Synthesis of New Benzopyrans Related to Podophyllotoxin

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Received May 1, 1989

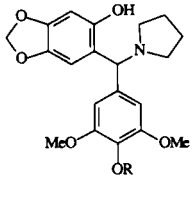
Mannich bases of types **1** or **8**, which are readily synthesized by condensation of 3,4-methylenedioxyphenol with aromatic aldehydes and pyrrolidine or piperazine, react with cyclic and acyclic β-diketones to yield benzopyrans. These benzopyrans are structurally similar to podophyllotoxin and like this drug some of the benzopyrans show *in vivo* anti-leukemic action in mice.

J. Heterocyclic Chem., **26**, 1349 (1989).

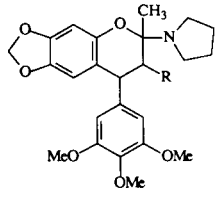
Pyrrolidinyl Mannich bases such as **1a** and **1c** react with acetone and other mono-ketonic reagents to give good yields of crystalline pyrrolidinylbenzopyrans of type **2**, which can be hydrolyzed in acidic media to form alcoholic benzopyrans of type **3** [1]. The benzopyran **3a** has some of the structural features of the anti-tumor drug podophyllotoxin **4a** [2,3] and, like podophyllotoxin, it is a potent anti-mitotic and tubulin-binding agent and is active *in vivo* against lymphocytic leukemia in mice [4]. These studies have now been extended to reactions of Mannich bases with acyclic and cyclic β-diketones. These reactions yield non-nitrogenous benzopyrans directly; the formation of intermediate pyrrolidinylbenzopyrans has not been detected.

The pyrrolidinyl-Mannich base **1a** reacts with 2,4-pentanedione in methanol to give a colorless crystalline product, $C_{22}H_{24}O_8$. This was identified as **5a** on the basis of its ^{1}H-nmr spectrum which, as in related benzopyrans of type **3**, show the methyl group at position 6 as a singlet at δ 1.57, and a methine proton (C_7) at δ 3.22 *trans*-coupled to a benzylic methine proton at δ 4.21. Structure **5a** was further confirmed by the ^{13}C-nmr spectrum which showed signals *inter al.* of two methyls (δ 27.5, δ 32.9), two aliphatic CH's (δ 44.2, δ 60.9 ppm) and an *O,N*-linked quaternary C (at δ 95.2). Treated with acidified methanol **5a** yields the crystalline *O*-methyl derivative **5b**.

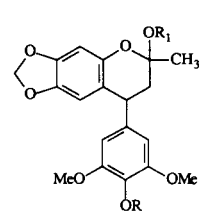
Reaction of **1a** with 2,4-pentanedione in aqueous acetic acid gave a crystalline mixture which was active *in vivo* against leukemia in National Cancer Institute screening tests. The mixture was separated into three compounds, one of which was identical to the methanol product **5a**. The molecular formula, $C_{22}H_{22}O_7$, and nmr spectrum of a second minor component indicated this to be **6a**, formed by dehydration of the alcoholic benzopyran **5a**. This structure was confirmed by conversion of pure **5a** to **6a** on warming with acetic and hydrochloric acids. The third and major component of the reaction product was identified as the acetoxy compound **7a**, formed by ring opening of the benzopyran **5a** in aqueous acetic acid. In accord with this structure the two methyl groups appeared in the ^{1}H-nmr spectrum as singlets at δ 2.12 and δ 2.27 (-$COCH_3$), and a CH_2 group as two doublets at δ 2.90 and δ 3.07, coupled to a benzylic CH group at δ 4.63. The ^{13}C-nmr confirmed the presence of two carbonyl groups (at δ 169.4, -$OCOCH_3$; at δ 206.1, -CH_2COCH_3). Alkaline hydrolysis of the acetate **7a** resulted in ring closure with formation of the anti-tumor



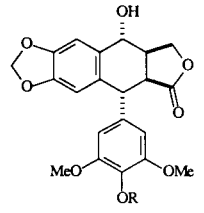
1a: $R_1 = R_2 = OCH_3$
1b: $R_1 = OCH_3$, $R_2 = OH$
1c: $R_1 = H$, $R_2 = OCH_3$



