Carbohydrate Research, 94 (1981) 115–118
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Note

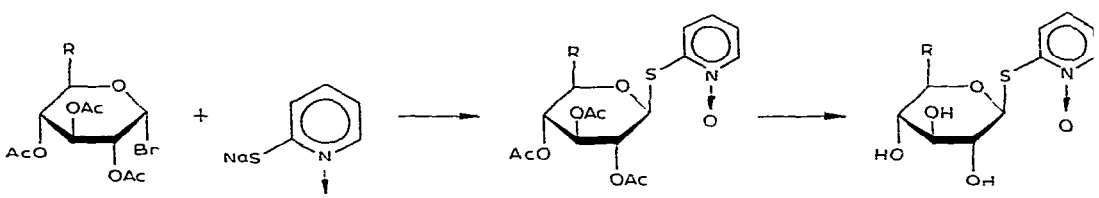
Synthesis of analogs of a metabolite of sodium 2-pyridinethiolate *N*-oxide (pyrithione)

DARYL E. WARDER
Department of Product Research and Development, Olin Corporation, New Haven, CT 06520 (U.S.A.)
(Received October 10th, 1980; accepted for publication in revised form, December 29th, 1980)

The widespread use of the sodium and zinc salts of 2-pyridinethiol *N*-oxide owing to their antibacterial and antifungal properties has prompted many studies[1–5] to determine the structure of the metabolites of the salts. Recently, Wedig *et al.*[1] identified methyl, ethyl, and butyl [(2-pyridyl *N*-oxide) 1-thio-β-D-glucopyranosid]-uronates as metabolites of zinc and sodium (3) 2-pyridinethiolate *N*-oxide (pyrithione) in swine, whereas Kabacoff *et al.*[4] had previously identified these glycosides as metabolites of the salts in rabbits.

The reaction of 2-pyridinethiol with methyl 2,3,4-(tri-*O*-acetyl-α-D-glucopyranosyl bromide)uronate (**2**) or 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**1**) using the analogous phenol fusions[6] as model systems proved unsuccessful, as did the condensation of **3** with methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranuronate, but the method of Matta *et al.*[7] was effective. The classical methods of *O*-deacylation[6] could not be used with methyl [(2-pyridyl *N*-oxide) 2,3,4-tri-*O*-acetyl-1-thio-β-D-glucopyranosid]uronate (**5**), but did succeed with (2-pyridyl *N*-oxide) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**4**). A milder *O*-deacetylation with methanol saturated with ammonia at 0° yielded [(2-pyridyl *N*-oxide) 1-thio-β-D-glucopyranosid]uronamide (**7**).

The successful condensation of **3** with **1** or **2** was highly dependent upon the solvent used, and the length of the reaction. The condensations were attempted in



1 R = CH_2OAc
2 R = CO_2Me

3

4 R = CH_2OAc
5 R = CO_2Me

6 R = CH_2OH
7 R = $CONH_2$

methanol or *N,N*-dimethylformamide. The reaction of **1** with **3** in *N,N*-dimethylformamide gave (2-pyridyl *N*-oxide) 1-thio-β-D-glucopyranoside (**6**) in high yields (66–72%) and in high purity, whereas the reaction of **2** with **3** in *N,N*-dimethylformamide gave **7** in high yields, but in low purity. This same reaction in methanol gave **7** in lower yields (36–48%), but in a much higher purity.

The method of deacylating **4** was too harsh for **5**, whereas the method of deacylating **5** did not preclude side-reactions with **4**, resulting in a crude sample of (2-pyridyl *N*-oxide) 1-thio-β-D-glucopyranoside (**6**), which was extremely difficult to purify. Compound **4** was deacylated in a methanol–0.25M sodium hydroxide solution, and then washed with water and methanol to give **6**. This procedure decomposed **5**, and, consequently, this compound was deacylated, at 0° in methanol saturated with ammonia, to give **7** in good purity. It should be noted that crude **5** produced in *N,N*-dimethylformamide solution was deacylated with this method to give highly pure **7**, whereas pure **5** produced in methanol solution gave, under these conditions, a crude sample of **7** that was extremely difficult to purify. The final products, (2-pyridyl *N*-oxide) 1-thio-β-D-glucopyranosiduronamide (**7**) and 1-thio-β-D-glucopyranoside (**6**), were slightly soluble in water at room temperature, but decomposed in water at elevated temperatures. The structures of **6** and **7** were confirmed by ^{13}C-n.m.r., mass, and i.r. spectrometry.

