[Chem. Pharm. Bull.
31(9)3039—3055(1983)]

Studies on the Chemical Constituents of Rutaceous Plants. L.[1]) Development of a Versatile Method for the Synthesis of Antitumor-Active Benzo[*c*]phenanthridine Alkaloids. (2).[1]) Preparation of 2-Aryl-1-tetralone Derivatives

HISASHI ISHII,* ERI KAWANABE, KEN-ICHI HARADA, TAKEO DEUSHI,
ETSUKO UEDA, TOSHIKO WATANABE, YUH-ICHIRO ICHIKAWA,
MITSUGI SAKAMOTO, TOSHIAKI ISHIDA, TSUTOMU TAKAHASHI
(deceased), KEIKO NAKAJIMA,
and TSUTOMU ISHIKAWA

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

(Received January 14, 1983)

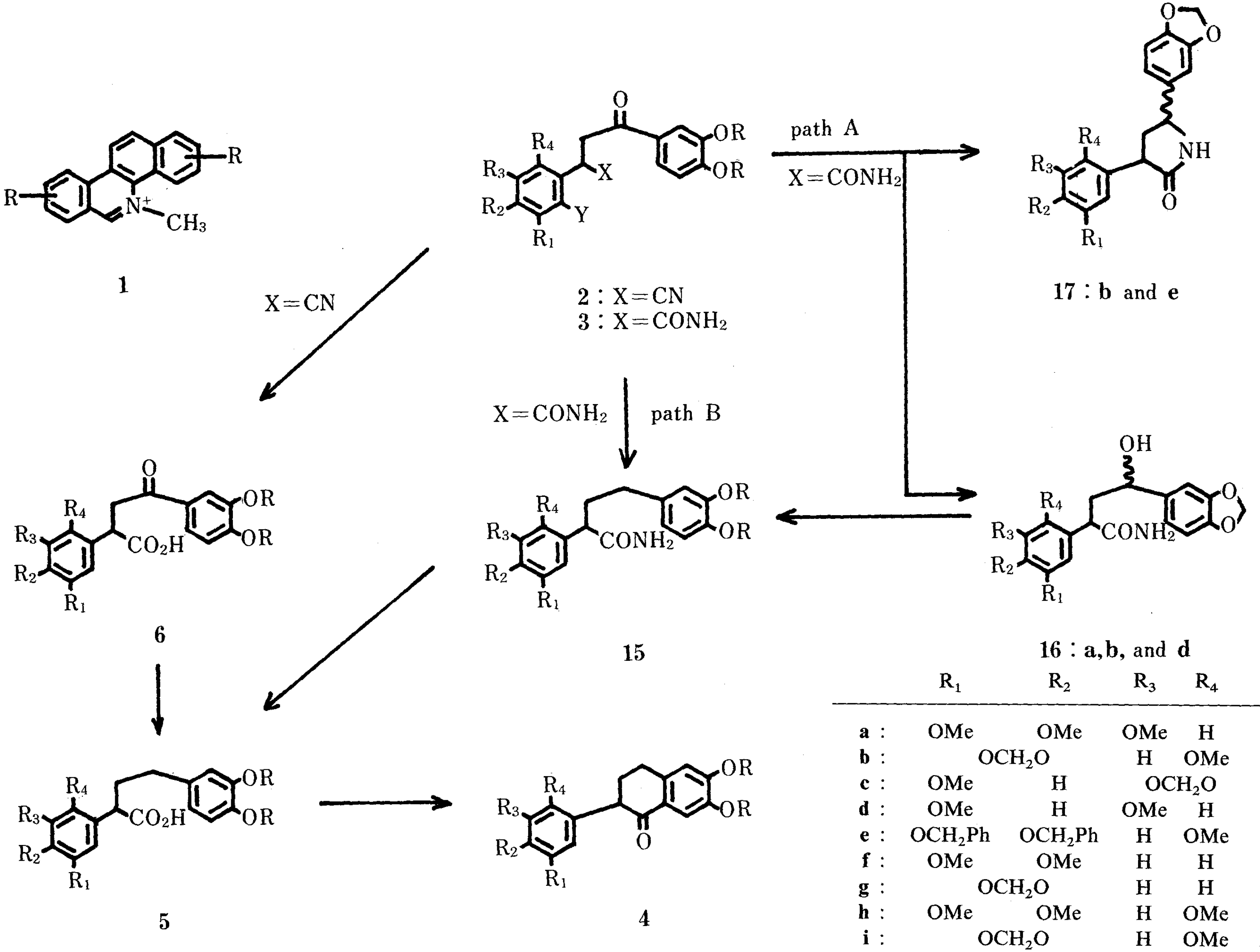
The synthetic pathway from 2,4-bisaryl-4-oxobutyramide (3) to 2-aryl-1-tetralone (4), which is the key intermediate in the Robinson synthesis of antitumor-active benzo[*c*]phenanthridine alkaloids was improved. Treatment of the model keto-amide (3a) under the reported basic conditions gave a γ-keto-α,β-unsaturated acid (9) and degradation products. Reduction of the 2,4-bisaryl-4-oxobutyramide (3) with sodium borohydride gave 2,4-bisaryl-4-hydroxybutyramide (16), which could easily be hydrogenolyzed to give 2,4-bisarylbutyramide (15). However, this transformation also tended to give a γ-lactam derivative (17), unfortunately. We succeeded in the direct hydrogenolysis of the 2,4-bisaryl-4-oxobutyramide (3) to the 2,4-bisarylbutyramide (15), which could be hydrolyzed to the corresponding acid (5) without difficulty. The direct hydrolysis of the 2,4-bisaryl-4-oxobutyronitrile (2) to the 2,4-bisaryl-4-oxobutyric acid (6) as reported by Cheng *et al.* was also examined. Ten 2-aryl-1-tetralones (4) required as starting materials for syntheses of various benzo[*c*]phenanthridine alkaloids were prepared.

Keywords——Robinson method improved; benzo[*c*]phenanthridine alkaloid; 2,4-bisaryl-4-oxobutyramide; 2,4-bisaryl-4-oxobutyric acid; 2,4-bisarylbutyric acid; 2-aryl-1-tetralone

It is well known that the Robinson synthetic sequence[2]) is a useful preparative method for benzo[*c*]phenanthridine alkaloids[3]) (1), including some showing antileukemic activity.[4]) In the preceding paper,[1b]) we reported syntheses of a number of 2,4-bisaryl-4-oxobutyronitriles (keto-nitriles) (2) and 2,4-bisaryl-4-oxobutyramides (keto-amides) (3), which are suitable starting materials for 2-aryl-1-tetralones (tetralones) (4), the key intermediates, *via* 2,4-bisarylbutyric acids (methylene-acids) (5). Treatment of these compounds (2 and 3) according to the Robinson synthetic method should give useful benzo[*c*]phenanthridine alkaloids and related compounds relevant to studies on the establishment of the structure of O_5-benzo[*c*]phenanthridine alkaloids and on the structure–activity relationship for antileukemic activity. In this report we describe our attempts to improve the synthetic sequence from the keto-amides (3) to the methylene-acids (5), and the syntheses of several tetralones (4).

Historically, Robinson *et al.*[2a]) hydrolyzed the keto-nitriles (2) by way of the keto-amides (3) to the corresponding 2,4-bisaryl-4-oxobutyric acids (keto-acids) (6) by treatment with mixed sulfuric and acetic acids followed by sodium hydroxide in aqueous ethanol. Then, the resulting keto-acids (6) were transformed into the desired methylene-acids (5) by Clemmensen reduction.

In our studies aimed at the development of a versatile synthetic method for antitumor-



	R_1	R_2	R_3	R_4	Y	2R
a :	OMe	OMe	OMe	H	H	CH_2
b :	OCH_2O		H	OMe	H	CH_2
c :	OMe	H	OCH_2O		H	CH_2
d :	OMe	H	OMe	H	H	CH_2
e :	OCH_2Ph	OCH_2Ph	H	OMe	H	CH_2
f :	OMe	OMe	H	H	H	CH_2
g :	OCH_2O		H	H	H	CH_2
h :	OMe	OMe	H	OMe	H	Me Me
i :	OCH_2O		H	OMe	H	Me Me
j :	OCH_2Ph	OMe	H	OMe	H	Me Me
k :	OCH_2O		H	OMe	Br	CH_2
l :	OMe	OMe	H	OMe	H	CH_2

Chart 1

active benzo[*c*]phenanthridine alkaloids, we used a trimethoxy derivative as a model compound for establishment of the reaction conditions in each step. In preliminary examination of the hydrolysis, we occasionally found that treatment of the keto-amide (**3a**) with a solution of sodium hydroxide in aqueous ethanol unexpectedly gave acetopiperone (**7**) and a mixture of several species of acid derivatives. Direct separation of the acid mixture by column chromatography on silica gel gave the desired keto-acid (**6a**) in only 44.7% yield along with the 3,4,5-trimethoxybenzoic acid (**8**) and an unexpected acid (**9**). Next, in order to examine the acid components of the reaction mixture in more detail, the crude acid portion of the reaction mixture was methylated by treatment with dimethyl sulfate and potassium carbonate in acetone. In this experiment, we obtained a minute amount of an additional acid (**10**) which remained unesterified on esterification, as well as three esters (**11**, **12**, and **13**) corresponding to the above three acids (**6a**, **8**, and **9**).

The molecular formula of the fourth acid (**10**) was established to be $C_{11}H_{12}O_6$ based on elemental analysis. In the infrared (IR) spectrum, this acid (**10**) shows carbonyl bands at 1755 and 1730 cm^{-1}. In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, three methoxy signals were observed at δ 3.90 and at δ 3.92 as 6H and 3H singlets. In addition, two aromatic protons appeared as a 2H singlet at δ 7.40. These data indicate that this product is 3,4,5-trimethoxyphenylglyoxylic acid$^{5)}$ (**10**).

The unexpected acid (**9**) gave elemental analyses in agreement with the molecular formula $C_{20}H_{18}O_8 \cdot 1/3C_6H_6$. In the ^{1}H-NMR spectrum, the acid (**9**) shows no aliphatic proton. In the ultraviolet (UV) spectrum, the acid (**9**) shows a characteristic absorption at 324 nm (log ε: 4.00). These data indicate the presence of an ene–dione system in the molecule. This observation suggested that a double bond was inserted between a γ-ketonic group and an amide function of the starting keto-amide (**3a**) by air-oxidation under basic conditions. In other words, the unexpected acid could be a γ-keto-α,β-unsaturated acid$^{6)}$ (**9**). This assumption was also supported by the observations that, when the hydrolysis of the keto-amide (**3a**) was carried out under argon, the yield of the desired keto-acid (**6a**) increased to 62.2%, while the yield became very poor when air was bubbled through the reaction mixture, as shown in Table I.

For the formation of the unsaturated keto-acid (**9**) from the starting keto-amide (**3a**), two possible pathways were envisaged. First, hydrolysis of the keto-amide (**3a**) might initially take place in the normal way and the resulting saturated keto-acid (**6a**) might undergo air-oxidation at the subsequent reaction stage to give the unsaturated keto-acid (**9**). However, this possibility was immediately ruled out by the fact that treatment of the saturated keto-acid (**6a**) in ethanolic sodium hydroxide solution with bubbling of air through the reaction mixture resulted in recovery of the starting material (**6a**) quantitatively. Therefore, we may assume

Table I. Hydrolysis of 4-(3,4-Methylenedioxyphenyl)-4-oxo-2-(3,4,5-trimethoxyphenyl)butyramide (**3a**) with Aqueous Ethanolic NaOH Solution (7% NaOH aq.: EtOH = 1 : 1)

Condition	Yields (%)			
	The keto-acid (**6a**)	The α,β-unsaturated γ-keto-acid (**9**)	Acetopiperone (**7**)	3,4,5-Trimethoxybenzoic acid (**8**)
In open apparatus	44.7	18.5	16.0	13.6
Under argon	62.2	+ (On TLC)	+ (On TLC)	—
With bubbling air	5.2	37.1	22.3	20.0

