reaction), the flask was immersed in a Woods' metal bath, which had been preheated to the appropriate temperature (see Table II). When a basic gas (presumably methylamine) was no longer being released, as indicated by litmus paper, the system was allowed to come to room temperature. Lactones VIa, VIb, and XIV crystallized and were recrystallized from appropriate solvents (see footnotes to Table II). Lactone XV was distilled.

The n.m.r. spectrum of lactone VIb showed a singlet at -222 ± 1 c.p.s. attributed to the methylene hydrogens and an aromatic multiplet between -420 and -450 c.p.s. The area ratio was 7.21 for aromatic hydrogens–CH_2 (calcd. 7.00). This spectrum was taken in carbon tetrachloride.

Hydrolysis of Hydroxyamide Va to Hydroxy Acid VIIa.—A sample of Va (5.1 g., 0.02 mole) in 50 ml. of 95% ethanol and 50 ml. of 6 *M* sodium hydroxide was refluxed until the evolution of methylamine ceased (10 hr.). After cooling, the reaction mixture was acidified with 12 *M* hydrochloric acid to give 4.65 g. (96%) of *o*-(2-phenyl-2-hydroxyethyl)benzoic acid, m.p. 115–118° and 123–124° after two recrystallizations from aqueous ethanol and drying *in vacuo*.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.37; H, 5.70.

A sample of VIIIa was reduced to the corresponding diol, which was cyclized to isochroman VIII as described recently.[4]

Hydrolysis of Hydroxyamide Vb to Hydroxy Acid VIIb.—A solution of 6.63 g. (0.02 mole) of Vb and 11.2 g. (0.20 mole) of potassium hydroxide in 30 ml. of ethanol and 40 ml. of water was refluxed for 10 hr. The ethanol was removed (rotary evaporator) and the residual aqueous mixture was washed with several portions of ether. Acidification of the aqueous solution afforded a gum, which was scratched to give 5.8 g. (91%) of *o*-(2,2-diphenyl-2-hydroxyethyl)benzoic acid (VIIb), m.p. 123.5–124.5° and 125.5–126° dec. after recrystallization from hexane–benzene–ethanol.

Anal. Calcd. for $C_{21}H_{18}O_3$: C, 79.22; H, 5.70. Found: C, 79.08; H, 5.73.

Cyclization of 4.2 g. of VIIb by heating it above its melting point *in vacuo* for several minutes afforded 3.7 g. (88%) of lactone VIb, m.p. 143.5–144° and 144–144.5° after recrystallization from hexane–ethanol.

Oxidation of 3.2 g. of VIIb with excess alkaline potassium permanganate afforded 0.7 g. (42%) of phthalic acid, m.p. 208–209°, undepressed on admixture with an authentic sample. The infrared spectra of the two samples were identical.

The Synthesis of Royal Jelly Acid and Its Homologs from Cycloalkanones[1]

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Two methods for the synthesis of royal jelly acid, *trans*-10-hydroxy-2-decenoic acid (Ia), from cyclooctanone are reported. Homologs of Ia were prepared utilizing one of the methods which involved an initial oxidation of a cycloalkanone to an ω-lactone (II). The resulting lactone was treated with sodioacetonitrile to produce a 3-keto-ω-hydroxynitrile (IX), which was reduced and hydrolyzed to afford the corresponding 3,ω-dihydroxycarboxylic acid (VIII). The latter was then dehydrated to give the desired ω-hydroxy-α,β-unsaturated carboxylic acid I.

Royal jelly is the remarkable substance, secreted by the common honey bee *Apis mellifira*, which is responsible for the ultimate differentiation of bee larva into queen bees.[2] One of the major components of royal jelly has been isolated[3] and identified[4] as *trans*-10-hydroxy-2-decenoic acid (Ia). This acid, commonly referred to as royal jelly acid, has been found to possess antibiotic[5] and antitumor activities.[6] In order to obtain homologs and analogs for the purpose of biological testing, a synthetic program was initiated for the synthesis of royal jelly acid utilizing a scheme which could be readily extended to similar compounds. The synthesis of the parent compound has been reported by a number of different groups.[7]

The methods for the preparation of royal jelly acid utilized in these laboratories involved the use of cyclooctanone as the starting material. This cyclic ketone was oxidized to the lactone IIa employing peroxytrifluoroacetic acid.[8] Two routes *via* the dihydroxy acid VIII were developed (Scheme I).

