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THE SYNTHESIS OF THE α-D-ANOMERS OF "HOMONUCLEOSIDES": DERIVATIVES OF 2,5-ANHYDRO-D-ALTRITOL

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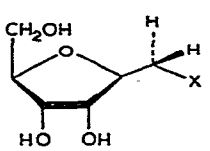
ABSTRACT

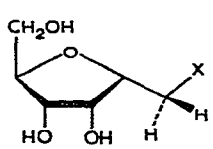
Reaction of 2,3,5-tri-*O*-benzyl-D-ribofuranosyl bromide with mercuric cyanide afforded an anomeric mixture of cyanides (**3**) and 1,4-anhydro-2,3,5-tri-*O*-benzyl-D-*erythro*-pent-1-enitol (**6**). Reduction of **3** with lithium aluminum hydride gave a pair of epimeric amines (**4** and **5**), which were separated by chromatography and characterized by conversion into the known 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-ureido-D-allitol (**7**) and its epimer, 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-ureido-D-altritol (**8**). Compound **8** and its precursor were used for the synthesis of various "α-homonucleosides".

INTRODUCTION

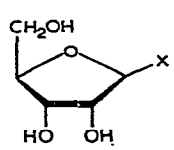
The synthesis of "homonucleosides" of the type A depicted in Chart I has been pursued vigorously[1–4]. The resemblance between the α-D-anomers of this series (B) in the conformation shown and the naturally occurring nucleosides (C) is quite strong. A similar observation by Robins and co-workers[5] was used as rationale for the synthesis of *S*-nucleosides of 8-mercaptopurines and 6-mercaptopyrimidines. The synthesis of nucleosides derived from 2,5-anhydro-D-altritol (B) was, therefore, undertaken.



