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Note

Synthesis of *C*-(3-nitro- and 3-amino-glycopyranosyl) derivatives of furan*

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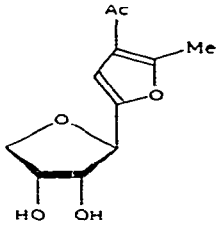
In connection with the preparation of *C*-glycosyl heterocycles, the Baer–Fischer reaction has been used in the ring expansion of the 2-β-D-erythrofuranosylfuran derivative **1**. Periodate oxidation of **1** gave the dialdehyde **2**, which has been reported[1,2] to exist as a monohydrate, with a 1,4-dioxane structure, although its configuration



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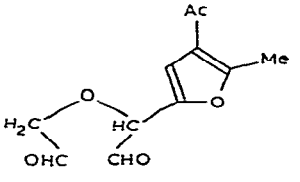

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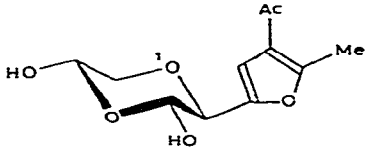
and conformation are not known. In this connection, we have used optical rotation data and ^{1}H-n.m.r. spectroscopy. Although great efforts[3–5] have been made to establish a correlation between molecular constitution and optical rotation, few practical applications have been described. We now report an application to the hydrate of **2**, that is in agreement with the spectroscopic results and indicates the structure **3**.



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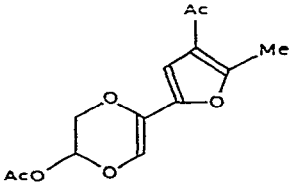

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*Synthesis of *C*-(3-Nitro- and 3-Amino-glycopyranosyl) Heterocycles, Part I.
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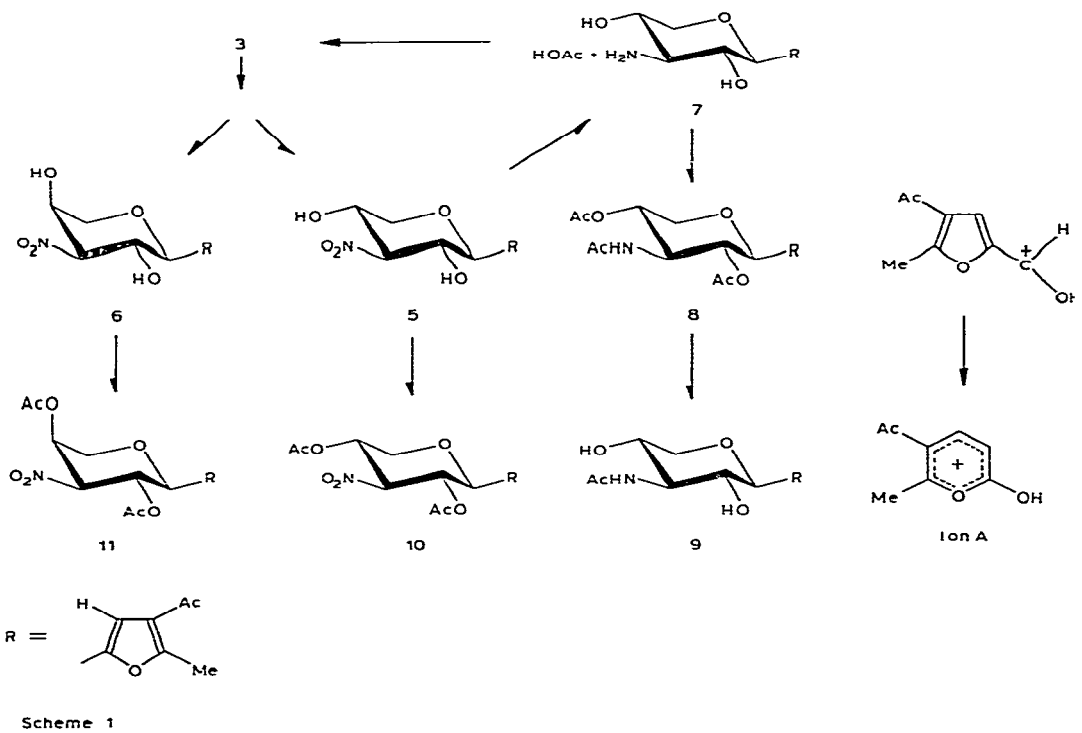
The ^{1}H-n.m.r. data ($J_{2,3}$ 8, $J_{5,6ax}$ 8, $J_{5,6eq}$ 3, and $J_{6ax,6eq}$ 11 Hz) for **3** indicate a $^5C_2$ conformation with the three bulky groups equatorial. The calculated $[M]_D$ value for this conformer, according to Brewster's parameters[4]*, is −50°; the experimental value was −46°. In contrast to the behaviour of **3** in pyridine solution[2], no mutarotation was observed in aqueous solutions. The supposition[6] about the (*R*) configuration at C-1 in **1**, and therefore the (*S*) configuration at C-2 in **3**, is valid.

