

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

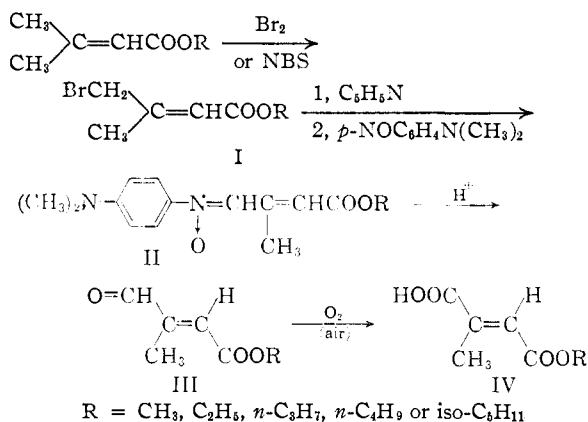
Synthesis of γ -Oxosenecioates. Flavor of Watermelon

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Homologous alkyl γ -oxosenecioates (III) have been prepared from γ -bromosenecioates (I) by means of Kröhnke's method *via* the corresponding nitrones II. In spite of the very close resemblance of the odor of ethyl γ -oxosenecioate to that of watermelon juice, the attempted isolation of the aldehydic ester from the latter has been unsuccessful.

Although the preparation of ethyl γ -oxosenecioate has been recorded,¹ the methods used were not suitable for preparation in quantity. In view of the potential use of these compounds as an isoprene unit in the synthesis of natural products an easier preparation has been sought and a new route leading to this class of esters, as shown in the accompanying flow-sheet, has been worked out.



γ -Bromosenecioates (I) were prepared from the corresponding senecioates by the action of free bromine highly diluted in carbon tetrachloride with simultaneous removal of hydrogen bromide.² The pyridinium salts of these bromoesters were then treated with *p*-nitrosodimethylaniline according to the method of Kröhnke³ to give the nitrones II. Hydrolysis of the nitrones afforded the desired aldehydic esters III in over-all yields of 33–45% based on the bromoesters I.

All of these esters formed yellowish oils which were easily autoxidized as evidenced by the change of refractive indices or better by the infrared absorptions. Samples which had been allowed to stand as a thin film on a watch glass showed the characteristic absorption of bonded carboxy in the 3000–2500 cm.⁻¹ region.⁴

The autoxidation of the methyl and ethyl esters (III, R = CH₃ or C₂H₅) gave solid products which melted after recrystallizations at 52–53° and 67–67.5°, respectively. They were found to

(1) (a) P. F. Wiley and O. Weaver, *THIS JOURNAL*, **77**, 3422 (1955); **78**, 808 (1956); (b) D. D. Phillips, *ibid.*, **76**, 5385 (1954).

(2) (a) This method is based on a patent of H. Schaltegger (U. S. Patent 2,790,757, April 30, 1957), which is concerned with the preparation of γ -bromocrotonate in this way. (b) For the preparation of γ -bromosenecioate by means of the ordinary bromination with N-bromosuccinimide see, for example, H. O. Huisman, A. Smit, S. Wromen and L. G. M. Fisscher, *Rec. trav. chim.*, **71**, 899 (1952).

(3) F. Kröhnke, *Angew. Chem.*, **65**, 605 (1953).

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen & Co., Ltd., London, 1958, p. 162.

be identical with the corresponding α -methyl or α -ethyl monoester of mesaconic acid (IV, R = CH₃ or C₂H₅).

The oxidation of the aldehydic methyl ester (III, R = CH₃) with silver oxide in ice-cooled aqueous alkali gave mesaconic acid (IV, R = H) as a sole isolable product in an 88% yield.

