added, and the mixture was stirred and refluxed for 7 hr. and allowed to remain at room temperature overnight. The mixture was poured into an equal volume of water and the layers were separated. The ether layer was washed free of alkaline substances with eight 20-ml. portions of water and dried (sodium sulfate). Removal of the ether *in vacuo* at room temperature left an oil (30.8 g.) which was fractionated. Isobutyrophenone (15.9 g., 54%) was recovered at 51° (0.5 mm.). A fraction boiling at 93–98° (0.4 mm.), 6.1 g., possessed an infrared spectrum that indicated it was a mixture of isobutyrophenone and 1-phenyl-6,6-dimethyl-2,7-dioxabicyclo[2.2.1]heptane (XVIII). Accordingly, a portion (5.0 g.) of this fraction was chromatographed from petroleum ether onto alumina (120 g., Alcoa F-20). Elution with petroleum ether gave 1.4 g. of isobutyrophenone (identified by comparing its infrared spectrum with the spectrum of an authentic sample), followed by 0.40 g. of XVIII. Additional XVIII, 1.34 g. (total, 1.74 g.), was obtained by elution with 9:1 petroleum ether–ether. A center fraction melted without further purification at 57.5–58.5°; mixture melting point with the 58°-melting solid obtained in procedure A was 57–57.5°. The infrared spectra of the two were identical. The total yield of pure XVIII by this method was 4% based on original isobutyrophenone taken. Attempts to isolate and to characterize any other products from this reaction were not made.

Action of Aqueous Base on the Bromohydrin (XIII).—A mixture of the bromohydrin (XIII, 1.5 g., 5.3×10^{-3} mole), 10% sodium hydroxide (2.5 ml., estimated 6.3×10^{-3} mole of sodium hydroxide), and dioxane (50 ml.) was stirred and refluxed for 4 hr. It was poured into water (1 l.), and this mixture was extracted with four 200-ml. portions of ether. The ether extracts were combined and washed with five 100-ml. portions of water and three 40-ml. portions of saturated sodium chloride. Removal of the ether at room temperature left an orange oil (1.22 g.) which was chromatographed from petroleum ether onto alumina (37 g., Alcoa F-20). Elution with petroleum ether and with 10:1 petroleum ether–ether gave 0.75 g. (50%) of a white solid, m.p. 99–100°, which proved to be starting material (bromohydrin) by comparing its infrared spectrum with that of an authentic sample. Elution with ether gave a white solid (0.36 g., 30%), melting at 97–98°, which was glycol XXI, according to its infrared spectrum. Material with analysis agreeing with XVIII was not isolated.

In another experiment in which the crude oil obtained from the reaction was heated on the steam bath before it was chromatographed, only the amorphous solid, identified by its infrared spectrum, also obtained in procedure A in the previous synthesis, was isolated.

Dimer of XVIII (XXIV).—In one experiment designed to prepare XVIII, silica gel (Baker, 80–200 mesh) was used instead of alumina as the adsorbant for chromatography. The silica gel, when mixed with water, liberated enough acid to test with indicator paper. The principal product (4 g. from an initial 5 g., 0.027 mole of unsaturated ketone X) was a white solid, m.p. 219–221°, after recrystallization from ligroin.

Anal. Calcd. for $C_{26}H_{32}O_4$: C, 76.44; H, 7.90. Found: C, 75.83, 75.96; H, 7.96, 8.03.

Our molecular weight determinations (cryoscopic in benzene), while giving reasonable results with naphthalene (Calcd. for $C_{10}H_8$: 128. Found: 125, 125, 118, 118.) and with *p*-dibromobenzene (Calcd. for $C_6H_4Br_2$: 236. Found: 223, 221, 224, 220.), gave low results for the dimer, $C_{26}H_{32}O_4$ (Calcd., 408. Found: 371, 342, 335.). That our product was indeed the dimer seemed evident from the work of Haller and Ramart-Lucas[19] who obtained a compound, $C_{26}H_{32}O_4$ (m.p. 214–215°; mol. wt. found, 396). Although they assigned structure XXIII to their compound, the origin was such that their 214–215°-melting material and our 219–221° substance were almost surely the same.

The compound did not react with bromine in carbon tetrachloride. In acetic acid it gave a positive periodic acid test.[21,22]

The infrared spectrum of the product (as a 5% solution in carbon tetrachloride/carbon disulfide) showed that it did not absorb between 1600 and 2800 or between 3100 and 4000 cm.$^{-1}$. Several sharp bands occurred between 970 and 1110 cm.$^{-1}$, the two strongest at 1050 and 1065 with others at 1115 (s), 1085 (m–s), 1035 (w), 1015 (m–s), 995 (w) and 980 cm.$^{-1}$ (w). Three sharp bands appeared at 705 (s), 748 (w), and 777 cm.$^{-1}$ (m). The spectrum was significantly different from either that of the "monomer" (XVIII) or of the amorphous material, both described earlier.

Acknowledgment.—We wish to express our gratitude to Dr. Donald P. Hollis and Varian Associates of Palo Alto, California, for the n.m.r. analyses.

The Structure of Isomaltol[1]

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Isomaltol is shown to be 3-hydroxy-2-furyl methyl ketone. Isomaltol *O*-methyl ether was ammonolyzed to produce both a pyrrole (3-methoxy-2-pyrrolyl methyl ketone) and a pyridine derivative (4-methoxy-2-methyl-3-pyridinol). Removal of the *O*-methyl group of the pyridinol gave the same 3-hydroxy-2-methyl-4-(1*H*)-pyridone that was obtained by ammonolysis of maltol *O*-methyl ether (3-methoxy-2-methyl-4*H*-pyran-4-one) to 3-methoxy-2-methyl-4-(1*H*)-pyridone, followed by removal of the *O*-methyl group. Oxidative degradation of the acetyl side chain of isomaltol *O*-methyl ether gave 3-methoxy-2-furoic acid, which was decarboxylated to the known 3-methoxyfuran. The acidity of isomaltol is attributed to a carboxylic acid-like resonance that extends from the carbonyl group to the enolic hydroxyl group and that diminishes the aromaticity of the furan nucleus. The infrared spectra indicate isomaltol to be strongly hydrogen bonded as a dimer in the crystalline state, and possibly also as a dimer, or intramolecularly, in organic solvents.

