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Bridged Lactones and Bridged Carbocyclic Systems from 2-(3,4,5-Trimethoxyphenyl)-4,5-dimethyl-Δ^4-cyclohexenecarboxylic Acid. Novel Mescaline Analogs[1]

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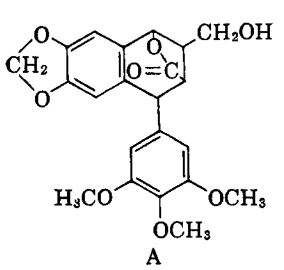
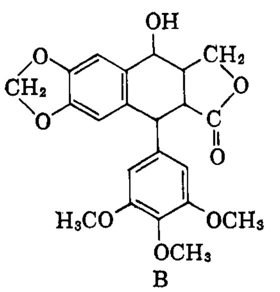
Treatment of 2-(3,4,5-trimethoxyphenyl)-4,5-dimethyl-Δ^4-cyclohexenecarboxylic acid (C) with methanesulfonic acid yielded a mixture of the γ- and δ-lactones D and E, and a mixture of bridged ring acids, consisting principally of trimethoxybenzodimethyl[2.2.2]bicyclooctanecarboxylic acid (F). The structure of F was established by conversion of the amine F-5 (which is a mescaline analog of unusual type), degradation of the amine *via* the oxide, and pyrolysis to 1,2,3-trimethoxy-8-methylnaphthalene (M). This was synthesized by an unambiguous method. The dimethoxyphenyl analog of C was converted by methanesulfonic acid to a similar mixture of compounds.

This work was commenced with the idea of making bridged lactones as analogs of podophyllotoxin, which at that time was assigned structure A; the activity of podophyllotoxin in inhibiting experimental tumors suggested the synthesis and screening of related compounds. Since that time, podophyllotoxin has been shown to have structure[3] B by degradation and synthesis. The study of lactones related to structure A has led to some bridged carbocyclic structures and to some novel compounds containing the mescaline structure, which are described in the present paper.

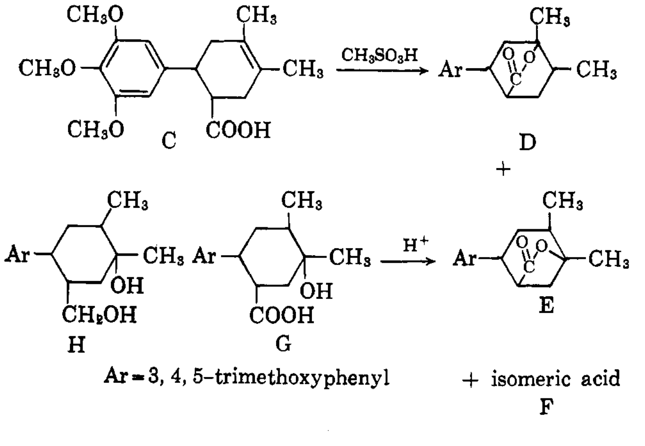


A



B

3,4,5-Trimethoxybenzaldehyde, prepared far more readily by treatment of N,N-dimethyl-3,4,5-trimethoxybenzamide with lithium diethoxyaluminum hydride[4] than by Rosenmund reduction of the acid chloride, was condensed with malonic acid to yield 3,4,5-trimethoxycinnamic acid[5]; 2,3-dimethylbutadiene added to this under pressure at 175° to form 2-(3,4,5-trimethoxyphenyl)-4,5-dimethyl-Δ^4-cyclohexenecarboxylic acid (C). Attempts to lactonize C with sulfuric acid, phosphoric acid, or hydrobromic acid were unsuccessful, but treatment with methanesulfonic acid yielded a mixture of lactones D and E and an acidic material, isomeric with the starting acid C.



The lactone mixture could be crystallized, but the melting point was not changed from 135–140° by further crystallization; the infrared spectrum (in Nujol) showed two peaks of nearly equal intensity at 1753 and 1725 cm.$^{-1}$. Chromatography on activity II alumina gave a homogeneous lactone, m.p. 156–157°, which, from its carbonyl band at 1720 cm.$^{-1}$, was given the δ-lactone structure D. When the two lactones are

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(1) Taken from the Ph.D. theses of R. G. Nelb (1949), Leo Zeftel (1951), and T. J. Perun (1963), University of Rochester. Aided in part by Grant E-1138 of the U. S. Public Health Service.

(2) National Science Foundation Cooperative Fellow, 1961–1962.

(3) J. L. Hartwell and A. W. Schrecker, *J. Am. Chem. Soc.*, **73**, 2909 (1951); **75**, 5916 (1953); **77**, 432 (1955); W. J. Gensler, C. M. Samour, S. Y. Wang, and F. Johnson, *ibid.*, **82**, 1714 (1960); W. J. Gensler and C. D. Gatsonis, *ibid.*, **84**, 1748 (1962).

(4) K. I. H. Williams, Ph.D. thesis, University of Rochester, 1959; H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, **81**, 502 (1959).

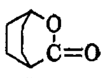
(5) K. H. Slotta and H. Heller, *Ber.*, **63**, 3042 (1930).

present in equal amounts a complex is formed which melts at 139–140° and which is not separated by chromatography on alumina.

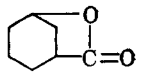
Saponification of the lactone mixture by base, followed by acidification, gave a 60% yield of a hydroxy acid, m.p. 191–193°; the fact that this hydroxy acid was converted to the γ-lactone E, m.p. 150–151°, with a carbonyl band in Nujol at 1753 cm.$^{-1}$, indicated that it was probably the γ-hydroxy acid G.

The n.m.r. spectra of the lactones D and E showed that they were indeed bridged across a dimethylcyclohexane ring. Both spectra showed one unsplit methyl peak, at about 8.55 τ, and one methyl peak split into a doublet at 8.95 τ. The presence of the two methyl peaks in both lactones showed that no skeletal rearrangement had occurred during the acid-catalyzed cyclization. The γ-lactone E was reduced by lithium aluminum hydride to a diol, m.p. 158–159°, presumably H, which also showed two methyl groups in the n.m.r. spectrum, one unsplit (8.48 τ) and one a doublet (8.83 τ).

