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A SYNTHETIC APPROACH TO ISOTETRANDRINE. I. 2,2′,3-TRIMETHOXY-4′,5-DICARBOXYDIPHENYL ETHER

WILSON M. WHALEY, LEE STARKER, AND MORTON MEADOW

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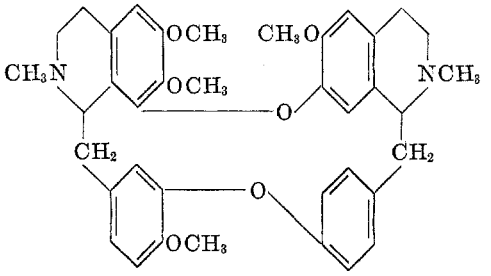
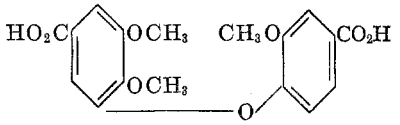
Numerous reports (1) over a period of years have claimed a high degree of antitubercular activity for some of the bis(benzylisoquinoline) alkaloids; however, samples purchased in Japan have failed to exhibit unusual tuberculostatic activity in this country (2, 3). In the meantime a program was begun to evolve methods of synthesizing the bis(benzylisoquinoline) alkaloids.



I



II

The work reported here is concerned with the initial step in a projected synthesis of isotetrandrine (I), the structure of which has recently been established (4). The diastereoisomers of isotetrandrine (tetrandrine and phaeanthine) as well as the unknown optical antipode will also be obtained in this synthesis. No macrocyclic bis(benzylisoquinoline) has ever been synthesized. The synthetic approach was devised prior to learning that Kondo (5) had performed similar preliminary experiments with the intention of synthesizing cepharanthine. Some experiments have also been conducted in this country (6), but difficulty was encountered in the Ullmann synthesis of the desired diphenyl ethers. The diphenyl ether II is a necessary intermediate to the synthesis. It has now been prepared in reasonably good yield and converted (7) to 2,2′,3-trimethoxy-4′,5-bis(2-aminoethyl)diphenyl ether. The latter should couple with 2-methoxy-4′,5-bis(carboxymethyl)diphenyl ether (8) to form a diamide capable of conversion to isotetrandrine and its isomers through the Bischler-Napieralski reaction followed by methylation and reduction.

Compounds of comparable complexity to 2,2′,3-trimethoxy-4′,5-dicarboxydiphenyl ether (II) have been prepared only in very low yields. 2′-Methoxy-2,3-methylenedioxy-4′,5-dicarboxydiphenyl ether (5) and 2-methoxy-2′-ethoxy-4,5,5′-tricarboxydiphenyl ether (9) were formed in yields of 10 and 2%,

respectively. In the former case, the methylenedioxy group should offer less steric hindrance than the methoxyl groups of II. Since a fairly large quantity of II was required, an extensive study was necessarily made of the Ullmann method of synthesis. Yields of less than 1% were encountered in the first attempts, but the technique finally adopted and described in the experimental section consistently gave yields in excess of 25%. Subsequent work has led to the realization that these conditions are not invariably applicable for the synthesis of all diphenyl ethers, but represent a useful starting point for exploratory work such as reported here.

Synthesis of diphenyl ethers possessing ester functions has usually been less efficient than synthesis of other types. King (9) has partly explained the low yields by showing that dehalogenation of the aryl halide and alkylation of the hydroxyl group (with the alkyl group of the ester) occur, sometimes consuming over half of the starting materials. In the thirty-eight experiments conducted by us, debromination of methyl 5-bromoveratrate was an important side reaction, yielding large quantities (30–70%) of methyl veratrate. As methyl veratrate would also have been the product of methylation of methyl vanillate by the ester groups according to King, an experiment was performed using the ethyl esters. No ethyl 3-methoxy-4-ethoxybenzoate was detected.

