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REVISION, BY PROTON, CARBON-13, AND NITROGEN-15 N.M.R. SPECTROSCOPY, OF THE STRUCTURE ASSIGNED A BIS(HEXOPYRANOSYL)-AMINE DERIVATIVE*

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ABSTRACT

Structural analysis of the acetylated, minor product of the reaction of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside with ammonia by high-field proton- and ^{13}C-n.m.r. spectroscopy, and also ^{15}N-n.m.r. spectroscopy, has shown that this acetyl derivative is bis(methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)amine, and not the *N*-acetyl derivative reported previously. The configuration and conformation of the bis(altropyranosid-3-yl)amine derivative have been determined, and its unusually large $^1J_{^{15}\mathrm{NH}}$ coupling constant is discussed.

INTRODUCTION

In 1943, Myers and Robertson reported[1] that reaction of ammonia with methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside affords a major yield of methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside and a minor yield of a second compound (*A*) which was presumed to be methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside. Formation of the 2,3-*trans*-diaxial adduct having the α-D-*altro* configuration would be expected to predominate in this reaction as a consequence of the operation of the Fürst–Plattner rule[2]. The structure of the 3-amino-α-D-*altro* derivative is well documented, and the compound has been widely used in synthetic studies of amino sugars[3,4]. The minor product *A* was isolated in approximately one percent yield as its crystalline acetyl derivative (*B*), m.p. 235°, $[\alpha]_D^{12}$ +45.5° in chloroform, which was presumed[1] to be methyl 2-acetamido-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside. The latter derivative was later synthesized by Wiggins[5] by an unequivocal route, and was shown to be different from

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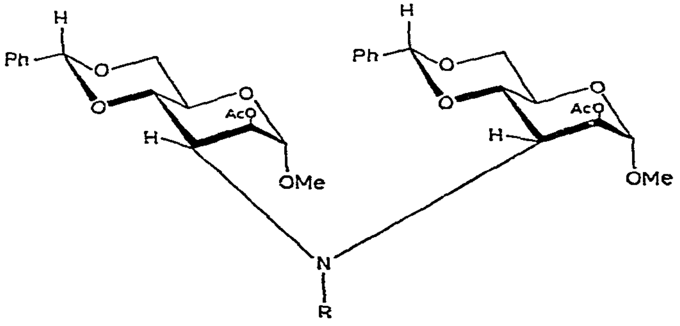
product *B*. He demonstrated[5] by elemental analysis and determination of molecular weight (630) that compound *B* was not a monomeric, amino sugar derivative, but that it contained one nitrogen atom combined with two aldose residues. Wiggins indicated[5] that the elemental analysis and mode of formation of *B* were consistent with its representation as either *N*-(methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-α-altropyranosid-3-yl)-*N*-(methyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-α-glucopyranosid-2-yl)acetamide, or as *N*,*N*-bis(methyl 2-*O*-acetyl 4,6-*O*-benzylidene-3-deoxy-α-altropyranosid-3-yl)acetamide. The latter structure was tentatively favored, because product *B* could also be synthesized in "quite good" yield (24 percent) by direct reaction of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside with methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside, followed by acetylation[5]. By analogy with the observed effects of anhydro-ring fission by simple reagents, it was suggested that both hexose parts of *B* would have the α-*altro* configuration. However, these parts were incorrectly depicted[5] as having opposite enantiomorphic configurations (D and L). As depicted previously[5], molecule *B* had a plane of symmetry, and would not have been optically active. Actually, both hexose parts of *B* must have the D configuration.

The minor product *A* has been inadvertently recorded as a monomeric 2-amino-2-deoxy-D-glucose derivative in three reviews of amino sugars[6-8] and as an iminobis(D-glucose) derivative in a more recent, comprehensive treatise[9].

RESULTS AND DISCUSSION

We now report a new structural (and conformational) analysis of the acetylated compound (*B*) that demonstrates that it is a secondary amine (**1**) and not the *N*-acetyl derivative (**2**). In fact, conventional elemental analysis does not distinguish structures **1** and **2**, and the molecular weight (630) determined by Wiggins for compound *B* agrees remarkably well with that (629.6) of the amine structure **1** and less well with the molecular weight (671.7) of the *N*-acetyl structure **2** proposed by him[5]. In our hands, the reaction of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-manno-



1 R = H
2 R = Ac

pyranoside with a limited quantity of ammonia afforded a lower yield of methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside, and then (after acetylation of the mother liquors), a substantially higher yield[10] (25 percent) of compound *B* than had been achieved previously[1,5].