The model bridged lactones I and J were prepared; their carbonyl frequencies, and those of D and E, are give in Table I.[6]



I



J

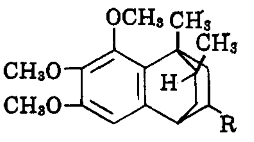
TABLE I

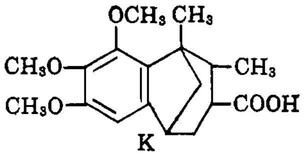
Lactone	Carbonyl absorption in CCl_4, cm.$^{-1}$
D	1748
E	1773
I	1754
J	1773

The treatment of C with reagent grade methanesulfonic acid for three hours gave approximately equal amounts of the lactone mixture D and E and of the isomeric acid F; the latter melted, after crystallization from ethanol–water, at 155–157°, and, after a further crystallization from carbon tetrachloride, at 159–160°.

The proportion of the lactone mixture and of the isomeric acid obtained depended on the conditions; the amount of isomeric acid was decreased by short reaction times, and increased, most strikingly, by the use of practical, instead of reagent grade methanesulfonic acid. The latter gave no lactone.

The n.m.r. spectrum of the isomeric acid showed the absence of vinyl protons and the presence of only *one* aromatic proton. One methyl group appeared as a singlet (8.46 τ), but the other methyl was present as a doublet (9.40 τ). The only structures consistent with the n.m.r. data are the bridged structures F and K. These structures can arise by nuclear alkylation by the tertiary carbonium ions formed by protonation at the two olefinic carbons in the cyclohexene ring.[7] The melting point of the once crystallized acidic material showed that the material was not pure; the methyl ester was therefore prepared, and it was found by gas chromatographic analysis that two components were present in a 9:1 ratio. It is possible that the 9:1 ratio was different in the mixture before recrystallization. It was expected that the 2,2,2-bicyclooctane system F would be favored over the 3,2,1 system K, and this expectation was supported by degradation; F was found to be the major component.

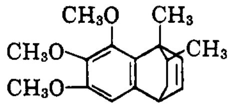




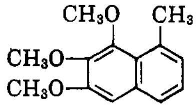
K

F-1, R = COOH
F-2, R = CON_3
F-3, R = N=C=O
F-4, R = $NHCOOCH_3$
F-5, R = NH_2
F-6, R = $NHCH_3$
F-7, R = $N(CH_3)_2$

The degradation was planned to consist of conversion of the carboxyl group in F to a tertiary amine, removal of the amino group to give the unsaturated compound L, and conversion of this by a reverse Diels–Alder reaction to the substituted naphthalene M and propylene.[8]

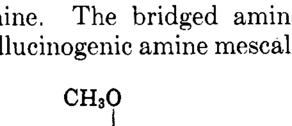


L

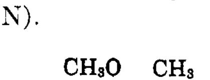


M

Conversion of the acid F-1 to the amine F-5 by the Schmidt reaction gave only a 38% yield. In an alternative procedure, the acid was converted to the azide F-2 through the mixed carboxylic–carbonic anhydride[9]; the azide was rearranged to the crystalline isocyanate F-3 by refluxing in toluene in 86% over-all yield from the acid, without the isolation of any intermediates. Acid hydrolysis of the isocyanate, which appeared to be unusually unreactive, gave a 47% yield of the crude amine F-5. The isocyanate was converted to the urethan F-4 in 97% yield by heating the toluene solution with methanol for five hours with triethylamine as catalyst. The slow rate of reaction of the isocyanate group with methanol required the use of the basic catalyst and of the long time of heating to complete the reaction. The urethan was hydrolyzed only slowly to the amine. The bridged amine F-5 is an analog of the hallucinogenic amine mescaline (N).



N



O

The samples of the amine F-5 obtained by various procedures were not homogeneous; the melting points varied, even after purification by sublimation. Thin layer chromatography of amine obtained by isocyanate hydrolysis showed two spots very close together, with

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(6) The preparation of the crystalline lactone I is described by N. R. Campbell and J. H. Hunt, *J. Chem. Soc.*, 1379 (1950); J was obtained crystalline by E. J. Boorman and R. P. Linstead, *ibid.*, 258 (1935); see also M. Kilpatrick and J. G. Morse, *J. Am. Chem. Soc.*, **75**, 1846 (1953).

(7) For analogous ring closures, see R. Grewe and A. Mondon, *Chem. Ber.*, **81**, 279 (1948); C. Schöpf, *Experientia*, **5**, 201 (1949); G. Wittig, H. Tenhaeff, W. Schoch, and G. Koenig, *Ann.*, **572**, 7 (1951).

(8) *Cf.* C. A. Grob, H. Kny, and A. Gagneux, *Helv. Chim. Acta*, **40**, 130 (1957); O. Diels and K. Alder, *Ber.*, **62**, 2343 (1929).

(9) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961); *cf.* D. S. Tarbell and J. A. Price, *ibid.*, **22**, 245 (1957).

the estimated ratio of areas about 4:1 or 5:1. It is unlikely that the Curtius rearrangement of F-2 to F-3 involves rearrangement of the carbon skeleton[10]; the variation in composition of the amine is probably due to differing rates of the various reactions involved, with compounds derived from the parent structures F and K.

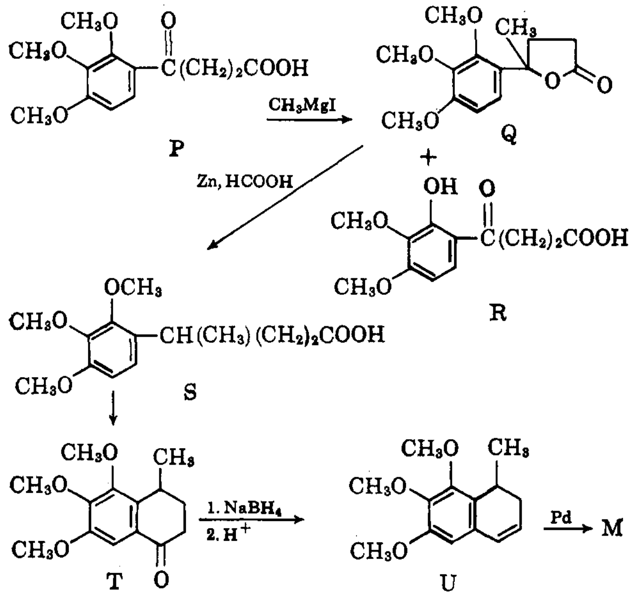
The primary amine was treated with formaldehyde–formic acid,[11] followed by refluxing with concentrated hydrochloric acid, to prepare the tertiary amine F-7. This yielded a mixture of amine salts, probably the hydrochlorides of trimethylamine and of F-7, and in addition 30% of a neutral oil, with a carbonyl band at 1710 cm.$^{-1}$ in the infrared, which was probably the ketone O. Milder reaction conditions with omission of the refluxing with concentrated acid yielded approximately equal amounts of the tertiary amine F-7 and the ketone O. This hydrolysis of the amino group during Clarke–Eschweiller methylation has been observed in other cases of bridged amines.[12] A mechanism has been suggested, involving hydrolysis of the imine.

