Studies on the Hypohalogenation of Long Chain α,β-Unsaturated Acids

ASHFAQUE A. ANSARI, FASIH AHMAD, and **S.M. OSMAN,**
Department of Chemistry, Aligarh Muslim University, Aligarh, India

ABSTRACT

As a result of hypohalogenation, a series of *erythro* 2(3)-halo-3(2)-hydroxy derivatives of C_{16}, C_{18} and C_{22} α, β-unsaturated acids have been prepared. The structures of the individual isomers were established by chemical and spectral methods. The major products were shown to be 2-halo-3-hydroxy alkanoic acids. Unlike internal halohydrins, the isomeric mixture of these derivatives of long chain α, β-unsaturated acids was successfully resolved by column chromatography.

INTRODUCTION

Reactions of long chain α, β-unsaturated fatty acids have received only limited study. Studies on hypohalogenation of fatty acids have been confined to the geometric pairs of C_{18} (oleic-elaidic [1-3], petroselinic-petroselaidic [4]) and C_{22} (erucic-brassidic [5]) olefinic acids. These investigations were aimed at explaining the configurational relationships that exist in the epoxy-, dihydroxy-, and halohydroxy acids. Although the chloro-, bromo-, and iodohydroxy derivatives of C_{18} and C_{22} unsaturated acids containing internal double bonds have been prepared in crystalline state, the product is always an inseparable mixture of two positional isomers, i.e., 9(10)-chloro-10(9)-hydroxystearic and 13(14)-chloro-14(13)-hydroxybehenic acids. The present work on the hypohalogenation of α, β-unsaturated acids was undertaken for two reasons. Firstly, there appeared to be no mention in the literature of the reactions of hypohalous acids on these compounds. Secondly, the earlier reports about the inseparability of the mixture of isomeric halohydrins suggested that the location of halohydroxy functions in the middle of the fatty acid chain may result in the formation of an eutectic mixture not separable by fractional crystallization or chromatography. It was therefore anticipated that if the olefinic bond was very close to the carboxyl function, the influence of carboxyl on the halohydroxy groups of the halohydrins would markedly affect their polarity, thereby enabling them to be separable chromatographically. This paper describes the first preparation of a series of chloro-, bromo, and iodohydrins from *trans*-2-hexadecenoic, -octadecenoic, and -docosenoic acids, and the establishment of their structures by chemical and spectral studies.

EXPERIMENTAL PROCEDURES

All the melting points are uncorrected. Infrared (IR) spectra were obtained with a Perkin-Elmer 221 spectrophotometer with CCl_4. Nuclear magnetic resonance (NMR) spectra were run in $CDCl_3$ on a Varian A60 NMR spectrometer with trimethylsilane (TMS) as the internal standard. Mass spectra were measured with an AEI MS-902 mass spectrometer using a direct insertion sample inlet system. Thin layer chromatographic plates were coated with Silica Gel G, and a mixture of petroleum ether:ether:acetic acid (80:20:1, v/v) was used as developing solvent. The spots were visualized by spraying with 50% chromic acid and subsequent heating.

MATERIALS AND METHODS

trans-2-Enoic acids of C_{16}, C_{18}, and C_{22} chain length were prepared according to the procedure of Palameta and Prostenik (6). The 2-enoic structure of the three parent acids and their geometry were established by IR, NMR, and mass spectrometry (7).

Hypochlorination of C_{16}, C_{18}, and C_{22} *trans*-2-Enoic Acids

The isomeric mixture of *erythro* 2(3)-chloro-3(2)-hydroxy acids of the three series of α, β-unsaturated acids were prepared according to the procedure of King (3).

General procedure: A 2% aqueous solution of the potassium salt of the appropriate *trans*-2-enoic acid (2.0 g) containing a 4% solution of potassium carbonate (50 ml) was cooled below 10 C and chlorine gas passed into the solution for 6 hr with occasional shaking. Excess of hypochlorous acid, formed in situ, was destroyed with 10% aqueous sodium thiosulphate solution and then acidified with 50% hydrochloric acid. The resulting product was extracted with ether, washed, and dried. After evaporation of the solvent, a pale yellow solid (2.2 g) was obtained which showed two distinct spots on a thin layer chromatographic (TLC) plate.

