ether–methanol gave 4-methylprogesterone (0.36 g.) as needles, m.p. 155–157°, [α]D +235°, λ_{max} 251 mμ (log ε 4.18); λ_{max} 5.84, 6.00 and 6.20 μ.

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.60; H, 9.69.

The fractions eluted with ether on crystallization from acetone–hexane yielded the hemi-ketal VIIId, m.p. 178–180°, [α]D +37°, λ_{max} 2.96 and 5.84 μ.

Anal. Calcd. for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71. Found: C, 76.14; H, 10.60.

REHOVOTH, ISRAEL

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

The Acid-catalyzed Rearrangement of Cinenic Acid. III.[1] Structure and Synthesis of the Lactonic Product

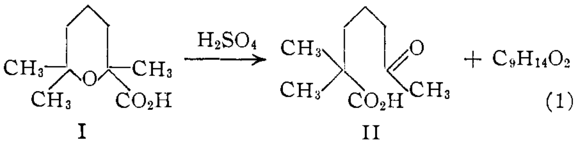
BY JERROLD MEINWALD AND HO CHIEN HWANG

RECEIVED DECEMBER 29, 1956

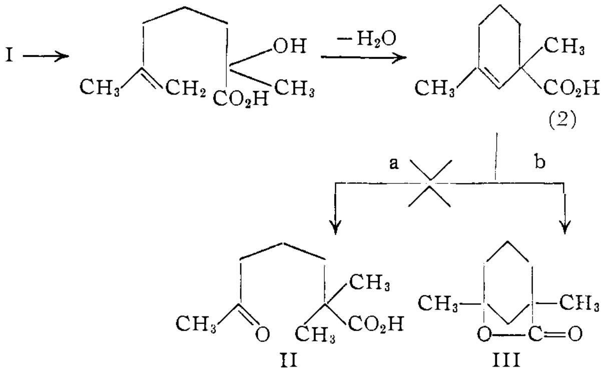
A crystalline lactone, isolated in 15% yield after treatment of α-cinenic acid (I) with concentrated sulfuric acid, has been shown to possess structure III. This lactone has been synthesized using a two-step procedure involving the Diels–Alder addition of isoprene to ethyl methacrylate and lactonization of the resultant adduct. The formation of III from I involves a reaction sequence which is unrelated to the carboxyl transfer process which produces geronic acid (II).

Introduction

As a continuation of our study of the acid-catalyzed rearrangements of α-cinenic acid (I), we have investigated the structure of the crystalline lactone, $C_9H_{14}O_2$, which is formed in about 15% yield when α-cinenic acid is isomerized to geronic acid (II) (see eq. 1).[2,3] The results of these synthetic and degradative studies are presented below.

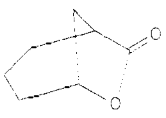


On the basis of a mechanism for the formation of II which is now known to be erroneous (eq. 2a), Rupe derived formula III[2] for the lactonic product (eq. 2b). The support for this formulation, aside from these "theoretical" considerations, came only from the observations that the lactone was saturated (therefore bicyclic) and that it could be hydrolyzed to a hydroxy-acid which dehydrated to regenerate the original lactone. Since this rather incomplete evidence in favor of III is weakened by the discovery that the formation of II involves a carboxyl transfer process rather than the path shown in equation 2,[4] we have sought a rigorous proof of the lactone structure.

