398. *α-Ketol Carboxylic Acids. Part I. 9-Hydroxy-10-keto- and 10-Hydroxy-9-keto-stearic Acids.*

By George King.

Interest in the α-ketol derivatives of the higher aliphatic acids has been stimulated during recent years by the suggestion that this type of compound may occur among the products of autoxidation of the higher unsaturated acids or their glycerides (Ellis, *J. Soc. Chem. Ind.*, 1926, **45**, 198T; Morrell and Marks, *J. Oil Col. Chem. Assoc.*, 1927, **10**, 197; Skellon, *J. Soc. Chem. Ind.*, 1931, **50**, 382T; Morrell and Davis, *ibid.*, 1936, **55**, 237, 261T), yet much uncertainty exists regarding the properties of these particular ketols, and the simple α-ketol derivatives of stearic acid do not appear to have hitherto been isolated.

Under favourable conditions the oxidation of oleic acid with alkaline permanganate affords an almost theoretical yield of 9 : 10-dihydroxystearic acid, m. p. 132° (Robinson and Robinson, J., 1925, **127**, 175; Lapworth and Mottram, *ibid.*, p. 1628). On the other hand, if an excess of alkali is avoided, the product for the most part corresponds in composition to a hydroxyketostearic acid (Holde and Marcusson, *Ber.*, 1903, **36**, 2658). It is now shown that in neutral solution this oxidation leads principally to the formation of a mixture of the two structurally isomeric 9 : 10-hydroxyketostearic acids. The individual isomerides have been isolated, their constitutions clearly established, and their properties examined in some detail. The conditions under which the two hydroxyketo-acids may be prepared in good yield from both oleic and elaidic acids may be summarised as follows : (1) The acid and potassium hydroxide should be in equivalent proportion, and the amount of potassium permanganate subsequently added approximately two mols. per mol. of oleic acid; (2) the concentration of the acid should not exceed 1 g. per litre of the reaction mixture; and (3) the duration of the oxidation should be 8—10 minutes, at 8—10° for oleic acid and 25° for elaidic acid.

In such circumstances commercial samples of oleic acid give a 30—40% yield of a mixture of *9-hydroxy-10-ketostearic* and *10-hydroxy-9-ketostearic acids*, together with 20—35% of dihydroxystearic acid, m. p. 132°. Elaidic acid similarly affords 55—60% of mixed hydroxyketostearic acids, and 10—20% of dihydroxystearic acid, m. p. 95°. The two hydroxyketostearic acids appear to be formed in about equal amounts, and repeated crystallisation of the product from 60% alcohol or petroleum–benzene yields a mixture of constant m. p. 64·5—65·5°. A separation is most conveniently effected through the semicarbazones.

9-Hydroxy-10-ketostearic acid (I), m. p. 74°, is characterised by a *semicarbazone*, m. p. 152°, and is oxidised smoothly by periodic acid at room temperature to nonoic acid and azelaic semialdehyde. The isomeride (II), m. p. 75·5° (*semicarbazone*, m. p. 138·5°), is oxidised under similar conditions to nonaldehyde and azelaic acid.

$$\text{(I.)}\quad CH_3\cdot[CH_2]_7\cdot CO\cdot CH(OH)\cdot[CH_2]_7\cdot CO_2H \longrightarrow CH_3\cdot[CH_2]_7\cdot CO_2H + CHO\cdot[CH_2]_7\cdot CO_2H$$

$$\text{(II.)}\quad CH_3\cdot[CH_2]_7\cdot CH(OH)\cdot CO\cdot[CH_2]_7\cdot CO_2H \longrightarrow CH_3\cdot[CH_2]_7\cdot CHO + CO_2H\cdot[CH_2]_7\cdot CO_2H$$