Isomaltol first was isolated from bread as a crystalline enol by Backe.[3] He obtained it in trace amounts from the steam distillate of a bread baked from a special flour that contained dried milk. He named the compound isomaltol because some of its properties were similar to those of isomeric maltol (3-hydroxy-2-methyl-4*H*-pyran-4-one). Backe suggested a 4-pyrone structure for isomaltol.

Hodge and Nelson[4] produced isomaltol β-D-galactopyranoside from lactose by the same reaction with secondary amine salts that gave the amino-hexose-reductones from hexoses.[5] The *O*-galactoside was easily hydrolyzed to yield Backe's isomaltol. How-

(1) Presented at the 139th National Meeting of the American Chemical Society, St. Louis, Mo., March, 1961.

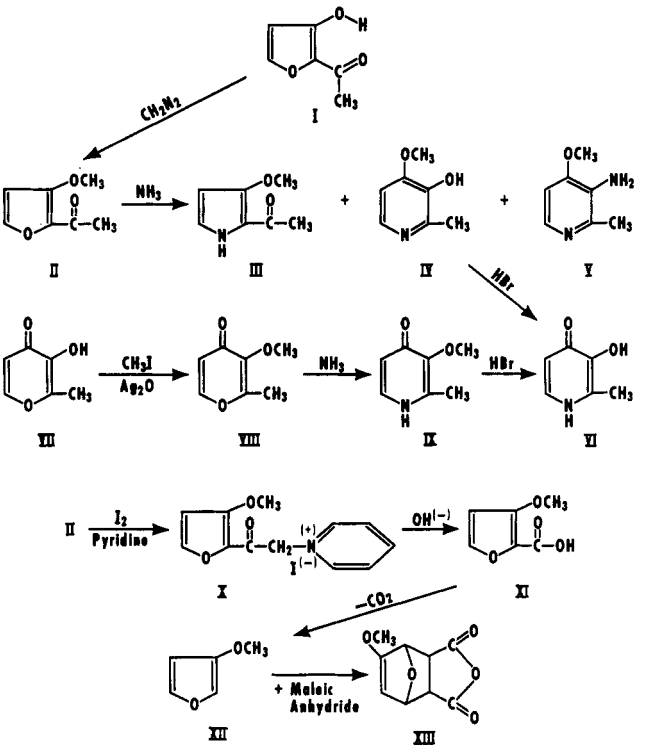
(2) A laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture; article is not copyrighted.

(3) A. Backe, *Compt. rend.*, **150**, 540 (1910); **151**, 78 (1910).

(4) J. E. Hodge and E. C. Nelson, *Cereal Chem.*, **38**, 207 (1961).

(5) (a) J. E. Hodge, U. S. Patent 2,936,308 (May 10, 1960); (b) J. E. Hodge, E. C. Nelson, and B. E. Fisher, unpublished results; (c) F. Weygand, H. Simon, and W. Bitterlich, and also J. E. Hodge and B. E. Fisher, *Tetrahedron*, **6**, 123 (1959).

CHART I

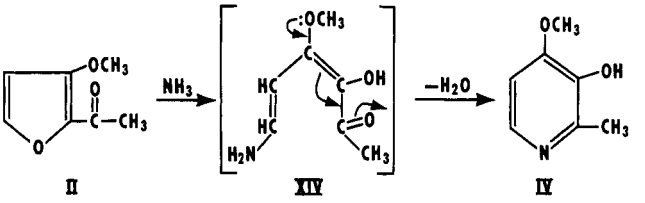


ever, from the instability of isomaltol to mineral acids (in contrast to the known stability of maltol and other 4-pyrones), the rather strong acidity of the enolic hydroxyl group, the demonstration of a reactive carbonyl group apart from the enol function, and the ultraviolet and infrared spectra, they concluded that isomaltol could not have the pyrone structure proposed by Backe. Instead, the 3-hydroxy-2-furyl methyl ketone structure (I) was proposed.[4] Proof of structure was undertaken because knowledge of the complex group of reactions involved in the browning decomposition of sugars by amine salts would be extended,[6] and because the strong caramel flavor of isomaltol indicated some possible uses as a flavoring agent.[7]

The structure (I) now has been proved by the series of transformations presented in Chart I. Ammonolysis of the *O*-methyl ether of isomaltol (II) gave the pyridinol derivative (IV), and, by demethylation of IV, 3-hydroxy-2-methyl-4-(1*H*)-pyridone (VI) was obtained. The same pyridone (VI) was synthesized by a known route (VII → VIII → IX → VI)[8] from maltol, for which the structure has been established unequivocally as 3-hydroxy-2-methyl-4*H*-pyran-4-one (VII).[8] Furthermore, degradation of the side chain of isomaltol *O*-methyl ether (II) through the pyridinium salt (X) and 3-methoxy-2-furoic acid (XI), with decarboxylation of XI, gave 3-methoxyfuran (XII).[9] Identity of the pyridones (VI) was shown by infrared spectra and X-ray diffraction patterns, by melting points, and by the melting point of a mixture of *O*-acetyl derivatives. Identity of our 3-methoxyfuran with that of Gronowitz and Sörlin was established by comparison of the infrared and n.m.r. spectra.[9]

Reaction of 3-methoxyfuran with maleic anhydride gave the crystalline adduct analyzing as XIII. However, several attempts to convert the adduct to the known 4-hydroxyphthalic anhydride with acetic anhydride and zinc chloride, or with hydrobromic acid in glacial acetic acid, were unsuccessful.

