601. *Aliphatic Acids. Part III.*[1] *The Preparation and Some Reactions of Halogenohydroxy-acids.*

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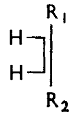
The preparation of isomeric pairs of *erythro-* and *threo*-6,7(7,6)- and -9,10(10,9)-chloro-, -bromo-, and -iodo-hydroxyoctadecanoic, and 13,14(14,13)-chloro-, -bromo-, and -iodo-hydroxydocosanoic acids is described, together with a study of their oxidation and the oxidation products. The reduction of these halogeno-oxo-acids with hydriodic acid and with sodium borohydride is also reported. The formation of *vic*-dioximes from the α-chloro- and α-bromo-oxo-acids is described.

Apart from King's work [2] on the halogenohydroxy-acids derived from *cis-* and *trans*-octadec-9-enoic acids, scant attention has been paid to the study of halogenohydrins of long-chain unsaturated acids. We have investigated this problem, and for comparison repeated King's work,[2] extending our studies to the halogenohydrins derived from *cis-* and *trans*-octadec-6-enoic and -docos-13-enoic acid.

[1] Part II, Julietti, McGhie, Rao, Ross, and Cramp, *J.*, 1960, 4514.
[2] King, *J.*, 1949, 1817.

Only two routes of preparative importance are available for the preparation of halogenohydroxy-acids. One involves the direct addition of the appropriate hypohalous acid to the olefinic acid.[2,3] Such addition is known to be *trans*:[4] the *cis*-olefin (I) gives the *threo*-halogenohydrin (II), whereas the *trans*-isomer (III) affords the *erythro*-halogenohydrin (IV) under similar conditions.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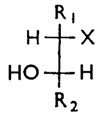
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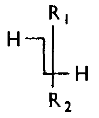
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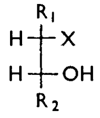
(IV)

[X = Halogen]

In King's experiments[2] the yields fall in the order Cl > Br > I. Also side reactions lead to ester acids and dihalides, the latter formed by nucleophilic attack of halide ion on the intermediate onium ion. In the preparation of the iodohydrins from *cis*- and *trans*-octadec-9-enoic acids King also isolated a mixture of 9(10)-oxo-octadecanoic acids. From our results the formation of such acids can be explained by oxidation of the initially formed iodohydrin to the iodo-ketone; the latter is then reduced to the ketone, a reaction which may well involve the solvent, or alternatively hydriodic acid which is almost certainly present. This is discussed more fully below.

The second route to halogenohydroxy-acids involves ring fission of an epoxide by the appropriate halogen acid;[2,5] it has been used throughout the present investigation, since in our experience undesirable side reactions are reduced to a minimum and very pure halogenohydrins are obtained in excellent yields. Current knowledge of epoxidation[5,6] and the fission of epoxide rings[7] indicates that *cis*- (I) and *trans*-olefins (III) will give *threo*- and *erythro*-halogenohydrins respectively, as in the direct addition of the hypohalous acid. The 9(10)-halogeno-10(9)-hydroxyoctadecanoic acids obtained from the epoxides had constants in good agreement with those reported by King[2] and by other workers,[5,8,9] as shown in Table 1. The only serious discrepancy is the value for *erythro*-9(10)-bromo-10(9)-hydroxyoctadecanoic acid. The melting point reported, 70—71°, is close to that of a 2 : 3 mixture of 9(10)-oxo-octadecanoic acids,[10] and we suggest that in this particular case, like that of the iodohydrins, some bromo-ketone was formed and on reductive elimination of bromine afforded a mixture of 9(10)-oxo-octadecanoic acids.

TABLE 1.

	threo		*erythro*	
Octadecanoic acids	M. p.	Lit.[2, 5, 8, 9]	M. p.	Lit.[2, 5, 8, 9]
9(10)-Chloro-10(9)-hydroxy- ...	35—41°	35°, 39—40°, 38—41°	53—58°	50°, 58—58·8°, 52—57°
9(10)-Bromo-10(9)-hydroxy- ...	16—18	15—18·5	56—58	70—71, 53—55
9(10)-Iodo-10(9)-hydroxy-	Oil	Oil	48—54	54—60, 64·5—65·5

The first report[11] of halogenohydroxy-derivatives from *cis*- and *trans*-octadec-6-enoic acids appeared when our work had been completed;[12] the two sets of results are included

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[3] Albitzky, *J. Russ. Phys. Chem. Soc.*, 1899, **31**, 76; 1902, **34**, 788; *J. prakt. Chem.*, 1900, **61**, 65; Nicolet and Poulter, *J. Amer. Chem. Soc.*, 1930, **52**, 1186; Naudet and Desnuelle, *Bull. Soc. chim. France*, 1950, 845.

