Pergamon

Tetrahedron 54 (1998) 10703–10712

TETRAHEDRON

Building Blocks from Sugars. Part 23.[1] Hydrophilic 3-Pyridinols from Fructose and Isomaltulose

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Received 30 April 1998; accepted 24 June 1998

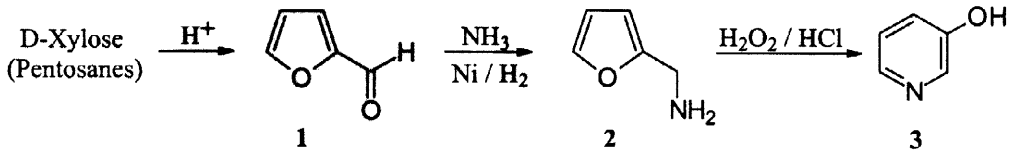
Abstract: Brief exposure to bromine in water-methanol at 0 °C smoothly and effectively converts furfurylamines with hydroxymethyl (**5**) or glucosyloxymethyl substituents (**16**) into the respective 6-substituted 3-pyridinols **9** and **19**, whereas the *N*-methyl-furfurylamines **10** and **17** elaborate the *N*-methyl-pyridinium betaines **13** and **22**. Combination of this multistep one-pot reaction with the large scale-feasible generation of hydroxymethylfurfural (**4**) from D-fructose and its *O*-glucosyl analog **15** from isomaltulose, together with their ready conversion into furfurylamines by reductive amination, opens up a preparatively satisfactory, 3-step "reaction channel" from inexpensive sugars to hydrophilic 3-pyridinols, of interest as intermediate chemicals for drugs of the pyridostigmine type and agrochemicals.

Keywords: Pyridines; Pyridinium Salts; Glycosides

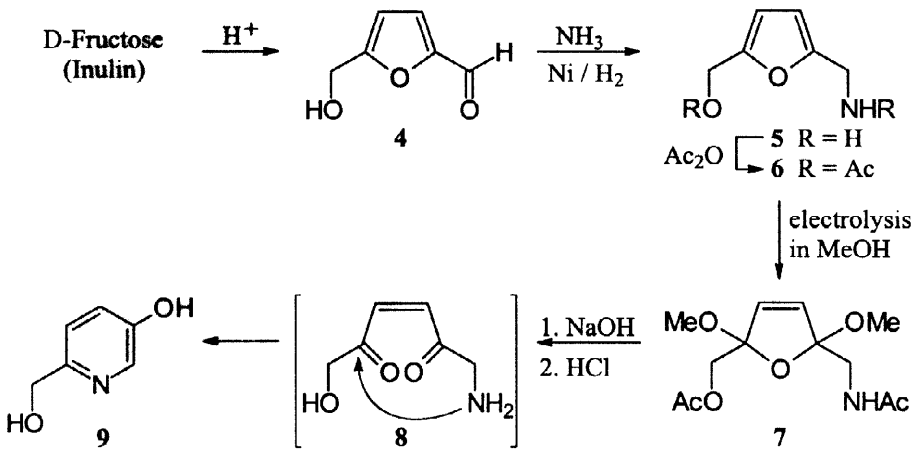
INTRODUCTION

As our fossile resources become less and as the pressure on our environment for using biomass-derived, CO_2-neutral raw materials is increasing, it is of principal importance to elaborate simple preparative procedures for the conversion of carbohydrates – they represent 95 % of the annually renewable biomass – into building blocks with industrial application profiles.[2,3] Despite substantial recent efforts towards this end,[2-4] the huge potential lying in high and low molecular weight carbohydrates is far from being fully exploited, one particular deficiency being the non-availability of appropriate methodology for their conversion into nitrogen heterocycles. Although the transformation of sugars into trace amounts of *N*-heterocycles occurs extensively on exposure of foodstuffs to heat (Maillard reaction[5]), and despite of the fact that various nitrogen heterocycles have been generated from saccharide derivatives,[6] procedures meeting preparative standards are scarce, one being the recently worked out three-step conversion of D-xylose, D-glucose or isomaltulose into pyrazoles with a versatile hydrophilic substitution pattern.[1,7] Another practicable 3-step sequence allows the conversion of pentosanes or pentoses into 3-pyridinol (**3**), involving acid-induced dehydration to furfural (**1**),[8] reductive amination to furfurylamine (→ **2**),[9] and subsequent oxidation with hydrogen peroxide,[10] the last step conceivably proceeding through the stage of a 2,5-dihydroxy-2,5-dihydrofurfurylamine, which elaborates the pyridine nucleus via dehydration to a 5-aminopentenal intermediate and intramolecular aldimine formation.