In the first method the lactone IIa was hydrolyzed and the resulting 8-hydroxyoctanoic acid (III) was converted to 8-acetoxyoctanoyl chloride (V). This acid chloride was allowed to react with ethyl sodioacetoacetate to give ethyl 3-keto-10-acetoxydecanoate (VI) after deacylation with ammonia.[9] Conversion of the keto ester VI to ethyl 3-hydroxy-10-acetoxydecanoate (VII) was accomplished by ruthenium-catalyzed hydrogenation.[10] Hydrolysis of VII followed by dehydration of the resulting 3,10-dihydroxydecanoic acid (VIIIa) utilizing acetic anhydride gave the unsaturated acid Ia which was identical with the naturally occurring acid[11] with respect to mixture melting point and infrared spectrum.

A shorter alternate method for the synthesis of the dihydroxy acid VIIIa from the lactone IIa was achieved by extending Hauser's method for the acylation of nitriles with esters.[12] The procedure used involved the treatment of the lactone IIa with 2 equiv. of sodioacetonitile to produce 3-keto-10-hydroxydecanitrile (IXa). This intermediate was converted to the acid

(1) Taken in part from the dissertation presented by J. F. Muren, Jan., 1961, to the Graduate School of the University of Wisconsin in partial fulfillment of the requirements for the Ph.D. degree.

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(6) G. F. Townsend, J. F. Morgan, and B. Hazlett, *Nature*, **183**, 1270 (1959).

(7) (a) G. I. Fray, R. H. Jaeger, and R. Robinson, *Tetrahedron Letters*, **No. 4**, 15 (1960); (b) G. I. Fray, R. H. Jaeger, E. D. Morgan, R. Robinson, and A. D. B. Sloan, *Tetrahedron*, **15**, 18 (1961); (c) S. A. Barker, A. B. Foster, D. C. Lamb, and L. M. Jackman, *ibid.*, **18**, 177 (1962); (d) M. Fujii, N. Koga, Y. Osawa, and K. Chuma, *Nippon Kagaku Zasshi*, **81**, 1782 (1960); (e) U. Schmidt and P. Grafen, *Ann.*, **656**, 97 (1962); (f) K. Sisido, M. Kawanisi, K. Kondo, T. Morimoto, A. Saito, and N. Hukue, *J. Org. Chem.*, **27**, 4073 (1962).

(8) R. Huisgen and H. Ott, *Tetrahedron*, **6**, 253 (1959).

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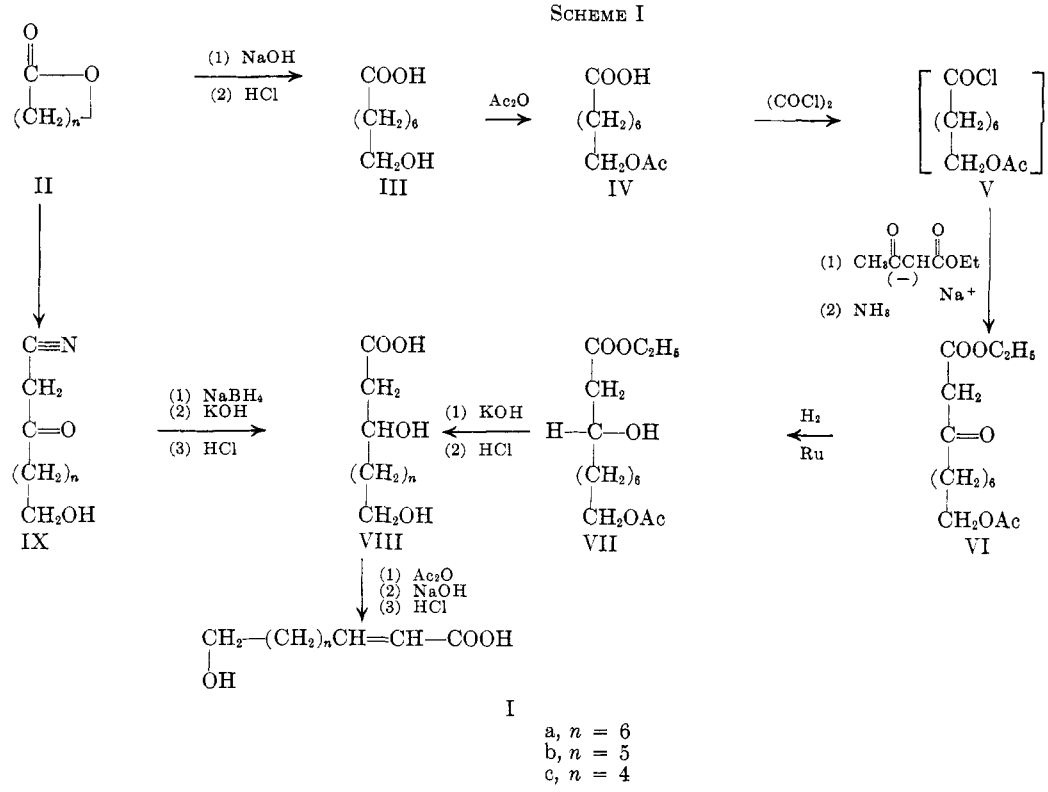
(11) We wish to thank Dr. S. D. Beck, Department of Entomology, University of Wisconsin, for providing a sample of natural royal jelly acid.

