Structure, Relative Conformation, and Synthesis of a Condensed Aromatic Antioxidant from the Acid Hydrolysis of Aminohexose Reductones

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The toxicity of aminohexose reductones, which form in the reactions of aldo- and ketohexoses with various secondary amines and contribute antioxidant properties to animal fats and vegetable oils, instigated the hydrolytic conversion of these compounds into amine-free products. A series of consecutive reactions occurred when these reductones were treated with dilute mineral acid at 25 °C, leading to the formation of C_{12}, C_{22}, and higher polymeric brown products. From either the secondary aminohexose reductones or the first-formed condensed product, [2-hydroxy-2-(2,3-dihydroxy-5-methyl-2-cyclopentenon-5-yl)-4-methyl-4-cyclopentene-1,3-dione], the compound 1,6a,11a(*S*,*R*),11b-tetrahydro-5,7,8-trihydroxy-3,6a(*S*,*R*),10,11b(*R*,*S*)-tetramethyldiindeno[7,1-*bc*:2,1-*e*]pyran-2,11-dione was formed in 25% yield. Ultraviolet, infrared, mass fragmentation, and ^{13}C and ^{1}H nuclear magnetic resonance spectra suggested a structure for the compound, and chemical evidence (alkaline hydrolysis, reduction, and dehydration reactions) supported the assignment. Confirmation of the structure was shown by dimerization of 4,5-dihydroxy-3,7-dimethyl-1*H*-indenone in dilute mineral acid to the diindenopyran. Also, dimerization produced the new pentacyclic ring system when 4,5-dihydroxy-3,6-dimethyl-1*H*-indenone was treated similarly. Preliminary X-ray analysis data showed that the 6a-methyl, 11a-proton, and 11b-methyl groups are in a cis-syn, cis-gauche arrangement.

The lipids in Maillard-browned foods are known to resist autoxidation better than those in unbrowned ones. Because only a few of the antioxidants have been identified, further product identifications are important for economic and nutritional reasons. Several antioxidants formed in model Maillard browning reactions were shown to be the antioxidant aminohexose reductones **1**[2-4] (Chart I); later, reductone **1a** was identified in a thermally induced browning reaction of 1-deoxy-1-piperidino-D-fructose.[5] The reductones **1a–c** possess excellent antioxidant properties in animal fats and vegetable oils,[6,7] but several deficiencies are inherent in these compounds and their anhydro derivatives. They are teratogenic to rats,[7,8] are decomposed in solution to form melanoidin-like polymers, and are destroyed at temperatures used for oil deodorization.[6] To improve the utility of these antioxidants, we undertook removal of the amine moiety; treatment in mineral acid (4 N HCl) did not yield the nonnitrogenous derivative but led to a 12-carbon reductone-like antioxidant (**2**)[9] and a 22-carbon compound with antioxidant properties.[10] Although phenols have been shown to form in trace amounts under rigorous conditions (high temperatures and extended reflux times) from glucose,[11] the phenol isolated in this study, with all carbons derived from the sugar, formed in very high yield at room temperature. Because polymers are also found in the same reaction, the chemistry of formation and identification of this antioxidant may provide clues to the production of melanoidins in processed foods.

Table I. Antioxidant Activity of Various Maillard-Browning Compounds[a]

compd	ratio rel to BHT[b,c]	compd	ratio rel to BHT[b,c]
BHA[c]	1.69	**3a**	0.66
1a[d]	0.94	propyl gallate	0.56
2	0.75		

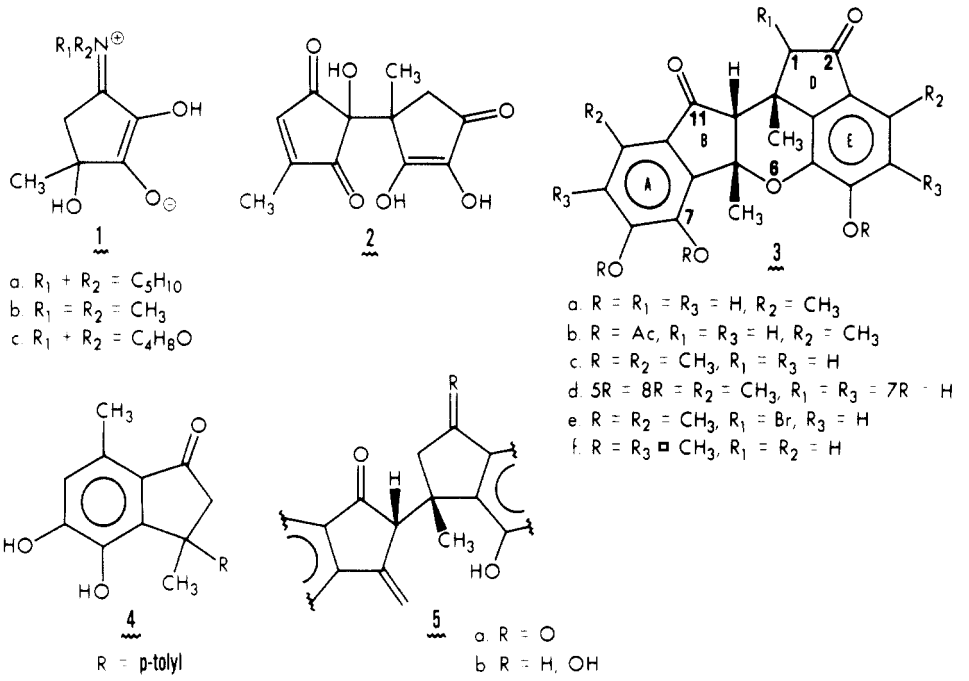
[a] Antioxidant free safflower oil was oxidized in the presence of a hemoglobin catalyst.[12,13] [b] Reaction time ratio: time required to remove 25% of the oxygen from the reaction. [c] BHT = butylated hydroxytoluene, BHA = butylated hydroxyanisol. [d] Piperidinohexose reductone.

The comparative antioxidant properties of **1a**, **2**, and **3a** are listed in Table I. On an equimolar basis, the example aminohexose reductone was nearly as active as butylated hydroxytoluene while the 12-carbon (**2**) and 22-carbon (**3a**) compounds were intermediate between propyl galate and piperidinohexose reductone.