Because the primary amine F-5 could not be converted to the tertiary amine F-7 in good yield, an alternative procedure was followed. The urethan F-4 was reduced by lithium aluminum hydride to the monomethylated amine F-6 in 75% yield, and this was converted to the tertiary amine by Clarke–Eschweiler methylation. The compounds F-6 and F-7 were not crystalline, but could be distinguished from each other and from the primary amine by thin layer chromatography.

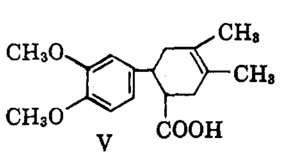
The N-oxide was prepared from F-7 by treatment with 30% hydrogen peroxide for two days, and was degraded by the Cope procedure[13] by heating at 170° for five hours *in vacuo;* dimethylhydroxylamine was isolated as the hydrochloride in 40% yield. The neutral material (isolated in 50% yield) was obtained crystalline after chromatography on alumina, m.p. 75–76°; the trinitrobenzene complex had m.p. 94–95°. The ultraviolet spectrum indicated that the material was a naphthalene derivative, and its analysis and melting point, and the melting point of the trinitrobenzene complex indicated that it was the known[14] 1,2,3-trimethoxy-8-methylnaphthalene (M). A sample of Haworth's material was not available for comparison, and the required trimethoxymethylnaphthalene was, therefore, synthesized.

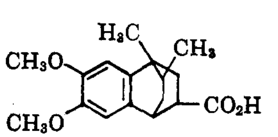
The isolation of the naphthalene M in good yield from the degradation establishes the structure of the main component of the isomeric acid as F-1; it is unlikely that the amine oxide derived from K would aromatize to a naphthalene derivative under the conditions (170°) involved in the Cope degradation.

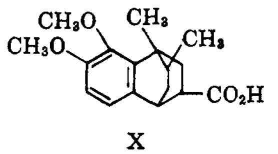
The naphthalene M was synthesized as follows. β-(2,3,4-Trimethoxybenzoyl)propionic acid (P)[15] was treated with methylmagnesium iodide to give the expected lactone Q, a viscous liquid with carbonyl absorption at 1770 cm.$^{-1}$. Some of the demethylated acid R was formed along with Q. Reduction of the lactone Q, which may have contained some demethylated acid, with zinc and formic acid[16] gave the valeric acid S, which could be obtained crystalline and analytically pure. The crude S could be used for cyclization with polyphosphoric acid to the tetralone T; this was reduced with sodium borohydride to the alcohol, which was dehydrated under acidic conditions to the dihydronaphthalene U. This material was treated with dimethyl sulfate and alkali to replace any methyl groups lost during the cyclization of S or in the later stages. Then it was aromatized by heating for two hours at 300° with palladium on charcoal; the product, after chromatography on alumina, melted at 73–74°, and showed no depression on mixture melting point with the naphthalene M, obtained by degradation of the acid F-1. Identity of the two samples of M was also indicated by the infrared and ultraviolet spectra.

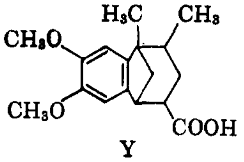


A less extended examination was made of the products from the action of methanesulfonic acid on the dimethoxyphenylcyclohexenecarboxylic acid V, which was prepared in a manner similar to that used for C.


V


W


X


Y

The acid V was obtained as a monohydrate; the water of hydration could be removed *in vacuo*, and treatment of the anhydrous acid with methanesulfonic acid gave a lactone mixture and an acidic material. The lactone mixture showed carbonyl bands in the same region in the infrared spectrum as the mixture of D and E, and hence was considered to be a mixture of the γ- and δ-lactones. The acidic material contained water of hydration, and melted, when anhydrous, at 135–145°;

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[10] E. S. Wallis and J. F. Lane, *Org. Reactions*, **3**, 272 (1946).

[11] H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

[12] W. E. Parkam, W. T. Hunter, R. Hanson, and T. Lahr, *ibid.*, **74**, 5646 (1952).

[13] A. C. Cope, T. T. Foster, and P. H. Towle, *ibid.*, 3929 (1949).

[14] R. D. Haworth, B. P. Moore, and P. L. Pauson, *J. Chem. Soc.*, 3271 (1949).

[15] P. D. Gardner, *J. Am. Chem. Soc.*, **76**, 4550 (1954); R. H. F. Manske and H. L. Holmes, *ibid.*, **67**, 95 (1945).

[16] R. L. Letsinger, J. D. Jamison, and A. S. Hussey, *J. Org. Chem.*, **26**, 97 (1961); M. S. Newman and K. Naiki, *ibid.*, **27**, 863 (1962).

its analysis showed it was isomeric with V. The n.m.r. spectrum showed that the two components were not the 2-position isomers W and X; there were two aromatic protons occurring in a single peak, indicating that the aromatic protons were in nearly identical environments. Therefore, the mixture was not a mixture of W and X, but more probably a mixture of W and Y.

It appears that a larger proportion of the 3,2,1 ring system was formed with the dimethoxy compound V than with the trimethoxy analog C. The methyl ester, prepared from a recrystallized sample of the mixture was shown by v.p.c. analysis to be a 55:45 mixture of two components, presumably W and Y. It appeared, however, that the original mixture was closer to a ratio of 2:1.

Experimental[17]

N,N-Dimethyl-3,4,5-trimethoxybenzamide.[4]—The crude 3,4,5-*trimethoxybenzoyl chloride*[18] *from* 76 g. of 3,4,5-trimethoxybenzoic acid was dissolved in 160 ml. of benzene, and the solution was cooled in an ice bath. Excess anhydrous dimethylamine (80 g., 1.8 moles) was distilled into the stirred solution through a delivery tube which extended below the surface. Water was added to dissolve the amine hydrochloride, the layers were separated, and the water layer was extracted with three portions of benzene. The combined benzene solution was dried and evaporated. The residue was dissolved in a mixture of 225 ml. of heptane and 70 ml. of benzene, and the solution was treated with Norit and allowed to cool. The white crystalline product obtained amounted to 65 g. (76%). The melting point was 76–77°.