Other observations during this study were: (a) rigorously anhydrous conditions are not necessary, though water in more than trace amounts is inhibitory; (b) addition of cupric acetate or pyridine was not beneficial in the few cases tried; (c) using diphenyl ether as a solvent is deleterious; (d) methyl 5-bromoveratrate gave better results than methyl 5-iodoveratrate. Use of the copper salt of methyl vanillate without metallic copper yielded no product (10); (e) the reaction may be run with large quantities, though Kondo (5) reported to the contrary for a similar compound; (f) it is desirable to use copper in at least equimolar quantities. Cuprous oxide may be used in place of copper, but cupric oxide may not. It is noteworthy that debromination was not lessened appreciably when the oxides were used, indicating that the copper is not responsible for dehalogenation; (g) temperatures ranging from 150–240° were tried, the optimum being about 180–185°; (h) an excess of the bromo ester was not beneficial.

EXPERIMENTAL[1]

Starting materials. Methyl and ethyl vanillate were prepared from vanillin (11). 5-Bromovanillin (12) was methylated (13) to form 5-bromoveratraldehyde which was oxidized (14) to 4-bromoveratric acid and converted to the methyl and ethyl esters in the usual manner. Methyl 5-iodoveratrate was prepared in the same way from 5-iodovanillin (15). Potassium methyl vanillate was formed from methyl vanillate and potassium methoxide in methanol; the methanol was removed by distillation and the salt was dried *in vacuo*. The sodium salt was prepared in the same way and the copper salt was prepared by metathesis of cupric sulfate and sodium methyl vanillate.

2,2',3-Trimethoxy-4',5-dicarboxydiphenyl ether (II). An intimate mixture of 70 g. (0.32 mole) of potassium methyl vanillate, 88 g. (0.32 mole) of methyl 5-bromoveratrate, and 20 g. (0.32 g.-atom) of copper[2] was heated at 180° for six hours in a 500-ml., round-

[1] Analyses by Galbraith Laboratories, Knoxville, Tenn. Melting points were obtained on a calibrated apparatus.

[2] Copper Lining Bronze XX, U. S. Bronze Powder Works, New York.

bottomed flask equipped with a reflux condenser and an inlet for dry nitrogen. The temperature was easily controlled with a metal bath contained in an electric heating mantle. Two such reaction mixtures were cooled and extracted with ether in a Soxhlet extractor for six hours. The extract was washed with 3% potassium hydroxide solution and water, dried over magnesium sulfate, and evaporated. Methyl veratrate was removed by distillation at 110°/0.6 mm. (83 g., 66%). The residue was saponified with methanolic potassium hydroxide by refluxing for three hours; the methanol was evaporated and water was added. After being washed with ether the aqueous solution was acidified to Congo Red with concentrated sulfuric acid. The oil which separated soon solidified. It was washed with water, leached with methanol, then dried, pulverized, and washed with water until the washings contained no further sulfate ion. The final product weighed 61.2 g. (27.4%) and melted at 245–249°. A sample which was sublimed at 200° (bath)/0.001 mm., then recrystallized from dioxane and water, melted at 250–251°. In this reaction the products isolated accounted for 93.4% of the initial methyl 5-bromoveratrate.

Anal. Calc'd for $C_{17}H_{16}O_8$: C, 58.62; H, 4.63.
Found: C, 58.67, 58.64; H, 4.53, 4.66.

During evaporation of the ethereal extract from the Soxhlet extractor there has been obtained a small amount of a sparingly soluble, white solid which melts at 284–286° after recrystallization from a mixture of ethanol and chloroform. The compound has not been identified.

Anal. Found: C, 59.39, 59.43; H, 4.46, 4.39.

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SUMMARY

2,2′,3-Trimethoxy-4′,5-dicarboxydiphenyl ether, an important intermediate for a projected synthesis of isotetrandrine, has been prepared in satisfactory yield. A study of the Ullmann synthesis of diphenyl ethers was necessary to find a useful technique for the preparation, and some general conclusions have been drawn concerning the Ullmann synthesis.

KNOXVILLE, TENNESSEE

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