Separation of isomeric erythro 2(3)-chloro-3(2)-hydroxy esters: The mixture of chlorohydroxy acids (2.2 g) was methylated by heating for 4 hr with anhydrous methanol (15 ml) in the presence of a catalytic amount of sulphuric acid. After the usual work-up, the mixture of methyl 2(3)-chloro-3(2)-hydroxy esters was passed over a column of Silica Gel G and eluted successively with a mixture of petroleum ether:ether (85:15 and 70:30, v/v). The TLC monitored fractions were combined and rechromatographed to give pure TLC homogenous samples of the individual isomers of chlorohydroxy esters. The yields of 2-chloro-3-hydroxy (2a, b, and c) and 3-chloro-2-hydroxy (3a, b, and c) derivatives were ca. 60% and 20%, respectively. The melting points and elemental analyses of each isomer are given in Table I.

Dechlorination of chlorohydroxy esters: The individual isomers of 2(3)-chloro-3(2)-hydroxy esters were dechlorinated by the method of Jungermann and Spoerri (8) to give the corresponding 2(3)-hydroxy alkanoic esters.

To the solution of chlorohydroxy ester (0.8 g) in 50 ml of glacial acetic acid, zinc amalgam (3.0 g) was added and the mixture refluxed for 6 hr and filtered. Dilution of the filtrate precipitated a solid which was extracted with ether, washed, and dried. Evaporation of ether gave a solid (0.6 g) which on crystallization from ethanol yielded a crystalline compound which was characterized as the 2- or 3-hydroxy alkanoic ester.

Each of the methyl 2-chloro-3-hydroxy derivatives (2a, b, and c) on dechlorination yielded the corresponding methyl 3-hydroxyhexadecanoate, -octadecanoate, and -docosanoate (8a, b, and c), which melted at 57, 61, and 70 C, respectively. On the other hand, the methyl 3-chloro-2-hydroxy compounds (3a, b, and c) on similar treatment gave the corresponding 2-hydroxy esters (9a, b, and c) melting at 60, 66, and 74 C, respectively. Co-chromatography of the hydroxy esters with the authentic samples gave a single spot, and mixed melting points were found to be undepressed. All the 2- and 3-hydroxy esters of C_{16}, C_{18}, and C_{22} acids showed IR (KBr) bands at 3,400-3,500 cm^{-1} characteristic of hydroxyl absorption.

Hypobromination of *trans*-2-Enoic acids

As a general method, 50 ml of sodium hypobromite

TABLE I

Carbon, Hydrogen Analysis of 2(3)-Halo-3(2)-Hydroxy Esters of C_{16}, C_{18}, and C_{22} α, β-Unsaturated Acids

Compound code	Formulae	Melting point (C)	C (%)		H (%)		X (%)	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
2a	$C_{17}H_{33}O_3Cl$	Liquid	63.76	63.71	10.31	10.30	10.93	10.90
3a		42	63.76	63.74	10.31	10.28	10.93	10.88
2b	$C_{19}H_{37}O_3Cl$	40	65.51	65.48	10.63	10.61	10.06	10.02
3b		57	65.51	65.46	10.63	10.58	10.06	10.00
2c	$C_{23}H_{45}O_3Cl$	55	68.31	68.26	11.14	11.11	8.66	8.61
3c		72	68.31	68.28	11.14	11.10	8.66	8.63
4a	$C_{17}H_{33}O_3Br$	Liquid	54.52	54.50	9.14	9.10	22.09	22.05
5a		45	54.52	54.48	9.14	9.12	22.09	22.03
4b	$C_{19}H_{37}O_3Br$	41	58.90	58.86	9.54	9.50	20.34	20.30
5b		58	58.90	58.88	9.54	9.52	20.34	20.32
4c	$C_{23}H_{45}O_3Br$	59	61.48	61.44	9.92	9.90	18.00	17.98
5c		74	61.48	61.42	9.92	9.88	18.00	17.96
6a	$C_{17}H_{33}O_3I$	Liquid	49.61	49.58	8.21	8.18	30.83	30.80
7a		49	49.61	49.57	8.21	8.17	30.83	30.78
6b	$C_{19}H_{37}O_3I$	43	51.81	51.75	8.41	8.37	28.87	28.85
7b		64	51.81	51.78	8.41	8.39	28.87	28.81
6c	$C_{23}H_{45}O_3I$	62	55.64	55.58	8.87	8.83	25.82	25.80
7c		75	55.64	55.60	8.87	8.85	25.82	25.78