Although compound *B* was found to display an ester carbonyl absorption at 1744 cm^{-1} in its infrared spectrum, no amide bands were found. The observation of a weak absorption at 3420 cm^{-1} suggested the possible presence of an NH group.

The proton-n.m.r. spectrum of *B* in chloroform-*d* solution at 60 MHz was not readily interpretable, and this solution was examined at successively higher frequencies (100, 220, and 360 MHz) until adequate dispersion was obtained. The spectra of solutions of *B* in chloroform-*d* show a broad, one-proton resonance at ~3 p.p.m. that disappears on equilibration of the solution with deuterium oxide, thus suggesting the presence of an NH (or OH) group. The broad resonance did not shift upfield on heating of the solution of *B* in chloroform-*d* from 31° to 55°, thus suggesting that the exchangeable proton is not hydrogen bonded. Spin-decoupling experiments at 100 MHz, and spectral integration at 60 and 220 MHz, establish that one of the ring-proton resonances (H-3) lies underneath the methoxyl signal, and that the signal of the exchangeable proton has one-half the intensity of that of each sugar ring-proton signal. The best spectral dispersion was obtained at 360 MHz for a solution of *B*

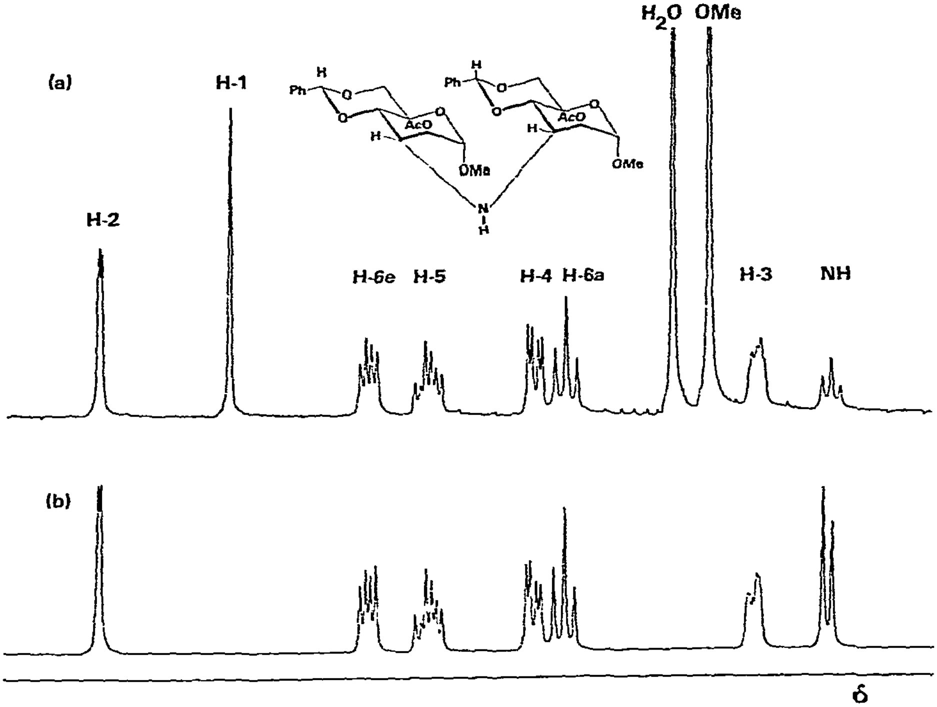


Fig. 1 Partial, proton-n m r. spectra of bis(methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)amine (*B*). [(a) Fourier-transform spectrum (8 scans) of a solution in dimethyl sulfoxide-d_6 at 360 MHz, and (b) computed spectrum.]

