Preparation of 3-Hydroxy- and 3-Methoxy-*N*-heteroaryl-2-methyl-4-pyridones

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A number of new 3-hydroxy- and 3-methoxy-2-methyl-4-pyridones substituted on the nitrogen atom with selected heterocycles has been prepared. Novel chelating properties of the hydroxy-compounds are expected.

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A fascinating aspect of heterocyclic chemistry is the ring interconversion of one heterocyclic system into another [1]. This frequently has been used for preparative purposes.

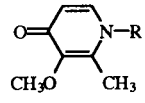
Possibly the most exploited preparation of 4-pyridones is accomplished by the reaction of the corresponding 4-pyrone with an aliphatic or an aromatic primary amine [2] by an ANRORC mechanism [3]. The same is true for the preparation of 3-hydroxy derivatives [4]. The reaction was adopted in our laboratory [5] to prepare a number of *N*-aryl-substituted 3-hydroxy-4-pyridones which turned out to be very useful [6] as complex forming ligands in spectral determination, solvent extraction and separation of many metal ions, *e.g.* galium from zinc [7]. All earlier studied 3-hydroxy-4-pyridones were *N*-phenyl-substituted derivatives. Substituents at the phenyl group did not influence chelating properties markedly [8] but small difference in solubility, and consequently in solvent extraction of metal ions was found.

Another reason for the preparation of various *N*-aryl-4-pyridones was found in the studies of restricted rotation about N–C bond and chromatographic separation of enantiomers of sterically hindered molecules of this type [9].

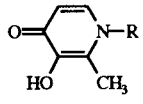
In the present paper we wish to report the preparation of hitherto undescribed *N*-heteroaryl-2-methyl-3-hydroxy-4-pyridones, which accomodates both research interests,

Table 1

3-Methoxy- and 3-Hydroxy-2-methyl-*N*-heteroaryl-4-pyridones



1,3,4,5



2a, 4a, 5a, 6a

No.	R	Mp °C	Yield % [a]	Formula	Analysis Calcd./Found %C	%H	%N	%S	Principal comon ir bands (cm^{-1}) [b] ν C=C [c]	ν C=O
1	2-pyridyl	135-136	17	$C_{12}H_{12}N_2O_2$	66.65 66.86	5.60 5.43	12.95 12.80		1620 (vs)	1560 (s)
2a	3-methyl-2-pyridyl	102-103	26	$C_{12}H_{12}N_2O_2$	66.65 66.42	5.60 5.38	12.95 12.72		1650 (vs)	1550 (m)
3	8-quinolil	205	31	$C_{16}H_{14}N_2O_2$	72.17 71.90	5.30 5.15	10.52 10.80		1620 (vs)	1560 (s)
4	5-methyl-3-isoxazolyl	94-95	60	$C_{11}H_{12}N_2O_3$	59.99 60.08	5.49 5.32	12.72 12.59		1620 (vs)	1575 (s)
4a	5-methyl-3-isoxazolyl	203-205	90 [d]	$C_{10}H_{10}N_2O_3$	58.25 58.52	4.89 4.85	13.59 13.74		1625 (vs)	1580 (vs)
5	2-benzothiazolyl	130-132	21	$C_{14}H_{12}N_2O_2S$	61.75 61.65	4.44 4.56	10.29 10.43	11.77 12.05	1620 (vs)	1580 (vs)
5a	2-benzothiazolyl	225 [e]	60 [d]	$C_{13}H_{10}N_2O_2S$	60.45 60.22	3.90 4.12	10.85 10.55	12.41 12.09	1620 (vs)	1570 (vs)
6a	2-benzoimidazolyl	223-225	25	$C_{13}H_{11}N_3O_2$	64.71 64.64	4.60 4.65	17.43 17.61		1600 (vs)	1475 (vs)

[a] After the product was chromatographed and recrystallized from appropriate solvent. [b] In potassium bromide discs. [c] Pyridone ring. [e] Sublimation. [d] Demethylation with hydrobromic acid.

that is (i) a study of novel type chelating agents and (ii) a study of restricted rotation about the N-C bond.

We believe that the heterocyclic substituent on the nitrogen atom should markedly influence not only the solubilities of metal ion complexes and its distribution between polar and non polar phases, but complex forming properties of hydroxypyridones through its electronic effects as well.

