

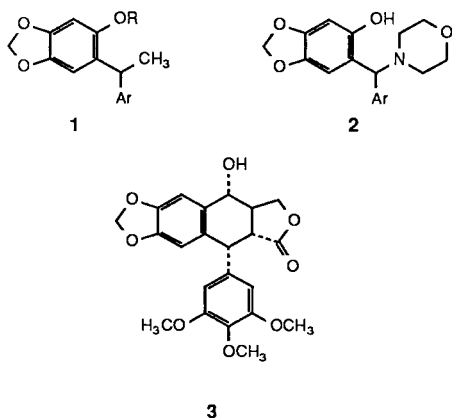
Leonard Jurd

Western Regional Research Center, Agricultural Research Service, U. S. Department of Agriculture,
Albany, California 94710
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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** ($R = \text{alkyl}$) 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



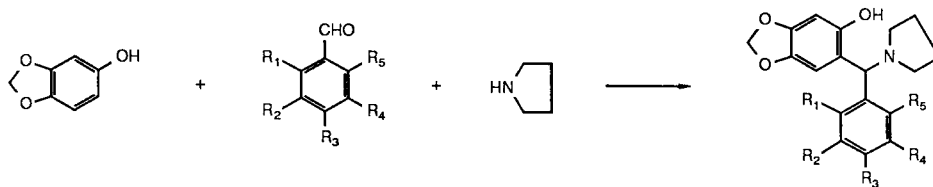
which is now in clinical use as an effective anti-cancer agent [4,5]. Like podophyllotoxin a number of these benzodioxoles have proved to be potent anti-mitotic and tubulin binding agents, and to be active *in vivo* against lymphocytic leukemia and other tumors in mice [6,7]. Pyrrolidine

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 piperidinyl 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 pyrrolidine 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



- 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, $R_1 = R_3 = R_5 = OCH_3, R_2 = R_4 = H$

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Table 1
Reactions of Pyrrolidine with Sesamol and Aromatic Aldehydes in Methanol

Product	mp °C	Yield %	Found (%) / Calcd. (%)			¹ H NMR (Deuteriochloroform)
			C	H	N	
4a C ₁₉ H ₂₁ O ₄ N	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 ₂ NCH ₂), 3.76 (OCH ₃), 4.21 (CH), 5.74 (d, J = 1 Hz and 5.82, d J = 1 Hz, OCH ₂ O), 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 ₄ N	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 ₂ NCH ₂), 3.75 (OCH ₃), 4.19 (CH), 5.73 (d, J = 1 Hz, OCH ₂ O), 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 ₅ N	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 ₂ NCH 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 ₂ O), 6.29-6.49 (m, 4 ArH), 7.42 (d, J = 8 Hz, ArH), 11.95 (OH)
4d C ₁₉ H ₁₉ O ₅ N	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 ₂ NCH ₂), 4.13 (CH), 5.73 (d, J = 1 Hz and 5.77 d, J = 1 Hz, OCH ₂ O), 5.86 (OCH ₂ O), 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 ₅ N	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 ₂ NCH ₂), 3.78 (OCH ₃), 4.97 (CH), 5.72 (d, J = 1 Hz, and 5.78 d, J = 1 Hz, OCH ₂ O), 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 ₅ NF	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 ₂ NCH ₂), 2.92 (N(CH ₃) ₂), 4.19 (CH), 5.74 (d, J = 1 Hz and 5.80 d, J = 1 Hz, OCH ₂ O), 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 ₁₈ O ₅ NF	112-113°	95	68.5 68.6	5.9 5.8		δ 1.82 (m, 2 CH ₂), 2.53 (m, CH ₂ NCH ₂), 4.21 (CH), 5.74 (d, J = 1 Hz and 5.80 d, J = 1 Hz, OCH ₂ O), 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 ₆ N	105-106°	55	[a]			δ 1.81 (m, 2 CH ₂), 2.52 (m, CH ₂ NCH 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 ₂ O), 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 ₆ N	148-149°	66	[a]			δ 1.73 (m, 2 CH ₂), 2.50 (m, CH ₂ NCH ₂), 3.60 (OCH ₃), 3.71 (OCH ₃), 3.79 (OCH ₃), 5.23 (CH), 5.78 (OCH ₂ O), 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 ¹³C 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 reaction can be rationalized on the basis that the pyrrolidine formed by dissociation of the Mannich base in solution (Scheme 2, a) rapidly reacts with the ketonic reagent to form an enamine (Scheme 2, b) which then recombine with the *ortho*-quinone methide in a Diels-Alder type reaction to yield the benzopyran (Scheme 2, c).

