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

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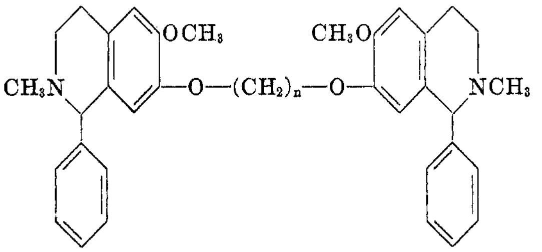
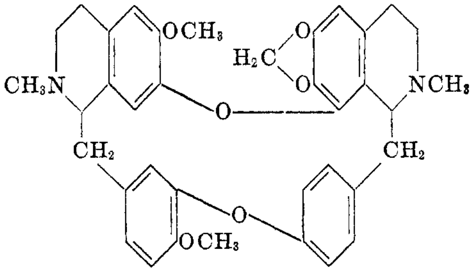
Japanese interest in cepharanthine (III, R + R′ = CH_2, or XII, the actual structure being undetermined) and isotetrandrine (III, R = R′ = CH_3) as tuberculostatic agents has led to the synthesis of numerous analogous compounds (26). Since none of the analogs have had two isoquinoline nuclei joined by 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 its O,N-dibenzoyl derivative (28). Cyclization to 1-phenyl-6-methoxy-7-benzoyloxy-3,4-dihydroisoquinoline was accomplished by the Bischler-Napieralski



XI



XII

reaction (29) using phosphorus pentachloride in chloroform (70% yield). The methiodide was reduced by lithium aluminum hydride to 1-phenyl-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (80%).

Conversion of the tetrahydroisoquinolinol to its polymethylene ethers was efficiently accomplished by the Williamson synthesis. Of the ethers prepared only the pentamethylene ether was easily crystallized. A similar Williamson synthesis was used to prepare 1,2-bis(2-methoxy-4-formylphenoxy)ethane in 65% yield along with some 3-methoxy-4-(β-bromoethoxy)benzaldehyde. The use of such dialdehydes to prepare compounds similar to XI was not further investigated.

EXPERIMENTAL[3]

Homovanillylamine hydrochloride. 3-Methoxy-4-hydroxy-β-nitrostyrene was prepared from vanillin and nitromethane (27). There was obtained 77–80% of product melting at 171–173°. Reduction with lithium aluminum hydride yielded 50–65% of homovanillylamine hydrochloride, m.p. 212–215°. Since the amine is amphoteric its isolation is laborious, but no better procedure could be devised than that of Burger (27).

O,N-Dibenzoylhomovanillylamine. Benzoylation of homovanillylamine hydrochloride by the Schotten-Baumann procedure, using aqueous sodium hydroxide and ether, afforded 87% of the dibenzoyl derivative, m.p. 129–131°. Buck (28) reported m.p. 129°.

Anal. Calc'd for $C_{23}H_{21}NO_4$: C, 73.60; H, 5.60.

Found: C, 73.60; H, 5.68.

1-Phenyl-6-methoxy-7-benzoyloxy-3,4-dihydroisoquinoline. A solution of 53.5 g. (0.145 mole) of O,N-dibenzoylhomovanillylamine and 75 g. of phosphorus pentachloride in 500 ml. of chloroform was allowed to stand for 8 days. The volatile material was removed *in vacuo* and the residue extracted with boiling water. Tar was removed by filtration; the filtrate was basified with ammonium hydroxide and allowed to stand overnight. The white dihydroisoquinoline was collected and recrystallized from dilute ethanol. There was obtained 35 g. (70%) of product, m.p. 192°.

Anal. Calc'd for $C_{23}H_{19}NO_3$: C, 77.31; H, 5.32; N, 3.92.

Found: C, 77.38; H, 5.31; N, 3.71.

Phosphorus oxychloride in refluxing toluene was not a suitable condensing agent, yielding only 10% of the desired dihydroisoquinoline. Isolation of benzoic acid was evidence of debenzoylation.

1-Phenyl-2-methyl-6-methoxy-7-benzoyloxy-3,4-dihydroisoquinolinium iodide. The dihydroisoquinoline (35 g., 0.098 mole) was dissolved in benzene; 30 ml. of methyl iodide was added, and the solution was refluxed until bumping became too vigorous to continue. The methiodide was collected, 15 ml. of methyl iodide was added to the filtrate, and it was refluxed for several hours longer. The precipitated methiodide was collected, making a total of 48 g. (98%) of yellow crystals. After recrystallization from dilute ethanol the product melted at 182–183°.

Anal. Calc'd for $C_{24}H_{22}INO_3 \cdot H_2O$: C, 55.71; H, 4.68; N, 2.71.

Found: C, 55.94; H, 4.35; N, 2.81.

