The Acid-catalyzed Reactions of 4-Chromanones with Formaldehyde[1)]

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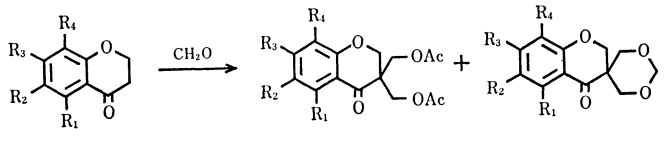
(Received October 2, 1978)

The reactions of several methyl substituted 4-chromanones, such as 4-chromanone (**1a**), 6-(**1b**), and 8-methyl-(**1c**), as well as 5,7-(**1d**) and 6,8-dimethyl-4-chromanone(**1e**) with formaldehyde were carried out in dioxane or mixed solutions of acetic acid and benzene or cyclohexane in the presence of sulfuric acid as a catalyst. The reactions involved an aldol condensation analogous to the Prins reaction, affording acetoxymethyl derivatives and 1,3-dioxanes. It was found that the formation of products was strongly influenced by the substituents on the 4-chromanones and solvents. In a mixed solution of acetic acid and benzene, **1b** and **1e** gave acetoxymethyl derivatives and 1,3-dioxanes, **1a** and **1c** only 1,3-dioxanes, and **1d** a resinous substance. In a dioxane solution, **1b** and **1e** gave 1,3-dioxanes, while **1c** gave a polymer. Bromination of **1e** in 35 and 96% sulfuric acids gave 3- and 5-bromo-6,8-dimethyl-4-chromanones, respectively. The acid-catalyzed reactions were compared with those in 96% sulfuric acid on the basis of the duterium exchange rates of 4-chromanones.

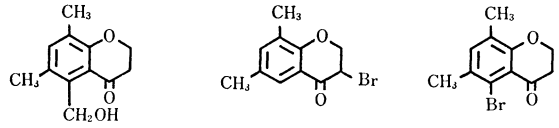
In previous papers,[2,3)] reports were given on the reactions of 4-chromanones with formaldehyde carried out in the presence of 96% sulfuric acid. The reaction products of 4-chromanone (**1a**), 6-(**1b**) as well as 8-methyl-(**1c**) and 5,7-dimethyl-4-chromanone (**1d**) with formaldehyde were the polymers linked by methylene bridges, while those of 6,8-dimethyl-4-chromanone (**1e**) were 5-hydroxymethyl-6,8-dimethyl-4-chromanone (**4**), along with small amounts of the methylene- and methyleneoxymethylene-bridged dimers.

The present investigation deals with the reactions of 4-chromanones with formaldehyde in dioxane or mixed solutions of acetic acid and benzene or cyclohexane in the presence of sulfuric acids as a catalyst. The reactions in 35% sulfuric acid are compared with those in 96% sulfuric acid.



1 **2** **3**

a; $R_1=R_2=R_3=R_4=H$
b; $R_1=R_3=R_4=H$, $R_2=CH_3$
c; $R_1=R_2=R_3=H$, $R_4=CH_3$
d; $R_1=R_3=CH_3$, $R_2=R_4=H$
e; $R_1=R_3=H$, $R_2=R_4=CH_3$
f; $R_1=R_3=R_4=H$, $R_2=CH_2C_6H_5$
g; $R_1=R_3=H$, $R_2=CH_2C_6H_5$, $R_4=CH_3$
h; $R_1=R_3=H$, $R_2=CH_2OAc$, $R_4=CH_3$



4 **5** **6**

Results and Discussion

Reaction Products of 4-Chromanones with Formaldehyde. The reactions of 4-chromanones with formaldehyde were carried out with different molar ratios of the reactants in a mixture of acetic acid and benzene in the presence of H_2SO_4 as a catalyst. The results are summarized in Table 1.

The reaction of **1a** with formaldehyde in a 1:3 molar ratio gave 6-benzylspiro(chroman-3,5′-[1,3]dioxane)-4-one (**3f**), and that in a 1:1 molar ratio caused the recovery of **1a** in 68% yield.

The reaction of **1b** with formaldehyde in a 1:1 molar ratio gave 3,3-bis(acetoxymethyl)-6-methyl-4-chromanone (**2b**) and that in a 1:3.3 molar ratio gave 6-methylspiro(chroman-3,5′-[1,3]dioxane)-4-one (**3b**).

