After adding, the reaction mixture was warmed to room temperature and then heated to 80 °C for 20 min. After cooling, the crude reaction mixture was neutralized with an aqueous saturated sodium bicarbonate solution and extracted with diethyl ether. The organic layer was dried ($MgSO_4$) and filtered. The solvent was evaporated under reduced pressure and the residue was distilled bulb-to-bulb at 0.05 torr (room temperature) into a receiver cooled by liquid nitrogen. Octenes were converted into the corresponding dibromoalkanes as described above. (−)-(*R*)-2-Fluorooctane was obtained by bulb-to-bulb distillation (0.05 torr, room temperature) as an inseparable mixture (0.4 g; 0.003 mol) with isomeric 3-fluorooctane: ^{19}F NMR ($CDCl_3$) 174 (m); ^{13}C NMR ($CDCl_3$, Me_4Si) {^1H}, general formula $C_4H_9C^dH_2C^cHYC^bHXC^aH_3$ (see Table II).

Fluorination of (+)-(*S*)-2-Octanol with FAR. A solution of 16.2 g (0.085 mol) of *N*-(2-chloro-1,1,2-trifluoroethyl)diethylamine[8] in 10 mL of anhydrous diethyl ether was added to a solution of 10 g (0.077 mol) of (+)-(*S*)-2-octanol in 30 mL of ether cooled to 0 °C. The reaction mixture was allowed to stand at 0 °C for 24 h, and then washed with an aqueous saturated sodium bicarbonate solution and water until neutral. The organic layer was dried ($MgSO_4$), concentrated, and distilled bulb-to-bulb at 15 torr (bath temperature 50 °C) into a receiver cooled to −75 °C to separate the diethylamide of chlorofluoroacetic acid. The volatile products were treated with bromine in the usual way. Distillation bulb-to-bulb at 0.01 torr (room temperature) afforded 4.5 g (0.034 mol) of (−)-(*R*)-2-fluorooctane.

In another experiment, the crude reaction mixture, after hydrolysis, was distilled on a spinning-band column (40 torr) to give (−)-(*R*)-2-fluorooctane free of octenes, in comparable yield and optical purity.

Fluorination of (+)-(*S*)-2-Octanol with DAST. A solution of 4.25 g (0.033 mol) of (+)-(*S*)-2-octanol in 6 mL of dichloromethane was added dropwise to a stirred solution of 5.18 g of DAST in 15 mL of methylene chloride cooled to −60 °C. The reaction mixture was slowly warmed to room temperature and stirred overnight. After washing with aqueous sodium bicarbonate and water until neutral, the organic layer was dried, concentrated, and distilled bulb-to-bulb at 0.01 torr (room temperature) to give a mixture of 2-fluorooctane and octenes. This mixture was treated by bromine in the usual way. Distillation on a small Vigreux column afforded 1.0 g (0.0076 mol) of (−)-(*R*)-2-fluorooctane.

Registry No. (−)-(*R*)-2-Octyl tosylate, 27770-99-6; (+)-(*S*)-2-fluorooctane, 56772-74-8; (+)-(*S*)-2-(trimethylsilyloxy)octane, 65500-76-7; (+)-(*S*)-2-octanol, 6169-06-8; (−)-(*R*)-2-fluorooctane, 54632-06-3; 3-fluorooctane, 20469-83-4.

Bromomaltol: Structure and Conversion to Novel Pyridone and Pyridine Derivatives

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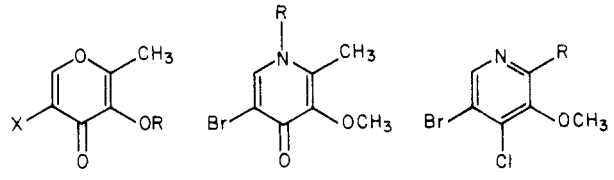
Maltol (**1**), known since 1862,[1] has been obtained from several plant, food, and beverage sources,[2] and by synthesis from methyl-α-furylcarbinol.[3] The mesylate of **1** was prepared several years ago.[4] In the present paper, we report bromination of maltol by *N*-bromosuccinimide (NBS) and by bromine, chemical and spectral data which establish structure of the bromination product, and conversion of the latter to new pyridone and pyridine derivatives.

Bromination of the methyl group of **1** with NBS is an obvious first step in functionalization. However, when **1** reacted with NBS in carbon tetrachloride containing benzoyl peroxide, there resulted a bromomaltol (**2**) which reacted with silver acetate–acetic anhydride to give an ester (**3**), which retained bromine. ^{13}C NMR data confirmed



1, X = R = H
2, X = Br; R = H
3, X = Br; R = Ac
4, X = Br; R = CH_3

5, R = H
9, R = CH_3

6, R = CH_3
7, R = CO_2H
8, R = H

a nuclear bromine; hence the acetoxyl group resulted from enolic hydroxyl acetylation, not from bromine displacement.

