Synthesis of 9-(3,4-Dimethoxyphenoxy)-1,2,10-trimethoxyaporphine

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Abstract □ The reactions leading to the preparation of a pentamethoxyaporphine, a synthetic precursor to the cytotoxic compounds isolated from the genus *Thalictrum*, are described.

Keyphrases □ 9-(3,4-Dimethoxyphenoxy)-1,2,10-trimethoxyaporphine—synthesis □ Aporphines, pentamethoxy—synthesis of 9-(3,4-dimethoxyphenoxy)-1,2,10-trimethoxyaporphine □ *Thalictrum* cytotoxic alkaloids, synthetic precursor—synthesis of 9-(3,4-dimethoxyphenoxy)-1,2,10-trimethoxyaporphine

The cytotoxic effects (1) of the alkaloids thalicarpine (2), hernandaline (3), thalmelatine, and other aporphine benzylisoquinoline alkaloids have been reported. The interest in these structures led us to seek an efficient synthetic route to thalicarpine. However, a recent total synthesis of this molecule (4), reported without experimental detail, prompted us to report our findings at this time and turn our attention toward other antitumor agents of interest synthetically.

DISCUSSION

The required aromatic halves of the diaryl ether III were both obtained by short processes from readily available materials. The intermediate 2-bromo-4-methyl-5-nitroanisole, I (Scheme I), was obtained in good yield (80%) by a Sandmeyer reaction. Baeyer-Villiger oxidation of veratraldehyde followed by ammonolysis of the formate ester gave the phenol II.

Heating a mixture of the bromo compound I and the phenol II with aqueous potassium hydroxide in dimethylformamide gave reasonable yields of the diaryl ether III. Unreacted I and the product III were separated and purified by column chromatography. Yields of III based on converted I were 40–50%.

Homoveratrylamine was converted into *N*-methyl-6,7-dimethoxy-3,4-dihydroisoquinolinium iodide, IV, by a three-step sequence of formylation in 98% formic acid (95% yield), cyclization with phosphorus pentachloride in chloroform (75%), and methylation with methyl iodide (94%).

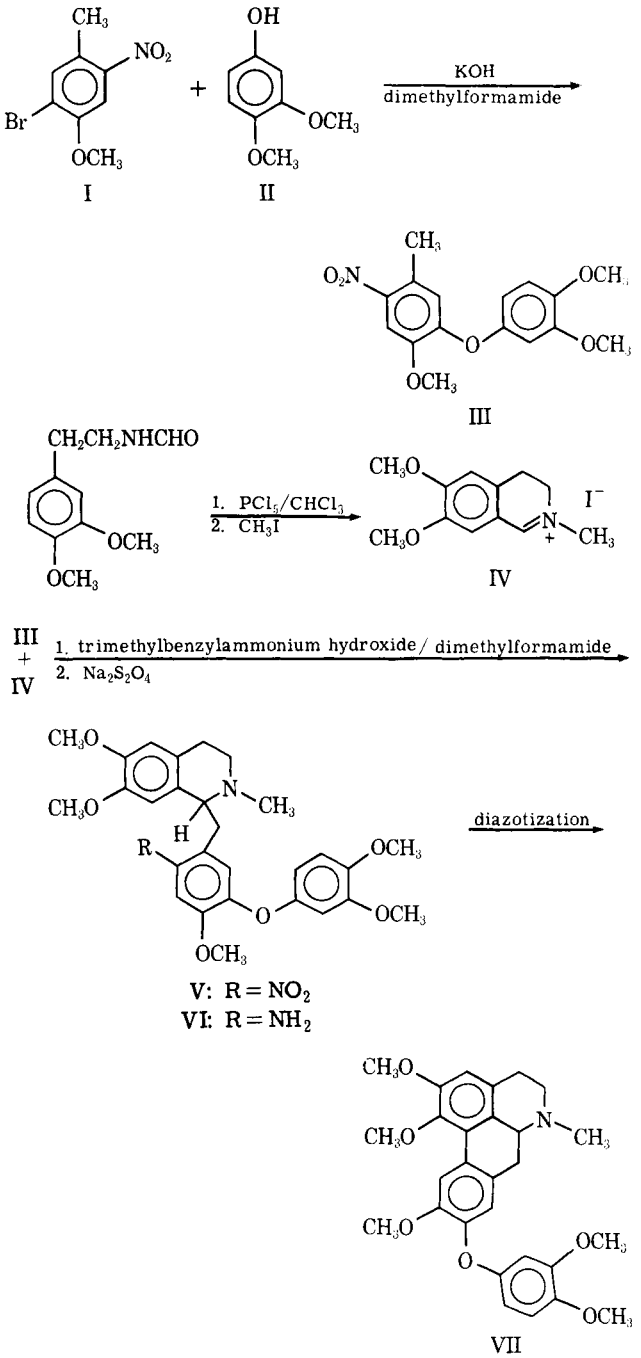
Several base and solvent pairs were investigated for the alkylation of IV with III. One of the most convenient systems was trimethylbenzylammonium hydroxide[1] in dry dimethylformamide. Conversion to V required long reaction times, but yields based on converted III were very good (>90%).