Similarly, the reactions of **1c** in 1:3.3 and 1:5 molar ratios gave 6-benzyl-8-methylspiro(chroman-3,5′-[1,3]-dioxane)-4-one (**3g**). The reaction in a 1:1 molar ratio afforded a small amount of product which was isolated

Table 1. Reaction of 4-chromanones with formaldehyde in a mixture of acetic acid and benzene in the presence of H_2SO_4 at 60 °C

Run	Chromanone, (mmol)	CH_2O/**1**, mole ratio	Acetic acid, ml	Benzene, ml	H_2SO_4, ml	Time, h	Product, (% yield)
1	**1a** (10)	3.0	15	50	1.0	6	**3f** (11)
2	**1b** (4.2)	1.0	5	30	0.5	4	**2b** (5)[a)]
3	**1b** (10)	3.3	15	50	1.0	16	**3b** (2)
4	**1c** (10)	3.3	15	50	1.0	16	**3g** (9)
5	**1c** (10)	5.0	15	50	1.0	16	**3g** (47)
6	**1d** (10)	1.0	10	50	1.0	5	b)
7	**1d** (10)	3.3	15	50	1.0	16	b)
8	**1e** (10)	1.0	10	50	1.0	6	**2e** (10), **3e** (3)
9	**1e** (100)	3.3	100	450	10.0	16	**3e** (70)

a) Yield determined by the ^{1}H-NMR spectrum. b) Resinous substance obtained (see Experimental).

Table 2. Solvent effect in the reaction of 4-chromanones with formaldehyde in the presence of H_2SO_4 at 60 °C

Run	Chromanone, (mmol)	CH_2O/**1**, mole ratio	Solvent, (ml)	H_2SO_4, ml	Time, h	Product, (% yield)
10	**1e** (50)	3.0	Propionic acid (50) Benzene (225)	5.0	7	**3e** (49)
11	**1e** (10)	3.3	Benzyl acetate (10) Benzene (50)	1.0	17	**3e** (12)
12	**1e** (10)	3.0	Acetic acid (20)	2.0	9	**3e** (32)
13	**1e** (10)	1.0	Acetic acid(6)	34.0	4	**4** (80)
14	**1e** (10)	1.0	Benzene (50)	1.0	4	a)
15	**1e** (10)	3.1	Dioxane (35)	5.0	6	**3e** (51)
16	**1e** (10)	1.0	Dioxane (10)	35.0	4	**4** (33)
17	**1b** (10)	3.1	Dioxane (35)	5.0	6	**3b** (30)
18	**1c** (10)	5.0	Acetic acid (10) Cyclohexane (50)	1.0	6	**3h** (2)
19	**1c** (10)	3.1	Dioxane (35)	5.0	6	b)

a) **1e** recovered in 95% yield. The reaction products were diphenylmethane and its homologues. b) A resinous product was obtained, yield 2.51 g.

with difficulty from the reaction mixture.

The reaction of **1e** with formaldehyde in a 1 : 1 molar ratio gave 3,3-bis(acetoxymethyl)-6,8-dimethyl-4-chromanone (**2e**) and 6,8-dimethylspiro(chroman-3,5′-[1,3]dioxane)-4-one (**3e**), while that in a 1 : 3.3 molar ratio gave **3e** in high yield. **3e** was changed into 6,8-dimethylspiro(chroman-3,5′-[1,3]dioxane)-4-ol (**3e′**) by use of sodium borohydride. The reaction of **1d**, however, gave a resinous substance.

The reactions were examined as regards the effects of the solvents and their acidity. The results are summarized in Table 2.

In the reaction of **1e** with formaldehyde, the use of propionic acid–benzene or benzyl acetate–benzene mixture, acetic acid, or dioxane as solvent gave **3e**, along with resinous substance. When the reaction was carried out in a benzene solution, diphenylmethane and its homologues were obtained, **1e** being recovered in 95% yield. The use of a large amount of H_2SO_4 (Runs 13 and 16) gave **4**, analogous to the case of the use of 96% H_2SO_4.[3]

The reaction of **1b** in dioxane gave only **3b**. The reaction of **1c** in a mixed solution of acetic acid and cyclohexane gave 6-acetoxymethyl-8-methylspiro-(chroman-3,5′-[1,3]dioxane)-4-one (**3h**), and that in dioxane a resinous material.

