biological and enzymatic properties of 9-(5,6-dideoxy-β-D-*ribo*-hex-5-enofuranosyl)adenine (**9**) and its enantiomer **14** to that of the enantiomeric forms of 9-(5-deoxy-β-*erythro*-pent-4-enofuranosyl)adenine reported recently.[3] Because of previous difficulties experienced during attempts to unsaturate preformed nucleosides without competitive side reactions, such as cyclonucleoside formation, the scheme of synthesis reported here again emphasizes the use of unsaturated sugar derivatives for the preparation of the desired nucleosides.

The desired starting material for the synthesis of nucleoside **9** was methyl 5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranoside (**5**). A preparation of **5** was reported a number of years ago by pyrolysis of methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranoside 5-*S*-methylxanthate (Chugaev reaction).[7] One problem with this approach was that methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranoside had to be prepared from L-rhamnose, a fairly expensive sugar. A more serious problem was that the product of the Chugaev reaction was contaminated with sulfur-containing byproducts, and **5** could only be purified by preparative GLC. Previous experience in this laboratory has demonstrated the ease of preparation of glycosides related to **5** starting from the parent hexoses.[5] D-Allose (**1**) was, therefore, required as the starting sugar for the preparation of **5**. D-Allose has been prepared in a number of laboratories by oxidation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose followed by reduction and hydrolysis of blocking groups. The ruthenium tetraoxide oxidation procedure of Baker et al.[8] appeared to be the best method; however, in the author's hands this procedure gave low yields (~25%) and required extensive chromatography to remove colored contaminants. Utilizing this procedure as a basis and applying certain advantageous aspects of various other methods in the literature,[9] a somewhat different oxidation procedure was worked out which is presented in the Experimental Section. The reduction of the oxidation product and removal of the isopropylidene groups were accomplished as described previously[8] and D-allose was obtained in high yield.

Treatment of D-allose (**1**) with a mixture of acetone, methanol, 2,2-dimethoxypropane, and an acid catalyst[10] gave methyl 2,3:5,6-di-*O*-isopropylidene-β-D-allofuranoside (**2**) (Scheme I). In previous work,[10,11] it had been found advantageous to skip the isolation of the fully blocked intermediate and to procede directly to the next product. Therefore, a repeat of the above followed by selective hydrolysis gave a 51% yield of crystalline methyl 2,3-*O*-isopropylidene-β-D-allofuranoside (**3**). A fair amount of over hydrolysis produced D-allose and the methyl glycoside, which were present in the aqueous phase after the extraction process. By using an anion-exchange resin in the hydroxide form to neutralize the acid, it was possible to recycle the aqueous phase through the entire process at least one time to raise the total yield to over 70%. Williams[12] has reported that the acid-catalyzed methanolysis of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose yielded both **2** and **3** as products. The physical data for **2** agreed well; however, **3** had been reported as a syrup. No elemental analysis was given and the optical rotations, which are not close, could not be compared in water due to the low solubility of crystalline **3**. The elemental analysis and NMR and IR spectra of **3** support the structure, as do the following reactions performed on it.

Treatment of **3** with methanesulfonyl chloride afforded methyl 2,3-*O*-isopropylidene-5,6-bis(*O*-methanesulfonyl)-β-D-allofuranoside (**4**) in 86% yield. Methyl 5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranoside (**5**) was

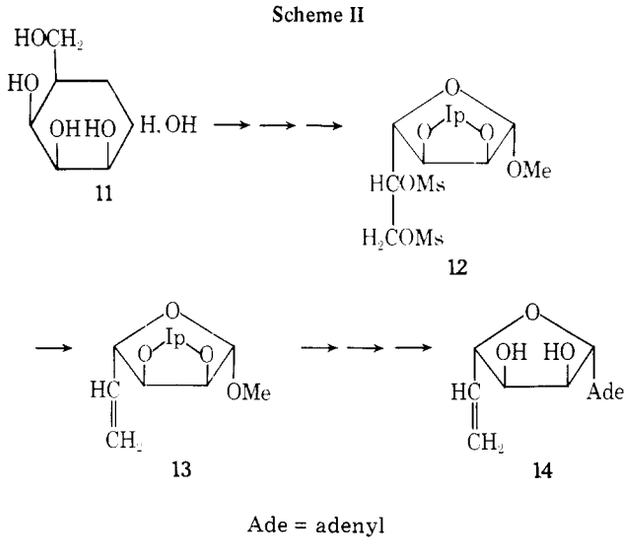
Scheme I



obtained from **4** with sodium iodide in boiling 2-butanone. The spectral data and optical rotation of **5**, which was a distillable liquid, compared favorably to the compound reported by Ryan et al.[7] The present synthesis has the distinct advantage that large quantities of **5** can be produced from D-glucose and purified by distillation without the problem of contaminating byproducts.