3,4,5-Trimethoxybenzaldehyde.—A solution of lithium aluminum diethoxydihydride was prepared following the procedure of Brown.[4] The ethyl acetate used was dried over potassium carbonate and distilled. A solution of 15.5 ml. of ethyl acetate in 170 ml. of anhydrous ether was added to a stirred and cooled solution of 6.0 g. of lithium aluminum hydride in 170 ml. of anhydrous ether over a period of 2 hr. The resulting solution was then forced up into a long-stemmed dropping funnel by the use of nitrogen pressure. This solution was added dropwise to a well stirred suspension of 63 g. (0.26 mole) of N,N-dimethyl-3,4,5-trimethoxybenzamide in 500 ml. of anhydrous ether over a period of 2 hr. while the reaction flask was cooled in an ice bath. The reaction mixture was allowed to warm to room temperature and was refluxed for 2 hr. It was then poured over a mixture of 700 g. of ice and 700 ml. of 10% sulfuric acid. Benzene (350 ml.) was added to dissolve the product, the layers were separated, and the aqueous phase was extracted with three 350-ml. portions of benzene. The benzene extracts were added to the benzene–ether solution, and this solution was dried and evaporated, leaving an orange oil residue. The residue was dissolved in hot ethanol-water (1:1), and the solution was treated with Norit and cooled. The colorless plates obtained amounted to 30.6 g. (60%) with m.p. 73–74°; lit.[19] m.p. 74–75°.

2-(3,4,5-Trimethoxyphenyl)-4,5-dimethyl-Δ^4-cyclohexenecarboxylic Acid (C).—In a high-pressure hydrogenation bomb was placed 60 ml. of anhydrous xylene, 24.6 g. of 3,4,5-trimethoxycinnamic acid,[5] 24.6 g. of 2,3-dimethylbutadiene, and 0.3 g. of hydroquinone. The bomb was heated at 175° in a rocker for 12 hr. The bomb was cooled, the contents poured out, and the inside washed out with portions of warm xylene. The combined xylene solution was heated on a steam bath, treated with Norit, and the filtered xylene solution was extracted with three 70-ml. portions of 10% sodium bicarbonate. In some runs a colloidal dispersion resulted. The bicarbonate solution was cooled in ice and acidified with dilute hydrochloric acid. The solid material obtained was recrystallized from ethanol–water (1:1) to give 21 g. (66%) of white, finely crystalline product with m.p. 137–138°.

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.42; H, 7.48.

The **methyl ester** melted, after crystallization from dilute methanol, at 74.5–75.5°.

Anal. Calcd. for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 67.91; H, 7.39.

The *p*-**nitrobenzyl ester** melted at 118.5–119.5°.

Anal. Calcd. for $C_{25}H_{29}NO_7$: C, 65.92; H, 6.42. Found: C, 65.53; H, 6.28.

Reaction of 2-(3,4,5-Trimethoxyphenyl)-4,5-dimethyl-Δ^4-cyclohexenecarboxylic Acid with Methanesulfonic Acid.—To 1.0 g. of 2-(3,4,5-trimethoxyphenyl)-4,5-dimethyl-Δ^4-cyclohexenecarboxylic acid (C) was added 6 ml. of reagent grade methanesulfonic acid. The solid dissolved quickly to give a reddish brown solution which was allowed to stand at room temperature for 3 hr. The reaction mixture was then poured onto 15 g. of cracked ice, and a white solid precipitated immediately. This material was filtered off, washed with water, and the sticky solid obtained was dissolved in about 20 ml. of ether.

A. The Tricyclic Acids (F and K).—The ether solution from the foregoing procedure was extracted with three portions of 10% sodium bicarbonate solution; the extracts were combined and acidified with dilute hydrochloric acid to give a sticky solid. This material was recrystallized from ethanol–water (1:1) to give 0.3 g. of white crystals with m.p. 155–157°. A second recrystallization from carbon tetrachloride gave fine white needles with m.p. 159–160°. The analysis was carried out on a sample of F recrystallized from dilute acetic acid.

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.29; H, 7.45.

The *p*-**nitrobenzyl ester** melted at 156–157° after crystallization from ethanol.

Anal. Calcd. for $C_{25}H_{29}NO_7$: C, 65.92; H, 6.42. Found: C, 65.68; H, 6.37.

Saponification of this ester produced the same acid from which it had been prepared.

The n.m.r. spectrum of the tricyclic acid F showed that there was only one aromatic hydrogen in the compound, and that the two methyl groups were not equivalent. One methyl group was unsplit, and the other was split into a doublet. The spectrum also showed the absence of vinyl protons.

The ultraviolet spectrum contained a maximum at 278 mμ (log ϵ 3.17) and end absorption at 210 mμ.

The methyl ester of the once-recrystallized tricyclic acid was prepared by refluxing a solution of the acid in methanol containing 2% sulfuric acid. The colorless needles obtained after recrystallization had m.p. 109–110°. A gas chromatographic analysis of the ester on a 5-ft. SE-30 column at 200° showed the presence of two compounds, presumably the methyl esters of F and K, in a 9:1 ratio.

B. The Mixture of δ- and γ-Lactones (D and E).—The ether solution remaining from the bicarbonate extraction was dried over magnesium sulfate and evaporated to give 0.35 g. of a sticky solid. This material was recrystallized from diluted methanol to give 0.2 g. of colorless crystals with m.p. 132–134°. Repeated recrystallizations from methanol gave nicely formed prisms which melted between 135 and 140°.

An infrared spectrum of this material in solution (1% in carbon tetrachloride) contained two peaks in the carbonyl region at 1775 and 1755 cm.$^{-1}$. An infrared spectrum of a Nujol mull contained carbonyl peaks at 1753 and 1720 cm.$^{-1}$. Elementary analysis of the lactone mixture agreed with the expected value for D or E.

The mixture of δ- and γ-lactones (200 mg.) was dissolved in a petroleum ether–benzene solution and chromatographed on a 30-g. column of activity grade II neutral alumina. Elution with 2% ether in benzene gave 85 mg. of material in seven fractions. The material in the early fractions (40 mg.) consisted of a single **lactone D** with m.p. 156–157°. The infrared spectrum (Nujol mull) contained a single carbonyl peak at 1720 cm.$^{-1}$. A solution infrared spectrum (carbon tetrachloride) contained a carbonyl peak at 1748 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found (D): C, 67.65; H, 7.85.

