Direct Conversion of Some Halogen Hydroxy Fatty Acids Into the Corresponding Methyl Esters of Ketoacids

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Abstract

Conditions have been established for converting some methyl esters of halogen hydroxy fatty acids to keto esters in high yields of 90% of isolated product, by the action of mercuric sulfate and sulfuric acid in methanol. Investigation of the same conversion using silver nitrate has shown the formation of dihydroxy acid parallel with the keto ester. The crude reaction mixture was separated into fraction by column chromatography.

Introduction

KING (1) HAS ESTABLISHED the partial conversion of 9(10), 10(9)-iodohydroxy stearic acid into 9(10)-keto stearic acid upon treatment with HgO in moist ether. Jungermann and Spoerri (2) have achieved indirect conversion of 9(10), 10(9)-chlorohydroxy stearic acid into the corresponding 9(10)-ketostearic acid. Maerker et al. (3) have found that methyl 9,10-epoxystearate can be converted into the corresponding methyl 9(10)-ketostearate with the aid of acid catalysts (aluminum chloride, boron fluoride, boron fluoride etherate) in dioxan.

We have established (4,5) that treatment of idohydroxy fatty acids or their methyl esters with silver acetate or potassium (sodium) acetate in glacial acetic acid leads to considerable yields of the corresponding keto fatty acids.

The purpose of the present work was to study the possibility of a direct quantitative conversion of the above-mentioned iodohydroxy fatty acids into the corresponding ketoacids using some other salt in acid medium (in our case, methanol solutions of mercuric sulfate and silver nitrate in the presence of sulfuric or nitric acid, respectively). On the other hand, it was of interest to determine the extent to which the mineral acid influences the above conversion. The behavior of chloro- and bromohydroxy stearic acids under equal reaction conditions was also to be investigated for the sake of comparison.

Experimental Procedure and Data

Materials

Methyl 9(10), 10(9)-iodohydroxy Stearate, I. This compound was prepared by treatment of pure methyl ester of oleic acid (n_D^{20} = 1.4525 and I.V. = 86.0) with hypoiodous acid, according to the method of Margosches for the determination of iodine value of fats (4–6). Anal. Calc'd for $C_{19}H_{37}O_3J$: C = 51.88%; H = 8.40%; found: C = 52.05% H = 8.50%.

Methyl 6(7), 7(6)-iodohydroxy Stearate, II. This was prepared as above, from pure methyl ester of petroselinic acid (n_D^{20} = 1.4530 and I.V. = 86.2). Calc'd for $C_{19}H_{37}O_3J$: C = 51.88%; H = 8.40%; found: C = 52.15%; H = 8.55%.

Methyl 13(14), 14(13)-iodohydroxy Behenate, III. This compound was prepared in the same way as above from pure methyl ester of erucic acid (n_D^{20} = 1.4560 and I.V. = 72.1. Anal. Calc'd for $C_{23}H_{45}O_3J$: C = 55.60%; H = 9.24%; found: C = 56.23%; H = 9.52%.

Methyl 9(10), 10(9)-bromohydroxy Stearate, IV. This was obtained from methyl 9,10-epoxy stearate (epoxy oxygen. Anal. Calc'd: 5.12; found: 5.02%) and hydrobromic acid by the method of Swern et al. (7). Anal. Calc'd for $C_{19}H_{37}O_3Br$ (398.4): C = 58.08%; H = 9.40%; found: C = 58.30%; H = 9.60%.

Methyl 9(10), 10(9)-chlorohydroxy Stearate, V. This was obtained in an analogous manner (7) from methyl 9,10-epoxy stearate and hydrochloric acid. Anal. Calc'd for $C_{19}H_{37}O_3Cl$ (349.0): C = 65.47%; H = 10.60%; found: C = 65.70%; H = 10.75%.

Methyl alcohol: A.R., dried over CaO.

Silica gel (Merck): a 80–100 mesh fraction, dried at 120C for 2 hr.

Benzene: A.R., dried over sodium.

Ethyl ether: A.R., dried over sodium.

Petroleum ether: bp 30–50C, freshly distilled.

All inorganic reagents were A.R.

Analysis and Description of the Products

Column chromatography was used for the quantitative separation of the reaction products according to the procedure of Maerker et al. (3). The methyl ester was eluated with 80 ml benzene (I fraction). The remaining part of the sample in the column was completely eluated with 50 ml ether (II fraction). After removal of ether from fraction II it was tested qualitatively for the presence of halogen by the Beilstein test. Dihydroxy acids were isolated and determined as follows.

The residue was refluxed for 1 hr with 30 cc of 0.5 N alcoholic KOH, converted to free acids with dilute sulfuric acid, extracted three times with 25 cc of ethyl ether, and the ether extract washed until neutral. The ether extract, which contained some insoluble dihydroxy acids was distilled to remove the ether. The residue was treated with five times its weight of petroleum ether, refluxed for 20 min, filtered hot, and washed with 10 cc of petroleum ether. The precipitate was dried and weighed as dihydroxy acid.