Direct bromination in three haloalkane solvents also was studied. Yields of **2** in both carbon tetrachloride and methylene chloride were approximately 30%. When **1** was reacted with excess bromine in 1,1,2,2-tetrachloroethane and the reaction mixture was swept continually with nitrogen, the yield of **2** was 58%. Sweeping with nitrogen removed not only oxygen, but also hydrogen bromide, which conceivably could interact with **1** and **2** to form insoluble oxonium salts.

The position of the chemically inert bromine was not apparent. Conversion of kojic acid to pyridine derivatives was structurally useful;[5] hence a multistep sequence leading to a known bromopyridine[6] was attempted. Bromomaltol was methylated to give the ether **4**. Reaction of **4** to give the pyridone (**5**) required only concentrated aqueous ammonia at room temperature, in contrast to procedures[7] using elevated temperature and pressure. Assignment of a pyridone structure to **5** is not unequivocally certain, for tautomerization to a pyridin-4-ol derivative is possible.[8] Reaction of phosphoryl chloride gave 2-methyl-3-methoxy-4-chloro-5-bromopyridine (**6**). The difference in melting points of **5** and **6** is striking: mp of **5**, 233 °C; mp of **6**, 35 °C. Oxidation of **6** with neutral permanganate gave the picolinic acid derivative (**7**), which was decarboxylated at 120 °C to yield the trisubstituted pyridine (**8**). ^1H NMR spectra of **6** and **8** contained peaks near δ 8.3, in satisfactory agreement with a value of δ 8.5 reported[9] for α-protons in pyridine derivatives. These data indicate tentatively that the bromine atom in **6** is bonded not to C(6) but to C(5). Hence the bromine atoms in **2** and **4** also must be bonded to C(5). A preliminary study of selective dehalogenation of the 4-chloro atom of **8** was attempted,[10] but insufficient **8** was available for thorough study.

In Table I are presented ^{13}C NMR data for bromomaltol (**2**) and 2-bromopyromeconic acid (2-bromo-3-hydroxy-4*H*-pyran-4-one).[11] Chemical shifts for these two bro-

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Table I. ^{13}C NMR Spectra[a] of Bromopyrones in Me_2SO-d_6

compd	C(2)	C(3)	C(4)	C(5)	C(6)	CH_3
bromomaltol	150.0 (1.1)[b]	141.2 (−1.4)[b]	167.7 (−4.4)[b]	110.8 (−2.4)[b]	152.9 (−1.4)[b]	13.9 (0.1)[b]
2-bromopyromeconic acid	129.7 (−10.2)[c]	145.0 (−1.4)[c]	171.4 (−1.5)[c]	113.6 (−0.6)[c]	156.0 (0.6)[c]	

[a] Chemical shifts in ppm downfield from Me_4Si. [b] Values in parentheses are differences in chemical shift relative to maltol values; cf ref 12. [c] Values in parentheses are differences in chemical shift relative to pyromeconic acid values; cf. ref 12.

mopyrones are compared with previously reported[12] values for maltol (1) and pyromeconic acid. The effect of the bromine at C(5) of **2** is evident both in a modest but significant upfield α-effect and in a larger β-effect involving depolarization of the carbonyl group and a resulting upfield shift of the C(4) resonance. The α-effect of the 2-bromo substituent in 2-bromopyromeconic acid is larger than that of the 3-bromo substituent in **2**.

Experimental Section

All melting points were taken by the capillary tube method and are uncorrected. Proton NMR spectra were observed with the aid of a Varian A-60 or A-60D spectrometer, with tetramethylsilane as internal standard. Infrared spectra were determined on a Perkin-Elmer Model 237 spectrophotometer. ^{13}C NMR spectra were run at 25.2 MHz on a Varian XL-100 instrument.

Maltol (1). Maltol was obtained from Aldrich Chemical Co., or from Fritzche Bros., Inc.

Bromomaltol (2). Method I: Reaction of Maltol with NBS. Maltol (50.4 g), 100 g of *N*-bromosuccinimide, and 0.5 g of benzoyl peroxide were placed in 500 mL of carbon tetrachloride and refluxed on a steam bath under UV irradiation for 30 min. The hot reaction mixture was filtered, the precipitate was discarded, and filtrate was stored for 24 h in a refrigerator. The product was collected, and boiling water (50 mL) was poured over the dried product on the filter paper. The water-insoluble yellow-orange product was dried, recyrstallized repeatedly from benzene (decanting from tar with each recrystallization), and precipitated by addition of Skellysolve B. Yields of bromomaltol, mp 148–151 °C, ranged from 8 to 30 g.

