Leonard Jurd

United States Department of Agriculture, Agricultural Research Service, Western Regional Research Center,
800 Buchanan Street, Albany, California 94710

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Pyrrolidine, morpholine and piperidine derived Mannich bases of types **1-3** react with acetone, propionaldehyde and butyraldehyde to form 2-methyl and 3-methylbenzopyrans of types **4-8**. Hydrolysis of these benzopyrans yields alcoholic benzopyrans which readily condense with a variety of amine, aniline and hydrazine derivatives to form diverse isomeric benzopyrans of types of **9** and **10**. The benzopyrans **4-9** which contain a 3,4,5-trimethoxyphenyl ring are active anti-tumor agents, particularly against human breast, CNS and colon cancer cell lines, total growth inhibition of these tumors often occurring *in vitro* at concentrations as low as 10^{-5}-10^{-6} moles/l. Because of their *in vitro* activities and unusual structures a number of these benzopyrans have been selected for *in vivo* Xenograft testing against breast and other susceptible human cancers.

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In Part **1** of this series it was reported [1] that the National Cancer Institute has made available to researchers a new, extensive *in vitro* screening program to detect potential anti-tumor agents. This program employs a panel of 60 human cancer cell lines of diverse types to measure the effects of bioactive compounds on cancer growth. Part **1** described the synthesis of a new class of heterocyclic benzylbenzodioxole lactones, many of which inhibited growth of some human cancers in the NCI procedure. Part **2** now reports the synthesis of a large number of novel methylenedioxybenzopyrans containing a variety of substituted amine and hydrazine groups. Many of these novel nitrogenous compounds selectively inhibit tumor growths *in vitro* and at this time a number have been chosen by NCI for further *in vivo* Xenograft testing against susceptible human cancers.

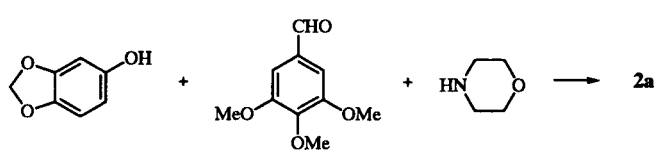
Chemistry.

Pyrrolidine Mannich bases **1** react with acetone and other ketones to form 2-methylbenzopyrans of type **4**, and with propionaldehyde to form 3-methylbenzopyrans of type **5**. In contrast to the pyrrolidines, similar morpholinyl and piperidinyl bases **2** and **3** do not react with monoketones and, in fact, can often be purified by crystallization from acetone-containing solvents. In this earlier work [2,3] only three propionaldehyde derived benzopyrans were synthesized, **viz. 5a**, **5b**, **5h**. Since acetone did not react with the morpholine and piperidine bases, the possible interaction of propionaldehyde with these bases was not further pursued at that time. However, a few of the above pyrrolidine compounds were active in the NCI mouse *in vivo* screening program then in use [4], and were also potent tubulin binding agents [5]; it was later found that the benzopyran **5h** showed interesting selective toxicity to some human breast cancer lines in the new *in vitro* screening programs. These observations indicated the desirability of greatly expanding these earlier synthetic studies to give a larger, more diverse pool of analogous benzopyrans containing other nitrogen ring systems and substituents such as those shown in **6**, **7**, **9**, and **10**.

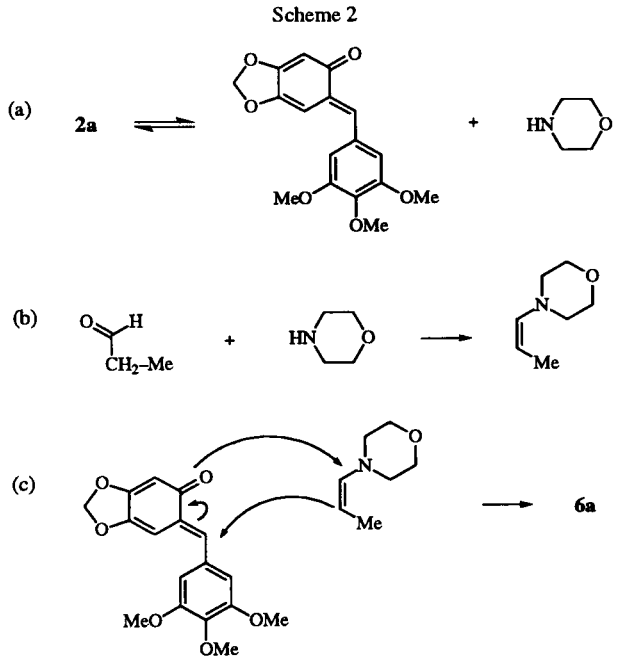
Thus, although acetone is inactive, it has now been found that propionaldehyde or butyraldehyde react very readily with the morpholine **2** and piperidine **3** Mannich bases to give high yields of benzopyrans **6**, **7** and **8**, corresponding to the pyrrolidine compounds **5**. For example, the morpholino compound **2a** dissolves in warm methanol to give a deep, yellow-orange colored solution. Addition of propionaldehyde leads to rapid decoloration and crystallization of a colorless product, $C_{24}H_{29}NO_7$. This product was assigned the benzopyran structure **6a** on the basis of its ^1H nmr spectrum, which shows the presence of a methyl group (doublet, δ 0.88, J = 7 Hz) coupled to a methine group (multiplet, δ 2.18). This methine group is, in turn, coupled to a benzylic methine which appears as a doublet (J = 12 Hz) at δ 3.55, and to a second (O,N linked) methine which appears as a doublet (J = 12 Hz) at δ 4.36. The magnitude of these couplings confirms the *trans-trans* stereochemistry shown in **6a**.

The Mannich bases used as starting materials for the preparation of benzopyrans **5**, **6** and **7** are easily synthesized [2,6] by reaction of 3,4-methylenedioxylphenol (sesamol) with an aromatic aldehyde and pyrrolidine, morpholine or piperidine in methanol, *e.g.* as in Scheme 1. These Mannich bases give orange colored solutions in warm solvents due to their dissociation to highly reactive *o*-quinone methides (Scheme 2a). The formation of novel benzopyrans on addition of propionaldehyde can then be rationalized on the

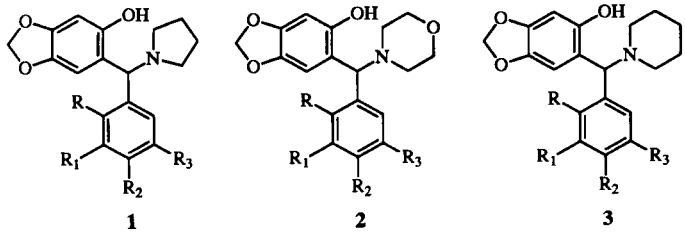
Scheme 1



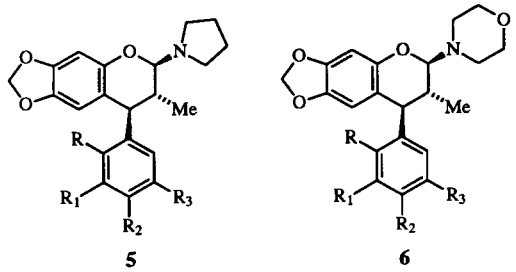
Scheme 2



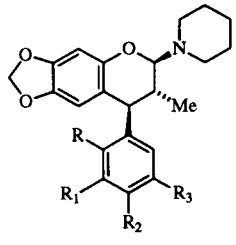
basis that the morpholine or other base, liberated by dissociation of the Mannich compound, rapidly reacts with the propionaldehyde to form an enamine (Scheme 2b); this undergoes a Diels-Alder reaction with the *o*-quinone methide to yield the benzopyran (Scheme 2c).