TABLE I

N.M.R. PARAMETERS[a] FOR BIS(METHYL 2-*O*-ACETYL-4,6-*O*-BENZYLIDENE-3-DEOXY-α-D-ALTROPYRANOSID-3-YL)AMINE

Solvent	*Parameter*	*Position*												*Ph*			
		1	*2*	*3*	*4*	*5*	*6*		*NH*	*OMe*	*CMe*	*C=O*	*Ph*CH	*1*	*2(6)*	*3(5)*	*4*
$(CD_3)_2SO$	^1H chemical shifts	4.58	4.92d[b]	3.22m	3.79q	4.07s	3.71t (6a)	4.22q (6e)	3.03t	3.34	1.98		5.62		7.40m	7.34m	7.34m
	^1H integrals	2	2	2	2	2	2	2	1	6	6		2		4	6	
	$J_{H,H}$	$J_{1,2}$ <0.5	$J_{2,3}$ 2.4	$J_{3,4}$ 3.5	$J_{4,5}$ 9.6	$J_{5,6e}$ 5.2	$J_{5,6a}$ 10.0	$J_{6e,6a}$ 9.9	$J_{3,NH}$ 8.5								
$CDCl_3$	^1H chemical shifts	4.59	5.04q	3.36	3.80q	4.22s	3.74t (6*a*)	4.28q (6*e*)	3.03[c]	3.35	1.95		5.52		7.44m	7.31m	7.31m
	^1H integrals	2	2	2	2	2[d]	2	2[d]	1[e]	6	6		2		4	6	
	$J_{H,H}$	$J_{1,2}$ 1.0	$J_{2,3}$ 2.8	$J_{3,4}$ 3.5	$J_{4,5}$ 9.4	$J_{5,6e}$ 5.1	$J_{5,6a}$ 9.4	$J_{6e,6a}$ 9.3									
	^{13}C chemical shifts[f]	99.0	72.7	55.5	77.8	58.3	69.2			55.2	21.0	169.3	102.0	137.9	126.4	128.2	128.9
$(CD_3)_2SO$	^{13}C chemical shifts[g]	98.2d[h]	72.1d	55.2d	77.0d	58.0d	68.1t			54.8q	20.6q	169.0	101.0d	137.9	126.2d	127.9d	128.6d
	$^1J_{^{13}C,H}$	174	156	142	142	149	147	147		144	129		163		161	162	158
$CDCl_3$	^{15}N chemical shift[i]								−354.4								
$(CD_3)_2SO$									−354.3								
	$J_{^{15}N,H}$				3.7				86.7								

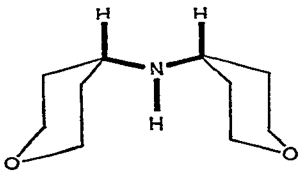
[a] ^1H and ^{13}C chemical shifts are given in p.p.m. from internal tetramethylsilane, and ^{15}N chemical shifts in p.p.m. from external $NH_4{}^{15}NO_3$ in saturated, aqueous solution. ^1H-chemical shifts and coupling constants (Hz) were measured by first order analysis of 360 MHz spectra. [b] Signal multiplicities: d, doublet; m, multiplet; q, quartet; s, sextet; t, triplet. [c] Broad singlet. [d] Unresolved. [e] At 220 MHz. [f] At 90.5 MHz. [g] At 22.6 MHz. [h] Signal multiplicities in off-resonance, proton-decoupled, ^{13}C-n.m.r. spectra. [i] At 9.1 MHz.

in dimethyl sulfoxide-d_6; this spectrum displays only one acetyl methyl signal, single methoxyl and benzylic proton signals, and a single set of proton signals for the sugar residues (see Fig. 1a). The singularity of these various signals at the highest available field-strength provides strong evidence that the two hexose parts of *B* are identical in structure and configuration.

The triplet at 3.03 p.p.m. (see Table I and Fig. 1a) displayed one-half the integrated intensity of each of the seven, fully resolved signals of the sugar protons (see Table I) and was assigned to the NH proton. The multiplicity of the NH signal, and the magnitudes of the spacings (8.5 Hz) in it, indicate that the NH proton is coupled to a vicinal H-3 on each of the pyranoid rings and that, in dimethyl sulfoxide-d_6 solution, NH proton exchange is relatively slow, presumably because of hydrogen bonding to the oxygen atoms of the solvent. The sugar-proton signals were assigned as indicated in Fig. 1a, and first-order analysis yielded the proton chemical shifts and coupling constants shown in Table I. The validity of the spectral analysis was confirmed by partial simulation of the 360-MHz spectrum of *B* (see Fig. 1b). As H-1 was not observably coupled to H-2 or H-3, it was excluded from the simulation, and the NH proton, together with H-2, H-3, H-4, H-5, H-6*e*, and H-6*a* of one pyranoid ring were simulated as a seven-spin subsystem. Good agreement between experimental and computed spectra (see Figs. 1a and 1b) was obtained, except for the NH signal, which, in the computed spectrum, lacked coupling to a second H-3. Coupling of H-1 with H-2 ($J_{1,2}$ 1.0 Hz) was observed for solutions of *B* in chloroform-*d*.