Method II: Reaction of Maltol with Bromine. A mixture of 30 g of maltol in 250 mL of 1,1,2,2-tetrachloroethane was heated on a steam bath in a three-neck flask fitted with reflux condenser, dropping funnel, and inlet tube for N_2. To the mixture at reflux, swept continually with N_2, was added dropwise 75 g of bromine over a period of 4 h; reflux was continued for an additional 6 h. The mixture was evaporated and the residue was washed with 200 mL of water for 2 h at room temperature. The insoluble product was collected, dried, and crystallized from benzene–Skellysolve B: yield 28 g (58%); mp 146–152 °C. Analytically pure bromomaltol, mp 152–153 °C, was obtained by sublimation at approximately 120 °C under water-pump vacuum; NMR (Me_2SO-d_6) δ 2.28 (s, $3CH_3$), 8.53 (s, 1, C(6)–H). Anal. Calcd for $C_6H_5BrO_3$: C, 35.15; H, 2.46; Br, 38.98. Found: C, 35.68; H, 2.57; Br, 38.80.

Bromomaltol also was prepared as above, except that only 1 equiv of bromine was used and the reaction mixture was not swept with nitrogen, in carbon tetrachloride (31% yield) and methylene chloride (~30% yield). In the latter, an insoluble product separated, possibly maltol hydrobromide, which was removed by filtration prior to product bromomaltol isolation.

Bromomaltol Acetate (3). A mixture of 10 g of bromomaltol, 8.2 g of silver acetate, and 200 mL of acetic anhydride was heated under reflux for 90 min. Insoluble silver compounds were removed from the hot mixture by filtration, and the filtrate was added slowly to a mechanically stirred ice–water mixture. Stirring was continued for 90 min. Liquid components were removed by flash evaporation, and the residue was dissolved in hot benzene. The benzene solution was decanted from tar and Skellysolve B was added. The mixture was cooled to give crystalline material, which was recrystallized from benzene–Skellysolve B: yield of colorless bromomaltol acetate, 7.5 g; mp 97–98 °C. Anal. Calcd for $C_8H_7BrO_4$: C, 38.88; H, 2.86; Br, 32.34. Found: C, 38.79, 38.94; H, 2.97, 2.94; Br, 32.64.

Bromomaltol Methyl Ether (4). To a solution of 16.4 g of bromomaltol in 300 mL of reagent acetone was added 60 g of anhydrous K_2CO_3. The mixture was heated to reflux and 9.28 g of dimethyl sulfate was added. Reflux was continued for 30 h, and the mixture was filtered hot. Solvent was removed and the residual oil was dissolved in 25 mL of ethyl ether (Norit A added). The filtrate was placed in a dry ice bath. The yellow solid which separated was collected and recrystallized from 125 mL of boiling Skellysolve B by decanting from colored residue and cooling the decantate. Colorless bromomaltol methyl ether resulted: yield 14.2 g (82%); mp 61–62 °C. Anal. Calcd for $C_7H_7BrO_3$: C, 38.36; H, 3.22; Br, 36.48. Found: C, 37.93; H, 3.31; Br, 36.46.

2-Methyl-3-methoxy-5-bromo-γ-pyridone (or 2-Methyl-3-methoxy-5-bromopyridin-4-ol) (5). To 50 mL of concentrated aqueous ammonia (28.8% NH_3) was added 11.0 g of bromomaltol methyl ether (4). The resulting suspension was stirred for 10 min at room temperature in a tightly stoppered flask; the pyrone dissolved. The dark-colored solution was stirred an additional 20 min, when a brown solid separated, and then for an additional 2.5 h. The reaction mixture was cooled and crude product was collected by filtration and dried in vacuo over P_2O_5. The product was dissolved in 50 mL of hot methanol, and 1.0 g of Norite A was added and shaken for several minutes. The hot suspension was filtered (Celite) and the filtrate was refrigerated. The crude was collected and recrystallized from 50 mL of methanol to give the colorless pyridone (or pyridin-4-ol) derivative (7.21 g; 66%): mp 232–233 °C. Anal. Calcd for $C_7H_8BrNO_2$: C, 38.51; H, 3.67; Br, 36.64; N, 6.42. Found: C, 38.24; H, 3.85; Br, 36.81; N, 6.40.

