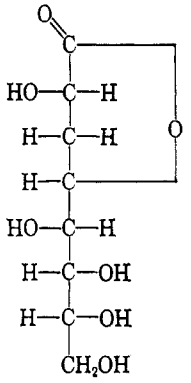
10.0. Both 3-deoxy-D-*arabino*-hexonic γ-lactone and **1** were devoid of resonance signal in this region while 2-*C*-methyl-D-*ribo*-pentonic γ-lactone showed the expected *C*-methyl signal as a singlet at τ 8.08. The lack of *C*-methyl signal in the p.m.r. spectrum of **1** eliminates the saccharinic acid structure and the metasaccharinic acid structure is established.

That **1** is a γ-lactone is indicated by its lack of mutarotation[2] and the presence of a band at 1765 cm.$^{-1}$ in the infrared.[8] The phenylhydrazide derivative of the octonic lactone is levorotatory and, by the phenylhydrazide rule,[9] the hydroxyl on C-2 is to the left in the Fischer projection formula. If one assumes the formation of the lactone *via* the Nef–Isbell mechanism,[6b,10] **1** is then 3-deoxy-D-*glycero*-D-*ido*-octonic γ-lactone.



1

It is interesting to note that Hudson's lactone rule[11] predicts the metasaccharinic acid structure as the only possibility for the octonic lactone. Its specific optical rotation was reported as +27° [2]; the γ-lactones of the two branched chain structures would both have negative optical rotations.

Experimental[12]

3-Deoxy-D-*glycero*-D-*ido*-octonic Phenylhydrazide.—A mixture of 3-deoxy-D-*glycero*-D-*ido*-octonic lactone (20 mg.), phenylhydrazine (25 mg.), and acetic acid (0.40 ml.) in water (1 ml.) was heated at 100° for 1 hr. The solution was cooled and concentrated *in vacuo* at 60° to an oil which crystallized upon addition of ethanol. The crystals (18 mg.) were collected, washed with ethanol, and dried. Two recrystallizations from methanol produced pure product, m.p. 153–154°, $[\alpha]^{20}D$ −8.8° (H_2O, *c* 1).

Anal. Calcd. for $C_{14}H_{22}O_7N_2$: C, 50.90; H, 6.71; N, 8.48. Found: C, 50.67; H, 6.68; N, 8.70.

Acknowledgment.—This work was done in the laboratories of Dr. H. E. Carter and was supported by Public Health Service grants.

(8) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 178.

(9) P. A. Levene, *J. Biol. Chem.*, **23**, 145 (1915); C. S. Hudson, *J. Am. Chem. Soc.*, **39**, 462 (1917); P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, **31**, 623 (1917).

(10) H. S. Isbell, *J. Res. Natl. Bur. Std.*, **32**, 45 (1944).

(11) C. S. Hudson, *J. Am. Chem. Soc.*, **32**, 338 (1910); E. Anderson, *ibid.*, **34**, 51 (1912).

(12) Proton magnetic resonance spectra were taken in deuterium oxide on a Varian A-60 instrument by the spectroscopy laboratory, Department of Chemistry.

Nucleosides. V. The Monomesylates of 1-(2′-Deoxy-β-D-lyxofuranosyl)thymine[1,2]

JEROME P. HORWITZ, JONATHAN CHUA, AND MICHAEL NOEL

The Rollin H. Stevens Memorial Laboratory, Detroit Institute of Cancer Research, Detroit, Michigan 48201

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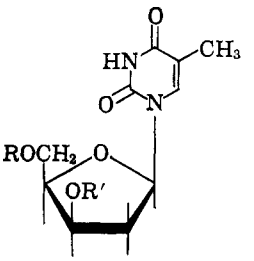
A recent study in this laboratory corrected the identity of 3′-*O*-mesyl- and 5′-*O*-mesylthymidine.[3] Efforts were then directed toward the synthesis of the corresponding mesylates of the 2′-deoxylyxosyl epimer (**4**) of thymidine. In fact, an unsuccessful attempt to prepare 1-(2′-deoxy-5′-*O*-mesyl-β-D-lyxofuranosyl)thymine (**5**) has since been recorded.[4] However, the simultaneous disclosure[4,5] of a practical route to 1-(2′-deoxy-β-D-lyxofuranosyl)thymine (**4**) by two laboratories provided an approach to the desired monomesyloxy derivatives.