EXPERIMENTAL

General methods. — Compound **2** was synthesized according to the method of Bollenback *et al.*[6] using a pyridine-catalyzed acetylation. Compound **1** was purchased from ICN K & K Laboratories Inc., Plainview, NY 11803, and **3** was supplied by the Olin Corp. All melting points are uncorrected. Elemental analyses were performed by the Analytical Dept. of the Olin Corp. ^{13}C-N.m.r. spectra were recorded with a 20-MHZ Varian CTF20 spectrophotometer for solutions in dimethyl sulfoxide and tetramethylsilane as the internal standard. Mass spectral data were obtained with a Finnigan mass spectrometer using the ammonia, chemical-ionization, positive-ion technique. I.r. spectra were recorded with a Perkin–Elmer 283 spectrophotometer equipped with a potassium bromide cell. All spectral data were obtained and interpreted by the Analytical Dept. of the Olin Corp.

(*2-Pyridyl* N-*oxide*) *2,3,4,6-tetra*-O-*acetyl-1-thio*-β-D-*glucopyranoside* (**4**). — To a solution of **1** (5 g, 2.2 mmol) in *N,N*-dimethylformamide in (45 mL) was added **3** (2.7 g, 18.1 mmol). This mixture was stirred for 3 days at room temperature, after which it was poured into water (700 mL), and stirred for 2 h. The precipitate was filtered off, washed with water, and dried *in vacuo* (40°) for 1 h to give **4** (3.7 g, 8.1 mmol, 66% yield) as a yellowish solid, m.p. 154–155°; ν_{max}^{KBr} 3130, 3040, 1615, 1535, 1140–1000 (sharp aromatic bands), 2965, 1380 (CH_3, stretching and bending), 1760 (broad ester CO), 1240 (broad CO_2 stretching), and 1100–1000 cm^{-1} (broad CO_2-C stretching); ^{13}C-n.m.r.: δ 174.4 (C-1, pyridine *N*-oxide C), 169.9–169.1

(4 CH_3CO), 141.2–134.5 (3 pyridine *N*-oxide C), 112.4 (C-2 pyridine *N*-oxide C), 101.8 (C-1 of Glc), 71.1–61.4 (5 Glc C), and 20.7–20.2 (4 CH_3CO).

Anal. Calc. for $C_{19}H_{23}NO_{10}S$: C, 49.89; H, 5.03; N, 3.06; S, 7.00. Found: C, 49.76; H, 5.07; N, 3.13; S, 6.75.

Methyl [*(2-pyridyl* N-*oxide) 2,3,4-tri-*O-*acetyl-1-thio-β-*D-*glucopyranosid*]*uronate* (**5**). — *Method* (*a*). To a solution of **2** (4.1 g, 10.3 mmol) in *N*,*N*-dimethylformamide (40 mL) was added **3** (2.24 g, 15 mmol), and the mixture was stirred overnight at room temperature. The solution was poured into water (600 mL) and stirred for 2 h. The precipitate was filtered off and washed with water, and then dried *in vacuo* (40°) to give crude **5** (2.5 g, 5.7 mmol, 55% yield), m.p. 163–167°.

Anal. Calc. for $C_{18}H_{21}NO_{10}S$: C, 48.76; H, 4.77; N, 3.16; S, 7.23. Found: C, 47.7; H, 4.76; N, 3.7; S, 6.72.

Method (*b*). To a solution of **2** (4 g, 10.1 mmol) in methanol (75 mL) was added **3** (2.24 g, 15 mmol). The solution was stirred overnight at room temperature. The precipitate was filtered off and dried under vacuum (40°) to give **5** (1.7 g, 38.17% yield), m.p. 170–171°; ^{13}C-n.m.r.: δ 174.4 (C-1 of pyridine *N*-oxide), 169.3–166.7 (4 CO), 141.0–134.6 (3 pyridine *N*-oxide C), 112.7 (C-2 of pyridine *N*-oxide), 101.6 (C-1 of sugar residue), 70.7–68.7 (3 C of sugar residue), 52.6 (OCH_2), and 20.7–20.1 (3 CH_2CO); ν_{max}^{KBr} 3130, 3040, 1615, 1535, 1140–1000 (sharp aromatic bands), 1760, 1750 (CH_3CO), 1730 (CH_3OCO), 1240 (doublet CO_2), and 1100–1000 cm^{-1} (COOC).

