Synthesis of Degradation Products of 2-(6-Hydroxy-2-methoxy-3,4-methylenedioxyphenyl)-benzofuran

BY ARTHUR F. WAGNER, EDWARD WALTON, ANDREW N. WILSON, JOHN OTTO RODIN, FREDERICK W. HOLLY, NORMAN G. BRINK AND KARL FOLKERS

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Several new compounds were obtained as degradation products from a new substance from yeast during the elucidation of its structure as 2-(6-hydroxy-2-methoxy-3,4-methylenedioxyphenyl)-benzofuran. The structures of these new degradation products were proved by synthesis and are: 1,5-dimethoxy-2,3-methylenedioxybenzene (VII), 5-ethoxy-1-methoxy-2,3-methylenedioxybenzene (IX), 1-ethoxy-5-methoxy-2,3-methylenedioxybenzene (XVII), 2,6-dimethoxy-3,4-methylenedioxybenzoic acid (XXX) and 4,6-dimethoxy-2,3-methylenedioxybenzoic acid ( XXXVIII).

The isolation of a new product from yeast has been described, and its structure has been shown to be 2-(6-hydroxy-2-methoxy-3,4-methylenedioxyphenyl)-benzofuran (I). In the elucidation of this structure, orientation of the substituents on the phenyl ring was determined by synthesis of degradation products. This paper describes syntheses of these new alkoxyalkoxyphenols, alkoxyalkoxybenzoic acids and their derivatives.

1,5-Dimethoxy-2,3-methylenedioxybenzene (VII) was synthesized from 1-methoxy-2,3-methylenedioxybenzene (III). Nitration of III gave 1-methoxy-2,3-methylenedioxy-5-nitrobenzene (IV), which was reduced to 3-methoxy-4,5-methylenedioxyaniline (V). Diazotization of V, followed by hydrolysis of the product, yielded 3-methoxy-4,5-methylenedioxyphenol (VI). Methylation of this phenol gave 1,5-dimethoxy-2,3-methylenedioxybenzene (VII).

The phenol VI also was converted to the ethyl ether, 5-ethoxy-1-methoxy-2,3-methylenedioxybenzene (IX), which in turn was converted to the dibromo derivative, 4,6-dibromo-1,5-dimethoxy-2,3-methylenedioxybenzene (VIII). The identity of VII and VIII with the corresponding degradation products showed the position of all the oxygen atoms and the location of the methylenedioxy group on the phenyl ring of the yeast product.

The phenol VI also was converted to the ethyl ether, 5-ethoxy-1-methoxy-2,3-methylenedioxybenzene (IX), which in turn was converted to the dibromo derivative, 4,6-dibromo-1,5-dimethoxy-2,3-methylenedioxybenzene (X). The identity of IX and X with corresponding degradation products located the position of the free hydroxy group in the yeast product.

The isomeric 1-ethoxy-5-methoxy-2,3-methylenedioxybenzene (XVII) was prepared from ethyl o-vanillin (XI) by the reaction sequence XI → XVII using methods described for the synthesis of the corresponding methyl ether X.

The position of attachment of the benzofuran nucleus to the benzene ring in the yeast product was demonstrated by characterization of 2,6-dimethoxy-3,4-methylenedioxybenzoic acid (XXX) as a degradation product. The structure of XXX was determined by characterization of the product with the yeast product.

(3) Since the completion of this work, the previously unknown 1,5-dimethoxy-2,3-methylenedioxybenzene (VII) was isolated as a degradation product of the isoflavone, tlatlancuayin by P. Crabbe, P. R. Leeming and C. Djerassi, THIS JOURNAL, 80, 5258 (1958). This synthesis confirms the structure of VII as deduced by these investigators and others.
(4) Although the same melting point is reported for the compound VII by both laboratories, the 4,6-dibromo derivative is obtained as an oil by Djerassi and his co-workers and as a crystalline compound (mp. 94-95°) in this laboratory.
(5) A. H. Salway, J. Chem. Soc., 1155 (1909) prepared both IV and V from 3-methoxy-4,5-methylenedioxybenzaldehyde (XIX) and determined the orientation of substituents.
(6) An alternative route to XVII would be by way of 2,3-methylenedioxy-5-nitrophenol. A. H. Salway, J. Chem. Soc., 1155 (1909) reported that this phenol was obtained by cleavage of the methoxyl group in 1-methoxy-2,3-methylenedioxy-5-nitrobenzene with aqueous ethanolic potassium hydroxide. We found, however, that the methylenedioxy group, not the methoxyl group, was cleaved under these conditions. Apparently an attack by ethoxide ion at the carbon atom para to the nitro group results in cleavage of the methylenedioxy group and entry of an ethoxyl group at the site of attack. On this basis, the product is 2-ethoxy-3-hydroxy-1-methoxy-5-nitrobenzene (XX).
was proved by synthesis. When 2-methoxy-3,4-methylenedioxybenzoic acid (XXXII) (croweac acid) was nitrated, 2-methoxy-3,4-methylenedioxy-6-nitrobenzoic acid (XXXIV) was obtained. The position of the nitro group was established by (i) consideration of the directive influence of the methylenedioxy group on aromatic substitution, (ii) reduction of the nitroacid XXXIV and subsequent decarboxylation to 3-methoxy-4,5-methylenedioxyaniline (V) and (iii) observation that carbonyl stretching frequencies throughout this series of compounds are in the region associated with a 6- rather than a 5-substituted benzoic acid ester.

