[CONTRIBUTION NO. 117 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

A SYNTHETIC APPROACH TO ISOTETRANDRINE.[1] II. 2,2′,3-TRIMETHOXY-4′,5-BIS(β-AMINOETHYL)DIPHENYL ETHER

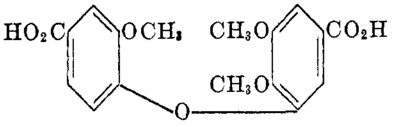
WILSON M. WHALEY,[2] LEE N. STARKER, AND WALTER L. DEAN

Received June 24, 1953

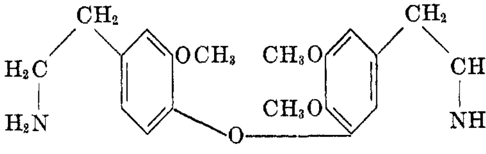
The first article (1) of this series related the synthesis of 2,2′,3-trimethoxy-4′,5-dicarboxydiphenyl ether (I), and the present paper deals with its conversion to 2,2′,3-trimethoxy-4′,5-bis(β-aminoethyl)diphenyl ether (II). The diamine (II) represents almost the entire bisisoquinoline portion of the isotetrandrine molecule (III, R = R′ = CH_3).

Conversion of the dicarboxy ether (I) to the diamino ether (II) was accomplished by the following reactions. Reduction of I to 2,2′,3-trimethoxy-4′,5-bis(hydroxymethyl)diphenyl ether with lithium aluminum hydride in tetrahydrofuran proceeded in nearly quantitative yield. Treatment of the dialcohol with thionyl chloride afforded the corresponding bis(chloromethyl) derivative in good yield. Difficulty was encountered in preparing the bis(cyanomethyl) compound from the dihalide and no sample of dinitrile could be obtained which did not contain a considerable percentage of residual chlorine. Substituting the bis(bromomethyl) compound for the chloro compound did not improve the reaction with potassium cyanide.

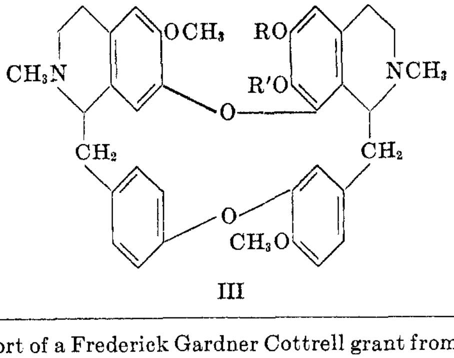
Lithium aluminum hydride reduction of the crude dinitrile resulted in a much lower yield (6%) of II than could be accounted for by the impurity of the dinitrile. It is known that formation of insoluble complexes during reduction of nitriles sometimes results in low yields (2). Reduction of the dinitrile with platnum oxide in acetic anhydride (3) afforded 30% of crude dihydrochloride.



I



II



III

---

[1] The financial support of a Frederick Gardner Cottrell grant from the Research Corporation and a Tennessee Eastman Company fellowship is gratefully acknowledged.

[2] Present address: Pabst Laboratories, Milwaukee 3, Wisconsin.

The dihydrochloride and dihydrobromide of the diamine II were prepared sufficiently pure for corroborative analysis, and the dibenzoyl derivative was also prepared.

Various attempts to apply the Arndt-Eistert homologation to the diacid chloride of I failed. One reason for this was an inability to perform a smooth conversion of I to its acid chloride and corresponding diazoketone. No product except tar could be obtained by the usual Arndt-Eistert procedure (4), the Wilds modification (5), or the Newman variation (6).

EXPERIMENTAL[3]

2,2′,3-Trimethoxy-4′,5-bis(hydroxymethyl)diphenyl ether. A cooled solution of 7.5 g. (0.2 mole) of lithium aluminum hydride in 300 ml. of dry tetrahydrofuran was treated dropwise with 6.42 g. (0.018 mole) of 2,2′,3-trimethoxy-4′,5-dicarboxydiphenyl ether dissolved in 150 ml. of tetrahydrofuran, after which the mixture was refluxed for 30 minutes. Excess lithium aluminum hydride was decomposed by careful addition of water, the flask being cooled in an ice-bath. The mixture was filtered and the residue was washed with four 100-ml. portions of tetrahydrofuran. Removal of the solvent *in vacuo* afforded 5.82 g. (99%) of a viscous oil which could not be distilled in a high-vacuum apparatus due to its tendency to resinify.

Anal. Calc'd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29.
Found: C, 63.50; H, 6.34.

2,2′,3-Trimethoxy-4′,5-bis(chloromethyl)diphenyl ether. A solution of 5.82 g. (0.018 mole) of the bis(hydroxymethyl) compound, 25 ml. of thionyl chloride, and 5 ml. of dry benzene was allowed to stand at room temperature for 2 hours. Excess thionyl chloride was removed *in vacuo* and two 5-ml. portions of benzene were successively added and distilled *in vacuo.* The residue was dark and viscous, weighing 5.42 g. (83%). It distilled at 90–100° (bath)/0.4 micron.

Anal. Calc'd for $C_{17}H_{18}Cl_2O_4$: C, 57.16; H, 5.08; Cl, 19.85.
Found: C, 57.51; H, 5.26; Cl, 19.55.

2,2′,3-Trimethoxy-4′,5-bis(cyanomethyl)diphenyl ether. In a flask equipped with a reflux condenser, stirrer, and dropping-funnel were heated 5.42 g. (0.015 mole) of the bis(chloromethyl) derivative, 100 ml. of acetone, and 50 ml. of ethylene glycol monoethyl ether. A solution of 3.0 g. (0.05 mole) of potassium cyanide in 50 ml. of water was added dropwise to the refluxing solution of the dichloride, after which the mixture was refluxed for 6 hours. After evaporation of the acetone from the filtered mixture, it was extracted three times with chloroform, the latter extract being washed ten times with water to remove the glycol ether. The dark oil (5.32 g.) was distilled at 130° (bath)/0.5 micron. Analysis of the product indicated about one-third of the starting material was converted to the bis(cyanomethyl) compound and one-third to the mono(cyanomethyl) compound.

Anal. Found: N, 4.36, 4.23; Cl, 2.86, 2.96.

Repetition of the above experiment using the bis(bromomethyl) derivative and refluxing for 9 or 21 hours also resulted in incomplete reaction with potassium cyanide.

Anal. Found: N, 5.18; Br, 2.96.

No identifiable product was obtained by treating the bis(bromomethyl) compound with cuprous cyanide in acetone.

2,2′,3-Trimethoxy-4′,5-bis(β-aminoethyl)diphenyl ether (II). A solution of 5.32 g. of lithium aluminum hydride in 100 ml. of dry tetrahydrofuran was refluxed and slowly treated with a solution of 4.83 g. of crude dinitrile in 20 ml. of tetrahydrofuran. The mixture was then refluxed for 2 hours. Following decomposition of excess lithium aluminum hydride with water, 300 ml. of 10% sulfuric acid was added. The aqueous phase was separated, washed

---

[3] Microanalyses by Galbraith Laboratories, Knoxville 17, Tennessee. Melting points determined on a calibrated apparatus.

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