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SYNTHESIS OF 5-ACETAMIDO-6,6-DIBROMO-5,6-DIDEOXY-6-NITROHEXOFURANOSE DERIVATIVES BY ADDITION AND SUBSTITUTION REACTIONS WITH *N*-BROMOACETAMIDE*†

WERNER RANK AND HANS H. BAER‡
Department of Chemistry, University of Ottawa, Ottawa (Canada K1N 6N5)
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ABSTRACT

N-Bromoacetamide, in the presence of a catalytic amount of sodium acetate, reacted smoothly with the nitroalkene moiety of 3-*O*-acetyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*xylo*-hex-5-enofuranose (**1**) by addition of bromine and an acetamido group across the olefinic double bond, with concomitant introduction of a second bromine atom at C-6. The preponderant product was 5-acetamido-3-*O*-acetyl-6,6-dibromo-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-glucofuranose (**3**). The β-L-*ido* isomer (**4**) and the 5-acetoxy analog (**2**) of **3** were isolated as minor products. Reaction of **1** with ammonia in tetrahydrofuran gave 5-acetamido-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-glucofuranose (**5**) and -β-L-idofuranose (**6**) in a ratio of 1:1.4. These compounds were converted into their 3-acetates (**7** and **8**) which, with *N*-bromoacetamide, underwent bromination at C-6 to give **3** and **4**, respectively. Configurations were allocated to the new products on the basis of circular dichroism.

INTRODUCTION AND RESULTS

Recently, we have found[2] that *N*-bromoacetamide (NBA), in the presence of a catalytic amount of sodium acetate, readily reacts with β-nitrostyrene by addition of bromine and an acetamido group across the olefinic double bond, with concomitant further bromination in the β-position. The resulting product is 2-acetamido-1,1-dibromo-1-nitro-2-phenylethane. The addition of NBA in this reaction appears to proceed by an ionic mechanism and thus differs from the light-induced reaction[3] of NBA with unactivated alkenes, which is thought to involve at least an initial radical step, and which leads to another type of adduct. Obviously, it is also different from the formation of bromohydrins[4] that occurs with NBA under certain conditions. In order

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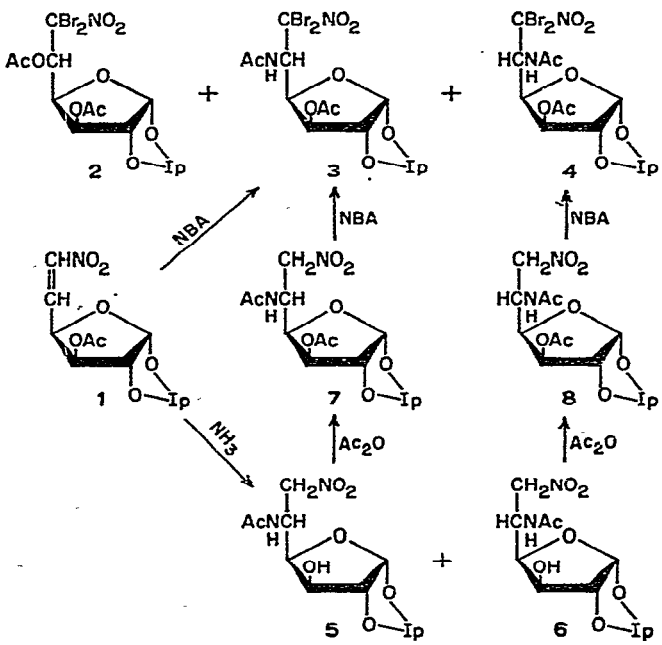
‡Author to whom correspondence should be addressed. We thank the National Research Council of Canada for financial support of this research.

to examine the utility of the new reaction in carbohydrate chemistry, the nitro-olefin 3-*O*-acetyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*xylo*-hex-5-enofuranose (**1**) was chosen for a first example, and it was found that introduction of an acetamido group at C-5 and of two bromine atoms at C-6 occurred with great ease[2]. The present paper records in greater detail these findings, as well as the chemical reactions and physical data that served to ascertain the structure of the products.