Bromination of 1e. The bromination of **1e** in acetic acid solution in the presence of H_2SO_4 gave 3-bromo-6,8-dimethyl-4-chromanone (**5**), while that in 96% H_2SO_4 gave 5-bromo-6,8-dimethyl-4-chromanone (**6**).

Deuterium Exchange of 4-Chromanones. Rates of the deuterium exchange of **1e** were observed by means of ^{1}H-NMR spectra. The results obtained in 35% D_2SO_4 (in CH_3CO_2D), 85% D_2SO_4 (in D_2O), and 96% D_2SO_4 are shown in Figs. 1a, 1b, and 1c, respectively. The deuterium atom % was calculated on the basis of the integral value in the C-2 methylene protons of **1e**. There is a clear difference between 1a and 1c. In 35% D_2SO_4, deuterium is incorporated into the C-3 methylene protons faster than the C-5 aromatic proton, while in the case of 96% D_2SO_4, the opposite tendency is

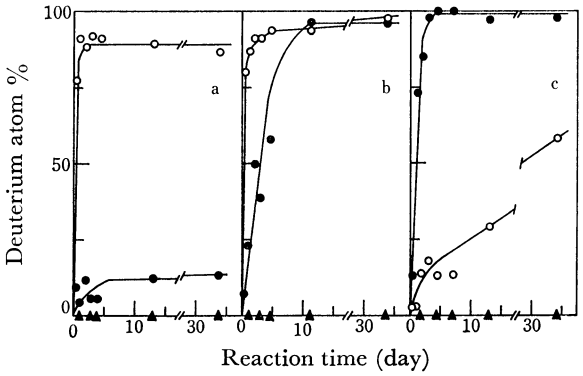


Fig. 1. Deuterium exchange of **1e** in various concentrations of D_2SO_4.
D_2SO_4 concentrations: a, 35% (in CH_3CO_2D); b, 85% (in D_2O); c, 96%. Exchange position: (○), C-3 methylene protons; (●), C-5 aromatic proton; (▲), C-7 aromatic proton.

Table 3. Deuterium exchange of 4-chromanones in 20% D_2SO_4 (in CH_3CO_2D) and 96% D_2SO_4 at 25 °C

Chromanone	Solvent[a]	Concn, wt %	Time	Deuterium atom % 3-,	6-,	8-,
1a	SA	15	3 h	86	0	0
			48 h	87	33	10
	S	15	24 h	5	15	2
			48 h	54	72	44
1b	SA	11	3 h	89	—	0
			48 h	86	—	6
	S	11	24 h	20	—	55
1c	SA	15	3 h	86	0	—
			48 h	89	60	—
	S	15	24 h	49	83	—
1d	SA	12	5 min	77	44[b]	
			3 h	100	73[b]	
			48 h	100	100[b]	
	S	12	3 h	3	91[b]	

a) SA=20% D_2SO_4 (in CH_3CO_2D), S=96% D_2SO_4. b) Signal not resolved to the 6- and 8-protons.

Table 4. ^{13}C-NMR spectra of **1e** in 96% H_2SO_4, 35% H_2SO_4 (in CH_3CO_2H), and $CDCl_3$[a]

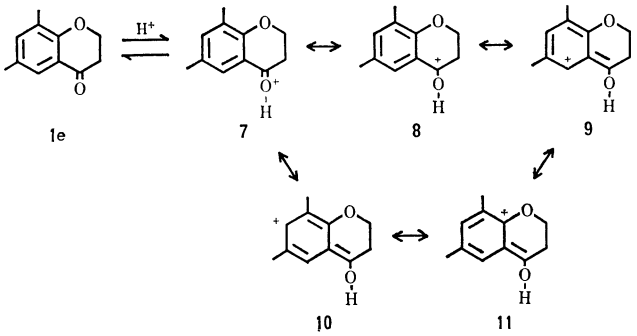
Solvent	Concn, wt %	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	6-CH_3	8-CH_3
96% H_2SO_4	11.9	65.7	31.4	202.7	125.0	133.9	151.9	129.9	168.0	114.6	19.5	14.3
35% H_2SO_4	17.9	67.4	37.4	197.6	125.0	131.1	140.3	128.1	160.2	120.5	20.4	15.5
$CDCl_3$	36.5	66.5	37.2	190.8	123.6	129.1	137.0	126.0	157.6	120.2	19.7	14.9
Δ_1		−0.8	−5.8	11.9	1.4	4.8	14.9	3.9	10.4	−5.6	−0.2	−0.6
Δ_2		0.9	0.2	6.8	1.4	2.0	3.3	2.1	2.6	0.3	0.7	0.6

