starting material. The remaining solid was dissolved in a minimium volume (about 4 ml.) of hot water under nitrogen, treated with charcoal, filtered under nitrogen, and allowed to crystallize at 5°. 5-Hydroxy-L-tryptophan was recovered as pale pink needles; 0.55 g., m.p. 273° dec., $[\alpha]_D^{22}$ −32.5° (c 1, water), $[\alpha]_D^{22}$ +16.0° (c 1, 4*N* HCl) (L-tryptophan, $[\alpha]_D^{23}$ −31.5° (c 1, water).[21] The filtrate was concentrated to yield an additional 0.11 g. In this manner, a total of 4.7 g. of 5-hydroxy-L-tryptophan (80% theor.) was obtained from 12.0 g. of N-carbobenzoxy-5-benzyloxy-L-tryptophan.

A sample was prepared for analysis by recrystallization from water under nitrogen.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.65; H, 5.44; N, 12.50.

5-Hydroxy-D-tryptophan. N-Carbobenzoxy-5-benzyloxy-D-tryptophan (2.0 g.) was reduced by the procedure described for the L-isomer to yield 0.60 g. (61% yield) of 5-hydroxy-D-tryptophan; m.p. 274° dec., $[\alpha]_D^{22}$ +32.2° (c 1, water).

A sample was prepared for analysis by recrystallization from water under nitrogen.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.86; H, 5.62; N, 12.50.

5-Hydroxy-L-tryptophan picrolonate. 5-Hydroxy-L-tryptophan (30 mg.) and 36 mg. of picrolonic acid were dissolved in 3 ml. of hot water under nitrogen. The yellow needles which formed on cooling were collected on a filter; 54 mg. (82% yield), m.p. 184–186° (dec.). For analysis, a portion was recrystallized three times from hot water, m.p. 184–186° (dec.).

Anal. Calcd. for $C_{21}H_{20}N_6O_8 \cdot H_2O$: C, 50.19; H, 4.41; N, 16.74. Found: C, 50.45; H, 4.57; N, 17.00.

SALT LAKE CITY, UTAH

(21) Greenberg, *Chemistry of the Amino Acids and Proteins*, C. C. Thomas, Springfield, Ill., 1945, p. 1177.

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

Potential Antimicrobial Agents. I. Alkyl 4-Oxo-2-alkenoates

HENRY M. WALTON

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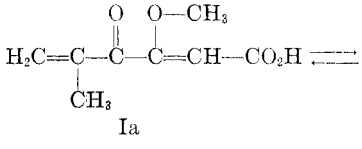
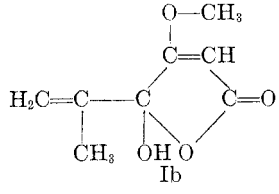
Alkyl 4-oxo-2-alkenoates were conveniently obtained by the retrogressive Diels-Alder reaction of their cyclopentadiene adducts. The requisite adducts were prepared through the interaction of alkylzinc chlorides and half ester chlorides of bicyclo-[2.2.1]5-heptene-2,3-dicarboxylic acid. The analogous reactions were also effected with anthracene adducts.

The structural elucidation of the antibiotic, penicillic acid (Ia, Ib)[1] and its synthesis[2] have

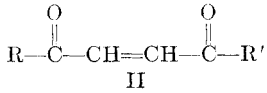


Ia



Ib

stimulated considerable interest in the antimicrobial activity associated with related classes of compounds, notably 4-oxo-2-alkenoic acids (IIa) and certain of their derivatives (IIb, c)



II

R = alkyl, aryl
IIa: R′ = OH
IIb: R′ = alkoxy
IIc: R′ = NH_2, NHR

This interest has focused mainly on β-aroylacrylic acids (IIa)[3a] and their derivatives, esters (IIb)[3b] and amides (IIc),[3c] since the availability of relatively convenient preparative methods in this area was conducive to their examination.

In pronounced contrast there is a lack of adequate preparative methods for the corresponding *aliphatic* analogs of penicillic acid, 4-oxo-2-alkenoic acids, and their derivatives. As a result the antimicrobial properties of but a few compounds of this type have been investigated. Esters of β-acetylacrylic acid[3b,4] and ethyl 4-oxo-2-hexenoate[5] have been shown to have good *in vitro* activity against a number of microorganisms.