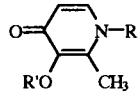
The reports of 4-pyridones having heterocyclic substituents on the nitrogen atom are quite rare, and as far as we know the only reported examples are the preparation of several *N*-pyridyl-4-pyridones containing the N-N bond between two heterocycles [10] and the isolation of 1-(4'-pyridyl)-4-pyridone as one of the photoproducts of 4-chloropyridine [11].

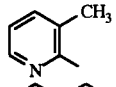
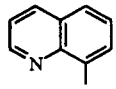
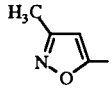
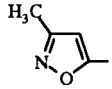
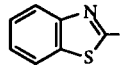
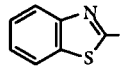
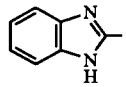
For the preparation of the title compounds **1-6**, (Table 1) the previously reported [6a,8] method of heating the reaction components in a Carrius tube was found preferable to other methods. The equimolar mixture of 3-hydroxy-4-pyrone ("Maltol") or its *O*-methyl derivative and an appropriate heterocyclic amine in water or water/methanol was heated for 24-48 hours at 150-160°, and purified by column chromatography and recrystallization. It should be pointed out that all the efforts to convert unmethylated 3-hydroxy-2-methyl-4-pyrone to *N*-heteroarylpyridone was unsuccessful in spite of the various procedures applied. The difference between the normal reaction with aniline or substituted anilines [8] on the one hand and heterocyclic amines on the other could possibly be caused by their basicity.

Heteroarylpyridones with a free hydroxyl group can be obtained by demethylation with hydrobromic acid or, in several instances, they were obtained as a result of spontaneous demethylation during the reaction or purification of the *O*-methyl derivative (Scheme 1). The pure compounds in Table 1, were processed using non-metallic laboratory ware and were characterized by elemental analyses, ir, ^1H and ^{13}C nmr spectra showing the characteristics

Table 2

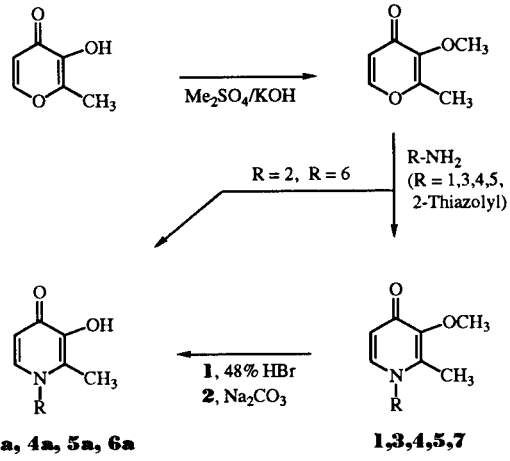
^1H NMR Spectra [a] of Methoxy- and Hydroxypyridones



Compound	R'	R	2-CH_3	R-CH_3	3-OCH_3	3-OH [b]	5-H	6-H	Others
1 [c]	CH_3		2.18 (s, 3H)	–	3.91 (s, 3H)	–	6.49 (d, 1H) J = 7.6	7.42 (d, 1H) J = 7.6	7.8-8.7 (m, 4H)
2a [c]	H		2.15 (s, 3H)	2.07 (s, 3H)	–	6.4 (bs, 1H)	6.57 (d, 1H) J = 5.8	6.65 (d, 1H) J = 5.8	7.3-8.8 (m, 3H)
3 [c]	CH_3		1.95 (s, 3H)	–	3.97 (s, 3H)	–	6.51 (d, 1H) J = 7.6	7.31 (d, 1H) J = 7.6	7.6-8.9 (m, 6H)
4 [c]	CH_3		2.25 (s, 3H)	2.55 (s, 3H)	3.90 (s, 3H)	–	6.44 (d, 1H) J = 7.6	7.34 (d, 1H) J = 7.6	6.18 (s, 1H)
4a [d]	H		2.15 (s, 1H)	2.5 (3H) [e]	–	4.2 (bs, 1H)	6.26 (d, 1H) J = 7.5	7.67 (d, 1H) J = 7.5	6.7 (s, 1H)
5 [c]	CH_3		2.39 (s, 3H)	–	3.93 (s, 3H)	–	6.49 (d, 1H) J = 7.6	7.58 (d, 1H) J = 7.6	7.9-8.1 (m, 4H)
5a [d]	H		2.28 (s, 3H)	–	–	3.4 (bs, 1H)	6.31 (d, 1H) J = 7.6	7.92 (d, 1H) J = 7.6	7.5-8.2 (m, 4H)
6a [d]	H		2.49 (s, 3H) [e]	–	–	3.8 (bs, 1H)	5.97 (d, 1H) J = 7.0	7.97 (d, 1H) J = 7.0	7.3-8.4 (m, 4H)
7 [c,f]	CH_3	H	2.42 (s, 3H)	–	3.79 (s, 3H)	–	6.43 (d, 1H) J = 7.0	7.52 (d, 1H) J = 7.0	–

