

[CONTRIBUTION FROM THE MERCK SHARP AND DOHME RESEARCH LABORATORIES, DIVISION OF MERCK AND CO., INC.]

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

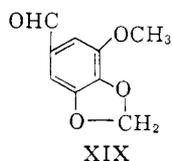
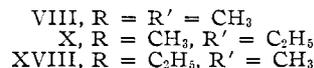
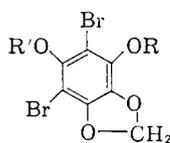
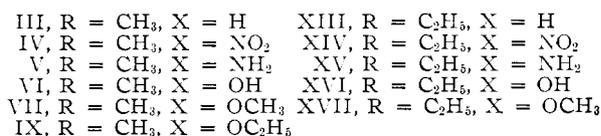
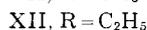
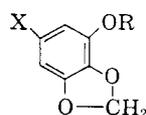
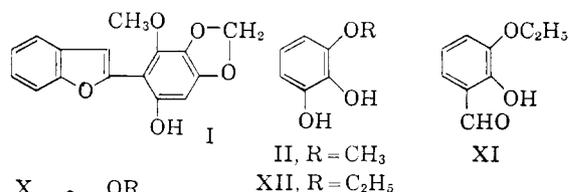
BY ARTHUR F. WAGNER, EDWARD WALTON, ANDREW N. WILSON, JOHN OTTO RODIN,
FREDERICK W. HOLLY, NORMAN G. BRINK AND KARL FOLKERS

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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,¹ and its structure has been shown^{1,2} 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 alkoxy-methylenedioxyphenols, alkoxy-methylenedioxybenzoic acids and their derivatives.

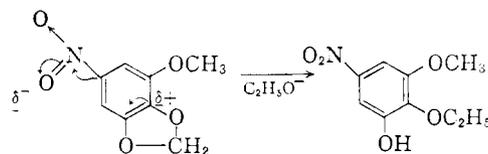
1,5-Dimethoxy-2,3-methylenedioxybenzene (VII) was synthesized³ from 1-methoxy-2,3-methylenedioxybenzene⁴ (III). Nitration of III gave 1-



methoxy-2,3-methylenedioxy-5-nitrobenzene⁵ (IV), which was reduced to 3-methoxy-4,5-methylenedioxyaniline⁵ (V). Diazotization of V, followed by hydrolysis of the product, yielded 3-methoxy-4,5-methylenedioxyphenol (VI).⁶ Methylation of this phenol gave 1,5-dimethoxy-2,3-methylenedioxybenzene (VII).³ Bromination of VII yielded the dibromo derivative, 4,6-dibromo-1,5-dimethoxy-2,3-methylenedioxybenzene (VIII).³ 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.²

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-5-ethoxy-1-methoxy-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.²

The isomeric 1-ethoxy-5-methoxy-2,3-methylenedioxybenzene (XVII)⁷ 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 characterization² of 2,6-dimethoxy-3,4-methylenedioxybenzoic acid (XXX) as a degradation product. The structure of XXX

(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) Since the completion of this work, the previously unknown 3-methoxy-4,5-methylenedioxyphenol (VI) was isolated as a degradation product of the isoflavone tlatlancuayin by P. Crabbé, P. R. Leeming and C. Djerassi, THIS JOURNAL, **80**, 5258 (1958). This synthesis confirms the structure of VI as deduced by these investigators and others.²

(7) 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 methoxy 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).

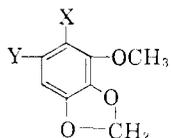
(1) M. Forbes, F. Zilliken, G. Roberts and P. Gyorgy, THIS JOURNAL, **80**, 385 (1958).

(2) M. A. P. Meisinger, F. A. Kuehl, Jr., E. L. Rickes, N. G. Brink and K. Folkers; M. Forbes, F. Zilliken and P. Gyorgy, *ibid.*, **81**, 4979 (1959).

(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. Crabbé, P. R. Leeming and C. Djerassi, THIS JOURNAL, **80**, 5258 (1958). This synthesis confirms the structure of VII as deduced by these workers and others.² 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 (m.p. 94-95°) in this Laboratory.

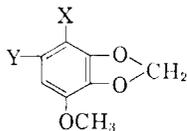
(4) K. N. Campbell, P. F. Hopper and B. K. Campbell, J. Org. Chem., **16**, 1736 (1951).

was proved by synthesis. When 2-methoxy-3,4-methylenedioxybenzoic acid (XXIII) (croweacid acid)⁸ was nitrated, 2-methoxy-3,4-methylenedioxy-6-nitrobenzoic acid (XXIV) was obtained. The position of the nitro group was established by (i) consideration of the directive influence of the methylenedioxy group on aromatic substitution,⁹ (ii) reduction of the nitroacid XXIV 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.¹⁰