Preparatively the esters of β-acetylacrylic acid constitute a special case due to their ready availability from levulinic acid.[6] Ethyl 4-oxo-2-hexe-

(1) T. H. Birkinshaw, A. E. Oxford, and H. Raistrick, *Biochem. J. London*, **30**, 394 (1936). Antibiotic activity: *cf.* references in Baron, *Handbook of Antibiotics*, Reinhold Publishing Corp., New York, 1950, p. 183.

(2) R. A. Raphael, *Nature*, **160**, 261 (1947).

(3a) B. J. Cramer, Wm. J. Moran, C. H. Nield, M. Edwards, Ch. I. Jarowski, and B. Puetzer, *J. Am. Pharm. Assoc. Sci. Ed.*, **37**, 439 (1948). D. Papa and E. Schwenk, U. S. Patent **2,562,208** [*Chem. Abstr.*, **46**, 2759 (1952)]; F. H. Kirchner, J. H. Bailey, and Ch. J. Cavallito, *J. Am. Chem. Soc.*, **71**, 1210 (1949).

(3b) R. L. Worral, Med. World Jan. 11, 1946; J. C. Thomas, U. S. Patent **2,532,579** [*Chem. Abstr.*, **45**, 1290 (1950)].

(3c) B. J. Cramer *et al.* (3a).

(4) See also S. Raymond, *J. Am. Chem. Soc.*, **72**, 4304 (1950).

(5) J. S. Mofatt, G. Newberry, and W. Webster, *J. Chem. Soc.*, 451 (1946).

(6) W. G. Overend, J. M. Turton and L. F. Wiggins, *J. Chem. Soc.*, 3500 (1950): Ethyl 4-oxo-2-pentenoate from ethyl levulinate in two steps and 45% over-all yield.

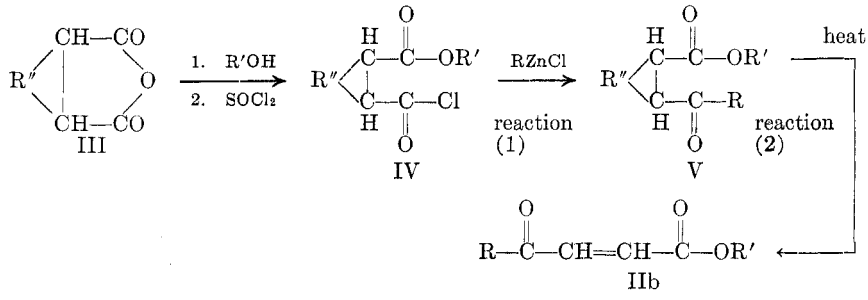
noate has been obtained from the silver salt of the acid by reaction with ethyl iodide.[5] The silver salt–alkyl iodide method may be considered a general one for the preparation of alkyl 4-oxo-2-alkenoates. However, the requisite 4-oxo-2-alkenoic acids remain relatively inaccessible. Mofatt and coworkers[5] devised three interesting methods for the preparation of 4-oxo-2-hexenoic acid which are probably capable of generalization. Subsequently Keskin[7] developed two general methods for the preparation of these acids. Unfortunately, all of these methods are laborious and result in poor over-all yields. The usefulness of the silver salt–alkyl iodide method is thereby severely limited.[8]

For these reasons further investigation of aliphatic analogs for penicillic acid appeared to require additional preparative methods. This paper deals with a new and apparently general method for the preparation of alkyl 4-oxo-2-alkenoates.

Much of the difficulty encountered in the construction of 4-oxo-2-alkenoic esters resides in their ethylenic double bond. When present in a starting material in conjugation with a carbonyl or ester group, its location militates against the employment of convenient methods which might otherwise be used to effect the desired variations in the radical R of structure II. On the other hand, in using saturated starting materials one cannot usually introduce this bond in a convenient and unequivocal manner.

In the present instance this difficulty was overcome by the use of Diels-Alder adducts of maleic anhydride with cyclopentadiene and anthracene, whose propensity for retrogression at elevated temperatures is well known.[9] These adducts were transformed into the corresponding adducts of 4-oxo-2-alkenoates which underwent the expected retrogression at elevated temperatures with the liberation of alkyl 4-oxo-2-alkenoates.[10] Attempts to effect this reaction sequence with furan adducts were unsuccessful.