1 **2** **3**

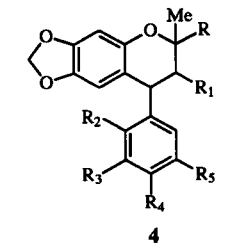


5 **6**



7

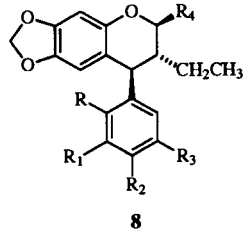
a, R = H; $R_1 = R_2 = R_3$ = OMe
b, R = $R_1 = R_3$ = H; R_2 = OMe
c, R = OMe; $R_1 = R_2 = R_3$ = H
d, R = R_1 = OMe; $R_2 = R_3$ = H
e, R = R_3 = H; $R_1 = R_2$ = OMe
f, R = R_3 = H; R_1, R_2 = OCH_2O
g, R = R_2 = OMe; $R_1 = R_3$ = H
h, R = OH; R_1 = OMe; $R_2 = R_3$ = H
i, R = $R_2 = R_3$ = H; R_1 = OMe
j, R = R_3 = H; R_1 = OMe; R_2 = OH
k, R = $R_1 = R_2$ = OMe; R_3 = H
l, R = OH; $R_1 = R_2 = R_3$ = H



4

a, R = N□; $R_1 = R_2$ = H; $R_3 = R_4 = R_5$ = OMe
b, R = OH; $R_1 = R_2$ = H; $R_3 = R_4 = R_5$ = OMe
c, R = HN–⬡; $R_1 = R_2$ = H; $R_3 = R_4 = R_5$ = OMe
d, R = N□; R_1 = Me; R_2 = H; $R_3 = R_4 = R_5$ = OMe
e, R = OH; R_1 = Me; R_2 = H; $R_3 = R_4 = R_5$ = OMe
f, R = N□; R_1 = Me; R_2 = OH; R_3 = OMe; $R_4 = R_5$ = H

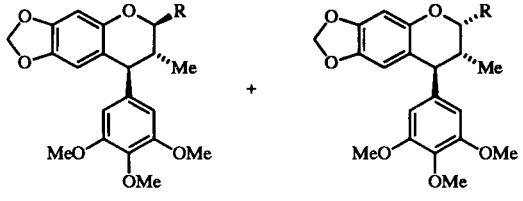
Attempts to prepare crystalline Mannich bases from other nitrogen compounds such as anilines, primary alkylamines and hydrazines by reactions similar to those shown in Scheme 1 have not been successful. Thus a different approach has been developed for the synthesis of related benzopyrans containing a widely diverse group of nitrogenous substituents. The pyrrolidine, morpholine and piperidine substituted benzopyrans **5**, **6** and **7** are easily hydrolysed [2] in warm aqueous acetic acid to give high yields of crystalline alcohols (hemiacetals), *e.g.* of type **9a**. The ^{1}H nmr spectra of these alcoholic products show that they are mixtures of *cis-trans* and *trans-trans* isomers, as shown in **9**, the *cis-trans* isomer sometimes being formed in predominant amounts. The *cis-trans* isomer is easily detected in these mixtures from the signal of its *O,O*-linked methine proton, which appears as a doublet with a small coupling (J = 2 Hz) downfield from the corresponding *trans-trans* coupled proton (J = 12 Hz) of the other isomer. Integration of these proton signals in the mixtures often allows assignment of other non-aromatic proton signals to either isomer; *e.g.* the ^{1}H nmr spectrum in deuteriochloroform of the alcoholic product **9a** from



8

a, R = H; $R_1 = R_2 = R_3$ = OMe; R_4 = –N⬡O
b, R = H; $R_1 = R_2 = R_3$ = OMe; R_4 = N□
c, R = OH; R_1 = OMe; $R_2 = R_3$ = H; R_4 = –N⬡O
d, R = OH; $R_1 = R_2 = R_3$ = H; R_4 = –N⬡O
e, R = $R_1 = R_3$ = H; R_2 = OMe; R_4 = –N⬡O

hydrolysis of **6a** indicates the presence of *cis-trans* and *trans-trans* isomers in a ratio of about 3:1. The *cis-trans* isomer shows a methyl (doublet at δ 0.94, J = 7 Hz) coupled to a methine proton (multiplet, δ 2.17) that is in turn coupled (*trans*) to the benzylic methine (doublet at δ 3.72, J = 12 Hz) and (*cis*) to the *O,O*-linked methine proton (doublet at δ 5.45, J = 2 Hz); the spectrum of the *trans-trans* isomer shows the methyl (doublet at δ 1.02, J = 7 Hz) coupled to a methine proton at δ 2.08, which is in turn coupled (*trans*) to a benzylic methine proton (doublet at δ 3.54, J = 12 Hz) and (*trans*) to an *O,O*-linked methine proton (doublet at δ 5.07, J = 12 Hz).



9

a, R = OH

b, R = HN-⬡

c, R = HN-⬡-OMe

d, R = HNNH-⬡

e, R = NEt_2

f, R = HN-⬡

g, R = $NHCH_2$-⬡

h, R = $NHCH_2CH_2$-⬡

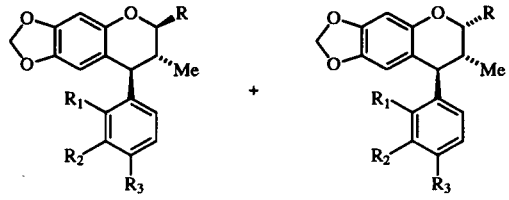
i, R = HN-⬡-COOH

j, R = HN-⬡-COOEt

k, R = $NHNHCONH_2$

l, R = $NHNHCSNH_2$

When these alcoholic benzopyran hydrolysis products are warmed with diverse amine and hydrazine derivatives they rapidly react to yield nitrogen substituted benzopyrans, *e.g.* **9a** reacts with *p*-methoxyaniline or phenylhydrazine in methanol to give the active *in vitro* tumor growth inhibitors **9c** and **9d** respectively. As in the case of the alcohols, each of these condensation products consists of a mixture of *cis-trans* and *trans-trans* isomers, the *O,N*-linked methine proton (doublet, J = 2 Hz) of the *cis-trans* isomer appearing downfield of the corresponding proton, (doublet, J = 9-12 Hz) of the *trans-trans* isomer. Although the separation of the pure *cis-trans* and *trans-trans* isomers has not yet been explored, this reaction sequence appears to offer simple access to an almost unlimited variety of nitrogenous benzopyrans. Thus the alcohol(s) **9a** has been condensed with diethylamine and primary amines such as cyclohexylamine, benzylamine and phenethylamine, aniline and hydrazine derivatives to give the crystalline products (**9b-9l**). All of these compounds inhibited growth of some tumors *in vitro* and, in fact, **9c** and **9d** were selected by NCI for *in vivo* testing with sensitive cancers. Benzopyrans with a differently substituted lateral phenyl ring were generally much less active growth inhibitors than 3,4,5-trimethoxyphenyl compounds. Some of these inactive or less active benzopyrans are shown in **10**.