1, R = $(C_6H_5)_3C$; R′ = H
2, R = $(C_6H_5)_3C$; R′ = CH_3SO_2
3, R = H; R′ = CH_3SO_2
4, R = R′ = H
5, R = CH_3SO_2; R′ = H

The mesylation of 1-(2′-deoxy-5′-*O*-trityl-β-D-lyxosyl)thymine (**1**), the direct precursor[4,5] of **4**, afforded the sulfonate **2** in high yield. Detritylation of **2** with anhydrous hydrogen chloride in chloroform at −5° gave 1-(2′-deoxy-3′-*O*-mesyl-β-D-lyxofuranosyl)-thymine (**3**) in 66% yield. Unimolar mesylation of **4** in a mixture of chloroform and pyridine at −5° produced a single[6] monomesylate (73% yield) with chromatographic (*cf.* Table I) and spectral (infrared) properties distinctly different from those of **3**. Accordingly, it is concluded that selective esterification of the primary (C′-5) alcohol function in **4** was effected and structure **5** is assigned to the product.

The acquisition of **2** provided the opportunity of studying the replacement of the mesyloxy group by nucleophiles such as azide, iodide, and benzoate ions. These transformations are of interest in view of the fact that recent studies have emphasized the difficulty of promoting the displacement of secondary sulfonates

(1) This work was supported in part by Research Grants CA-02903 and CY-5943 from the National Cancer Institute, Public Health Service, and in part by an institutional grant from the United Foundation of Greater Detroit allocated through the Michigan Cancer Foundation.

(2) Presented, in part, before the Division of Medicinal Chemistry, 144th National Meeting, American Chemical Society, Los Angeles, Calif., April, 1963.

(3) J. P. Horwitz, J. A. Urbanski, and J. Chua, *J. Org. Chem.*, **27**, 3300 (1962).

(4) J. P. Horwitz, J. Chua, J. A. Urbanski, and M. Noel, *ibid.*, **28**, 942 (1963).

(5) J. J. Fox and N. C. Miller, *ibid.*, **28**, 936 (1963).

(6) The same reaction conditions applied to thymidine produced a mixture of mesylates.

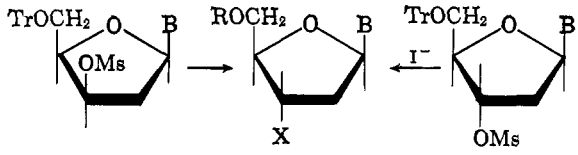
TABLE I

$R_{thymidine}$ VALUES FOR THE MONOMESYLATES OF 1-β-D-(2′-DEOXYALDOPENTOFURANOSYL)THYMINE[a]

Thymine derivative	Solvent system[b] A	B
3′-*O*-Mesylthymidine	1.02	1.52
3	0.82	1.06
5′-*O*-Mesylthymidine	0.92	1.19
5	0.90	1.37

[a] Ascending thin-layer chromatograms were run on silica gel G (Research Specialties Co.). The compounds were located on the chromatogram either by ultraviolet light alone or in conjunction with a fluorescein–bromine spray technique [J. G. Kirchner, J. M. Miller, and G. J. Keller, *Anal. Chem.*, **23**, 420 (1951)]. Each chromatogram included thymidine and the results represent the average of several determinations. [b] Two solvent systems were employed: A, *n*-butyl alcohol–water (86:14); and B, benzene–ethanol (7:3).

of cyclic carbohydrate derivatives in the absence of anchimeric assistance to the reaction.[7-10] A *cis* relationship between the aglycon and mesyloxy moieties in **2** obviously precludes the possibility of participation by the 2-carbonyl of the pyrimidine in these replacements.



