Solution of the problem concerning the relations of components of aconites and their kinds or their circumstances must be acted by cooperation of chemists and botanists. However, the author's observations in wild states of many kinds maintain the opinion that many kinds recorded as many species hitherto are thought to be almost local forms, there are merely a few species in Japanese aconites. And then, the opinion accords with hitherto mentioned results of statistical studies.

At last, internal structures of tuberous roots of Japanese aconites resemble closely each other and are almost impossible to discriminate definitely, as expressing in this series of studies, so native tuberous roots must not be used for medicine except after the strict determinations of toxicity and pharmacological actions. Therefore, in order to utilize native Japanese aconites, pharmacological studies must be performed on crude drugs which are prepared by detoxication of poisonous tuberous roots or from cultivation of nontoxic plants, namely *A. luciduscul*um NAKAI, *A. sanyoense* NAKAI and its var. *tonense* NAKAI, and two unidentified kinds growing in Shimoburo in Shimokita Peninsula and Mt. Takao in Tokyo Prefecture.

The author expresses his deep gratitude to Prof. K. Kimura and Dr. J. Okada of Kyoto University for their guidance throughout the course of these studies. The author also expresses his gratitude to President T. Ukai of this College, to Emeritus Prof. E. Ochiai, and to Prof. F. Maekawa of University of Tokyo and Mr. A. Ueno of this College for valuable advices and encouragements. He is indebted to Drs. I. Igura, H. Ageta, T. Kikuchi, Messrs. K. Hosoi, T. Satomi, S. Gomi, Z. Mizuochi, Misses Y. Amano, K. Tujimoto, R. Yamamoto, Mr. M. Fujita, Miss K. Iwase and many co-operating persons for collection of acontites, and to Mr. T. Ohmura for conveyance of literature. Furthermore many forest offices of each locality in this country co-operated for collection of native aconites, to whom the author's thanks are expressed.

Summary

By combining the results from previous papers, Japanese aconites are devided into several structural types by use of average results conveniently.

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44. Takahiro Nakamura, Yasuhiro Murase, Ryozo Hayashi, and Yonekichi Endo : Studies on the Total Synthesis of *dl*-Colchiceine.[1] I. Synthesis of 3-Hydroxy-9,10,11-trimethoxy-1,2,3,4,6,7-hexahydro-5*H*-dibenzo[*a*,*c*]cycloheptatrien-5-one.

(*Takamine Laboratory, Sankyo CO., Ltd.*[*1])

The structure of colchicine, the chief alkaloid of *Colchicum autumnale* L., has been established as formula (I). Absolute configuration of the amido group in the B-ring was determined by Corrodi and others,[2] the structure of the C-ring was proposed by Šantavý and Čech,[3] and confirmed by X-ray defraction work by Pepinsky and others.[4]

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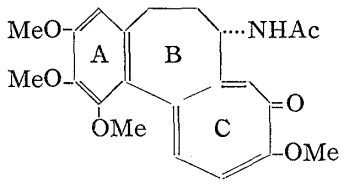
1) A part of this work has been published as brief communications in This Bulletin, 8, 843 (1960); 9, 81 (1961).
2) H. Corrodi, E. Hardegger : Helv. Chim. Acta, 38, 2030 (1955).
3) J. Čech, Fr. Šantavý : Collection Czechoslov. Chem. Communs., 14, 532 (1949).
4) M. V. King, J. L. de Vries, R. Pepinsky : Acta Cryst., 5, 437 (1952).



(I)

Total synthesis of colchicine was finally achieved by Eschenmoser and others.[5] and by van Tamelen and others[6] in 1959. Reports published to date on the synthesis of colchicine and related compounds may be classified into two kinds, the one of making the A- and B-rings first, followed by formation of the C-ring, and the other of makihg the A- and C-rings first, followed by cyclization of the B-ring. The total synthesis of the foregoing two workers followed the first method. Many reported[7] have been made on the latter method but they are all still incomplete.

The synthesis planned in this laboratory is the latter method of forming the A- and C-rings first and then the B-ring is cyclized to form the colchicine ring. Further, it was planned to form the six-membered ketone C-ring first and to extend this into a seven-membered ketone ring. As a preliminary experiment, Pechmann condensation of ethyl 2-oxo-5-hydroxycyclohexanecarboxylate (Ⅲ) was attempted.

(Ⅲ) was obtained by Dieckmann cyclization of diethyl 4-hydroxypimelate (Ⅱ), obtained by the reduction of diethyl γ-oxo-pimelate.[8] This γ-hydroxy compound (Ⅱ) undergoes dealcoholation on distillation and the majority forms a γ-lactone (Ⅱ′), since the infrared spectrum of undistilled, crude (Ⅱ) exhibits absorptions for hydroxyl at 2.83 μ and ester carbonyl at 5.76 μ, while that of the liquid (Ⅱ′) obtained by distillation at $b.p_{0.015}$ 112° shows a new absorbtion at 5.62 μ for γ-lactone, besides absorption for ester carbonyl at 5.76 μ, and the absorption at 2.83 μ for hydroxyl is no longer present. Consequently, this product is a γ-lactone, i.e. ethyl 5-oxo-tetrahydro-2-furanpropionate (Ⅱ′). Therefore, (Ⅱ) was submitted to the Dieckmann reaction with sodium hydride without distillation and (Ⅲ) was successfully obtained.

The Pechmann condensation of (Ⅲ) and pyrogallol, with phosphoryl chloride, methanesulfonic acid, or 75% sulfuric acid as the condensation agent, afforded scaly crystals (Ⅳ). The best yield was obtained by the use of phosphoryl chloride. The infrared spectrum of (Ⅳ) exhibits a new strong absorption at 5.96 μ, assumed to correspond to coumarin carbonyl and it was therefore considered to be a coumarin compound. The Pechmann condensation would result in formation of a coumarin or chromone compound but it is clear that (Ⅳ) is a coumarin compound since ring cleavage of (Ⅳ) with alkali gives coumaric acid, without formation of *o*-hydroxy ketone or *o*-hydroxy acid, and its acidification reverts it to (Ⅳ). Application of alkali and dimethyl sulfate to the coumarin compound (Ⅳ) affords coumaric acid, i.e. 2-(2,3,4-trimethoxyphenyl)-5-hydroxy-1-cyclohexenecarboxylic acid (Ⅴ). The foregoing experiments have proved that the 5-hydroxy compound can be utilized for the Pechmann reaction.

