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3,4-Methylenedioxyphenol (sesamol) condenses with pyrrolidine and aromatic aldehydes to yield Mannich bases of type **4**. The Mannich bases react readily with ketonic reagents to form pyrrolidinylbenzopyran derivatives which provide a simple route to antimitotic and bioactive heterocyclic analogs of the anti-cancer drug, podophyllotoxin.

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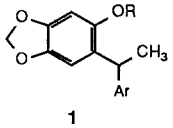
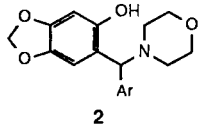
Benzyl-1,3-benzodioxole derivatives of types **1** (R = alkyl) and **2** were originally synthesized as potential insect growth regulators and sterilants [1,2,3]. These substances have some of the structural features of the antimitotic natural product, podophyllotoxin **3**, a glycosidic derivative of



1



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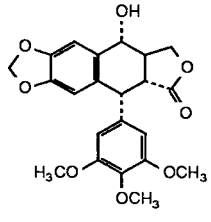


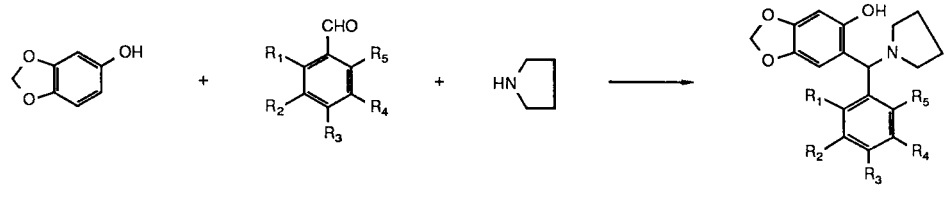
3

which is now in clinical use as an effective anti-cancer agent [4,5]. Like podophyllotoxin a number of these benzodioxoles have proved to be potent anti-mitotic and tubulin binding agents, and to be active *in vivo* against lymphocytic leukemia and other tumors in mice [6,7]. Pyrrolidine analogs of **2** have now been synthesized. It has been found that the pyrrolidine compounds undergo an unusual, facile reaction with ketonic reagents to yield cyclic products which provide a simple route to bioactive, synthetic heterocyclic analogs of podophyllotoxin. This unexpected synthetic sequence is particularly interesting since the related morpholinyl and piperdinyl Mannich bases of type **2** do not react with ketonic reagents and are, in fact, most conveniently purified by crystallization from acetone-alcohol solvent mixtures.

The pyrrolidine Mannich bases listed in Table 1 were prepared in good yields by heating equimolecular quantities of sesamol and pyrrolidine with the appropriate aromatic aldehyde in methanol (Scheme 1).

The pyrrolidine compounds of type **4** form highly colored yellow or orange solutions in both protic and aprotic solvents due to their ready dissociation to *ortho*-quinone methides (*e.g.* Scheme 2, (a)). Addition of a ketonic solvent or a reagent such as ethyl acetoacetate results in decoloration due to a rapid reaction sequence which leads to the formation of colorless, cyclic benzopyran derivatives. For example, the pyrolidine base **4f** reacts readily with 2-butanone in methanol to yield a colorless, crystalline product, $C_{25}H_{31}O_6N$. This was identified as **5d** on the basis of its ^1H nmr spectrum which shows the presence of an un-

Scheme 1



4

4a, $R_3 = OCH_3$, $R_1 = R_2 = R_4 = R_5 = H$
b, $R_2 = OCH_3$, $R_1 = R_3 = R_4 = R_5 = H$
c, $R_1 = R_3 = OCH_3$, $R_2 = R_4 = R_5 = H$
d, $R_2R_3 = OCH_2O$, $R_1 = R_4 = R_5 = H$
e, $R_1 = OH$, $R_2 = OCH_3$, $R_3 = R_4 = R_5 = H$
f, $R_2 = R_3 = R_4 = OCH_3$, $R_1 = R_5 = H$
g, $R_3 = N(CH_3)_2$, $R_1 = R_2 = R_4 = R_5 = H$
h, $R_3 = F$, $R_1 = R_2 = R_4 = H$
i, $R_1 = R_2 = R_3 = OCH_3$, $R_4 = R_5 = H$
j, $R_1 = R_3 = R_5 = OCH_3$, $R_2 = R_4 = H$

Table 1

Reactions of Pyrrolidine with Sesamol and Aromatic Aldehydes in Methanol

Product	mp °C	Yield %	Found (%)/Calcd. (%) C	H	N	^{1}H NMR (Deuteriochloroform)
4a $C_{19}H_{21}O_4N$	87°	81	69.7 69.7	6.5 6.5	4.3 4.3	δ 1.81 (m, 2 CH_2), 2.53 (m, CH_2NCH_2), 3.76 (OCH_3), 4.21 (CH), 5.74 (d, J = 1 Hz and 5.82, d J = 1 Hz, OCH_2O), 6.39 (ArH), 6.41 (ArH), 6.80 (d, J = 9 Hz, 2 ArH), 7.37 (d, J = 9 Hz, 2 ArH), 11.90 (OH)
4b $C_{19}H_{21}O_4N$	91-92°	80	69.8 69.7	6.4 6.5	4.3 4.3	δ 1.81 (m, 2 CH_2), 2.55 (m, CH_2NCH_2), 3.75 (OCH_3), 4.19 (CH), 5.73 (d, J = 1 Hz, OCH_2O), 6.41 (2 ArH), 6.76 (dd, J = 8.2 Hz, ArH), 6.96-7.32 (m, 3 ArH)
4c $C_{20}H_{23}O_5N$	118-119°	84	67.0 67.2	6.4 6.5	3.8 3.9	δ 1.76 (m, 2 CH_2), 2.57 (m, CH_2NCH_2), 3.73 (OCH_3), 3.79 (OCH_3), 4.91 (CH), 5.72 (d, J = 1 Hz and 5.77, d, J = 1 Hz, OCH_2O), 6.29-6.49 (m, 4 ArH), 7.42 (d, J = 8 Hz, ArH), 11.95 (OH)
4d $C_{19}H_{19}O_5N$	129-130°	87	66.6 66.8	5.6 5.6	4.1 4.1	δ 1.78 (m, 2 CH_2), 2.51 (m, CH_2NCH_2), 4.13 (CH), 5.73 (d, J = 1 Hz and 5.77 d, J = 1 Hz, OCH_2O), 5.86 (OCH_2O), 6.36 (ArH), 6.37 (ArH), 6.55-7.05 (m, 3 ArH), 6.55-7.05 (m, 3 ArH), 12.22 (OH)
4e $C_{19}H_{21}O_5N$	162-163°	88	66.4 66.5	6.1 6.2	3.9 4.1	δ 1.75 (m, 2 CH_2), 2.60 (m, CH_2NCH_2), 3.78 (OCH_3), 4.97 (CH), 5.72 (d, J = 1 Hz, and 5.78 d, J = 1 Hz, OCH_2O), 6.35 (ArH), 6.54 (ArH), 6.62-6.85 (m, 2 ArH), 7.07-7.25 (m, ArH), 8.42 (OH)
4g $C_{20}H_{24}O_3NF$	153-154°	66	70.3 70.6	7.0 7.1	8.1 8.2	δ 1.79 (m, 2 CH_2), 2.53 (m, CH_2NCH_2), 2.92 ($N(CH_38)_2$, 4.19 (CH), 5.74 (d, J = 1 Hz and 5.80 d, J = 1 Hz, OCH_2O), 6.39 (2 ArH), 6.63 (d, J = 9 Hz, 2 ArH), 7.29 (d, J = 9 Hz, 2 ArH), 11.50 (OH)
4h $C_{18}H_{16}O_3NF$	112-113°	95	68.5 68.6	5.9 5.8		δ 1.82 (m, 2 CH_2), 2.53 (m, CH_2NCH_2), 4.21 (CH), 5.74 (d, J = 1 Hz and 5.80 d, J = 1 Hz, OCH_2O), 6.37 (ArH), 6.41 (ArH), 6.84 (d, J = 9 Hz, ArH), 6.95 (d, J = 9 Hz, ArH), 7.33 (d, J = 9 Hz, ArH), 7.42 (d, J = 9 Hz, ArH)
4i $C_{21}H_{25}O_6N$	105-106°	55	[a]			δ 1.81 (m, 2 CH_2), 2.52 (m, CH_2NCH_2), 3.75 (OCH_3), 3.80 (OCH_3), 3.92 (OCH_3), 4.80 (CH), 5.72 (d, J = 1 Hz and 5.78 d, J = 1 Hz, OCH_2O), 6.36 (ArH), 6.44 (ArH), 6.58 (d, J = 9 Hz, ArH), 7.28 (d, J = 9 Hz, ArH)
4j $C_{21}H_{25}O_6N$	148-149°	66	[a]			δ 1.73 (m, 2 CH_2), 2.50 (m, CH_2NCH_2), 3.60 (OCH_3), 3.71 (OCH_3), 3.79 (OCH_3), 5.23 (CH), 5.78 (OCH_2O), 6.00 (d, J = 2 Hz, ArH), 6.08 (d, J = 2 Hz, ArH), 6.25 (ArH), 6.32 (ArH)