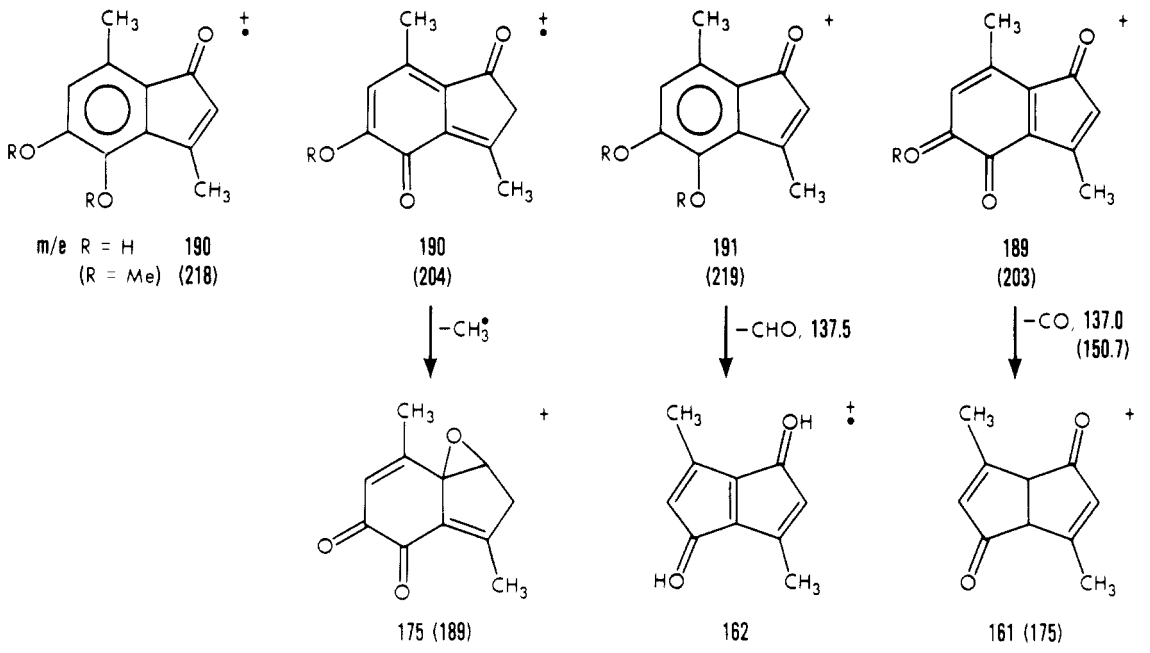
The infrared spectrum of **3a** showed it to be polyhydric (3400–3200 cm^{-1}, br) and to possess an aryl ketone (1678 cm^{-1}, s). These assignments were confirmed when **3a** was converted to a tri-*O*-methyl ether with disappearance of the hydroxyl band and the shift of the ketone to 1690 cm^{-1}. The ultraviolet maxima for the nonreductone were very intense [214 nm (ϵ 16 600), 238 (23 000), 283 (12 300), and 310 (4160)] and indicated a highly conjugated chromophore; furthermore, the absorbances at 238 and 310 nm undergo a bathochromic shift to 256 and 330 nm, respectively, in aqueous sodium hydroxide solution, and the absorbance at 283 shifts to 270 nm. The two different types of shifts indicate conflicting structural assignments for the hydroxyls; ortho- and meta-substituted phenols

(1) The mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products not mentioned.
(2) J. E. Hodge and C. E. Rist, *J. Am. Chem. Soc.*, **75**, 316 (1953).
(3) J. E. Hodge and B. E. Fisher, *Chem. Eng. News*, **32**, 1436 (1954).
(4) F. Weygand, H. Simon, W. B. Bitterlich, J. E. Hodge, and B. E. Fisher, *Tetrahedron*, **6**, 123 (1959).
(5) F. D. Mills, B. G. Baker, and J. E. Hodge, *Carbohydr. Res.*, **15**, 205 (1970).
(6) (a) J. E. Hodge and C. D. Evans, U.S. Patent 2 806 794 (1957). (b) C. D. Evans, H. A. Moser, P. M. Cooney, and J. E. Hodge, *J. Am. Oil Chem. Soc.*, **35**, 84 (1958).
(7) A. M. Ambrose, D. J. Robbins, and F. deEds, *Proc. Soc. Exp. Biol. Med.*, **106**, 656 (1961).
(8) W. Cutting, A. Furst, D. Read, G. Read, and H. Parkman, *Proc. Soc. Exp. Biol. Med.*, **104**, 381 (1960).
(9) F. D. Mills, J. E. Hodge, W. K. Rohwedder, and L. W. Tjarks, *J. Org. Chem.*, **38**, 2512 (1973).
(10) F. D. Mills, J. E. Hodge, and L. W. Tjarks, Abstracts, 178th National Meeting of the American Chemical Society, Washington, DC, Sept 1979, No. CARB 75.
(11) K. Olsson, P.-A. Pernemaln, and O. Theander, *Acta Chem. Scand., Ser. B*, **B32**, 249 (1978).
(12) D. L. Berner, J. A. Conte, and G. A. Jacobson, *J. Am. Oil Chem. Soc.*, **51**, 292 (1974).
(13) W. M. Cort, *Food Technol.*, **28**, 60 (1974).

Chart I



Scheme I



shift to longer wavelengths (red shift) while *p*-hydroxy phenols move to lower wavelengths (blue shift).[14] The presence of an ortho-substituted phenol was indicated by a positive test with Tillmans' reagent [(2,6-dichloroindolyl)phenol].[15]

The proton magnetic resonance spectrum of **3a** indicated four methyl groups (two aliphatic, δ 2.10 and 1.52, and two aromatic, δ 2.30 and 2.26), a methine (δ 2.98), two methylenes (δ 4.58 and 2.42), and two coupled aromatic hydrogens (ortho to the ring methyls δ 6.55 and 6.62). The large coupling constant (18 Hz) of the methylene protons indicates they are situated between a carbonyl group and a chiral center or a second carbon with sp^2 bonding.[16] The isolated methylene moiety was confirmed by decoupling experiments. The presence of three *O*-methyl groups was shown by the center of the three chemical shifts at δ 3.88. Consequently, the remaining oxygens were present as carbonyls and an ether or as a carbonyl and two ethers. The ^{13}C proton-decoupled spectrum of the ether derivative indicated the latter choice. The spectrum consists of 25 lines: two carbonyl carbon signals (observed furthest downfield); 12 aromatic resonances, the two highest field ones being doublets before decoupling; a quaternary carbon signal (no previous splitting); a methine-containing carbon signal (a doublet previously); three methyl signals for the *O*-methyl ethers; a methylene carbon signal (previous triplet); a second quaternary carbon signal upfield; four

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(16) C. H. Depuy, C. E. Lyons, and C. B. Rodewald, *J. Chem. Eng. Data*, 11, 102 (1966).