10

a, R = R_1 = OH; R_2 = OMe; R_3 = H

b, R = HN-⬡ ; R_1 = OH; R_2 = OMe: R_3 = H

c, R = HNNH-⬡ ; R_1 = OH; R_2 = OMe: R_3 = H

d, R = $NHNHCONH_2$; R_1 = OH; R_2 = OMe; R_3 = H

e, R = OH; R_1 = R_2 = OMe; R_3 = H

f, R = HN-⬡ ; R_1 = R_2 = OMe; R_3 = H

g, R = HN-⬡-OMe ; R_1 = R_2 = OMe; R_3 = H

h, R = $NHNHCONH_2$; R_1 = R_2 = OMe; R_3 = H

i, R = R_1 = OH; R_2 = R_3 = H

j, R = OH; R_1 = R_2 = H; R_3 = OMe

k, R = HNNH-⬡ ; R_1 = R_2 = H; R_3 = OMe

On the basis of the results obtained in their *in vitro* screening program [7,8] the NCI selected a relatively large number of the nitrogenous and alcoholic benzopyrans for further *in vivo* Xenograft testing against breast and other human cancers. Benzopyrans of interest [9] included **4b**, **4d**, **5a**, **5h**, **6a**, **9a**, **9c** and **9d**.

EXPERIMENTAL

The nmr spectra were determined in deuteriochloroform with TMS as internal standard on a Nicolet NT-WB 200 FT instrument at 200 MHz (^1H) and at 50 MHz (^{13}C). Analyses were performed in a commercial laboratory. Melting points are uncorrected.

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

A mixture of the morpholino compound **2a** (1.0 g) [4] and propion aldehyde (1.0 g) in methanol (5 ml) was heated to boiling. Within five minutes the reaction mixture became almost colorless and colorless crystals separated. Heating was continued for 30 minutes, the mixture was cooled, and the crystals were collected. Recrystallized from acetone-methanol the benzopyran **6a** separated as colorless needles, m.p. 201-202° (0.99 g, 91%); ^{1}H nmr: δ 0.88 (d, J = 7 Hz, CH_3), 2.18 (m, CH), 2.76 (m) and 3.02 (m) (-CH_2-N-CH_2-), 3.55 (d, J = 12 Hz, CH), 3.75 (m, -CH_2-O-CH_2-), 3.82 (2 OCH_3), 3.86 (OCH_3), 4.36 (d, J = 12 Hz, CH), 5.80 (d, J = 1 Hz) and 5.82 (d, J = 1 Hz) (OCH_2O), 6.08 (ArH), 6.32 (2ArH), 6.38 (ArH); ^{13}C nmr: δ 15.2 (CH_3), 36.5 (CH), 47.6 ($N(CH_2)_2$), 51.8 (CH), 56.2 (2 OCH_3), 60.7 (OCH_3), 67.2 ($O(CH_2)_2$), 96.7 (O-CH-N), 98.1 (CH), 100.8 (OCH_2O), 106.3 (CH), 108.3 (2 CH), 117.4 (C), 136.5 (C), 139.5 (C), 141.3 (C), 146.7 (C), 149.7 (C), 153.4 (2C) .

Anal. Calcd. for $C_{24}H_{29}NO_7$: C, 65.0; H, 6.6. Found: C, 65.2; H, 6.6.

A mixture of **2a** and *n*-butyraldehyde reacted similarly in warm methanol to give benzopyran **8a** which crystallized from acetone-methanol as colorless needles, mp 179-180° (86%); ^{1}H nmr: δ 0.87 (t, J = 7 Hz, CH_3), 1.27 (m) and 1.55 (m) (CH_2), 2.17 (m, CH), 2.75 (m) and 3.02 (m) (-CH_2-N-CH_2-), 3.72 (m, -CH_2-OCH_2-, CH), 3.78 (OCH_3), 3.83 (2 OCH_3), 4.47 (d, J = 12 Hz, CH), 5.81 (d, J = 1 Hz) and 5.83 (d, J = 1 Hz) (OCH_2O), 6.08 (ArH), 6.33 (2 ArH), 6.37 (ArH).

Anal. Calcd. for $C_{25}H_{31}NO_7$: C, 65.6; H, 6.8. Found: C, 65.7; H, 7.0.

A mixture of the piperidine Mannich base **3a** (1.0 g) and propionaldehyde (1.0 g) warmed similarly in methanol gave the benzopyran **7a** as colorless needles, mp 187-188° (80%); ^{1}H nmr: δ 0.86 (d, J = 7 Hz, CH_3), 1.57 (m, 3 CH_2), 2.19 (m, CH), 2.67 (m) and 2.98 (m) (-CH_2-N-CH_2-), 3.53 (d, J = 12 Hz, CH), 3.82 (2 OCH_3), 3.86 (OCH_3), 4.36 (d, J = 12 Hz, CH), 5.78 (d, J = 1 Hz), and 5.83 (d, J = 1 Hz) (OCH_2O), 6.08 (ArH), 6.33 (2 ArH), 6.36 (ArH).

Anal. Calcd. for $C_{25}H_{31}NO_6$: C, 68.0; H, 7.1. Found: C, 67.7; H, 7.3.

6-[(2-Hydroxy-3-methoxyphenyl)-4-morpholinylmethyl]-1,3-benzadioxol-5-ol **2h**.

A solution of sesamol (2.8 g), 2-hydroxy-3-methoxybenzaldehyde (3.0 g) and morpholine (1.74 g) in methanol (20 ml) was heated under reflux for 3 hours. On cooling colorless crystals separated. Recrystallized from chloroform-methanol the morpholino compound **2h** separated as colorless, glistening prisms, mp 178° (5.2 g, 72%); ^{1}H nmr: δ 2.56 (m) and 2.70 (m) (CH_2NCH_2), 3.74 (m, CH_2OCH_2), 3.87 (OCH_3), 5.03 (CH), 5.77 (d, J = 1 Hz) and 5.83 (d, J = 1 Hz) (OCH_2O), 6.39 (ArH), 6.54 (ArH), 6.72-6.83 (m, 2ArH), 7.04 (dd, J = 2, 8 Hz, ArH), 11.22 (br s, 2 OH).

Anal. Calcd. for $C_{19}H_{21}NO_6$: C, 63.5; H, 5.9; N, 3.9. Found: C, 63.7; H, 5.9; N, 3.8.

1-[7,8-Dihydro-7-methyl-8-(2-hydroxy-3-methoxyphenyl)-6*H*-1,3-dioxolo[4,5-*g*][1]benzopyran-6-yl]morpholine **6h**.

A mixture of the morpholino Mannich base **2h** (0.6 g) and propionaldehyde (0.6 g) in methanol (5 ml) was heated for 15 minutes on a steam-bath. Within a few minutes all of **2h** passed into solution. At the end of the reaction colorless crystals had begun to separate. After cooling, the product was collected and recrystallized from acetone-methanol. The benzopyran **6h** separated as colorless needles, mp 111-112° (0.5 g); ^{1}H nmr: δ 0.88 (d, J = 7 Hz, CH_3), 2.26 (m, CH), 2.76 (m) and 3.01 (m) (CH_2NCH_2), 3.50 (H_2O, OH), 3.73 (m, CH_2OCH_2), 3.92 (OCH_3), 4.26 (br m, CH), 4.40 (d, J = 12 Hz, CH), 5.78 (OCH_2O), 6.07 (ArH), 6.37 (ArH), 6.61-6.78 (m, 3ArH).