In order to prepare nucleoside **9**, it was necessary to exchange the blocking groups of **5** for ester groups. The isopropylidene group was removed in boiling methanol containing the acid form of an ion-exchange resin.[13] The hydroxyl groups were benzoylated, giving methyl 2,3-di-*O*-benzoyl-5,6-dideoxy-β-D-*ribo*-hex-5-enofuranoside (**6**), and acetolysis afforded the 1-*O*-acetate **7**. The benzoate groups precluded isomerization at C-2 of the sugar during the acetolysis reaction.[14] The sugar derivative **7** was condensed with 6-benzamidochloromercuripurine by the titanium tetrachloride method[5,15] and the blocking groups of the nucleoside **8** were removed in hot methanolic sodium methoxide. The crystalline product **9** was purified by chromatography on an ion-exchange column[16] and obtained in 44% yield from **7**. The elemental analysis and UV, IR, and NMR spectra indicated that **9** was an N-9 substituted adenine hexofuranosyl nucleoside. However, the H-1′ proton was obscured by overlapping of the multiplet from H-5′ so that no decision concerning the anomeric configuration could be made. It was expected that **9** would have the β-D configuration because of the directive effect of the benzoyl group at C-2 during the coupling reaction.[17] Since the optical rotation of **9** offered no basis for a decision, it was converted to the isopropylidene derivative **10** and the NMR spectrum recorded

Scheme II



Ade = adenyl

again. The anomeric proton was still not clearly defined; however, the $\Delta\delta$ value of the α- and γ-methyl groups of the isopropylidene group was 0.22. Imbach[18] has stated that values of $\Delta\delta > 0.18$, when recorded in Me_2SO-d_6, are indicative of the β-D configuration, which has been assigned to **9**.[19]

The starting sugar for the preparation of the enantiomeric nucleoside **14** was D-talose (**11**) (Scheme II). The preparation of methyl 2,3-*O*-isopropylidene-5,6-bis(*O*-methanesulfonyl)-α-D-talofuranoside (**12**) followed the preparation of the D-mannose isomer[10] more closely than the D-allose isomer **4** in that the intermediates were not isolated. Attempts were made to purify and crystallize methyl 2,3:5,6-di-*O*-isopropylidene-α-D-talofuranoside and methyl 2,3-*O*-isopropylidene-α-D-talofuranoside, but these substances did not crystallize and the purification process decreased yields. Therefore, the entire reaction sequence to **12** from **11** was performed without isolation of intermediates. Similar to the case of D-allose, the aqueous phase after selective hydrolysis was recycled one time and, following mesylation, a 60% total overall yield of **12** from D-talose was obtained.

Treatment of **12** with sodium iodide in 2-butanone gave methyl 5,6-dideoxy-2,3-*O*-isopropylidene-β-L-*ribo*-hex-5-enofuranoside (**13**). From this point on, the synthesis of **14** was achieved in the same manner as described for **9**.

Experimental Section[20]

D-Allose (1). To a 1-L Morton flask was added 10 g of sodium bicarbonate, 50 mL of water, and 1 g of ruthenium dioxide hydrate,[21] and the mixture was stirred magnetically. Sodium metaperiodate (5 g) was added and the insoluble black ruthenium dioxide was converted to the soluble yellow-orange ruthenium tetraoxide. Carbon tetrachloride (200 mL) was added followed by 50 g of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose,[22] which was added in small portions over 1 h. During this time a solution containing 55 g of sodium metaperiodate in 500 mL of water was added intermittently in small portions to the well-stirred mixture to maintain the yellow-orange color. After each addition of the sugar derivative the formation of black ruthenium dioxide could be observed around the dissolving crystals. After all of the sugar derivative and sodium metaperiodate solution had been added the orange solution was stirred until ruthenium dioxide was regenerated. Solid sodium metaperiodate was added in 3–5-g portions from time to time to regenerate the orange color until a total of 20 g had been added. TLC using 1:1 chloroform–ether indicated that the reaction was complete in 4–5 h. The mixture was treated with 50 mL of 2-propanol for 0.5 h, filtered through a pad of Celite-545, and the orange organic layer separated. The aqueous layer was extracted with chloroform (8 × 150 mL) and combined with the main organic layer, and the solvents were removed by evaporation, leaving a yellow crystalline mass. The reduction of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofurano-3-ulose hydrate to 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (41.6 g, 83% yield from 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose) and subsequent hydrolysis to obtain D-allose (95% yield) was conducted as described by Baker et al.[8]