5) J. Schreiber, W. Leingruber, M. Pesaro, P. Schudel, T. Threlfall, A. Eschenmoser: Angew. Chem., **71**, 637 (1959); Helv. Chim. Acta, **44**, 540 (1961).
6) E.E. van Tamelen, J.A. Spencer, Jr., D.A. Allen, Jr., R.L. Oevis: J. Am. Chem. Son., **81**, 6341 (1959).
7) H. Rapoport, A.R. Williams, M.E. Cisney: J. Am. Chem. Soc., **73**, 1414 (1951); J.W. Cook, J. Jack, J.D. Loudon: J. Chem. Soc., **1951**, 1397; V. Boekelheide, F.C. Pennington: J. Am. Chem. Soc., **74**, 1558 (1952); H.J.E. Loewenthal: J. Chem. Soc., **1953**, 3962, **1958**, 1367; C.D. Gutsche, F.A. Fleming: J. Am. Chem. Soc., **76**, 1771 (1954); T. Nozoe, K. Takase, Y. Kitahara, K. Doi: Paper presented at the 132nd National Meeting of the American Chemical Society, New York, 1957; K. Takase, T. Meguro, H. Akiyama, T. Nozoe: Paper presented at the 11th Annual Meeting of the Chemical Society of Japan, 1958; H.J.E. Loewenthal, P. Rana: Proc. Chem. Soc., **1958**, 114.
8) Org. Syntheses, **33**, 25 (1953).

The Pechmann condensation of (III) and 3-methoxy-4,5-dihydroxyhydrocinnamic acid (VII) was attempted but the condensation did not take place, due probably to the interference of the carboxyethyl group in (VII). This has shown that a coumarin compound with carboxyethyl group in 1-positon cannot be obtained directly from the Pechmann condensation.

The Pechmann condensation of (III) with 1-O-methylpyrogallol[9] as in the case of pyrogallol gave the coumarin compound (VIII), although the yield was best, in this case, with the use of methanesulfonic acid.*[2] The infrared spectrum of (VIII) exhibited absorption at 5.92 μ, assumed to be that of coumarin carbonyl, and its ultraviolet spectrum had absorption maxima at 262 and 315 mμ. Ring cleavage of (VIII) with alkali and methylation of its product with dimethyl sulfate gave a compound identical with the above-mentioned coumaric acid, 2-(2,3,4-trimethoxyphenyl)-5-hydroxy-1-cyclohexenecarboxylic acid (V), obtained from the coumarin compound (IV).

Allylation of this coumarin compound (VIII) and the Claisen rearrangement of this 4-allyloxy compound (IX) resulted in the rearrangement of the allyl group to the *para*(1)-position to form the 1-allyl compound (X) soluble in alkali. This allyl compound (X) was heated with alkali to effect isomerization and 1-(propenyl)compound (XI) was obtained. The infrared spectrum of (XI) no longer contained the allyl absorptions at 10.41 and 10.96 μ present in (X) but showed a strong absorption at 10.26 μ for a propenyl group.

Application of 1 mole of ozone in the cold to the 1-propenyl compound (XI) afforded 1-formyl compound (XII), soluble in sodium hydrogen sulfite solution. Infrared spectrum of (XII) showed absorptions for an aldehyde at 6.02 μ and coumarin carbonyl at 5.86 μ, which suggests that ozone had oxidized the double bond in the propenyl side chain to form an aldehyde, without attacking the double bond in the coumarin ring. Application of more than 1 mole of ozone results in the attack of the coumarin ring and the product is an uncrystallizable oil. The phenolic hydroxyl in the 4-position of the 1-formyl compound (XII) is highly acidic, as in vanillin, and the compound is soluble in sodium hydrogen carbonate.

Treatment of the 1-formyl compound (XII) with alkali and then with dimethyl sulfate, as in the case of the coumarin compound (IV), gives the coumaric acid of (XII), the cyclohexenecarboxylic acid (XIII), which indicates that the 1-formyl compound (XII) has a coumarin ring. The infrared spectrum of this coumaric acid (XIII) exhibits absorptions for alcoholic hydroxyl at 2,92 μ, carboxylic acid at 3.8~4.0 μ, for α,β-unsaturated carboxylic acid at 5.92 μ, and for aldehyde at 5.94 μ, which fact endorses (XII) as an aldehyde compound with a coumarin ring. Attempt to change the carboxyl in (XIII) to a methyl-ketone group ended fruitless.

Heating of the 1-formyl compound (XII) with malonic acid at 50° for 22 hours resulted in Knoevenagel condensation to form the carboxylic acid derivative (XIV), which was found to be a dicarboxylic acid and not the objective monocarboxylic acid from its analytical values. This 1-(2,2-dicarboxyethylene) compound (XIV) was hydrogenated and heated to effect decarboxylation, from which a monocarboxylic acid was obtained to show that the original (XIV) was a dicarboxylic acid. Attempt to obtain the monocarboxylic acid directly from the 1-formyl compound (XII) by the Knoevenagel condensation by the usual reaction did not materialize.

Catalytic reduction of (XIV) over palladium-charcoal catalyst resulted in absorption of one mole of hydrogen. The ultraviolet spectrum of this hydrogenation product (XV) shows strong absorption maxima at 266 and 329 mμ, suggesting that a conjugated double bond still remains. Loewenthal[10] did not succeed in the reduction of 2-(2,3,4-trimethoxy-

*[2] Cf. V. Boekelheide and F.C. Pennington's work in Footnote (7).

9) Org. Syntheses, **26**, 90 (1946).

10) H.J.E. Loewenthal: J. Chem. Soc., **1953**, 3962; **1962**, 1367.