On several attempts at reduction of the nitroacid XXXIV, decarboxylation also took place. In order to minimize this reaction, the acid was esterified prior to reduction and the resulting methyl 2-methoxy-3,4-methylenedioxy-6-nitrobenzoate (XXXV) was reduced catalytically to methyl 6-amino-2-methoxy-3,4-methylenedioxybenzoic acid (XXXVI). This amine was characterized by acetylation to methyl 6-acetamido-2-methoxy-3,4-methylenedioxybenzoate (XXXVII). Diazotization of the amine XXXVI and then hydrolysis gave methyl 6-hydroxy-2-methoxy-3,4-methylenedioxybenzoate (XXXVIII). Methylation of the phenol XXXVIII in alkaline solution gave methyl 2,6-dimethoxy-3,4-methylenedioxybenzoate (XXXIX), which was hydrolyzed in hot alkaline solution to 2,6-dimethoxy-3,4-methylenedioxybenzoic acid (XXX).

In the course of this work, an isomeric acid, 4,6-dimethoxy-2,3-methylenedioxybenzoic acid (XXXII), was also synthesized. When 4-methoxy-2,3-methylenedioxybenzoic acid (XXXI) was nitrated, 4-methoxy-2,3-methylenedioxy-6-nitrobenzoic acid (XXXII) was obtained. The orientation of the substituents of XXXII is based on the fact that (i) heating at 200-250°C at atmospheric pressure yields the decarboxylated product 1-methoxy-2,3-methylenedioxy-5-nitrobenzene (IV) in about 15% yield and (ii) the carbonyl stretching frequencies of successively derived compounds are in the region associated with a 6- rather than a 5-substituted benzoic acid ester. The nitroacid XXXIII was esterified to methyl 4-methoxy-2,3-methylenedioxy-6-nitrobenzoate (XXXIII). Reduction of the nitroester XXXIII gave the amine, methyl 6-amino-4-methoxy-2,3-methylenedioxybenzoate (XXXIV), which was further characterized by acetylation to methyl 6-acetamido-4-methoxy-2,3-methylenedioxybenzoate (XXXV). When methyl 6-amino-4-methoxy-2,3-methylenedioxybenzoate (XXXIV) was diazotized and then hydrolyzed in steam, methyl 6-hydroxy-4-methoxy-2,3-methylenedioxybenzoate (XXXV) was obtained. Treatment of the phenol XXXV with alkali and dimethyl sulfate unexpectedly gave a mixture of products containing little or no methylated product.

The synthesis of 4,6-dimethoxy-2,3-methylenedioxybenzoic acid (XXXVIII) finally was accomplished when 1,5-dimethoxy-2,3-methylenedioxybenzene (VII) was brominated to 1-bromo-4,6-dimethoxy-2,3-methylenedioxybenzene (XXXVII), which after treatment with n-butylthium followed by carbonation, gave 4,6-dimethoxy-2,3-methylenedioxybenzoic acid (XXXVIII).

These various compounds were prepared in other attempts to synthesize 2,6-dimethoxy-3,4-methylenedioxybenzoic acid (XXX). When 3-


(9) For a discussion of the role of the methylenedioxy group in orientation of aromatic substituents, see R. T. Arnold and P. Bondwell, THIS JOURNAL, 1942.


(11) The orientation of the substituents of this acid rests upon the orientation of the substituents of the nitro compound XXIV and the fact that no migrations would be predicted in the series of transformations (from nitro group to methyl ether). In further support of this structure, it should be noted that the only other orientation possible from this reaction sequence would be that of acrylic acid (2,5-dimethoxy-3,4-methylenedioxybenzoic acid). That the product was not acrylic acid was established by melting points and infrared spectra.

(12) The orientation of the bromo compound XXXVII is based upon the orientation of the acid XXXVIII. The orientation of the acid XXXVIII is determined by the fact that of the two possible products of the reaction, one had already been prepared from croweac acid (above). Since this product is not the same, it follows that its structure is 4,6-dimethoxy-2,3-methylenedioxybenzoic acid.
methoxy-4,5-methylenedioxyaniline (V) was brominated with one equivalent of bromine in the presence of hydrogen bromide, a mixture of products was obtained, and 2-bromo-3-methoxy-4,5-methylenedioxyaniline (XXXIX) was isolated by chromatography. Location of the halogen was accomplished by reductive diazotization to give 1-bromo-2-methoxy-3,4,5-methylenedioxybenzene (XL). Metallation of XL with n-butyllithium and then carbonation gave the known crocuse acid (XXIII).