0040-4020/98/$ - see front matter
PII: S0040-4020(98)00634-6



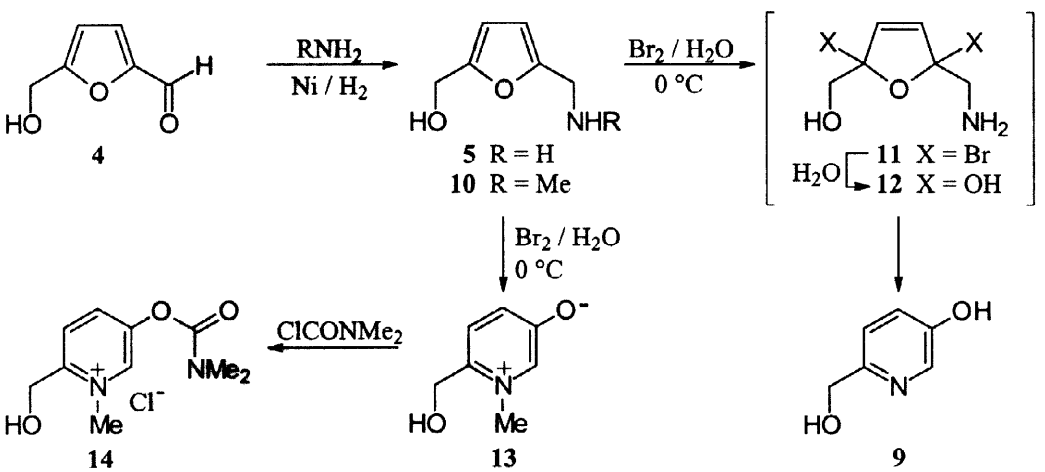
This straightforward 3-step protocol for the acquisition of **3** from pentoses is contrasted with a six-step procedure required for the conversion of D-fructose into 6-hydroxymethyl-3-pyridinol (**9**)[11] – considerably more laborious, since the oxidative conditions usable for **2** → **3** (30 % H_2O_2 in 3 N HCl, 30 min reflux[10]) cannot be applied to a furfurylamine such as **5**, carrying readily oxidizable hydroxyl groups; hence, *N*- and *O*-blocking (**5** → **6**) had to precede oxidation, which was effected electrochemically in methanol (→ **7**) and entailed deacetylation and acetal-hydrolysis before cyclization to the pyridine ring could take place :[11]



As D-xylose-derived 3-pyridinol (**3**) figures prominently as an intermediate chemical for the preparation of herbicides,[12] insecticides,[13] and cholinergic drugs of the pyridostigmine type,[14] we considered it of interest to provide a more direct and efficient protocol for the conversion of suitable hexoses or disaccharides into pyridinols with hydroxymethyl (e.g. **9**) or glucosyloxymethyl residues (e.g. **19**), as their biologically relevant derivatives would not only have an improved resorbability but a higher biodegradability as well. As a result, we here detail oxidative conditions that allow the direct, one-pot conversion of **5** or even glucosyloxymethyl-substituted furfurylamines (e.g. **16**) into the corresponding 3-pyridinols **9** and **19**, to opening up a simple, large scale-adaptable 3-step "reaction channel" to hydrophilic pyridines from D-fructose and isomaltulose.

RESULTS AND DISCUSSION

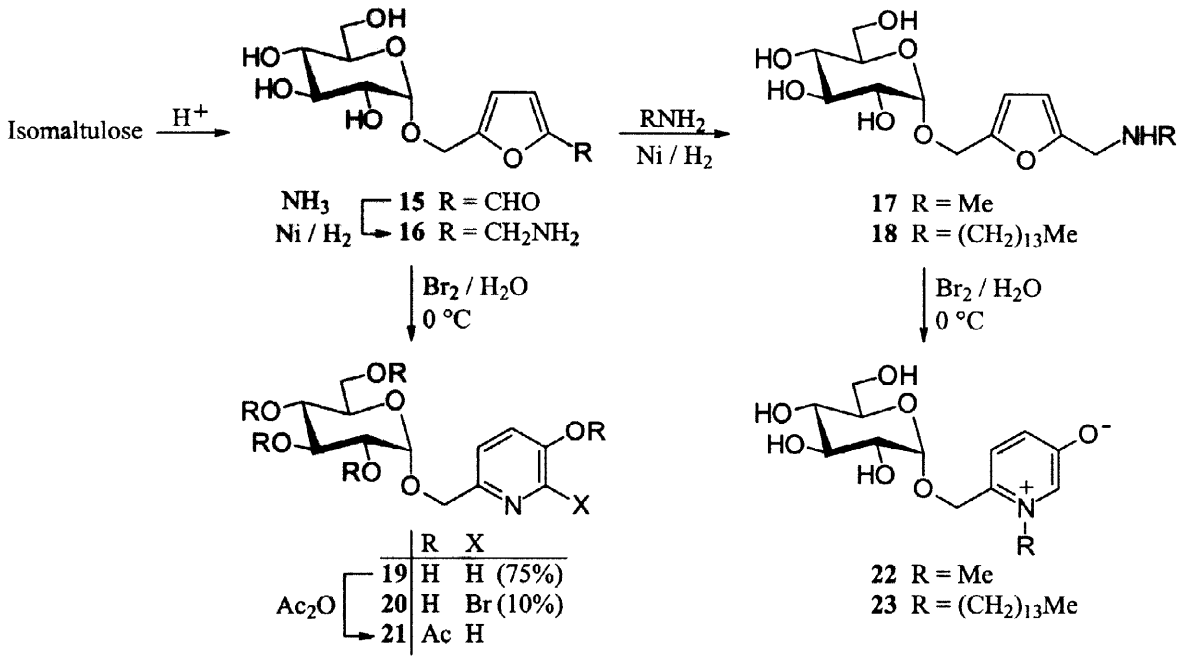
Various oxidants were evaluated for effecting a one pot-conversion of 5-hydroxymethyl-furfurylamine (**5**) to pyridinol **9** : chlorine or bromine in water, i.e. hypochlorous and hypobromous acid generated *in situ*, *N*-bromosuccinimide in dimethyl sulfoxide or dioxane in the presence of water or followed by its addition, and others. Best results were obtained by simply exposing **5** to bromine in water/methanol at 0 °C for 45 min, affording the 3-pyridinol **9** in crystalline form in an 85 % yield. That the hydroxymethyl group survives these oxidative conditions is not unexpected, as bromine water is long known to convert aldohexoses into their aldonic acids without harming primary and secondary hydroxyl functions;[15] surprising though is, that the entire multistep conversion occurs under these exceedingly mild conditions, i.e. 1,4-addition of bromine (→ **11**), hydrolysis of the dibromide to the cyclic bis-hemiketal **12**, elimination of water to the respective open-chain 2,5-diketone, and the concluding cyclo-imine formation with elaboration of the pyridine ring.