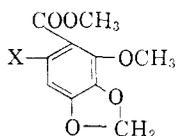
XXI. X = CHO, Y = H

XXIII. X = COOH, Y = H

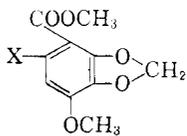
XXIV. X = COOH, Y = NO₂

XXII. X = CHO, Y = H

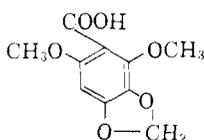
XXXI. X = COOH, Y = H

XXXII. X = COOH, Y = NO₂XXV. X = NO₂XXVI. X = NH₂XXVII. X = NHCOCH₃

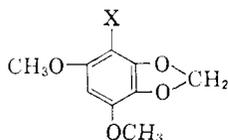
XXVIII. X = OH

XXIX. X = OCH₃XXXIII. X = NO₂XXXIV. X = NH₂XXXV. X = NHCOCH₃

XXXVI. X = OH



XXX



XXXVII. X = Br

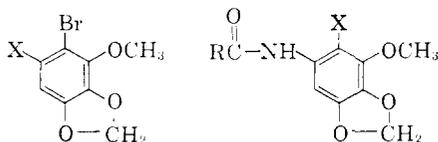
XXXVIII. X = COOH

On several attempts at reduction of the nitro acid XXIV, 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 (XXV) was reduced catalytically to methyl 6-amino-2-methoxy-3,4-methylenedioxybenzoate (XXVI). This amine was characterized by acetylation to methyl 6-acetamido-2-methoxy-3,4-methylenedioxybenzoate (XXVII). Diazotization of the amine XXVI and then hydrolysis gave methyl 6-hydroxy-2-methoxy-3,4-methylenedioxybenzoate (XXVIII). Methylation of the phenol XXVIII in alkaline solution gave methyl 2,6-dimethoxy-3,4-

methylenedioxybenzoate (XXIX), which was hydrolyzed in hot alkaline solution to 2,6-dimethoxy-3,4-methylenedioxybenzoic acid (XXX).¹¹

In the course of this work, an isomeric acid, 4,6-dimethoxy-2,3-methylenedioxybenzoic acid (XXXVIII), 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° 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 XXXII 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 (XXXVI) was obtained. Treatment of the phenol XXXVI 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*-butyllithium followed by carbonation, gave 4,6-dimethoxy-2,3-methylenedioxybenzoic acid (XXXVIII).¹²

XXXIX, X = NH₂

XL, X = H

XLI, R = CH₃, X = HXLII, R = CH₃, X = BrXLIII, R = CF₃, X = HXLIV, R = CF₃, X = BrXLV, R = C₆H₅CH₂, X = HXLVI, R = C₆H₅CH₂O, X = Br

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

(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 apioic acid (2,5-dimethoxy-3,4-methylenedioxybenzoic acid). That the product was not apioic 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 croweacid (above). Since this product is not the same, it follows that its structure is 4,6-dimethoxy-2,3-methylenedioxybenzoic acid.

(8) A. R. Penfold, G. R. Ramage and J. L. Simonsen, *J. Chem. Soc.*, 756 (1938).

(9) For a discussion of the role of the methylenedioxy group in orientation of aromatic substituents, see R. T. Arnold and F. Bordwell, *THIS JOURNAL*, **64**, 2983 (1942).

(10) L. W. Duncanson, J. F. Grove and J. Zealley, *J. Chem. Soc.*, 1331 (1953); I. M. Hunsberger, *THIS JOURNAL*, **72**, 5626 (1950); R. S. Rasmussen and R. R. Brattain, *ibid.*, **71**, 1073 (1949); M. St. C. Flett, *J. Chem. Soc.*, 1441 (1948); and W. Gordy, *THIS JOURNAL*, **60**, 605 (1938).

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-methylenedioxybenzene (XL). Metallation of XL with *n*-butyllithium and then carbonation gave the known croweic acid⁸ (XXIII).

1-Acetamido-3-methoxy-4,5-methylenedioxybenzene (XLI) was prepared by the acetylation of 3-methoxy-4,5-methylenedioxyaniline (V). Bromination of XLI with one equivalent of bromine gave 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-4,5-methylenedioxy-1-trifluoroacetamidobenzene (XLIII) and its corresponding 2-bromo derivative XLIV and 1-carbobenzyloxyamino-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 bromoacetamido compound XLII.

Acknowledgment.—We are indebted to Mr. R. N. Boos and associates for elemental analyses and to Mr. R. W. Walker and Dr. N. R. Trenner for infrared spectra.

Experimental

1-Methoxy-2,3-methylenedioxy-5-nitrobenzene (IV).—Twelve grams of 1-methoxy-2,3-methylenedioxybenzene¹³ (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. (68%) of 1-methoxy-2,3-methylenedioxy-5-nitrobenzene, m.p. 145–146°.

Anal. Calcd. for C₈H₇NO₅ (197.14): C, 48.74; H, 3.58; N, 7.11. Found: C, 49.03; H, 3.50; N, 7.21.

2(or 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 55–65° 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 311 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° (0.3 mm.), melted at 101–102°.

Anal. Calcd. for C₉H₁₁NO₅ (213.19): C, 50.70; H, 5.20; N, 6.57; -OCH₃, 35.6. Found: C, 50.42; H, 4.90; N, 6.57; -OCH₃, 36.1.

3-Methoxy-4,5-methylenedioxyaniline (V).—A suspension of 5 g. (26 mmoles) 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 5 g. of catalyst (5% palladium-on-Darco).

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, 3.8 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°.

Anal. Calcd. for C₈H₉NO₃ (167.16): C, 57.48; H, 5.43; N, 8.38. Found: C, 57.44; H, 5.40; N, 8.48.

3-Methoxy-4,5-methylenedioxyphenol (VI).—A suspension of 1.6 g. (10 mmoles) 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 cooled and extracted with two 200-ml. portions of ether. After the ether solution had been dried and concentrated, 1.2 g. of product was obtained. Distillation of the crude product at 130° (0.3 mm.) yielded 530 mg. of the phenol, m.p. 89–93°. Recrystallization of the product from ether-petroleum ether gave 3-methoxy-4,5-methylenedioxyphenol, m.p. 89–91°.

Anal. Calcd. for C₈H₉O₄ (168.14): C, 57.15; H, 4.80. Found: C, 57.55; H, 5.11.