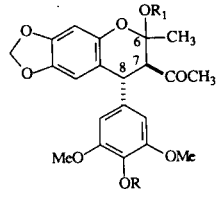
2: R = H, CH_3, or CO_2Et



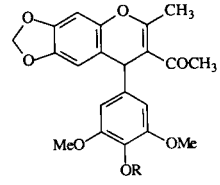
3a: $R = CH_3$, $R_1 = H$
3b: $R = R_1 = H$
3c: $R = H$, $R_1 = CH_3$



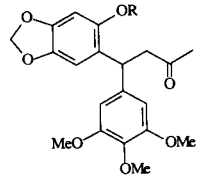
4a: $R = CH_3$
4b: R = H



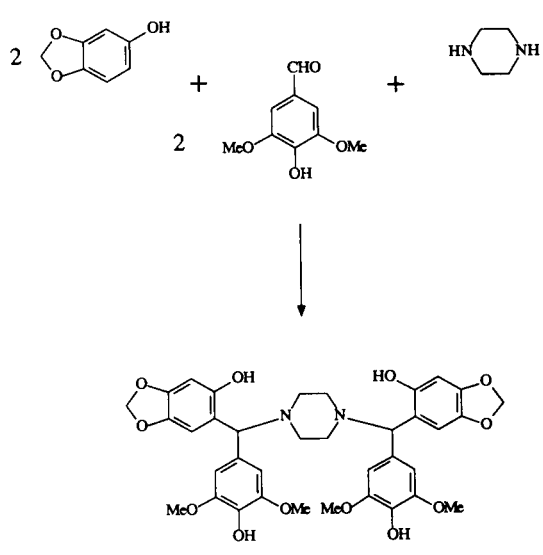
5a: $R = CH_3$, $R_1 = H$
5b: $R = R_1 = CH_3$
5c: $R = R_1 = H$
5d: $R = H$, $R_1 = CH_3$



6a: $R = CH_3$
6b: R = H



7a, $R = COCH_3$
7b, $R = CH_3$



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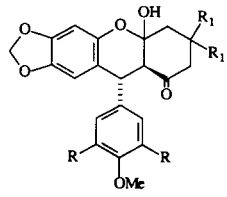
benzopyran **3a**.

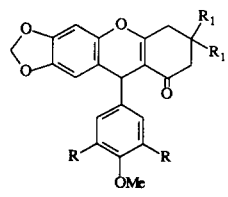
The demethylated podophyllotoxin derivative **4b** forms the basis for an anti-tumor drug in current clinical use; a glycosidic derivative of **4b** is being used against some small cell lung tumors [2]. Condensation of 2,4-pentanedione with Mannich bases has now provided a route to the hitherto inaccessible analogous demethylated benzopyran **3b**. Thus, reaction of 3,4-methylenedioxyphenol, piperazine, and 4-hydroxy-3,5-dimethoxybenzaldehyde gave the Mannich base **8**. Treatment of **8** with 2,4-pentanedione in aqueous acetic gave high yields of the phenolic benzopyran **5c** which was hydrolyzed with alkali to give the crystalline, desired phenolic benzopyran **3b**. Acid catalyzed dehydration of **3b** yielded **6b**.

The reaction of pyrrolidinyl Mannich bases with cyclic β-diketones in methanol is similar to their reaction with 2,4-pentanedione and leads to alcoholic benzopyrans. Thus, the Mannich bases **1a** and **1c** react with 1,3-cyclohexanedione and with dimedone in methanol solutions to give the alcoholic benzopyrans **9a**, **9b**, **9c** and **9d** respectively. Reactions in aqueous acetic acid may yield dehydrated products, depending on the solubility of the initially formed alcoholic benzopyrans in the medium. Thus, reactions of the Mannich base **1a** with these β-diketones in aqueous acetic acid yield the dehydrated products **10a** and **10b**. The Mannich base **1c**, however, reacts with these cyclic β-diketones in aqueous acetic acid, as in methanol, to yield the highly insoluble alcoholic benzopyrans **9c** and **9d**. These benzopyrans form and precipitate very rapidly from the aqueous acetic acid media.

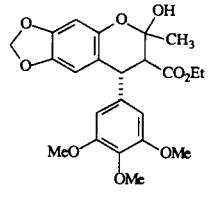
The reaction of β-ketoesters is quite different with pyrrolidinyl Mannich bases in the two different media. In methanol, as previously reported [1], Mannich bases such as **1a** react with ethyl acetoacetate to form pyrrolidinyl benzopyrans of type **2**. In aqueous acetic acid, on the other hand, the reaction of **1a** with ethyl acetoacetate gives good yields of the alcoholic benzopyran **11**. Alkaline hydrolysis of **11** leads to ring opening and reclosure to yield the dihydrocoumarin derivative **12**.