1-Acetamido-3-methoxy-4,5-methylenedioxybenzene (XL) was prepared by the acetylation of 1-acetamido-2-bromo-3-methoxy-4,5-methylenedioxybenzene (XLII). The position of the halogen was established by identity of the product with the acylation product of 2-bromo-3-methoxy-4,5-methylenedioxyaniline (XXXIX).

Both 3-methoxy-1,5-methylenedioxy-1-trifluoromethylbenzene (XLIII) and its corresponding 2-bromo derivative XLIV and 1-carbobenzyloxy-amino -3-methoxy-4,5-methylenedioxybenzene (XLV) and its 2-bromo derivative XLVI were prepared in a similar manner. The orientation of the bromo substituent in XLIV and XLVI was based on analogy with the bromoaacetamido compound XLII.

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Experimental

1-Methoxy-2,3-methylenedioxy-5-nitrobenzene (IV).—Twelve grams of 1-methoxy-2,3-methylenedioxybenzene (III) was added dropwise to 95 ml. of cold, stirred, concentrated nitric acid. A few minutes after the addition was complete, 900 ml. of ice-water was added, and the product (12.8 g., m.p. 130-141°) was filtered and washed with water. Recrystallization of the product from 400 ml. of ethanol gave 10.5 g. (98%) of 1-methoxy-2,3-methylenedioxy-5-nitrobenzene, m.p. 145-146°.


2-(3-Ethoxy-3-or 2)-hydroxy-1-methoxy-5-nitrobenzene (XX).—A suspension of 500 mg. of 1-methoxy-2,3-methylenedioxy-5-nitrobenzene (IV) in 22 ml. of 10% ethanolic potassium hydroxide and 3 ml. of water was heated at 55-60° under nitrogen for 1 hour. The reaction mixture was diluted with 50 ml. of water and was filtered. The filtrate was acidified, concentrated under reduced pressure, and extracted with ether. Concentration of the ether extract yielded 3.11 mg. of (2 or 3)-ethoxy-3-(or 2)-hydroxy-1-methoxy-5-nitrobenzene, m.p. 101°. A sample, recrystallized from water and sublimed at 110-120° (0.5 mm.), melted at 101-102°.


3-Methoxy-4,5-methylenedioxyaniline (V).—A suspension of 3 g. (26 minutes) of 1-methoxy-2,3-methylenedioxy-5-nitrobenzene (IV) in 200 ml. of methanol (containing 1 g. of anhydrous hydrogen chloride) was shaken at room temperature in an atmosphere of hydrogen in the presence of 9 g. of catalyst (5% palladium-on-Debro). The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in water, the solution was neutralized with alkali, and the product was isolated by extraction with three 150-ml. portions of ether. After the combined ether extracts had been dried and concentrated, 3.9 g. of product, m.p. 78-80°, was isolated. Purification of the product by sublimation at 100-120° (0.3 mm.) yielded 3.4 g. of 3-methoxy-4,5-methylenedioxyaniline, m.p. 78-80°.


3-Methoxy-4,5-methylenedioxyphenol (VI).—A suspension of 1.6 g. (10 moles) of 3-methoxy-4,5-methylenedioxyaniline (V) in 50 ml. of water was cooled to 0°. The mixture was acidified with 8 ml. of 5 N sulfuric acid, and a solution of 0.7 g. of sodium nitrite in 6 ml. of water was added slowly to the stirred mixture. The unreacted nitrous acid was decomposed by the addition of urea.

The solution of the diazonium sulfate was added dropwise through a jet of steam into a boiling solution of 100 g. of copper sulfate in 100 ml. of water. The aqueous mixture was dissolved in 300 ml. of ether, and the solution was acidified with 12% H₂SO₄. The ether solution was washed with 5% sodium carbonate solution and water. The ether extract was dried and concentrated. Purification of the product by sublimation at 100-120° (0.3 mm.) yielded 3.4 g. of product, m.p. 89-91°.

Anal. Calc'd. for C₁₀H₁₀O₃ (197.17): C, 48.74; H, 3.58; Br, 45.78.

3-Methoxy-4,6-dibromo-5-ethoxy-2,3-methylenedioxybenzene (VIII).—A solution of 63 mg. of 3-methoxy-4,5-methylenedioxyphenol (VI) in 10 ml. of 2 N sodium hydroxide was treated in the course of 30 minutes with five 0.2-ml. portions of dimethyl sulfoxide. The reaction mixture was extracted with two 20-ml. portions of ether. Concentration of the ether extract yielded 44 mg. of product, m.p. 41-42°, which on recrystallization from 2 ml. of petroleum ether yielded 30 mg. of 3,5-dimethoxy-3,5-dimethylenedioxybenzene, m.p. 41-42°.