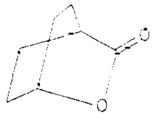


Structure Proof

The rearrangement of I was carried out as previously described, and a crystalline lactone, m.p. 50–51°, was obtained from the neutral portion of the product. A Kuhn–Roth determination indicated the presence of two C-methyl groups. The infrared spectrum of the crystalline lactone (in Nujol) showed a maximum at 5.60 μ. More significantly, in chloroform solution the lactone showed maximal absorption at 5.67 μ. Since these findings were in accord with the proposed structure, an independent synthesis of this structure was undertaken as the simplest method of unambiguous identification. The method chosen for the synthesis is outlined in Chart 1. Diels–Alder addition of isoprene to ethyl methacrylate gave a *mixture* of adducts, not easily separable into its individual components by fractional distillation. The formation of both of the theoretically possible products was anticipated, and ensured the success of the synthesis. Treatment of the mixture with sulfuric acid in acetic acid gave a mixture of lactones, from which III, m.p. 50–51°, and IV, m.p. 48–49°, were isolated by distillation and purified by crystallization. These were the lactones to be expected from acid-catalyzed cyclization following Markownikoff's rule. In accord with the structural assignments, III showed lactonic absorption at 5.67 μ (in chloroform) while IV showed absorption at 5.80 μ (in chloroform). The reported carbonyl bands for the known models



VI



VII

VI and VII are at 5.67 and 5.76 μ, respectively.[5] Finally, III was degraded in good yield to *m*-xylene (identified by conversion to its trinitro derivative, as well as by its infrared and ultraviolet spectra) by

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[1] Presented at the 131st National Meeting, American Chemical Society, Miami, Florida, April, 1957. For the previous paper in this series see J. Meinwald and C. C. Cornwall, THIS JOURNAL, **77**, 5991 (1955).

[2] H. Rupe and C. Liechtenhan, *Ber.*, **41**, 1278 (1908).

[3] H. Rupe and H. Hirschmann, *Helv. Chim. Acta*, **16**, 505 (1933).

[4] J. Meinwald, THIS JOURNAL, **77**, 1617 (1955).

[5] R. Grewe, A. Heinke and C. Sommer, *Chem. Ber.*, **89**, 1978 (1956).

heating with a barium oxide–palladium-on-charcoal mixture. Similarly, degradation of IV gave rise to a good yield of *p*-xylene.