B = thymine
Tr = $(C_6H_5)_3C$
MS = CH_3SO_2

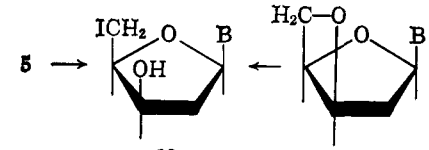
6, R = Tr; X = N_3
7, R = H; X = N_3
8, R = H; X = NH_2·HCl
9, R = Tr; X = I
10, R = H; X = I
11

Treatment of **2** with lithium azide in N,N-dimethylformamide at 100° for 3 hr. led to a solid that was characterized by a strong azide absorption at 4.76 μ and the disappearance of mesylate absorption at 7.35 and 8.48 μ. The crude[11] product (**6**), on detritylation, gave a crystalline solid (62% yield based on **2**) with properties consistent with those of 1-(3′-azido-2′,3′-dideoxy-β-D-*erythro*-pentosyl)thymine (3′-azido-3′-deoxythymidine, **7**). The latter, on catalytic reduction, gave 3′-amino-3′-deoxythymidine (**8**),[12] which was isolated as a hydrochloride.

The interaction of **2** and sodium iodide in acetone at 100° for 16 hr. gave a product identical in every respect with the known 3′-deoxy-3′-iodo-5′-*O*-tritylthymidine (**9**) obtained from 3′-*O*-mesyl-5′-*O*-tritylthymidine[13] (**11**). Moreover, **9**, obtained by either route, yielded the same 3′-deoxy-3′-iodo nucleoside (**10**) on detritylation. It was originally assumed[13] that the action of sodium iodide on **11** led to 3′-iodo derivative of the "down" or *ribo* configuration. The present findings lend credence to the original structural assignment and provide additional support for the view[5] that displacement on **11** by iodide ion proceeds through a 2,3′-anhydro nucleoside under acid catalysis.

Treatment of **2** with sodium benzoate in refluxing DMF led only to partial replacement of the sulfonyloxy group after 70 hr. It is apparent, then, that the displacement of this function requires the use of strong nucleophilic reagents under forcing conditions. The present observations are in accord with the concept that ring sulfonates are, in general, relatively unreactive in the absence of neighboring group participation.[7-9]

The synthesis of **5** provided an alternate route to an iodo nucleoside (**13**) obtained in a previous study[4] from the action of sodium iodide on 1-(2′-deoxy-3′,5′-epoxy-β-D-lyxofuranosyl)thymine (**12**). It was suggested that opening of the epoxide ring in **12** occurred as a result of attack at C′-5 to form 1-(2′,5′-dideoxy-5′-iodo-β-D-lyxosyl)thymine (**13**). It was found that **5**, on treatment with sodium iodide in butanone, yielded an identical product.



B = thymine

Experimental[14]

1-(2′-Deoxy-3′-*O*-mesyl-5′-*O*-trityl-β-D-lyxosyl)thymine (2).—To a cold solution of 9.0 g. (18.6 mmoles) of **1**[4,5] in 50 ml. dry pyridine was added 4.2 ml. (57.2 mmoles) of methanesulfonyl chloride and the reaction mixture was held at 0° for 16 hr. The amber solution was then allowed to reach room temperature and held there for 3 hr.[15] The reaction mixture was again cooled to 0°, treated with *ca.* 2 ml. of ice–water, refrigerated for an additional hour, and finally poured slowly, with vigorous stirring, into 1.5 l. of ice–water. After 1 hr. of stirring the product was collected, air-dried, and crystallized from ethanol, 9.25 g (80% yield), m.p. 108–110°. Material in this form was sufficiently pure for succeeding transformations. Three recrystallizations from ethanol provided analytical material, m.p. 116–118°, $[\alpha]^{26}D$ −14° (*c* 0.5, ethanol); $\lambda^{EtOH}_{max,\ min}$ 266 mμ (ε 10,000), 243 (5015).

Anal. Calcd. for $C_{30}H_{30}N_2O_7S \cdot C_2H_5OH$: C, 63.34; H, 5.98; N, 4.61. Found: C, 63.05; H, 5.38; N, 4.94.