A



B

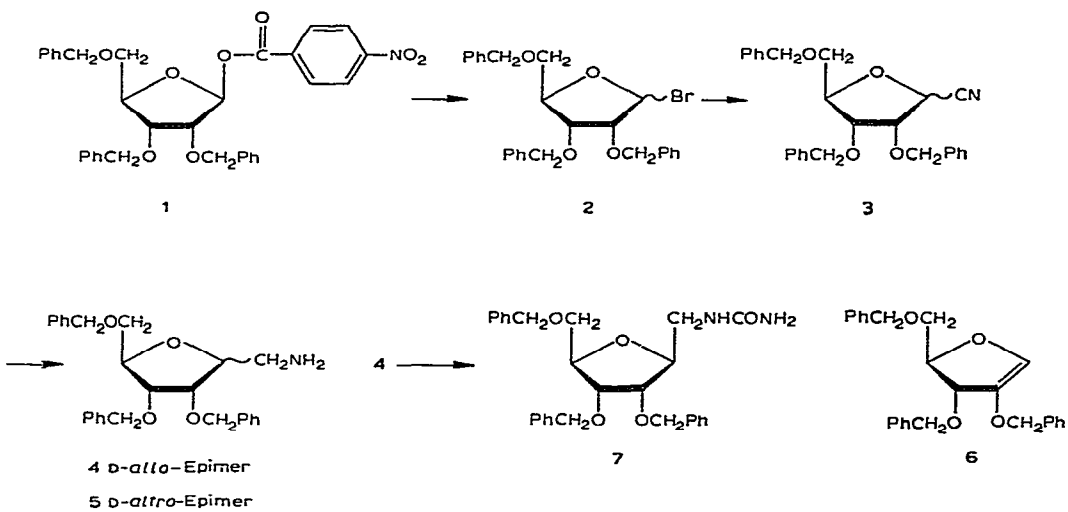


C

natural nucleoside

X= heterocyclic base attached in the usual way

An abundant supply of 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-β-D-ribose* made possible the scheme outlined in Chart II. Generation of the glycosyl halide **2** according to the procedure of Barker and Fletcher[6], and treatment of **2** with mercuric cyanide in nitromethane, gave an anomeric mixture of cyanides **3**. Reduction of **3** with lithium aluminum hydride in tetrahydrofuran gave an epimeric mixture of amines (**4** and **5**), separated by chromatography on a column of silica gel. A crystalline by-product *presumably* 1,4-anhydro-2,3,5-tri-*O*-benzyl-D-*erythro*-pent-1-enitol (**6**), resulting from the elimination of hydrogen bromide from **2** during the conversion **2**→**3**, was also isolated at this stage. Syrupy **4** reacted with nitrourea in ethanol to give crystalline 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-ureido-D-allitol (**7**), identical with that prepared by the method of Bobek and Farkaš[1] by an unequivocal route starting from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribose. This conversion established that the other syrupy member of the epimeric pair of amines (**4** and **5**) was 1-amino-2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-D-altritol (**5**). Compound **4** has also been reported by Ogawa and co-workers[7] as an oil, obtained by a multi-stage synthesis starting from 3-*O*-benzyl-1,2,5,6-di-*O*-cyclohexylidene-α-D-allose.

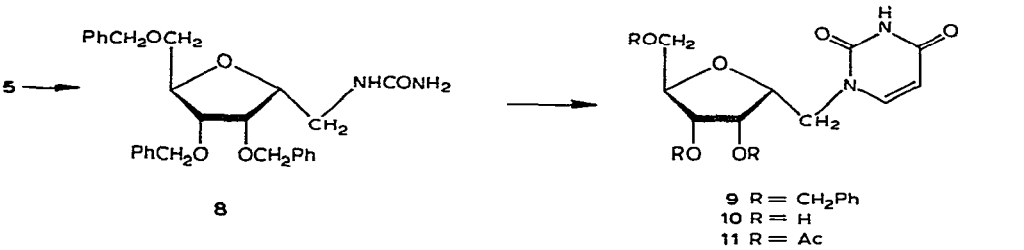


Compound **5** was converted into both purine and pyrimidine "homonucleosides" of type B (chart III). For the pyrimidine series, treatment of **5** with nitrourea provided the crystalline epimer of **7**, namely 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-ureido-D-altritol (**8**). Ring closure of **8** by the 3-ethoxyacryloyl chloride method[1] gave the protected uracil derivative **9**. Purification of crude **9** by column chromatography on silica gel afforded material that was hydrogenated over 10% palladium chloride on barium sulfate. Acetylation of the resulting crude 1-(2,5-anhydro-1-

*The author thanks Dr. E. J. Watson and Dale H. LaBar of this laboratory for their assistance in the preparation of this compound according to the procedure given in ref. 6.

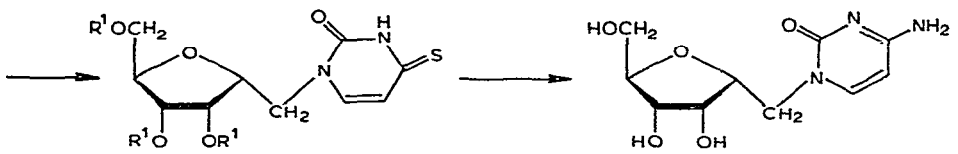
deoxy-D-altritol-1-yl)uracil (**10**) with acetic anhydride–pyridine gave a crude tri-*O*-acetyl derivative (**11**) that was readily purified by chromatography on a column of silica gel. Treatment of a portion of homogeneous, syrupy **11** with sodium methoxide in methanol gave crystalline **10**.

The remaining portion of **11** was treated with phosphorus pentasulfide in pyridine[8], and the syrupy product **12** was purified by chromatography on a column