[a] Chemical shifts are given in ppm (δ) relative to internal TMS; Coupling constants (J) are given in Hz. [b] Very broad signal. [c] In deuteriochloroform. [d] In DMSO-d_6. [e] Partly overlapped by the solvent (dimethyl sulfoxide multiplet). [f] The sole isolable product in condensation reaction of methoxymaltol with 2-aminothiazole.

Scheme 1



2a, 4a, 5a, 6a **1,3,4,5,7**

R = **1**) 2-pyridyl, **2**) 3-methyl-2-pyridyl, **3**) 8-quinolyl, **4**) 5-methyl-3-isoxazolyl, **5**) 2-benzothiazolyl, **6**) 2-benzimidazolyl, **7**) H

presented in Tables 1-3.

An anomalous case was found in the reaction of *O*-methylmaltol with 2-aminothiazole. The only isolable product was unsubstituted 2-methyl-3-methoxy-4-pyridone (**7**). In fact, instead of the expected transformation of the *N*-thiazolyl derivative, 2-aminothiazole played the role of a formal nitrogen donor. It is difficult at the present time to propose a reaction pathway, however, exactly the same result was obtained when *O*-methylmaltol was allowed to react with adenine [12].

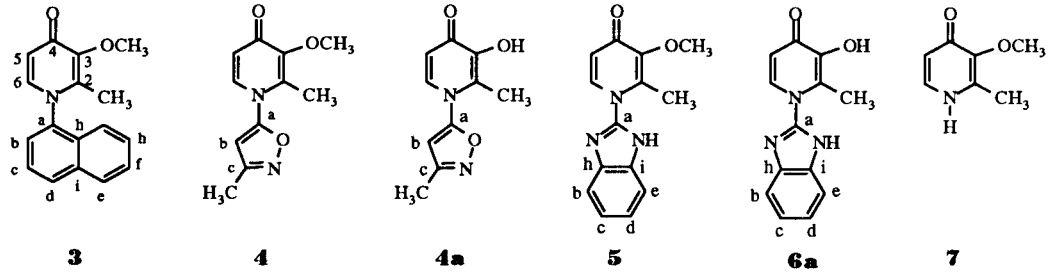
Spectroscopic Properties.

The ir spectra of *N*-heteroarylpyridones all show intense, broad peaks near 1620 and 1550-1580 cm^{-1}. The later are assigned, by analogy [13], primarily to ν (C=O). The former are assigned (Table 1) to pyridone ν (C=C) ring modes [10]. The compounds with a 3-hydroxy group, **2a**, **4a**, **5a**, **6a**, exhibit a broad or very broad band in the 3000 cm^{-1} region characteristic for a hydrogen bonded hydroxyl group [13b,14].

The ^1H nmr spectra of hydroxy and methoxy pyridones provide good evidence for the proposed structures (Table 2). The chemical shifts and J values are as expected [15]. The most obvious difference between hydroxy and methoxypyridones is the presence of a broad or a very broad deuterium exchangeable signal of the hydroxy group in the region δ = 3.40-6.40 for the hydroxy compounds.