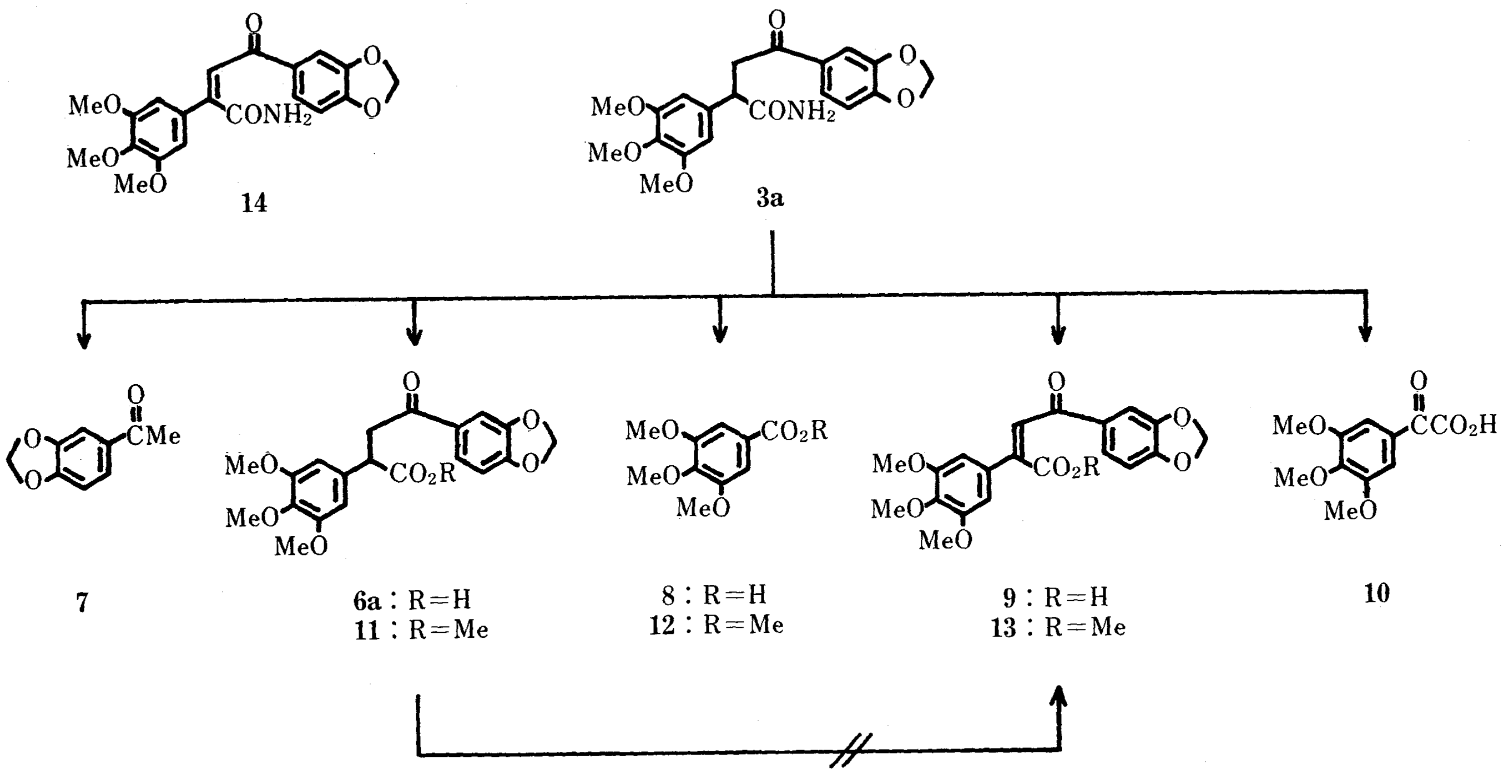


Chart 2

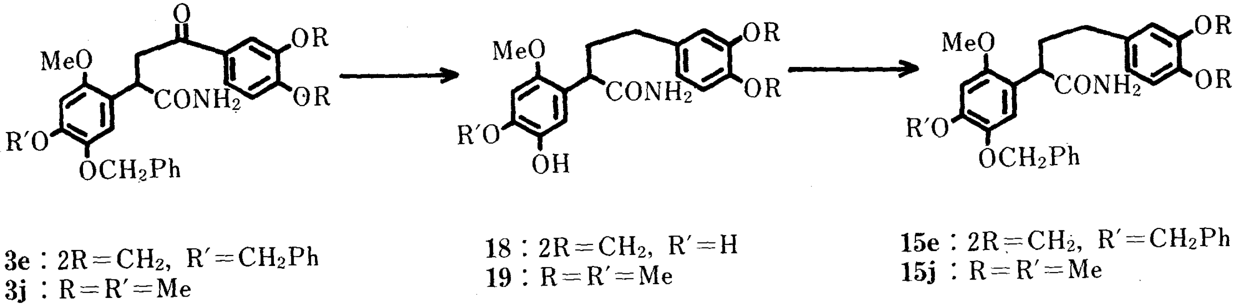


Chart 3

that hydrolysis of the keto-amide (**6a**) must be preceded by air-oxidation to the trimethoxy-γ-keto-α,β-unsaturated amide[6] (unsaturated keto-amide) (**14**).

Consequently, this observation led us to conclude that our results on the hydrolysis[7] of the keto-amide (**3a**) under basic conditions were explicable by supposing that hydrolysis of the keto-amide competed with air-oxidation at the initial stage of the reaction. Then, retro-aldol condensation of the resulting unsaturated keto-amide (**14**) provided acetopiperone (**7**) and 3,4,5-trimethoxyphenylglyoxylic acid (**10**). Since Mauthner[5] reported that 3,4,5-trimethoxyphenylglyoxylic acid (**10**) was converted into 3,4,5-trimethoxybenzoic acid (**8**) by treatment with base, the presence of the latter (**8**) in our reaction mixture is accounted for.

Since, in addition, hydrolysis of some other keto-amides (**3**) gave reaction mixtures, which showed no evidence for the formation of the corresponding saturated keto-acids (**6**) even on thin-layer chromatography (TLC), it seemed that hydrolysis of the keto-amide (**3**) under basic conditions might have a narrow applicability for synthesis of the methylene-acid (**5**). These observations stimulated us to improve the reaction sequence from the keto-amide (**3**) to the methylene-acid (**5**) in the Robinson method.

Initially, we aimed at converting the keto-amide (**3**) into the methylene-amide (**15**) by hydrogenolysis of the keto-amide (**3**). However, when commercial 10% palladium-carbon was used as a catalyst, the hydrogenolysis of the keto-amides (**3**) took a long time or resulted in recovery of the starting materials (**3**). Therefore, we attempted to reduce the keto-amides (**3**) to the corresponding alcohols (hydroxy-amides) (**16**), which would be expected to be more labile on hydrogenolysis. On examination of the reduction of the keto-amide (**3**) with sodium borohydride, two keto-amides (**3a** and **3d**) provided only the desired hydroxy-amides (**16a** and **16d**) as diastereomeric mixtures. However, in the case of the keto-amide (**3b**), the desired hydroxy-amide (**16b**) was obtained as a sole product in a relatively small-scale operation. In the large-scale operation, however, a relatively small amount of a diastereomeric mixture of the undesired cyclized product (**17b**) was isolated in addition to a diastereomeric mixture of the desired hydroxy-amide (**16b**) as the main product. Hydrogenolysis of these hydroxy-amides (**16a**, **16b**, and **16d**) on commercial palladium-charcoal proceeded smoothly to give the desired methylene-amides (**15a**, **15b**, and **15d**). Moreover, reduction of the keto-amide (**3e**) with sodium borohydride gave only a diastereomeric mixture of the undesired γ-lactams (**17e**) which was separable into the epimeric components (*trans*- or *cis*-**17e**). These results indicate that the hydroxy-amides (**16**) tend to cyclize to form a diastereomeric mixture of the undesired γ-lactams (**17**) during post-treatment of the reaction mixture, depending upon the species of the starting keto-amide (**3**) and the scale of operation. Further, even when only a desired hydroxy-amide (**16**) was obtained as the sole product, in several cases, difficulty was found in purifying the desired product because of the formation of a diastereomeric mixture by induction of an extra chiral center at the site of the newly formed secondary alcohol.

In the course of examination of catalytic reduction of the keto-amide (**3**), we incidentally found that catalytic hydrogenation of a solution of the keto-amide (**3**) in acetic acid in the presence of a relatively large volume of palladium chloride solution[8] and a calculated amount of charcoal for formation of 10% palladium-charcoal smoothly provided the desired methylene-amides (**15**). Therefore, seven desired methylene-amides (**15a—c**, and **15f—i**) were prepared by this method. In the case of the keto-amide (**3b**), the cyclized product (**17b**) was also produced even by this method.

In order to extend the Robinson method to the synthesis of phenolic benzo[*c*]phenanthridine alkaloids, we applied the above method to the keto-amides (**3e** and **3j**) having a benzyloxy group in the molecule. Unfortunately, in these cases, all attempts to prevent hydrogenolysis of their benzyloxy groups failed. Thus, the desired methylene-amides (**15e** and **15j**) were prepared by re-benzylation of the phenolic amides (**18** and **19**).

We also examined hydrogenolysis of the keto-amide (**3k**) having a bromine atom in the

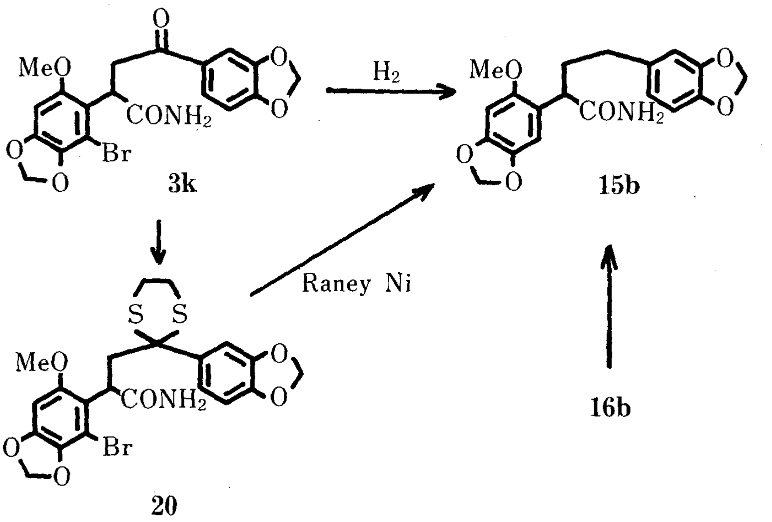


Chart 4

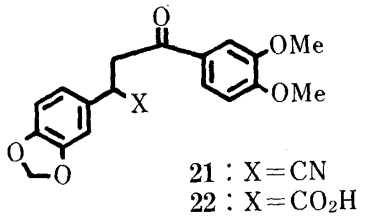


Chart 5

molecule. In this case, elimination of the bromine atom took place as expected to give the methylene-amide (**15b**) which was obtained on the hydrogenolysis of the hydroxy-amide (**16b**). Thus, the keto-amide (**3k**) was converted to the dithioketal (**20**) by treatment with ethanedithiol. Desulfurization of the dithioketal (**20**) also resulted in elimination of the bromine atom, providing the debrominated methylene-amide (**15b**).

Finally, these methylene-amides (**15a**—**j**) were hydrolyzed by treatment with ethanolic potassium hydroxide solution to give the desired methylene-acids (**5a**—**j**) in good yields without difficulty.

On the other hand, in 1973, Cheng *et al.*[2b)] reported direct hydrolysis of the keto-nitrile (**2f**) and a related compound (**21**) to the corresponding keto-acids (**6f** and **22**) under basic conditions in a one-pot reaction. However, their reported results seem to be in conflict with our conclusion. Thus, we examined hydrolysis of the keto-nitrile (**2a**) according to their procedure. When heated in a solution of 6.5% sodium hydroxide in aqueous ethanol for 11 h, the keto-nitrile (**2a**) was transformed into the desired keto-acid (**6a**) in 76.1% yield. It should be emphasized here that the heating must be prolonged and continuous. Otherwise, undefined precipitates are formed. This product was insoluble in most solvents containing aqueous ethanol (the reaction solvent) even on warming. Moreover, the desired keto-acid (**6a**) could not be obtained by further re-heating of the product as a suspension in 6.5% sodium hydroxide aqueous ethanolic solution. These experimental results seem to suggest that the mechanism of hydrolysis of the keto-nitrile (**2**) to the keto-acid (**6**) is different from that of the keto-amide (**3**) to the desired keto-acid (**6**). The structure of the undefined product formed remains to be solved.

General applicability of Cheng's method was confirmed by the preparation of ten keto-acids (**6a**—**c**, **6e**—**j**, and **6l**). Hydrogenolysis of these keto-acids except for those having a benzyloxy group (**6e** and **6j**) smoothly gave the desired methylene-acids (**5a**—**c**, **5f**—**i**, and **5l**).

Finally, treatment of nine methylene-acids (**5a**—**d**, **5f**—**i**, and **5l**) having no benzyloxy group with phosphorus oxychloride provided the corresponding tetralones (**4a**—**d**, **4f**—**i**, and **4l**). Although the same treatment of the benzyloxy-methylene-acid (**5e**) gave a mixture showing many spots on TLC, the desired tetralone (**4e**) could be prepared by treatment with thionyl chloride under ice-cooling.

Syntheses of benzo[*c*]phenanthridine alkaloids from these tetralone derivatives will be described in the near future.

Experimental

Instruments, *etc.*, were as described in the preceding paper.[1b] In the assignment of the ^{1}H-NMR spectra of the tetralones (**4**), the methylene-acids (**5**), the keto-acids (**6**), and the methylene-amides (**15**), the same numbering system as described in the preceding paper[1b] was applied.

Hydrolysis of 4-(3,4-Methylenedioxyphenyl)-4-oxo-2-(3,4,5-trimethoxyphenyl)butyramide (3a) with Sodium Hydroxide in Aqueous Ethanol——According to the reported procedure,[2a] a solution of the keto-amide (**3a**) (0.30 g) in a mixture of EtOH (3.5 ml) and 7% NaOH aq. (3.5 ml) was refluxed for 6 h. After cooling, the mixture was diluted with water and extracted with benzene. The benzene extract and the aqueous layer were separately worked up.

i) Acetopiperone (**7**): The benzene extract was dried over K_2CO_3 and evaporated to dryness *in vacuo*. Recrystallization of the residue from benzene–hexane or cyclohexane–Et_2O gave colorless prisms (0.021 g), mp 84—86 °C (lit.[1b] mp 85—87 °C). This material was identical with an authentic sample of acetopiperone[1b] (**7**).