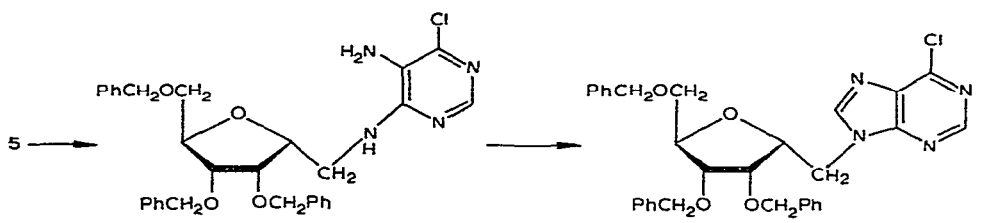
8

9 R = CH_2Ph
10 R = H
11 R = Ac



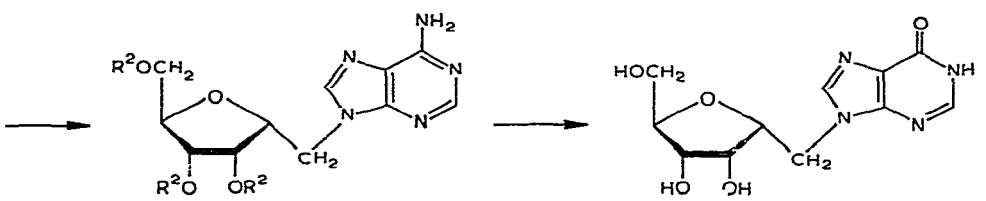
12 R^1 = Ac
13 R^1 = H

14



15

16



17 R^2 = CH_2Ph
18 R^2 = H

19

of silica gel. Removal of the protecting groups from **12** gave crystalline 1-(2,5-anhydro-1-deoxy-D-altritol-1-yl)-4-thiouracil (**13**). Treatment of **13** with methanolic ammonia at 100° gave crude 1-(2,5-anhydro-1-deoxy-D-altritol-1-yl)cytosine (**14**). Purification by ion-exchange chromatography on Dowex-50 resin afforded crystalline **14**.

In the purine series, the method of Montgomery and Hewson[2] was employed. Compound **5** was allowed to react with 5-amino-4,6-dichloropyrimidine and the product **15** was purified by column chromatography on silica gel. Ring closure of **15** gave crude **16** which, upon treatment with methanolic ammonia at 100°, gave crude 9-(2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-D-altritol-1-yl)adenine. Extensive purification by column chromatography on silica gel and alumina afforded crystalline **17**. Removal of the protecting groups by hydrogenation over palladium chloride[9] gave crystalline 9-(2,5-anhydro-1-deoxy-D-altritol-1-yl)adenine (**18**).

Deamination of **18** with nitrous acid followed by ion-exchange chromatography on Dowex-1 formate gave crystalline 9-(2,5-anhydro-1-deoxy-D-altritol-1-yl) hypoxanthine (**19**).

EXPERIMENTAL

General methods. — Melting points were determined with a Thomas–Hoover capillary melting-point apparatus and are uncorrected. Optical rotations were measured in an 0.5-dm tube with a Carl Zeiss LEP A2 photoelectric precision polarimeter. I.r. spectra were recorded with a Perkin–Elmer Model 21 recording i.r. spectrophotometer. U.v. spectra were recorded with a Perkin–Elmer Model 450 u.v.–visible–near i.r. spectrophotometer. P.m.r. spectra were measured with appropriate internal standards of tetramethylsilane or sodium 4,4-dimethyl-4-silapentane-1-sulfonate with a Varian A-60 n.m.r. spectrometer.

Mass spectra, unless otherwise stated, were recorded in the chemical-ionization (c.i.) mode with isobutane as the reagent plasma at 0.5 torr pressure and source temperatures between 200 and 350°. Data were recorded at low resolution with an AEI MS-902 mass spectrometer equipped with a Scientific Research Industries dual c.i.-e.i. source. All samples entered the source via a direct-insertion probe. Components on t.l.c. plates were detected by u.v. light. SilicAR 7GF (Mallinckrodt) plates were used for t.l.c. Silica gel (J. T. Baker) and alumina (Merck) were of chromatographic grade. Solvent proportions were by volume. Evaporations were performed under diminished pressure at 35°.