Formation of the Hydroxy Acid G by Saponification of the Lactone Mixture.—Some of the recrystallized mixture of δ- and γ-lactones (170 mg.) was heated on the steam bath in 10 ml. of 2

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[17] All melting points are uncorrected. Microanalyses are by V. Landeryou in this laboratory and by Micro-Tech Laboratories. Infrared spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer. The ultraviolet spectra were taken on a Beckman DU spectrophotometer. Nuclear magnetic resonance spectra were obtained on a 60-Mc. Varian instrument. We are indebted to Dr. L. D. Colebrook for the n.m.r. spectra and for assistance in their interpretation.

[18] Prepared following Rapoport, *et al.*, *J. Am. Chem. Soc.*, **73**, 1414 (1951).

[19] D. S. Tarbell, H. T. Huang, and H. R. V. Arnstein, *ibid.*, **70**, 4181 (1948).

N sodium hydroxide until it all dissolved (2.5 hr.). The cooled solution was then acidified with dilute hydrochloric acid, and the precipitate was collected and washed with portions of warm ether. The amount of hydroxy acid obtained was 110 mg., m.p. 191–193°.

Anal. Calcd. for $C_{18}H_{26}O_6$: C, 63.89; H, 7.75. Found: C, 63.56; H, 7.52.

Lactonization of the Hydroxy Acid G.—The hydroxy acid (100 mg.) was dissolved in 2 ml. of glacial acetic acid while warmed on a steam bath. Five drops of 10% sulfuric acid was added, and the solution was heated on the steam bath for 30 min. The solution was diluted with 2 ml. of water and cooled in the refrigerator. The colorless crystals that formed were filtered off to give 50 mg. of the γ-**lactone E**, m.p. 150–151°. The melting point of this lactone was depressed by mixture with the δ-lactone D.

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found (E): C, 67.77; H, 7.52.

The infrared spectrum of lactone E showed a single carbonyl peak at 1753 cm.$^{-1}$; in carbon tetrachloride the carbonyl peak was at 1775 cm.$^{-1}$ when measured on a Perkin-Elmer Model 21 spectrometer; with a Perkin-Elmer Model 421, the compound in carbon tetrachloride showed a doublet at 1787 and 1775 cm.$^{-1}$.

Preparation of the Tricyclic Amine F-5 from the Tricyclic Acid F-1 by a Schmidt Reaction.—The reaction was conducted in a 100-ml. three-neck flask equipped with a stirrer, dropping funnel, and reflux condenser. A gas outlet tube was connected to the top of the condenser, and the tube led to a column of water in a graduate cylinder inverted in a beaker of water. The tricyclic acid F-1 (1.0 g.) was dissolved in 10 ml. of chloroform and to the stirred and cooled solution was added 2 ml. of concentrated sulfuric acid. The hydrazoic acid solution[20] (3.0 ml.) was then added dropwise to the reaction mixture. The mixture was allowed to warm to room temperature, and the reaction was stopped when 140 cc. of gas was collected in the water column. At this time the sulfuric acid layer was colored dark brown. The acid layer was separated from the chloroform and poured into 15 ml. of ice–water. The brown precipitate which formed was collected, and it amounted to 0.67 g. (m.p. 180–185°).

The solid was placed in an aqueous sodium hydroxide solution, ether was added, and the mixture was stirred with a magnetic stirrer. The yellow ether layer was separated and the brown aqueous solution was extracted with two more portions of ether. The ether extracts were combined, dried, and evaporated to give 0.35 g. (38%) of yellow oil which solidified overnight in the refrigerator. This material was sublimed under aspirator vacuum at an oil-bath temperature of 140° to give fine white crystals with m.p. 112–115°.

The hydrochloride of this amine was prepared, and it was recrystallized from ethyl acetate–methanol to give colorless needles with m.p. 204–208°.

Anal. Calcd. for $C_{17}H_{26}O_3NCl$: C, 62.28; H, 7.99. Found: C, 62.17; H, 8.05.

Reaction of the Tricyclic Amine F-5 with Formaldehyde and Formic Acid.[21]—A round bottom flask containing 110 mg. of the crude tricyclic amine was cooled in ice, while 0.2 ml. of 90% formic acid and 0.2 ml. of 38% formaldehyde were added separately. The reaction mixture was then heated on a steam bath under a reflux condenser for 20 hr. At the beginning of the last hour of heating, 0.04 ml. of concentrated hydrochloric acid was added. The solvent was removed under vacuum and a 25% sodium hydroxide solution was added to the yellow residue. A volatile amine was produced, and a yellow solid remained undissolved in the basic solution. Ether was added to dissolve the solid, and the aqueous solution was extracted with two more portions of ether. The ether solution was extracted with three portions of 10% hydrochloric acid and then dried over sodium sulfate. The ether solution was evaporated to give 33 mg. of a pale yellow oil which showed carbonyl absorption in the infrared at 1710 cm.$^{-1}$. A small portion of this neutral material was treated with 2,4-dinitrophenylhydrazine reagent. A precipitate was formed, but it could not be purified.

The acid extract was evaporated and the residue was treated with ethyl acetate to give a white solid which gave a positive chloride test with silver nitrate. A recrystallization from ethyl acetate-methanol gave colorless needles with m.p. 170–175° dec.

Another batch of crude tricyclic amine was treated with formaldehyde and formic acid for 10 hr., and the reaction was not heated with hydrochloric acid during the last hour. Work-up of this reaction gave nearly equal amounts of the ketone and the N,N-dimethyltricyclic amine F-7.