The aqueous layer was acidified with 10% HCl aq. and extracted with $CHCl_3$. The chloroform solution was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was chromatographed on SiO_2 with $CHCl_3$ and then $CHCl_3$–MeOH (20 : 1—4 : 1, v/v). The eluate was divided into three fractions, the less polar eluate with $CHCl_3$, the more polar eluate with $CHCl_3$, and the eluate with the mixed solvent.

ii) 3,4,5-Trimethoxybenzoic Acid (**8**): The less polar eluate with $CHCl_3$ gave colorless needles (0.023 g), mp 176—177 °C (lit.[9] mp 167 °C), which were recrystallized from benzene or MeOH. This material was identical with a sample of 3,4,5-trimethoxybenzoic acid (**8**) which was prepared in our laboratory according to the reported method.[9]

iii) 4-(3,4-Methylenedioxyphenyl)-4-oxo-2-(3,4,5-trimethoxyphenyl)butyric Acid (**6a**): The more polar eluate with $CHCl_3$ gave colorless pillars (0.14 g), mp 207—209 °C, which were recrystallized from $CHCl_3$–MeOH or acetone–hexane. *Anal.* Calcd for $C_{20}H_{20}O_8$: C, 61.85; H, 5.19. Found: C, 61.62: H, 5.17. IR ν_{max} cm^{-1}: 2650 (OH) br, 1705 and 1670 (CO). ^{1}H-NMR ($CDCl_3$ + 1 drop of CD_3OD) δ: 3.18 (1H, dd, J=17.0 and 4.0 Hz, $CHC\underline{H}_AH_BCO$), 3.81 (1H, dd, J=17.0 and 10.0 Hz, $CHCH_A\underline{H}_BCO$), 3.83 (3H, s, OCH_3), 3.87 (6H, s, $OCH_3 \times 2$), 4.21 (1H, dd, J=10.0 and 4.0 Hz, $ArC\underline{H}CH_2$), 6.02 (2H, s, OCH_2O), 6.58 (2H, s, C_2- and C_6-H), 6.83 (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).

iv) 4-(3,4-Methylenedioxyphenyl)-4-oxo-2-(3,4,5-trimethoxyphenyl)-2-butenoic Acid (The Unsaturated Keto-acid) (**9**): The eluate with $CHCl_3$–MeOH (20 : 1—4 : 1, v/v) gave yellow needles (0.056 g), mp 151—152 °C, which were recrystallized from MeOH–benzene. *Anal.* Calcd for $C_{20}H_{18}O_8 \cdot 1/3C_6H_6$: C, 64.07; H, 4.89. Found: C, 64.53; H, 4.96. IR ν_{max} cm^{-1}: 3220 (OH), 1730 (CO). UV λ_{max} (log ε): 236 (4.25) sh, 2.86 (3.88) sh, 324 (4.00). ^{1}H-NMR (acetone-d_6) δ: 3.75 (3H, s, OCH_3), 3.85 (6H, s, $OCH_3 \times 2$), 6.01 (2H, s, OCH_2O), 6.85 (1H, d, J=8.5 Hz, $C_{5'}$-H), 7.00—7.40 (7H, m, arom. H, OH, and/or olefinic H), 7.71 (1H, s, arom. H or olefinic H).

Methylation of the Keto-acid (6a) [Methyl 4-(3,4-Methylenedioxyphenyl)-4-oxo-2-(3,4,5-trimethoxyphenyl)-butyrate (The Keto-ester) (11)]——A mixture of the keto-acid (**6a**) (0.081 g), K_2CO_3 (0.055 g), and Me_2SO_4 (0.04 ml) in acetone (3.2 ml) was stirred at room temperature for 40 min. The mixture was poured onto ice-water and extracted with $CHCl_3$. The chloroform solution was washed with 5% $NaHCO_3$ aq., dried over K_2CO_3, and evaporated to dryness *in vacuo*. Recrystallization of the residue from $CHCl_3$–MeOH gave colorless prisms (0.080 g), mp 136—138 °C. *Anal.* Calcd for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51. Found: C, 62.76; H, 5.52. IR ν_{max} cm^{-1}: 1725 and 1675 (CO). ^{1}H-NMR δ: 3.15 (1H, dd, J=17.0 and 3.5 Hz, $COC\underline{H}_AH_BCHAr$), 3.70 and 3.81 (each 3H, s, OCH_3), 3.85 (6H, s, $OCH_3 \times 2$), 3.60—4.40 (2H, m, $COCH_A\underline{H}_BC\underline{H}Ar$), 6.01 (2H, s, OCH_2O), 6.52 (2H, s, C_2- and C_6-H) 6.81 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.41 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.57 (1H, dd, J=8.0 and 2.0 Hz, $C_{6'}$-H).

Methylation of the Unsaturated Keto-acid (9) [Methyl 4-(3,4-Methylenedioxyphenyl)-4-oxo-2-(3,4,5-trimethoxyphenyl)-2-butenoate (The Unsaturated Keto-ester) (13)]——Dimethyl sulfate (0.036 ml) and K_2CO_3 (0.055 g) were added to a solution of the unsaturated keto-acid (**9**) (0.074 g) in acetone (1.5 ml). The mixture was stirred at room temperature for 1 h, diluted with water, and extracted with $CHCl_3$. The chloroform solution was washed with 5% $NaHCO_3$ aq., dried over K_2CO_3, and evaporated to dryness *in vacuo*. Recrystallization of the residue from $CHCl_3$–MeOH or MeOH gave yellow needles (0.069 g), mp 156.5—157.5 °C. *Anal.* Calcd for $C_{21}H_{20}O_8$: C, 62.99; H, 5.04. Found: C, 63.09; H, 5.07. IR ν_{max} cm^{-1}: 1745 and 1730 (CO). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 and 1660 (CO). UV λ_{max} (log ε): 242 (4.15), 351 (4.29). ^{1}H-NMR δ: 3.87 (12H, s, $OCH_3 \times 4$), 6.02 (2H, s, OCH_2O), 6.75 (2H, s, C_2- and C_6-H), 6.83 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.14 (1H, s, COCH=CAr), 7.44 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.58 (1H, dd, J=8.0 and 2.0 Hz, $C_{6'}$-H).

Product Analysis of the Acidic Portion in Hydrolysis of the Keto-amide (3a) after Esterification——A solution of the keto-amide (**3a**) (3.00 g) in a mixture of EtOH (35 ml) and 7% NaOH aq. (35 ml) was refluxed for 10 h. After cooling, the mixture was diluted with water and extracted with benzene. The benzene extract and the aqueous layer were separately worked up.

i) Acetopiperone (**7**): The benzene extract gave colorless prisms (0.227 g), mp 80—86 °C, when treated as described in the corresponding section in the above item. This material was identical with an authentic sample of acetopiperone[1b] (**7**).

The aqueous layer was acidified with 10% HCl aq. and extracted with $CHCl_3$. The chloroform solution was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was dissolved in acetone (50 ml). After addition of

K_2CO_3 (1.74 g) and Me_2SO_4 (1.28 ml), the mixture was stirred at room temperature for 4 h, poured onto ice-water, and extracted with $CHCl_3$. The chloroform solution was washed with 5% $NaHCO_3$ aq., dried over K_2CO_3, and evaporated to dryness *in vacuo*. Column chromatography of the residue on SiO_2 with benzene–AcOEt (100 : 1, v/v) followed by benzene–AcOEt (50 : 1—20 : 1, v/v) gave three fractions.

ii) Methyl 3,4,5-Trimethoxybenzoate (**12**): The eluate with benzene–AcOEt (100 : 1, v/v) gave colorless prisms (0.21 g), mp 84—86 °C, which were recrystallized from MeOH. This material was identical with a sample of methyl 3,4,5-trimethoxybenzoate[1b)] (**12**) which was prepared in our laboratory.

iii) The Keto-ester (**11**): The eluate with benzene–AcOEt (50 : 1, v/v) gave pale yellow needles (1.52 g), mp 136—138 °C, which were recrystallized from MeOH–$CHCl_3$. This material was identical with a sample of the keto-ester (**11**) derived from the keto-acid (**6a**).

iv) The Unsaturated Keto-ester (**13**): The eluate with benzene–AcOEt (20 : 1, v/v) gave yellow needles (0.36 g), mp 156.5—157.5 °C, which were recrystallized from MeOH. This material was identical with a sample of the unsaturated keto-ester (**13**) derived from the keto-acid (**9**).

v) 3,4,5-Trimethoxyphenylglyoxylic Acid (**10**): The mother liquor from the extraction after the esterification and the 5% $NaHCO_3$ aq. washings were combined, made acidic with 10% HCl aq., and extracted with $CHCl_3$. The chloroform solution was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was dissolved in Et_2O and the insoluble material was filtered off. The ethereal solution was evaporated again. Recrystallization of the residue from benzene gave pale yellow prisms (0.016 g), mp 164—166 °C (lit.[5)] mp 155—156 °C). *Anal.* Calcd for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04. Found: C, 54.98; H, 5.03. IR ν_{max} cm^{-1}: 3200—2900 (OH), 1755 and 1730 (CO). ^1H-NMR ($CDCl_3$ + a few drops of CD_3OD) δ: 3.90 (6H, s, $OCH_3 \times 2$), 3.92 (3H, s, OCH_3), 3.90—4.20 (1H, br, OH), 7.40 (2H, s, arom. H × 2).

Treatment of the Keto-acid (6a) in Dilute Sodium Hydroxide Solution under Air-bubbling——A solution of the keto-acid (**6a**) (0.10 g) in EtOH (1.2 ml) and 7% NaOH aq. (1.2 ml) was refluxed for 5.5 h while air was bubbled through the reaction mixture. The reaction mixture was extracted with benzene. The aqueous layer was acidified with 10% HCl aq. and extracted with $CHCl_3$. The chloroform solution was dried over $MgSO_4$ and evaporated to dryness *in vacuo* to give colorless prisms (0.098 g), mp 208—210 °C. This material was identical with a sample of the starting material (**6a**).

A Diastereomeric Mixture of 4-Hydroxy-4-(3,4-methylenedioxyphenyl)-2-(3,4,5-trimethoxyphenyl)butyramide (16a)——A solution of the keto-amide (**3a**) (0.10 g) and $NaBH_4$ (0.040 g) in MeOH (2 ml) was stirred at room temperature for 2 h. After the reaction was completed, the reaction mixture was evaporated under reduced pressure. The residue was dissolved in a large amount of water and extracted with AcOEt. The organic layer was dried over K_2CO_3 and evaporated to dryness *in vacuo* to give a colorless amorphous mass (0.10 g). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540 and 3420 (NH_2 and OH), 1670 (CO).

Reduction of 2-(2-Methoxy-4,5-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyramide (3b) with Sodium Borohydride——i) A Diastereomeric Mixture of 4-Hydroxy-2-(2-methoxy-4,5-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)butyramide (**16b**): Sodium borohydride (9.50 g) was added portionwise to a stirred suspension of the keto-amide (**3b**) (11.6 g) in MeOH (300 ml) at room temperature and the reaction mixture was left to stand at room temperature for 8 h. The reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in water and extracted with AcOEt. The organic layer was dried over K_2CO_3 and evaporated to dryness *in vacuo*. Recrystallization of the residue from Et_2O–EtOH gave colorless needles (10.1 g), mp 152—154 °C. *Anal.* Calcd for $C_{19}H_{19}NO_7$: C, 61.12; H, 5.13; N, 3.75. Found: C, 61.38; H, 5.09; N, 3.69. IR ν_{max} cm^{-1}: 3500—3100 (OH and NH_2), 1655 (CO). ^1H-NMR (DMSO-d_6) δ: 1.70 and 2.15 (each 1H, m, $CHC\underline{H}_2CH$), 3.73 (3H, s, OCH_3), 3.93 (1H, m, $ArC\underline{H}CH_2$), 4.28 (1H, m, $CH_2C\underline{H}(O)Ar$), 5.10 (1H, d, J = 4.8 Hz, OH), 5.89 and 5.93 (each 2H, s, OCH_2O), 6.70—6.80 (7H, m, arom. H × 5 and $CONH_2$).

ii) A Diastereomeric Mixture of 3-(2-Methoxy-4,5-methylenedioxyphenyl)-5-(3,4-methylenedioxyphenyl)-2-pyrrolidinone (**17b**) (Large-scale Operation): Treatment of a solution of the starting keto-amide (**3b**) (39.0 g) in MeOH (800 ml) with $NaBH_4$ (25.0 g) as described above gave the desired hydroxy-amide (**16b**) (27.1 g). The residue obtained from the mother liquor of recrystallization was chromatographed on Al_2O_3 (neutral, grade II) with $CHCl_3$. The eluate with $CHCl_3$ gave the starting material (**3b**) (1.27 g). The subsequent eluate with $CHCl_3$–AcOEt (1 : 1, v/v) provided colorless prisms (1.99 g), mp 196—198 °C, which were recrystallized from MeOH–$CHCl_3$ or benzene–$CHCl_3$. *Anal.* Calcd for $C_{19}H_{17}NO_6$: C, 64.22; H, 4.82; N, 3.94. Found: C, 63.98; H, 4.76; N, 3.83. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (NH), 1700 (CO). ^1H-NMR δ: 1.80—2.22 and 2.60—3.00 (each 1H, m, $CHC\underline{H}_2CH$), 3.78 (3H, s, OCH_3), 3.74—4.04[10)] (1H, m, $ArC\underline{H}CH_2$), 4.62 (1H, dd, J = 10.0 and 7.0 Hz, $CH_2C\underline{H}(N)Ar$), 5.85 and 5.92 (each 2H, s, OCH_2O), 6.06 (1H, br s, NH), 6.51 (1H, s, C_3-H), 6.68 and 6.87 (each 1H, s, arom. H), 6.77 (2H, s, arom. H × 2).

Subsequent elution with AcOEt and/or EtOH gave a further amount (7.50 g) of the desired hydroxy-amide (**16b**) (total yield: 34.6 g).

Reduction of 2-(3,5-Dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyramide (3d) with Sodium Borohydride [A Diastereomeric Mixture of 2-(3,5-Dimethoxyphenyl)-4-hydroxy-4-(3,4-methylenedioxyphenyl)butyramide (16d)]——Sodium borohydride (5.07 g) was gradually added to a stirred solution of the keto-amide (**3d**) (5.00 g) in dioxane (300 ml) at room temperature. The reaction mixture was stirred at room temperature for 8 h, then the solvent was distilled off. The residual mixture was dissolved in water and extracted with AcOEt. The organic layer was dried over K_2CO_3 and evaporated to give a colorless oil (5.02 g), which was subjected to hydrogenolysis of the hydroxy group without purification.