Anal. Calcd. for $C_{22}H_{25}NO_6$: C, 66.2; H, 6.3. Found: C, 66.2; H, 6.5.

Benzopyran **6l**.

The morpholino Mannich base **2l**, was prepared by refluxing sesamol (28 g), *o*-hydroxybenzaldehyde (24.4 g) and morpholine (17.4 g) in methanol (40 ml) for an hour. The product crystallized on cooling. Recrystallized from chloroform-methanol **2l** separated as hard, colorless prisms, mp 172-173° (51.0 g); ^{1}H nmr: δ 2.53 (br s, CH_2NCH_2), 3.76 (CH_2OCH_2), 5.02 (CH), 5.84 (OCH_2O), 6.36 (ArH), 6.72 (ArH), 6.81 (m, 2ArH), 7.13 (m, 2ArH).

Anal. Calcd. for $C_{18}H_{19}NO_5$: C, 65.6; H, 5.8. Found: C, 65.1; H, 5.9.

A solution of **2l** (1.0 g) and propionaldehyde (0.5 g) in warm methanol was heated until the yellow color had disappeared (10 minutes). On cooling, colorless crystals separated. Recrystallized from acetone-methanol the benzopyran **6l** was obtained as colorless needles, mp 222-223° (0.8 g, 73%); ^{1}H nmr: δ 0.94 (d, J = 7 Hz, CH_3), 1.57 (OH), 2.38 (m, CH), 2.73 (m) and 2.98 (m) (CH_2NCH_2), 3.72 (m, CH_2OCH_2, CH), 4.33 (d, J = 12 Hz, CH), 5.83 (OCH_2O), 6.20 (ArH), 6.40 (ArH), 6.80 (dd, J = 2, 8 Hz, ArH), 6.89 (m, ArH), 7.15 (m, 2ArH).

Anal. Calcd. for $C_{21}H_{23}NO_5$: C, 68.3; H, 6.3. Found: C, 68.3; H, 6.5.

Warmed with butyraldehyde the morpholino compound **2l** gave the benzopyran **8d**. This crystallized from acetone-methanol in colorless, glistening needles, mp 188-189°; ^{1}H nmr: δ 0.98 (t, J = 7 Hz, CH_3, 1.50 (m, CH_2), 2.31 (m, CH), 2.62 (m) and 2.90 (m) CH_2NCH_2), 3.70 (m, CH_2OCH_2), 4.03 (d, J = 11 Hz, CH), 4.31 (d, J = 11 Hz, CH), 5.80 (d, J = 1 Hz) and 5.82 (d, J = 1 Hz) (OCH_2O), 6.24 (ArH), 6.41 (ArH), 6.78 (dd, J = 2, 8 Hz, ArH), 6.88 (m, ArH), 7.12 (m, 2 ArH).

Anal. Calcd. for $C_{22}H_{25}NO_5$: C, 68.9; H, 6.6. Found: C, 68.8; H, 6.8.

Synthesis of Other New Benzopyrans of Types **5**, **6**, **7**, and **8**.

Applying procedures similar to those described above, the following new benzopyrans were synthesized by reaction of the appropriate Mannich base **1**, **2** or **3** with propionaldehyde or butyraldehyde in methanol.

Benzopyran **5d** was obtained as colorless soft needles from acetone-methanol, mp 122-123°; ^{1}H nmr: δ 0.88 (d, J = 7 Hz, CH_3), 1.81 (m, 2 CH_2), 2.07 (m, CH), 2.89 (m) and 3.0 (m) (-CH_2-N-CH_2-), 3.85 (2 OCH_3), 4.27 (d, J = 11 Hz, CH), 4.67 (d, J = 11 Hz, CH), 5.78 and 5.80 (OCH_2O), 6.05 (ArH), 6.36 (ArH), 6.62 (m, ArH), 6.82 (m, ArH), 6.90 (ArH).

Anal. Calcd. for $C_{23}H_{27}NO_5$: C, 69.5; H, 6.9. Found: C, 69.3; H, 6.9.

Benzopyran **5f** was obtained as colorless, glistening prisms, mp 173-174°; ^{1}H nmr: δ 0.90 (d, J = 7 Hz, CH_3), 1.82 (m, 2 CH_2), 2.03 (m, CH), 2.94 (m) and 3.03 (m) (-CH_2-N-CH_2-), 3.53 (d, J = 12 Hz, CH), 4.63 (d, J = 12 Hz, CH), 5.81 (OCH_2O), 5.94 (OCH_2O), 6.07, (ArH), 6.37 (ArH), 6.56 (d, J = 2 Hz, ArH), 6.65 (dd, J = 2, 8 Hz, ArH), 6.74 (d, J = 8 Hz, ArH).

Anal. Calcd. for $C_{22}H_{23}NO_5$: C, 69.3; H, 6.1. Found: C, 69.0; H, 6.2.

Benzopyran **5i** was obtained as colorless needles, mp 116-117°; ^{1}H nmr: δ 0.88 (d, J = 7 Hz, CH_3), 1.82 (m, 2 CH_2), 2.11 (m, CH), 2.94 (m) and 3.03 (m) (-CH_2-N-CH_2-), 3.58 (d, J = 12 Hz, CH), 3.78 (OCH_3), 4.64 (d, J = 12 Hz, CH), 5.78 (d, J = 1 Hz) and 5.80 (d, J = 1 Hz), (OCH_2O), 6.07 (ArH), 6.37 (ArH), 6.68 (m, ArH), 6.77 (m, ArH), 7.23 (m, ArH).

Anal. Calcd. for $C_{22}H_{25}NO_4$: C, 71.9; H, 6.9. Found: C, 71.5; H, 7.1.

Benzopyran **6b** was obtained as colorless needles from acetone-methanol, mp 173-174°; ^{1}H nmr: δ 0.84 (d, J = 7 Hz, CH_3), 2.14 (m, CH), 2.76 (m) and 3.00 (m) (-CH_2-N-CH_2-), 3.55 (d, J = 12 Hz, CH), 3.68 (m, -CH_2OCH_2-), 3.79 (OCH_3) 4.37 (d, J = 12 Hz, CH), 5.70 (d, J = 1 Hz) and 5.72 (d, J = 1 Hz) (OCH_2O), 6.03 (ArH), 6.38 (ArH), 6.85 (d, J = 9 Hz, 2 ArH), 7.04 (d, J = 9 Hz, 2 ArH).

Anal. Calcd. for $C_{22}H_{25}NO_5$ C, 68.9; H, 6.6. Found: C, 69.0; H, 6.8.

Benzopyran **6c** was obtained as colorless prisms, mp 177-178°: ^{1}H nmr: δ 0.86 (d, J = 7 Hz, CH_3), 2.22 (m, CH), 2.76 (m) and 3.00 (m) (-CH_2-N-CH_2-), 3.86 (m, OCH_3, CH), 4.39 (d, J = 12 Hz, CH), 5.78 (d, J = 1 Hz) and 5.80 (d, J = 1 Hz) (OCH_2O), 5.98 (ArH), 6.37 (ArH), 6.90 (m, 3 ArH), 7.22 (m, ArH).