Acetylation of **3** in pyridine yielded a crystalline, racemic, unsaturated monoacetate (**4**). Similar behaviour has been observed in a phenylosotriazole analogue[7].

The reaction of **3** with nitromethane in water gave two isomeric 3-deoxy-3-nitropentopyranosides with the β-D-*xylo* (major product, **5**) and α-L-*arabino* (minor product, **6**) configurations. Baer and Fischer, dealing with similar reactions of dialdehydes derived from pentoses[8], supposed that neutral forms of nitro derivatives with HO-2,4 *cis* were formed from the corresponding sodium salt *via* proton attack on the side of the ring opposite to the hydroxyl groups. Thus, the β-D-*ribo* isomer was formed preferentially. In the present case, however, attack on the sodium derivative must occur on the same side as the hydroxyl groups, which means that the steric control is determined by the nature of the substituent at C-1, rather than the orientation of the hydroxyl groups. In both cases, the processes seem to be thermodynamically controlled.



Scheme 1

*The parameter used for C-2 in the furan ring is the same as that given by Brewster for the hydroxymethylene group in hexopyranosides.

We are not aware of any conformational study of the Baer–Fischer nitroglycosides, but, for the β-D-ribopyranoside, the anomeric effect, the equatorial orientation of the nitro group, and the possibility of a hydrogen bond between the hydroxyl groups can be regarded as stability factors for the $^1C_4$ conformation. A molecular rotation of −213° was calculated for this conformer, which agrees well with the experimental value (−226°); for the $^4C_1$ conformer, the calculated value is −145°.

Compound **5** has no anomeric effect, and the two bulky groups, furyl and nitro, must be equatorial. This requirement leads to the order of stability β-D-*xylo* > α-L-*arabino* > β-D-*lyxo* > α-L-*ribo* configuration in the $^4C_1$ conformation. This interpretation accords with the ^{1}H-n.m.r. data for **5**, namely, $J_{1,2} = J_{3,4} = 10$ Hz. X-Ray diffraction studies confirm this conformation in the crystalline form[9].

The α-L-*arabino* configuration for the minor product **6** is another difference in comparison with the Baer–Fischer results. They reported that the major (β-D-*ribo*) and minor (β-D-*xylo*) products came from the same sodium salt. In our furan derivative, however, the major and minor products must be formed from different sodium salts. The most stable $^4C_1$ conformation ($J_{1,2}$ 10, $J_{2,3}$ 10, $J_{3,4}$ 3.5, $J_{4,5ax}$ 1.5, and $J_{4,5eq}$ 2 Hz) for the α-L-*arabino* isomer also accords with the equatorial disposition of the bulky groups.

Reduction of **5** with zinc and acetic acid gave **7**, which was subsequently transformed into the triacetyl derivative **8**. The ^{1}H-n.m.r. data for **8** indicated a $^4C_1$ conformation ($J \geq 10$ Hz in methyl sulfoxide). *O*-Deacetylation of **8** gave **9**. Treatment of **5** and **6** with acetyl chloride gave the 2,4-diacetates **10** and **11**, respectively. The possibility of epimerisation at C-1 in the condensation of **3** with nitromethane was ruled out when periodate oxidation of the amine **7** gave the dialdehyde **3**.

