[Chem. Pharm. Bull. 31(9)3024—3038(1983)]

Studies on the Chemical Constituents of Rutaceous Plants. XLIX.[1] Development of a Versatile Method for the Synthesis of Antitumor-Active Benzo[*c*]phenanthridine Alkaloids. (1). Preparation of Various 2,4-Bisaryl-4-oxobutyronitriles and 2,4-Bisaryl-4-oxobutyramides

Hisashi Ishii,* Tsutomu Ishikawa, Takeo Deushi, Ken-Ichi Harada, Toshiko Watanabe, Etsuko Ueda, Toshiaki Ishida, Mitsugi Sakamoto, Eri Kawanabe, Tsutomu Takahashi (deceased), Yuh-Ichiro Ichikawa, Kazue Takizawa, Takeshi Masuda, and Ih-Sheng Chen

Faculty of Pharmaceutical Sciences, Chiba University, 1–33, Yayoi-cho, Chiba 260, Japan

(Received January 14, 1983)

For the sake of establishment of a versatile synthetic method for benzo[*c*]phenanthridine alkaloids, improvement of the Robinson synthetic method was examined. Thirteen chalcones (**7a**—**m**) were prepared by condensation of two acetophenone derivatives (**15** and **16**) with eleven benzaldehyde derivatives (**19a**—**k**) as fundamental starting materials. Hydrocyanation of these chalcones (**7a**—**l**) except one (**7m**) gave the corresponding 2,4-bisaryl-4-oxobutyronitriles (**8a**—**l**). Eleven 2,4-bisaryl-4-oxobutyramides (**9a**—**k**) were also prepared.

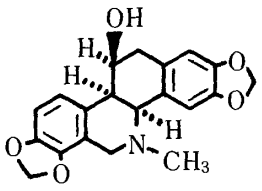
Keywords——synthesis; Robinson pathway improved; antileukemic activity; chalcone; hydrocyanation; 2,4-bisaryl-4-oxobutyronitrile; 2,4-bisaryl-4-oxobutyramide

It is well known that benzo[*c*]phenanthridine alkaloids[2] naturally occur in Papaveraceous (several species) and in Rutaceous [*Xanthoxylum* (*Fagara*) and *Toddalia*] plants. Alkaloids of this kind can be classified into two groups, one having a partially hydrogenated benzo[*c*]phenanthridine skeleton [*e.g.* chelidonine (**1**)] (group I) and the other having a fully aromatized one (group II). The latter can be subdivided into the 7,8-oxygenated alkaloid group [*e.g.* chelerythrine (**2**)] (group IIa) and the 8,9-oxygenated one [*e.g.* nitidine (**3**)] (group IIb). All of the alkaloids belonging to group I have oxygen functions at the C_7 and C_8 positions and have been isolated only from Papaveraceous plants. Among the fully aromatized alkaloids, 7,8-oxygenated ones occur in both Papaveraceous and Rutaceous plants, while 8,9-oxygenated ones occur only in Rutaceous plants.

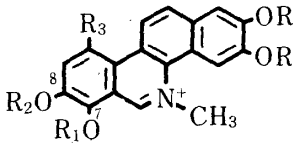
In 1971, Wall *et al.*[3] reported that nitidine (**3**) shows antileukemic activity against L1210 mouse leukemia. One year later, Farnsworth *et al.*[4] found that fagaronine (**4**), one of the 8,9-oxygenated alkaloids, also shows a high order of activity against P388 leukemia in mice, but sanguinarine (**5**), one of the 7,8-oxygenated alkaloids, is not effective.[5] These reports stimulated us to investigate the structure–activity relationship among these alkaloids and related compounds. For this purpose, a practical synthetic method for benzo[*c*]phenanthridine alkaloids and related compounds was required.

Robinson *et al.*[6b] reported the first success in the synthesis of this type of alkaloid in 1950 (Chart 2). Although, it has been applied to total syntheses of various naturally occurring alkaloids and/or their derivatives [chelerythrine[7] (**2**), nitidine[8] (**3**), and avicine[9] (**6**)] with

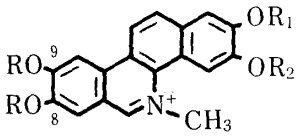
group I group IIa group IIb



1

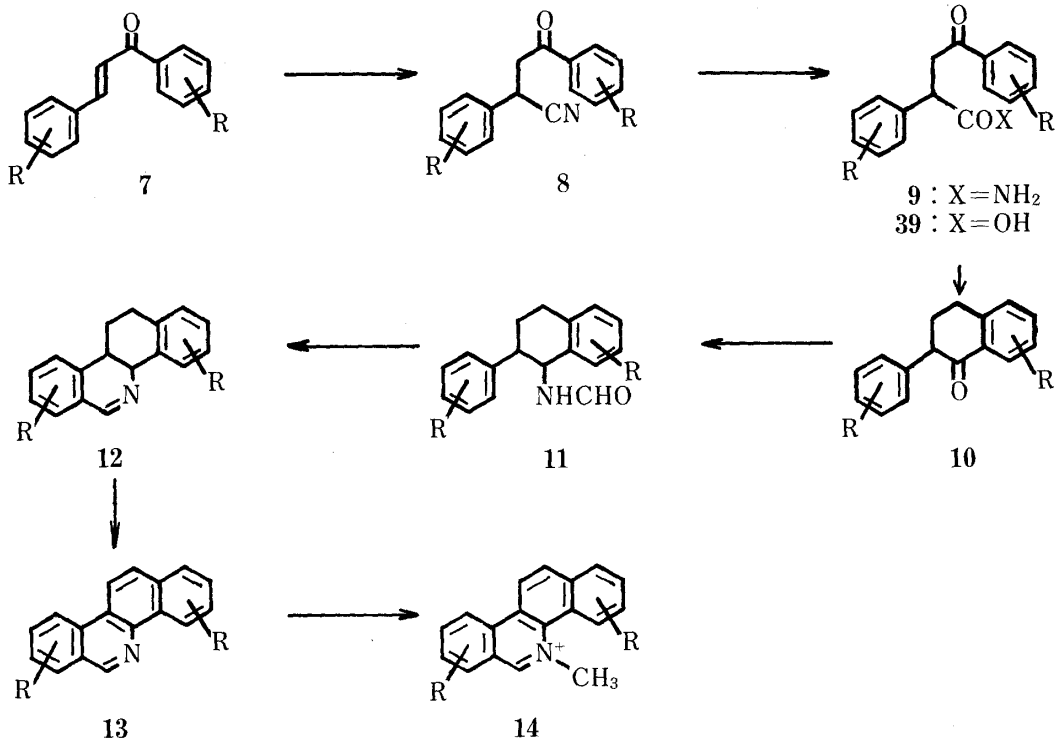


2 : 2R=CH_2, R_1=R_2=CH_3, R_3=H
5 : 2R=R_1+R_2=CH_2, R_3=H
17 : R=CH_3, R_1+R_2=CH_2, R_3=OCH_3
18 : R=R_1=R_2=CH_3, R_3=OCH_3



3 : R=CH_3, R_1+R_2=CH_2
4 : R=R_2=CH_3, R_1=H
6 : 2R=R_1+R_2=CH_2

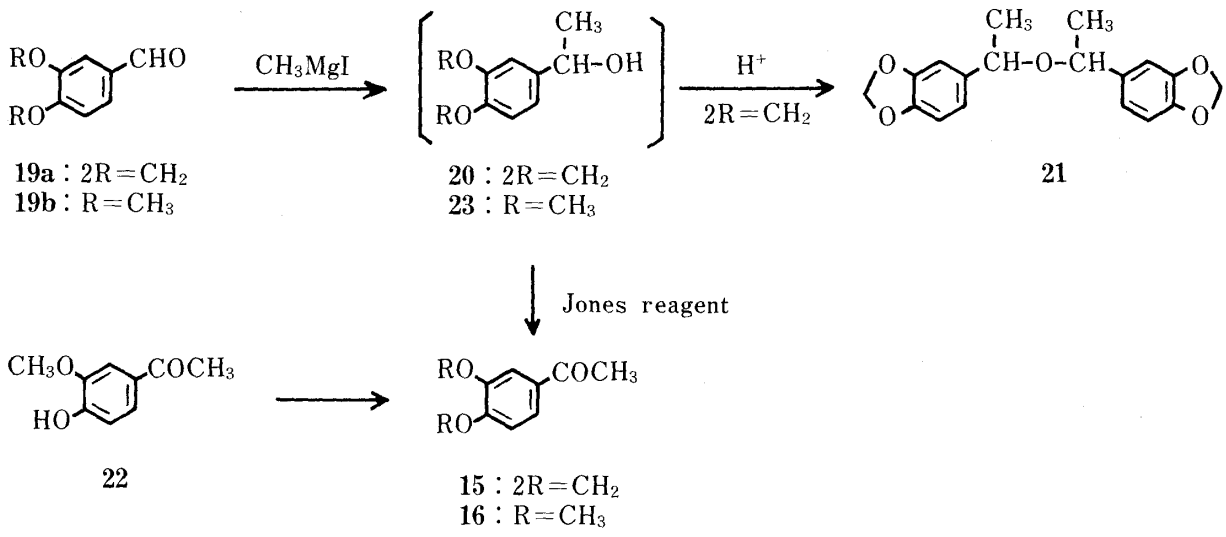
Chart 1



7 8 9 : X=NH_2 39 : X=OH 10 11 12 13 14

Chart 2

some minor modifications, this reaction sequence still involves five troublesome steps: i) synthesis of the 2-aryl-1-tetralone derivative (**10**) from the chalcone (**7**) *via* 2,4-bisaryl-4-oxobutyronitrile (**8**), ii) preparation of the 1-formamido-1,2,3,4-tetrahydronaphthalene (**11**) from the tetralone (**10**), iii) Bischler–Napieralski reaction of the formamide (**11**), iv) aromatization of the Bischler–Napieralski product (**12**), and v) quaternization of the benzo[*c*]phenanthridine skeleton (**13**) by *N*-alkylation. We therefore tried to establish a versatile synthetic pathway for this type of alkaloids and related compounds by improvement of this reaction sequence. In this paper, we describe syntheses of various 2,4-bisaryl-4-oxobutyronitriles (**8**) and 2,4-bisaryl-4-oxobutyramides (**9**), the fundamental starting materials in this reaction sequence.



19a : 2R=CH_2
19b : R=CH_3

20 : 2R=CH_2
23 : R=CH_3

21

22

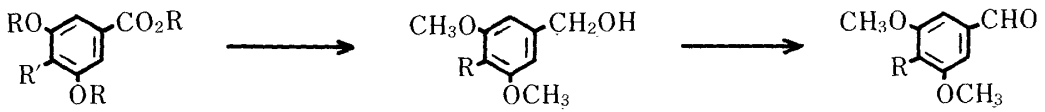
15 : 2R=CH_2
16 : R=CH_3

Chart 3

As materials for syntheses of the starting chalcones (**7**) two acetophenone derivatives (**15** and **16**) were prepared. Acetopiperone (**15**) is the most commonly required starting acetophenone (which will be led to the alkaloid ring D) inasmuch as all of the known benzo[*c*]phenanthridine alkaloids except three [fagaronine (**4**), sanguirubine (**17**), and sanguilutine (**18**)] have a methylenedioxy group at the 2,3-positions in the D ring. In spite of the expectation that acetopiperone (**15**) could be prepared by treatment of piperonal (**19a**) with methyl magnesium iodide followed by oxidation of the resulting alcohol (**20**), many research groups have avoided the Grignard reaction of piperonal (**19a**) because of erroneous descriptions in the literature.[10-12] Actually, Mameli[10] and Béhal[11] independently claimed at the beginning of this century that the Grignard reaction of piperonal (**19a**) resulted in formation of a dimerized product (**21**), bis-1-(3,4-methylenedioxyphenyl)diethyl ether, because of facile dimerization[12] of the secondary alcohol (**20**), 1-(3,4-methylenedioxyphenyl)ethanol, under basic conditions. Moreover, Klages[13] recommended isolation of the complex formed by the Grignard reaction by filtration, followed by hydrolysis with a large amount of water. Consequently, some earlier research groups[8a,8c,14] working on the synthesis of benzo[*c*]phenanthridine alkaloids prepared acetopiperone (**15**) by other methods. However, we doubted the early reports, since, generally speaking, this type of dimerization takes place not under basic conditions, but under acidic conditions. The desired secondary alcohol (**20**) was confirmed to be stable under basic conditions, whereas it readily dimerized on treatment with mineral acid even at room temperature. The complex isolated by filtration of the Grignard reaction mixture could be easily decomposed by an aqueous solution of ammonium chloride to give the corresponding secondary alcohol (**20**), which was convertible into acetopiperone (**15**) by treatment with Jones reagent without formation of the dimerized product (**21**) in excellent yield [overall 70—84%].

