An Unexpected Conformational Preference in a Sugar Derivative

R. S. GLASS[1] AND T. WILLIAMS*

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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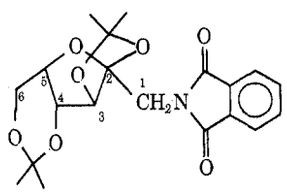
This paper presents a suggestion for the conformation of 1-phthalimido-1-deoxy-2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (**1**) derived from nmr studies.



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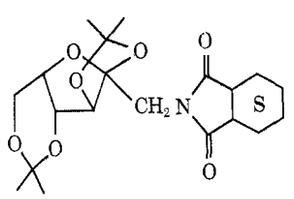
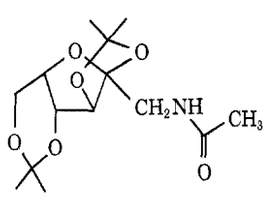
Specifically, the C_2–O bond of the isopropylidene ring is predominantly transcoplanar with the C_1–N bond in the favored rotamer.

Phthalimide **1** was prepared from 1-*O*-*p*-toluenesulfonyl-2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose. Chemical proof for the structure was obtained by conversion to the corresponding known primary amine.[2]

The nmr spectrum of phthalimide **1** reveals one methyl group resonating at unusually high field (Table I, **1** *vs.* **2**–**4**). Furthermore, the position of this methyl





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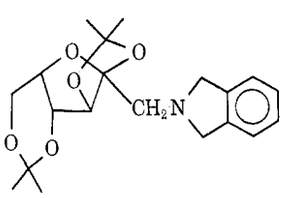

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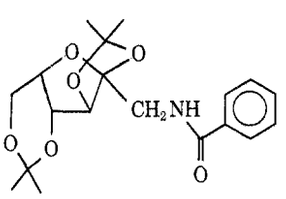

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peak of **1** in DMSO-d_6 solution does not change upon 32-fold dilution, but moved downfield from δ 0.67 at 27° to 0.77 at 100° while no change occurred for other methyl bands. Thus, one methyl group is shielded intramolecularly by the phthalimide moiety. Shielding by an anisotropic benzene ring is well documented[3] and this effect has been used to determine stereochemistry and conformation[4] of aromatic compounds.

(1) University of Arizona, Tucson, Arizona.

(2) K. Tokuyama, *Bull. Chem. Soc. Jap.*, **37**, 1133 (1964). This amine was also prepared by reduction of the azide obtained from sodium azide and the same tosylate.

(3) J. A. Pople, *J. Chem. Phys.*, **24**, 1111 (1956); C. E. Johnson, Jr., and F. A. Bovey, *ibid.*, **29**, 1012 (1958).

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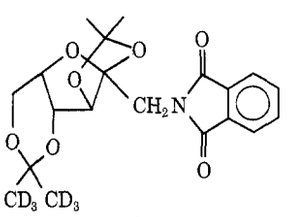
TABLE I

NMR CHEMICAL SHIFTS

Compd	Solvent	δ, Methyl groups			
1	DMSO-d_6	0.65	1.21	1.29	1.41
	CD_3OD	0.67	1.28	1.32	1.44
	Acetone-d_6	0.72	1.25	1.35	1.41
	$CDCl_3$	0.82	1.29	1.33	1.48
	C_6D_6	0.82	0.92	1.20	1.38
	C_6D_5N	0.91	1.29	1.31	1.51
2	$CDCl_3$	1.27	1.35	1.39	1.44
3	$CDCl_3$	1.35	1.40	1.43	1.46
4	DMSO-d_6	1.25	1.34	1.39	1.42
	$CDCl_3$	1.38	1.43	1.43	1.50
5	DMSO-d_6	1.06	1.19	1.32	1.36
	$CDCl_3$	1.03	1.38	1.42	1.50
6	DMSO-d_6		1.20		1.38
	Acetone-d_6		1.25		1.41
	C_6D_6			1.17	1.37
	C_6D_5N		1.27		1.48

When a catalytic amount of perchloric acid was added to a solution of **1** in acetone-d_6 and the nmr spectrum was measured at various times, the high-field methyl peak as well as one other methyl band disappeared rapidly, and the nmr and mass spectra of the deuterated compound are consistent with its formulation as 1-phthalimido-1-deoxy-2,3-mono-*O*-isopropylidene-4,6-mono-*O*-hexadeuterioisopropylidene-α-L-sorbofuranose (**6**).



