72. *Experiments on the Synthesis of Carbonyl Compounds. Part III. Addition of Ethyl Acetoacetate to Ethyl Sorbate.*

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Addition of ethyl acetoacetate to ethyl sorbate has been realised and the product (I) reduced and degraded to (±)-7-*keto*-5-*methyloctanoic acid* (III). The structure of (III) has been proved by reduction to (±)-5-*methyloctanoic* acid (IV) which has been synthesised by an independent route.

IN connection with another investigation we wished to prepare 7-keto-5-methyloctanoic acid, $CH_3CO{\cdot}CH_2{\cdot}CH{\cdot}Me{\cdot}[CH_2]_3{\cdot}CO_2H$. It seemed possible that a convenient method for the preparation of this material was by way of the keto-diester (I) which would result from a Michael addition of ethyl acetoacetate to ethyl sorbate :

$$\begin{tikzcd}
\mathrm{CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et + CHMe{:}CH{\cdot}CH{:}CH{\cdot}CO_2Et} \arrow[r] & \mathrm{CH_3{\cdot}CO{\cdot}CH(CO_2Et){\cdot}CHMe{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CO_2Et}\ \text{(I.)} \arrow[d] \\
\text{(III.)}\ \mathrm{CH_3{\cdot}CO{\cdot}CH_2{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CO_2H} & \mathrm{CH_3{\cdot}CO{\cdot}CH(CO_2Et){\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CO_2Et}\ \text{(II.)} \arrow[l]
\end{tikzcd}$$

There appears to be no recorded instance in the literature of the addition of ethyl acetoacetate to sorbic esters, although malonic and cyanoacetic esters have been used and been found to give products corresponding, predominantly, to 1 : 4-addition (Vorländer, *Annalen*, 1906, **345**, 228; Kohler and Butler, *J. Amer. Chem. Soc.*, 1926, **48**, 1036; Farmer and Healey, *J.*, 1927, 1060; Farmer and Mehta, *J.*, 1930, 1610; Bloom and Ingold, *J.*, 1931, 2765).

In *tert.*-butanolic solution in the presence of potassium *tert.*-butoxide the reaction furnished the unsaturated *keto*-diester (I) in excellent yield. This was catalytically reduced with the aid of palladised strontium carbonate to the corresponding saturated *keto*-diester (II) which on hydrolysis with constant-boiling hydrochloric acid yielded (±)-7-*keto*-5-*methyloctanoic acid* (III), characterised as its *semicarbazone*, p-*bromophenacyl* and *ethyl* ester. The structure and homogeneity of (III) were proved by unequivocal synthesis of the corresponding saturated acid (IV) (p-*bromophenacyl* ester), obtained in almost theoretical yield by the modified Wolff–Kishner reduction (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) and synthesised as follows.

$$\begin{tikzcd}
\underset{\text{(V.)}}{\mathrm{CH_3{\cdot}CO{\cdot}[CH_2]_3{\cdot}Cl}} \arrow[r, "\mathrm{PrMgBr}"] & \underset{\text{(VI.)}}{\mathrm{CH_3{\cdot}CPr{:}CH{\cdot}[CH_2]_3{\cdot}Cl}} \arrow[r, "\mathrm{H_2-PtO_2}"] & \underset{\text{(VII.)}}{\mathrm{CH_3{\cdot}CHPr{\cdot}[CH_2]_3{\cdot}Cl}} \arrow[r, "\mathrm{KCN-}", "\mathrm{KOH}"'] & {} \\
& & \mathrm{CH_3{\cdot}CHPr{\cdot}[CH_2]{\cdot}_3CO_2H}\ \text{(IV.)} &
\end{tikzcd}$$

1-Chloropentan-4-one (V) and *n*-propylmagnesium bromide (cf. Cason, Brewer, and Pippen, *J. Org. Chem.*, 1948, **13**, 239—248) gave 5-*methylhept*-4-*enyl chloride* (VI), separated from unchanged ketone by oximation of the ketone, followed by distillation, and then reduced using Adams's catalyst and treated, without isolation, with potassium cyanide and then sodium hydroxide to give (±)-5-*methyloctanoic acid*, identical with the acid resulting from (III).

The evidence presented herein leaves, in our opinion, no doubt of the homogeneity or structure of (III). For the keto-esters (I) and (II) the position is not so clear, as complete absence of the analogous products formed by 1 : 2-addition cannot be assumed.

EXPERIMENTAL.

Ethyl 6-*Keto*-5-*methylhept*-2-*ene*-1 : 5-*dicarboxylate*.—Ethyl acetoacetate (98 g., 0·75 mol.) and ethyl sorbate (53 g., 0·38 mol.) were added to absolute *tert.*-butanol (150 ml.) in which potassium (2·5 g.) had been dissolved, and the mixture was refluxed in an oil-bath at 110—120° for 12 hours. The cold solution was poured into dilute sulphuric acid, and the oil taken up in benzene. After removal of the solvent and unreacted materials by distillation, the *ethyl* ester was obtained as an almost colourless oil (78 g., 75%), b. p. 120°/0·5 mm., n_D^{20} 1·4530 (Found : C, 61·9; H, 8·2. $C_{14}H_{22}O_5$ requires C, 62·2; H, 8·2%). It gave a deep-red colour with aqueous-alcoholic ferric chloride and absorbed bromine with great avidity.

Ethyl 6-*Keto*-5-*methylheptane*-1 : 5-*dicarboxylate* (II).—The unsaturated ester (I) (86 g.) was hydrogenated in alcohol in the presence of palladised strontium carbonate (3 g., 12%) until hydrogenation was complete (1 mol.). After removal of catalyst and solvent, the saturated *keto*-diester distilled as a colourless oil, b. p. 118°/0·2 mm., n_D^{20} 1·4479 (Found : C, 61·9; H, 9·2. $C_{14}H_{24}O_5$ requires C, 61·7; H, 8·8%).