9a : R = OCH_3, R_1 = H
9b : R = OCH_3, R_1 = CH_3
9c : R = R_1 = H
9d : R = H, R_1 = CH_3



10a : R = OCH_3, R_1 = H
10b : R = OCH_3, R_1 = CH_3
10c : R = R_1 = H



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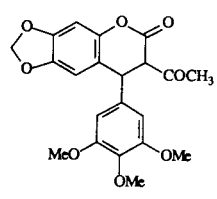

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EXPERIMENTAL

The ^{1}H-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 analytical laboratory. Melting points are uncorrected.

Reaction of **1a** with 2,4-Pentanedione.

(a) In methanol: A solution of **1a** [1] (3.8 g) and 2,4-pentanedione (2 g) in methanol (20 ml) was heated under reflux for 2 hours. The colorless solid which separated was recrystallized from acetone-methanol to yield **5a** as colorless needles, mp 197-198° (1.8 g).

(b) In aqueous acetic acid: A solution of **1a** (15 g) and 2,4-pentanedione (30 g) in acetic acid (75 ml) and water (15 ml) was heated on a steam-bath for one hour, diluted with water (500 ml) and filtered. Analysis (tlc) of the solid product showed the presence of three components, subsequently identified as **5a**, **7a** and **6a**. The product was dissolved in acetone and the solution concentrated to 50 ml whereupon **5a** crystallized (4.5 g). The acetone filtrate was reheated to boiling, diluted with methanol and concentrated to 50 ml, whereupon crude **7a** separated (10.5 g).

The methanol filtrate from **7a** was warmed and diluted with an equal volume of water, whereupon **6a** crystallized (1.52 g).

The ring-opened, major product **7a** formed in the aqueous acetic acid reaction was purified by repeated crystallization from methanol. It was obtained as colorless needles, mp 137-138°; ^{1}H-nmr: δ 2.12 (CH_3), 2.27 (CH_3), 2.90 (d, J = 4 Hz and 3.07, d, J = 4 Hz, CH_2), 3.82 (3 OCH_3), 4.64 (dd, J = 4, 4 Hz, CH), 5.94 (OCH_2O), 6.38 (2 ArH), 6.56 (ArH), 6.62 (ArH); ^{13}C-nmr: δ 20.7 (CH_3), 30.3 (CH_3), 39.2 (CH), 48.8 (CH_2), 56.0 (2 OCH_3), 60.7

(OCH_3), 101.6 (OCH_2O), 104.2 (CH), 104.8 (2 CH), 107.0 (CH), 128.4 (C), 136.6 (C), 138.1 (C), 141.8 (C), 145.5 (C), 146.2 (C), 153.0 (2 C), 169.4 ($OCOCH_3$), 206.1 (CO CH_3).

Anal. Calcd. for $C_{22}H_{24}O_8$: C, 63.5; H, 5.8. Found: C, 63.5; H, 5.8.

The acetoxy compound **7a** (5.0 g) was refluxed with dimethyl sulfate (2.5 ml), potassium carbonate (8 g), acetone (50 ml) and methanol (20 ml) for one hour, concentrated and diluted with water. The oily product crystallized from methanol to give the methyl ether **7b** as colorless needles, mp 116-117° (4.2 g); ^{1}H-nmr: δ 2.08 (CH_3), 3.04 (d, J = 7 Hz, CH_2), 3.74 (OCH_3), 3.78 (OCH_3), 3.80 (2 OCH_3), 4.85 (t, J = 7 Hz, CH), 5.86 (OCH_2O), 6.45 (ArH), 6.50 (ArH), 6.58 (ArH).

Anal. Calcd. for $C_{21}H_{24}O_7$: C, 64.9; H, 6.2. Found: C, 65.0; H, 6.1.

Compound **7a** (0.2 g) was dissolved in warm 50% aqueous methanol (10 ml) containing 10% aqueous sodium hydroxide (1 ml). The solution was acidified with acetic acid and the solid product was recrystallized from wet methanol **3a** was obtained as colorless needles, mp 100-101°, identical in all respects (mmp, ^{1}H-nmr, tlc) with the previously described [1] product.