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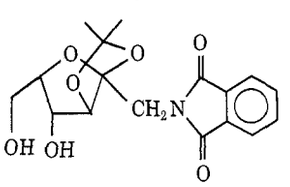

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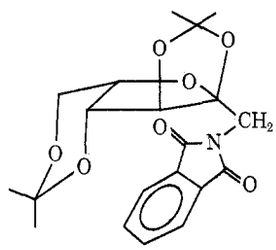
That exchange occurred in the 4,6 position was confirmed by selective acid-catalyzed hydrolysis of **6** to give a monoisopropylidene derivative **7** free of deuterium and identical with that obtained by partial hydrolysis of **1**. The nmr spectrum of **7** in DMSO-d_6 displays a doublet and a triplet which disappear on addition of deuterium oxide. This confirms the presence[5] of a primary and a secondary alcohol, as in structure **7**.

Consideration of molecular models of **1** reveals that only one methyl group in the 4,6-isopropylidene bridge can be shielded by the aromatic ring of the phthalimide moiety. This shielding may be achieved in the conformation depicted below. The reason for the importance of this conformation merits comment.

The most impressive conformational changes in phthalimide **1** are brought about by ring flip of the 1,3-dioxane ring and rotation about the C_1–C_2 and C_1–N

(5) D. E. Greer and M. M. Mocek, *J. Chem. Educ.*, **40**, 358 (1963).



single bonds. The 1,3-dioxane ring in the conformation shown above is in the energetically more favorable chair form.[6] Of the three staggered conformations about C_1–C_2, only the one shown should result in shielding[3,4,7] of a methyl group of the 4,6-isopropylidene group. To achieve the amount of shielding observed, phthalimide **1** must spend a considerable portion of its time in the conformation shown above. Dreiding molecular models reveal that the center of the methyl group is approximately 4 Å from the center of the benzene ring, and from this is predicted[3] a shielding of 0.8 ppm. The experimental values (0.5 to 0.6 ppm, compound **1** *vs.* **2**, **3**, and **4** in Table I) were in good agreement. The other conformers might be destabilized by steric or dipolar interactions of the carbonyl groups or the conformer shown might be stabilized by some interaction. Since none of the methyl groups in isoindoline **4** resonate at high field, the first explanation may not apply. Although it is possible that the nitrogen is tetrahedral in **4** (sp^3 hybridized) but trigonal[8] in **1** (sp^2), the methylene protons of **4** are magnetically equivalent, suggesting trigonal hybridization. Thus, an intriguing possibility is that some interaction stabilizes the conformation shown. The oxygens of the 1,3-dioxane ring are very close to the carbonyl carbons of the phthalimide moiety. This may result in favorable intramolecular interaction, *e.g.*, dipolar interaction. A similar explanation was offered to explain an unusual conformational preference in substituted aziridines.[3] Such an interaction is not possible with isoindoline **4**, and this may account for the lack of substantial shielding of a methyl group in this compound.

Interestingly, one methyl group in benzamide **5** appears to absorb at slightly higher field than expected. Perhaps, effects similar to that proposed for phthalimide **1** are operative here, but hydrogen bonding, which is possible in benzamide **5** but not in phthalimide **1**, is likely to be of much importance.[9]

Experimental Section

Melting points were taken with a Thomas-Hoover capillary melting point apparatus and are not corrected. The ir spectra were recorded on a Perkin-Elmer 621 spectrophotometer, the uv spectra on a Cary 15 spectrometer, the nmr spectra on a Varian HA-100 spectrometer, and the mass spectra on a CEC 21-110 spectrometer.