In order to synthesize sanguirubine (**17**) and sanguilutine (**18**), acetoveratrone (**16**) was prepared by methylation[15] of commercially available acetovanillone (**22**) and from veratraldehyde (**19b**) according to the same reaction sequence as in the case of acetopiperone (**15**).

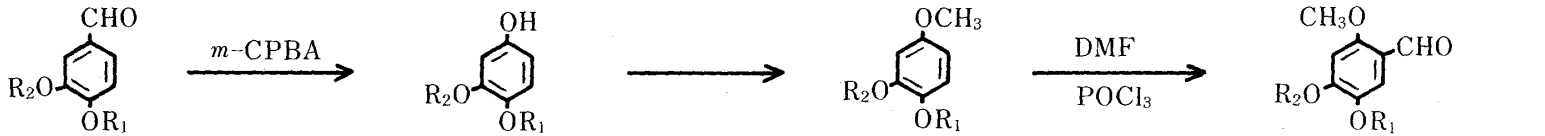
Several benzaldehyde derivatives other than piperonal (**19a**) and veratraldehyde (**19b**) were also prepared for use as synthetic starting materials. i) 3,5-Dimethoxybenzaldehyde[16] (**19c**) was prepared by methylation of 3,5-dihydroxybenzoic acid (**24**) with dimethyl sulfate in acetone in the presence of potassium carbonate followed by reduction with lithium aluminium hydride and by oxidation with Collins reagent[17] in 80.3% overall yield. ii) 3,4,5-Trimethoxybenzaldehyde[18] (**19d**) was also prepared by methylation of gallic acid (**27**) with



24 : R=R′=H
25 : R=CH_3, R′=H
27 : R=H, R′=OH
28 : R=CH_3, R′=OCH_3

26 : R=H
29 : R=OCH_3

19c : R=H
19d : R=OCH_3

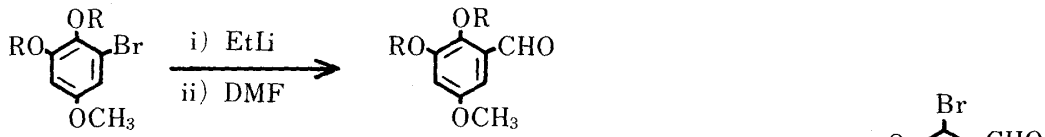


34 : R_1=R_2=CH_2Ph
35 : R_1=CH_2Ph, R_2=CH_3

36 : R_1=R_2=CH_2Ph
37 : R_1=CH_2Ph, R_2=CH_3

30 : R_1+R_2=CH_2
31 : R_1=R_2=CH_3
38 : R_1=R_2=CH_2Ph
39 : R_1=CH_2Ph, R_2=CH_3

19e : R_1+R_2=CH_2
19f : R_1=R_2=CH_3
19h : R_1=R_2=CH_2Ph
19i : R_1=CH_2Ph, R_2=CH_3

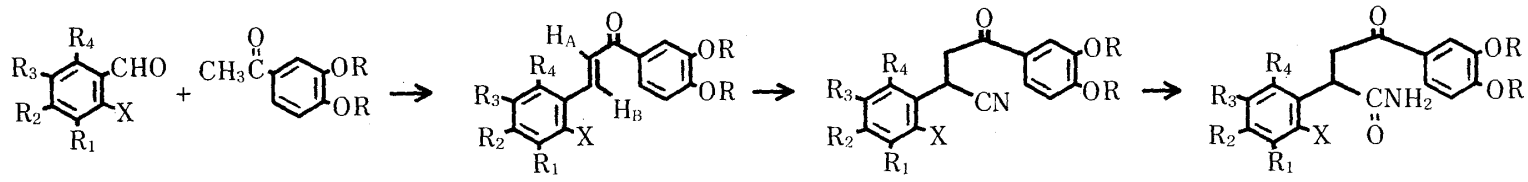


32 : 2R=CH_2
33 : R=CH_3

19g : 2R=CH_2
19k : R=CH_3

19j

Chart 4



19a—k **15** or **16** **7** **8** **9**

Chalcone (7)	Chemical shifts of olefinic protons of chalcones			Substituents							Keto nitrile (8)	Keto amide (9)
	H_A	H_B	J(Hz)	R_1	R_2	R_3	R_4	X	R	R		
7a	7.26	7.73	16.0	OCH_2O		H	H	H	CH_2		**8a**	**9a**
7b	7.31	7.73	16.0	OCH_3	OCH_3	H	H	H	CH_2		**8b**	**9b**
7c	7.39	7.68	16.0	OCH_3	H	OCH_3	H	H	CH_2		**8c**	**9c**
7d	7.31	7.69	16.0	OCH_3	OCH_3	OCH_3	H	H	CH_2		**8d**	**9d**
7e	7.31	8.09	16.0	OCH_2O		H	OCH_3	H	CH_2		**8e**	**9e**
7f	7.40	7.98	16.0	OCH_2Ph	OCH_2Ph	H	OCH_3	H	CH_2		**8f**	**9f**
7g	7.16—7.68	8.00	15.5	OCH_2Ph	OCH_3	H	OCH_3	H	CH_3	CH_3	**8g**	**9g**
7h	7.38	8.10	16.0	OCH_2O		H	OCH_3	H	CH_3	CH_3	**8h**	**9h**
7i	7.44	8.03	16.0	OCH_3	OCH_3	H	OCH_3	H	CH_3	CH_3	**8i**	**9i**
7j	7.92	8.05	15.0	OCH_2O		H	OCH_3	Br	CH_2		**8j**	**9j**
7k	7.66		—	OCH_3	H	OCH_2O		H	CH_2		**8k**	**9k**
7l	7.36	8.01	16.0	OCH_3	OCH_3	H	OCH_3	H	CH_2		**8l**	—
7m	7.51	8.09	16.0	OCH_3	H	OCH_3	OCH_3	H	CH_2		—	—

Chart 5

the same reagent followed by reduction with Vitride[19] and by oxidation[20] with pyridinium dichromate[21] (PDC) in 80.7% overall yield. iii) 2-Methoxy-4,5-methylenedioxy-[22] (**19e**) and 2,4,5-trimethoxy-[23] (**19f**) benzaldehydes were obtained by Vilsmeier–Haack reaction of *O*-methylsesamol[22] (**30**) and 1,2,4-trimethoxybenzene[24] (**31**), respectively. iv) 5-Methoxy-2,3-methylenedioxy- (**19g**) and 2,3,5-trimethoxy-[25] (**19k**) benzaldehydes were derived from 5-methoxy-2,3-methylenedioxy[26]- (**32**) and 2,3,5-trimethoxy[27]- (**33**) bromobenzenes by treatment with ethyl lithium followed by formylation with *N*,*N*-dimethylformamide (DMF).

In the course of our synthetic study of the 7,8-oxygenated benzo[*c*]phenanthridine alkaloids, some 2-aryl-1-tetralones having a hydroxy group at the C_3 position or a bromine atom at the C_2 position of the aryl substituent were required. For this purpose, 3,4-dibenzyloxybenzaldehyde[28] (**34**) and benzylvanillin (**35**) were converted into 3,4-dibenzyloxyanisole (**38**) and 4-benzyloxy-1,3-dimethoxybenzene (**39**), respectively, by Baeyer–Villiger oxidation followed by methylation. Vilsmeier–Haack reaction of these products provided 4,5-dibenzyloxy-2-methoxybenzaldehyde[29] (**19h**) and 5-benzyloxy-2,4-dimethoxybenzaldehyde (**19i**). 2-Bromo-6-methoxy-3,4-methylenedioxybenzaldehyde[26] (**19j**) was used a representative of 2-bromobenzaldehyde derivatives, which would be useful starting materials for synthesis of 7,8-oxygenated alkaloids *via* the Robinson synthetic sequence with minor modifications.[7]

The thirteen chalcones (**7a**—**m**) shown in Chart 5 were prepared by condensation of the acetophenone (**15** or **16**) with the aldehyde (**19a**—**k**) using sodium hydroxide in alcohol according to the reported procedure.[6] In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, each of these chalcones (**7**) except one (**7k**) shows a pair of doublets having *J* values of 15—16 Hz due to olefinic protons at relatively low field, indicating that these desired chalcones (**7**) are *trans*. However, the 5-methoxy-2,3;3′,4′-bis(methylenedioxy)chalcone (**7k**) shows, instead of a pair of doublets, a 2H singlet at δ 7.66. Since this signal raised some doubt as to whether the assignment of a *trans* configuration to the chalcone (**7k**) was appropriate, the related chalcone (**7m**), in which the 2,3-methylenedioxy group of the questionable chalcone (**7k**) was replaced with two methoxy groups, was prepared from acetopiperone (**15**) and 2,3,5-trimethoxybenzaldehyde (**19k**). In the ^{1}H-NMR spectrum, the newly prepared chalcone (**7m**) clearly shows two doublets having *J* values of 16.0 Hz at δ 7.51 and 8.09, demonstrating a *trans* configuration. Comparison of the ultraviolet (UV) spectrum of the questionable chalcone (**7k**) with that of the newly prepared chalcone (**7m**) suggested the *trans* configuration for the questionable chalcone (**7k**). Therefore, the 2H singlet at δ 7.66 in the ^{1}H-NMR spectrum of the chalcone (**7k**) can reasonably be assigned to its olefinic protons. It is of interest that the signals of the α- and β-protons in an α,β-unsaturated ketone were observed at the same chemical shift in this case.

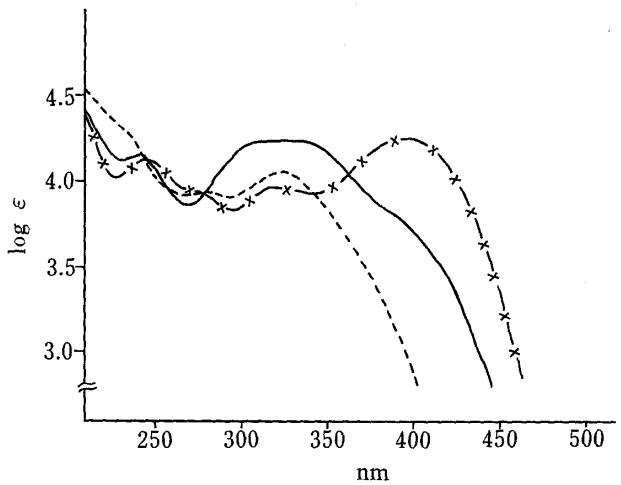


Fig. 1.

——, the 5-methoxy-2,3-methylenedioxychalcone (**7k**); – – – –, the 2,3,5-trimethoxychalcone (**7m**); —×—, the 2-methoxy-4,5-methylenedioxychalcone (**7e**).

The desired twelve 2,4-bisaryl-4-oxobutyronitriles (**8a**—**l**) were obtained by cyanation of these chalcones (**7a**—**l**) without any difficulty according to the reported procedure[6,8a,8b] in excellent yields.

In the Robinson synthetic sequence,[6,8a,8b,9] the 2,4-bisaryl-4-oxobutyronitriles (**8**) were hydrolyzed to the corresponding keto-amides (**9**) by treatment with mixed sulfuric and acetic acids. Similar treatment of the eleven keto-nitriles (**8a**—**k**) shown in Chart 5 according to the reported procedure[6,8a,8b] provided the desired 2,4-bisaryl-2-oxobutyramides (**9**). Syntheses of benzo[*c*]phenanthridine alkaloids from these keto-nitriles (**8**) or keto-amides (**9**) according to our modification of the Robinson synthetic pathway will be reported in subsequent papers.

Experimental

All melting points were measured on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. Infrared (IR) and UV spectra were recorded on a Hitachi EPI-G3 spectrometer (in Nujol) and on a Hitachi 340 spectrophotometer (as solutions in 95% ethanol), respectively. ^{1}H-NMR spectra[30] were recorded on a JEOL JNM-4H-100 spectrometer in deuteriochloroform, with tetramethylsilane as an internal reference. Mass spectra (MS) were measured on a Hitachi RMU-6E spectrometer at 70 eV chamber voltage with a direct inlet system. For chromatography (column), silicic acid (100 mesh), Mallinckrodt Chemical Works, Silica gel 60 (70—230 mesh ASTM), Merck, and aluminium oxide (neutral, grade I), Woelm, and for preparative thin layer chromatography (TLC), Silica gel GF_{254}, Merck, were used. All identification of products was done by IR and TLC comparisons, and by mixed melting point determination. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; br, broad; dif, diffused; sh, shoulder. The assignment of NH or OH signals was confirmed by disappearance of the signals after addition of deuterium oxide.