Table II. Electron Impact Mass Fragmentation

compd	m/e (relative intensity)
3a	380 (5), 191 (35), 190 (100), 189 (16), 175 (16), 162 (16), 161 (27), 147 (13), 119 (12), 115 (11), 91 (17), 79 (7), 77 (6)
3b[a]	464 (10), 275 (27), 274 (16), 233 (56), 232 (25), 191 (70), 190 (100), 162 (15), 161 (11), 43 (54)
3c	422 (27), 407 (11), 219 (39), 218 (100), 205 (30), 204 (67), 203 (14), 176 (6), 175 (9), 161 (3), 133 (4)
3d	408 (14), 219 (6), 218 (16), 206 (9), 205 (71), 204 (100), 189 (6), 176 (7), 175 (5), 161 (6), 133 (5)
3e	502 (5), 500 (5), 422 (8), 421 (6), 220 (4), 219 (28), 218 (100), 204 (26), 203 (30), 175 (15), 161 (4), 115 (5), 85 (6), 83 (24), 82 (11), 80 (11)
3f	422 (43), 407 (2), 219 (29), 218 (100), 205 (45), 204 (83), 203 (14), 176 (12), 175 (18), 161 (6), 148 (9), 133 (4)
4	282 (68), 267 (51), 239 (12), 191 (20), 190 (100), 178 (6), 162 (11), 152 (4), 119 (5), 117 (4), 115 (7), 105 (4), 91 (11)
5a	422 (35), 407 (5), 220 (6), 219 (29), 218 (100), 206 (10), 205 (47), 204 (57), 203 (21), 189 (14), 176 (8), 161 (8), 156 (6), 133 (7), 77 (7)
5b	424 (21), 406 (7), 236 (16), 235 (31), 234 (85), 221 (59), 220 (69), 219 (60), 218 (81), 206 (66), 205 (100), 203 (44), 193 (17), 189 (40), 177 (40), 176 (37), 175 (39), 149 (49), 115 (36)
6	426 (2), 408 (19), 393 (6), 392 (8), 391 (24), 390 (85), 375 (27), 220 (18), 219 (11), 205 (19), 204 (14), 203 (19), 202 (33), 191 (13), 190 (41), 189 (61), 115 (15), 86 (44), 85 (71), 84 (77), 83 (100)
7	390 (100), 375 (30), 218 (5), 203 (7), 202 (10), 189 (13), 173 (5), 149 (81), 119 (5)
8	408 (34), 393 (10), 391 (13), 390 (38), 375 (15), 360 (4), 279 (42), 220 (27), 219 (26), 205 (29), 204 (14), 203 (27), 202 (36), 191 (19), 190 (61), 189 (100), 175 (11), 174 (12), 173 (15), 149 (25), 129 (13), 113 (12), 112 (14), 69 (19)

[a] No parent ion.

methyl signals, two aromatic and two aliphatic (all four were quartets before decoupling).

Analytical and high-resolution mass spectral analyses show a molecular ion for **3a** at 380 amu with a composition of $C_{22}H_{20}O_6$. Definitive structural information was obtained from some of the fragments (Table II) of **3a** and its per-*O*-methyl derivative **3c**. All ion compositions were verified by high-resolution analyses, and some routes of formation were indicated by appropriate metastable ions (Scheme I).

In the mass spectrum of **3a**, the fragment at *m/e* 190 represents two different halves of the molecule, which result from a retro-Diels–Alder cleavage of the dihydropyran ring. When the tri-*O*-methyl derivative is similarly examined, two peaks are found at *m/e* 218 (a gain of 28 amu) and 204 (a gain of 14 amu) with relative intensities of 100% and 67%. These data suggest the positioning of two hydroxyl groups on one portion of the molecule and one on the other half. Also, the lack of a tetra-*O*-methyl or -acetyl derivative suggests that one oxygen atom is tied into a heterocyclic ring. The peak at *m/e* 191 (**3a**; *m/e* 219, **3c**) represents Diels–Alder cleavage with a proton transfer (McLafferty rearrangement), and the fragment at *m/e* 189 (**3a**; *m/e* 203, **3c**) represents the one that surrendered the proton, before or during cleavage. The intensities of these latter peaks are lower but still significant, because they also indicate a symmetrical or dimeric phenol. An *m/e* 189 ion (AB rings) also is found in the permethyl ether spectrum, and it is assumed to originate from *m/e* 204. The peak at *m/e* 191 loses CO, as shown by the metastable ion at *m/e* 137.5, to yield *m/e* 162. With **3c**, the peak expected at *m/e* 219 is present, but *m/e* 190 is absent, indicating that the interpretation for this route is correct (CO from the benzene nucleus). The fragment at *m/e* 189 (formed from the D/E rings of **3a**) also loses CO (metastable at *m/e* 137.0) to form the *m/e* 161 ion. Examination of the pattern of **3c** shows this route to still exist, as demonstrated by the ion at *m/e* 175 (metastable *m/e* 150.7), again indicating the CO expulsion occurs when an unsubstituted hydroxy group is present. The fragmentation of these two compounds complements the NMR information; together they establish the diindenopyran ring system, leaving only the positional assignment of the aromatic methyl groups in doubt.

In summary, the phenol is a cyclized dimer and has one of its oxygens tied up in a heterocyclic ring; the latter assumption is supported by the lack of formation of any tetra-O-substituted derivatives. The spectral data and the two derivatives **3b** and **3c** established the presence of an ortho-substituted phenol, two carbonyls, an ether joined to a second toluene fragment, a single tertiary carbon, and two quaternary carbons (the one further downfield, on the basis of carbon resonance data, is bonded to a highly electronegative atom).[17]

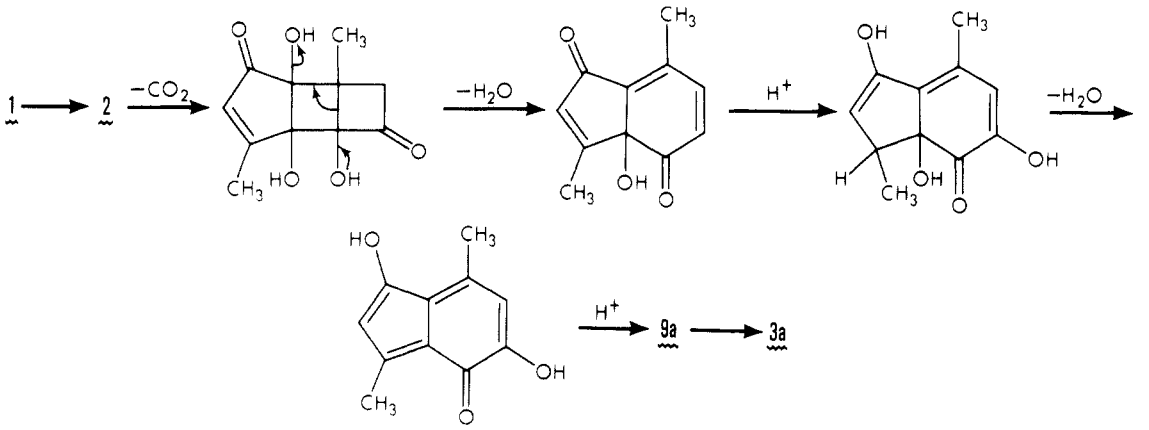
Some chemistries were tried in order to confirm and add to the knowledge of the structure; most did not yield identifiable products. Those that did still did not allow an assignment of the exact structure of the aromatic nuclei, although additional information was obtained that strengthened the diindenopyran assignment. Bromination of **3c** produced **3e**; the position of attack was verified by both proton and carbon-13 nuclear magnetic resonance, and this reaction tended to support the structure assigned to the two carbonyl-containing rings. Partial methylation of **3a** yielded **3d**; the base fragment at *m/e* 204 indicates that rings A and E each contain a single *O*-methyl ether group. The appearance of *m/e* 218, which has a greatly reduced intensity relative to the fragment from **3c**, could originate from the loss of a hydrogen atom and a methyl migration from C(11b) to the B ring during cleavage of the molecule. The lowered intensity also suggests that none of the ions contain two *O*-methyl ether moieties. Also, the ^{1}H NMR shifts for the methyl ether protons at C(5) and C(8) should be nearly alike, and in the pattern for **3d** the expected resonance (upfield assignment) for the C(7) methyl ether is absent.