Reduction of 2-(4,5-Dibenzyloxy-2-methoxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyramide (3e) with Sodium Borohydride——A mixture of the keto-amide (**3e**) (0.12 g) and $NaBH_4$ (0.065 g) in abs. EtOH (13.5 ml) was refluxed for 5 h and then evaporated to dryness *in vacuo*. The residue was dissolved in water and extracted with $CHCl_3$. The chloroform solution was dried over K_2CO_3 and evaporated to dryness *in vacuo*. The residue was purified by column chromatography on SiO_2 with $CHCl_3$ followed by preparative TLC on SiO_2 with benzene–AcOEt (3 : 5, v/v) to give two main components.

i) *trans*-3-(4,5-Dibenzyloxy-2-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)-2-pyrrolidinone (*trans*-**17e**): Recrystallization of the less polar fraction from EtOH gave colorless needles (0.026 g), mp 165—167 °C.[11] *Anal.* Calcd for $C_{32}H_{29}NO_6$: C, 73.41; H, 5.58; N, 2.68. Found: C, 73.25; H, 5.59; N, 2.67. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3450 (NH), 1700 (CO). ^{1}H-NMR δ: 2.10—2.70 (2H, m, CHC$\underline{H}_2$CH), 3.71 (3H, s, OCH_3), 3.90 (1H, dd, J=10.0 and 8.0 Hz, ArC$\underline{H}$CH$_2$), 4.65 (1H, dd, J=8.0 and 5.0 Hz, CH$_2$C$\underline{H}$(N)Ar), 5.05 and 5.13 (each 2H, s, OCH$_2$Ph), 5.94 (2H, s, OCH$_2$O), 6.20 (1H, s, NH), 6.55 (1H, s, C$_3$-H), 6.75—6.80 (4H, m, C$_6$-, C$_{2'}$-, C$_{5'}$-, and C$_{6'}$-H), 7.35 (10H, m, arom. H × 10).

ii) *cis*-3-(4,5-Dibenzyloxy-2-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)-2-pyrrolidinone (*cis*-**17e**): Recrystallization of the more polar fraction from EtOH gave colorless needles (0.045 g), mp 177—178 °C. *Anal.* Calcd for $C_{32}H_{29}NO_6$: C, 73.41; H, 5.58; N, 2.68. Found: C, 73.19; H, 5.62; N, 2.63. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3450 (NH), 1700 (CO). ^{1}H-NMR δ: 1.80—2.20 and 2.50—2.95 (each 1H, m, CHC$\underline{H}_2$CH), 3.75 (3H, s, OCH$_3$), 3.80[10] (1H, dd, J=12.0 and 10.0 Hz, ArC$\underline{H}$CH$_2$), 4.60 (1H, dd, J=10.0 and 7.0 Hz, CH$_2$C$\underline{H}$(N)Ar), 5.06 and 5.11 (each 2H, s, OCH$_2$Ph), 5.93 (2H, s, OCH$_2$O), 6.00 (1H, s, NH), 6.55 (1H, s, C$_3$-H), 6.76—6.85 (4H, m, C$_6$-, C$_{2'}$-, C$_{5'}$-, and C$_{6'}$-H), 7.35 (10H, m, arom. H × 10).

General Method for Hydrogenolysis of the Hydroxy-amide (16) to the Methylene-amide (15)——A solution of the hydroxy-amide (**16**) in AcOH containing a small portion of 70% $HClO_4$ was hydrogenated over 5% Pd-C at room temperature under atmospheric pressure until absorption of hydrogen ceased. After removal of the catalyst by filtration, the filtrate was evaporated to dryness *in vacuo*. After addition of a large quantity of water, the residue was extracted with Et_2O. The ethereal solution was washed with 5% $NaHCO_3$ aq., dried over K_2CO_3, and then evaporated to dryness *in vacuo*. Recrystallization of the residue from an appropriate solvent provided the desired material (**15**).

4-(3,4-Methylenedioxyphenyl)-2-(3,4,5-trimethoxyphenyl)butyramide (15a)——The general method was applied to a solution of the hydroxy-amide (**16a**) (0.10 g) in AcOH (2 ml) with 70% $HClO_4$ (0.02 ml) and 5% Pd-C (0.023 g). Colorless pillars (0.060 g), mp 127—130 °C (benzene–hexane or MeOH–H$_2$O). *Anal.* Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.32; H, 6.22; N, 3.89. IR $\nu_{\max}$ cm^{-1}: 3400 and 3190 (NH$_2$), 1645 (CO). ^{1}H-NMR δ: 1.70—2.70 (4H, m, CHC$\underline{H}_2$C$\underline{H}_2$Ar), 3.21 (1H, m, ArC$\underline{H}$CH$_2$), 3.78 (3H, s, OCH$_3$), 3.81 (6H, s, OCH$_3$ × 2), 5.40—5.74 (2H, m, NH$_2$), 5.87 (2H, s, OCH$_2$O), 6.44 (2H, s, C$_2$- and C$_6$-H), 6.50—6.67 (3H, m, arom. H × 3).

2-(2-Methoxy-4,5-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)butyramide (15b)——The general method was applied to a solution of the hydroxy-amide (**16b**) (10.0 g) in AcOH (125 ml) with 70% $HClO_4$ (2.5 ml) and 5% Pd-C (3 g). Colorless prisms (7.1 g), mp 113—114 °C (EtOH). *Anal.* Calcd for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36, N. 3.92. Found: C, 63.48; H, 5.35; N, 3.87. IR $\nu_{\max}$ cm^{-1}: 3475 and 3180 (NH$_2$), 1675 (CO). ^{1}H-NMR δ: 1.70—2.65 (4H, m, CHC$\underline{H}_2$C$\underline{H}_2$Ar), 3.60—3.90[10] (1H, m, ArC$\underline{H}$CH$_2$), 3.76 (3H, s, OCH$_3$), 5.20—5.78 (2H, m, NH$_2$), 5.89 (4H, s, OCH$_2$O × 2), 6.50—6.80 (5H, m, arom. H × 5).

2-(3,5-Dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)butyramide (15d)——The general method was applied to a solution of the crude hydroxy-amide (**16d**) (5.02 g) in AcOH (30 ml) with 70% $HClO_4$ (0.3 ml) and 5% Pd-C (1.0 g). Colorless pillars (3.98 g), mp 140—142 °C (CH$_2$Cl$_2$–cyclohexane). *Anal.* Calcd for $C_{19}H_{21}NO_5$: C, 66.69; H, 6.20; N, 3.86. Found: C, 66.46; H, 6.16; N, 4.08. IR $\nu_{\max}$ cm^{-1}: 3430 and 3175 (NH$_2$), 1675 (CO). ^{1}H-NMR δ: 1.70—2.70 (4H, m, CHC$\underline{H}_2$C$\underline{H}_2$Ar), 3.28 (1H, m, ArC$\underline{H}$CH$_2$), 3.79 (6H, s, OCH$_3$ × 2), 5.30—5.75 (2H, br s, NH$_2$), 5.90 (2H, s, OCH$_2$O), 6.30—6.45 and 6.45—6.80 (each 3H, m, arom. H × 3).

General Method for Direct Hydrogenolysis of the Keto-amide (3) to the Methylene-amide (15)——An aqueous solution of $PdCl_2$[8] and a corresponding amount of Norit for preparation of 10% palladium-charcoal were added to a solution of the keto-amide (**3**) in AcOH. The mixture was hydrogenated at room temperature under atmospheric pressure until absorption of hydrogen ceased. After removal of the catalyst by filtration, the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in an organic solvent (CHCl$_3$ or Et$_2$O). The solution was washed with 5% NaHCO$_3$ aq., dried over K$_2$CO$_3$, and then evaporated to dryness *in vacuo*. If necessary, the γ-lactam (**17**) formed during hydrogenation as a by-product was removed by column chromatography of the residue on SiO$_2$ using an appropriate solvent. Recrystallization of the crude product from a suitable solvent gave the desired product (**15**).

4-(3,4-Methylenedioxyphenyl)-2-(3,4,5-trimethoxyphenyl)butyramide (15a)——The general method was applied to a solution of the keto-amide (**3a**) (26.3 g) in AcOH (1 l) with PdCl$_2$ aq. solution (66 ml) and Norit (5.94 g). Colorless needles (24.1 g), mp 135—137 °C (benzene–hexane or H$_2$O–MeOH). This material was identical with a sample of the methylene-amide (**15a**) which was prepared *via* the hydroxy-amide (**16a**) from the keto-amide (**3a**).

2-(2-Methoxy-4,5-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)butyramide (15b)——i) 2-(2-Methoxy-4,5-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)butyramide (**15b**): The general method was applied to a solution of the keto-amide (**3b**) (14.4 g) in AcOH (830 ml) with $PdCl_2$ aq. solution (78 ml) and Norit (6.30 g). The crude product was purified by column chromatography on SiO_2 with benzene–AcOEt (2 : 1, v/v) to give colorless prisms (9.74 g), mp 114—116 °C (EtOH or EtOH–Et_2O). This material was identical with a sample of the methylene-amide (**15b**) which was prepared *via* the hydroxy-amide (**16b**) from the keto-amide (**3b**).

ii) 3-(2-Methoxy-4,5-methylenedioxyphenyl)-5-(3,4-methylenedioxyphenyl)-2-pyrrolidinone (**17b**): Further elution with $CHCl_3$ gave colorless prisms (1.334 g), mp 196—198 °C (MeOH–$CHCl_3$). This material was identical with the sample of the γ-lactam (**17b**) which was obtained on the reduction of the keto-amide (**3b**) with $NaBH_4$ as described above.

2-(5-Methoxy-2,3-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)butyramide (15c)——The general method was applied to a solution of the keto-amide (**3c**) (0.10 g) in AcOH (15 ml) with $PdCl_2$ aq. solution (1.75 ml) and Norit (0.18 g). Colorless needles[12] (0.094 g), mp 139—142 °C (benzene–cyclohexane). *Anal.* Calcd for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 64.02; H, 5.39; N, 3.90. IR ν_{max} cm^{-1}: 3427 and 3150 (NH_2), 1678 (CO). ^1H-NMR δ: 2.00—2.64 (4H, m, $CHC\underline{H}_2C\underline{H}_2Ar$), 3.53 (1H, m, $ArC\underline{H}CH_2$), 3.75 (3H, s, OCH_3), 5.69 (2H, br s, NH_2), 5.89 and 5.91 (each 2H, s, OCH_2O), 6.31 and 6.42 (each 1H, d, J=3.0 Hz, C_4- and C_6-H), 6.59 (1H, dd, J=8.0 and 1.5 Hz, $C_{6'}$-H), 6.66 (1H, d, J=1.5 Hz, $C_{2'}$-H), 6.72 (1H, d, J=8.0 Hz, $C_{5'}$-H).

2-(3,4-Dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)butyramide (15f)——The general method was applied to a solution of the keto-amide (**3f**) (1.01 g) in AcOH (15 ml) with $PdCl_2$ aq. solution (4 ml) and Norit (0.36 g). The crude product was purified by column chromatography on SiO_2 with benzene followed by $CHCl_3$ as solvents. Colorless needles (0.65 g), mp 130—132 °C (benzene). *Anal.* Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.32; H, 6.10; N, 3.81. IR ν_{max} cm^{-1}: 3420 and 3200 (NH_2), 1675 (CO). ^1H-NMR δ: 1.60—2.68 (4H, m, $CHC\underline{H}_2C\underline{H}_2Ar$), 3.30 (1H, m, $ArC\underline{H}CH_2$), 3.86 (6H, s, $OCH_3 \times 2$), 5.40 and 5.64 (each 1H, br s, NH_2), 5.88 (2H, s, OCH_2O), 6.48—7.00 (6H, m, arom. H × 6).

2,4-Bis(3,4-methylenedioxyphenyl)butyramide (15g)——The general method was applied to a solution of the keto-amide (**3g**) (1.00 g) in AcOH (150 ml) with $PdCl_2$ aq. solution (19 ml) and Norit (1.71 g). Colorless prisms (0.87 g), mp 103—113 °C (benzene–hexane). *Anal.* Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.24; N, 4.28. Found: C, 65.87; H, 5.20; N, 4.20. IR ν_{max} cm^{-1}: 3410 and 3210 (NH_2), 1650 (CO). ^1H-NMR δ: 2.00—2.60 (4H, m, $CHC\underline{H}_2C\underline{H}_2Ar$), 3.26 (1H, br s, $ArC\underline{H}CH_2$), 5.48 (2H, br s, NH_2), 5.86 and 5.91 (each 2H, s, OCH_2O), 6.54—6.68 (3H, m, arom. H × 3), 6.72 (2H, s, arom. H × 2), 6.78 (1H, s, arom. H).

4-(3,4-Dimethoxyphenyl)-2-(2,4,5-trimethoxyphenyl)butyramide (15h)——The general method was applied to a solution of the keto-amide (**3h**) (5.91 g) in AcOH (60 ml) with $PdCl_2$ aq. solution (28 ml) and Norit (2.10 g). Colorless cotton-like needles (5.38 g), mp 119—138 °C (benzene). *Anal.* Calcd $C_{21}H_{27}NO_6$: C, 64.76; H, 6.99; N, 3.60. Found: C, 64.62; H, 7.08; N, 3.67. IR ν_{max} cm^{-1}: 3420 and 3200 (NH_2), 1650 (CO). ^1H-NMR δ: 1.72—2.68 (4H, m, $CHC\underline{H}_2C\underline{H}_2Ar$), 3.79 and 3.82 (each 6H, s, $OCH_3 \times 2$), 3.86 (3H, s, OCH_3), 3.70—3.96[10] (1H, m, $ArC\underline{H}CH_2$), 5.46 and 5.66 (each 1H, br s, NH_2), 6.50 (1H, s, C_3-H), 6.56—6.80 (3H, m, arom. H × 3), 6.81 (1H, s, C_6-H).

4-(3,4-Dimethoxyphenyl)-2-(2-methoxy-4,5-methylenedioxyphenyl)butyramide (15i)——The general method was applied to a solution of the keto-amide (**3i**) (3.46 g) in AcOH (60 ml) with $PdCl_2$ aq. solution (13.8 ml) and Norit (1.24 g). Colorless cotton-like needles (3.17 g), mp 131—132 °C (MeOH–$CHCl_3$). *Anal.* Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.09; H, 6.21; N, 3.99. IR ν_{max} cm^{-1}: 3420 and 3200 (NH_2), 1635 (CO). ^1H-NMR δ: 1.72—2.68 (4H, m, $CHC\underline{H}_2C\underline{H}_2Ar$), 3.74 (3H, s, OCH_3), 3.82 (6H, s, $OCH_3 \times 2$), 3.64—3.96[10] (1H, m, $ArC\underline{H}CH_2$), 5.57 (2H, br s, NH_2), 5.85 and 5.87 (each 1H, dif. s, OCH_2O), 6.48 (1H, s, C_3-H), 6.54—6.76 (3H, m, arom. H × 3), 6.78 (1H, s, C_6-H).