[4] de la Mare, *Quart. Rev.*, 1949, **3**, 126, and references therein.

[5] Swern, *J. Amer. Chem. Soc.*, 1948, **70**, 1235.

[6] Witnauer and Swern, *J. Amer. Chem. Soc.*, 1950, **72**, 3364; Braun, *ibid.*, 1929, **51**, 228.

[7] Kuhn and Ebel, *Ber.*, 1925, **59**, 919; Böeseken, *Rec. Trav. chim.*, 1928, **47**, 683; Esafor, *J. Gen. Chem., U.S.S.R.*, 1937, **7**, 1403; Wilson and Lucas, *J. Amer. Chem. Soc.*, 1936, **58**, 2396.

[8] Atherton and Hilditch, *J.*, 1943, 204.

[9] Morrell and Phillips, *J. Soc. Chem. Ind.*, 1940, **59**, 147.

[10] Grey, McGhie, and Ross, *J.*, 1960, 1502.

[11] Farooq, Osman, and Siddiqui, *Rec. Trav. chim.*, 1961, **80**, 415.

[12] Cramp, Thesis, London, 1958.

in Table 2. The isomeric 6(7)-halogeno-7(6)-hydroxyoctadecanoic acids are sparingly soluble in hexane at 0°, the *threo*-isomers being the more soluble; they are converted by 0·1N-sodium hydroxide at room temperature into the respective 6,7-epoxyoctadecanoic acids from which they were derived.

TABLE 2.

	threo		*erythro*	
Octadecanoic acids	M. p.	Lit.[11]	M. p.	Lit.[11]
6(7)-Chloro-7(6)-hydroxy-	62—64°	59—60°	43—45°	55—56°
6(7)-Bromo-7(6)-hydroxy-	48—52	36—37	55—56	55—56
6(7)-Iodo-7(6)-hydroxy-	71—73	69—70	57—59	56—57

The ready availability of *cis*- and *trans*-13,14-epoxydocosanoic acids[1] caused us to investigate their reaction with halogen acids. Only scattered references to the 13(14)-halogeno-14(13)-hydroxydocosanoic acids appear in the literature. Our results are summarized in Table 3.

TABLE 3.

	threo		*erythro*	
Docosanoic acids	M. p.	Lit.	M. p.	Lit.
13(14)-Chloro-14(13)-hydroxy-	48°	47—48° [13, 14]	63—64°	62—63° [13, 14]
13(14)-Bromo-14(13)-hydroxy-	37	—	57	—
13(14)-Iodo-14(13)-hydroxy-	13—15	Oil [15]	38—40	—

Little attention has been paid to the oxidation of halogenohydrins to halogenoketones, and the latter have usually been obtained by halogenation of the appropriate ketone. We explored this oxidation. The only reports of halogenoketones derived from long-chain acids (apart from a patent reference[16]) are those of Myddleton *et al.*,[17] who obtained 9(10)-bromo-10(9)-oxo-octadecanoic and 13(14)-bromo-14(13)-oxodocosanoic acids as viscous oils. We first used chromic acid in acetic acid or *N*-bromosuccinimide for the oxidation but later found Kiliani's chromic acid in acetone more convenient,* and so obtained crystalline chloro- and bromo-ketones in high yields (see Table 4).

TABLE 4.

	M. p. of chloro-ketone		M. p. of bromo-ketone	
Parent acid	From *threo*-alcohol	From *erythro*-alcohol	From *threo*-alcohol	From *erythro*-alcohol
9(10)-Halogeno-10(9)-hydroxyoctadecanoic	40—47°	38—45°	41—45°	48·5—49·5°
6(7)-Halogeno-7(6)-hydroxyoctadecanoic...	52—55	52·5	52—53	52—54
13(14)-Halogeno-14(13)-hydroxydocosanoic	50—55	50—55	56—59	56·5—59·5

The racemic chloro- and bromo-ketones derived from any pair of isomeric *threo*- and *erythro*-halogenohydrins have similar melting points. The isomeric optically active *cis*- and *trans*-9,10-epoxyoctadecanoic acids, however, give chloro-ketones of m. p. 36—38·5°; $[\alpha]_D$ +1·8°, and m. p. 48—49°, $[\alpha]_D$ −33·5°, respectively.