5-Ethoxy-1-methoxy-2,3-methylenedioxybenzene (IX).—A solution of 63 mg. of 3-methoxy-4,5-methylenedioxyphenol (VI) in 10 ml. of 2 N sodium hydroxide at 50-70° was treated with five 0.2-ml. portions of diethyl sulfate. After 45 minutes, the ether was removed by distillation. Sublimation of the product at 120° (0.3 mm.), followed by recrystallization from petroleum ether, yielded 19 mg. of 4,6-dibromo-5-ethoxy-2,3-methylenedioxybenzene, m.p. 93-94°.


4,6-Dibromo-1,5-dimethoxy-2,3-methylenedioxybenzene (VII).—A solution of 15 mg. of 1,5-dimethoxy-2,3-methylenedioxybenzene (VII) in 0.5 ml. of acetic acid. The solution was cooled and excess bromine was removed by distillation. Sublimation of the product at 120° (0.3 mm.), followed by recrystallization from petroleum ether, yielded 19 mg. of 4,6-dibromo-5-ethoxy-2,3-methylenedioxybenzene, m.p. 41-42°.

of 6% hydrogen peroxide solution in the manner described for the oxidation of o-vanillin.

The distillate (b.p. 80-75° (0.5 mm.)) from 135 g. of product was a mixture of solid and oil, which was washed with petroleum ether to remove the water. Recrystallization of the solid from 75 ml. of benzene–petroleum ether (2:1) yielded 40 g. of pyrogallo-1-ethyl ether, m.p. 95-98°. Five recrystallizations of the product from benzene, followed by vacuum evaporation, raised the melting point to 98-99°.

Found: C, 59.52; H, 5.71.

The titrous acid had been consumed. Successive portions were not added until most of the titrous acid had been consumed. After 15 minutes the reaction mixture was poured onto 311 g. of water and extracted with five 75-ml. portions of chloroform. Concentration of the chloroform solution and distillation of the residual oil (0.75 g.) at 80-110° (0.5 mm.) yielded 150 mg. of distillate, which partially crystallized upon cooling. Three recrystallizations of the product from ether–petroleum ether, followed by sublimation, gave 3-ethoxy-4,5-methylenedioxyphenol, m.p. 81-82°.

Found: C, 63.95; H, 5.53.

1-Ethoxy-5-methoxy-2,3-methylenedioxybenzene (XVII).—Dimethyl sulfate (1 ml.) was added in small portions to a solution of 57 mg. of 3-ethoxy-4,5-methylenedioxyphenol (XVI) in 10 ml. of 2 N sodium hydroxide at room temperature. About 30 minutes after the last addition, the reaction mixture was extracted with ether. Removal of the ether yielded 34 mg. of crude product (m.p. 40-45°), which after sublimation and recrystallization from petroleum ether, gave 1-ethoxy-5-methoxy-2,3-methylenedioxybenzene, m.p. 43-44°.

4,6-Dibromo-1-ethoxy-5-methoxy-2,3-methylenedioxybenzene (XVIII).—A solution of 27 mg. of 1-ethoxy-5-methoxy-2,3-methylenedioxybenzene (XVII) in 0.5 ml. of acetic acid was treated dropwise with bromine in acetic acid until an excess of bromine was present. The acetic acid was removed at reduced pressure, and sublimation of the residue gave 37 mg. of 4,6-dibromo-1-ethoxy-5-methoxy-2,3-methylenedioxybenzene, m.p. 87-89°.

The distillate (2.1) was saturated with sodium chloride and extracted with four 100-ml. portions of ether. Concentration of the product from benzene, followed by vacuum evaporation, raised the melting point to 98-99°.

Anal. Caled. for C6H13BrO3 (217.03): C, 37.70; H, 5.60; Br, 45.40. Found: C, 37.66; H, 5.43; Br, 45.27.

2-Methoxy-3,4-methylenedioxybenzaldehyde (XXI) and 4-Methoxy-2,3-methylenedioxybenzaldehyde (XXII).—Recrystallization of 1-methoxy-2,3-methylenedioxybenzene (XIII) with phosphorous oxychloride and dimethylylmethanethiol (or N-methylformanilide) to 2-methoxy-3,4-methylenedioxybenzaldehyde (XXI) is described in the literature. It was found that the product of 27 g. of X and 4-methoxy-2,3-methylenedioxybenzaldehyde (XXII). These isomers were separated by chromatography.

The solution of 150 g. of reaction product in 60 ml. of benzene was chromatographed on a column (15 x 50 cm.) of acid-washed alumina (7 kg.). Elution with benzene (35.1) gave 63 g. of 2-methoxy-3,4-methylenedioxybenzaldehyde (XXI), m.p. 97-105°. Elution with chloroform (3.3 g., m.p. 117°) was washed with 50 ml. of 2.5 N sodium hydroxide. Concentration of the ether solution of 40 g. of product from benzene, followed by recrystallization from petroleum ether, gave 1-ethoxy-2-methoxy-3,4-methylenedioxybenzaldehyde (XXI), m.p. 118-120°.