*2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-ureido-*D*-allitol* (**7**) *and 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-ureido-*D*-altritol.* — 2,3,5-Tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-β-D-ribose[6] (**1**, 120 g) was dissolved in dry (Drierite) dichloromethane (500 ml) and the solution was cooled in an acetone–ice bath. Dry hydrogen bromide gas was passed into the solution for approximately 5 min. The precipitated *p*-nitrobenzoic acid was rapidly removed by filtration and the filter was washed with dichloromethane. The yellow filtrate was evaporated below room temperature and the resulting red syrup was subjected to vacuum (oil pump) for 5 min. The syrup was dissolved in

dry (Drierite) nitromethane (500 ml) and added to mercuric cyanide (170 g). The mixture, suitably protected from moisture, was cooled and swirled in an ice–acetone bath for a few min. The mixture was then stirred rapidly with a magnetic stirrer for 2 days at room temperature. The mixture was filtered and the filtrate evaporated to a syrup. The syrup was dissolved in chloroform and the solution washed consecutively with aqueous potassium iodide solution, water, ice-cold potassium carbonate solution, and water (four times). The dried magnesium sulfate solution was evaporated to give 103.5 g of a brown syrup containing the anomeric cyanides (**3**).

The syrup was dissolved in tetrahydrofuran (500 ml) and the solution was added dropwise to a stirred suspension of lithium aluminum hydride (40 g) in tetrahydrofuran (1.5 l) over the course of 10 min. The mixture was stirred and heated for 1 h under reflux. Concentrated ammonia solution (150 ml) was added to the cooled, stirred solution, and the mixture was filtered. The filter cake was stirred with further quantities of concentrated ammonia solution and tetrahydrofuran, and the mixture was filtered again. The combined filtrates were evaporated to low volume. The two-phase mixture was extracted with chloroform and the organic layer was dried (magnesium sulfate), and evaporated to a syrup.

The crude mixture of epimeric amines (**4** and **5**) was dissolved in chloroform and applied to a column (77 × 6.0 cm) of silica gel prepacked in chloroform. The fractions were of the following volumes: 1–6, 500 ml; 7–12, 150 ml; 13–16,200 ml and 17–23, 300 ml. The fractionation was monitored by t.l.c. with solvent system *A**.

Fractions **5** and **6** were evaporated to a syrup that crystallized spontaneously. Trituration with ether gave 10.26 g (12%) of a crude by-product, 1,4-anhydro-2,3,5-tri-*O*-benzyl-D-*erythro*-pent-1-enitol (**6**), m.p. 109–110°. Recrystallization from ethyl acetate–ether gave pure product, m.p. 109–110°; mass spectrum M^+ 402 (e.i.).

Anal. Calc. for $C_{26}H_{26}O_4$: C, 77.59; H, 6.51. Found: C, 77.69; H, 6.79.

This compound was homogeneous by t.l.c. with chloroform as developer.

Fractions 12–23 were pooled and evaporated to give 16.7 g (18%) of homogeneous, syrupy 1-amino-2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-D-allitol (**4**).

Elution of the column with a suitable volume of methanol gave the epimeric amine. Evaporation gave 34.6 g (38%) of essentially homogeneous, syrupy 1-amino-2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-D-altritol (**5**); mass spectrum MH^+ 434.

A mixture of **4** (16.70 g) and nitrourea (4.0 g) in ethanol (100 ml) was warmed gently, with swirling until solution occurred, and the solution was heated for 1.5 h under reflux. The reaction mixture was filtered through Celite and the filtrate was evaporated to a syrup. Crystallization from chloroform–ether gave 9.00 g. (49%) of 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-ureido-D-allitol (**7**), m.p. 89–90°, $[\alpha]_D^{26}$ +18.7° (*c* 1.02, ethanol), having an i.r. (KBr) spectrum identical with that of authentic material prepared in this laboratory by the method of Bobek and Farkaš[1]. These authors recorded $[\alpha]_D^{25}$ +16.7° (*c* 0.5, ethanol) for **7**.

*A mixture of equal volumes of chloroform and concentrated ammonia solution were shaken in a separatory funnel. The lower layer was used for development. The upper phase was placed in an isolated vessel in the developing tank to maintain the concentration of ammonia in the organic phase.