1-(2′-Deoxy-3′-*O*-mesyl-β-D-lyxofuranosyl)thymine (3).—To a solution of 2.0 g. (3.76 mmoles) of **2** (once recrystallized) in 25 ml. of chloroform, chilled to 0°, was added a cold solution of chloroform (22 ml.) containing 5.4 mequiv. of dry hydrogen chloride, and the mixture was held at −5° for 16 hr. The solution was decanted from an oil that lined the reaction vessel and the oil then triturated with cold chloroform. The addition of a small quantity (*ca.* 10 ml.) of ethanol and scratching effected solidification of the oil. The amorphous solid was collected, washed with cold ethanol, and air-dried, 0.735 g. (61%), m.p. 156–158° dec. Evaporation of the original chloroform solution in a stream of air left a residue which, on recrystallization from ethanol, gave an additional crop (0.055 g., 5%) of solid, m.p. 157–160° dec. Recrystallization of the first crop from ethanol gave material, m.p. 161–162°, in the form of transparent plates, $[\alpha]^{26}D$ −40° (*c* 0.5, ethanol); $\lambda^{EtOH}_{max\ min}$ 265 mμ (ε 10,550), 234 (2500); λ^{KBr}_{max} 7.35, 8.48 μ (sulfonate).

Anal. Calcd. for $C_{11}H_{16}N_2O_7S$: C, 41.24; H, 5.04; N, 8.75. Found: C, 41.19; H, 5.16; N, 8.92.

1-(2′-Deoxy-5′-*O*-mesyl-β-D-lyxofuranosyl)thymine (5).—To a solution of 1.53 g. (6.32 mmoles) of **4**[4,5] in 5 ml. of dry pyridine

(7) For a summary of earlier work related to this subject, see S. R. Tipson, *Advan. Carbohydrate Chem.*, **8**, 107 (1953).

(8) B. R. Baker and A. H. Haines, *J. Org. Chem.*, **28**, 438 (1963).

(9) M. L. Wolfrom, J. Bernsmann, and D. Horton, *ibid.*, **27**, 4505 (1962).

(10) W. M. Zu Reckendorf and W. A. Bonner, *Tetrahedron*, **19**, 1711 (1963).

(11) No attempt was made to purify this product.

(12) The synthesis of this compound by an alternate route was recently announced by N. C. Miller and J. J. Fox, Abstracts of Papers, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963, p. 21D.

(13) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 816 (1955).

(14) Melting points are corrected. Infrared spectra were recorded by a Perkin-Elmer Model 21 spectrophotometer (KBr) and ultraviolet spectra by a Cary Model 11 spectrophotometer. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(15) It was found that mesylation was incomplete after 16 hr. at 0°.

cooled to −12° was added dropwise with magnetic stirring and over a period of 0.5 hr. a solution of 0.54 ml. (7.4 mmoles) of methanesulfonyl chloride in 3 ml. of chloroform. The reaction mixture was held overnight (16 hr.) at −5°. Methanol (5 ml.) was then added and the solution evaporated to dryness *in vacuo*. This procedure was repeated twice with ethanol after which the residue crystallized from the same solvent as colorless irregular prisms, 1.45 g. (73% yield), m.p. 142–145° dec. Two recrystallizations from ethanol provided analytical material, m.p. 148–149°, $[\alpha]^{26}D$ +10° (*c* 0.5, ethanol); $\lambda_{max,\ min}^{EtOH}$ 266 mμ (ε 9700), 234 (2230).

Anal. Calcd. for $C_{11}H_{16}N_2O_7S$: C, 41.24; H, 5.04; N, 8.75. Found: C, 41.47; H, 5.00; N, 8.73.

3′-Azido-3′-deoxythymidine (7).—A solution of 3.27 g. (6.7 mmoles) of **2** in 20 ml. of DMF containing 1.0 g. of lithium azide[16] was stirred for 3 hr. at 100° under an atmosphere of nitrogen. The cooled reaction mixture was poured, with stirring, into 600 ml. of ice–water and the product (**6**) was collected. The air-dried, off-white solid (3.4 g.), which showed a prominent azide peak (λ_{max}^{KBr} 4.76 μ), was dried (P_2O_5) for 4 hr. at 50° (0.1 mm.) and used without further purification.

