and dried. There was obtained 4.4 g. (32%) of 2-methoxy-4′,5-dicarboxydiphenyl ether melting at 292–300°. After recrystallization from ethanol the product melted at 296–297°. The reported (9, 10) melting points are 313–314° and 302–306°.

2-Methoxy-4′,5-diacetyldiphenyl ether (IV). In a flask equipped with a reflux condenser and an inlet tube for dry nitrogen were placed 19.5 g. (0.096 mole) of the potassium salt of isoacetovanillone, 19 g. (0.096 mole) of 4-bromoacetophenone and 6.1 g. (0.096 g.-atom) of copper bronze. The mixture was maintained at 180–185° for 6 hours, cooled, and then the solid mass was crushed in a mortar. During extraction of the mass in a Soxhlet extractor for 20 hours, a yellow solid crystallized from the ethereal extract. There was obtained 16.5 g. (61%) of product melting at 138–143°. Decolorization with charcoal and two recrystallizations from ethanol yielded a white, crystalline solid, m.p. 144–145°.

Anal. Calc'd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67.
Found: C, 71.79; H, 5.62.

Haloform reaction of 2-methoxy-4′,5-diacetyldiphenyl ether. A solution of 2.6 g. (0.065 mole) of sodium hydroxide and 5.1 g. (0.032 mole) of bromine in 180 ml. of water was heated at 60° for 3 hours with 1 g. (0.0035 mole) of 2-methoxy-4′,5-diacetyldiphenyl ether in 25 ml. of methanol. The methanol was removed by distillation, 0.5 ml. of acetone was added to destroy excess hypobromite, and the bromoform was removed by boiling the solution. After cooling, the solution was further basified by the addition of 0.5 g. of sodium hydroxide, and was extracted twice with chloroform. Acidification of the aqueous phase precipitated a fine solid. Recrystallization three times from ethanol yielded a white product melting at 312–314°. It was purer than the sample of 2-methoxy-4′,5-dicarboxydiphenyl ether prepared by the Ullmann reaction and the melting point agreed with that of Späth (10).

2-Methoxy-4′,5-bis(carboxymethyl)diphenyl ether (VI). A mixture of 5.66 g. (0.02 mole) of 2-methoxy-4′,5-diacetyldiphenyl ether, 1.95 g. (0.06 g.-atom) of sulfur, and 5.2 g. (0.06 mole) of morpholine was heated cautiously for 1 hour and then allowed to reflux for 13 hours. The reaction mixture was hydrolyzed by refluxing for 6 hours with a mixture of 25 ml. of acetic acid, 5 ml. of sulfuric acid, and 4 ml. of water. The solution was diluted with water and cooled. The dark solid which separated was dissolved in sodium hydroxide solution, cooled to 3°, and acidified with sulfuric acid. The precipitated solid was dissolved in dioxane and decolorized with charcoal three times, then the dioxane was removed by distillation. The residue was recrystallized from ether by the Soxhlet-extractor technique, yielding 2.0 g. (32%) of tan solid, m.p. 175–178°. The compound has been reported to melt at 177°, 173°, and 172–174° (7–9).

Anal. Calc'd for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10.
Found: C, 64.36; H, 5.05.

SUMMARY

2-Methoxy-4′,5-bis(carboxymethyl)diphenyl ether, corresponding to the diphenyl ether moiety of the isotetrandrine structure, was prepared by a Willgerodt reaction with 2-methoxy-4′,5-diacetyldiphenyl ether. The latter and 2-methoxy-4′,5-dicarboxydiphenyl ether were prepared by appropriate Ullmann diphenyl ether syntheses.

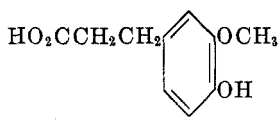
IV. 2,2′,3-TRIMETHOXY-4′,5-BIS(β-CARBOXYETHYL)DIPHENYL ETHER AND RELATED COMPOUNDS

WILSON M. WHALEY, MORTON MEADOW, AND WALTER L. DEAN

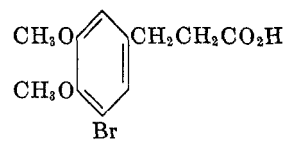
The synthesis of 2,2′,3-trimethoxy-4′,5-bis(β-aminoethyl)diphenyl ether (II) was described in Part II of this series. Due to the meager yield of diamine obtained in that synthesis, alternative routes have been investigated.

The bis(β-carboxyethyl) derivative IX was prepared so that it could be degraded to the desired diamine II. The intermediates required for the Ullmann diphenyl ether synthesis were hydroferulic acid (VII) and β-(5-bromo-3,4-dimethoxyphenyl)propionic acid (VIII). The former was prepared in excellent yield by reduction of ferulic acid in alkali with Raney nickel alloy, no demethylation being observed in the reaction (13).