(12) C. J. Eby and C. R. Hauser, *J. Am. Chem. Soc.*, **79**, 723 (1957).

SCHEME I



VIIIa by sodium borohydride reduction followed by vigorous hydrolysis with potassium hydroxide.

The above procedure involving the reaction of an active methylene with a lactone appeared to be satisfactory for the production of homologs of royal jelly acid. The lactones derived by Baeyer–Villiger oxidation of cycloheptanone and cyclohexanone were converted to *trans*-9-hydroxy-2-nonenoic acid (Ib) and *trans*-8-hydroxy-2-octenoic acid (Ic) by utilizing the described sequence of reactions. The physical constants for the intermediates in these sequences are listed in Table I.

Experimental[13]

Preparation of the ω-Lactones II.—The following general procedure was utilized in the preparation of octano lactone (IIa), heptano lactone (IIb), and hexano lactone (IIc).

Dry methylene chloride was prepared by distillation from phosphorus pentoxide. Anhydrous disodium hydrogen phosphate was finely powdered in a mortar and dried 16 hr. at 120° before use.

Trifluoroacetic anhydride (The Matheson Co.) (102 ml., 0.72 mole) was added over the course of 30 min. from a cooled dropping funnel to a stirred suspension, cooled in ice, of 16.4 ml. (0.60 mole) of 90% hydrogen peroxide (Becco Chemical Div.) in 100 ml. of dry methylene chloride. Stirring was continued for an additional 30 min. The resulting peroxytrifluoroacetic acid solution was added over a 1-hr. period from a cooled dropping funnel to a vigorously stirred suspension of 160 g. of anhydrous disodium hydrogen phosphate in 400 ml. of dry methylene chloride containing 0.4 mole of the ketone. The reaction mixture was cooled to 0° during the addition, stirred for an additional 3 hr. at 0°, and stirred at room temperature for 3 hr. The insoluble salts were removed by filtration. When these salts were granular, as was the case in most runs, they were washed thoroughly with methylene chloride. On some occasions the salts were sticky and in these runs they were dissolved in water (600 ml.) and extracted with three 100-ml. portions of methylene chloride. In either case all of the methylene chloride solutions were combined and washed twice with 100-ml. portions of 10% sodium carbonate solution. After drying and removal of the methylene chloride, the residual oil was distilled at reduced pressure to give the lactones.

8-Hydroxyoctanoic Acid (III).—A mixture of 14.2 g. (0.1 mole) of ω-octanolactone and 40 ml. of 3 *N* aqueous sodium hydroxide was refluxed until the two-layer system became homogeneous. The reaction mixture was cooled, washed once with methylene chloride, cooled in an ice bath, and acidified to pH 3 with concentrated hydrochloric acid. A white solid precipitated and was collected by filtration after standing for 1 hr. Ether extraction of the mother liquor was necessary for recovery of the remaining hydroxy acid. The total yield of crude 8-hydroxyoctanoic acid was 14.7 g. (92%). Three recrystallizations from ethylene dichloride yielded tiny white needles, m.p. 61.0–61.5° (lit.[14] m.p. 58–58.5°).

