2-Deoxy Sugars. VIII. Nucleosides Derived from 2-Deoxy-D-allopyranose (2-Deoxy-D-*ribo*-hexopyranose)[1]

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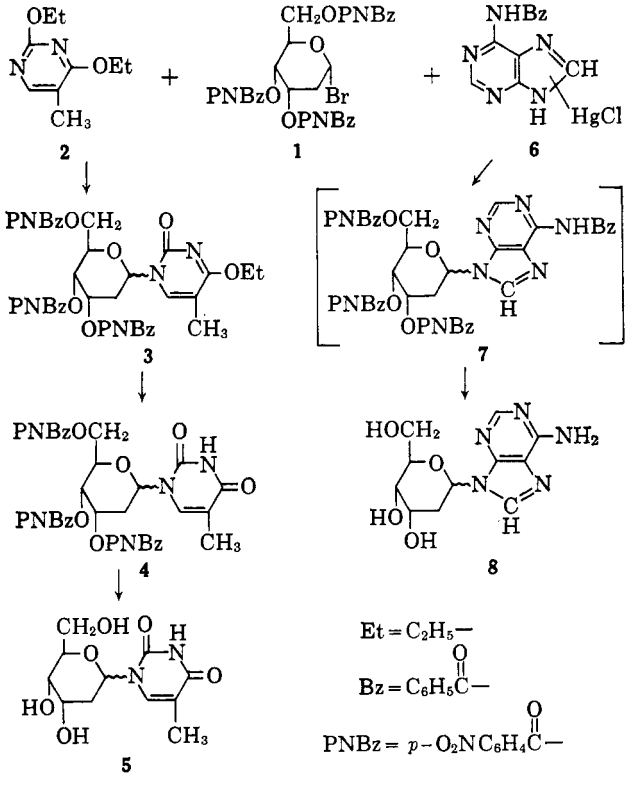
Received February 17, 1964

As a continuation of our earlier work[3] on the direct synthesis of potential, anticancer nucleosides using stable crystalline *p*-nitrobenzoylglycosyl halides of 2-deoxy sugars, we investigated the preparation of additional nucleosides to contain as the carbohydrate component 2-deoxy-D-allopyranose (2-deoxy-D-*ribo*-hexopyranose). This paper deals with the preparation of 9-(2-deoxy-D-*ribo*-hexopyranosyl)adenine (**8**) and 1-(2-deoxy-D-*ribo*-hexopyranosyl)thymine (**5**). The latter nucleoside is of especial interest owing to a recent discovery[4] that 1-(2-deoxy-D-*arabino*-hexopyranosyl)thymine, prepared for the first time in this laboratory,[3] is a powerful and apparently specific inhibitor of pyrimidine nucleoside phosphorylase, obtained from Ehrlich's ascites tumor cells. Because the new nucleoside (**5**) and "2-deoxyglucosyl thymine"[3,4] differ only with respect to the configuration of the hydroxyl group about C-3 of the sugar moiety, it is considered that **5** might display an equivalent or even superior biological activity.



The coupling of 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*ribo*-hexosyl bromide (**1**)[5] and 2,4-diethoxy-5-methylpyrimidine (**2**) took place readily to give crystalline, protected nucleoside **3** which was de-ethylated to give the nitrobenzoylated intermediate **4**, which was likewise crystalline. Deacylation of **4** by means of ethanolic ammonia gave amorphous, hygroscopic 1-(2-deoxy-D-*ribo*-hexopyranosyl)thymine (**5**) in 18% yield based on the bromide **1**.

The bromide reacted also with chloromercuri-6-benzamidopurine (**6**) which resulted in amorphous, protected nucleoside **7**, a fraction of which was insoluble in chloroform. The chloroform extract was purified by column chromatography and, after deacylation with ethanolic ammonia, gave crude nucleoside **8** which was further purified *via* its picrate salt. This resulted in 8.4% (based on **1**) of pure 9-(2-deoxy-D-*ribo*-hexopyranosyl)adenine hemihydrate (**8**), having $[\alpha]_D$ +74.9°.

The chloroform-insoluble material obtained from the protected nucleoside **7** was treated in a similar manner and gave 3.2% (based on **1**) of nucleoside **8** as a monohydrate, having $[\alpha]_D$ +49.5°. Because the ultraviolet absorption spectra and the chromatographic behavior of the two adenine nucleosides are the same, additional studies will be required to determine whether the latter material is the alternate anomeric form of **8**.