The reaction sequence is represented as follows:



R″ = 3,5-cyclopenteno- or 9,10-anthraceno-.

In preliminary work this reaction sequence was studied with adducts of maleic anhydride with cyclopentadiene, anthracene, and furan. The crude ester chlorides (IV) resisted all attempts at purification by crystallization or distillation and were used as such. Reaction 1 failed with furan adducts. Complex reaction mixtures were obtained which, undoubtedly, derived in part from the attack of the ester chloride group, in the presence of magnesium chloride and/or zinc chloride, upon the allylic ether oxygen of the furan adducts. Reaction 1 was successful with cyclopentadiene and with anthracene adducts. The use of cyclopentadiene adducts, however, appeared to be conducive to better over-all yields. Accordingly they were used in most cases.

The expected thermal instability of cyclopentadiene adducts (V) became apparent during their distillation. Even under 1-mm. pressure most members of the series distilled with varying degrees of retrogression; those having a molecular weight 306 or higher underwent complete retrogression when their distillation was attempted. The presence of alkyl 4-oxo-2-alkenoates in the distillates of their adducts (V) was reflected by analyses and in some cases confirmed by isolation. Table I lists distilled products of reaction 1 which, from their analyses, are inferred to consist wholly or predominantly of keto ester adducts (V).

When desired, the retrogressive Diels-Alder reaction 2 was effected at 180–200° under reduced pressure. This pyrolysis was also carried out to advantage with *crude* adducts (V). The method was thereby reduced to a single step based on ester chloride adducts (IV). In the case of methyl esters

(7) F. L. Breusch and H. Keskin, *Arch. Biochem.*, **18**, 305 (1948); H. Keskin, *Rev. fac. sci. univ. Istanbul*, **15A** (1), 54 (1950), *cf. Chem. Abstr.*, **45**, 2904 (1951).

(8) While this work was under way R. E. Bowman and W. D. Fordham, *J. Chem. Soc.*, 3945 (1952), published an elegant new synthesis of ketonic compounds, a variant of which afforded ethyl *trans*-4-oxo-2-heptadecenoate from β-carboethoxyacrylyl chloride and di(2-)pyranyl dodecylmalonate. The authors consider the method to be limited to the preparation of ethyl esters. Attempts at this Laboratory to apply it to the preparation of lower homologs met with little success.

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

(10) A similar reaction sequence resulting in vinyl ketones *via* their anthracene adducts was recently described by Tatsuyo Shono and Ryohei Oda, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **58**, 276 (1955); *Bull. Inst. Chem. Research Kyoto Univ.*, **33**, 58 (1955) [*Chem. Abstr.*, **50**, 4102, 14681 (1956)].

TABLE I

KETO ESTERS (V). (CYCLOPENTADIENE ADDUCTS)

R	R′	B.P. °C./Mm.	Formula	Analyses[a] C Calcd.	C Found	H Calcd.	H Found
n-C_3H_7	CH_3	102–104/0.4	$C_{13}H_{18}O_3$	70.25	69.80	8.16	8.04
n-C_4H_9	CH_3	122/2	$C_{14}H_{20}O_3$	71.16	71.00	8.53	8.04
i-C_4H_9	CH_3	108/1[b]	$C_{14}H_{20}O_3$	71.16	70.46	8.53	8.21
n-C_4H_9	C_2H_5	128–130/1	$C_{15}H_{22}O_3$	71.97	71.26	8.86	8.61
n-C_4H_9	C_3H_7	139–142/2	$C_{16}H_{24}O_3$	72.69	71.09	9.15	8.68
n-C_5H_{11}	CH_3	133–140/1.2[b]	$C_{15}H_{22}O_3$	71.97	70.51	8.86	8.41
n-C_6H_{13}	CH_3	131–135/1.3[b]	$C_{16}H_{24}O_3$	72.69	71.01	9.15	8.61
n-C_6H_{13}	C_2H_5	142/1.5	$C_{17}H_{26}O_3$	73.34	71.76	9.42	9.01

[a] See Table II for calculated composition of the corresponding 4-oxo-2-alkenoates. [b] Crystalline material deposited in the distillate, isolated and identified as the corresponding methyl 4-oxo-2-alkenoate.