Attempts to form the β-D-*ribo* isomer under conditions similar to those employed by Baer–Fischer (*i.e.*, anhydrous solvents and low temperature) were unsuccessful.

EXPERIMENTAL

General. — Melting points were determined with an Electrothermal melting-point apparatus, and are uncorrected. I.r. spectra were recorded for KBr discs with a Unicam SP 1000 spectrometer or a Spektralphotometer IMR-16. U.v. spectra were recorded for methanolic solutions, using a Perkin–Elmer 124 spectrometer. ^{1}H-N.m.r. spectra were recorded with Perkin–Elmer–Hitachi R-20 B (60 MHz) or Bruker HFX-100, -200, or -400 spectrometers. Chemical shifts (first order) are given on the δ scale with first-order couplings in Hz. Mass spectra were recorded with a Hewlett–Packard model 5930 A spectrometer. Optical rotations were measured with a Perkin–Elmer 141 polarimeter.

Solutions were concentrated below 50° under diminished pressure. T.l.c. was performed on Silica Gel G (Merck) with detection by charring with sulfuric acid.

(2S,3R,5S)-2-(4-Acetyl-5-methyl-2-furyl)-3,5-dihydroxy-1,4-dioxane (**3**). — This compound, obtained as reported[1,10], had $[\alpha]_D^{20}$ −19° (*c* 0.5, water; no mutaro-

tation), $[M]_D$ −46° (calc. −50°). ^{1}H-N.m.r. data (100 MHz): acetone-d_6, δ 6.72 (s, 1 H, H-β), 5.88–5.70 (bs, 2 H, HO-3,5, exchangeable with D_2O), 5.14–4.94 (bs, 2 H, H-3,5), 4.05 (d, 1 H, $J_{2,3}$ 8 Hz, H-2), 3.88–3.71 (dd, 1 H, $J_{6eq,5}$ 3, $J_{6eq,6ax}$ 11 Hz, H-6*eq*), 3.38–3.15 (dd, 1 H, $J_{6ax,5}$ 8 Hz, H-6*ax*), 2.55 (s, 3 H, Me), and 2.37 (s, 3 H, Ac); acetone-d_6–D_2O, δ 5.10–4.94 (dd, 2 H, $J_{3,2}$ 8, $J_{5,6ax}$ 8, $J_{5,6eq}$ 3 Hz, H-3,5). Mass spectrum: *m/z* 224 ($M^+ - H_2O$), 209 (224 — Me), 153 (Ion A; see Scheme 1), and 43 (Ac, 100%).

5-Acetoxy-2-(4-acetyl-5-methyl-2-furyl)-1,4-dioxene (**4**). — Compound **3** (470 mg, 19.4 mmol) was treated with acetic anhydride (10 mL) and pyridine (10 mL) for 12 h at ~5°, to give **4** (104 mg, 20.1%), m.p. 115° (from ethanol), $[\alpha]_D^{30}$ 0° (*c* 1, methanol); ν_{max} 3140, 3020, 2960, 1760, 1690, 1610, 1590, 1570, 1235, 1125, 1040, and 955 cm^{-1}; λ_{max}^{MeOH} 266 (ε 12.3 × 10^3) and 210 nm (ε 8.3 × 10^3). ^{1}H-N.m.r. data (60 MHz, $CDCl_3$): δ 6.45 (s, 1 H, H-β), 6.42 (s, 1 H, H-3), 6.25 (t, 1 H, $J_{5,6} = J_{5,6'}$ = 2 Hz, H-5), 4.1 (dd, 1 H, $J_{6,6'}$ 12 Hz, H-6), 3.95 (dd, 1 H, H-6'), 2.5 (s, 3 H, Me), 2.3 (s, 3 H, Ac), and 2.08 (s, 3 H, AcO-5). Mass spectrum: *m/z* 266 (M^+), 251 (M^+ — Me), 224 ($M^+ - COCH_2$), 207 (M^+ — OAc), and 195 (224 — CHO).