Leditschke[10] demonstrated that formation of 3-pyridinols by ammonolysis of 2-acylfurans is a general reaction. Others[11,12] have isolated both 2-methyl-3-pyridinol and methyl 2-pyrrolyl ketone after heating 2-furyl methyl ketone in aqueous or alcoholic ammonia. When 2-furyl methyl ketone is ammonolyzed in aqueous ammonia, the 3-pyridinol is isolated in 47% yield with a very low yield of the pyrrole derivative.[13] In contrast, aqueous ammonolysis of isomaltol *O*-methyl ether gave only 1.2% of 4-methoxy-2-methyl-3-pyridinol (IV), and 24% of 3-methoxy methyl 2-pyrrolyl ketone (III). Ammonolysis of II in aqueous methanol gave 2.0% of IV, 25% of III, and 0.4% of an unidentified compound of empirical formula $C_7H_{10}N_2O$. A plausible explanation for the low yield of IV is that the flow of electrons from the methoxyl oxygen of the postulated intermediate XIV decreases the electropositive character



of the carbonyl carbon. This decrease impedes nucleophilic attack of the nitrogen atom on the carbonyl carbon.

The pyrrole derivative (III) gave a positive color reaction with Ehrlich reagent and a blood-red color by the well-known pine splinter test. Structure III is supported by ultraviolet and infrared spectra. The ultraviolet absorption spectrum of III in methanol discloses a single peak at 290 mμ with E_m (l. mole^{-1} cm.$^{-1}$) 21,300. This peak coincides with the major peak reported for methyl 2-pyrrolyl ketone in methanol at 290 mμ, E_m 16,400.[14] The minor peak at 251 mμ, E_m 4100 that was reported for methyl 2-pyrrolyl ketone did not appear in the spectrum of III. However, disappearance of the minor peak (with a corresponding increase in the extinction coefficient of the major peak) also occurs when the furan nucleus is substituted with a methoxyl group in the β-position. For example, 2-furyl methyl ketone in methanol gives E_m 15,000 at 268 mμ and E_m 2500 at 226 mμ,[15] whereas, 3-methoxy-2-furyl methyl ketone (II) in methanol gives only one peak with E_m 17,400 at 281 mμ.[4] The infrared spectrum of III shows N–H stretching vibrations at 3495 and 3270 cm.$^{-1}$ and carbonyl stretching at 1640–1645

(6) J. E. Hodge, B. E. Fisher, and E. C. Nelson, *Am. Soc. Brewing Chemists Proc.*, 84 (1963).

(7) J. E. Hodge and H. A. Moser, *Cereal Chem.*, **38**, 221 (1961).

(8) A. Peratoner and A. Tamburello, *Gazz. chim. ital.*, **36**, 33, 50 (1906).

(9) Shortly after our presentation of this synthesis of 3-methoxyfuran (Abstracts, 139th National Meeting of the American Chemical Society, St. Louis, Mo., March, 1961, p. 1D), G. Gronowitz and G. Sörlin [*Acta Chem. Scand.*, **15**, 1419 (1961); *Arkiv Kemi*, **19**, 515 (1962)] published a synthesis of 3-methoxyfuran from 3-iodofuran. Comparisons of the infrared and n.m.r. spectra were made by correspondence with Dr. Gronowitz, who kindly provided the spectra he had obtained before they were published.

(10) H. Leditschke, *Chem. Ber.*, **86**, 123 (1953).

(11) A. P. Dunlop and S. Swadesh, U. S. Patent 2,636,882 (April 28, 1953); U. S. Patent 2,672,461 (March 16, 1954).

(12) H. Sugisawa and K. Aso, *Chem. Ind.* (London), 887 (1958).

(13) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953, p. 667.

(14) U. Eisner and P. H. Gore, *J. Chem. Soc.*, 922 (1958).

(15) Spectra were measured at this laboratory by Mr. C. A. Glass.

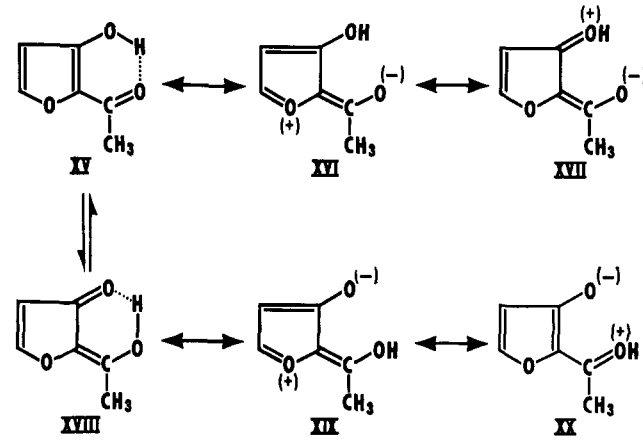
cm.$^{-1}$. This conforms to the recorded spectrum of methyl 2-pyrrolyl ketone, which shows N–H vibrations at 3425 and 3270 and carbonyl stretching at 1640 cm.$^{-1}$.[16] Furthermore, the band of III at 1515 cm.$^{-1}$ is in the region (1475–1600 cm.$^{-1}$) assigned to a ring vibration of pyrroles.[16] The methoxyl group of III was indicated by a clear, sharp band at 2830 cm.$^{-1}$, a frequency assigned to the C–H stretching vibrations of methoxyl groups.[17]

Huebner's method[18] for the paper chromatographic separation and identification of pyridines indicated the ammonolysis product, $C_7H_{10}N_2O$, to be a pyridine derivative. Proof of structure was not attempted because of the limited quantity of material available; however, *a priori* reasoning allows tentative assignment of the 3-amino-4-methoxy-2-picoline structure (V).