(0.35 M) was added to the potassium salt of *trans*-2-enoic acid (2.5 g) in 100 ml water. The solution was then kept at room temperature for 2 hr with occasional shaking. The solution was acidified with dilute sulphuric acid, any excess of bromine was destroyed with sodium sulphite solution, and the product was extracted with ether. Subsequent evaporation of the ether gave a mixture of *erythro* 2(3)-bromo-3(2)-hydroxy acids (2.8 g).

The mixture of bromohydroxy acids was esterified by heating with an excess of anhydrous methanol in the presence of acidic catalyst (H_2SO_4). The esters were then fractionated into two components, 2-bromo-3-hydroxy (4a, b, and c, 40%) and 3-bromo-2-hydroxy (5a, b, and c, 15%) esters by column chromatography using petroleum ether and ether as eluents. Each individual isomer (Table I) showed a positive test for bromine and had characteristic IR absorptions (CCl_4) at 3,400-3,500 (Br, OH) and 800-715 cm^{-1} (C-Br) (9).

Debromination of bromohydroxy esters: The *erythro* 2(3)-bromo-3(2)-hydroxy derivatives of C_{16}, C_{18}, and C_{22} *trans*-2-enoic acids were subjected to debromination by a procedure similar to that of dechlorination. The corresponding 2-hydroxy and 3-hydroxy alkanoic esters had the same melting points and IR absorptions as reported earlier in the dechlorination procedure.

Hypoiodination of *trans*-2-Enoic Acids

The *erythro*-2(3)-iodo-3(2)-hydroxy acids of the three *trans*-2-enoic acids were prepared following the procedure of Conforth and Green (10).

trans-2-Enoic acid (4.0 g) was dissolved in ethanol (50 ml) and treated with iodine (2.6 g), potassium iodate (1.08 g), water (75 ml), and concentrated sulphuric acid (1 ml). After keeping for 8 hr at room temperature, the mixture was extracted with ether, washed, and dried. Evaporation of the solvent gave an isomeric mixture of 2(3)-iodo-3(2)-hydroxy acids (4.4 g) as a yellow product. The methyl esters of iodohydroxy acids were fractionated by column chromatography to afford the individual isomers, i.e., methyl 2-iodo-3-hydroxy (6a, b, and c, 40%) and methyl 3-iodo-2-hydroxy (7a, b, and c, 15%) derivatives. Each of the iodohydrins (Table II) showed IR absorption (CCl_4) at 3,400-3,500 (OH) and 820-710 cm^{-1} (C-I) (9).