Anal. Caled. for C11H12O6 (250.21): C, 47.56; H, 4.80; N, 3.60. Found: C, 47.51; H, 4.65; N, 3.51.

3-Ethoxy-4,5-methylenedioxyaniline (XV).—A suspension of 2.1 g. (10 mmoles) of 1-ethoxy-2,3-methylenedioxy-5-nitrobenzene (XIV) in 2.5 ml. of 2 N hydrochloric acid was treated with hydrochloric acid, 1.02 g. of crookeacic acid, l.l.p. 1.59-1.75, was obtained. The mixture was filtered and the filtrate, oil concentrated under reduced pressure, was washed with 50 ml. of 2.5 N sodium hydroxide. Concentration of the ether solution and distillation of the residue (1.5 g.) at 100-110° (0.5 mm.) yielded 1.1 g. (61%) of 3-ethoxy-4,5-methylenedioxyaniline, m.p. 41-43°. Recrystallization of the product from ether–petroleum ether raised the melting point to 43-44°.

Anal. Caled. for C11H12O6 (250.21): C, 47.56; H, 4.80; N, 3.60. Found: C, 47.51; H, 4.65; N, 3.51.

3-Ethoxy-5-methylenedioxyphenol (XVI).—A solution of 0.4 g. (5.5 mmoles) of sodium nitrite in 10 ml. of water was added to 0.5 ml. portions of sodium bromide to 2-Methoxy-3,4-methylenedioxybenzaldehyde (XXVII) was added. The mixture was filtered and 2.7 ml. of 1 N hydrochloric acid was added from a burette. The mixture was stirred for 30 minutes and then was diluted with 30 ml. of water. The mixture was filtered, dissolved in ether, and washed with aqueous sodium bicarbonate solution. The bicarbonate extracts were acidified to pH 2 with hydrochloric acid. The mixture was extracted three times with ether, and the combined ether extracts were then extracted with ether–petroleum ether to give an aqueous solution of sodium bicarbonate. The bicarbonate extracts were added to pH 2 with hydrochloric acid and 25 mg. of crocetine acid, m.p. 158°, was precipitated.


2-Methoxy-3,4-methylenedioxybenzoic Acid (Crownac Acid) (XXIII). (A) From 1-Bromo-2-methoxy-3,4-methylenedioxybenzene (XII).—A solution of 80 g. (0.4 mmole) of 1-bromo-2-methoxy-3,4-methylenedioxybenzene (XI) in 1.5 ml. of dry ether was cooled to -70°, and 0.4 ml. of a 1 N solution of n-butylithium in ether (0.4 mmole) was added. After 15 minutes the reaction mixture was poured onto 75-80° Dried Ice. Water (5 ml.) was added, and the mixture was acidified to pH 2 with hydrochloric acid. The mixture was extracted three times with ether, and the combined ether extracts were then extracted with ether–petroleum ether to give an aqueous solution of sodium bicarbonate. The bicarbonate extracts were added to pH 2 with hydrochloric acid and 25 mg. of crocetine acid, m.p. 158°, was precipitated.


(B) From 2-Methoxy-3,4-methylenedioxybenzaldehyde (Crownac Aldehyde) (XXIII).—A mixture consisted of 80 g. (0.4 mmole) of 2-methoxy-3,4-methylenedioxybenzaldehyde (XXVII) was added. The reaction mixture was stirred for 10 minutes. The mixture was filtered, and the ether was removed at reduced pressure. After the alkaline solution had been extracted with ether and acidified with hydrochloric acid, 1.02 g. of crocetine acid, m.p. 159-160°, was obtained.

2-Methoxy-3,4-methylenedioxy-5-nitrobenzene (XXIII).—A solution of 80 g. (0.4 mmole) of 4-methoxy-2,3-methylenedioxybenzaldehyde (XIV) in 0.5 ml. of cold concentrated nitric acid was treated dropwise with nitric acid. The reaction mixture was stirred about 10 minutes and then was diluted with 20 ml. of ethanol-water yielding 390 mg. of 2-Methoxy-3,4-methylenedioxy-5-nitrobenzene (XXIII), m.p. 190-192°, was obtained.

Anal. Caled. for C15H15N3O6 (361.30): C, 49.82; H, 3.10. Found: C, 49.76; H, 3.06.


Methyl 2-Methoxy-3,4-methylenedioxy-6-nitrobenzoic Acid (XXV).—Four grams of 2-methoxy-3,4-methylenedioxy-6-nitrobenzonic acid (XXV) was suspended in 100 ml. of ether, and 850 mg. of diazomethane in 50 ml. of ether was added slowly. The excess diazomethane was decomposed with acetic acid, and the ether solution was concentrated under reduced pressure. The residue was dissolved in chloroform, and the solution was washed with aqueous sodium bicarbonate. Concentration of the chloroform solution and recrystallization of the residue (3.9 g.) from methanol yielded 3.6 g. of methyl 2-methoxy-3,4-methylenedioxy-6-nitrobenzoic acid, m.p. 115-117°, \(\text{C}_9\text{H}_7\text{NO}_6\) 5.76 µ.