When **1** (1 mol.) was allowed to react at 25° with NBA (2.2 mol.) in acetone containing a small amount of sodium acetate, a solid mixture of products was isolated in 95% yield. A minor component was separated by chromatography and proved to be 3,5-di-*O*-acetyl-6,6-dibromo-6-deoxy-1,2-*O*-isopropylidene-6-nitro-α-D-glucofuranose (**2**). The bulk of the material consisted of the two acetamido sugars, 5-acetamido-3-*O*-acetyl-6,6-dibromo-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-glucofuranose (**3**) and -β-L-idofuranose (**4**), in proportions of 80–85% and 15–20%, respectively; the product ratio was estimated on the basis of n.m.r. and polarimetric data after pure **3** and **4** had become available for comparison. Fractional crystallization gave **3** and **4** in yields of 65 and 6%, respectively. The n.m.r. data of the products (Table I) were consistent with the constitutions depicted. Unambiguous structural proof was obtained for **3** and **4** by an alternative synthesis (see below), and the configurations could thereby be allocated. The by-product **2** was not investigated in the same detail, but its coupling constant $J_{4,5}$ indicated configurational identity with **3** rather than **4**.

Treatment of **1** with ammonia in tetrahydrofuran effected amination with concomitant O→N acetyl migration, in accordance with a reaction pattern well-estab-

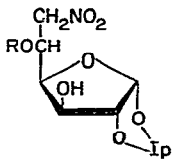
TABLE I

NUCLEAR MAGNETIC RESONANCE DATA AT 100 MHZ IN CHLOROFORM-*d*

Compound	*Chemical shifts*[a] (τ)								*Couplings*[a] (*Hz*)			
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*O-Ac*	*N-Ac*	*C-Me*	$J_{1,2}$	$J_{3,4}$	$J_{4,5}$	$J_{5,NH}$
2	4.19 d	5.62 d	4.69 d	5.50 q	3.87 d	7.88, 7.91	—	8.54, 8.72	3.5	3	9	—
3[b]	4.20 d	5.64 d	4.62 d	5.53 q	4.45 t	7.90	8.03	8.54, 8.74	3.5	3	9.7	9.7
4	4.07 d	5.55 d	4.68 d	5.42 d	4.52 d	7.97	7.99	8.54, 8.71	3.5	3.5	0	9.5
5	4.11 d	5.45 d				—	7.96	8.59, 8.73	3.5			
6[b]	4.10 d	5.52 d				—	8.06	8.57, 8.73	3.5			
7	4.10 d	5.51 d	4.66 d			7.92	8.07	8.54, 8.72	3.5	2.5		
8	4.09 d	5.49 d	4.71 d			7.95	8.02	8.54, 8.72	3.5	3		

[a]Signal multiplicities are indicated for ring protons as d (doublet), t (triplet), or q (quartet), as seen at a sweep width of 1000 Hz. The chemical shifts and couplings for H-1 to H-4 agree well with data reported (ref. 14) for configurationally related 1,2:5,6-di-*O*-isopropylidenehexofuranoses. Coupling between H-2 and H-3 was too small to be observed. The spectra of **5**–**8** were complicated due to the presence of hydrogen at C-6, so that some signals could not be analyzed. [b]In $CDCl_3$ solution with added $(CD_3)_2SO$.

lished in carbohydrate nitro-olefins[5]. Column chromatography of the resulting mixture of 5-epimers gave 40% of amorphous 5-acetamido-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-glucofuranose (**5**) and 56% of its crystalline β-L-*ido* isomer (**6**). In a similar amination of the 1,2-*O*-cyclohexylidene analog of **1**, Paulsen[6] obtained the corresponding α-D-*gluco* and β-L-*ido* derivatives in a ratio of 3:1. The reason for these differing product ratios is not clear; at any rate, the addition of ammonia was, in both reactions, associated with lesser stereoselectivity than that of NBA. Acetylation of **5** and **6** furnished their crystalline 3-acetates **7** and **8**, and these were brominated in high yield by NBA in the manner previously applied to saturated nitro sugars[7]. The resulting dibromonitro sugars (**3** from **7** and **4** from **8**) were identical in every respect with the products obtained from **1** in the one-step operation.



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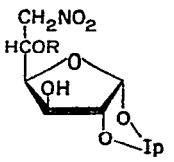
13 R = Me



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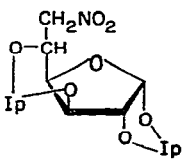

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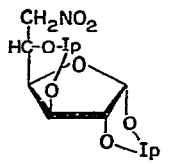