[a] Elemental analysis not obtained.

coupled methyl group (singlet at δ 1.36), a methyl group (δ 0.84) coupled to a methine proton (δ 2.18) which is in turn coupled to a second, benzylic methine proton at δ 3.46 (doublet, J = 12 Hz). The magnitude of this coupling indicates that the two methine protons have a *trans* configuration as shown in **5d**. This structure was further confirmed by the ^{13}C nmr spectrum which showed signals *inter al.* of two methyls (14.6, 18.0 ppm), two aliphatic CH's (41.6, 49.8 ppm), and of an *O,N*-linked quaternary C (at 93.8 ppm).

The formation of benzopyrans of type **5d** in this reac tion can be rationalized on the basis that the pyrrolidin formed by dissociation of the Mannich base in solutio (Scheme 2, a) rapidly reacts with the ketonic reagent t form an enamine (Scheme 2, b) which then recombine with the *ortho*-quinone methide in a Diels-Alder type reac tion to yield the benzopyran (Scheme 2, c).

Pyrrolidinylbenzopyran derivatives formed in thes ketone-Mannich base reactions can be hydrolyzed b warming in aqueous acetic acid to yield the correspondin

Table 2

Products from Reactions of Ketones with Mannich Bases

Reactants	Product	mp °C	Yield %	Found (%)/Calcd. (%) C	H	N	^{1}H NMR (Deuteriochloroform)
4a + Acetone	**7a** $C_{22}H_{25}O_4N$	144°	77	71.8 71.9	6.8 6.9	3.7 3.8	δ 1.47 (CH_3), 1.73 (m, 2 CH_2), 2.10 (m, CH_2), 2.92 (m, CH_2NCH_2), 3.73 (OCH_3), 3.97 (dd, J = 8.12 Hz, CH), 5.74 (OCH_2O), 6.12 (ArH), 6.33 (ArH), 6.81 (d, J = 8 Hz, 2 ArH), 7.12 (d, J = 8 Hz, 2 ArH)
7a + $H_3O^{\oplus}$	**7b** $C_{18}H_{18}O_5$	112-113°	66	69.0 68.0	5.7 5.8		δ 1.57 (CH_3), 2.12 (m, CH_2), 3.0 (OH), 3.74 (OCH_3), 4.12 (dd, J = 6, 13 Hz), 5.73 (d, J = 1 Hz and 5.79 d, J = 1 Hz, OCH_2O), 6.17 (ArH), 6.34 (ArH), 6.82 (d, J = 9 Hz, 2 ArH), 7.12 (d, J = 9 Hz, 2 ArH)
7a + $CH_3OH_2^{\oplus}$	**7c** $C_{19}H_{20}O_5$	81-82°		69.5 69.5	6.1 6.1		δ 1.50 (CH_3), 2.07 (m, CH_2), 3.28 (OCH_3), 3.78 (OCH_3), 4.13 (dd, J = 6, 13 Hz, CH), 5.80 (OCH_2O), 6.18 (ArH), 6.40 (ArH), 6.82 (2 ArH), 7.11 (2 ArH)
4a + 2-Butanone	**7d** $C_{23}H_{27}O_4N$	136-137°	79	72.6 72.4	7.1 7.1	3.7 3.7	δ 0.78 (d, J = 6 Hz, CH_3), 1.74 (m, 2 CH_2), 2.16 (m, CH), 2.96 (m, CH_2NCH_2), 3.44 (d, J = 12 Hz, CH), 3.76 (OCH_3), 5.73 (OCH_2O), 6.01 (ArH), 6.30 (ArH), 6.79 (d, J = 9 Hz, 2 ArH), 7.03 (d, J = 9 Hz, 2 ArH)
7d + $H_3O^{\oplus}$	**7e** $C_{19}H_{20}O_5$	143-144°	81	69.7 69.5	6.1 6.1		δ 0.90 (d, J = 6 Hz, CH_3), 1.62 (CH_3), 1.97 (m, CH), 2.63 (OH), 3.65 (d, J = 12 Hz, CH), 3.78 (OCH_3), 5.77 (d, J = 1 Hz and 5.81 d, J = 1 Hz, OCH_2O), 6.07 (ArH), 6.37 (ArH), 6.84 (d, J = 9 Hz, 2 ArH), 7.07 (d, J = 9 Hz, 2 ArH)
7d + $CH_3OH_2^{\oplus}$	**7f** $C_{20}H_{22}O_5$	162-163°		70.2 70.3	6.5 6.5		δ 0.85 (d, J = 6 Hz, CH_3), 1.53 (CH_3), 1.95 (m, CH), 3.26 (OCH_3), 3.63 (d, J = 12 Hz, CH), 3.78 (OCH_3), 5.78 (OCH_2O), 6.06 (ArH), 6.37 (ArH), 6.82 (d, J = 9 Hz, 2 ArH), 7.04 (d, J = 9 Hz, 2 ArH)
4a + Ethyl acetoacetate	**7g** $C_{25}H_{29}O_6N$	132-133°	82	68.6 68.3	6.6 6.6	3.2 3.2	δ 0.96 (t, J = 6 Hz, CH_3), 1.55 (CH_3), 1.73 (m, 2 CH_2), 3.05 (m, CH_2NCH_2), 3.20 (d, J = 12 Hz, CH), 3.74 (OCH_3), 3.92 (q, J = 6 Hz, CH_2), 4.23 (d, J = 12 Hz, CH), 5.78 (OCH_2O), 6.10 (ArH), 6.33 (ArH), 6.78 (d, J = 9 Hz, 2 ArH), 7.05 (d, J = 9 Hz, 2 ArH)
4a + Propionaldehyde	**7h** $C_{22}H_{25}O_4N$	152-153°	96	71.8 71.9	6.8 6.9	3.8 3.8	δ 0.86 (d, J = 6 Hz, CH_3), 1.77 (m, 2 CH_2), 2.08 (m, CH), 2.97 (m, CH_2NCH_2), 3.52 (d, J = 11 Hz, CH), 3.78 (OCH_3), 4.63 (d, J = 9 Hz, CH), 5.77 (OCH_2O), 6.04 (ArH), 6.37 (ArH), 6.84 (d, J = 9 Hz)
7h + $H_3O^{\oplus}$	**7i** $C_{18}H_{18}O_5$	138-139°	85	68.8 69.0	5.8 5.8		δ 0.89 (d, J = 6 Hz, CH_3), 2.09 (m, CH), 3.18 (m, OH), 3.53 (d, J = 12 Hz, CH), 3.80 (OCH_3), 5.40 (d, J = 2 Hz, CH), 5.79 (OCH_2O), 6.12 (ArH), 6.39 (ArH), 6.82 (d, J = 9 Hz, 2 ArH), 7.07 (d, J = 9 Hz, 2 ArH)