Methyl 2,3:5,6-Di-*O*-isopropylidene-β-D-allofuranoside (2). A mixture containing 1 g (5.55 mmol) of D-allose (**1**), 5 mL of 2,2-dimethoxypropane, 3.3 mL of methanol, 3.3 mL of acetone, and 0.1 mL of concentrated hydrochloric acid was heated under reflux for 2 h. The mixture was cooled to room temperature and neutralized with 3 mL of saturated sodium bicarbonate solution. An additional 10 mL of water was added and enough methanol to dissolve the precipitate that formed. The organic solvents were evaporated and the product crystallized from the water. The crystals were filtered off, washed with water, and air dried: 0.838 g (55% yield). Recrystallization from methanol–water gave clear, colorless micaceous platelets: mp 66–66.5 °C; $[\alpha]^{25}_D$ −54.3° (*c* 1.36, chloroform) [lit.[12] mp 67–68 °C; $[\alpha]^{23}_D$ −54° (*c* 0.19, chloroform)].

Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.09. Found: C, 56.95; H, 8.13.

Methyl 2,3-*O*-Isopropylidene-β-D-allofuranoside (3). A mixture containing 22 g (0.122 mol) of D-allose, 110 mL of 2,2-dimethoxypropane, 73 mL of acetone, 73 mL of methanol, and 2.2 mL of concentrated hydrochloric acid was boiled under reflux for 2 h. The orange solution was cooled to room temperature and poured into 220 mL of water. The organic solvents were evaporated (30 °C), during which process crystals of **2** began forming. The amount of water was readjusted to 220 mL and 220 mL of methanol was added. The crystals dissolved, 5.5 mL of concentrated hydrochloric acid was added, and the solution was kept at room temperature for 3.5 h. The acid was neutralized with Amberlite IR-45 (OH^-) anion-exchange resin and the resin was removed by filtration and washed with 200 mL of 1:1 methanol–water. The filtrate was evaporated to about 125 mL of water and extracted with chloroform (4 × 70 mL), and the chloroform extracts were combined and dried. The solvent was evaporated and the residue crystallized from a mixture of ethyl acetate (20 mL) and petroleum ether (bp 30–60 °C, 60 mL) to afford 14.03 g of **3**. An additional 0.5 g was crystallized from the mother liquor for a 51% yield.

The original water layer was evaporated and the residue dried by coevaporation several times with absolute ethanol. The residue, which weighed 13.8 g, was treated with 69 mL of 2,2-dimethoxypropane, 46 mL of methanol, 46 mL of acetone, and 1.4 mL of concentrated hydrochloric acid, and boiled under reflux for 2 h. The rest of the procedure was the same as above except that neutralization of the acid was effected with saturated sodium bicarbonate solution. An additional 5.88 g of **3** was obtained for a total of 20.42 g (71%). These crystals were satisfactory for use in the next step.

In a separate experiment 1 g of **1** was converted to **3** in 51% yield and recrystallized from ethyl acetate–petroleum ether to obtain microcrystals; mp 100–100.5 °C; $[\alpha]^{25}_D$ −66.8° (*c* 1.37, methanol); IR (KBr) ν_{max} 3340 (OH), 1384 cm^{-1} (*gem*-dimethyl); NMR (acetone-d_6) δ 4.87 (br s, 1, OH), 4.75 (s, 1, H-1), 4.42 (d, 1, $J_{2,3}$ = 6 Hz, H-2), 4.02 (d, 1, $J_{2,3}$ = 6 Hz, H-3), 3.83–3.40 (m, 5, H-4, H-5, H-6a, H-6b, OH), 3.20 (s, 3, OMe) 1.33, 1.21 (both s, 6, *gem*-dimethyl). A previous paper[12] reported **3** as a syrup having $[\alpha]^{25}_D$ −43° (*c* 0.35, water).

Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.74. Found: C, 51.35; H, 7.73

Methyl 2,3-*O*-Isopropylidene-5,6-bis(*O*-methanesulfonyl)-β-D-allofuranoside (4). To a solution of **3** (20.4 g, 87 mmol) in 102 mL of dry pyridine, chilled in an ice bath, was added 31 mL of methanesulfonyl chloride dropwise. The mixture was stirred for 2 h at room temperature, chilled again, and 45 mL of water was added very slowly. Crystallization of the product began and after 1 h the contents of the flask was transferred to a beaker containing 1 L of water and stirred for 20 min. The crystals were filtered off, washed copiously with water, and air dried: 29.34 g (86% yield). This material was satisfactory for the next reaction. Recrystallization of a sample (1.46 g) from ethanol–water afforded 1.21 g of needles: mp 102–103 °C; $[\alpha]^{25}_D$ −25.9° (*c* 1.38, chloroform); IR (KBr) ν_{max} 1374 (*gem*-dimethyl), 1350, 1170 cm^{-1} (sulfonyl), no OH; NMR (acetone-d_6) δ 5.00–3.93 (series of unresolved, complex multiplets, 7 sugar protons), 3.33 (s, 3, OMe), 3.18, 3.12 (both s, 6, methanesulfonyl), 1.40, 1.27 (both s, 6, *gem*-dimethyl). The NMR spectrum very closely resembled that of other isomers of this type.