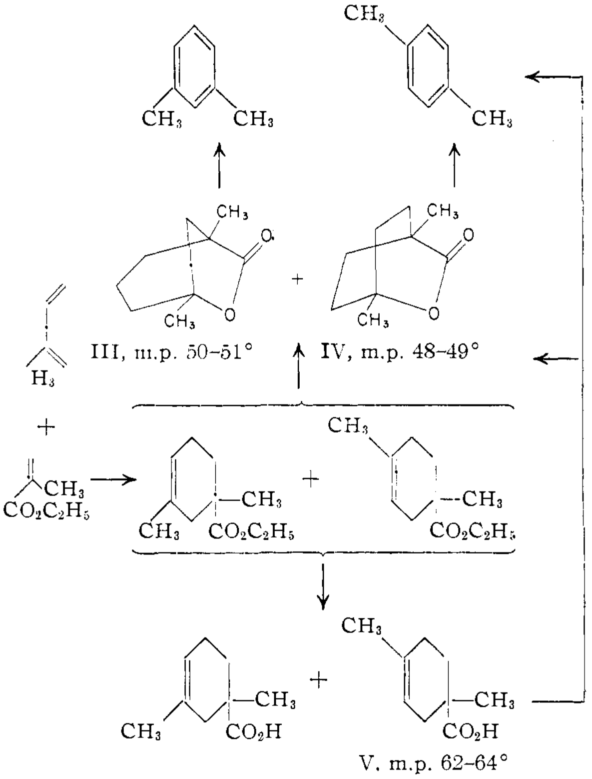


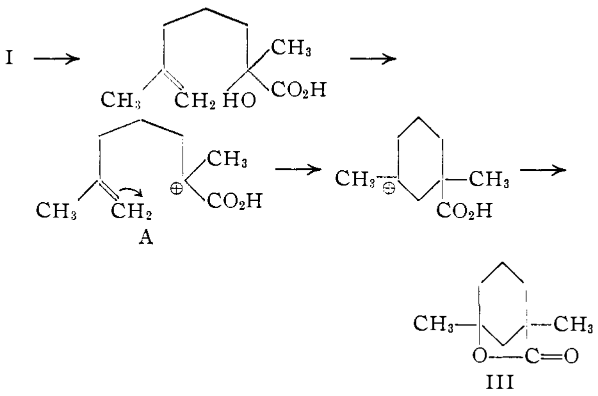
CHART 1

In an effort to separate the hydrolysis and lactonization steps, and to characterize the acid intermediates, a base hydrolysis of the original adduct mixture was carried out. A liquid mixture of acids was obtained, which gave rise to a mixture of lactones on acid treatment. (Chromatography of this mixture produced III and IV, but this procedure for preparing the lactones was much more tedious than that described previously.) The acid V, m.p. 62–64°, was isolated from the crude adduct hydrolyzate by virtue of the fact that it slowly crystallized from the mixture of acids. Its structure was proven by degradation to *p*-xylene and cyclization to the δ-lactone, IV. Unfortunately, it was impossible to characterize the acid precursor to the γ-lactone, III.

An authentic sample of lactone III was now available from these synthetic experiments, and a direct comparison with the neutral α-cinenic acid product was possible. Indistinguishable infrared spectra and an undepressed mixture melting point proved these two samples to be identical. The melting point of the γ-lactone III was depressed strongly upon admixture with the δ-lactone IV.

Concluding Remarks

The transformation of I to III would seem to proceed by the series of steps outlined in equation 3, the essential features of which were present in Rupe's suggestion. It should be pointed out, however, that this sequence is not entirely satisfactory. It would be possible to circumvent the rather unattractive intermediate (A) by postulating a cyclization *concerted* with loss of the hydroxyl group. In any event, it is apparent that this reaction is quite unrelated to the carboxyl transfer reaction responsible for the production of geronic acid (II), and that II and III do not have a common carbocyclic precursor as previously postulated.[2] Nevertheless, insofar as the structure and genesis of III is concerned, these results pay tribute to Rupe's organic chemical intuition.



Acknowledgment.—The authors are indebted to the National Science Foundation, whose support in the form of a Research Grant has made this research possible.

Experimental

Rearrangement of α-Cinenic Acid.—The rearrangement of 30 g. of I was carried out as described previously.[2-4] A neutral fraction weighing 12.1 g. was obtained from the reaction product by the usual extraction procedures. This material yielded a crystalline solid on chilling. Recrystallization from 30–60° petroleum ether gave 4.6 g. (15%) of white plates, m.p. 50–51°. The infrared spectrum of this material showed maxima at 5.60 μ in Nujol and 5.67 μ in $CHCl_3$ solution.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15; $-CH_3$, 19.4. Found: C, 69.86; H, 9.03; $-CH_3$, 10.83.

Addition of Isoprene to Ethyl Methacrylate.—Two hundred grams (1.76 moles) of ethyl methacrylate, 120 g. (1.76 moles) of freshly distilled isoprene and 2 g. of hydroquinone were placed in a steel bomb, heated at 200° overnight, and cooled to room temperature. The crude reaction product (316 g.) was subjected to distillation at diminished pressure. A small amount of unreacted ethyl methacrylate (27 g.) was recovered. A mixture (24 g.) of ethyl methacrylate and adduct was collected below 65° (3 mm.) and the main portion of adduct (263 g.) was collected over the range 66–72° (2.3–2.5 mm.). The infrared spectrum of this adduct was free of the sharp maximum at 6.10 μ characteristic of ethyl methacrylate. The yield, based on unrecovered dienophile, corresponded to 95%. Slow redistillation of the main fraction failed to separate the two isomeric esters, but gave an analytical sample, b.p. 71–72° (2.5 mm.).

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.53; H, 9.84. Found: C, 72.73; H, 9.94.

