

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

The Wound Hormones of Plants. V. The Synthesis of Some Analogs of Traumatic Acid

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In view of the fact that traumatic acid, Δ^1 -decene-1,10-dicarboxylic acid,¹ is only one of several factors involved in the growth phenomena associated with the bean test² it was considered desirable to investigate the chemical and physiological properties of some traumatic acid analogs. The problem seems especially interesting because various observations during the isolation of this hormone led to the suspicion that closely related physiologically active substances might be present in plant materials. The present paper describes the synthesis of a number of unsaturated dibasic acids which are being investigated from the point of view of their activity as plant wound hormones.³

Acids of the type $\text{HOOC}(\text{CH}_2)_n\text{CH}=\text{CH}-\text{COOH}$ (I) and $\text{HOOC}(\text{CH}_2)_n\text{H}=\text{CH}-\text{CH}_2-\text{COOH}$ (II) were prepared by the condensation of the desired aldehyde-ester $\text{ROOC}(\text{CH}_2)_n\text{CHO}$ with malonic acid followed by hydrolysis of the ester group. Decarboxylation of the substituted malonic acids took place during the condensation reaction. It was found, in agreement with the findings of Linstead in the unsaturated monobasic acid series,⁴ that when pyridine was used as a condensing agent type (I) formed the chief product, while dimethylaniline or triethanolamine led to the formation of type (II). Although several other condensing agents and a variety of experimental conditions were tried, in every case difficulty was experienced in separating the desired products from the reaction mixture in the pure state. Both recrystallization and distillation of the esters were rather inefficient and led to low yields. The partial esterification method used for separating the Δ^1 and Δ^2 unsaturated monobasic acids⁵ was tried and found to be more tedious and less effective than a chromatographic adsorption method. Using charcoal as an adsorbent and ether as a solvent it was found that a

satisfactory separation of types (I) and (II) could be effected easily and this method was used in purifying the reaction products.

In order to study the effect on wound hormone activity of a double bond further removed from the carboxyl group in this series, Δ^6 -undecene-1,11-dicarboxylic acid was prepared. This synthesis involved the preparation of 6-undecanone-1,11-dicarboxylic acid followed by reduction and conversion of the resulting hydroxy acid to the desired product. Attempts to prepare keto acids of this type from the half esters $\text{ROOC}(\text{CH}_2)_n-\text{COOH}$ by passing them over various catalysts or heating their salts either led to exceedingly poor yields or failed entirely. Accordingly acetone-dicarboxylic ester was di-alkylated by treatment with sodium ethylate and *o*-iodovaleric ester; the reaction went smoothly, though slowly, in the same manner as in the case of acetone-dipropionic acid.⁶ Some difficulty was encountered in the reduction of 6-undecanone-1,11-dicarboxylic acid: catalytic reduction using platinum oxide was very slow and other methods tried such as the use of sodium and ethyl alcohol⁷ gave unsatisfactory yields. Since the iodo acid prepared from the 6-undecanol-1,11-dicarboxylic acid failed to crystallize, it was converted directly to the unsaturated acid by heating with alcoholic potassium hydroxide. Oxidation of the product of this reaction with potassium permanganate gave the expected degradation products confirming the structure as Δ^6 -undecene-1,11-dicarboxylic acid.

$\Delta^{1,7}$ -Octadiene-1,8-dicarboxylic acid was prepared from α,α' -dibromosebacic ester by the action of dimethylaniline and was converted to Δ^1 -octene-1,8-dicarboxylic acid by adding half the calculated quantity of hydrogen and separating the resulting mixture by chromatographic analysis.

The physiological activities of these compounds will be reported elsewhere. It may be said here that all the acids prepared show wound hormone activity when tested in the presence of the stand-

(1) J. English, Jr., J. Bonner and A. J. Haagen-Smit, *THIS JOURNAL*, **61**, 3434 (1939).

(2) J. Bonner and J. English, Jr., *Plant Physiol.*, **13**, 331 (1938).

(3) The physiological testing is being carried out by Professor James Bonner at the California Institute of Technology.

(4) R. P. Linstead, E. G. Nobler and E. J. Boorman, *J. Chem. Soc.*, 557 (1933).

(5) J. J. Sudborough and E. R. Thomas, *ibid.*, **99**, 2307 (1911).

(6) H. v. Pechman and N. V. Sidgwick, *Ber.*, **37**, 3816 (1904).

(7) G. M. Robinson, *J. Chem. Soc.*, 745 (1930).

ard co-factor mixture,⁸ and in all cases the unsaturated acids are more active than the corresponding saturated compounds.

Experimental

Preparation of Aldehyde-esters.—(a) Ethyl hydrogen sebacate was heated on the steam-bath with the calculated amount of thionyl chloride until the evolution of gases ceased and the mixture was then fractionally distilled under reduced pressure. Sebacyl ethyl ester chloride, b. p. 129–130° (1 mm.), was obtained in 82% yield.

Anal. Calcd. for C₁₂H₂₁O₃Cl: C, 58.0; H, 8.48. Found: C, 57.8; H, 8.50.