The oxidation of the iodohydrins under similar conditions proved anomalous. The iodo-ketones were too labile for isolation, being rapidly converted into the saturated oxo-acids. This is not altogether unexpected, since it is well known, not only that iodo-ketones are readily reduced with loss of iodine affording the ketone, but also that attempts at dehydroiodination give the same result.[18]

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* We thank Dr. M. Rosenberger for the initial experiments.

[13] Bauer and Bähr, *J. prakt. Chem.*, 1929, **122**, 201.

[14] Hashi, *J. Soc. Chem. Ind., Japan*, 1936, **39**, 469B.

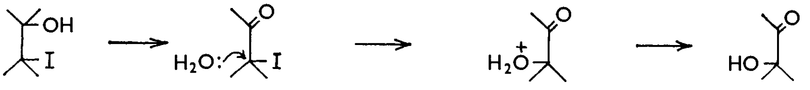
[15] Holde and Gorgas, *Ber.*, 1925, **58**, 1071.

[16] U.S.P. 2,396,969/1946.

[17] Myddleton and Barrett, *J. Amer. Chem. Soc.*, 1927, **49**, 2258; Myddleton, Berchem and Barrett *ibid.*, p. 2264; Myddleton, Barrett, and Seager, *ibid.*, 1930, **52**, 4405.

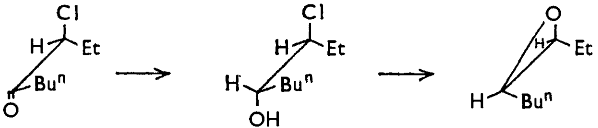
[18] Rosenkranz, Mancera, Gatica, and Djerassi, *J. Amer. Chem. Soc.*, 1950, **72**, 4077.

In one instance, oxidation of the isomeric iodohydrins derived from *cis*- and *trans*-octadec-6-enoic acids with *N*-bromosuccinimide afforded 6,7-dioxo-octadecanoic acid in poor yield. This might result from the ketol, which in turn would be further oxidised to the dioxo-acid. The formation of the ketol may be the result of a reaction sequence as illustrated.



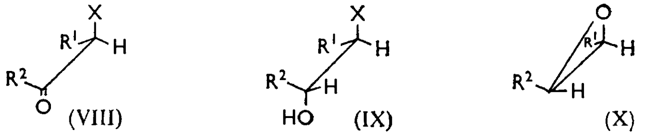
The halogeno-oxo-acids were readily reduced by hydriodic acid to the saturated oxo-acids;[17] thus 6(7)-chloro- and -bromo-7(6)-oxo-octadecanoic acid gave 6(7)-oxo-octadecanoic acid; 9,10-halogeno-10(9)-oxo-octadecanoic acids afforded 9(10)-oxo-octadecanoic acid; and 13(14)-chloro- and -bromo-14(13)-oxodocosanoic acids gave 13(14)-oxodocosanoic acid.

Although particular attention has been paid to the reduction of α-halogeno-ketones in the steroid field, little attention has been paid to aliphatic compounds apart from isolated examples. Recently, however, Cornforth and his collaborators[19] reduced 3-chloro-octan-4-one (V) with sodium borohydride to a chlorohydrin which with alkali afforded 3,4-epoxyoctane (VII) containing 80—85% of the *cis*-epoxide. Thus, the chlorohydrin must possess predominantly the *threo*-configuration (VI), and consequently the borohydride reduction must follow the course predicted by Cram's rule.[20]



(V) (VI) (VII)

We had already observed that the halogeno-ketones described above are reduced by sodium borohydride to, predominantly, the *threo*-halogenohydrin, that is converted by alkali into the oxides containing about 80% of the *cis*-epoxide. The interpretation of such reductions requires consideration of the nature and size of the groups attached to the asymmetric carbon atom α to the carbonyl group. The halogen atom, possessing the largest relative lateral diameter of the three substituents, results in the preferred conformation (VIII) for the halogenoketo-acids, which would result in predominant formation of the *threo*-halohydrin (IX) and of the *cis*-epoxide (X).