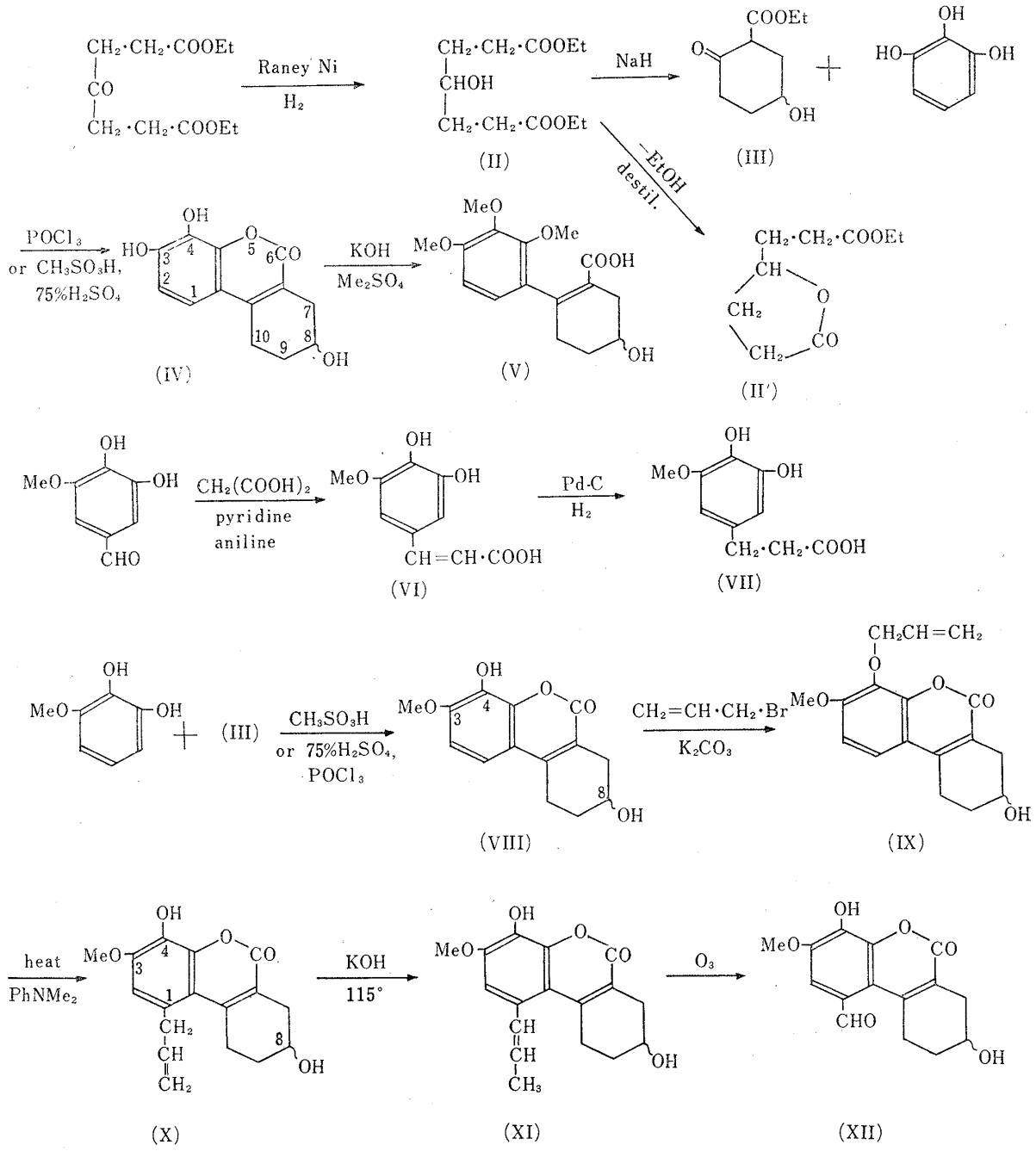


Chart 1. (1)

phenyl)-1-cyclohexenecarboxylic acid either over Adams platinum in neutral solution or over Raney Nickel in alkaline solution, and finally obtained cyclohexanecarboxylic acid by reduction with metallic lithium in liquid ammonia. The double bond in the coumarin ring of (XIV), which is structurally similar to the above acid, is assumed to be more resistant to reduction over palladium-charcoal in neutral solution and the hydrogenation is more likely to occur in the ethylenic double boud in the side chain. In general, infrared absorption of carbonyl in Ph-O-CO-CH_2CH_2-R is likely to be in a shorter wavelength region than that in Ph-O-CO-CH=CH-R[11] and, if the hydrogeation of the 1-(2,2-dicarboxyethylene) compound (XIV) had occurred in the coumarin ring, its carbonyl absorp-

11) L. J. Bellamy: "The Infra-red Spectra of Complex Molecules," 178 (1958). Methuen & Co., London.

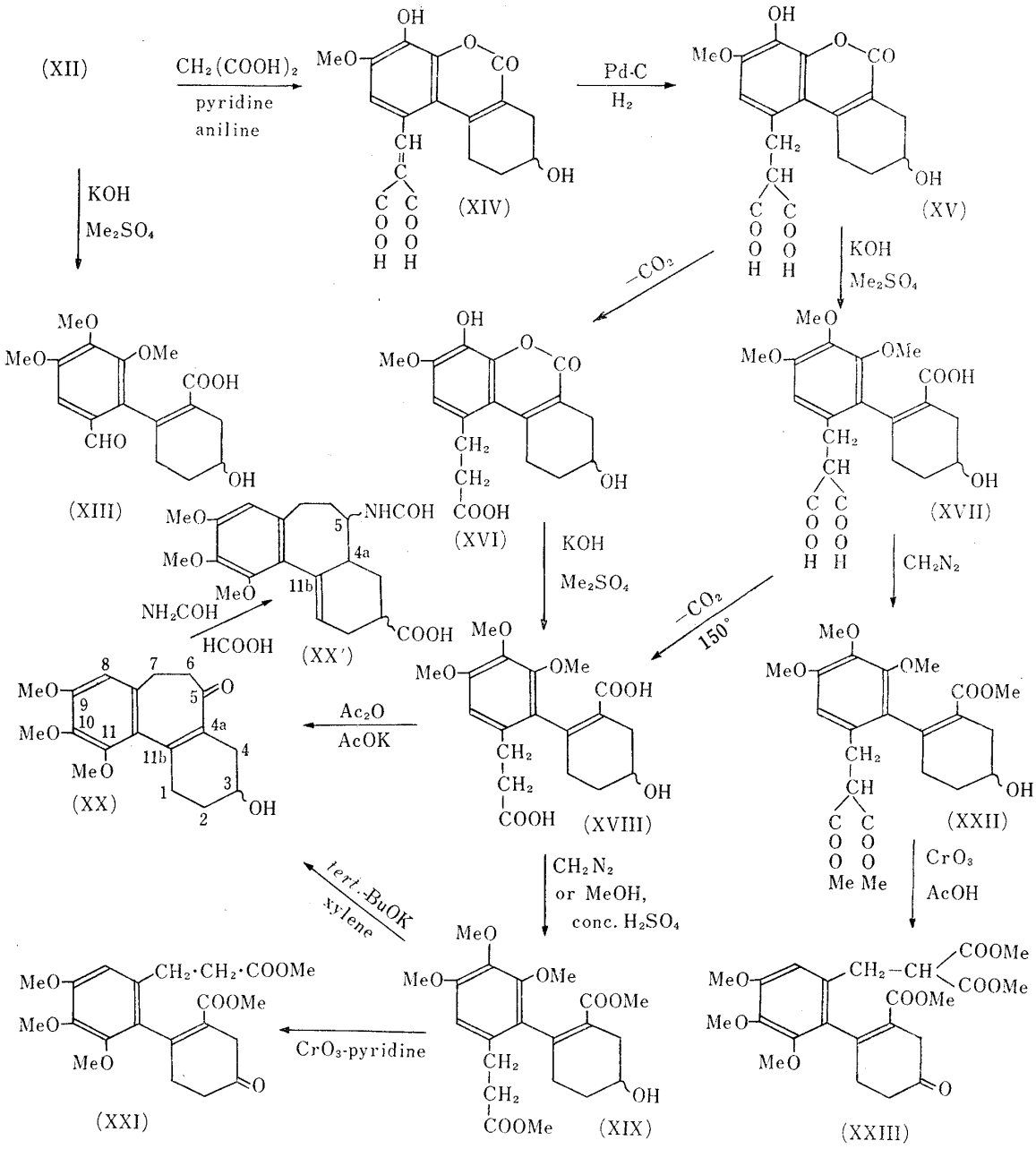


Chart 1. (2)