Isomaltol reacts as a strongly acidic enol. It gives an immediate deep red color with ferric chloride, and it liberates carbon dioxide from sodium bicarbonate solution.[4] It has one-tenth the acidity of acetic acid (pK_a 5.7 determined by electrometric titration). In ether solution isomaltol reacts rapidly with diazomethane to give II in 68% yield.[4] Whereas 2-furyl methyl ketone is very easily hydrogenated with a platinum catalyst,[19] isomaltol resisted hydrogenation under 3 atm. of hydrogen pressure at 25 and at 60° in the presence of prereduced platinum oxide catalyst. No significant uptake of hydrogen was observed.[20]

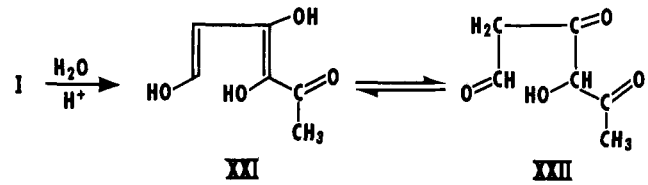
The only well-characterized β-hydroxyfurans that have been shown to exist predominantly in the enol form are diethyl and dimethyl 3,4-dihydroxy-2,5-furan dicarboxylate.[21,22] Hoehn[23] alkylated the dimethyl ester with dimethyl sulfate and isolated both mono- and dimethoxy derivatives of the dienol. Stable disodium and diammonium salts of the dienol also were isolated from the diethyl ester. No keto derivatives were reported. On the other hand, a series of 2-alkyl-3-hydroxyfurans prepared recently have been shown to exist almost completely in the keto form.[22] The side-chain β-carbonyl groups in the furan-2,5-dicarboxylic esters, therefore, can be considered to induce enolization of the ring carbonyl groups. In view of the stronger electron-withdrawing property of the acetyl carbonyl of isomaltol in comparison with the carbonyl of these esters, the existence of isomaltol as an enol is not surprising. However, a question arises on the mode of induction of enolization and stabilization of the enol by the carbonyl group. Does it occur by intramolecular hydrogen bonding of the conjugate chelate type,[24] as suggested by Dunlop and Peters[21]; or does it occur without such bonding, by resonance stabilization, as in carboxylic acids and vinylogs of carboxylic acids like "*trans* fixed" β-diketones?[25]

The relatively strong acidity of isomaltol coupled with its resistance to hydrogenation indicates that resonance through the enol and β-carbonyl functions is probably more important than the enol–chelate structure in stabilizing the enol form. Much weaker acidity and a much slower reaction with diazomethane would exist if only the intramolecularly bonded structures XV and XVIII were present.[24] Some structures that would



contribute to the resonance hybrid are given by XV, XVI, XVII, and (especially if intramolecular hydrogen bonding does occur) XVIII, XIX, and XX. The strong acidity suggests a relatively high contribution of structures XVII and XX and corresponding resonance structures of the anion.[25b,26]

Isomaltol in water alone at pH 3.5 reduces a limited amount of 2,6-dichloroindophenol in the cold in the manner of *aci*-reductones.[4] Hydrolysis of the furan ring[27] would yield the enediol-α-carbonyl compound XXI with strong acidic and reducing properties. Ex-



istence of the reductone XXI in water does not satisfactorily explain the observed acidity of isomaltol, however, because isomaltol is strongly acidic in ether solution as shown by its rapid methylation with diazomethane.[4] Hydrolysis of isomaltol by strong acid, as in the Elek–Harte method of determining acetyl groups,[28] gives a nearly quantitative yield of acetic acid together with a small amount of formic acid.[4] Both acids would be produced by C–C bond hydrolyses in the open-chain β-triketone XXII.

Evidence for a hydrogen-bonded conjugate chelate structure, such as XV ⇌ XVIII, was sought by meas-

(16) U. Eisner and R. L. Erskine, *J. Chem. Soc.*, 971 (1958).

(17) H. B. Hinbest, G. D. Meakins, B. Nicholls, and A. A. Waglund, *ibid.*, 1462 (1957).

(18) C. F. Huebner, *Nature*, **167**, 119 (1951).

(19) T. Kariyone, *J. Pharm. Soc. Japan*, **515**, 1 (1925); *Chem. Abstr.*, **20**, 412 (1926).

(20) By E. C. Nelson of this laboratory.

(21) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953, p. 180 ff.

(22) (a) C. H. Eugster, K. Allner, and R. E. Rosenkranz, *Chimia* (Aarau), **15**, 516 (1961); (b) C. H. Eugster, R. E. Rosenkranz, K. Allner, and A. Hoffman, *Angew. Chem.*, **73**, 737 (1961); (c) R. E. Rosenkranz, K. Allner, R. Good, W. v. Phillipsborn, and C. H. Eugster, *Helv. Chim. Acta*, **46**, 1259 (1963).

(23) W. M. Hoehn, *Iowa State Coll. J. Sci.*, **11**, 66 (1936).

(24) (a) B. Eistert, F. Arndt, L. Loewe, and E. Ayca, *Chem. Ber.*, **84**, 156 (1951); (b) B. Eistert and E. Merkel, *ibid.*, **86**, 895 (1953); (c) B. Eistert, W. Reiss, and H. Wurzler, *Ann.*, **650**, 133 (1961); (d) A. Schönberg and A. Mustafa, *J. Chem. Soc.*, 746 (1946).

(25) (a) B. Eistert and W. Reiss, *Chem. Ber.*, **87**, 92, 108 (1954); (b) B. Eistert and F. Geiss, *Tetrahedron*, **7**, 1 (1959).

(26) R. B. Woodward and G. Small, Jr., *J. Am. Chem. Soc.*, **72**, 1297 (1950).

(27) Because of the resonance that extends to two electronegative oxygen atoms outside the ring, the aromaticity of the ring is diminished. Increased double bond character within the ring promotes hydrolysis of the vinyl ether linkage under mildly acidic conditions. Hydrolysis to the reductone was not observed in cold alkaline solutions.[4]

(28) A. Elek and R. A. Harte, *Ind. Eng. Chem., Anal. Ed.*, **8**, 267 (1936).

urements of the infrared spectra in various media.[15] In the crystalline state in potassium bromide disks (Fig. 1A), isomaltol does show broad, merged, and strongly shifted bands for the hydroxyl and carbonyl stretching vibrations at 3100–2650 and 1610–1550 cm.$^{-1}$, respectively; however, these bands should not be interpreted as representing the chelated structure XV. According to Martin,[29] these wide bands are too strong to represent intramolecular hydrogen bonding of a conjugate chelate type. They closely resemble bands that correspond to O–H· · ·O bonding in dimers of carboxylic acids.[29–31] No such strong, shifted bands appear in the spectrum of isomaltol in carbon tetrachloride solution (Fig. 1B).