The values of the vicinal-proton coupling-constants of *B* (see Table I) are similar to values reported previously for α-D-altropyranosides[4] and to those measured more recently at 360 MHz for methyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-α-D-altropyranoside[11]. These values confirm that both pyranoid parts of *B* have the α-*altro* configuration, and indicate that both adopt the $^4C_1$(D) conformation. Typical values of $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$ for 4,6-*O*-benzylidene derivatives having the α-*gluco*, α-*allo*, and α-*manno* configurations are characteristically different[4] from those of such derivatives of the α-*altro* configuration, and the former configurations may be discounted.

The magnitudes of the coupling constants $J_{3,NH} = J_{3',NH} = 8.5$ Hz afford some evidence for the relative, stereochemical orientation of the pyranoid rings of *B*. These coupling constants may be expected to conform to a Karplus relationship[12], and the values of 8.5 Hz may be interpreted as representing pairs of vicinal protons having either *transoid* or *cisoid* orientations. Pairwise combinations of these orientations indicate the possibility of conformers having *trans-cis*, *cis-trans*, *cis-cis*, and



1a

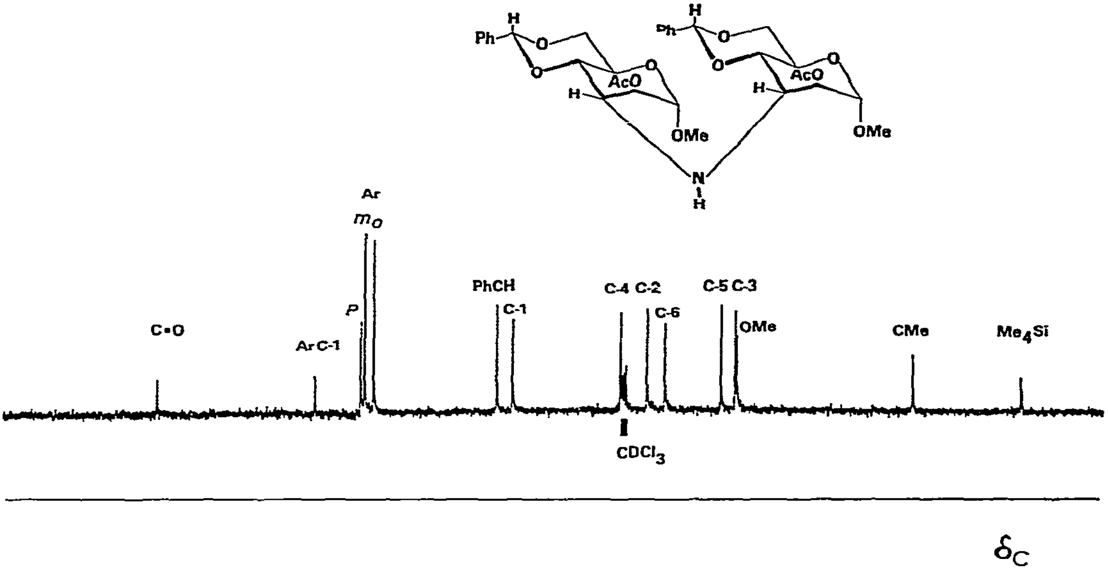


Fig. 2. Fourier-transform, ^{13}C-n m r. spectrum (49 scans) of bis(methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)amine (*B*) in chloroform-*d* at 90 5 MHz.

trans-trans orientations of the proton pairs H-3–NH and H-3′–NH. In principle, each of these conformers could exist in two diastereomeric forms, depending on the stereochemistry about the nitrogen atom. Inspection of molecular models of *B* revealed that the *trans-cis, cis-trans,* and *cis-cis* conformers all contain at least one eclipsed interaction between carbon atoms in different hexose rings. As the *trans-trans* conformer (**1a**) does not contain such interactions, it should be favored.

The carbon-13 n.m.r. spectra of *B* show only single acetyl methyl, methoxyl, and benzylic carbon signals, and only single sets of signals for the aromatic and sugar carbon nuclei, even at the highest frequency (90.5 MHz) available to us; this spectrum (see Fig. 2) provides confirmatory evidence that the hexose parts of *B* are identical (for ^{13}C data, see Table I).