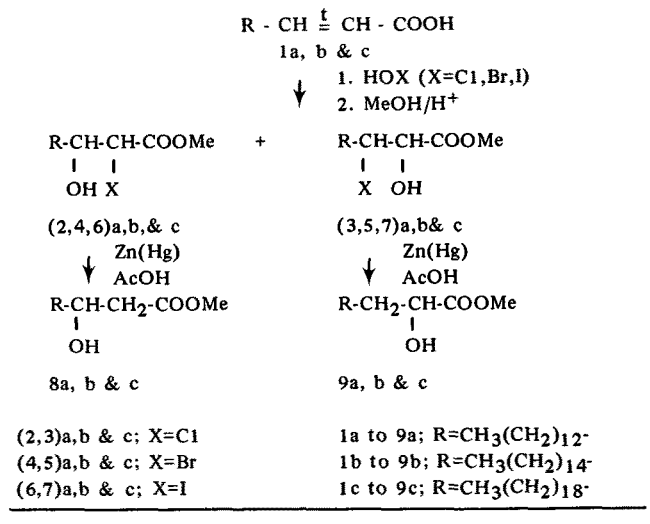
Deiodination of iodohydroxy derivatives: The individual isomers, methyl iodohydroxy alkanoic esters, were subjected to dehalogenation as described earlier. The corresponding 2-hydroxy and 3-hydroxy alkanoic esters were found to possess identical melting points, IR spectra, and TLC mobility similar to those of the 2- and 3-hydroxy esters obtained during the dechlorination of the chlorohydroxy derivatives.

RESULTS AND DISCUSSION

In continuation of our earlier study (7) on the 2,3-diols of long chain α, β-unsaturated acids, the present work describes the results (Scheme 1) of the reaction of hypohalous acids with C_{16}, C_{18}, and C_{22} *trans*-2-enoic acids. The mixture of isomeric halohydrins has been successfully separated by column chromatography. Some observations regarding the separability of the isomeric mixture of halohydrins by chromatography and their spectral data are discussed below.

The *erythro* 2(3)-chloro-3(2)-hydroxy derivatives of the three *trans*-2-enoic acids were prepared by the method of King (3).

SCHEME I



trans-2-Docosenoic acid (1c) on hypochlorination afforded a yellowish product which showed two distinct

TABLE II

Spectral Data for 2(3)-Halo-3(2)-Hydroxy Esters[a]

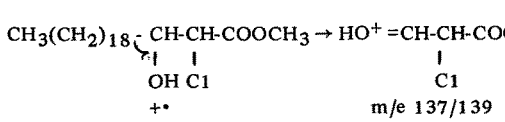
Compound code	IR(cm^{-1})			NMR (τ)		
	OH	C=O(ester)	C-X	-CH-OH	-CH-OH	CH-X
2a	3450	1740	820	7.1	5.85	5.15
3a	3525	1750	800	7.0	5.90	5.00
4a	3500	1740	800	7.2	5.85	5.30
5a	3525	1745	800	7.0	5.95	5.10
6a	3450	1745	730	7.2	5.90	5.60
7a	3525	1750	715	7.1	5.80	5.55
2b	3450	1730	730	7.2	5.88	5.60
3b	3475	1735	720	7.2	5.90	5.50
4b	3450	1740	725	7.2	5.95	5.60
5b	3500	1745	720	7.2	5.85	5.55
6b	3450	1735	730	7.4	5.90	5.60
7b	3500	1740	720	7.3	5.80	5.55
2c	3525	1740	750	7.1	5.85	5.15
3c	3570	1750	820	7.0	5.90	5.00
4c	3450	1735	720	7.2	5.80	5.60
5c	3500	1745	715	7.2	5.85	5.50
6c	3400	1735	720	7.3	5.80	5.60
7c	3425	1740	710	7.2	5.75	5.55

[a]From infrared (IR) spectra it is obvious that 2-halo-3-hydroxy derivatives show a greater degree of hydrogen bonding as anticipated than the corresponding 3-halo-2-hydroxy esters. In the nuclear magnetic resonance (NMR) spectra, the signals of protons attached to chlorine and hydroxyl containing carbons appeared as unresolved multiplets. The methine signals of -CH-Cl appeared downfield, which may be attributed to the deshielding effect of chlorine substituents.