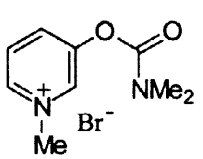
The procedure can also be applied fo furfurylamines with secondary amino groups, which are readily prepared by replacing ammonia with a primary amine in the reductive amination, e.g. **4** → **10** (91 %). Thus, when exposing **10** to bromine water, the *N*-methyl-3-oxidopyridinium betaine **13** is obtained (78 %). Through selective carbamoylation of the pyridine-3-OH ($ClCONMe_2$ in pyridine, 2 h at 0 °C), **13** is cleanly converted (82 %) into **14**, a 6-hydroxymethyl analog of the parasympathomimetic pyridostigmine (**24**, cf. below).

Gratifyingly, the bromine water treatment for the conversion of furfurylamines to 3-pyridinols is also applicable to analogs carrying glycoside residues, as the acidity building up through generation of HBr during the bromination is not sufficient to cleave the glycosidic linkage. Accordingly, the 5-glucosyloxymethyl-furfurylamine (**16**) – readily accessible from technically produced[16] isomaltulose by acid dehydration to the respective furfural **15**,[17] and ensuing reductive amination[17] – gave the 6-glucosyloxymethyl-3-pyridinol (**19**), isolable in 75 % yield as an amorphous product, yet readily characterizable as such or as its highly crystalline

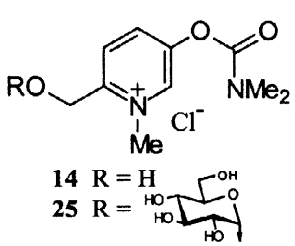
pentaacetate **21**. The conversion **16** → **19**, however, is accompanied by a side product (10 %) that proved to be the 2-bromo derivative **20**, obviously formed by bromination of **19**.



Exposing glucosylated furfurylamines with secondary amino groups to bromine water at 0 °C, e.g. the *N*-methyl and *N*-tetradecyl derivatives **17** and **18**, the respective *N*-alkyl pyridinium betaines **22** and **23** are smoothly elaborated. Here too, the selective 3-*O*-carbamoylation of **22** is readily accomplished, to provide the now highly hydrophilic pyridostigmine analog **25**. Both analogs, **14** and **25**, exhibited cholinesterase inhibitory activities similar to that of pyridostigmine (**24**), whereas preliminary evaluation of the surface and interfacial tension properties of the *N*-tetradecyl-pyridinium salt **23** showed it to have a critical micell concentration of 0.126 mmol/L, comparable to those of technical sugar tensides[18] and long-chain pyridinium salts.[19]



Pyridostigmine
(**24**)



EXPERIMENTAL

General. Melting points (uncorrected values): Bock monoskop instrument. Spectral measurements: Perkin-Elmer 241 (rotations), Varian MAT 311 A (MS), and Bruker WM 300 instruments (^{1}H at 300, ^{13}C NMR at 75.5 MHz, respectively). TLC on Kieselgel 60 F_{254} plastic sheets (Merck) was used to monitor the reactions and to ascertain the purity of the products; detection was effected with UV-light or by charring with sulfuric acid. Column chromatography: Kieselgel 60 (63-200 mesh, Macherey-Nagel).

6-Hydroxymethyl-3-pyridinol (9). A solution of 5-hydroxymethyl-2-furfurylamine (**5**)[11] (2.00 g, 15.7 mmol) in 20 mL of water was cooled to 0 °C, and a M solution of bromine in MeOH (19 mL, 1.2 molar equiv.) was added dropwise with stirring over a period of 15 min. After another 30 min the mixture was allowed to warm to rt, and was neutralized by the addition of a weakly basic ion exchange resin (Amberlite IRA-68, OH^- form). The residue obtained after evaporation of the filtrate *in vacuo* was purified by elution from a silica gel column (4 × 28 cm) with 6:1 EtOH-2.5 % aqueous NH_3. Evaporation of the eluate to dryness and crystallization from acetonitrile gave 1.66 g (85 %) of **9** as colorless needles; mp 124-125 °C (ref.: mp 123-125 °C[11] and 124-125 °C[20]. ^{1}H NMR (DMSO-d_6): δ 4.48 (s, 2 H, 6-CH_2), 4.54 (s, 1 H, 6-CH_2OH), 7.27 (dd, 1 H, H-4), 7.32 (d, 1 H, H-5), 8.09 (d, 1 H, H-2), 10.0 (br s, 1 H, 3-OH); $J_{2,4}$ = 2.5, $J_{4,5}$ = 8.5 Hz. ^{13}C NMR (DMSO-d_6): δ 63.4 (6-CH_2), 121.3, 123.3 (C-4, C-5), 135.8 (C-2), 151.6, 152.4 (C-3, C-6). MS (FD): *m/z* 125 (M^+). *Anal.* Calcd for $C_6H_7NO_2$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.62; H, 5.68; N, 11.08.