tion should have shifted to the shorter wave-length region. Actually, however, the absorption bands that could be assigned to coumarin carbonyl in (XIV), its hydrogenation product (XV), and its decarboxylated product (XVI) are respectively at 6.00, 6.06, and 6.08 μ, the shift being rather to the longer wave-length region, and this fact indicates that the coumarin ring has not been saturated. Further, if the ethylenic double bond still remains, decarboxylation should give a *trans*-cinnamic acid, with infrared absorption of CH in -CH=CH-, but there is no strong absorption corresponding to it at 10.3~10.4 μ in the decarboxylated compound (XVI). The foregoing evidences also indicate the presence of a coumarin ring in 1-(2,2-carboxyethyl) compound (XV), In addition, as will be described later, the formation of the cyclized B-ring ketone compound (XX) from (XVIII) and (XIX) by the Dieckmann intramolecular condensation indicates that there is an active methylene group in the hydrogenated product (XV), i.e. absence of a double bond in the side chain. Consequently, conjugated double bond in (XV) shows the presence of a coumarin ring.

The decarboxylated product (XVI) had been obtained by heating 1-(2,2-dicarboxyethyl) compound (XV) at 150° for 20 hours and this is 3-methoxy-6-oxo-4,8-dihydroxy-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*, *d*]pyran-1-propionic acid (XVI), which was not obtained directly by the Pechmann condensation, following the method of Boekelheide and others.[8] If this decarboxylation is carried out after ring-cleavage of the coumarin ring, the reaction is completed in 1~2 hours at 150°. In this case, 1-(2,2-dicarboxyethyl) compound (XV) is treated with alkali to open its coumarin ring and methylated with dimethyl sulfate by which the coumaric acid, 2-[2,3,4-trimethoxy-6-(2,2-dicarboxyethyl)phenyl]-5-hydroxy-1-cyclohexenecarboxylic acid (XVII), is obtained, as in the case of the coumarin compound (IV), and decarboxylation of (XVII) gives the 6-(2-carboxyethyl) compound (XVIII), which is also obtained by ring-opening of the coumarin compound (XVI), followed by methylation.

Esterification of (XVIII) and Dieckmann condensation results in cyclization, and subsequent saponification and decarboxylation yields a neutral substance which must be a ketone compound (XX) since it forms a 2,4-dinitrophenylhydrazone. The same ketone compound is obtained by heating the dicarboxylic acid (XVII) in acetic anhydride to effect dehydration and decarboxylation, though the yield is smaller than that from the Dieckmann condensation. The infrared absorption of (XX) exhibits absorptions for α,β-unsaturated conjugated carbonyl at 6.00 μ and for hydroxyl at 2.86 μ, which indicates that there is a double bond common to B- and C-rings in (XX). The presence of a double bond conjugated to the phenyl group in (XX) can be understood from the following fact. The amide compound (XX′), obtained by the Leuckart reaction of (XX), has absorption maxima at 218 and 249 mμ in its ultraviolet spectrum, and this spectrum is the same as that characteristic to tricyclic amide compound possessing a colchicine spectrum, which will be described in the following paper. Consequently, the presence of a double bond conjugated to the phenyl group in (XX′) is reliable and its position is considered to be the same as that described in the following paper. Therefore, the compound (XX′) should be 3-formyloxy-5-formamido-9,10,11-trimethoxy-2, 3, 4, 4a, 6, 7-hexahydro-5*H*-dibenzo[*a*, *c*]cycloheptatriene. It is certain, therefore, that a double bond conjugated to phenyl group is also present in (XX) and its position is assumed to be 4a-11b from the fact that infrared spectrum of (XX) exhibits absorption for α,β-unsaturated conjugated carbonyl at 6.00 μ. However, the ultraviolet spectrum of (XX) has absorption maxima at 235 and 283 mμ (log ε 3.56), and a shoulder at 308 mμ (log ε 3.40), which dose not give enough evidence to suggest the double bond at 4a-11b position. On the other hand, compounds with α,β-unsaturated carbonyl, like (V), (XVII), and (XVIII), show absorption maximum in the region of 270~280 mμ, and the absorption maximum at 283 mμ and a shoulder at 308 mμ in (XX) are not sufficient evidence to deny the presence of a double bond at 4a-11b position. It may therefore be assumed from infrared data that the double bond in (XX) is at 4a-11b.

The tricyclic ketone compound, 3-hydroxy-9,10,11-trimethoxy-1,2,3,4,6,7-hexahydro-5*H*-dibenzo[*a*, *c*]cycloheptatrien-5-one (XX), has now been synthesized and the next step would be the troponlonization of the C-ring. In a tricyclic ketone compound like (XX), the ketone group in the B-ring (or even if changed to an amino group) would interfere in the extension of the C-ring and it was considered better to form a seven-membered ring ketone first and followed by cyclization of the B-ring.

Oxidation of the dicarboxylic ester (XIX) and tricarboxylic ester (XXII) with chromium trioxide in pyridine or acetic acid respectively afforded a cyclohexenone compound (XXI) and (XXIII), both of which produced a large amount of reddish orange precipitate on reaction with 2,4-dinitrophenylhydrazine, indicating that they are ketone compounds. Application of diazomethane to these six-membered ketone compounds (XXI and XXIII) failed to cause their reaction and attempt was made for ring enlargement by the Tiffeneau reac-

tion,[12] which is side to be effective with unsaturated ring ketones. Attempt was first made to change the ketone group to aminomethyl-alcohol group but derivation to cyanohydrin was unsuccessful. Attempt to form a nitromethyl-alcohol group with methyl nitrite also failed. Attempted ring enlargement of cyclohexene compounds (XXI and XXIII) to cycloheptenone compounds all ended fruitless.

Experimental*3

Diethyl 4-Hydroxypimelate (II)——A solution of 200 cc. of diethyl γ-oxopimelate dissolved in 200 cc. of MeOH, added with 100 g. of Raney-Ni W-5, was hydrogenated at ordinary temperature and pressure, by which 1 mole of H_2 was absorbed in 7~8 hr. Raney-Ni was filtered off, MeOH was evaporated from the filtrate at below 40°, and the residual liquid was dried at 40°/1 mm. Hg, from which 200 g. of a colorless liquid was obtained. *Anal.* Calcd. for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 55.06; H, 8.20. IR $\lambda_{max}^{liq.}$ μ: 2.83 (OH), 5.76 (ester-CO).