4c + 2-Butanone	**12d** $C_{24}H_{29}O_5N$	144-145°	75	70.1 70.1	7.0 7.1	3.4 3.4	δ 0.78 (d, J = 6 Hz, CH_3), 1.34 (CH_3), 1.76 (m, 2 CH_2), 2.14 (m, CH), 2.96 (m, CH_2NCH_2), 3.76 (OCH_3), 3.81 (OCH_3), 4.22 (d, J = 12 Hz, CH), 5.72 (OCH_2O), 6.01 (ArH), 6.22-6.52 (3 ArH), 6.82 (d, J = 8 Hz, ArH)
12d + $H_3O^{\oplus}$	**12e** $C_{20}H_{22}O_6$	129-130°	92	67.2 67.0	6.2 6.2		δ 0.90 (d, J = 6 Hz, CH_3), 1.62 (CH_3), 2.12 (m, 2 CH_2), 3.47 (OH), 3.80 (2 OCH_3), 4.14 (m, CH), 5.77 (d, J = 1 Hz and 5.80 d, J = 1 Hz, OCH_2O), 6.10 (ArH), 6.32-6.58 (m, 3 ArH), 6.90 (m, ArH)

Table 2 (continued)

Reactants	Product	mp °C	Yield %	Found (%)/Calcd. (%) C	H	N	^{1}H NMR (Deuteriochloroform)
12e + $CH_3OH_2^{\oplus}$	**12f** $C_{21}H_{22}O_6$	143-144°		67.9 67.7	6.5 6.5		δ 0.84 (d, J = 6 Hz, CH_3), 1.52 (CH_3), 2.08 (m, 2 CH_2), 3.25 (OCH_3), 3.75 (OCH_3), 4.20 (m, CH), 7.7 (OCH_2O), 6.06 (ArH), 6.32-6.52 (m, 3 ArH), 6.90 (m, ArH)
4c + Propionaldehyde	**12h** $C_{23}H_{27}O_5N$	119-120°	65	69.6 69.5	6.8 6.8	3.5 3.5	δ 0.86 (d, J = 6 Hz, CH_3), 1.72 (m, 2 CH_2), 2.14 (m, CH), 2.94 (m, CH_2NCH_2), 3.74 (2 OCH_3), 4.10 (d, J = 12 Hz, CH), 4.64 (d, J = 9 Hz, CH), 5.74 (OCH_2O), 6.01 (ArH), 6.32-6.56 (3 ArH), 6.90 (d, J = 8 Hz, ArH)
4c + Ethyl Acetoacetate	**12g** $C_{26}H_{31}O_7N$	123-124°	70	66.6 66.5	6.6 6.7	2.9 3.0	δ 0.96 (t, J = 6 Hz, CH_3), 1.49 (CH_3), 1.74 (m, 2 CH_2), 3.10 (m, CH_2NCH_2), 3.52 (d, J = 12 Hz, CH), 3.80 (2 OCH_3), 3.94 (q, J = 6 Hz, CH_2) 4.90 (d, J = 12 Hz, CH), 5.78 (OCH_2O), 6.11 (ArH), 6.32-6.54 (m, 3 ArH), 7.0 (m, ArH)
4c + Cyclohexanone	**12j** $C_{26}H_{31}O_5N$	157-158°	87	71.5 71.4	7.2 7.1	3.2 3.2	δ 1.08-1.84 (m, 6 CH_2), 2.14 (m, CH), 2.82 (m, CH_2NCH_2), 3.75 (OCH_3), 3.81 (OCH_3), 4.54 (d, J = 12 Hz, CH), 5.70 (OCH_2O), 6.02 (ArH), 6.22-6.48 (m, 3 ArH), 6.82 (d, J = 8 Hz, ArH)
4c + Cyclopentanone	**12l** $C_{25}H_{29}O_5N$	131-132°	91	70.9 70.9	6.9 6.9	3.3 3.3	δ 1.56 (m, 5 CH_2), 2.06 (m, CH), 2.70 (m, CH_2NCH_2), 3.79 (OCH_3), 3.80 (OCH_3), 4.02 (d, J = 9 Hz, CH), 5.82 (OCH_2O), 6.15 (ArH), 6.31-6.55 (m, 3 ArH), 6.95 (d, J = 8 Hz, 2 ArH)
4d + 2-Butanone	**9d** $C_{23}N_{25}O_5N$	147-148°		70.0 69.9	6.4 6.4	3.4 3.5	δ 0.82 (d, J = 6 Hz, CH_3), 1.33 (CH_3), 1.74 (m, 2 CH_2), 2.05 (m, CH), 2.94 (m, CH_2NH_2), 3.44 (d, J = 12 Hz, CH), 5.74 (OCH_2O), 5.88 (OCH_2O), 6.06 (ArH), 6.29 (ArH), 6.54 (ArH), 6.68 (m, 2 ArH)
4e + Acetone	**8a** $C_{22}H_{25}O_5N$	184-185°	83	68.7 68.9	6.5 6.6	3.3 3.6	δ 1.43 (CH_3), 1.78 (m, 2 CH_2), 2.20 (m, CH_2), 2.94 (m, CH_2NCH_2), 3.84 (OCH_3), 4.52 (m, CH), 5.78 (OCH_2O), 6.27 (ArH), 6.36 (ArH), 6.72 (m, 3 ArH)
4e + 2-Butanone	**8d** $C_{23}H_{27}O_5N$	170-171°	61	69.5 69.5	6.8 6.8	3.5 3.5	δ 0.87 (d, J = 6 Hz, CH_3), 1.36 (CH_3), 1.71 (m, 2 CH_2), 2.25 (m, CH), 2.96 (m, CH_2NCH_2), 3.84 (OCH_3), 4.31 (d, J = 12 Hz, CH), 5.76 (OCH_2O), 6.10 (ArH), 6.32 (ArH), 6.73 (m, 3 ArH)
4e + Propionaldehyde	**8h** $C_{22}H_{25}O_5N$	132-133°	76	69.0 68.9	6.6 6.6	3.6 3.6	δ 0.89 (d, J = 6 Hz, CH_3), 1.73 (m, 2 CH_2), 2.24 (m, CH), 2.92 (m, CH_2NCH_2), 3.85 (OCH_3), 4.10 (d, J = 12 Hz, CH), 4.63 (d, J = 8 Hz, CH), 5.70 (OCH_2O), 5.90 (OH), 6.08 (ArH), 6.35 (ArH), 6.74 (m, 3 ArH)
4e + Ethyl Acetoacetate	**8g** $C_{25}H_{29}O_7N$	114-115°	76	65.9 65.9	6.4 6.4		δ 0.94 (t, J = 6 Hz, CH_3), 1.54 (CH_3), 1.73 (m, 2 CH_2), 3.05 (m, CH_2NCH_2), 3.32 (d, J = 13 Hz, CH), 3.84 (OCH_3), 3.90 (m, CH and CH_2), 4.90 (OH), 5.78 (OCH_2O), 6.12 (ArH), 6.32 (ArH), 6.72 (m, 3 ArH)
4f + Ethyl acetoacetate	**5g** $C_{27}H_{33}O_8N$	129-130°	89	64.7 64.9	6.5 6.7	2.6 2.8	δ 0.93 (t, J = 7 Hz, CH_3), 1.52 (CH_3), 1.70 (m, 2 CH_2), 3.05 (m, CH_2NCH_2), 3.13 (d, J = 12 Hz, CH), 3.73 (2 OCH_3), 3.78 (OCH_3), 3.92 (q, J = 7 Hz, CH_2), 4.18 (d, J = 12 Hz, CH), 5.74 (d, J = 1 Hz and 5.78 d, J = 1 Hz, OCH_2O), 6.16 (ArH), 6.32 (3 ArH)