2-Hydroxymethyl-5-(methylaminomethyl)furan (10). In a hydrogenation vessel a solution of 10.00 g (79.3 mmol) of hydroxymethylfurfural (**4**)[21] in 100 mL of aqueous $MeNH_2$ (40 %) was stirred for 30 min at rt, followed by the addition of Raney nickel (3 g) and vigorous shaking in a hydrogen atmosphere for 30 h. The catalyst was filtered off, washed with MeOH, and the filtrate was concentrated *in vacuo*. Bulb tube distillation (0.5 mbar, bath temp. 120-130 °C) yielded 10.19 g (91 %) of **10** as a colorless liquid. ^{1}H NMR (DMSO-d_6): δ 2.26 (s, 3 H, Me), 3.58 (s, 2 H, 5-CH_2), 3.76 (br s, 2 H, OH, NH), 4.35 (s, 2 H, 2-CH_2), 6.14, 6.18 (2 d, 1 H each, H-3, H-4); $J_{3,4}$ = 3.1 Hz. ^{13}C NMR (DMSO-d_6): δ 35.6 (Me), 47.8 (5-CH_2), 55.9 (2-CH_2), 107.3, 107.6 (C-3, C-4), 153.8, 154.4 (C-2, C-5). MS (FD): *m/z* 141 (M^+). *Anal.* Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.23; H, 7.85; N, 9.96.

6-Hydroxymethyl-1-methyl-3-oxidopyridinium betaine (13). To a cooled (0 °C) solution of furfurylamine (**10**) (2.40 g, 17.0 mmol) in 80 mL of water was added dropwise a M solution of bromine in MeOH (25 mL) over a period of 30 min and stirring was continued for 1 h. The resulting mixture was neutralized by the addition of a strongly basic ion exchange resin (Amberlite IRA-400, OH^- form), filtered and evaporated to dryness. Purification by elution from a silia gel column (3.5 × 26 cm) with 6:1 EtOH-2.5 % aqueous NH_3 furnished 1.85 g of **13** (78 %) as an uniform amorphous solid. ^{1}H NMR (DMSO-d_6): δ 3.98 (s, 1 H, Me), 4.48 (s, 2 H, 6-CH_2), 5.78 (s, 1 H, OH), 6.83 (dd, 1 H, H-4), 7.22 (d, 1 H, H-5), 7.38 (d, 1 H, H-2); $J_{2,4}$ = 2.9, $J_{4,5}$ = 9.0 Hz. ^{13}C NMR (DMSO-d_6): δ 43.2 (Me), 58.6 (6-CH_2), 127.5 (C-5), 131.8 (C-6), 132.3 (C-4),

135.6 (C-2), 167.9 (C-3). **MS (FD): *m/z* 139 (M^+).** *Anal.* Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.22; H, 6.75; N, 9.95.

3-(*N,N*-Dimethylcarbamoyloxy)-6-hydroxymethyl-1-methylpyridinium chloride (14). To a cooled (0 °C) suspension of 900 mg (6.6 mmol) of **13** in dry pyridine (50 mL) was added dropwise 0.6 mL (6.6 mmol) of *N,N*-dimethylcarbamoyl chloride. After 2 h the ice bath was removed and the suspension was stirred for an additional hour at rt. Subsequently, few drops of water were added, and the now clear solution was evaporated to dryness. The residue was purified by dissolving it in dry ethanol followed by precipitation with dry ether: 1.30 g (82 %) of pyridinol carbamate **14** as colorless and hygroscopic crystals. ^{1}H NMR (DMSO-d_6): δ 2.97, 3.10 (2 s, 3 H each, NMe_2), 4.30 (s, 3 H, 1-Me), 4.89 (d, 2 H, 6-CH_2), 6.80 (t, 1 H, OH), 8.19 (d, 1 H, H-5), 8.52 (dd, 1 H, H-4), 9.34 (d, 1 H, H-2); $J_{2,4}$ = 2.1, $J_{4,5}$ = 8.9, J_{CH_2OH} = 5.7 Hz. ^{13}C NMR (DMSO-d_6): δ 36.4, 36.8 (NMe_2), 43.7 (1-Me), 58.8 (6-CH_2), 126.1 (C-5), 139.1 (C-4), 140.6 (C-2), 148.2 (C-6), 152.5 (C-3), 155.9 (CO). MS (FD): *m/z* 211 (M^+). ***Anal.*** Calcd for $C_{10}H_{15}N_2O_3^+$ Cl^-: C, 48.69; H, 6.13; N, 11.36. Found: C, 48.27; H, 6.30; N, 11.38.