(VIII) (IX) (X) [X = Cl or Br]

We therefore studied the reduction of the 9(10)-chloro- and -bromo-10(9)-oxo-octadecanoic acids. Reduction of 9(10)-chloro-10(9)-oxo-octadecanoic acid, and treatment of the product with alkali, gave a product of m. p. 55° (m. p. 56—57° after recrystallization). From the melting point–composition curves due to Swern,[6] this corresponds to a product containing more than 75% of *cis*-9,10-epoxyoctadecanoic acid (more than 80% after recrystallization); this supports the hypothesis already presented. Similarly, the results obtained by the reduction of 6(7)-chloro- and -bromo-7(6)-oxo-octadecanoic and 13(14)-chloro- and -bromo-14(13)-oxodocosanoic acids indicate the formation of the respective *cis*-epoxides in a yield above 80%, the infrared spectra of the epoxides confirming the

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[19] Cornforth, Cornforth, and Mathew, *J.*, 1959, 112.

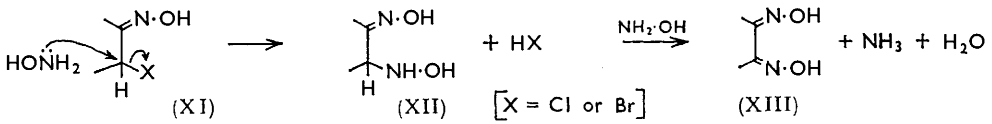
[20] Cram and Elhafez, *J. Amer. Chem. Soc.*, 1952, **74**, 5828.

melting point–composition curve data. Further support was obtained by using the optically active 9(10)-chloro-10(9)-oxo-octadecanoic acid, which afforded an epoxide, m. p. 55—57°, $[\alpha]_D$ +1·8°. Since pure *cis*- and *trans*-9,10-epoxyoctadecanoic acids have $[\alpha]_D$ +0·34° and $[\alpha]_D$ +23·6°, respectively, this indicates a *cis*-epoxide of 93·6% purity.

These experiments provide yet another route for the conversion of a *trans*- into the isomeric *cis*-epoxide.

An attempt to characterize these halogeno-ketones by reaction with hydroxylamine, led, not to the expected α-halogeno-oximes, but to dioximes, identical with those derived from the respective α-dioxo-acids. Thus, for example, 9(10)-chloro-10(9)-oxo-octadecanoic acid gave a dioxime identical with the known dioxime of 9,10-dioxo-octadecanoic acid. This result was not unexpected, since the original preparation of an oxime from hydroxylamine resulted from Meyer and Janny's study[21] of the action of hydroxylamine on 1,1-dichloroacetone, which afforded the dioxime of methyl glyoxal. More recently, Belcher *et al.*[22] have reported the preparation of *vic*-dioximes from α-bromo-ketones by their reaction with hydroxylamine. Here, as we observed, the yields of the dioximes were of the order 30—50%, even when a large excess of hydroxylamine was employed.

The results thus obtained may be explained by initial formation of the halogeno-oxime (XI) which then undergoes nucleophilic attack to form the hydroxylamine (XII),



and this is then oxidized to the *vic*-dioxime by a third molecule of hydroxylamine. This mechanism shows a formal similarity to that originally suggested by Fischer for osazone formation. We have observed the presence of ammonia formed in the reaction, which lends support to our suggestions.

EXPERIMENTAL

All known compounds were identified by direct comparison with authentic specimens. Melting points, unless otherwise stated, are uncorrected.

Chloro- and Bromo-hydroxy-acids.—The preparation of *threo*-9(10)-chloro-10(9)-hydroxy-octadecanoic acid is typical. *cis*-9,10-Epoxyoctadecanoic acid (3 g.), suspended in ether (100 ml.), was shaken with hydrochloric acid (6 ml.) for 30 min. The lower layer was removed, and the ether washed free from mineral acid; removal of the ether afforded an oil, which solidified on cooling. Crystallization from hexane gave *threo*-9(10)-chloro-10(9)-hydroxyoctadecanoic acid (2·9 g.) as needles, m. p. 35—41°.

By this procedure, with the same quantities of material, *cis*-9,10-epoxyoctadecanoic acid gave *threo*-9(10)-bromo-10(9)-hydroxyoctadecanoic acid (2·8 g.), m. p. 16—18°.