Pyrrolidinylbenzopyran derivatives formed in these ketone-Mannich base reactions can be hydrolyzed by warming in aqueous acetic acid to yield the corresponding

Table 2
Products from Reactions of Ketones with Mannich Bases

Reactants	Product	mp °C	Yield %	Found (%) / Calcd. (%)			¹ H NMR (Deuteriochloroform)
				C	H	N	
4a + Acetone	7a C ₂₂ H ₂₅ O ₄ N	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 ₂ NCH ₂), 3.73 (OCH ₃), 3.97 (dd, J = 8.12 Hz, CH), 5.74 (OCH ₂ O), 6.12 (ArH), 6.33 (ArH), 6.81 (d, J = 8 Hz, 2 ArH), 7.12 (d, J = 8 Hz, 2 ArH)
7a + H ₃ O [⊕]	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 ₂ O), 6.17 (ArH), 6.34 (ArH), 6.82 (d, J = 9 Hz, 2 ArH), 7.12 (d, J = 9 Hz, 2 ArH)
7a + CH ₃ OH ₂ [⊕]	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 ₂ O), 6.18 (ArH), 6.40 (ArH), 6.82 (2 ArH), 7.11 (2 ArH)
4a + 2-Butanone	7d C ₂₃ H ₂₇ O ₄ N	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 ₂ NCH ₂), 3.44 (d, J = 12 Hz, CH), 3.76 (OCH ₃), 5.73 (OCH ₂ O), 6.01 (ArH), 6.30 (ArH), 6.79 (d, J = 9 Hz, 2 ArH), 7.03 (d, J = 9 Hz, 2 ArH)
7d + H ₃ O [⊕]	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 ₂ O), 6.07 (ArH), 6.37 (ArH), 6.84 (d, J = 9 Hz, 2 ArH), 7.07 (d, J = 9 Hz, 2 ArH)
7d + CH ₃ OH ₂ [⊕]	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 ₂ O), 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 ₆ N	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 ₂ NCH 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 ₂ O), 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 ₄ N	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 ₂ NCH ₂), 3.52 (d, J = 11 Hz, CH), 3.78 (OCH ₃), 4.63 (d, J = 9 Hz, CH), 5.77 (OCH ₂ O), 6.04 (ArH), 6.37 (ArH), 6.84 (d, J = 9 Hz)
7h + H ₃ O [⊕]	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 ₂ O), 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 ₅ N	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 ₂ NCH ₂), 3.76 (OCH ₃), 3.81 (OCH ₃), 4.22 (d, J = 12 Hz, CH), 5.72 (OCH ₂ O), 6.01 (ArH), 6.22-6.52 (3 ArH), 6.82 (d, J = 8 Hz, ArH)
12d + H ₃ O [⊕]	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 ₂ O), 6.10 (ArH), 6.32-6.58 (m, 3 ArH), 6.90 (m, ArH)

Table 2 (continued)