1-Phenyl-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline. To a solution of 7.3 g. (0.192 mole) of lithium aluminum hydride in 1 l. of ether was slowly added 48 g. (0.096 mole) of the methiodide described above. The mixture was refluxed several hours and allowed to stand overnight. It was titrated with 19 ml. of water to form a grey, granular precipitate which was removed. The ethereal solution was evaporated to a small volume to obtain 14.5 g. of the desired product. The grey precipitate which had been removed was extracted in a Soxhlet extractor for 4 days to obtain 6.5 g. of product. The tetrahydroisoquinoline (21 g., 80%) was recrystallized from ether. The clear, colorless plates melted at 155–156°.

Anal. Calc'd for $C_{17}H_{19}NO_2$: C, 75.80; H, 7.11; N, 5.20.

Found: C, 75.50; H, 7.17; N, 5.11.

7,7′-Ethylenedioxybis(1-phenyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline) (XI, n = 2). The tetrahydroisoquinoline (2 g., 0.0074 mole) was dissolved in 0.42 g. (0.0074 mole) of potassium hydroxide in 50 ml. of water, then 0.7 g. (0.0037 mole) of ethylene bromide in 50 ml. of dioxane was added, and the solution was refluxed for 48 hours. The dioxane and water were distilled, water was added, and the mixture was extracted successively with ether and chloroform. When the ethereal solution was dried over potassium hydroxide there was precipitated the potassium salt of the 7-isoquinolinol, which was removed. Treatment of the filtrate with dry hydrogen chloride yielded 0.6 g. of the dihydrochloride of the desired product. The chloroform extract was dried over magnesium sulfate, filtered, and treated with dry hydrogen chloride. The product (1.4 g.) was collected, making 2.0 g. (85%) of the dihydrochloride. An analytical sample of the free base was prepared by adding ammonium hydroxide to an aqueous solution of the dihydrochloride, extracting the precipitate with ether, evaporating the ether, subliming the residue in a high vacuum, and recrystallizing the sublimate seven times from 2-propanol and water. The sample melted at 149–150°.

Anal. Calc'd for $C_{36}H_{40}N_2O_4 \cdot 1/2C_3H_7OH$: C, 75.73; H, 7.46; N, 4.71.
Found: C, 75.46; H, 7.76; N, 4.80.

7,7′-Trimethylenedioxybis(1-phenyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline) (XI, n = 3). The method used for the ethylenedioxy compound was followed, but the free base was crystallized from acetone and water without prior sublimation. It melted at 138–140°.

Anal. Calc'd for $C_{37}H_{42}N_2O_4$: C, 76.78; H, 7.31; N, 4.84.
Found: C, 76.60; H, 7.33; N, 4.84.

7,7′-Tetramethylenedioxybis(1-phenyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline) (XI, n = 4). Prepared by the method used for the trimethylene compound, the product was crystallized from acetone and melted at 132–133°.

Anal. Calc'd for $C_{38}H_{44}N_2O_4$: C, 76.98; H, 7.48; N, 4.73.
Found: C, 76.61; H, 7.70; N, 4.58.

7,7′-Pentamethylenedioxybis(1-phenyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline) (XI, n = 5). Prepared by the method used for the trimethylene compound, the product was crystallized from acetone and water. It melted at 86–87°, resolidified at about 100°, then melted again at 121–122°.

Anal. Calc'd for $C_{39}H_{46}N_2O_4$: C, 77.18; H, 7.64; N, 4.62.
Found: C, 77.09; H, 7.54; N, 4.64.

1,2-Bis(2-methoxy-4-formylphenoxy)ethane. The following procedure was the best of several tried. To a solution of 3.7 g. of potassium hydroxide in 100 ml. of ethanol were added 10 g. of vanillin and 6.2 g. of ethylene dibromide. The mixture was refluxed for 25 hours. After distillation of the alcohol, water was added and the whole was extracted with petroleum ether. The precipitated solid was collected, washed with acetone, and recrystallized from chloroform and ethanol. There was obtained 7 g. (65%) of product melting at 180–181°.

Anal. Calc'd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.46.
Found: C, 65.25; H, 5.47.

Evaporation of the petroleum ether extract afforded white needles of 3-methoxy-4-(β-bromoethoxy)benzaldehyde. After recrystallization from dilute 2-propanol it melted at 69–70°.

Anal. Calc'd for $C_{10}H_{11}BrO_3$: C, 46.33; H, 4.25.
Found: C, 46.41; H, 4.25.

SUMMARY

A series of 7,7′-polymethylenedioxybis(1-phenyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinolines) has been prepared by the reaction of polymethylene dihalides with the potassium salt of 1-phenyl-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline. Preparation of the intermediates and of related compounds is described.