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The configurational correlation of the new compounds was based on their Cotton effects. Satoh and co-workers[8] have studied o.r.d. and c.d. of numerous epimeric pairs of acyclic 1-nitro polyols, including 2-acetamido derivatives. They have established that the Cotton effect in this type of compound depends solely on the absolute configuration of the carbon atom adjacent to the nitromethyl group: the effect is negative in 1-deoxy-1-nitroalditols having the *R* configuration at C-2, and positive in those having the *S* configuration at C-2. We have found that this rule also applies to 6-deoxy-6-nitrohexofuranose derivatives, with C-5 being the determinant, asymmetric carbon atom. Thus, in each of the known 5-epimeric pairs **9** and **10**, **11** and **12**, and **13** and **14**, the D-*gluco* compound (*R* at C-5) was found to display a negative, and the L-*ido* compound (*S* at C-5) a positive, Cotton effect (Fig. 1 and Experimental). It is noteworthy that neither the involvement of the carbon chain in a furanoid structure nor the attachment of one or two isopropylidene acetal rings to the molecule invalidates the rule. The c.d. of **7** and **8** (Fig. 1) could therefore be used with confidence to allocate to these new compounds the configurations indicated. The dibromo compounds **3** and **4** had been interrelated chemically with **7** and **8**, respectively, by means of reactions that did not involve C-5, and hence their configurations, too, were thereby established. Interestingly, and in full accord with the rule, **3** and **4** exhibited a reversal of the Cotton effect. It was positive in **3** and negative in **4** since introduction of bromine at C-6 interchanges the priorities of C-4 and -6 and thus inverts the absolute configuration of C-5, even though the conventional D-*gluco* and L-*ido* designations remain unaffected.

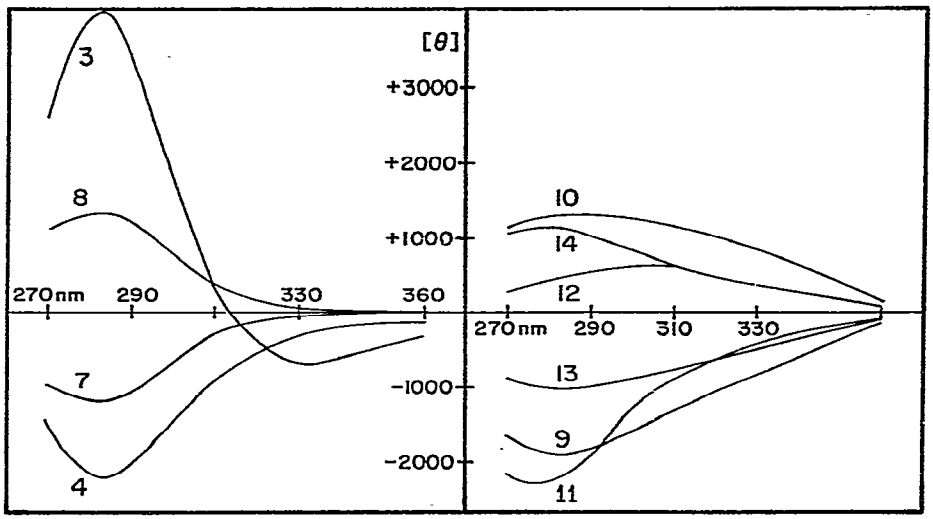

Fig. 1. Circular dichroism of 6-deoxy-6-nitrohexofuranose derivatives.

Reductive debromination by sodium borohydride[7,9] readily converted **3** into **7**. Since acetamidonitro compounds like **7** generally pose no problems in catalytic hydrogenation to diamino derivatives[5], the addition of NBA to sugar nitro-olefins followed by reduction would represent a new approach to vicinal diamino sugars. An advantage of this approach over the simpler sequence comprising addition of ammonia (with concurrent or subsequent *N*-acetylation) and reduction may not be apparent at first sight. However, we have alluded above to differential stereoselectivities that may exist in the two routes, and it is in this regard especially that the NBA method has in fact proved very valuable, in applications to be reported elsewhere[10].

EXPERIMENTAL

Melting points were determined in capillaries in an electrically heated aluminum block and are uncorrected. Solvents used for t.l.c. and column chromatography with silica gel were: *A*, benzene–ethyl acetate (1:10); *B*, benzene–methanol (9:1). Optical rotations were measured with a Perkin–Elmer 141 automatic polarimeter at ~23°. The n.m.r. data were obtained with a Varian HA-100 spectrometer (lock signal, tetramethylsilane). Infrared spectra were recorded from Nujol mulls on a Beckman IR 20 instrument, unless otherwise indicated. The c.d. curves (Fig. 1) were obtained with a Jasco ORD/UV-5 instrument. Compounds **1**[11], **9**–**12**[12], **13**[13], and **14**[13] were prepared by the literature procedures.