Anal. Calcd. for \(\text{C}_9\text{H}_7\text{NO}_6\): C, 47.34; H, 3.70; N, 5.49. Found: C, 47.60; H, 4.02; N, 5.59.

Methyl 6-Amino-2-methoxy-3,4-methylenedioxybenzoate (XXVI).—A suspension of 1.5 g. of methyl 2-methoxy-3,4-methylenedioxy-6-nitrobenzoic acid (XXV) and 3 g. of catalyst (5% Pd-on-Darco) in 80 ml. of methanol containing 1 g. of hydrogen chloride was shaken at room temperature in an atmosphere of hydrogen.16 The reaction mixture was filtered, and the methanol solution was concentrated under reduced pressure. The residue was neutralized with aqueous sodium bicarbonate solution; and the product (1 g.), isolated by extraction with ether, was purified by sublimation at 120-130° (0.5 mm.). Recrystallization of the sublimed product from benzene gave 300 mg. of methyl 6-amino-2-methoxy-3,4-methylenedioxybenzoate, m.p. 80-82°, \(\text{C}_9\text{H}_{13}\text{NO}_6\) 5.97 µ.

Anal. Calcd. for \(\text{C}_9\text{H}_{13}\text{NO}_6\): C, 53.33; H, 4.92; N, 5.24. Found: C, 53.31; H, 5.00; N, 5.38.

Methyl 6-Amino-4-methoxy-2-methoxy-3,4-methylenedioxybenzoate (XXVII).—A solution of 60 mg. of methyl 6-amino-2-methoxy-3,4-methylenedioxybenzoate (XXVI) in 1 ml. of pyridine was treated at room temperature with 1 ml. of freshly prepared silver oxide, 18 ml. of ethanol, and 18 ml. of 5% sodium hydroxide for 1 hour. The methanol was removed under reduced pressure, and the solution was acidified to pH 3 with mineral acid. The product (118 mg.) isolated by extraction with chloroform and concentration of the chloroform solution and recrystallization from methanol, raised the melting point to 203-205°, \(\text{C}_9\text{H}_{13}\text{NO}_6\) 5.8-5.84 µ.

Anal. Calcd. for \(\text{C}_9\text{H}_{13}\text{NO}_6\): C, 53.93; H, 4.90; N, 5.47. Found: C, 53.98; H, 4.95; N, 5.54.

Methyl 2-Hydroxy-6-methoxy-2,3-methylenedioxybenzoate (XXVIII).—A suspension of 441 mg. of methyl 6-amino-2-methoxy-3,4-methylenedioxybenzoate (XXVI) in 10 ml. of water was stirred at 0° while 2 ml. of 25% sulfuric acid was added. The solution was treated with a solution of 138 mg. of sodium nitrite in 2 ml. of water. After the excess nitrous acid had been decomposed with urea, the solution was diluted to 30 ml. with water and was added dropwise through a jet of steam into a boiling solution of copper sulfate.

The reaction mixture was cooled and extracted with ether. The ether solution, after being washed with aqueous sodium bicarbonate and concentrated under reduced pressure, yielded a 280-mg. residue. Purification of the product by chromatography on alumina followed by recrystallization from ethanol gave 75 mg. of methyl 2-hydroxy-2,3-methylenedioxy-6,4-methylenedioxybenzoate, m.p. 81-82°, \(\text{C}_9\text{H}_{13}\text{NO}_6\) 5.01 µ. Sublimation of the product, followed by recrystallization from methanol, raised the melting point to 83-84°.

Anal. Calcd. for \(\text{C}_9\text{H}_{13}\text{NO}_6\): C, 53.17; H, 4.49. Found: C, 53.10; H, 4.46.

2,6-Dimethoxy-3,4-methylenedioxybenzoic Acid (XXX).—A solution of 57 mg. of methyl 6-hydroxy-2-methoxy-3,4-methylenedioxybenzoic acid (XXVIII) in 10 ml. of 2 N sodium hydroxide was stirred and treated with 1 ml. of dimethyl sulfate. After about 15 minutes, an additional 10 ml. of 2 N sodium hydroxide and 1 ml. of dimethyl sulfate were added. After 30 minutes the alkaline solution was extracted with ether; and the ether solution, on concentration under reduced pressure, yielded 59 mg. of methyl 2,6-dimethoxy-3,4-methylenedioxybenzoic acid. The rest of the product was an orange diazo compound of unknown structure. Reduction of the acid XXIV in glacial acetic acid using 5% Pd on Darco catalyst gave about 10% of the decarboxylated product, 1-acetamido-3-methoxy-4-methylenedioxybenzene (V) and 10% of 6-amino-2-methoxy-3,4-methylenedioxybenzoic acid. The rest of the product was an orange diazo compound of unknown structure. Reductive amination of XXIV gave a mixture of decarboxylated product, 1-acetamido-3-methoxy-4-methylenedioxybenzene and 6-amino-2-methoxy-3,4-methylenedioxybenzoic acid. A mixture was also obtained from reduction of XXV in the presence of minimal acid. 

