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A NEW REACTION OF N-BROMOACETAMIDE: FACILE ADDITION TO α-NITROALKENES

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Recently we have described[2] the use of N-bromoacetamide (NBA) as an efficient agent for α-bromination of secondary nitroalkane groupings in carbohydrates. The brominations were performed in aqueous methanol solution in the presence of sodium acetate. In connection with these studies the question arose in what way NBA would react with nitroalkenes. We now report that, in acetone or aqueous acetone solution and in the presence of a catalytic amount of sodium acetate, NBA adds itself smoothly at room temperature and in the dark across the olefinic bond to give β-acetamido-α-bromo-α-nitroalkanes. If the nitro group is situated in a terminal position, the α-hydrogen atom is replaced by another bromine atom and β-acetamido-α,α-dibromo-α-nitro derivatives are obtained. Thus, β-nitrostyrene gave,[3] in 65 % yield, 2-acetamido-1,1-dibromo-1-nitro-2-phenylethane as colorless crystals from ethanol-water, m.p. 129-130°(dec.), (Anal. for $C_{10}H_{10}Br_2N_2O_3$. Found: C, 32.85; H, 2.89; N, 7.64; Br, 43.55). I.r. bands in Nujol: 3310 (NH), 1660 (amide I), 1570 (NO_2), and 1520 cm^{-1}(amide II). N.m.r. data (100 MHz, in $CDCl_3$): τ 2.64 (m, 5H, phenyl), 3.70 (1H, benzylic, d with $J_{CH, NH}$ 10 Hz, collapsing to s on D_2O exchange), 7.97 (s, 3H, N-acetyl). Removal of the bromine by borohydride[4] gave the known[5] 2-acetamido-1-nitro-2-phenylethane, m.p. 137-138° (yield, 90 %).

The addition reaction fails if the sodium acetate catalyst is omitted. Likely it is of ionic character and is promoted by the activating effect of the nitro group. According to a recent review[6], N-bromocarboxamides generally do not add to unsaturated hydrocarbons that lack activation. On the other hand, Wolfe and Awang[7] obtained adducts of NBA with several alkenes in the course of a detailed study leading to a reinterpretation of the Wohl reaction which had previously been assumed to give allylic bromination. However, their additions were performed in refluxing carbon tetrachloride under conditions of photolysis. It was considered that a radical reaction of NBA with itself produces N,N-dibromoacetamide which then adds ionically to the olefins, giving isolable 2-bromoalkyl N-bromoacetimidates, $BrCR_2—CR_2—O—C(CH_3)=NBr$. That is to say, the amide moiety becomes attached through its oxygen, whereas in our case a C—N bond is formed.

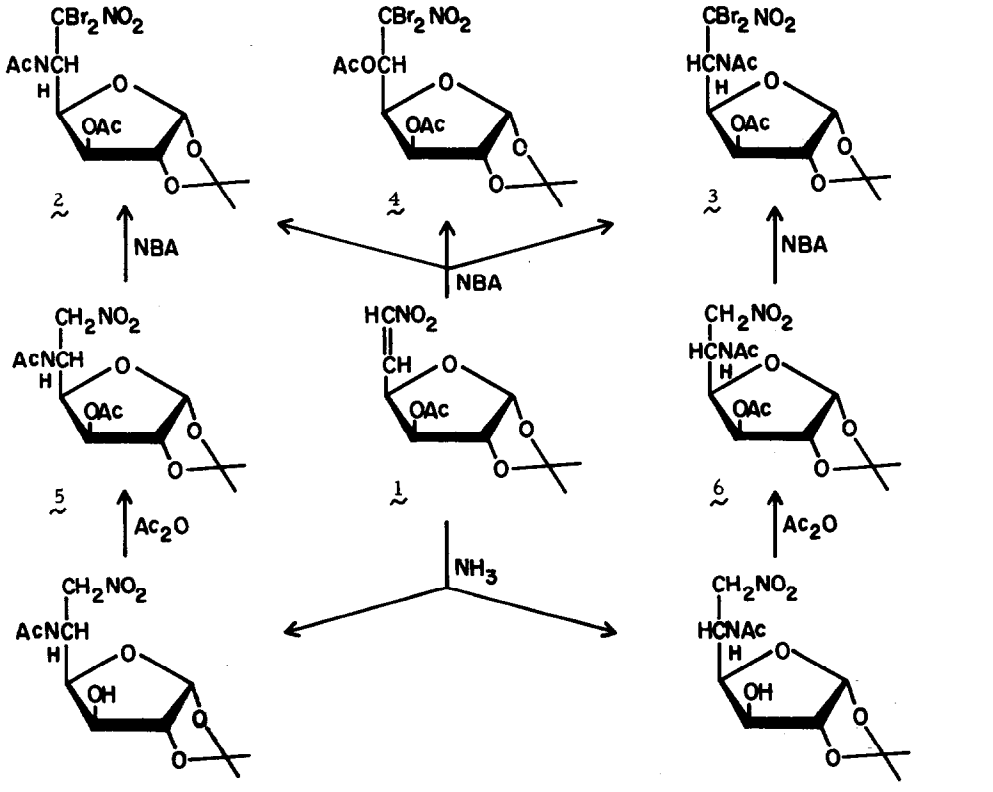
In a first application of our reaction to carbohydrates, the nitroolefin 3-O-acetyl-5,6-