The proton-decoupled, natural-abundance nitrogen-15 n.m.r. spectra of solutions of *B* in either chloroform-*d* or dimethyl sulfoxide-d_6 consist of sharp singlets (see Fig. 3a) having nitrogen-15 chemical-shifts* of −354.4 and −354.3 p.p.m., respectively (from external $NH_4{}^{15}NO_3$), that are similar to the nitrogen-14 chemical-shift (−351 ±3 p.p.m.) reported[13] for dibutylamine, and also to the nitrogen-15 chemical-shifts (approximately −361 p.p.m.) recorded for *primary* amino sugar derivatives[14]. *N*-Acetylation of an amino sugar causes a substantial shift (~90 p.p.m.) of the nitrogen resonance to lower field, which is more than sufficient to distinguish an amide from an amine[14].

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*Chemical shifts to lower frequency than the reference line are recorded herein as negative, so as to be consistent with current ASTM recommendations.

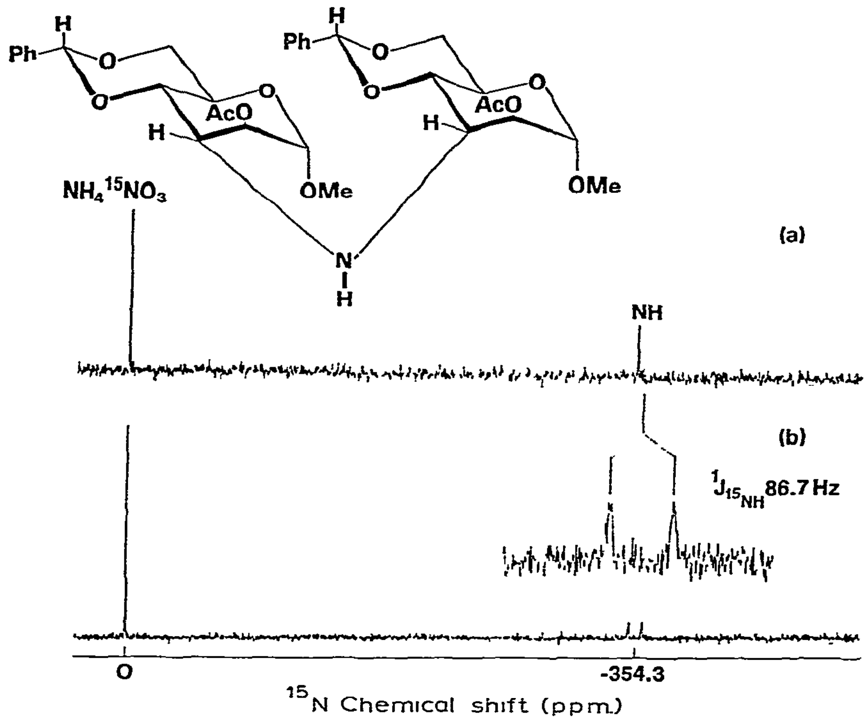
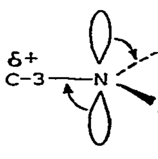


Fig 3. Fourier-transform, ^{15}N-n m r. spectra of bis(methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)amine (*B*) in dimethyl sulfoxide-d_6 at 9.1 MHz. [(a) Proton-decoupled spectrum (16,000 scans), and (b) proton-coupled spectrum (284,151 scans).]

Definitive evidence for the presence of an NH group in *B* is afforded by its proton-coupled, nitrogen-15 n.m.r. spectra. The spectrum of *B* in chloroform-*d* solution was found to be a broadened doublet, which suggested an intermediate rate of chemical exchange of the NH proton. As the spacing (78 Hz) in the doublet could not legitimately be assumed to represent the true value of the coupling constant $^{1}J_{^{15}\mathrm{NH}}$, the proton-coupled, ^{15}N spectrum of *B* in dimethyl sulfoxide-d_6 solution was determined, as, in it, chemical exchange of the NH proton could be expected to be less rapid. This spectrum (see Fig. 3b) displays a doublet of multiplets containing several sharp lines. The major spacing ($^{1}J_{^{15}\mathrm{NH}}$ 86.7 Hz) in this doublet is substantially larger than the value (~70 Hz) that would be expected[15] for nominal, sp^3 hybridization of the nitrogen atom. It seems possible that steric repulsion of the altropyranoid parts of *B* causes enlargement of the tetrahedral C-3–N–C-3′ angle, thus causing