2-(4,5-Dibenzyloxy-2-methoxyphenyl)-4-(3,4-methylenedioxyphenyl)butyramide (15e)——i) Hydrogenolysis of the Keto-amide (**3e**) [2-(4,5-Dihydroxy-2-methoxyphenyl)-4-(3,4-methylenedioxyphenyl)butyramide (**18**)]: A $PdCl_2$ aq. solution (96 ml) and Norit (9.6 g) were added to a solution of the keto-amide (**3e**) (8.00 g) in a mixture of AcOEt (400 ml) and EtOH (240 ml). The mixture was hydrogenated at room temperature under atmospheric pressure until absorption of hydrogen ceased. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo* to give an oily product (hydroxy-methylene-amide) (**18**) (6.60 g). This material was so labile that the crude material was used for the subsequent step without purification.

ii) Benzylation of the Hydroxy-methylene-amide (**18**) [2-(4,5-Dibenzyloxy-2-methoxyphenyl)-4-(3,4-methylenedioxyphenyl)butyramide (**15e**)]: A mixture of the above oily product (**18**) (6.60 g), benzyl chloride (4.46 ml), and anhydrous K_2CO_3 (3.96 g) in abs. EtOH (13.2 ml) was refluxed for 8 h under argon. The mixture was poured into a large amount of water and extracted with $CHCl_3$. The chloroform solution was washed with 5% NaOH aq., dried over K_2CO_3, and then evaporated to dryness *in vacuo*. Column chromatography of the residue on alumina (basic, grade I) with $CHCl_3$ gave colorless plates (4.83 g), mp 94—95 °C, which were recrystallized from benzene–hexane. *Anal.* Calcd for $C_{32}H_{31}NO_6$: C, 73.12; H, 5.95; N, 2.67. Found: C, 73.21; H, 5.98; N, 2.66. IR ν_{max} cm^{-1}: 3375 and 3190 (NH_2), 1652 (CO). ^1H-NMR δ: 1.70—2.50 (4H, m, $CHC\underline{H}_2C\underline{H}_2Ar$), 3.73 (3H, s, OCH_3), 3.60—3.85[10] (1H, m, $ArC\underline{H}CH_2$), 5.06 and 5.14 (each 2H, s, OCH_2Ph), 5.30 and 5.55 (each 1H, br s, NH_2), 5.88 (2H, s, OCH_2O), 6.45—6.70 (4H, m, arom. H × 4), 6.89 (1H, s, C_6-H), 7.35 (10H, dif. s, arom. H × 10).

2-(5-Benzyloxy-2,4-dimethoxyphenyl)-4-(3,4-dimethoxyphenyl)butyramide (15j)——i) Hydrogenolysis of 2-(5-Benzyloxy-2,4-dimethoxyphenyl)-4-(3,4-dimethoxyphenyl)-4-oxobutyramide (**3j**) [4-(3,4-Dimethoxyphenyl)-2-(5-hydroxy-2,4-dimethoxyphenyl)butyramide (**19**)]: The general method was applied to a solution of the keto-amide (**3j**) (5.01 g) in AcOH (50 ml) with $PdCl_2$ aq. solution (10 ml) and Norit (0.90 g). Colorless prisms (3.92 g), mp 150—152 °C (EtOH). *Anal.* Calcd for $C_{20}H_{25}NO_6$: C, 63.98; H, 6.71; N, 3.73. Found: C, 63.74; H, 6.68; N, 3.65. IR ν_{max} cm^{-1}: 3480 (OH), 3200 (NH_2), 1670 (CO). ^{1}H-NMR δ: 1.80—2.64 (4H, m, CHC$\underline{H}_2$C$\underline{H}_2$Ar), 3.54—4.00[10] (1H, m, ArC$\underline{H}$CH$_2$), 3.76 and 3.84 (each 3H, s, OCH_3), 3.80 (6H, s, OCH_3 × 2), 5.56 (2H, br s, NH_2), 5.68 (1H, s, OH), 6.46 (1H, s, C_3-H), 6.54—6.80 (3H, m, arom. H × 3), 6.88 (1H, s, C_6-H).

ii) Benzylation of the Hydroxy-methylene-amide (**19**) [2-(5-Benzyloxy-2,4-dimethoxyphenyl)-4-(3,4-dimethoxyphenyl)butyramide (**15j**)]: A mixture of the hydroxy-methylene-amide (**19**) (2.90 g), benzyl chloride (1.1 ml), and anhydrous K_2CO_3 (0.85 g) in abs. EtOH (15 ml) was refluxed for 1.5 h. The mixture was diluted with water and extracted with $CHCl_3$. The chloroform solution was washed with 5% NaOH aq., dried over K_2CO_3, and then evaporated to dryness *in vacuo*. Recrystallization of the residue from benzene gave colorless fine needles (3.69 g), mp 147—149 °C. *Anal.* Calcd for $C_{27}H_{31}NO_6$: C, 69.66; H, 6.71; N, 3.01. Found: C, 69.79; H, 6.81; N, 3.07. IR ν_{max} cm^{-1}: 3400 and 3220 (NH_2), 1650 (CO). ^{1}H-NMR δ: 1.68—2.04 (1H, m, CHC$\underline{H}_A$H$_B$CH$_2$), 2.20—2.56 (3H, m, CHCH$_A\underline{H}_B$C$\underline{H}_2$Ar), 3.76 and 3.85 (each 3H, s, OCH_3), 3.80 (6H, s, OCH_3 × 2), 3.52—3.92[10] (1H, m, ArC$\underline{H}$CH$_2$), 5.00 (2H, s, OCH_2Ph), 5.48 (2H, br s, NH_2), 6.48 (1H, s, C_3-H). 6.56—6.90 (4H, m, arom. H × 4), 7.18—7.44 (5H, m, arom. H × 5).

Hydrogenolysis of 2-(2-Bromo-6-methoxy-3,4-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyramide (3k)——The general method described for hydrogenolysis of the keto-amides (**3**) was applied to a solution of the bromo-keto-amide (**3k**) (0.45 g) in AcOH (45 ml) with $PdCl_2$ aq. solution (6 ml) and Norit (0.60 g). Colorless needles (0.35 g), mp 112—113 °C (EtOH). This material was identical with a sample of 2-(2-methoxy-4,5-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)butyramide (**15b**).

2-(2-Bromo-6-methoxy-3,4-methylenedioxyphenyl)-4-ethylenedithio-4-(3,4-methylenedioxyphenyl)butyramide (20)——A mixture of the keto-amide (**3k**) (1.00 g) and ethanedithiol (2 ml) in AcOH (20 ml) involving $BF_3 \cdot Et_2O$ (2 ml) was left to stand at room temperature for 4 d. The mixture was poured into water and extracted with Et_2O. The ethereal solution was washed with 5% NaOH aq., dried over K_2CO_3, and then evaporated to dryness *in vacuo*. The oily residue was chromatographed on Al_2O_3 (Brockmann) with $CHCl_3$ to give colorless plates (0.92 g), mp 104—107 °C, which were recrystallized from benzene. After being dried over P_2O_5, this product melted at 163—165 °C. *Anal.* Calcd for $C_{21}H_{20}BrNO_6S_2$: C, 47.91; H, 3.82; N, 2.66. Found: C, 47.83; H, 3.77; N, 2.69. IR ν_{max} cm^{-1}: 3450 (NH_2), 1685 (CO). ^{1}H-NMR δ: 2.90—3.50 (6H, m, methylenic H), 3.72 (3H, s, OCH_3), 4.10 (1H, m, ArC$\underline{H}$CH$_2$), 5.30 (2H, br s, NH_2), 5.88 and 5.96 (each 2H, s, OCH_2O), 6.36 (1H, s, C_3-H), 6.56 (1H, d, J=8.5 Hz, $C_{5'}$-H), 7.04 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.12 (1H, dd, J=8.5 and 2.0 Hz, $C_{6'}$-H). MS m/z: 527 ($M^+ + 2$, 118.4% of M^+), 525 (M^+), 225 (base peak).

Desulfurization of the Dithioketal (20) with Raney Nickel——Raney nickel[13] prepared from the alloy (3.0 g) two days before was added to a solution of the dithioketal (**20**) (0.20 g) in abs. EtOH (10 ml). The suspension was refluxed for 4 h. After removal of the catalyst by filtration, the catalyst was washed with $CHCl_3$. The filtrate and the washings were combined and evaporated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$, and the solution was washed with water, dried over K_2CO_3, and then evaporated to dryness *in vacuo*. Recrystallization of the residue from EtOH gave colorless needles (0.120 g), mp 109—110 °C. This material was identical with a sample of 2-(2-methoxy-4,5-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)butyramide (**15b**).

General Method for Hydrolysis of the Methylene-amide (15) to the Methylene-acid (5)——A concentrated aqueous solution of KOH was added to a solution of the methylene-amide (**15**) in EtOH. The mixture was refluxed, diluted with a large quantity of water, made acidic with HCl aq., and then extracted with Et_2O or $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. Recrystallization of residue afforded the desired product (**5**).

4-(3,4-Methylenedioxyphenyl)-2-(3,4,5-trimethoxyphenyl)butyric Acid (5a)——The general method was applied to a solution of the methylene-amide (**15a**) (1.01 g) in EtOH (30 ml) with 33% KOH aq. (20.8 ml). Refluxing was required for 7.5 h. Colorless needles (0.95 g), mp 125—127 °C (benzene–hexane or MeOH–H_2O). *Anal.* Calcd for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found: C, 64.09; H, 5.94. IR ν_{max} cm^{-1}: 3160 (OH), 1700 (CO). ^{1}H-NMR δ: 1.90—2.70 (4H, m, CHC$\underline{H}_2$C$\underline{H}_2$Ar), 3.46 (1H, t, J=7.5 Hz, ArC$\underline{H}$CH$_2$), 3.82 (3H, s, OCH_3), 3.84 (6H, s, OCH_3 × 2), 5.90 (2H, s, OCH_2O), 6.52 (2H, s, C_2- and C_6-H), 6.60—6.75 (3H, m, arom. H × 3), 9.74 (1H, br s, COOH).

2-(2-Methoxy-4,5-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)butyric Acid (5b)——The general method was applied to a solution of the methylene-amide (**15b**) (3.55 g) in EtOH (106 ml) with 33% KOH aq. (71 ml). Refluxing was required for 10 h. Light brown oil (3.24 g). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200—2800 (OH), 1700 (CO). ^{1}H-NMR δ: 1.80—2.60 (4H, m, CHC$\underline{H}_2$C$\underline{H}_2$Ar), 3.71 (3H, s, OCH_3), 3.95 (1H, t, J=6.5 Hz, ArC$\underline{H}$CH$_2$), 5.84 (4H, s, OCH_2O × 2), 6.40—6.80 (5H, m, arom. H × 5), 9.72 (1H, br s, COOH).

2-(5-Methoxy-2,3-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)butyric Acid (5c)——The general method was applied to a solution of the methylene-amide (**15c**) (1.51 g) in EtOH (45 ml) with 33% KOH aq. (30 ml). Refluxing was needed for 24 h. Colorless needles (1.51 g), mp 135—138 °C ($CHCl_3$–hexane or MeOH–H_2O). *Anal.* Calcd for $C_{19}H_{18}O_6$: C, 63.68; H, 5.06. Found: C, 63.83; H, 5.07. IR ν_{max} cm^{-1}: 3200—2800 (OH), 1710 (CO). ^1H-NMR[14] δ: 2.00—2.68 (4H, m, $CHC\underline{H}_2C\underline{H}_2Ar$), 3.60—3.84[10] (1H, m, $ArC\underline{H}CH_2$), 3.73 (3H, s, OCH_3), 5.89 (4H, s, OCH_2O × 2), 6.31 (1H, d, J=3.0 Hz, C_4-H), 6.42 (1H, d, J=3.0 Hz, C_6-H), 6.50—6.80 (3H, m, arom. H × 3).

2-(3,5-Dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)butyric Acid (5d)——The general method was applied to a solution of the methylene-amide (**15d**) (0.050 g) in EtOH (1 ml) with 60% KOH aq. (1 ml). Refluxing was needed for 2 h. Colorless pillars (0.034 g), mp 117—119 °C (benzene–hexane). *Anal.* Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.45; H, 5.87. IR ν_{max} cm^{-1}: 3070 (OH), 1700 (CO). ^1H-NMR δ: 1.80—2.60 (4H, m, $CHC\underline{H}_2C\underline{H}_2Ar$), 3.47 (1H, t, J=7.0 Hz, $ArC\underline{H}CH_2$), 3.89 (6H, s, OCH_3 × 2), 5.90 (2H, s, OCH_2O), 6.37 (1H, t, J=2.0 Hz, C_4-H), 6.44 (2H, d, J=2.0 Hz, C_2- and C_6-H), 6.48—6.78 (3H, m, arom. H × 3), 9.23 (1H, br s, COOH).

2-(4,5-Dibenzyloxy-2-methoxyphenyl)-4-(3,4-methylenedioxyphenyl)butyric Acid (5e)——The general method was applied to a solution of the methylene-amide (**15e**) (0.10 g) in EtOH (4.5 ml) with 33% KOH aq. (3 ml). Refluxing was needed for 12 h. Colorless needles (0.089 g), mp 97—98 °C (benzene–hexane). *Anal.* Calcd for $C_{32}H_{30}O_7$: C, 72.99; H, 5.74. Found: C, 73.13; H, 5.85. IR ν_{max} cm^{-1}: 3200—2600 (OH), 1720 (CO). ^1H-NMR δ: 1.60—2.50 (4H, m, $CHC\underline{H}_2C\underline{H}_2Ar$), 3.70 (3H, s, OCH_3), 3.90 (1H, dif. t, J=8.0 Hz, $ArC\underline{H}CH_2$), 5.06 and 5.14 (each 2H, s, OCH_2Ph), 5.88 (2H, s, OCH_2O), 6.44—6.80 (5H, m, arom. H × 4 and COOH), 6.88 (1H, s, arom. H), 7.20—7.60 (10H, m, arom. H × 10).