In dilute carbon tetrachloride and in bromoform and tetrachloroethylene solutions, the hydroxyl stretching band of isomaltol lies at 3295 ± 5 cm.$^{-1}$; therefore, the hydroxyl group is not free. The hydroxyl group of phenols, *p*-acylphenols, and catechols is free in dilute carbon tetrachloride solutions, and the O–H stretching band occurs in the 3760–3580-cm.$^{-1}$ region.[32–34] Because dilutions from 1.4 down to 0.1% in the organic solvents did not alter the frequency or form of the isomaltol hydroxyl band, this stability rules out intermolecular hydrogen bonding of the type observed in liquid *p*-hydroxyacetophenone,[35] but which is lost in dilute carbon tetrachloride solution.[33]

The hydroxyl band of isomaltol in carbon tetrachloride (Fig. 1B) is relatively weak, broadened, and merged with the C–H bands. This band is just as broad and weaker in the more polar bromoform and tetrachloroethylene solvents. Weakness and breadth of a hydroxyl band, with shift into the C–H region and with no significant shift in three solvents of differing polarity,[36] are indications of intramolecular hydrogen bonding of a conjugate chelate type.[29] Some additional evidence was obtained in the region of carbonyl absorption.

The carbonyl band of 2-furyl methyl ketone in carbon tetrachloride lies at 1700 cm.$^{-1}$; 3-methoxylation (II) shifts the band to 1685 cm.$^{-1}$, and 3-hydroxylation (I) shifts the band by 45 to 1655 cm.$^{-1}$. The shifts to lower wave numbers for both the hydroxyl and carbonyl frequencies are not so great as the shifts observed for *o*-acylphenols and catechols,[31–35] but the carbonyl shift of 45 cm.$^{-1}$ does approach that of 55 cm.$^{-1}$ observed for 2-acetyl-1-naphthol in carbon tetrachloride,[37] and a 45-cm.$^{-1}$ shift observed for the same compound in chloroform.[33] Only a 28-cm.$^{-1}$ shift was observed for 2-acetyl-3-naphthol.[37] Methoxylation eliminates the possibility of conjugate chelation, yet a small shift is observed. Such a shift was observed also for *o*-methoxyacetophenone and was attributed to resonance of the type exemplified by XVI and XVII, structures which presumably exist also for the *O*-methyl ether.[35]

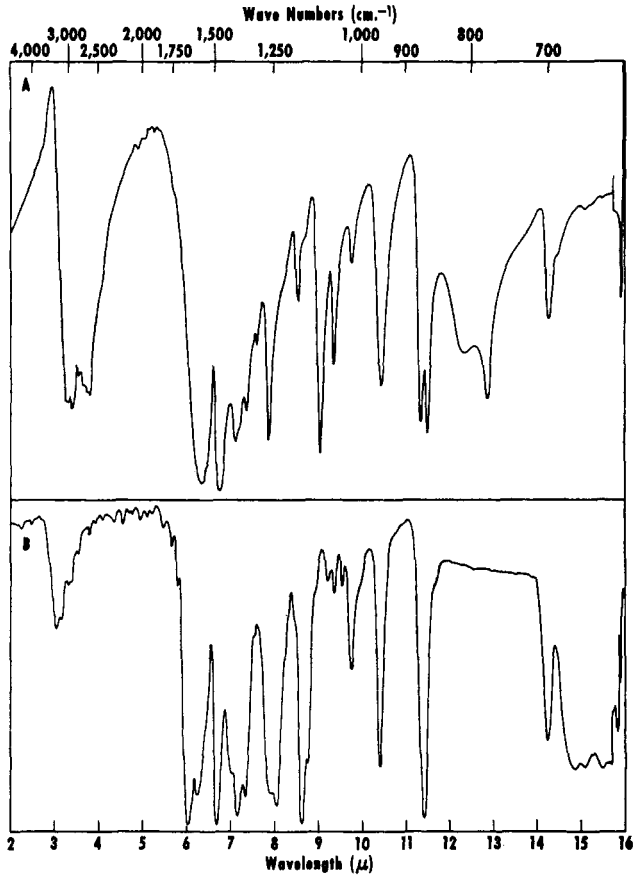


Fig. 1.—Infrared spectra of isomaltol (A) in potassium bromide disks, 14.0 g./l., and (B) in carbon tetrachloride solution, 13.5 g./l.

Carpenter and Snyder[38] found that a dimeric 2-carboethoxy-3-hydroxythiophene derivative, quite analogous to isomaltol, gave in chloroform a hydroxyl band at 3290 cm.$^{-1}$, the same frequency given by isomaltol in bromoform. As with isomaltol, no evidence was obtained from the infrared spectra for a breakdown of the thiophene dimer in organic solvents upon dilution. Therefore, the relatively small frequency shifts observed could be due to an unusually stable hydrogen-bonded dimer of the type proposed by Carpenter and Snyder, to intramolecular conjugate chelation, or to the unusual combination of furan and enolized β-diketone resonance systems. Further investigation of this matter, using infrared and n.m.r. measurements, is in progress with the collaboration of C. A. Glass of this laboratory.

Experimental

Materials and Methods. Isomaltol and isomaltol *O*-methyl ether were prepared by the methods previously described.[4] The maltol used was an especially purified commercial product, m.p. 160–161.5°. 2-Furyl methyl ketone was prepared by the method of Hartough and Kosak,[39] redistilled, and sublimed for the infrared analyses.