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

Recrystallized from acetone-methanol **5a** separated as colorless needles, mp 197-198°; ^{1}H-nmr: δ 1.57 (CH_3), 1.90 ($COCH_3$), 3.22 (d, J = 12 Hz, CH), 3.80 (2 OCH_3), 3.83 (OCH_3), 4.04 (OH), 4.21 (d, J = Hz, OCH_2O), 5.79 (d, J = 1 Hz and 5.86, d, J = 1 Hz, OCH_2O), 6.17 (ArH), 6.36 (2 ArH), 6.42 (ArH); ^{13}C nmr: δ 27.5 (CH_3), 32.9 (CH_3), 44.2 (CH), 56.2 (2 OCH_3), 60.5 (OCH_3), 60.9 (CH), 95.2 (O-C-OH), 98.7 (CH), 101.1 (OCH_2O), 107.6 (2 CH), 108.0 (CH), 115.9 (C), 136.7 (C), 137.3 (C), 142.1 (C), 145.9 (C), 147.1 (C), 153.6 (2C), 212.5 (CO).

Anal. Calcd. for $C_{22}H_{24}O_8$: C, 63.5; H, 5.8. Found: C, 63.5; H, 5.8.

A solution of **5c** (0.42 g) in methanol (20 ml) containing a drop of concentrated hydrochloric acid was heated to boiling for 10 minutes, concentrated and cooled. The colorless product (0.39 g) was collected and recrystallized from acetone-methanol to give the methyl ether **5b** as colorless needles, mp 230-231°; ^{1}H-nmr: δ 1.56 (CH_3), 2.0 ($COCH_3$), 3.16 (d, J = 6 Hz, CH), 3.20 (OCH_3), 3.77 (2 OCH_3), 3.83 (OCH_3), 4.43 (d, J = 6 Hz, CH), 5.84 (OCH_2O), 6.17 (ArH), 6.37 (2 ArH), 6.42 (ArH).

Anal. Calcd. for $C_{23}H_{26}O_8$: C, 64.1; H, 6.1. Found: C, 64.2; H, 6.1.

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

Compound **6a**, isolated as a minor product in the reaction of 2,4-pentanedione with **1a** in acetic acid, was also prepared by heating a solution of **5a** (3 g) in acetic acid (5 ml) containing a drop of concentrated hydrochloric acid. Addition of water precipitated **6a** (2.6 g). Recrystallized from acetone-methanol **6a** was obtained as colorless, brittle needles, mp 167-168°; ^{1}H-nmr: δ 2.06 (CH_3), 2.38 (CH_3), 3.80 (3 OCH_3), 4.82 (CH), 5.86 (d, J = 1 Hz and 5.89, d, J = 1 Hz, OCH_2O), 6.41 (2 ArH), 6.53 (2 ArH); ^{13}C-nmr: δ 19.9 (CH_3), 30.1 (CH_3), 42.6 (CH), 56.1 (2 OCH_3), 60.7 (OCH_3), 98.0 (CH), 101.3 (OCH_2O), 104.6 (2 CH), 107.0 (CH), 113.5 (C), 116.6 (C), 136.9 (C), 141.5 (C), 143.5 (C), 144.2 (C), 146.8 (C), 153.4 (C), 158.6 (2C), 198.7 (CO).

Reaction of 3,4-Methylenedioxyphenol with Piperazine and 3,5-Dimethoxy-4-hydroxybenzaldehyde.

A solution of 3,4-methylenedioxyphenol (2.8 g), 3,5-dimethxoy-4-hydroxybenzaldehye (3.64 g) and piperazine (1.72 g) in methanol (10 ml) was refluxed for 3 hours. The crystalline product which separated on cooling was recrystallized from acetone to give the piperazinyl derivative **8** as colorless needles, mp 239-240° (6.2 g, 90%); ^{1}H-nmr (in pyridine-d_5): δ 2.63 (m, 4 CH_2), 3.79 (4 OCH_3), 4.52-4.80 (m, 40 H, 2 CH), 5.83 (2 OCH_2O), 6.77 (2 ArH), 6.89 (2 ArH), 7.06 (4 ArH).

Anal. Calcd. for $C_{36}H_{38}O_{12}N_2$: C, 62.6; H, 5.6; N, 4.1. Found: C, 62.1; H, 5.6; N, 4.1.

7-Acetyl-7,8-Dihydro-8-(3,5-dimethoxy-4-hydroxyphenyl-6-methyl-6*H*-1,3-dioxolo[4,5-*g*][1]benzopyran-6-ol **5c**.