Anal. Calcd for $C_{12}H_{22}O_{10}S_2$: C, 36.91, H, 5.68; S, 16.43. Found: C, 36.93; H, 5.68; S, 16.42.

Methyl 5,6-Dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranoside (5). A mixture containing 29.4 g (75.5 mmol) of **4**, 83 g (0.55 mol) of sodium iodide, and 650 mL of 2-butanone was boiled under reflux for 39 h. The mixture was cooled to room temperature and filtered, and the solvent was evaporated. The liquid residue was

dissolved in 175 mL of chloroform, washed with 10% aqueous sodium thiosulfate solution (250 mL; then 2 × 175 mL) and water, (200 mL) and dried. After evaporation of the chloroform, the oil was dissolved in methanol and decolorized with activated charcoal.[23] The methanol was evaporated and the oil distilled to yield 13.14 g (87%): bp 79–80 °C (3.5 mmHg); $[\alpha]^{26}_D$ −61.0° (*c* 1.64, chloroform) [lit.[7] bp 104–105 °C (17 mmHg), $[\alpha]^{24}_D$ −57.9° (chloroform)]; IR (film) ν_{max} 3015, 2780 (=C-H stretching), 1682, 1635 (C=C), 1374 (d, *gem*-dimethyl), 992, 907 cm^{-1} (=CH bending); NMR (chloroform-*d*) 6.0–4.97 (complex m, 3, H-5, H-6a, H-6b), 4.90 (s, 1, H-1), 4.57 (m, 3, H-2, H-3, H-4), 3.25 (s, 3, OMe), 1.43, 1.27 (both s, 6, *gem*-dimethyl).

9-(5,6-Dideoxy-β-D-*ribo*-hex-5-enofuranosyl)adenine (9). To a solution containing 8 g (40 mmol) of **5** in 240 mL of methanol was added 80 g of Amberlite IR-120 (H^+) cation-exchange resin.[13,24] The well-stirred mixture was heated under reflux for 3.5 h, cooled to room temperature, and filtered by suction through a pad of Celite-545. The solids were washed with 200 mL of methanol, the methanol was evaporated, and a yellow syrup remained. The syrup was dissolved in 112 mL of dry pyridine, chilled in an ice bath, and 19 mL of benzoyl chloride was added, dropwise, to the stirring mixture. After 1 h the flask was stored at room temperature for 16 h, chilled again in an ice bath, and the contents treated with 7 mL of methanol[25] dropwise. After 0.5 h in the ice bath; the flask was kept at room temperature for 2.5 h, and then the contents was diluted with 100 mL of chloroform and transferred to a separatory funnel. The organic solution was washed with 250 mL of ice water, and the aqueous layer was back-extracted one time with 40 mL of chloroform. The chloroform solution was washed with 250 mL of saturated sodium bicarbonate solution and 250 mL of water and evaporated. The residue, which contained methyl benzoate, was suspended in 50 mL of 1:1 methanol–water and the solvents were evaporated. This process was repeated four times and removed all but traces of methyl benzoate. The syrupy residue was dried by coevaporation with absolute ethanol (4 × 50 mL) to afford 13.2 g (90% yield from **5**) of an orange syrup, methyl 2,3-di-*O*-benzoyl-5,6-dideoxy-β-D-*ribo*-hex-5-enofuranoside (**6**): NMR (chloroform-*d*) δ 8.07–7.00 (m, phenyl), 3.42 (s, OMe).

The entire sample (36 mmol) was dissolved in a mixture of glacial acetic acid (81 mL) and acetic anhydride (8.1 mL), chilled in an ice bath, and 3.8 mL of concentrated sulfuric acid was added dropwise. The mixture was kept at room temperature for 16 h, poured into 200 mL of ice, and the mixture was stirred until the ice melted. A gum had settled out, which was dissolved by stirring in 100 mL of chloroform, and the chloroform solution was separated in a separatory funnel. The aqueous layer was extracted with chloroform (2 × 50 mL) and the extracts were combined. The chloroform solution was washed with water (2 × 200 mL), saturated sodium bicarbonate solution (200 mL), and again with water (200 mL), and dried. Evaporation of the solvent and several coevaporations with benzene to remove traces of acetic acid afforded a colorless syrup, 14.34 g of 1-*O*-acetyl-2,3-di-*O*-benzoyl-5,6-dideoxy-D-*ribo*-hex-5-enofuranose (**7**): NMR (chloroform-*d*) δ 2.03 (acetyl), no methoxyl.