Table 2 (continued)

Reactants	Product	mp °C	Yield %	Found (%)/Calcd. (%) C	H	N	^{1}H NMR (Deuteriochloroform)
5g + $H_3O^{\oplus}$	**5q** $C_{23}H_{26}O_9$	184°	63	61.8 61.9	5.8 5.8		δ 1.0 (t, J = 7 Hz, CH_3), 1.62 (CH_3), 2.96 (d, J [5] 12 Hz, CH), 3.78 (2 OCH_3), 3.84 (OCH_3), 4.01 (q, J = 7 Hz, CH_2CH_3), 4.31 (d, J = 12 Hz, CH), 5.80 (d, J = 1 Hz and 5.86, J = 10 Hz, OCH_2O), 6.20 (ArH), 6.37 (2 ArH), 6.40 (ArH)
5q + $CH_3OH_2^{\oplus}$	**5r** $C_{24}H_{28}O_9$	182-183°	90	62.6 62.6	6.1 6.1		δ 1.04 (t, J = 7 Hz, CH_3), 1.58 (CH_3), 2.96 (d, J = 12 Hz, CH), 3.26 (OCH_3), 3.74 (2 OCH_3), 3.80 (OCH_3), 4.02 (q, J = 7 Hz, CH_2CH_3), 4.44 (d, J = 12 Hz, CH), 5.80 (d, J = 1 Hz and 5.83 d, J = 1 Hz, OCH_2O), 6.18 (ArH), 6.38 (2 ArH), 6.41 (ArH)
5q + HOAc, HCl	**6s** $C_{23}H_{24}O_8$	117-118°	95	64.5 64.5	5.6 5.6		δ 1.07 (t, J = 7 Hz, CH_3), 2.41 (CH_3), 3.73 (OCH_3), 3.78 (2 OCH_3), 4.08 (q, J = 7 Hz, CH_2CH_3), 4.82 (CH), 3.83 (d, J = 1 Hz and 3.87 d, J = 1 Hz, OCH_2O), 6.30 (2 ArH), 6.44 (ArH), 6.52 (ArH)
4f + Propionaldehyde	**5h** $C_{24}H_{29}O_6N$	181-182°	94	67.7 67.4	6.7 6.7	3.3 3.3	δ 0.88 (d, J = 6 Hz, CH_3), 1.80 (m, 2 CH_2), 2.04 (m, CH), 2.96 (m, CH_2NCH_2), 3.48 (d, J = 9 Hz, CH), 3.78 (2 OCH_3), 3.81 (OCH_3), 4.62 (d, J = 9 Hz, CH), 5.74 (d, J = 1 Hz and 5.78 d, J = 1 Hz, OCH_2O), 6.07 (ArH), 6.33 (2 ArH), 6.37 (ArH)
5h + $H_3O^{\oplus}$	**5i** $C_{20}H_{22}O_7$	173-174°	91	64.1 64.2	5.8 5.9		δ 1.13 (d, J = 6 Hz, CH_3), 2.49 (m, CH), 3.71 (2 OCH_3), 3.91 (OCH_3), 4.20 (d, J = 14 Hz, CH), 5.83 (OCH_2O), 6.50 (ArH), 6.68 (ArH), 6.74 (2 ArH)
4f + Cyclohexanone	**5j** $C_{27}H_{33}O_6N$	169-179°	86	69.6 69.4	7.1 7.1	3.0 3.0	d 1.20-1.86 (m, 6 CH_2), 2.19 (d, J = 11 Hz, CH), 2.70-3.00 (m, CH_2NCH_2), 3.76 (2 OCH_3), 3.82 (OCH_3), 3.93 (d, J = 11 Hz, CH), 5.72 (d, J = 1 Hz and 5.77 d, J = 1 Hz, OCH_2O), 6.06 (ArH), 6.28 (ArH), 6.33 (2 ArH)
4f + Cyclopentanone	**5l** $C_{26}H_{31}O_6N$	145-146°	88	68.6 68.6	6.8 6.9	2.9 3.1	δ 1.32-2.25 (m, 5 CH_2), 2.37-3.03 (m, CH_2NCH_2), 3.55 (d, J = 9 Hz, CH), 3.80 (2 OCH_3), 3.85 (OCH_3), 5.77 (d, J = 1 Hz and 5.80 d, J = 1 Hz, OCH_2O), 6.14 (ArH), 6.42 (ArH), 6.45 (2 ArH)
4g + Acetone	**10a** $C_{23}H_{28}O_3N_2$	169-170°	66	72.2 72.6	7.4 7.4	7.2 7.4	δ 1.48 (CH_3), 1.73 (m, 2 CH_2), 2.12 (m, CH), 2.86 ($N(CH_3)_2$), 2.95 (m, CH_2NCH_2), 3.92 (dd, J = 6, 12 Hz, CH), 5.74 (OCH_2O), 6.18 (ArH), 6.32 (ArH), 6.56 (2 ArH), 7.04 (2 ArH)
10a + $H_3O^{\oplus}$	**10b** $C_{19}H_{21}O_4N$	123-124°	80	69.5 69.7	6.4 6.5	4.3 4.3	δ 1.57 (CH_3), 2.10 (m, CH_2), 2.91 ($N(CH_3)_2$), 3.42 (OH), 4.05 (dd, J = 6, 12 Hz, CH), 5.76 (OCH_2O), 6.21 (ArH), 6.35 (ArH), 6.67 (2 ArH), 7.05 (2 ArH)
4g + 2-Butanone	**10d** $C_{24}H_{30}O_3N_2$	163-164°		73.2 73.1	7.8 7.7	7.1 7.1	δ 0.80 (d, J = 6 Hz, CH_3), 1.32 (CH_3), 1.74 (m, 2 CH_2), 2.20 (m, CH), 2.92 ($N(CH_3)_2$), 2.95 (m, CH_2NCH_2), 3.38 (d, J = 12 Hz, CH), 5.74 (OCH_2O), 6.06 (ArH), 6.64 (d, J = 9 Hz, 2 ArH), 6.96 (d, J = 9 Hz, 2 ArH)
4g + Ethyl acetoacetate	**10g** $C_{26}H_{32}O_5N_2$	175-176°	69	69.0 69.0	7.1 7.1	6.2 6.2	δ 0.94 (t, J = 6 Hz, CH_3), 1.54 (CH_3), 1.72 (m, 2 CH_2), 2.88 ($N(CH_3)_2$), 3.06 (m, CH_2NCH_2, CH), 4.0 (m, CH_2, CH), 5.76 (OCH_2O), 6.16 (ArH), 6.31 (ArH), 6.61 (2 ArH), 6.96 (2 ArH)