Distillation of (II) resulted in dealcoholation to form γ-lactone (II') as colorless liquid, b.$p_{0.005}$ 134.5°. *Anal.* Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.66; H, 8.01. IR $\lambda_{max}^{liq.}$ μ: 5.62 (CO in γ-lactione), 5.76 (ester-CO), 5.84.

Ethyl 2-Oxo-5-hydroxycyclohexanecarboxylate (III)——To a mixture of 28.3 g. (1.2 moles) of NaH in 330 cc. of dehyd. Et_2O, 25 cc. of a solution of 227 g. of (II) dissolved in 1.1 L. of dehyd. benzene was added in one portion, by which a vigorous reaction occured. When the reaction subsided, the remainder of the solution was added dropwise during 1 hr. into the solution warmed at 42° and the mixture was stirred at 42° for 8 hr. After allowing the mixture to stand over night at room temperature, 104 cc. of AcOH was added with stirring, followed by 104 cc. of H_2O. The whole was shaken thoroughly, a mixture of benzene and Et_2O was separated, and washed consecutively with H_2O, saturated solution of 60 g. of $NaHCO_3$, and H_2O. After drying, the solvent was evaporated and left 104 g. (57%) of a colorless liquid, b.$p_{0.1}$ 123°. Distillation was carried out in flask with a short neck and in several portions so that one distillation was finished within 15 min., at a temperature of the bath below 145°. *Anal.* Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.98; H, 7.52. IR $\lambda_{max}^{liq.}$ μ: 2.93 (OH), 5.76 (ester-CO), 5.84 (aliphatic ketone), 6.02 (chelated CO), 6.20 (enolic C=C). 2,4-Dinitrophenylhydrazone of (III): Yellow needles (from EtOH), m.p. 164°. *Anal.* Calcd. for $C_{15}H_{18}O_7N_4$: C, 49.18; H, 4.95; N, 15.30. Found: C, 49.24; H, 5.23; N, 15.13.

3,4,8-Trihydroxy-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*, *d*]pyran-6-one (IV)——A solution of 1.3 g. of pyrogallol and 1.1 g. of (III) dissolved in 8 cc. of dehyd. benzene, added with 0.27 cc. of $POCl_3$, was boiled for 5 hr., cooled, and benzene was decanted. The residue was washed with benzene, diluted with 50 cc. of H_2O, and the precipitate was collected by filtration. This was washed with water, dried, and recrystallized twice from EtOH to 0.9 g. (60%) of scaly crystals, m.p. 288°. *Anal.* Calcd. for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.52; H, 4.89. IR λ_{max}^{Nujol} μ: 2.96, 3.10 (OH), 5.96 (coumarin-CO).

2-(2,3,4-Trimethoxyphenyl)-5-hydroxy-1-cyclohexenecarboxylic Acid (V)——To a solution of 0.2 g. of (IV) dissolved in 3 cc. of 20% KOH solution, heated with stirring on a steam bath, in N_2 stream, 2.5 cc. of Me_2SO_4 and 13 cc. of 20% KOH solution were added alternately in drops during 3 hr. After standing the mixture over night, the mixture was filtrated, the filtrate was acidified, and extracted with AcOEt. The extract solution was washed with H_2O. dried, and AcOEt was evaporated. The residue was recrystallized from petr. ether and Et_2O to prisms, m.p. 159°. *Anal.* Calcd. for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54. Found: C, 62.32; H, 6.65. IR λ_{max}^{Nujol} μ: 2.92 (OH), 3.7~3.9 (OH in COOH), 5.96 (CO in C=C-COOH). UV: λ_{max}^{EtOH} 284 mμ (log ε 3.57).

3-Methoxy-4,5-dihydroxycinnamic Acid (VI)——A mixture of 16 g. of 3-methoxy-4,5-dihydroxybenzaldehyde[13] and 20 g. of malonic acid with 13.5 cc. of pyridine, added with 2 cc. of aniline, was allowed to stand at room temperature for 2 days. The mixture was then warmed at 50° for 30 min., cooled, acidified with 10% HCl, and extracted with Et_2O. The extract solution was washed with H_2O, dried, and Et_2O was evaporated. The residue was washed with H_2O and recrystallized from H_2O to 10.3 g. (51%) of needles, m.p. 182°. *Anal.* Calcd. for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80. Found: C, 57.40; H, 4.87. IR λ_{max}^{Nujol} μ: 2.74, 2.87, 2.98 (OH), 3.70, 3.85 (COOH), 5.97 (CO in C=C-COOH). UV λ_{max}^{EtOH} mμ (log ε): 237 (4.24), 322 (4.26).

3-Methoxy-4,5-dihydroxyhydrocinnamic Acid (VII)——A solution of 2 g. of $PdCl_2$ dissolved in 140 cc. of dli. HCl was mixed with 40 g. of (VI) and the mixture was shaken in H_2 stream at ordinary temperature and pressure, by which 4.5 L. of H_2 was absorbed in 4 hr. The solution was filtered,

*3 All m.p.s and b.p.s are uncorrected.

12) A. C. Cope, R. D. Smith: J. Am. Chem. Soc., **78**, 1012 (1956).

13) W. Bradley, R. Robinson, G. Schwarzenbach: J. Chem. Soc., **1930**, 811.

the filtrate was extracted with Et_2O, and the extract solution was washed with H_2O. Et_2O was evaporated and residual oil was recrystallized from Et_2O and petr. ether to 32 g. (80%) of needles, m.p. 95°. *Anal.* Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.65; H, 5.47. IR λ_{max}^{Nujol} μ: 2.96 (OH), 3.65~3.90 (COOH), 5.84 (CO in COOH). UV: λ_{max}^{EtOH} 272 mμ (log ε 3.12).

3-Methoxy-4,8-dihydroxy-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*, *d*]pyran-6-one (VIII)——A solution of 290 g. of 1-O-methylpyrogallol and 376.3 g. of (III) dissolved in 1.16 L. of cold $MeSO_3H$ was allowed to stand at room temperature for 20 hr. This was poured into 5.8 L. of ice-water, crystals that separated out were collected by filtration, washed with water, and dried to 530 g. (quantitative) of needles, m.p. 260°. Recrystallization from EtOH raised the m.p. to 261°. *Anal.* Calcd. for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38. Found: C, 64.39; H, 5.59. IR λ_{max}^{Nujol} μ: 2.93 (OH), 5.92 (coumarin-CO). UV λ_{max}^{EtOH} mμ (log ε): 262 (4.11), 315 (4.14).

