719. *The Oxidation of Carboxylic Acids containing a Tertiary Carbon Atom. Part II.**

By J. Kenyon and M. C. R. Symons.

Two procedures have been described in Part I * whereby branched-chain carboxylic acids $RR'CH\cdot[CH_2]_n\cdot CO_2H$ are converted into the corresponding hydroxy-acids $RR'C(OH)\cdot[CH_2]_n\cdot CO_2H$, the prescribed oxidants being (*a*) potassium permanganate in concentrated alkaline solution ($n = 0$ or 2) and (*b*) potassium manganate in dilute alkaline solution ($n = 2$). Applied to optically active carboxylic acids, oxidations by method (*a*) result in complete loss of optical activity, whereas those by method (*b*) result in complete retention of activity. It is postulated that the radical ion $RR'\dot{C}\cdot[CH_2]_n\cdot CO_2^-$ and the lactone $RR'\overline{C\cdot[CH_2]_2\cdot CO}_2$ are the respective intermediates in these reactions which, together, constitute an example of an oxidation which may proceed either by a single two-electron change or by two consecutive one-electron changes.

The behaviour of several optically active branched-chain carboxylic acids of type $RR'CH\cdot[CH_2]_n\cdot CO_2H$, in which $n = 0$ or 2, R = Me, and R' = Et or Ph, when subjected to oxidation by (*a*) potassium permanganate in concentrated alkaline solution and (*b*) potassium manganate in dilute alkaline solution, has been studied. In Part I,* it was reported that the use of permanganate afforded good yields of the corresponding hydroxy-acids $RR'C(OH)\cdot[CH_2]_n\cdot CO_2H$ when $n = 0$ or 2, whilst the use of manganate led to good yields of the corresponding hydroxy-acids, when $n = 2$. It is now shown that the products obtained from optically active acids by oxidation with permanganate are devoid of optical activity, whereas with manganate there is no loss of activity. Since both reactants and products are optically stable in hot concentrated alkaline solution, the two reactions must proceed by different mechanisms.

There is considerable evidence (contributed largely by McKenzie *et al.*) that extensive racemisation occurs during the alkaline hydrolysis of α-substituted carboxylic esters, and

---

* The communication "The Oxidation of Carboxylic Acids containing a Tertiary Carbon Atom," *J.*, **1953**, 2129, is regarded as Part I.

Kenyon and Young (*J.*, 1940, 216) have found that such esters readily racemise in the presence of sodium ethoxide. This racemisation, which may be a consequence either of the formation of the ion $RR'\overset{-}{C}{\cdot}CO_2Et$ or of a series of inversions in which the solvent participates (Dewar, " Electronic Theory of Organic Chemistry," Oxford Univ. Press, London, 1949, p. 110), is not observed when optically active branched-chain carboxylic acids are heated for several hours in concentrated alkaline solution. This precludes any mechanism involving an initial ionization of the type:

$$RR'CH{\cdot}[CH_2]_n{\cdot}CO_2^- + OH^- \longrightarrow RR\,C{\cdot}[CH_2]_n{\cdot}CO_2^- + H_2O$$

followed by an electron-transfer reaction as postulated by Drummond and Waters (*J.*, 1953, 435) for oxidations by alkaline permanganate. It may, therefore, be concluded that the first step in either mechanism is an attack by the oxidant at the " tertiary " hydrogen atom, leading to its removal as an atom or negative ion. Removal of hydrogen as an atom would result in the radical ion $RR'\dot{C}{\cdot}[CH_2]_n{\cdot}CO_2^-$ becoming kinetically free during the reaction, with consequent extensive racemisation. Since, in reactions with permanganate the oxidant undergoes a one-electron change and the hydroxy-acids obtained are devoid of optical activity, it is postulated that such reactions proceed by a free-radical mechanism.

On the other hand, removal of hydrogen, together with both its bonding electrons, would result in formation of a zwitterion of type $RR'\overset{+}{C}{\cdot}[CH_2]_n{\cdot}CO_2^-$. The behaviour of optically active halogeno-carboxylic acids (Hughes, *Quart. Reviews*, 1951, **5**, 255) shows that the formation of an intermediate of this type results in complete inversion of configuration about the positive carbon atom. Since, during reactions with manganate, the oxidant undergoes a two-electron change and there is no loss of optical activity during the reaction, it is concluded that these oxidations probably proceed by this alternative mechanism.