1,5-Dimethoxy-2,3-methylenedioxybenzene (VII).—A solution of 100 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 sulfate. The reaction mixture was extracted with two 20-ml. portions of ether. Concentration of the ether extracts gave 44 mg. of product, m.p. 41–42°, which on recrystallization from 2 ml. of petroleum ether yielded 30 mg. of 1,5-dimethoxy-2,3-methylenedioxybenzene, m.p. 41–42°.

Anal. Calcd. for C₉H₁₀O₄ (182.17): C, 59.33; H, 5.53. Found: C, 59.82; H, 5.70.

4,6-Dibromo-1,5-dimethoxy-2,3-methylenedioxybenzene (VIII).—A slight excess of bromine in acetic acid solution was added dropwise to a solution of 15 mg. of 1,5-dimethoxy-2,3-methylenedioxybenzene (VII) in 0.5 ml. of acetic acid. The solvent and excess bromine were removed by distillation. Sublimation of the product at 120° (0.3 mm.), followed by recrystallization from petroleum ether, yielded 13 mg. of 4,6-dibromo-1,5-dimethoxy-2,3-methylenedioxybenzene, m.p. 93–94°.

Anal. Calcd. for C₉H₈Br₂O₄ (339.99): C, 31.80; H, 2.37; Br, 47.00. Found: C, 31.80; H, 2.30; Br, 47.79.

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. About 45 minutes after the last addition, the product was extracted into ether. Concentration of the ether extracts yielded 60 mg. of crude product, which after three recrystallizations from petroleum ether, yielded 36 mg. of 5-ethoxy-1-methoxy-2,3-methylenedioxybenzene, m.p. 54–55°. A sample was sublimed prior to analysis.

Anal. Calcd. for C₁₀H₁₂O₄ (196.20): C, 61.21; H, 6.17. Found: C, 61.62; H, 6.05.

4,6-Dibromo-5-ethoxy-1-methoxy-2,3-methylenedioxybenzene (X).—A solution of 21 mg. of 5-ethoxy-1-methoxy-2,3-methylenedioxybenzene (IX) in 0.5 ml. of acetic acid was treated with a slight excess of bromine in acetic acid. Concentration of the solution and sublimation of the residue under reduced pressure yielded 31 mg. of product, m.p. 74–75°. Two recrystallizations of the product from petroleum ether yielded 4,6-dibromo-5-ethoxy-1-methoxy-2,3-methylenedioxybenzene, m.p. 74–75°.

Anal. Calcd. for C₁₀H₁₀Br₂O₄ (354.02): C, 33.92; H, 2.84; Br, 45.15. Found: C, 33.86; H, 2.60; Br, 44.63.

Pyrogallol-1-ethyl Ether (XII).—One hundred sixty-six grams (1 mole) of crude ethyl *o*-vanillin (XI) in 500 ml. of 2 *N* sodium hydroxide was oxidized with 710 ml. (1.25 moles)

(13) The method described (ref. 4) for the preparation of III was modified by running the reaction in a rocking autoclave. Under these conditions methylene bromide was superior to methylene iodide as evidenced by increased yields (from ~16% with methylene iodide to ~32% with methylene bromide) and easier isolation of the product.

of 6% hydrogen peroxide solution in the manner described¹⁴ for the oxidation of *o*-vanillin.

The distillate (b.p. 60–75° (0.5 mm.)) from 135 g. of product was a mixture of solid and oil, which was washed with petroleum ether to remove the oil. Recrystallization of the solid from 75 ml. of benzene-petroleum ether (2:1) yielded 40 g. of pyrogallol-1-ethyl ether, m.p. 95–98°. Five recrystallizations of the product from benzene, followed by vacuum sublimation, raised the melting point to 98–99°.

Anal. Calcd. for C₈H₁₀O₃ (154.16): C, 62.32; H, 6.54; OC₂H₅, 29.2. Found: C, 62.75; H, 6.65; OC₂H₅, 32.48.

1-Ethoxy-2,3-methylenedioxybenzene (XIII).—A mixture of 31 g. (0.2 mole) of pyrogallol-1-ethyl ether (XII), 110 ml. of methanol, 6 g. of Tobin bronze, 64 g. (0.24 mole) of methylene iodide, 22 g. (0.4 mole) of potassium hydroxide and 30 ml. of water was heated in a pressure vessel at 105° for 10 hours.⁴

The product was isolated by steam distillation, and the distillate (2 l.) was saturated with sodium chloride and extracted with four 450-ml. portions of chloroform. The chloroform solution was dried and concentrated under reduced pressure giving 24 g. of an oil. The oil, in 400 ml. of ether, was washed with 50 ml. of 2.5 *N* sodium hydroxide.

Concentration of the ether solution gave a residual oil (19 g.), which on distillation gave three fractions: 9.8 g. of unreacted methylene iodide (b.p. 71–73° (17 mm.)), *n*_D²⁰ 1.7, 0.7 g. of an intermediate fraction, and 7.3 g. (22%) of 1-ethoxy-2,3-methylenedioxybenzene (b.p. 115–123° (17 mm.)), *n*_D²⁰ 1.5345).

1-Ethoxy-2,3-methylenedioxy-5-nitrobenzene (XIV).—1-Ethoxy-2,3-methylenedioxybenzene (XIII) (3.3 g., 20 mmoles) was added dropwise to 27 ml. of cold, stirred, concentrated nitric acid. The product began to separate almost immediately. The mixture was stirred for a few minutes after the final addition, and 270 ml. of ice-water was added. The product isolated by filtration (3.3 g., m.p. 109–117°) was washed with water. Recrystallization of the product from 55 ml. of ethanol gave 2.6 g. (62%) of 1-ethoxy-2,3-methylenedioxy-5-nitrobenzene, m.p. 119–120°.

