Syntheses of 2-Acetyl-3-hydroxy-1-*n*-propylpyrrole from Isomaltol and 1-*n*-Alkyl-3-hydroxy-2-methyl-4-pyridones from Maltol

J. Bartulin

Departamento de Quimica, Universidad de Concepcion,
Casilla 3-C, Concepcion, Chile

J. Belmar

Departamento de Quimica, Universidad Federico Santa Maria,
Casilla 110-V, Valparaiso, Chile

H. Gallardo

Departamento de Fisica, Universidade Federal de Santa Catarina,
Trindade, Florianopolis, SC, 88049 Brasil

G. Leon*

Instituto de Quimica, Universidad Catolica de Valparaiso,
Casilla 4059, Valparaiso, Chile

Received August 12, 1991

2-Acetyl-3-hydroxyfuran (**2**) reacts with *n*-propylamine affording 2-acetyl-3-hydroxy-1-*n*-propylpyrrole (**3**) in 63% yield. The transformation of 2-methyl-3-hydroxy-4-pyrone (**4**) into 1-*n*-alkyl-3-hydroxy-2-methyl-4-pyridones is achieved by benzylation of the 3-hydroxyl group whereupon the product reacts with ammonia and the corresponding pyridone is obtained. The pyridone is alkylated with alkyl bromides and after hydrobromic acid in acetic acid cleavage of the 3-position ether function, 1-*n*-alkyl-3-hydroxy-2-methyl-4-pyridones are obtained in 48% overall yield.

J. Heterocyclic Chem., **29**, 1017 (1992).

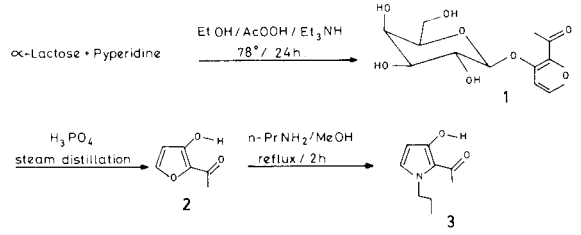
Isomaltol (**2**) and maltol (**4**) are trivial names for 2-acetyl-3-hydroxyfuran and 3-hydroxy-2-methyl-4-pyrone. These compounds had been found in cereals and bread [1-4]. Backe [5,6] isolated isomaltol from cookies and proposed a pyrone structure. Hodge and Nelson [4] designed a synthesis of isomaltol that involved the deshydration of lactose in the presence of pyridine and steam distillation of the *O*-galactosylisomaltol (**1**) obtained from a phosphoric acid medium to yield **2**. They also proposed the furan type structure for **2** that is currently accepted.

Maltol (**4**), a derivative of γ-pyrone had been extracted from natural sources as baked cereals, roasting malt, chicory and coffee among several others [1,8,9,10].

Furan [7] and γ-pyrones [11] can be transformated in pyrrole and pyridones or into the corresponding *N*-alkyl substituted derivative depending on whether the substrates are made to react with ammonia or primary amines. It would be expected that isomaltol and maltol were able to undergo similar transformations. This paper describes the transformation of isomaltol into 1-*n*-propyl-2-acetyl-3-hydroxypyrrole and that of maltol into 1-*n*-alkyl-3-hydroxy-2-methyl-4-pyridones.

Scheme 1 shows the synthetic route followed in the preparation of 2-acetyl-3-hydroxy-1-*n*-propylpyrrol (**3**). Isomaltol was synthesized adapting the method described by Hodge and Nelson [4]. The yields were different from those reported, *i.e.*, higher in the first step (94%) and lower (16%) in the acid hydrolysis of **1**. The low yield in the second step (**1** → **2**) is a drawback, but the synthesis proposed is still interesting because α-lactose is readily available and because **3** is obtained from **2** and *n*-propylamine at room temperature in 63% yield.