(16) Reduction of the acid XXIV in glacial acetic acid using 5% Pd on Darco catalyst gave about 10% of the decarboxylated product, 3-methoxy-4,5-methylenedioxyaniline (VI) and 10% of 6-amino-2-methoxy-3,4-methylenedioxybenzoic acid. The rest of the product was an orange diazo compound of unknown structure. Reductive amination of XXIV gave a mixture of decarboxylated product, 1-acetamido-3-methoxy-4-methylenedioxybenzene and 6-amino-2-methoxy-3,4-methylenedioxybenzoic acid. A mixture was also obtained from reduction of XXV in the presence of minimal acid.
Methyl 6-Hydroxy-4-methoxy-2,3-methylenedioxybenzoate (XXXV).—A suspension of 278 mg. of methyl 6-amino-4-methoxy-2,3-methylenedioxybenzoate (XXXIV) in 9 ml. of 10% hydrochloric acid was added dropwise to a water bath at 50°. The product, a deep yellow solid, was filtered, washed, and dried. The yield was 176 mg. of 6-Hydroxy-4-methoxy-2,3-methylenedioxybenzoic acid, m.p. 140-150°.

Recrystallization of the product from ethanol gave 70 mg. of 6-Hydroxy-4-methoxy-2,3-methylenedioxybenzoic acid, m.p. 160-170°.

Anal. Calcd. for C_{10}H_{10}O_{6}: C, 53.10; H, 4.46.

Found: C, 53.31; H, 4.59.

4,6-Dimethoxy-2,3-methylenedioxybenzoic Acid (XXXVIII).—A solution of 282 mg. (1.6 mmole) of 4,6-dimethoxy-2,3-methylenedioxybenzene (VII) in a mixture of 3 ml. of glacial acetic acid and 1 ml. of carbon tetrachloride was cooled to 0°, and a solution of 250 mg. (1.6 mmole) of bromine in 2 ml. of glacial acetic acid was added over a period of 15 minutes. The solvents were removed at reduced pressure, and the residue was extracted with three 10-ml. portions of boiling petroleum ether (b.p. 30-60°). Concentration of the petroleum ether extract gave 245 mg. (80%) of 1-bromo-4,6-dimethoxy-2,3-methylenedioxybenzene (XXVIII), m.p. 80-85°. A small sample, recrystallized from petroleum ether, melted at 85-89°.

Anal. Calcd. for C_{10}H_{10}BrO (226.18): C, 54.88; H, 4.46; Br, 49.50.

A solution of 100 mg. (0.4 mmole) of 1-bromo-4,6-dimethoxy-2,3-methylenedioxybenzene (XXXVII) in 25 ml. of absolute ether was cooled to -50°, and 0.8 ml. (0.8 mmole) of n-butyllithium in ether was added. After about 10 minutes, the temperature was lowered to -70°, and dry carbon dioxide was passed into the mixture for 5 minutes. The reaction mixture was then allowed to warm up to 0° under an atmosphere of carbon dioxide.

Water was added to the mixture, and the layers were separated. The aqueous phase, after extraction with ether, was cooled to about -15°, and the solution was decanted and poured into ice. The product (780 mg.) was filtered, washed, and dried. Recrystallization of the product from ethanol gave 350 mg.

1-Acetamido-2-bromo-3-methoxy-4,5-methylenedioxybenzene (XXVII).—A solution of 275 mg. of methyl &amino-2-bromo-3-methoxy-4,5-methylenedioxybenzene, m.p. 113-110°, was added to a cooled solution of 440 mg. (2.1 mmole) of trifluoroacetic anhydride in 5 ml. of pyridine. The reaction mixture was kept at room temperature overnight. The mixture was acidified with hydrochloric acid, and the product was extracted with five 10-ml. portions of boiling petroleum ether (b.p. 30-60°). The solution was added to 1 ml. of 25% sulfuric acid and then to 3 ml. of 25% sodium bicarbonate, and concentrated. The residue was extracted with 100 ml. of cold water, was filtered, and concentrated. Recrystallization of the product from ethanol gave 50 mg. (53%) of 1-acetamido-2-bromo-3-methoxy-4,5-methylenedioxybenzene, m.p. 167-168°.

Anal. Calcd. for C_{10}H_{10}BrO (288.11): C, 54.62; H, 4.90; Br, 49.50.

1-Acetamido-2-bromo-3-methoxy-4,5-methylenedioxybenzene (XXVI).—A solution of 334 mg. of trifluoroacetic anhydride in 1 ml. of pyridine was cooled to 0°, and 0.2 ml. of acetamide was added. The solution was kept at room temperature overnight. A few grams of ice was added, and the mixture was acidified with hydrochloric acid. The product (170 mg., 90%), m.p. 160-165°, was filtered, washed, and dried. The melting point of the compound was unchanged on admixture with a sample of 1-acetamido-2-bromo-3-methoxy-4,5-methylenedioxybenzene prepared by bromination of 1-acetamido-3-methoxy-4,5-methylenedioxybenzene.