Anal. Calcd. for C₉H₈NO₅ (211.17): C, 51.19; H, 4.30; N, 6.63. Found: C, 50.91; H, 4.58; N, 6.30.

3-Ethoxy-4,5-methylenedioxyaniline (XV).—A suspension of 2.1 g. (10 mmoles) of 1-ethoxy-2,3-methylenedioxy-5-nitrobenzene (XIV), 2.5 ml. (12 mmoles) of 4.7 *N* methanolic hydrogen chloride, 2 g. of 5% palladium-on-Darco and 80 ml. of methanol was shaken at 25° in an atmosphere of hydrogen.

The mixture was filtered and the filtrate, on concentration at reduced pressure, gave 2.2 g. of solid. The solid was suspended in 100 ml. of water. The mixture was neutralized with 2.5 *N* sodium hydroxide, and was extracted with four 100-ml. portions of ether. 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. Calcd. for C₉H₁₁NO₃ (181.19): C, 59.66; H, 6.12; N, 7.73. Found: C, 59.95; H, 5.89; N, 7.86.

3-Ethoxy-4,5-methylenedioxyphenol (XVI).—A solution of 0.4 g. (5.5 mmoles) of sodium nitrite in 10 ml. of water was added in 0.5-ml. portions to a stirred suspension of 1.0 g. (5.5 mmoles) of 3-ethoxy-4,5-methylenedioxyaniline (XV) in 30 ml. of water and 0.8 ml. of concentrated sulfuric acid at 0° until a permanent excess of nitrous acid was detected. Successive portions were not added until most of the nitrous acid had been consumed.

The cold solution of diazonium sulfate was dropped through a jet of steam into boiling water. The aqueous solution was saturated with sodium chloride 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°.

Anal. Calcd. for C₉H₁₀O₄ (182.17): C, 59.33; H, 5.53. Found: C, 59.52; H, 5.71.

(14) A. R. Surrey, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 759.

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 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°.

Anal. Calcd. for C₁₀H₁₀Br₂O₄ (354.02): C, 33.92; H, 2.84; Br, 45.15. Found: C, 34.03; H, 2.70; Br, 45.52.

2-Methoxy-3,4-methylenedioxybenzaldehyde (XXI) and 4-Methoxy-2,3-methylenedioxybenzaldehyde (XXII).

Formylation of 1-methoxy-2,3-methylenedioxybenzene (III) with phosphorus oxychloride and dimethylformamide (or *N*-methylformanilide) to 2-methoxy-3,4-methylenedioxybenzaldehyde (XXI) is described in the literature.¹⁵ We found that the product was a mixture of XXI and 4-methoxy-2,3-methylenedioxybenzaldehyde (XXII). These isomers were separated by chromatography.

A solution of 150 g. of reaction product in 600 ml. of benzene was chromatographed on a column (15 × 50 cm.) of acid-washed alumina (7 kg.). Elution with benzene (35 l.) gave 65 g. of 2-methoxy-3,4-methylenedioxybenzaldehyde (XXI), m.p. 97–105°. Recrystallization of the product from ethanol raised the melting point to 103–105°. Further elution with chloroform (35 l.) gave 54 g. of 4-methoxy-2,3-methylenedioxybenzaldehyde (XXII), which on recrystallization from ethanol, melted at 85–86°.

2-Methoxy-3,4-methylenedioxybenzoic Acid (Croweac Acid) (XXIII). (A) From 1-Bromo-2-methoxy-3,4-methylenedioxybenzene (XL).—A solution of 90 mg. (0.4 mmole) of 1-bromo-2-methoxy-3,4-methylenedioxybenzene (XL) in 1.5 ml. of dry ether was cooled to –70°, and 0.4 ml. of a 1 *N* solution of *n*-butyllithium in ether (0.4 mmole) was added. After 15 minutes the reaction mixture was poured onto an excess of crushed Dry 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 in turn extracted twice with an aqueous solution of sodium bicarbonate. The bicarbonate extracts were acidified to pH 2 with hydrochloric acid and 25 mg. of croweac acid, m.p. 158°, precipitated.

Anal. Calcd. for C₉H₈O₅ (196.15): C, 55.11; H, 4.11. Found: C, 55.86; H, 4.13; neut. equiv., 191.

(B) From 2-Methoxy-3,4-methylenedioxybenzaldehyde (Croweac Aldehyde) (XXI).—A mixture of 1.12 g. (6.2 mmoles) of 2-methoxy-3,4-methylenedioxybenzaldehyde (XXI), 1.52 g. (6.5 mmoles) of freshly prepared silver oxide, 20 ml. of ethanol and 20 ml. of 5% sodium hydroxide was refluxed for 10 minutes. The mixture was filtered, and the ethanol was removed under reduced pressure. After the alkaline solution had been extracted with ether and acidified with hydrochloric acid, 1.02 g. of croweac acid, m.p. 159–160°, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.77 μ , was obtained.

2-Methoxy-3,4-methylenedioxy-6-nitrobenzoic Acid (XXIV).—2-Methoxy-3,4-methylenedioxybenzoic acid (croweac acid) (XXIII) (680 mg.) was added in portions to 6 ml. of cold concentrated nitric acid. The reaction mixture was stirred about 10 minutes and then was diluted with 35 ml. of water. The product was filtered, dissolved in ether, and extracted with aqueous sodium bicarbonate solution. The bicarbonate extract was acidified to pH 3 and the product (500 mg.), m.p. 185–192°, after recrystallization from ethanol-water yielded 390 mg. of 2-methoxy-3,4-methylenedioxy-6-nitrobenzoic acid, m.p. 190–192°, $\lambda_{\text{max}}^{\text{NaOH}}$ 5.83 μ .