A mixture of **5** (34.6 g) and nitrourea (8.4 g) in ethanol (250 ml) was allowed to react as described for **4**. The reaction solution was treated with charcoal and filtered through Celite. The filtrate was evaporated and the resulting syrup was crystallized chloroform–ether to give 15.1 g (32%) of crude (m.p. 118–120°) 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-ureido-D-altritol (**8**). Recrystallization gave pure **8**, m.p. 122–123°, $[\alpha]_D^{26}$ +52.2° (*c* 1.03, ethanol), MH^+ 477.

Anal. Calc. for $C_{28}H_{32}N_2O_5$: C, 70.57; H, 6.77; N, 5.88. Found: C, 70.47; H, 6.89; N, 5.77.

This product was homogeneous by t.l.c. with (1:1) chloroform–ethyl acetate as developer.

*1-(2,5-Anhydro-1-deoxy-*D*-altritol-1-yl)uracil* (**10**). — To 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-ureido-D-altritol (**8**, 14.0 g) in dichloromethane (50 ml) and pyridine (30 ml) was added 3-ethoxyacryloyl chloride[1] in dichloromethane (40 ml). The solution was protected from moisture and kept for 2 days at room temperature. The resulting red solution was diluted with ethyl acetate and the organic layer washed with several portions of 5% potassium hydrogen sulfate until the washings were acidic. The organic layer was then washed with saturated sodium hydrogen carbonate solution, and dried (magnesium sulfate). Evaporation produced a syrup that was dissolved in glacial acetic acid (150 ml) containing concentrated hydrochloric acid (15 ml). The mixture was kept overnight at room temperature and then heated for 1 h at 60°. Evaporation gave a red syrup, which was dissolved in ethyl acetate. The solution was washed with saturated sodium hydrogen carbonate solution, dried (magnesium sulfate), and evaporated to a syrup (crude **9**).

The crude product was dissolved in chloroform and applied to the top of a column (82 × 6.0 cm) of silica gel prepacked in chloroform. The column was eluted with chloroform and 500-ml fractions were collected (fractions 12–14 were of 250 ml volume). The fractionation was monitored by t.l.c. with (7:3) chloroform–ethyl acetate as developer. Fractions 12–21 were pooled and evaporated to give 8.30 g (53%) of purified **9**.

The protected nucleoside **9** (8.23 g) in 95% ethanol was added to a prereduced suspension of 10% palladium on barium sulfate (4.0 g) in 95% ethanol (200 ml) and the mixture was hydrogenated at atmospheric pressure until hydrogen uptake had ceased. Examination by t.l.c. with 4:1 ethyl acetate–methanol revealed essentially one component. The mixture was filtered through Celite and the filter was washed with ethanol. The filtrate and washings were evaporated to give 4.20 g of crude **10** as a foam.

The foam (4.00 g) was mixed with acetic anhydride (40 ml) and pyridine (40 ml), and the solution was protected from moisture and kept overnight at room temperature. The solution was poured onto ice and the mixture extracted with dichloromethane. The extract was washed consecutively with 2M hydrochloric acid, water, saturated sodium hydrogen carbonate solution, and water. The dried (magnesium sulfate) solution showed two components (t.l.c. with ethyl acetate as developer).

The solution was evaporated onto silica gel and the dry powder was added to the top of a dry column (48 × 5.3 cm) of silica gel to make a column 54 × 5.3 cm. The column was eluted with chloroform and 200-ml fractions were collected. Fractions 29–33, which contained the slower-moving, major component, were pooled and evaporated to give 4.90 g (83% from **9**) of **11** as a foam.