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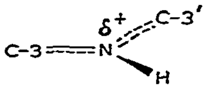

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some rehybridization of the nitrogen orbitals towards a bonding arrangement that is intermediate between sp^3 and sp^2, but perhaps closer to sp^2. Withdrawal of the electrons in the unused, p orbital of the nitrogen atom (see 3) by the combined inductive effects of the substituents on the sugar rings could account for the low basicity[16] of B (see 4). The value $^{1}J_{^{15}N,H}$ 86.7 Hz for B is only slightly smaller than the values (91–93 Hz) reported[14,17,18] for acetamido sugar derivatives, in which the nitrogen atom appears to be substantially sp^2 hybridized. Nevertheless, the observation of a wide, nitrogen-15 doublet for B clearly indicates the direct attachment of one hydrogen atom to the nitrogen atom. The smaller spacings (3.7 Hz) in the proton-coupled, nitrogen-15 spectrum (see Fig. 3b) of B probably represent vicinal coupling of the axially oriented, nitrogen-15 nucleus with the *trans*-coplanar H-4 and H-4′. The magnitude of this coupling is similar to that ($^{3}J_{3,^{15}N}$ 3.5 Hz) observed recently for methyl 2-acetamido-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-α-D-mannopyranoside-2-^{15}N in studies of the angular dependence of vicinal, nitrogen-15–proton coupling[11].

A limited number of other poly(hexosyl)amines have been reported, including derivatives of bis-[19,20] and tris[20]-(6-deoxy-D-galactopyranos-6-yl)amine, bis(2-acetamido-2-deoxy-D-glucopyranosyl)amines[16,21] (C), and bis(methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-glucopyranosid-2-yl)amine[22], and its reduction product, bis(methyl 3-amino-2,3-dideoxy-α-D-glucopyranosid-2-yl)amine[22] (D). Previous attempts to acylate the imino nitrogen atoms of compounds C and D have also been unsuccessful[16,22], and these results have been attributed to the weak basicity of the NH group, or steric hindrance, or both[16,22]. We have observed that compound A is not *N*-acetylated by treatment with a mixture of equal volumes of acetic anhydride and pyridine for 4.5 h at 95–100°, conditions that are more vigorous than those employed by Wiggins[5]. On the other hand, no difficulty was experienced in preparation[19] of a benzoyl derivative (or nitrosamine) from bis(6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl)amine, in which the imino group is bonded to two primary carbon atoms. Thus, lack of reactivity towards *N*-acylation seems to be a general property of bis(hexosyl)amines in which the imino group is bonded to *two* secondary carbon atoms.

The bis(hexosyl)amines are extreme examples of *N*-alkylated amino sugar derivatives. This general class of compounds is of interest in connection with current efforts to block mechanisms of bacterial resistance to the aminoglycoside antibiotics[23].

EXPERIMENTAL*

General. — Proton-n.m.r. spectra were recorded in the continuous-wave mode at 60, 100, and 220 MHz by using Varian Associates A-60, HA-100, and HR-220 spectrometers, respectively, and in the pulse, Fourier-transform (F.t.) mode at

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*Mention of commercial equipment in this article does not imply recommendation or endorsement by the National Bureau of Standards

360 MHz, by means of a Bruker Instruments spectrometer, model WH-360. ^{13}C-N.m.r. spectra were recorded in the F.t. mode at 22.6 and 90.5 MHz with Bruker HFX-11 and WH-360 spectrometers, respectively. ^{15}N-N.m.r. spectra were obtained in the F.t. mode at 9.1 MHz with the Bruker HFX-11 spectrometer.

Solutions of compound *B* (210 mg) in 0.4–0.9 mL of solvent contained in 5-mm sample-tubes were used for proton-n.m.r., 210–250 mg in 0.8–2 mL in 5- or 10-mm tubes for ^{13}C-n.m.r., and 0.5–1.4 g in 2–4 mL in 15-mm tubes for ^{15}N-n.m.r. spectroscopy. Quadrature phase-detection was employed for all F.t. spectra. I.r. spectra were recorded with a Unicam model S.P. 100 spectrometer.

