436. *The Oxidation of Carboxylic Acids Containing a Tertiary Carbon Atom.*

By J. KENYON and M. C. R. SYMONS.

Contrary to the commonly held view, hydroxy-carboxylic acids $RR'C(OH)\cdot[CH_2]_n\cdot CO_2H$ are obtained from the corresponding branched-chain carboxylic acids by potassium permanganate in dilute alkaline solution only in limited yield and only when $n = 2$. When $n = 0$ or 2, the use of permanganate in *concentrated* alkaline solution gives yields of 50—90%. When $n = 2$, replacing permanganate by manganate in dilute alkaline solution gives the hydroxy-acids in 70—80% yield. Neither procedure leads to β-hydroxy-acids.

FOR study of the mechanism of replacement by hydroxyl of a hydrogen atom attached to a tertiary carbon atom, a reaction was chosen which is given in many textbooks as a general method for the preparation of hydroxy-carboxylic acids (*e.g.*, Rodd, " Chemistry of Carbon Compounds," Elsevier, Amsterdam, 1951, p. 780), namely, the oxidation of branched-chain carboxylic acids by the use of potassium permanganate in dilute alkaline solution :

$$RR'CH\cdot[CH_2]_n\cdot CO_2H \longrightarrow RR'C(OH)\cdot[CH_2]_n\cdot CO_2H$$

The factual basis for this general method is, however, somewhat slender. Hydroxy-acids constitute only a small part of the oxidation products of branched-chain carboxylic acids (Meyer, *Annalen*, 1883, **219**, 234; **220**, 1; Miller, *ibid.*, 1880, **200**, 261; Ladenburg and Rugheimer, *Ber.*, 1880, **13**, 373; Fittig and Bredt, *Annalen*, 1881, **208**, 59; Fittig and Thron, *ibid.*, 1899, **304**, 285), and, since 1899, only two references to the use of this reaction have been found, neither of which reports the formation of the expected products (Lawrence, *J.*, 1899, 531; *Proc.*, 1900, 1541; 1901, 47; Linstead and Mann, *J.*, 1930, 2064).

Nevertheless, attempts have been made to convert several carboxylic acids into the corresponding hydroxy-acids by the use of the prescribed reagents (see 3rd col. of Table).

Oxidation of carboxylic acids to hydroxy-carboxylic acids.

		Yield (%) of hydroxy-acid by use of		
No.	Acid oxidized	$KMnO_4$ in dil. NaOH	$KMnO_4$ in conc. NaOH	K_2MnO_4 in dil. NaOH
1	$CHMeEt\cdot CO_2H$	trace	80	0
2	$CHMePh\cdot CO_2H$	,,	90	0
3	$CHMe_2\cdot CH_2\cdot CO_2H$	0	0	0
4	$CHMeEt\cdot CH_2\cdot CO_2H$	0	0	0
5	$CHMeEt\cdot CH_2\cdot CH_2\cdot CO_2H$	10	70	80
6	$CHMePh\cdot CH_2\cdot CH_2\cdot CO_2H$	10	50	70
7	$CHMeBu\cdot CH_2\cdot CH_2\cdot CO_2H$	—	60	70

Acids nos. 1, 4, 5 underwent little or no oxidation with the following reagents: H_2O_2 (30%) in H_2O, AcOH, or $H\cdot CO_2H$: $K_2Cr_2O_7$ in dil. H_2SO_4 at 100°: $KMnO_4$ in boiling $COMe_2$ for 12 hr. Acid no. 2 underwent rapid reaction with Fenton's reagent at room temperature with copious evolution of CO_2: acetophenone (20%) and unchanged material (50%) were isolated. Acids nos. 1 and 5 appeared to be completely degraded to CO_2 by CrO_3 in AcOH and Ac_2O.

In each instance, a quantity of potassium permanganate was consumed equivalent to that required for the oxidation of the acid to the corresponding hydroxy-acid but only very snall quantities of the corresponding α-hydroxy-acids, no β-hydroxy-acids, and less than 10% of the theoretical quantity of γ-hydroxy-acids could be isolated. The formation of large quantities of carbonate, and the recovery of about 50% of unchanged starting material, showed that the main oxidation was deep-seated and that the reaction is unsatisfactory as a general preparative method. Experiments at lower temperatures and greater dilutions were no more satisfactory.

Numerous attempts to effect the desired type of oxidation by other oxidants were uniformly unsuccessful (see footnotes to Table). The conditions employed for oxidation with potassium dichromate were similar to those used by Lawrence (*J.*, 1899, 531), in the conversion of *iso*propylsuccinic acid into terebic acid and of *iso*propylglutaric acid into terpenylic acid, but differed in that the reaction mixture was not homogeneous.