The hydroxyketostearic acids exhibit normal properties, and show no tendency to enolise under ordinary conditions. They are unimolecular in solution. They reduce Fehling's and ammoniacal silver nitrate solutions readily on heating, and are oxidised in the cold by chromic acid in acetic acid to the diketone, stearoxylic acid, whereas with hot acid permanganate nonoic and azelaic acids are the main products. Nascent hydrogen slowly reduces 9-hydroxy-10-ketostearic acid to dihydroxystearic acid, m. p. 132°, but the isomeride is particularly resistant to reduction. Interconversion of the two isomerides occurs when the hydroxyketo-acids are dissolved in dilute alkali solution, equilibrium being reached in 24—36 hours at room temperature, or within a few minutes at 100°. Autoxidation, although extremely slow in weakly alkaline solution, becomes appreciable when a solution of the acids in concentrated alkali is heated in the presence of air, and is still more pronounced in boiling alcoholic potassium hydroxide, nonoic and azelaic acids being the principal products (cf. Weissberger *et al.*, *Annalen*, 1933, **502**, 53; J., 1935, 223). 2 : 4-Dinitrophenylhydrazine gives an *osazone*, m. p. 146·5°, identical with that prepared from stearoxylic acid.

The mechanism of the formation of the hydroxyketostearic acids remains obscure, since the two dihydroxy-acids are practically unaffected by permanganate under the conditions outlined above. Hence the assumption that the latter are intermediates in this process appears to be untenable.

It has been suggested (Hilditch, J., 1926, 1828; Hilditch and Lea, J., 1928, 1576) that the dihydroxystearic acids, m. p.'s 132° and 95°, are structurally related to elaidic and oleic acids respectively, and that the "inversion" which occurs during the oxidation of the latter acids with alkaline permanganate may be attributed to the alkalinity of the medium. In the present investigation, although the oxidations were carried out under substantially neutral conditions (p_H *ca.* 8·5), and excess of alkali was carefully avoided, of the two dihydroxy-acids, that of m. p. 132° was formed exclusively as a by-product from oleic acid, that of m. p. 95° from elaidic acid.

EXPERIMENTAL.

Oxidation of Oleic Acid to a Mixture of 9 : 10-*Hydroxyketostearic Acids.*—A solution of oleic acid (5 g.) in water (1 l.) containing the theoretical quantity of *N*-potassium hydroxide (17·75 ml.) was diluted to 5 l. and cooled to 8°, and potassium permanganate (5·5 g.) in cold water (250 ml.) rapidly added with shaking. After 10 minutes the solution was decolourised with sodium hydrogen sulphite (30 g.) in water (150 ml.), followed by 5*N*-hydrochloric acid (60 ml.). The precipitate was collected, washed, dried in a vacuum, and digested with chloroform (50 ml.). When the resulting solution was cooled in ice, dihydroxystearic acid (1·2 g.) separated. This was removed and the filtrate was washed, dried, and evaporated. Light petroleum (200 ml., b. p. 40—60°), added to the warm (molten) residue, and subsequent cooling in ice during 24 hours, precipitated crude hydroxyketostearic acid. This was collected, redissolved in cold chloroform (10 ml.), and filtered from a trace of insoluble matter, and the solvent removed. The warm residue was again treated with light petroleum (150 ml.), and the product (1·7 g.) was crystallised several times from 60% alcohol, from which it separated in hexagonal and rhombic plates, m. p. 64—65° [Found : C, 68·6; H, 10·7; *M*, by titration, 313; *M* (Rast), 331; *M*, cryoscopic in acetic acid, 289. Calc. for $C_{18}H_{34}O_4$: C, 68·8; H, 10·9%; *M*, 314].

The dihydroxystearic acid crystallised from alcohol in rhombic plates, m. p. and mixed m. p. 131°, sparingly soluble in ether (Found : equiv., 316. Calc. for $C_{18}H_{36}O_4$: equiv., 316).

Evaporation of the petroleum mother-liquors left a pale yellow, semi-solid residue (1·2 g.), iodine value 20, which reduced alkaline permanganate, and presumably consisted of unchanged oleic acid together with saturated acids which were present in the original commercial acid.

Oxidation of Elaidic Acid.—The method was precisely similar to that described above, except that the reaction was carried out at 25°. 5 G. of elaidic acid, m. p. 45°, afforded 3·0 g. of hydroxyketostearic acids, m. p. 64°, and 0·6 g. of dihydroxystearic acid, m. p. and mixed m. p. with a specimen prepared from oleic acid (Hilditch, *loc. cit.*) 94·5° (Found : equiv., 315). The petroleum mother-liquors left on evaporation a solid (0·5 g.), m. p. 41—45°, consisting mainly of unchanged elaidic acid.