The above ester chloride was reduced according to the method of Rosenmund⁹ in boiling xylene solution. No catalyst "poison" was found necessary and the reduction was complete in about three hours; yield 70–80% of the theoretical of ethyl θ -aldehyde-nonanoate, b. p. 130° (2 mm.).

(b) Methyl oleate, methyl undecylate and methyl erucate were ozonized in acetic acid solution¹⁰ and the ozonides decomposed directly by treating the solution with zinc dust and water.¹¹ The yields of aldehyde-esters so obtained ranged from 50 to 60% of the theoretical.

Preparation of Unsaturated Acids.—(a) The Δ^1 unsaturated acids were prepared by adding the desired aldehyde-ester to a solution of an equivalent amount of dry malonic acid in 2–3 times its weight of pyridine at room temperature. The mixture was allowed to stand for three to five days, after which time the evolution of carbon dioxide had practically ceased. After being heated on the steam-bath for three hours to complete the reaction, the mixture was acidified and extracted with ether. The crude mixture of acid-esters thus obtained was hydrolyzed with 2 *N* alcoholic sodium hydroxide and the mixture of dibasic acids precipitated with dilute hydrochloric acid. In order to purify the product it was dissolved in ether (dried over calcium chloride) and passed through a column packed with an intimate mixture of carbon (Merck Decolorizing) and an equal weight of Supercel (Hyflo Supercel, Johns-Manville). An amount of carbon equal to 4–5 times the weight of product was found to be sufficient. The columns were developed by dry ether followed by a mixture of three parts of ether to one of acetone. The adsorbed acids were thus washed completely through the columns, the less strongly adsorbed materials, consisting of some low melting side products containing the Δ^2 -acid, coming through first followed by the Δ^1 -acid in a fairly pure state. Further recrystallization from dilute alcohol or acetic acid was always necessary to obtain a pure product. The yields ranged from 30 to 50% of the theoretical quantity.

(b) The Δ^2 -unsaturated acids were prepared in exactly the same manner, using dimethylaniline instead of pyridine, and adding sufficient dry methanol to give a homogeneous reaction mixture. In this case also chromatographic adsorption on charcoal followed by recrystalliza-

tion from dilute alcohol or acetic acid was used to purify the product. In each case the Δ^2 -acid was found more soluble in ether and less strongly adsorbed on carbon than the corresponding Δ^1 -acid. The melting points and analyses of the compounds prepared in this manner are given in Table I.

(c) Δ^1 -Nonene-1,9-dicarboxylic acid was also prepared by the method recently reported by Bergmann¹² utilizing pure azelaic semi-aldehyde, b. p. 151 (1.5 mm.), instead of the crude oxidation product used by him. This aldehyde-acid was prepared from U. S. P. oleic acid by conversion to dihydroxystearic acid, followed by a lead tetraacetate oxidation.¹³ The condensation was carried out exactly as described by that author and the product, after eight recrystallizations from carbon tetrachloride and dilute alcohol, was identical with that obtained by method (a), melting at 103° rather than at 94° as reported by Bergmann.

TABLE I

Dicarboxylic acid	M. p., ^a °C.	Calcd.		Found	
		C	H	C	H
Δ^1 -Nonene-1,9-	103	61.7	8.96	61.7	9.03
Δ^2 -Nonene-1,9-	90	61.7	8.96	61.9	8.70
Δ^1 -Decene-1,10-	165
Δ^2 -Decene-1,10-	109	63.2	8.78	63.4	8.94
Δ^1 -Tridecene-1,13-	108.5	66.7	9.62	66.4	9.69
Δ^2 -Tridecene-1,13-	104	66.7	9.62	66.5	9.54

^a All melting points are corrected.

$\Delta^{1,7}$ -Octadiene-1,8-dicarboxylic Acid.—Ethyl α, α' -dibromosebacate,¹⁴ 40 g., b. p. 188–192 (2 mm.), prepared by the action of bromine on sebacyl chloride followed by treatment with ethyl alcohol, was mixed with 30 g. of dimethylaniline and heated in an oil-bath at 180° for sixteen hours. The solution was then cooled, added to an excess of cold dilute hydrochloric acid and extracted with ether. The ether solution was dried, the ether evaporated, and the resulting mixture of esters fractionally distilled. The fraction boiling between 151 and 168° at 1 mm. was hydrolyzed with 2 *N* sodium hydroxide to give 10 g. of crude unsaturated acid. The pure $\Delta^{1,7}$ -octadiene-1,8-dicarboxylic acid, m. p. 236–239° with decomposition, was obtained by washing with a little cold ether and recrystallizing from acetic acid.

Anal. Calcd. for C₁₀H₁₄O₄: C, 60.6; H, 7.07. Found: C, 60.6; H, 7.00.