Reactants	Product	mp °C	Yield %	Found (%) / Calcd. (%)			¹ H NMR (Deuteriochloroform)
				C	H	N	
12e + CH ₃ OH ₂ [⊕]	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 ₂ O), 6.06 (ArH), 6.32-6.52 (m, 3 ArH), 6.90 (m, ArH)
4c + Propionaldehyde	12h C ₂₃ H ₂₇ O ₅ N	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 ₂ NCH ₂), 3.74 (2 OCH ₃), 4.10 (d, J = 12 Hz, CH), 4.64 (d, J = 9 Hz, CH), 5.74 (OCH ₂ O), 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 ₇ N	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 ₂ NCH 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 ₂ O), 6.11 (ArH), 6.32-6.54 (m, 3 ArH), 7.0 (m, ArH)
4c + Cyclohexanone	12j C ₂₆ H ₃₁ O ₅ N	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 ₂ NCH ₂), 3.75 (OCH ₃), 3.81 (OCH ₃), 4.54 (d, J = 12 Hz, CH), 5.70 (OCH ₂ O), 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 ₅ N	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 ₂ NCH ₂), 3.79 (OCH ₃), 3.80 (OCH ₃), 4.02 (d, J = 9 Hz, CH), 5.82 (OCH ₂ O), 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 ₅ N	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 ₂ NH ₂), 3.44 (d, J = 12 Hz, CH), 5.74 (OCH ₂ O), 5.88 (OCH ₂ O), 6.06 (ArH), 6.29 (ArH), 6.54 (ArH), 6.68 (m, 2 ArH)
4e + Acetone	8a C ₂₂ H ₂₅ O ₅ N	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 ₂ NCH ₂), 3.84 (OCH ₃), 4.52 (m, CH), 5.78 (OCH ₂ O), 6.27 (ArH), 6.36 (ArH), 6.72 (m, 3 ArH)
4e + 2-Butanone	8d C ₂₃ H ₂₇ O ₅ N	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 ₂ NCH ₂), 3.84 (OCH ₃), 4.31 (d, J = 12 Hz, CH), 5.76 (OCH ₂ O), 6.10 (ArH), 6.32 (ArH), 6.73 (m, 3 ArH)
4e + Propionaldehyde	8h C ₂₂ H ₂₅ O ₅ N	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 ₂ NCH ₂), 3.85 (OCH ₃), 4.10 (d, J = 12 Hz, CH), 4.63 (d, J = 8 Hz, CH), 5.70 (OCH ₂ O), 5.90 (OH), 6.08 (ArH), 6.35 (ArH), 6.74 (m, 3 ArH)
4e + Ethyl Acetoacetate	8g C ₂₅ H ₂₉ O ₇ N	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 ₂ NCH 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 ₂ O), 6.12 (ArH), 6.32 (ArH), 6.72 (m, 3 ArH)
4f + Ethyl acetoacetate	5g C ₂₇ H ₃₃ O ₆ N	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 ₂ NCH 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 ₂ O), 6.16 (ArH), 6.32 (3 ArH)

Table 2 (continued)

Reactants	Product	mp °C	Yield %	Found (%) / Calcd. (%)			¹ H NMR (Deuteriochloroform)
				C	H	N	
5g + H ₃ O [⊕]	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 = 12 Hz, CH), 3.78 (2 OCH ₃), 3.84 (OCH ₃), 4.01 (q, J = 7 Hz, CH ₂ CH ₃), 4.31 (d, J = 12 Hz, CH), 5.80 (d, J = 1 Hz and 5.86, J = 10 Hz, OCH ₂ O), 6.20 (ArH), 6.37 (2 ArH), 6.40 (ArH)
5q + CH ₃ OH ₂ [⊕]	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 ₂ CH ₃), 4.44 (d, J = 12 Hz, CH), 5.80 (d, J = 1 Hz and 5.83 d, J = 1 Hz, OCH ₂ O), 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 ₂ CH ₃), 4.82 (CH), 3.83 (d, J = 1 Hz and 3.87 d, J = 1 Hz, OCH ₂ O), 6.30 (2 ArH), 6.44 (ArH), 6.52 (ArH)
4f + Propionaldehyde	5h C ₂₄ H ₂₉ O ₆ N	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 ₂ NCH 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 ₂ O), 6.07 (ArH), 6.33 (2 ArH), 6.37 (ArH)
5h + H ₃ O [⊕]	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 ₂ O), 6.50 (ArH), 6.68 (ArH), 6.74 (2 ArH)
4f + Cyclohexanone	5j C ₂₇ H ₃₃ O ₆ N	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 ₂ NCH 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 ₂ O), 6.06 (ArH), 6.28 (ArH), 6.33 (2 ArH)
4f + Cyclopentanone	5l C ₂₆ H ₃₁ O ₆ N	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 ₂ NCH 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 ₂ O), 6.14 (ArH), 6.42 (ArH), 6.45 (2 ArH)
4g + Acetone	10a C ₂₃ H ₂₈ O ₃ N 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 ₂ NCH ₂), 3.92 (dd, J = 6, 12 Hz, CH), 5.74 (OCH ₂ O), 6.18 (ArH), 6.32 (ArH), 6.56 (2 ArH), 7.04 (2 ArH)
10a + H ₃ O [⊕]	10b C ₁₉ H ₂₁ O ₄ N	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 ₂ O), 6.21 (ArH), 6.35 (ArH), 6.67 (2 ArH), 7.05 (2 ArH)
4g + 2-Butanone	10d C ₂₄ H ₃₀ O ₃ N 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 ₂ NCH ₂), 3.38 (d, J = 12 Hz, CH), 5.74 (OCH ₂ O), 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 ₅ N 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 ₂ NCH ₂), 4.0 (m, CH ₂ , CH), 5.76 (OCH ₂ O), 6.16 (ArH), 6.31 (ArH), 6.61 (2 ArH), 6.96 (2 ArH)

Table 2 (continued)