TABLE II

ALKYL 4-OXO-2-ALKENOATES (IIb)

R	R′	B.P. °C./Mm. or M.P. °C.	Formula	Analyses C Calcd.	C Found	H Calcd.	H Found
n-C_4H_9	CH_3O	104–105.5°/9 35–36°[a]	$C_9H_{14}O_3$	63.51	63.49	8.22	7.94
i-C_4H_9	CH_3O	123–127°/28	$C_9H_{14}O_3$	63.51	62.93	8.22	7.92
n-C_4H_9	C_2H_5O	131–134°/15	$C_{10}H_{16}O_3$	65.19	64.51	8.76	8.17
n-C_5H_{11}	CH_3O	48.5°[a]	$C_{10}H_{16}O_3$	65.09	65.09	8.76	9.00
n-C_6H_{13}	CH_3O	52°[a]	$C_{11}H_{18}O_3$	66.64	66.40	9.15	8.86
cyclo-C_6H_{11}	CH_3O	56–57°[b]	$C_{11}H_{16}O_3$	67.32	66.99	8.22	7.63
n-C_6H_{13}	C_2H_5O	157–158°/14	$C_{12}H_{20}O_3$	67.89	67.91	9.50	9.56
n-C_8H_{17}	C_2H_5O	133–141°/1.2	$C_{14}H_{24}O_3$	69.97	68.81	10.07	9.60
n-C_8H_{17}	n-C_3H_7O	149°/1.5	$C_{15}H_{26}O_3$	70.82	71.17	10.29	9.94
$(CH_3)(C_6H_{13})CH$—	CH_3O	105–108°/1	$C_{13}H_{22}O_3$	68.99	69.35	9.80	9.50

[a] Recrystallized from low boiling petroleum ether. [b] Recrystallized from ligroin, b.p. 66–75°.

yields of 30–60% were obtained. Table II lists alkyl 4-oxo-2-alkenoates prepared by the new method.

Methyl 4-oxo-2-octenoate had λ_{max}^{MeOH} 220 mμ, ε 14,500; reported for methyl 4-oxo-2-pentenoate[4] and for methyl *trans*-4-oxo-2-heptadecenoate,[8] λ_{max} 222 mμ.

Positive structure proof for methyl 4-oxo-2-nonenoate prepared by the new method was afforded by comparing it with a specimen obtained from the silver salt of the known 4-oxo-2-nonenoic acid[7] and methyl iodide. The melting points of the esters were: *via* adducts (IV, V), 48°; *via* the silver salt, 46.5°. No melting point depression resulted from their admixture.

EXPERIMENTAL

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

Half esters of bicyclo[2.2.1]5-heptene-2,3-dicarboxylic acid. (a) Without catalyst. A mixture of bicyclo[2.2.1]5-heptene-2,3-dicarboxylic anhydride (328.4 g., 2.0 moles) and methanol (85 g., 2.65 moles) was heated under reflux. After 2 hr. a clear solution was obtained. Heating was continued for 1 hr. during which the solution attained a temperature of 115°. After cooling to 50°, the solution was seeded. Crystallization was allowed to proceed for several hours at 50° and finally at room temperature. The crystalline mass was slurried with 300 ml. isopropyl ether, filtered with suction, and washed once with 100 ml. isopropyl ether and twice with low boiling petroleum ether. The air-dried material melted at 103.5–105° and weighed 320 g. (yield 82%). By working up the mother liquors, a small amount of additional material (20.5 g.) of m.p. 102–103° was obtained. This represents a modification of the method of L. M. Rice and E. E. Reid[11] who reported the melting point of 102–103°.

(b) With potassium acetate catalyst. A mixture of bicyclo[2.2.1]5-heptene-2,3-dicarboxylic anhydride (164 g., 1.0 mole), methanol (100 g., 3.1 moles) and potassium acetate (1.0 g., 0.01 mole) was warmed briefly on the steam bath with occasional swirling until a clear solution was obtained. When the solution had returned to room temperature it was seeded and allowed to crystallize for several hours. The crystalline mass was filtered with suction, washed carefully with 30 g. methanol, and air-dried. The resulting product represented a yield of 42%. The combined methanolic solutions were used to convert additional anhydride (1.0 mole) into methyl half esters by the same procedure. By repetition of this process, a series of crops was obtained which varied between 0.9 and 1.1 moles of half ester and melted within 1 degree of the reported melting point.[11] With several repetitions and final concentration of the mother liquors on the steam bath, over-all yields exceeding 95% were obtained.