3,4-Methylenedioxyacetophenone (Acetopiperone) (15)——A solution of piperonal (**19a**) (9.98 g) in abs. Et_2O (60 ml) was added dropwise at 5 °C to a stirred solution of MeMgI prepared from MeI (11 ml) in abs. Et_2O (45 ml) and Mg metal (3.25 g). The mixture was allowed to stand at room temperature for 45 min. The resulting precipitate was collected by filtration, washed with abs. hexane, and then suspended in water. After addition of Et_2O, the suspension was clarified by addition of 20% NH_4Cl aq. and extracted with Et_2O. The ethereal layer was collected, washed with sat. NaCl aq., dried over K_2CO_3, and evaporated *in vacuo*. The oily residue [*ca.* 10.7 g; 1-(3,4-methylenedioxyphenyl)ethanol] was dissolved in acetone (300 ml). Jones reagent[31] (51 ml) was added to the stirred solution below 10 °C and stirring was then continued for a further 1 h. After decomposition of the excess reagent with MeOH, the mixture was poured into a large quantity of water and extracted with Et_2O. The ethereal solution was washed with 5% $NaHCO_3$ aq., dried over K_2CO_3, and evaporated to dryness *in vacuo*. Recrystallization of the residue from cyclohexane–Et_2O or benzene–hexane gave colorless prisms (8.99 g), mp 85—87 °C (lit. mp 85 °C;[6a] mp 86—87 °C;[7] mp 87 °C;[13] mp 84—85 °C[14]). IR ν_{max} cm^{-1}: 1665 (CO).

3,4-Dimethoxyacetophenone (Acetoveratrone) (16)——i) Methylation of Acetovanillone (**22**): A solution of commercial acetovanillone (**22**) (39.4 g) in 10% KOH aq. (150 ml) was heated at 55 °C and then Me_2SO_4 (30 ml) was added to the mixture for 5 min. The reaction was brought to completion by using additional 10% KOH aq. (270 ml) and Me_2SO_4 (44 ml), then the excess Me_2SO_4 was decomposed with 10% KOH aq. (330 ml). The mixture was extracted with Et_2O. The ethereal solution was dried over K_2CO_3 and evaporated to dryness. Distillation of the residue at 136—138 °C (4 mmHg) gave colorless prisms (36.9 g), mp 48—50 °C (lit.[15] mp 48—49 °C), which were recrystallized from Et_2O–hexane. IR ν_{max} cm^{-1}: 1665 (CO).

ii) Grignard Reaction of Veratraldehyde (**19b**) with Methyl Magnesium Iodide Followed by Jones Oxidation: A solution of MeMgI in abs. Et_2O was prepared by addition of a solution of MeI[32] (7.5 ml) in abs. Et_2O (50 ml) to Mg metal[32] (2.47 g). A solution of veratraldehyde (**19b**) (1.00 g) in abs. Et_2O[32] (50 ml) was added dropwise to the MeMgI solution at 5 °C with stirring. The mixture was stirred at room temperature for 45 min. The resulting precipitate was collected by filtration, washed with abs. hexane, and then suspended in water. After dilution with Et_2O, the suspension was clarified by addition of 20% NH_4Cl aq. and extracted with Et_2O. The ethereal layer was collected, dried over K_2CO_3, and evaporated *in vacuo*. The oily residue [*ca.* 0.91 g; 1-(3,4-dimethoxyphenyl)ethanol] was dissolved in acetone (18.3 ml). Jones reagent[31] (3.5 ml) was added to the stirred solution below 5 °C and stirring was then continued for a further 1 h at 5—10 °C. After decomposition of the excess reagent with MeOH, the mixture was poured into a large quantity of water and extracted with Et_2O. The ethereal solution was washed with 5% $NaHCO_3$ aq., dried over K_2CO_3, and evaporated to dryness *in vacuo*. Recrystallization of the residue from hexane–Et_2O gave colorless prisms (0.58 g), mp 44—47 °C, which were identical with a sample prepared by the above method.

3,5-Dimethoxybenzaldehyde (19c)——i) Methyl 3,5-Dimethoxybenzoate (**25**): A solution of 3,5-dihydroxybenzoic acid (**24**) (1.01 g) and Me_2SO_4 (4 ml) in acetone (20 ml) containing K_2CO_3 (5.02 g) was refluxed for 4 h. After removal of K_2CO_3 by filtration, the excess reagent was decomposed with conc. NH_4OH aq. The mixture was diluted

with a large quantity of water and extracted with Et_2O. The ethereal solution was washed with water, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. Recrystallization of the residue from MeOH–H_2O gave colorless pillars (1.16 g), mp 41 °C (lit. mp 42—44 °C[33a]; mp 41 °C[33b]).

ii) 3,5-Dimethoxybenzyl Alcohol (**26**): A suspension of $LiAlH_4$ (1.22 g) in abs. Et_2O (12.8 ml) was gradually added to a solution of the ester (**25**) (5.02 g) in abs. Et_2O (19.4 ml). The suspension was refluxed for 3 h. After decomposition of the excess of the $LiAlH_4$ with wet Et_2O followed by water, the ethereal layer was separated. The ethereal layer was dried over K_2CO_3 and evaporated to dryness *in vacuo* to give colorless needles (4.58 g), mp 48 °C (lit.[16] mp 47—48 °C).

iii) 3,5-Dimethoxybenzaldehyde (**19c**): A solution of the alcohol (**26**) (5.04 g) in CH_2Cl_2 (100 ml) was added to the complex prepared from CrO_3 (17.9 g) and pyridine (28.3 g) in CH_2Cl_2 (400 ml). The mixture was stirred at room temperature for 15 min. The precipitate was removed by decantation and washed with Et_2O. The organic layers were combined and diluted with Et_2O. After being washed with 5% NaOH aq., 5% HCl aq., 5% $NaHCO_3$ aq., and sat. NaCl aq. successively, the ethereal solution was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was chromatographed on Al_2O_3 with benzene to give colorless pillars (4.37 g), mp 46—47 °C (lit.[16] mp 45—46 °C).

3,4,5-Trimethoxybenzaldehyde (19d)——i) Methyl 3,4,5-Trimethoxybenzoate (**28**): A solution of gallic acid·H_2O (**27**) (29.9 g) in DMF (100 ml) was added to a suspension of K_2CO_3 (97 g) in DMF (200 ml) with vigorous stirring. Dimethyl sulfate (66 ml) was added dropwise to the above mixture at 20—25 °C. After completion of the addition, the mixture was stirred at room temperature for 2.5 h. The above procedure was repeated using a further amount of K_2CO_3 (44 g) and Me_2SO_4 (30 ml), then the reaction mixture was stirred at room temperature for a further 4.5 h, poured into water, and extracted with Et_2O. The ethereal solution was dried over K_2CO_3 and evaporated to dryness. Recrystallization of the residue from MeOH gave pale yellow prisms (32.7 g), mp 85—86 °C (lit.[34] mp 83—84 °C). IR ν_{max} cm^{-1}: 1710 (CO).

ii) 3,4,5-Trimethoxybenzyl Alcohol (**29**): A solution of the ester (**28**) (9.86 g) in abs. benzene (40 ml) was added dropwise to Vitride[19] (22 ml) under ice cooling. After the mixture had been stirred at room temperature for a further 1 h, the complex was decomposed with 25% H_2SO_4 aq. (290 ml). The benzene layer was separated from the aqueous layer, which was extracted with benzene. The organic layers were combined, washed with 5% $NaHCO_3$ aq., and then dried over $MgSO_4$. Evaporation of the benzene solution gave an oily product (7.84 g). IR ν_{max} cm^{-1}: 3500 (OH).

iii) 3,4,5-Trimethoxybenzaldehyde (**19d**): Pyridinium dichromate[21] [$(C_5H_5N^+H)_2 \cdot Cr_2O_7^{2+}$] (16.9 g) was added to a solution of the crude alcohol (**29**) (5.92 g) in dry CH_2Cl_2 (43 ml) at 18—19 °C with stirring. After stirring at room temperature for 3.5 h, further PDC (3.38 g) was added to the mixture and the whole was stirred at room temperature for 4 h. The reaction mixture was diluted with benzene and the diluted solution was filtered through a column packed with Celite 545 with the aid of an air-pump. Evaporation of the benzene filtrate under reduced pressure gave colorless prisms (5.74 g), mp 76—78 °C (lit.[18] mp 77 °C), which were recrystallized from benzene–hexane. IR ν_{max} cm^{-1}: 1680 (CO).

2-Methoxy-4,5-methylenedioxybenzaldehyde (19e)——Phosphorus oxychloride (26 ml) was added to a solution of *O*-methylsesamol[22] (**30**) (34.60 g), bp 110—115 °C (22 mmHg) [lit.[22] bp 110—114 °C (18 mmHg)], in DMF (67 ml) under ice cooling for 1.5 h. After the addition, the mixture was heated at 80 °C for 1 h with stirring, then cooled. Saturated AcONa aq. (170 ml) was added to the reaction mixture under ice cooling to give colorless needles (36.4 g), mp 115—117 °C (lit.[22] mp 111.5—112 °C), which were recrystallized from EtOH. IR ν_{max} cm^{-1}: 1650 (CO).

2,4,5-Trimethoxybenzaldehyde (19f)——Phosphorus oxychloride (5.5 ml) was added to a stirred solution of 1,2,4-trimethoxybenzene[24] (**31**) (8.42 g) in DMF (17 ml) under ice cooling. After the addition, the mixture was heated at 80 °C for 1 h with stirring, then cooled. Saturated AcONa aq. (30 ml) was added to the reaction mixture under ice cooling to give colorless needles (9.80 g), mp 114—115.5 °C (lit.[23] mp 114 °C), which were recrystallized from EtOH. IR ν_{max} cm^{-1}: 1660 (CO). ^{1}H-NMR δ: 3.83, 3.88, and 3.92 (each 3H, s, OCH_3), 6.44 and 7.26 (each 1H, s, C_3- and C_6-H), 10.23 (1H, s, CHO).

5-Methoxy-2,3-methylenedioxybenzaldehyde (19g)——A solution of EtBr (3.3 ml) in abs. Et_2O (12 ml) was added to a suspension of Li metal (0.40 g) in abs. Et_2O (13 ml) between −20 and −30 °C for 10 min with stirring. When the Li metal had completely dissolved, a solution of 5-methoxy-2,3-methylenedioxybromobenzene[26] (**32**) (5.10 g) in abs. Et_2O (15 ml) was added dropwise to the solution at −20——30 °C. The mixture was stirred at the same temperature for 1.4 h, then a mixed solution of DMF (19 ml) and abs. Et_2O (20 ml) was added and the reaction mixture was allowed to stand at room temperature for 2 h, poured into water, and extracted with Et_2O. The ethereal solution was dried over K_2CO_3 and evaporated to dryness.

A solution of $NaHSO_3$ (21.5 g) in water (33 ml) was added to the residue and the mixture was heated at 100 °C for 2 h to give the bisulfite compound as a precipitate. The precipitate was collected by filtration, washed with benzene, and dissolved in water (70 ml). The aqueous solution was made alkaline with 10% NaOH aq. (13 ml), heated at 100 °C for 30 min, then cooled. The resulting precipitate was collected by filtration and recrystallized from MeOH to give slightly yellow needles (2.62 g), mp 79—80 °C. *Anal.* Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 59.91; H, 4.37. IR ν_{max} cm^{-1}: 1685 (CO). ^{1}H-NMR δ: 3.79 (3H, s, OCH_3), 6.08 (2H, s, OCH_2O), 6.68 (2H, s, arom. H), 10.11 (1H, s, CHO).