Similarly, *cis*-6,7-epoxyoctadecanoic acid afforded threo-6(7)-*chloro*-7(6)-*hydroxy*- (2·1 g.), m. p. 62—64° (Found: C, 64·1; H, 10·8; Cl, 10·7. $C_{18}H_{35}ClO_3$ requires C, 64·6; H, 10·5; Cl, 10·6%), and threo-6(7)-*bromo*-7(6)-*hydroxy-octadecanoic acid* (3·1 g.), m. p. 48—52° (Found: C, 57·3; H, 9·4; Br, 20·7. $C_{18}H_{35}BrO_3$ requires C, 57·0; H, 9·3; Br, 21·1%). *cis*-13,14-Epoxydocosanoic acid gave *threo*-13(14)-chloro-14(13)-hydroxy- (3·3 g.), m. p. 48° (Found: C, 67·8; H, 10·7; Cl, 9·3. Calc. for $C_{22}H_{43}ClO_3$: C, 67·6; H, 11·1; Cl, 9·1%), and threo-13(14)-*bromo*-14(13)-*hydroxy-docosanoic acid* (3·2 g.), m. p. 37° (Found: C, 60·5; H, 9·8; Br, 18·6. $C_{22}H_{43}BrO_3$ requires C, 60·7; H, 10·0; Br, 18·4%).

The isomeric *trans*-oxides gave the following results: *trans*-9,10-Epoxyoctadecanoic acid gave *erythro*-9(10)-chloro-10(9)-hydroxy- (3·2 g.), m. p. 53—58°, and *erythro*-9(10)-bromo-10(9)-hydroxy-octadecanoic acid (3·5 g.), m. p. 56—58°. *trans*-6,7-Epoxyoctadecanoic acid yielded erythro-6(7)-*chloro*-7(6)-*hydroxy*- (2·0 g.), m. p. 43—45° (Found: C, 64·5; H, 10·6; Cl, 10·4.

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[21] Meyer and Janny, *Ber.*, 1882, **15**, 1165.

[22] Belcher, Hoyle, and West, *J.*, 1958, 2743.

$C_{18}H_{35}ClO_3$ requires C, 64·5; H, 10·5; Cl, 10·6%), and erythro-6(7)-*bromo*-7(6)-*hydroxy-octadecanoic acid* (3 g.), m. p. 55—56° (Found: C, 57·3; H, 9·8; Br, 21·2. $C_{18}H_{35}BrO_3$ requires C, 57·0; H, 9·3; Br, 21·1%). Similarly, *trans*-13,14-epoxydocosanoic acid afforded erythro-13(14)-*chloro*-14(13)-*hydroxy*- (3 g.), m. p. 63—64° (Found: C, 67·5; H, 11·1; Cl, 9·0. $C_{22}H_{43}ClO_3$ requires C, 67·6; H, 11·1; Cl, 9·1%), and erythro-13(14)-*bromo*-14(13)-*hydroxy-docosanoic acid* (3 g.), m. p. 37° (Found: C, 61·1; H, 10·0; Br, 18·5. $C_{22}H_{43}BrO_3$ requires C, 60·7; H, 10·0; Br, 18·4%).

Iodohydroxy-acids.—The method employed was a modification of that used for the chloro- and bromo-hydroxy-acids; the preparation of 9(10)-iodo-10(9)-hydroxyoctadecanoic acid is typical. *trans*-9,10-Epoxyoctadecanoic acid (2 g.) in ether (100 ml.) was shaken with freshly distilled hydriodic acid (55% w/w; 2 ml.) at 0° for 30 min. The aqueous layer was removed and the ethereal solution washed free of mineral acid; the residue, on removal of the ether, crystallized from hexane at 0° affording *erythro*-9(10)-iodo-10(9)-hydroxyoctadecanoic acid (2 g.), as needles, m. p. 48—54°.

By an identical procedure, *cis*-9,10-epoxyoctadecanoic acid afforded *threo*-9(10)-iodo-10(9)-hydroxyoctadecanoic acid as an uncrystallizable oil.