*Bis(methyl 2-O-acetyl-4,6-O-benzylidene-3-deoxy-α-*D*-altropyranosid-3-yl)amine* (B). — A mixture of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside[24] (50 g), methanol (150 mL), and concentrated ammonium hydroxide (200 mL, *d* 0.88) was heated in a stainless-steel autoclave for 7 h at 140°, and was then evaporated to a solid; this was dissolved in methanol, decolorized, the solution evaporated, and the product crystallized from methanol, to give methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside as plates (33 g, 62%), m.p. 187–189°. Recrystallization from methanol yielded material with m.p. 188–190°, undepressed on admixture with an authentic specimen of the 3-amino derivative.

The mother liquors were dissolved in hot, dry pyridine (75 mL), acetic anhydride (75 mL) was added, and the solution was heated for 4.5 h at 95–100°. The mixture was cooled, poured into ice-water (~750 mL), and extracted with chloroform (2 × 100 mL), and the combined extracts were successively washed with 2M hydrochloric acid, saturated sodium hydrogencarbonate solution, and water, dried ($CaSO_4$), and evaporated, affording a solid that was dissolved in ethanol, and decolorized, and then recrystallized twice from aqueous ethanol, to give compound *B* as thick needles (15.2 g; 25% based on the 2,3-anhydro derivative), m.p. 236–237°. Further recrystallizations from aqueous ethanol, and then ethanol, gave material with m.p. 241–242°, $[\alpha]_{\lambda}^{20}$ +45.2, +46.6, +52.0, +84.7, and +124.7° at λ 589, 578, 546, 436, and 365 nm, respectively (*c* 2.12, $CHCl_3$); ν_{max}^{Nujol} 3420 (weak, NH) and 1744 cm^{-1} (strong, ester C=O); lit.[5] m.p. 237–238°, $[\alpha]_D$ +45.3° (in $CHCl_3$); and lit.[1] m.p. 235°, $[\alpha]_D^{12}$ +45.5° (in $CHCl_3$).

Anal. Calc. for $C_{32}H_{39}NO_{12}$: C, 61.04: H, 6.24, N, 2.22. Found: C, 60.90; H, 6.40; N, 2.20.

Spectral assignments and simulation. — In the proton-n.m.r. spectra of *B* in chloroform-*d* solution, the quartet at δ 5.04 was assigned to H-2, because, of the pyranose-ring protons, the proton in geminal relationship to an acetoxyl group could be expected to resonate at lowest field. On irradiation of H-2 (frequency-swept, spin-decoupling at 100 MHz), the singlet at δ 4.59 sharpened up and was assigned to H-1. Irradiation at the frequency of the methoxyl signal removed the larger spacing ($J_{2,3}$ 2.8 Hz) from the H-2 quartet, thus indicating (*a*) that the H-3 resonance lies underneath the methoxyl signal (see also, the integrals in Table I), and (*b*) the assignment of H-4. The proton-n.m.r. spectrum of *B* at 360 MHz was simulated on a Nicolet

Instrument Corporation minicomputer, model BNC-12, by using the ITRCAL program.

Assignments for the Ph*C*H, C-1–C-6, OMe, and C*Me* signals in the ^{13}C-n.m.r. spectra of *B* were determined by selective proton-decoupling at 90 MHz, using proton-irradiation frequencies that had been calculated from the proton chemical-shifts of *B* in dimethyl sulfoxide-d_6 at 360 MHz. The assignments of the C-6, OMe, C*Me*, C=O, and aromatic C-1, ^{13}C-resonances were confirmed by off-resonance proton-decoupling and by proton-coupled spectra obtained, with retention of the nuclear Overhauser effect, by means of gated irradiation of the protons[25] at 90 MHz (for signal multiplicities in the off-resonance, proton-decoupled spectrum, see Table I). Except for C-2 and C-5, the ^{13}C assignments for *B* resemble those of methyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-α-D-altropyranoside, the ^{13}C-n.m.r. spectrum of which has been assigned by selective proton-decoupling and ^{15}N isotopic-labeling[11]. The benzylic carbon and pyranose C-1 signals of *B* were also distinguished by the significantly different values of $^{1}J_{^{13}\mathrm{CH}}$ (see Table I) that were measured from the proton-coupled spectrum. These values are similar to those measured previously for the 2-deoxy-2-phthalimido-α-D-altropyranoside derivative[11].

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