Accordingly, attention was again directed to potassium permanganate in alkaline solution. Since the required oxidation represents a two-electron change (as distinct from the reduction of permanganate to manganese dioxide, which is a three-electron change), it was expected that the reaction process might be considerably simplified by (*a*) greatly increasing the concentration of alkali so that the permanganate could be reduced only as far as manganate (a one-electron change) and (*b*) using potassium manganate in dilute alkaline solution (reduction to manganese dioxide is then a two-electron change). Each of these modifications proved partly successful (see Table): method (*a*) gave very good yields of α- and γ-hydroxy-acids, but still no β-hydroxy-acids; method (*b*) gave good yields of γ-hydroxy-acids but no α- or β-hydroxy-acids. The most satisfactory method of preparing γ-hydroxy-acids from γ-branched-chain carboxylic acids is by a combination of the two procedures. This differs from the more usual oxidation with potassium permanganate in dilute alkaline solution in that, by suitable adjustment of the concentration of alkali, the two stages in reduction ($MnO_4' \longrightarrow MnO_4'' \longrightarrow MnO_2$) are consecutive and not simultaneous.

The failure to isolate even small quantites of β-hydroxy-acids may be due to the ready formation of substituted acrylic acids, which would rapidly be oxidised further under the conditions employed. The isolation of ketones RR'CO and large quantities of carbon dioxide from the products supports this suggestion.

EXPERIMENTAL

Preparation of Branched-chain Carboxylic Acids.—α-Methylbutyric acid, prepared in 61% yield from malonic ester, had b. p. 63—64°/2 mm. (Found : equiv., 102·3. Calc. for $C_5H_{10}O_2$: equiv., 102); its *p*-bromophenacyl ester had m. p. 54·5° (Kenyon and Ross, *J.*, 1951, 3410, give m. p. 55°).

β-Methylvaleric acid, similarly prepared in 65% yield, had b. p. 63°/1 mm. (Found : equiv., 115·8. Calc. for $C_6H_{12}O_2$: equiv., 116); its *p*-bromophenacyl ester had m. p. 36·5° (Sabetay and Panouse, *Compt. rend.*, 1947, **225**, 887, give m. p. 36°).

4-Methylhexanoic acid, prepared in 53% yield, had b. p. 85°/2 mm. (Found: equiv., 130. Calc. for $C_7H_{14}O_2$: equiv., 130); its p-*bromophenacyl* ester formed plates, m. p. 63—64° (Found : Br, 24·55. $C_{15}H_{19}O_3Br$ requires Br, 24·4%); its S-*benzylthiuronium* salt formed plates, m. p. 142° (Found : N, 9·65. $C_{15}H_{24}O_2N_2S$ requires N, 9·5%).

4-Methyloctanoic acid was prepared from 4-hydroxy-4-methyloctanoic lactone (see below) by Cason's procedure (*J. Amer. Chem. Soc.*, 1944, **66**, 1764). The lacton e(18 g.) and thionyl chloride (50 g.) in benzene (30 c.c.) were heated under reflux for 3 hr., then mixed with absolute ethanol (100 c.c.) and saturated at 0° with hydrogen chloride. Distillation of the product yielded ethyl 4-methyloctenoate (41·1 g.), b. p. 76—79°/3 mm., together with unchanged lactone (2 g.), b. p. 90—93°/2 mm. Hydrogenation of this (10 g.) in absolute ethanol (100 c.c.) at low pressure in the presence of platinum oxide (0·15 g.) during 0·5 hr. gave the saturated ester (7·9 g.; b. p. 108°/2 mm.) and thence by hydrolysis 4-methyloctanoic acid (6 g.), b. p. 110°/2 mm. (Found : equiv., 158·3. Calc. for $C_9H_{18}O_2$: equiv., 158). The S-*benzylthiuronium* salt formed needles, m. p. 135° (Found : N, 8·7. $C_{17}H_{28}O_2N_2S$ requires 8·65%).

α-Phenylpropionic acid (Campbell and Kenyon, *J.*, 1946, 25) gave a S-*benzylthiuronium* salt, plates, m. p. 146° (Found : N, 8·9. $C_{19}H_{24}O_2N_2S$ requires 8·9%).

α-Phenylpropionic acid (15 g.) in ethereal solution was reduced by lithium aluminium hydride (4·75 g.), and the resulting hydratropyl alcohol (11·9 g.; b. p. 62—63°/0·1 mm.) converted by phosphorus tribromide into hydratropyl bromide (12·6 g.; b. p. 49°/0·1 mm.), which, by condensation with malonic ester in the usual way, afforded γ-phenyl-*n*-valeric acid (5·6 g.), b. p. 98°/0·1 mm. [S-*benzylthiuronium* salt, plates, m. p. 134° (Found : N, 8·1. $C_{19}H_{24}O_2N_2S$ requires N, 8·1%)].

Preparation of Hydroxy-acids and Lactones.—α-Hydroxy-α-methylbutyric acid, prepared from ethyl methyl ketone (*via* the bisulphite compound and the cyanohydrin) in 63% yield, had b. p. 117·5°/12 mm., m. p. 69·5—70·5° (after sublimation) (Found : equiv., 117·2. Calc. for $C_5H_{10}O_3$: equiv., 118).

β-Hydroxy-β-methyl-*n*-valeric acid, prepared from ethyl bromoacetate and ethyl methyl ketone in 68% yield, had b. p. 138—139°/18 mm. (Found : equiv., 131·3. Calc. for $C_6H_{12}O_3$: equiv., 132).