Preparation of the Tricyclic Isocyanate F-3.—The procedure used was similar to one used by Weinstock.[9] The tricyclic acid F-1 (1.3 g.) was placed in 1.0 ml. of water and acetone was added until solution occurred. The solution was stirred with a magnetic stirrer and cooled in an ice–salt bath while triethylamine (0.73 ml.) in 10 ml. of acetone was added. A solution of ethyl chloroformate (0.50 ml., 0.005 mole) in 2.0 ml. of acetone was then added slowly. During this addition, the solution became milky white. The mixture was stirred for 0.5 hr. while cooled at 0°, and then a solution of sodium azide (0.34 g.) in 2.0 ml. of water was added. The reaction gave good yields only with sodium azide purchased from Matheson Coleman and Bell. The reaction mixture first became clear and then became milky white again. The mixture was stirred at 0° for 1.5 hr. and then poured into ice–water. An oil first separated from the cloudy solution, and it then solidified. The azide was extracted from the aqueous mixture into three portions of toluene and the combined toluene extracts were dried. The toluene solution was then added slowly to a flask equipped with a stirrer while the flask was heated on a steam bath. When the evolution of gas had ceased, the toluene solution was evaporated to give 1.1 g. (86%) of pale yellow plates with m.p. 105–109°. The infrared spectrum (Nujol) of this material contained a peak at 2222 cm.$^{-1}$ due to the isocyanate group.[22]

Preparation of the Methylcarbamate F-4.—The toluene solution obtained in a preparation of the isocyanate was concentrated to about 25 ml., and 10 ml. of methanol and 1 drop of triethylamine were added. The solution was heated on the steam bath under a reflux condenser for 5 hr. Evaporation of the solution left 1.18 g. of viscous pale yellow material. The infrared spectrum contained an N–H peak at 3260 cm.$^{-1}$ and a carbonyl peak at 1690 cm.$^{-1}$. The material later crystallized to give almost colorless prisms with m.p. 115–120°. The yield was 97%.

Preparation of the Tricyclic Amine F-5 from the Isocyanate.—The tricyclic isocyanate F-3 (1.1 g.) was refluxed for 2.5 hr. in 8 ml. of 20% hydrochloric acid. The solid went into solution after a short time during the heating. Evaporation of the solution gave 1.2 g. of a glassy material, which was dissolved in water and the solution filtered. The aqueous solution was then stirred with ether and enough 20% sodium hydroxide was added to make it strongly basic. The basic solution was extracted twice more with ether and the pale purple ether solution obtained was dried over magnesium sulfate. Evaporation of the ether solution gave 0.47 g. (47%) of viscous yellow-orange liquid which solidified after standing a few days. After some seed crystals of the amine were placed on the cold finger of the sublimation apparatus, the material was sublimed under aspirator vacuum at an oil-bath temperature of 140°. The material was sublimed in batches totaling 0.3 g. to give 0.2 g. of fine white crystals with m.p. 104–109°.

Anal. Calcd. for $C_{17}H_{25}O_3N$: C, 70.07; H, 8.65. Found: C, 70.06; H, 8.57.

Thin-layer chromatography of this amine (1% in ethanol) on silica gel G, using 1-butanol–acetic acid–water solvent, produced a separation of the two isomers. The ratio of the areas of the spots appeared to be 4:1 or 5:1. The R_f values were 0.65 and 0.69, respectively.

Preparation of the Tricyclic Amine F-5 from the Methylcarbamate.—The crude methylcarbamate (1.1 g.) was placed in 5 ml. of 10% sodium hydroxide, and 5 ml. of ethanol was added to give a clear solution. The solution was refluxed for 4 hr., and the ethanol was evaporated to leave an oil in the reaction solution. The mixture was extracted three times with ether and the ether was dried. Evaporation gave an oil which showed carbonyl absorption in the infrared.

The oil was redissolved in basic aqueous ethanol and refluxed for 12 hr. more. Work-up as before gave 0.5 g. of oil which solidified overnight. This material still showed some carbonyl absorption in the infrared. The material was sublimed to give white crystals with m.p. 110–114°. Treatment with phenyl isothiocyanate gave the phenylthiourea derivative, which was recrystallized to give fine white needles with m.p. 185–188°.

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(20) H. Wolff, *Org. Reactions*, **3**, 327 (1946).

(21) M. L. Moore, *ibid.*, **5**, 323 (1949).

(22) H. Hoyer, *Chem. Ber.*, **89**, 2677 (1956).

Preparation of the N-Methyl Tricyclic Amine F-6.—The methylcarbamate F-4 (1.05 g.) was dissolved in 15 ml. of anhydrous ether, and the solution was added dropwise to a stirred solution of 0.23 g. of lithium aluminum hydride in 15 ml. of anhydrous ether. The reaction mixture was refluxed for 21 hr. and was decomposed with wet ether. Enough 50% potassium hydroxide solution was added to form an aqueous layer containing the aluminum salts. The ether solution was separated and the aqueous layer was extracted with two more portions of ether. The ether solution was dried over potassium carbonate and evaporated to give 0.7 g. of viscous orange liquid. An attempt to sublime some of this material failed to give any crystalline product. The material gave a positive Hinsberg test for a secondary amine but failed to give a derivative with phenyl isothiocyanate. Thin-layer chromatography of this amine (1% in ethanol) using the 1-butanol–acetic acid–water solvent gave a single spot with R_f value 0.58.

Preparation of the N,N-Dimethyl Tricyclic Amine F-7.—The N-methyl tricyclic amine F-6 (0.5 g.) was placed in a flask with 0.45 ml. of 90% formic acid and 0.3 ml. of 38% formaldehyde. This mixture was heated on a steam bath under a reflux condenser for 8 hr. The flask was cooled, 0.28 ml. of 6 *N* hydrochloric acid was added, and the excess of formaldehyde and formic acid was removed under vacuum. Water was added to the residue and the aqueous solution (containing some insoluble material) was extracted with two portions of ether. This ether solution was dried and evaporated to give 0.06 g. of neutral oil which was not characterized.

The aqueous solution was stirred with ether, while enough sodium hydroxide solution was added to make it strongly basic. The solution was extracted with two more portions of ether and the ether solution was dried. Evaporation of the ether gave 0.4 g. of pale yellow viscous liquid.

Thin layer chromatography of this material (1% in ethanol) using the 1-butanol–acetic acid–water solvent gave a single spot with R_f value 0.46.

Thin layer chromatography of mixtures of the tricyclic amine, N-methyl tricyclic amine, and N,N-dimethyl tricyclic amine gave three distinct spots at precisely the same R_f values as determined individually.

Preparation and Decomposition of the N-Oxide of the N,N-Dimethyl Tricyclic Amine F-7.—The N,N-dimethyltricyclic amine F-7 (350 mg.) was dissolved in 1 ml. of methanol, 0.45 ml. of 30% hydrogen peroxide was added to the cooled solution, and the reaction solution was allowed to stand for 24 hr. at room temperature. Another 0.45 ml. of 30% hydrogen peroxide was added, and the solution was allowed to stand for 24 hr. more. The excess peroxide was decomposed with platinum foil (1 cm.^{2}). When the decomposition slowed down after standing overnight, a small drop of an aqueous solution of catalase was added.