3-Methoxy-4-allyloxy-8-hydroxy-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*, *d*]pyran-6-one (IX)——A solution of 120 g. of (VIII), 47.7 cc. of allyl bromide, 63.15 g. of K_2CO_3, and 8.3 g. of NaI dissolved in a mixture of 8.35 L. of MeOH and 4.77 L. of H_2O was boiled for 8 hr., 23.85 cc. of allyl bromide and 31.58 g. of K_2CO_3 were added, and the mixture was further boiled for 8 hr. MeOH was evaporated and the residual solution was extracted with benzene. The extract was washed with 4% NaOH solution and H_2O, dried, and benzene was evaporated. The white needle crystals that separated were collected by filtration, washed with benzene, and dried to 91 g. (66%) of needles, m.p. 112°. Further crop of 8.2 g. of crystals was obtained from the benzene mother liquor. *Anal.* Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.44; H, 5.73.

1-Allyl-3-methoxy-4,8-dihydroxy-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*, *d*]pyran-6-one (X)——A mixture of 367.9 g. of (IX) and 1.104 L. of N,N-dimethylaniline was boiled in N_2 atmosphere for 6 hr. and allowed to stand over night. The needle crystals that precipitated out were collected by filtration, washed with AcOEt, and dried to 320 g. (87%) of crystals, m.p. 182°. *Anal.* Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00; O, 26.46. Found: C, 67.51; H, 5.98; O, 26.81. IR λ_{max}^{Nujol} μ: 3.00 (OH), 3.24, 5.98 (coumarin-CO), 10.41, 10.96 (allylic C=C).

1-Propenyl-3-methoxy-4,8-dihydroxy-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*, *d*]pyran-6-one (XI)——A solution of 248 g. of KOH dissolved in 745 cc. of MeOH was heated and MeOH was allowed to distil out until the internal temperature reached 110°. The mixture was cooled while passing N_2 gas, 82.6 g. of (X) was added and the mixture was heated and MeOH was allowed to distil out until the internal temperature reached 110~115°. The mixture was boiled at 110~120° for 6 hr., cooled to 65°, and acidified with 10% HCl. Passage of N_2 gas was stopped and the mixture was allowed to stand over night. The crystals that separated out were collected, the filtrate was extracted with AcOEt, and the extract solution was washed with H_2O. Evaporation of AcOEt left crystals which were combined with the former crystals, washed with AcOEt, and 60.6 g. (73.5%) of white needles, m.p. 229°, were obtained. *Anal.* Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.23; H, 6.37. IR λ_{max}^{Nujol} μ: 2.96 (OH), 5.94 (coumarin-CO), 6.04 (C=C), 10.26 (propenyl).

1-Formyl-3-methoxy-4,8-dihydro-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-6-one (XII)——A solution of 15 g. of (XI) dissolved in a mixture of 70 cc. of MeOH and 940 cc. of CH_2Cl_2 was chilled to −60° and 2.4 g. (1 mole) of O_3 was passed during 1.5 hr. At the end of this period, 20% aqueous solution of 135 g. of $NaHSO_3$ was added, the mixture was shaken, and $NaHSO_3$ solution was washed with CH_2Cl_2. The aqueous solution was filtered, acidified with 60% H_2SO_4, aerated at room temperature for 15 min., warmed at 50°, and aerated for 1 hr. to remove SO_2 gas completely. The white crystals that precipitated out were collected by filtration, washed with H_2O, and dried to 10.4 g. (67.7%) of pale yellow microcrystals, m.p. 250°. Recrystallization from AcOEt raised the m.p. to 253°. *Anal.* Calcd. for $C_{15}H_{14}O_6$: C, 62.06; H, 4.86; O, 33.07. Found: C, 62.01; H, 5.09; O, 32.66. IR λ_{max}^{Nujol} μ: 2.96 (OH), 5.86 (coumarin-CO), 6.02 (CHO).

2-(2,3,4-Trimethoxy-6-formylphenyl)-5-hydroxy-1-cyclohexenecarboxylic Acid (XIII)——A mixture of 1.5 g. of (XII), 14.4 cc. of Me_2SO_4, and 100 cc. of 20% KOH solution was treated as for the preparation of (V) and 1.04 g. (60%) of a residue was obtained. This was recrystallized from AcOEt and petr. ether to white needles, m.p. 156°. *Anal.* Calcd. for $C_{17}H_{20}O_7$: C, 60.71; H, 5.99. Found: C, 61.03; H, 5.85. IR λ_{max}^{Nujol} μ: 2.92 (OH), 3.8~4.0 (COOH), 5.92 (CO in C=C-COOH), 5.94 (CHO). 6.10 (C=C).

α-Carboxy-3-methoxy-6-oxo-4,8-dihydroxy-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*, *d*]pyran-1-acrylic Acid (XIV)——A mixture of 139 g. of (XII), 101 g. of malonic acid, 2.05 L. of pyridine, and 48.8 cc. of aniline was warmed at 50° for 22 hr. Pyridine was distilled off at below 60°, residual solution was acidified with 15% HCl, and the yellowish brown crystals that separated out were collected by filtration. The crystals were washed with water and dried to 160.6 g. (87.6%) of crystals melting at 252° with decomposition. The crystals were dissolved in $NaHCO_3$ solution and acidification of this solution separated needle crystals. This product was recrystallized from MeOH to yellow needles, m.p. 260° (decomp.). *Anal.* Calcd. for $C_{18}H_{16}O_9$: C, 57.45; H, 4.29; O, 38.27. Found: C, 57.47; H, 4.44; O, 38.10. IR λ_{max}^{Nujol} μ: 2.92 (OH), 3.7~3.9 (COOH), 5.78 (CO in COOH), 6.00 (coumarin-CO), UV λ_{max}^{EtOH} mμ (log ε): 259 (4.17), 332 (4.06).

α-Carboxy-3-methoxy-6-oxo-4,8-dihydroxy-7,8,9,10-tetrahydro-6*H*-dibenzo[*b,d*]pyran-1-propionic Acid (XV)——A solution of 15 g. of (XIV) dissolved in 400 cc. of MeOH was hydrogenated over 8 g. of 5% Pd-C and 1.2 moles of H_2 was absorbed in 1 hr. The catalyst was filtered off, MeOH was evaporated from the filtrate, and 13.6 g. (90%) of white needles separated. The crystals were dissolved in water and acidification afforded needle crystals, m.p. 248°. *Anal.* Calcd. for $C_{18}H_{18}O_9$: C, 57.14; H, 4.80. Found: C, 56.97; H, 5.13. IR λ_{max}^{Nujol} μ: 2.91 (OH), 3.7~3.9 (COOH), 5.80 (CO in COOH), 6.06 (coumarin-CO). UV λ_{max}^{EtOH} mμ (log ε): 266 (4.10), 329 (4.10).