Reduction of the nitro group in V was accomplished by a very convenient method, wherein an aqueous solution of the hydrochloride salt was treated with sodium hydrosulfite with the product VI isolated as the dihydrochloride. The diazotization of VI successfully gave the aporphine VII but in poor yield.

Compounds I–VII were evaluated in the leukemia L-1210 rodent tumor system following standard National Cancer Institute, Chemotherapy, protocols (7). None of the compounds tested was active in the doses and regimens employed.

EXPERIMENTAL

2-Bromo-4-methyl-5-nitroanisole (I)—A suspension of 5-methyl-4-nitro-*o*-anisidine (50.0 g.) in 48% aqueous hydrobromic acid (473 ml.) was stirred for 0.5 hr. at room temperature to disperse the acid-insoluble amine thoroughly. The stirred suspension was treated at room temperature with a solution of sodium nitrite (19.2 g.) in water (100 ml.). Urea (1.0 g.) was added after 5 min. Cuprous oxide (30 g.) was added after an additional 5 min. A cool water bath was used to moderate this slightly exothermic step. The



Scheme I—Synthesis of Aporphine VII

[1] Triton B.

product appears within moments as a light-colored precipitate. The product was collected by filtration (sintered glass) after 0.5 hr., washed with water, 0.5 *N* sodium hydroxide solution, and then more water. It was then dissolved in benzene. The benzene solution was dried, filtered, and concentrated to a dark oil which was distilled *in vacuo* to give 53.9 g. (80%) of product. One recrystallization from 95% ethanol gave light-yellow crystals, m.p. 85–86°. Further recrystallization from the same solvent raised the melting point to 89–90° [lit. (4) m.p. 91–92°].

Anal.—Calc. for $C_8H_8BrNO_3$: C, 39.05; H, 3.28; Br, 32.47; N, 5.69. Found: C, 38.96; H, 3.09; Br, 32.48; N, 5.65.

3,4-Dimethoxyphenol (II)—A solution of veratraldehyde (120 g.) and *p*-toluenesulfonic acid monohydrate (0.16 g.) in anhydrous ether (500 ml.) was treated with *m*-chloroperoxybenzoic acid (154.2 g.). Spontaneous reflux began after 0.5 hr. and ceased in 1.25 hr. After 3 hr., *m*-chlorobenzoic acid began precipitating; after 18 hr., the mixture was filtered. The filter cake was dissolved in 10% sodium sulfite solution and extracted with ether, and the extract was added to the filtrate. The solution was washed with three portions of 10% sodium sulfite solution, twice with water, and dried over anhydrous sodium sulfate. The ether was removed on a steam bath. Trituration of the residual oil with absolute ethanol caused rapid crystallization of 55.0 g. (42%) of the formate ester, m.p. 56–57°. NMR ($CDCl_3$), p.p.m.: 8.24 (s, 1, OCHO), 6.94–6.58 (m, 3, ArH), and 3.84 (s, 6, OCH_3).

The formate ester (47.4 g.) was dissolved in concentrated ammonium hydroxide (210 ml.) under nitrogen. After 1 hr., the light-yellow solution was poured onto ice (100 g.) and acidified under nitrogen with concentrated hydrochloric acid (130 ml.). The cooled solution was filtered to give 30.2 g. of beige crystals. The filtrate was extracted with ether to give an additional 4.95 g. of II (total 87%). The combined crops were distilled *in vacuo* (107° at 0.006 torr to 150° at 0.06 torr) to give a colorless product, m.p. 79–80° [lit. (5) m.p. 78–80°].