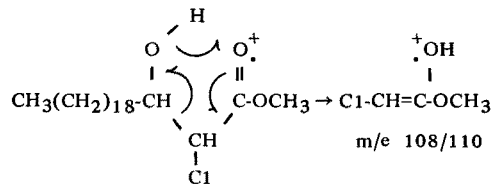
spots on a TLC plate. Chromatographic resolution of its methyl esters yielded two crystalline solids, the major one (2c) melting at 55 C and the minor one (3c) at 72 C. The chlorohydroxy structures of the products 2c and 3c were deduced from the combustion data (Table I) and IR and NMR spectra (Table II) of the pure compounds.

To assign definite positions to the chloro and hydroxyl functions in the two methyl chlorohydroxydocosanoates, each isomer was converted by an unequivocal method (dechlorination by amalgamated zinc) (8) to the corresponding hydroxy esters. Thus, compounds 2c and 3c on dechlorination yielded two methyl hydroxydocosanoates melting at 70 C and 74 C, respectively. The hydroxy esters were subsequently identified as methyl 3-hydroxy and methyl 2-hydroxydocosanoates (8c and 9c) by comparison of the TLC mobility, mixed melting points, and IR spectra of the authentic samples. Taken together, these data clearly established that the low melting product is *erythro* methyl 2-chloro-3-hydroxydocosanoate (2c) and the high melting isomer possesses the structure corresponding to *erythro* methyl 3-chloro-2-hydroxydocosanoate (3c).

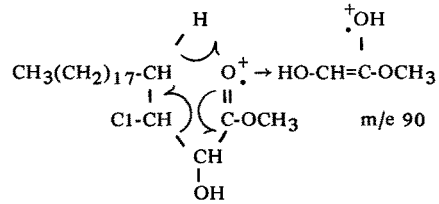
The above structures of 2c and 3c were further supported by the mass spectra of isomeric chlorohydroxy esters. The mass spectrum (Fig. 1) of methyl 2-chloro-3-hydroxydocosanoate 2c showed no molecular ion peak (M^+) at m/e 403/405, but showed the expected peaks at m/e 369 (M-Cl), 309 (369-$C_2H_4O_2$), and 253 (281-C_2H_4). The spectrum is dominated by chlorine-containing doublets at m/e 137/139 and m/e 108/110 (peak at m/e 108 almost equal in intensity to the base peak m/e 43). The appearance of ion peaks at m/e 137/139 is expected to originate from the fragmentation indicated below.



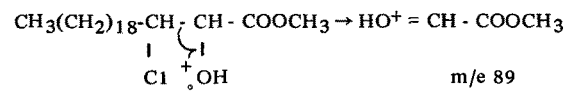
The strong peaks at m/e 108/110 could be explained by a McLafferty rearrangement involving a six-membered hydrogen bonded species as shown below:



The other isomeric derivative, methyl 3-chloro-2-hydroxydocosanoate 3c, also showed no molecular ion peak (M^+) in its mass spectrum (Fig. 2). The spectrum displayed the same fragmentation pattern as that of 2-chloro-3-hydroxy isomer. The two major structure revealing peaks were observed at m/e 90 (relatively of medium intensity as compared to base peak at m/e 43) and at m/e 89 of low intensity. The appearance of ion peak at m/e 90 of medium intensity could be due to the lack of hydrogen bonding and McLafferty rearrangement as shown below:



The ion peak at m/e 89 may arise due to the fragmentation indicated below:



Thus, the mass spectral data supported the structures of isomeric chlorohydroxy acids assigned on the basis of chemical, IR, and NMR studies.

The C_{16} and C_{18} *trans*-2-enoic acids were also subjected to hypochlorination. The mixtures of isomeric methyl 2(3)-chloro-3(2)-hydroxyhexadecanoates and -octadecanoates were separated and the individual isomers characterized by following the same procedure as outlined above (Scheme 1).