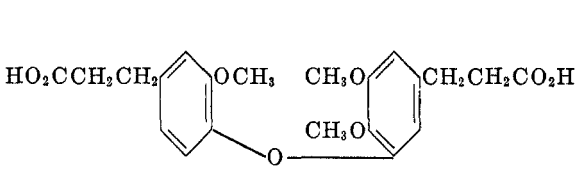
Synthesis of the bromo acid VIII was less easily accomplished. Bromination of hydroferulic acid gave a mixture of the 5-bromo and 6-bromo derivatives as shown by methylation and oxidation to the bromoveratric acids. 6-Bromohydroferulic acid and β-(6-bromo-3,4-dimethoxyphenyl)propionic acid were separated but the 5-isomers were not. 5-Bromovanillin was converted to 5-bromoferulic acid (14) and reduced to 5-bromohydroferulic acid by sodium amalgam in an alkaline medium (28% yield). Raney nickel alloy in alkali debrominated 5-



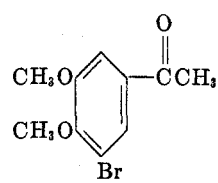
VII



VIII



IX



X

bromoferulic acid before reducing the double bond. Methods involving reduction with red phosphorus and iodides or iodine also failed (15). Low-temperature methylation (16) of 5-bromohydroferulic acid yielded VIII in good yield.

An Ullmann reaction between the potassium salt of methyl hydroferulate and methyl β-(5-bromo-3,4-dimethoxyphenyl)propionate afforded 28% of IX along with 35% of methyl β-(3,4-dimethoxyphenyl)propionate, which resulted from debromination of the 5-bromo compound.

5-Bromoacetoveratrone (X) was prepared in 17% yield by the reaction of dimethylcadmium with 5-bromoveratroyl chloride, in 29% yield by the reaction of diazomethane with 5-bromoveratraldehyde according to Mosettig's procedure (17) for acetopiperone, and in 46% yield by the reaction of methylmagnesium iodide with 5-bromoveratronitrile under forcing conditions. The product of the Grignard reaction, however, contained 15% of the debrominated product, acetoveratrone. It had been intended to condense acetovanillone with 5-bromoacetoveratrone under Ullmann conditions and subject the expected 2,2′,3-trimethoxy 4′,5-diacetyldiphenyl ether to a Willgerodt reaction to obtain a useful two-carbon side chain, but the condensation failed.

EXPERIMENTAL[3]

Hydroferulic acid (VII). To a well-stirred solution of 50 g. (0.26 mole) of ferulic acid (18) in 1.5 l. of 10% sodium hydroxide solution was added 100 g. of Raney nickel alloy over a period of 20 minutes. The reaction mixture was filtered and the Raney nickel was washed with two 25-ml. portions of water. The united filtrates were poured into 700 ml. of concentrated hydrochloric acid and then were evaporated until oily droplets of hydroferulic acid were visible. The cooled concentrate was extracted with three portions of a 2:1 benzene-ether mixture. The combined extracts were concentrated, and the crystals which deposited weighed 48.0–50.5 g. (95–100%), m.p. 90–91°. The reported (19, 20) melting points are 89–90° and 90°.

Methyl hydroferulate. A mixture of 50 g. (0.25 mole) of hydroferulic acid, 500 ml. of dry methanol, and 10 ml. of concentrated sulfuric acid was refluxed for 14 hours, excess methanol was removed by distillation, and then water was added to the residue. The oil which separated was extracted with three portions of ether, and the combined extracts were dried over magnesium sulfate, and filtered. Evaporation of the ether and distillation of the residue yielded 48.5 g. (96%) of methyl hydroferulate, b.p. 148–150°/3–4 mm.

Anal. Calc'd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71.

Found: C, 62.98; H, 6.79.

The ester was converted to its potassium salt by treatment with potassium methoxide in methanol.

Bromination of hydroferulic acid. Hydroferulic acid was brominated in glacial acetic acid at room temperature. The reaction mixture was diluted with water, decolorized with charcoal, and concentrated to one-half its original volume. The crystals of 6-bromohydroferulic acid which separated were recrystallized several times from dilute ethanol and melted at 138–139°.

Anal. Calc'd for $C_{10}H_{11}BrO_4$: C, 43.66; H, 4.03.

Found: C, 43.60; H, 3.90.