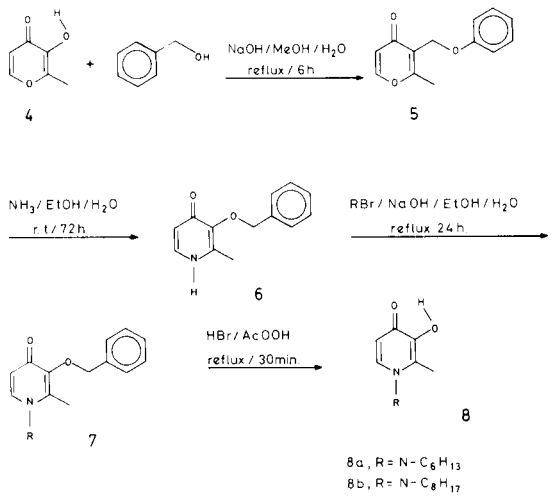
Scheme 1



The reaction of maltol (**4**) with primary amines did not afford the *N*-alkylated pyridone (**8**). The conditions were: a) reflux of an ethanolic solution with equimolar quantities of **4** and the *n*-alkylamine, and b) an equimolar mixture of **4** and the *n*-alkylamine heated at 120° for 24 hours in a closed vessel. Both methods yielded mixtures of hardly isolable and identificable products. Scheme 2 shows the route that allows the preparation of compounds **8** with an overall yield of 48%, it involves the *O*-benzylation of **4**, the resulting ether **5** reacts with ammonia to produce the pyridone **7** that is easily alkylated with *n*-alkyl bromides. After cleaving the ether function the *N*-alkyl-3-hydroxy-2-methylpyridone **8** is obtained. Two compounds were synthesized in this way, **8a** the *N*-hexyl derivative and **8b** the *N*-octyl derivative, the parent compound of the last one, **7b**, was not characterized, but its formation is obvious because **8b** could be prepared and characterized as described.

The syntheses herein described provide a simple method to prepare **3** and **8**. Considering the readily availability of the starting materials the yields in these reactions are very good, only the steps **2** → **3** and **5** → **8** are

Scheme 2



considered because the preparation of the other compounds is already reported and their preparation is of no additional interest. For the same reason the characterization of the compounds was not exhaustive, and only a minimal amount of information was used to characterize them. Spectroscopic data, and elemental analyses are given in Experimental and are in agreement with the proposed structures.

EXPERIMENTAL

Elemental analyses were performed at Laboratorio de Microanalysis, Departamento de Quimica, Universidad de Concepcion. Melting points were determined on a Koffler microscope and are uncorrected. The nmr spectra were recorded with a Varian T 60-A (^{1}H) and CFT-20 (^{13}C) spectrometers using tetramethylsilane as the internal reference and various deuterated solvents depending upon the solubilities of each compound. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quarted, m = multiplet). The ir spectra were measured with a Perkin Elmer 577 spectrophotometer. Absorption frequencies are quoted in reciprocal centimeters.

O-Galactosylisomaltol (**1**). Modified Literature Procedure [4].

In a three necked, round-bottom flask equipped with a mechanical stirrer, reflux condenser and dropping funnel, charged with 300 ml of ethanol, 360.32 g (1 mole) of lactose monohydrate was dispersed; 99 ml (1 mole) of piperidine was added at once and then 44 ml (1 mole) of glacial acetic acid was added dropwise during 15 minutes while a good stirring was maintained. After the dropping funnel was removed and a thermometer was fitted. The reaction mixture was heated to 78° and 50 ml of triethylamine was added. Ten or twelve hours later another 50 ml of triethylamine was added in order to maintain the alkalinity of the reacting mixture. Heating was continued for 24 hours. The solution was cooled to 5° with a water-ice bath, diluted with 300 ml of ethanol and stirred one hour. The product was filtered, washed with ethanol and again stirred with this solvent and filtered. The solid was crushed before drying over calcium chloride in a vacuum desiccator and crystallized from methanol, yield 74%, mp 204.5°: ir (potassium bromide): ν OH 3430, ν CO 1640, ν C=C 1595; cmr (DMSO-d_6): 183.79 (C=O), four signals for the isomaltol ring, 152.64 (C-1'), 146.97 (C-5'), 137.19 (C-2'), 102.75 (C-4'), seven signals for the galactosyl ring, 104.99 (C-1), 75.78 (C-5), 73.15 (C-3), 70.19 (C-2), 68.07 (C-4), 60.37 (C-6), 27.16 (C-β).

Anal. Calcd. for $C_{12}H_{16}O_8$: C, 50.00; H, 5.60. Found: C, 50.27; H, 5.83.

Isomaltol (**2**). Modified Literature Procedure [4].