Since the ethyl γ -oxosenecioate (III, R = C₂H₅) gave a single 2,4-dinitrophenylhydrazone, as confirmed by paper chromatography, and no evidence was obtained on the formation of isomers, it appeared plausible to conclude that this aldehydic ester (III) was a fairly pure *trans* compound with respect to the two carbonyl groups.⁵

Other methods for preparing the oxosenecioate also were examined, but found less satisfactory. The direct oxidation of ethyl senecioate with selenium dioxide according to the method of Bohlmann and Inhoffen⁶ gave an oil with disagreeable odor in a 5% yield, which afforded the 2,4-dinitrophenylhydrazone of ethyl γ -oxosenecioate (III) in a 3% yield, both based on the senecioate. Treatment of ethyl γ -bromosenecioate (I, R = C₂H₅) with dimethyl sulfoxide by the method of Kornblum and co-workers⁷ failed to give any oxidation product under various conditions.

Ethyl γ -oxosenecioate prepared according to the flowsheet has an odor strongly resembling that of watermelon juice.⁸ The same odor is perceptible upon treatment of the odorless, analytically pure semicarbazone with 15% sulfuric acid. The other esters had similar odors which were fainter and sweeter as the length of the alkyl chains increased. Because of the odor similarity, isolation of ethyl γ -oxosenecioate from watermelon juice was attempted but without success. In view of the easy oxidation of this ester to α -monoethyl mesaconate it was thought advisable to attempt isolation of this ester from the watermelon juice but this too failed. Acetaldehyde and acetone were shown to be

(5) It should be added that the corresponding acid, *i.e.*, γ -oxosenecioic acid, exists in its pseudo-acid form. This fact has been confirmed by the infrared spectrum in accord with the statement of Wiley and Weaver (ref. 1a) and shows that the configuration of the double bond apparently is transformed into *cis* during the hydrolysis process. The facile *cis-trans* rearrangement makes it desirable to obtain more conclusive evidence on the configuration of the γ -oxosenecioates by determining the nuclear magnetic resonance spectra. For example see R. Morris, C. A. Vernon and R. F. M. White, *Proc. Chem. Soc.*, 303 (1958); J. A. Elvidge, *J. Chem. Soc.*, 474 (1959).

(6) F. Bohlmann and E. Inhoffen, *Chem. Ber.*, **89**, 1276 (1956).

(7) N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand and W. M. Weaver, *THIS JOURNAL*, **79**, 6562 (1957).

(8) Regarding this close resemblance of the odor of ethyl γ -oxosenecioate to that of watermelon juice, all of the scientists who visited our laboratory agreed with us. Among these people are Professor Jerrold Meinwald of Cornell University, Ithaca, N. Y., and Doctor John A. Leighty of Eli Lilly & Co., Indianapolis, Ind.

TABLE I
 γ -OXOSENECIOATES (III)

R	B.p.		n_D^{20} ^a	Yield, % ^b	Formula	Analyses, ^c %			
	°C.	Mm.				Calcd.		Found	
CH ₃ ^d	56-57	7	1.4645	41.4	C ₆ H ₃ O ₃	56.24	6.29	56.18	6.63
C ₂ H ₅ ^{e,f}	51-53	4.5	1.4597	45.7	C ₇ H ₁₀ O ₃	59.14	7.09	58.83	7.22
<i>n</i> -C ₃ H ₇	62.5-63	4.7	1.4600	42.3	C ₈ H ₁₂ O ₃	61.52	7.75	59.03	7.33
<i>n</i> -C ₄ H ₉	83-84	6	1.4589	39.2	C ₉ H ₁₄ O ₃	63.51	8.29	62.54	8.27
<i>iso</i> -C ₅ H ₁₁	82-84	4.7	1.4609	33.5	C ₁₀ H ₁₆ O ₃	65.19	8.75	63.02	8.49