4,5-Dibenzyloxy-2-methoxybenzaldehyde (19h)——i) 3,4-Dibenzyloxyphenol (**36**): A solution of 3,4-dibenzyl-

oxybenzaldehyde [28] (**34**) (70.0 g), mp 83—85 °C (lit.[28] mp 87.5—89 °C), in abs. $CHCl_3$ (150 ml) was added to a solution of *m*-chloroperbenzoic acid (45.5 g) in $CHCl_3$ (550 ml) under ice cooling. The mixture was allowed to stand at room temperature overnight and the excess of the peracid was decomposed with Na_2SO_3 (10.0 g). After removal of the precipitate by filtration, the filtrate was evaporated to dryness *in vacuo*. A solution of KOH (20.0 g) in MeOH (280 ml) was added to the residue. The mixture was stirred at room temperature for 2 h and then evaporated to dryness *in vacuo*. The residue was dissolved in water. After addition of an excess of dry ice, the aqueous solution was extracted with Et_2O. The ethereal solution was dried over $MgSO_4$ and evaporated to dryness. Recrystallization of the residue from benzene gave colorless needles (57.6 g), mp 111—112 °C (lit.[35] mp 110.5—111.5 °C), IR ν_{max} cm^{-1}: 3250 (OH).

ii) 3,4-Dibenzyloxyanisole (**38**): Dimethyl sulfate (111.4 ml) was added to a solution of 3,4-dibenzyloxyphenol (**36**) (68.2 g) in MeOH (120 ml). The mixture was stirred at 70—80 °C for 30 min and the pH of the reaction mixture was kept slightly alkaline by addition of 50% NaOH aq. (80 ml). After decomposition of the excess reagent with 50% NaOH aq. (50 ml), the mixture was extracted with Et_2O. The ethereal solution was washed with 5% NaOH aq., dried over K_2CO_3, and evaporated to dryness. Recrystallization of the residue from cyclohexane–hexane gave colorless needles (70.1 g), mp 55—57.5 °C. *Anal.* Calcd for $C_{21}H_{20}O_3$: C, 78.72; H, 6.29. Found: C, 78.92; H, 6.31. ^{1}H-NMR δ: 3.72 (3H, s, OCH_3), 5.07 and 5.12 (each 2H, s, OCH_2Ph), 6.34 (1H, dd, J=9.0 and 3.0 Hz, C_6-H), 6.55 (1H, d, J=3.0 Hz, C_2-H), 6.85 (1H, d, J=9.0 Hz, C_5-H), 7.40 (10H, dif. s, arom. H).

iii) 4,5-Dibenzyloxy-2-methoxybenzaldehyde (**19h**): Phosphorus oxychloride (3.8 ml) was added to dry DMF (13.6 ml) under ice cooling. The mixture was stirred at room temperature for 30 min, then cooled again to 0 °C. A solution of 3,4-dibenzyloxyanisole (**38**) (12.4 g) in dry DMF (10 ml) was added to the above solution below 10 °C, and the mixture was stirred at room temperature for 4 d and poured into ice-cooled saturated Na_2CO_3 aq. The resulting precipitate was collected by filtration. Recrystallization of the precipitate from cyclohexane gave colorless needles (12.9 g), mp 86—87 °C[36] (lit.[29] mp 69—70 °C). *Anal.* Calcd for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.76; H, 5.80. IR ν_{max} cm^{-1}: 1668 (CO). ^{1}H-NMR δ: 3.82 (3H, s, OCH_3), 5.11 and 5.24 (each 2H, s, OCH_2Ph), 6.52 (1H, s, C_3-H), 7.40 (11H, dif. s, arom. H), 10.22 (1H, s, CHO).

5-Benzyloxy-2,4-dimethoxybenzaldehyde (19i)——i) 4-Benzyloxy-3-methoxyphenol (**37**): Commercial hydrogen peroxide (35% in H_2O: 43.5 ml) was added to 85% HCOOH (180 ml) under ice cooling with stirring. The mixture was stirred at room temperature for 1 h. After addition of a solution of benzylvanillin (**35**) (75.0 g) in 98% HCOOH (200 ml) at 0 °C with stirring, the above solution was stirred at 0 °C for a further 3 h. After decomposition of the excess reagent with Na_2SO_3 (70 g), the mixture was poured onto ice and extracted with Et_2O. The ethereal solution was concentrated to *ca.* 500 ml and 5% NaOH aq. (550 ml) was added. The mixture was vigorously stirred at room temperature for 30 min. The aqueous solution was separated from ether and the ethereal solution was washed with 5% NaOH aq. The original 5% NaOH aq. solution and the washings were combined and acidified with 10% HCl aq. The resulting precipitate was collected by filtration. Recrystallization of the precipitate from Et_2O–hexane gave slightly brown needles (61.2 g), mp 87—88 °C (lit. mp 86—87 °C,[37a] mp 87 °C[37b]).

ii) 4-Benzyloxy-1,3-dimethoxybenzene (**39**): A 50% aqueous solution of NaOH (130 ml) was slowly added to a solution of 4-benzyloxy-3-methoxyphenol (**37**) (57.1 g) in MeOH (200 ml) containing Me_2SO_4 (71 ml) over a period of 1 h. The reaction proceeded exothermically with refluxing. After the addition, the mixture was refluxed for 40 min, poured into water, and extracted with Et_2O. The ethereal solution was washed with 10% NaOH aq., dried over K_2CO_3, and evaporated to dryness. Recrystallization of the residue from Et_2O–hexane gave colorless needles (57.8 g), mp 45—45.5 °C. *Anal.* Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.72; H, 6.65. ^{1}H-NMR δ: 3.73 and 3.84 (each 3H, s, OCH_3), 5.03 (2H, s, OCH_2Ph), 6.28 (1H, dd, J=9.0 and 3.0 Hz, C_6-H), 6.48 (1H, d, J=3.0 Hz, C_2-H), 6.76 (1H, d, J=9.0 Hz, C_5-H), 7.20—7.48 (5H, m, arom. H).

iii) 5-Benzyloxy-2,4-dimethoxybenzaldehyde (**19i**): A solution of $POCl_3$ (24 ml) in DMF (80 ml) was stirred at room temperature for 30 min. A solution of 4-benzyloxy-1,3-dimethoxybenzene (**39**) (57.8 g) in DMF (100 ml) was added to the above solution at room temperature. The mixture was heated at 55 °C for 6 h and poured into ice-cooled saturated Na_2CO_3 aq. The precipitate was collected by filtration. Recrystallization of the precipitate from benzene–hexane gave colorless fine needles (61.0 g), mp 103—104 °C. *Anal.* Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.43; H, 5.93. IR ν_{max} cm^{-1}: 1660 (CO). ^{1}H-NMR δ: 3.88 and 3.92 (each 3H, s, OCH_3), 5.05 (2H, s, OCH_2Ph), 6.45 (1H, s, C_3-H), 7.18—7.52 (6H, m, arom. H), 10.23 (1H, s, CHO).

2,3,5-Trimethoxybenzaldehyde (19k)——A solution of EtBr (24 ml) in abs. Et_2O (125 ml) was added to a suspension of Li metal (4.35 g) in abs. Et_2O (190 ml) between −20 and −30 °C over 10 min with stirring. After the Li metal had completely dissolved, a solution of 2,3,5-trimethoxybromobenzene[27] (**33**) (5.10 g) in abs. Et_2O (125 ml) was added dropwise to the above solution between −20 and −30 °C. After the mixture had been stirred at the same temperature for 1.4 h, a mixture of DMF (62.6 ml) and abs. Et_2O (190 ml) was added. The whole was stirred for 1 h, then poured into a large quantity of water. After Et_2O extraction, the ethereal solution was dried over K_2CO_3 and evaporated to dryness. Distillation of the residue at 140—148 °C (5 mmHg) gave colorless needles, mp 60—64 °C [lit. mp 71 °C;[25a] mp 61—62 °C;[25b] mp 63 °C[25c]].

General Method for Syntheses of Chalcone Derivatives (7)——Equivalent amounts of an acetophenone (**15** or **16**) and a benzaldehyde (**19**) were dissolved in a minimum amount of EtOH. The mixture was made alkaline with NaOH

aq. and allowed to stand at room temperature overnight. The precipitate was collected by filtration. Recrystallization from a suitable solvent gave the desired product.

3,4;3′,4′-Bis(methylenedioxy)chalcone (7a)——The general method was applied to a solution of acetopiperone (**15**) (0.50 g) and piperonal (**19a**) (0.46 g) in EtOH (8.2 ml) with 10% NaOH aq. (0.82 ml). Yellow needles (0.68 g), mp 177.5—178.5 °C (benzene–hexane) (lit.[9] mp 174 °C). IR ν_{max} cm^{-1}: 1670 (CO). ^{1}H-NMR (DMSO-d_6) δ: 6.09 and 6.14 (each 2H, s, OCH_2O), 6.95 (1H, d, J=8.5 Hz, $C_{5'}$-H), 7.05 (1H, d, J=8.0 Hz, C_5-H), 7.30 (1H, dd, J=8.0 and 2.0 Hz, C_6-H), 7.59 (1H, d, J=16.0 Hz, CH=CHCO), 7.63 and 7.66 (each 1H, d, J=2.0 Hz, C_2- and $C_{2'}$-H), 7.80 (1H, d, J=16.0 Hz, ArCH=CH), 7.84 (1H, dd, J=8.5 and 2.0 Hz, $C_{6'}$-H).

3,4-Dimethoxy-3′,4′-methylenedioxychalcone (7b)——The general method was applied to a solution of acetopiperone (**15**) (70.0 g) and veratraldehyde (**19b**) (78.0 g) in EtOH (350 ml) with 10% NaOH aq. (112 ml). Yellow prisms (122.2 g), mp 137—139 °C (benzene–hexane) (lit. mp 133—135 °C;[6a] mp 135 °C;[8a] mp 133—135 °C[8c]). IR ν_{max} cm^{-1}: 1640 (CO). ^{1}H-NMR δ: 3.91 and 3.94 (each 3H, s, OCH_3), 6.02 (2H, s, OCH_2O), 6.86 (2H, d, J=8.2 Hz, C_5- and $C_{5'}$-H), 7.13 (1H, dif. d, J=2.0 Hz, C_2-H), 7.19 (1H, d, J=8.2 Hz, C_6-H), 7.31 (1H, d, J=16.0 Hz, CH=CHCO), 7.54 (1H, dd, J=8.2 and 2.0 Hz, $C_{6'}$-H), 7.65 (1H, s, $C_{2'}$-H), 7.73 (1H, d, J=16.0 Hz, ArCH=CH).

3,5-Dimethoxy-3′,4′-methylenedioxychalcone (7c)——The general method was applied to a solution of acetopiperone (**15**) (19.8 g) and 3,5-dimethoxybenzaldehyde (**19c**) (20.0 g) in EtOH (300 ml) with 10% NaOH aq. (70 ml). Pale yellow pillars (27.9 g), mp 105—107 °C (EtOH). *Anal.* Calcd for $C_{18}H_{16}O_5$: C, 69.18; H, 5.17. Found: C, 69.22; H, 5.16. IR ν_{max} cm^{-1}: 1640 (CO) sh. ^{1}H-NMR δ: 3.84 (6H, s, $OCH_3\times2$), 6.04 (2H, s, OCH_2O), 6.48 (1H, t, J=2.0 Hz, C_4-H), 6.73 (2H, d, J=2.0 Hz, C_2- and C_6-H), 6.86 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.39 (1H, d, J=16.0 Hz, CH=CHCO), 7.48 (1H, d, J=1.5 Hz, $C_{2'}$-H), 7.61 (1H, dd, J=8.0 and 1.5 Hz, $C_{6'}$-H), 7.68 (1H, d, J=16.0 Hz, ArCH=CH).

3,4,5-Trimethoxy-3′,4′-methylenedioxychalcone (7d)——The general method was applied to a solution of acetopiperone (**15**) (8.4 g) and 3,4,5-trimethoxybenzaldehyde (**19d**) (10.0 g) in EtOH (140 ml) with 10% NaOH aq. (13.8 ml). Yellow needles (15.0 g), mp 154—156 °C (EtOH). *Anal.* Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.38; H, 5.23. IR ν_{max} cm^{-1}: 1665 (CO). ^{1}H-NMR δ: 3.88 (3H, s, OCH_3), 3.92 (6H, s, $OCH_3\times2$), 6.50 (2H, s, OCH_2O), 6.85 (2H, s, C_2- and C_6-H), 6.91 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.31 (1H, d, J=16.0 Hz, CH=CHCO), 7.52 (1H, d, J=1.5 Hz, $C_{2'}$-H), 7.63 (1H, dd, J=8.0 and 1.5 Hz, $C_{6'}$-H), 7.69 (1H, d, J=16.0 Hz, ArCH=CH).