8-Acetoxyoctanoic Acid (IV).—A suspension of 12.8 g. (0.08 mole) of 8-hydroxyoctanoic acid in 30 ml. of acetic anhydride was treated with 1.0 ml. of concentrated sulfuric acid. The mixture became warm and the solid acid slowly dissolved. After standing overnight, the solution was poured into 50 ml. of ice–water, stirred for 1 hr., and extracted with ether. The ether extract was thoroughly washed with water and dried, and the solvent was removed. Distillation of the residue yielded 15.3 g. (94%) of 8-acetoxyoctanoic acid, a colorless liquid, b.p. 126–127° (0.07 mm.), $n^{22}D$ 1.4432.

Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.40; H, 8.97. Found: C, 59.77; H, 8.90.

Ethyl 3-Keto-10-acetoxydecanoate (VI).—An ethyl sodioacetoacetate suspension in 200 ml. of dry benzene was prepared from 11.7 g. (0.09 mole) of ethyl acetoacetate (Eastman Organic Chemicals) and 4.32 g. (0.09 mole) of 50% sodium hydride dispersion (Metal Hydrides, Inc.), which had been washed free of oil with dry benzene. A solution of 8-acetoxyoctanoyl chloride was prepared by adding 43 ml. of freshly distilled oxalyl chloride to 16.2 g. (0.08 mole) of 8-acetoxyoctanoic acid (IV) in 60 ml. of dry benzene. Excess oxalyl chloride and solvent were removed *in vacuo* while the flask was swirled in a warm water bath. Two successive 10-ml. portions of benzene were added and removed in a similar manner.

(13) All melting points were obtained on a Fisher-Johns or a Thomas–Hoover melting point apparatus and are uncorrected. Infrared data were recorded on a Beckman IR-5 infrared spectrophotometer. Microanalyses were conducted by Huffman Microanalytical Laboratories, Wheatridge, Colo. Unless otherwise stated, the removal of solvents was carried out under reduced pressure and drying of a solution of a compound, or mixture of compounds, in an organic solvent refers to the use of anhydrous magnesium sulfate powder (reagent grade).

(14) P. Chuit and J. Hausser, *Helv. Chim. Acta*, **12**, 466 (1929).

TABLE I

Compd.	Yield, %	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
			$CH_2(CH_2)_nCCH_2C{\equiv}N$ (OH; O)						
IXa	73	67–68	$C_{10}H_{17}NO_2$	65.54	9.35	7.64	65.52	7.47	9.26
IXb	41	42–43	$C_9H_{15}NO_2$	Unstable					
IXc	43	41–42	$C_8H_{13}NO_2$	Unstable					
			$CH_2(CH_2)_nCHCH_2COOH$ (OH; OH)						
VIIIa	49	84–85	$C_{10}H_{20}O_4$	58.80	9.87		59.08	9.88	
VIIIb	48	70–71	$C_9H_{18}O_4$	56.82	9.54		57.13	9.36	
VIIIc	32	60–62	$C_8H_{16}O_4$	54.53	9.15		54.48	8.95	
			$CH_2(CH_2)_nCH{=}CH{-}COOH$ (OH)						
Ia	82	65.5–66[a]	$C_{10}H_{18}O_3$	64.49	9.74		64.57	9.75	
Ib	40	63–64[b]	$C_9H_{16}O_3$	62.76	9.37		62.55	9.21	
Ic	32	55–56	$C_8H_{14}O_3$	60.74	8.92		60.87	8.64	

[a] Lit.[5] m.p. 64–65°. [b] Lit.[7f] m.p. 63–64°.

The pale yellow acid chloride was dissolved in 30 ml. of benzene and added dropwise to the ethyl sodioacetoacetate suspension, cooled to 5°, while vigorous stirring was maintained. The addition was completed in 30 min.; the reaction mixture was allowed to warm slowly to room temperature and finally refluxed or an additional 15 min. The total reaction time was 1 hr.

