Mannich Base Derivatives of Bioactive Benzyl-1,3-benzodioxo-5-ols

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3,4-Methylenedioxyphenol (sesamol) reacts with equimolecular quantities of an aromatic aldehyde and morpholine or piperidine in methanol to give Mannich bases **7** and **8**, related to insect growth regulators and anti-leukemic and antimitotic benzyl-1,3-benzodioxole derivatives.

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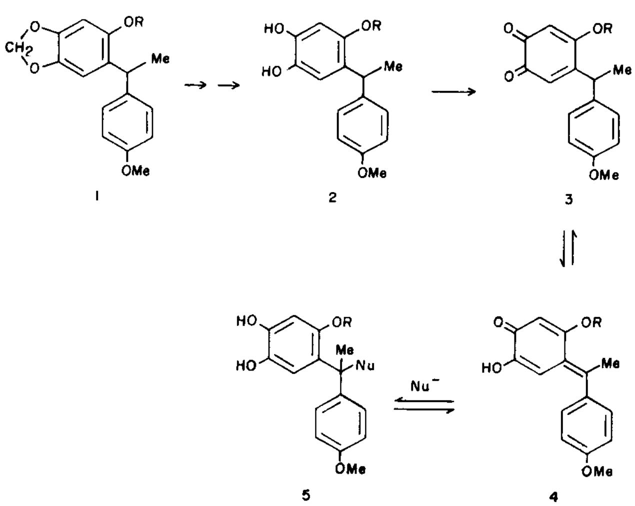
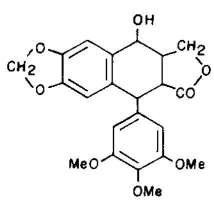
Benzyl-1,3-benzodioxole derivatives of type **1** (R = Me, ethyl or allyl) are growth regulators which show anti-juvenile hormone activity in some insects [1,2], sterilize female housefly (*Musca domestica*), screwworm fly (*Cochliomyia hominivorax*) and Tsetse fly (*Glossina morsitans morsitans*) species [3,4,5], and disrupt the mating behavior of the Mediteranean fruit fly (*Ceratitis capitata*) [6]. Furthermore, standard anti-tumor screening tests at the National Cancer Institute have confirmed that some of these benzyl-1,3-benzodioxole derivatives are active *in vivo* against P-388 lymphocytic leukemia and other tumors, and like podophyllotoxin 6, an anti-tumor drug now in clinical use, they are potent tubulin binders and anti-mitotic agents [7].

It has been suggested [3] that the biological activity of these benzyl-1, 3-benzodioxoles might be due to their oxidative conversion *in vivo* to reactive quinones **3** or quinone methide **4** alkylating agents (Scheme 1). For this reason it was of interest to synthesize and evaluate Mannich bases of benzyl-1,3-benzodioxoles potentially capable of undergoing elimination reactions leading to ortho-quinone methides which could theoretically alkylate cellular components (Scheme 2). Morpholinyl and piperidinyl Mannich bases of types **7** and **8** have now been readily synthesized in good yields by reacting sesamol with

Scheme 1





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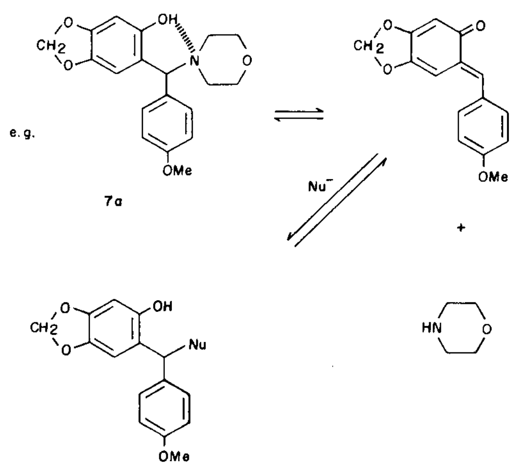
Scheme 2



equimolecular quantities of morpholine or piperidine and the appropriate aromatic aldehyde in methanol (Scheme 3). These new Mannich bases are listed in Table 1 or are described in the Experimental section. Structures were assigned on the basis of elemental analyses and their ^1H nmr spectra.