The sugar derivative **7** (14.3 g, 36 mmol), 21.4 g (45 mmol) of 6-benzamidochloromercuripurine, 21.4 g of Celite-545, and 1250 mL of 1,2-dichloroethane were set up to reflux and 250 mL of solvent was removed through a take-off adapter in order to eliminate traces of moisture. A solution containing 5.2 mL (47 mmol) of titanium tetrachloride in 200 mL of fresh, dry 1,2-dichloroethane was added and the mixture was refluxed for 22 h with efficient stirring and protected from moisture. The mixture was cooled to room temperature, treated with 700 mL of saturated sodium bicarbonate solution, stirred for 1.5 h, and filtered through a pad of Celite-545. The filter cake was washed with 250 mL of hot 1,2-dichloroethane, the filtrate was placed in a separatory funnel, and the organic layer separated. Evaporation of the solvent left a brown foam, which was dissolved in 200 mL of chloroform, and the solution was washed with 30% aqueous potassium iodide solution (2 × 200 mL) and saturated sodium chloride solution (300 mL). The chloroform solution was dried and evaporated, yielding a brown, foamy, stiff gum weighing 18.3 g. The gum was dissolved in 300 mL of methanol, 48 g of 1 N methanolic sodium methoxide was added, and the mixture was boiled under reflux for 1.5 h. When the solution was chilled, precipitation of a tan solid occurred, which was filtered off, washed with cold methanol, and air dried. This material (3.5 g) was dissolved in 50 mL of hot 30% aqueous methanol and placed on top of a column[26] (56 × 1.8 cm) of BioRad AG 1-X2 (200–400 mesh, OH^-). Fractions (19 mL) were collected, and at tube number 68 the solvent was changed to 60% aqueous methanol and 16-mL fractions were collected. The dark-colored material stayed at the top of the column and only a few very minor UV absorbing peaks were observed. The main UV peak was in tubes 53–134, which were pooled and the solvents evaporated. The product was crystallized from ethanol to give 2.679 g in two crops. Recrystallization from acetone afforded 2.616 g of white needles in two crops.

The original methanol filtrate was adjusted to neutral pH with Amberlite CG-120 (H^+) ion-exchange resin and the mixture was filtered through a pad of Celite. The methanol was evaporated and 50-mL portions of water were coevaporated three times to remove methyl benzoate as an azeotrope. The residue was dissolved in 50 mL of 30% aqueous methanol and placed on a fresh column (60 cm × 1.8 cm) of the same resin used above. Fractions (15 mL) were collected and the solvent changed to 60% aqueous methanol at tube number 88. The major UV peak corresponded to tubes 73–160. These were pooled, the solvents evaporated, and the residue was crystallized from ethanol in two crops, affording 1.850 g. Recrystallization from acetone gave 1.603 g of white needles in three crops, identical with the above product by melting point, mixture melting point, and IR spectrum. The total yield of **9** was 4.219 g (44% from **7**): mp 190–191 °C; $[\alpha]^{28}_D$ +5.4° (*c* 0.837, 1 N hydrochloric acid); UV max (pH 1) 256.5 (ε 15 025), (H_2O) 259 (ε 14 780), (pH 13) 259 nm (ε 15 180); UV min (pH 1) 230 (ε 5000), (H_2O) 227 (ε 2190), (pH 13) 231.5 (ε 3885); NMR (Me_2SO-d_6) δ 8.17, 8.03 (both s, 2, H-8, H-2). 7.13 (br s, 2, NH_2), 6.03–5.67 (m, 2, H-1′, H-5′), 5.53–4.93 (complex m, 4, 2′-OH, 3′-OH, H-6′a, H-6′b), 4.77–4.43 (m, 1, H-2′), 4.40–3.97 (complex m, 2, H-4′, H-3′).

Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.60. Found: C, 50.38; H, 5.09; N, 26.73.