Anal. Calc. for $C_{18}H_{21}NO_{10}S$: C, 48.76; H, 4.77; N, 3.16; S, 7.23. Found: C, 48.68; H, 4.52; N, 3.04; S, 7.01.

(2-Pyridyl N-*oxide) 1-thio-β-*D-*glucopyranoside* (**6**). — Compound **4** (4 g, 88 mmol) was dissolved in methanol (100 mL) and 0.25M sodium hydroxide (50 mL), and the solution was kept overnight in the refrigerator. The solvents were removed under diminished pressure (50°). The residue was treated with methanol and the solid was filtered off, washed with water, then methanol, and dried under vacuum (40°) for a few hours to give **6** (0.3 g 10 mmol, 11.8% yield), m.p. 183–184°; ^{13}C-n.m.r.: δ 173.7 (C-1 of pyridine *N*-oxide), 141.6–135.4 (3 pyridine *N*-oxide C), 113.8 (C-2 of pyridine *N*-oxide), 106.7 (C-1 of sugar residue), 77.3–69.1 (4 C of sugar residue), and 60.6 (C-6 of sugar residue); m.s.: *m/z* 290 (M + 1) and 274 (M — O + 1); ν_{max}^{KBr} 3500–3000 (strong O + H stretch), 1610, 1535, 1100–1000 (sharp aromatic bands), 1230 (N→O stretch), and 1100–1000 cm^{-1} (broad C-O ether stretch).

Anal. Calc. for $C_{11}H_{15}NO_6S$: C, 45.67; H, 5.19; N, 4.84; S, 11.07. Found: C, 45.55; H, 5.15; N, 4.80; S, 10.88.

[*(2-Pyridyl* N-*oxide) 1-thio-β-*D-*glucopyranosid*]*uronamide* (**7**). — A solution of **5** (6 g, 13.6 mmol obtained by method *a*) in methanol (500 mL) at 0° was saturated with ammonia, and stirred for 4 h at 0°. The solvent was removed under diminished pressure (45°) until a precipitate formed, which was filtered off and dried under vacuum (40°) to give **7** (0.9 g, 3.0 mmol, 21.9% yield), m.p. 187–188°; ^{13}C-n.m.r.: δ 174 (CO), 170.5 (C-1 of pyridine *N*-oxide), 141.4–136.16 (3 pyridine *N*-oxide C), 113.57 (C-2 of pyridine *N*-oxide), 105.7 (C-1 of sugar residue), and 75.79–70.79 (4 C of sugar residue); m.s.: *m/z* 303 (M + 1); ν_{max}^{KBr} 3410, 3340 (primary amide NH

stretching), 1694 (CO of primary amide), 1640 (primary amine band), 1610, 1530, 1114–1000 (sharp aromatic bands), and 1100–100 cm^{-1} (broad C-O stretching).

Anal. Calc. for $C_{11}H_{14}N_2O_6S$: C, 43.71; H, 4.64; N, 9.27; S, 10.6. Found: C, 43.89; H, 4.64; N, 9.42; S, 10.35.

ACKNOWLEDGMENTS

Special thanks are due Doug A. Farmer and Sam I. Trotz for their support.

REFERENCES

1 J. H. WEDIG, C. MITOMA, R. A. HOWD, AND D. W. THOMAS, *Toxicol. Appl. Pharmacol.*, 43 (1978) 373–379.
2 M. D. ADAMS, J. H. WEDIG, R. L. JORDAN, L. W. SMITH, R. HENDERSON, AND J. F. BORZELLECA, *Toxicol. Appl. Pharmacol.*, 36 (1976) 523–531.
3 H. C. S. HOWLETT AND N. J. VAN ABBE, *J. Soc. Cosmet. Chem.*, 26 (1975) 3–15.
4 B. L. KABACOFF, C. M. FAIRCHILD, AND C. BURNETT, *Food Cosmet. Toxicol.*, 9 (1971) 519–526.
5 B. H. MIN, C. PAREKH, L. GOLDBERG, AND E. W. MCCHESNEY, *Food Cosmet. Toxicol.*, 8 (1970) 161–166.
6 G. N. BOLLENBACK, J. W. LONG, D. G. BENJAMIN, AND J. A. LINDQUIST, *J. Am. Chem. Soc.*, 77 (1955) 3310–15.
7 K. L. MATTA, R. N. GIROTRA, AND J. J. BARLOW, *Carbohydr. Res.*, 43 (1975) 101–109.