The hydroxyl group in these Mannich bases is strongly hydrogen bonded to the nitrogen atom. In their spectra, therefore, the OH proton signal appears at very low fields (δ 11.50-12.60). The ^1H nmr spectra, furthermore, indicate that as a result of the hydrogen bonding the Mannich bases may assume fairly rigid conformations in which the H3, H5 and H2, H6 protons of the phenyl ring are non-equivalent. Thus, in the spectrum of **7k** the chemical shifts of the H3 and H5 protons are δ 6.90 and δ 7.00, and of the H2 and H6 protons, δ 7.32 and δ 7.38. Similarly, for compound **7h** the H3 and H5 protons of the 2,4,6-trimethoxyphenyl ring do not appear as a singlet but as meta coupled doublets at δ 6.06 and δ 6.17.

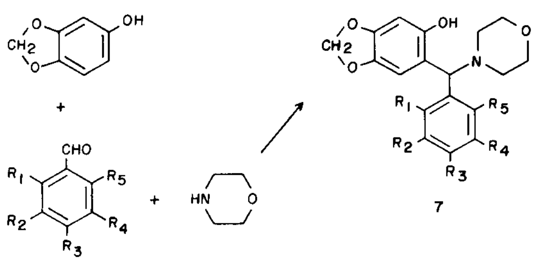
Table 1

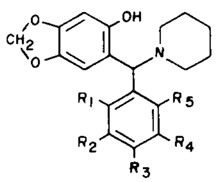
Reactions of Sesamol with Amines and Aldehydes in Methanol

