and zinc chloride (63.5 g.) in ether (about 50 ml.). The above ester chloride solution in benzene was added and the resulting mixture was stirred overnight at 45°. After cooling, it was decomposed by the addition with stirring of dilute (1:3) hydrochloric acid and filtered. The clear benzene solution was separated, washed with water, and concentrated on the steam bath. The resulting residue was dissolved in warm isopropyl ether; the ensuing crystallization was slow. When it appeared complete, the crystalline material was filtered off and recrystallized from the same solvent, m.p. 104° (27 g., 21% yield on the basis of the half ester used).

Anal. Calcd. for $C_{23}H_{24}O_3$: C, 79.28; H, 6.94. Found: C, 79.22; H, 6.91.

Saponification with alcoholic alkali afforded a quantitative yield of the keto acid, m.p. 220–225°.

Anal. Calcd. for $C_{22}H_{22}O_3$: C, 79.01; H, 6.63; neut. equiv. 334. Found: C, 78.93; H, 6.58; neut. equiv. 336.

Methyl 4-oxo-2-octenoate by pyrolysis of methyl 9,10-dihydro-9,10-ethanoanthracene-12-n-valeryl-11-carboxylate (V). The adduct (7.0 g., 0.02 mole) was pyrolyzed at 260° under about 15-mm. pressure. The resulting distillate consisted of a solid (anthracene) and a yellow oil. The distillate was taken up in low boiling petroleum ether; the solution was filtered and partly concentrated. The concentrate deposited impure methyl 4-oxo-2-octenoate (m.p. 26°, 2.0 g., 59% crude yield). Recrystallization from the same solvent raised the melting point to 35°. No depression of the melting point resulted from admixture of the ester with a specimen of the ester obtained *via* the cyclopentadiene adduct (V).

Methyl 4-oxo-2-nonenoate from 4-oxo-2-nonenoic acid. 4-Oxo-2-nonenoic acid[7] (5.2 g., 0.031 mole) was dissolved in the calculated amount of 1*N* sodium hydroxide, and an excess of 40% silver nitrate solution was added. The precipitated silver salt was filtered off, washed with water and methanol, and dried at 40° *in vacuo* (6.8 g., 80% yield). A mixture of the silver salt, methanol (15 ml.), and methyl iodide (4.5 g., 0.032 mole) was heated under reflux for 2 hr. The solid material was removed by filtration and washed with a little methanol. The combined methanolic solutions were concentrated *in vacuo*. The residue was extracted with low boiling petroleum ether and the extract partly evaporated and allowed to crystallize. After two recrystallizations from low boiling petroleum ether, the ester melted at 45–46°.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 65.92; H, 8.54.

No depression of the melting point resulted upon admixture with a specimen of the ester, m.p. 48.5°, obtained *via* the cyclopentadiene adduct.

Acknowledgment. The author is indebted to Mr. S. J. Tassinari of this Laboratory who carried out the microanalyses, and to Dr. A. M. Vogel of the Chemistry Department, Adelphi College, Garden City, N. Y. for the ultraviolet absorption measurements.

OAKDALE, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES DIVISION, NATIONAL DAIRY PRODUCTS CORPORATION]

Potential Antimicrobial Agents. II. 4-Hydroxy-2,4-alkadienoic Acid γ-Lactones[1]

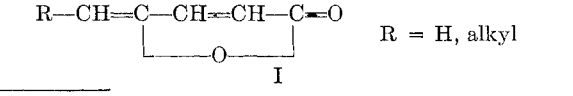
HENRY M. WALTON

Received September 17, 1956

A new method is described for the synthesis of 4-hydroxy-2,4-alkadienoic acid γ-lactones (protoanemonin analogs) in two steps: (1) Synthesis of cyclopentadiene and anthracene adducts of 4-oxo-2-alkenoic acids, followed by (2), lactonization and retrogressive Diels-Alder reaction of the resulting lactones. The facile saponification of the lactones also completes a new synthesis of 4-oxo-2-alkenoic acids.

Protoanemonin[2–4] and patulin,[5] both broad-spectrum antibiotics, are 4-hydroxy-2,4-alkadienoic acid γ-lactones, protoanemonin (I, R = H) being the simplest possible compound of this structure.