Experimental

All melting points were determined using a Kofler hot stage. All paper and t.l.c. chromatograms were carried out by an ascending technique employing saturated aqueous ammonium sulfate–2-propanol–water (2:28:70).

1-(2-Deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-D-*arabino*-hexopyranosyl)-4-ethoxy-5-methyl-2(1*H*)-pyrimidone (3).—An intimate mixture of 750 mg. (1.11 mmoles) of 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*ribo*-hexopyranosyl bromide (**1**) and 750 mg. (4.03 mmoles) of 2,4-diethoxy-5-methylpyrimidine (**2**) was heated at 55° for 24 hr. under a reduced pressure of 20 mm. After cooling, the melt was crushed and extracted five times with 50-ml. portions of ether. The crude, protected nucleoside **3** amounting to 500 mg. was recrystallized from chloroform–ethanol (1:1), giving 335 mg. of pure **3**, m.p. 276–276.5°.

Anal. Calcd. for $C_{34}H_{29}NO_{15}$: C, 54.61; H, 3.91; N, 9.37. Found: C, 54.37; H, 4.28; N, 8.92.

1-(2-Deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-D-*ribo*-hexopyranosyl)-thymine (4).—To a solution of the 335 mg. of protected nucleoside **3** obtained in the preceding preparation in 40 ml. of chloroform–ethanol (1:1) was added 6 ml. of 20% methanolic hydrogen chloride. The mixture was stirred under the exclusion of moisture overnight, after which the solvent was evaporated *in vacuo*. Recrystallization of the residue from chloroform–ethanol gave 270 mg. of pure **4**, m.p. 317–320°.

Anal. Calcd. for $C_{32}H_{25}N_5O_{15}$: C, 53.41; H, 3.50; N, 9.73. Found: C, 53.55; H, 3.92; N, 8.60.

1-(2-Deoxy-D-*ribo*-hexopyranosyl)thymine (5).—The 270 mg. of de-ethylated, acylated nucleoside **4** obtained in the preceding experiment was dissolved in 27 ml. of absolute ethanol saturated with ammonia at 0°, and the solution was stirred for 24 hr. in a closed flask. The clear solution was evaporated to dryness and the residue was washed three times with 50-ml. portions of ether. It was then dissolved in 50 ml. of water and was extracted with three 50-ml. portions of chloroform. After separating, the aqueous layer was evaporated to dryness, giving 54 mg. of pure nucleoside **5** as an amorphous, hygroscopic powder, m.p. 116–126°, $[\alpha]^{25}_D$ +68.7° (*c* 2.73, methanol), $\lambda^{H_2O}_{max}$ 267 mμ (log ε 3.80), ν^{KBr}_{max} 1665 cm.$^{-1}$ (—NHCO—). When chromatographed on paper the nucleoside **5** traveled as a single spot ($R_{thymine}$ 1.07).

9-(2-Deoxy-D-*ribo*-hexopyranosyl)adenine (8).—To a solution of 2.28 g. (3.38 mmoles) of the bromide (**1**) in 50 ml. of dry dichloromethane was added 1.44 g. (3.04 mmoles) of chloromercuri-6-benzamidopurine (**6**) and the mixture was stirred for 24 hr. at room temperature. After filtering the mercury salts, the filtrate was evaporated under reduced pressure giving 2.2 g. of crude, pro-

(1) This work was supported largely by U. S. Public Health Service Grant CY-4288.

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(3) W. W. Zorbach and G. J. Durr, *J. Org. Chem.*, **27**, 1474 (1962).

(4) P. Langen and G. Etzold, *Biochem. Z.*, **339**, 190 (1963).