The methyl esters obtained were identified by their IR spectra (max. at 1710 cm^{-1} for the keto group and 1745 cm^{-1} for the ester group) as well as by means of elementary analysis and analysis of the semicarbazone of the corresponding ketoacids. Other data were also obtained as follows:

1. a) Methyl 9(10)-ketostearate, $C_{19}H_{36}O_3$ (312.5), mp 38–41C (literature values (8), methyl 9-ketostearate, mp 47.5C; methyl 10-ketostearate, mp 46C); n_D^{40} = 1.4425; Anal. Calc'd: C = 73.0; H = 11.54; found: C = 72.65; H = 11.56.

b) 9(10)-ketostearic acid, mp 66–69C (literature values (2) mp 66–69C); semicarbazone, $C_{19}H_{37}O_3N_3$ (355.5), mp 101–103C; Anal. Calc'd: N = 11.80; found: N = 11.65.

2. a) Methyl 6(7)-ketostearate, $C_{19}H_{36}O_3$ (312.5), mp 37–40C (literature values (8), methyl 6-ketostearate, mp 46.5C, methyl 7-ketosterate, mp 49.0C); n_D^{40} = 1.4428. Anal. Calc'd: C = 73.0; H = 11.54; found: C = 72.75; H = 11.50.

b) 6(7)-ketostearic acid, $C_{18}H_{34}O_3$ (298.5), mp

TABLE I

No.	Molar ratio $HgSO_4$/I	Conc of H_2SO_4 (N)	Time, hr	Temp, C	Product composition		
					Methyl 9(10)-keto stearate	Methyl 9,10-dihydroxy stearate	Other compounds
1	.....	0.5	3	70	12	....	88[a]
2	.....	5.0	3	70	8	....	92[a]
3	2:1	....	3	70	67	21	12[a]
4	2:1	....	10	22	62	19	19[a]
5	2:1	0.05	3	70	75	12	13
6	1:1	0.5	3	70	80	....	20[a]
7	2:1	0.5	3	70	94	....	6
8	3:1	0.5	3	70	93	....	7
9	2:1	5.0	3	70	85	....	15
10	2:1	0.5	6	22	60	....	40[a]
11	2:1	0.5	10	22	93	....	7
12	2:1	0.5	12	22	95	....	5

[a] The products contained halogen.

67–70C (literature values (8), 6-ketostearic acid, mp 87.0C; 7-keto stearic acid, mp 83.0C); semicarbazone, $C_{19}H_{37}O_3N_3$ (355.5), mp 100–102C; Anal. Calc'd: N = 11.80; found: N = 11.60.

3. a) Methyl 13(14)-ketobehenate, $C_{23}H_{44}O_3$ (368.6), mp 50–53C; n_D^{60} = 1.4390; Anal. Calc'd: C = 75.15; H = 12.06; found: C = 75.02; H = 11.85.

b) 13(14)-ketobehenic acid, $C_{22}H_{42}O_3$ (354.6), mp 81–85C (literature values (8), 14-ketobehenic acid, mp 84.5C); semicarbazone, $C_{23}H_{45}O_3N_3$ (411.6), mp 104–105C; Anal. Calc'd: N = 10.20; found: N = 10.10.

The dihydroxy acids obtained were identified by their melting points and by analysis as follows:

1. 9,10-dihydroxy stearic acid, $C_{18}H_{36}O_4$ (316.5), mp 129–131C (literature value (8) 131C); Anal. Calc'd: C = 68.40; H = 11.40; found: C = 68.20; H = 11.35.

2. 6,7-dihydroxystearic acid, $C_{18}H_{36}O_4$ (316.5), mp 122–124C (literature value (9) 124C) Anal. Calc'd: C = 68.40; H = 11.40; found: C = 68.25; H = 11.40.

3. 13,14-dihydroxybehenic acid, $C_{22}H_{44}O_4$ (374.6), mp 130–132C (literature value (10), 132C). Anal. Calc'd: C = 70.63; H = 11.74; found: C = 70.40; H = 11.60.

Procedures

Reaction of Methyl Esters of Halogen Hydroxy Fatty Acids with Mercuric Sulfate

The amount of 4.00 g (0.00908 mole) of I or II (or 3.70 g of III, 3.56 g of IV and 3.17 g of V, respectively) was dissolved in 100 ml of 0.5 N sulfuric acid (in absolute methanol). 5.40 g (0.01816 mole) mercuric sulfate was added to the solution. The mixture was refluxed for 3 hr (with III, 3 hr; IV, 5 hr; V, 7 hr) or stirred at room temperature for 10–12 hr (III, 10–12 hr; IV, 18 hr; V, 24 hr), then filtered using a Büchner funnel. The precipitate was washed with ether and the filtrate transferred to a separatory funnel, diluted with water and extracted with ether. The ether extract was washed with water until neutral reaction, then passed to an Erlenmeyer flask and saturated over a 20-min period with hydrogen sulfide until the complete removal of the mercuric ions from the solution. The latter was filtered to remove the mercuric sulfide, the precipitate was extracted with ether, and the mixture was repeatedly washed with a solution of potassium iodide (10%), then with water. It was subsequently dried with sodium sulfate, after which the ether was distilled off. The following crude products were obtained: 2.70 g of I; 2.70 g of II; 2.65 g of III; 2.65 g of IV; 2.60 g of V. All products contained methyl ketostearate (92–95%) but no dihydroxy acids. The above procedure was varied by changing some of the reaction conditions using methyl 9(10), 10(9)-iodohydroxy stearate as a model compound. The results are given in Table I.