Since therapeutic use of these antibiotics appears to be precluded by their toxicity it seemed of interest to examine similar compounds in order to determine the relation of their structure to antimicrobial activity and toxicity.



I

When this investigation was undertaken protoanemonin was the only lactone of type I which had been synthesized. The most practicable synthesis of protoanemonin had been devised by Shaw[4] who obtained the lactone in 30% yield by lactonization of the readily available β-acetylacrylic acid. Although the lactonization of other 4-oxo-2-alkenoic acids might prove feasible, attempts in this direction appeared unpromising since these acids remain relatively inaccessible.[6,7]

(1) Preceding paper in this series: H. M. Walton, *J. Org. Chem.*, **22**, 308 (1957).

(2) For references concerning the physiological properties of this antibiotic see L. J. Haynes, *Quart. Rev.*, **2**, 46 (1948).

(3) Earlier findings concerning the physiological properties of this antibiotic were substantially confirmed by K. Rotter and Gruber, *Mitt. Versuchsanstalt Gärungsgewerbe u. Insts. angew. Mikrobiol. Hochschule Bodenkult.*, **3**, 56 (1949); [*Chem. Abstr.*, **47**, 7094 (1953)].

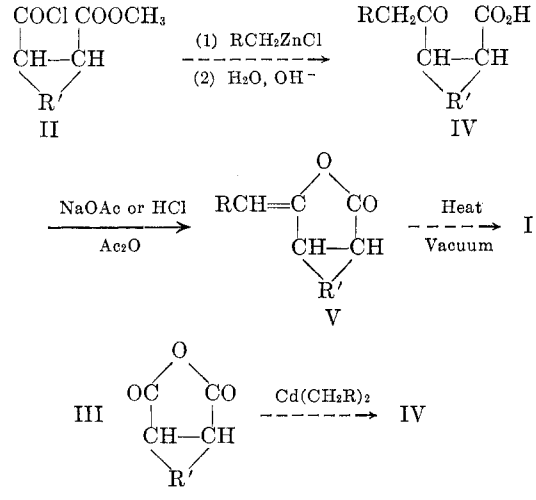
(4) Structure, *cf.* E. Shaw, *J. Am. Chem. Soc.*, **68**, 2510 (1946).

(5) R. B. Woodward and G. Singh, *J. Am. Chem. Soc.*, **71**, 758 (1949).

(6) For references concerning general methods of preparation for 4-oxo-2-alkenoic acids see (1).

(7) While this work was in progress, K. N. Campbell, C. D. Gordon and B. K. Campbell, Abstracts of Papers, 122nd Meeting, Am. Chem. Soc., Atlantic City 1952, p. 12L, outlined the synthesis of two lactones (I), R = *n*-propyl and R = *n*-amyl, by another route involving, *i. a.*, lactonization of 4-oxo-alkanoic acids, bromination of the resulting ketenol lactones and dehydrobromination.

A new method was, therefore, developed for the synthesis of lactones (I) which is based on Diels-Alder adducts of 4-oxo-2-alkenoic acids with cyclopentadiene and anthracene (IV). These adducts had become conveniently available through saponification of the corresponding esters obtained during an earlier investigation.[1] Lower molecular weight keto acid adducts (IV) proved also capable of preparation through the reaction of bicyclo-[2.2.1]5-heptene-2,3-dicarboxylic anhydride (III) with cadmium alkyls.



(II, IV: R′ = 3,5-cyclopenteno or 9,10-anthraceno; III: R′ = 3,5-cyclopenteno)

The corresponding lactones (V) represent adducts of 4-hydroxy-2,4-alkadienoic acid γ-lactones and it was reasonable to expect these lactone adducts to undergo retrogression[8] at elevated temperatures with the liberation of the desired lactones (I). This reaction scheme proved feasible.

could also be brought about by employing mixtures that resulted from the addition of small amounts of hydrochloric acid to acetic anhydride. However, this method appears to be limited to lower molecular weight members of the series (up to, and including, R = *n*-propyl). Attempts to apply acidic lactonizing conditions to higher homologs failed also when stronger, anhydrous acids (sulfuric, perchloric) in acetic anhydride were used.