2-(α-D-Glucopyranosyloxymethyl)-5-(methylaminomethyl)furan (17). In a hydrogenation vessel, Raney nickel (2 g) was added to a solution of 5.00 g (17.4 mmol) of 5-glucosyloxymethyl-furfural (**15**)[17] in 60 mL of aqueous $MeNH_2$ (40 %), and the mixture was stirred for 3 d in a hydrogen atmosphere. Subsequently, the catalyst was filtered off and washed thoroughly with MeOH. Freed from the solvent *in vacuo* gave a residue which was purified by elution from a silica gel column (5 × 30 cm) with 6:1 EtOH-2.5 % aqueous NH_3. Evaporation of the solvents from the appropriate eluates gave 4.70 g (90 %) of **17** as an uniform solid foam; $[\alpha]_D^{20}$ +128 (*c* 1.0, MeOH). ^{1}H NMR (DMSO-d_6): δ 2.27 (s, 3 H, Me), 3.07 (t, 1 H, H-4'), 3.21 (dd, 1 H, H-2'), 3.38 (m, 1 H, H-5'), 3.39 (t, 1 H, H-3'), 3.45, 3.63 (2 dd, 1 H each, 2 H-6'), 3.63 (s, 2 H, 5-CH_2), 4.3 (br s, 5 H, 4 OH, NH), 4.36, 4.52 (2 d, 1 H each, 2-CH_2), 4.74 (d, 1 H, H-1'), 6.22, 6.35 (2 d, 1 H each, H-3, H-4); $J_{3,4}$ = 3.1, $J_{gem(2\text{-}CH_2)}$ = 12.8, $J_{1',2'}$ = 3.6, $J_{2',3'}$ = 9.6, $J_{3',4'}$ = 9.2, $J_{4',5'}$ = 9.2, $J_{5',6'}$ = 5.7 and < 1.0, $J_{6',6'}$ = 11.4 Hz. ^{13}C NMR (DMSO-d_6): δ 35.1 (Me), 47.2 (5-CH_2), 60.1 (2-CH_2), 60.8 (C-6'), 70.2 (C-4'), 71.7 (C-2'), 72.8 (C-3'), 73.1 (C-5'), 97.6 (C-1'), 107.6, 110.2 (C-3, C-4), 150.2, 153.8 (C-2, C-5). MS (FD): *m/z* 303 (M^+). *Anal.* Calcd for $C_{13}H_{21}NO_7$: C, 51.48; H, 6.98; N, 4.62. Found: C, 51.40; H, 6.92; N, 4.70.

2-(α-D-Glucopyranosyloxymethyl)-5-(*n*-tetradecylaminomethyl)furan (18). To a solution of 5.02 g (17.4 mmol) of glucosyloxymethyl-furfural (**15**)[17] in 80 mL of CH_2Cl_2 was added *n*-tetradecylamine (5.70 g, 26.1 mmol) and the mixture was refluxed for 1 h. Subsequently, the solution was cooled (0 °C), followed by the addition of $NaBH_4$ (1.56 g, 17.4 mmol) and stirring for 20 h at rt. Decomposition of excessive $NaBH_4$ by the addition of few drops of HOAc and removal of the solvent *in vacuo* left a residue, which was purified first by elution from an ion exchange resin column (Amberlite IRA-410, OH^- form, 4 x 17 cm) with MeOH and finally by elution from silica gel (4 x 30 cm) with 5:1 acetone-H_2O: 7.80 g (92 %) of **18** as a colorless solid foam; $[\alpha]_D^{20}$ +77 (*c* 1.2, MeOH). ^{1}H NMR (DMSO-d_6): δ 0.83 (t, 3 H, Me), 1.23 (br s, 22 H, $[CH_2]_{11}$), 1.36 (m, 2 H,

NCH_2CH_2), 2.45 (t, 2 H, NCH_2CH_2), 3.05 (t, 1 H, H-4'), 3.18 (dd, 1 H, H-2'), 3.35 (m, 1 H, H-5'), 3.36 (t, 1 H, H-3'), 3.43, 3.61 (2 dd, 1 H each, 2 H-6'), 3.60 (s, 2 H, 5-CH_2), 4.33, 4.49 (2 d, 1 H each, 2-CH_2), 4.71 (d, 1 H, H-1'), 6.14, 6.30 (2 d, 1 H each, H-3, H-4); $J_{3,4}$ = 3.1, $J_{gem(2\text{-}CH_2)}$ = 12.8, J_{CH_2,CH_3} = 6.8, J_{NCH_2,CH_2} = 6.5, $J_{1',2'}$ = 3.6, $J_{2',3'}$ = 9.6, $J_{3',4'}$ = 9.2, $J_{4',5'}$ = 9.2, $J_{5',6'}$ = 5.6 and 1.0, $J_{6',6'}$ = 11.4 Hz. ^{13}C NMR (DMSO-d_6): δ 13.9 (Me), 22.0-31.3 ($[CH_2]_{12}$), 45.7 (NCH_2CH_2), 48.6 (5-CH_2), 60.2 (2-CH_2), 60.8 (C-6'), 70.2 (C-4'), 71.8 (C-2'), 72.8 (C-3'), 73.2 (C-5'), 97.6 (C-1'), 107.0, 110.1 (C-3, C-4), 150.0, 154.8 (C-2, C-5). MS (FD): *m/z* 485 (M^+). *Anal.* Calcd for $C_{26}H_{47}NO_7$: C, 64.30; H, 9.75; N, 2.88. Found: C, 64.39; H, 9.94; N, 2.78.