Δ^1 -Octene-1,8-dicarboxylic Acid.—An alcohol solution of $\Delta^{1,7}$ -octadiene-1,8-dicarboxylic acid, 2 g., was shaken at atmospheric pressure with hydrogen in the presence of platinum (platinum oxide previously reduced in the presence of solvent alone) until one mole of hydrogen had been absorbed. At this point the reduction was interrupted, the alcohol evaporated, and the product treated with 350 cc. of dry ether. About 0.5 g. of unchanged starting material was insoluble in this amount of ether. The filtered solution was then passed through a column of 10 g. of carbon as before. Sebacyl acid, 0.3 g., followed by 0.11 g. of an intermediate fraction appeared in the filtrate before the Δ^1 -octene-1,8-dicarboxylic acid came through. The

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(9) K. W. Rosenmund, *Ber.*, **51**, 585 (1918).

(10) C. R. Noller and R. Adams, *This Journal*, **48**, 1074 (1926).

(11) F. C. Whitmore and J. M. Church, *ibid.*, **54**, 3710 (1932).

(12) F. Bergmann, *ibid.*, **62**, 3255 (1940).

(13) J. T. Scanlan and D. Swern, *ibid.*, **62**, 2305 (1940).

(14) H. L. Le Sueur and P. Haas, *J. Chem. Soc.*, **97**, 180 (1910).

yield was 0.6 g. of material melting at 168–171°; after recrystallization from acetic acid the pure product melted at 173°.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 60.0; H, 8.00. Found: C, 59.9; H, 7.88.

6-Undecanone-1,11-dicarboxylic Acid.—This compound was prepared by the alkylation of acetone dicarboxylic ester as described by von Pechman and Sidgwick⁶ using ethyl iodovalerate.¹⁵ About eight hours of refluxing was required to complete each stage of the alkylation as judged by the neutrality of the reaction mixture. It was not found possible to distill the tetracarboxylic esters first formed without serious decomposition so the product was isolated by hydrolysis of all material boiling above 150° (1 mm.). This was carried out by refluxing the material with four times its weight of concentrated hydrochloric acid for six to eight hours, during which time decarboxylation took place, and purifying the resulting 6-undecanon-1,11-dicarboxylic acid by recrystallization from water or dilute alcohol. The product may also be purified by distillation of its ethyl ester, b. p. 180 (0.5 mm.). A 52% yield of 6-undecanon-1,11-dicarboxylic acid melting at 114° was obtained.

Anal. Calcd. for $C_{13}H_{22}O_6$: C, 60.4; H, 8.56. Found: C, 60.3; H, 8.32.

5-Nonanone-1,9-dicarboxylic acid, m. p. 111°, was prepared in the same manner as above, using α -iodobutyric ester in the alkylation reaction.

Anal. Calcd. for $C_{11}H_{18}O_6$: C, 57.4; H, 7.83. Found: C, 57.0; H, 7.66.

6-Undecanol-1,11-dicarboxylic acid was prepared by reduction of the corresponding keto acid using platinum oxide and a pressure of 30–40 pounds of hydrogen. A mixture of equal volumes of ether and alcohol was found to be a suitable solvent. The reduction was very slow, requiring from two to six days depending on the activity and amount of the catalyst; it was found necessary to use an amount of platinum oxide equal to one-fifth or more of the weight of the keto acid in order to get a reasonable rate of reduction. The yield of pure hydroxy acid m. p. 102–103 was nearly quantitative.

Anal. Calcd. for $C_{13}H_{24}O_6$: C, 60.0; H, 8.85. Found: C, 59.8; H, 8.88.

5-Nonanol-1,9-dicarboxylic acid was prepared as above from the corresponding keto acid, m. p. 95°.

Anal. Calcd. for $C_{11}H_{20}O_6$: C, 56.9; H, 8.70. Found: C, 56.4; H, 8.50.

Δ^5 -Undecene-1,11-dicarboxylic acid was prepared by heating 6-undecanol-1,11-dicarboxylic acid with a slight excess of phosphorus triiodide on the steam-bath for three hours. The iodo acid obtained by ether extraction of the reaction mixture did not crystallize and was directly converted to the unsaturated acid by refluxing with 25% alcoholic potassium hydroxide for three hours. The product was isolated by ether extraction of the acidified reaction mixture followed by chromatographic analysis and recrystallization from a mixture of benzene and petroleum ether. Δ^5 -Undecene-1,11-dicarboxylic acid melts at 72°.

Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.5; H, 9.09. Found: C, 64.6; H, 9.24.

Several attempts to prepare Δ^4 -nonene-1,9-dicarboxylic acid by this method failed to give a significant amount of pure product. There was found a considerable portion of neutral material as well as a mixture of liquid unsaturated acids that did not yield to the usual methods of separation.

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Summary

1. A method for the synthesis of unsaturated acids of the type $HOOC(CH_2)_nCH=CHCOOH$ and $HOOC(CH_2)_nCH=CH-CH_2COOH$ has been developed and several representatives of these types were prepared.

2. Δ^5 -Undecene-1,11-dicarboxylic acid and $\Delta^{1,7}$ -octadiene-1,8-dicarboxylic acid also have been prepared.

3. These acids are found to be active plant wound hormones.

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(15) A. S. Carter, *THIS JOURNAL*, **60**, 1968 (1928).