Anal. Calcd. for C₉H₇NO₇ (241.15): C, 44.82; H, 2.93; N, 5.81. Found: C, 44.92; H, 3.02; N, 5.68.

(15) W. B. Brownell and A. W. Weston, THIS JOURNAL, **73**, 4971 (1951).

Methyl 2-Methoxy-3,4-methylenedioxy-6-nitrobenzoate (XXV).—Four grams of 2-methoxy-3,4-methylenedioxy-6-nitrobenzoic acid (XXIV) 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-nitrobenzoate, m.p. 115–117°, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.76 μ .

Anal. Calcd. for $\text{C}_{10}\text{H}_9\text{NO}_7$ (255.18): C, 47.06; H, 3.56; N, 5.49. Found: C, 47.34; H, 3.70; N, 5.28.

Methyl 6-Amino-2-methoxy-3,4-methylenedioxybenzoate (XXVI).—A suspension of 1.5 g. of methyl 2-methoxy-3,4-methylenedioxy-6-nitrobenzoate (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. 86–88°, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.97 μ .

Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{NO}_6$ (225.20): C, 53.33; H, 4.92; N, 6.22. Found: C, 53.41; H, 5.00; N, 6.86.

Methyl 6-Acetamido-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 acetic anhydride. After about 12 hours the solution was poured into ice-water and acidified to pH 3. The mixture was extracted with ether. Concentration of the ether solution and recrystallization of the residue from methanol gave 34 mg. of methyl 6-acetamido-2-methoxy-3,4-methylenedioxybenzoate, m.p. 116–117°, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.92 μ .

Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{NO}_6$ (267.23): C, 53.93; H, 4.90; N, 5.24. Found: C, 53.98; H, 4.95; N, 5.47.

Methyl 6-Hydroxy-2-methoxy-3,4-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 290-mg. residue. Purification of the product by chromatography on alumina followed by recrystallization from ethanol gave 75 mg. of methyl 6-hydroxy-2-methoxy-3,4-methylenedioxybenzoate, m.p. 81–82°, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 6.01 μ . Sublimation of the product, followed by recrystallization from methanol, raised the melting point to 83–84°.

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_6$ (226.18): C, 53.10; H, 4.46. Found: C, 53.17; H, 4.49.

2,6-Dimethoxy-3,4-methylenedioxybenzoic Acid (XXX).—A solution of 57 mg. of methyl 6-hydroxy-2-methoxy-3,4-methylenedioxybenzoate (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-methylenedioxybenzoate (XXIX).

Forty-two milligrams of methyl 2,6-dimethoxy-3,4-methylenedioxybenzoate was refluxed in aqueous methanolic sodium hydroxide for 1 hour. The methanol was removed under reduced pressure, and the solution was acidified to pH 3. The product (27 mg.) was extracted with ether. Several recrystallizations of the product from ether-petroleum ether gave 12 mg. of 2,6-dimethoxy-3,4-methylenedioxybenzoic acid, m.p. 156–157°, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.85 μ .

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_6$ (226.18): C, 53.10; H, 4.46. Found: C, 53.22; H, 4.67.

4-Methoxy-2,3-methylenedioxybenzoic Acid (XXXI).—A mixture of 0.93 g. (5.1 mmoles) of 4-methoxy-2,3-methylenedioxybenzaldehyde (XXII), 1.26 g. (5.3 mmoles) of freshly prepared silver oxide, 18 ml. of ethanol and 18 ml. of 5% sodium hydroxide was refluxed for 15 minutes. The mixture was filtered, and the ethanol was removed under reduced pressure. After the alkaline solution had been extracted with ether and acidified with hydrochloric acid, 0.91 g. of 4-methoxy-2,3-methylenedioxybenzoic acid, m.p. 250–255°, $\lambda_{\text{max}}^{\text{dioxane}}$ 5.85 μ , was obtained.

4-Methoxy-2,3-methylenedioxy-6-nitrobenzoic Acid (XXXII).—The 4-methoxy-2,3-methylenedioxybenzoic acid (XXXI) (0.9 g., 4.6 mmoles) was added in portions to 8 ml. of cold concentrated nitric acid. The reaction mixture was stirred for about 5 minutes and was diluted with 60 ml. of water. The product, isolated by filtration, was washed with water and dissolved in chloroform. The chloroform solution was extracted with aqueous sodium bicarbonate. The bicarbonate extract was acidified, and the product was filtered. Recrystallization of this material from ethanol-water yielded 0.7 g. of 4-methoxy-2,3-methylenedioxy-6-nitrobenzoic acid, m.p. 201–205°. A second recrystallization from ethanol raised the melting point of the product to 203–205°, $\lambda_{\text{max}}^{\text{dioxane}}$ 5.8–5.84 μ .

Anal. Calcd. for $\text{C}_9\text{H}_7\text{O}_7\text{N}$ (241.15): C, 44.82; H, 2.93; N, 5.81. Found: C, 44.96; H, 3.16; N, 6.05.

Methyl 4-Methoxy-2,3-methylenedioxy-6-nitrobenzoate (XXXIII).—A solution of 102 mg. of diazomethane in 6 ml. of ether was added to a suspension of 500 mg. of 4-methoxy-2,3-methylenedioxy-6-nitrobenzoic acid (XXXII) in 20 ml. of ether. 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 solution. Concentration of the chloroform solution and recrystallization of the residue (550 mg.) from methanol yielded 490 mg. of methyl 4-methoxy-2,3-methylenedioxy-6-nitrobenzoate, m.p. 145–147°, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.76 μ .