^a The refractive indices of γ -oxosenecioates are apt to show a remarkable rise as a result of the facile autoxidations. ^b Based on the corresponding γ -bromosenecioates (I). ^c Owing to the autoxidation which was apparently evidenced by weight increase during the sampling for microanalysis, some of the analytical data were not entirely satisfactory, but those of carbonyl derivatives as listed in Tables II and III were in good accordance with the calculated values. ^d Infrared absorptions (NaCl plates): 2955, 2840, 2705, 1722, 1695, 1664, 1460, 1443, 1438, 1400, 1360, 1331, 1289, 1270, 1227, 1185, 1164, 1115, 1095, 1040, 983, 913, 875 and 836 cm.⁻¹. ^e Infrared absorptions (NaCl plates): 3000, 2960, 2848, 2720, 1720, 1690, 1660, 1465, 1448, 1438, 1409, 1389, 1364, 1350, 1330, 1285, 1240, 1215, 1175, 1160, 1113, 1095, 1045, 1035, 982, 957, 947, 875 and 828 cm.⁻¹. ^f The recorded^{1a} b.p. is 51° (2 mm.) and n_D^{20} is 1.4569.

TABLE II

2,4-DINITROPHENYLHYDRAZONES OF γ -OXOSENECIOATES

R	M.p., °C.	Formula	Analyses, %			
			Calcd.		Found	
CH ₃	224-225	C ₁₂ H ₁₂ N ₄ O ₆	46.76	3.92	46.67	4.23
C ₂ H ₅	200 ^a	C ₁₃ H ₁₄ N ₄ O ₆	48.45	4.38	48.73	4.50
<i>n</i> -C ₃ H ₇	193-193.7	C ₁₄ H ₁₆ N ₄ O ₆	50.00	4.80	49.41	4.74
<i>n</i> -C ₄ H ₉	166	C ₁₅ H ₁₈ N ₄ O ₆	51.42	5.18	51.67	5.28
<i>i</i> -C ₅ H ₁₁	160	C ₁₆ H ₂₀ N ₄ O ₆	52.74	5.53	52.85	5.67

^a The recorded m.p. is 199-200° (ref. 1a) or 183-185° (ref. 1b).

TABLE III

SEMICARBAZONES OF γ -OXOSENECIOATES

R	M.p., °C.	Formula	Analyses, %			
			Calcd.		Found	
CH ₃	223 dec.	C ₇ H ₁₁ N ₃ O ₃	45.40	5.99	45.10	6.00
C ₂ H ₅	208	C ₈ H ₁₃ N ₃ O ₃	48.23	6.58	48.07	6.61
<i>n</i> -C ₃ H ₇	193.5-194.5	C ₉ H ₁₅ N ₃ O ₃	50.69	7.09	50.41	7.04
<i>n</i> -C ₄ H ₉	178-179	C ₁₀ H ₁₇ N ₃ O ₃	52.85	7.54	53.07	7.59
<i>i</i> -C ₅ H ₁₁	192-193	C ₁₁ H ₁₉ N ₃ O ₃	54.75	7.92	55.00	7.90

present in watermelon juice by their isolation as 2,4-dinitrophenylhydrazones. Control experiments with ethyl γ -oxosenecioate indicated that failure to isolate it from the juice was not due to destruction during isolation.

Experimental⁹

Methyl γ -Bromosenecioate.—The bromination of methyl senecioate was carried out by means of bromine highly diluted in carbon tetrachloride with simultaneous removal of hydrogen bromide from the reaction mixture.^{2a} The physical properties and yields are given in Table IV together with those of other bromoesters prepared similarly. The infrared spectra and refractive indices of some of the γ -bromosenecioates thus obtained were compared with those prepared by the ordinary method of bromination with *N*-bromosuccinimide^{2b} and found to be identical.