Ice–water (40 ml.) and 10 ml. of 3 *N* aqueous hydrochloric acid were stirred into the reaction mixture and the layers were allowed to separate. The aqueous phase was washed thoroughly with ether, and the ether and benzene solutions were combined, washed once with water, dried, and concentrated to about 100 ml.

The solution of crude ethyl 2-acetyl-3-keto-10-acetoxy decanoate was treated with dry ammonia gas at 0° for 40 min., allowed to stand at room temperature for 30 min., warmed on a steam bath for 10 min. to drive off most of the excess ammonia, and shaken with 30 ml. of 3 *N* hydrochloric acid. After the layers had separated, the organic phase was washed with water, sodium bicarbonate solution, and water again. Removal of the solvent left a yellow oil, which was distilled under reduced pressure. The main fraction was collected from 108–161° (1.0 mm.). Redistillation of this fraction yielded 11.7 g. (54%) of ethyl 3-keto-10-acetoxydecanoate, b.p. 139–140° (0.09 mm.), $n^{25}D$ 1.4468. The infrared spectrum (liquid film) showed bands at 5.75, 5.82, 6.08, 6.13, and 8.03 μ.

Anal. Calcd. for $C_{14}H_{24}O_5$: C, 61.75; H, 8.88. Found: C, 62.17; H, 8.85.

Ethyl 3-Hydroxy-10-acetoxydecanoate (VII).—Hydrogenation of 8.17 g. (0.030 mole) of ethyl 3-keto-10-acetoxydecanoate in 90 ml. of absolute ethanol was effected by shaking the solution with 0.8 g. of ruthenium oxide (Engelhard Industries) at room temperature and a means pressure of 3 atm. in a Parr hydrogenation apparatus. Hydrogen uptake was quite slow during the initial 8 hr. of shaking, accelerated appreciably thereafter, and stopped after 1 mole equiv. had been absorbed (40 hr.). The catalyst was removed by filtration through a bed of Celite and washed with ethanol. Removal of the solvent left a dark oil which, on distillation at reduced pressure, yielded 7.30 g. (90%) of ethyl 3-hydroxy-10-acetoxydecanoate, a colorless liquid, b.p. 165–166° (1.0 mm.), $n^{24}D$ 1.4488. The infrared spectrum (liquid film) showed bands at 2.86, 5.74, and 8.03 μ.

Anal. Calcd. for $C_{14}H_{26}O_5$: C, 61.28; H, 9.55. Found: C, 61.64; H, 9.49.

Preparation of 3,10-Dihydroxydecanoic Acid (VIIa) by Hydrolysis of Ethyl 3-Hydroxy-10-acetoxydecanoate (VII).—A solution of 6.05 g. (0.022 mole) of ethyl 3-hydroxy-10-acetoxydecanoate in 50 ml. of 1 *N* alcoholic potassium hydroxide was heated under reflux for 3 hr. The alkaline reaction mixture was cooled, diluted for 25 ml. of water, and concentrated to approximately 25 ml. *in vacuo*. After being washed once with ether, the aqueous solution was carefully acidified to pH 3 with concentrated hydrochloric acid. Filtration of the white solid acid and subsequent crystallization from chloroform yielded 3.64 g. (81%) of the desired product, m.p. 88–89°.

Anal. Calcd. for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.40; H, 9.70.

Preparation of 3-Keto-ω-hydroxynitriles (IX).—3-Keto-10-hydroxydecanitrile (IXa), 3-keto-9-hydroxynonanitrile (IXb), and 3-keto-8-hydroxyoctanitrile (IXc) were prepared by the following method.