The solution was transferred to a flask connected to a vacuum distillation apparatus. The methanol was removed under vacuum at room temperature and then the remaining solution was heated at 75° under 15-mm. pressure to remove the water (collected in a Dry Ice trap). The remaining material was heated for 5 hr. at 170° under 15-mm. pressure; it became brown during this time. Colorless material was collected in the Dry Ice trap. Nothing was collected in the receiving flask from the water condenser.

Ether and a 2 *N* solution of hydrochloric acid were added to the material in the trap and the two layers were shaken and separated. The ether solution was shaken with another portion of 2 *N* hydrochloric acid, and the combined acid solutions were extracted with two portions of ether. This procedure was also followed in working up the material in the pot.

The dried ether solution from the trap was evaporated, leaving no material. The acid solution was evaporated to give 33 mg. of white solid, m.p. 100–103°. Recrystallization from ethanol–ether gave colorless rods of N,N-dimethylhydroxylamine hydrochloride with m.p. 107–108°.[23] The yield of this material was 40% based on recovered starting material.

The acid solution from the pot was evaporated to give a glassy material. This was dissolved in water, and the solution was made strongly basic and extracted with ether. The dried ether solution was evaporated to give 70 mg. of the amine starting material.

The dried ether solution from the pot was evaporated to give 100 mg. of orange oil which showed mainly carbon–hydrogen peaks in the infrared. The ultraviolet spectrum contained maxima at 236 mμ ($\log \epsilon$ 4.42), 280 (3.46), 312 (2.75) sh, and 328 (2.67). A 35-mg. portion of this material was chromatographed on activity grade II alumina, and 25 mg. of colorless oil was obtained. A portion of this material was crystallized from hexane to give 5 mg. of colorless prisms, m.p. 75–76°; lit.[14] melting point of 1,2,3-trimethoxy-8-methylnaphthalene is 73–75°.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.23; H, 7.05.

A derivative with *s*-trinitrobenzene was prepared and crystallized from methanol to give orange plates with m.p. 94–95°; lit.[14] m.p. 91.5–93°.

Reaction of β-(2,3,4-Trimethoxybenzoyl)propionic Acid (P) with Methylmagnesium Iodide.—To 0.5 g. of magnesium turnings was added 15 ml. of anhydrous ether and 5 g. of methyl iodide. When the reaction was complete, the solution was added dropwise to a stirred solution of 2.0 g. of β-(2,3,4-trimethoxybenzoyl)propionic acid[15] in 50 ml. of dry benzene. A yellow complex separated as the Grignard reagent was added. The reaction mixture was stirred at room temperature for 4 hr. and then refluxed for 3 hr. The complex was decomposed with 10% hydrochloric acid. The organic layer was separated, and the aqueous solution was extracted with four portions of ether. The organic solutions were combined and extracted with three portions of 10% sodium carbonate solution. The organic solution was dried over anhydrous copper sulfate and evaporated to give 0.8 g. of viscous orange liquid which showed lactone carbonyl absorption in the infrared at 1770 cm.$^{-1}$. This lactone Q of γ-hydroxy-γ-(2,3,4-trimethoxyphenyl)valeric acid was not purified further but was used directly in the next reaction.

The combined sodium carbonate extracts were acidified with hydrochloric acid to give 0.25 g. of brown solid. This material was recrystallized from water–ethanol with Norit treatment to give pale yellow needles of β-(2-hydroxy-3,4-dimethoxybenzoyl)-propionic acid (R) with m.p. 154–155°; lit.[24] m.p. 152°.

Anal. Calcd. for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.63; H, 5.62.

γ-(2,3,4-Trimethoxyphenyl)valeric Acid (S).—The crude lactone of γ-hydroxy-γ-(2,3,4-trimethoxyphenyl)valeric acid (0.2 g.) was refluxed for 12 hr. with 3 ml. of 90% formic acid, 0.5 ml. of water, and 0.5 g. of zinc dust, then cooled and filtered. The formic acid solution was diluted with water and was placed in the refrigerator. After about 7 days a colorless crystalline solid separated. The amount was 70 mg. with m.p. 75–76°.

Anal. Calcd. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.64; H, 7.55.

4-Methyl-5,6,7-trimethoxy-1-keto-1,2,3,4-tetrahydronaphthalene (T).—The crude γ-(2,3,4-trimethoxyphenyl)valeric acid (300 mg.) was heated with 10 g. of polyphosphoric acid at 70–80° for 30 min. At the end of this time the color of the reaction mixture was an orange-brown. The reaction mixture was worked up with 30 g. of ice–water, and the cloudy solution was allowed to stand in the refrigerator for a few days. The aqueous solution was then poured off, and the remaining sticky material was dissolved in ether.

The ether solution was extracted with three portions of 10% sodium carbonate solution and then dried over magnesium sulfate. Evaporation of the ether gave 60 mg. of a yellow oil which contained a carbonyl peak in the infrared spectrum at 1670 cm.$^{-1}$. The infrared spectrum also contained a broad hydroxyl peak at 3390 cm.$^{-1}$. This indicated that the product was partially demethylated. The material could not be purified by chromatography or attempted crystallization.

1-Methyl-6,7,8-trimethoxy-1,2-dihydronaphthalene (U).—The crude tetralone (60 mg.) was dissolved in 5 ml. of methanol, and to this solution was added 100 mg. of sodium borohydride in aqueous methanol. The reaction mixture was stirred at room temperature for 14 hr. and then refluxed for 30 min. To this solution was added 4 ml. of 1 *N* hydrochloric acid, and the solution was stirred for 1.5 hr. The methanol was removed under vacuum and ether was added to the cloudy solution. The layers were separated and the aqueous solution was extracted with three portions of ether. The ether solutions were combined, dried, and evaporated to give 50 mg. of semisolid. The infrared spectrum contained no carbonyl peak and had two broad hydroxyl peaks at 3400 and 3240 cm.$^{-1}$. This hydroxy compound (50 mg.) was placed in 5 ml. of 10% sulfuric acid, and enough ethanol was added to effect solution. The solution was heated on a steam

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[23] A. C. Cope, R. A. Pike, and C. F. Spencer, *J. Am. Chem. Soc.*, **75**, 3212 (1953).

[24] P. Mitter and S. De, *J. Indian Chem. Soc.*, **16**, 35 (1939).

bath under a reflux condenser for 4 hr. Most of the ethanol was then removed under vacuum leaving a milky white aqueous solution.