2-(3,4-Dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)butyric Acid (5f)——The general method was applied to a solution of the methylene-amide (**15f**) (0.50 g) in EtOH (15 ml) with 33% KOH aq. (10 ml). Refluxing was needed for 10 h. Slightly brown oil[2b,c,d] (0.52 g). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 (CO). ^1H-NMR δ: 1.90—2.68 (4H, m, $CHC\underline{H}_2C\underline{H}_2Ar$), 3.48 (1H, dif. t, J=7.0 Hz, $ArC\underline{H}CH_2$), 3.86 (6H, s, OCH_3 × 2), 5.87 (2H, s, OCH_2O), 6.48—7.00 (6H, m, arom. H × 6), 8.64 (1H, br, COOH).

2,4-Bis(3,4-methylenedioxyphenyl)butyric Acid (5g)——The general method was applied to a solution of the methylene-amide (**15g**) (8.13 g) in EtOH (245 ml) with 33% KOH aq. (165 ml). Refluxing was needed for 11 h. Colorless oil[2e] (8.16 g). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500—3150 (OH), 1710 (CO). ^1H-NMR δ: 1.80—2.60 (4H, m, $CHC\underline{H}_2C\underline{H}_2Ar$), 3.45 (1H, t, J=7.0 Hz, $ArC\underline{H}CH_2$), 5.88 and 5.91 (each 2H, s, OCH_2O), 6.46—6.84 (6H, m, arom. H × 6), 6.88—7.40 (1H, br, COOH).

4-(3,4-Dimethoxyphenyl)-2-(2,4,5-trimethoxyphenyl)butyric Acid (5h)——The general method was applied to a solution of the methylene-amide (**15h**) (6.69 g) in EtOH (200 ml) with 33% KOH aq. (135 ml). Refluxing was needed for 15 h. Light brown oil (6.89 g), a part of which was purified by distillation, bp 265—270 °C (1 mmHg). *Anal.* Calcd for $C_{21}H_{26}O_7$: C, 64.60; H, 6.71. Found: C, 64.40; H, 6.90. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 (CO). ^1H-NMR δ: 1.80—2.64 (4H, m, $CHC\underline{H}_2C\underline{H}_2Ar$), 3.74, 3.76, and 3.82 (each 3H, s, OCH_3), 3.80 (6H, s, OCH_3 × 2), 3.60—4.04[10] (1H, m, $ArC\underline{H}CH_2$), 6.43 (1H, s, C_3-H), 6.52—6.68 (3H, m, arom. H × 3), 6.75 (1H, s, C_6-H), 10.46 (1H, br s, COOH).

4-(3,4-Dimethoxyphenyl)-2-(2-methoxy-4,5-methylenedioxyphenyl)butyric Acid (5i)——The general method was applied to a solution of the methylene-amide (**15i**) (2.72 g) in EtOH (82 ml) with 33% KOH aq. (55 ml). Refluxing was needed for 15 h. Colorless prisms (2.69 g), mp 117—120 °C (benzene–hexane). *Anal.* Calcd for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found: C, 64.17; H, 5.92. IR ν_{max} cm^{-1}: 1680 (CO). ^1H-NMR δ: 1.84—2.72 (4H, m, $CHC\underline{H}_2C\underline{H}_2Ar$), 3.72 (3H, s, OCH_3), 3.84 (6H, s, OCH_3 × 2), 3.99 (1H, t, J=7.0 Hz, $ArC\underline{H}CH_2$), 5.87 (2H, s, OCH_2O), 6.50 (1H, s, C_3-H), 6.56—6.92 (4H, m, arom. H × 4), 7.64—8.70 (1H, br s, COOH).

2-(5-Benzyloxy-2,4-dimethoxyphenyl)-4-(3,4-dimethoxyphenyl)butyric Acid (5j)——The general method was applied to a solution of the methylene-amide (**15j**) (3.06 g) in EtOH (90 ml) with 33% KOH aq. (60 ml). Refluxing was needed for 20 h. Colorless prisms (2.99 g), mp 134—136 °C (EtOH). *Anal.* Calcd for $C_{27}H_{30}O_7$: C, 69.51; H, 6.48. Found: C, 69.32; H, 6.70. IR ν_{max} cm^{-1}: 3250—2800 (OH), 1740 (CO). ^1H-NMR δ: 1.80—2.60 (4H, m, $CHC\underline{H}_2C\underline{H}_2Ar$), 3.76 and 3.85 (each 3H, s, OCH_3), 3.82 (6H, s, OCH_3 × 2), 3.60—4.08[10] (1H, m, $ArC\underline{H}CH_2$), 5.01 (2H, s, OCH_2Ph), 6.49 (1H, s, C_3-H), 6.52—6.82 (3H, m, arom. H × 3), 6.84 (1H, s, C_6-H), 7.16—7.52 (5H, m, arom. H × 5).

General Method for Direct Hydrolysis of the Keto-nitrile (2) to the Keto-acid (6) under Basic Conditions——The keto-nitrile (**2**) was suspended in a solution of NaOH in aqueous EtOH. If necessary, dioxane was added to the above suspension (or solution). When heated at *ca.* 100 °C under argon, the suspension became clear. Heating was continued[15] until a blue-black precipitate could not be formed by addition of *ca.* 10% HCl aq. to a portion of the reaction solution. After completion of the reaction had been thus confirmed, the reaction mixture was made acidic with 10% HCl aq. and then extracted with $CHCl_3$ (or Et_2O). The organic layer was dried over $MgSO_4$ and then evaporated to dryness *in vacuo*. Recrystallization of the residue from the appropriate solvent gave the desired keto-acid (**6**).

4-(3,4-Methylenedioxyphenyl)-4-oxo-2-(3,4,5-trimethoxyphenyl)butyric Acid (6a)——The general method was applied to a suspension of the keto-nitrile (**2a**) (0.10 g) in H_2O (1.2 ml) containing NaOH (0.11 g) and EtOH (0.5 ml). Refluxing was needed for 11 h. Colorless prisms (0.08 g), mp 207—209 °C (EtOH–benzene). This material was identical with a sample of 4-(3,4-methylenedioxyphenyl)-4-oxo-2-(3,4,5-trimethoxyphenyl)butyric acid (**6a**) which was obtained by hydrolysis of the keto-amide (**3a**) with an aqueous ethanolic solution as described above.

2-(2-Methoxy-4,5-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyric Acid (6b)——The general method was applied to a suspension of the keto-nitrile (**2b**) (0.80 g) in H_2O (10 ml) containing EtOH (3.5 ml) and NaOH (0.91 g). Refluxing was needed for 8 h. Colorless prisms (0.67 g), mp 186—188.5 °C ($CHCl_3$–EtOH). *Anal.* Calcd for $C_{19}H_{16}O_8$: C, 61.29; H, 4.33. Found: C, 61.08; H, 4.37. IR ν_{max} cm^{-1}: 1690 and 1665 (CO). ^{1}H-NMR (pyridine-d_5) δ: 3.34 (1H, dd, $J=18.0$ and 4.0 Hz, $CHC\underline{H}_AH_BCO$), 3.70 (3H, s, OCH_3), 4.22 (1H, dd, $J=18.0$ and 10.0 Hz, $CHCH_A\underline{H}_BCO$), 5.25 (1H, dd, $J=10.0$ and 4.0 Hz, $ArC\underline{H}CH_2$), 5.90 and 5.94 (each 1H, d, $J=1.0$ Hz, OCH_2O), 5.97 (2H, s, OCH_2O), 6.78 (1H, s, C_3-H), 6.88 (1H, d, $J=8.0$ Hz, $C_{5'}$-H), 7.30 (1H, s, C_6-H), 7.69 (1H, d, $J=2.0$ Hz, $C_{2'}$-H), 7.75 (1H, dd, $J=8.0$ and 2.0 Hz, $C_{6'}$-H).

2-(5-Methoxy-2,3-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyric Acid (6c)——The general method was applied to a suspension of the keto-nitrile (**2c**) (0.30 g) in H_2O (3.7 ml) containing EtOH (1.3 ml) and NaOH (0.34 g). Refluxing was needed for 3.5 h. The crude product was collected from the acidified mixture by filtration. Colorless prisms (0.21 g), mp 158—160.5 °C (MeOH). *Anal.* Calcd for $C_{19}H_{16}O_8$: C, 61.29; H, 4.33. Found: C, 60.95; H, 4.20. IR ν_{max} cm^{-1}: 1715 and 1685 (CO). ^{1}H-NMR δ: 3.23 (1H, dd, $J=18.0$ and 5.0 Hz, $CHC\underline{H}_AH_BCO$), 3.73 (3H, s, OCH_3), 3.82 (1H, dd, $J=18.0$ and 9.5 Hz, $CHCH_A\underline{H}_BCO$), 4.43 (1H, dd, $J=9.5$ and 5.0 Hz, $ArC\underline{H}CH_2$), 5.90 and 6.00 (each 2H, s, OCH_2O), 6.30 (1H, d, $J=2.0$ Hz, C_4-H), 6.39 (1H, d, $J=2.0$ Hz, C_6-H), 6.81 (1H, d, $J=8.0$ Hz, $C_{5'}$-H), 7.40 (1H, d, $J=2.0$ Hz, $C_{2'}$-H), 7.55 (1H, dd, $J=8.0$ and 2.0 Hz, $C_{6'}$-H), 9.88 (1H, br s, COOH).

2-(4,5-Dibenzyloxy-2-methoxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyric Acid (6e)——The general method was applied to a suspension of the keto-nitrile (**2e**) (0.25 g) in H_2O (5.5 ml) containing EtOH (2.5 ml), dioxane (3 ml), and NaOH (0.39 g). Colorless prisms (0.13 g), mp 149.5—151.5 °C (benzene–hexane). *Anal.* Calcd for $C_{32}H_{28}O_8$: C, 71.10; H, 5.22. Found: C, 70.96; H, 5.14. IR ν_{max} cm^{-1}: 1690 and 1665 (CO). ^{1}H-NMR$^{14)}$ δ: 3.04 (1H, dd, $J=18.0$ and 5.0 Hz, $CHC\underline{H}_AH_BCO$), 3.70 (1H, dd, $J=18.0$ and 9.0 Hz, $CHCH_A\underline{H}_BCO$), 3.74 (3H, s, OCH_3), 4.60 (1H, dd, $J=9.0$ and 5.0 Hz, $ArC\underline{H}CH_2$), 5.07 and 5.13 (each 2H, s, OCH_2Ph), 6.01 (2H, s, OCH_2O), 6.59 (1H, s, C_3-H), 6.82 (1H, d, $J=8.5$ Hz, $C_{5'}$-H), 6.93 (1H, s, C_6-H), 7.20—7.64 (12H, m, arom. H × 12).

2-(3,4-Dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxobutyric Acid (6f)——The general method was applied to a suspension of the keto-nitrile (**2f**) (10.0 g) in H_2O (130 ml) containing EtOH (46 ml) and NaOH (11.8 g). Refluxing was needed for 10 h. The crude product, mp 188.5—191 °C,$^{16)}$ was collected from the acidified mixture by filtration and recrystallized from EtOH to give colorless prisms (8.70 g), mp 182—184 °C (lit. mp 178—179 °C;$^{2b)}$ mp 172 °C;$^{2c)}$ mp 188—189 °C$^{2d)}$). *Anal.* Calcd for $C_{19}H_{18}O_7$: C, 63.68; H, 5.06. Found: C, 63.30; H, 5.13. IR ν_{max} cm^{-1}: 1690 and 1670 (CO). ^{1}H-NMR$^{14)}$ δ: 3.20 (1H, dd, $J=17.0$ and 5.0 Hz, $CHC\underline{H}_AH_BCO$), 3.77 (1H, dd, $J=17.0$ and 9.5 Hz, $CHCH_A\underline{H}_BCO$), 3.84 and 3.87 (each 3H, s, OCH_3), 4.28 (1H, dd, $J=9.5$ and 5.0 Hz, $ArC\underline{H}CH_2$), 5.99 (2H, s, OCH_2O), 6.82 (2H, d, $J=8.0$ Hz, C_5- and $C_{5'}$-H), 6.88—7.02 (2H, m, C_2- and C_6-H), 7.42 (1H, d, $J=2.0$ Hz, $C_{2'}$-H), 7.56 (1H, dd, $J=8.0$ and 2.0 Hz, $C_{6'}$-H).

2,4-Bis(3,4-methylenedioxyphenyl)-4-oxobutyric Acid (6g)——The general method was applied to a suspension of the keto-nitrile (**2g**) (0.20 g) in H_2O (2.6 ml) containing NaOH (0.24 g) and EtOH (1 ml). Refluxing was needed for 10 h. Colorless prisms (0.19 g), mp 174—177 °C (benzene–hexane) (lit.$^{2e)}$ mp 169—170 °C). *Anal.* Calcd for $C_{18}H_{14}O_7$: C, 63.16; H, 4.12. Found: C, 63.03; H, 4.08. IR ν_{max} cm^{-1}: 1705 and 1660 (CO). ^{1}H-NMR ($CDCl_3+CD_3OD$) δ: 3.17 (1H, dd, $J=18.0$ and 5.0 Hz, $CHC\underline{H}_AH_BCO$), 3.79 (1H, dd, $J=18.0$ and 10.0 Hz, $CHCH_A\underline{H}_BCO$), 4.20 (1H, dd, $J=10.0$ and 5.0 Hz, $ArC\underline{H}CH_2$), 5.92 and 6.03 (each 2H, s, OCH_2O), 6.67—7.02 (4H, m, arom. H × 4), 7.40 (1H, d, $J=2.0$ Hz, $C_{2'}$-H), 7.69 (1H, dd, $J=8.0$ and 2.0 Hz, $C_{6'}$-H).