Methyl β -[*N*-(*p*-Dimethylaminophenyl)-nitrono]-crotonate [N-(*p*-Dimethylaminophenyl)- α -(2-methoxycarbonyl-1-methylvinyl)-nitrono].—To a solution of 38.6 g. (0.2 mole) of methyl γ -bromosenecioate in 40 ml. of dry benzene 19 g. (0.24 mole) of pyridine was added. The resulting mixture was stirred at room temperature for 2 hours and then at 60-70° (bath temperature) for an additional 4 hours. After cooling the mixture the upper layer which consisted of benzene and excess pyridine was discarded by decantation. The lower layer contained the resulting pyridinium salt and formed a semi-solid, to which a solution of 30 g. (0.2 mole) of *p*-nitrosodimethylaniline in 300 ml. of methanol was added.¹⁰ The mixture then was treated with 200 ml. of 1 *N*

(9) Melting points and boiling points were uncorrected. Infrared spectra were obtained with a double beam recording spectrophotometer (Oyo-kōken model D-101, Tōkyō, Japan).

(10) When ethanol was used as a solvent according to the method of F. Kröhnke, a transesterification took place and the corresponding

TABLE IV

 γ -BROMOSENECIOATES (I)

R	B.p.		n_D^{20}	Yield, % ^a
	°C.	Mm.		
CH ₃ ^b	78-85	8.0	1.5051	73.4
C ₂ H ₅ ^c	73-82	6.0	1.4935	75.4
<i>n</i> -C ₃ H ₇	93-102	5.0	1.4892	83.5
<i>n</i> -C ₄ H ₉	100-107	4.5	1.4870	77.2
<i>i</i> -C ₅ H ₁₁	109-116	5.1	1.4800	76.8

^a The yields are those of bromination with free bromine in carbon tetrachloride. ^b Infrared spectrum (NaCl plates): 3055, 2980, 2950, 2920, 2845, 1770, 1743, 1720, 1710, 1650, 1637, 1430, 1387, 1377, 1356, 1278, 1250, 1230, 1212, 1187, 1155, 1100, 1037, 992, 956, 923, 883, 861, 832 and 733 cm.⁻¹. ^c Infrared spectrum (NaCl plates): 3055, 2980, 2950, 2918, 2880, 1780, 1745, 1721, 1715, 1650, 1445, 1388, 1375, 1366, 1349, 1277, 1251, 1231, 1215, 1155, 1110, 1095, 1040, 990, 958, 887, 862, 824 and 733 cm.⁻¹.

sodium hydroxide solution which was added dropwise in the course of about 1 hour under stirring and cooling in an ice-bath. After all of the alkaline solution was introduced, stirring and cooling was continued for an additional 4 hours. The brown crystals of the crude nitrono which separated were collected and the mother liquor was evaporated to dryness *in vacuo*. For the analyses a sample was recrystallized twice from benzene; m.p. 132.5°.

Anal. Calcd. for C₁₄H₁₈N₂O₃: C, 64.10; H, 6.92. Found: C, 64.20; H, 6.95.

Other β -[*N*-(*p*-dimethylaminophenyl)-nitrono]-crotonates were prepared similarly and subjected to the hydrolysis without any purification. The nitrono of the ethyl ester, *i.e.*, ethyl β -[*N*-(*p*-dimethylaminophenyl)-nitrono]-crotonate [= *N*-(*p*-dimethylaminophenyl)- α -(2-ethoxycarbonyl-1-methylvinyl)-nitrono], could also be isolated in a crystalline form, m.p. 90°.

Anal. Calcd. for C₁₅H₂₀N₂O₃: C, 65.48; H, 7.48. Found: C, 65.19; H, 7.30.

Methyl γ -Oxosenecioate.—The crude crystals of nitrono and the viscous oil which remained upon concentrating the mother liquor and contained a substantial amount of the nitrono were combined and the whole was suspended in 400 ml. of ether. To this mixture 200 ml. of 6 *N* sulfuric acid was added gradually during 30 minutes under stirring and cooling in an ice-bath. After continued stirring for an additional 1.5 hours at the same temperature, the organic layer was separated and the aqueous layer was extracted three times with ether. The combined ethereal solution was washed twice with sodium bicarbonate solution and then once with water, dried over anhydrous sodium sulfate and the solvent was distilled off. Distillation of the residue under reduced pressure gave 10.6 g. (41.4% based on γ -bromosenecioate) of methyl γ -oxosenecioate, b.p. 56-57° (7 mm.).