(5) W. W. Zorbach and W. Bühler, *Ann. Chem.*, **670**, 116 (1963).

tected nucleoside **7** which was then treated with chloroform, leaving 1.0 g. of insoluble material. After evaporation of the solvent, the chloroform-soluble material was placed on a column (3 × 26 cm.) of 80 g. of silicic acid (Fisher reagent grade, activated for 1 hr. at 105°) and was eluted with chloroform–methanol (95:5), 2.5-ml. eluates being collected. The desired material, amounting to 240 mg., appeared in fractions 141–200, and was then dissolved in 40 ml. of absolute ethanol saturated with ammonia at 0°. After stirring in a closed flask for 24 hr., the insoluble material was filtered and the filtrate was evaporated to dryness. The residue was dissolved in 10 ml. of methanol, 100 mg. of picric acid was added, and, after standing for 5 hr., the resulting yellow salt was collected. It was next treated in water for 18 hr. with 10 ml. of Amberlite IR-45 ion-exchange resin and, after filtering, the clear solution was evaporated to dryness at 30°. Recrystallization of the residue from 95% ethanol gave 80 mg. (8.4% based on 1) of pure 9-(2-deoxy-D-*ribo*-hexopyranosyl)-adenine (**8**) as a hemihydrate, m.p. 159–164°, $[\alpha]^{23}D$ +74.9° (*c* 0.833, methanol), $\lambda_{max}^{H_2O}$ 259.5 mμ (log ε 4.22). When chromatographed on paper the nucleoside **8** traveled as a single spot ($R_{adenine}$ 1.11). On t.l.c. chromatograms the R_f value was 0.75.

Anal. Calcd. for $C_{11}H_{15}N_5O_4 \cdot 0.5\ H_2O$: C, 45.51; H, 5.55; N, 24.12. Found: C, 45.43; H, 5.97; N, 24.29.

Anomeric (?) Nucleoside 8.—The chloroform-insoluble fraction of the protected nucleoside **7** obtained in the preceding experiment was placed on a column (3 × 26 cm.) of 60 g. of silicic acid (activated for 1 hr. at 105°) and 40 g. of Celite 505, similarly dried. Elution, in 2.5-ml. fractions, was carried out using ethyl acetate, and from fractions 21–36 there was obtained 500 mg. of material which was deacylated and treated in the same manner as that described in the foregoing experiment. The white powder obtained was recrystallized from 95% ethanol giving 30 mg. (3.2% based on 1) of hydrated nucleoside, m.p. 143–150°, $[\alpha]^{23}D$ +49.5° (*c* 0.370, methanol), $\lambda_{max}^{H_2O}$ 260 mμ (log ε 4.10). When chromatographed on paper, the material traveled as a single spot ($R_{adenine}$ 1.11). On t.l.c. chromatograms the R_f value was 0.75.

Anal. Calcd. for $C_{11}H_{15}N_5O_4 \cdot H_2O$: C, 44.14; H, 6.72; N, 23.40. Found: C, 44.87; H, 6.00; N, 23.54.

Acknowledgment.—For the elemental analyses the authors are indebted to Miss Paula Parisius, Microanalytical Laboratory, LC, NIAMD, National Institutes of Health, Bethesda, Maryland, under the direction of Mr. H. G. McCann.

3,3′-Diphenyl-1,1′-bibenzo[*c*]thienyl

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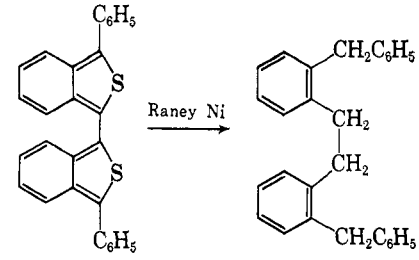
Received September 12, 1963

In a survey of known derivatives of benzo[*c*]thiophene[1] our attention was directed to a red compound, m.p. 237°, obtained by heating *o*-benzoylbenzoic acid with phosphorus pentasulfide,[2] which was reported to be 1-phenylbenzo[*c*]thiophene. Since 1,3-diphenylbenzo[*c*]thiophene, for which the structure is firmly established,[3] is yellow and melts at 118–119°, the color and melting point of the supposed 1-phenylbenzo[*c*]-thiophene seemed out of line. Investigation has shown this compound to be 3,3′-diphenyl-1,1′-bibenzo[*c*]-thienyl (I).



I II

Structure proof was accomplished by desulfurization of I to *o,o′*-dibenzylbibenzyl (II).

This structure assignment was supported by examination of the mass spectrum, which had a parent peak at 418 (98%) and a peak at mass 354 ascribable to the loss of two sulfur atoms. This shows that the original molecular weight determination (223 and 239 found[2]) must have been in error.