3-Methoxy-6-oxo-4,8-dihydroxy-7,8,9,10-tetrahydro-6*H*-dibenzo[*b, d*]pyran-1-propionic Acid (XVI)——One gram of (XV) was heated at 140~150° at 1 mm. Hg for 20 hr. to effect decarboxylation. When cooled, this was dissolved in $NaHCO_3$ solution, filtered, and the filtrate was acidified, from which 0.85 g. of white needles, m.p. 245°, separated. *Anal.* Calcd. for $C_{17}H_{18}O_7$: C, 61.07; H, 5.43; O, 33.50. Found: C, 61.06; H, 5.56; O, 33.27. IR λ_{max}^{Nujol} μ: 2.96 (OH), 5.91 (CO in COOH), 3.7~3.9 (COOH), 6.08 (coumarin-CO).

2-[2,3,4-Trimethoxy-6-(2,2-dicarboxyethyl)phenyl]-5-hydroxy-1-cyclohexenecarboxylic Acid (XVII)——Treatment of 36 g. of (XV), 260 cc. of Me_2SO_4, and 1.77 L. of 20% KOH, as for the preparation of (V), and recrystallization of the product from AcOEt gave 18.05 g. (46.7%) of needles, m.p. 183° (decomp.). *Anal.* Calcd. for $C_{20}H_{24}O_{10}$: C, 56.60; H, 5.70. Found: C, 56.52; H, 5.56. IR λ_{max}^{Nujol} μ: 2.93 (OH), 3.7~4.0 (COOH), 5.84 (CO in COOH), 6.06 (C=C). UV: λ_{max}^{EtOH} 274 mμ (log ε 3.42).

2-[2,3,4-Trimethoxy-6-(2-carboxyethyl)phenyl]-5-hydroxy-1-cyclohexenecarboxylic Acid (XVIII)——Decarboxylation was effected by heating 460 mg. of (XVII) at 150°/1mm. Hg for 2 hr. and 412 mg. of the product was recrystallized from AcOEt and pert. ether to prisms, m.p. 184°. *Anal.* Calcd. for $C_{19}H_{24}O_8$: C, 59.99; H, 6.36. Found: C, 59.97; H, 6.36. IR λ_{max}^{Nujol} μ: 3.18 (OH), 3.7~4.0 (COOH), 5.88 (CO in COOH), 6.12 (C=C). UV: λ_{max}^{EtOH} 274 mμ (log ε 3.32).

Treatment of 897 mg. of (XVI) with 14.4 cc. of Me_2SO_4 and 100 cc. of 20% KOH solution as for the preparation of (V) afforded 514 mg. (53%) of (XVIII), which showed no depression of m.p. on admixture with the decarboxylation product of (XVII).

Methyl 2-[2,3,4-Trimethoxy-6-(2-methoxycarbonylethyl)phenyl]-5-hydroxy-1-cyclohexenecarboxylate (XIX)——CH_2N_2 generated from 1 g. of nitrosomethyltosylamide at room temperature was passed through a solution of 208 mg. of (XVIII) dissolved in a mixture of 1.4 cc. of MeOH and 14 cc. of Et_2O, the mixture was allowed to stand for 1 hr., and the solvent was evaporated to leave 226 mg. of a liquid. Molecular distillation of this liquid afforded a viscous liquid at $b.p_{0.001}$ 240° (bath temp.), in a quantitative yield. *Anal.* Calcd. for $C_{21}H_{28}O_8$: C, 61.75; H, 6.91. Found: C, 61.89; H, 7.11. IR $\lambda_{max}^{CCl_4}$ μ: 2.82 (OH), 5.80 (CO in COOH), 6.06 (C=C).

A mixture of 41.2 g. of (XVIII), 320 cc. of MeOH, and 13.7 cc. of conc. H_2SO_4 was boiled for 18 hr., 1.1 L. of benzene was added, and 800 cc. was distilled off. Benzene was further added, benzene solution was separated, and washed with H_2O, 1% KOH solution, and H_2O. After drying, benzene evaporated and 41.1 g. (93%) of liquid thereby obtained was submitted to molecular distillation to obtain colorless liquid (XIX), $b.p_{0.001}$ 230~240° (bath temp.).

3-Hydroxy-9,10,11-trimethoxy-1,2,3,4,6,7-hexahydro-5*H*-dibenzo[*a, c*]cycloheptatrien-5-one (XX)——a) In N_2 stream, 1.04 g. of metallic K was dissolved in a mixture of 20 cc. of *tert*-BuOH and xylene by boiling, 650 cc. of xylene was added, and the solvent was distilled off until the boiling reached 138.5°. A solution of 3.6 g. of (XIX) dissolved in 60 cc. of xylene was added dropwise into the former xylene solution while boiling with stirring, stopping the addition after 27 cc., 39 cc., and 60 cc., had been added to distill off the solvent until the boiling temperature reached 138.5°. After the third distillation was completed, the whole mixture was boiled with stirring for 20 hr., cooled, acidified with dil. HCl, and passage of N_2 gas was stopped. The aqueous solution was extracted with benzene, the organic solvent layer was combined with this benzene layer, and the combined solution was washed with water. Evaporation of the solvent afforded 2 g. of crude β-keto-carboxylate, which was dissolved in a mixture of 5 g. of KOH, 90 cc. of MeOH, and 10 cc. of H_2O, and the mixture was boiled for 2 hr. This was acidified, filtered, and MeOH was evaporated from the filtrate. The residue was dissolved in benzene solution was washed with 3% KOH solution and H_2O, dried, and benzene was evaporated, leaving 0.6 g. of a solid. This residue was treated with 9 g. of alumina, the column was washed with 300 cc. of petr. ether, and further eluted with a mixture (1:1) of petr. ether and benzene. Evaporation of the solvent from the eluate furnished 126 mg. (4.5%) of reddish yellow liquid. Its recrystallization from hydrous MeOH gave white needles, m.p. 84°. *Anal.* Calcd. for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.83; H, 6.76. UV λ_{max}^{EtOH} mμ (log ε): 235 (4.11), 283 (3.56). IR λ_{max}^{Nujol} μ: 2.86 (OH), 6.00 (conjugated CO).