7-*Keto*-5-*methyloctanoic Acid* (III).—The foregoing ester (69 g.) was refluxed with concentrated hydrochloric acid and water (200 ml. of each) until evolution of carbon dioxide ceased (6 hours). The oil was taken up in benzene, the residue remaining after removal of solvent was refluxed for 2 hours with sodium hydroxide (100 ml.; 5N.), and the solution was steam-distilled. Acidification of the residue furnished an oil which was isolated in the usual manner. 7-*Keto*-5-*methyloctanoic acid* was obtained thereby as a viscous oil (33 g., 75%), b. p. 114°/0·1 mm., n_D^{20} 1·4528 (Found : C, 62·8; H, 9·5%; equiv., 173. $C_9H_{16}O_3$ requires C, 62·8; H, 9·4%; equiv., 172). The p-*bromophenacyl* ester, crystallised from aqueous alcohol, had m. p. 60—61° (Found : C, 54·7; H, 5·6. $C_{17}H_{21}O_4Br$ requires C, 55·3; H, 5·7%), and the *semicarbazone* crystallised from ethyl acetate–dioxan in tiny prisms, m. p. 146—147° (Found : N, 17·7. $C_{10}H_{19}O_3N_3$ requires N, 18·3%).

Ethyl 7-*Keto*-5-*methyloctanoate*.—A mixture of the acid (55 g.), ethanol (100 ml.), benzene (100 ml.), and sulphuric acid (2 g.) was distilled through a Fenske column fitted with a phase-separator until no further separation took place. The cooled residue was washed with water, sodium hydrogen carbonate solution, and water successively. After removal of solvent, the *ester* was obtained as a colourless oil which distilled at 91—92°/0·5 mm. and had n_D^{20} 1·4362 (62 g., 97%) (Found : C, 65·7; H, 10·0. $C_{11}H_{20}O_3$ requires C, 66·0; H, 10·1%).

Wolff-Kishner Reduction of (III).—The foregoing keto-acid (10 g.) was reduced with sodium hydroxide (5 g.), hydrazine hydrate (13 ml.; 60%), and 2 : 2′-dihydroxydiethyl ether (75 ml.) in the manner described by Huang-Minlon (*loc. cit.*), and the reduced acid, (±)-5-*methyloctanoic acid*, isolated as an oil (9 g.), b. p. 150°/30 mm., n_D^{20} 1·4355 (Found : C, 68·1; H, 11·5%; equiv., 158. $C_9H_{18}O_2$ requires C, 68·3; H, 11·4%; equiv., 158). The *p*-bromophenacyl ester crystallised from aqueous alcohol in colourless plates, m. p. 46—46·5°, undepressed by admixture with the material prepared synthetically.

Synthesis of (±)-5-*Methyloctanoic Acid*.—1-Chloro-5-methylheptene (VI) was prepared as described by Cason *et al.* (*loc. cit.*) for the higher homologue, using *n*-propyl bromide (80 g.), magnesium (16 g.), and 1-chloropentan-4-one (80 g.; freshly distilled). The product boiled at 70—73°/22 mm. and contained about 15% of ketone (oxime value). The crude product (41 g.) was thoroughly shaken with a solution of hydroxylamine hydrochloride (20 g.) in water (100 ml.), sufficient sodium hydroxide solution being added from time to time to keep the aqueous solution alkaline to *p*-bromophenol-blue. When no further alkali was needed, the chloro-compound was extracted with benzene. The organic layer was washed with water, dried ($CaCl_2$), and distilled to give the *chloro-olefin* as a colourless, mobile liquid (36 g.), b. p. 72°/22 mm., n_D^{20} 1·4514, possessing an unpleasant odour (Found : C, 65·5; H, 10·3. $C_8H_{15}Cl$ requires C, 65·5; H, 10·2%).

The above chloro-compound (34 g., 0·23 mol.) was hydrogenated in 95% ethanol in the presence of Adams's catalyst (0·2 g.). Absorption of hydrogen was extremely rapid and finally stopped when a total of 6·3 l. had been absorbed (theory, 5·2 l.). After removal of catalyst by filtration, the filtrate was carefully neutralised with 10N-sodium hydroxide, the amount of the latter being in accord with that required if the excess of hydrogen was used to displace chlorine as hydrogen chloride. A solution of potassium cyanide (32 g.) in water (50 ml.) was then added to the filtrate containing the saturated chloro-compound together with potassium iodide (5 g.) and ethanol (150 ml.), and the mixture digested on the steam-bath for 30 hours. After cooling, the supernatant liquid was decanted from the solid material which was washed with fresh ethanol (50 ml.). Sodium hydroxide (50 ml.; 10N.) was added to the combined alcoholic extracts, and the solution refluxed for a further 30 hours. Water was then added and the mixture steam-distilled to remove a small amount of an evil-smelling material, presumably the *iso*cyanide. Acidification (fume-cupboard) of the residue yielded (±)-5-methyloctanoic acid which was isolated in the usual manner as an oil, b. p. 150°/30 mm., n_D^{20} 1·4355 (Found : C, 68·2; H, 11·5%). The yield of this acid was 24 g. (66% based on chloro-olefin, or 81% if allowance is made for the extra hydrogen consumed during the hydrogenation of the chloro-olefin resulting in the formation of the corresponding paraffin).

The p-*bromophenacyl* ester separated from aqueous alcohol in colourless plates, m. p. 46—46·5° (Found: C, 57·6; H, 6·9. $C_{17}H_{23}O_3Br$ requires C, 57·5; H, 6·5%).

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