Synthesis of N^4-(5-Methoxy-7-benzofuranyl)-1,4-pentanediamine, An Oxygen Isostere of Primaquine [1]

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N^4-(5-Methoxy-7-benzofuranyl)-1,4-pentanediamine, an oxygen isostere of primaquine was synthesized and found devoid of antimalarial activity.

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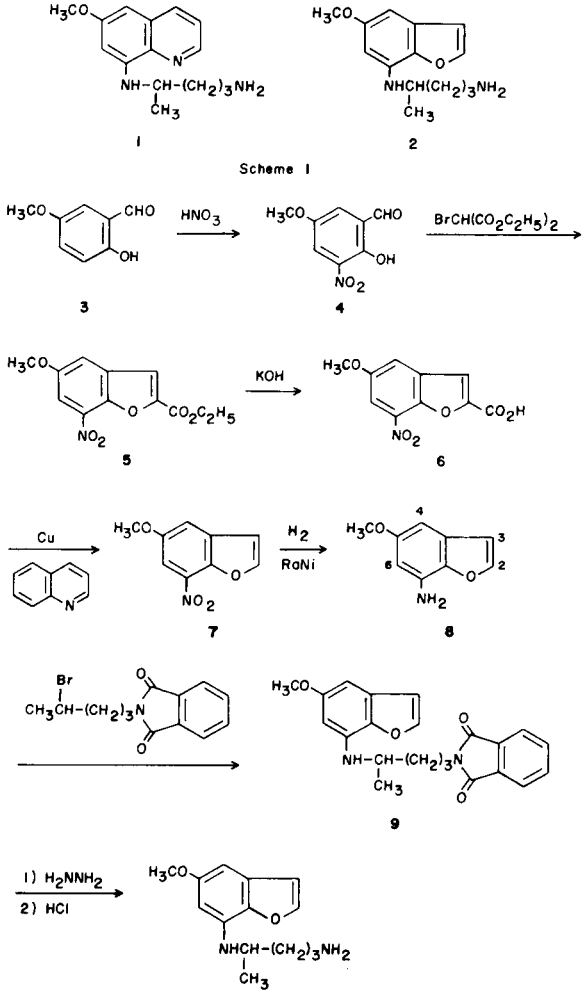
From all the effort [2-4] which has been devoted to find a compound with greater radical curative activity and better tolerability than primaquine (**1**) nothing has emerged to replace the 8-aminoquinoline structure.

Surprisingly, little has been done to vary the nature of the heterocycle itself, and we became interested in preparing bioisosteres of primaquine. This report describes the synthesis of the oxygen isostere namely N^4-(5-methoxy-7-benzofuranyl)-1,4-pentanediamine (**2**) which was prepared as shown in Scheme I.



Nitration of 2-hydroxy-5-methoxybenzaldehyde (**3**) afforded 2-hydroxy-5-methoxy-3-nitrobenzaldehyde (**4**) [5] which was allowed to condense with diethyl bromopropanedioate to form 5-methoxy-7-nitro-2-benzofurancarboxylic acid ethyl ester (**5**). This material was hydrolyzed with potassium hydroxide, and the resulting 5-methoxy-7-nitro-2-benzofurancarboxylic acid (**6**) was decarboxylated in the presence of copper and quinoline to afford 5-methoxy-7-nitrobenzofuran (**7**) [6]. Catalytic hydrogenation over Raney nickel produced 5-methoxy-7-benzofuranamine (**8**).

Reaction of 5-methoxy-7-benzofuranamine (**8**) with 2-(4-bromopentyl)-1*H*-isoindole-1,3(2*H*)-dione [7] afforded 2-[4-[(5-methoxy-7-benzofuranyl)amino]pentyl]-1*H*-isoindole-1,3(2*H*)-dione (**9**). Treatment with hydrazine and then with hydrochloric acid afforded the desired **2** which was isolated as the phosphate salt.

Compounds **2** and **8** were administered in a single subcutaneous dose to mice infected with a normal drug sensitive strain of *Plasmodium berghei* [8] and were found devoid of antimalarial activity even at doses up to 640 mg/kg. Inactivity against the blood stages of the parasite is not unexpected for an 8-aminoquinoline related structure. Unfortunately testing in a primate model to reflect activity against the tissue stages has not been available.

EXPERIMENTAL

All melting points (uncorrected) were taken on a Thomas-Hoover capillary melting-point apparatus. The ir spectra were recorded on a Digilab FTIR-14D spectrophotometer in potassium bromide discs. The nmr spectra were recorded on a Bruker WH90 MHz or a Varian EM390 MHz spectrophotometer in hexadeuterio-dimethyl sulfoxide and in δ parts per million relative to tetramethylsilane.