Other γ -oxosenecioates were prepared similarly, the physical constants together with analyses being listed in Table I.

ethyl ester was obtained. See A. Funke and P. Karrer, *Helv. Chim. Acta*, **32**, 1016 (1949).

Those of 2,4-dinitrophenylhydrazones¹¹ and semicarbazones are given in Tables II and III, respectively.

The 2,4-dinitrophenylhydrazone of ethyl γ -oxoseneioate was submitted to the chromatographic separation on a paper impregnated with *N,N*-dimethylformamide, decalin saturated with the amide being used as a mobile phase.¹² After about 20 hours development a single spot (R_f 0.07) was observed. When the developing solvent was replaced with 30% tetrahydrofuran in ligroin (b.p. 80–100°),¹³ the R_f value was 0.83, but the spot still remained single and the presence of other substances with different R_f values was not ascertained.

α -Methyl and α -Ethyl Monoesters of Mesaconic Acid.—A sample of methyl and ethyl γ -oxoseneioates was allowed to stand as a thin film on a watch-glass for about 1 week at room temperature. The autoxidation products solidified and melted at 51–52.5° and 65–66.5°, respectively. One recrystallization of each crude product from petroleum ether gave white crystals of α -methyl monoester, m.p. 52–53° (lit. 52°¹⁴), and α -ethyl monoester, m.p. 67–67.5° (lit. 67°¹⁴) of mesaconic acid, which afforded correct analyses for carbon and hydrogen.

Oxidation of Methyl γ -Oxoseneioate with Silver Oxide.—A solution of 7 g. (0.041 mole) of silver nitrate in 15 ml. of water was treated with a solution of 3.5 g. (0.0875 mole) of sodium hydroxide in 15 ml. of water under stirring. To the resulting suspension of silver oxide in water a solution of 2.5 g. (0.0195 mole) of methyl γ -oxoseneioate in 50 ml. of ether was added dropwise under continued stirring and ice-cooling, the reaction temperature being kept below 15°. After the addition was completed, stirring was continued for an additional 1 hour. The solids were removed by filtration and the filtrate was acidified with concentrated hydrochloric acid. The organic layer was separated, the aqueous one being saturated with sodium chloride and extracted with ether. The combined ethereal solutions were washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and evaporated to give 2.25 g. (88.5%) of colorless crystals with m.p. 191–200°.

The infrared spectrum of the crude oxidation product was completely identical with that of mesaconic acid and the absorptions characteristic of citraconic acid were absent; thus, the absorptions of the crude oxidation product and those of authentic specimen of mesaconic acid were 1700, 1680, 1638, 1351, 1297, 1265, 1233, 1132, 1017, 930, 914, 825 and 778 cm^{-1} (Nujol mull), while those of authentic specimens of citraconic acid were 1720, 1700, 1680, 1635,

(11) Prepared according to R. L. Shriner and R. C. Fuson, "The Systematic Identifications of Organic Compounds," J. Wiley and Sons, Inc., New York, N. Y., 1948, pp. 170–171.

(12) I. Panayotov, *Perfumery Essent. Oil Record*, **49**, 233 (1958); see also L. Horner and W. Kirmse, *Ann.*, **597**, 48 (1955).

(13) R. G. Rice, G. J. Keller and J. G. Kirchner, *Anal. Chem.*, **23**, 194 (1951).

(14) R. Anschütz and J. Drugman, *Ber.*, **30**, 2649 (1897).

1337, 1315, 1282, 1246, 1227, 1133, 1041, 1028, 926, 891, 820 and 765 cm^{-1} (Nujol mull).