Lactonization of the Diels–Alder Adduct to III and IV. A.—Several techniques were used to prepare the desired lactones. In one experiment, the adduct (1 g.) was boiled with 50% sulfuric acid for about two days. The neutral product (85%) from this experiment was chromatographed on a Magnesol–Celite (1:1) column, using 30–60° petroleum ether as solvent. The early fractions showed carbonyl absorption at 5.80 μ, while later fractions showed a 5.65 μ maximum. Fractions showing chiefly γ-lactone absorption were combined and recrystallized to give about 7% of fine, colorless, platelike crystals, m.p. 50–51°, mixture m.p. with cinenic acid product 50–51°. The infrared spectra of the rearrangement product and the synthetic lactone were indistinguishable.

Some crystalline δ-lactone was obtained from an early fraction. It showed m.p. 48–49° after sublimation.

B.—The following technique gave both III and IV as crystalline products in reasonable yield. Ten grams of adduct was dissolved in 30 ml. of glacial acetic acid and 1 ml. of concentrated sulfuric acid was added. After standing at room temperature for 96 hours, the honey-colored reaction mixture was neutralized with saturated sodium bicarbonate solution. The neutral product was isolated by ether extraction in the usual manner, and 7 g. (83%) of lactone mixture was obtained. Vacuum distillation separated this mixture into two main fractions, b.p. 70-72° (1.5 mm.) and 79–81° (1.0 mm.), respectively. These products solidified on cooling, the lower boiling cut yielding 2.9 g. of γ-lactone (m.p. 50-51° after recrystallization from petroleum ether) and the higher boiling giving 4.0 g. of δ-lactone (m.p. 48–49° after recrystallization from petroleum ether).

The δ-lactone was resublimed to yield an analytical sample, m.p. 48–49°. It had a single sharp maximum in chloroform at 5.80 μ.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.91; H, 9.00.

Degradation of III to *m*-Xylene.—One gram (0.006 mole) of III (m.p. 50–51°) was ground to a fine powder and mixed thoroughly with 300 mg. of 10% palladium–charcoal and 3.0 g. of barium oxide. The mixture was placed in a 25-ml. distilling flask and heated gently over a micro-flame. The product, *m*-xylene, came over readily as a colorless liquid. The yield was 0.55 g. (80%). For complete identification of this product, infrared and ultraviolet spectra were taken and a nitro derivative was prepared. Maxima at 13.00, 13.75 and 14.50 μ in the infrared[6] and at 259, 265.4, 268.8 and 272.5 mμ in the ultraviolet,[7] all characteristic of *m*-xylene, were observed. Nitration of 500 mg. of the degradation product using 2 ml. of concentrated sulfuric acid and 2 ml. of fuming nitric acid, and keeping the mixture at 100° for 20 minutes, gave a white precipitate when the reaction mixture was poured onto ice. After recrystallization from 95% ethanol, fine, pale yellow, needles, m.p. 177–180° (lit.[8] 182°), were obtained. A melting point of 177–181° was observed on admixture with an authentic sample of 2,4,-6-trinitro-*m*-xylene.

Degradation of IV to *p*-Xylene.—Five hundred mg. (0.003 mole) of IV (m.p. 48–49°) was degraded in a fashion parallel to that described above. A yield of 300 mg. (88%) of *p*-xylene was obtained. The product was identified by its characteristic infrared (12.58, 13.72, 14.41 μ)[9] and ultraviolet (260.7, 266.1, 269.0, 275.0 mμ)[10] spectra.

Base Hydrolysis of the Diels–Alder Adduct.—Forty grams (0.22 mole) of the Diels–Alder adduct was refluxed with 210 ml. of 5% potassium hydroxide solution for 70 hours. Not all the ester had been hydrolyzed at this point, and 8.5 g. of starting material was recovered by ether extraction. The reaction mixture was then acidified with hydrochloric acid and extracted with five 100-ml. portions of ether. The ether layer was washed with water, dried over anhydrous magnesium sulfate and evaporated. Vacuum distillation of the residual acid gave a main fraction (21.9 g., 82% yield on basis of ester converted), b.p. 104–105° (1.0 mm.). Using a 70-cm. Podbielniak column, no evidence for separation of isomers was obtained. On cooling, however, the acid slowly deposited crystals of V. These crystals were collected and washed with petroleum ether. The crude material, m.p. 60-64°, gave an analytical sample, m.p. 62–64°, on vacuum sublimation.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.84; H, 8.91.