5-(3,4-Dimethoxyphenoxy)-4-methoxy-2-nitrotoluene (III)—A solution of potassium hydroxide (9.60 g.) in water (5.0 ml.) was added dropwise to a stirred solution of I (40.0 g.) and II (27.6 g.) in dimethylformamide (25.0 ml.) under nitrogen. The mixture was heated for 8 hr. at 126°. Additional II (6.28 g.) and potassium carbonate (5.62 g.) were added, and heating was continued for 6 hr. The cooled mixture was diluted with ethyl acetate and washed with dilute sodium hydroxide, dilute hydrochloric acid, and saturated aqueous sodium chloride solutions. After drying (anhydrous sodium sulfate) and filtration, the solution was evaporated *in vacuo* to give 47.5 g. of a black syrup. Two chromatographs on basic alumina (benzene and benzene–petroleum ether, 1:1) gave 11.58 g. of I, m.p. 85–88°, and 17.61 g. of III (48%). Recrystallization of III from 95% ethanol gave light-yellow crystals, m.p. 127–128° [lit. (4) m.p. 127–128°]. NMR ($CDCl_3$), p.p.m: 7.72 (s, 1, ArH), 6.86 [d, 1 (J_o = 9 Hz.), ArH], 6.62 (s, 1, ArH), 6.56 [d, 1 (J_m = 2.5 Hz.), ArH], 6.54 [q, 1 (J_o = 9 Hz., J_m = 2.5 Hz.), ArH], 3.94 (3, s, OCH_3), 3.87 (3, s, OCH_3), 3.82 (3, s, OCH_3), and 2.23 (3, s, CH_3).

Anal.—Calc. for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39. Found: C, 60.33; H, 5.44; N, 4.27.

***N*-Methyl-6,7-dimethoxy-3,4-dihydroisoquinolinium Iodide (IV)**—Homoveratrylamine was purified by distillation *in vacuo* (94–97° at 6–7 × 10^{-3} torr). The colorless amine (72.57 g.) was refluxed with 98% formic acid (100 ml.) for 40 min., and then the excess formic acid was distilled (83 ml. collected). The clear, colorless residue was diluted with chloroform and washed with two portions of water, dilute sodium bicarbonate, and saturated aqueous sodium chloride solutions. The chloroform solution was dried over anhydrous sodium sulfate, filtered, concentrated, and distilled *in vacuo* to obtain 79.36 g. (94%) of viscous, nearly colorless oil. When the Bischler-Napieralski cyclization was carried out in benzene or toluene solution with phosphorus oxychloride, the best yield obtained was 40%. When phosphorus pentachloride in chloroform was used, the product was obtained in much better yield and quality. Phosphorus pentachloride (48.1 g.) was added to a solution of homoveratrylamine formamide (40.3 g.) in chloroform (200 ml.) at room temperature. After 65 hr., anhydrous ether (250 ml.) was added, causing a yellow precipitate of the hydrochloride salt. The precipitate was filtered, washed with ether, redissolved in chloroform, filtered, and reprecipitated with anhydrous ether to give 33.6 g. (75%) of product. The free base was obtained by basification of an aqueous solution with concentrated ammonium hydroxide. Extraction with benzene and removal of the solvent gave a light-yellow oil which was essentially homogeneous on TLC. The free base (4.47 g.) was placed in a pressure bottle. A test tube containing methyl iodide (5 g.) was placed upright in the pressure bottle which was then sealed. Inverting the bottle mixed the two components. A vigorous reaction ensued which produced a light-yellow crystalline solid. The mixture was warmed 0.5 hr. on a steam bath, cooled, and triturated with anhydrous ether; the resulting light-yellow crystals were filtered to give 7.3 g. (94%) of IV, m.p. 187–193° [lit. (6) m.p. 210–212°]. NMR (D_2O), p.p.m.: 8.72 (s, 1, ArH), 7.08 (s, 1, ArH), 3.96 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 3.76 (s, 3, NCH_3), 3.24 [t, 2 (J = 8 Hz.), NCH_2], and 2.88 [t, 2 (J = 8 Hz.), $ArCH_2$]. This material was found to be suitable for the next step without further purification. In larger scale reactions, a different procedure was useful. The free base (70.7 g.) containing chloroform (7 ml.) was placed in a pressure bottle which was cooled in a dry ice–acetone bath. Cold methyl iodide (57.7 g.) was added, the pressure vessel was sealed, and the mixture was allowed to warm to room temperature. The product was triturated with a mixture of benzene and ether and filtered to give 99.5 g. (81%) of product, m.p. 189–196°.