Experimental[4]

3,3′-Diphenyl-1,1′-bibenzo[*c*]thienyl (I).—This compound was prepared as described by O'Brochta and Lowy[2] (termed 2-phenyl-3,4-benzothiophene). Deep red needle-like crystals of I, m.p. 236–237°, were obtained in 15% yield; infrared spectrum: 3.28, 6.26, 6.69, 6.92, 7.34, 7.57, 8.29, 9.23, 9.68, 10.80, 11.70, 11.89, 13.1 (broad), 13.4 (very broad), and 14.4 (very broad) μ; mass spectrum: parent peak at 418 (98%) and peak at 354, due to loss of both sulfur atoms. No peaks attributable to (isotopic) oxygen.

Anal. Calcd. for $C_{28}H_{18}S_2$: C, 80.37; H, 4.33; S, 15.30. Found: C, 79.67; H, 4.31; S, 15.50. Reported in ref. 2: C, 80.01, 80.29; H, 4.72, 4.73; S, 15.02.

Desulfurization of I with Raney Nickel.—A mixture of 1.7 g. (4.1 mmoles) of I, approximately 20 g. of Raney nickel, and 50 ml. of 95% ethanol was refluxed for 2 days. The insoluble residue was removed by filtration, and the filtrate was concentrated until solid material crystallized. Recrystallization from 95% ethanol afforded 1.0 g. (68%) of a white crystalline compound, m.p. 97–98°, identified as *o,o′*-dibenzylbibenzyl (II) by comparison with an authentic sample, synthesized as described below. The infrared spectra were identical in all respects, and the mixture melting point was undepressed.

***o*-Benzylbenzyl Alcohol** (IV).—This compound was prepared from *o*-benzylbenzoic acid[5] as described by Speeter.[6] IV was obtained as a colorless liquid, b.p. 147–148° (1 mm.), $n^{20}D$ 1.5942, lit.[6] b.p. 148–151° (3 mm.). Upon standing at room temperature, the alcohol solidified. Recrystallization from hexane gave white needle-like crystals of IV, m.p. 37–38°; infrared spectrum: broad O–H at 3.0, 6.22, 6.70, 6.89, 9.6–10.0 (broad bands), 13.2–13.7 (broad bands), and 14.5 μ.

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 85.26; H, 7.18.

The **phenylurethan derivative** melted at 60–61°, lit.[6] m.p. 77–78°; infrared spectrum: 3.08 (N–H), 5.92 (C=O), 6.25, 6.56, 6.94, 7.62, 8.05, 8.16, 9.43, 13.16, 13.85, and 14.50 μ.

Anal. Calcd. for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 80.16; H, 6.33; N, 4.56.

***o*-Benzylbenzyl Bromide** (V).—To a solution of 12.8 g. (64.6 mmoles) of IV in 20 ml. of benzene, cooled in an ice bath, was added dropwise 6.0 g. (22 mmoles) of phosphorus tribromide over a 15-min. period. The mixture was stirred overnight while coming to room temperature and allowed to stand until a total reaction time of 24 hr. had elapsed. Work-up in the usual manner afforded 17.0 g. of a crude oily product which crystallized when placed in a Dry Ice–acetone bath. Recrystallization from hexane gave 13.0 g. (77.1%) of white needle-like crystals of V, m.p. 40–42°. Further recrystallization from hexane gave the analytical sample, m.p. 42–43°. V gave an immediate

(1) The parent compound has been synthesized recently by R. Mayer, *et al.*, *Angew. Chem.*, **74**, 118 (1962); *Angew. Chem., Intern. Ed. Eng.*, **1**, 115 (1962).

(2) J. O'Brochta and A. Lowy, *J. Am. Chem. Soc.*, **61**, 2765 (1939).

(3) See H. D. Hartough and S. L. Meisel, "Compounds with Condensed Thiophene Rings," Interscience Publishers, Inc., New York, N. Y., 1954, pp. 169–170.

(4) Carbon, hydrogen, and nitrogen analyses were by Miss Hilda Beck. Sulfur analysis was by Micro-Tech Laboratories, Skokie, Ill. All infrared spectra were taken in potassium bromide pellets.

(5) E. L. Martin, *J. Am. Chem. Soc.*, **58**, 1441 (1936).

(6) M. E. Speeter, U. S. Patent 2,759,934; *Chem. Abstr.*, **51**, 2044 (1957).