*5-Acetamido-3-*O*-acetyl-6,6-dibromo-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-*α*-*D*-glucofuranose* (**3**) *and -β-*L*-idofuranose* (**4**). — (*a*) *From* **1**. A solution of **1** (273 mg, 1 mmol.) in acetone (20 ml) containing NBA (300 mg, 2.2 mmol.) and sodium acetate (10 mg) was stirred in the dark at room temperature. After 90 min, t.l.c. (solvent *A*)

revealed that **1** had almost completely disappeared, but stirring was allowed to continue overnight. Water (20 ml) was then added, and much of the acetone was removed by evaporation. A white solid which was thereby deposited was filtered off, washed with cold water, and dried. This crude material (466 mg) showed 1 major spot of intermediate mobility as well as a slower and a faster moving minor spot in t.l.c. (solvent *A*). The fast-moving component was isolated by column chromatography on silica gel (20 g), using solvent A; it proved to be the diacetate **2** (24 mg, 5.4%; see a subsequent section). The more slowly moving, minor component (**4**) was not separated on the column from the main product (**3**). The mixture eluted (419 mg) showed $[\alpha]_D$ +32.1° (*c* 0.7, methanol), and n.m.r. signals at τ 4.45 and 4.52 given by H-5 of **3** and **4**, respectively, revealed the proportion of **3** to be 80–85% (integration at 250-Hz sweep width). Recrystallization of the mixture from ethyl acetate–petroleum ether gave pure **3** (323 mg, 77% of the mixture; 65% based on **1**), m.p. 193–194°, $[\alpha]_D$ +51.3° (*c* 0.6, methanol). Characteristic i.r. bands were at 3370 (NH), 1720 (OAc), 1685 (amide I), 1580 (NO_2), and 1520 cm^{-1} (amide II).

Anal. Calc. for $C_{13}H_{18}Br_2N_2O_8$ (490.1): C, 31.85; H, 3.70; Br, 32.60. Found: C, 32.04; H, 3.86; Br, 32.33.

The residue obtained from the mother liquor of **3** was repeatedly recrystallized from ethyl acetate–petroleum ether to give pure **4** (29 mg, 5.9% based on **1**), m.p. 158–160°, $[\alpha]_D$ −53° (*c* 0.6, methanol). The i.r. spectrum was superimposable on that of **4** obtained from **8** (see below).

(*b*) **4** *from* **8**. To a solution of **8** (110 mg) in methanol (10 ml) was added NBA (100 mg) and a saturated, aqueous solution (1 ml) of sodium acetate. The mixture was stirred at room temperature for 1 h and then diluted with water (10 ml). A white deposit, which appeared on partial evaporation of the solution, was collected, washed with cold water, and dried. Recrystallization from ethyl acetate–petroleum ether gave **4** (148 mg, 91%), m.p. 160–161°, $[\alpha]_D$ −54° (*c* 0.7, methanol). Characteristic i.r. bands were at 3275 (NH), 1750 (OAc), 1670 (amide I), 1580 (NO_2), and 1525 cm^{-1} (amide II).

Anal. Calc. for $C_{13}H_{18}Br_2N_2O_8$ (490.1): C, 31.85; H, 3.70; Br, 32.60. Found: C, 32.09; H, 3.87; Br, 32.37.

(*c*) **3** *from* **7**. Bromination of **7** (110 mg), as described above for **8**, gave **3** (138 mg, 85%), m.p. 191–192°, $[\alpha]_D$ +52° (*c* 0.4, methanol). The i.r. spectrum was identical with that of **3** obtained from **1**.

*3,5-Di-*O*-acetyl-6,6-dibromo-6-deoxy-1,2-*O*-isopropylidene-6-nitro-α-*D*-glucofuranose* (**2**). — The product isolated chromatographically [see (*a*) above] showed m.p. 136–138° and $[\alpha]_D$ +15.4° (*c* 0.3, methanol). I.r. bands were at 1760 and 1740 (OAc), and at 1590 cm^{-1} (NO_2). Amide bands were absent. A mass spectrum showed strong fragment peaks around *m/e* 476 (with an isotopic pattern typical of a dibromo compound), probably arising from loss of CH_3 from the molecule (mol. wt. 491). The n.m.r. spectrum (Table I) was consistent with structure **2**, but, like the relatively low $[\alpha]_D$ value, suggested the possibility that some of the β-L-*ido* isomer was present.

*5-Acetamido-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-*D*-glucofuranose* (**5**) *and -β-*L*-idofuranose* (**6**). — A solution of **1** (273 mg) in tetrahydrofuran (20 ml) was

stirred with conc., aqueous ammonia (5 ml) for 15 min, after which time t.l.c. (solvent *B*) indicated that all of **1** had been consumed and that two slow-moving products were present. The reaction mixture was diluted with water (20 ml) and evaporated with addition of several portions of ethanol. The crystalline residue was chromatographed on silica gel (20 g) with solvent *B*. Fractions containing solely the more mobile product gave **5** (115 mg, 40%) as a brittle glass that could not be crystallized, $[\alpha]_D$ +5.4° (*c* 0.7, methanol); ν_{max} (neat film) 3330 (NH, OH), 1655 (amide I), 1550 (NO_2), and 1530 cm^{-1} (amide II).