The lactonization methods were successful when applied to keto acid adducts (IV) possessing an α-methylene group. Branching in the α-position apparently interferes with lactonization since attempts to lactonize the simplest α-branched keto acid adduct (IV) ($(CH_3)_2CH$— instead of RCH_2—) were unsuccessful.

Lactone adducts (V) were obtained as colorless high-boiling oils of considerable heat instability. Except in the case of the lowest molecular weight members of the series, they distilled with decomposition, *i.e.*, presumably retrogression,[8] even under low pressures (1 mm.).

The lactone adducts (V) with cyclopentadiene and anthracene underwent retrogression in a preparatively satisfactory manner at 180–200° and 240–260°, respectively. Higher over-all yields of lactones (I) were obtained when *crude* rather than purified lactone adducts (V) were subjected to pyrolysis.

The following yields of lactones (I) were obtained: From lactone adducts (V), 70–85%; from keto acid adducts (IV) without isolation of the intermediate lactone adducts (V), 50–80%; on the basis of half ester chlorides (II) yields were generally 25–40%.

The alkadienoic lactones (I) were obtained as

TABLE I

KETO ACID ADDUCTS (IV)

R	M.P. °C.	Formula	Analyses[a] C Calcd.	C Found	H Calcd.	H Found
CH_3	102–103[b]	$C_{11}H_{14}O_3$	68.03	67.41	7.27	7.04
C_2H_5	83–85[c]	$C_{12}H_{16}O_3$	69.20	69.36	7.75	7.94
[d]	85–86[c]	$C_{12}H_{16}O_3$	69.20	69.07	7.75	7.43
n-C_3H_7	87–88[c,e]	$C_{13}H_{18}O_3$	70.24	70.12	8.16	7.98
i-C_3H_7	122[b]	$C_{13}H_{18}O_3$	70.24	70.07	8.16	8.10
n-C_4H_9	93–94[f]	$C_{14}H_{20}O_3$	71.16	71.50	8.53	8.48
n-C_5H_{11}	85[c,g]	$C_{15}H_{22}O_3$	71.97	72.23	8.86	8.54
n-$C_{11}H_{23}$	86.5–87[c,h]	$C_{21}H_{34}O_3$	75.40	74.94	10.27	9.99

[a] Neutral equivalents found 100–101% of theory. [b] Recrystallized from isopropyl ether. [c] Recrystallized from ligroin, b.p. 60–90°. [d] $(CH_3)_2CH$ instead of RCH_2. [e] Semicarbazone from aqueous dioxane, m.p. 209–211°, dec. Calcd. for $C_{14}H_{23}N_3O_3$: C, 56.25; H, 7.80. Found: C, 56.27 H, 7.47. [f] Recrystallized from isopropyl ether-ligroin. [g] Semicarbazone from aqueous alcohol, m.p. 183–184.5°. Calcd. for $C_{16}H_{25}N_3O_3$: C, 62.51; H, 8.20. Found: C, 62.52; H, 7.98. [h] Semicarbazone from aqueous alcohol, m.p. 130–131°. Calcd. for $C_{22}H_{37}N_3O_3$: C, 67.49; H, 9.52. Found: C, 67.70; H, 9.25.

Generally, the keto acid adducts (IV) were lactonized in refluxing acetic anhydride containing small amounts of sodium acetate. Lactonization

(8) For a discussion of the retrogressive Diels-Alder reaction see M. C. Kloetzel, *Org. Reactions*, **4**, 9 (1948).

colorless oils of pleasant, characteristic odor. They lack the lachrymatory and vesicant properties of their parent compound, protoanemonin. The new lactones (I), on storage under nitrogen at room temperature, showed only a moderate discoloration,

TABLE II

LACTONES (I)