Anal. Calcd. for $\text{C}_{10}\text{H}_9\text{NO}_7$ (255.18): C, 47.06; H, 3.56; N, 5.49. Found: C, 47.12; H, 3.36; N, 5.55.

Methyl 6-Amino-4-methoxy-2,3-methylenedioxybenzoate (XXXIV).—A suspension of 490 mg. of methyl 4-methoxy-2,3-methylenedioxy-6-nitrobenzoate (XXXIII) and 1 g. of catalyst (5% Pd-on-Darco) in a mixture of 25 ml. of methanol and 1 ml. of concentrated hydrochloric acid was shaken at room temperature in an atmosphere of hydrogen. The reaction mixture was warmed and filtered, and the filtrate was concentrated at reduced pressure. The residue was neutralized with aqueous sodium bicarbonate solution, and the product was extracted with ether. Concentration of the ether extract and recrystallization of the product (250 mg.) from benzene gave 210 mg. of methyl 6-amino-4-methoxy-2,3-methylenedioxybenzoate, m.p. 164–166°, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.92 μ .

Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{NO}_6$ (225.20): C, 53.33; H, 4.92; N, 6.22. Found: C, 53.36; H, 4.75; N, 6.76.

Methyl 6-Acetamido-4-methoxy-2,3-methylenedioxybenzoate (XXXV).—A solution of 100 mg. of methyl 6-amino-4-methoxy-2,3-methylenedioxybenzoate (XXXIV) in 2 ml. of pyridine was treated at room temperature with 1 ml. of acetic anhydride. After about 12 hours the mixture was poured into water and the solution was acidified to pH 3. The product (118 mg.) isolated by extraction with chloroform was recrystallized from benzene-petroleum ether. A second crystallization of the product from ethanol yielded 40 mg. of methyl 6-acetamido-4-methoxy-2,3-methylenedioxybenzoate, m.p. 203–204°, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.97 μ .

Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{NO}_6$ (267.23): C, 53.93; H, 4.90; N, 5.24. Found: C, 54.22; H, 4.71; N, 5.45.

(16) Reduction of the acid XXIV in glacial acetic acid using a 5% Pd on Darco catalyst gave about 10% of the decarboxylated product, 3-methoxy-4,5-methylenedioxyaniline (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 acetylation of XXIV gave a mixture of decarboxylated product, 1-acetamido-3-methoxy-4,5-methylenedioxybenzene and 6-acetamido-2-methoxy-3,4-methylenedioxybenzoic acid. A mixture was also obtained from reduction of XXIV in the presence of mineral acid.

Methyl 6-Hydroxy-4-methoxy-2,3-methylenedioxybenzoate (XXXVI).—A suspension of 278 mg. of methyl 6-amino-4-methoxy-2,3-methylenedioxybenzoate (XXXIV) in 9 ml. of water was stirred at 0° while 1 ml. of 25% sulfuric acid was added. A solution of 98 mg. of sodium nitrite in 1 ml. of water was added dropwise. After the excess nitrous acid had been decomposed with urea, the solution was diluted to a 30-ml. volume 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, gave a 215-mg. residue. Purification of the product by chromatography on alumina and recrystallization from ethanol gave 70 mg. of methyl 6-hydroxy-4-methoxy-2,3-methylenedioxybenzoate, m.p. 176–177°, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.99 μ .

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_6$ (226.18): C, 53.10; H, 4.46. Found: C, 53.31; H, 4.36.

4,6-Dimethoxy-2,3-methylenedioxybenzoic Acid (XXXVIII).—A solution of 285 mg. (1.6 mmoles) of 1,5-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 mmoles) 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. (60%) of 1-bromo-4,6-dimethoxy-2,3-methylenedioxybenzene (XXVII), m.p. 80–85°. A small sample, recrystallized from petroleum ether, melted at 86–89°.

Anal. Calcd. for $\text{C}_9\text{H}_9\text{BrO}_4$ (261.08): Br, 30.62. Found: Br, 29.29.

A solution of 100 mg. (0.4 mmole) of 1-bromo-4,6-dimethoxy-2,3-methylenedioxybenzene (XXVII) in 25 ml. of absolute ether was cooled to –50°, and 0.8 ml. (0.8 mmole) of 1 *N* *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 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 3 extractions with ether, was acidified to about pH 2 with dilute hydrochloric acid, and 11 mg. (13%) of 4,6-dimethoxy-2,3-methylenedioxybenzoic acid, m.p. 140–150°, was obtained. Recrystallization of the product from ether–petroleum ether and sublimation at 150° (0.3 mm.) gave the pure acid, m.p. 173.5–174°, $\lambda_{\text{max}}^{\text{KBr}}$ 5.77 μ .

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_6$ (226.18): C, 53.10; H, 4.46. Found: C, 53.26; H, 4.55.

2-Bromo-3-methoxy-4,5-methylenedioxyaniline (XXXIX).—A solution of 2.3 g. (14.2 mmoles) of bromine in 20 ml. of glacial acetic acid was added dropwise to a cold (15°), stirred suspension of 2.5 g. (14.2 mmoles) of 3-methoxy-4,5-methylenedioxyaniline (V) in 100 ml. of acetic acid containing 30 g. of hydrogen bromide. Petroleum ether (100 ml.) was added to the reaction mixture and the solid was filtered, washed, and dried. The product was suspended in 100 ml. of cold water and neutralized with sodium hydroxide. The mixture was extracted with ether; concentration of the ether solution gave a 2.9-g. residue.