The isolation of **4** from the reaction of **3c** with aluminum chloride in toluene is significant because its identification supports, chemically, the dimer structure of **3a** and also suggests an intermediate for the synthesis of **3a** or **3c**. Because addition of solvent to 1*H*-indenones was previously observed in the 2-alkylated derivatives,[18] **4** most likely forms via the transient 4,5-dihydroxy-3,7-dimethyl-1*H*-indenone. In this instance, **3c** undergoes demethylation and a retro-Diels–Alder reaction before solvent addition. Aqueous permanganate oxidations yielded

(17) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, 1972, Chapter 3.

(18) M. B. Floyd and G. R. Allen, Jr., *J. Org. Chem.*, **35**, 2647 (1970).

Scheme II

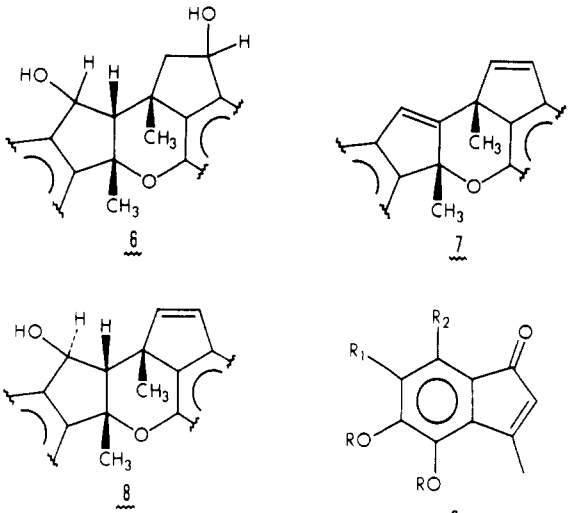


little isolable products from **3c**, but **5a** was isolated in small yield from an alkaline oxidation in *tert*-butyl alcohol. Because the methyl group at C(6a) is destroyed, the isolation of **5a** also allowed the assignment of the carbon-13 chemical shifts for the methyl groups of **3c**; formation of the *exo*-methylene group caused one of the lower field methyls to disappear and, by anology, assignment of the others was made. Finally, the reaction demonstrated that the dihydropyran ring could open easily under alkaline conditions and that isomerization would play a role in other alkaline reactions. When **3c** was treated with lithium aluminum hydride, the expected diol **6** (35%) was isolated (Chart II). Also, the dihydropyran ring opened and produced **5b**. No specificity was observed in reduction of the C(2) carbonyl, but the influence of the chiral center at C(11a) induced a stereospecific reduction, as demonstrated by the large coupling constant (6 Hz) for the vicinal protons in ring B of compound **6**, that produced trans adjacent protons at C(11) and C(11a). As a result, the newly formed hydroxyl group is in a less sterically hindered position. Repeating the reaction and dehydrating the isolate with dimethyl sulfoxide produced **7** and **8**, each being derived from **6**.

Because the physiochemical and chemical reaction studies did not provide sufficient information to establish a complete structure for racemic **3a**, 1,6a(*S*,*R*),11a,11b-tetrahydro-5,7,8-trihydroxy-4,6a(*S*,*R*),9,11b(*R*,*S*)-tetramethyldiindeno[7,1-*bc*:2,1-*e*]pyran-2,11-dione, a total synthesis of the compound was undertaken. The selection of intermediate **9a** was based on the high reactivity of indenones to 1,4 electro- and nucleophilic attack,[18] the isolation of **4**, and the plausible production of **9a** from the hydrolysis of **2**; the latter compound is known to decarboxylate in mineral acids. After oxidation of **2**, which has been shown to form from **1**,[9] a rearrangement and several dehydrations would lead to **9a** (Scheme II). At this time, no reason can be suggested for the specificity of formation of a 3-methyl-1*H*-indenone intermediate in preference to the 2-methyl isomer.

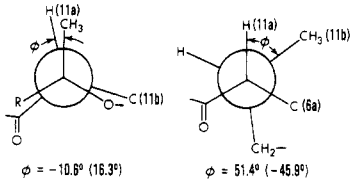
Compound **9a** then would form the dimer by 1,4-addition of the phenol and an intramolecular Michael condensation. Indenone **9a** was prepared from **9b**,[10,19] and the free phenol was self-condensed in dilute mineral acid. After O-methylation, which improved the ease of isolation and chromatographic separation, **3c** was isolated in 25% yield. Its mass spectrum (fragments and normalized intensities) and the nuclear magnetic resonance data are identical with those obtained from the carbohydrate-derived phenol. Additional support for the assigned structure

Chart II



a R = R_1 = H, R_2 = CH_3
b R = Ac, R_1 = H, R_2 = CH_3
c R = Ac, R_1 = CH_3, R_2 = H

is present in the spectral data for the isomeric diidenopyran **3f**. The comparative mass spectra of **3c** and **3f** (Table II) are nearly identical, but the nuclear magnetic resonance data significantly differ so that **3f** could be excluded from consideration. Compound **3c** had aromatic methyl proton resonances at δ 2.43 and 2.47, while those for **3f** are at δ 2.15 and 2.21; the aromatic ring protons for the former are at δ 6.78 and 6.46 and those for latter are at δ 7.09 and 7.02, clearly enough difference for isomer identification. Finally, because the present information is insufficient to indicate a conformational assignment, Drieding models were used to indicate the conformation of carbons 6a, 11a, and 11b. Two preferred arrangements are suggested. One has the B and C rings cis fused with



ϕ = −10.6° (16.3°) ϕ = 51.4° (−45.8°)

the proton at C(11a) anti to the methyl on C(11b); as a result, the molecule would be nearly linear, and the dihydropyran ring would be in the boat form. The second choice also has the A and B rings with a cis fusion, but in this example the C(11a) proton and the C(11b) methyl are in a gauche arrangement. This conformation similarly

(19) F. D. Mills, *J. Org. Chem.*, **46**, 2389 (1981).

produces a dihydropyran ring in the boat form, and this molecule has one aromatic ring bent back toward the other (basketlike); steric and existing electronic effects indicate no preferred configurational arrangement. Following a preliminary report on the diindenopyran structure,[10] a second compound with the former conformation was described.[20] Now, our initial X-ray crystallographic work supports the latter selection (above structures) for **3c**;[21] the complete study will be published at a later date.

With the identification of **3a** and synthesis of it and of **3f**, the acid hydrolysis of aminohexose reductones that produces a reductic acid **2** and a subsequent 1*H*-indenopyran is more fully understood, and a new ring system has been identified and synthesized.[10] The chemistry uncovered also indicates that indenones play a role in polymer formation in nonenzymic browning reactions that are acid catalyzed.