Table 3

^{13}C NMR Spectra [a] of some Methoxy- and Hydroxypyridones



3 **4** **4a** **5** **6a** **7**

Carbon	**3** [b]	**4** [b]	**5** [c]	**7** [c]	**4a** [c]	**6a** [c]
2	143.7 (*s*)	147.3 (*s*)	149.1 (*s*)	145.4 (*s*)	144.7 (*s*)	148.8 (*s*)
3	141.9 (*s*)	139.7 (*s*)	146.5 (*s*)	139.2 (*s*)	127.1 (*s*)	134.5 (*s*)
4	174.1 (*s*)	174.0 (*s*)	173.0 (*s*)	171.7 (*s*)	172.4 (*s*)	159.5 (*s*)
5	116.9 (d)	117.2 (d)	116.7 (d)	115.5 (d)	111.3 (d)	113.4 (d)
6	139.2 (d)	137.9 (d)	138.9 (d)	134.8 (d)	136.9 (d)	125.7 (d)
3-OCH_3	59.5 (q)	59.3 (q)	58.9 (q)	58.3 (q)	–	–
2-CH_3	13.7 (q)	12.9 (q)	13.4 (q)	13.6 (q)	11.9 (q)	15.5 (q)
c-CH_3	–	13.4 (q)	–	–	12.1 (q)	–
a [d]	139.3 (*s*)	173.1 (*s*)	160.0 (*s*)	–	170.3 (*s*)	149.2 (*s*)
b [d]	136.4 (d)	100.3 (d)	123.5 (d)	–	99.9 (d)	115.1 (d) [f]
c [d]	126.2 (d)	161.3 (*s*)	127.3 (d)	–	161.1 (*s*)	121.5 (d) [e]
d [c]	122.5 (d)	–	126.7 (d)	–	–	121.5 (d) [e]
e [d]	130.3 (d)	–	122.8 (d)	–	–	115.1 (d) [f]
f [d]	129.4 (d)	–	–	–	–	–
g [d]	152.0 (d)	–	–	–	–	–
h + 1 [d]	147.3 (*s*) and 128.4 (*s*)	–	139.4 (*s*) and 135.2 (*s*)	–	–	126.7 (*s*)

[a] Chemical shift given in ppm (δ) relative to internal TMS. Peak multiplicities in off resonace decoupled spectra are represented by (*s*) singlet, (d) doublet and (q) quartet. [b] In deuteriochloroform. [c] In DMSO-d_6. [d] Tentative assignment. [e] $C_c + C_d$. [f] $C_b + C_e$.

EXPERIMENTAL

Melting points were determined on an Original Kofler Mikroheiztisch apparatus (Reichert, Wien) and are not corrected. Infrared spectra were taken in potassium bromide pellets with a Perkin-Elmer 297 Infracord Spectrophotometer. Proton nmr spectra were obtained using a Varian CFT-20 spectrometer with tetramethylsilane as the internal standard. The ^{13}C nmr spectra were taken on Jeol FX-100 FT instrument at 25.05 MHz. Mass spectra were recorded on a Varian Mat-CH7 spectrometer operating at 70 eV by direct insertion probe. 3-Methoxy-2-methyl-4-pyrone (bp 118-120°/18 Torr) was prepared by methylation of 3-hydroxy-2-methyl-4-pyrone (Maltol) "Fluka" with dimethyl sulphate according to a reported procedure [16,17].

General Procedure.

N-Heteroaryl-3-methoxy-2-methyl-4-pyridones **1**, **3**, **4** and **5** and Heteroaryl-3-hydroxy-2-methyl-4-pyridones **2a**, **4a**, **5a** and **6a**.

A mixture of 3-methoxy-2-methyl-4-pyrone (0.01-0.02 mole) and the appropriate heterocyclic amine (0.011-0.022 mole) in 20-40 ml of water/methanol 5:1, **2a**, **3** and **5** or water for the other preparations was heated in a sealed thick walled glass tube at 150-160° for 24 hours. After solvent evaporation under reduced pressure, the product was purified by repeated column chromatography on silica gel (eluent stated), and was recrystallized (solvent stated). The yields varried from 17-90% [18].

Demethylation.

The crude methoxy derivative obtained on evaporation was heated for 1 hour under reflux with 48 per cent hydrobromic acid. The product after neutralization separated and was recrystallized from the appropriate solvent [19].

Attempted Preparation of Hydroxy Compounds **2a**, **4a**, **5a** and **6a** from 3-Hydroxy-2-methyl-4-pyridone (Maltol).

Procedure A.

A mixture of maltol (0.02 mole) and heterocyclic amine (0.022 mole) in 50 ml of 1% hydrochloric acid was heated under reflux for 24 hours. Only the starting compounds were isolated and no other products were detected.

Procedure B.

Maltol (0.02 mole) and heterocyclic amine (0.022 mole) in water was heated in a sealed glass tube at 150-160° for 48 hours. After the usual work up procedures no products except starting compounds were detected.

N-(2-Pyridyl)-3-methoxy-2-methyl-4-pyridone (**1**).