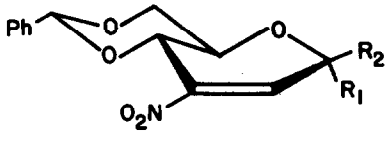
dideoxy-1,2-O-isopropylidene-6-nitro-α-D-xylo-hex-5-enofuranose[8] (1, 1 mmol) with NBA (2.2 mmol) and sodium acetate (0.12 mmol) in acetone afforded[9] the crystalline α-D-gluco product 2 in 65 % yield; m.p. 193-194°, $[\alpha]_D^{25}$ +52° in MeOH. Recrystallization of the mother liquor material from ethyl acetate-petroleum ether gave the β-L-ido isomer 3 in 6 % yield; m.p. 160-161°, $[\alpha]_D^{25}$ -54° in MeOH. Prior to isolation, the product ratio 80-85 % 2 to 15-20% 3 was found by n.m.r. and polarimetric measurements. Another minor product (5 %), which was first removed from the crude mixture by silica gel chromatography with benzene – ethyl acetate (1 : 10), was the diacetate 4; m.p. 136-138°, $[\alpha]_D^{25}$ +15.4° in MeOH. It was noticed in several similar experiments that such by-products may arise to varying degrees depending upon the amount of sodium acetate provided in the reaction medium. Evidently, acetate ion competes with the reactive acetamido species in the addition to the double bond. Again, omission of NaOAc resulted in failure of NBA to add to the double bond.

Compounds 2, 3, and 4 gave analytical, n.m.r., and i.r. data consistent with their constitutions. Of special diagnostic value were the 100-MHz n.m.r. signals for H-5, which were a triplet in 2 (τ 4.45, $J_{4,5} = J_{5,NH}$ = 10 Hz), a doublet in 3 (τ 4.52, $J_{4,5}$ = 0, $J_{5,NH}$ = 10 Hz), and a doublet in 4 (τ 3.87, $J_{4,5}$ = 9 Hz). Furthermore, 2 and 3 were synthesized from 1 by an alternative route involving conventional[10] amination (with NH_3 in aqueous tetrahydrofuran) accompanied by O-3 → N-5 acetyl migration, reacetylation of OH-3, and dibromination at C-6 with NBA and sodium acetate in aqueous methanol. By this route, 2 and 3 were obtained in a ratio of 1 : 1.4, i.e., stereoselectivity was diminished and its order reversed.

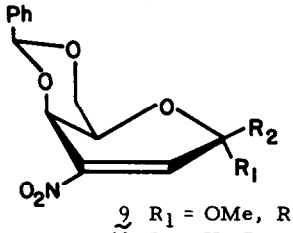
The configurations of 2 and 3 were assigned on the basis of circular dichroism. The bromine-free acetamidonitro compounds 5 and 6 as well as their known 3,5-dihydroxy, 3-hydroxy-5-methoxy, and 3,5-isopropylidenedioxy analogs all were found to exhibit a negative Cotton effect when C-5 had the R configuration (D-gluco series), and a positive Cotton effect when C-5 had the S configuration (L-ido series), in accordance with the rule of Satoh and coworkers.[11] These authors have correlated the Cotton effects in 1-deoxy-1-nitroalditols (including 2-acetamido derivatives) with the absolute configuration of the carbon atom adjacent to the nitromethyl group. Evidently, involvement of the polyol chain in such cyclic structures as furanose and isopropylidene acetal rings does not invalidate the rule. Now the dibromo compound having the D-gluco configuration (2) and that having the L-ido configuration (3) — which configurations were assignable on the grounds of chemical correlation with 5 and 6 — showed a reversal of Cotton effects. The effect was positive in 2 and negative in 3. This was to be expected since introduction of bromine at C-6 inverts the absolute configuration of C-5 due to priority interchange of C-6 and C-4.