9-(5,6-Dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranosyl)adenine (10). Nucleoside 9 (100 mg, 0.38 mmol) was suspended in a mixture containing 30 mL of acetone and 3 mL of 2,2-dimethoxypropane, and 0.64 g of *p*-toluenesulfonic acid monohydrate was added. After stirring for 4 h at room temperature, the orange solution was poured into a stirring solution of 1 g of sodium bicarbonate in 10 mL of water. The precipitate was removed by filtration, and the solvents were evaporated. The residue was triturated with 25 mL of chloroform, the mixture filtered, and the chloroform evaporated. The syrupy residue crystallized after standing for 2 days at room temperature. Recrystallization from ethanol afforded 53 mg (46% yield) of **10:** mp 182.5–183.5 °C with a wet appearance at 178 °C; NMR (Me_2SO-d_6) δ 8.18, 8.10 (both s, H-8, H-2), 7.23 (br s, NH_2), 1.55, 1.33 (both s, Δδ = 0.22, *gem*-dimethyl).

Anal. Calcd for $C_{14}H_{17}N_5O_3$: C, 55.47; H, 5.65; N, 23.09. Found: C, 55.20; H, 5.50; N, 22.84.

Methyl 2,3-*O*-Isopropylidene-5,6-bis(*O*-methanesulfonyl)-α-D-talofuranoside (12). D-Talose (**11**) was prepared from D-galactal[27] by the method of Bilik and Kučár.[28] A mixture containing 19.8 g (0.11 mol) of D-talose, 100 mL of 2,2-dimethoxypropane, 70 mL of acetone, 70 mL of methanol, and 2 mL of concentrated hydrochloric acid was boiled under reflux for 2 h, cooled, diluted with 200 mL of water, and the organic solvents evaporated below 30 °C. Methanol (200 mL) and 5 mL of concentrated hydrochloric acid were added and the mixture was kept at room temperature for 4 h. The pH was adjusted to neutrality with Amberlite IR-45 (OH^-) and the resin was removed by filtration and washed thoroughly with 1:1 methanol–water. The solvents were evaporated until about 200 mL of water remained. Continuous extraction of the water layer with ethyl acetate was carried out for 5 days.[29] Evaporation of the dried solution gave an orange syrup (17.34 g). The aqueous layer was recycled through this process as described for the D-allose isomer, and an additional 4.34 g of crude methyl 2,3-*O*-isopropylidene-α-D-talofuranoside was obtained. The two preparations were used separately in the following mesylation step.

To a solution containing the 17.34 g of syrup in 90 mL of dry pyridine, chilled in an ice bath, was added 24 mL of methanesulfonyl chloride dropwise. The reaction was allowed to proceed for 2 h at room temperature, the mixture was chilled again, and 40 mL of water was added very slowly. After 15 min of stirring the mixture was diluted with an additional 150 mL of water and extracted with chloroform (3 × 75 mL). The chloroform extracts were combined, washed with saturated sodium bicarbonate solution (2 × 175 mL) and water (175 mL), and dried, and the solvent was evaporated. Coevaporation with small portions of toluene gave a syrup which was crystallized from ethanol after seeding.[30] A yield of 20.48 g of white needles was obtained. Treatment of the 4.34-g sample of syrup with 6 mL of methanesulfonyl chloride in 25 mL of pyridine and similar processing afforded an additional 5.22 g of **12**, for a total yield of 25.70 g (60% from **11**): mp 74.5–75.5 °C; $[\alpha]^{25}_D$ +37.2° (*c* 1.20, chloroform); IR (KBr) ν_{max} 1384, 1360, 1346 (overlapping broad peaks, *gem*-dimethyl, sulfonyl), 1179 cm^{-1} (sulfonyl); NMR (chloroform-*d*) δ 5.10–3.90 (series of complex multiplets, 7 sugar protons), 3.37 (s, 3, OMe), 3.10, 3.05 (both s, 6, methanesulfonyl), 1.48, 1.32 (both s, 6, *gem*-dimethyl).

Anal. Calcd for $C_{12}H_{22}O_{10}S_2$: C, 36.91; H, 5.68; S, 16.43. Found: C, 37.00; H, 5.59; S, 16.45.

Methyl 5,6-Dideoxy-2,3-*O*-isopropylidene-β-L-*ribo*-hex-5-enofuranoside (13). Methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methanesulfonyl-α-D-talofuranoside (**12**, 12.5 g, 32 mmol), 35 g of sodium iodide, and 275 mL of 2-butanone were heated under reflux for 26 h. The mixture was worked up in a similar manner as in the preparation of **5** to afford 4.33 g (67.5% yield) of a clear, colorless liquid after distillation: bp 85–87 °C (3 mmHg), $[\alpha]^{25}_D$ +61.0° (*c* 1.53, chloroform). The IR and NMR spectra of **13** were identical with **5**.

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 59.92; H, 7.94.