R	B.P. °C.	Mm.	Formula	Analyses[a] C Calcd.	C Found	H Calcd.	H Found	n_D^{25}
CH_3[b]	94–95	10	$C_6H_8O_2$	65.44	65.58	5.49	5.56	1.5316
n-C_3H_7[c]	65–67	1	$C_8H_{10}O_2$	69.54	69.51	7.30	7.16	1.5182
	118–120	17						
i-C_3H_7	110–113	11	$C_8H_{10}O_2$	69.54	69.35	7.30	7.07	1.5085
n-C_4H_9	131–132	18	$C_9H_{12}O_2$	71.02	70.20	7.94	7.72	
n-C_5H_{11}	154–156	18	$C_{10}H_{14}O_2$	72.26	72.45	8.49	7.87	1.5088

[a] Saponification equivalents found were 100–103% of theory. [b] Cyclopentadiene adduct: b.p. 119–124°/0.8 mm. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.87. Found: C, 74.46; H, 6.73. [c] Anthracene adduct: m.p. 176° (from methyl ethyl ketone). Calcd. for $C_{22}H_{20}O_2$: C, 83.52; H, 6.37. Found: C, 83.67; H, 6.35.

apparently without occurrence of appreciable dimerization.

The alkadienoic lactones (I) underwent the usual tests for unsaturation and gave a positive Legal test. Their ultraviolet absorption was consistent with values reported for patulin,[4] λ_{max} 276 mμ and desoxypatulin,[4] λ_{max} 273 mμ. 4-Hydroxy-2,4-nonadienoic acid γ-lactone had $\lambda_{max}^{isopropyl\ alcohol}$ 275 mμ, ε 17,700; 4-hydroxy-2,4-decadienoic acid γ-lactone had $\lambda_{max}^{isopropyl\ alcohol}$ 280 mμ, ε 15,700.

Lactones (I) were easily saponified. Saponification followed by acidification afforded known 4-oxo-2-alkenoic acids,[7] thus confirming the carbon skeletal structures of lactones (I) as obtained by the present method. Yields of 60–70% of 4-oxo-2-alkenoic acids were realized from lactones (I).

4-Oxo-2-alkenoic acids were also obtained in small yields by direct pyrolysis of keto acid adducts (IV).

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus; the thermometer was calibrated with Keufler "Testsubstanzen." Boiling points are uncorrected.

Bicyclo[2.2.1]5-heptene-3-propionyl-2-carboxylic acid (IV). (*R* = *ethyl*, *R″* = *3,5-cyclopenteno-*) *from II and diethyl cadmium.* The preparation of the Grignard reagent, its reaction with cadmium chloride and the subsequent condensation with II were conducted under dry nitrogen. An efficient stainless steel stirrer and a Teflon bearing were used.

Ethylmagnesium bromide was prepared in the usual way from magnesium (24.3 g., 1 atom) and ethyl bromide (122 g., 1.14 moles) in ether (500 ml.). Cadmium chloride (96 g., 0.525 mole) was added in several portions to the Grignard solution (ice bath). The mixture was then stirred briefly at room temperature. Stirring was maintained throughout the following operations. The mixture was heated for 30 min. under reflux. A solution of II (109.5 g., 0.67 mole) in benzene (700 ml.) was added rapidly. The reaction temperature was raised to about 80° by distilling off ether and replacing it with benzene; three fractions of distillate were collected, namely, up to 62°, 62–74°, and 74–77°; at 62°, 74°, and at 77°, the original volume of the distilling mixture was restored by the addition of benzene (a total of 850 ml.). Following this, the mixture was heated under reflux for 4 hr., cooled, and decomposed by the slow addition, with external cooling, of 3*N* hydrochloric acid (300 ml.). The separated aqueous layer was extracted with benzene. The combined benzene solutions were washed with water and extracted with 10% potassium carbonate solution (750 ml.). The separated basic extract was acidified with 3*N* hydrochloric acid. The resulting mixture was stirred briefly. The precipitated crude product was filtered, washed with water, and air-dried. Recrystallization from acetone afforded colorless crystals, m.p. 101.5–103.5° (yield 34 g.). A second crop, m.p. 101.5–102° (17 g., total yield 35%), was obtained from the recrystallization mother liquors.

Lactones (V). (*R″* = *3,5-cyclopenteno-*). The lactones were isolated from their crude concentrates by distillation under 1 mm. pressure. Their preparation and, when desired, their pyrolysis followed the procedures described below.