Anal. Calcd. for $C_{22}H_{25}NO_5$: C, 68.9; H, 6.6. Found: C, 68.9; H, 6.7.

Benzopyran **6d** was obtained as brittle needles from methanol, mp 165°; ^{1}H nmr: δ 0.85 (d, J = 7 Hz, CH_3), 2.17 (m, CH), 2.75 (m) and 3.00 (m) (-CH_2-N-CH_2-), 3.73 (m, -CH_2OCH_2-), 3.87 (OCH_3), 3.88 (OCH_3), 4.31 (d, J = 10 Hz, CH), 4.44 (d, J = 10 Hz, CH), 5.78 and 5.80 (OCH_2O), 6.03 (ArH), 6.38 (ArH), 6.57 (m, ArH), 6.81 (m, ArH), 6.98 (m, ArH).

Anal. Calcd. for $C_{23}H_{27}NO_6$: C, 66.8; H, 6.6. Found: C, 67.0; H, 6.8.

Benzopyran **6e** was obtained as colorless needles, mp 179-180°; ^{1}H nmr: δ 0.88 (d, J = 7 Hz, CH_3), 2.17 (m, CH), 2.76 (m) and 3.04 (m) (-CH_2-N-CH_2-), 3.5 (d, J = 12 Hz, CH), 3.82 (OCH_3), 3.88 (OCH_3), 4.36 (d, J = 12 Hz, CH), 5.80 (d, J = 1 Hz) and 5.82 (d, J = 1 Hz) (OCH_2O), 6.06 (ArH), 6.37 (ArH), 6.57 (d, J = 2 Hz, ArH), 6.72 (dd, J = 2, 8 Hz, ArH), 6.82 (d, J = 8 Hz, ArH).

Anal. Calcd. for $C_{23}H_{27}NO_6$: C, 66.8; H, 6.6. Found: C, 66.7; H, 6.8.

Benzopyran **6f** was obtained as colorless needles, mp 179-180°; ^{1}H nmr: δ 0.86 (d, J = 7 Hz, CH_3), 2.12 (m, CH), 2.76 (m) and 2.95 (m) (-CH_2-N-CH_2-), 3.54 (d, J = 12 Hz, CH) 3.73 (m, -CH_2OCH_2-), 4.33 (d, J = 12 Hz, CH), 5.81 (d, J = 1 Hz) and 5.82 (d, J = 1 Hz) (OCH_2O), 5.94 (OCH_2O), 6.07 (ArH), 6.36 (ArH), 6.54 (d, J = 2 Hz, ArH), 6.48 (dd, J = 2, 8 Hz, ArH), 6.74 (d, J = 8 Hz, ArH).

Anal. Calcd. for $C_{22}H_{23}NO_6$: C, 66.5; H, 5.8. Found: C, 66.2; H, 6.1.

Benzopyran **6g** was obtained as colorless needles, mp 163-164°; ^{1}H nmr: δ 0.84 (d, J = 7 Hz, CH_3), 2.17 (m, CH), 2.75 (m) and 3.01 (m) (-CH_2-N-CH_2-), 3.72 (m, -CH_2OCH_2-), 3.80 (2 OCH_3), 4.27 (br d, J = 11 Hz, CH), 4.38 (br d, J = 11 Hz, CH), 5.67 (d, J = 1 Hz) and 5.69 (d, J = 1 Hz) (OCH_2O), 6.02 (ArH), 6.36 (ArH), 6.43-6.52 (m, 2 ArH), 6.88 (d, J = 8 Hz, ArH).

Anal. Calcd. for $C_{23}H_{27}NO_6$: C, 66.8; H, 6.6. Found: C, 66.6; H, 6.5.

Benzopyran **6j** was obtained as colorless needles, mp 212-213°; ^{1}H nmr: δ 0.87 (d, J = 7 Hz, CH_3), 2.14 (m, CH), 2.76 (m) and 3.02 (m) (-CH_2-N-CH_2-), 3.53 (d, J = 12 Hz, CH), 3.74 (m, CH_2OCH_2), 3.84 (OCH_3), 4.36 (d, J = 12 Hz, CH), 5.57 (br s, OH), 5.79 (d, J = 1 Hz) and 5.81 (d, J = 1 Hz) (OCH_2O), 6.06 (ArH), 6.37 (ArH), 6.53 (d, J = 2 Hz, ArH), 6.67 (dd, J = 2, 8 Hz, ArH), 6.84 (d, J = 8 Hz, ArH).

Anal. Calcd. for $C_{22}H_{25}NO_6$: C, 66.1; H, 6.3. Found: C, 65.9; H, 6.4.

Benzopyran **6k** was obtained as colorless prisms, mp 117-119°; ^{1}H nmr: δ 0.84 (d, J = 7 Hz, CH_3), 2.16 (m, CH), 2.76 (m) and 3.02 (m) (-CH_2-N-CH_2-), 3.72 (m, CH_2OCH_2), 3.84 (3 OCH_3, CH), 5.78 (d, J = 1 Hz) and 5.80 (d, J = 1 Hz) (OCH_2O), 6.03 (ArH), 6.37 (ArH), 6.65 (2 ArH).

Anal. Calcd. for $C_{24}H_{29}NO_7$: C, 65.0; H, 6.6. Found: C, 65.1; H, 6.8.

Benzopyran **7b** was obtained as colorless needles from methanol, mp 183-184°; ^{1}H nmr: δ 0.83 (d, J = 7 Hz, CH_3), 1.53 (m, 3 CH_2), 2.17 (m, CH), 2.66 (m) and 2.97 (m) (-CH_2-N-CH_2-), 3.54 (d, J = 12 Hz, CH), 3.80 (OCH_3), 4.36 (d, J = 12 Hz, CH), 5.78 (d, J = 1 Hz) and 5.80 (d, J = 1 Hz) (OCH_2O), 6.03 (ArH), 6.36 (ArH), 6.84 (d, J = 9 Hz, 2 ArH), 7.04 (d, J = 9 Hz, 2 ArH).

Anal. Calcd. for $C_{23}H_{27}NO_4$: C, 72.4; H, 7.1. Found: C, 72.4; H, 7.3.

Benzopyran **7f** was obtained as colorless, hard needles, mp 182-183°; ^{1}H nmr: δ 0.84 (d, J = 7 Hz, CH_3), 1.54 (m, 3 CH_3), 2.16 (m, CH), 2.67 (m) and 2.95 (m) (-CH_2-N-CH_2-), 3.54 (d, J = 12 Hz, CH), 4.35 (d, J = 12 Hz, CH), 5.79 (d, J = 1 Hz) and 5.80 (d, J = 1 Hz) (OCH_2O), 5.95 (OCH_2O), 6.07 (ArH), 6.36 (ArH), 6.55 (d, J = 2 Hz, ArH), 6.66 (dd, J = 2, 8 Hz, ArH), 6.76 (d, J = 8 Hz, ArH).

Anal. Calcd. for $C_{23}H_{25}NO_5$: C, 69.8; H, 6.4. Found: C, 69.6; H, 6.4.