4-Hydroxy-4-methylhexanoic lactone, prepared from ethylmagnesium bromide and ethyl lævulate by Cason's method (*loc. cit.*) in 61% yield; had b. p. 73°/0·5 mm. (Found : equiv., 127·6. Calc. for $C_7H_{12}O_2$: equiv., 128). The S-*benzylthiuronium* salt of the hydroxy-acid formed plates, m. p. 142° (Found : N, 9·4. $C_{15}H_{24}O_3N_2S$ requires N, 9·0%).

Atrolactic acid, prepared from acetophenone in 61% yield, had, after sublimation, m. p. 91·3—91·6° (Found : equiv. 165·7. Calc. for $C_9H_{10}O_3$: equiv., 166); its S-*benzylthiuronium* salt formed plates, m. p. 160° (Found : N, 8·6. $C_{17}H_{20}O_3N_2S$ requires N, 8·4%).

4-Hydroxy-4-methyloctanoic lactone, prepared from *n*-butylmagnesium bromide and ethyl lævulate in 60% yield, had b. p. 84°/1 mm. (Found : equiv., 156. Calc. for $C_9H_{16}O_2$: equiv., 156); the S-*benzylthiuronium* salt of the hydroxy-acid formed needles, m. p. 116·5—117° (Found : N, 8·25. $C_{17}H_{28}O_3N_2S$ requires N, 8·3%).

γ-Phenyl-γ-valerolactone, prepared from phenylmagnesium bromide and ethyl lævulate in 45% yield, had b. p. 123°/1 mm. The hydroxy-acid, obtained as a precipitate from an aqueous solution of its sodium salt on acidification at 0°, separated from light petroleum in needles, m. p. 103·5—104° (Found : equiv., 194·3. Calc. for $C_{11}H_{18}O_3$: equiv., 194); its S-*benzylthiuronium* salt formed plates, m. p. 127° (Found : N, 7·8. $C_{19}H_{24}O_3N_2S$ requires N, 7·8%).

Oxidations.—" AnalaR " potassium permanganate and sodium or potassium hydroxide were used. The products were identified by conversion into the *p*-bromophenacyl esters or benzylthiuronium salts (mixed m. p. determinations).

(a) *With potassium permanganate in dilute alkaline solution.* In earlier experiments, the general procedure recommended by Meyer (*loc. cit.*) was followed. In later experiments, variations of temperature and concentration were made but only 4-methylhexanoic acid underwent oxidation in the desired way, to give 4-hydroxy-4-methylhexanoic lactone in 8·6% yield. In all cases, much unchanged material was recovered, with carbon dioxide and other products of deep-seated oxidation. The results are in the Table.

(b) *With potassium manganate in dilute alkaline solution.* The following general procedure was adopted. Potassium manganate was prepared by heating a solution of potassium permanganate (6·3 g., 0·04 mol.) and potassium hydroxide (40 g.) in water (150 c.c.) on a steam-bath until the solution became green (30 min.). The cooled solution was partly neutralised with sulphuric acid (100 c.c.; 6N), the carboxylic acid (0·04 mol.) added, and the green solution kept at 90° until the green colour was discharged (10—30 min.). After removal of manganese dioxide, the solution was extracted with ether, and the aqueous layer acidified and again extracted with ether. This extract was dried ($MgSO_4$), the solvent evaporated off, and the product distilled under reduced pressure. When γ-hydroxy-acids were formed, the product was kept in a desiccator *in vacuo* over potassium hydroxide in order to convert them into lactones. The crude lactone was exhaustively shaken with saturated sodium hydrogen carbonate solution and then with ether. The ethereal layer was washed with water, dried ($MgSO_4$), and freed from solvent. The aqueous layer was acidified and treated in like manner. The results are in the Table.

(c) *With potassium permanganate in concentrated alkaline solution.* The following general procedure was adopted. The acid (0·02 mol.) in water (50 c.c.) containing potassium hydroxide (40 g.) was vigorously shaken with a solution (100 c.c.) of potassium permanganate (6·3 g., 0·04 mol.) and potassium hydroxide (20 g.), added drop-wise at 40° ($\pm$ 1°) during about 20 min. The resulting green solution was cooled in ice and shaken with sulphur dioxide until colourless, after which the manganese dioxide was removed. The products were isolated, as in (b) above. The results are in the Table.

(d) *Oxidation of γ-branched-chain acids by procedures* (b) *and* (c) *consecutively.* A solution of the acid (0·02 mol.) and potassium hydroxide (40 g.) in water (50 c.c.) was vigorously shaken at 40° with a solution (100 c.c.) containing potassium permanganate (2·1 g., 0·0167 mol.) and potassium hydroxide (6 g.), added drop-wise during *ca.* 6 min. The resulting green solution was partly neutralised with sulphuric acid (100 c.c.; 6N) and kept at 90° during 10 min., by which time the green colour was discharged. The products were isolated as in (b) above, the yields of γ-hydroxy-acids being between 70 and 80%.

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

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, March* 11*th*, 1953.]