1-Phthalimido-1-deoxy-2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (1).—1-*O*-*p*-Toluenesulfonyl-2,3:4,5-di-*O*-isopropylidene-α-L-sorbofuranose[10] (1.64 g, 4.00 mmol) and potassium phthalimide (0.833 g, 4.50 mmol) in *N*,*N*-dimethylformamide (35 ml) were heated at reflux for 48 hr[11] and cooled, the solvent was removed *in vacuo*, and the residue was diluted with water (30 ml) and extracted with six 50-ml portions of ether. The ethereal extract was dried (anhydrous Na_2SO_4), filtered, concentrated to dryness, chromatographed on silica gel, and recrystallized from ether–pentane to give 0.683 g (43%) of crystalline phthalimide **1**: mp 148–150°, mp of analytical sample 152.5–153°; $[\alpha]^{25}D$ −21.7° (*c* 0.96, $CHCl_3$); ir (KBr) 2990, 2910, 1770, 1720, 1400 cm^{-1}; uv max (C_2H_5OH) 219.5 mμ (ε 41,300), 233 (12,500), 241.5 (9150), 293.5 (1780).

Anal. Calcd for $C_{20}H_{23}NO_7$: C, 61.69; H, 5.95; N, 3.60. Found: C, 61.44; H, 5.88; N, 3.68.

Hyrazinolysis.[12]—A solution of **1** (712 mg, 1.83 mmol), 85% hydrazine hydrate (1.4 ml), and 95% ethanol (5.5 ml) was heated at reflux for 2 hr and cooled. A solution of sodium hydroxide (600 mg) in water (3.5 ml) was added, and the reaction mixture was extracted with four 20-ml portions of ether. The ethereal extract was washed with four 2-ml portions of water, dried (anhydrous K_2CO_3), concentrated to dryness, and chromatographed on silica gel to give 206 mg (43%) of a solid which was identical with authentic 1-amino-1-deoxy-2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose[2] by mixture melting point, tlc, ir, and nmr spectra.

Hexahydrophthalimide 2 was prepared according to general procedure[13] as colorless prisms: mp 52–54° from pentane; nmr ($CDCl_3$) δ 1.30–2.00 (m, 8, 4 CH_2), 2.97 (m, 2, CHCH), 4.00 (s, 5, CH + 2 CH_2), 4.24, 4.60 (s, 2, 2 CH).

Anal. Calcd for $C_{20}H_{29}NO_7$: C, 60.74; H, 7.39; N, 3.54. Found: C, 60.52; H, 7.47; N, 3.58.

Acetamide 3.—To a cooled solution of 1-amino-1-deoxy-2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (207 mg, 0.800 mmol) in pyridine (1.25 ml) was added acetic anhydride (1.50 ml). The solution was stirred at room temperature for 24 hr, concentrated to dryness, and crystallized from ether to give crystalline acetamide **3** (220 mg, 91%): mp 146–148°; $[\alpha]^{25}D$ −62.2° (*c* 2.27, C_2H_5OH); mass spectrum *m/e* 301; ir ($CHCl_3$) 3445, 2995, 1660, 1508, 1380 cm^{-1}; nmr ($CDCl_3$) δ 1.97 (s, 3, CH_3CO), 6.09 (broad, 1, NH).

Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69. Found: C, 56.08; H, 7.83.

Isoindoline 4 was prepared according to general procedure[14] as a colorless oil: nmr ($CDCl_3$) δ 3.22 (s, 2, CH_2N), 4.00–4.13 (m, 3, CH + CH_2), 4.15 (s, 4, CH_2NCH_2), 4.28 (d, 1, J = 2.5 Hz, CH), 4.47 (s, 1, CH).

Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.39; H, 7.60; N, 3.87.

Benzamide 5.—To a solution of 1-amino-1-deoxy-2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (129 mg, 0.50 mmol) in pyridine (0.2 ml) at 0° was added dropwise with stirring a solution of benzoyl chloride (81.3 mg, 0.58 mmol) in pyridine (0.4 ml) and the mixture was allowed to warm to room temperature during 2 hr. After removal of pyridine by evaporation under reduced pressure, aqueous copper sulfate and chloroform were added. The chloroform layer was washed with aqueous copper sulfate and water, dried (anhydrous Na_2SO_4), concentrated to dryness (205 mg), and chromatographed on silica gel plates. Elution with 9:1 (v/v) chloroform–methanol gave an oil: yield 184 mg; ir ($CHCl_3$) 3455, 1670 cm^{-1}; nmr ($CDCl_3$) δ 3.70–4.20 (m, 5, CH + 2 CH_2), 4.25 (d, 1, J = 2 Hz, CH), 4.49 (s, 1, CH), 6.53 (broad, 1, NH), 7.43 (m, 3, aromatic), 7.89 (m, 2, aromatic).