Table 2 (continued)

Reactants	Product	mp °C	Yield %	Found (%)/Calcd. (%) C	H	N	^{1}H NMR (Deuteriochloroform)
4h Acetone	**11a** $C_{21}H_{22}O_3NF$	132°	85	70.9 71.0	6.3 6.2		δ 1.48 (CH_3), 1.74 (m, 2 CH_2), 2.04 (m, CH) + 2.94 (m, CH_2NCH_2), 4.02 (dd, J = 6, 12 Hz, CH), 5.75 (OCH_2O), 6.10 (ArH), 6.34 (ArH), 6.92 (2 ArH), 7.16 (2 ArH)
4i + 2-Butanone	**13d** $C_{25}H_{31}O_6N$	115-116°	61	[a]			δ 0.94 (d, J = 7 Hz, CH_3), 149 (CH_3), 1.73 (m, 2 CH_2), 2.20 (m, CH), 2.97 (m, CH_2NCH_2), 3.80 (OCH_3), 3.88 (OCH_3), 3.93 (OCH_3), 4.10 (d, J = 12 Hz, CH), 5.76 (OCH_2O), 6.02 (ArH), 6.32 (ArH), 6.64 (2 ArH)
13d + $CH_3OH_2^{\oplus}$	**13f** $C_{22}H_{26}O_7$	142-143°		[a]			δ 0.85 (d, J = 7 Hz, CH_3), 1.52 (CH_3), 2.08 (m, CH), 3.22 (OCH_3), 3.74 (2 OCH_3), 3.84 (OCH_3), 5.78 (OCH_2O), 6.08 (ArH), 6.40 (ArH), 6.67 (2 ArH)
4j + 2-Butanone	**14d** $C_{25}H_{21}O_6N$	151-152°	95	[a]			δ 0.80 (d, J = 7 Hz, CH_3), 1.37 (CH_3), 1.76 (m, 2 CH_2), 2.70 (m, CH), 2.98 (m, CH_2NCH_2), 3.46 (OCH_3), 3.78 (OCH_3), 3.82 (OCH_3), 4.25 (d, J = 12 Hz, CH), 5.72 (d, J = 1 Hz and 5.78 (d, J = 1 Hz, OCH_2O), 6.07 (ArH), 6.18 (d, J = 1 Hz, ArH), 6.21 (d, J = 1 Hz, ArH), 6.30 (ArH)
14d + $H_3O^{\oplus}$	**14e** $C_{21}H_{24}O_7$	185-186°	74	[a]			δ 0.82 (d, J = 7 Hz, CH_3), 1.57 (CH_3), 2.42 (m, CH), 3.47 (OCH_3), 3.81 (2 OCH_3), 4.42 (d, J = 12 Hz, CH), 4.82 (OH), 5.71 (d, J = 1 Hz and 5.78 d, J = 1 Hz, OCH_2O), 6.04 (ArH), 6.07 (d, J = 2 Hz, ArH), 6.19 (d, J = 2 Hz, ArH), 6.30 (ArH)
14e + $CH_3OH_2^{\oplus}$	**14f** $C_{22}H_{26}O_7$	143-144°	96	[a]			δ 0.80 (d, J = 7 Hz, CH_3), 1.47 (CH_3), 2.39 (m, CH), 3.22 (OCH_3), 3.38 (OCH_3), 3.72 (2 OCH_3), 4.38 (d, J = 12 Hz, CH), 3.70 (d, J = 1 Hz and 3.75 d, J = 1 Hz, OCH_2O), 6.04 (ArH), 6.11 (d, J = 1 Hz, ArH), 6.17 (d, J = 1 Hz, ArH), 6.33 (ArH)
5l + $H_3O^{\oplus}$	**5n** $C_{22}H_{24}O_7$	159-160°	74	66.2 66.0	5.9 6.0		δ 1.30-2.52 (m, 7H), 3.48 (d, J = 9 Hz, CH), 3.78 (2 OCH_3), 3.85 (OCH_3), 5.84 (OCH_2O), 6.17 (ArH), 6.43 (2 ArH), 6.50 (ArH)
5n + $CH_3OH_2^{\oplus}$	**5o** $C_{23}H_{26}O_7$	183-184°		66.7 66.6	6.3 6.3		δ 1.31-2.52 (m, 7H), 3.34 (OCH_3), 3.44 (d, J = 8.0 Hz, CH), 3.78 (2 OCH_3), 3.85 (OCH_3), 5.82 (OCH_2O), 6.13 (ArH), 6.47 (2 ArH), 6.53 (ArH)
5n + $KHSO_4$	**6p** $C_{22}H_{22}O_6$	187-188°	74	69.2 69.1	5.8 5.8		δ 1.89 (m, CH_2), 2.06 (m, CH_2), 2.53 (m, CH_2), 3.78 (3 OCH_3), 4.29 (CH), 5.85 (OCH_2O), 6.35 (3 ArH), 6.48 (ArH)