The product **11** (2.40 g) was dissolved in anhydrous methanol (100 ml) containing dissolved sodium (0.2 g) and the solution was kept overnight at room temperature with protection from moisture. The solution was neutralized by portionwise addition of Dowex-50 (H^+, X2, 50–100) resin. The resin was removed by filtration and washed with methanol. The filtrate and washings were evaporated to a syrup. The syrup was extracted with hot abs. ethanol and the extract was evaporated to a syrup. Warming the syrup with ethyl acetate and allowing the solution to stand gave crude, crystalline **11**; yield 1.49 g (90%), m.p. 144–149°. The compound was dissolved in methanol and the solution was decolorized. Evaporation and crystallization of the resulting syrup twice from methanol–ethanol (seeding) gave pure **10**; m.p. 149–150°, $[\alpha]_D^{25}$ +101.1° (*c* 1.10, water); λ_{max}^{pH1} 264 (8.30 × 10^3), λ_{min}^{pH1} 230 (1.75 × 10^3), λ_{max}^{pH11} 261 (6.13 × 10^3), λ_{min}^{pH11} 240 nm (3.94 × 10^3); p.m.r. (D_2O): δ 5.87 (d, $J_{5,6}$ 8.0 Hz, H-5), 7.73 (d, H-6); mass spectrum MH^+ 259.

Anal. Calc. for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.57; H, 5.72; N, 10.63.

*1-(2,5-Anhydro-1-deoxy-*D*-altritol-1-yl)-4-thiouracil* (**13**). — The remainder of **11** (2.50 g) was dissolved in reagent-grade pyridine (100 ml) and phosphorus pentasulfide (6.0 g) was added. The mixture was stirred and heated for 6 h under reflux. The solution was evaporated to smaller volume and water was added. The mixture was extracted with chloroform and the extract was washed consecutively with water, 2M hydrochloric acid, saturated sodium hydrogen carbonate solution, and water. The dried ($MgSO_4$) solution was evaporated to give 2.26 g of crude **12** as a yellow foam.

A solution of **12** in chloroform was evaporated onto silica gel to give a dry, free-running powder, which was added to the top of a column (44 × 3.5 cm) to give a column 53 × 3.5 cm. The column was eluted with chloroform and 200-ml fractions were collected. Fractions 6–11 were evaporated to give 2.22 g of a yellow syrup. The syrup was dissolved in methanol (75 ml) containing dissolved sodium (0.2 g). The solution was protected from moisture, kept for 2 h at room temperature, and then was neutralized by the portionwise addition of Dowex-50 X2, (H^+, 50–100) resin. The resin was removed and washed with methanol. The solution and washings were evaporated to a yellow syrup, which crystallized from abs. ethanol to give yellow crystals of **13**; yield 1.22 g (66%), m.p. 183–185°. The product was dissolved in methanol and the solution decolorized. Evaporation to a syrup and crystallization from abs. ethanol gave 1.12 g of pure **13**; m.p. 184–186°, $[\alpha]_D^{25}$ +154.8° (*c* 1.09, water); λ_{max}^{pH1} 243 (4.03 × 10^3), 331 (2.21 × 10^4), λ_{min}^{pH1} 274 (1.34 × 10^3), λ_{max}^{pH11} 314 nm (1.94 × 10^4); p.m.r. (D_2O): δ 6.51 (d, $J_{5,6}$ 7.0 Hz, H-5), 7.57 (d, H-6); mass spectrum MH^+ 275.

Anal. Calc. for $C_{10}H_{14}N_2O_5S$: C, 43.77; H, 5.14; N, 10.21; S, 11.69. Found: C, 43.65; H, 5.42; N, 9.94; S, 11.34.