A mixture of the piperazinyl derivative **8** (5 g) and 2,4-pentanedione (10 g) in acetic acid (10 ml) and water (2 ml) was heated on a steam bath for 10 minutes. Compound **8** rapidly dissolved and a new product separated. Water was added and the product was collected (5.2 g). Repeated recrystallized from acetone gave **5c** as colorless needles, mp 209-210° to a deep orange liquid; ^{1}H-nmr: δ 1.53 (CH_3), 1.85 (CH_3), 3.19 (d, J = 14 Hz, CH), 3.80 (2 OCH_3), 3.97 (OH), 4.16 (d, J = 14 Hz, CH), 5.47 (OH), 5.77 (d, J = 1 Hz and 5.84, d, J = 1 Hz, OCH_2O), 6.16 (ArH), 6.25 (2 ArH), 6.30 (ArH).

Anal. Calcd. for $C_{21}H_{22}O_8$: C, 62.7; H, 5.5. Found: C, 62.6; H, 5.6.

A solution of **5c** (1.3 g) in methanol (50 ml) containing a drop of concentrated hydrochloric acid was concentrated and cooled. Colorless crystals separated. Recrystallized from acetone-methanol the *O*-methyl derivative **5d** was obtained as colorless needles, mp 232-233° (1.0 g); ^{1}H-nmr: δ 1.54 (CH_3), 2.05 (CH_3), 3.14 (d, J = 12 Hz, CH), 3.30 (OCH_3), 3.82 (2 OCH_3), 4.42 (d, J = 12 Hz, CH), 5.45 (OH), 5.84 (OCH_2O), 6.17 (ArH), 6.37 (2 ArH), 6.42 (ArH).

Anal. Calcd. for $C_{22}H_{24}O_8$: C, 63.5; H, 5.8. Found: C, 63.6; H, 5.8.

7-Acetyl-8-(3,5-dimethoxy-4-hydroxyphenyl)-6-methyl-8*H*-1,3-dioxolo[4,5-*g*][1]benzopyran **6b**.

A solution of **5c** (1.6 g) in acetic acid (4 ml) containing 4 drops of concentrated hydrochloric acid was heated briefly to boiling and then diluted with water. The solid product was recrystallized from acetone-methanol to give **6b** as colorless, soft needles, mp 172-173° (1.2 g); ^{1}H-nmr: δ 2.13 (CH_3), 2.37 (CH_3), 3.80 (2 OCH_3), 4.78 (CH), 5.41 (OH), 5.82 (d, J = 1 Hz and 5.87, d, J = 1 Hz, OCH_2O), 6.40 (2 ArH), 6.59 (2 ArH); ^{13}C-nmr: δ 2.13 (CH_3), 2.37 (CH_3), 3.80 (2 OCH_3), 4.78 (CH), 5.41 (OH), 5.82 (d, J = 1 Hz and 5.8 d, J = 1 Hz, OCH_2O), 6.40 (2 ArH), 6.59 (2 ArH); ^{13}C-nmr: δ 19.9 (CH_3), 30.1 (CH_3), 42.4 (CH), 56.3 (2 OCH_3), 97.9 (CH), 101.3 (OCH_2O), 104.4 (2 ArH), 107.0 (CH), 113.6 (C), 116.8 (C), 133.8 (C), 137.8 (C), 143.4 (C), 144.2 (C), 146.8 (C), 147.2 (2C), 158.4 (C), 199.1 (CO).

Anal. Calcd. for $C_{21}H_{20}O_7$: C, 65.6; H, 5.2. Found: C, 65.5; H, 5.2.

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

A solution of **5c** (15 g) in methanol (50 ml) was diluted with 10% aqueous sodium hydroxide and the intense blue-colored solution was refluxed for 20 minutes. Water (500 ml) was added and the solution acidified with acetic acid (40 ml). The solid pro-

duct was recrystallized from aqueous methanol to yield **3b** as colorless needles, mp 154-155° (12.5 g); ^{1}H-nmr: δ 1.61 (CH_3), 1.84-2.37 (m, CH_2), 2.75 (d, J = 2 Hz, OH), 3.79 (2 OCH_3), 4.08 (dd, = 13.5 Hz, C*H*CH_2), 5.46 (OH), 5.76 (d, J = 2 Hz and 5.82, d, J = 2 Hz, OCH_2O), 6.22 (ArH), 6.37 (ArH), 6.42 (2 ArH).