Phthalimide 6 from 1 by Ketone Exchange.—To phthalimide **1** (40 mg) in acetone-d_6 (0.4 ml) was added perchloric acid (71–72%, 0.5 ml) and the nmr spectra were taken after 20 min, 3.7 hr, and 24 hr.

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(8) G. S. D. King, *J. Chem. Soc. B*, 1224 (1966); P. Groth, *Acta Chem. Scand.*, **23**, 1076 (1969).

(9) Rotational freedom in benzamide **5** may be limited by partial double bond character of the amide N–C bond and by orbital overlap between the π orbital of the benzene ring and those of the amide group. See A. H. Lewin and M. Frucht, *Tetrahedron Lett.*, 1079 (1970), and references cited therein.

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(11) M. S. Gibson and R. W. Bradshaw, *Angew. Chem., Int. Ed. Engl.*, **7**, 919 (1968).

(12) H. S. Mosher, *J. Amer. Chem. Soc.*, **68**, 1565 (1946).

(13) A. J. McAlees and R. McCrindle, *J. Chem. Soc. C*, 2425 (1969); M. Prostenik, M. Munk-Weinert, and D. E. Sunko, *J. Org. Chem.*, **21**, 406 (1956).

(14) J. Bornstein, S. C. Lashua, and A. P. Boisselle, *J. Org. Chem.*, **22**, 1255 (1957).

Time	δ, Methyl groups			
0 min	0.72	1.25	1.35	1.41
20 min	0.71[a]	1.22	1.32[a]	1.40
3.7 hr		1.21		1.41
24 hr		1.22		1.40

[a] Peak height is *ca.* 20% that of sample before addition of $HClO_4$.

The above sample was poured into water and extracted with chloroform. The extracts were dried (anhydrous Na_2SO_4), concentrated, and recrystallized from ether to give **6**: mp 149–152°; nmr (acetone-d_6) δ 3.70–4.50 (m, 6), 4.76 (s, 1), 7.88 (s, 4); mass spectrum *m/e* 395.

1-Phthalimido-1-deoxy-2,3-*O*-isopropylidene-α-L-sorbofuranose (7) by Hydrolysis of 6.—A solution of **6** (46 mg, 0.12 mmol), glacial acetic acid (1.0 ml), and water (0.5 ml) was stirred at room temperature for 86 hr. Pyridine was then added and the solution was concentrated to dryness and extracted with ether. The extract was dried (anhydrous Na_2SO_4), filtered, and concentrated to dryness to give **7** as an oil which was crystallized from benzene to give 23 mg (55%) of **7**, mp and mmp with later sample 175–178°, ir and nmr spectra identical within experimental error to data below.

By Hydrolysis of 1.—Phthalimide **1** (500 mg, 1.29 mmol), hydrolyzed and worked up in the same way as **6**, afforded from benzene crystals of **7**: mp 178–181°; $[\alpha]^{25}D$ −4.5° (*c* 1.05, C_2H_5OH); ir ($CHCl_3$) 3455, 1777, 1720, 1714, 1425, 1398 cm^{-1}; uv max (C_2H_5OH) 220.5 mμ (ε 46,000), 234 (14,100 infl), 242 (10,000), 293.5 (2200); nmr (DMSO-d_6) δ 1.10, 1.36 (s, 6, 2 CH_3), 3.40–4.20 (m, 5, CH + CH_2), 4.46 (s, 1, CH), 4.44 (t, 1, *J* = 6 Hz, exchanged by D_2O addition, CH_2OH), 5.01 (d, 1, *J* = 4.5 Hz, exchanged by D_2O addition, CHOH), 7.85 (s, 4, aromatic).