Semicarbazones of 9 : 10-*Hydroxyketostearic Acids.*—Repeated fractional crystallisation from a number of solvents having failed to effect any separation of the mixture of hydroxyketo-acids, m. p. 64—65°, the mixed acids (4 g.) were converted into a mixture of semicarbazones, which formed readily in the cold during 48 hours and crystallised from alcohol in needles and rhombohedra, m. p. 130—140° (cf. Holde and Marcusson, *loc. cit.*). The product (5 g.) was digested with ethylene dichloride (500 ml.), and the hot solution rapidly filtered (filtrate A). The insoluble residue (2·5 g.), consisting of the *semicarbazone* of 9-hydroxy-10-ketostearic acid, crystallised from aqueous alcohol in small flat prisms, m. p. 152°, sparingly soluble in cold alcohol and ether (Found : C, 61·8; H, 9·9; equiv., 371. $C_{19}H_{37}O_4N_3$ requires C, 61·5; H, 10·0%; equiv., 371).

Filtrate (A) gave, on cooling in ice, a precipitate of the *semicarbazone* of 10-hydroxy-9-ketostearic acid (2·3 g.), which crystallised from absolute alcohol in colourless needles, m. p. 138·5° (Found : C, 61·9; 9·8%).

9-*Hydroxy*-10-*ketostearic Acid.*—The semicarbazone of m. p. 152° (5 g.) was hydrolysed by boiling with 2*N*-hydrochloric acid (500 ml.) and formaldehyde (5 ml. of 38% solution) for 15 minutes. The *acid* (3·5 g.) crystallised from aqueous alcohol in colourless plates, m. p. 74° (Found : C, 68·9; H, 10·8%; equiv., 314).

10-*Hydroxy*-9-*ketostearic Acid.*—The semicarbazone, m. p. 138·5° (5 g.), gave on hydrolysis an *acid* (3·5 g.), crystallising from aqueous alcohol in colourless plates, m. p. 75·5° (Found : C, 69·0; H, 10·8%; equiv., 314). A mixture of this acid with an equal quantity of 9-hydroxy-10-ketostearic acid melted at 65°.

Both acids dissolved readily in most organic solvents, although less readily in carbon tetrachloride and very sparingly in light petroleum. No coloration was obtained with ferric chloride or sodium nitroprusside, nor was there any appreciable absorption of bromine or iodine in acid solution (iodine values of 1—2 were found).

2 : 4-Dinitrophenylhydrazine in sulphuric acid, added to a solution of either acid in 80% alcohol, gave after 48 hours a nearly quantitative yield of the *dinitrophenylosazone*, which crystallised from alcohol–chloroform in orange needles, m. p. 146·5° alone or mixed with the product obtained in a similar manner from stearoxylic acid [Found : N, 16·3; *M* (Rast), 686. $C_{30}H_{40}O_{10}N_8$ requires N, 16·7%; *M*, 672]. This osazone was sparingly soluble in alcohol and ether, but soluble in chloroform. In alcoholic sodium hydroxide it formed an intensely violet solution.

Oxidation of 9 : 10-*Hydroxyketostearic Acids with Periodic Acid.*—By the technique described by Clutterbuck and Reuter (J., 1935, 1467), preliminary experiments were carried out to ascertain whether these α-ketol acids react quantitatively with periodic acid according to the equation:

$$R{\cdot}CO{\cdot}CH(OH){\cdot}R' + HIO_4 = R{\cdot}CO_2H + R'{\cdot}CHO + HIO_3$$

It was found that oxygen equivalent to 105% of the theoretical quantity was absorbed during 48 hours at room temperature, and the amount of potassium periodate required for the following oxidative processes was calculated accordingly.