2,4-Dinitrophenylhydrazone of (XX): Reddish yellow crystals (from MeOH), m.p. 101°. *Anal.* Calcd. for $C_{24}H_{26}O_8N_4$: C, 57.82; H, 5.26; N, 11.24. Found: C, 57.96; H, 5.03; N, 11.34.

b) A solution of 300 mg. of (XVIII) dissolved in a mixture of 20 cc. of Ac_2O and 0.6 g. of AcOK in N_2 stream was boiled for 2 hr., Ac_2O was distilled off until the boiling temperature reached 138°, and the residual solution was boiled further for 20 hr. Ac_2O was distilled off below 50°, the residue

was dissolved in 5% MeOH-KOH, the solution was made sufficiently alkaline, and boiled for 2 hr. The solution was diluted with H_2O, MeOH was evaporated, and extracted with benzene. The extract solution was washed with water, dried, and benzene was evaporated to leave ca. 150 mg. of an oily substance. This residue was adsorbed on a column of 5 g. of alumina, the column was washed with 7 cc. of a mixture (1:1) of petr. ether and benzene, and eluted with 20 cc. of the same mixture and 10 cc. of benzene. Evaporation of the solvent from the eluate afforded 30 mg. of needles, m.p. 80°. Recrystallization from hydrous MeOH gave pale yellow needles, m.p. 84°, undepressed on admixture with (XX), m.p. 84°, obtained by the foregoing method (a). *Anal.* Calcd. for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.51; H, 6.89.

3-Formyloxy-5-formamido-9,10,11-trimethoxy-2,3,4,4a,6,7-hexahydro-5*H*-dibenzo[*a*,*c*]cycloheptatriene (XX′)——A solution of 1 g. of (XX) dissolved in a mixture of 20 cc. of NH_2CHO and 10 cc. of HCOOH in N_2 stream was heated at 130~160° for 1 hr. and at 160~180° for 1 hr. while distilling off HCOOH, the mixture was maintained at 180°, and 10 cc. of HCOOH was added dropwise during 4 hr. When cooled, N_2 gas was stopped, the mixture was extracted with benzene, and the benzene extract was washed con secutively with H_2O, 5% NaOH solution, H_2O, 5% HCl, and H_2O. Evaporation of benzene afforded 403 mg. of brown powder which was passed through a column of 8 g. of alumina, the column was washed with 160 cc. of benzene, and eluted with 80 cc. of 0.5% EtOH-benzene mixture. Evaporation of the solvent from the eluate gave 147 mg. of a residue from which needle crystals separated on standing. Recrystallization from AcOEt gave colorless needles, m.p. 161°. *Anal.* Calcd. for $C_{20}H_{25}O_6N$: C, 63,98; H, 6.71; N, 3.73. Found: C, 64.37; H, 7.11; N, 3.80. IR $\lambda_{max}^{KBr}\mu$: 3.03 (NH), 5.78 (O-CO), 5.92, 6.03 (NH-CO), 6.45 (NH). UV λ_{max}^{EtOH} mμ (log ε): 218 (4.64), 249 (4.18); λ_{max}^{EtOH} 237 (4.08).

Methyl 2-[2,3,4-Trimethoxy-6-(2-methoxycarbonylethyl)phenyl]-5-oxo-1-cyclohexenecarboxylate (XXI)——A solution of 41.1 g. of (XIX) dissolved in 411 cc. of pyridine was added into the solution of 41.1 g. of CrO_3 dissolved in 411 cc. of pyridine and the mixture was allowed to stand at room temperature for 20 hr. The mixture was shaken with 1.6 L. of benzene, diluted with 1 L. of H_2O, and benzene solution was separated. The benzene solution was washed with H_2O and benzene was evaporated to leave 43.4 g. of a residue. The residue was dissolved in benzene, the solution was washed consecutively with dil. HCl, H_2O, $NaHCO_3$ solution, and H_2O, dried, and benzene was evaporated. Molecular distillation of 25.1 g. (60%) of the residue so obtained afforded yellow viscous liquid at $b.p_{0.001}$ 190° (bath temp.). Yield, 20.2 g. (49.3%). *Anal.* Calcd. for $C_{21}H_{26}O_8$: C, 62.08; H, 6.45. Found: C, 62.12; H, 6.41. UV: λ_{max}^{EtOH} 274 mμ (log ε 3.38).

Methyl 2-[2,3,4-Trimethoxy-6-(2,2-dimethoxycarbonylethyl)phenyl]-5-hydroxy-1-cyclohexenecarboxylate (XXII)——CH_2N_2 generated from 4 g. of nitrosomethyltosylamide was passed through the solution of 1 g. of (XVII) dissolved in a mixture of 5 cc. of MeOH and 30 cc. of Et_2O at room temperature and the solvent was evaporated to leave 1.1 g. of pale yellow liquid. Molecular distillation of this residue afforded colorless liquid of $b.p_{0.001}$ 190° (bath temp.). *Anal.* Calcd $C_{23}H_{30}O_{10}$: C, 59.22; H, 6.48. Found: C, 59.26; H, 6.52. IR $\lambda_{max}^{liq.}\mu$: 2.84 (OH), 5.76 (CO in COOH), 6.08 (C=C).

Methyl 2-[2,3,4-Trimethoxy-6-(2,2-dimethoxycarbonylethyl)phenyl]-5-oxo-1-cyclohexenecarboxylate (XXIII)——A solution of 1.025 g. of (XXII) dissolved in a mixture of 10 cc. of AcOH and 1 cc. of H_2O was cooled to 12° and added dropwise into a mixture of 1 g. of CrO_3 in 10 cc. of AcOH and 1 cc. of H_2O during 10 min. at 12°. The mixture was allowed to stand at 17° for 1.5 hr., CrO_3 was decomposed with aqueons solution of 2 g. of Na_2SO_3, and the solvent was evaporated at below 50°. The residue was dissolved in benzene, this solution was washed with H_2O, 5% K_2CO_3, and H_2O, dried, and benzene was evaporated to leave 398 mg. (39%) of a yellow liquid. This residue was passed through a column of 10 g. of alumina, the column was eluted with a mixture (2:1) of benzene and petr. ether, and evaporation of the solvent from the eluate afforded a pale yellow liquid. It formed a large amount of reddish orange precipitate with 2,4-dinitrophenylhydrazine. *Anal.* Calcd. for $C_{23}H_{28}O_{10}$: C, 59.47; H, 6.08. Found: C, 59.21; H, 6.10. IR $\lambda_{max}^{liq.}\mu$: 5.72 (ester-CO), 5.80 (aliphatic ketone-CO).

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Summary

3-Hydroxy-9, 10, 11-trimethoxy-1, 2, 3, 4, 6, 7-hexahydro-5*H*-dibenzo[*a*, *c*]cycloheptatrien-5-one (XX) was synthesized from ethyl 2-oxo-5-hydroxycyclohexanecarboxylate (III) in 11 steps. Attempt to enlarge the six-membered C-ring in (XX) to a seven-membered ring did not materialize.

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