Experimental Section

Melting points were recorded on a Thomas-Hoover Unimelt apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer Model 612 spectrophotometer from solutions in chloroform or from KBr disks. The mass spectra (Table II) were determined with a Nuclide 12-90-DF double-focusing spectrometer at 70 eV, and either a direct or heated inlet (150–200 °C) was used. The ^{1}H NMR spectra were recorded with a Varian HA-100 or XL-100 instrument, employing various sweep widths (50, 100, 500 Hz) in coupling constant determinations. A Bruker WH-90 spectrometer was used to record the ^{13}C NMR spectra, and, as with the proton studies, chloroform-*d* or methanol-d_4, with tetramethylsilane as an internal standard, were the solvents employed. The UV spectra were measured on a Beckmann Model DB recording spectrophotometer from either absolute or 95% ethanolic solutions. The optical rotation was measured on a Beckmann automatic recording polarimeter, Model 1169, from an absolute ethanol solution. In the antioxidant evaluations, the dissolved oxygen was measured with a Gilson Oxygraph, Model K-1C.

Antioxidant Testing. The inhibitory effect of **3a** relative to other antioxidants was measured by using a rapid oxygen uptake method.[12,13] The analysis was modified so that only 2 mL of tocopherol- and peroxide-free safflower oil emulsions were needed. The time for each sample to reach an arbitrary oxygen value, after catalyst addition, was used to relate the effectiveness of each sample. Emulsions were made from 10 g of oil, 89 g of water, and 1 g of Tween 20. Hemoglobin (68 mg 100 mL^{-1}) solutions were made weekly, and the concentration of the antioxidants in ethanol was 0.05 μg μL^{-1}. Each antioxidant (40 μL) was added to 2 mL of emulsion, and then 0.25 μL of catalyst was added. The reaction temperature was maintained at 35 °C, and the oxygen content was measured after 3 min.

***N*-(1-Methyl-1,2,3-trihydroxycyclopent-2-en-4-ylidene)-piperidinium Betaine (N→2 or 3), Piperidinohexose Reductone (1).** Piperidino-, morpholino-, and (*N*,*N*-dimethylamino)hexose reductones were prepared in ethanol from the respective amine and D-glucose.[22]

2-Hydroxy-2-(2,3-dihydroxy-5-methyl-2-cyclopentenon-5-yl)-4-methyl-4-cyclopentene-1,3-dione (2). Compound **1** was used to prepare **2**.[9]

(±)-1,6a,11a,11b-Tetrahydro-5,7,8-trihydroxy-3,6a,10,11b-tetramethyldiindeno[7,1-*bc*:2,1-*e*]pyran-2,11-dione (3a). Piperidinohexose reductone **1a** (106 g) was dissolved in 900 mL of 6 M hydrochloric acid. After filtration, the solution was blanketed with nitrogen, stoppered, and allowed to stand in the dark for 60 days. The precipitate that formed was isolated by filtration and washed with water (75 mL). The solid **3a** (32.4 g) was recrystallized from EtOH: mp 257 °C; 17% yield; IR (KBr disk) 3410–2900 (OH, br), 1675, 1650, 1625, 1590, 1570 (sh) cm^{-1}; UV (EtOH) λ 214 nm (ε 16 590), 238 (23 110), 283 (12 280), 310 (4160); mass of parent ion calcd for $C_{22}H_{20}O_6$ 380.1260, found 380.1247; ^{1}H NMR(CD_3OD) δ 6.56 and 6.42 (2 H, aromatic, pair of doublets, J = 1 Hz), 4.58 (1 H, geminal methylene d, J_{gem} = 18 Hz), 2.98 (1 H, methine s), 2.42 (1 H, geminal d, J_{gem} = 18 Hz), 2.30 (3 H, aromatic methyl), 2.26 (3 H, aromatic methyl), 2.10 [3 H, methyl at C(6a)], 1.52 [3 H, methyl at C(11b)]; $[\alpha]^{23}_D$ +0.01 (EtOH).

Anal. Calcd for $C_{22}H_{20}O_6 \cdot C_2H_5OH$: C, 67.59; H, 6.15. Found C, 67.55; H, 6.22.

Compound **3a** was also produced from **1b** (46–54%, 2 M HCl, 6 months) and **1c** (20%, 0.1 M HCl, 3 months).

Compound 3a from 2. Reductone **2** (0.5 g) was added to 100 mL of 2 M hydrochloric acid. The mixture was covered with nitrogen, the flask was stoppered, and the solution was stirred in the dark for 7 days. Compound **3a** was isolated by filtration, and the precipitate was recrystallized from ethanol to give product **3a**, 40% yield (superimposible ^{1}H NMR, ^{13}C NMR, and mass spectra).

(±)-1,6a,11a,11b-Tetrahydro-5,7,8-triacetoxy-3,6a,10,11b-tetramethyldiindeno[7,1-*bc*:2,1-*e*]pyran-2,11-dione (3b). Diindenopyran **3a** (0.5 g) was dissolved in 12 mL of pyridine containing 3.0 g of acetic anhydride. The resulting solution was heated on a steam bath for 2 h, cooled, and poured onto 120 mL of ice. The precipitate was isolated by filtration and recrystallized from chloroform–hexane and then from ethanol to give 0.59 g of **3b**: mp 206–208 °C; IR (KBr disk) 2910, 1775, 1703, 1600, 1490 cm^{-1}; ^{1}H NMR, δ 7.06 and 6.56 (2 H, aromatic, finely split), 4.10 (1 H, geminal d, J_{gem} = 18 Hz), 2.99 (1 H, methine s), 2.52 (1 H, geminal d, J = 18 Hz), 2.48 (6 H, acetoxy methyl), 2.42 (3 H, acetoxy methyl), 2.32 (3 H, aromatic methyl), 2.26 (3 H, aromatic methyl), 2.06 [3 H, methyl on C(11b)].

Anal. Calcd for $C_{26}H_{26}O_9$: C, 66.26; H, 5.36; CH_3CO, 25.49. Found C, 66.37; H, 5.33; CH_3CO, 25.17.

(±)-1,6a,11a,11b-Tetrahydro-5,7,8-trimethoxy-3,6a,10,11b-tetramethyldiindeno[7,1-*bc*:2,1-*e*]pyran-2,11-dione (3c). Compound **3a** (5 g) was added to 100 mL of anhydrous acetone that contained 5 g of potassium carbonate. The mixture was brought to reflux, and 5 g of methyl iodide was added; after 4 h, an additional 2 g of methyl iodide was added. After an additional reflux of 12 h, the reaction was cooled and filtered. The solvent was then removed (under vacuum), and the residue was crystallized from methanol: 5.4 g; mp 110–111 °C; mass of parent ion calcd for $C_{25}H_{26}O_6$ 422.1720, found 422.1783; ^{1}H NMR δ 6.64 (1 H, aromatic), 6.48 (1 H, aromatic), 4.17 (1 H, methylene d, J_{gem} = 18 Hz), 4.08, 3.87, and 3.75 (9 H, 3 methoxyls), 2.90 (1 H, methine s), 2.46 (1 H, methylene d), 2.44 and 2.40 (6 H, aromatic methyls, J = 0.5 Hz), 2.19 [3 H, C(6a) methyl], 1.52 [3 H, C(11b) methyl]; ^{13}C NMR (carbon number) (C) 203.9 and 201.6 (2 and 11), 158.6, 152.7, 149.5, 146.7, 144.6, 134.7, 132.9, 127.6, 124.9 (2a, 3, 5, 5a, 6b, 7, 8, 10, 10a, 10b), 116.6 and 114.4 (both d, 4 and 9), 85.3 (6a), 63.1 (11a), 61.1, 56.2, 56.0 (OMe), 49.3 (Cl), 37.8 (11b), 29.4 and 28.1 (methyl carbons on 6a and 11b, respectively), 18.5 and 17.5 ppm (methyl carbons on 5 and 10).