Methylation of the product with dimethyl sulfate and potassium hydroxide in methanol yielded white needles of β-(6-bromo-3,4-dimethoxyphenyl)propionic acid which after recrystallization from benzene melted at 119°. The reported (21) melting point is 118–119°.

5-Bromoferulic acid. A mixture of 40 g. (0.17 mole) of 5-bromovanillin (22), 54 g. (0.52 mole) of malonic acid, 170 ml. of dry pyridine, and 1.5 ml. of piperidine was heated on the steam-cone for 90 minutes and then poured into a stirred mixture of 300 ml. of concentrated hydrochloric acid and crushed ice. The solid which separated was collected and washed successively with 5% hydrochloric acid and water. After drying it weighed 43 g. (91%), m.p. 250–252° (decomp.). After three recrystallizations from 95% ethanol, the melting point was 257–258° (decomp.). The reported (14) melting point of the bromo acid is 246° (decomp.).

Anal. Calc'd for $C_{10}H_9BrO_4$: C, 43.98; H, 3.32; OCH_3, 11.36.

Found: C, 43.95; H, 3.38; OCH_3, 11.43.

5-Bromohydroferulic acid. To a vigorously stirred solution of 15 g. (0.055 mole) of 5-bromoferulic acid in 210 ml. of 10% sodium hydroxide was added 135 g. of 2.5% sodium amalgam (23) over a period of 1 hour. Stirring was continued for 30 minutes, then the reaction mixture was decanted from the mercury and filtered. The mercury was washed with water and the united filtrate and washings were extracted with ether, which was discarded. The aqueous layer was poured into 350 ml. of concentrated hydrochloric acid, 200 ml. of water was added, and the resultant mixture was extracted with three portions of benzene. The benzene extract was washed with water, filtered, and concentrated. The concentrate deposited 4.2 g. (28%) of a white solid, m.p. 110–112°. Two recrystallizations from benzene and one from 50% ethanol raised the melting point to 115–116°.

Anal. Calc'd for $C_{10}H_{11}BrO_4$: C, 43.66; H, 4.03.

Found: C, 43.82; H, 4.10.

β-(5-Bromo-3,4-dimethoxyphenyl)propionic acid (VIII). To a cooled solution of 4.2 g.

(0.015 mole) of 5-bromohydroferulic acid in 14 ml. of methanol was added 4.1 g. (0.032 mole(of dimethyl sulfate, and the mixture was cooled to −5°. The cooling bath was then removed and a solution of 3.85 g. (0.075 mole) of potassium hydroxide in water was added over a period of 15 minutes. After refluxing the reaction mixture for 90 minutes, the methanol was removed by distillation and water was added to the residue. Acidification with concentrated hydrochloric acid precipitated the bromo acid, which was extracted with a 2:1 benzene-ether mixture. The extract was washed with water and concentrated. The concentrate yielded 3.2 g. (73%) of β-(5-bromo-3,4-dimethoxyphenyl)propionic acid which after decolorization and recrystallization from benzene had m.p. 119–119.3°.

Anal. Calc'd for $C_{11}H_{13}BrO_4$: C, 45.69; H, 4.53.

Found: C, 45.69; H, 4.43.

Methyl β-(5-bromo-3,4-dimethoxyphenyl)propionate. The acid was esterified (93% yield) according to the procedure described for preparing methyl hydroferulate. The ester had a b.p. 150°/1 mm.

Anal. Calc'd for $C_{12}H_{15}BrO_4$: C, 47.53; H, 4.99.

Found: C, 47.79; H, 4.93.

2,2',3-Trimethoxy-4',5-bis(β-carboxyethyl)diphenyl ether (IX). The diphenyl ether was prepared under Ullmann conditions previously described (1). Heating equimolar quantities of potassium methyl hydroferulate, methyl β-(5-bromo-3,4-dimethoxyphenyl)propionate, and copper bronze for 6 hours at 180–185° and distillation of the extract of the reaction mixture yielded 35% of methyl β-(3,4-dimethoxyphenyl)propionate. Distillation of the saponified residue at 214–247° (bath)/0.6 micron afforded 28% of a clear, yellow liquid.

Anal. Calc'd for $C_{21}H_{24}O_8$: C, 62.37; H, 5.98.

Found: C, 62.28; H, 6.29.

5-Bromoacetoveratrone (X). *Procedure A.* Dimethylcadmium was allowed to react with 5-bromoveratroyl chloride according to the procedure described by Cason and Prout (24). The residual oil was distilled to yield 17% of a light-yellow liquid, b.p. 122–125°/1 mm.

Anal. Calc'd for $C_{10}H_{11}BrO_3$: C, 46.35; H, 4.28; Br. 30.84.

Found: C, 46.33; H, 4.38; Br, 30.86.

