with chloroform, concentrated to half its original volume, and again washed with chloroform. Basification of the aqueous solution with sodium hydroxide resulted in precipitation of alumina, which was separated by filtration. The filtrate was extracted with chloroform and the alumina was extracted for 4 hours with chloroform in a Soxhlet extractor. Evaporation of the extracts yielded 0.3 g. of the crude diamine II.

A portion of the diamine, in benzene, was converted to its dihydrochloride by dry hydrogen chloride.

Anal. Calc'd for $C_{19}H_{28}Cl_2N_2O_4$: C, 54.42; H, 6.70; N, 6.68.
Found: C, 54.25; H, 6.92; N, 6.42.

Catalytic reduction of the bis(cyanomethyl) compound with platinum oxide in acetic anhydride according to Carothers and Jones (3) required 16 hours for nearly theoretical absorption of hydrogen. The intermediate diacetyl derivative was hydrolyzed with concentrated hydrochloric acid. The base freed by addition of sodium hydroxide was dissolved in benzene and treated with hydrogen bromide, yielding 30% of tan dihydrobromide, m.p. 120–130° (decomp.).

Anal. Calc'd for $C_{19}H_{28}Br_2N_2O_4 \cdot C_6H_6$: C, 51.20; H, 5.84; N, 4.78.
Found: C, 51.21; H, 5.86; N, 4.98.

Benzoylation by the Schotten-Baumann procedure converted the diamine to an amorphous dibenzoyl derivative which was apparently associated with two molecules of benzene.

Anal. Calc'd for $C_{33}H_{34}N_2O_6 \cdot 2C_6H_6$: C, 76.03; H, 6.52.
Found: C, 75.61; H, 6.21.

SUMMARY

2,2′,3-Trimethoxy-4′,5-bis(β-aminoethyl)diphenyl ether has been synthesized from 2,2′,3-trimethoxy-4′,5-dicarboxydiphenyl ether by (a) reduction of the diacid to a dialcohol, (b) conversion of the dialcohol to a dihalide, (c) formation of a dinitrile from the dihalide, and (d) reduction of the dinitrile. The yields of the last two processes were low and various attempts to improve them have been unsuccessful.

III. 2-METHOXY-4′,5-BIS(CARBOXYMETHYL)DIPHENYL ETHER

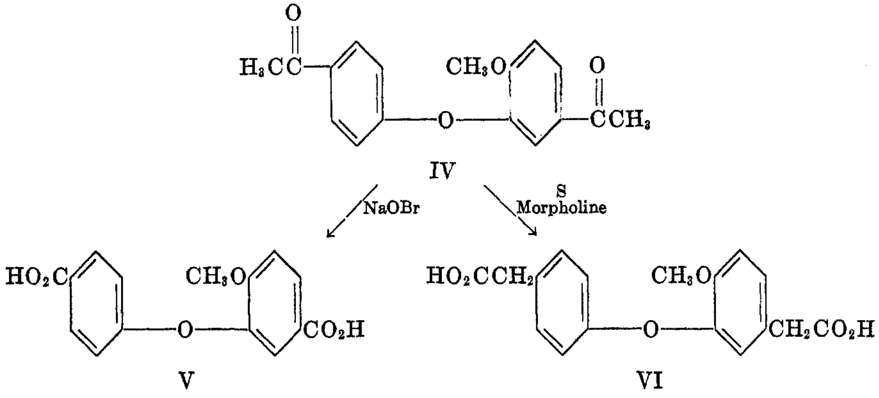
WILSON M. WHALEY, WALTER L. DEAN, AND LEE N. STARKER

The first paper (1) of this series described a synthesis of 2,2′,3-trimethoxy-4′,5-dicarboxydiphenyl ether, an important intermediate for preparing the bisisoquinoline portion of the isotetrandrine molecule. This paper describes the preparation of 2-methoxy-4′,5-bis(carboxymethyl)diphenyl ether (VI), which will form the diphenyl ether moiety of the alkaloid. The diphenyl ether VI has been synthesized by other workers (7–9), but the method described here is more convenient.

The first preparation of VI was by the Ullmann condensation of potassium methyl 4-hydroxyphenylacetate and methyl 3-bromo-4-methoxyphenylacetate (7), in unstated yield. It has also been synthesized (8, 9) through a double Arndt-Eistert reaction on the diacid chloride of 2-methoxy-4′,5-dicarboxydiphenyl ether (V). Preparation of V has been achieved by oxidation of the corresponding dimethyldiphenyl ether (9) and by the Ullmann synthesis using methyl 4-bromobenzoate and potassium methyl isovanillate (62% yield) (10).

2-Methoxy-4′,5-diacetyldiphenyl ether (IV) was prepared in 61% yield by an *Ullmann reaction* with 4-bromoacetophenone and the potassium salt of isoacetovanillone. Its identity was confirmed by conversion to V through the haloform reaction. A dual Willgerodt reaction converted the diketone IV into an oily bis(thiomorpholide) which was hydrolyzed to the desired diacetic acid VI in 32% yield.

Considerable importance can be attached to the yields obtained in forming a diphenyl ether (V) from methyl 3-bromoanisate and potassium methyl 4-hydroxybenzoate. Much better yields resulted (10) when the same ether was prepared from methyl 4-bromobenzoate and potassium methyl isovanillate, and when a similar ether (IV) was prepared from 4-bromoacetophenone and potassium isoacetovanillone. Since the Ullmann reaction must involve displacement of a bromide ion by a phenolic anion,[4] it will always be desirable to use the less hindered and more highly activated bromide, when the two possible starting materials are of equal availability.



EXPERIMENTAL[3]

Starting materials. Isoacetovanillone (m.p. 91.5–93°) was prepared (26%) by acetylating guaiacol with acetic anhydride and sulfuric acid, followed by saponification of the ester (11). The isoacetovanillone and methyl 4-hydroxybenzoate were converted to their potassium salts by treatment with potassium methoxide in methanol. Bromination of anisic acid yielded 77% of 3-bromoanisic acid (10) (m.p. 211–212°), which was esterified (89%) with absolute methanol and sulfuric acid; the methyl ester melted at 94–95° (12).

2-Methoxy-4',5-dicarboxydiphenyl ether (V). A mixture of 12.25 g. (0.048 mole) of methyl 3-bromoanisate, 7.2 g. (0.048 mole) of potassium methyl 4-hydroxybenzoate, and 0.25 g. (0.004 g.-atom) of copper bronze[5] was finely ground in a mortar and then heated at 190–200° for 4 hours. The mixture was extracted with five 50-ml. portions of ether. The extract was washed with potassium hydroxide solution, then with water, and dried over sodium sulfate. Distillation yielded 5.0 g. (60%) of methyl anisate boiling at 93–96°/2 mm. and melting at 45–46°. The distillation residue was saponified by refluxing for 8 hours with 3% methanolic potassium hydroxide solution. After distillation of the methanol, water was added, and the solution was acidified with sulfuric acid. The precipitated product was washed with water

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[4] The reaction is not actually so simple; the catalytic effect of copper and its derivatives is unexplained.

[5] Copper Lining Bronze XX, United States Bronze Powder Works, New York, New York.

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.