Similarly, *cis*-6,7-epoxyoctadecanoic acid gave threo-6(7)-*iodo*-7(6)-*hydroxyoctadecanoic acid* (2·2 g.), m. p. 71—73° (Found: C, 51·0; H, 8·3; I, 30·2. $C_{18}H_{35}IO_3$ requires C, 50·7; H, 8·3; I, 29·8%), and *trans*-6,7-epoxyoctadecanoic acid afforded erythro-6(7)-*iodo*-7(6)-*hydroxy-octadecanoic acid* (1·9 g.), m. p. 57—59° (Found: C, 50·8; H, 8·4; I, 29·8%). *cis*-13,14-Epoxydocosanoic acid yielded threo-13(14)-*iodo*-14(13)-*hydroxydocosanoic acid* (1·9 g.), m. p. 13—15° (Found: C, 54·3; H, 8·9; I, 26·2. $C_{22}H_{43}IO_3$ requires C, 54·7; H, 9·0; I, 26·3%), and *trans*-13,14-epoxydocosanoic acid gave erythro-13(14)-*iodo*-14(13)-*hydroxydocosanoic acid*, m. p. 38—40° (Found: C, 55·2; H, 8·7; I, 25·8%).

Conversion of Halohydrins into the Respective Epoxy-acids.—The yields in such conversions were of the order of 90—98%. The general procedure is exemplified in the case of *threo*-9(10)-chloro-10(9)-hydroxyoctadecanoic acid. The acid (1 g.) was dissolved in sodium hydroxide (0·1N; 200 ml.). After 1 hr. the solution was diluted with water and carefully acidified with acetic acid. The solid which separated was washed with distilled water, dried azeotropically with benzene, and finally crystallized from hexane to give *cis*-9,10-epoxyoctadecanoic acid, m. p. 58·5°, identical in all respects with an authentic specimen.

Similarly, the *threo*-9(10)-bromo- and -iodo-10(9)-hydroxyoctadecanoic acids afforded *cis*-9,10-epoxyoctadecanoic acid. The isomeric *erythro*-9(10)-halogeno-10(9)-hydroxyoctadecanoic acids gave *trans*-9,10-epoxyoctadecanoic acid, m. p. 55·4°.

In like manner, the *threo*-6(7)-halogeno-7(6)-hydroxyoctadecanoic acids, and the *threo*-13(14)-halogeno-14(13)-hydroxydocosanoic acids afforded *cis*-6,7-epoxyoctadecanoic acid, m. p. 63·5°.

The isomeric *erythro*-halogenohydroxy-acids gave *trans*-6,7-epoxyoctadecanoic acid, m. p. 67—68°, and *trans*-13,14-epoxydocosanoic acid, m. p. 70·0°.

Oxidation of Chloro- and Bromo-hydroxy-acids.—The general procedure is illustrated in the case of *erythro*-9(10)-chloro-10(9)-hydroxyoctadecanoic acid. The *erythro*-acid from *trans*-9,10-epoxyoctadecanoic acid (3·0 g.) was dissolved in " AnalaR " acetone (60 ml.), and shaken for 15 min. at room temperature with Kiliani's chromic acid (10 ml.). The excess of oxidant was destroyed with 1% sodium hydrogen sulphite, and the product isolated by ether extraction. The usual procedure, followed by crystallization from light petroleum (b. p. 40—60°) at 0°, gave 9(10)-*chloro*-10(9)-*oxo-octadecanoic acid* (2·0 g.), needles, m. p. 40—47° (Found: C, 65·2; H, 10·1; Cl, 10·2. $C_{18}H_{33}ClO_3$ requires C, 65·0; H, 10·0; Cl, 10·7%).

By this method and with the same quantities of reagents *threo*-9(10)-chloro-10(9)-hydroxy-afforded 9(10)-*chloro*-10(9)-*oxo-octadecanoic acid* (2 g.), m. p. 40—45° (Found: C, 65·0; H, 9·8; Cl, 10·5%), and *erythro*-9(10)-bromo-10(9)-hydroxy- gave 9(10)-*bromo*-10(9)-*oxo-octadecanoic acid* (1·8 g.), m. p. 48·5—49·5° (Found: C, 57·6; H, 8·8; Br, 21·4. $C_{18}H_{33}BrO_3$ requires C, 57·3; H, 8·8; Br, 21·2%); *threo*-9(10)-bromo-10(9)-hydroxy-acid gave 9(10-)-*bromo* 10(9)-*oxo-octadecanoic acid* (1·6 g.), m. p. 41—45° (Found: C, 57·3; H, 8·7; Br, 20·7%); *erythro*-6(7)-chloro-7(6)-hydroxy- gave 6(7)-*chloro*-7(6)-*oxo-octadecanoic acid* (1·9 g.), m. p. 52—55° (Found: C, 64·7; H, 10·0; Cl, 10·7. $C_{18}H_{33}ClO_3$ requires C, 65·0; H, 10·0; Cl, 10·7%), and *threo*-6(7)-chloro-7(6)-hydroxy- yielded 6(7)-*chloro*-7(6)-*oxo-octadecanoic acid* (1·75 g.), m. p. 52—55° (Found: C, 64·7; H, 10·0; Cl, 10·5%); *erythro*-6(7)-bromo-7(6)-hydroxy- afforded 6(7)-*bromo*-7(6)-*oxo-octadecanoic acid* (2·0 g.), m. p. 52—54° (Found: C, 57·1; H, 8·5; Br, 20·8.