A suspension of 14.5 g (0.05 mole) of **1** in 200 ml of 85% phosphoric acid was steam distillated. One liter of distillated was collected and extracted with chloroform. To the residue of the distillation a 1:1 mixture of diethyl ether-petroleum ether was added and the solid crushed. The extracts were collected and concentrated to dryness in a rotatory evaporator. The product was crystallized from benzene, yield 16%, mp 98-98.5°; ir (potassium bromide): ν OH 3130, ν CO 1685, ν C=C 1590; pmr (deuteriochloroform): 8.7 (s, 1H, OH), 7.35 (d, 1H, H-5), 6.33 (d, 1H, H-4), 2.45 (s, 3H, Me).

Anal. Calcd. for $C_6H_6O_3$: C, 57.14; H, 4.80. Found: C, 57.29; H, 4.94.

2-Acetyl-3-hydroxy-1-*n*-propylpyrrole (**3**).

A solution containing 6.93 g (0.05 mole) of **2** and 5 ml (0.055 mole) of *n*-propylamine in 80 ml of methanol was heated to reflux during 8 hours. The solvent was evaporated under reduced pressure and the product was crystallized from chloroform, yield 63%, mp 84-85°; ir (potassium bromide): ν OH 3150, ν C=O 1630, ν C=C 1565; pmr (perdeuteriomethanol): 7.65 (d, 1H, H-5), 6.43 (d, 1H, H-4), 4.97 (s, 1H, OH), 4.05 (t, 2H, CH_2 to N), 2.41 (s, 3H, MeC=O), 1.70 (m, 2H, CH_2 β to N), 0.95 (t, 3H, Me γ to N).

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.83. Found: C, 64.02; H, 7.68.

N-Alkyl-2-methyl-3-hydroxy-4-pyridone (**4**).

Method 1.

n-Alkylamine (0.07 mole) was added to a solution of 7.6 g (0.06 mole) of **4** in 250 ml of ethanol. The solution was heated to reflux during 15 hours and then the solvent evaporated under reduced pressure.

Method 2.

An autoclave containing 0.06 mole of *n*-alkylamine, 7.6 g (0.06 mole) of **4** and 100 ml of ethanol was heated at 120° during 24 hours. Then the solvent was evaporated under reduced pressure.

Methods 1 and 2 afford materials that were not identified because of their complex nature.

Method 3. As Described in Scheme 2.

3-Benzyloxy-2-methyl-4-pyrone (**5**). Modified Literature Procedure [12].

A solution containing 22.2 g (0.16 mole) of **4**, 6.8 g (0.17 mole) of sodium hydroxide, 23 ml (0.20 mole) of benzyl chloride, 25 ml of water and 210 ml of methanol was refluxed during 6 hours and allowed to stand overnight. Most of the solvent was evaporated under reduced pressure; 45 ml of water was added to this crude material and it was extracted twice with 100 ml of methylene chloride. The organic extracts were collected, washed with 5% sodium hydroxide and 100 ml of water, dried with magnesium sulfate and filtered. The material obtained by evaporating the

solvent was used without further purification in the next stage, yield 92%; pmr (carbon tetrachloride): 7.67 (d, 1H, H-6), 7.36 (m, 5H, H-arom), 6.30 (d, 1H, H-5), 5.13 (s, 2H, OCH_2), 2.01 (s, 3H, Me).

3-Benzyloxy-2-methyl-4(1*H*)-pyridone (**6**). Modified Literature Procedure [12].

A solution containing 15.3 g (0.075 mole) of **5**, 160 ml of 25% ammonia and 80 ml of ethanol were stirred at room temperature during 3 days. The solution was concentrated under reduced pressure and some acetone was added, the solid was filtered and crystallized from ethanol, yield 80%, mp 162-163°; ir (potassium bromide): ν N-H 3260, ν C=O 1670.

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.52; H, 6.08. Found: C, 72.43; H, 6.35.

Alkylation of 3-Benzyloxy-2-methyl-4(1*H*)-pyridone.

A solution containing 23.5 g (0.125 mole) of **6**, 0.125 mole of *n*-alkyl bromide, 5 g (0.125 mole) of sodium hydroxide, 25 ml of water and 200 ml of ethanol were heated to reflux during 24 hours. The solution was concentrated under reduced pressure and extracted with diethyl ether. On washing the ethereal phase with water, the product precipitates. After drying it was crystallized from benzene, yield 95%.