a) Chemical shifts are reported in ppm relative to Me_4Si. Δ_1=(96% H_2SO_4–$CDCl_3$) and Δ_2=(35% H_2SO_4–$CDCl_3$) are the chemical shift differences.

observed. It was found that the deuterium atom % of the C-5 position in 35% D_2SO_4 is in equilibrium at 10%, but that of the C-3 methylene in 96% D_2SO_4 slowly increases with time. The results of the deuterium exchange of other 4-chromanones are summarized in Table 3. 20% D_2SO_4 preferentially leads to exchange of the C-3 methylene protons, and 96% D_2SO_4 leads to the aromatic protons, but the difference between 20% D_2SO_4 and 96% D_2SO_4 is not as large as in the case of **1e**. The deuterium exchange of **1c** in 20% D_2SO_4 occurred in the order 3>6>8, and that in 96% D_2SO_4 in the order 6>3>8.

*^{13}C-NMR Spectra of **1e**.* Table 4 gives the carbon-13 chemical shifts obtained in 96% H_2SO_4, 35% H_2SO_4 (in CH_3CO_2H), and $CDCl_3$, as well as the chemical shift differences, Δ_1 and Δ_2, between H_2SO_4 solutions and $CDCl_3$ solution. Assigments of resonance positions to individual carbon atoms were made on the basis of substituent effects,[4] splitting patterns in proton coupled spectra, and internal consistency. A positive Δ indicates that the resonance is deshielded in H_2SO_4 relative to $CDCl_3$. In 96% H_2SO_4, larger deshielding trends of 10—15 ppm are observed for C-4, C-7, and C-9. Deshielding of 6.8 ppm for C-4 is observed in 35% H_2SO_4 solution.

The observed chemical shift trends in 96% H_2SO_4 are interpreted to result predominantly from protonation of the carbonyl oxygen (**7**) (Scheme 1). A deshielding effect is associated with a loss of charge density for carbons of similar hybridization.[5]

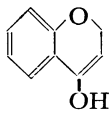


Scheme 1.

Reaction Path. Some papers on the acid-catalyzed condensation of cycloalkanones with formaldehyde[6] have reported the formation of hydroxymethyl derivatives and 1,3-dioxanes.

In the reactions of 4-chromanones with formaldehyde in solvents in the presence of sulfuric acid, the condensation products for the C-3 position were obtained even though **1a**, **1b**, and **1c** gave the aromatic substituted products containing 1,3-dioxanes. The deuterium exchange of 4-chromanones in various concentrations of sulfuric acid suggests that the C-3 methylene protons are more reactive than the aromatic protons.

These results obtained in the low concentrations of sulfuric acid can be explained by the aldol condensation mechanism.[7] The intermediate enol (**12**) is formed by the direct removal of a proton from the protonated intermediate (**8**) by bases (HSO_4^- and/or $CH_3CO_2^-$), reacting with hydroxymethyl cation($\overset{+}{C}H_2OH$)[8] to produce hydroxymethyl derivatives. Diacetates were obtained when the molar quantity of formaldehyde as against that of 4-chromanones was small.



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Bromination of **1e** in 35 and 96% H_2SO_4 using molecular bromine as an electrophilic substituting agent gave 3- and 5-bromo derivatives, respectively. The different reactivity of 4-chromanones in various concentrations of sulfuric acid might be utilized in synthetic reactions by use of other electrophilic agents.

The aromatic substituted products formed by the addition of formaldehyde to the benzene rings of 4-chromanones proceeds by an electrophilic aromatic substitution.

The results given in Table 1 suggest that the methyl substituents attached to the 6- and/or 8-positions of 4-chromanones play an important role in the formation of aromatic substituted products. **1e** fixed by the two methyl groups gave 3-substituted products only, **1d** containing the reactive 6- and 8-positions a polymer, while **1a** gave the 6-benzyl product. The results are also in line with the rates of deuterium exchange.