The crude product in 25 ml. of benzene was chromatographed on 150 g. of acid-washed alumina. Elution with benzene yielded 0.3 g. of 2,6-dibromo-3-methoxy-4,5-methylenedioxyaniline,¹⁷ R_f 0.95.¹⁸

Further elution with benzene gave 1.6 g. (65% based on starting material consumed) of 2-bromo-3-methoxy-4,5-methylenedioxyaniline, m.p. 80–86°, R_f 0.72. Two recrystallizations from ether raised the melting point of the product to 86–87°.

Anal. Calcd. for $\text{C}_8\text{H}_8\text{BrNO}_2$ (246.07): C, 39.05; H, 3.28; N, 5.69; Br, 32.48. Found: C, 39.28; H, 3.24; N, 5.78; Br, 31.04.

(17) Based on halogen analysis. *Anal.* Calcd. for $\text{C}_8\text{H}_7\text{Br}_2\text{NO}_2$ (324.98): Br, 48.9. Found: Br, 48.6.

(18) All R_f values were obtained by radial papergrams on Whatman 3MM paper developed with the upper phase of a cyclohexane–benzene–methanol–water (4:1:4:1) system. Zones were detected by spraying with dilute aqueous potassium permanganate.

Elution with chloroform gave 0.7 g. of starting material, R_f 0.27.

1-Bromo-2-methoxy-3,4-methylenedioxybenzene (XL).—A solution of 850 mg. (3.4 mmoles) of 2-bromo-3-methoxy-4,5-methylenedioxyaniline (XXXIX) in 10 ml. of water and 0.8 ml. of concentrated sulfuric acid was diazotized at 0° with a solution of 235 mg. of sodium nitrite in 1 ml. of water. The solution of the diazonium sulfate was added slowly to 200 ml. of boiling methanol. The mixture was concentrated at reduced pressure, and the aqueous residue was extracted three times with ether. The combined ether extracts were washed with sodium bicarbonate solution, dried, and concentrated. Recrystallization of the residue (740 mg.) from methanol–water and then from petroleum ether gave 1-bromo-2-methoxy-3,4-methylenedioxybenzene, m.p. 49–49.5°.

Anal. Calcd. for $\text{C}_8\text{H}_7\text{O}_3\text{Br}$ (231.06): C, 41.58; H, 3.05; Br, 34.59; CH_3O , 13.43. Found: C, 41.83; H, 3.35; Br, 34.57; CH_3O , 12.56.

1-Acetamido-3-methoxy-4,5-methylenedioxybenzene (XLI).—Three milliliters of acetic anhydride was added to a solution of 960 mg. of 3-methoxy-4,5-methylenedioxyaniline (V) in 5 ml. of pyridine. The reaction mixture was kept at room temperature overnight. It was poured onto ice, and the mixture was acidified with hydrochloric acid. The product (910 mg.), after two recrystallizations from ethanol, gave 600 mg. of 1-acetamido-3-methoxy-4,5-methylenedioxybenzene, m.p. 154–156°.

Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{NO}_4$ (209.20): C, 57.41; H, 5.30; N, 6.70. Found: C, 57.87; H, 5.10; N, 6.78.

1-Acetamido-2-bromo-3-methoxy-4,5-methylenedioxybenzene (XLII) (A) From 1-Acetamido-3-methoxy-4,5-methylenedioxybenzene (XLI).—A solution of 334 mg. (2.1 mmoles) of bromine in 4 ml. of glacial acetic acid was added dropwise to a cooled solution of 440 mg. (2.1 mmoles) of the 1-acetamido-3-methoxy-4,5-methylenedioxybenzene (XLI) in 10 ml. of glacial acetic acid. Crystallization occurred during the addition of the bromine solution. The mixture was filtered, and the crystals (600 mg.), m.p. 160–165°, were washed and dried. Recrystallization of the product from ethanol gave 350 mg. (58%) of 1-acetamido-2-bromo-3-methoxy-4,5-methylenedioxybenzene, m.p. 167–168°.

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{BrNO}_4$ (288.11): C, 41.69; H, 3.50; N, 4.86; Br, 27.74. Found: C, 41.65; H, 3.64; N, 4.90; Br, 28.08.

(B) From 2-Bromo-3-methoxy-4,5-methylenedioxyaniline (XXXIX).—A solution of 103 mg. of 2-bromo-3-methoxy-4,5-methylenedioxyaniline (XXXIX) in 1 ml. of dry pyridine was cooled to 0°, and 0.2 ml. of acetic anhydride 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 (108 mg., 90%), m.p. 166–167°, was filtered, washed with water, 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-trifluoroacetamidobenzene (XLIII).—Trifluoroacetic anhydride (2.2 g.) was added to a solution of 584 mg. (3.5 mmoles) of 3-methoxy-4,5-methylenedioxyaniline (V) in 9 ml. of pyridine. The reaction mixture, after being kept at room temperature overnight, was poured onto ice, and the product (780 mg.) was filtered. After recrystallization from ethanol and sublimation at 110–120° (0.5 mm.), 370 mg. of 3-methoxy-4,5-methylenedioxy-1-trifluoroacetamidobenzene, m.p. 125–126°, was obtained.

Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{F}_3\text{NO}_4$ (263.17): C, 45.62; H, 3.06; N, 5.32. Found: C, 46.12; H, 3.05; N, 5.80.

2-Bromo-3-methoxy-4,5-methylenedioxy-1-trifluoroacetamidobenzene (XLIV).—A solution of 159 mg. of bromine in 1 ml. of glacial acetic acid was added dropwise to a solution of 275 mg. of 3-methoxy-4,5-methylenedioxy-1-trifluoroacetamidobenzene (XLIII) in 2 ml. of glacial acetic acid. The product, which precipitated on the addition of water, was filtered. One recrystallization of the product from ethanol gave 170 mg. of 2-bromo-3-methoxy-4,5-methylenedioxy-1-trifluoroacetamidobenzene, m.p. 113–116°.