9-(5,6-Dideoxy-β-L-*ribo*-hex-5-enofuranosyl)adenine (14). The preparation of **14** from **13** proceeded exactly as already described for the preparation of **9**. From 2.5 g of **13**, 4.89 g of methyl 2,3-di-*O*-benzoyl-5,6-dideoxy-β-L-*ribo*-hex-5-enofuranoside was obtained and this was acetolyzed to 1-*O*-acetyl-2,3-di-*O*-benzoyl-L-*ribo*-hex-5-enofuranose (4.16 g). Both of these compounds had NMR spectra which were virtually identical with their enantiomers. The 1-*O*-acetate (4.16 g, 10.5 mmol) was condensed with 6.2 g (13.1 mmol) of 6-benzamidochloromercuripurine in 450 mL of 1,2-dichloroethane as described for the synthesis of **9**. After workup, 4.48 g of tan foam was obtained. The blocking groups were removed with sodium methoxide, the methyl benzoate was removed as a water azeotrope, and the product was purified on a column[16] (33 × 2 cm) as described before.[31] The contents of the tubes containing the main UV peak were combined and crystallization from ethanol gave 1.201 g in two crops. Two recrystallizations from acetone yielded 0.998 g (36% from the 1-*O*-acetate) of needles, mp 191–191.5 °C. The sample required drying to 100 °C under high vacuum in a drying pistol (phosphorus pentaoxide) to remove traces of acetone and water. The IR spectrum of **14** was identical with **9**.

Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.60. Found: C, 49.79; H, 5.00; N, 26.46.

Registry No.—**1**, 2595-97-3; **2**, 28642-53-7; **3**, 28642-54-8; **4**, 65969-34-8; **5**, 29325-28-8; **6**, 65969-35-9; **7**, 65969-36-0; **8**, 66008-58-0; **9**, [65969-37-1; **10**, 65969-38-2; **11**, 2595-98-4; **12**, 65969-39-3; **13**, 65969-40-6; **14**, 65969-41-7; 1,2:5,6-di-*O*-isopropylidene-2-D-glucofuranose, 582-52-5; 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofurano-3-ulose, 2847-00-9; 6-benzamidochloromercuripurine, 17187-65-4; methyl 2,3-*O*-isopropylidene-α-D-talofuranoside, 65969-42-8; methyl 2,3-di-*O*-benzoyl-5,6-dideoxy-β-L-*ribo*-hex-5-enfuranoside, 65969-43-9; 1-*O*-acetyl-2,3-di-*O*-benzoyl-5,6-dideoxy-L-*ribo*-hex-5-enofuranose, 65969-44-0.