Benzopyran **8b** was obtained as colorless needles, mp 103°; ^{1}H nmr: δ 0.86 (t, J = 7 Hz, CH_3), 1.32 (m) and 1.57 (m) (CH_2), 1.82 (m, 2 CH_2), 2.08 (m, CH), 2.96 (m) and 3.03 (m) (-CH_2-N-CH_2-), 3.83 (2 OCH_3), 3.84 (d, J = 12 Hz, CH), 3.86 (OCH_3), 4.76 (d, J = 12 Hz, CH), 5.79 (d, J = 1 Hz) and 5.82 (d, J = 1 Hz) (OCH_2O), 6.12 (ArH), 6.35 (2 ArH), 6.37 (ArH).

Anal. Calcd. for $C_{25}H_{31}NO_6$: C, 68.0; H, 7.1. Found: C, 67.6; H, 7.2.

Benzopyran **8c** was obtained as colorless needles, mp 165-166°; ^{1}H nmr: δ 0.88 (t, J = 7 Hz, CH_3), 1.25 (m) and 1.50 (m) (CH_2), 2.35 (m, CH), 2.76 (m) and 3.00 (m) (-CH_2-N-CH_2-), 3.74 (m, CH_2OCH_2) 3.90 (OCH_3), 4.39 (br s, CH), 4.49 (d, J = 12 Hz, CH), 5.78 (OCH_2O), 5.83 (OH), 6.09 (ArH), 6.36 (ArH), 6.60 (m, ArH), 6.78 (m, 2 ArH).

Anal. Calcd. for $C_{23}H_{27}NO_6$: C, 66.8; H, 6.6. Found: C, 66.7; H, 6.8.

Benzopyran **8e**, colorless felted needles, mp 154-155°; ^{1}H nmr: δ 0.83 (t, J = 7 Hz, CH_3), 1.26 (m) and 1.50 (m) (CH_2), 2.14 (m, CH), 2.76 (m) and 3.02 (m) (-CH_2-N-CH_2-), 3.73 (m, CH_2OCH_2), 3.86 (d, J = 12 Hz, CH), 4.48 (d, J = 12 Hz, CH), 5.79 (OCH_2O), 6.06 (ArH), 6.37 (ArH), 6.85 (d, J = 8 Hz, 2 ArH), 7.06 (d, J = 8 Hz, 2 ArH).

Anal. Calcd. for $C_{23}H_{27}NO_5$: C, 69.5; H, 6.9. Found: C, 69. 5; H, 7.1.

Benzopyran **9a**.

A solution of the benzopyranylpyrrolidine **5a** in warm acetic acid (10 ml) and water (5 ml) was heated on a steam-bath for 30 minutes and slowly diluted with more water (10 ml). The product rapidly crystallized (4.17 g). Recrystallized from acetone-

methanol the mixed isomeric alcohols **9a** were obtained as colorless needles, mp 173-174°; *cis-trans* isomer ^{1}H nmr: δ 0.94 (d, J = 7 Hz, CH_3), 2.17 (m, CH), 2.60 (br s, OH), 3.72 (d, J = 12 Hz, CH), 3.82 (2 OCH_3), 3.86 (OCH_3), 5.45 (d, J = 2 Hz, CH), 5.86 (OCH_2O), 6.18 (ArH), 6.33 (ArH), 6.36 (2 ArH); *trans-trans* isomer ^{1}H nmr: δ 1.02 (d, J = 7 Hz, CH_3), 2.08 (m, CH), 3.54 (d, J = 12 Hz, CH), 3.82 (2 OCH_3), 3.86 (OCH_3), 5.07 (d, J = 12 Hz, CH), 5.82 (OCH_2O), 6.13 (ArH), 6.41 (2 ArH), 6.43 (ArH). The spectrum previously reported [2] for **9a** was obtained in pyridine d5; isomers could not be clearly distinguished in this solvent.

Anal. Calcd. for $C_{20}H_{22}O_7$: C, 64.2; H, 5.9. Found: C, 64.1; H, 5.8.

A solution of alcohol **9a** (1.0 g) and aniline (0.75 g) in methanol (5 ml) was heated on a steam-bath for 45 minutes and cooled. The product crystallized (0.81 g) and was recrystallized from acetone-methanol to give the benzopyran **9b** as colorless needles, mp 183-184°; *cis-trans* isomer ^{1}H nmr: δ 1.06 (d, J = 7 Hz, CH_3), 2.41 (m, CH) 3.67 (m, CH), 3.82 (2 OCH_3), 3.86 (OCH_3), 5.43 (d, J = 2 Hz, CH), 5.82 (OCH_2O), 6.28 (ArH), 6.37 (3 ArH), 6.82 (m, 3 ArH), 7.25 (m, 2 ArH); *trans-trans* isomer ^{1}H nmr: δ 1.07 (d, J = 7 Hz, CH_3), 2.29 (m, CH), 3.67 (m, CH), 3.82 (2 OCH_3), 3.86 (OCH_3) 5.17 (d, J = 9 Hz), 5.86 (OCH_2O), 6.18 (ArH), 6.37 (2 ArH), 6.41 (ArH), 6.82 (3 ArH), 7.25, (2 ArH).

Anal. Calcd. for $C_{26}H_{27}NO_6$: C, 69.5, H, 6.1. Found: C, 69.2; H, 6.2.

A mixture of the alcohol **9a** (5 g) and *p*-anisidine (5 g) in methanol (25 ml) was warmed for 30 minutes and cooled. The crystalline product (4.4 g) was recrystallized from acetone-methanol to give **9c** as colorless needles, mp 183-184°; *cis-trans* isomer (45%) ^{1}H nmr: δ 1.03 (d, J = 7 Hz, CH_3), 2.39 (m, CH) 3.64 (d, J = 12 Hz, CH), 3.75 (OCH_3), 3.80 (2 OCH_3), 3.85 (OCH_3), 5.34 (d, J = 2 Hz, CH), 5.82 (OCH_2O), 6.28 (ArH), 6.36 (2 ArH), 6.38 (ArH); 6.81 (4, ArH); *trans-trans* isomer ^{1}H nmr: δ 1.04 (d, J = 7 Hz, CH_3), 2.17 (m, CH), 3.66 (d, J = 12 Hz, CH), 3.76 (OCH_3), 3.80 (2 OCH_3) 3.86 (OCH_3), 5.07 (d, J = 10 Hz, CH), 5.86 (OCH_2O), 6.17 (ArH), 6.36 (2 ArH), 6.40 (ArH), 6.81 (m, 4 ArH).

Anal. Calcd. for $C_{27}H_{29}NO_7$: C, 67.6; H, 6.1. Found: C, 67.2; H, 6.3.