Experimental

General. Melting points are uncorrected. IR spectra were obtained on a Hitachi EPI-G2 spectrometer, ^{1}H-NMR spectra on a JEOR Model PS-100 spectrometer with tetramethylsilane(Me_4Si) as an internal standard, and ^{13}C-NMR spectra on a JNM-FX60 spectrometer. Chemical shifts in $CDCl_3$ and 35% H_2SO_4 (in CH_3CO_2H) were measured using Me_4Si as an internal standard. Chemical shifts in 96% H_2SO_4 were obtained relative to external $CDCl_3$ and converted into the Me_4Si scale by the relationship $\delta Me_4Si=\delta CDCl_3+$

77.1. Mass spectra were determined on a Hitachi RUM-6 mass spectrometer operating at 70 eV. Molecular weight was determined with a Mechrolab Model 301A vapor pressure osmometer in *N,N*-dimethylformamide at 65 °C.

Materials. 4-Chromanones were prepared from phenols according to the published procedure.[2,9] Commercial 1,3,5 trioxane, sulfuric acids, and solvents were used.

Reactions of 4-Chromanones with Formaldehyde. The general procedure is as follows. To a mixture of acetic acid and benzene were added 4-chromanones, 1,3,5-trioxane, and H_2SO_4 in this order, and the mixture was stirred at 60 °C. The reaction mixture was poured into cold water, and extracted with benzene. The benzene solution was washed with aqueous sodium hydroxide, aqueous hydrochloric acid, and water successively. After removal of the solvents, the residual oil was separated by column chromatography on silica gel (Wakogel C-200; developing solvent, chloroform) to some fractions in which the first fractions were starting 4-chromanones, unless otherwise stated. The reaction conditions and products of these reactions are given in Tables 1 and 2.

From ***1a***. The reaction of **1a** with formaldehyde in a 1:3 molar ratio gave a pale yellow oil from the second fraction. The fraction could not be separated further. However, it gave **3f** containing a small amount of **1a**.

3f: IR (neat) 2770, 1670, 1090, 1040, 840, 705 cm^{-1}; ^1H NMR (CCl_4) δ=7.57 (1H, d, J=3.0 Hz, 5-H), 7.10 (5H, m, Ph), 7.06 (1H, dd, 7-H), 6.76 (1H, d, J=9.0 Hz, 8-H), 4.75 (2H, AB-q, J=6.0 Hz, $-OCH_2O-$), 4.53 (2H, s, 2-H), 3.88 (4H, s, $-CH_2O-$), 3.84 (2H, s, 6-CH_2); MS *m/e* 310 (M^+, 60), 211 (100).

From ***1b***. The reaction product obtained in a 1:1 molar ratio was subjected to fractional distillation under reduced pressure. From the first fraction unreacted **1b** was recovered at 86—87 °C/0.5 mmHg, and from the second fraction a yellow viscous oil at 165—166 °C/0.5 mmHg, which was separated by column chromatography to give a mixture of **2b** and **1b**. The distillation residue was a mixture of **3b** and other unknown products. The third fraction of the product obtained in a 1:3.3 molar ratio gave a pale yellow oil, which crystallized after being left to stand overnight. The crystals were recrystallized from cyclohexane to give **3b**.

2b: Oil; IR (neat) 1730, 1680, 1040, 880, 830 cm^{-1}; MS *m/e* 306 (M^+, 5), 174 (100).

3b: Mp 93—94 °C; IR (KBr) 2780, 1680, 1100, 1030, 890, 825 cm^{-1}; ^1H-NMR (CCl_4) δ=7.50 (1H, d, J=2.7 Hz, 5-H), 7.18 (1H, dd, 7-H), 6.80 (1H, d, J=9.1 Hz, 8-H), 4.76 (2H, AB-q, J=6.4 Hz, $-OCH_2O-$), 4.54 (2H, s, 2-H), 3.89 (4H, s, $-CH_2O-$), 2.29 (3H, s, 6-CH_3); MS *m/e* 234 (M^+, 41), 135 (100). Found: C, 66.45; H, 5.97%. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02%.