Product	mp °C	Yield %	Found (%)/Calcd. (%) C	H	N	^{1}H NMR (Deuteriochloroform)
7b $C_{20}H_{23}O_6N$	164-165°	87	64.5 64.3	6.2 6.2	3.8 3.8	δ 2.48, m, CH_2NCH_2; 3.70, m, CH_2OCH_2; 3.82, OCH_3; 4.17, CH; 5.84, d, J = 1 Hz and 5.88, d, J = 1 Hz, OCH_2O; 6.36, ArH; 6.39, ArH; 6.67-7.00, 3 ArH
7c $C_{19}H_{19}O_6N$	151°	93	63.9 63.9	5.4 5.4	3.9 3.9	δ 2.49, m, CH_2NCH_2; 3.70, m, CH_2OCH_2; 4.18, CH; 5.74, m, 2 OCH_2O; 6.16, ArH; 6.32, ArH; 6.53-6.90, m, 3 ArH; 11.55, OH
7d $C_{20}H_{23}O_6N$	141-142°	97	64.4 64.3	6.3 6.2	3.7 3.7	δ 2.52, m, CH_2NCH_2; 3.70, m, CH_2OCH_2; 3.83, OCH_3; 3.90, OCH_3; 4.96, CH; 5.78, d, J = 1 Hz and 5.82, d, J = 1 Hz, OCH_2O; 6.38, ArH; 6.43, ArH; 6.72-7.32, m, 4 ArH
7e $C_{19}H_{21}O_5N$	114-115°	65	66.7 66.5	6.1 6.2	4.1 4.1	δ 2.53, m, CH_2NCH_2; 3.66, m, CH_2OCH_2; 3.84, OCH_3; 5.05, CH; 5.73, d, J = 1 Hz and 5.78, d, J = 1 Hz, OCH_2O; 6.37, ArH; 6.44, ArH; 6.75-7.57, m, 4 ArH
7f $C_{20}H_{23}O_6N$	162-163°	96	64.3 64.3	6.3 6.2	3.6 3.7	δ 2.53, m, CH_2NCH_2; 3.67, m, CH_2OCH_2; 3.75, OCH_3; 3.82, OCH_3; 4.96, CH; 5.73, d, J = 1 Hz and 5.80, d, J = 1 Hz, OCH_2O; 6.34-6.53, m, 4 ArH; 7.32, d, J = 9 Hz, ArH
7g $C_{21}H_{25}O_7N$	164-165°	81	62.6 62.5	6.3 6.25	3.5 3.5	δ 2.57, m, CH_2NCH_2; 3.73, m, CH_2OCH_2; 3.81, OCH_3; 3.87, OCH_3; 3.95, OCH_3; 4.89, CH; 5.78, d, J = 1 Hz and 5.84, d, J = 1 Hz, OCH_2O; 6.43, 2 ArH; 6.63, d, J = 9 Hz, ArH; 7.22 d, J = 9 Hz, ArH; 11.75 OH
7h $C_{21}H_{25}O_7N$	163-164°	84	62.6 62.5	6.25 6.25	3.4 3.5	δ 2.48, m, CH_2NCH_2; 3.65, OCH_3; 3.72, CH_2OCH_2; 3.78, OCH_3; 3.87, OCH_3; 5.26, CH; 5.72, d, J = 1 Hz and 5.77, d, J = 1 Hz, OCH_2O; 6.06, d, J = 2 Hz, ArH; 6.17, d, J = 2 Hz, ArH; 6.30, ArH; 6.36, ArH
7i $C_{21}H_{25}O_7N$	123-124°	75	62.7 62.5	6.4 6.3	3.5 3.5	δ 2.52, m, CH_2NCH_2; 3.73, m, CH_2OCH_2; 3.82, OCH_3; 4.15, CH; 5.78, d, J = 1 Hz and 5.82, d, J = 1 Hz, OCH_2O; 6.41, 2 ArH; 6.67, 2 ArH
7j $C_{20}H_{24}O_4N_2$	133-134°	67	67.3 67.4	6.8 6.8	7.8 7.9	δ 2.42, m, CH_2NCH_2; 2.84, $N(CH_3)_2$; 3.63, m, CH_2OCH_2; 4.13, CH; 5.66, d, J = 1 Hz and 5.73, d, J = 1 Hz, OCH_2O; 6.32, ArH; 6.36, ArH; 6.56, d, J = 9 Hz, 2 ArH; 7.16, d, J = 9 Hz, 2 ArH
7k $C_{22}H_{28}O_4N_2$	118-119°	68	68.9 68.7	7.3 7.3	7.2 7.3	δ 1.10, t, J = 6 Hz, CH_3; 2.48, m, CH_2CH_2; 3.27, q, J = 6 Hz, CH_2; 3.60, m, CH_2OCH_2; 4.17, CH; 5.73, d, J = 1 Hz and 5.78, d, J = 1 Hz, OCH_2O; 6.37, 2 ArH; 6.56, d, J = 9 Hz, 2 ArH; 7.17, d, J = 9 Hz, 2 ArH
7l $C_{18}N_{18}O_4NF$	123-124°	78	65.3 65.2	5.6 5.5		δ 2.45, m, CH_2NCH_2; 3.71, m, CH_2OCH_2; 4.22, CH; 5.35, d, J = 1 Hz and 5.80, d, J = 1 Hz, OCH_2O; 6.33, ArH; 6.39, ArH; 6.90, d, J = 9 Hz, ArH; 7.00, d, J = 9 Hz, ArH; 7.32, d, J = 9.0 Hz, ArH; 7.38, d, J = 9 Hz, ArH; 11.50, OH
7m $C_{18}H_{18}O_4NCl$	124-125°	76	62.2 62.2	5.3 5.2		δ 2.43, m, CH_2CH_2; 3.70, m, CH_2CH_2; 4.19, CH; 5.72, d, J = 1 Hz and 5.79, d, J = 1 Hz, OCH_2O; 6.32, ArH; 6.38, ArH; 7.14-1.61, m, 4 ArH
8a $C_{20}H_{23}O_4N$	119-120°	73	70.5 70.4	6.8 6.8	4.1 4.1	δ 1.53, m, 3 CH_2; 2.41, CH_2NCH_2; 3.74, OCH_3; 4.30, CH; 5.72, d, J = 1 Hz and 5.76, d, J = 1 Hz, OCH_2O; 6.31, ArH; 6.40, ArH; 6.80, d, J = 9 Hz, 2 ArH; 7.27, d, J = 9 Hz, 2 ArH
8c $C_{20}H_{21}O_5N$	152-153°	83	67.6 67.6	6.1 6.0	3.9 3.9	δ 1.53, m, 3 CH_2; 2.32, m, CH_2NCH_2; 4.24, CH; 5.72, d, J = 1 Hz and 5.77, d, J = 1 Hz, OCH_2O; 5.87, OCH_2O; 6.31, ArH; 6.38, ArH; 6.68-6.95, 3 ArH
8f $C_{21}H_{25}O_5N$	162-163°	94	67.9 67.9	6.7 6.8	3.7 3.8	δ 1.49, m, 3 CH_2; 2.45, m, CH_2NCH_2; 3.72, OCH_3; 3.80, OCH_3; 5.03, CH; 5.72, d, J = 1 Hz and 5.76, d, J = 1 Hz, OCH_2O; 6.28-6.50, m, 4 ArH; 7.28, d, J = 9 Hz, ArH; 12.38, OH
8j $C_{21}H_{26}O_3N_2$	125-126°	68	71.1 71.2	7.4 7.4	7.9 7.9	δ 1.54, m, 3 CH_2; 2.43, m, CH_2NCH_2; 2.92, OCH_3; 4.30, CH; 5.73, d, J = 1 Hz and 5.77, d, J = 1.0 Hz, OCH_2O; 6.34, ArH; 6.37, ArH; 6.63, d, J = 9 Hz, 2 ArH; 7.20, d, J = 9 Hz, 2 ArH
8l $C_{19}H_{20}O_3NF$	132-133°	76	69.3 69.3	6.2 6.1		δ 1.49, m, CH_2NCH_2; 2.36, CH_2OCH_2; 4.28, CH; 5.71, d, J = 1 Hz and 5.75, d, J = 1 Hz, OCH_2O; 6.27, ArH; 6.48, ArH; 6.87, d, J = 9 Hz, ArH; 6.97, d, J = 9 Hz, ArH; 7.27, d, J = 9 Hz, ArH; 7.33, d, J = 9 Hz, ArH

