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Note

Formation of a common imidazole derivative from several 2-acetamido-2-deoxy-*N*-*p*-tolyl-β-D-glycosylamines under acetolyzing conditions

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Under acteolyzing conditions, *N*-acetyl-*p*-toluidine has been isolated in up to 92% yield from *N*-*p*-tolyl-β-D-glycosylamines and in less than 2% yield from 2-acetamido-2-deoxy-*N*-*p*-tolyl-β-D-glycosylamines[1]. An imidazole derivative (**1**) has been isolated from the reaction products of 2-acetamido-2-deoxy-*N*-*p*-tolyl-β-D-glucosylamine[2] (**2**), and it has been concluded that the presence of an acetamido group at C-2 in glycosylamines stabilizes the glycosylamine linkage toward acetolysis because of the formation of **1**.

We now report that **1** is produced as a common product from 2-acetamido-2-deoxy -*N*-*p*-tolyl-β-D-galactosylamine (**3**) and -D-mannosylamine (**4**), and 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-*N*-*p*-tolyl-β-D-glucosylamine (**5**) under the same acetolyzing conditions.

Small-scale experiments were performed at room temperature under various acetolyzing conditions, and the formation of **1** (R_F 0.45) was analyzed by t.l.c. (Solvent A). Treatment of **2** with various mixtures of acetic acid–acetic anhydride and with acetic anhydride did not afford **1**, but treatment with mixtures of acetic anhydride–concentrated sulfuric acid afforded traces of **1**. At a higher temperature (50°), decomposition of the carbohydrate moiety occurred to give colored products, but no **1**. At lower temperature (~5°), numerous products, including **1**, were produced. The maximal yield of **1** (up to 27.4%) was obtained in the reaction with 10:10:1 (v/v) acetic acid–acetic anhydride–concentrated sulfuric acid for 90 h at room temperature.

As shown in Table I, the imidazole derivative (**1**) was isolated in 18–27% yield. The derivatives (**1**) produced from **2**, **3**, **4**, and **5** were indistinguishable from each other on the basis of their physical constants (no mixed melting-point depression), elemental analysis, retention time by g.l.c., R_F value in t.l.c., fragmentation pattern showing M^+ at 460) in m.s., proton signals in p.m.r. spectra (measured in Me_2SO-d_6, $CDCl_3$, and C_6D_6), and i.r. absorption (KBr). This compound (**1**) gave a positive Ehrlich diazo reaction for imidazole[3], and showed i.r. absorptions at 1750 (C=O of *O*-acetyl), 1230 (C–O of *O*-acetyl), and 830 cm^{-1} (*p*-disubstituted phenyl, but no

TABLE I

IMIDAZOLE DERIVATIVES ISOLATED FROM SEVERAL 2-ACETAMIDO-2-DEOXY-*N*-*p*-TOLYL-β-D-GLYCOSYLAMINES

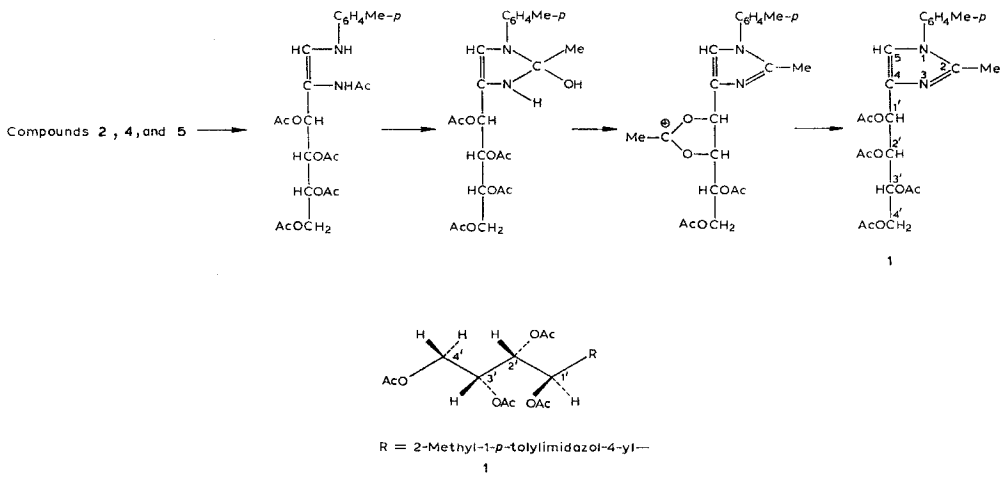
N-p-*Tolyl derivative*	*Imidazole derivative*[a]						
	Yield (%)	*M.p.* (*degrees*)	$[\alpha]_D^{21}$ (*degrees*)[b]	*Retention time of g.l.c.*[c]	*Found* (%)[d]		
					C	*H*	*N*
2-Acetamido-2-deoxy-β-D-glucosylamine (**2**)[e]	22[f]	164.5–165.5	+3	6.8	59.68	6.04	5.93
2-Acetamido-2-deoxy-β-D-galactosylamine (**3**)	18	166	+3	6.8	59.86	6.11	6.13
2-Acetamido-2-deoxy-β-D-mannosylamine (**4**)	24	166	+2	6.8	60.12	6.24	6.21
2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucosylamine (**5**)	27.4	165–166	+3	6.8	59.90	6.19	6.15