2-Methoxy-4,5;3′,4′-bis(methylenedioxy)chalcone (7e)——The general method was applied to a solution of acetopiperone (**15**) (9.20 g) and 6-methoxypiperonal (**19e**) (10.0 g) in EtOH (150 ml) with 10% NaOH aq. (15 ml). Yellow needles (16.5 g), mp 205.5—206.5 °C (dioxane–EtOH). *Anal.* Calcd for $C_{18}H_{14}O_6$: C, 66.25; H, 4.32. Found: C, 66.13; H, 3.97. IR ν_{max} cm^{-1}: 1650 (CO). UV λ_{max} nm (log ε): 246 (4.12), 310 (4.01), 399 (4.28). ^{1}H-NMR δ: 3.82 (3H, s, OCH_3), 5.95 and 6.02 (each 2H, s, OCH_2O), 6.52 and 7.08 (each 1H, s, C_3- and C_6-H), 6.85 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.31 (1H, d, J=16.0 Hz, CH=CHCO), 7.49 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.61 (1H, dd, J=8.0 and 2.0 Hz, $C_{6'}$-H), 8.09 (1H, d, J=16.0 Hz, ArCH=CH).

4,5-Dibenzyloxy-2-methoxy-3′,4′-methylenedioxychalcone (7f)——The general method was applied to a solution of acetopiperone (**15**) (6.25 g) and 4,5-dibenzyloxy-2-methoxybenzaldehyde (**19h**) (13.3 g) in EtOH (68 ml) with 10% NaOH aq. (13.7 ml). Recrystallization of the crude product from a large quantity of MeOH or $CHCl_3$–hexane gave yellow needles (17.4 g), mp 118—119 °C. *Anal.* Calcd for $C_{31}H_{26}O_6$: C, 75.29; H, 5.30. Found: C, 75.35; H, 5.24. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1653 (CO). ^{1}H-NMR δ: 3.81 (3H, s, OCH_3), 5.12 and 5.21 (each 2H, s, OCH_2Ph), 6.04 (2H, s, OCH_2O), 6.54 (1H, s, C_3-H), 6.87 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.40 (12H, dif. s, CH=CHCO and arom. H), 7.48 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.58 (1H, dd, J=8.0 and 2.0 Hz, $C_{6'}$-H), 7.98 (1H, d, J=16.0 Hz, ArCH=CH).

5-Benzyloxy-2,4,3′,4′-tetramethoxychalcone (7g)——The general method was applied to a solution of acetoveratrone (**16**) (20.0 g) and 5-benzyloxy-2,4-dimethoxybenzaldehyde (**19i**) (30.0 g) in EtOH (100 ml) with 10% NaOH aq. (40 ml). Yellow prisms (43.5 g), mp 128—131 °C (EtOH). *Anal.* Calcd for $C_{26}H_{26}O_6$: C, 71.87; H, 6.03. Found: C, 71.66; H, 6.01. IR ν_{max} cm^{-1}: 1645 (CO). ^{1}H-NMR δ: 3.89 and 3.93 (each 3H, s, OCH_3), 3.96 (6H, s, $OCH_3\times2$), 5.10 (2H, s, OCH_2Ph), 6.50 (1H, s, C_3-H), 6.92 (1H, d, J=10.0 Hz, $C_{5'}$-H), 7.16—7.68 (9H, m, CH=CHCO and arom. H), 8.00 (1H, d, J=15.5 Hz, ArCH=CH).

2,3′,4′-Trimethoxy-4,5-methylenedioxychalcone (7h)——The general method was applied to a solution of acetoveratrone (**16**) (26.7 g) and 6-methoxypiperonal (**19e**) (26.8 g) in EtOH (350 ml) with 10% NaOH aq. (55 ml). Yellow needles (44.0 g), mp 173—174 °C (MeOH–$CHCl_3$). *Anal.* Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.68; H, 5.34. IR ν_{max} cm^{-1}: 1650 (CO). ^{1}H-NMR δ: 3.84 (3H, s, OCH_3), 3.96 (6H, s, $OCH_3\times2$), 5.94 (2H, s, OCH_2O), 6.52 and 7.10 (each 1H, s, C_3- and C_6-H), 6.90 (1H, d, J=8.5 Hz, $C_{5'}$-H), 7.38 (1H, d, J=16.0 Hz, CH=CHCO), 7.59 (1H, s, $C_{2'}$-H), 7.64 (1H, dd, J=8.5 and 2.0 Hz, $C_{6'}$-H), 8.10 (1H, d, J=16.0 Hz, ArCH=CH).

2,3′,4,4′,5-Pentamethoxychalcone (7i)——The general method was applied to a solution of acetoveratrone (**16**) (4.68 g) and 2,4,5-trimethoxybenzaldehyde (**19f**) (5.08 g) in EtOH (40 ml) with 10% NaOH aq. (12 ml). Yellow needles (8.24 g), mp 145—147 °C (EtOH). *Anal.* Calcd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 67.03; H, 6.21. IR ν_{max} cm^{-1}: 1645 (CO). ^{1}H-NMR δ: 3.89 (9H, s, $OCH_3\times3$), 3.95 (6H, s, $OCH_3\times2$), 6.48 and 7.10 (each 1H, s, C_3- and C_6-H), 6.89 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.44 (1H, d, J=16.0 Hz, CH=CHCO), 7.56—7.72 (2H, m, arom. H), 8.03 (1H, d, J=16.0 Hz, ArCH=CH).

2-Bromo-6-methoxy-3,4;3′,4′-bis(methylenedioxy)chalcone (7j)——The general method was applied to a solution

of acetopiperone (**15**) (15.7 g) and 2-bromo-6-methoxy-3,4-methylenedioxybenzaldehyde[26] (**19j**) (25.0 g) in EtOH (2500 ml) with 10% NaOH aq. (250 ml). Yellow needles (25.4 g), mp 188—190 °C ($CHCl_3$–hexane). *Anal.* Calcd for $C_{18}H_{13}BrO_6$: C, 53.36; H, 3.23. Found: C, 53.38; H, 3.22. IR ν_{max} cm^{-1}: 1655 (CO). ^{1}H-NMR δ: 3.91 (3H, s, OCH_3), 6.00 and 6.04 (each 2H, s, OCH_2O), 6.56 (1H, s, C_3-H), 6.88 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.53 (1H, d, J=1.0 Hz, $C_{2'}$-H), 7.64 (1H, dd, J=8.0 and 1.0 Hz, $C_{6'}$-H), 7.90 (1H, d, J=15.0 Hz, CH=CHCO), 8.05 (1H, d, J=15.0 Hz, ArCH=CH).

5-Methoxy-2,3;3′,4′-bis(methylenedioxy)chalcone (7k)——The general method was applied to a solution of acetopiperone (**15**) (7.50 g) and 5-methoxy-2,3-methylenedioxybenzaldehyde (**19g**) (9.85 g) in EtOH (90 ml) with 30% KOH aq. (15 ml). In this case, after the reaction was completed, dilution of the reaction mixture with a large amount of water was required. Yellow needles (13.9 g), mp 130—131 °C (benzene). *Anal.* Calcd for $C_{18}H_{14}O_6$: C, 66.25; H, 4.32. Found: C, 66.19; H, 4.36. IR ν_{max} cm^{-1}: 1644 (CO). ^{1}H-NMR δ: 3.79 (3H, s, OCH_3), 6.05 and 6.07 (each 2H, s, OCH_2O), 6.40 and 6.54 (each 1H, d, J=2.5 Hz, C_4- and C_6-H), 6.89 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.54 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.65 (1H, dd, J=8.0 and 2.0 Hz, $C_{6'}$-H), 7.66 (2H, s, ArCH=CHCO).

2,4,5-Trimethoxy-3′,4′-methylenedioxychalcone (7l)——The general method was applied to a solution of acetopiperone (**15**) (16.8 g) and 2,4,5-trimethoxybenzaldehyde (**19f**) (20.0 g) in EtOH (300 ml) with 10% NaOH aq. (37.0 ml). Yellow prisms (29.8 g), mp 112—114 °C (benzene–hexane). *Anal.* Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.70; H, 5.25. IR ν_{max} cm^{-1}: 1650 (CO). ^{1}H-NMR δ: 3.86 (6H, s, $OCH_3\times2$), 3.91 (3H, s, OCH_3), 6.00 (2H, s, OCH_2O), 6.47 and 7.07 (each 1H, s, C_3- and C_6-H), 6.82 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.36 (1H, d, J=16.0 Hz, CH=CHCO), 7.46 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.58 (1H, dd, J=8.0 and 2.0 Hz, $C_{6'}$-H), 8.01 (1H, d, J=16.0 Hz, ArCH=CH).

2,3,5-Trimethoxy-3′,4′-methylenedioxychalcone (7m)——The general method was applied to a solution of acetopiperone (**15**) (0.13 g) and 2,3,5-trimethoxybenzaldehyde (**19k**) (0.15 g) in EtOH (2.2 ml) with 10% NaOH aq. (0.34 ml). Yellow needles (0.228 g), mp 127—128 °C (benzene–hexane). *Anal.* Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.71; H, 5.33. IR ν_{max} cm^{-1}: 1655 (CO). ^{1}H-NMR[38] δ: 3.86 (6H, s, $OCH_3\times2$), 3.88 (3H, s, OCH_3), 6.59 and 6.73 (each 1H, d, J=3.0 Hz, C_4- and C_6-H), 6.91 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.51 (1H, d, J=16.0 Hz, CH=CHCO), 7.54 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.67 (1H, dd, J=8.0 and 2.0 Hz, $C_{6'}$-H), 8.09 (1H, d, J=16.0 Hz, ArCH=CH).

General Method for Hydrocyanation of the Chalcone (7) [2,4-Bisaryl-4-oxobutyronitrile (8)]——The starting chalcone (**7**) was dissolved in a minimum amount of hot ethyl cellosolve ($EtOCH_2CH_2OH$) containing AcOH. An aqueous solution of KCN was added to the mixture at about 120 °C. The mixture was heated at the same temperature with monitoring by TLC, and finally poured into a large amount of water. The precipitate was collected by filtration and recrystallized from a suitable solvent.

2,4-Bis(3,4-methylenedioxyphenyl)-4-oxobutyronitrile (8a)——The general method was applied to a solution of the chalcone (**7a**) (11.0 g) in ethyl cellosolve (77 ml) containing AcOH (2.8 ml) with a solution of KCN (5.50 g) in H_2O (9.9 ml). The reaction time was 15 min. Slightly brown needles (11.0 g), mp 142—143 °C (EtOH) (lit.[9] mp 141 °C). IR ν_{max} cm^{-1}: 2260 (CN), 1670 (CO). ^{1}H-NMR δ: 3.34 and 3.63 (each 1H, dd, J=17.5 and 7.0 Hz, $CHCH_2CO$), 4.45 (1H, t, J=7.0 Hz, $ArCHCH_2$), 5.96 and 6.04 (each 2H, s, OCH_2O), 6.70—6.94 (4H, m, arom. H), 7.38 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.48 (1H, dd, J=8.0 and 2.0 Hz, $C_{6'}$-H).

2-(3,4-Dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyronitrile (8b)——The general method was applied to a solution of the chalcone (**7b**) (50.0 g) in ethyl cellosolve (200 ml) containing AcOH (11 ml) with a solution of KCN (23.5 g) in H_2O (75 ml). The reaction time was 20 min. Colorless leaflets (50.8 g), mp 146—148 °C (MeOH–$CHCl_3$) (lit. mp 144—146 °C;[6a] mp 146 °C,[8a] mp 145—146 °C[8b]). IR ν_{max} cm^{-1}: 2240 (CN), 1670 (CO). ^{1}H-NMR δ: 3.37 and 3.64 (each 1H, dd, J=17.0 and 7.0 Hz, $CHCH_2CO$), 3.86 and 3.89 (each 3H, s, OCH_3), 4.48 (1H, t, J=7.0 Hz, $ArCHCH_2$), 6.01 (2H, s, OCH_2O), 6.81 (2H, d, J=8.0 Hz, C_5- and $C_{5'}$-H), 6.90 (1H, s, C_2-H), 6.96 and 7.47 (each 1H, dd, J=8.0 and 2.0 Hz, C_6- and $C_{6'}$-H), 7.37 (1H, d, J=2.0 Hz, $C_{2'}$-H).