Recrystallizations of the oxidation product from water gave a pure sample, m.p. 202°, mixed m.p. with mesaconic acid 202°. This also afforded correct analyses for carbon and hydrogen.

Volatile Carbonyl Constituents of a Watermelon Fruit.—An ordinary watermelon (*Citrullus vulgaris* Schrad.) fruit which weighed 6.5 kg. was found to consist of following parts: 2.4 kg. of rind, 0.08 kg. of seeds, 0.22 kg. of pressed cake and 3.8 kg. of juice. Concentrating the juice under reduced pressure gave 3.65 kg. of distillate and 0.14 kg. of red, viscous residue. The whole distillate was acidified with 200 ml. of concentrated sulfuric acid under stirring at 0–5° and then treated with an alcoholic solution of 0.8 g. of 2,4-dinitrophenylhydrazine. After standing overnight 350 mg. of yellow precipitates were collected by filtration and the mother liquor was extracted with ether. The ethereal extracts gave an additional 200 mg. of crystalline solid containing a small amount of oily product. Several recrystallizations of the combined dinitrophenylhydrazone mixture from ethanol containing ethyl acetate gave 380 mg. of yellow crystals melting at 168°, which were identified as 2,4-dinitrophenylhydrazone of acetaldehyde by means of a mixed m.p. with the authentic specimen.

The mother liquors of recrystallizations were concentrated and dissolved in a mixture of benzene-ether (10:1). This solution was chromatographed on activated alumina and the resulting fractions were examined by means of paper chromatography.¹²

The chromatography was carried out on a paper impregnated with *N,N*-dimethylformamide and developed with decalin saturated with the amide. The paper then was sprayed with sodium hydroxide solution in order to locate the spots.

Following fractions were isolated by the column-chromatography: fraction 1: Elution with petroleum ether gave a very small amount of light yellow needles melting at 91°, the R_f value on the paper being 0.9. This substance could not be identified due to the low yield.

Fraction 2: Elution with a mixture of petroleum ether-benzene (1:2) gave an additional 50 mg. of 2,4-dinitrophenylhydrazone of acetaldehyde. The total amount of the dinitrophenylhydrazone amounts to 430 mg. so that the content of acetaldehyde based on the whole fruit is 12 p.p.m.

Fraction 3: Elution with a mixture of benzene-ether (10:1) gave a very small amount of reddish-yellow crystals. The crystals afforded two spots on a paper chromatography. The R_f values were 0.2 and 0.3, respectively, in accord with the values of pure 2,4-dinitrophenylhydrazones of acetaldehyde and acetone, respectively, which were chromatographed under the same conditions. The acetone 2,4-dinitrophenylhydrazone could not be isolated.

Fraction 4: Elution with ethanol gave a brown oil which could neither be crystallized nor identified.

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[CONTRIBUTION NO. 558 FROM THE CENTRAL RESEARCH DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS AND CO.]

Fluoroketones. I

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Fluoroketones have been shown to be versatile intermediates for the synthesis of new fluorine-containing structures. Ketals of unusual thermal and chemical stability have been prepared by a novel base-promoted ketalization. The synthesis was extended to dioxolanes, dioxanes, oxazolidines, oxathiolanes and their carbonyl-containing analogs. Fluoroketones reacted with diazomethane to give high yields of stable epoxides, and condensed readily with active methylene compounds and metallic acetylides. The chemistry of the condensation products was briefly examined.

Although a great number of partially and completely fluorinated ketones has been prepared by a variety of standard methods, the reported chemistry of these ketones,¹ most of which contained hydrogen-bearing α -carbons, does not re-

fect the inherent reactivity of the unusually modified carbonyl function. Observations made in these laboratories pointed out the desirability of

(1) P. Tarrant in J. H. Simons, "Fluorine Chemistry," Vol. 11, Academic Press, Inc., New York, N. Y., 1954, pp. 213–320.