3-Methoxy-4,5-methylenedioxy-1-trifluoracetamidobenzene (XLIII).—Trifluoroacetic anhydride (2.2 g.) was added to a solution of 584 mg. (3.5 mmole) of 3-methoxy-4,5-methylenedioxybenzene (V) in 9 ml. of pyridine. The reaction mixture, after being kept at room temperature overnight, was poured onto ice, and the product (280 mg.) was filtered. After recrystallization from ethanol and sublimation at 110-120° (0.5 mm.), 370 mg. of 3-methoxy-4,5-methylenedioxy-1-trifluoracetamidobenzene, m.p. 125-126°, was obtained.

Anal. Calcd. for C_{10}H_{10}FNO (293.17): C, 45.62; H, 3.05; N, 5.32. Found: C, 45.12; H, 3.05; N, 5.80.

2-Bromo-3-methoxy-4,5-methylenedioxy-1-trifluoracetamidobenzene (XLIV).—A solution of 150 mg. of bromine in 1 ml. of glacial acetic acid was added dropwise to a solution of 275 mg. of 3-methoxy-4,5-methylenedioxybenzene (XXXVIII) in 2 ml. of pyridine. The reaction mixture, after being kept at room temperature overnight, was poured onto ice, and the product (170 mg.) was filtered. One recrystallization of the product from ethanol gave 70 mg. of 2-bromo-3-methoxy-4,5-methylenedioxy-1-trifluoracetamidobenzene, m.p. 115-116°.
The Polysaccharides of Yellow Birch (Betula lutea). II. The Constitution of the Main Hemicellulose

By T. E. Timell

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The general chemical composition of the wood of yellow birch (Betula lutea) has been determined. Alkaline extraction of the wood yielded a hemicellulose, which on partial hydrolysis gave p-galacturonic acid, glucuronic acid, 4-O-methyl-d-glucuronic acid, and 2-O(4-O-methyl-a-D-glucopyranosyluronic acid)-D-xylopyranose and an aldopenturonic acid. A crystalline tetraacetate of the methyl ester glycolide of the aldobiouronic acid was prepared and fully characterized. Hydrolysis of two fully methylated hemicellulose samples yielded a mixture of 2-O- and 3-O-methyl-D-xylose, 2,3,4-tri-O-methyl-D-glucose and 2,3,4-tri-O-methyl-D-xylopyranose in molar ratios of 3:109:1:11 and 3:89:1:9. The number-average degrees of polymerization of the methylated hemicelluloses were 102 and 81 and that of the original polysaccharide 192. On the basis of this and other evidence it is suggested that this 4-O-methyl-D-glucuronoxylan consists of a linear framework of approximately 190 1,4-linked D-xylopyranose residues, with, on the average, every tenth residue carrying a single, terminal side chain of 4-O-methyl-D-glucuronic acid attached glycosidically to the 2-position of the xylose.

Yellow birch is the most important hardwood species in the northeastern part of this continent, although it has lately suffered severely from attack of birch dieback. In a previous investigation the molecular properties of its cellulose component were dealt with. This paper is concerned with an identification of the uronic acids obtained on partial hydrolysis of the main hemicellulose constituent and with its constitution and molecular weight.

Alkaline extraction of the wood gave a hemicellulose in a yield of 17.5%, somewhat lower than the xylan content of the wood, 20.1%. The sugar mixture obtained on hydrolysis of the hemicellulose was resolved on a column of anion exchange resin to yield D-xylose, which crystallized, two monouronic acids, a mono-O-methyl uronic acid, and an aldopenturonic acid. One of the monouronic acids corresponded on the paper chromatogram to glucuronic acid-glucuronolactone. The other acid was converted to D-galactose, identified through its crystalline 1-methyl-1-phenylhydrazone derivative, and was therefore D-galacturonic acid. The third monouronic acid was identified by reduction if its ester glycoside with lithium aluminium hydride, to 4-O-methyl-D-glucose, characterized as its phenylasazone derivative.

2-Bromo-1-carbobenzyloxyamino-3-methoxy-4,5-methylenedierythrohexybenzene (XLVI).—A solution of 304 mg. of bromine in 2 ml. of acetic acid was added slowly to a solution of 580 mg. (1.9 mmoles) of 1-carbobenzyloxyamino-3-methoxy-4,5-methylenedierythrohexybenzene (XLV) in 4 ml. of acetic acid. The reaction mixture was diluted with water, and the product was filtered. Two recrystallizations from ethanol gave 300 mg. of 2-bromo-1-carbobenzyloxyamino-3-methoxy-4,5-methylenedierythrohexybenzene, m.p. 93-97°.

[Contribution from The Division of Industrial and Cellulose Chemistry, McGill University, and the Wood Chemistry Division, Pulp and Paper Research Institute of Canada]