A solution of sodium hydroxide in water was added to the mixture until the oily material dissolved and the solution was basic. Dimethyl sulfate (5 drops) was then added and the solution was heated on a steam bath for 30 min. Enough sodium hydroxide solution was added to make the reaction solution basic again, 5 drops more of dimethyl sulfate were added, and the solution was heated for 30 min. more. At the end of this time an oil had separated from the reaction mixture. The basic solution was extracted with three portions of ether, and the ether solution was dried and evaporated to give 35 mg. of an orange oil which had only a small hydroxyl peak in the infrared. The ultraviolet spectrum contained maxima at 224 mμ (log ϵ 4.34), 269 (3.88), 276 (3.87) sh, and 307 (3.22) sh.

1,2,3-Trimethoxy-8-methylnaphthalene (M).—The dihydronaphthalene was heated with 5 mg. of 10% palladium on charcoal under nitrogen for 2 hr. at 280–310°. The product was dissolved in benzene, the solution was filtered, the charcoal was washed with more benzene, and the combined benzene solution was evaporated to give 18 mg. of orange oil. The infrared spectrum of this material was essentially identical to the infrared spectrum of the crude material obtained in the decomposition of the N-oxide from F-7. The ultraviolet spectrum of this material showed maxima at 235 mμ (log ϵ 4.55), 280 (3.59), 313 (3.06) sh, and 328 (2.95). The material was dissolved in benzene–petroleum ether and eluted through activity grade II alumina. A yellow oil (9 mg.) was obtained which was crystallized from hexane to give 4 mg. of yellow crystals, m.p. 73–74°; lit.[14] m.p. 73–75°. A mixture melting point of this material with the recrystallized material from the N-oxide decomposition was 73–74°.

2-(3,4-Dimethoxyphenyl)-4,5-dimethyl-Δ^4-cyclohexenecarboxylic Acid (V).—In a small high-pressure hydrogenation bomb were placed 60 ml. of anhydrous xylene, 24 g. of 3,4-dimethoxycinnamic acid,[25] 23.8 g. of 2,3-dimethylbutadiene, and 0.3 g. of hydroquinone. The bomb was heated at 175° in a rocker for 13 hr. The bomb was then opened, the contents poured out, and the solid remaining in the bomb was washed out with portions of warm xylene. The solid was filtered off and the xylene solution was allowed to stand. More solid precipitated and this too was filtered off and added to the other solid material. This material was recrystallized from ethanol–water (1:1) to give white needles with m.p. 92–97°.

The xylene solution was extracted with 10% sodium bicarbonate solution, but this was unsatisfactory because of the formation of colloidal dispersions. Extraction with lithium carbonate solution also produced the same results. The extract solutions that were obtained (after settling) were acidified to give a white solid. This was recrystallized from ethanol–water (1:1) to give the same white needles obtained previously.

The infrared spectrum of this material contained a strong hydroxyl peak at 3300 cm.$^{-1}$. The neutralization equivalent (308) and analysis indicated that the product was a hydrate.

Anal. Calcd. for $C_{17}H_{22}O_4 \cdot H_2O$: C, 66.21; H, 7.85. Found: C, 66.13; H, 7.73.

The total yield of this hydrated product was 19.2 g. (62%).

A sample of this material was heated in a drying pistol with refluxing acetone under aspirator vacuum for 48 hr. The material obtained had m.p. 107–108°. The infrared spectrum contained no peak at 3300 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.40; H, 7.82.

Reaction of 2-(3,4-Dimethoxyphenyl)-4,5-dimethyl-Δ^4-cyclohexenecarboxylic Acid with Methanesulfonic Acid.—A 1.0-g. sample of the hydrate of 2-(3,4-dimethoxyphenyl)-4,5-dimethyl-Δ^4-cyclohexenecarboxylic acid was heated in a drying pistol under aspirator vacuum for 48 hr. The material obtained (0.95 g.) melted at 107–108°.

The anhydrous acid was placed in 6 ml. of reagent grade methanesulfonic acid. The solid dissolved immediately to give a cherry red solution. The solution was allowed to stand at room temperature for 3 hr., during which time the color became dark brown. The reaction solution was poured over 15 g. of cracked ice, and the white precipitate was collected and dissolved in ether.

A. The Dimethoxy Tricyclic Acids W and Y.—The ether solution was extracted with three portions of 10% sodium bicarbonate, and the extracts were combined and acidified with dilute hydrochloric acid. The solid obtained was recrystallized from ethanol–water (1:1) to give 0.57 g. of white crystalline product. The material melted low and over a large range, and the infrared spectrum (Nujol) contained a peak at 3400 cm.$^{-1}$. Some of this material was heated under aspirator vacuum in a drying pistol for 60 hr., and the solid obtained had m.p. 135–145°. The infrared spectrum contained no peak at 3400 cm.$^{-1}$. Recrystallization of some of this acid from carbon tetrachloride gave colorless needles with m.p. 80–90°. When heating was continued with the melting point block, square crystals formed in the melt and these crystals remelted at 135–145°. Chromatography of the acid melting at 135–145° on silica gel gave material which had the same melting-point range as the unchromatographed material.

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.61; H, 7.50.

The methyl ester of the dimethoxy tricyclic acid was prepared by refluxing a solution of the acid in methanol containing 2% sulfuric acid. The colorless liquid obtained was chromatographed on silica gel. All fractions of material obtained had identical infrared spectra. The chromatographed material was crystallized from an ethanol–water solution to give colorless prisms with m.p. 87–92°.

A gas chromatographic analysis of the ester on a 5-ft. SE-30 column at 195° showed the presence of two compounds in relative amounts of 45% and 55%.

The n.m.r. spectrum of the ester confirmed the ratio of the two compounds as determined by the gas chromatographic analysis.

B. The Lactone Mixture.—The ether solution remaining from the bicarbonate extraction was dried over magnesium sulfate and evaporated to give 0.05 g. of pale yellow oil which could not be crystallized.

When a sample of the hydrate of the cyclohexenecarboxylic acid was used in place of the anhydrous acid, 0.1 g. of neutral solid was obtained from the ether solution. A recrystallization of this material from dilute methanol gave white crystals with m.p. 138–143°. An infrared spectrum of this material as a Nujol mull contained a peak in the carbonyl region at 1722 cm.$^{-1}$, with a shoulder at 1755 cm.$^{-1}$.

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(25) Prepared in 60% yield by condensation of veratricaldehyde with malonic acid in pyridine with piperidine catalyst, m.p. 183–184°. G. Lock and E. Bayer, *Ber.*, **72**, 1070 (1939), report m.p. 181°.