Compound **3a** (1.0 g) in 20 mL of methanol was treated with diazomethene (prepared from 3.5 g of *N*-(nitrosomethyl)urea). The reaction was allowed to stand for 12 h. Finally, the solvent was removed and the residue recrystallized from methanol to give 877 mg of **3c**.

Preparation of 3c from 4,5-Diacetoxy-2,3-dihydro-3,7-dimethyl-1*H*-indenone (9b). Indenone **9b** (100 mg) was stirred with 4.47 mL of 0.18 M sodium methoxide in methanol for 30 s under a blanket of nitrogen. The reaction was neutralized with 2×10^{-4} M hydrochloric acid, and the solvent was removed. The residue was taken up in 3 mL of dioxane containing 2 drops of concentrated hydrochloric acid; an additional 6 mL of 2 M hydrochloric acid was added. The reaction mixture was stirred for 132 h in the dark. After neutralization with solid potassium carbonate, the solvent was removed from the mixture by azeotropic distillation with ethanol. The resulting residue was methylated with methyl iodide/potassium carbonate, and the product, 140 mg after filtration and solvent removal, was chromatographed on two 2-mm-thick silica gel preparative plates. Each was developed with 25% (v/v) ethyl acetate in benzene. The zone that chromatographed the same as the standard was removed and extracted with chloroform: 38 mg; 25% yield; mp 257 °C.

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Infrared, ^1H NMR, mass, and ^{13}C NMR spectra were superimposible with those of **3c** that was derived from the aminohexose reductone **1a**.

(±)-7-Hydroxy-5,8-dimethoxy-1,6a,11a,11b-tetrahydro-3,6a,10,11b-tetramethyldiindeno[7,1-*bc*:2,1-*e*]pyran-2,11-dione (3d). Ether **3d** was isolated from the 3-h reaction of **3a** with diazomethane. Preparative thin-layer chromatography on 2.2-mm-thick silica plates (toluene) gave the product: 61 mg (40%); mp 230–232d °C; ^1H NMR δ 6.62 and 6.54 (2 H, aromatic, finely split), 3.94 (3 H, methoxyl), 3.87 (3 H, methoxyl), 3.60 (1 H, methylene d, J_{gem} = 19 Hz), 3.04 (1 H, methine s), 2.55 (1 H, methylene d), 2.46 (3 H, aromatic methyl), 2.42 (3 H, aromatic methyl), 2.06 [3 H, C(6a) methyl], 1.54 [3 H, C(11b) methyl].

(±)-1-Bromo-1,6a,11a,11b-tetrahydro-5,7,8-trimethoxy-3,6a,10,11b-tetramethyldiindeno[7,1-*bc*:2,1-*e*]pyran-2,11-dione (3e). Ether **3c** (30 mg) was dissolved in 20 mL of chloroform. An equimolar amount of bromine in 10 mL of chloroform was added with stirring over 30 min. After 3.5 h, the reaction mixture was extracted once with 5% sodium carbonate and water. The organic phase was separated and dried (sodium sulfate). Subsequent filtration, solvent removal, and crystallization of the crude product yielded **3e**: 28 mg; mp 203–205 °C (chloroform–hexane); IR 2840, 1720 (s), 1695 (vs), 1635, 1600, 1580 cm^{-1}; mass of parent ion calcd for $C_{25}H_{25}BrO_6$ 502.0835, found 502.0829; ^1H NMR δ 6.68 (1 H, aromatic), 6.51 (1 H, aromatic), 6.19 [1 H, C(1) methine], 4.08 (3 H, methoxyl), 3.90 (3 H, methoxyl), 3.76 (3 H, methoxyl), 2.92 [1 H, methine, C(11a)], 2.40 (3 H, aromatic methyl), 2.98 (3 H, aromatic methyl), 2.19 [3 H, methyl at C(6a)], 1.51 [3 H, methyl at C(11b)]; ^{13}C NMR (carbon number) 201.2 and 195.2 (2 and 11), 159.0, 153.1, 146.8, 145.1, 144.7, 139.2, 137.2, 133.7, 126.2, (2a, 3, 5, 5a, 6b, 7, 8, 10, 10a, 11b), 116.9 and 114.8 (both d, 4 and 9), 84.9 (6a), 61.4 (11a), 61.2 (OMe), 58.9d (1), 56.3 (OMe), 56.0 (OMe), 41.4 (11b), 28.3 and 28.0 (6a- and 11b-methyls), 18.5 and 17.6 ppm (methyls on 3 and 10).

(±)-1,6a,11a,11b-Tetrahydro-5,7,8-trimethoxy-4,6a,9,11b-tetramethyldiindeno[7,1-*bc*:2,1-*e*]pyran-2,11-dione (3f). 4,5-Diacetoxy-3,6-dimethyl-1*H*-indenone, (**9c**, 546 mg) was added to 18.3 mL of 0.12 M sodium methoxide in methanol. The workup procedure followed the one used for the dimerization of **3b**.

The isolated chloroform-soluble extract was chromatographed on a 40-g dry-packed silica gel column with 10% ethyl acetate in toluene as the developing solvent; 15-mL fractions were collected, and fractions 22–30 contained **3f**: 67 mg (16% yield); mp 172–174 °C (from ethyl acetate–hexane); IR (KBr disk) 3010, 2938, 2850, 1688, 1625, 1595, 1575 cm^{-1}; mass of parent ion calcd for $C_{25}H_{26}O_6$ 422.1720, found 422.1670; ^1H NMR δ 7.04 and 6.96 (2 H, aromatic), 4.04 (1 H, methylene d, J_{gem} = 18 Hz), 4.03, 3.98, and 3.80 (9 H, methoxyl), 2.96 (1 H, methine s), 2.48 (1 H, methylene d), 2.19 and 2.17 [6 H, aromatic methyls on C(12) and C(15)], 2.06 [3 H, C(6a) methyl], 1.54 [3 H, C(11b) methyl]; ^{13}C NMR (carbon number) 203.1 and 201.2 (2 and 11), 158.6, 152.3, 150.4, 148.8, 144.3, 141.9, 136.3, 132.5, and 128.5 (two resonances) (2a, 3, 5, 5a, 6b, 7, 8, 10, 10a, 11b, singlets), 119.5 and 118.5 (both d, 4 and 9), 85.9 (6a, s), 62.9 (11a, d), 60.6, 60.3, and 59.7 (methoxyls), 48.7 (1, t), 38.3 (11b, s), 2.92 and 27.9 (methyls on 6a and 11b, both q), 16.9 and 16.3 ppm (methyls on 4 and 9).