Warmed with phenylhydrazine (1.0 g) in methanol (5 ml) for 20 minutes the alcohol **9a** (1.0 g) gave the benzopyran **9d** which crystallized from acetone-methanol as slightly yellow needles, mp 165-166° (1.0 g); *cis-trans* isomer (30%) ^{1}H nmr: δ 1.03 (d, J = 7 Hz, CH_3), 2.24 (m, CH) 3.52 (d, J = 12 Hz, CH), 3.80 (OCH_3), 3.82 (2 OCH_3), 4.88 (d, J = 2 Hz, CH), 5.82 (OCH_2O), 6.25 (ArH), 6.33 (2 ArH), 6.43 (ArH), 6.80 (m, ArH), 6.99 (m, 2 ArH), 7.24 (m, 2 ArH); *trans-trans* isomer (70%) ^{1}H nmr: δ 1.07 (d, J = 7 Hz, CH_3), 2.12 (m, CH), 3.56 (d, J = 12 Hz, CH), 3.82 (2 OCH_3), 3.86 (OCH_3) 4.59 (d, J = 10 Hz, CH), 5.87 (OCH_2O), 6.10 (ArH), 6.33 (2 ArH), 6.49 (ArH), 6.80 (m, ArH), 6.99 (m, 2 ArH), 7.24 (m, 2 ArH).

Anal. Calcd. for $C_{26}H_{28}N_2O_6$: C, 67.2, H, 6.1. Found: C, 67.4; H, 6.0.

Reaction with diethylamine occurs much more slowly. However, when refluxed with diethylamine (1 g) in methanol (3 ml) for 24 hours alcohol **9a** (0.5 g) yields the *trans-trans* isomer **9e** (0.4 g), mp 151-152°. Formation of the *cis-trans* isomer was not detected; ^{1}H nmr: δ 0.86 (d, J = 6 Hz, CH_3), 1.12 (t, J = 6 Hz, 2 CH_3), 2.18 (m, CH), 2.85 (m, 2 CH_2), 3.54 (d, J = 11 Hz, CH), 3.82 (2 OCH_3), 3.86 (OCH_3), 4.54 (d, J = 10 Hz, CH), 5.82 (OCH_2O), 6.08 (ArH), 6.33 (2 ArH), 6.51 (ArH).

Anal. Calcd. for $C_{24}H_{31}NO_6$: C, 67.1; H, 7.3. Found: C, 66.9; H, 7.3.

Warmed with cyclohexylamine (1.0 g) **9a** (1.0 g) gave benzopyran **9f** (1.0 g) as colorless felted needles, mp 153-154°, the ratio of isomers being 1:1.

Anal. Calcd. for $C_{26}H_{33}NO_6$: C, 68.5; H, 7.3. Found: C, 68.1; H, 7.2.

Heated similarly with benzylamine **9c** gave the benzopyran **9g**, as colorless needles, mp 135-136°, isomer ratio 1:1.

Anal. Calcd. for $C_{27}H_{29}NO_6$: C, 69.9; H, 6.3. Found: C, 69.9; H, 6.1.

Heated in methanol with 2-phenylethylamine **9a** gave benzopyran **9h** as colorless needles, mp 113-115°, the ratio of isomers being 1:1.

Warmed with *p*-aminobenzoic acid in methanol for 45 minutes **9a** formed almost quantitatively crystalline anilide **9i** which crystallized from acetone-methanol as colorless needles, mp 224-225°; the product consisted of a mixture of the *cis-trans* and *trans-trans* isomer in a ratio of approximately 1:2.

Anal. Calcd. for $C_{27}H_{27}NO_8$: C, 65.7; H, 5.5. Found: C, 65.5; H, 5.3.

The ethyl ester **9j** of this anilide, prepared by reaction of **9a** with ethyl *p*-aminobenzoate crystallized from methanol as colorless needles, mp 98-102°, the ratio of isomers being 1:1; *cis-trans* ^{1}H nmr: δ 0.92 (d, J = 6 Hz, CH_3), 1.35 (t, J = 6 Hz, CH_3), 2.13 (m, CH), 3.70 (d, J = 12 Hz, CH), 3.80 (2 OCH_3), 3.86 (OCH_3), 4.35 (q, J = 6 Hz, CH_2), 5.44 (d, J = 2 Hz, CH), 5.81 (OCH_2O), 6.18 (ArH), 6.34 (2 ArH), 6.40 (ArH), 6.62 (d, J = 9 Hz, 2 ArH), 7.89 (d, J = 9 Hz, 2 ArH); *trans-trans* ^{1}H nmr: δ 1.00 (d, J = 6 Hz, CH_3), 1.35 (t, J = 6 Hz, CH_3), 2.06 (m, CH), 3.52 (d, J = 12 Hz, CH), 3.80 (2 OCH_3), 3.86 (OCH_3), 4.35 (q, J = 6 Hz, CH_2), 5.07 (d, J = 12 Hz, CH), 5.86 (OCH_2O), 6.13 (ArH), 6.37 (2 ArH), 6.42 (ArH), 6.62 (d, J = 9 Hz, 2 ArH), 7.89 (d, J = 9 Hz, 2 ArH).

A solution of **9a** (1.0 g), semicarbazide hydrochloride (0.56 g) and powdered potassium hydroxide (0.28 g) in methanol (5 ml) was heated for 15 minutes and slowly diluted with water. The crystalline product was recrystallized from acetone-methanol to give the benzopyran **9k** as colorless needles, mp 179-180°; ^{1}H nmr spectrum showed the product contained approximately 40% of the *cis-trans* isomer and 60% of the *trans-trans* isomer.

Anal. Calcd. for $C_{21}H_{25}N_3O_7$: C, 58.5; H, 5.8. Found: C, 58.7; H, 5.9.

Treated similarly with thiosemicarbazide hydrochloride **9a** gave the benzopyran **9l** as colorless needles, mp 163-164°; ^{1}H nmr showed this product also contained about 40% of the *cis-trans* isomer and 60% of the *trans-trans* isomer.

Hydrolysis of Benzopyran **6h**.

A solution of the benzopyran **6h** (21 g) in warm acetic acid (40 ml) and water (20 ml) was heated on a steam bath for two hours and slowly diluted with more water (60 ml) during this period. Colorless crystals separated. After cooling, the product (16.5 g), 95% was collected and recrystallized once from acetone-methanol to give the alcohols **10a** as colorless needles, mp 148-157°; *cis-trans* isomer ^{1}H nmr: δ 0.96 (d, J = 7 Hz, CH_3), 2.39 (m, CH), 2.75 (br s, 2 OH), 3.91 (OCH_3), 4.27 (d, J = 11 Hz, CH), 5.43 (d, J = 2.0 Hz, CH), 5.83 (OCH_2O), 6.21 (ArH), 6.42 (ArH), 6.60 (m, ArH), 6.78 (m, 2 ArH); *trans-trans* isomer ^{1}H nmr: δ 1.03 (d, J = 7 Hz, CH_3), 2.27 (m, CH), 2.75 (br s, 2 OH),

4.13 (d, J = 11 Hz, CH), 5.13 (d, J = 10 Hz, CH), 5.79 (OCH_2O), 6.17 (ArH), 6.45 (ArH), 6.60 (m, ArH), 6.78 (m, 2 ArH).

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.4; H, 5.5. Found: C, 65.5; H, 5.6.

A solution of the alcohol **10a** (1.0 g) and aniline **1g** in methanol (5 ml) was heated for 30 minutes. On standing the benzopyran crystallized (0.9 g). Recrystallized from methanol **10b** was obtained as colorless, brittle needles, mp 168-170°.

Anal. Calcd. for $C_{24}H_{23}NO_5$: C, 71.1; H, 5.7. Found: C, 70.8; H, 5.9.