Reactants	Product	mp °C	Yield %	Found (%) / Calcd. (%)			¹ H NMR (Deuteriochloroform)
				C	H	N	
4h Acetone	11a C ₂₁ H ₂₂ O ₃ NF	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 ₂ NCH ₂), 4.02 (dd, J = 6, 12 Hz, CH), 5.75 (OCH ₂ O), 6.10 (ArH), 6.34 (ArH), 6.92 (2 ArH), 7.16 (2 ArH)
4i + 2-Butanone	13d C ₂₂ H ₃₁ O ₆ N	115-116°	61	[a]			δ 0.94 (d, J = 7 Hz, CH ₃), 1.49 (CH ₃), 1.73 (m, 2 CH ₂), 2.20 (m, CH), 2.97 (m, CH ₂ NCH ₂), 3.80 (OCH ₃), 3.88 (OCH ₃), 3.93 (OCH ₃), 4.10 (d, J = 12 Hz, CH), 5.76 (OCH ₂ O), 6.02 (ArH), 6.32 (ArH), 6.64 (2 ArH)
13d + CH ₃ OH ₂ [⊕]	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 ₂ O), 6.08 (ArH), 6.40 (ArH), 6.67 (2 ArH)
4j + 2-Butanone	14d C ₂₂ H ₂₁ O ₆ N	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 ₂ NCH 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 ₂ O), 6.07 (ArH), 6.18 (d, J = 1 Hz, ArH), 6.21 (d, J = 1 Hz, ArH), 6.30 (ArH)
14d + H ₃ O [⊕]	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 ₂ O), 6.04 (ArH), 6.07 (d, J = 2 Hz, ArH), 6.19 (d, J = 2 Hz, ArH), 6.30 (ArH)
14e + CH ₃ OH ₂ [⊕]	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 ₂ O), 6.04 (ArH), 6.11 (d, J = 1 Hz, ArH), 6.17 (d, J = 1 Hz, ArH), 6.33 (ArH)
5l + H ₃ O [⊕]	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 ₂ O), 6.17 (ArH), 6.43 (2 ArH), 6.50 (ArH)
5n + CH ₃ OH ₂ [⊕]	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 ₂ O), 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 ₂ O), 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.

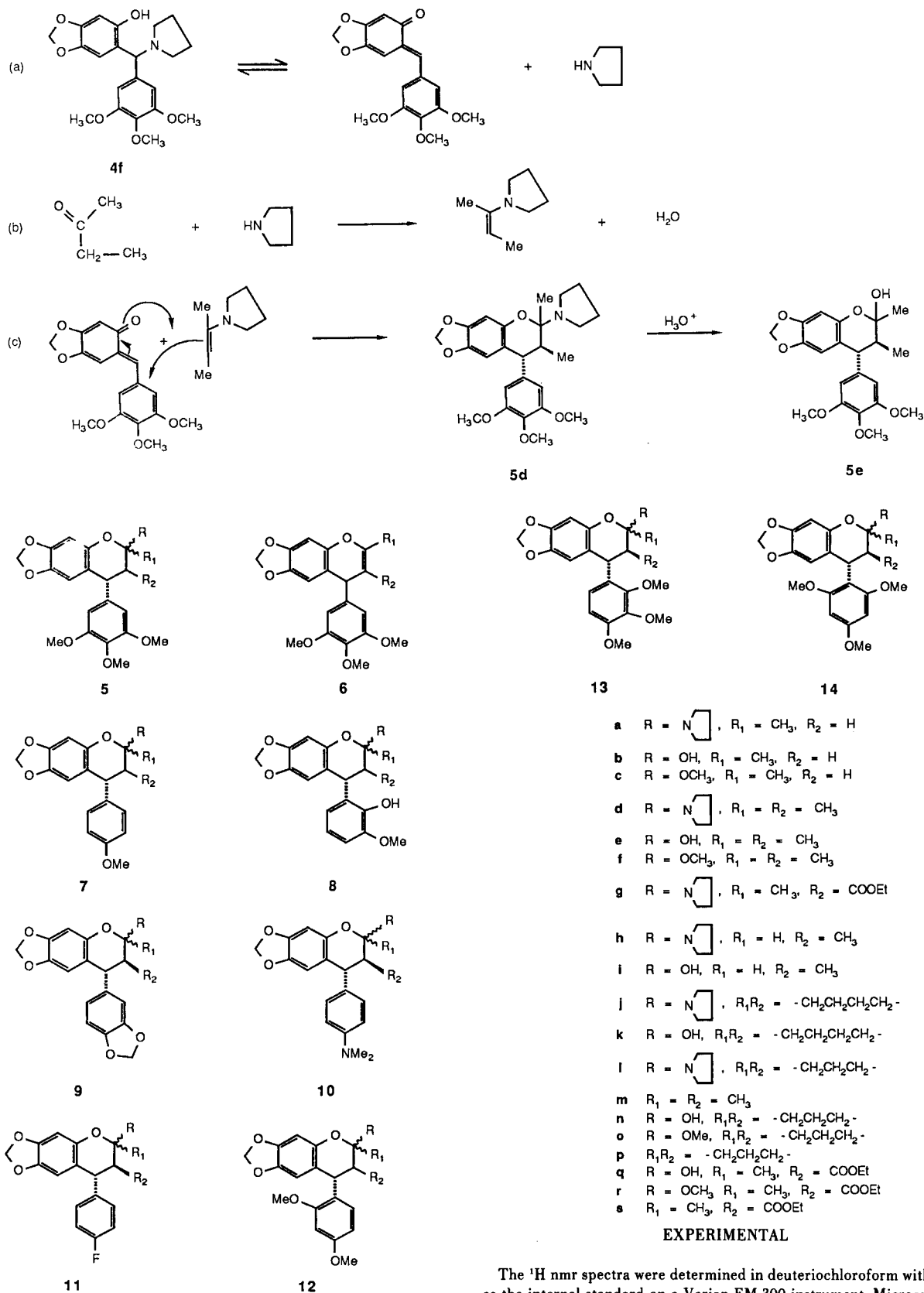
alcohols. Thus, hydrolysis of **5d** and of **5a**, the product from acetone and **4f**, gives the alcohols **5e** and **5b** respectively (Scheme 2, c). These alcohols may be readily converted into methyl ethers such as **5f** and **5c** or dehydrated to compounds of type **6**.