References and Notes

(1) This work was supported by Grant CA 13802 from the National Cancer Institute, National Institutes of Health.
(2) J. R. McCarthy, Jr., R. K. Robins, and M. J. Robins, *J. Am. Chem. Soc.*, **90**, 4993 (1968); E. J. Prisbe, J. Smejkal, J. P. H. Verheyden, and J. G. Moffatt, *J. Org. Chem.*, **41**, 1836 (1976); N. Suciu and L. M. Lerner, *Carbohydr. Res.*, **44**, 112 (1975).
(3) L. M. Lerner, *Carbohydr. Res.*, **53**, 177 (1977).
(4) L. M. Lerner, *J. Org. Chem.*, **37**, 470, 473 (1972).
(5) L. M. Lerner, *Carbohydr. Res.*, **44**, 13 (1975).
(6) A. Bloch, unpublished data.
(7) K. J. Ryan, H. Arzoumanian, E. M. Acton, and L. Goodman, *J. Am. Chem. Soc.*, **86**, 2503 (1964).
(8) D. C. Baker, D. Horton, and C. G. Tindall, Jr., *Methods Carbohydr. Chem.*, **7**, 3 (1976); *Carbohydr. Res.*, **24**, 192 (1972).
(9) For an excellent review of ruthenium tetraoxide oxidation, see: D. G. Lee and M. van den Engh in "Oxidation in Organic Chemistry", Part B, W. S. Trahanovsky, Ed., Academic Press, New York, N.Y., 1973, p 177
(10) M. E. Evans and F. W. Parrish, *Carbohydr. Res.*, **28**, 359 (1973).
(11) L. M. Lerner, *J. Org. Chem.*, **40**, 2400 (1975); *Carbohydr. Res.*, 44, 116 (1975).
(12) J. M. Williams, *Carbohydr. Res.*, **13**, 281 (1970).
(13) This method was suggested by Dr. V. K. Srivastava of this laboratory.
(14) L. M. Lerner, *Carbohydr. Res.*, **38**, 328 (1974); E. J. Reist, L. Goodman, R. R. Spencer, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 3962 (1958); E. J. Reist, L. Goodman, and B. R. Baker, *ibid.*, **80**, 5775 (1958).
(15) B. R. Baker, R. E. Schaub, J. P. Joseph, and J. H. Williams, *J. Am. Chem. Soc.*, **77**, 12 (1955); J. Prokop and D. H. Murray, *J. Pharm. Sci.*, **54**, 359 (1965).
(16) C. A. Dekker, *J. Am. Chem. Soc.*, **87**, 4027 (1965).
(17) B. R. Baker in Ciba Foundation Symposium, "Chemistry and Biology of Purines", G. E. W. Wolstenholme and C. M. O'Connor, Ed., Little, Brown and Co., Boston, Mass., 1957, p 120.
(18) J.-L. Imbach, *Ann. N.Y. Acad. Sci.*, **255**, 177 (1975); B. Rayner, C. Tapiero, and J.-L. Imbach, *Carbohydr. Res.*, **47**, 195 (1976).
(19) It should be noted that this method was worked out for ribofuranose nucleosides and may not be applicable here. For example, some discrepancies have been found when C-5′ has a substituent.[18]
(20) Elemental analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich., or by the Baron Consulting Co., Orange, Conn. Moist organic solutions were dried over anhydrous magnesium sulfate and evaporations were performed on a rotary evaporator under reduced pressure with a bath temperature of 40–45 °C unless specified otherwise. TLC was performed on silica gel G plates of 0.25-mm thickness, prepared with Desaga equipment. The NMR spectra were recorded on a Varian T-60A spectrometer with Me_4Si as the internal reference. IR and UV spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer and a Beckman DK-2 spectrophotometer, respectively. Optical rotations were determined with a Rudolph polarimeter. A Kofler micro hot stage was used to determine melting points as corrected values.
(21) Ruthenium dioxide hydrate was purchased from Engelhard Industries, Newark, N.J. It was used without any special treatment or activation.
(22) 1,2:5,6-Di-*O*-isopropylidene-β-D-glucofuranose was purchased from Pfanstiehl Laboratories, Inc., Waukegan, Ill.
(23) If this step is omitted, the colored material will distill with **5**.
(24) The resin was suspended in methanol and after 15 min the solvent was decanted. This process was repeated three times before the resin was used.
(25) If water was used, a large amount of benzoic anhydride was formed. The latter could be removed by treatment with methanol–pyridine solution for several days to form methyl benzoate.
(26) It is advisable to use a jacketed column in order to apply heat, if necessary, because the nucleoside tends to crystallize during early stages of chromatography. A hot-air blower (hair drier) was found to be a useful alternative for heating just the upper regions of the column.
(27) D-Galactal was purchased from Raylo Chemical, Ltd., Edmonton, Alberta, Canada.
(28) V. Bilik and S. Kucar, *Carbohydr. Res.*, **13**, 311 (1970).
(29) Extraction of the aqueous layer using a separatory funnel with either chloroform or ethyl acetate produced a hopeless emulsion. It was desirable not to add salts so that the sugar in the aqueous layer could be easily recycled through the reaction sequence.
(30) Seed crystals were originally obtained from a small-scale reaction by scratching the product in a mixture of methanol and water.
(31) No significant crystallization of the nucleoside in the methanolysis solution occurred in this case, therefore, only one column was necessary.

Diels–Alder Approach to Naphthocyclobutenes and Anthrocyclobutenes

Randolph P. Thummel,* Wesley E. Cravey, and Wutichai Nutakul

Department of Chemistry, University of Houston, Houston, Texas 77004

Received September 20, 1977

The [2 + 4] cycloaddition of benzyne with 1,2-dimethylenecyclobutane or 1-vinylcyclobutene leads to the formation of an adduct which can be dehydrogenated with DDQ to provide naphtho[*b*]cyclobutene or naphtho[*a*]cyclobutene, respectively. Similar reaction of 2,3-dehydronaphthalene with these same two dienes provides analogous cycloadducts which can then be oxidized to anthro[*a*]cyclobutene and anthro[*b*]cyclobutene. Pyrolysis of 1,4-dihydronaphtho[*b*]cyclobutene provides a ring-opened diene which can undergo further cycloaddition. Other oxidative routes to naphtho[*b*]cyclobutene are presented.

The preparation of annelated aromatic systems is often best accomplished by the utilization of synthetic techniques in which the fused ring portion of the molecule comprises one of the initial reacting partners. This species can then undergo cycloaddition or condensation reactions to build up the aromatic nucleus. We have demonstrated the utility of this ap-

0022-3263/78/1943-2473$01.00/0