2-(3,5-Dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyronitrile (8c)——The general method was applied to a solution of the chalcone (**7c**) (9.7 g) in ethyl cellosolve (75 ml) containing AcOH (3.04 ml) with a solution of KCN (4.58 g) in H_2O (12 ml). The reaction time was 15 min. Pale yellow plates (8.85 g), mp 81—84 °C (EtOH). *Anal.* Calcd for $C_{19}H_{17}NO_5$: C, 67.26; H, 5.03; N, 4.09. Found: C, 67.25; H, 5.05; N, 4.13. IR ν_{max} cm^{-1}: 2235 (CN), 1660 (CO). ^{1}H-NMR δ: 3.36 (1H, dd, J=18.0 and 7.0 Hz, $CHCH_AH_BCO$), 3.63 (1H, dd, J=18.0 and 8.0 Hz, $CHCH_AH_BCO$), 3.81 (6H, s, $OCH_3\times2$), 4.46 (1H, dd, J=8.0 and 7.0 Hz, $ArCHCH_2$), 6.03 (2H, s, OCH_2O), 6.37 (1H, t, J=1.5 Hz, C_4-H), 6.52 (2H, d, J=1.5 Hz, C_2- and C_6-H), 6.82 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.38 (1H, d, J=1.5 Hz, $C_{2'}$-H), 7.47 (1H, dd, J=8.0 and 1.5 Hz, $C_{6'}$-H).

4-(3,4-Methylenedioxyphenyl)-4-oxo-2-(3,4,5-trimethoxyphenyl)butyronitrile (8d)——The general method was applied to a solution of the chalcone (**7d**) (10.0 g) in ethyl cellosolve (70 ml) containing AcOH (2.6 ml) with a solution of KCN (4.4 g) in H_2O (small amount). The reaction time was 15 min. Colorless needles (8.3 g), mp 132—134 °C (EtOH or EtOH–$CHCl_3$). *Anal.* Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.19; N, 3.79. Found: C, 64.91; H, 5.19; N, 3.79. IR ν_{max} cm^{-1}: 2240 (CN), 1680 (CO). ^{1}H-NMR δ: 3.35 and 3.63 (each 1H, dd, J=17.5 and 6.5 Hz, $CHCH_2CO$), 3.80 (3H, s, OCH_3), 3.85 (6H, s, $OCH_3\times2$), 4.47 (1H, t, J=6.5 Hz, $ArCHCH_2$), 6.02 (2H, s, OCH_2O), 6.59 (2H, s, C_2- and C_6-H), 6.82 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.38 (1H, d, J=1.5 Hz, $C_{2'}$-H), 7.49 (1H, dd, J=8.0 and 1.5 Hz, $C_{6'}$-H).

2-(2-Methoxy-4,5-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyronitrile (8e)——The general method was applied to a solution of the chalcone (**7e**) (18.6 g) in ethyl cellosolve (450 ml) containing AcOH (3.9 ml) with a solution of KCN (7.45 g) in H_2O (30 ml). The reaction time was 15 min. Colorless prisms (18.2 g), mp 130—133.5 °C (EtOH–$CHCl_3$). *Anal.* Calcd for $C_{19}H_{15}NO_6$: C, 64.58; H, 4.28; N, 3.96. Found: C, 64.74; H, 4.37; N, 3.96. IR ν_{max} cm^{-1}: 2250 (CN), 1670 (CO). ^{1}H-NMR δ: 3.32 (1H, dd, J=17.5 and 7.5 Hz, $CHC\underline{H}_A\underline{H}_BCO$), 3.54 (1H, dd, J=17.5 and 10.0 Hz, $CHCH_A\underline{H}_BCO$), 3.80 (3H, s, OCH_3), 4.64 (1H, dd, J=10.0 and 7.5 Hz, $ArC\underline{H}CH_2$), 5.93 and 6.04 (each 2H, s, OCH_2O), 6.53 and 6.93 (each 1H, s, C_3- and C_6-H), 6.82 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.41 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.52 (1H, dd, J=8.0 and 2.0 Hz, $C_{6'}$-H).

2-(4,5-Dibenzyloxy-2-methoxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyronitrile (8f)——The general method was applied to a solution of the chalcone (**7f**) (0.90 g) in ethyl cellosolve (12 ml) containing AcOH (0.5 ml) with a solution of KCN (1.40 g) in H_2O (2.7 ml). The reaction time was 30 min. Colorless needles (0.70 g), mp 133—134 °C (EtOH). *Anal.* Calcd for $C_{31}H_{27}NO_6$: C, 73.69; H, 5.22; N, 2.69. Found: C, 73.63; H, 5.19; N, 2.56. IR ν_{max} cm^{-1}: 2230 (CN), 1672 (CO). ^{1}H-NMR δ: 3.25 (1H, dd, J=18.0 and 6.0 Hz, $CHC\underline{H}_A\underline{H}_BCO$), 3.48 (1H, dd, J=18.0 and 9.0 Hz, $CHCH_A\underline{H}_BCO$), 3.75 (3H, s, OCH_3), 4.60 (1H, dd, J=9.0 and 6.0 Hz, $ArC\underline{H}CH_2$), 5.09 and 5.14 (each 2H, s, OCH_2Ph), 6.02 (2H, s, OCH_2O), 6.53 and 7.06 (each 1H, s, C_3- and C_6-H), 6.80 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.39 (12H, dif. s, arom. H).

2-(5-Benzyloxy-2,4-dimethoxyphenyl)-4-(3,4-dimethoxyphenyl)-4-oxobutyronitrile (8g)——The general method was applied to a solution of the chalcone (**7g**) (40.5 g) in ethyl cellosolve (150 ml) containing AcOH (6.5 ml) with a solution of KCN (14.1 g) in H_2O (40 ml). The reaction time was 40 min. Colorless cotton-like needles (38.1 g), mp 105—108 °C (EtOH). *Anal.* Calcd for $C_{27}H_{27}NO_6$: C, 70.27; H, 5.90; N, 3.04. Found: C, 70.53; H, 5.93; N, 3.04. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240 (CN), 1670 (CO). ^{1}H-NMR δ: 3.32 (1H, dd, J=17.5 and 6.0 Hz, $CHC\underline{H}_A\underline{H}_BCO$), 3.54 (1H, dd, J=17.5 and 8.0 Hz, $CHCH_A\underline{H}_BCO$), 3.81, 3.85, 3.88, and 3.91 (each 3H, s, OCH_3), 4.62 (1H, dd, J=8.0 and 6.0 Hz, $ArC\underline{H}CH_2$), 5.04 (2H, s, OCH_2Ph), 6.49 and 7.02 (each 1H, s, C_3- and C_6-H), 6.83 (1H, d, J=9.0 Hz, $C_{5'}$-H), 7.22—7.60 (7H, m, arom. H).

4-(3,4-Dimethoxyphenyl)-2-(2-methoxy-4,5-methylenedioxyphenyl)-4-oxobutyronitrile (8h)——The general method was applied to a solution of the chalcone (**7h**) (44.0 g) in ethyl cellosolve (600 ml) containing AcOH (8.8 ml) with a solution of KCN (16.7 g) in H_2O (40 ml). The reaction time was 2 h. Colorless needles (43.8 g), mp 156—158 °C. *Anal.* Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.19; N, 3.79. Found: C, 64.77; H, 5.21; N, 3.91. IR ν_{max} cm^{-1}: 2250 (CN), 1665 (CO). ^{1}H-NMR δ: 3.37 (1H, dd, J=18.0 and 6.0 Hz, $CHC\underline{H}_A\underline{H}_BCO$), 3.59 (1H, dd, J=18.0 and 7.5 Hz, $CHCH_A\underline{H}_BCO$), 3.79, 3.90, and 3.92 (each 3H, s, OCH_3), 4.64 (1H, dd, J=7.5 and 6.0 Hz, $ArC\underline{H}CH_2$), 5.88 (2H, s, OCH_2O), 6.49 and 6.92 (each 1H, s, C_3- and C_6-H), 6.84 (1H, d, J=8.5 Hz, $C_{5'}$-H), 7.47 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.48 (1H, dd, J=8.5 and 2.0 Hz, $C_{6'}$-H).

4-(3,4-Dimethoxyphenyl)-4-oxo-2-(2,4,5-trimethoxyphenyl)butyronitrile (8i)——The general method was applied to a solution of the chalcone (**7i**) (7.47 g) in ethyl cellosolve (30 ml) containing AcOH (1.44 ml) with a solution of KCN (2.71 g) in H_2O (10 ml). The reaction time was 50 min. Slightly brown needles (7.02 g), mp 154—156 °C (EtOH–$CHCl_3$). *Anal.* Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.07; H, 6.00, N, 3.55. IR ν_{max} cm^{-1}: 2250 (CN), 1680 (CO). ^{1}H-NMR δ: 3.40 (1H, dd, J=17.0 and 6.0 Hz, $CHC\underline{H}_A\underline{H}_BCO$), 3.62 (1H, dd, J=17.0 and 8.0 Hz, $CHCH_A\underline{H}_BCO$), 3.84, 3.86, 3.89, 3.91, and 3.93 (each 3H, s, OCH_3), 4.68 (1H, dd, J=8.0 and 6.0 Hz, $ArC\underline{H}CH_2$), 6.54 and 7.01 (each 1H, s, C_3- and C_6-H), 6.87 (1H, d, J=9.0 Hz, $C_{5'}$-H), 7.51 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.52 (1H, dd, J=9.0 and 2.0 Hz, $C_{6'}$-H).

2-(2-Bromo-6-methoxy-3,4-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyronitrile (8j)——The general method was applied to a solution of the chalcone (**7j**) (10.0 g) in ethyl cellosolve (100 ml) containing AcOH (2.2 ml) with a solution of KCN (4.40 g) in H_2O (8 ml). The reaction time was 30 min. Colorless needles (10.0 g), mp 144—146 °C (MeOH–benzene). *Anal.* Calcd for $C_{19}H_{14}BrNO_6$: C, 52.79; H, 3.26; N, 3.24. Found: C, 53.03; H, 3.12; N, 3.49. IR ν_{max} cm^{-1}: 2250 (CN), 1682 (CO). ^{1}H-NMR δ: 3.25 (1H, dd, J=18.0 and 6.0 Hz, $CHC\underline{H}_A\underline{H}_BCO$), 3.90 (1H, dd, J=18.0 and 9.0 Hz, $CHCH_A\underline{H}_BCO$), 3.90 (3H, s, OCH_3), 5.06 (1H, dd, J=9.0 and 6.0 Hz, $ArC\underline{H}CH_2$), 6.00 and 6.04 (each 2H, s, OCH_2O), 6.55 (1H, s, C_5-H), 6.84 (1H, d, J=9.0 Hz, $C_{5'}$-H), 7.44 (1H, d, J=1.5 Hz, $C_{2'}$-H), 7.55 (1H, dd, J=9.0 and 1.5 Hz, $C_{6'}$-H).

2-(5-Methoxy-2,3-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyronitrile (8k)——The general method was applied to a solution of the chalcone (**7k**) (5.35 g) in ethyl cellosolve (18.7 ml) containing AcOH (1.1 ml) with a solution of KCN (2.13 g) in H_2O (7.7 ml). The reaction time was 2 h. Purification of the crude material by column chromatography on Al_2O_3 using benzene as a solvent followed by recrystallization from MeOH gave colorless prisms (4.51 g), mp 104—107 °C. *Anal.* Calcd for $C_{19}H_{15}NO_6$: C, 64.58; H, 4.28; N, 3.96. Found: C, 64.31; H, 4.30; N, 3.90. IR ν_{max} cm^{-1}: 2245 (CN), 1680 (CO). ^{1}H-NMR δ: 3.46 (1H, dd, J=18.0 and 7.0 Hz, $CHC\underline{H}_A\underline{H}_BCO$), 3.68 (1H, dd, J=18.0 and 7.5 Hz, $CHCH_A\underline{H}_BCO$), 3.77 (3H, s, OCH_3), 4.54 (1H, dd, J=7.5 and 7.0 Hz, $ArC\underline{H}CH_2$), 5.95 and 6.04 (each 2H, s, OCH_2O), 6.43, 6.45, and 7.43 (each 1H, d, J=2.0 Hz, C_4-, C_6-, and $C_{2'}$-H), 6.85 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.54 (1H, dd, J=8.0 and 2.0 Hz, $C_{6'}$-H).