From ***1c***. The yellow oils obtained in 1:3.3 and 1:5 molar ratios in a mixed solution of acetic acid and benzene were separated into three fractions. A crystalline product (**3g**) was isolated from the second fraction, and a small amount of polymer from the third fraction. The first fraction of the product obtained in a 1:5 molar ratio in a mixture of acetic acid and cyclohexane gave **3h**.

3g: Mp 153—154 °C (from ligroin); IR (KBr) 2760, 1670, 1100, 1040, 830, 700 cm^{-1}; ^1H-NMR (CCl_4) δ=7.42 (1H, d, 5-H), 7.04 (1H, d, 7-H), 7.12 (5H, m, Ph), 4.78 (2H, AB-q, J=6.1 Hz, $-OCH_2O-$), 4.58 (2H, s, 2-H), 3.91 (2H, s, $-CH_2O-$), 3.48 (2H, s, 6-CH_2), 2.22 (3H, s, 8-CH_3); MS *m/e* 324 (M^+, 93), 225 (100). Found: C, 74.29; H, 6.32%. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.22%.

3h: Mp 99—99.5 °C (from ligroin); IR (KBr) 2780, 1680, 1095, 1035, 1025, 820 cm^{-1}; ^1H-NMR (CCl_4) δ=7.52 (1H, d, 5-H), 7.26 (1H, d, 7-H), 4.87 (2H, s, 6-CH_2), 4.75 (2H, AB-q, J=6.0 Hz, $-OCH_2O-$), 4.60 (2H, s, 2-H), 3.89 (4H, s, $-CH_2O-$), 2.26 (3H, s, 8-CH_3), 2.00 (3H, s, $COCH_3$); MS *m/e* 306 (M^+, 77), 207 (100). Found: C, 62.80; H, 5.83%. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92%.

From ***1d***. The reaction product obtained in a 1:1 molar ratio gave a resinous substance which could be isolated with difficulty from the reaction mixture: yield 1.5 g; mp 80 °C; molecular weight 420; IR (KBr) 1670, 1100, 1020 cm^{-1}. The absorption due to benzyl group at 3.9 ($C\underline{H}_2Ph$) and 7.2 (Ph) ppm was observed by the ^1H-NMR spectrum. The reaction product obtained in a 1:3 molar ratio gave a resinous substance: yield 2.7 g; mp 100 °C; molecular weight 630; IR (KBr) 1725, 1660, 1095, 1030 cm^{-1}. The absorption due to the benzyl group at 3.9 ($C\underline{H}_2Ph$) and 7.2 (Ph) ppm, and the 1,3-dioxane ring at 5.0 and 4.8 ($-OCH_2O-$) ppm was observed by the ^1H-NMR spectrum.

From ***1e***. The reaction products obtained in Runs 8, 9, 10, 11, and 12 were isolated by column chromatography to three fractions. The second white crystalline fraction and the third yellow oil fraction gave **3e** and **2e**, respectively. The reaction mixtures in Runs 13, 15, and 16 were extracted with chloroform and recrystallized from ligroin to give **3e** or **4**.

2e: Yellow oil; IR (neat) 1730, 1670, 1030, 870 cm^{-1}; ^1H-NMR (CCl_4) δ=7.44 (1H, d, 5-H), 7.04 (1H, d, 7-H), 4.35 (2H, s, 2-H), 4.24 (4H, s, $-CH_2OCO-$), 2.26 (3H, s, 6-CH_3), 2.08 (3H, s, 8-CH_3), 2.00 (6H, s, $-OCOCH_3$); MS *m/e* 320 (M^+, 37), 148 (100). Found: C, 63.98; H, 6.30%. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29%.