1-[5-(3,4-Dimethoxyphenoxy)-4-methoxy-2-nitrobenzyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline Hydrochloride (V)—A solution of III (2.84 g.), IV (2.67 g.), and trimethylbenzylammonium hydroxide (3.54 g. of 40% methanolic solution) in 50 ml. of dimethylformamide was stirred under nitrogen for 135 hr. at room temperature. The reaction mixture was diluted with ethyl acetate (150 ml.), washed four times with 100-ml. portions of water, extracted with three 100-ml. portions of 0.2 *N* hydrochloric acid, and washed once more with water (50 ml.). Unreacted III was recovered from the ethyl acetate solution by evaporation of the solvent after drying over anhydrous sodium sulfate. The recovered III was crystallized once from ethanol to give 0.65 g., m.p. 125–126°. The product, V, was extracted as the hydrochloride salt from the combined aqueous acid extracts with four 100-ml. portions of chloroform. The combined chloroform extracts were dried (anhydrous sodium sulfate), concentrated to dryness, and triturated with anhydrous ether to give a light-tan powder (3.60 g., 94% based on converted III). Recrystallization from absolute ethanol gave the pure bright-yellow hydrochloride salt, m.p. 128–130°. NMR ($CDCl_3$), p.p.m.: 7.75 (s, 1, ArH), 6.80 [d, 1 (J_o = 9 Hz.), ArH], 6.60 [d, 1 (J_m = 2.5 Hz.), ArH], 6.60 (s, 1, ArH), 6.38 [m, 1 (J_o = 9 Hz., J_m = 2.5 Hz.), ArH], 6.31 (s, 1, ArH), 5.58 (s, 1, ArH), 3.94 (s, 3, OCH_3), 3.83 (s, 3, OCH_3), 3.81 (s, 3, OCH_3), 3.78 (s, 3, OCH_3), 3.44 (s, 3, OCH_3), and 2.92 (s, 1, CH_3).

Anal.—Calc. for $C_{28}H_{33}ClN_2O_8$: C, 59.94; H, 5.93; N, 4.99. Found: C, 59.78; H, 6.19; N, 4.78.

9-(3,4-Dimethoxyphenoxy)-1,2,10-trimethoxyaporphine Hydrochloride (VII)—Sodium hydrosulfite (250 mg.) was added to a stirred solution of the hydrochloride salt V (200 mg.) in 7.0 ml. of water. Aqueous 6 *N* hydrochloric acid (5 drops) was added after 5 min. The aqueous solution was treated with activated charcoal[2], filtered through diatomaceous earth[3], and extracted with chloroform four times. The combined extracts were dried (anhydrous sodium sulfate), filtered, and concentrated to dryness. Trituration with dry ether gave VI as a dihydrochloride, m.p. 167–170.5° (180 mg., 90%). NMR($CDCl_3$), p.p.m.: 7.54 (s, 1, ArH), 6.67 [d, 1 (J_o = 9 Hz.), ArH], 6.6–6.5 (m, 2, ArH), 6.3–5.8 (m, 3, ArH), 4.9–4.5 (broad, 3, NH_3^+), 3.88 (s, 3, OCH_3), 3.82 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 3.78 (s, 3, OCH_3), 3.61 (s, 3, OCH_3), 4–3.5 (broad, 5, CH_2), 3.2–2.6 (broad, 2, CH_2), and 3.04 (s, 3, NCH_3). M^+ *m/e* 492,494.

A solution of the dihydrochloride of VI (12.7 g.) in methanol (235 ml.) and 3 *N* sulfuric acid (135 g.) was cooled to below 5° and treated with a solution of sodium nitrite (2.2 g.) in water (10 ml.). The cold solution was stirred for 0.5 hr. and diluted with 10 *N* sulfuric acid (120 ml.), and the resulting solution was heated on a steam bath for 0.5 hr. Zinc powder (25 g.) was added in small portions to the hot solution, and this suspension was refluxed another 35 min. The hot reaction mixture was filtered through diatomaceous earth (sintered-glass filter), and the filter was washed with hot water. The washings and the yellow filtrate were combined, chilled, and extracted with four 300-ml. portions of chloroform. The combined chloroform extracts were washed with saturated aqueous sodium chloride, dried (anhydrous sodium sulfate), filtered, and evaporated to dryness, giving 10 g. of an amorphous semisolid material. This was dis-

[2] Norite.
[3] Celite.