4-(3,4-Methylenedioxyphenyl)-4-oxo-2-(2,4,5-trimethoxyphenyl)butyronitrile (8l)——The general method was applied to a solution of the chalcone (**7l**) (22.2 g) in ethyl cellosolve (88 ml) containing AcOH (4.4 ml) with a solution of KCN (8.4 g) in H_2O (22 ml). The reaction time was 1 h. Colorless prisms (19.7 g), mp 164—165 °C (MeOH–

$CHCl_3$). *Anal.* Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.19; N, 3.79. Found: C, 65.12; H, 5.23; N, 3.76. IR ν_{max} cm^{-1}: 2260 (CN), 1680 (CO). ^{1}H-NMR δ: 3.35 (1H, dd, J=17.5 and 6.0 Hz, $CHC\underline{H}_A\underline{H}_BCO$), 3.58 (1H, dd, J=17.5 and 8.0 Hz, $CHCH_A\underline{H}_BCO$), 3.85, 3.87, and 3.90 (each 3H, s, OCH_3), 4.66 (1H, dd, J=8.0 and 6.0 Hz, $ArC\underline{H}CH_2$), 6.02 (2H, s, OCH_2O), 6.53 and 6.99 (each 1H, s, C_3- and C_6-H), 6.82 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.40 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.51 (1H, dd, J=8.0 and 2.0 Hz, $C_{6'}$-H).

General Method for Syntheses of the Keto-Amides (9) from the Keto-Nitriles (8)——Mixed acid [conc. H_2SO_4–AcOH (1 : 3, v/v)] was added dropwise to a solution or suspension of the keto-nitrile (**8**) in AcOH at room temperature. The mixture was stirred at room temperature for 20—30 min, then poured into a large quantity of water. The precipitate was collected by filtration and recrystallized from a suitable solvent to give the desired keto-amide (**9**).

2,4-Bis(3,4-methylenedioxyphenyl)-4-oxobutyramide (9a)——The general method was applied to a solution of the keto-nitrile (**8a**) (5.00 g) in AcOH (80 ml) with the mixed acid (6.8 ml). Colorless prisms (5.10 g), mp 169—171 °C (EtOH) (lit.[9] mp 164 °C). IR ν_{max} cm^{-1}: 3470, 3230 (NH_2), 1670, 1650 (CO). ^{1}H-NMR (DMSO-d_6) δ: 3.04 (1H, dd, J=17.0 and 4.0 Hz, $CHC\underline{H}_A\underline{H}_BCO$), 3.60—4.10 (2H, m, $ArC\underline{H}CH_A\underline{H}_BCO$), 5.96 and 6.10 (each 2H, s, OCH_2O), 6.75 (1H, br s, $N\underline{H}$(H)), 6.82 (2H, s, arom. H), 6.95 (1H, s, arom. H), 7.01 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.42 (1H, br s, $N\underline{H}$(H)), 7.44 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.64 (1H, dd, J=8.0 and 2.0 Hz, $C_{6'}$-H).

2-(3,4-Dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyramide (9b)——The general method was applied to a solution of the keto-nitrile (**8b**) (1.00 g) in AcOH (25 ml) with the mixed acid (1.89 ml). Colorless needles (1.11 g), mp 188—190 °C (EtOH–$CHCl_3$) (lit. mp 177 °C;[8a] mp 178—180 °C[6a,8b]). IR ν_{max} cm^{-1}: 3420, 3180 (NH_2), 1685, 1645 (CO). ^{1}H-NMR δ: 3.09 (1H, dd, J=17.0 and 4.5 Hz, $CHC\underline{H}_A\underline{H}_BCO$), 3.73—4.06[39] (1H, m, $CHCH_A\underline{H}_BCO$), 3.83 and 3.85 (each 3H, s, OCH_3), 4.17 (1H, dd, J=8.5 and 4.5 Hz, $ArC\underline{H}CH_2$), 5.53 (2H, br s, NH_2), 5.97 (2H, s, OCH_2O), 6.70—6.96 (4H, m, arom. H), 7.40 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.56 (1H, dd, J=8.5 and 2.0 Hz, $C_{6'}$-H).

2-(3,5-Dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyramide (9c)——The general method was applied to a solution of the keto-nitrile (**8c**) (12.0 g) in AcOH (83 ml). In this experiment, instead of the mixed acid, conc. H_2SO_4 (12 ml) was used. Colorless plates (9.97 g), mp 200—202 °C (EtOH). *Anal.* Calcd for $C_{19}H_{19}NO_6$: C, 64.14; H, 5.39; N, 3.84. Found: C, 63.86; H, 5.36; N, 3.92. IR ν_{max} cm^{-1}: 3420, 3190 (NH_2), 1680sh, 1640 (CO). ^{1}H-NMR (DMSO-d_6) δ: 2.60—3.20 (1H, m $CHC\underline{H}_A\underline{H}_BCO$), 3.75—4.10 (2H, m, $ArC\underline{H}CH_A\underline{H}_BCO$), 3.75 (6H, s, $OCH_3\times2$), 6.08 (2H, s, OCH_2O), 6.28 (1H, t, J=2.0 Hz, C_4-H), 6.52 (2H, d, J=2.0 Hz, C_2- and C_6-H), 6.66 and 7.31 (each 1H, dif. s, NH_2), 6.91 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.48 (1H, d, J=1.0 Hz, $C_{2'}$-H), 7.52 (1H, dd, J=8.0 and 1.0 Hz, $C_{6'}$-H).

4-(3,4-Methylenedioxyphenyl)-4-oxo-2-(3,4,5-trimethoxyphenyl)butyramide (9d)——The general method was applied to a solution of the keto-nitrile (**8d**) (28.2 g) in AcOH (200 ml) with the mixed acid (17 ml). Colorless needles (28.4 g), mp 202—203 °C (EtOH or $CHCl_3$–MeOH). *Anal.* Calcd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62. Found: C, 61.96; H, 5.51; N, 3.64. IR ν_{max} cm^{-1}: 3400, 3160 (NH_2), 1680, 1645 (CO). ^{1}H-NMR δ: 3.08 (1H, dd, J=16.3 and 3.8 Hz, $CHC\underline{H}_A\underline{H}_BCO$), 3.81 (3H, s, OCH_3), 3.83 (6H, s, $OCH_3\times2$), 3.75—4.25 (2H, m, $ArC\underline{H}CH_A\underline{H}_BCO$), 5.63 (2H, br s, NH_2), 6.01 (2H, s, OCH_2O), 6.58 (2H, s, C_2- and C_6-H), 6.82 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.42 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.58 (1H, dd, J=8.0 and 2.0 Hz, $C_{6'}$-H).

2-(2-Methoxy-4,5-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyramide (9e)——The general method was applied to a solution of the keto-nitrile (**8e**) (16.1 g) in AcOH (140 ml) with the mixed acid (10 ml). Recrystallization of the crude product from MeOH–$CHCl_3$ gave pure crystals (15.1 g). The dimorphism of this compound, colorless needles, mp 120—125 °C, and colorless prisms, mp 177—179 °C, was confirmed by a cross-seeding experiment. *Anal.* Calcd for $C_{19}H_{17}NO_7 \cdot 1/3CHCl_3$: C, 56.48; H, 4.25; N, 3.41. Found: C, 56.28; H, 4.08; N, 3.30. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540, 3425 (NH_2), 1680 (CO). ^{1}H-NMR δ: 3.06 (1H, dd, J=18.0 and 4.4 Hz, $CHC\underline{H}_A\underline{H}_BCO$), 3.81 (3H, s, OCH_3), 3.90 (1H, dd, J=18.0 and 8.0 Hz, $CHCH_A\underline{H}_BCO$), 4.56 (1H, dd, J=8.0 and 4.4 Hz, $ArC\underline{H}CH_2$), 5.30 and 5.85 (each 1H, m, NH_2), 5.89 and 6.01 (each 2H, s, OCH_2O), 6.53 (1H, s, C_3-H), 6.81 (1H, d, J=8.0 Hz, $C_{5'}$-H), 6.84 (1H, s, C_6-H), 7.44 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.60 (1H, dd, J=8.0 and 2.0 Hz, $C_{6'}$-H).

2-(4,5-Dibenzyloxy-2-methoxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyramide (9f)——The general method was applied to a solution of the keto-nitrile (**8f**) (0.25 g) in AcOH (2.5 ml) with the mixed acid (0.5 ml). Colorless plates (0.26 g), mp 165.5—167 °C (EtOH). *Anal.* Calcd for $C_{32}H_{29}NO_7$: C, 71.23; H, 5.42; N, 2.60. Found: C, 71.26; H, 5.42; N, 2.56. IR ν_{max} cm^{-1}: 3450, 3240, 3190 (NH_2), 1679, 1650 (CO). ^{1}H-NMR δ: 2.94 (1H, dd, J=16.5 and 5.0 Hz, $CHC\underline{H}_A\underline{H}_BCO$), 3.77 (3H, s, OCH_3), 3.85 (1H, dd, J=16.5 and 9.0 Hz, $CHCH_A\underline{H}_BCO$), 4.52 (1H, dd, J=9.0 and 5.0 Hz, $ArC\underline{H}CH_2$), 5.07 and 5.14 (each 2H, s, OCH_2Ph), 5.30 and 5.75 (each 1H, br s, NH_2), 6.01 (2H, s, OCH_2O), 6.55 (1H, s, C_3-H), 6.81 (1H, d, J=8.0 Hz, $C_{5'}$-H), 6.92 (1H, s, C_6-H), 7.40 (11H, dif. s, arom. H), 7.55 (1H, dd, J=8.0 and 2.0 Hz, $C_{6'}$-H).

2-(5-Benzyloxy-2,4-dimethoxyphenyl)-4-(3,4-dimethoxyphenyl)-4-oxobutyramide (9g)——The general method was applied to a solution of the keto-nitrile (**8g**) (25.1 g) in AcOH (260 ml) with the mixed acid (12 ml). Colorless cotton-like needles (24.5 g), mp 142—144 °C (EtOH). *Anal.* Calcd for $C_{27}H_{29}NO_7$: C, 67.63; H, 6.10; N, 2.92. Found: C, 67.24; H, 6.07; N, 2.88. IR ν_{max} cm^{-1}: 3450, 3375, 3225 (NH_2), 1660 (CO). ^{1}H-NMR δ: 3.03 (1H, dd, J=17.0 and 5.0 Hz, $CHC\underline{H}_A\underline{H}_BCO$), 3.72—4.08[39] (1H, m, $CHCH_A\underline{H}_BCO$), 3.84, 3.86, 3.88, and 3.92 (each 3H, s, OCH_3), 4.54 (1H, dd, J=9.0 and 5.0 Hz, $ArC\underline{H}CH_2$), 5.03 (2H, s, OCH_2Ph), 5.32 and 5.74 (each 1H, br s, NH_2), 6.51 (1H, s, C_3-H), 6.84 (1H, d, J=8.0 Hz, $C_{5'}$-H), 6.90 (1H, s, C_6-H), 7.20—7.68 (7H, m, arom. H).

4-(3,4-Dimethoxyphenyl)-2-(2-methoxy-4,5-methylenedioxyphenyl)-4-oxobutyramide (9h)——The general method was applied to a solution of the keto-nitrile (**8h**) (3.41 g) in AcOH (80 ml) with the mixed acid (1.9 ml). The collected precipitate was dissolved in $CHCl_3$, and the solution was washed with sat. $NaHCO_3$ aq., dried over K_2CO_3, and evaporated to dryness *in vacuo*. Recrystallization of the residue from MeOH–$CHCl_3$ gave colorless needles (3.55 g), mp 188—190 °C. *Anal.* Calcd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62. Found: C, 61.87; H, 5.47; N, 3.58. IR ν_{max} cm^{-1}: 3500, 3370 (NH_2), 1660 (CO). ^{1}H-NMR δ: 3.12 (1H, dd, J=18.0 and 5.0 Hz, $CHCH_AH_BCO$), 3.80, 3.88, and 3.91 (each 3H, s, OCH_3), 3.72—4.06[39] (1H, m, $CHCH_AH_BCO$), 4.57 (1H, dd, J=9.0 and 5.0 Hz, $ArCHCH_2$), 5.44 and 5.85 (each 1H, br s, NH_2), 5.85 (2H, s, OCH_2O), 6.51 (1H, s, C_3-H), 6.83 (1H, s, C_6-H), 6.84 (1H, d, J=8.5 Hz, $C_{5'}$-H), 7.48 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.62 (1H, dd, J=8.5 and 2.0 Hz, $C_{6'}$-H).