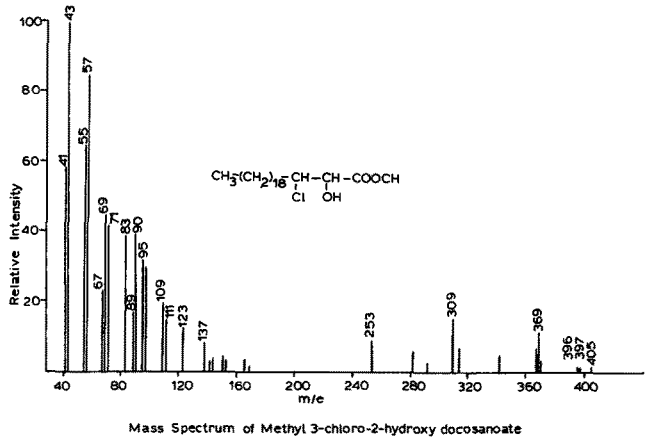


FIG. 1. Mass spectrum of methyl 2-chloro-3-hydroxy docosanoate.

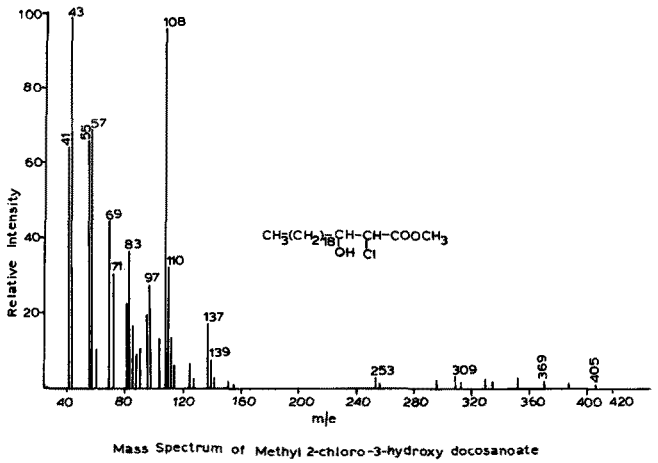


FIG. 2. Mass spectrum of methyl 3-chloro-2-hydroxy docosanoate.

Hypobromination of all the three C_{16}, C_{18}, and C_{22} α, β-unsaturated acids was carried out according to the procedure of King (3). The 2(3)-iodo-3(2)-hydroxy derivatives of the three acids were prepared following the method of Conforth and Green (10). In each case the product obtained by the hypohalogenation gave two distinct spots on an analytical TLC plate. The mixture of isomeric 2(3)-halo-3(2)-hydroxy acids after methylation was resolved into two chromatographically homogenous products by column chromatography. The structures of the separated halohydrins were then established by characterization of the hydroxy acids obtained by dehalogenation. Thus, the 2-halo-3-hydroxy esters of *trans*-2-hexadecenoic,-octadecenoic, and -docosenoic acids on dehalogenation yielded the corresponding 3-hydroxy esters. On the other hand, the 3-halo-2-hydroxy esters on similar treatment gave the respective 2-hydroxy esters. The assignment of structures to the individual halohydroxy esters was further supported by the IR and NMR spectra of the pure compounds (Table II).

A few comments regarding the observations described above are worth mentioning. The amenability of the isomeric mixture of the 2(3)-halo-3(2)-hydroxy esters to chromatographic separation can be ascribed to the effect of the ester group on the polarity of the halohydroxy function.

The effect of the ester carbonyl on the adjacent halohydroxy function is clearly discernible in the separability of isomeric halohydrins by column chromatography. Unlike halohydrins of internal double bonds, the polarity of 2(3)-halo-3(2)-hydrins is greatly affected by the adjacent ester carbonyl group. The separability of these isomeric halohydrins can be possibly explained by effective intramolecular hydrogen bonding between C_3-OH and ester carbonyl function (7). These assumptions find support in the IR spectra of the isomeric halohydrins (Table II), where chelation is much more pronounced in 2-halo-3-hydroxy esters. Also, the carbonyl frequency of ester carbonyl group decreases as is expected. Hence, the internal halohydrins resist resolution whereas the 2(3)-halo-3(2)-hydrins are easily separable on chromatography.

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