2-Methyl-3-methoxy-4-chloro-5-bromopyridine (6). To 50 mL of phosphoryl chloride was added 4.35 g of **5**. The resulting suspension was refluxed for 3 h, with protection from atmospheric moisture. The solution was cooled, poured onto 50 g of crushed ice, and stirred vigorously until excess $POCl_3$ decomposed. The mixture was basified with solid $NaHCO_3$ and extracted with ether (3 × 20 mL). The extract was dried over anhydrous sodium bisulfite, and solvent was removed by flash evaporation. The residual oil was dissolved in 10 mL of methanol, water was added to turbidity, and the mixture was cooled for at least 12 h. The colorless product was collected by filtration: maximum yield 3.1 g (65%); mp 34–35 °C, repeated crystallization from methanol–water did not raise the melting point; NMR (CCl_4) δ 2.46 (s, 3, CH_3), 3.84 (s, 3, OCH_3), 8.31 (1, C(6)–H). Anal. Calcd for $C_7H_7BrClNO$: C, 35.55; H, 2.98; N, 5.92. Found: C, 35.68, H, 3.09; N, 5.86.

3-Methoxy-4-chloro-5-bromopyridine (8). To 5 g of 2-methyl-3-methoxy-4-chloro-5-bromopyridine in 50 mL of water at reflux was added 9.0 g of $KMnO_4$ in five portions over a 6-h period. After each addition, the condenser tube was washed with 10 mL of water to return permanganate and very volatile starting material to the reaction vessel. The mixture was filtered hot, and the MnO_2 was washed on the filter with 100 mL of hot water in five portions. The combined washings and filtrate were evaporated in vacuo to 50 mL and acidified to pH 3.0 with concentrated HCl, and the mixture was refrigerated. The crude 3-methoxy-4-chloro-5-bromopicolinic acid (7) was collected and dried in vacuo over P_2O_5: yield 2.5 g; mp 141–143 °C. The picolinic acid derivative could not be purified bacause of ready decarboxylation, even in ethanol–water during attempted recrystallization. A sample of the acid was heated to 120 °C and the evolved gases were passed through lime water; a voluminous precipitate of calcium carbonate resulted.

The crude 7 (2 g) was placed in a sublimation apparatus and heated to 120–130 °C in an oil bath. The colorless sublimate was

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collected until only a trace of colored residue remained. The sublimate was recrystalized from 10 mL of petroleum ether, bp 37–55 °C; chilling of the solution in dry ice gave 0.98 g (81%) of colorless 3-methoxy-4-chloro-5-bromopyridine (8): mp 97–98 °C; NMR (CCl_4) δ 4.00 (s, 3, OCH_3), ~8.35 (evident only by integration, 2, C(2) and C(6) protons). Anal. Calcd for $C_6H_5BrClNO$: C, 32.39; H, 2.27; N, 6.30. Found: C, 32.42; H, 2.31; N, 6.36.

***N*,2-Dimethyl-3-methoxy-5-bromo-γ-pyridone (9).** A solution prepared by dissolving 1 g of bromomaltol methyl ether and 20 mL of 40% aqueous methylamine in 25 mL of ethanol was refluxed for 3 h. The solvent was evaporated by flash evaporation. The residue was dissolved in 10 mL of hot chloroform and shaken with 1 g of Norite A, the mixture was filtered, and the filtrate was evaporated in vacuo. The tarry residue was extracted with 5-mL portions of hot toluene twice, the combined extracts were refrigerated, and product was collected. The solid then was recrystallized repeatedly from 5–10 mL of benzene to give 0.8 g (77%) of the colorless pyridone: mp 172–173 °C. Anal. Calcd. for $C_6H_{10}BrNO_2$: C, 41.38; H, 4.34; Br, 34.43; N, 6.03. Found: C, 41.54; H, 4.35; Br, 34.20; N, 6.30.

Acknowledgment. This work was supported in part by a grant (AI-01703) from the National Institutes of Health, U.S. Public Health Service. The XL-100 NMR instrument used in this investigation was purchased with funds from NSF grant GP 10293. Both grants are gratefully acknowledged.

Registry No. 1, 118-71-8; 2, 71001-54-2; 3, 71001-55-3; 4, 71001-56-4; 5, 71001-57-5; 6, 71001-58-6; 7, 71001-59-7; 8, 71001-60-0; 9, 71001-61-1.