The slower fractions furnished crystalline **6** (163 mg, 56%) that was recrystallized from ethyl acetate–petroleum ether; m.p. 179–180°, $[\alpha]_D$ −32.8° (*c* 0.3, methanol); ν_{max} 3380, 3340 (NH, OH), 1665 (amide I), 1545 (NO_2), and 1510 cm^{-1} (amide II).

Anal. Calc. for $C_{11}H_{18}N_2O_7$ (290.3): C, 45.51; H, 6.25; N, 9.65. Found: C, 45.43; H, 6.38; N, 9.69.

*5-Acetamido-3-*O*-acetyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-*D*-glucofuranose* (**7**). — (*a*) *From* **5**. Acetic anhydride (6 ml) and pyridine (12 ml) were added to a suspension of **5** (490 mg) in ether (15 ml). The reaction mixture was kept overnight in a refrigerator and then evaporated with addition of several portions of ethanol. The product was recrystallized from ethyl acetate–pentane to give **7** (500 mg, 89%), m.p. 86–88°, $[\alpha]_D$ +12.6° (*c* 0.7, methanol); ν_{max} 3300–3250 (NH), 1750 (OAc), 1660 (amide I), 1555 (NO_2), and 1545 cm^{-1} (amide II).

Anal. Calc. for $C_{13}H_{20}N_2O_8$ (332.3): C, 46.98; H, 6.07; N, 8.43. Found: C, 46.86; H, 6.19; N, 8.25.

(*b*) *From* **3**. Sodium borohydride (50 mg) was added to a solution of **3** (100 mg) in ethanol (10 ml). After 15 min, complete disappearance of **3** was revealed by t.l.c. (solvent *A*). The reaction mixture was slightly acidified with 2M acetic acid, diluted with water (10 ml), and concentrated by partial evaporation. The white precipitate was filtered off, washed with cold water, dried, and recrystallized from ethyl acetate–pentane to give **7** (61 mg, 90%), m.p. 87–88°. The i.r. spectrum was identical with that of **7** obtained from **5**.

*5-Acetamido-3-*O*-acetyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-β-*L*-idofuranose* (**8**). — Compound **6** (160 mg) was acetylated as described for **5**. Analytically pure **8** (183 mg, 92%), obtained from ethyl acetate–pentane, had m.p. 119–120°, $[\alpha]_D$ −33.4° (*c* 0.7, methanol). The i.r. spectrum was similar to that of **7**.

Anal. Calc. for $C_{13}H_{20}N_2O_8$ (332.3): C, 46.98; H, 6.07; N, 8.43. Found: C, 46.85; H, 6.17; N, 8.55.

Circular dichroism data. — Ellipticities ($[\theta]$) are given in parentheses after wavelengths (nm).

Compound **3**: 270 (~ +2600), 283 (~ +4000, extremum), 290 (+3710), 310 (+250), 330 (−630), 332 (−682), 360 (−330). Compound **4**: 270 (~ −1450), 284 (~ −2200, extremum), 290 (−2026), 310 (−890), 330 (−330), 360 (−140). Compound **7**: 270 (−990), 283 (−1182, extremum), 290 (−1080), 310 (−320), 330 (−40), 360 (0). Compound **8**: 270 (+1130), 282 (+1352, extremum), 290 (+1220), 310

(+365), 330 (+40), 360 (0). Compound **9**: 270 (−1640), 283 (−1888, extremum), 290 (−1785), 310 (−1280), 330 (−785), 360 (−150). Compound **10**: 270 (+1125), 284 (+1326, extremum), 290 (+1290), 310 (+1190), 330 (+840), 360 (+150). Compound **11**: 270 (−2160), 277 (−2289, extremum), 290 (−1910), 310 (−830), 330 (−445), 360 (−80). Compound **12**: 270 (+270), 290 (+510), 307 (+647, extremum), 310 (+630), 330 (+440), 360 (+85). Compound **13**: 270 (−870), 283 (−1024, extremum), 290 (−970), 310 (−730), 330 (−490), 360 (−100). Compound **14**: 270 (+1045), 280 (+1150, extremum), 290 (+1015), 310 (+660), 330 (+430), 360 (+75).

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