The alcohol **10a** reacted similarly with phenylhydrazine in methanol. The product **10c** crystallized from acetone-methanol as cream colored needles, mp 177-180°.

Anal. Calcd. for $C_{24}H_{24}N_2O_5$: C, 68.6; H, 5.8. Found: C, 68.8; H, 5.9.

A mixture of the alcohol **10a** (0.8 g), semicarbazide hydrochloride (0.56 g) and powdered potassium hydroxide (0.28 g) in methanol (5 ml) was heated for ten minutes and diluted with water. The product was collected and recrystallized from acetone-methanol to give **10d** as cream colored needles, mp 221-222° (0.5 g).

Anal. Calcd. for $C_{19}H_{21}N_3O_6$: C, 58.9; H, 5.5. Found: C, 59.2; H, 5.6.

Hydrolysis of Benzopyran **6d**.

A solution of the benzopyran **6d** (15.5 g) in acetic acid (25 ml) and water (10 ml) was heated on a steam-bath for 2 hours during which time the product crystallized. Water was added and the product was collected (12.3 g). Recrystallized from acetone-methanol the isomeric alcohols (ratio 3:1) **10e** were obtained as colorless needles, mp 140-141°; *cis-trans* isomer ^{1}H nmr: δ 0.93 (d, J = 7 Hz, CH_3), 2.31 (m, CH), 3.00 (br s, OH), 3.89 (2 OCH_3), 4.27 (d, J = 12 Hz, CH), 5.43 (d, J = 2 Hz, CH), 5.83 (OCH_2O), 6.15 (ArH), 6.40 (ArH), 6.63 (m, ArH), 6.83 (m, ArH); 7.00 (m, ArH); *trans-trans* isomer ^{1}H nmr: δ 1.02 (d, J = 7 Hz, CH_3), 2.17 (m, CH), 3.00 (br s, OH), 3.89 (2 OCH_3), 4.12 (d, J = 12 Hz), 5.12 (d, J = 10 Hz, CH), 5.80 (OCH_2O), 6.10 (ArH), 6.42 (ArH), 6.63 (m, ArH), 6.83 (m, ArH), 7.00 (m, ArH).

Anal. Calcd. for $C_{19}H_{20}O_6$: C, 66.3; H, 5.9. Found: C, 66.6; H, 6.1.

Warmed with aniline in methanol in the usual way **10e** gave the benzopyran **10f** which crystallized from acetone as colorless needles, mp 203-204°; *cis-trans/trans-trans* isomer ratio, 1:1.

Anal. Calcd. for $C_{25}H_{25}NO_5$: C, 71.6; H, 6.0. Found: C, 71.6; H, 6.2.

Warmed with *p*-methoxyaniline **10e** gave the benzopyran **10g** which crystallized from acetone-methanol as brittle, cream colored needles, mp 164-165°; ratio of isomers, 1:1.

Anal. Calcd. for $C_{26}H_{27}NO_6$: C, 69.5; H, 6.1. Found: C, 69.5; H, 6.2.

Heated with semicarbazide hydrochloride and potassium hydroxide in methanol **10e** gave the benzopyran **10h**. This crystallized from acetone-methanol as colorless needles, mp 210-212°; *trans-trans* isomer predominated in a ratio of 5: 1.

Anal. Calcd. for $C_{20}H_{23}N_3O_6$: C, 59.8; H, 5.8. Found: C, 59.8; H, 5.9.

Benzopyran **10j**.

As previously reported aqueous acetic acid hydrolysis [2] of the benzopyran **5b** yields the benzopyran **10j**. Reinvestigation of the ^{1}H nmr spectrum at higher field shows that although the crude product is mostly the *cis-trans* isomer (80%) it does contain about 20% of the *trans-trans* isomer: *cis-trans* isomer ^{1}H nmr: δ 0.89 (d, J = 6 Hz, CH_3) 2.09 (m, CH), 3.18 (br s, OH), 3.74 (d, J = 12 Hz, CH), 3.82 (OCH_3), 5.42 (d, J = 2 Hz, CH), 5.81 (OCH_2O), 6.14 (ArH), 6.38 (ArH), 6.85 (d, J = 9 Hz, 2 ArH), 7.07 (d, 9 Hz, 2 ArH); *trans-trans* isomer ^{1}H nmr: δ 0.97 (d, J = 6 Hz, CH_3) 2.02 (m, CH), 3.18 (br s, OH), 3.55 (d, J = 12 Hz, CH), 3.81 (OCH_3), 5.07 (d, J = 10 Hz, CH), 5.78 (OCH_2O), 6.05 (ArH), 6.40 (ArH), 6.85 (d, J = 9 Hz, 2 ArH), 7.03 (d, J = 9 Hz, 2 ArH).

Warmed in methanol with a variety of amines and hydrazines the benzopyran **10j** forms crystalline nitrogenous benzopyrans in the usual way. For example, with phenylhydrazine it yields the benzopyran **10k** which crystallizes from methanol as colorless needles, mp 160-162°; *cis-trans* isomer (30%) ^{1}H nmr: δ 1.04 (d, J = 7 Hz, CH_3) 2.28 (m, CH), 3.57 (d, J = 12 Hz, CH), 3.78 (OCH_3), 4.86 (d, J = 2 Hz, CH), 5.86 (OCH_2O), 6.18 (ArH); 6.48 (ArH), 6.82 (m, 3 ArH), 7.00 (m, 4 ArH), 7.21 (m, 2 ArH); *trans-trans* isomer 70% ^{1}H nmr: δ 1.00 (d, J = 7 Hz, CH_3) 2.07 (m, CH), 3.54 (d, J = 12 Hz, CH), 3.78 (OCH_3), 4.58 (d, J = 12 Hz, CH), 5.81 (OCH_2O), 6.04 (ArH) 6.42 (ArH), 6.82 (m, 3 ArH), 7.00 (m, 4 ArH), 7.21 (m, 2 ArH).

Anal. Calcd. for $C_{24}H_{24}N_2O_4$: C, 71.3; H, 6.0. Found: C, 71.0; H, 6.2.

Benzopyran **4c**.

A solution of the alcohol **4b** [2] (1.0 g) and aniline (1.0 g) in methanol (5 ml) was warmed for 30 minutes. The crystalline product was recrystallized from acetone-methanol to give the benzopyran **4c** as colorless needles, mp 152-153° (0.85 g); ^{1}H nmr: δ 1.69 (CH_3), 2.18 (m), and 2.37 (m, CH_2), 3.78 (NH), 3.83 (2 OCH_3), 3.86 (OCH_3), 4.17 (m, CH), 5.80 (d, J = 1 Hz) and 5.88 (d, J = 1 Hz, OCH_2O), 6.18 (ArH), 6.44 (2 ArH), 6.47 (ArH), 6.86 (m, ArH), 7.00 (m, 2 ArH), 7.19 (m, 2 ArH).

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4b (381578), **4c** (669887), **4d** (371010), **4f** (375504), **5a** (375501), **5h** (375503), **6a** (666217), **6h** (666214), **6g** (666220), **7a** (666237), **7h** (667923), **8b** (666227), **9a** (381586), **9c** (667931), **9d** (667925), **9e** (667928), **9f** (675365), **9g** (675363), **9h** (675362), **9i** (675367). **9j** (675368), **9k** (667932), **10d** (667933).