4-(3,4-Dimethoxyphenyl)-4-oxo-2-(2,4,5-trimethoxyphenyl)butyramide (9i)——The general method was applied to a solution of the keto-nitrile (**8i**) (7.02 g) in AcOH (180 ml) with the mixed acid (3.9 ml). Colorless cotton-like needles (6.80 g), mp 186—188 °C (EtOH–$CHCl_3$). *Anal.* Calcd for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.23; H, 6.27; N, 3.44. IR ν_{max} cm^{-1}: 3455, 3350, 3240 (NH_2), 1670 (CO). ^{1}H-NMR δ: 3.14 (1H, dd, J=17.0 and 6.0 Hz, $CHCH_AH_BCO$), 3.56—4.12[39] (1H, m, $CHCH_AH_BCO$), 3.79, 3.82, 3.85, 3.87, and 3.90 (each 3H, s, OCH_3), 4.58 (1H, dd, J=9.0 and 6.0 Hz, $ArCHCH_2$), 5.44 and 5.80 (each 1H, br s, NH_2), 6.49 (1H, s, C_3-H), 6.83 (1H, d, J=9.0 Hz, $C_{5'}$-H), 6.86 (1H, s, C_6-H), 7.47 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.60 (1H, dd, J=9.0 and 2.0 Hz, $C_{6'}$-H).

2-(2-Bromo-6-methoxy-3,4-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyramide (9j)——The general method was applied to a solution of the keto-nitrile (**8j**) (10.0 g) in AcOH (50 ml). In this experiment, instead of the mixed acid, conc. H_2SO_4 (5 ml) was used. The reaction time was 5 min. Colorless needles (8.99 g), mp 228—230 °C (dec.) ($CHCl_3$–hexane). *Anal.* Calcd for $C_{19}H_{16}BrNO_7$: C, 50.68; H, 3.58; N, 3.11. Found: C, 50.36; H, 3.59; N, 3.04. IR ν_{max} cm^{-1}: 3490, 3375 (NH_2), 1690, 1680 (CO). ^{1}H-NMR (CF_3COOH) δ: 3.50 (1H, dd, J=17.0 and 5.0 Hz, $CHCH_AH_BCO$), 3.88 (3H, s, OCH_3), 4.18 (1H, dd, J=17.0 and 8.0 Hz, $CHCH_AH_BCO$), 5.14 (1H, dd, J=8.0 and 5.0 Hz, $ArCHCH_2$), 6.05 and 6.09 (each 2H, s, OCH_2O), 6.66 (1H, s, C_3-H), 6.95 (1H, d, J=9.0 Hz, $C_{5'}$-H), 7.51 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.76 (1H, dd, J=9.0 and 2.0 Hz, $C_{6'}$-H). MS m/z: 451 (M^++2, 102.8% of M^+), 449 (M^+, 11.2%), 149 (100%).

2-(5-Methoxy-2,3-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyramide (9k)——The general method was applied to a solution of the keto-nitrile (**8k**) (4.51 g) in AcOH (36 ml) with the mixed acid (18 ml). Colorless prisms (3.47 g), mp 212 °C (EtOH). *Anal.* Calcd for $C_{19}H_{17}NO_7$: C, 61.45; H, 4.61; N, 3.77. Found: C, 61.31; H, 4.55; N, 3.66. IR ν_{max} cm^{-1}: 3425, 3200 (NH_2), 1667, 1690sh (CO). ^{1}H-NMR[40] (CF_3COOH) δ: 3.98 (3H, s, OCH_3), 3.74 (1H, dd, J=17.0 and 5.5 Hz, $CHCH_AH_BCO$), 4.16 (1H, dd, J=17.0 and 8.2 Hz, $CHCH_AH_BCO$), 4.62 (1H, dd, J=8.2 and 5.5 Hz, $ArCHCH_2$), 6.04 and 6.10 (each 2H, s, OCH_2O), 6.62 and 6.68 (each 1H, d, J=2.5 Hz, C_4- and C_6-H), 6.97 (1H, d, J=8.5 Hz, $C_{5'}$-H), 7.53 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.80 (1H, dd, J=8.5 and 2.0 Hz, $C_{6'}$-H).

References and Notes

1) This work was presented in part at the 16th Symposium on the Chemistry of Natural Products, Osaka, October 1972 [H. Ishii, T. Deushi, and K.-I. Harada, Symposium Papers, p. 327] and in part at the 9th Congress of Heterocyclic Chemistry, Fukuoka, October 1976 [H. Ishii, T. Deushi, K.-I. Harada, M. Sakamoto, K. Nakajima, E. Ueda, T. Ishida, and T. Ishikawa, Abstracts of Papers, p. 136]; Part XLVIII; H. Ishii, T. Ishikawa, M. Mihara, and M. Akaike, *Yakugaku Zasshi*, **103**, 279 (1983).
2) For a review of the chemistry of these alkaloids, see R. H. F. Manske, "The Alkaloids," Vol. 4, ed. by R. H. F. Manske, Academic Press, New York·London, 1954, p. 253; R. H. F. Manske, *ibid.*, Vol. 7, 1959, p. 430; R. H. F. Manske, *ibid.*, Vol. 10, 1968, p. 485; F. Šantavý, *ibid.*, Vol. 12, 1970, p. 417; V. Preininger, *ibid.*, Vol. 15, 1975, p. 241; F. Šantavý, *ibid.*, Vol. 17, 1979, p. 493; H. Ishii and T. Ishikawa, *Yakugaku Zasshi*, **101**, 663 (1981).
3) M. E. Wall, M. C. Wani, and Y. L. Taylor, Abstracts, 162nd National Meeting of the American Chemical Society, Washington D. C., Sept. 1971, MEDI 34; Abstracts of the Third International Congress of Heterocyclic Chemistry: B, Sendai, Japan, 1971, p. 29.
4) W. M. Messmer, M. Tin-Wa, H. H. S. Fong, C. Bevelle, N. R. Farnsworth, D. J. Abraham, and J. Trojánek, *J. Pharm. Sci.*, **61**, 1858 (1972); M. Tin-Wa, C. L. Bell, C. Bevelle, H. H. S. Fong, and N. R. Farnsworth, *ibid.*, **63**, 1476 (1974).
5) F. R. Stermitz, K. A. Larson, and D. K. Kim, *J. Med. Chem.*, **16**, 939 (1973); F. R. Stermitz, J. P. Gillespie, L. G. Amoros, R. Romero, T. A. Stermitz, K. A. Larson, S. Earl, and J. E. Ogg, *ibid.*, **18**, 708 (1975).
6) *a*) T. Richardson, R. Robinson, and E. Seijo, *J. Chem. Soc.*, **1937**, 835; *b*) A. S. Bailey, R. Robinson, and R. S. Staunton, *ibid.*, **1950**, 2277.
7) A. S. Bailey and C. R. Worthing, *J. Chem. Soc.*, **1956**, 4535.
8) *a*) H. R. Arthur and Y. L. Ng, *J. Chem. Soc.*, **1959**, 4010; *b*) K. W. Gopinath, T. R. Govindachari, P. C. Parthasarathy, and N. Viswanathan, *ibid.*, **1959**, 4012; *c*) T. Kametani, K. Kigasawa, M. Hiiragi, and O. Kusama, *J. Heterocycl. Chem.*, **10**, 31 (1973); *d*) K.-Y. Zee-Cheng and C. C. Cheng, *ibid.*, **10**, 85 (1973).

9) K. W. Gopinath, T. R. Govindachari, and N. Viswanathan, *Tetrahedron*, **14**, 322 (1961).
10) E. Mameli, *Gazz. Chim. Ital.*, **34I**, 360, 372; **34II**, 170 (1904) [*Beilstein*, **19**, 69 (1934)].
11) M. Béhal, *Bull. Soc. Chim. Fr.*, **25**, 275 (1901) [*Beilstein*, **19**, 69 (1934)].
12) E. Mameli, *Gazz. Chim. Ital.*, **34II**, 177 (1904) [*Beilstein*, **19**, 69 (1934)].
13) A. Klages, *Chem. Ber.*, **36**, 3584 (1903).
14) K. W. Gopinath, T. R. Govindachari, K. Nagarajan, and N. Viswanathan, *J. Chem. Soc.*, **1957**, 4760.
15) E. Neitzel, *Chem. Ber.*, **24**, 2863 (1891).
16) F. Mauthner, *J. Prakt. Chem.*, **100**, 176 (1920); F. Mauthner, *J. Chem. Soc.*, **120**, I, 32 (1921); R. Adams, S. MacKenzie, Jr., and S. Loewe, *J. Am. Chem. Soc.*, **70**, 664 (1948); R. Adams, M. Harfenist, and L. Loewe, *ibid.*, **71**, 1624 (1949).
17) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, **1968**, 3363; R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970); E. J. Corey and W. Suggs, *Tetrahedron Lett.*, **1975**, 2647.
18) A. Heffter and R. Capellmann., *Chem. Ber.*, **38**, 3634 (1905).
19) A 70% solution of sodium bis(2-methoxyethoxy)aluminium hydride [$NaAlH_2(OCH_2CH_2OCH_3)_2$] in benzene: Eastman Kodak Co., Ltd.
20) We also tried the oxidation of the alcohol (**29**) with Jones reagent. In the case of PDC, the desired benzaldehyde (**19d**) was obtained almost quantitatively, but in the case of Jones reagent, the yield of the desired product (**19d**) was decreased to 82.5% due to over-oxidation. For the oxidation of benzyl alcohols to the corresponding benzaldehydes, PDC is almost always the preferred reagent in our experience.
21) E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, **1979**, 399.
22) K. Fukui and M. Nakayama, *Nippon Kagaku Zasshi*, **84**, 606 (1963).
23) L. Gattermann and F. Eggers, *Chem. Ber.*, **32**, 289 (1899).
24) E. Hardegger, K. Steiner, E. Widmer, H. Corrodi, Th. Schmidt, H. P. Knoepfel, W. Rieder, H. J. Meyer, F. Kugler, and H. Gempeler, *Helv. Chim. Acta*, **47**, 1996 (1964).
25) *a*) L. E. Smith and F. B. LaForge, *J. Am. Chem. Soc.*, **53**, 3072 (1931); *b*) J. R. Merchant, R. M. Naik, and A. J. Mountwalla, *J. Chem. Soc.*, **1957**, 4142; *c*) W. Baker, N. C. Brown, and J. A. Scott, *ibid.*, **1939**, 1922.
26) H. Ishii, E. Ueda, K. Nakajima, T. Ishida, T. Ishikawa, K.-I. Harada, I. Ninomiya, T. Naito, and T. Kiguchi, *Chem. Pharm. Bull.*, **26**, 864 (1978).
27) H. W. Dorn, W. H. Warren, and J. L. Bullock, *J. Am. Chem. Soc.*, **61**, 144 (1939).
28) K. Kametani and S. Kano, *Yakugaku Zasshi*, **72**, 1081 (1952).
29) J. Daly, L. Horner, and B. Witkop, *J. Am. Chem. Soc.*, **83**, 4787 (1961). Their reaction sequence involves an unsatisfactory step as regards yield [demethylenation of 2-methoxy-4,5-methylenedioxybenzaldehyde (53.2%)].
30) The numberings used in the assignment of ^{1}H-NMR signals of the chalcones (**7**), the keto-nitriles (**8**), and the keto-amides (**9**) are as follows:

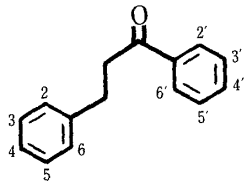


Chart 6

31) Jones reagent was prepared by the addition of conc. H_2SO_4 (61 ml) to a solution of CrO_3 (70 g) in H_2O (500 ml).
32) Dilution and a large excess of MeMgI were absolutely necessary. Otherwise, the starting material (**19b**) was recovered as a co-precipitate with the resulting Grignard complex.
33) *a*) J. Herzig and S. Epstein, *Monatsh. Chem.*, **29**, 661 (1908); *b*) C. Bülow and G. Riess, *Chem. Ber.*, **35**, 3900 (1902).
34) F. W. Semmler, *Chem. Ber.*, **41**, 1768 (1908).
35) M. Wenke, V. Trcka, L. Blaha, J. Hodrova, and J. Weichet, Czech. Patent 131157 (1969) [*Chem. Abstr.*, **72**, P111007*p* (1970)].
36) This substance melted at 69—70 °C and solidified again.
37) *a*) A. Paulsen, *Medd. Norsk. Farm. Selskap*, **22**, 11 (1959) [*Chem. Abstr.*, **55**, 3499*a* (1961)]; *b*) T. B. H. McMurry and C. Y. Theng, *J. Chem. Soc.*, **1960**, 1491.
38) This ^{1}H-NMR spectrum was recorded on a Hitachi R-24B machine (60 MHz) in $CDCl_3$.
39) The precise splitting pattern of this signal could not be observed because of overlapping with the signals due to a methoxy group.
40) This material is sparingly soluble in various solvents. CF_3COOH had to be used as a solvent for the ^{1}H-NMR measurement. However, this material gradually decomposed in the solvent.