(±)-4,5-Dihydroxy-3,7-dimethyl-3-*p*-tolyl-1*H*-indenone (4). Ether **3c** (50 mg) was added to 30 mL of anhydrous toluene that contained 100 mg of aluminum chloride; the mixture was refluxed for 3.5 h. After the mixture cooled, ice and 8 mL of 6 M hydrochloric acid were added. The organic phase was separated and dried (sodium sulfate). Chromatography on a 2-mm-thick silica gel preparative plate, employing 15% ethyl acetate in chloroform as the developing solvent, yielded a single intense zone. The zone was removed and extracted with chloroform: 44 mg; mp 134–136 °C (chloroform–hexane); ^1H NMR, δ 7.15 (2 H, *p*-tolyl aromatic, broadened s), 7.10 (2 H, *p*-tolyl aromatic), 6.78 (1 H, aromatic), 2.88 (1 H, methylene d, J_{gem} = 19 Hz), 2.71 (1 H, methylene d), 2.54 (3 H, tolyl methyl), 2.28 [3 H, C(7) methyl], 1.82 [3 H, C(3) methyl]. When the spectrum was obtained from a benzene solution, the aromatic region contained a broadened multiplet at δ 7.19 and a nine-line pattern centered at δ 6.94. The *p*-tolylmethyl group was present as two singlets at δ 2.10 and 2.02 (3 *h* total) in a 40/60 ratio; the alkyl methyl likewise was split 40/60 into two peaks. This evidence indicated **4** was an enantiomeric mixture.

(±)-2-(2,3-Dihydro-4-hydroxy-3,7-dimethyl-5-methoxy-1*H*-indenonyl)-2,3-dihydro-4,5-dimethoxy-7-methyl-3-methylene-1*H*-indenone (5a). Ether **3c** (300 mg) was added to 4 mL of 2 M sodium hydroxide that contained 0.112 g of potassium permanganate; enough *tert*-butyl alcohol was added to solubilize **3c**. The solution was refluxed, and two additions of permanganate were made (each 0.1 g) 1 h apart; the total reflux time was 4 h. After filtration, the solution was concentrated in vacuo. Water (50 mL) was added, and the solution was acidified (HCl). Two 25-mL extractions with chloroform yielded, after drying (sodium sulfate), 160 mg of oil. The total isolate was applied to two, 2-mm-thick silica gel preparative plates; each was developed with 7/18 (v/v) ethyl acetate–hexane. An intermediate zone containing the major component was removed, and the organic component was isolated by extraction with ethyl acetate in a Soxhlet apparatus and gave 66 mg of **5a** (the product did not crystallize): IR 1590, 1615, 1600 cm^{-1}; ^1H NMR($CDCl_3$–C_6H_6) δ 6.44 (2 H, aromatic), 6.10 (1 H, *exo*-methylene m, decoupling showed proton coupled to methine at position 2 and methylene protons, J = 1 Hz), 5.84 (1 H, hydroxy, br), 4.50 (1 H, *exo*-methylene), 4.05 [1 H, methine at C(2)], 3.62, 3.54, and 3.52 (9 H, methoxyls), 2.62 and 2.57 (6 H, aromatic methyls), 2.31 [1 H, C(2) methylene d, J_{gem} = 18 Hz], 2.08 [1 H, C(2) methylene d], 1.98 [3 H, methyl at C(11b)]; ^{13}C NMR (carbon number) 205.2 and 203.4 (2 and 11), 157.9, 146.4, 142.3, 140.2, 139.9, 135.8, 131.3, 128.7, and 127.9 (aromatic), 115.6 (d, aromatic), 115.6 (t, *exo*-methylene), 112.8 (d, aromatic), 59.5 (d, 2), 56.5, 56.4, and 55.4 (methoxyls), 47.6t (1), 44.3 (s, 3), 24.9 (q, methyl on 3), 18.6 and 18.1 ppm (aromatic C-methyls).

2-(2,3-Dihydro-1,4-dihydroxy-3,7-dimethyl-5-methoxy-1*H*-indenyl)-2,3-dihydro-4,5-dimethoxy-7-methyl-3-methylene-1*H*-indenone (5b). This compound was a coproduct in and was isolated from the reaction of **3c** with lithium aluminum hydride that yielded **6**. Indenone **5b** was isolated from the slower moving zone: 28 mg; mp 152–155 °C; ^1H NMR 6.50 (2 H, aromatic), 5.98 (1 H, *exo*-methylene, broadened t, becomes a doublet when the other methylene proton is irradiated), 5.78 [1 H, C(1) hydroxyl], 4.40 (1 H, *exo*-methylene, broadened t), 3.92 (3 H, methoxyl), 3.91 [1 H, center of C(2) methine, m], 3.86 (3 H, methoxyl), 3.56 (3 H, methoxyl), 2.95 (3 H, aromatic methyl), 3.50 (3 H, aromatic methyl), 2.11 [2 H, center of C(2) methylene m], 1.70 [3 H, C(3) methyl].

2,11-Dihydroxy-1,6a,11a,11b-tetrahydro-5,7,8-trimethoxy-3,6a,10,11b-tetramethyldiindeno[7,1-*bc*:2,1-*e*]pyran (6). Compound **3c** (210 mg) was added to a 10% equivalent excess of lithium aluminum hydride in 30 mL of anhydrous tetrahydrofuran. The resulting mixture was refluxed for 3 h. After the mixture cooled, ice–water and dilute sulfuric acid were added, and then the mixture was extracted with ether. The combined ether extract was dried (sodium sulfate) and concentrated to a light oil. Preparative thin-layer chromatography on silica gel, using 15% ethyl acetate in benzene (v/v), yielded two major zones. Removal of the faster moving organic component with chloroform produced **6**: 74 mg (35%); mp 120–122 °C; ^1H NMR δ ($CDCl_3$–C_6D_6), 6.60 and 5.38 (2 H, aromatic), 5.22 [1 H, C(2) methine finely split and broadened t], 4.71 [1 H, C(11) methine br d, J_{vic} = 6 Hz], 4.02, 3.79, and 3.61 (9 H, methoxyls), 2.54 [2 H, center of seven line pattern, C(1) methylene], 2.30 [3 H, C(6a) methyl], 2.20 and 2.12 (6 H, aromatic methyl), 1.40 [3 H, C(11b) methyl].