3-Benzyloxy-1-*n*-hexyl-2-methyl-4-pyridone (**7a**).

This compound was synthesized as described above, yield 95%, mp 46°; ir (potassium bromide): ν C=O 1625, ν C=C 1520, C-O-C 1170; cmr (perdeuteriomethanol): 186.03 (C=O), 158.29 (C-3), 156.04 (C-6), 152.74 (C-2), four signals at 149.99, 141.99, 141.00, 120.02 (6C, C-aromatics), 85.93 (C-5), 66.79 (α to N), 44.02 (OCH_2), 24.62 (C-7), five signals at 43.07, 38.38, 35.06, 26.26, 12.12 corresponding to the alkyl chain.

Anal. Calcd. for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42. Found: C, 75.81; H, 8.64.

1-*n*-Hexyl-3-hydroxy-2-methyl-4-pyridone (**8a**).

A solution containing 25 g (0.12 mole) of **7a** and 80 ml of 40% hydrobromic and in acetic acid is gently heated with a water bath during 30 minutes. The product was filtered and crystallized from benzene, yield 70%, mp 57-58°; ir (potassium bromide): ν OH 3550, ν C=O 1625; pmr (deuteriochloroform): 7.32 (d, 1H, H-6), 6.88 (s, 1H, OH), 6.43 (d, 1H, H-5), 3.90 (t, 2H, CH_2 α to N), 2.39 (s, 3H, Me), 1.29 (m, 8H, four methylenes), 0.89 (t, 3H, Me); cmr (deuteriochloroform): 169.51 (C=O), 146.38 (C-3), 136.63 (C-6), 128.80 (C-2), 111.42 (C-5), 54.01 (CH_2 α to N), six signals at 31.25, 30.86, 25.99, 22.45 and 11.81 corresponding to the alkyl chain and 13.86 (C-7).

Anal. Calcd. for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15. Found: C, 68.34; H, 9.32.

1-*n*-Octyl-3-hydroxy-2-methylpyridone (**8b**).

This compound was synthesized as described for **7a**, yield 73%, mp 55-56°; ir (potassium bromide): ν C=O 1610, ν C=C 1570; pmr (deuteriochloroform): 7.93 (d, 1H, H-6), 7.73 (s, 1H, OH), 6.64 (d, 1H, H-5), 3.99 (t, 2H, CH_2 α to N), 2.46 (s, 3H, Me), 1.26 (m, 12H, six methylenes), 0.83 (t, 3H, Me); cmr (perdeuteriobenzene): 153.30 (C=O), 145.99 (C-3), 142.16 (C-6), 140.14 (C-2), 105.96 (C-5), 68.93 (CH_2 α to N), seven signals at 32.23, 29.68, 29.17, 26.17, 23.05 and 14.27 corresponding to the alkyl chain, 18.17 (Me at C-2 in the ring).

Anal. Calcd. for $C_{14}H_{23}NO_2$: C, 70.84; H, 9.76. Found: C, 70.49; H, 9.62.

Acknowledgements.

The authors are pleased to thank the Universidad de Concepcion and "Deutscher Akademischer Austauschdienst" for financial support.

REFERENCES AND NOTES

[1] A. Backe, *Compt. Rend.*, **150**, 540 (1910).
[2] A. Backe, *Compt. Rend.*, **151**, 78 (1910).
[3] H. C. Sherman, *J. Ind. Eng. Chem.*, **2**, 24 (1910).
[4] J. E. Hodge and E. L. Nelson, *Cereal Chem.*, **38**, 207 (1961).
[5] A. R. Katritzky, *Chimia*, **24**, 134 (1970).
[6] P. Y. Curtin, *Rec. Chem. Prog.*, **15**, 111 (1954).
[7] R. M. Ackerson, An Introduction to the Chemistry of Heterocyclic Compounds, Interscience Publishers, New York, NY, 2nd Ed, 1967.
[8] A. Paratoner and A. Tamburello, *Gazz. Chim. Ital.*, **36**, 33 (1966).
[9] S. Palton and R. J. Flipse, *Science*, **125**, 1087 (1957).
[10] J. Brand, *Ber.*, **27**, 806 (1984).
[11] J. W. Armit and T. J. Nolan, *J. Chem. Soc.*, 3023 (1931).
[12] R. L. Harris, *Aust. J. Chem.*, **29**, 1329 (1976).