[a]N.m.r. data (Me_2SO-d_6): δ 5.83 (d, 1 proton, H-1′, $J_{1',2'}$ 8.0 Hz), 5.59 (q, 1 proton, H-2′, $J_{2',3'}$ 3.0 Hz), 5.02 (m, 1 proton, $J_{3',4'}$ 4.7 Hz), 4.29 (q, 1 proton, $J_{3',4''}$ 6.8 Hz), 4.00 (q, 1 proton, H-4″, $J_{4',4''}$ 12.0 Hz), 7.27 (s, 1 proton, H-5), 7.20 (m, 4 protons, Ph-1), 2.28 (s, 3 protons, Me-Ar-1), 2.18 (s, 3 protons, Me-2), 2.00, 1.98, 1.92, 1.88 (s, 3 protons each, OAc-Me). N.m.r. data ($CDCl_3$): δ 6.03 (d, 1 proton, H-1′, $J_{1',2'}$ 8.0 Hz), 5.87 (q, H-2′, $J_{2',3'}$ 2.0 Hz), 5.23 (m, 1 proton, $J_{3',4'}$ 5.0 Hz), 4.25 (q, 1 proton, H-4′, $J_{3',4'}$ 7.0 Hz), 3.97 (q, 1 proton, H-4″, $J_{4',4''}$ 11.6 Hz), 6.95 (s, 1 proton, H-5), 7.24 (m, 4 protons, Ph-1), 2.44 (s, 3 protons, Me-Ar-1), 2.31 (s, 3 protons, Me-2), 2.12, 2.07, 2.05, 2.02 (s, 3 protons each, OAc-Me). [b]*c* 1.0, chloroform. [c]Relative to *N*-acetyl-*p*-toluidine. [d]Calc. for $C_{23}H_{28}N_2O_8$: C, 59.99; H, 6.13; N, 6.08. [e]Reported in Ref. 2. [f]The yield is higher than our previous one (12% yield in Ref. 2) because of improved better technique.

i.r. absorptions at 3300–3500 (OH, NH), ~1650 (C=O of *N*-acetyl) or ~1650 cm^{-1} (NH of *N*-acetyl).

With regard to the configuration at the three chiral carbon centers, the values $J_{1',2'}$ 8.0, $J_{2',3'}$ 2.0–3.0, and $J_{3',4'}$ 4.7–5.0 Hz observed in the p.m.r. spectra (Me_2SO–d_6 and $CDCl_3$) accord with an antiparallel relationship of H-1′ and H-2′, and a gauche disposition of H-2′ and H-3′ (Table I). Each of these signal assignments was confirmed by double irradiation. On the basis of these data, we have tentatively assigned the D-*lyxo* configuration (in the planar, zigzag conformation) to the acyclic side-chain of **1**, through consideration of reported values for 1,2,3,4-tetraacetoxybutyl derivatives having the D-*arabino*, D-*lyxo*, D-*ribo*, and D-*xylo* configurations[4–6], although the configuration should be conclusively verified by chemical means.

Formation of the imidazole is considered to occur by 1,2-enolization and dehydration reactions, and the configurational inversion at C-4 of **2**, **4**, and **5** (C-2′ of **1**) may proceed by way of a cyclic acetoxonium ion[7] (see Scheme for proposed intermediates).



The reaction products, as indicated by t.l.c. (Solvent A), consisted of **1** (R_F 0.47), *N*-acetyl-*p*-toluidine (R_F 0.29), 2-acetamido-2-deoxy-1,3,4,6-tetra-*O*-acetyl-D-glucose (R_F 0.22), and various other products (R_F 0.55, 0.37, 0.26, 0.18, 0.12, 0.08, and 0.05). These unknown products are considered to be intermediates that include the imidazole derivative of the original configuration, but these were not further studied because they were difficult to separate.

EXPERIMENTAL

General methods. — Melting points were measured on a Yanagimoto apparatus (SP-2) and are uncorrected. P.m.r. spectra were recorded at 60 MHz with a Hitachi NMR R-24 spectrometer and at 90 MHz with a Hitachi Perkin–Elmer R-22 spectro-

meter, and tetramethylsilane was used as the internal reference and lock. Specific rotations were measured with a Yanagimoto OR-50 automatic polarimeter and a cell of path length 1.0 cm. G.l.c. analyses were carried out at 230° on a Shimadzu GC-5A apparatus equipped with a hydrogen flame-ionization detector and with a stainless-steel column (4 mm × 3 m) packed with 5% OV-17 on Celite 545 (AW-DMCS) 80–120 mesh; nitrogen was the carrier gas and the flow-rate was 60 ml/min. Mass spectra were recorded at 190° with a Hitachi RMS-4 mass spectrometer operating at an ionization potential of 70 eV.

T.l.c. was performed on plates of Merck Silica Gel G with two solvents: A, 9:1 (v/v) benzene–methanol and B, 17:3 (v/v) benzene–methanol. The components were detected by viewing under u.v. light, and then by spraying the plates with concentrated sulfuric acid and heating them at ~120°.

2-Acetamido-2-deoxy-*N*-*p*-tolyl-β-D-glycosylamines having the *galacto* (**3**), *gluco* (**2**), and *manno* (**4**) configurations, and 2-acetamido-3,4,6-tri-*O*-acetyl-β-D-glucosylamine (**5**) were prepared by conventional methods and had physical constants in agreement with published values.

*4-(1,2,3,4-Tetraacetoxylbutyl)-2-methyl-1-*p*-tolylimidazole* (**1**). — Samples (1.0 g) of **2**, **3**, **4**, and **5** were dissolved in a mixture of acetic anhydride (10 ml), acetic acid (10 ml), and concentrated sulfuric acid (1 ml) with stirring at 0°. The solutions were kept for 3 h at this temperature, and then for 90 h at room temperature. Compound **1** was isolated from the mixture by chromatography on a column (1.5 × 32 cm) of silica gel 60 (70–230 mesh, ASTM, Merck) that was eluted with 19:1 (v/v) benzene–acetone as described in our previous paper[2]. The fractions were monitored by t.l.c. Compound **1** was crystallized and recrystallized from ethanol–ether.

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