To a solution of 3.4 g. (6.7 mmoles) of **6** in 5 ml. of chloroform cooled to 0° was added 36 ml. of a cold chloroform solution containing 8.6 mmoles of hydrogen chloride. The cloudy reaction mixture was refrigerated for 1 hr. and then poured into 5 ml. of a saturated solution of sodium bicarbonate. The two-phase mixture was evaporated to dryness in a stream of air and the residue triturated with four 10-ml. portions of acetone. The acetone extract was treated with Norit and concentrated to *ca.* one-half of the original volume. The addition of petroleum ether (b.p. 30–60°) caused the slow deposition of the product in the form of a mat of colorless needles, 1.34 g. (62% yield based on **2**), m.p. 106–112°. Recrystallization of the product from ether did not change the melting point. However, material of m.p. 119–121° was obtained after drying at 100° (1×10^{-2} mm.) for 16 hr., $[\alpha]^{25}D$ +99° (*c* 0.5, water); λ_{max}^{KBr} 4.76 μ (azide); $\lambda_{max,\ min}^{H_2O}$ 266.5 mμ (ε 11,650), 234.5 (2610).

Anal. Calcd. for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.21. Found: C, 44.98; H, 4.74; N, 26.22.

3′-Amino-3′-deoxythymidine Hydrochloride (8).—A solution of 0.6 g. (1.9 mmoles) of **7** in 25 ml. of ethanol containing 0.25 g. of platinum oxide was shaken under 3 atm. of hydrogen for 2.5 hr. The catalyst was removed by filtration; the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in 5 ml. of 2-propanol and to this solution was added an equal volume of cold, saturated 2-propanolic hydrogen chloride. The salt that was deposited was collected, 0.35 g. (57% yield), m.p. 240–245° dec. Two recrystallizations from methanol–2-propanol provided an analytical sample, m.p. 248–249° dec., $[\alpha]^{25}D$ +11° (*c* 0.58, H_2O); $\lambda_{max,\ min}^{H_2O}$ 265.5 mμ (ε 10,015), 234.5 (2320).

Anal. Calcd. for $C_{10}H_{16}N_8O_4Cl$: C, 43.24; H, 5.80; N, 15.13. Found: C, 43.07; H, 6.12; N, 14.83.

3′-Deoxy-3′-iodo-5′-*O*-tritylthymidine (9) from 2.—A solution of 0.335 g. of **2** and 0.2 g. (1.33 mmoles) of anhydrous sodium iodide in 15 ml. of dry acetone was heated at 100° in a pressure bottle for 15 hr. The inorganic salts were removed and the filtrate was evaporated to dryness *in vacuo*. The residue was triturated with water and the yellow amorphous solid was collected. The product crystallized from acetone–methanol in the form of colorless cubes, 0.13 g. (37% yield), m.p. 145–148° (lit.[13] m.p. 147°). Recrystallization from the same solvent system raised the melting point to 148–150°, $[\alpha]^{25}D$ +59° (*c* 0.42, acetone); $\lambda_{max,\ min}^{EtOH}$ 266 mμ (ε 10,110), 244 (4650).

From 3′-*O*-Mesyl-5′-*O*-tritylthymidine (11).—A solution of 0.335 g. (0.6 mmoles) of **11** and 0.2 g. (1.3 mmoles) of anhydrous sodium iodide in 15 ml. of acetone was treated in a pressure bottle at 100° for 18 hr.[17] The work-up and recrystallization of the product was identical with that described above, 0.15 g. (44% yield), m.p. and m.m.p. 148–150°, $[\alpha]^{24}D$ +59° (*c* 0.51, acetone); $\lambda_{max,\ min}^{EtOH}$ 266 mμ (ε 10,500), 244 (4900).

Samples of **9** obtained by the two routes gave 3′-deoxy-3′-iodothymidine (**10**) as a colorless crystalline solid on detritylation with 80% acetic acid, m.p. 166–167° dec. (lit.[13] m.p. 166–167° dec.).