6-(α-D-Glucopyranosyloxymethyl)-3-pyridinol (19). To a cooled (0 °C) solution of 5-glucosyloxymethyl-2-furfurylamine (**16**)[17] (2.71 g, 9.4 mmol) in 20 mL of water was added dropwise a M solution of bromine in MeOH (14 mL, 1.5 molar equiv.) over a period of 20 min. After an additional 1 h at this temp., the solution was neutralized with a weakly basic ion exchange resin (Amberlite IRA-68, OH^- form). Filtration and and evaporation of the filtrate yielded a residue, of which tlc revealed to contain **19** and its 2-bromo derivative **20** (R_f 0.13 and 0.35, resp., in 6:1 acetone-water), in an approximate 7:1 ratio. Separation was effected by elution from a silica gel column (4 × 28 cm) with 6:1 acetone-H_2O (second fraction cf. below). Removal of the solvents from the eluate with R_f 0.13 (6:1 acetone-water) afforded 2.4 g (75 %) of **19** as an uniform solid foam; $[\alpha]_D^{20}$ +108 (*c* 1.2, MeOH). ^{1}H NMR (DMSO-d_6): δ 3.11 (t, 1 H, H-4'), 3.26 (dd, 1 H, H-2'), 3.45 (m, 2 H, H-3', H-5'), 3.52, 3.63 (2 d, 1 H each, 2 H-6'), 4.42, 4.65 (2 d, 1 H each, 6-CH_2), 4.56 (br s, 1 H, OH), 4.78 (d, 1 H, H-1'), 4.85 (br s, 1 H, OH), 4.93 (m, 2 H, 2 OH), 7.19 (dd, 1 H, H-4), 7.38 (d, 1 H, H-5), 8.08 (d, 1 H, H-2), 9.89 (s, 1 H, 3-OH); $J_{2,4}$ = 2.8, $J_{4,5}$ = 8.5, $J_{gem(6\text{-}CH_2)}$ = 12.5, $J_{1',2'}$ = 3.6, $J_{2',3'}$ = 9.6, $J_{3',4'}$ = 8.6, $J_{4',5'}$ = 8.6, $J_{6',6'}$ = 9.7 Hz. ^{13}C NMR (DMSO-d_6): δ 60.8 (C-6'), 68.8 (6-CH_2), 70.2 (C-4'), 71.8 (C-2'), 72.9 (C-3'), 73.2 (C-5'), 98.1 (C-1'), 122.4, 122.5 (C-4, C-5), 136.7 (C-2), 148.0 (C-6), 152.7 (C-3). MS (FD): *m/z* 288 (MH^+). *Anal.* Calcd for $C_{12}H_{17}NO_7$: C, 50.17; H, 5.96; N, 4.88. Found: C, 50.20; H, 5.98; N, 4.76.

2-Bromo-6-(α-D-glucopyranosyloxymethyl)-3-pyridinol (20). The fraction eluted next in the above column separation (R_f 0.35 in 6:1 acetone-water) gave, upon evaporation of the solvents *in vacuo*, 0.36 g (10 %) of **20** as colorless crystals of mp 185 °C and $[\alpha]_D^{20}$ +93 (*c* 0.8, MeOH). ^{1}H NMR (DMSO-d_6): δ 3.10 (t, 1 H, H-4'), 3.25 (dd, 1 H, H-2'), 3.42 (m, 2 H, H-3', H-5'), 3.50, 3.63 (2 d, 1 H each, 2 H-6'), 4.42, 4.61 (2 d, 1 H each, 6-CH_2), 4.47 (br s, 1 H, OH), 4.75 (br s, 1 H, OH), 4.77 (d, 1 H, H-1'), 4.85 (br s, 2 H, 2 OH), 7.30 (d, 1 H, H-5), 7.41 (d, 1 H, H-4), 10.69 (br s, 1 H, 3-OH); $J_{4,5}$ = 8.1, $J_{gem(6\text{-}CH_2)}$ = 12.9, $J_{1',2'}$ = 3.6, $J_{2',3'}$ = 9.6, $J_{3',4'}$ = 9.0, $J_{4',5'}$ = 9.0, $J_{6',6'}$ = 10.3 Hz. ^{13}C NMR (DMSO-d_6): δ 60.8 (C-6'), 68.0 (6-CH_2), 70.2 (C-4'), 71.8 (C-2'), 73.0 (C-3'), 73.2 (C-5'), 98.1 (C-1'), 122.3, 122.7 (C-4, C-5), 129.2 (C-2), 148.3 (C-6), 150.3 (C-3). MS (FD): *m/z* 368 ($M[^{81}Br]H^+$), 366 ($M[^{79}Br]H^+$). *Anal.* Calcd for $C_{12}H_{16}BrNO_7 \cdot H_2O$: C, 37.52; H, 4.72; N, 3.65. Found: C, 37.49; H, 4.75; N, 3.64.