(a) Potassium periodate (1·55 g.) in water (100 ml.), acidified with *N*-sulphuric acid (exactly 100 ml.), was added to 9-hydroxy-10-ketostearic acid (2 g.) in alcohol (300 ml.). After 48 hours *N*-potassium hydroxide (exactly 100 ml.) was added, and the liquid steam-distilled. Zinc sulphate, added to the carefully neutralised distillate, precipitated zinc nonoate (0·9 g. Calc., 1·2 g.), crystallising from alcohol in plates, m. p. and mixed m. p. with an authentic specimen 133°. The slightly turbid liquid left after the steam-distillation was treated with potassium iodide (10 g.), acidified with 2*N*-hydrochloric acid, and the liberated iodine titrated with thiosulphate (to remove iodate). On addition of Brady's reagent, the 2 : 4-*dinitrophenylhydrazone* of azelaic semialdehyde separated (1·4 g. Calc., 2·24 g.), which crystallised from methyl alcohol in short, thick, orange blades, m. p. 120°, sparingly soluble in alcohol at 0° (Found : C, 51·5; H, 6·0; N, 15·6. $C_{15}H_{20}O_6N_4$ requires C, 51·1; H, 5·7; N, 15·9%). This dissolved readily in aqueous sodium hydroxide, forming a deep red solution from which it was recovered on acidification.

(b) 10-Hydroxy-9-ketostearic acid (2 g.) was oxidised by periodic acid in a similar manner. After 48 hours the solution was made slightly alkaline and steam-distilled. Addition of Brady's reagent to the distillate precipitated the dinitrophenylhydrazone of nonaldehyde (1·29 g. Calc., 2·04 g.), which crystallised from absolute alcohol in golden-yellow needles, m. p. 106—106·5° (cf. Allen, *J. Amer. Chem. Soc.*, 1930, **52**, 2955; Nunn and Smedley-Maclean, *Biochem. J.*, 1935, **29**, 2744) (Found : C, 56·1; H, 6·9; N, 17·6. Calc. for $C_{15}H_{22}O_4N_4$: C, 55·9; H, 6·9; N, 17·4%). The liquid remaining after the steam-distillation was acidified with 2*N*-sulphuric acid, evaporated to small bulk, and extracted several times with ether. Removal of the ether left almost pure azelaic acid (1·1 g. Calc., 1·2 g.), which crystallised from water in colourless plates, m. p. and mixed m. p. 107° (Found : equiv., 94·5. Calc. for $C_9H_{16}O_4$: equiv., 94).

Oxidation of the Hydroxyketo-acids to Stearoxylic Acid.—9-Hydroxy-10-ketostearic acid (0·5 g.) was added to chromic acid (0·25 g.) in glacial acetic acid (25 ml.). After 24 hours at room temperature the addition of water precipitated stearoxylic acid, which crystallised from 80% alcohol in pale yellow laminæ (0·23 g.), m. p. 85·5° (Found : equiv., 310. Calc. for $C_{18}H_{32}O_4$: equiv., 312). The isomeride behaved similarly on oxidation.

Oxidation to Nonoic and Azelaic Acids.—A mixture of the hydroxyketostearic acids (2 g.), 2*N*-sulphuric acid (50 ml.), and potassium permanganate (2 g.) was refluxed for 10 minutes, and the volatile acid was distilled in steam. Light petroleum extracted from the oily distillate nonoic acid (0·55 g.), which readily solidified to a crystalline mass on cooling in ice (Found : equiv., by analysis of the silver salt, 158. Calc. for $C_9H_{18}O_2$: equiv., 158). The zinc salt crystallised from alcohol in plates, m. p. and mixed m. p. 133°. The liquid remaining after the steam-distillation was warmed with concentrated hydrochloric acid (20 ml.) to dissolve oxides of manganese, filtered, cooled, and thoroughly extracted with ether. After washing and drying, the ethereal solution was evaporated to small bulk. On addition of several vols. of light petroleum, azelaic acid (0·75 g.) separated; it crystallised from water in colourless plates, m. p. and mixed m. p. 107° (Found : equiv., 94·5). The individual isomerides gave identical results.

Reduction to Dihydroxystearic Acid.—Zinc–copper couple (10 g.) was added to 9-hydroxy-10-ketostearic acid (0·4 g.) in alcohol (10 ml.) acidified with acetic acid (4 ml.), and the whole kept at 60—70° during 48 hours. Small quantities of 50% acetic acid and a few drops of copper sulphate solution were added from time to time during a further 24 hours. After addition of concentrated hydrochloric acid (5 ml.), the solution was heated to the b. p., filtered, and diluted with water. The acid obtained was crystallised from acetone containing a little dilute hydrochloric acid, washed with cold chloroform (5 ml.), and recrystallised from alcohol, from which dihydroxystearic acid (0·05 g.) separated in rhombic plates, m. p. and mixed m. p. 131°. The greater part of the hydroxyketo-acid remained unreduced and was recovered from the chloroform washings.