A suspension of 0.5 mole of sodium amide[15] in 600 ml. of liquid ammonia was prepared in a 1-l., three-necked, round-bottomed flask equipped with a sealed stirrer, a dropping funnel, and a reflux condenser. To the stirred suspension was added during 5 min. a solution of 26.2 ml. (0.50 mole) of redistilled acetonitrile in 25 ml. of anhydrous ether. After 5 min. a solution of 0.25 mole of the ω-lactone in 25 ml. of ether was added as rapidly as feasible (about 5 min.); stirring was continued 1 hr. As the reaction mixture thickened, more ether was added to facilitate stirring. The ammonia was removed rapidly on the steam bath as ether was being added to keep the volume at approximately 500 ml. The reaction mixture was then cautiously poured with stirring into 500 g. of crushed ice. The two layers were separated and the cold aqueous solution of the sodio-β-ketonitrile was filtered. After washing the filter paper with ice–water, the combined filtrate and washings were acidified with iced 3 *N* hydrochloric acid. The liberated β-ketonitrile was extracted with three 200-ml. portions of ethyl acetate. The ethyl acetate extract was washed with four 25-ml. portions of saturated sodium bicarbonate solution and dried. The solvent was removed at room temperature on a rotary-type evaporator. The resulting oil was treated with 100 ml. of ether. On re-evaporation under reduced pressure, allowing the evaporating ether to cool the flask, the ketonitrile crystallized. The ketonitrile was recrystallized by dissolving it in diethyl ether at room temperature and then cooling to 0°. The ketonitriles, especially IXb and IXc, are unstable and should be stored in the cold. The infrared spectrum ($CHCl_3$) showed bands at 2.77, 2.88, 4.42, and 5.77 μ.

Preparation of 3,ω-Dihydroxy Acids (VIII).—The following method was used for the preparation of 3,10-dihydroxydecanoic acid (VIIIa), 3,9-dihydroxynonanoic acid (VIIIb), and 3,8-dihydroxyoctanoic acid (VIIIc), from the corresponding ketonitriles IX.

To a stirred solution of 0.0218 mole of the 3-keto-ω-hydroxynitrile, in 40 ml. of 80% methanol, was slowly added 1.00 g. (0.0264 mole) of sodium borohydride (Metal Hydrides, Inc.), and the solution was stirred for 12 hr. at room temperature. The solution was concentrated at reduced pressure to 10 ml. and 10 ml. of water was added. The two phases were transferred to a separatory funnel with the aid of small portions of ethyl acetate and the aqueous phase was extracted with three 25-ml. portions of ethyl acetate. The combined ethyl acetate extracts were dried, and removal of the solvent at reduced pressure left a clear oil whose infrared spectrum showed the absence of a car-

(15) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 461 (1943).

bonyl but the presence of nitrile (4.42 μ) and hydroxyl (2.95 μ) groups. The crude 3,ω-dihydroxynitrile was dissolved in 30 ml. of 15% ethanol containing 2.50 g. (0.045 mole) of analytical reagent potassium hydroxide, and the clear solution refluxed. After 20 hr. the solution was concentrated to half its original volume and extracted with two 20-ml. portions of ethyl acetate. The resulting aqueous solution was cooled in ice, acidified to pH 1 (hydrion paper) with 37% hydrochloric acid, and extracted with three 25-ml. portions of ethyl acetate. The ethyl acetate solution was dried and removal of the solvent gave the crude acid which was recrystallized from chloroform.

Preparation of *trans*-ω-Hydroxy-α,β-Unsaturated Acids (I).—*trans*-10-Hydroxy-2-decenoic acid (Ia), *trans*-9-hydroxy-2-nonenoic acid (Ib), and *trans*-8-hydroxy-2-octenoic acid (Ic) was prepared by the following method.

A mixture of 0.007 mole of the 3,ω-dihydroxy acid and 10 ml. of acetic anhydride was heated at 150° for 4 hr. Acetic acid was allowed to distil as it formed. The solvent was removed as thoroughly as possible, and the residual oil refluxed for 1 hr. with 50 ml. of 1 *N* alcoholic potassium hydroxide. Water was added, the bulk of the ethanol was removed, and the solution washed with ether and acidified. The aqueous phase was thoroughly extracted with ether, the ethereal phase was washed with water and dried, and the solvent was removed. The acids were recrystallized to constant melting point from diethyl ether–petroleum ether (b.p. 40–60°).

The infrared spectrum ($CHCl_3$) exhibited bands at 5.90, 6.06, and 10.2 μ. In the 60-Mc. n.m.r. spectrum (recorded on a Varian A-60 instrument) of the acids in $DCCl_3$, a doublet centered at δ 5.85 (p.p.m.)., with a J value of 18 c.p.s., was observed, indicating the *trans* configuration of the double bond.