3-Acetoxy-6-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyloxymethyl)pyridine (21). Pyridinol **19** (500 mg, 1.74 mmol) was added to a cooled suspension of freshly molten NaOAc (2.0 g) in 5 mL of acetic

anhydride, the mixture was stirred at rt overnight and subsequently quenched by pouring into a cooled, satd. $NaHCO_3$ solution (50 mL). Addition of CH_2Cl_2 (50 mL), separation of the organic phase, washing with water (50 mL), drying ($MgSO_4$), and removal of the solvent *in vacuo* gave a residue which crystallized on trituration with methanol: 615 mg (71 %) of **21** as colorless needles; mp 108-110 °C; $[\alpha]_D^{20}$ +106 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.02, 2.03, 2.07, 2.10, 2.35 (5 s, 3 H each, 5 Ac-CH_3), 4.06, 4.28 (2 dd, 1 H each, 2 H-6'), 4.10 (ddd, 1 H, H-5'), 4.67, 4.85 (2 d, 1 H each, 6-CH_2), 4.95 (dd, 1 H, H-2'), 5.10 (dd, 1 H, H-4'), 5.23 (d, 1 H, H-1'), 5.56 (dd, 1 H, H-3'), 7.49 (dd, 1 H, H-5), 7.52 (dd, 1 H, H-4), 8.37 (dd, 1 H, H-2); $J_{2,4}$ = 2.2, $J_{2,5}$ = 1.0, $J_{4,5}$ = 8.6, $J_{gem(6\text{-}CH_2)}$ = 13.4, $J_{1',2'}$ = 3.7, $J_{2',3'}$ = 10.2, $J_{3',4'}$ = 9.6, $J_{4',5'}$ = 10.2, $J_{5',6'}$ = 4.2 and 2.2, $J_{6',6'}$ = 12.4 Hz. ^{13}C NMR ($CDCl_3$): δ 61.8 (C-6'), 67.7 (C-5'), 68.5 (C-4'), 70.2 (6-CH_2), 70.3 (C-3'), 70.7 (C-2'), 95.8 (C-1'), 121.9 (C-5), 130.0 (C-4), 142.8 (C-2), 146.6 (C-6), 153.3 (C-3); Ac-CH_3 around 21.0, Ac-*C*O around 170 ppm. *Anal.* Calcd. for $C_{22}H_{27}NO_{12}$: C, 53.12; H, 5.47; N, 2.82. Found: C, 53.04; H, 5.50; N, 2.81.

6-(α-D-Glucopyranosyloxymethyl)-1-methyl-3-oxidopyridinium betaine (22). A solution of 1.93 g (6.4 mmol) of **17** in 50 mL of water was neutralized by the addition of 3.2 mL of hydrochloric acid (2 N) and cooled to 0 °C. Subsequently, a M solution of methanolic bromine (12.7 mL) was added dropwise over a period of 30 min, the resulting mixture was neutralized with a weakly basic ion exchange resin (Amberlite IRA-68, OH^- form) and filtered. The filtrate was evaporated to dryness and the residue was purified by elution from a silica gel column (3.5 × 20 cm) with 6:1 EtOH-2.5 % aqueous NH_3: 1.76 g (91%) of **22** as an uniform amorphous solid; $[\alpha]_D^{20}$ +115 (*c* 1.0, MeOH). ^{1}H NMR (DMSO-d_6): δ 3.10 (t, 1 H, H-4'), 3.25 (dd, 1 H, H-2'), 3.38 (m, 1 H, H-5'), 3.42 (t, 1 H, H-3'), 3.47, 3.65 (2 dd, 1 H each, 2 H-6'), 4.08 (s, 3 H, Me), 4.54, 4.71 (2 d, 1 H each, 6-CH_2), 4.72 (d, 1 H, H-1'), 4.9 (br s, 4 H, 4 OH), 6.99 (dd, 1 H, H-4), 7.38 (d, 1 H, H-5), 7.66 (d, 1 H, H-2); $J_{2,4}$ = 2.5, $J_{4,5}$ = 9.0, $J_{gem(6\text{-}CH_2)}$ = 13.0, $J_{1',2'}$ = 3.6, $J_{2',3'}$ = 9.6, $J_{3',4'}$ = 8.9, $J_{4',5'}$ = 9.2, $J_{5',6'}$ = 5.4 and <1.0, $J_{6',6'}$ = 11.7 Hz. ^{13}C NMR (DMSO-d_6): δ 44.0 (Me), 60.8 (C-6'), 63.9 (6-CH_2), 70.1 (C-4'), 71.7 (C-2'), 73.2 (C-3'), 73.3 (C-5'), 98.0 (C-1'), 129.0 (C-5), 129.3 (C-6), 131.8 (C-4), 136.7 (C-2), 167.6 (C-3). MS (FD): *m/z* 301 (M^+).