Discussion.—Reactions between branched-chain carboxylic acids and permanganate in dilute alkaline solution are slow, even at elevated temperatures, and result in extensive degradation of the acid: when the concentration of alkali is high, the reaction is rapid, proceeds at room temperature, and leads to hydroxy-acids, which are not further attacked. Although it is possible that the change in mode of reaction is due to the stabilisation of the manganate ion by the alkali, this can hardly account for the marked change in the rate of oxidation. It may be that a new mode of attack is involved which is related to the large increase in the rate of decomposition of permanganate with increase in concentration of alkali:

$$4KMnO_4 + 4KOH \longrightarrow 4K_2MnO_4 + 2H_2O + O_2$$

It has been postulated that the first stage in this decomposition involves the formation of a free hydroxyl radical:

$$MnO_4^- + OH^- \longrightarrow MnO_4^{2-} + {\cdot}OH$$

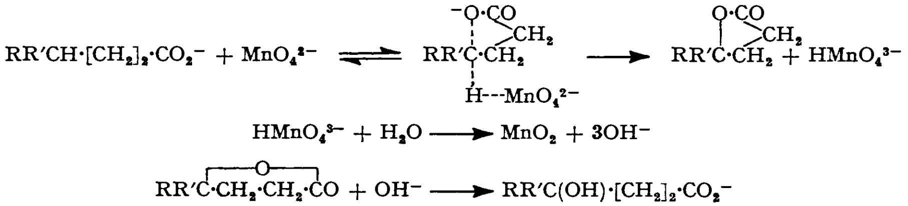
(Stamm, " Newer Methods of Volumetric Chemical Analysis," transl. by Oesper, Van Nostrand Co. Inc., New York, 1938; Symons, *Research*, 1953, **6**, 5S), and a recent kinetic study (*J.*, in the press) supports the view that this primary step is followed by the formation of the $\cdot O^-$ radical ion:

$${\cdot}OH + OH^- \rightleftharpoons {\cdot}O^- + H_2O$$

Accordingly, it is postulated that for reactions with permanganate, the active oxidant is the free hydroxyl radical or the $\cdot O^-$ radical ion:

$$RR'CH{\cdot}[CH_2]_n{\cdot}CO_2^- + {\cdot}OH \longrightarrow RR'\dot{C}{\cdot}[CH_2]_n{\cdot}CO_2^- + H_2O$$
$$RR'\dot{C}{\cdot}[CH_2]_n{\cdot}CO_2^- + {\cdot}OH \longrightarrow RR'C(OH){\cdot}[CH_2]_n{\cdot}CO_2^-$$

Although oxidation of γ-branched-chain carboxylic acids by manganate gives good yields of γ-hydroxy-acids, that of α- or β-branched-chain acids results in extensive degradation of the molecule. It may be that in strongly alkaline solution zwitterions containing positive α- or β-carbon atoms readily eliminate a proton to form substituted acrylate ions, which would be susceptible to further attack, but that the removal of a hydride ion from the γ-carbon atom is facilitated by a simultaneous nucleophilic attack by the $\cdot CO_2^-$ group on the γ-carbon atom to give a γ-lactone, which would then be hydrolysed to the salt of a stable hydroxy-acid:



$$HMnO_4^{3-} + H_2O \longrightarrow MnO_2 + 3OH^-$$

In general, no evidence relating to the mechanism of oxidation by potassium permanganate in dilute alkaline solution ($MnO_4^- \longrightarrow MnO_2$) has been obtained. However, oxidation of optically active 4-methylhexanoic acid ($CO_2H = 1$) by this reagent yielded 4-hydroxy-4-methylhexanoic acid in small quantities, which possessed a rotatory power considerably smaller than that required for complete retention of optical activity. It is therefore possible that both types of reaction contributed to its formation. However, since the hydroxy-acid is unaffected by permanganate, and since the main part of the reaction consisted of a deep-seated oxidation, it is inferred that neither process contributes extensively to the main reaction.

The most cogent evidence in favour of the dual mechanisms resides in their complementary nature. Thus, it is expected that one mechanism would result in slight, and the other in extensive, racemisation: and two procedures have been found which exhibit these characteristics to the fullest extent.