Anal. Calcd. for $C_{19}H_{20}O_7$: C, 63.3; H, 5.6. Found: C, 63.6; H, 5.6.

Recrystallized from methanol containing a drop of concentrated hydrochloric acid, **3b** was converted into the *O*-methyl derivative **3c** which separated from methanol as colorless needles, mp 165-166°; ^{1}H-nmr: δ 1.52 (CH_3), 1.75-2.34 (m, CH_2), 3.28 (OCH_3), 3.81 (2 OCH_3), 4.08 (dd, J = 13, 6 Hz, *CH* CH_2), 5.46 (OH), 5.79 (d, J = 2 Hz and 5.83, d, J = 2 Hz, OCH_2O), 6.22 (ArH), 6.42 (3 ArH).

Reaction of **1a** with 1,3-Cyclohexanediones.

(a) In aqueous acetic acid: A mixture of **1a** (3 g) and 1,3-cyclohexanedione (6 g) in acetic acid (15 ml) and water (5 ml) was heated on a steam-bath for 30 minutes and diluted with water. The product crystallized from methanol to yield **10a** as colorless needles, mp 182° (3.6 g); ^{1}H-nmr: δ 2.04 (m, CH_2), 2.38 (m, CH_2), 2.64 (m, CH_2), 3.74 (OCH_3), 3.79 (2 OCH_3), 4.87 (CH), 5.88 (OCH_2O), 6.42 (2 ArH), 6.51 (ArH), 6.58 (ArH); ^{13}C-nmr: δ 20.3 (CH_2), 27.7 (CH_2), 36.9 (CH_2), 38.1 (CH), 55.96 (2 OCH_3), 60.54 (OCH_3), 97.7 (CH), 101.4 (OCH_2O), 104.9 (2 CH), 107.9 (CH), 113.9 (C), 117.1 (C), 136.5 (C), 141.7 (C), 143.8 (C), 144.6 (C), 146.7 (C), 152.9 (C), 165-9 (C), 196.8 (CO).

Anal. Calcd. for $C_{23}H_{22}O_7$: C, 67.4; H, 5.4. Found: C, 67.3; H, 5.4.

Warmed with hydroxylamine hydrochloride and pyridine **10a** formed an oxime, which crystallized from methanol as colorless needles, mp 211-212°; ^{1}H-nmr: δ 1.88 (m, CH_2), 2.46 (m, CH_2), 2.89 (m, CH_2), 3.76 (3 OCH_3), 4.73 (CH), 5.82 (d, J = 1 Hz and 5.86, d, J = 1 Hz, OCH_2O), 6.40 (2 ArH), 6.50 (ArH), 6.52 (ArH), 8.59 (OH).

Anal. Calcd. for $C_{24}H_{25}O_6N$: C, 68.1; H, 5.9; N, 3.3. Found: C, 68.2; H, 5.9; N, 3.2.

Compound **1a** (2 g) reacted with dimedone (4 g) in aqueous acetic acid under similar conditions to yield **10b** which crystallized from methanol as colorless, brittle needles, mp 153-154° (2.2 g); ^{1}H-nmr: δ 1.04 (CH_3), 1.12 (CH_3), 2.23 (CH_2), 2.51 (CH_2), 3.78 (3 OCH_3), 4.82 (CH), 5.76 (d, J = 1 Hz and 5.79, d, J = 1 Hz, OCH_2O), 6.42 (2 ArH), 6.53 (ArH), 6.67 (ArH).

Anal. Calcd. for $C_{25}H_{26}O_7$: C, 68.5; H, 6.0. Found: C, 68.6; H, 5.9.

(b) In methanol: A solution of **1a** (5 g) and dimedone (5 g) in methanol (20 ml) was refluxed for 30 minutes and diluted with water. The gummy product was collected and crystallized from methanol to yield **9b** as colorless glistening prisms, mp 157-158° (3.5 g); ^{1}H-nmr (in pyridine-d_5): δ 1.02 (CH_3), 1.36 (CH_3), 2.20-2.60 (m, $2CH_2$, OH), 3.68 (2 OCH_3), 3.87 (OCH_3), 3.94 (d, J = 12 Hz, CH), 5.60 (d, J = 12 Hz, CH), 5.82 (d, J = 1 Hz and 5.87, J = 1 Hz, OCH_2O), 6.67 (ArH), 6.88 (ArH), 7.02 (2 ArH).