Compound **1** was obtained from *O*-methylmaltol (2.2 g, 0.016 mole) and 2-aminopyridine (1.6 g, 0.018 mole) in 20 ml of water after elution with ethyl acetate-acetone-methanol (10:10:1), mp 135-136°; ir: [20] 3400 (s), 3100-2600 (m, b), 1620 (vs), 1560 (vs), 1540 (s), 1450 (s), 1420 (s), 1380 (m), 1275 (vs), 1265 (vs), 1240 (w), 1210 (s), 1165 (s), 1045 (m), 1010 (w), 990 (m), 980 (m), 830 (s), 795 (s) and 750 (m) cm^{-1}.

N-(3-Methyl-2-pyridyl)-3-hydroxy-2-methyl-4-pyridone (**2a**).

This compound was obtained from *O*-methylmaltol (2.8 g, 0.02 mole) and 2-amino-3-methylpyridine (3.1 g, 0.03 mole) in 40 ml of a water-methanol mixture (10:1) after elution with ethyl acetate-acetone (10:1), mp 102-103°; ir: [20] 3220-2300 (s, b), 1650 (vs), 1620 (m), 1550 (m), 1530 (m), 1460 (m), 1425 (w), 1385 (s), 1310 (w), 1245 (w), 1130 (w), 1040 (w), 985 (w), 960 (w), 915 (w), 870 (w), 765 (s) and 740 (s) cm^{-1}.

N-(8-Quinolyl)-3-methoxy-2-methyl-4-pyridone (**3**).

This compound was obtained from *O*-methylmaltol (2.0 g, 0.0014 mole) and 8-aminoquinoline (2.3 g, 0.015 mole) in 20 ml of methanol-water (1:1) after elution with ethyl acetate-acetone (3:1) followed by recrystallization from ethyl acetate, colourless crystals, mp 205°; ir: [20] 3450 (s), 3100-2200 (s, b), 1620 (vs), 1560-1540 (vs, b), 1480-1460 (s, b), 1420 (m), 1390 (vs), 1320 (vs), 1275 (vs), 1220 (s), 1210 (s), 1155 (m), 1070 (m), 1060-1030 (m, b), 985 (s), 955 (w), 920 (w), 865 (m), 835 (vs), 818 (vs), 800 (s), 780 (s), 758 (m) and 705 (w) cm^{-1}.

N-(5-Methyl-3-isoxazolyl)-3-methoxy-2-methyl-4-pyridone (**4**).

This compound was obtained from *O*-methylmaltol (2.8 g, 0.02 mole) and 3-amino-5-methylisoxazole (2.2 g, 0.022 mole) in 20 ml of water after elution with chloroform-acetone (1:1) followed by recrystallization from ether-ethanol (10:1), mp 94-95°; ir: [20] 3200-2800 (m, b), 1620 (vs), 1575 (vs), 1540 (s), 1525 (v), 1460 (s), 1425 (vs), 1380 (w), 1275 (m), 1255 (s), 1210 (s), 1150 (s), 1050 (w), 980 (w), 965 (w), 920 (m), 845 (w), 830 (m), 760 (w), 730 (w) and 710 (m) cm^{-1}.

N-(5-Methyl-3-isoxazolyl)-3-hydroxy-2-methyl-4-pyridone (**4a**).

By Demethylation of **4**.

Crude **4** (1.0 g) was heated under reflux in 48% hydrobromic acid (5 ml) for 1 hour. After evaporation to a small volume, water was added and filtered, then the solution neutralized with sodium carbonate. The product was extracted into chloroform. On evaporation of the dried solution (anhydrous magnesium sulphate) crystalline **4a** (0.95 g), mp 180-185° was obtained. After repeated recrystallization from water-ethanol pure **4a** melted at 203-205°; ir: [20] 3300-2000 (s, b), 1625 (vs), 1580 (vs), 1525 (m), 1490 (s), 1430 (vs), 1370 (s), 1300 (s), 1250 (m), 1225 (s), 1210 (vs), 1120 (s), 1075 (s), 1020 (m), 950 (m), 925 (m), 840 (m), 835 (m), 760 (w), 740 (m), 725 (m), 710 (m) and 675 (m) cm^{-1}.

N-(2-Benzothiazolyl)-3-methoxy-2-methyl-4-pyridone (**5**).