*1-(2,5-Anhydro-1-deoxy-*D*-altritol-1-yl)cytosine* (**14**). — 1-(2,5-Anhydro-1-deoxy-D-altritol-1-yl)-4-thiouracil (**13**, 0.70 g) was dissolved in methanol (100 ml) presaturated with ammonia at 0° and the solution was heated in a steel bomb overnight at 100°. The product was filtered through Celite and the filtrate evaporated to a syrup. The syrup was dissolved in water and added to a column (34 × 2.2 cm) of Dowex-50 (H^+, X2, 50–100), and the column was washed with water (400 ml). The column was eluted with 3% aqueous ammonium hydroxide solution and 50-ml fractions were collected. Fractions 4–7 were evaporated to give a crystalline solid; yield 0.60 g (91%), m.p. 211–215°. Two recrystallizations from methanol with decolorization gave pure **14**; m.p. 220–221°, $[\alpha]_D^{25}$ +121.5° (*c* 1.06, water); λ_{max}^{pH1} 280 (1.29×10^4), λ_{min}^{pH1} 239 (1.07×10^3), λ_{max}^{pH7} 272 (8.60×10^3), λ_{min}^{pH7} 246 (4.56×10^3), λ_{max}^{pH11} 270 (8.60×10^3), λ_{min}^{pH11} 246 (4.56×10^3); p.m.r. (D_2O): δ 5.98 (d, $J_{5,6}$ 7.5 Hz, H-5), 7.62 (d, H-6).

Anal. Calc. for $C_{10}H_{15}N_3O_5$: C, 46.69; H, 5.88; N, 16.34. Found: C, 46.70; H, 6.21; N, 15.91.

*9-(2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-*D*-altritol-1-yl)adenine* (**17**). — To crude 1-amino-2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-D-altritol (**5**, 25.3 g) was added 5-amino-4,6-dichloropyrimidine (9.56 g) and butanol (350 ml, dried over Linde 4A sieves), and the mixture was stirred until it was homogeneous. Triethylamine (8.2 ml) was added, and the mixture was stirred and heated for 48 h at 105° under reflux with an oil bath. The mixture was evaporated to a syrup and the syrup was extracted with chloroform. The extract was washed (thrice) with water, and dried (magnesium sulfate). The solution was evaporated to a syrup and examined by t.l.c. with (4:1) chloroform–ethyl acetate as developer. Two components were observed. The slower-moving one gave a positive test with sulfuric acid (charring) and Draggendorf spray, and the faster-moving one migrated with a marker of 5-amino-4,6-dichloropyrimidine.

The syrup was dissolved in chloroform and added to the top of a column (56 × 5.3 cm) of silica gel prepacked in chloroform. The column was eluted with chloroform and 200-ml fractions were collected. Fractions 12–32 (slow component) were evaporated to a syrup.

Fractions 5–11, which contained both components, were rechromatographed on another column. Further processing of mixed material from this column on a third column yielded complete separation of the material, so that a total of 17.2 g of the slow-moving component (crude **15**), was isolated as a dark syrup.

Crude **15** was dissolved in ethyl orthoformate (85 ml) and concentrated hydrochloric acid (3.6 ml) was added. The solution was stirred for 3 days at room temperature. The solution was evaporated to dryness under vacuum (oil pump) at room temperature. Toluene was then evaporated from the residue and the syrup resulting was kept under vacuum (oil pump) for 2 h. The dried syrup (crude **16**) was dissolved in methanol (200 ml) presaturated at 0° with ammonia, and the solution was sealed in a steel bomb and heated overnight at 100°. The solution was evaporated to a

syrup, which was dissolved in chloroform, washed with brine (thrice), and dried (magnesium sulfate).

The solution containing **17** was applied to a column (62 × 5.3 cm) of silica gel prepacked in chloroform. Initially, the column was eluted with chloroform. Fractions 1–5 were of 500-ml volume and fractions thereafter were of 300-ml volume. The fractionation was monitored by t.l.c. with (9:1) ethyl acetate–methanol as developer. At fraction 21 the solvent was changed to (9:1) chloroform–methanol. Fractions 11–33 were pooled and evaporated to a syrup that was dissolved in chloroform and applied to a column (62 × 5.2 cm) of alumina prepacked in chloroform. The column was eluted with chloroform, and 500-ml fractions were collected from 1–5 and 300-ml fractions thereafter. Fractions 6–45 were evaporated to give 12.5 g of a dark syrup, which was subjected to further purification on a column of silica gel in the manner outlined previously. The resulting syrup crystallized on standing. Crystallization (seeding) from ethyl acetate–ether gave 6.80 g of **17**, m.p. 95–98°. The mother liquors yielded another crop (1.17 g), m.p. 92–95°. The two crops were combined and dissolved in ethyl acetate. The solution was decolorized and evaporated to smaller volume. Addition of ether and seeds gave 7.70 g (24%) of crude **17**, m.p. 98–100°. Recrystallization gave pure product; m.p. 98–100°; p.m.r.(Me_2SO-d_6): δ 8.17 (s), 8.35 (s, 2 and 8 protons); mass spectrum MH^+ 552.