1-(2′,5′-Dideoxy-5′-iodo-β-D-lyxosyl)thymine (13) from 5.—A solution of 0.32 g. (1 mmole) of **5** and 0.3 g. (2 mmoles) of anhydrous sodium iodide in 15 ml. of butanone was refluxed for 17 hr. under an atmosphere of nitrogen. The inorganic salts were removed by filtration and the solution was evaporated to dryness *in vacuo*. The residue was triturated with *ca.* 5 ml. of ice–water; the solid was collected and then recrystallized from ethanol, 0.20 g. in two crops (57% yield), m.p. 154–157° dec. A second recrystallization from ethanol provided an analytical sample, m.p. 156–157° dec., $[\alpha]^{25}D$ −38° (*c* 0.53, ethanol); $\lambda_{max,\ min}^{EtOH}$ 266 mμ (ε 10,930), 234 (3160).

Anal. Calcd. for $C_{10}H_{13}N_2O_4I$: C, 34.11; H, 3.72; N, 7.96. Found: C, 34.11; H, 3.78; N, 7.81.

From 12.—A solution of 1.0 g. (4.5 mmoles) of **12**[4] and 2.0 g. (13.3 mmoles) of sodium iodide in 25 ml. of butanone containing 0.4 ml. of glacial acetic acid was refluxed under an atmosphere of nitrogen for 16 hr. The inorganic salts were removed; the filtrate was evaporated to dryness *in vacuo*. The gummy residue solidified on trituration with *ca.* 5 ml. of ice–water. The solid was collected, washed with two 5-ml. portions of water, and sucked dry, 1.04 g. (66% yield), m.p. 156–157° dec. The product obtained by this procedure gave spectrophotometric and polarimetric data identical with that obtained above.

(16) J. P. Horwitz, A. J. Tomson, J. A. Urbanski, and J. Chua, *J. Org. Chem.*, **27**, 3045 (1962).

(17) A reaction period of 2 hr. as employed by the English workers (see ref. 13) gave **9** in only 24% yield.

Monoglucose Derivatives of Gentisic Acid

A. ZANE AND S. H. WENDER

Chemistry Department, University of Oklahoma, Norman, Oklahoma

Received January 17, 1964

A glucoside of gentisic acid (2,5-dihydroxybenzoic acid) has been found to accumulate in sunflower leaves that have become deficient in boron.[1] As the position of attachment of the glucose unit in the unknown glucoside was not determined, synthesis of the hitherto unknown monoglucosides of gentisic acid for use as reference standards was undertaken. Gentisic acid-5-β-D-glucopyranoside (I), gentisic acid-2-β-D-glucopyranoside (II), and 1-*O*-gentisoyl-β-D-glucopyranose (III) have been prepared.

Glucosides I and II were obtained from their known methyl esters[2] by de-esterification with barium hydroxide. Compound III was produced by the condensation of 2,5-dibenzyloxybenzoyl chloride with the sodium salt of 4,6-*O*-benzylidene-α-D-glucopyranose in chloroform, followed by the catalytic reduction of the product. It was then purified on a polyamide column. Acetylation of III produced the hexaacetate, 1-*O*-(2′,5′-diacetylgentisoyl)-β-D-glucopyranose tetraacetate. This derivative was identical with that obtained by the condensation of gentisic acid diacetate with tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of silver oxide and quinoline. Steps in the preparation of monoglucosides of gentisic acid are summarized in Fig. 1.

Experimental

Melting points are not corrected and were taken in open capillary tubes. No efforts were made to obtain maximum possible yields.

2,5-Dibenzyloxybenzoic Acid.—To a solution of 61.6 g. (0.4 mole) of gentisic acid in 800 ml. of absolute ethyl alcohol was added 228 ml. of freshly distilled benzyl chloride, followed by 332 g. of anhydrous potassium carbonate. The mixture was refluxed for 20 hr. under anhydrous conditions and cooled to room

(1) R. Watanabe, W. Chorney, J. Skok, and S. Wender, *Phytochemistry*, in press.

(2) G. Wagner, *Arch. Pharm.*, **291**, 278 (1958).