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The Course of the Michael–Aldol Synthesis. I. The Formation of Cyclopentanediones[1]

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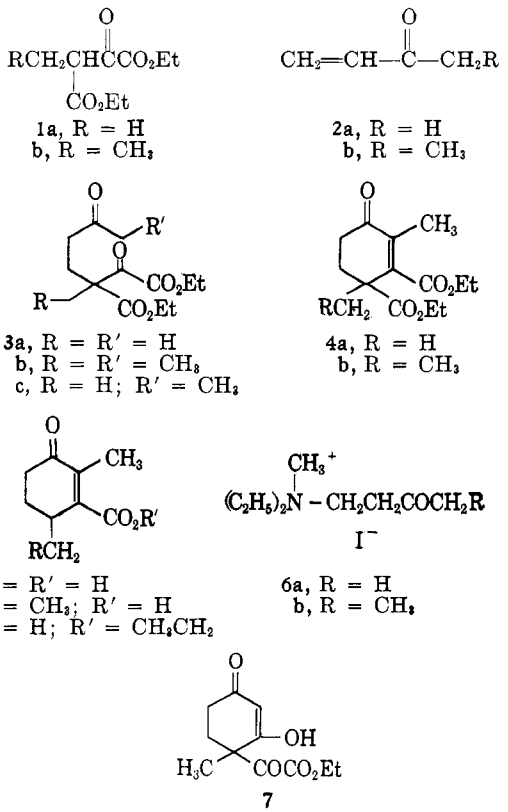
The reaction of ethyl α-ethoxalylpropionate with methyl vinyl ketone (or as reported with the corresponding Mannich base methiodide) in the presence of sodium ethoxide leads not to a cyclohexanedione or cyclohexenone but instead to an acetylcyclopentane-1,2-dione. The structure of this material and its hydrolysis product is discussed and the use of other unsaturated carbonyl compounds is illustrated.

In the course of a projected synthesis of ψ-santonin we wished to prepare the cyclohexenone carboxylic acid, **5a**. The obvious route to such a system appears to be the Michael addition of an enolate to an unsaturated ketone to yield a 1,5-diketone followed by an intramolecular aldol condensation to produce the cyclohexenone. In the case at hand the components of such a sequence would be ethyl α-ethoxalylpropionate (**1a**) and ethyl vinyl ketone (**2b**) or its equivalent. The expected stepwise path to the desired cyclic ketone should then be **1a** + **2b** → **3c** → **4a** → **5a**.

This general type of synthesis is well documented[3] and in this case two closely similar sequences have been carried out. Martin and Robinson[4] reported the reaction of the sodium salt of **1a** with the Mannich base methiodide **6a**. They isolated in unspecified yield an acidic material for which they suggested the cyclohexanedione **7**. In an almost totally analogous sequence, Büchi and Warnhoff[5a,b] obtained the expected keto acid **5b**, from the homologous starting materials **1b** and **6b**. Neglecting for the moment the validity of the structural assignments of these compounds the following points may be noted. The experimental procedures for the two cases are similar. In each, a sodium alkoxide in benzene–alcohol solution (ethanol in the first example and methanol in the second) is used for the initial condensation. Although **3b** was isolated in a crude



form and converted to the cyclic product (**5b**) by treatment with aqueous base, Martin and Robinson effected cyclization of their intermediate by adding a second mole of sodium ethoxide to the solution presumably containing **3a**. Despite these apparently small differences in procedure, the products in the two cases are very different structurally. Elemental analysis alone

(1) The authors gratefully acknowledge the support of this research by the National Institutes of Health, Grant No. GM 10509-01.

(2) Taken in part from the Ph.D. Thesis of J. A. Hartman, Wayne State University, 1963.

(3) For a review of this subject, see E. D. Ginsburg and R. Pappo, *Org. Reactions*, **10**, 179 (1959).

(4) R. H. Martin and R. Robinson, *J. Chem. Soc.*, 1866 (1949).

(5) (a) G. Büchi and E. W. Warnhoff, *J. Am. Chem. Soc.*, **81**, 4443 (1959); (b) the authors have kindly supplied us with the details of their experimen tal procedures.