$C_{18}H_{33}BrO_3$ requires C, 57·3; H, 8·8; Br, 21·2%), and *threo*-6(7)-bromo-7(6)-hydroxy- gave 6(7)-*bromo*-7(6)-*oxo-octadecanoic acid* (1·5 g.), m. p. 52—53° (Found: C, 57·4; H, 9·0; Br. 20·8%).

In the docosanoic acid series the following results were obtained: *erythro*-13(14)-Chloro-14(13)-hydroxy- gave 13(14)-*chloro*-14(13)-*oxo-docosanoic acid* (1·9 g.), m. p. 50—55° (Found: C, 68·0; H, 10·6; Cl, 9·0. $C_{22}H_{41}ClO_3$ requires C, 67·9; H, 10·6; Cl, 9·1%), and *threo*-13(14)-chloro-14(13)-hydroxy- yielded 13(14)-*chloro*-14(13)-*docosanoic acid* (1·9 g.), m. p. 50—55° (Found: C, 67·9; H, 10·5; Cl, 8·7%); *erythro*-13(14)-bromo-14(13)-hydroxy- gave 13(14)-*bromo*-14(13)-*oxo-docosanoic acid* (2·2 g.), m. p. 56·5—59·5° (Found: C, 60·9; H, 9·5; Br, 18·4%), and *threo*-13(14)-bromo-14(13)-hydroxy- afforded 13(14)-*bromo*-14(13)-*oxo-docosanoic acid* (2·1 g.), m. p. 56—59° (Found: C, 60·9; H, 9·8; Br, 18·0%).

Reduction of Halogeno-oxo-acids with Sodium Borohydride.—The following procedure was used throughout. The acid (0·5 g.) in methanol (40 ml.) was treated with sodium borohydride (0·3 g.) at room temperature. After 1 hr. the solution was just acidified with 5% acetic acid, and the product isolated by ether extraction. The washed and dried (Na_2SO_4) ethereal solution was evaporated, and the residue was heated under reflux with potassium hydroxide (2%, 50 ml.) for 30 min. The alkaline solution was worked up as described above to give the epoxide, which was crystallized from light petroleum (b. p. 40—60°). In this way, 9(10)-chloro- and bromo-10(9)-oxo-octadecanoic acids afforded a product having m. p. 55°, raised on further crystallization to 56—57°. This corresponds to 9,10-epoxyoctadecanoic acid containing >80% of the *cis*-acid (Found: C, 72·3; H, 11·2. Calc. for $C_{18}H_{34}O_3$: C, 72·5; H, 11·5%). With the 6(7)-halogeno-7(6)-oxo-octadecanoic acids the intermediate chloro- and bromo-hydrins were isolated as solids, m. p. 55—57° and 53—54°, respectively, in fair agreement with values found for *threo*-6(7)-chloro- and bromo-7(6)-hydroxyoctadecanoic acids.

Treatment with alkali afforded a product having m. p. 58—60°; this corresponds to a 6,7-epoxyoctadecanoic acid containing >90% of the *cis*-acid.

The intermediate chloro- and bromo-hydrins obtained by the borohydride reduction of the 13(14)-halogeno-14(13)-oxodocosanoic acids had m. p.s 42—44° and 36—37°, respectively, in close agreement with the values found for *threo*-13(14)-chloro- and bromo-14(13)-hydroxy-docosanoic acids.

Alkali treatment afforded a product, m. p. 54°, which on further crystallization from hexane had m. p. 60°, corresponding to a content of >75% of *cis*-13,14-epoxydocosanoic acid (Found: C, 74·4; H, 11·7. Calc. for $C_{22}H_{42}O_3$: C, 74·5; H, 11·9%).