The stereoselectivity of the NBA addition reaction proved particularly useful in 2,3-unsaturated 3-nitrohexopyranosides where it provided facile access to derivatives of 2,3-

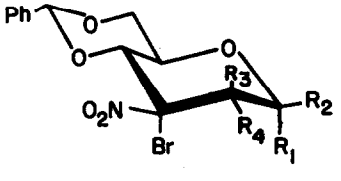




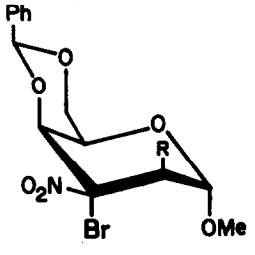
7 R_1 = OMe, R_2 = H
8 R_1 = H, R_2 = OMe



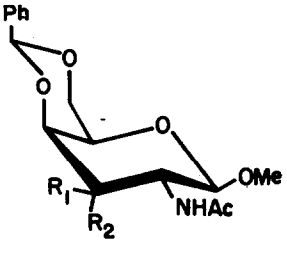
9 R_1 = OMe, R_2 = H
10 R_1 = H, R_2 = OMe



11a R_1 = OMe, R_2 = R_4 = H, R_3 = NHAc
11b R_1 = OMe, R_2 = R_4 = H, R_3 = OAc
12a R_1 = R_3 = H, R_2 = OMe, R_4 = NHAc
12b R_1 = R_3 = H, R_2 = OMe, R_4 = OAc



13a R = NHAc
13b R = OAc



14 R_1 = NO_2, R_2 = Br
15 R_1 = Br, R_2 = NO_2

diamino-2,3-dideoxyhexoses.

Thus, the nitroolefinic glycosides 7 - 9 gave high yields (55-83%) of acetamidobromo adducts 11a (m.p. 127-129°, $[\alpha]_D$ +46° in chlf.), 12a (m.p. 205-206°, $[\alpha]_D$ -70° in chlf.), and 13a (m.p. 175-176°, $[\alpha]_D$ +19.1° in chlf.), respectively. These were accompanied by smaller proportions (15-34 %) of the corresponding acetoxybromo adducts 11b (m.p. 152-153°, $[\alpha]_D$ +10.5° in chlf.), 12b (m.p. 223-225°, $[\alpha]_D$ -69° in chlf.), and 13b (m.p. 226-226°, $[\alpha]_D$ +31.5° in chlf.). In every case the C-2 substituent entered trans to the C-1 methoxyl group. The configuration of the products on the geminally substituted C-3 could not be rigorously established, but the depicted choice, with equatorial orientation of the nitro group, appears very probable on the basis of chemical considerations and some spectroscopic evidence (2). The olefin 10 behaved exceptional in that it afforded two 3-epimeric adducts in about 45 % yield each: 14 (m.p. 190-191°, $[\alpha]_D$ -20.5° in DMF) and 15 (dec.p. 188-189°, $[\alpha]_D$ +86.6° in chlf.). Debromination of 11a, 12a, 13a, 14, and 15 by sodium borohydride readily furnished vicinal acetamidonitro derivatives for which the α-D-manno, β-D-gluco, α-D-talo, and β-D-galacto configurations were established by n.m.r. spectra and comparison with, or conversion into, known compounds. The acetamidonitro glycosides are convenient preparative intermediates for the synthesis of 2,3-diamino sugars (10). Derivatives of 2,3-diamino-2,3-dideoxy-D-talose were obtained for the first time starting from 13a. Extensions of the NBA addition to include other N-halamides are being investigated.

References and Notes

1. (a) From whose Ph.D. thesis (University of Ottawa, 1971) this paper was abstracted. (b) To whom inquiries should be directed.
2. H. H. Baer and W. Rank. Can. J. Chem., 51, 2001 (1973).
3. β-Nitrostyrene (298 mg, 2 mmol), NBA (600 mg, 4.4 mmol), and sodium acetate (20 mg) were stirred in acetone (20 ml) under exclusion of light at room temperature for 6-8 h.
4. D. C. Iffland and G. X. Criner. J. Am. Chem. Soc., 75, 4047 (1953). See also ref. 2.
5. G. Stefanovic, J. Bojanovic, and K. Sirotanovic. J. Org. Chem., 17, 1110 (1952).
6. R. S. Neale. Synthesis, 1 (1971).
7. S. Wolfe and D. V. C. Awang. J. Am. Chem. Soc., 89, 5287 (1967); Can. J. Chem., 49, 1384 (1971).
8. H. H. Baer and W. Rank. Can. J. Chem., 43, 3330 (1965).
9. At room temperature, the reaction was revealed by t.l.c. to be nearly complete after 90 min, but it was allowed to continue for several hours.
10. H. H. Baer. Advan. Carbohydr. Chem. Biochem., 24, 67 (1969). For a similar amination of the 1,2-cyclohexylidene analog of 1, see H. Paulsen, Ann., 665, 166 (1963).
11. C. Satoh, A. Kiyomoto, and T. Okuda. Carbohydr. Res., 5, 140 (1967); C. Satoh and A. Kiyomoto. Carbohydr. Res., 7, 138 (1968).