6-(α-D-Glucopyranosyloxymethyl)-1-*n*-tetradecyl-3-oxidopyridinium betaine (23). To a solution of **18** (1.33 g, 2.7 mmol) in water (50 mL) was added 2 N HCl until *pH* 4 was reached and the mixture was cooled to 0 °C. Subsequently, 4.11 mL of a M solution of bromine in methanol was added dropwise over a period of 2 h. Purification as described above for **17** → **22** yielded 0.68 g (52 %) of **23** as a light brown amorphous powder; $[\alpha]_D^{20}$ +76 (*c* 1.0, MeOH). ^{1}H NMR (DMSO-d_6): δ 0.85 (t, 3 H, Me), 1.30 (m, 22 H, $[CH_2]_{11}$), 1.83 (m, 2 H, NCH_2CH_2), 3.09 (t, 1 H, H-4'), 3.24 (dd, 1 H, H-2'), 3.37 (m, 1 H, H-5'), 3.40 (t, 1 H, H-3'), 3.46, 3.65 (2 dd, 1 H each, 2 H-6'), 4.26 (m, 2 H, NCH_2CH_2), 4.50, 4.68 (2 d, 1 H each, 6-CH_2), 4.74 (d, 1 H, H-1'), 5.1 (m, 4 H, 4 OH), 6.92 (dd, 1 H, H-4), 7.34 (d, 1 H, H-5), 7.58 (d, 1 H, H-2); $J_{2,4}$ = 2.6, $J_{4,5}$ = 9.0, $J_{gem(6\text{-}CH_2)}$ = 12.9, J_{CH_2,CH_3} = 6.8, $J_{1',2'}$ = 3.5, $J_{2',3'}$ = 9.5, $J_{3',4'}$ = 9.2, $J_{4',5'}$ = 9.0, $J_{5',6'}$ = 5.8 and <1.0, $J_{6',6'}$ = 11.6 Hz. ^{13}C NMR (DMSO-d_6): δ = 13.9 (Me), 22.0-31.2 $[CH_2]_{12}$), 55.9 (1-CH_2), 60.8 (C-6'), 63.5 (6-CH_2), 70.1 (C-4'), 71.6 (C-2'),

73.2 (C-3'), 73.4 (C-5'), 98.0 (C-1'), 127.3 (C-5), 129.7 (C-6), 132.2 (C-4), 135.6 (C-2), 168.2 (C-3). MS (FD): m/z = 483 (M^+).

3-(*N,N*-Dimethylcarbamoyloxy)-6-(α-D-glucopyranosyloxymethyl)-1-methylpyridinium chloride (25). A suspension of 712 mg (2.4 mmol) of **22** in 1:1 dry pyridine/dry DMF (80 mL) was cooled (0 °C), 0.22 mL (2.4 mmol) of *N,N*-dimethylcarbamoyl chloride was added, and stirring was continued for 5 h at 0 °C. Subsequently, the solution was hydrolyzed with few drops of water, evaporated to dryness and purificated from a cellulose column (Avicel, Merck, 4 × 25 cm) with 4:4:1 EtOAc-EtOH-H_2O to afford 830 mg (86 %) of **25** as an uniform solid foam; $[\alpha]_D^{20}$ +99 (*c* 1.1, MeOH). ^{1}H NMR (DMSO-d_6): δ 2.98, 3.11 (2 s, 3 H each, NMe_2), 3.15 (dd, 1 H, H-4'), 3.31 (dd, 1 H, H-2'), 3.40 (m, 1 H, H-5'), 3.49, 3.64 (2 dd, 1 H each, 2 H-6'), 3.53 (t, 1 H, H-3'), 4.31 (s, 3 H, 1-Me), 4.59 (t, 1 H, 6'-OH), 4.88 (d, 1 H, H-1'), 4.95, 5.10 (2 d, 1 H, each, 6-CH_2), 5.03 (d, 1 H, 3'-OH), 5.13 (d, 1 H, 4'-OH), 5.25 (d, 1 H, 2'-OH), 8.38 (d, 1 H, H-5), 8.57 (dd, 1 H, H-4), 9.30 (d, 1 H, H-2); $J_{2,4}$ = 2.3, $J_{4,5}$ = 8.9, $J_{gem(6\text{-}CH_2)}$ = 15.4, $J_{1',2'}$ = 3.6, $J_{2',3'}$ = 9.7, $J_{3',4'}$ = 9.2, $J_{4',5'}$ = 9.2, $J_{5',6'}$ = 5.3 and 1.0, $J_{6',6'}$ = 10.1, $J_{2',2'\text{-}OH}$ = 6.3, $J_{3',3'\text{-}OH}$ = 4.6, $J_{4',4'\text{-}OH}$ = 5.2, $J_{6',6'\text{-}OH}$ = 5.8 Hz. ^{13}C NMR (DMSO-d_6): δ 36.2, 36.7 (NMe_2), 45.0 (1-Me), 60.6 (C-6'), 63.6 (6-CH_2), 69.9 (C-4'), 71.6 (C-2'), 73.0 (C-3'), 73.5 (C-5'), 98.2 (C-1'), 126.7 (C-5), 138.9 (C-4), 141.2 (C-2), 148.5 (C-6), 151.5 (C-3), 152.2 (CO). MS (FD): m/z = 373 (M^+).

Acknowledgements. This work was financially supported by the Südzucker AG, Mannheim/Ochsenfurt and by a grant (94 NR 078-F) from the Ministry of Nutrition, Agriculture and Forestry, Bonn, administered by the Fachagentur Nachwachsende Rohstoffe, Gülzow.

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