Reduction of Halogeno-oxo-acids with Hydriodic Acid.—The method described below was used throughout. The halogeno-oxo-acid (1 g.) in ethanol (25 ml.) was treated with a solution of potassium iodide (2·5 g.) in the minimum of water, and to the mixture was added hydrochloric acid (2·5 ml.). The mixture was heated under reflux for 15 min. and then cooled rapidly in ice; the colour due to iodine was discharged by the dropwise addition of a 20% solution of sodium thiosulphate. This procedure was repeated at 5-min. intervals until no further liberation of iodine took place. The product was isolated by dilution with water followed by ether extraction. After the usual processing and removal of ether, the residue was crystallized from acetone at 0°, to give the oxo-acid. In this manner, the 9(10)-chloro- and -bromo-10(9)-oxo-octadecanoic acids afforded 9(10)-oxo-octadecanoic acid (0·8 g.), m. p. 72·0°, identical with an authentic specimen prepared from 9,10-octadecynoic acid. Similarly the 6(7)-chloro- and -bromo-7(6)-oxo-octadecanoic acids afforded 6(7)-oxo-octadecanoic acid (0·7 g.), m. p. 70—72°, identical with a specimen prepared from *cis*-octadec-6-enoic acid. Likewise, the 13(14)-chloro- and -bromo-14(13)-oxo-docosanoic acids afforded 13(14)-oxodocosanoic acid (0·8 g.), m. p. 83·0°, identical with the product obtained either by hydration of 13,14-docosynoic acid, or by hydration of *cis*-docos-13-enoic acid followed by oxidation.

Attempted Oxidation of Hydroxyiodo-acids to Iodo-oxo-acids.—Oxidation according to the method used for the chloro- and bromo-hydroxy-acids, gave, in poor yields, the saturated oxo-acid as the only identifiable product. Using *N*-bromosuccinimide, we isolated, from the 6(7)-iodo-7(6)-hydroxyoctadecanoic acids, 6,7-dioxo-octadecanoic acid.

The hydroxyiodo-acid (5 g.) in ethyl acetate (150 ml.) was heated [23] under reflux with *N*-bromosuccinimide (5 g.); the product (0·4 g.), m. p. 97—99°, was 6,7-dioxo-octadecanoic acid, and no other identifiable material was isolated.

Reaction of α-Halogeno-acids with Hydroxylamine.—The acid (1 g.) was heated under reflux

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[23] Cramp, Julietti, McGhie, Rao, and Ross, *J.*, 1960, 4260.

for 1 hr. with an alcoholic solution of hydroxylamine [from hydroxylamine hydrochloride (3 g.) and sodium acetate (4 g.) in alcohol (30 ml.), heated for 15 min., and the precipitated sodium chloride removed]. The dioxime was isolated by dilution with water, extraction with ethyl acetate, washing with water, and evaporation. The residue was crystallized from ethanol to give the pure dioxime.

Following this procedure, the 6(7)-chloro- and -bromo-7(6)-oxo-octadecanoic acids afforded 6,7-dihydroxyimino-octadecanoic acid (0·4 g. and 0·35 g., respectively), m. p. 173—174° (lit., m. p. 166—167°) [24] (Found: C, 63·0; H, 10·2; N, 8·0. Calc. for $C_{18}H_{34}N_2O_4$: C, 63·1; H, 10·0; N, 8·2%); the 9(10)-chloro- and -bromo-10(9)-oxo-octadecanoic acids gave 9,10-dihydroxyimino-octadecanoic acid (0·3 g. and 0·45 g., respectively), m. p. 155—156° (lit.,[25] m. p. 153—154°) (Found: C, 63·3; H, 9·9; N, 8·1%); and the 13(14)-chloro- and -bromo-14(13)-oxo-docosanoic acids yielded 13,14-dihydroxyiminodocosanoic acid (0·25 g. and 0·4 g., respectively), m. p. 148—149° (lit.,[25] m. p. 144—145°) (Found: C, 66·5; H, 10·5; N, 7·2. Calc. for $C_{22}H_{42}N_2O_4$: C, 66·3; H, 10·6; N, 7·0%).

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[24] Arnaud, *Compt. rend.*, 1902, **134**, 548.

[25] Spieckermann, *Ber.*, 1895, **28**, 277.