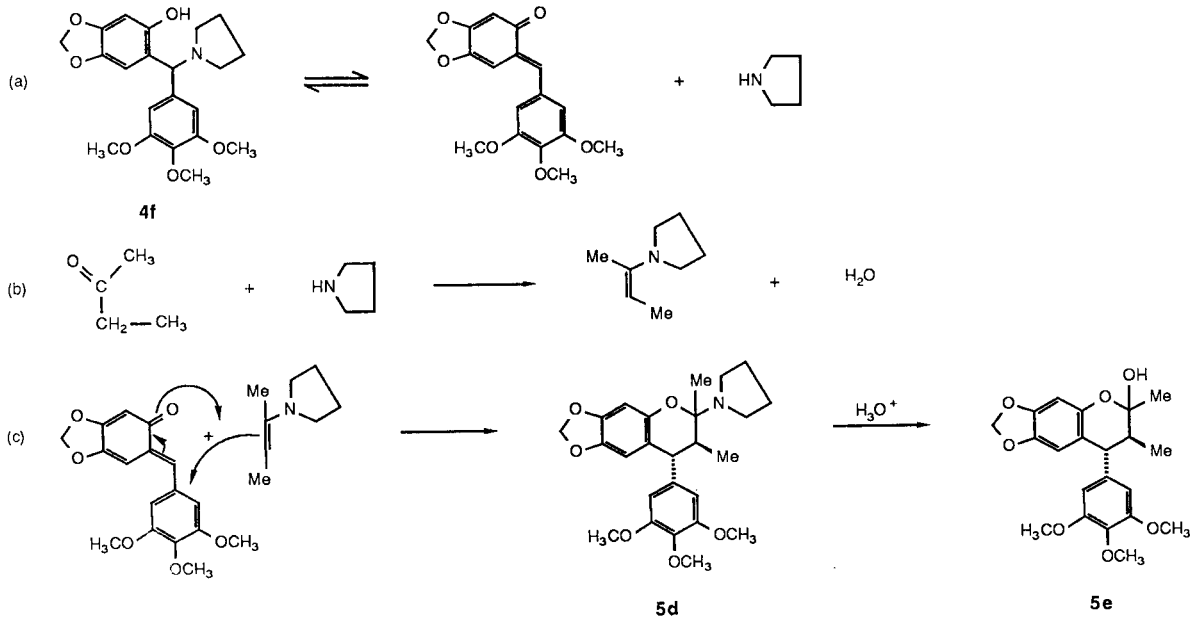
[a] These compounds were analyzed by high resolution mass spectrometry: **13d**, meas. M^+ 441.2126, Calcd. M^+ 441.2151; **13f**, meas. M^+ 402.1682, Calcd. M^+ 402.1678; **14d**, meas. M^+ 441.2141, Calcd. M^+ 441.2151; **14e**, meas. M^+ 388.1508, Calcd. M^+ 388.1522; **14f**, meas. M^+ 402.1664, Calcd. M^+ 402.1678.

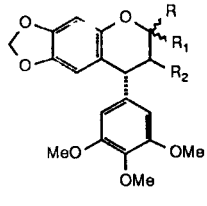
alcohols. Thus, hydrolysis of **5d** and of **5a**, the product from acetone and **4f**, gives the alcohols **5e** and **5b** respectively (Scheme 2, c). These alcohols may be readily converted into methyl ethers such as **5f** and **5c** or dehydrated to compounds of type **6**.

The alcohols **5e** and **5b**, and their methyl derivatives **5f** and **5c**, are structurally similar to podophyllotoxin and like this drug they have proven to be effective tubulin binders and anti-mitotic agents, and to be active *in vivo* against lymphocytic leukemia [7].

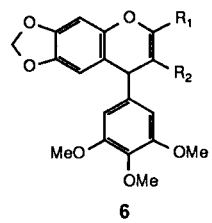
Other Mannich bases in Table 1 reacted with ketonic reagents to form similar benzopyran derivatives, which are listed in Table 2. In contrast to **5b** and **5e**, the benzopyrans in this table did not show anti-tumor activity.

Scheme 2

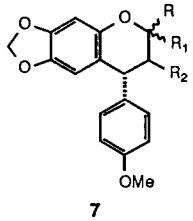




5



6



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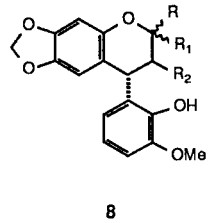

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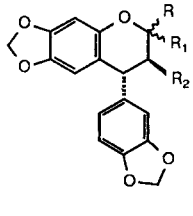

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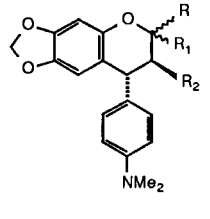
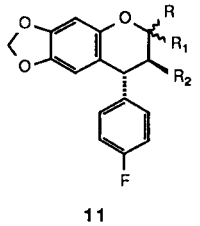
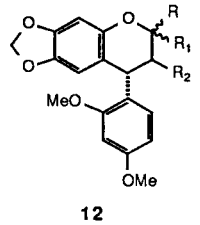


10



11



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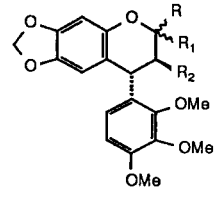

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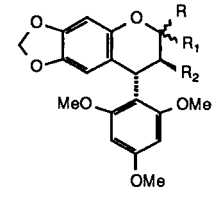