Anal. Calc. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.29. Found: C, 58.72; H, 5.58.

Reaction of **3** *with nitromethane.* — To a solution of **3** (19.37 g, 0.08 mol) in water (800 mL) was added nitromethane (4.3 mL, 0.08 mol), followed by 2M potassium hydroxide (4 mL, 0.008 mol). The mixture was stirred at 45°. After 1 h, the white solid (11.8 g) was collected and washed with cold water. The filtrate was neutralised with Amberlite IR-120 (H^-) resin and then extracted with ethyl acetate (5 × 300 mL). The extracts were dried (Na_2SO_4) and kept at 0°, yielding more solid (1.78 g, total yield 59.5%). T.l.c. (2:1 ethyl acetate–hexane) of this solid revealed two products having R_F 0.42 (**5**) and 0.34 (**6**).

The mother liquor was concentrated, to give a syrupy residue (8.67 g, 38%), which t.l.c. showed to contain **5** (major), **6** (second), and three more products (R_F 0.26, 0.19, and 0.09) in smaller amounts. The mixture was eluted from a column of silica gel with ethyl acetate–hexane (1.5:1), to give **5** (1966 mg) and **6** (678 mg).

4-Acetyl-2-(3-deoxy-3-nitro-β-D-xylopyranosyl)-5-methylfuran (**5**) had m.p. 185–190° (dec.), $[\alpha]_D^{29}$ −51° (*c* 1, methanol); ν_{max} 3520, 3350, 3100, 2960, 2920, 2850, 1655, 1605, 1560, 1550, 1140, 1070, and 980 cm^{-1}; λ_{max}^{MeOH} 265 (ε 5.6 × 10^3) and 212 nm (ε 15.1 × 10^3). For ^{1}H-n.m.r. data, see Table I. Mass spectrum: *m/z* 285 (M^+), 270 (M^+ — Me), 256 (M^+ — CHO), 242 (M^+ — Ac), 239 ($M^+ - NO_2$), 221 ($M^+ - H_2O - NO_2$), 153 (Ion A, see Scheme 1), and 43 (Ac, 100%).

Anal. Calc. for $C_{12}H_{15}NO_7$: C, 50.52; H, 5.30. Found: C, 50.08; H, 5.35.

4-Acetyl-2-(3-deoxy-3-nitro-α-L-arabinopyranosyl)-5-methylfuran (**6**) had m.p. 210° (dec.), $[\alpha]_D^{29}$ +6° (*c* 1, methanol); ν_{max} 3540, 3280, 3100, 2980, 2960, 2940, 2860, 1655, 1600, 1550, 1540, 1360, 1065, and 955 cm^{-1}; λ_{max}^{MeOH} 265 (ε 5.1 × 10^3) and 208 nm (ε 25.3 × 10^3). For ^{1}H-n.m.r. data, see Table I. Mass spectrum: *m/z* 285 (M^+), 270 (M^+ — Me), 256 (M^+ — CHO), 242 (M^+ — Ac), 239 ($M^+ - NO_2$), 221 ($M^+ - H_2O - NO_2$), 153 (Ion A, see Scheme 1), and 43 (Ac, 100%).

Anal. Found: C, 51.12; H, 5.40.

TABLE I

^{1}H-N.M.R. DATA (δ SCALE)