Infrared absorptions were determined in a Perkin-Elmer Model 21[40] twin-beam spectrometer with rock salt prism. The solvents used were spectral grade. Approximately 0.1 *M* solutions were

(29) A. E. Martin, *Nature*, **166**, 474 (1950).
(30) R. S. Rasmussen, D. D. Tunnicliff, and R. R. Brittain, *J. Am. Chem. Soc.*, **71**, 1068 (1949).
(31) M. St. C. Flett, *J. Chem. Soc.*, 962 (1951).
(32) L. L. Ingraham, J. Corse, G. F. Bailey, and F. Stitt, *J. Am. Chem. Soc.*, **74**, 2297 (1952).
(33) N. M. Cullinane, R. A. Woolhouse, and V. V. Bailey-Wood, *Rec. trav. chim.*, **80**, 116 (1961).
(34) W. I. Awad, M. F. El-Neweihy, and S. F. Selim, *J. Org. Chem.*, **25**, 1333 (1960).
(35) H. L. Hergert and E. F. Kurth, *J. Am. Chem. Soc.*, **75**, 1622 (1953).
(36) L. J. Bellamy and H. E. Hallam, *Trans. Faraday Soc.*, **55**, 220 (1959).
(37) I. M. Hunsberger, *J. Am. Chem. Soc.*, **72**, 5626 (1950).
(38) W. Carpenter and H. R. Snyder, *ibid.*, **82**, 2592 (1960).
(39) H. D. Hartough and A. I. Kosak, *ibid.*, **69**, 3093 (1947).
(40) Mention of instrument models and makers does not constitute endorsement by the U. S. Department of Agriculture over similar products not mentioned.

exposed in 1.0-mm. cells with automatic compensation for the absorption of the solvent. The potassium bromide pellets of isomaltol were 1.22 mm. thick, containing 0.1 *M* concentrations of the sample. The n.m.r. spectrum of 3-methoxyfuran was recorded on a Varian A-60 spectrometer.

All melting points were determined in capillary tubes and are corrected.

3-Methoxy-2-pyrrolyl Methyl Ketone (III).—Isomaltol *O*-methyl ether (II), 14.0 g. (0.1 mole), was dissolved in methanol (150 ml.) and concentrated ammonium hydroxide (150 ml.); the solution was heated in an autoclave at 140–145° for 20 hr. After cooling, the dark brown solution was washed from the autoclave with distilled water and concentrated at reduced pressure to *ca.* 100 ml. The crystals which separated were collected, and the filtrate was acidified to congo red with concentrated hydrochloric acid and extracted with three 50-ml. portions of benzene. The combined extracts were dried over anhydrous magnesium sulfate and evaporated to a crystalline residue. This material was added to the initial crystals, and the entire crop was recrystallized twice from water with the aid of charcoal to yield colorless needles, 3.5 g. (25%), of 3-methoxy-2-pyrrolyl methyl ketone, m.p. 115–116°. The compound gave a positive pine splinter test and a blood-red color with Ehrlich reagent, and had λ_{max}^{MeOH} 290 mμ (ε 21,300); $\nu_{max}^{CCl_4}$ 3500, 3270 (N–H); 2960 (C–H of C–CH_3); 2833 (C–H of O–CH_3); 1653–1625 (C:O); and 1515 $cm.^{-1}$ (pyrrole).

Anal. Calcd. for $C_7H_9NO_2$: C, 60.4; H, 6.52; N, 10.1; OCH_3, 22.3. Found: C, 60.4; H, 6.42; N, 10.1; OCH_3, 22.1.

Benzylidene Derivative of III.—3-Methoxy-2-pyrrolyl methyl ketone, 1.3 g., and benzaldehyde, 1.0 g. in 10% potassium hydroxide (20 ml.), were heated on a steam bath for 1 hr. The crystalline product which separated on cooling was recrystallized from aqueous ethanol, yielding 1.0 g. (45%) of 3-methoxy-2-pyrrolyl styryl ketone, m.p. 151–152°.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.77; N, 6.16. Found: C, 73.7; H, 5.61; N, 6.24.

3-Amino-4-methoxy-2-picoline (?) (V).—The aqueous mother liquor from the isolation of 3-methoxy-2-pyrrolyl methyl ketone was made alkaline with 50% potassium hydroxide and evaporated to dryness at reduced pressure. The residue was dissolved partially in boiling benzene (200 ml.). After evaporation of the benzene, the oily crystalline material which remained was purified by sublimation at 120° (3 mm.). Two recrystallizations from toluene gave 60 mg. of glistening flakes, m.p. 102–104.5°.

Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.9; H, 7.24; N, 20.3; OCH_3, 22.5. Found: C, 61.1; H, 7.37; N, 19.9; OCH_3, 21.9; *C*-methyl,[41] 0.90 per 138.2 mol. wt.

4-Methoxy-2-methyl-2-pyridinol (IV).—The undissolved residue from the boiling benzene extraction was taken up in water (20 ml.), acidified with acetic acid, evaporated to dryness at reduced pressure, and extracted with boiling benzene (200 ml.). After removal of the solvent, the gummy residue was purified by sublimation at 120° (3 mm.) and recrystallized from toluene, yielding 270 mg. of 4-methoxy-2-methyl-3-pyridinol as colorless needles, m.p. 161–163°. The melting point was raised to 162.5–163.5° after one additional recrystallization from toluene, and the product showed λ_{max}^{MeOH} 310 mμ (ε 1270) and 270 (4980); in 0.1 *N* methanolic sulfuric acid, λ_{max} 277 mμ (ε 9730) and 242 (3280); in 0.1 *N* methanolic potassium hydroxide, λ_{max} 290 mμ (ε 7010) and 252 (7930).

Anal. Calcd. for $C_7H_9NO_2$: C, 60.4; H, 6.52; N, 10.1. Found: C, 60.4; H, 6.38; N, 10.2; *C*-methyl,[41] 0.57 per 139 mol. wt.

Ammonolysis of isomaltol *O*-methyl ether (II), 5.0 g., in 100 ml. of concentrated ammonium hydroxide at 140° for 20 hr. yielded III, 1.2 g. (24%); IV, 60 mg. (1.2%); and V, 50 mg. (not purified).