Degradation of V to *p*-Xylene.—Five hundred mg. (0.003 mole) of V yielded 200 mg. (58%) of colorless distillate when subjected to palladium–charcoal and barium oxide degradation, as described above. The infrared spectrum of the product was indistinguishable from that of authentic *p*-xylene.

Lactonization of V.—A solution of 2.76 g. (0.018 mole) of V in 10 ml. of glacial acetic acid and 0.25 ml. of concentrated sulfuric acid was allowed to stand at room temperature overnight. The neutral product was isolated in the usual way, and appeared as long needles as soon as the ether was taken off. The yield was 1.9 g. (69%). Recrystallization from 30–60° petroleum ether gave pure white needles, m.p. 48–49°.

ITHACA, NEW YORK

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[6] F. D. Rossini, *et al.*, "Infrared Spectral Data," American Petroleum Institute Research Project 44, Carnegie Institute of Technology, Pittsburgh, Pennsylvania, 1955, Serial No. 311.

[7] "Ultraviolet Spectral Data," American Petroleum Institute Research Project 44, Carnegie Institute of Technology, Pittsburgh, Pennsylvania, 1946, Serial No. 56.

[8] I. M. Heilbron, "Dictionary of Organic Compounds," 2nd ed. Vol. IV, Oxford University Press, New York, N. Y., 1953, p. 627.

[9] See reference 6, spectrum Serial No. 312.

[10] See reference 7, spectrum Serial No. 57.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

The Synthesis of β-(3-Methoxy-2,6-dinitrophenyl)-D,L-alanine and β-(3-Methoxy-4,6-dinitrophenyl)-D,L-alanine. Proof of the Structures of Two Isomeric Dinitro-*m*-tyrosines

BY ERNEST L. JACKSON

RECEIVED DECEMBER 29, 1956

β-(3-Methoxy-2,6-dinitrophenyl)-D,L-alanine and β-(3-methoxy-4,6-dinitrophenyl)-D,L-alanine have been synthesized from 3-methoxy-2,6-dinitrobenzaldehyde and 3-methoxy-4,6-dinitrobenzaldehyde. These two amino acids have been correlated with two of the β-(3-methoxydinitrophenyl)-D,L-alanines that were obtained by way of the nitration of *m*-tyrosine, thus proving two of the nitration products to be β-(3-hydroxy-2,6-dinitrophenyl)-D,L-alanine and β-(3-hydroxy-4,6-dinitrophenyl)-D,L-alanine.

The nitration of *m*-tyrosine has been shown[1] to produce three crystalline isomers of β-(3-hydroxydinitrophenyl)-D,L-alanine which upon acetylation yielded three isomers of N-acetyl-β-(3-hydroxydinitrophenyl)-D,L-alanine; methylation of two of these compounds afforded two isomers of N-acetyl-β-(3-methoxydinitrophenyl)-D,L-alanine methyl ester. Hydrolysis and deacetylation of these two methyl esters gave the two isomeric β-(3-methoxydinitrophenyl)-D,L-alanines. The present paper describes the third isomer of β-(3-methoxydinitrophenyl)-D,L-alanine and its N-acetyl methyl ester; it also establishes the orientation of the nitro groups for two of the isomers by their comparison with the authentic compounds which have been synthesized from 3-methoxy-2,6-dinitrobenzaldehyde and 3-methoxy-4,6-dinitrobenzaldehyde, the structures of which were proved by Hodgson and Beard[2] and by Tröger and Eicker.[3]

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[1] E. L. Jackson, THIS JOURNAL, **77**, 4860 (1955).

[2] H. H. Hodgson and H. G. Beard, *J. Chem. Soc.*, 2375 (1927).

[3] J. Tröger and C. Eicker, *J. prakt. Chem.*, [2] **116**, 17 (1927).