Compounds **4-7** were prepared following literature procedures [2,3].

5-Methoxy-7-benzofuranamine Monohydrochloride (**8**).

A solution of 6.9 g (0.036 mole) of 5-methoxy-7-nitrobenzofuran in 100 ml of methanol and 100 ml of tetrahydrofuran was hydrogenated over 0.6 g of Raney nickel at an initial pressure of 51.7 psi and at room temperature for 21 hours and then concentrated to dryness under vacuum. Trituration of the oil with 2-propanol containing hydrogen chloride afforded 5.0 g (70%) of **8** as the hydrochloride salt, mp 210-213°; nmr: δ = 8.07 (d, 1H, H-2), 7.09 (d, 1H, H-4 or 6, exchanged by addition of deuterium oxide), 6.95 (m, 2H, H-4 or 6 which is exchanged by addition of deuterium oxide and H-3), 3.80 (s, 3H, CH_3).

Anal. Calcd. for $C_9H_9NO_2$·HCl: C, 54.14; H, 5.05; N, 7.02; Cl^-, 17.76.

Found: C, 54.06; H, 5.02; N, 6.98; Cl^-, 17.98.

*N*⁴-(5-Methoxy-7-benzofuranyl)-1,4-pentanediamine Phosphate (1:1) (**2**).

A solution of 3.0 g (0.015 mole) of 5-methoxy-7-benzofuranamine hydrochloride in 20 ml of water was made basic with ammonium hydroxide and extracted with ether. The ether was washed, dried, and concentrated to dryness under vacuum. The residue was combined with 1.6 g (0.005 mole) of 2-(4-bromopentyl)-1*H*-isoindole-1,3(2*H*)-dione [4] and heated at 120° for 1.5 hours. The mixture was allowed to cool, an additional 1.3 g (0.004 mole) of the bromo compound was added. The mixture was again heated with stirring at 120° for 2 hours, allowed to cool, taken up in water and dichloromethane, and filtered. The organic layer was separated, washed with water and with saturated sodium choride solution, dried over magnesium sulfate, and concentrated to dryness. The residue was chromatographed over 105 g of silica eluting first with 250 ml of dichloromethane and then with a 2% solution of ethyl acetate in dichloromethane. Fractions containing product, R_f (silica-4% ethyl acetate in dichloromethane) = 0.6, were concentrated to dryness and combined to afford 2.0 g of product, contaminated with 5-methoxy-7-benzofuranamine, R_f = 0.5. The nmr spectra confirmed the presence of the desired 2-[4-[(5-methoxy-7-benzofuranyl)amino]pentyl]-1*H*-isoindole-1,3(2*H*)-dione (**9**).

A mixture of 2.0 g of the crude **9** and 1 ml of 85% hydrazine in 30 ml of methanol was heated under reflux for 3 hours, allowed to cool, combined with 15 ml of 1*N* hydrochloric acid, heated under reflux for 1 hour, and concentrated under vacuum to remove the methanol. The concentrate was treated with 10% sodium hydroxide until its *p*H was about 4.5 and was then extracted with ether. The *p*H of the aqueous layer was adjusted to 7 with sodium hydroxide and extraction was repeated. Finally, the *p*H was adjusted to 10. The solution was extracted with ether and this last extract was washed, dried, and concentrated. The residue was dissolved in ether and combined with 0.4 ml of 85% phosphoric acid in 3 ml of ethanol. The resulting gummy precipitate was triturated successively with ether, 2-propanol, acetone, and methanol and then recrystallized from methanol ether to give 0.6 g (19% from compound **8**) of **2**, mp 187-193° dec; nmr: δ = 7.81 (d, 1H, H-2), 6.73 (d, 1H, H-3), 6.33 (d, 1H, H-7 or H-5), 6.09 (d, 1H, H-5 or H-7), 3.70 (s, 3H, OCH_3), 3.6 (m, 1H, -C*H*), 2.72 (m, 2H, -CH_2NH$_2$), 1.61 (m, 4H, -(CH_2)$_2$-), 1.10 (d, 3H, CH_3).

Anal. Calcd. for $C_{14}H_{20}N_2O_2 \cdot H_3PO_4$: C, 48.55; H, 6.69; N, 8.09. Found: C, 48.30; H, 6.94; N, 7.93.

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REFERENCES AND NOTES

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[8] The parenteral antimalarial screening was carried out by Dr. Leo Rane and Mrs. D. S. Rane of the University of Miami and test results were supplied through the courtesy of Dr. T. R. Sweeney and Dr. E. A. Steck of Walter Reed Army Institute for Research. For a descciption of the test method, see: T. S. Osdene, P. B. Russell and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).