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



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%); ¹H-nmr: δ 1.80 (m, CH₂CH₂), 2.52 (m, CH₂NCH₂), 3.80 (OCH₃), 3.88 (2OCH₃), 4.09 (CH, 5.74, d, J = 1 Hz and 5.78, d, J = 1 Hz, OCH₂O), 6.38 (2ArH), 6.67 (2ArH), 12.00 (broad, OH).

Anal. Calcd. for C₂₁H₂₅NO₆: 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)-6H-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°; ¹H nmr: δ 0.84 (d, J = 6 Hz, CH CH₃), 1.36 (CH₃), 1.78 (m, CH₂CH₂), 2.18 (m, CH CH₃), 2.98 (m, CH₂NCH₂), 3.46 (d, J = 12 Hz, CH), 3.78 (2OCH₃), 3.85 (OCH₃), 5.75 (d, J = 1 Hz and 5.78, d, J = 1 Hz, OCH₂O), 6.08 (ArH), 6.31 (ArH), 6.35 (2ArH); ¹³C nmr: δ 14.6, (CH₃), 18.0, (CH₃), 24.3, (2CH₂), 41.6, (CH-CH₂), 44.3, (CH₂NCH₂), 49.8 (CH), 56.1 (2OCH₃), 60.8 (OCH₃), 93.8 (O-C-N), 98.3 (CH), 100.6 (OCH₂O), 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 C₂₆H₃₁O₈N: 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)-6H-1,3-dioxolo[4,5-g][1]benzopyran-6-ol **5e**.