Procedure B. When 5-bromoacetoveratrone was prepared by treating 5-bromoveratraldehyde with diazomethane according to Mosettig's procedure (17) for preparing acetopiperone from piperonal, there was obtained 29% of a white semisolid, b.p. 122–124°/1 mm.

Anal. Found: C, 46.35; H, 4.20.

The ketone formed a *2,4-dinitrophenylhydrazone* in ethyl acetate which when recrystallized from the same solvent had m.p. 234–235°.

Anal. Calc'd for $C_{16}H_{15}BrN_4O_6$: C, 43.75; H, 3.44.

Found: C, 43.83; H, 3.45.

Procedure C. To a solution of methylmagnesium iodide prepared from 11.64 g. (0.48 mole) of magnesium turnings and 68 g. (0.48 mole) of methyl iodide in 1.35 l. of di-*n*-butyl ether was added 38.8 g. (0.16 mole) of solid 5-bromoveratronitrile (25), the temperature of the Grignard solution being raised to 70° before addition of the nitrile. The reaction mixture was vigorously stirred at 70° for 6 hours and then decomposed by pouring into a mixture of crushed ice and sulfuric acid. After vigorously stirring the mixture for 2 hours on a steam-plate, the mixture was cooled and the layers were seprated. The aqueous layer was extracted with ether and the extract was washed successively with 0.2 *N* sodium hydroxide and water. The ether was removed by distillation and the residue was distilled to yield 19.0 g. (46%) of a white solid, b.p. 135–138°/1.5 mm., m.p. 53–62°.

Anal. Found: C, 49.14, 48.81; H, 4.79, 5.02.

The analytical data correspond to a mixture of 85% of the desired product and 15% of the debrominated compound, acetoveratrone.

The 2,4-dinitrophenylhydrazone exhibited the same characteristics (melting point and mixture melting point) as the 2,4-dinitrophenylhydrazone prepared in *Procedure B.*

It is noteworthy that methylmagnesium iodide failed to react with 5-bromoveratronitrile in a medium of refluxing ether, unchanged 5-bromoveratronitrile being recovered.

No 2,2′,3-trimethoxy-4′,5-diacetyldiphenyl ether could be isolated from the reaction products when 5-bromoacetoveratrone and the potassium salt of acetovanillone were subjected to the Ullmann reaction. All attempts to obtain the diacetyldiphenyl ether by varying the conditions were unsuccessful. Debromination played a large part in all of the attempted syntheses.

SUMMARY

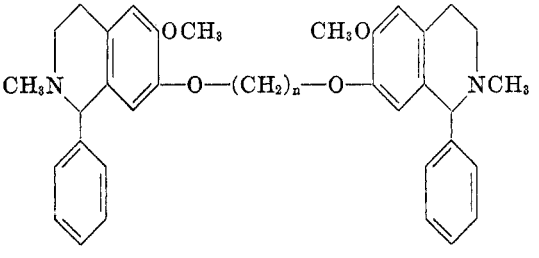
A synthesis of 2,2′,3-trimethoxy-4′,5-bis(β-carboxyethyl)diphenyl ether in 28% yield from potassium methyl hydroferulate and methyl β-(5-bromo-3,4-dimethoxyphenyl)propionate under Ullmann conditions is described, as is the preparation of the necessary intermediates. Three methods of preparing 5-bromoacetoveratrone are also described.

V. SOME SIMPLE ANALOGS

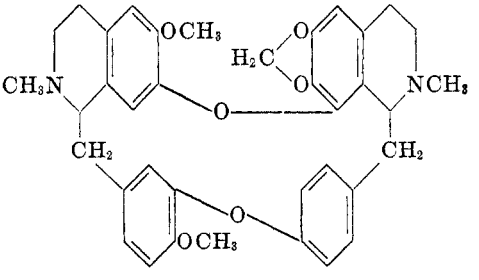
WILSON M. WHALEY AND CHARLES N. ROBINSON

Japanese interest in cepharanthine (III, R + R′ = CH_2, or XII, the actual structure being undetermined) and isotetrandrine (III, R = R′ = CH_3) as tuberculostatic agents has led to the synthesis of numerous analogous compounds (26). Since none of the analogs have had two isoquinoline nuclei joined by ether linkages to their benzo rings, a series of such compounds (XI) has been prepared for bacteriological evaluation.

Homovanillylamine was prepared according to Burger (27) and converted to



XI



XII

its O,N-dibenzoyl derivative (28). Cyclization to 1-phenyl-6-methoxy-7-benzoyloxy-3,4-dihydroisoquinoline was accomplished by the Bischler-Napieralski