EXPERIMENTAL

The preparation and characterisation of the racemic forms of the reactants and products, and the general procedures used for oxidation, are described in Part I (*loc. cit.*).

Preparation of Optically Active Branched-chain Carboxylic Acids.—(+)-α-Methylbutyric acid, prepared from a mixture of (−)-2-methylbutanol obtained from fusel oil (Le Couteur, Kenyon, and Rohan, *J. Appl. Chem.*, 1951, **1**, 341) and (±)-2-methylbutanol, had b. p. 64°/2 mm., α_D^{20} +6·2° (*l*, 1·0) (optical purity 35·5%).

(−)-α-Phenylpropionic acid, partially resolved *via* its strychnine salt (Ott and Kramer, *Ber.*, 1935, **68**, 1651), had b. p. 96—97°/0·1 mm., α_D^{20} −9·07° (*l*, 0·5) (optical purity 17·5%).

(+)-γ-Phenylvaleric acid, prepared from (−)-α-phenylpropionic acid, α_D^{20} −9·07° (*l*, 0·5), had m. p. 16°, b. p. 98°/0·1 mm., α_D^{20} +1·84° (*l*, 0·5). [The optical purity calculated from the datum of Levene and Marker (*J. Biol. Chem.*, 1935, **110**, 329) is 17·5%, thus indicating that no racemisation occurred during the synthesis.]

(+)-4-Methylhexanoic acid, prepared from a mixture of (−)-2-methylbutanol (20%) and (±)-2-methylbutanol (80%) by conversion into the bromide, followed by a malonic ester synthesis, had b. p. 85°/2 mm., α_D^{20} +1·00° (*l*, 0·5) (optical purity 20%).

Preparation of Optically Active Hydroxy-carboxylic Acids.—(+)-α-Hydroxy-α-phenylpropionic acid, partially resolved *via* its quinine salt (Wren and Wright, *J.*, 1921, **119**, 798), had m. p. 112°, α_D^{20} +1·2° (*l*, 2; *c*, 5 in abs. EtOH).

(+)- and (−)-γ-Phenyl-γ-valerolactone were prepared from the brucine salt of the hydroxy-acid. Brucine (13·6 g.) was dissolved in an ice-cold solution of the (±)-hydroxy-acid (6·8 g.) in aqueous ethanol (75%), and some solvent removed *in vacuo*, since, when heated, the brucine salt tends to decompose into brucine and the lactone. After 7 days, the separated crystals (A) were removed [3·4 g.; m. p. 95° (decomp.)]. After removal of three further crops, obtained by evaporation under reduced pressure, the mother-liquors were partially evaporated and cooled to 0°, and the separated crystals (B) dissolved in water and acidified at 0° with dilute hydrochloric acid. The precipitated γ-hydroxy-γ-phenylvaleric acid, m. p. 120°, by repeated distillation with benzene, was converted into the γ-lactone, b. p. 99°/0·1 mm., α_D^{20} +27·9° (*l*, 0·5). Similarly, the final mother-liquors from (B) gave (+)-γ-phenyl-γ-valerolactone, α_D^{20} +27·8° (*l*, 0·5). Three recrystallisations of crop (A) from 75% alcohol gave (−)-γ-phenyl-γ-valerolactone, b. p. 103°/0·5 mm., α_D^{20} −27·95° (*l*, 0·5). Recrystallisation of the brucine salt did not alter the rotatory power of the lactone.

(−)-4-Hydroxy-4-methylhexanoic lactone was prepared from the (−)-1-phenylethylamine salt of the hydroxy-acid. Since no reaction occurred when 1-phenylethylamine was warmed with the lactone, and since the hydroxy-acid is very readily lactonised, the following procedure was adopted. A vigorously stirred, ice-cold mixture of ether and an aqueous solution of the sodium salt of the hydroxy-acid was acidified with dilute hydrochloric acid, and the ethereal solution of the liberated hydroxy-acid immediately added to an ethereal solution of an equivalent quantity of (−)-1-phenylethylamine, $\alpha_{\rm D}^{20}$ −44·7° (*l*, 1·0). The precipitated salt, m. p. 112°, was recrystallised five times from acetone, the resulting needles, m. p. 122·5°, were dissolved in water, the solution was cooled and acidified, and the liberated hydroxy-acid extracted with ether. Repeated distillation with benzene to ensure complete lactonisation gave (−)-4-hydroxy-4-methylhexanoic lactone, b. p. 64°/0·5 mm., $\alpha_{\rm D}^{20}$ −7·2° (*l*, 0·5). Two further crystallisations altered neither the m. p. of the salt nor the rotation of the lactone.