Compound	*H-1* ($J_{1,2}$)	*H-2* ($J_{2,3}$)	*H-3* ($J_{3,4}$)	*H-4* ($J_{4,5ax}$) ($J_{4,5eq}$) ($J_{4,3}$)	*H-5eq* ($J_{5eq,5ax}$) ($J_{5eq,4}$)	*H-5ax* ($J_{5ax,5eq}$) ($J_{5ax,4}$)	*HO-2* ($J_{HO-2,2}$)	*HO-4* ($J_{HO-4,4}$)	*H-β*	*Me*	*Ac*	*HN* ($J_{HN,3}$)	*NAc*	*AcO-2*	*AcO-4*
5[a]	4.24d (10)	4.09m (10)	4.57st (10)	3.98m (11) (5.5)	3.84q (11)	3.31st	5.95d (7)	5.87d (6)	6.84s	2.49s	2.33s				
6[a]	4.11d (10)	4.51m (10)	4.79q (3.5)	4.25bs	3.76q (12) (2)	3.69q (—) (1.5)	5.69d (6.5)	5.60d (5)	6.84s	2.49s	2.35s				
8[b]	4.58d (10)	5.08st (10.5)	4.23m (10.5)	4.86m (10.8) (5.4)	3.99q (10.8)	3.50st			6.71s	2.50s	2.35s	7.94d (10)	2.19s	2.04s	1.77s
9[c]				4.5–3.0					6.7s	2.4s	2.3s		2.0s		
10[d]	4.9d (10)	5.6st (10)	(4.7–4.1)m unresolved	5.4m (10) (5) (10)	(4.7–4.1)m unresolved	3.3st (10) (—)			6.6s	2.5s	2.3s			2.0s	1.9s
11[d]	(5.0–4.6)(bs) (10)	6.0st (10)	(5.0–4.6)dd(bs) (3)	5.6bs	4.2d(bs) (11)	3.7d(bs)			6.6s	2.5s	2.3s			2.0s	1.8s

[a]400 MHz, Me_2SO-d_6. [b]200 MHz, Me_2SO-d_6. [c]60 MHz, D_2O. [d]60 MHz, $CDCl_3$.

4-Acetyl-2-(2,4-di-O-acetyl-3-deoxy-3-nitro-β-D-xylopyranosyl)-5-methylfuran (**10**). — To a suspension of **5** (0.1 g, 0.35 mmol) in acetic acid (6 mL) was added acetyl chloride (6 mL) followed by heating for 15 min at 50°. The solution was concentrated, and acetic acid was removed by repeated evaporation of methanol from the residue which was then crystallised from ethyl acetate–hexane (1 : 1), to give **10** as white needles (88 mg, 67.9%), m.p. 130–133°, $[\alpha]_D^{22}$ −28° (*c* 1, methanol); ν_{max} 3110, 2960, 1755, 1745, 1670, 1605, 1575, 1560, 1370, and 1030 cm^{-1}. For ^{1}H-n.m.r. data, see Table I. Mass spectrum: *m/z* 369 (M^+), 354 (M^+ − Me), 326 (M^+ − Ac), 294 (M^+ − Me − HOAc), 285 (M^+ − $COCH_2$ − $COCH_2$), 281 (M^+ − $COCH_2$ − NO_2), 239 (285 − NO_2), 153 (Ion A, see Scheme 1), and 43 (Ac, 100%).

Anal. Calc. for $C_{16}H_{19}NO_9$: C, 52.03; H, 5.18; N, 3.79. Found: C, 52.21; H, 5.11; N, 3.77.

4-Acetyl-2-(2,4-di-O-acetyl-3-deoxy-3-nitro-α-L-arabinopyranosyl)-5-methylfuran (**11**). — Compound **6** (86 mg, 0.3 mmol) was acetylated, as described above, to yield **11** as a syrup. For ^{1}H-n.m.r. data, see Table I.

4-Acetyl-2-(3-amino-3-deoxy-β-D-xylopyranosyl)-5-methylfuran (**7**). — To a suspension of **5** (0.8 g, 2.8 mmol) in acetic acid (80 mL) and water (16 mL) was added zinc (16 g). The mixture was stirred for 45 min at 55° and then for 3 h at room temperature, and filtered, and the zinc ions were removed as the sulfide. The solution was concentrated, and acetic acid was removed by repeated evaporation of methanol from the residue. T.l.c. (2 : 1 ethyl acetate–hexane) of the syrupy product **7** (725 mg, 82.3%) revealed no **5**.