Lactones (V). (*R″* = *9,10-anthraceno-*). A mixture of keto acid adduct (IV, R = *n*-propyl[1]); (14 g., 0.042 mole), acetic anhydride (56 g., distilled from sodium acetate) and sodium acetate (0.40 g., 0.005 mole) was heated for 17 hr. under reflux in a nitrogen atmosphere. The solvent was distilled *in vacuo* (water bath). A buff-colored solid was left which was digested with a small amount of methyl ethyl ketone and filtered. Digestion and filtration were repeated once. The lactone (VI), m.p. 176° (8.0 g., 60% yield) crystallized from the combined filtrates at room temperature.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.52; H, 6.37. Found: C, 83.67; H, 6.35.

After prolonged standing at 5°, the mother liquors deposited additional lactone (4.5 g.) which raised the total yield to 93%.

Lactones (I) *from keto acid adducts* (IV). (*A*) *From cyclopentadiene adducts* (*R″* = *3,5-cyclopenteno-*), *use of hydrochloric acid–acetic anhydride mixture.* Bicyclo[2.2.1]5-heptene-3-propionyl-2-carboxylic acid (IV, R = ethyl; 17.5 g., 0.09 mole) was added to a mixture of acetic anhydride (35 g.) and concentrated hydrochloric acid (1.8 g.) and stirred until solution had occurred (30 min.). The solution was allowed to stand at room temperature for several hours. It was filtered to remove traces of solid, and concentrated *in vacuo*. The residue was pyrolytically distilled under about 70 mm. pressure, and the distillation completed under 15 mm. pressure. Redistillation of the pyrolysate yielded the lactone as a colorless oil, b.p. 91–96°/12 mm. (7.25 g., yield 63%).

Anal. Calcd. for $C_6H_6O_2$: C, 65.44; H, 5.49; 2 double bonds. Found: C, 65.58; H, 5.56; hydrogen uptake, 2.0 moles.

(*B*) *From cyclopentadiene adducts* (*R″* = *3,5-cyclopenteno-*), *use of sodium acetate in acetic anhydride.* A mixture of bicyclo[2.2.1]5-heptene-3-*n*-valeryl-2-carboxylic acid (IV, R = *n*-butyl; 55.5 g., 0.25 mole), sodium acetate (1.1 g., 0.013 mole) and acetic anhydride (278 g., distilled from sodium acetate) was heated under reflux for 5 hr. in a nitrogen atmosphere. The solvent was distilled off *in vacuo* through a short Vigreux column and redistilled in the same

manner. The distillation residues were combined and taken up in ether. Undissolved solid material was removed by filtration and washed with ether. The combined ethereal solutions were concentrated *in vacuo*. The concentrate was pyrolyzed under 110 mm. pressure and the distillation terminated under 20 mm. pressure. Most of the pyrolysate was obtained at 165–170°/110 mm. Toward the end of this and similar pyrolysis runs, small amounts of solid material were obtained which were identified as 4-oxo-2-alkenoic acids, corresponding to keto acid adducts (IV). Distillation of the pyrolysate gave a fraction, b.p. 123–127°/17 mm., which upon redistillation yielded the lactone as a colorless oil, b.p. 110–111°/10 mm. (20.15 g., yield 59%); sapon. equiv. calcd. and found: 138.

In a repeat run in which the stripped and redistilled solvent was used, a 68% yield, b.p. 119–121°/15 mm., was obtained.

(*C*) *From anthracene adducts* (*R″ = 9,10-anthraceno-*). Lactone (VI), (8.0 g., 0.025 mole) was pyrolyzed at 240–260° under 12 mm. pressure. The distillate consisted of copious amounts of anthracene and a yellow oil. Low boiling petroleum ether was added to the mixture, and the solution was filtered and concentrated. Distillation yielded a colorless oil, b.p. 110–112°/11 mm. (1.9 g., yield 54%); sapon. equiv. calcd., 138; found, 142.