3-Hydroxy-2-methyl-4(1*H*)-pyridone (VI).—4-Methoxy-2-methyl-3-pyridinol (190 mg.) was dissolved in 48% hydrobromic acid (3 ml.) and heated in a sealed tube at 140° for 4 hr. The solution was concentrated to a crystalline mass which was dissolved in 5 ml. of distilled water and neutralized with sodium bicarbonate. The crystals that separated on cooling to 5° were recrystallized from water, yielding 60 mg. which decomposed above 250° without melting. An alcohol solution of the compound gave an initial red color with alcoholic ferric chloride. The red color changed to violet and then to blue on further addition of ferric chloride solution. The compound showed λ_{max}^{MeOH} 278 mμ (ε 13,500); in 0.1 *N* methanolic sulfuric acid, λ_{max} 274 mμ (ε 8600) and 242 (3080); in 0.1 *N* methanolic potassium hydroxide, λ_{max} 306 mμ (ε 4090), 275 (5355), and 247 (5570).

Anal. Calcd. for $C_6H_7NO_2$: C, 57.6; H, 5.64; N, 11.2. Found: C, 57.9; H, 5.60; N, 11.2.

3-Methoxy-2-methyl-4*H*-pyran-4-one (VIII).—Maltol, 25.2 g. (0.2 mole), was dissolved in dimethylformamide (150 ml.), and 85.2 g. (0.6 mole) of methyl iodide was added.[42] Moist silver oxide (45 g.) was added portionwise while the solution was stirred vigorously. The flask was stoppered and mechanically shaken for 44 hr. The mixture was filtered through kieselguhr, then diluted with 500 ml. of distilled water; potassium cyanide (20 g.) was added, and the solution was extracted with chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate, and the solvent was evaporated to a residual oil. This crude residue was chromatographed on an acid-washed aluminum oxide column (150 g.) and distilled at reduced pressure, yielding 11.2 g. (40%) of colorless hygroscopic liquid, b.p. 78–79° (4 mm), $n^{21}D$ 1.5168, λ_{max}^{MeOH} 259 mμ (ε 9,840).

Anal. Calcd. for $C_7H_8O_3$: C, 60.0; H, 5.71; OCH_3, 22.2. Found: C, 59.7; H, 5.83; OCH_3, 22.0.

3-Methoxy-2-methyl-4(1*H*)-pyridone (IX).—3-Methoxy-2-methyl-4*H*-pyran-4-one (4.0 g.) dissolved in concentrated ammonium hydroxide (120 ml.) was heated on a steam bath for 2 hr. The solvent was removed at reduced pressure, and the crude product was recrystallized from acetone, yielding 2.0 g. (50%) of 3-methoxy-2-methyl-4(1*H*)-pyridone, m.p. 155–156.5°, lit.[8] 149°; λ_{max}^{MeOH} 266 mμ (ε 13,370); in 0.1 *N* methanolic sulfuric acid, λ_{max} 259 mμ (ε 5320) and 241 (5580); in 0.1 *N* methanolic potassium hydroxide, λ_{max} 245 mμ (ε 10,130).

Anal. Calcd. for $C_7H_9NO_2$: C, 60.4; H, 6.52; N, 10.1. Found: C, 59.5; H, 6.56; N, 10.1; *C*-methyl,[41] 0.87 per 139 mol. wt.

3-Hydroxy-2-methyl-4(1*H*)-pyridone (VI).—3-Methoxy-2-methyl-4(1*H*)-pyridone (1.5 g.) dissolved in 48% hydrobromic acid (30 ml.) was heated in a sealed tube 3.5 hr. at 140°. The solution was concentrated to a crystalline salt which was dissolved in distilled water (25 ml.) and neutralized with sodium bicarbonate. The crystals, which separated on cooling to 5°, were recrystallized from water to yield 970 mg. (72%) of 3-hydroxy-2-methyl-4(1*H*)-pyridone which decomposed above 250° without melting. The infrared spectrum and X-ray diffraction pattern were identical with those of 3-hydroxy-2-methyl-4(1*H*)-pyridone from IV. The product showed λ_{max}^{MeOH} 278 mμ (ε 13,400); in 0.1 *N* methanolic sulfuric acid, λ_{max} 274 mμ (ε 7970) and 242 (2870); in 0.1 *N* methanolic potassium hydroxide, λ_{max} mμ (ε 4020), 275 (5080), and 247 (5240).

Anal. Calcd. for $C_6H_7NO_2$: C, 57.6; H, 5.64; N, 11.2. Found: C, 57.3; H, 5.64; N, 11.2.

Acetyl Derivative of VI. A.—3-Hydroxy-2-methyl-4(1*H*)-pyridone (50 mg.) from IX in 0.5 ml. of acetic anhydride was heated 0.5 hr. on a steam bath. The excess acetic anhydride and acetic acid were removed in a vacuum desiccator over potassium hydroxide pellets, and the sirupy residue was sublimed at 170–180° (2.5 mm.). Recrystallization of the sublimate from ethyl acetate gave 36 mg. of colorless 3-acetoxy-2-methyl-4(1*H*)-pyridone, m.p. 205–208°, lit.[8] 204–205°. An aqueous solution of the compound did not give a color with ferric chloride solution.

Anal. Calcd. for $C_8H_9NO_3$: N, 8.38. Found: N, 8.41.

B.—3-Hydroxy-2-methyl-4(1*H*)-pyridone (50 mg.) from IV, treated with acetic anhydride as in A, gave 10 mg. of 3-acetoxy-2-methyl-4(1*H*)-pyridone, m.p. 204–208°. A mixture melting point with the *O*-acetyl derivative of A showed no depression.

Anal. Calcd. for $C_8H_9NO_3$: N, 8.38. Found: N, 8.53.

3-Methoxy-2-furoylmethylpyridinium Iodide (X).—Isomaltol *O*-methyl ether, 14.0 g. (0.1 mole), was dissolved in dry pyridine (35 ml.), then 25.4 g. (0.1 mole) of iodine was added.[43] The mixture was heated 0.5 hr. on a steam bath. The crystals that formed at 5° overnight were collected, washed with ether and ethanol, and recrystallized from aqueous ethanol to yield 16.0 g. (40%) with m.p. 203° dec.

Anal. Calcd. for $C_{12}H_{12}INO_3$: C, 41.8; H, 3.50; N, 4.06. Found: C, 41.9; H, 3.63; N, 4.10.