Conventional acetylation of **7** gave 2-(3-acetamido-2,4-di-*O*-acetyl-3-deoxy-β-D-xylopyranosyl)-4-acetyl-5-methylfuran (**8**; 663 mg, 75.6%), m.p. 225–227° (from methanol), $[\alpha]_D^{27}$ −66° (*c* 1, methanol), R_F 0.41 (t.l.c., 5 : 1 benzene–ethanol); ν_{max} 3300, 3110, 3070, 2930, 1750, 1740, 1675, 1655, 1600, 1560, 1535, 1295, 1070, and 940 cm^{-1}; λ_{max}^{MeOH} 264 (ε 4.3 × 10^3) and 209 nm (ε 19.1 × 10^3). For ^{1}H-n.m.r. data, see Table I. Mass spectrum: *m/z* 382 (M^+ + 1), 366 (M^+ − Me), 321 (M^+ − HOAc), 306 (M^+ − Me − HOAc), 261 (321 − HOAc), 153 (Ion A, see Scheme 1), and 43 (Ac, 100%).

Anal. Calc. for $C_{18}H_{23}NO_8$: C, 56.68; H, 6.07. Found: C, 57.17; H, 6.25.

2-(3-Acetamido-3-deoxy-β-D-xylopyranosyl)-4-acetyl-5-methylfuran (**9**). — To a solution of **8** (1 g, 2.6 mmol) in methanol (200 mL) was added a solution of sodium methoxide (94 mg, 1.74 mmol) in methanol (2 mL). The mixture was stored at room temperature for 3 h, neutralised with Amberlite IR-120 (H^+) resin, and concentrated to 5 mL, to give **9** (756 mg, 97%), m.p. 222–223° (dec.), $[\alpha]_D^{20}$ −99° (*c* 1, water); ν_{max} 3380, 3300, 3260, 3100, 2850, 1660, 1650, 1610, 1535, 1300, and 1230 cm^{-1}; λ_{max}^{MeOH} 266 (ε 3.5 × 10^3) and 209 nm (ε 19.3 × 10^3). For ^{1}H-n.m.r. data, see Table I. Mass spectrum: *m/z* 297 (M^+), 282 (M^+ − Me), 153 (Ion A, see Scheme 1), and 43 (Ac, 100%).

Anal. Calc. for $C_{14}H_{19}NO_6$: C, 56.55; H, 6.44. Found: C, 56.49; H, 6.79.

Further reactions of **3** *with nitromethane.* — (*a*) To a solution of **3** (2.42 g, 10 mmol) and nitromethane (2.7 mL, 0.05 mol) in ethanol (25 mL) at −10° was slowly

added, with stirring, a solution of sodium methoxide (0.7 g, 13 mmol) in methanol (10 mL). After 2 h, the mixture was slowly acidified with acetic acid at −10°. The mixture then contained (t.l.c.) almost exclusively **5** and **6**.

(*b*) To a solution of **3** (0.1 g, 0.41 mmol) and nitromethane (0.2 mL, 3.72 mmol) in ethanol (15 mL) at −15° was slowly added, with stirring, a solution of sodium ethoxide (59 mg, 0.87 mmol) in ethanol (10 mL). After 2 h, the cold solution was neutralised with Amberlite IR-120 (H^+) resin. T.l.c. then revealed almost exclusively a mixture of **5** (major) and **6** (minor).

Attempted epimerisation at C-3 of **5**. — To a solution of **5** (0.1 g, 0.35 mmol) in methanol (15 mL) at −77° was slowly added a solution of sodium methoxide (0.47 g, 8.7 mmol) in methanol (7 mL). After 30 min, the mixture was neutralised at −77° with Amberlite IR-120 (H^+) resin. Only **5** was detectable by t.l.c.

Periodate oxidation of **7**. — To a solution of **1** (24 mg) in water (2 mL) at 20° {$[\alpha]_D^{20}$ −116° (*c* 1.2, water)} was added sodium periodate (35 mg). After 10 min, the specific rotation of the solution was −17°. In the final solution, **3** was the only product detectable by t.l.c.

To a solution of **7** (40 mg) in water (4 mL) at 20° {$[\alpha]_D^{20}$ −25° (*c* 1, water)} was added sodium periodate (145 mg). After 10 min, the specific rotation of the solution was −16°. T.l.c. showed that the final solution contained only **3**.

ACKNOWLEDGMENTS

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