Anal. Calc. for $C_{32}H_{33}N_5O_4$: C, 69.67; H, 6.03; N, 12.70. Found: C, 69.92; H, 5.85; N, 12.60.

*9-(2,5-Anhydro-1-deoxy-*D*-altritol-1-yl)adenine* (**18**). — To prereduced palladium chloride (2.70 g) in anhydrous methanol (250 ml) was added 9-(2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-D-altritol-1-yl-adenine (**17**, 3.0 g) in methanol (200 ml). The mixture was hydrogenated at atmospheric pressure until uptake of hydrogen ceased. The catalyst was removed and washed with methanol. The solution and washings were neutralized by portionwise addition of Dowex 2X8, (HCO_3^-, 50–100). The resin was removed and washed with methanol. The solution and washings were evaporated to small volume. Addition of ethanol and evaporation afforded 1.35 g (89%) of crystals of crude **18**, m.p. 264–266°. Recrystallization from water afforded pure product; m.p. 264–266°, $[\alpha]_D^{25}$ +78.0° (*c* 1.08, dimethyl sulfoxide); λ_{max}^{pH1} 259 (14.2×10^3), λ_{min}^{pH1} 232 (3.70×10^3), $\lambda_{max}^{H_2O}$ 260 (14.2×10^3), $\lambda_{min}^{H_2O}$ 227 (2.56×10^3); p.m.r. (Me_2SO-d_6): δ 8.12 (s), 8.17 (s, 2 and 8 protons); mass spectrum MH^+ 282.

Anal. Calc. for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.38; N, 24.90. Found: C, 46.77; H, 5.32; N, 24.92.

*9-(2,5-Anhydro-1-deoxy-*D*-altritol-1-yl)hypoxanthine* (**19**). — To a stirred suspension of 9-(2,5-anhydro-D-altritol-1-yl)adenine (**18**, 0.50 g) in water (100 ml) containing sodium nitrite (1.8 g) was added glacial acetic acid until a pH value of 3.6 was reached. The reaction vessel was loosely stoppered and the solution was stirred overnight at 5° to achieve solution. The solution was then kept for 6 days at room temperature. The pH of the solution was adjusted to 9 and the solution was added to a column (30 × 3.7 cm) of Dowex-1X2, (formate, 100–200). The column was washed with water until the effluent was neutral. The column was eluted with a formic acid

solution (10 ml of formic acid per 2 litres) and 300-ml fractions were collected. Fractions 1–5, which contained u.v.-absorbing material, were evaporated to afford a crystalline solid (crude **19**). This material was dissolved in water and the solution was decolorized. The solution was evaporated to smaller volume and the product crystallized by addition of ethanol and warming; yield 0.49 g (98%), m.p. 270–272°, $[\alpha]_D^{25}$ +82.6° (*c* 1.05, dimethyl sulfoxide); λ_{max}^{pH1} 249 (1.09×10^4); λ_{min}^{pH1} 221 (2.85×10^3), $\lambda_{max}^{H_2O}$ 250 (1.22×10^4), $\lambda_{min}^{H_2O}$ 223 (3.36×10^3), λ_{min}^{pH11} 253 (1.34×10^4), λ_{min}^{pH11} 226 (2.58×10^3); p.m.r. (Me_2SO-d_6): δ 8.09 (s, 2 and 8 protons); mass spectrum MH^+ 283.

Anal. Calc. for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; N, 19.85. Found: C, 46.42; H, 5.02; N, 19.94.

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