Anal. Calcd. for $C_{25}H_{28}O_8$: C, 65.8; H, 6.2. Found: C, 65.6; H, 6.3.

Compound **1a** (0.25 g) reacted similarly when warmed with 1,3-cyclohexanedione (0.5 g) in methanol (2 ml). Addition of water gave a gummy product which crystallized from methanol to give the **9a** as colorless needles, mp 178° (0.18 g); ^{1}H-nmr: δ 2.16 (m, 3 CH_2), 2.90 (OH), 3.05 (d, J = 12 Hz, CH), 3.78 (3 OCH8), 4.40 (d, J = 12 Hz, CH), 5.82 (d, J = 1 Hz and 5.85, d, J = 1 Hz, OCH_2O), 6.22 (ArH), 6.35 (ArH), 6.47 (2 ArH). When warmed with acetic acid this product was dehydrated to give colored crystals, mp 182°, identical with the product **10a**.

Reaction of **1c** with 1,3-Cyclohexanediones.

(a) A mixture of **1c** (6 g), 1,3-cyclohexanedione (12 g), acetic acid (20 ml) and water (5 ml) was heated on a steam bath causing rapid separation of a crystalline product. After 30 minutes water was added and the product was recrystallized from acetone-methanol to yield **9c** as colorless needles, mp 222-223° (7.3 g). An identical product was obtained by warming **1c** and the 1,3-cyclohexanedione in methanol; ^{1}H-nmr (deuteriochloroform-DMSO-d_6, 50%): δ 1.74-2.38 (m, 3 CH_2), 2.97 (d, J = 12 Hz, CH), 3.72 (OCH_3), 4.37 (d, J = 12 Hz, CH), 5.29 (d, J = 1.5 Hz, OH), 5.77 (OCH_2O), 6.10 (ArH), 6.32 (ArH), 6.76 (d, J = 9 Hz, 2 ArH), 7.14 (d, J = 9 Hz, 2 ArH).

Anal. Calcd. for $C_{21}H_{20}O_6$: C, 68.5; H, 5.5. Found: C, 68.6; H, 5.4.

Warmed with aqueous methanolic sodium hydroxide, diluted with water, and acidified, the above product was dehydrated to yield **10c**. This crystallized from acetone-methanol as glistening, colorless needles, mp 180-181°; ^{1}H-nmr: δ 2.06 (m, CH_2), 2.42 (m, CH_2). 2.66 (m, CH_2), 3.80 (OCH_3), 4.88 (CH), 5.96 (d, J = 1 Hz and 5.98, d, J = 1 Hz, OCH_2O), 6.44 (ArH), 6.52 (ArH), 6.62 (ArH).

Reaction of **1a** with Ethyl Acetoacetate.

A solution of **1a** (6 g) and ethyl acetoacetate (6 g) in acetic acid (20 ml) and water (5 ml) was heated briefly to boiling and then on a steam-bath for one hour. Addition of excess of water precipitated a colorless solid which was crystallized from methanol to yield **11** as colorless needles, mp 184° (5.5 g). This product was identical (mmp, ^{1}H-nmr) with the product previously prepared [1] by hydrolysis of a pyrrolidine intermediate.

A solution of **11** (2 g) in methanol (4 ml) and 10% aqueous sodium hydroxide (2 ml) was refluxed for 5 minutes, diluted with water and acidified with acetic acid. The product was recrystallized from methanol to yield the dihydrocoumarin derivative **12** as colorless, felted needles, mp 167-168° (1.0 g); ^{1}H-nmr: δ 2.21 (CH_3), 3.78 (2 OCH_3), 3.80 (OCH_3), 3.94 (d, J = 7 Hz, CH), 4.54 (d, J = 7 Hz, CH), 5.92 (OCH_2O), 6.33 (ArH), 6.42 (ArH), 6.62 (ArH); ^{13}C-nmr: δ 29.6 (CH_3), 43.1 (CH), 56.2 (2 OCH_3), 60.3), 60.8 (CH), 98.7 (CH), 101.8 (OCH_2O), 104.7 (2 CH), 107.6 (CH), 116.3 (C), 134.6 (C), 144.9 (C), 145.0 (C), 147.8 (C), 153.7 (2C), 165.0 (CO), 199.7 (CO).

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