In accordance with Scheme 2 these Mannich bases yield highly pigmented yellow or orange solutions in protic and aprotic solvents due to the ease with which they dissociate to give ortho-quinone methides. Two of the compounds showed moderate *in vivo* anti-tumor activity against P-388 lymphocytic leukemia. Standard national Cancer Institute

Scheme 3





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a, $R_3 = OCH_3$, $R_1 = R_2 = R_4 = R_5 = H$
b, $R_2 = R_3 = OCH_3$, $R_1 = R_4 = R_5 = H$
c, $R_2 = R_3 = OCH_2O$, $R_1 = R_4 = R_5 = H$
d, $R_1 = R_2 = OCH_3$; $R_3 = R_4 = R_5 = H$
e, $R_1 = OCH_3$, $R_2 = R_3 = R_4 = R_5 = H$
f, $R_1 = R_3 = OCH_3$; $R_2 = R_4 = R_5 = H$
g, $R_1 = R_2 = R_3 = OCH_3$; $R_4 = R_5 = H$
h, $R_1 = R_3 = R_5 = OCH_3$; $R_2 = R_4 = H$
i, $R_2 = R_3 = R_4 = OCH_3$; $R_1 = R_5 = H$
j, $R_3 = NMe_2$; $R_1 = R_2 = R_4 = R_5 = H$
k, $R_3 = NEt_2$; $R_1 = R_2 = R_4 = R_5 = H$
l, $R_3 = F$; $R_1 = R_2 = R_4 = R_5 = H$
m, $R_3 = Cl$; $R_1 = R_2 = R_4 = R_5 = H$

protocols confirmed that compounds **7a** and **8i** were active, with T/C = 120 and 134%, respectively. T/C represents the ratio of the survival time of treated to control mice [8]. The tubulin binding and anti-mitotic properties of these bases will be described elsewhere.