Anal. Calcd for $C_{17}H_{19}NO_7$: C, 58.45; H, 5.48; N, 4.01. Found: C, 58.62; H, 5.47; N, 4.03.

Registry No.—**1**, 35170-82-2; **2**, 35170-83-3; **3**, 35170-84-4; **4**, 35192-04-2; **5**, 35170-85-5; **6**, 35170-86-6; **7**, 35170-87-7.

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Preferential Cleavage of an Aromatic Methylenedioxy Group in the Presence of Methoxyls with Boron Trichloride

S. TEITEL,* J. O'BRIEN, AND A. BROSSI

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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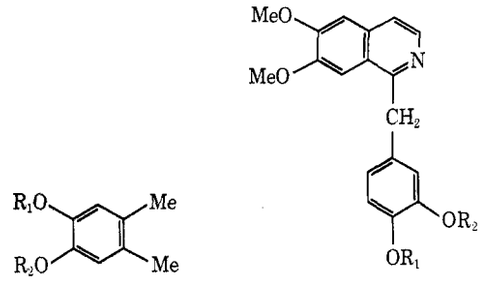
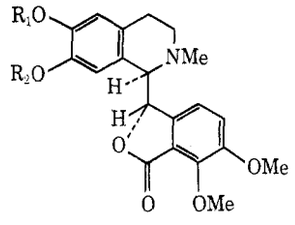
In connection with our studies on the transformation of phthalideisoquinolines into rheadans,[1] the methylenedioxy dimethoxy-substituted alkaloid (−)-β-hydrastine (**3a**) was deetherified with boron tribromide to the tetraphenol and methylated to the tetramethoxy phthalide (−)-cordrastine II[2] (**3c**). We now report a novel and more facile synthesis of **3c** based on the preferential O-demethylenation of **3a** with boron trichloride[3] followed by methylation of the resulting diphenol **3b**.



1a–c **2a–c**



3a–c

a, $R_1 + R_2 = -CH_2-$
b, $R_1 = R_2 = H$
c, $R_1 = R_2 = Me$

The type and extent of deetherification of model compounds treated with boron trichloride in methylene chloride was influenced by the ratio of substrate to reagent as well as the reaction temperature and time. By proper selection of conditions, cleavage of a methylenedioxy group in preference to aromatic methoxyls could be achieved. For example, treatment of 4,5-methylenedioxy-*o*-xylene (**1a**)[4] at room temperature with either 1 or 2 equiv of boron trichloride for 64 and 3 hr, respectively, gave 4,5-dimethylcatechol (**1b**)[5] in 80% yield while cleavage of 4,5-dimethoxy-*o*-xylene (**1c**)[5] required either higher temperatures or longer reaction times to effect ether cleavage. Similarly, while both the methylenedioxy-substituted isoquinoline **2a**[6] and its methoxy analog papaverine (**2c**) were converted by treatment with 2 molar equiv of the reagent for 5 hr at room temperature into a mixture of phenolic materials, only **2a** was cleanly cleaved at 4° to yield 78% 3′,4′-O-demethylpapaverine (**2b**)[7] while **2c** was recovered unchanged.

To further illustrate the synthetic applicability of preferential *O*-demethylenation, commercially available (−)-β-hydrastine (**3a**) was treated with 2 mol of boron trichloride in methylene chloride at room temperature for 6 hr to afford 81% the diphenol **3b**. Reaction of **3b** with diazomethane provided the tetra-

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(2) S. Teitel, J. O'Brien, and A. Brossi, *J. Org. Chem.*, **37**, 1879 (1972).

(3) Boron trichloride has been used in the selective scission of cyclic acetals [T. G. Bonner and N. M. Saville, *J. Chem. Soc.*, 2851 (1960)] and in the preferential O-demethylenation of certain podophyllotoxins [E. Schreier, *Helv. Chim. Acta*, **47**, 1529 (1964); H. MacLean and B. F. MacDonald, *Can. J. Chem.*, **47**, 457 (1969)]. Its selective action parallels that of aluminum bromide in nitrobenzene [E. Mosettig and A. Burger, *J. Amer. Chem. Soc.*, **52**, 2988 (1930)].

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