2,4-Octadienoic acid by saponification of 4-hydroxy 2,4-octadienoic acid γ-lactone. The lactone (1.35 g., 0.0098 mole) was dissolved in a little acetone, and treated with 1*N* sodium hydroxide (10 ml.). Enough acetone was added to the mixture to make it homogeneous. After standing at room temperature for 15 min. the solution was neutralized to the phenolphthalein end point with 0.1*N* hydrochloric acid, extracted twice with small amounts of methylene chloride, acidified with 3*N* hydrochloric acid and extracted with ether. The ethereal solution was separated, washed with water, and allowed to evaporate at room temperature. The residue was taken up in a small amount of isopropyl ether containing a trace of iodine. Crystallization began within a few hours; when it appeared complete, the mass was filtered, washed with a mixture of isopropyl ether and low boiling petroleum ether and finally with petroleum ether. Air-drying resulted in a 64% yield (0.98 g.) of colorless needles, m.p. 108° (reported[9] m.p. 105–106°); neut. equiv. calcd. and found: 156.

Acknowledgment. The author is indebted to Mr. S. J. Tassinari for the reported microanalyses, and to Mr. Berruti for ultraviolet absorption data.

OAKDALE, N. Y.

(9) F. L. Breusch and H. Keskin, *Arch. Biochem.*, **18**, 314 (1948).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES DIVISION, NATIONAL DAIRY PRODUCTS CORPORATION]

Potential Antimicrobial Agents. III. 4-Methylamino-2,4-alkadienoic Acid γ-Lactams[1]

HENRY M. WALTON

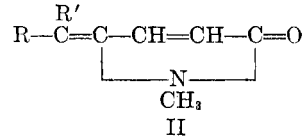
Received September 17, 1956

4-Methylamino-2,4-alkadienoic acid γ-lactams are structurally analogous to the antibiotic, protoanemonin. For this new class of lactams, a convenient one-step method of preparation is presented, consisting of the reaction of Grignard reagents with N-methylbicyclo[2.2.1]5-heptene-2,3-dicarboximide, followed by pyrolysis of the resulting Diels-Alder lactam adducts.

The structures of protoanemonin[2] and patulin[3] have attracted attention to 4-hydroxy-2,4-alkadienoic acid γ-lactones (I) as potential antimicrobial agents.[4] The preceding paper in this series[1] describes a general method for the preparation of lactones (I). It seemed also of interest to determine what effect the replacement of the lactone ring oxygen by nitrogen might have on physiological action.

This paper is concerned with the preparation of a new class of lactams (II) structurally analogous to lactones (I), in which the N-methyl group takes the place of the lactone ring oxygen.

The method presented here is based on the use of

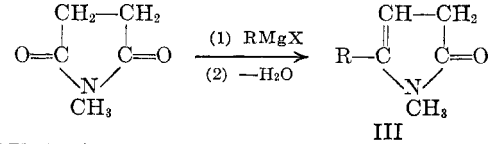


II

R, R′ = H, alkyl, cycloalkyl

the Diels-Alder adduct of N-methyl maleimide and cyclopentadiene, N-methylbicyclo[2.2.1]5-heptene-2,3-dicarboximide (IV), which is easily accessible, through reaction of the commercially available bicyclo[2.2.1]5-heptene-2,3-dicarboxylic anhydride[5] with methylamine.

Lukes[6] has shown that Grignard reagents react with N-methyl succinimide to yield lactams (III):



III

(1) Preceding paper in this series: H. M. Walton, *J. Org. Chem.*, **22**, 312 (1957).

(2) E. Shaw, *J. Am. Chem. Soc.*, **68**, 2510 (1946).

(3) R. B. Woodward and G. Singh, *J. Am. Chem. Soc.*, **71**, 758 (1949).

(4) For a discussion of the antimicrobial activity of unsaturated lactones, see L. J. Haynes, *Quart. Rev.*, **2**, 46 (1948); C. J. Cavallito, Antibiotics from Plants, in C. M. Suter, *Medicinal Chemistry*, John Wiley and Sons, New York, 1951, Vol. I, pp. 224–235.

(5) Nadic Anhydride, National Aniline Division, Allied Chemical and Dye Corporation.

(6) R. Lukes, *Coll. Czechoslov. Chem. Comm.*, **1**, 119 (1929); *Chem. Abstr.*, **23**, 4469 (1929).