Compound **5** was obtained from *O*-methylmaltol (3.4 g, 0.025 mole) and 2-aminobenzothiazole (4.0 g, 0.028 mole) in 50 ml of water-methanol (10:1) after elution with ethyl acetate-acetone (3:1). After recrystallization from ethanol-water (1:5), colourless crystals, mp 130-132° were obtained; ir: [20] 3100 (m), 3000-2000 (m, b), 1620 (vs), 1580 (vs), 1530 (m), 1500 (vs), 1450 (m), 1420 (vs), 1380 (m), 1360 (m), 1300 (m), 1275 (s), 1245 (s), 1225 (s), 1200 (s), 1150 (m), 1140 (w), 1100 (m), 1060 (m), 1040 (m), 1010 (m), 986 (s), 960 (m), 950 (m), 860 (m), 840 (vs), 816 (s), 775 (vs), 758 (w), 746 (w), 735 (m), 708 (m) and 685 (w) cm^{-1}.

N-(2-Benzothiazolyl)-3-hydroxy-2-methyl-4-pyridone (**5a**).

By Demethylation of **5**.

Crude **5** (1.0 g) was heated for 1 hour with 5 ml of 48% hydrobromic acid. The mixture was evaporated to a volume of about 2 ml, diluted with water and neutralized with sodium carbonate solution. Crude **5a** crystallized from the neutralized (sodium carbonate) solution. Analytically pure **5a**, mp 225° was obtained by repeated recrystallization from chloroform; ir: [20] 3120 (s), 3300-2200 (m, b), 1620 (s), 1570 (vs), 1525 (w), 1495 (m), 1470 (m), 1420 (m), 1370 (m), 1300 (s), 1260 (m), 1245 (s), 1225 (m), 1205 (s), 1190

(m), 1115 (w), 1100 (w), 1070 (m), 1040 (m), 1010 (w), 985 (m), 938 (w), 920 (w), 880 (s), 865 (w), 828 (vs), 762 (vs), 725 (m), 715 (w), 704 (w) and 696 (w) cm^{-1}.

N-(2-Benzoimidazolyl)-3-hydroxy-2-methyl-4-pyridone (**6a**).

This compound was obtained from *O*-methylmaltol (2.1 g, 0.015 mole) and 2-aminobenzoimidazole (2.3 g, 0.017 mole) in 40 ml of water. To the reaction mixture crushed ice was added and the excess starting compounds removed by acidification with diluted hydrochloric acid followed by extraction with ether and chloroform. The aqueous solution was alkalized with sodium carbonate and extracted with ether and with chloroform. After evaporation of the chloroform extract, 25% of crude **6a** crystallized spontaneously. Recrystallization from ethyl acetate-acetone (10:1) yielded pure **6a**, mp 223-225°; ir: [20] 3300-3200 (m, b), 1680 (vs), 1600 (vs), 1575 (vs), 1540 (vs), 1470 (s), 1450 (s), 1420 (m), 1320 (w), 1300 (s), 1250 (m), 1225 (s), 1160 (w), 1130 (w), 1100 (m), 1060 (w), 1025 (w), 1005 (m), 990 (s), 925 (w), 880 (m), 860 (m), 830 (m), 810 (s), 765 (s), 745 (s), 708 (w) and 696 (w) cm^{-1}.

3-Methoxy-2-methyl-4-pyridone (**7**).

This compound was obtained from *O*-methylmaltol (2.0 g, 0.014 mole) and 2-aminothiazole (2.2 g, 0.022 mole) in 40 ml of water after elution with ethyl acetate-acetone-methanol (6:2:1). Recrystallization from ethyl acetate-ethanol (2:1) afforded **7**, mp 146-147°; ir: [20] 3320 (s), 3100-2400 (m, b), 1660 (w), 1620 (s), 1550 (m), 1520 (s), 1480 (vs), 1440 (s), 1375 (s), 1260 (s), 1230 (m), 1210 (s), 1165 (m), 1140 (m), 1080 (w), 1050 (m), 1000 (s), 960 (m), 950 (w), 900 (w), 856 (w), 835 (s), 820 (s), 770 (m) and 690 (m) cm^{-1}; ms: m/z (%) 139 ($M^{+\cdot}$, 100), 124 (55), 109 (12), 96 (71), 67 (11), 55 (37) and 42 (64).

Anal. Calcd. for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.60; H, 6.75; N, 10.30.

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[19] Ten ml of hydrobromic acid per 0.01 mole of starting *O*-methylmaltol was used.

[20] Other spectral data and elemental analyses are tabulated.