(+)-4-Hydroxy-4-methylhexanoic lactone was prepared from the brucine salt of the hydroxy-acid. This salt, prepared as described for the 1-phenylethylamine salt, had m. p. 91°, raised to 97·5° after ten recrystallisations from acetone. Decomposition of the resulting needles gave (+)-4-hydroxy-4-methylhexanoic lactone, b. p. 64°/0·1 mm., $\alpha_{\rm D}^{20}$ +7·15° (*l*, 0·5). The m. p. of the salt and the rotation of the lactone were not altered by two further recrystallisations.

Oxidations.—(a) *With potassium permanganate in concentrated alkaline solution.* (+)-α-Methylbutyric acid, $\alpha_{\rm D}^{20}$ +3·1° (*l*, 0·5), gave α-hydroxy-α-methylbutyric acid, b. p. 117°/11 mm., m. p. and mixed m. p. 71°, $\alpha_{\rm D}^{20}$ 0·00° (Found : equiv., 117·1. Calc. for $C_5H_{10}O_3$: equiv., 118).

(−)-α-Phenylpropionic acid, $\alpha_{\rm D}^{20}$ −9·07° (*l*, 0·5), gave α-hydroxy-α-phenylpropionic acid, m. p. and mixed m. p. 89°, $\alpha_{\rm D}^{20}$ 0·00° (*l*, 0·5) (Found : equiv., 166·5. Calc. for $C_9H_{10}O_3$: equiv., 166).

(+)-4-Methylhexanoic acid, $\alpha_{\rm D}^{20}$ +1·00° (*l*, 0·5), gave 4-hydroxy-4-methylhexanoic acid, which, after repeated distillation with benzene, gave the lactone, b. p. 65°/0·5 mm., $\alpha_{\rm D}^{20}$ 0·00° (*l*, 0·5) (Found : equiv., 128·3. Calc. for $C_7H_{12}O_2$: equiv., 128).

(+)-γ-Phenylvaleric acid, $\alpha_{\rm D}^{20}$ +1·84° (*l*, 0·5), gave γ-hydroxy-γ-phenylvaleric acid, b. p. 82°/0·1 mm., m. p. and mixed m. p. 104·5° (Found : equiv., 194. Calc. for $C_{11}H_{14}O_3$: equiv., 194), which, after repeated distillation with benzene, gave the (±)-lactone, b. p. 122°/1·0 mm., $\alpha_{\rm D}^{20}$ 0·00° (*l*, 0·5).

(b) *With potassium manganate in dilute alkaline solution.* (+)-4-Methylhexanoic acid, $\alpha_{\rm D}^{20}$ +2·00° (*l*, 1·0), gave (+)-4-hydroxy-4-methylhexanoic lactone, b. p. 85°/2 mm., $\alpha_{\rm D}^{20}$ +1·43° (*l*, 1·0) (Found : equiv., 126·9).

(+)-γ-Phenylvaleric acid, $\alpha_{\rm D}^{20}$ +1·84° (*l*, 0·5), gave γ-hydroxy-γ-phenylvaleric acid, b. p. 102°/1 mm., m. p. 107·5—111·5° (Found : equiv., 194·1. Calc. for $C_{11}H_{14}O_3$: equiv., 194), converted by repeated distillation with benzene into the (+)-lactone, b. p. 123°/1 mm., $\alpha_{\rm D}^{20}$ +4·99° (*l*, 0·5).

(c) *With potassium permanganate in dilute alkaline solution.* (+)-4-Methylhexanoic acid, $\alpha_{\rm D}^{20}$ +2·00° (*l*, 1·0), gave (+)-4-hydroxy-4-methylhexanoic lactone, b. p. 85°/2 mm., $\alpha_{\rm D}^{20}$ +0·61° (*l*, 1·0) (Found : equiv., 127·6).

Thanks are expressed to Imperial Chemical Industries Limited for a grant.

BATTERSEA POLYTECHNIC, LONDON, S.W.11.
[Present address (of M. C. R. S.), UNIVERSITY OF SOUTHAMPTON.]

[*Received, June 24th,* 1953.]