3e: Mp 146.5—148 °C (from acetone); IR (KBr) 2760, 1660, 1100, 1030, 880 cm^{-1}; ^1H-NMR (CCl_4) δ=7.34 (1H, d, 5-H), 7.08 (1H, d, 7-H), 4.78 (2H, AB-q, J=6.0 Hz, $-OCH_2O-$), 4.56 (2H, s, 2-H), 3.90 (4H, s, $-CH_2O-$), 2.26 (3H, s, 6-CH_3), 2.22 (3H, s, 8-CH_3); MS *m/e* 248 (M^+, 69), 149 (100); ^{13}C-NMR ($CDCl_3$) δ=192.4 (s, 4-C), 157.7 (s, 9-C), 138.5 (d, 7-C), 130.3 (s, 6-C), 127.0 (s, 8-C), 124.3 (d, 5-C), 119.2 (s, 10-C), 94.0 (t, 2′-C), 69.7 (t, 2-C), 67.5 (t, 4′- and 6′-C), 45.2 (s, 3-C), 20.3 (q, 6-CH_3), 15.3 (q, 8-CH_3). The assignments are based on the data of Chauhan and Still,[10] and the procedure of Levy and Nelson.[11] Found: C, 67.61; H, 6.49%. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50%.

4: Mp 95—97 °C (lit,[9] mp 95—97 °C). The structure of this product was confirmed by ^1H-NMR and mass spectra.

Reduction of ***3e***. Sodium borohydride (0.14 g, 3.6 mmol) was added to **3e** (1.24 g, 5 mmol) in ethanol (20 ml). The mixture was heated under reflux at 80 °C for 4 h. The reaction mixture was neutralized with acetic acid and then extracted with ether. The ether layer was washed with aqueous sodium hydroxide, aqueous hydrochloric acid, and water and then dried *in vacuo*. The residue was recrystallized from hexane to give **3e′** in a 68% yield: mp 109 °C; IR (KBr) 3400, 2760, 1030, 870 cm^{-1}; ^1H-NMR (CCl_4) δ=6.76 (2H, bd, 5- and 7-H), 4.70 (2H, AB-q, J=6.1 Hz, $-OCH_2O-$), 4.12 (2H, AB-q, J=10.1 Hz, 2-H), 3.67 (4H, AB-q, J=12.1 Hz, $-CH_2O-$), 4.22 (1H, s, OH), 3.80 (1H, s, 4-H), 2.22 (3H, s, 6-CH_3), 2.14 (3H, s, 8-CH_3); MS *m/e* 250 (M^+, 71), 150 (100). Found: C, 66.94; H, 7.39%. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%.

Preparation of ***5***. To a solution of 96% H_2SO_4 (5 ml) and acetic acid (50 ml) was added **1e** (1.76 g, 10 mmol), and the mixture was cooled in an ice-bath. A solution of bromine (0.80 g, 10 mmol) and acetic acid (5 ml) was then added dropwise over a period of 30 min to the mixture with stirring, and the mixture was stirred for 30 min at 0 °C. The reaction mixture was poured into water and extracted with benzene. The organic layer was washed with aqueous sodium hydroxide and water, and dried *in vacuo* to give a yellow oil. The oil

was recrystallized twice from ligroin to give **5**: yield 17%; mp 86—87 °C, IR (KBr) 1680, 1020, 890, 550 cm^{-1}; ^1H-NMR (CCl_4) δ=7.46 (1H, d, 5-H), 7.10 (1H, d, 7-H), 4.54 (2H, d, J=4.5 Hz, 2-H), 4.42 (1H, t, 3-H), 2.27 (3H, s, 6-CH_3), 2.21 (3H, s, 8-CH_3); MS *m/e* 254 (M^+, 31), 148 (100). Found: C, 51.77; H, 4.33; Br, 31.16%. Calcd for $C_{11}H_{11}O_2Br$: C, 51.79; H, 4.35; Br, 31.32%.

Preparation of ***6***. **1e** (3.52 g, 20 mmol) was dissolved in 96% H_2SO_4 (30 ml), and the mixture was cooled in an ice-bath. Bromine (3.2 g, 40 mmol) was added over a period of 30 min to the mixture with stirring, and the mixture was stirred for 30 min at 0 °C. The reaction mixture was treated as described in the preparation of **5**. The product was recrystallized three time from ligroin to give **6**: yield 23%; mp 102—103 °C; IR (KBr) 1680, 1020, 870, 570 cm^{-1}; ^1H-NMR (CCl_4) δ=7.08 (1H, s, 7-H), 4.49 (2H, t, J=6.0 Hz, 2-H), 2.76 (2H, t, 3-H), 2.32 (3H, s, 6-CH_3), 2.14 (3H, s, 8-CH_3); MS *m/e* 254 (M^+, 100), 226 (83). Found: C, 51.63; H, 4.24; Br, 31.23%.

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