EXPERIMENTAL

The ^{1}H nmr spectra were determined in deuteriochloroform with TMS as the internal standard on a Varian EM-390 instrument. Microanalyses were performed in the Center's Structural Analysis Research Unit. Melting points were determined in unsealed capillaries and are uncorrected.

6-[(4-Methoxyphenyl)-4-morpholinylmethyl]-1,3-benzodioxol-5-ol (**7a**).

A solution of sesamol (13.4 g), morpholine (8.7 g) and 4-methoxybenzaldehyde (13.6 g) in methanol (40 ml) was heated under reflux for 4 hours. A mass of colorless crystals separated. These were collected and recrystallized form acetone-methanol to give 27 g (79%) of the morpholinyl compound **7a** as colorless needles, mp 141-142°; nmr (deuteriochloroform): δ 2.45 (m, $-CH_2NCH_2-$, 4H), 3.65 (m, $-CH_2OCH_2-$, 4H), 3.74 (s, OCH_3, 3H), 4.17 (s, OH, 1H), 5.71 and 5.77 (d, J = 1 Hz, and d, J = 1 Hz, $-OCH_2O-$, 2H), 6.32 (s, ArH, 1H), 6.38 (s, ArH, 1H), 6.78 (d, J = 8 Hz, 2 ArH, 2H), 7.27 (d, J = 8 Hz, 2 ArH, 2H), 11.62 (s, OH, 1H); ^{13}C nmr: δ 52.0 (CH_2NCH_2), 55.1 (OCH_3), 66.8 (CH_2OCH_2), 75.8 (CH), 98.9 (C), 100.7 (OCH_2O), 108.3 (C), 114.2 (2 CH), 116.2 (C), 129.6 (2 CH), 131.3 (C), 140.4 (C), 147.4 (C), 151.1 (C), 159.3 (C).

Anal. Calcd. for $C_{19}H_{21}O_5N$: C, 66.5; H, 6.2; N, 4.1. Found: C, 66.6; H, 6.3; N, 4.1.

Morpholinyl compounds listed in Table 1 were prepared similarly.

6-[(3,4,5-Trimethoxyphenyl)-1-piperidinylmethyl]-1,3-benzodioxol-5-ol (**8i**).

A solution of sesamol (2.26 g), 3,4,5-trimethoxybenzaldehyde (3.92 g) and piperidine (1.70 g) in methanol (20 ml) was heated under reflux for 2 hours and concentrated to an oil. On keeping for a day the oil crystallized. Recrystallized from acetone-methanol 6.9 g (95%) of **8i** separated as colorless needles which melt at 137-138° to a yellow liquid; nmr (deuteriochloroform): δ 1.53 (m, 6H), 2.42 (m, CH_2NCH_2, 4H), 3.78 (s, OCH_3, 3H), 4.16 (s, CH, 1H), 5.73 and 5.76 (d, J = 1 Hz, and d, J = 1 Hz, OCH_2O, 2H), 6.32 (s, ArH, 1H), 6.63 (s, ArH, 2H), 6.67 (s, ArH, 1H), 12.27 (s, OH, 1H).

Anal. Calcd. for $C_{19}H_{21}O_5N$: C, 65.8; H, 6.8; N, 3.5. Found: C, 65.7; H, 6.9; N, 3.5.

The piperidinyl compounds listed in Table 1 were prepared similarly.

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