The method is applicable to the preparation of the corresponding ethyl and n-propyl esters. Half esters of furan adducts were obtained similarly.

Bicyclo[2.2.1]5-heptene-2-carbalkoxy-3-carbonylchlorides (IV). The half ester was allowed to react at room tempera-

(11) L. M. Rice and E. E. Reid, *J. Am. Chem. Soc.*, 74, 3955 (1952).

ture with a 30–40% molar excess of thionyl chloride. The reaction was completed with warming to 40–50° (water bath) during 10–30 min. Volatile components of the mixture were removed under 10–15-mm. pressure at room or slightly elevated temperatures. A small amount of benzene was added to the residue and concentration *in vacuo* was repeated. Almost colorless to light straw-colored noncrystallizing oils were obtained which darkened slowly upon standing. Attempted distillation resulted in regeneration of the anhydride adduct (III) and, presumably, in the formation of alkyl chloride. A small sample of the oil was dissolved in acetone and hydrolyzed by the dropwise addition of water; the neutralization equivalent of the solution was usually found to be about 103% of theory. Yields of ester chloride adducts (IV), calculated on this basis, were 97–100%. High yields of regenerated half esters could be isolated from hydrolysis mixtures.

Furan analogs prepared in this manner darkened much more rapidly.

Methyl bicyclo[2.2.1]5-heptene-3-n-valeryl-2-carboxylate (V). The requisite ester chloride was prepared as above using 250 g. (1.27 moles) of the methyl half ester and 195 g. (1.65 moles) of thionyl chloride. The ester chloride was obtained as a straw-colored oil which weighed 279 g.; its neutralization equivalent was: calcd., 107.3; found, 109. The yield was quantitative.

The preparation of the Grignard reagent, its reaction with zinc chloride, and the condensation with ester chloride were carried out under dry nitrogen by a modification of the method of Jones.[12] An efficient stainless steel stirrer and a Teflon bearing were used.

Stirring was maintained throughout the following operations. A stock solution of 1.74*N* *n*-butylmagnesium chloride (1000 ml.) containing traces of methylmagnesium iodide, was added gradually with stirring to zinc chloride (237 g., 1.74 moles) in ether (about 350 ml.). Following the addition, the mixture was heated under reflux for 1 hr. Ether (700 ml.) was distilled off and benzene (1000 ml.) was added to the distillant. The replacement of ether by benzene was continued by alternate distillation of solvent (750 and 375 ml. of distillate) and replenishment of the distillation residue by equivalent volume of benzene. The final vapor temperature was 75°. The freshly prepared ester chloride, dissolved in 580 ml. benzene, was added gradually, with *vigorous* stirring, to the cooled alkylzinc chloride reagent. By suitable external cooling the temperature of the reaction mixture was kept at 42°. When the addition was completed, the mixture was kept at 40° for 4 hr. It was allowed to cool and stand at room temperature overnight. The mixture was decomposed by the slow addition, with external cooling, of 3*N* hydrochloric acid. The aqueous layer was separated and extracted with benzene. The combined benzene solutions were washed several times wi h water and once with sodium bicarbonate solution. The washed benzene solutions were stirred during several hours with potassium carbonate (50 g.), filtered, and allowed to evaporate at room temperature. Vacuum fractionation of the residue afforded a fore-fraction, b.p. 100–120°/2 mm., a main fraction consisting of a pale yellow oil, b.p. 122°/2 mm. (196 g.), which was followed by a darker yellow oil, b.p. 130°/2 mm.–145°/4 mm. (dec.). A small amount (10.6 g.) of the main fraction was set aside for saponification. The remainder of the main fraction was redistilled and yielded a pale yellow oil, b.p. 122°/2 mm. (176 g.).

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.00; H, 8.21.

The distillation residue was combined with the fore-fraction and the dark oil previously obtained. The combined fractions were distilled and afforded additional material, b.p. 122°/2 mm., which raised the total yield to 70%.

Methyl 4-oxo-2-octenoate by pyrolysis of methyl bicyclo-[2.2.1]5-heptene-3-n-valeryl-2-carboxylate (V). The adduct (21.0 g., 0.089 mole) was pyrolyzed by subjecting it to two distillations under about 50-mm. pressure at a stillpot temperature of 180°. Vacuum fractionation of the pyrolysate yielded an oil, b.p. 104–109°/9 mm., which crystallized. The material was recrystallized from low boiling petroleum ether, m.p. 35–36°.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.22. Found: C, 63.49; H, 7.94.