4-(3,4-Dimethoxyphenyl)-4-oxo-2-(2,4,5-trimethoxyphenyl)butyric Acid (6h)——The general method was applied to a suspension of the keto-nitrile$^{17)}$ (**2h**) (0.49 g) in H_2O (5.5 ml) containing EtOH (2.2 ml) and NaOH (0.50 g). Refluxing was needed for 1.5 h. Recrystallization of the crude material from benzene–EtOH gave colorless prisms (0.47 g), mp 101 °C (softened at 89 °C). *Anal.* Calcd for $C_{21}H_{24}O_8 \cdot C_2H_5OH$: C, 61.32; H, 6.71. Found: C, 61.24; H, 6.76. IR ν_{max} cm^{-1}: 1725 and 1665 (CO). UV λ_{max} nm (log ε): 229.5 (4.40), 277 (4.11), 295.5 (4.07). ^{1}H-NMR δ: 1.21 (3H, t, $J=7.5$ Hz, $C\underline{H}_3CH_2OH$), 3.14 (1H, dd, $J=18.0$ and 4.5 Hz, $CHC\underline{H}_AH_BCO$), 3.56—4.20 (18H, m, $CHCH_A\underline{H}_BCO$, $OCH_3 \times 5$, and $CH_3C\underline{H}_2OH$), 4.59 (1H, dd, $J=9.5$ and 4.5 Hz, $ArC\underline{H}CH_2$), 5.59 (2H, br s, COOH and $CH_3CH_2O\underline{H}$), 6.50 (1H, s, C_3-H), (6.81 (1H, s, C_6-H), 6.81 (1H, d, $J=8.5$ Hz, $C_{5'}$-H), 7.49 (1H, d, $J=2.0$ Hz, $C_{2'}$-H), 7.55 (1H, dd, $J=8.5$ and 2.0 Hz, $C_{6'}$-H).

4-(3,4-Dimethoxyphenyl)-2-(2-methoxy-4,5-methylenedioxyphenyl)-4-oxobutyric Acid (6i)——The general method was applied to a suspension of the keto-nitrile (**2i**) (10.0 g) in H_2O (120 ml) containing EtOH (40 ml) and NaOH (10.2 g). Refluxing was needed for 2 h. The crude product, mp 192—197 °C,$^{16)}$ was collected from the acidified reaction mixture by filtration. Colorless prisms (10.1 g), mp 190—193 °C (benzene). *Anal.* Calcd for $C_{20}H_{20}O_8$: C, 61.85; H, 5.19. Found: C, 61.37; H, 5.11. IR ν_{max} cm^{-1}: 1700 and 1670 (CO). ^{1}H-NMR$^{14)}$ δ: 3.14 (1H, dd, $J=18.0$ and 5.0 Hz, $CHC\underline{H}_AH_BCO$), 3.76 (3H, s, OCH_3), 3.60—4.10$^{10)}$ (1H, m, $CHCH_A\underline{H}_BCO$), 3.91 (6H, s, $OCH_3 \times 2$), 4.59 (1H, dd, $J=9.0$ and 5.0 Hz, $ArC\underline{H}CH_2$), 5.86 (2H, s, OCH_2O), 6.49 (1H, s, C_3-H), 6.77 (1H, s, C_6-H), 6.82 (1H, d, $J=8.5$ Hz, $C_{5'}$-H), 7.49 (1H, s, $C_{2'}$-H), 7.53 (1H, dd, $J=8.5$ and 2.0 Hz, $C_{6'}$-H).

2-(5-Benzyloxy-2,4-dimethoxyphenyl)-4-(3,4-dimethoxyphenyl)-4-oxobutyric Acid (6j)——The general method was applied to a suspension of the keto-nitrile (**2j**) (0.60 g) in H_2O (7.2 ml) containing NaOH (0.54 g), EtOH (2.4 ml), and dioxane (7 ml). Refluxing was needed for 4 h. The crude product was collected from the acidified reaction mixture by filtration. Colorless prisms (0.52 g), mp 139—140.5 °C (benzene–hexane). *Anal.* Calcd for $C_{27}H_{28}O_8$: C, 67.49; H, 5.87. Found: C, 67.31; H, 5.79. IR ν_{max} cm^{-1}: 1695 and 1670 (CO). ^{1}H-NMR$^{14)}$ δ: 3.08 (1H, dd, $J=18.0$ and 5.0 Hz,

$CHC\underline{H}_AH_BCO$), 3.71 (1H, dd, J=18.0 and 9.0 Hz, $CHCH_A\underline{H}_BCO$), 3.80, 3.86, 3.88, and 3.92 (each 3H, s, OCH_3), 4.60 (1H, dd, J=9.0 and 5.0 Hz, $ArC\underline{H}CH_2$), 5.02 (2H, s, OCH_2Ph), 6.51 (1H, s, C_3-H), 6.82 (1H, d, J=8.0 Hz, $C_{5'}$-H), 6.86 (1H, s, C_6-H), 7.20—7.64 (2H, m, arom. H × 2).

4-(3,4-Methylenedioxyphenyl)-4-oxo-2-(2,4,5-trimethoxyphenyl)butyric Acid (6l)——The general method was applied to a suspension of the keto-nitrile (**2l**) (16.3 g) in H_2O (195 ml) containing EtOH (65 ml) and NaOH (16.4 g). Refluxing was needed for 4 h. The crude material was collected by filtration from the acidified reaction mixture. Colorless prisms (15.4 g), mp 141—143 °C (MeOH). *Anal.* Calcd for $C_{20}H_{20}O_8$: C, 61.85; H, 5.19. Found: C, 61.81; H, 5.22. IR ν_{max} cm^{-1}: 1740 and 1680 (CO). ^{1}H-NMR δ: 3.09 (1H, dd, J=18.0 and 5.0 Hz, $CHC\underline{H}_AH_BCO$), 3.77 (1H, dd, J=18.0 and 9.0 Hz, $CHCH_A\underline{H}_BCO$), 3.81 (6H, s, OCH_3 × 2), 3.86 (3H, s, OCH_3), 4.59 (1H, dd, J=9.0 and 5.0 Hz, $ArC\underline{H}CH_2$), 5.98 (2H, s, OCH_2O), 6.51 (1H, s, C_3-H), 6.78 (1H, d, J=8.5 Hz, $C_{5'}$-H), 6.80 (1H, s, C_6-H), 7.39 (1H, d, J=2.0 Hz, $C_{2'}$-H), 7.54 (1H, dd, J=8.5 and 2.0 Hz, $C_{6'}$-H), 8.80—9.60 (1H, br s, COOH).

General Method for Hydrogenolysis of the Keto-acid (6) to the Methylene-acid (5)——An aqueous solution of $PdCl_2$[8] and a corresponding amount of Norit for preparation of 10% palladium-charcoal were added to a solution of the keto-acid (**6**) in AcOH. The mixture was hydrogenated at room temperature under atmospheric pressure until absorption of hydrogen ceased. After removal of the catalyst by filtration, the filtrate was evaporated to dryness *in vacuo* and the residue was dissolved in an organic solvent ($CHCl_3$ or Et_2O). The solution was washed with sat. NaCl aq. solution, dried over $MgSO_4$, and then evaporated to dryness *in vacuo*. Recrystallization of the residue from an appropriate solvent afforded the desired product (**5**). Each product was identical with a sample of the methylene-acid (**5**), which was prepared *via* hydrolysis of the corresponding methylene-amide (**15**).

4-(3,4-Methylenedioxyphenyl)-2-(3,4,5-trimethoxyphenyl)butyric Acid (5a)——The general method was applied to a solution of the keto-acid (**6a**) (0.050 g) in AcOH (2 ml) with $PdCl_2$ aq. solution (0.2 ml) and Norit (0.018 g). Colorless needles (0.043 g), mp 122—126 °C (benzene–hexane).

2-(2-Methoxy-4,5-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)butyric Acid (5b)——The general method was applied to a solution of the keto-acid (**6b**) (0.50 g) in AcOH (40 ml) with $PdCl_2$ aq. solution (2 ml) and Norit (0.18 g). Colorless oil (0.50 g).

2-(5-Methoxy-2,3-methylenedioxyphenyl)-4-(3,4-methylenedioxyphenyl)butyric Acid (5c)——The general method was applied to the keto-acid (**6c**) (0.039 g) in AcOH (0.6 ml) with $PdCl_2$ aq. solution (0.78 ml) and Norit (0.072 g). Colorless prisms (0.026 g), mp 135—138 °C ($CHCl_3$–hexane).

2-(3,4-Dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)butyric Acid (5f)——The general method was applied to a solution of the keto-acid (**6f**) (16.7 g) in AcOH (600 ml) with $PdCl_2$ aq. solution (67 ml) and Norit (6.03 g). Slightly brown oil[2b,c,d] (17.5 g).

2,4-Bis(3,4-methylenedioxyphenyl)butyric Acid (5g)——The general method was applied to a solution of the keto-acid (**6g**) (3.20 g) in AcOH (130 ml) with $PdCl_2$ aq. solution (12.8 ml) and Norit (1.15 g). Colorless oil[2e] (3.16 g).

4-(3,4-Dimethoxyphenyl)-2-(2,4,5-trimethoxyphenyl)butyric Acid (5h)——The general method was applied to a solution of the keto-acid (**6h**) (0.20 g) in AcOH (6 ml) with $PdCl_2$ aq. solution (0.8 ml) and Norit (0.072 g). Colorless oil (0.17 g), bp 265—270 °C (1 mmHg).

4-(3,4-Dimethoxyphenyl)-2-(2-methoxy-4,5-methylenedioxyphenyl)butyric Acid (5i)——The general method was applied to a solution of the keto-acid (**6i**) (10.2 g) in AcOH (350 ml) with $PdCl_2$ aq. solution (41 ml) and Norit (3.67 g). Colorless prisms (9.10 g), mp 117—120 °C (benzene–hexane).

4-(3,4-Methylenedioxyphenyl)-2-(2,4,5-trimethoxyphenyl)butyric Acid (5l)——The general method was applied to a solution of the keto-acid (**6l**) (10.0 g) in AcOH (100 ml) with $PdCl_2$ aq. solution (40 ml) and Norit (3.61 g). Colorless oil (11.1 g). A part of this oil was purified by distillation [bp 240—245 °C (2 mmHg)]. *Anal.* Calcd for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found: C, 63.97; H, 6.04. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (CO). ^{1}H-NMR δ: 1.70—2.68 (4H, m, $CHC\underline{H}_2C\underline{H}_2Ar$), 3.56—4.08[10] (1H, m, $ArC\underline{H}CH_2$), 3.79, 3.82, and 3.88 (each 3H, s, OCH_3), 5.88 (2H, s, OCH_2O), 6.53 (1H, s, C_3-H), 6.40—6.88 (3H, m, arom. H × 3), 6.81 (1H, s, C_6-H), 8.00—8.88 (1H, br s, COOH).

General Method for Synthesis of the 2-Aryl-1-tetralone (4) from the Methylene-acid (5)——A mixture of the methylene-acid (**5**) and $POCl_3$ in abs. $CHCl_3$ was refluxed, poured into water, and then extracted with $CHCl_3$. The organic layer was washed with 5% $NaHCO_3$ aq., dried over K_2CO_3, and then evaporated to dryness *in vacuo*. Recrystallization of the residue from a suitable solvent gave the desired product (**4**).

6,7-Methylenedioxy-2-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (4a)——The general method was applied to a solution of the methylene-acid (**5a**) (21.4 g) in abs. $CHCl_3$ (110 ml) with $POCl_3$ (67 ml). The reaction time was 3 h. Colorless needles (18.3 g), mp 189—191 °C ($CHCl_3$–MeOH). *Anal.* Calcd for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.94; H, 5.68. IR ν_{max} cm^{-1}: 1665 (CO). ^{1}H-NMR δ: 2.20—2.50 (2H, m, C_3-H_2), 2.85—3.05 (2H, m, C_4-H_2), 3.62 (1H, t, J=7.5 Hz, C_2-H), 3.80 (9H, s, OCH_3 × 3), 5.98 (2H, s, OCH_2O), 6.35 (2H, s, $C_{2'}$- and $C_{6'}$-H), 6.64 and 7.50 (each 1H, s, C_5- and C_8-H).

2-(2-Methoxy-4,5-methylenedioxyphenyl)-6,7-methylenedioxy-3,4-dihydronaphthalen-1(2*H*)-one (4b)——The general method was applied to a solution of the methylene-acid (**5b**) (3.24 g) in abs. $CHCl_3$ (20 ml) with $POCl_3$ (10.5 ml). The reaction time was 105 min. Colorless prisms (1.96 g), mp 162—165 °C (MeOH–$CHCl_3$ or benzene–cyclohexane). In this case, purification by column chromatography on Al_2O_3 with benzene was carried out. *Anal.* Calcd for $C_{19}H_{16}O_6$: C, 67.05; H, 4.75. Found: C, 67.12; H, 4.76. IR ν_{max} cm^{-1}: 1675 (CO). UV λ_{max} nm (log ε): 235 (4.35), 276 (3.93), 310 (4.08). ^{1}H-NMR δ: 2.05—2.50 (2H, m, C_3-H_2), 2.70—3.10 (2H, m, C_4-H_2), 3.68 (3H, s, OCH_3), 3.91 (1H, dd, J=11.0 and 5.0 Hz, C_2-H), 5.87 and 5.98 (each 2H, s, OCH_2O), 6.52, 6.54, 6.65, and 7.49 (each 1H, s, $C_{3'}$-, $C_{6'}$-, C_5-, and C_8-H).