14

a R = N, R_1 = CH_3, R_2 = H
b R = OH, R_1 = CH_3, R_2 = H
c R = OCH_3, R_1 = CH_3, R_2 = H
d R = N, R_1 = R_2 = CH_3
e R = OH, R_1 = R_2 = CH_3
f R = OCH_3, R_1 = R_2 = CH_3
g R = N, R_1 = CH_3, R_2 = COOEt
h R = N, R_1 = H, R_2 = CH_3
i R = OH, R_1 = H, R_2 = CH_3
j R = N, R_1R_2 = $-CH_2CH_2CH_2CH_2-$
k R = OH, R_1R_2 = $-CH_2CH_2CH_2CH_2-$
l R = N, R_1R_2 = $-CH_2CH_2CH_2-$
m R_1 = R_2 = CH_3
n R = OH, R_1R_2 = $-CH_2CH_2CH_2-$
o R = OMe, R_1R_2 = $-CH_2CH_2CH_2-$
p R_1R_2 = $-CH_2CH_2CH_2-$
q R = OH, R_1 = CH_3, R_2 = COOEt
r R = OCH_3 R_1 = CH_3, R_2 = COOEt
s R_1 = CH_3, R_2 = COOEt

EXPERIMENTAL

The ^1H nmr spectra were determined in deuteriochloroform with TMS as the internal standard on a Varian EM-300 instrument. Microanalyses

were performed in the Center's Structural Analysis Research Unit. Melting points were determined in unsealed capillaries and are uncorrected.

6-[(3,4,5-Trimethoxyphenyl)-1-pyrrolidinylmethyl]-1,3-benzodioxol-5-ol **4f**.

A solution of sesamol (2.8 g), 3,4,5-trimethoxybenzaldehyde (4.0 g) and pyrrolidine (1.2 g) in methanol (20 ml) was heated under reflux for 30 minutes and allowed to stand for a day. The colorless crystals which separated were collected and recrystallized from chloroform-methanol. Compound **4f** separated as colorless, hard prisms, mp 103-104° (7.1 g, 92%); ^{1}H-nmr: δ 1.80 (m, CH_2CH_2), 2.52 (m, CH_2NCH_2), 3.80 (OCH_3), 3.88 ($2OCH_3$), 4.09 (CH, 5.74, d, J = 1 Hz and 5.78, d, J = 1 Hz, OCH_2O), 6.38 (2ArH), 6.67 (2ArH), 12.00 (broad, OH).

Anal. Calcd. for $C_{21}H_{25}NO_6$: C, 65.1; H, 6.5; N, 3.6. Found: C, 64.9; H, 6.4; N, 3.5.

1-[7,8-Dihydro-6,7-dimethyl-8-(3,4,5-trimethoxyphenyl)-6*H*-1,3-dioxolo[4,5-*g*][1]benzopyran-6-yl]pyrrolidine **5d**.

A solution of **4f** (5 g) in 2-butanone (5 ml) and methanol (10 ml) was heated on a steam-bath for 30 minutes. The solution was concentrated, diluted with more methanol and cooled. Compound **5d** separated as colorless needles (3.28 g, 68%). Recrystallization from acetone-methanol gave **5d** as colorless brittle needles, mp 141-142°; ^{1}H nmr: δ 0.84 (d, J = 6 Hz, CH C*H*$_3$), 1.36 (CH_3), 1.78 (m, CH_2CH_2), 2.18 (m, C*H* CH_3), 2.98 (m, CH_2NCH_2), 3.46 (d, J = 12 Hz, CH), 3.78 ($2OCH_3$), 3.85 (OCH_3), 5.75 (d, J = 1 Hz and 5.78, d, J = 1 Hz, OCH_2O), 6.08 (ArH), 6.31 (ArH), 6.35 (2ArH); ^{13}C nmr: δ 14.6, (CH_3), 18.0, (CH_3), 24.3, ($2CH_2$), 41.6, (C*H*-CH_2), 44.3, (CH_2NCH_2), 49.8 (CH), 56.1 ($2OCH_3$), 60.8 (OCH_3), 93.8 (O-C-N), 98.3 (CH), 100.6 (OCH_2O), 106.3 (CH), 108.4 (2CH), 116.6 (C), 136.6 (C), 136.6 (C), 140.1 (C), 140.7 (C), 146.6 (C), 149.9 (2C), 153.0 (C).

Anal Calcd. for $C_{26}H_{31}O_6N$: C, 68.0; H, 7.1; N, 3.2. Found: C, 68.1; H, 7.0; N, 3.1.

7,8-Dihydro-6,7-dimethyl-8-(3,4,5-trimethoxyphenyl)-6*H*-1,3-dioxolo-[4,5-*g*][1]benzopyran-6-ol **5e**.

A solution of the benzopranylpyrrolidine **5d** (2.5 g) in glacial acetic acid (2 ml) and water (4 ml) was heated on a steam bath for one hour. Colorless crystals separated. Excess water was added and the product collected and washed well in water. Recrystallized from acetone-benzene **5e** was obtained as colorless needles, mp 183-184° (2.15 g, 98%); ^{1}H-nmr: δ 0.93 (d, J = 6 Hz, CHC*H*$_3$), 1.63 (CH_3), 2.10 (m, OH and CHC*H*$_3$), 3.62 (d, J = 12 Hz, CH), 3.78 ($2OCH_3$), 3.83 (OCH_3), 5.77 (d, J = 1 Hz and 5.82, d, J = 1 Hz, OCH_2O), 6.13 (ArH), 6.36 (3ArH); ^{13}C-nmr: δ 14.1 (CH_3), 27.4 (CH_3), 42.3 (*C*HCH$_3$), 46.5 (CH), 56.2 ($2OCH_3$), 60.9 (OCH_3), 98.4 (CH), 98.9 (O-C-OH), 100.8 (OCH_2O), 106.4 (2CH), 108.6 (CH), 118.2 (C), 136.7 (C), 139.4 (C), 146.1 (C), 146.6 (2C), 147.7 (C), 153.2 (C).

Anal. Calcd. for $C_{21}H_{24}O_7$: C, 64.9; H, 6.2. Found: C, 64.4; H, 6.2.

7,8-Dihydro-6,7-dimethyl-6-methoxy-8-(3,4,5-trimethoxyphenyl)-6*H*-1,3-dioxolo[4,5-g][1]benzopyran **5f**.

A solution of the alcohol **5e** (0.15 g) in methanol (2 ml) containing a drop of concentrated hydrochloric acid was heated briefly to boiling and allowed to cool. The colorless crystals which separated (0.12 g) were collected and recrystallized from methanol to **5f** as colorless soft needles, mp 179-180°; ^{1}H-nmr: δ 0.88 (d, J = 6 Hz, CHC*H*$_3$), 1.57 (CH_3), 2.04 (m, C*H*CH_3), 3.28 (OCH_3), 3.64 (d, J = 12 Hz, CH), 3.80 ($2OCH_3$), 3.86 (OCH_3), 5.81 (d, J = 1 Hz and 5.85, d, J = 1 Hz, OCH_2O), 6.14 (ArH), 6.37 (2ArH), 6.41 (ArH); ^{13}C-nmr: δ 13.9 (CH_3), 21.5 (CH_3), 43.4 (*C*HCH$_3$), 46.6 (CH), 50.0 (OCH_3), 56.6 ($2OCH_3$), 60.9 (OCH_3), 98.2 (CH), 100.7 (C), 101.0 (OCH_2O), 106.4 (2CH), 108.6 (CH), 119.1 (C), 136.6 (C), 139.7 (C), 141.6 (C), 146.1 (C), 146.1 (C), 153.2 (C).