Pyrolysis of the distillation residue afforded additional material, b.p. 107–109°/9 mm. (2.0 g.; total yield, 11.4 g., 76%).

At somewhat higher pressures (80–100 mm.) pyrolysis of the lower molecular weight adducts tended to be complete in one to two passes. Also, distilled higher molecular weight "adducts" appeared to pyrolyze more readily, perhaps because of their initial admixture of material identical with the pyrolysis product.

Bicyclo[2.2.1]5-heptene-3-n-valeryl-2-carboxylic acid.[13] The portion of the once-distilled methyl ester that was set aside for saponification (10.6 g., 0.045 mole), potassium hydroxide (1.25 g., 0.022 mole), potassium carbonate (5.0 g., 0.036 mole), water (70 ml.), and methanol (85 ml.) were mixed and heated under reflux for 15 min. A portion of the solvent (65 ml.) was distilled off and heating under reflux continued for 4.5 hr. The solution was allowed to cool and stand at room temperature overnight. Addition of water to the cooled solution did not produce cloudiness. The solution was acidified by the addition of 3*N* hydrochloric acid. The resulting crystalline precipitate was filtered with suction and washed thoroughly with water and low boiling petroleum ether. After air-drying, the product had a melting point of 87–88° (8.1 g., 81% yield). On recrystallization from ligroin (b.p. 66–75°) the melting point was unchanged.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.12; H, 7.98.

Crude keto ester adducts (V) also can be saponified satisfactorily. In some cases higher over-all yields, on the basis of ester chlorides (IV), of keto acid adducts were obtained when the crude rather than the purified ester adducts (V) were subjected to saponification.

9,10-Dihydro-9,10-ethanoanthracene-12-carbomethoxy-11-carboxylic acid. A sodium methylate solution was prepared by reacting sodium (2.45 g., 0.1 atom) with methanol (100 ml.). The warm solution was stirred and 9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic anhydride (III) (27.6 g., 0.1 mole) was added to it in several portions. When the anhydride had dissolved, methanol was removed *in vacuo*. The residual syrup was taken up in water (100 ml.) and acidified with 3*N* hydrochloric acid. A curdy precipitate was obtained which gradually crystallized on being stirred with water. The crystallized material was filtered with suction and washed with water. Recrystallization from benzene yielded the methyl half ester, m.p. 209–210° (27.6 g., 90% yield).

Anal. Calcd. for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23; neut. equiv. 308. Found: C, 74.40; H, 5.32; neut. equiv. 305.

9,10-Dihydro-9,10-ethanoanthracene-12-carbomethoxy-11-carbonylchloride (IV). A mixture of the half ester (111 g., 0.364 mole), thionyl chloride (55 g., 0.463 mole) and methylene chloride (200 ml.) was heated under reflux for 12 hr. following which the reaction mixture was concentrated *in vacuo* (water bath). The residue was dissolved in benzene (50 ml.) and the resulting solution again concentrated *in vacuo*. This procedure was repeated once more. The resulting crude ester chloride was dissolved in benzene for use in the following reaction. The benzene solution weighed 220 g., neut. equiv. 351.

*Methyl 9,10-dihydro-9,10-ethanoanthracene-12-n-valeryl-11-*carboxylate (V). *n*-Butylzinc chloride was prepared as described from 1.90*N* *n*-butylmagnesium bromide (242 ml.)

(12) R. G. Jones, *J. Am. Chem. Soc.*, **69**, 2350 (1947).

(13) For additional keto acid adducts and derived semicarbazones see Table I, following paper in this series, *J. Org. Chem.*, **22**, 313 (1957).

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.

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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

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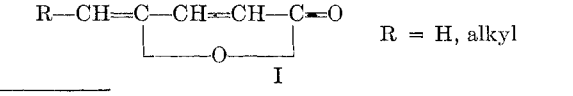
A new method is described for the synthesis of 4-hydroxy-2,4-alkadienoic acid γ-lactones (protoanemonin analogs) in two steps: (1) Synthesis of cyclopentadiene and anthracene adducts of 4-oxo-2-alkenoic acids, followed by (2), lactonization and retrogressive Diels-Alder reaction of the resulting lactones.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