(±)-6a,11b-Dihydro-5,7,8-trimethoxy-3,6a,10,11b-tetramethyldiindeno[7,1-*bc*:2,1-*e*]pyran (7). Compound **3c** (100 mg) was added to ether containing 10% THF (30 mL). A 10% excess of lithium aluminum hydride was carefully added, and the mixture was refluxed for 3 h. After the usual workup, the light oil was mixed with 2.5 mL of dimethyl sulfoxide, and the solution was heated at 115 °C for 2 h. The cooled mixture was then added to 50 mL of ice–water. The aqueous solution was extracted with chloroform once, and the extract was worked up to yield 75 mg of oil. The isolate was applied to a 2-mm-thick silica gel preparative plate and was then developed with 15% ethyl acetate in benzene (v/v). Two major zones were present after chromatography. After removal of the organic components, the faster moving zone contained **7**: 59 mg (oil); ^1H NMR δ 6.68 (1 H, vinyl d, J = 5 Hz), 6.62 (1 H, vinyl d), 6.46 (2 H, aromatic), 6.20 (1 H, vinyl s), 4.06, 3.78, and 3.74 (9 H, methoxyls), 2.77 [3 H, methyl on C(6a)], 2.12 (6 H, aromatic methyls), 1.61 [3 H, methyl on C(11b)].

11-Hydroxy-6a,11a,11b-trihydro-5,7,8-trimethoxy-3,6a,10,11b-tetramethyldiindeno[7,1-*bc*:2,1-*e*]pyran (8). Compound 8 was isolated as a coproduct with 7 in the reduction and subsequent dehydration of **3c**. This product was isolated from the slower moving zone in the preparative thin-layer chromatographic separation: 16 mg (oil); ^{1}H NMR δ 6.77 (1 H, olefinic, J = 6 Hz), 6.54 (1 H, aromatic), 6.52 (1 H, olefinic), 6.38 (1 H, aromatic), 4.02 (3 H, methoxyl), 3.78 (3 H, methoxyl), 3.68 [1 H, C(11) methine d, J = 6 Hz], 3.63 (3 H, methoxyl), 2.82 [1 H, C(11a) methine d, J = 6 Hz], 2.29 (3 H, aromatic methyl), 2.22 (3 H, aromatic methyl), 2.10 [3 H, methyl at C(11b)], 1.46 [3 H, methyl at C(6a)].

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Registry No. 1a, 39994-32-6; **1b**, 78018-35-6; **1c**, 39994-33-7; **2**, 78004-33-8; **3a**, 78004-34-9; **3b**, 78004-35-0; **3c**, 78004-36-1; **3d**, 78004-37-2; **3e**, 78004-38-3; **3f**, 78018-36-7; **4**, 78004-39-4; **5a**, 78018-37-8; **5b**, 78018-38-9; **6**, 78004-40-7; **7**, 78004-41-8; **8**, 78004-42-9; **9b**, 77028-56-9; **9c**, 77028-54-7; propyl gallate, 121-79-9.

Nucleosides. 120. Syntheses of 2′-Deoxy-ψ-isocytidine and 2′-Deoxy-1-methyl-ψ-uridine from ψ-Uridine[1]

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2′-Deoxy-ψ-isocytidine (**9**, R = H) and 2′-deoxy-1-methyl-ψ-uridine (**6**), *C*-nucleoside isosteres of deoxycytidine and thymidine, were synthesized by two different procedures. Treatment of ψ-uridine (**1**) with α-acetoxyisobutyryl chloride gave a mixture containing the 2′-chloro-2′-deoxyribosyl (**2**) and 3′-chloro-3′-deoxyxylosyl (**3**) *C*-nucleosides. After hydrodehalogenation of the mixture with n-Bu_3SnH, a mixture was obtained from which 2′-deoxy-ψ-uridine (**4**) and its 3′-deoxy isomer **5** were isolated. Compound **4** was converted into 2′-deoxy-1-methyl-ψ-uridine (**6**) by trimethylsilylation followed by treatment with methyl iodide. The mixture containing **4** and **5** was directly treated with DMF dimethyl acetal. 2′-Deoxy-1,3-dimethyl-ψ-uridine (**7**) and the 3′-deoxy analogue (**8**) were obtained from the mixture. Treatment of **7** with guanidine gave an α,β mixture of 2′-deoxy-ψ-isocytidine from which the β isomer (**9**, R = H) was isolated in low yield. Compound **8** was converted into 3′-deoxy-ψ-isocytidine (**10**) by treatment with guanidine. In the second procedure, **1** was converted into 1-methyl-ψ-uridine (**11**) which was tritylated to **12** and then thiocarbonylated to give the cyclic thionocarbonate **13**. Upon treatment of **13** with n-Bu_3SnH, three products, the 2′,3′-olefinic nucleoside **14**, 2′-deoxy-1-methyl-5′-*O*-trityl-ψ-uridine (**15**), and the 3′-deoxy *C*-nucleoside **16**, were obtained in 18%, 45%, and 25% yields, respectively. De-O-tritylation of **15** and **16** afforded the 2′-deoxy (**6**) and 3′-deoxy (**17**) analogues of 1-methyl-ψ-uridine, respectively, in good yield. Compound **15** was further methylated to 2′-deoxy-1,3-dimethyl-5′-*O*-trityl-ψ-uridine (**18**), and subsequent treatment with guanidine afforded an α,β mixture of the 2′-deoxy-ψ-isocytidine derivatives. The components were readily separated into pure isomers by chromatography. 2′-Deoxy-ψ-isocytidine (**9**, R = H) was obtained in high yield after de-O-tritylation of the β isomer **9** (R = Tr).

ψ-Isocytidine[2,3] was shown to have marked activity against several mouse leukemias that are sensitive or resistant to arabinofuranosylcytosine in vivo as well as in vitro.[4] This *C*-nucleoside is converted into the triphosphate in mouse, P815, and liver cells and incorporated into RNA.[5,6] The radioactivity of ψ-isocytidine-2-^{14}C was also found to be incorporated into the DNA of P815 or of mouse liver cells but to a much lesser extent.[5,6] Phase I clinical studies at this Center, however, showed[7] that ψ-isocytidine caused severe hepatotoxicity in humans.

Recently, we reported[8] the synthesis of the 2′-deoxy analogue of ψ-isocytidine from ψ-uridine. In preliminary tissue culture experiments, this analogue showed growth inhibitory activity against P815 cells. Whereas the growth inhibitory activity of ψ-isocytidine is reversed by cytidine (not by deoxycytidine), the activity of 2′-deoxy-ψ-isocytidine is reversed by deoxycytidine but not by cytidine. In this report, we describe details of our original syntheses of 2′-deoxy-ψ-isocytidine (a 2′-deoxy analogue of antileukemic ψ-isocytidine and also a *C*-nucleoside isostere of deoxycytidine) and 2′-deoxy-1-methyl-ψ-uridine (a *C*-nucleoside analogue of thymidine). We also report herein an alternate and more practical synthesis of these 2′-deoxy-*C*-nucleosides.

ψ-Uridine (**1**, Scheme I) was treated with α-acetoxyisobutyryl chloride[9] or acetylsalicyloyl chloride.[10] An intractable mixture containing the 2′-chloro (**2**) and 3′-chloro (**3**) derivatives was obtained which, without purification, was treated with tri-n-butyltin hydride and 2,2′-azobis(2-methylpropionitrile)[11] in boiling dimethoxyethane. Two products were isolated in crystalline form from the reaction mixture. One of these products (mp 216–217 °C) gave a

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