solved in water, basified with potassium carbonate, and extracted with benzene. The free base was obtained by chromatography on basic alumina. Elution with benzene and methylene chloride gave 0.85 g. (8%) of VII, which was converted to the hydrochloride salt and recrystallized from *n*-butanol to give an analytical sample decomposing at 213–215°. NMR($CDCl_3$ + D_2O), p.p.m.: 8.15 (s, 1, ArH), 6.85 [d, 1, (J_o = 9 Hz.), ArH], 6.68 (s, 2, ArH), 6.67 [d, 1, (J_m = 5 Hz.), ArH], 6.55 [q, 1, (J_o = 9 Hz., J_m = 5 Hz.), ArH), 3.90 (s, 6, OCH_3), 3.88 (s, 3, OCH_3), 3.85 (s, 3, OCH_3), 3.70 (s, 3, OCH_3), 3.9–3.7 (broad, 2, CH_2), 3.5–2.7 (m, 4, CH_2), 2.94 (s, 3, NCH_3). M^+ *m/e* 475,477.

Anal.—Calc. for $C_{28}H_{32}ClNO_6$: C, 65.43; H, 6.28; N, 2.73. Found: C, 65.19; H, 6.20; N, 2.96.

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Synthesis of Pyrazine Derivatives as Potential Hypoglycemic Agents

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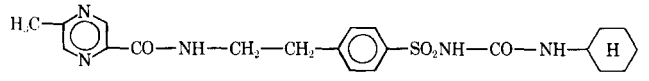
Abstract □ A series of new pyrazine derivatives was synthesized and screened for hypoglycemic activity. Some of these compounds showed weak activity at high dosage levels. Pyrazinoyl-4-ethylthiosemicarbazide was active both in mice and rats.

Keyphrases □ Pyrazine derivatives—synthesized and screened as potential hypoglycemic agents □ Hypoglycemic agents, potential—synthesis and pharmacological screening of pyrazine derivatives □ Pyrazinoyl-4-ethylthiosemicarbazide—synthesis, tested as potential hypoglycemic agent

Previous reports from this laboratory on hypoglycemic drugs showed that certain substituted pyrazine phenylsulfonylureas possess high antidiabetic activity at very low dosage levels. The most favorable compound of this series was *N*-{4-[β-(5-methylpyrazine-2-carboxamido)ethyl]benzenesulfonyl}-*N'*-cyclohexylurea or glipizide (I) (1–4).

Contrary to the other known phenyl-substituted sulfonylureas, the pyrazineamide moiety of this molecule shows a certain hypoglycemic activity (5). Based on this observation, the authors synthesized a series of pyrazine derivatives without the sulfonyl moiety in the molecule for screening for hypoglycemic activity.

Among other derivatives, compounds obtained by introduction of the pyrazine moiety into compounds not belonging to the sulfonylurea class were studied,



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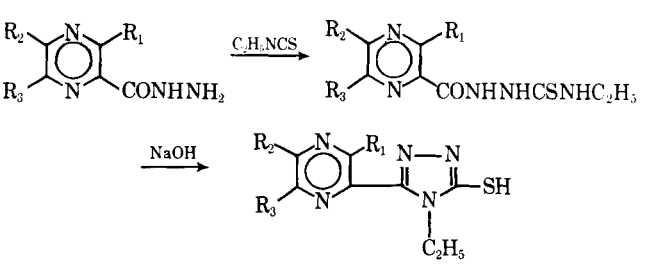
whose antidiabetic activity was known from the literature. It was hoped that this activity could be increased. Thus, the authors synthesized 5-pyrazinyl-4-alkyl-4*H*-1,2,4-triazole-3-thiols. The corresponding 5-phenyl derivatives, according to Mhasalkar *et al.* (6), showed a hypoglycemic activity comparable to tolbutamide. In this paper the synthesis of some corresponding pyrazine oxadiazoles and thiadiazoles is also described.

3-Mercapto-5-(2-pyrazinyl)-4-ethyl-4*H*-1,2,4-triazoles were synthesized from the corresponding thiosemicarbazides by cyclization with sodium hydroxide, according to Girard (7), to obtain the 3-mercapto-1,2,4-triazoles from acyl thiosemicarbazides. The requisite thiosemicarbazides were obtained by reacting acid hydrazides and ethyl isothiocyanate as shown in Scheme I.

2-Mercapto-5-(2-pyrazinyl)-1,3,4-thiadiazoles were obtained from potassium salts of the corresponding 3-pyrazinoyldithiocarbazic acid by cyclization with concentrated sulfuric acid, according to Young and Wood (8). Potassium salts were obtained by treating the requisite hydrazides with carbon disulfide and potassium



Scheme I