Anal. Calcd. for $C_{22}H_{26}O_7$: C, 65.7; H, 6.5. Found: C, 65.7; H, 6.4.

Under similar conditions a solution of **5e** (0.15 g) in warm ethanolic hydrogen chloride (1 ml) deposited the ethyl derivative (0.14 g). Recrystallized from acetone-ethanol the *ethoxy* derivative (**5e**, R = OC_2H_5) separated as colorless, glistening prisms, mp 184-185°; ^{1}H-nmr: δ 0.86 (d, J = 6 Hz, CHC*H*$_3$), 1.0 (t, J = 7 Hz, CH_2CH_3), 1.74-2.25 (m, C*H*CH_3), 3.53 (q, J = 7 Hz, C*H*$_2$CH$_3$), 3.60 (d, J = 12 Hz, CH), 3.77 ($2OCH_3$), 3.83 (OCH_3), 5.78 (OCH_2O), 6.10 (ArH), 6.35 (3ArH).

Anal. Calcd. for $C_{23}H_{28}O_7$: C, 66.3; H, 6.8. Found: C, 66.2; H, 6.7.

6,7-Dimethyl-8-(3,4,5-trimethoxyphenyl)-8*H*-1,3-dioxolo[4,5-*g*][1]benzopyran **6m**.

An intimate mixture of **5e** (1.2 g) and powdered potassium bisulfate (3 g) was warmed to melting. After 5 minutes water was added and the product was collected and recrystallized from acetone-methanol to give **6m** as colorless needles, mp 148-149° (1.0 g); ^{1}H-nmr: δ 1.48 (CH_3), 1.94 (CH_3), 3.77 ($3OCH_3$), 4.13 (CH), 5.80 (OCH_2O), 6.32 (ArH), 6.37 (2ArH), 6.43 (ArH); ^{13}C-nmr: δ 16.1 (CH_3), 16.2 (CH_3), 47.4 (CH), 56.1 ($2OCH_3$), 60.8 (OCH_3), 97.6 (CH), 101.0 (OCH_2O), 104.3 (C), 105.1 (2CH), 107.5 (CH), 115.5 (C), 136.6 (C), 141.8 (C), 141.9 (C), 142.9 (C), 145.1 (C), 146.5 (C), 153.2 (C).

Anal. Calcd. for $C_{21}H_{22}O_6$: C, 68.1; H, 6.0. Found: C, 68.2; H, 6.0.

1-[7,8-Dihydro-6-methyl-8-(3,4,5-trimethoxyphenyl)-6*H*-1,3-dioxolo-[4,5-*g*][1]benzopyran-6-yl]pyrrolidine **5a**.

A solution of **4f** (50 g) in warm acetone was diluted with methanol and concentrated on the steam-bath. On cooling, colorless crystals separated. Recrystallized from acetone-methanol **5a** was obtained as colorless needles, mp 158-159° (46 g, 84%); ^{1}H-nmr: δ 1.52 (CH_3), 1.78 (m, $2CH_2$), 2.14 (m, CH), 2.97 (m, CH_2NCH_2), 3.82 ($2OCH_3$), 3.87 (OCH_3), 4.02 (d, J = 12 Hz, CH), 5.78 (d, J = 1 Hz and 5.84, d, J = 1 Hz, OCH_2O), 6.22 (ArH), 6.34 (ArH), 6.43 (2ArH).

Anal. Calcd. for $C_{24}H_{29}O_6N$: C, 67.4; H, 6.8; N, 3.3. Found: C, 67.1; H, 6.7; N, 2.9.

7,8-Dihydro-6-methyl-8-(3,4,5-trimethoxyphenyl)-6*H*-1,3-dioxolo[4,5-*g*]-[1]benzopyran-6-ol **5b**.

A solution of **5a** (1.0 g) in 50% aqueous acetic acid (2 ml) was heated on a steam-bath for 15 minutes, diluted with water (2.0 ml) and allowed to cool. The oily product rapidly crystallized. It was recrystallized from methanol to give **5b** as almost colorless, small needles, mp 100-101° (0.6 g); ^{1}H-nmr: δ 1.64 (CH_3), 1.98 (d, J = 14 Hz and 2.24, dd, J = 6, 14 Hz, CH_2), 3.48 (OH), 3.82 ($2OCH_3$), 3.86 (OCH_3), 4.15 (dd, J = 6, 14 Hz, CH), 5.80 (d, J = 1 Hz and 5.86, d, J = 1 Hz, OCH_2O), 6.26 (ArH), 6.31 (ArH), 6.45 (2ArH); ^{13}C-nmr: δ 29.1 (CH_3), 39.2 (CH), 41.0 (CH_2), 56.1 ($2OCH_3$), 60.8 (OCH_3), 96.3 (O-C-OH), 98.5 (CH), 100.8 (OCH_2O), 105.7 (2CH), 108.1 (CH), 116.9, 136.7, 139.9, 141.7, 146.7, 146.8 (6C's), 153.3 (2C's).

Anal. Calcd. for $C_{20}H_{22}O_7$: C, 64.1; H, 5.9. Found: C, 63.9; H, 5.6.

Compound **5b** was recrystallized from methanol containing a drop of concentrated hydrochloric acid. The *O*-methyl derivative **5c** separated as colorless needles, mp 152-153°; ^{1}H-nmr: δ 1.53 (CH_3), 2.22 (m, CH), 3.29 (OCH_3), 3.78 ($2OCH_3$), 3.86 (OCH_3), 4.09 (dd, J = 6, 12 Hz, CH), 5.79 (d, J = 1 Hz and 5.85, d, J = 1 Hz, OCH_2O), 6.25 (ArH), 6.43 (3ArH).

Anal. Calcd. for $C_{21}H_{24}O_7$: C, 64.9; H, 6.2. Found: C, 65.1; H, 6.1.

Crystallized from ethanolic hydrogen chloride **5b** gave the *O*-ethyl derivative **5b** (R = OEt), mp 149-150°; ^{1}H-nmr: δ 1.06 (t, J = 6 Hz, CH_3), 1.52 (CH_3), 2.09 (m, CH), 3.78 ($2OCH_3$), 3.82 (OCH_3), 4.21 (dd, J = 6, 12 Hz, CH), 5.78 (d, J = 1 Hz and 5.83, d, J = 1 Hz, OCH_2O), 6.18 (ArH), 6.32 (ArH), 6.37 (2ArH).

Anal. Calcd. for $C_{22}H_{26}O_7$: C, 65.7; H, 6.5. Found: C, 65.8; H, 6.5.

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