Anal. Calcd. for $C_{10}H_7BrF_3NO_4$ (342.09): C, 35.11; H, 2.06; Br, 23.37; N, 4.10. Found: C, 35.21; H, 2.20; Br, 23.23; N, 4.40.

1-Carbobenzyloxyamino-3-methoxy-4,5-methylenedioxybenzene (XLV).—Carbobenzyloxy chloride (3.2 g.) was added to a cooled solution of 510 mg. (3.1 mmoles) of 3-methoxy-4,5-methylenedioxyaniline (V) in 8 ml. of pyridine. The reaction mixture, after being kept overnight at room temperature, was poured onto ice, and the product was filtered. After one recrystallization of the product from ethanol, 1-carbobenzyloxyamino-3-methoxy-4,5-methylenedioxybenzene (820 mg.), m.p. 90–93°, was obtained.

Anal. Calcd. for $C_{16}H_{15}NO_5$ (301.29): C, 63.78; H, 5.02; N, 4.65. Found: C, 64.24; H, 5.12; N, 4.63.

2-Bromo-1-carbobenzyloxyamino-3-methoxy-4,5-methylenedioxybenzene (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-methylenedioxybenzene (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-methylenedioxybenzene, m.p. 93–97°.

Anal. Calcd. for $C_{16}H_{14}BrNO_5$ (380.20): C, 50.55; H, 3.71; Br, 21.03; N, 3.68. Found: C, 50.98; H, 3.37; Br, 20.01; N, 3.95.

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The Polysaccharides of Yellow Birch (*Betula lutea*). II. The Constitution of the Main Hemicellulose¹

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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 D-galacturonic acid, glucuronic acid, 4-O-methyl-D-glucuronic acid, 2-O-(4-O-methyl- α -D-glucopyranosyluronic acid)-D-xylopyranose and an aldatriouronic acid. A crystalline tetraacetate of the methyl ester methyl glycoside 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-di-O-methyl-D-xylose, 2,3,4-tri-O-methyl-D-xylose and 2-O-(2,3,4-tri-O-methyl- α -D-glucopyranosyluronic acid)-3-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-methylglucuronoxylan consists of a linear framework of approximately 190 1,4-linked β -D-xylopyranose residues, with, on the average, every tenth residue carrying a single, terminal side chain of 4-O-methyl- α -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.² In a previous investigation³ 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 resin⁴ to yield D-xylose, which crystallized, two monouronic acids, a mono-O-methyl uronic acid, an aldobiouronic acid and an aldatriouronic 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 aluminum hydride^{5,6} to 4-O-methyl-D-glucose, characterized as its phenylosazone deriva-

tive,^{7,8} and was therefore 4-O-methyl-D-glucuronic acid. The aldatriouronic acid was chromatographically identical to similar compounds obtained from milkweed floss⁹ and white elm wood¹⁰ and yielded the same hydrolysis products. Glucuronic acid has previously been encountered in hydrolyzates from the woods of trembling aspen¹¹ and black spruce.¹² Aldotriouronic acids composed of 4-O-methyl-D-glucuronic acid and two xylose residues have been isolated from several wood species.^{10,13}

The methoxyl content and equivalent weight of the aldobiouronic acid, $[\alpha]^{20}_D + 104^\circ$, corresponded to that of a mono-O-methylated aldobiouronic acid containing a pentose and a hexuronic acid residue. Its infrared spectrum was identical to that of an authentic sample of 2-O-(4-O-methyl- α -D-glucopyranosyluronic acid)-D-xylopyranose.¹⁴ Reduction of its ester glycoside and hydrolysis yielded 4-O-methyl-D-glucose and D-xylose. When the ester glycoside of the fully methylated aldobiouronic acid was similarly reduced and hydrolyzed, 3,4-di-O-methyl-D-xylose and 2,3,4-tri-O-methyl-D-glucose were obtained, both of which

(7) R. Schinle, *Ber.*, **65**, 315 (1932).

(8) J. Munro and E. G. V. Percival, *J. Chem. Soc.*, 873 (1935).

(9) F. W. Barth and T. E. Timell, *THIS JOURNAL*, **80**, 6320 (1958).

(10) J. K. Gillham and T. E. Timell, *Can. J. Chem.*, **36**, 1467 (1958).

(11) J. K. N. Jones, E. Merler and L. E. Wise, *ibid.*, **35**, 634 (1957).

(12) A. R. N. Gorrod and J. K. N. Jones, *J. Chem. Soc.*, 2522 (1954).

(13) J. K. Hamilton and N. S. Thompson, *THIS JOURNAL*, **79**, 6464 (1957).

(14) C. P. J. Glaudemans and T. E. Timell, *ibid.*, **80**, 941, 1209 (1958).

(1) Paper presented at the Symposium on Wood Hemicelluloses before the Division of Cellulose Chemistry at the 136th Meeting of the American Chemical Society in Atlantic City, N. J., September, 1959.

(2) T. E. Timell, *Pulp Paper Mag. Can.*, **58**, No. 1, 97 (1957).

(3) T. E. Timell, *ibid.*, **59**, No. 8, 139 (1958).

(4) J. K. Gillham and T. E. Timell, *Can. J. Chem.*, **36**, 410 (1958).

(5) M. Abdel-Akher and F. Smith, *Nature*, **166**, 1037 (1950).

(6) F. Smith, *J. Chem. Soc.*, 2646 (1951).