(41) W. F. Barthel and F. B. LaForge, *Ind. Eng. Chem., Anal. Ed.*, **16**, 434 (1944).

(42) Method of R. Kuhn, I. Löw, and H. Trischmann, *Chem. Ber.*, **88**, 1492 (1955).

(43) Method of L. C. King, *J. Am. Chem. Soc.*, **66**, 894 (1944).

3-Methoxy-2-furoic Acid (XI).—3-Methoxy-2-furoylmethylpyridinium iodide (10.0 g.) was dissolved in 80 ml. of 6% aqueous potassium hydroxide. The solution was heated on a steam bath 5 min., cooled, and acidified with dilute hydrochloric acid. The acidified solution was extracted with three 100-ml. portions of ether, and the ether extracts were dried over anhydrous sodium sulfate. After distillation of the solvent at atmospheric pressure, 750 mg. of 3-methoxy-2-furoic acid, m.p. 161–163° dec., was obtained. A sample for analysis was recrystallized twice from ether and had m.p. 169–170° dec.; λ_{max}^{MeOH} 258 mμ (ε 14,500); ν_{max}^{KBr} 3365 w, 3125–2780 s, 2700–2530 s (O–H · · · O); 1710–1667 vs (C:O); 1610 vs (furan); 1495 vs cm.$^{-1}$ (furan).

Anal. Calcd. for $C_6H_6O_4$: C, 50.7; H, 4.26; OCH_3, 21.8; neut. equiv., 142.1. Found: C, 50.4; H, 4.23; OCH_3, 22.3; neut. equiv., 143.3.

Methyl 3-Methoxy-2-furoate (Methyl Ester of XI).—Crude 3-methoxy-2-furoic acid (500 mg.) was dissolved in dry tetrahydrofuran (10 ml.), and an ether solution of diazomethane was added. The solvents were removed on a steam bath, and the crude ester was recrystallized from ether–petroleum ether, yielding 320 mg. (58%) of methyl 3-methoxy-2-furoate, m.p. 51.5–52.5°.

Anal. Calcd. for C_7H_8O: C, 53.9; H, 5.17. Found: C, 53.9; H, 5.16.

3-Methoxyfuran (XII).—3-Methoxy-2-furoic acid (2.3 g.) was dissolved in 12 ml. of dry quinoline in a 50-ml. distilling flask. Cupric oxide catalyst (0.3 g.) was added, and the mixture was heated to boiling. The colorless liquid which distilled was dried over anhydrous sodium sulfate and redistilled twice. The yield of colorless volatile liquid, b.p. 109–110° (760 mm.), was 985 mg. (62%); $n^{20}D$ 1.4499; ν_{max} 3135 m (furan C–H); 2930 s, 2825 m (C–H); 1605 vs (furan C=C); 1515 s, 1468 s, 1458 s, 1395 vs, 1247 s, 1198 m, 1173 vs, 1070 vs, 1010 vs, 970 s, 865 vs, 764–746 vs, and 687 w cm.$^{-1}$; n.m.r. (CCl_4): τ 6.33 (OCH_3), 3.82 (C_4H), 2.92 (C_5H), 2.78 (C_2H).

Anal. Calcd. for $C_5H_6O_2$: C, 61.2; H, 6.17. Found: C, 61.6; H, 6.33.

4-Methoxy-3,6-*endo*-oxo-1,2,3,6-tetrahydrophthalic Anhydride (XIII).—3-Methoxyfuran (0.56 g.) dissolved in ether (10 ml.) was added to a solution of maleic anhydride (0.56 g.) in ether (10 ml.). The solution was kept at 5° overnight. The crystalline Diels–Alder adduct was washed with ether and air-dried to a weight of 0.6 g. (45%), m.p. 97–99°.

Anal. Calcd. for $C_9H_8O_5$: C, 55.1; H, 4.11. Found: C, 55.0; H, 4.32.

3-Methoxy-2-furyl Styryl Ketone.—Isomaltol *O*-methyl ether, 28.0 g. (0.2 mole), was dissolved in ethanol (150 ml.) and distilled water (120 ml.). Benzaldehyde, 21.0 g. (0.2 mole), was added and the solution was cooled to 5°. Sodium hydroxide (10 g. in 30 ml. water) was added while the solution was stirred mechanically. Stirring was continued for 6 hr. at 0°, and the crystals were collected and washed with cold 50% aqueous ethanol. The product was recrystallized from 50% ethanol, yielding 15.5 g. (68%) of pale yellow needles, m.p. 80–82.5°. A sample for analysis was recrystallized twice from 50% ethanol and had m.p. 84–85°.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.7; H, 5.30. Found: C, 73.7; H, 5.41.

3-*p*-Toluenesulfonyloxy-2-furyl Methyl Ketone.—Isomaltol, 6.3 g. (0.05 mole), and *p*-toluenesulfonyl chloride, 10.5 g. (0.055 mole), were dissolved in dry pyridine (100 ml.) at 0°. The solution was kept at room temperature for 72 hr., then the pyridine was removed by distillation at reduced pressure. The residue was taken up in chloroform (100 ml.), extracted with dilute hydrochloric acid, dilute potassium carbonate solution, and distilled water. After drying the chloroform phase over anhydrous magnesium sulfate, the solvent was removed at reduced pressure, and the crude crystals were recrystallized from absolute ethanol, yielding 9.0 g. (64%) of product with m.p. 62–65°. The melting point was raised to 69–70° after one additional recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_{12}O_5S$: C, 55.7; H, 4.31. Found: C, 55.8; H, 4.46.

An attempt to cleave the tosyl ester to 2-furyl methyl ketone by a Kenner desoxygenation was unsuccessful.[44]

3-Methoxy-2-furyl Methyl Ketone Oxime.—The oxime was prepared from isomaltol *O*-methyl ether and hydroxylamine hydrochloride by the method described by Vargha for 2-furyl methyl ketone.[45] The yield was 80% and the melting point was 124–125°.

Anal. Calcd. for $C_7H_9NO_3$: C, 54.2; H, 5.85; N, 9.03. Found: C, 54.7; H, 5.91; N, 9.17.

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