Similar attempts to reduce 10-hydroxy-9-ketostearic acid yielded only traces of dihydroxystearic acid, m. p. 132°, and in neither case was any dihydroxy-acid, m. p. 95°, isolated.

Isomerisation in Alkaline Solution.—9-Hydroxy-10-ketostearic acid was dissolved in a considerable excess of *N*/10-sodium hydroxide and portions of the solution were removed at intervals for examination. The products obtained on acidification were crystallised once from 60% alcohol. Equilibrium was reached in 24 hours, the product then melting at 63—64°. This was shown to consist of a mixture of the two isomeric hydroxyketo-acids by conversion into the semicarbazones, and separation in the manner already described. When the experiment was repeated at 100°, equilibrium was established within 5 minutes. Similar results were obtained with 10-hydroxy-9-ketostearic acid, but at room temperature about 36 hours were required to complete the interconversion.

Autoxidation.—For the following experiments a mixture of the hydroxyketo-acids melting at 65° was used.

(a) The acid (0·3163 g.) was refluxed with *N*/10-sodium hydroxide (25 ml.) for 30 minutes. 14·7 Ml. of *N*/10-sulphuric acid (calc., 14·9 ml.) were then required to neutralise the excess of alkali, and the acid was recovered nearly quantitatively.

(b) The acid (0·5 g.) was refluxed with 10% sodium hydroxide solution (15 ml.) for 5 hours. No colour developed during the process, and on acidification most (0·4 g.) of the acid was recovered unchanged.

(c) The acid (1 g.) was heated with 40% potassium hydroxide solution (12 ml.) for 6 hours at 100° in a large flask sealed with a bung carrying a mercury manometer. An orange colour developed, 48 ml. of oxygen (N.T.P.) being absorbed (calc. for oxidation to stearoxylic acid, 35·7 ml.; for complete oxidation to nonoic and azelaic acids, 71·3 ml.). Acidification produced a reddish-brown oil, from which about 0·1 g. each of nonoic and azelaic acids was isolated. The semi-solid residue was not fully identified.

(d) The acid (0·4 g.) was refluxed with *N*/4-alcoholic potassium hydroxide (20 ml.) for 3 hours while a slow current of air free from carbon dioxide was passed through the apparatus. After removal of the alcohol on the water-bath, the liquid was acidified with 2*N*-sulphuric acid and steam-distilled. Zinc sulphate, added to the neutralised distillate, precipitated zinc nonoate (0·1 g.), which crystallised from alcohol in plates, m. p. and mixed m. p. 133°. The liquid containing non-volatile acids was filtered while hot from a little insoluble matter, cooled, and extracted several times with ether. Removal of the solvent left slightly impure azelaic acid (0·13 g.), which, after recrystallising twice from water, melted at 106—107° (Found: equiv., 95·0). No oxalic acid was found in the remaining aqueous portion.

Attempted Oxidation of Dihydroxystearic to Hydroxyketostearic Acids.—(a) Dihydroxystearic acid (3·16 g.), m. p. 132°, was dissolved in the theoretical amount of *N*/20-potassium hydroxide (200 ml.) and diluted to 3 l. Potassium permanganate (3 g.) in water (300 ml.) was added, and the whole maintained at 25° during 1 hour. After decoloration with sodium hydrogen sulphite (25 g.) and 5*N*-hydrochloric acid (60 ml.), 3·04 g. of dihydroxystearic acid were recovered unchanged, traces only of ketol being found.

(b) Dihydroxystearic acid (3·16 g.), m. p. 95°, was treated in a similar manner. 3·06 G. were recovered unchanged.

The author gratefully acknowledges the helpful criticism and suggestions of Dr. G. W. Ellis, O.B.E.

ST. MARY'S HOSPITAL MEDICAL SCHOOL, LONDON, W. 2. [*Received, October 8th,* 1936.]