2-(5-Methoxy-2,3-methylenedioxyphenyl)-6,7-methylenedioxy-3,4-dihydronaphthalen-1(2*H*)-one (4c)——The general method was applied to a solution of the methylene-acid (**5c**) (3.00 g) in abs. $CHCl_3$ (15 ml) with $POCl_3$ (9.3 ml). The reaction time was 2 h. Colorless pillars (2.08 g), mp 144—147 °C (EtOH). *Anal.* Calcd for $C_{19}H_{16}O_6$: C, 67.05; H, 4.75. Found: C, 66.92; H, 4.72. IR ν_{max} cm^{-1}: 1675 (CO). ^{1}H-NMR δ: 2.10—2.64 (2H, m, C_3-H_2), 2.98 (2H, dd, J=10.0 and 5.0 Hz, C_4-H_2), 3.70 (3H, s, OCH_3), 3.73 (1H, dd, J=10.5 and 5.5 Hz, C_2-H), 5.85 and 5.98 (each 2H, s, OCH_2O), 6.11 and 6.40 (each 1H, d, J=2.5 Hz, $C_{6'}$- and $C_{4'}$-H), 6.66 and 7.51 (each 1H, s, C_5- and C_8-H).

The starting material (**5c**) (0.74 g) was recovered from the $NaHCO_3$ washings.[18)]

2-(3,5-Dimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydronaphthalen-1(2*H*)-one (4d)——The general method was applied to a solution of the methylene-acid (**5d**) (0.10 g) and $POCl_3$ (1 ml) without $CHCl_3$ as a solvent. The reaction time was 4 min. Colorless pillars (0.055 g), mp 92—95 °C (benzene–hexane). *Anal.* Calcd for $C_{19}H_{18}O_5$: C, 69.92; H, 5.56. Found: C, 69.82; H, 5.59. IR ν_{max} cm^{-1}: 1665 (CO). ^{1}H-NMR (CCl_4) δ: 2.30 (2H, q, J=6.5 Hz, C_3-H_2), 2.88 (2H, t, J=6.5 Hz, C_4-H_2), 3.51 (1H, t, J=6.5 Hz, C_2-H), 3.72 (6H, s, $OCH_3 \times 2$), 5.95 (2H, s, OCH_2O), 6.17 (3H, dif. s, arom. H × 3), 6.54 and 7.41 (each 1H, s, C_5- and C_8-H).

2-(3,4-Dimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydronaphthalen-1(2*H*)-one (4f)——The general method was applied to a solution of the methylene-acid (**5f**) (17.5 g) in abs. $CHCl_3$ (85 ml) with $POCl_3$ (52.5 ml). The reaction time was 3 h. Colorless prisms (11.5 g), mp 176—177.5 °C (MeOH–$CHCl_3$) (lit. mp 170—172 °C;[2b)] mp 165 °C;[2c)] mp 171—172 °C[2d)]). *Anal.* Calcd for $C_{19}H_{18}O_5$: C, 69.92; H, 5.56. Found: C, 69.80; H, 5.53. IR ν_{max} cm^{-1}: 1665 (CO). ^{1}H-NMR δ: 2.20—2.50 (2H, m, C_3-H_2), 2.80—3.10 (2H, m, C_4-H_2), 3.66 (1H, t, J=8.0 Hz, C_2-H), 3.86 (6H, s, $OCH_3 \times 2$), 5.97 (2H, s, OCH_2O), 6.65 and 7.49 (each 1H, s, C_5- and C_8-H), 6.68 (1H, d, J=2.0 Hz, $C_{2'}$-H), 6.70 (1H, dd, J=8.5 and 2.0 Hz, $C_{6'}$-H), 6.82 (1H, d, J=8.5 Hz, $C_{5'}$-H).

6,7-Methylenedioxy-2-(3,4-methylenedioxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (4g)——The general method was applied to a solution of the methylene-acid (**5g**) (4.82 g) in abs. $CHCl_3$ (25 ml) with $POCl_3$ (15.4 ml). The reaction time was 4.2 h. Colorless needles (3.86 g), mp 176—179 °C (benzene–hexane) (lit.[2e)] mp 170—171 °C). IR ν_{max} cm^{-1}: 1650 (CO). ^{1}H-NMR δ: 2.16—2.50 (2H, m, C_3-H_2), 2.80—3.10 (2H, m, C_4-H_2), 3.67 (1H, dd, J=9.0 and 7.5 Hz, C_2-H), 5.90 and 5.98 (each 2H, s, OCH_2O), 6.30—6.86 (4H, m, arom. H × 4), 7.48 (1H, s, C_8-H).

6,7-Dimethoxy-2-(2,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (4h)——The general method was applied to a solution of the crude oily methylene-acid (**5h**) (6.89 g) in abs. $CHCl_3$ (35 ml) with $POCl_3$ (21 ml). The reaction time was 2 h. Colorless prisms (4.45 g), mp 152—154 °C (EtOH). *Anal.* Calcd for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Found: C, 67.71; H, 6.50. IR ν_{max} cm^{-1}: 1675 (CO). ^{1}H-NMR δ: 2.08—2.60 (2H, m, C_3-H_2), 2.79—3.14 (2H, m, C_4-H_2), 3.58—4.08[10)] (1H, m, C_2-H), 3.74, 3.78, 3.88, 3.92, and 3.94 (each 3H, s, OCH_3), 6.55, 6.63, 6.68, and 7.56 (each 1H, s, $C_{3'}$-, $C_{6'}$-, C_5-, and C_8-H).

6,7-Dimethoxy-2-(2-methoxy-4,5-methylenedioxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (4i)——The general method was applied to a solution of the methylene-acid (**5i**) (8.36 g) in abs. $CHCl_3$ (42 ml) with $POCl_3$ (25 ml). The reaction time was 2 h. Colorless prisms (6.00 g), mp 209—211 °C (MeOH–$CHCl_3$). *Anal.* Calcd for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.12; H, 5.55. IR ν_{max} cm^{-1}: 1655 (CO). ^{1}H-NMR δ: 2.02—2.54 (2H, m, C_3-H_2), 2.82—3.10 (2H, m, C_4-H_2), 3.70, 3.91, and 3.94 (each 3H, s, OCH_3), 3.82—4.06[10)] (1H, m, C_2-H), 5.86 (2H, s, OCH_2O), 6.54 (2H, s, $C_{3'}$- and $C_{6'}$-H), 6.66 and 7.55 (each 1H, s, C_5- and C_8-H).

6,7-Methylenedioxy-2-(2,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (4l)——The general method was applied to a solution of the crude oily acid (**5l**) which was prepared from the keto-acid (**6l**) (10.0 g) by hydrogenolysis in abs. $CHCl_3$ (50 ml) with $POCl_3$ (29 ml). The reaction time was 3 h. Colorless prisms (7.31 g), mp 137—139 °C (MeOH–$CHCl_3$). *Anal.* Calcd for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.68; H, 5.53. IR ν_{max} cm^{-1}: 1680 (CO). ^{1}H-NMR δ: 2.00—2.58 (2H, m, C_3-H_2), 2.72—3.12 (2H, m, C_4-H_2), 3.54—4.04[10)] (1H, m, C_2-H), 3.72, 3.78, and 3.87 (each 3H, s, OCH_3), 5.97 (2H, s, OCH_2O), 6.54, 6.62, 6.66, and 7.51 (each 1H, s, $C_{3'}$-, $C_{6'}$-, C_5-, and C_8-H).

Cyclization of 2-(4,5-Dibenzyloxy-2-methoxyphenyl)-4-(3,4-methylenedioxyphenyl)butyric Acid (5e) [2-(4,5-Dibenzyloxy-2-methoxyphenyl)-6,7-methylenedioxy-3,4-dihydronaphthalen-1(2*H*)-one (4e)]——A mixture of the methylene-acid (**5e**) (0.10 g) with $SOCl_2$[19)] (0.48 ml) was stirred for 30 min under ice-cooling. The excess of $SOCl_2$ was evaporated off at room temperature under reduced pressure. The residue [IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1800 (COCl), nil (COOH)] was dissolved in dry $CHCl_3$ (0.5 ml). After addition of $SnCl_4$ (0.09 ml), the solution was stirred for 30 min under ice-cooling, poured onto ice water, and extracted with $CHCl_3$. The chloroform solution was washed with sat. $NaHCO_3$ aq., dried over $MgSO_4$, and evaporated to dryness *in vacuo*. After purification of the residue by preparative TLC on SiO_2 ($CHCl_3$, *Rf*=0.3), recrystallization of the crude material from benzene–hexane gave colorless needles (0.072 g), mp 139—141 °C. *Anal.* Calcd for $C_{32}H_{28}O_6$: C, 75.57; H, 5.55. Found: C, 75.66; H, 5.52. IR ν_{max} cm^{-1}: 1670 (CO). ^{1}H-NMR δ: 2.00—2.44 (2H, m, C_3-H_2), 2.80—3.00 (2H, m, C_4-H_2), 3.65 (3H, s, OCH_3), 3.88 (1H, dd, J=10.0 and 5.0 Hz, C_2-H), 5.00 and 5.12 (each 2H, s, OCH_2Ph), 5.96 (2H, s, OCH_2O), 6.57, 6.64, 6.68, and 7.50 (each 1H, s, $C_{3'}$-, $C_{6'}$-, C_5- and C_8-H), 7.32 (10H, m, arom. H × 10).

References and Notes

1) *a*) 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]; *b*) Part XLIX, H. Ishii, T. Ishikawa, T. Deushi, K.-I. Harada, T. Watanabe, E. Ueda, T. Ishida, M. Sakamoto, E. Kawanabe, T. Takahashi, Y.-I. Ichikawa, K. Takizawa, T. Masuda, and I.-S. Chen, *Chem. Pharm. Bull.*, **31**, 3024 (1983).

2) *a*) T. Richardson, R. Robinson, and E. Seijo, *J. Chem. Soc.*, **1937**, 835; *b*) K.-Y. Zee-Cheng and C. C. Cheng, *J. Heterocycl. Chem.*, **10**, 85, 867 (1973); R. K. -Y. Zee-Cheng and C. C. Cheng, *J. Med. Chem.*, **18**, 66 (1975); K. Y. Zee-Cheng and C.-C. Cheng, U. S. Patent Appl. 557183 (1975) [*Chem. Abstr.*, **86**, 171705p (1977)]; *c*) H. R. Arthur and Y. L. Ng, *J. Chem. Soc.*, **1959**, 4010; *d*) K. W. Gopinath, T. R. Govindachari, P. C. Parthasarathy, and N. Viswanathan, *ibid.*, **1959**, 4012; *e*) K. W. Gopinath, T. R. Govindachari, and N. Viswanathan, *Tetrahedron*, **14**, 322 (1961).

3) 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).

4) 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; 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); 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).

5) F. Mauthner, *Chem. Ber.*, **41**, 920 (1908).

6) A detailed discussion on the mechanism of formation of the unsaturated keto-acid (**9**) including the evidence for actual intervention of the unsaturated keto-amide (**14**) during the reaction and the assignment of the geometrical structure of the unsaturated keto-acid (**9**) will be published in the near future.

7) For example, heating of a suspension of the 2-methoxy-4,5-methylenedioxy-γ-keto-amide (**3i**) (0.20 g) in a mixture of EtOH (15 ml) and 7% NaOH aq. (3.3 ml) for 10 h gave a reaction mixture showing no spot corresponding to the γ-keto-acid (**6i**).

8) Anhydrous palladium chloride (1.0 g) was dissolved in concentrated hydrochloric acid (2.5 ml) and water (6.0 ml). Then, the total volume of the resulting solution was made up to 60 ml by addition of water.

9) F. Mauthner, "Organic Syntheses," Coll. Vol. I, 2nd ed., ed. by A. H. Blatt, John Wiley and Sons, Inc., New York, 1956, p. 537.

10) The precise splitting pattern of this signal could not be observed because of overlapping with the signals due to a methoxy group.

11) The crystal form of this material changed from needles to plates at 144—145 °C and the latter melted at 165—167 °C.

12) This material was so poorly soluble in Et_2O that the crude material was collected by addition of water followed by filtration in a large scale experiment.

13) H. Adkins and H. R. Billica, *J. Am. Chem. Soc.*, **70**, 695 (1948); H. R. Billica and H. Adkins, "Organic Syntheses," Coll. Vol. III, ed. by E. C. Horning, John Wiley and Sons, Inc., New York, 1955, p. 176.

14) In the ^{1}H-NMR spectra of the keto-acids (**6**), no signal due to the proton of a carboxylic acid could be observed. This phenomenon may be ascribed to hydrogen bonding between the proton and the ketonic oxygen.

15) Continuous heating of the reaction mixture was absolutely required for completion of the reaction. When heating was stopped during the reaction, an undefined by-product which was insoluble in most solvents was formed.

16) The melting point of the crude material is higher than that of the recrystallized product. This phenomenon may be explained by dimorphism, because the IR spectrum of the crude material is slightly different from that of the recrystallized product, although the former showed only one spot having the same *Rf* value as that of the latter on TLC.

17) In another run, hydrolysis of the keto-nitrile (**2h**) (1.00 g) in H_2O (11.0 ml) containing EtOH (4.5 ml) and NaOH (1.04 g) according to the general method without argon gave the keto-acid (0.66 g) (**6h**). The mother liquor of recrystallization of the keto-acid (**6h**) gave 4-(3,4-dimethoxyphenyl)-4-oxo-2-(2,4,5-trimethoxyphenyl)-2-butenoic acid as red needles (0.060 g), mp 185—187 °C (dec.), which were recrystallized from EtOH. *Anal.* Calcd for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51. Found: C, 62.43; H, 5.65. IR ν_{max} cm^{-1}: 1730 and 1640 (CO). ^{1}H-NMR δ: 3.67, 3.69, 3.81, 3.85, and 3.89 (each 3 H, s, OCH_3), 6.38, 6.64, and 7.60 (each 1 H, s, C_3-, C_6- and COCH$=$CAr), 6.76 (1 H, d, $J=8.5$ Hz, $C_{5'}$-H), 7.34 (1 H, d, $J=2.0$ Hz, $C_{2'}$-H), 7.52 (1 H, dd, $J=8.5$ and 2.0 Hz, $C_{6'}$-H), 7.30—

7.90 (1 H, br s, COOH).

18) The cyclization of the methylene-acid (**5c**) under stronger conditions such as PCl_5-$SnCl_4$ or prolonged heating of the reaction mixture did not give a better result.

19) Treatment of the methylene-acid (**5e**) with $POCl_3$ in $CHCl_3$ or without solvent provided a mixture showing many spots on TLC.