Reaction of Methyl 9(10), 10(9)-iodohydroxy Stearate (I) with Silver Nitrate

4.00 g (0.00908 mole) of I dissolved in 100 ml of 0.5 N nitric acid (methanol) was added to 3.10 g (0.01816 mole) of silver nitrate. The mixture was refluxed for 3 hr or stirred at room temperature for 10–12 hr, then filtered on a Büchner funnel. The precipitate was washed with ether, diluted with water and extracted with ether, then washed with water until a neutral reaction was given and dried over sodium sulfate, after which the ether was removed by distillation. Yield: 2.80 g of crude product with the following composition: methyl ketostearate (65–66%), dihydroxy stearic acid (16–18%) and a residue of approximately 15–20%. This procedure was repeated with variations in time, temperature, or the silver nitrate/methyl iodohydroxy ester ratio. The results are given in Table II.

Results and Discussion

Direct conversion of methyl esters of halogen hydroxy fatty acids into the corresponding keto acids

TABLE II

No.	Molar ratio $AgNO_3$/I	Conc of HNO_3 (N)	Time, hr	Temp, C	Product composition		
					Methyl 9(10)-keto stearate	Methyl 9,10-dihydroxy stearate	Other compounds
1	.....	0.5	3	70	12	....	88[a]
2	.....	5.0	3	70	10	....	90[a]
3	2:1	0.5	3	70	57	15	28[a]
4	1:1	0.5	3	70	55	13	32[a]
5	2:1	0.5	3	70	65	18	17
6	3:1	0.5	3	70	63	19	18
7	2:1	0.5	6	22	47	11	42[a]
8	2:1	0.5	10	22	65	16	19
9	2:1	0.5	12	22	66	16	18

[a] The product contained halogen.

is achieved using mercuric sulfate in the presence of sulfuric acid. When increasing the concentration of sulfuric acid in the solution, the yield of keto acid decreases (See experiment 9, Table I). Decrease in the concentration of sulfuric acid entails not only a decrease in the yield of keto acid but the formation of dihydroxy acid as well (Experiment No. 5, Table I). This is, perhaps, associated with the formation of mercuric oxide from the mercuric sulfate (when the sulfuric acid in the solution is insufficient). The mercuric oxide favors the formation of dihydroxy acid. This has been established by King (1).

An analogous reaction using silver nitrate in the presence of nitric acid always leads to the formation of dihydroxy acid (Table II). The highest yield of methyl 9(10)-ketostearate (65%) was obtained after boiling of the reaction mixture for 3 hr using the molar ratio silver nitrate/iodohydroxy stearic acid = 2:1 or employing the same molar ratio and stirring the reaction mixture at room temperature for 10–12 hr.

The conditions ensuring the highest yields of methyl 9(10)-ketostearate (when mercuric sulfate is employed as shown in Table I, experiments 7 and 12) were used for the preparation of methyl 6(7)-ketostearate and methyl 13(14)-ketobehenate from the corresponding iodohydroxy derivatives of the methyl esters of the petrolesilinic and erucic acids as well as for the conversion of methyl 9(10), 10(9)-chloro- and 9(10), 10(9)-bromohydroxy stearates into methyl 9(10)-ketostearate. We have established that the extent of conversion of the halogen hydroxy acids into keto acids is independent of the halogen atom position in the molecule. The yield depends, however, on the kind of halogen atom. This gave us the possibility of preparing the keto esters from the corresponding iodohydroxy derivatives most easily (in high yields: $\sim$ 90%). Under the same conditions, the conversion of methyl 9(10), 10(9)-chlorohydroxy stearate reached 60–65%, and that of 9(10), 10(9)-bromohydroxy stearic acid, 75–80%. This was not unexpected since the strength of bonding between the halogen atom and the molecule of the halohydrin decreases in the order chloro-, bromo- iodohydroxy derivatives due to the increase in atomic weight of the halogen atom. To obtain higher yields (above 90%) of methyl keto stearate from the above chloro- or bromohydroxy derivatives, we had to prolong the reaction: 7 hr boiling or 24 hr stirring at room temperature for the chloroderivatives and 5 hr boiling or 18 hr stirring for the bromoderivative.

In conclusion, it should be pointed out that partial formation of methyl ketostearate is also observed when boiling the iodohydroxy derivatives alone in acid medium in the absence of mercuric sulfate (silver nitrate). The yield is, however, negligible (see experiments No. 1 and 2 in Tables I and II). It amounts to approximately 10% and is not influenced by the concentration of the acid used.

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