A solution of the benzopyranpyrrolidine **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%); ¹H-nmr: δ 0.93 (d, J = 6 Hz, CHCH₃), 1.63 (CH₃), 2.10 (m, OH and CHCH₃), 3.62 (d, J = 12 Hz, CH), 3.78 (2OCH₃), 3.83 (OCH₃), 5.77 (d, J = 1 Hz and 5.82, d, J = 1 Hz, OCH₂O), 6.13 (ArH), 6.36 (3ArH); ¹³C-nmr: δ 14.1 (CH₃), 27.4 (CH₃), 42.3 (CHCH₃), 46.5 (CH), 56.2 (2OCH₃), 60.9 (OCH₃), 98.4 (CH), 98.9 (O-C-OH), 100.8 (OCH₂O), 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 C₂₂H₂₆O₇: 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)-6H-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°; ¹H-nmr: δ 0.88 (d, J = 6 Hz, CHCH₃), 1.57 (CH₃), 2.04 (m, CHCH₃), 3.28 (OCH₃), 3.64 (d, J = 12 Hz, CH), 3.80 (2OCH₃), 3.86 (OCH₃), 5.81 (d, J = 1 Hz and 5.85, d, J = 1 Hz, OCH₂O), 6.14 (ArH), 6.37 (2ArH), 6.41 (ArH); ¹³C-nmr: δ 13.9 (CH₃), 21.5 (CH₃), 43.4 (CHCH₃), 46.6 (CH), 50.0 (OCH₃), 56.6 (2OCH₃), 60.9 (OCH₃), 98.2 (CH), 100.7 (C), 101.0 (OCH₂O), 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 C₂₂H₂₆O₇: 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 = OC₂H₅) separated as colorless, glistening prisms, mp 184-185°; ¹H-nmr: δ 0.86 (d, J = 6 Hz, CHCH₃), 1.0 (t, J = 7 Hz, CH₃CH₂), 1.74-2.25 (m, CHCH₃), 3.53 (q, J = 7 Hz, CH₂CH₃), 3.60 (d, J = 12 Hz, CH), 3.77 (2OCH₃), 3.83 (OCH₃), 5.78 (OCH₂O), 6.10 (ArH), 6.35 (3ArH).

Anal. Calcd. for C₂₃H₂₈O₇: C, 66.3; H, 6.8. Found: C, 66.2; H, 6.7.

6,7-Dimethyl-8-(3,4,5-trimethoxyphenyl)-8H-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); ¹H-nmr: δ 1.48 (CH₃), 1.94 (CH₃), 3.77 (3OCH₃), 4.13 (CH), 5.80 (OCH₂O), 6.32 (ArH), 6.37 (2ArH), 6.43 (ArH); ¹³C-nmr: δ 16.1 (CH₃), 16.2 (CH₃), 47.4 (CH), 56.1 (2OCH₃), 60.8 (OCH₃), 97.6 (CH), 101.0 (OCH₂O), 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 C₂₁H₂₂O₆: C, 68.1; H, 6.0. Found: C, 68.2; H, 6.0.

1-[7,8-Dihydro-6-methyl-8-(3,4,5-trimethoxyphenyl)-6H-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%); ¹H-nmr: δ 1.52 (CH₃), 1.78 (m, 2CH₂), 2.14 (m, CH), 2.97 (m, CH₂NCH₂), 3.82 (2OCH₃), 3.87 (OCH₃), 4.02 (d, J = 12 Hz, CH), 5.78 (d, J = 1 Hz and 5.84, d, J = 1 Hz, OCH₂O), 6.22 (ArH), 6.34 (ArH), 6.43 (2ArH).

Anal. Calcd. for C₂₄H₂₉O₆N: 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)-6H-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); ¹H-nmr: δ 1.64 (CH₃), 1.98 (d, J = 14 Hz and 2.24, dd, J = 6, 14 Hz, CH₂), 3.48 (OH), 3.82 (2OCH₃), 3.86 (OCH₃), 4.15 (dd, J = 6, 14 Hz, CH), 5.80 (d, J = 1 Hz and 5.86, d, J = 1 Hz, OCH₂O), 6.26 (ArH), 6.31 (ArH), 6.45 (2ArH); ¹³C-nmr: δ 29.1 (CH₃), 39.2 (CH), 41.0 (CH₂), 56.1 (2OCH₃), 60.8 (OCH₃), 96.3 (O-C-OH), 98.5 (CH), 100.8 (OCH₂O), 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 C₂₀H₂₂O₇: 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°; ¹H-nmr: δ 1.53 (CH₃), 2.22 (m, CH), 3.29 (OCH₃), 3.78 (2OCH₃), 3.86 (OCH₃), 4.09 (dd, J = 6, 12 Hz, CH), 5.79 (d, J = 1 Hz and 5.85, d, J = 1 Hz, OCH₂O), 6.25 (ArH), 6.43 (3ArH).

Anal. Calcd. for C₂₁H₂₄O₇: 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°; ¹H-nmr: δ 1.06 (t, J = 6 Hz, CH₃), 1.52 (CH₃), 2.09 (m, CH), 3.78 (2OCH₃), 3.82 (OCH₃), 4.21 (dd, J = 6, 12 Hz, CH), 5.78 (d, J = 1 Hz and 5.83, d, J = 1 Hz, OCH₂O), 6.18 (ArH), 6.32 (ArH), 6.37 (2ArH).

Anal. Calcd. for C₂₂H₂₆O₇: C, 65.7; H, 6.5. Found: C, 65.8; H, 6.5.

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