Alkyl Nitrate Nitration of Active Methylene Compounds. Nitration of Alicyclic Ketimines[1]

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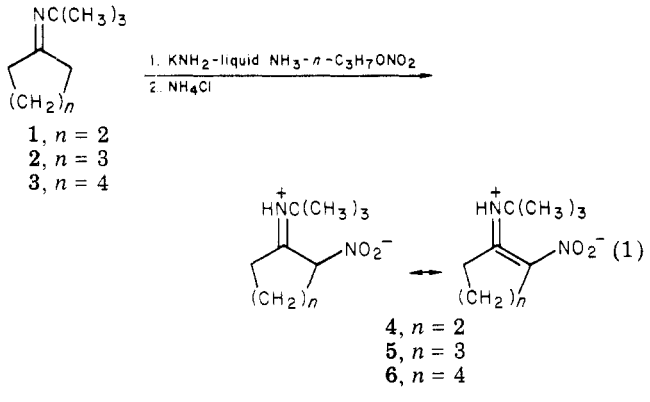
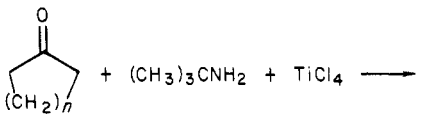
In continuation[2] of our studies of the alkyl nitrate nitration, we now report on its application to the preparation of 1-nitro-2-(*tert*-butylamino)cycloalkenes **4–6** directly from the corresponding alicyclic *tert*-butyl imines **1–3** (eq 1).



(1)

Compounds **1–3** were obtained in about 50% yield by an adaptation of the method by Weingarten et al.[3] (eq 2). The presence of the tautomeric enamine structure was



1-3 + $(CH_3)_3CNH_3^+ \cdot Cl^-$ + TiO_2 (2)

indicated only in *N*-cyclohexylidene-*tert*-butylamine (**2**). The NMR spectrum of **2** showed a triplet at 5.60 ppm (0.12 proton) due to the vinyl proton and two singlets for the *tert*-butyl group at 1.30 and 1.24 ppm (total of nine protons), indicating respectively the imine and enamine forms. A signal at 4.21 ppm for the vinyl proton was also reported for *N*-cyclohexylidene-*n*-butylamine.[4]

The nitration reaction in eq 1 was carried out in the potassium amide–liquid ammonia system employing conditions which were found to be optimum in the nitration of aldimines.[5] The molar ratio of imine to base to nitrating agent employed was 1:2:1.5, and ammonium chloride was used in the acidification step. Nitration of **1-3** gave 1-nitro-2-(*tert*-butylamino)cyclopentene (**4**), 1-nitro-2-(*tert*-butylamino)cyclohexene (**5**), and 1-nitro-2-(*tert*-butylamino)cycloheptene (**6**) in yields of 35, 44, and 50%, respectively. Only mononitration products were detected in these nitrations.

The formation of compound **4** is of interest in view of the fact that attempts to prepare 2-nitrocyclopentanone by the alkyl nitrate nitration of cyclopentanone were unsuccessful. Mainly, dipotassium 2-ketocyclopentane-1,3-dinitronate, the aldol condensation product, 2-(1-hydroxycyclopentyl)cyclopentanone, and amyl 5-nitropentanoate, arising from ring opening, were obtained.[6]

At ambient temperatures, **4** showed resistance to hydrolysis in 95% ethanolic hydrochloric acid. No changes in its UV spectrum were observed after 27 days. Compound **4** might be a useful synthetic intermediate as a substitute for 2-nitrocyclopentanone.

Spectra of Compounds 4–6. A study of the NMR spectra of compounds **4–6** indicated the presence of the dipolar structure. In $CDCl_3$ the presence of the iminium proton in compounds **4–6** was indicated at 10.17, 12.00, and 12.20 ppm, respectively. Addition of $(CD_3)_2SO$ to $CDCl_3$ solutions of compounds **4–6** did not affect the positions of these peaks. The iminium proton in pyridinium bromide has been reported to fall at 12.57 ppm.[7]

The ring protons of **4–6** appeared as two multiplets at about 1.80 and 2.80 ppm. The latter was assigned to the methylene groups adjacent to the iminium and nitronate groups.

The IR spectra (CCl_4) of compounds **4–6** showed the C=N absorptions as very strong bands in the region of 1595–1615 cm^{-1}. The expected absorptions for the nitronate group appeared at 1215–1245 (asymmetric stretch) and at 1120–1180 cm^{-1} (symmetric stretch).[8]

Absorptions due to the NH group were absent. Similar observations have been reported for several aminonitro olefins containing a secondary amino group and were attributed to intramolecular hydrogen bonding.[9] Similar hydrogen bonding in the dipolar structure A might account for the absence of absorption characteristic of the iminium group in **4–6**. The observed broad absorption of the iminium proton in the NMR spectra of **4–6** (vide supra) is further indication of structure A.

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