CI.—*A Synthesis of Certain Higher Aliphatic Compounds. Part III. A Variation of the Keto-acid Synthesis, constituting an Improved Method for the Extension of Normal Carbon Chains.*

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IN Part I of this series (Robinson and Robinson, J., 1925, **127**, 175), the synthesis of normal long-chain keto-acids,

$$CH_3{\cdot}[CH_2]_m{\cdot}CH_2{\cdot}CO{\cdot}[CH_2]_n{\cdot}CO_2H,$$

by the hydrolysis of condensation products of the form

$$CH_3{\cdot}[CH_2]_m{\cdot}C(CO{\cdot}CH_3)(CO_2Et){\cdot}CO{\cdot}[CH_2]_n{\cdot}CO_2Et$$

was described; the process gave only moderately satisfactory yields, owing to the fact that a varying but always a relatively considerable amount of the acid, $CO_2H{\cdot}[CH_2]_n{\cdot}CO_2H$, was recovered. Underlying this problem, the factors influencing the direction of fission of β-diketones are of fundamental importance, since it is clear that the recovery of the dibasic acid is due to hydrolysis initiated by the stage $CH_3{\cdot}[CH_2]_m{\cdot}C(CO{\cdot}CH_3)(CO_2Et){\cdot}CO{\cdot}[CH_2]_n{\cdot}CO_2Et \longrightarrow CH_3{\cdot}[CH_2]_m{\cdot}CH(CO{\cdot}CH_3){\cdot}CO_2Et + CO_2H{\cdot}[CH_2]_n{\cdot}CO_2Et$, which competes with the desired direction of change in which the acetyl group is removed as acetic acid.

An example of such competition of acyl groups in the hydrolysis of β-diketones has been quantitatively studied by Bradley and Robinson (J., 1926, 2356), who found in a series of substituted dibenzoylmethanes, $R{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}R'$, that hydrolysis by alkalis

occurred with production of the stronger of the acids, $R{\cdot}CO_2H$ and $R'{\cdot}CO_2H$, in preponderating amount.

This suggested two methods for the improvement of the yields in the keto-acid syntheses, namely, (*a*) the use of a β-ketonic ester, $R{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et$, such that $R{\cdot}CO_2H$ is a stronger acid than acetic acid, and (*b*) the acylation of a substituted ethyl acetoacetate by the group related to the weakest possible acid; this could clearly be achieved by removing the terminal carboxyl group from the acyl group and introducing it at the end of the alkyl chain. Thus, an acid $CH_3{\cdot}[CH_2]_m{\cdot}CH_2{\cdot}CO{\cdot}[CH_2]_n{\cdot}CO_2H$ can be obtained by the hydrolysis of the complexes

$$CH_3{\cdot}[CH_2]_m{\cdot}C(CO{\cdot}CH_3)(CO_2Et){\cdot}CO{\cdot}[CH_2]_n{\cdot}CO_2Et$$

or $CO_2Et{\cdot}[CH_2]_{n-1}{\cdot}C(CO{\cdot}CH_3)(CO_2Et){\cdot}CO{\cdot}[CH_2]_{m+1}{\cdot}CH_3$, and it was anticipated that the latter method would give the better yield because the dibasic acids are stronger than the fatty acids. In view of the accessibility of ethyl acetoacetate, practical effect has been given to the proposal (*b*) only, and actually the new process constitutes a great improvement and is applicable to the transformation of an acid $R{\cdot}CO_2H$ into $R{\cdot}CO{\cdot}CH_2{\cdot}[CH_2]_n{\cdot}CO_2H$, the accessory starting points being ethyl acetoacetate and $Br{\cdot}[CH_2]_n{\cdot}CO_2Et$. It is known (Le Sueur and Withers, J., 1915, **107**, 738) that Clemmensen's method (*Ber.*, 1913, **46**, 1837) can be advantageously used for the reduction of long-chain keto-acids, so we may proceed from $R{\cdot}CO_2H$ to $R{\cdot}[CH_2]_{n+2}{\cdot}CO_2H$ in a few simple stages, and can then repeat the process. The number of carbon atoms added in each stage of extension is limited only by the relative inaccessibility of the required ω-bromo-acids, but ethyl ω-bromodecoate can be obtained from sebacic acid and ethyl ω-bromoundecoate from undecenic acid (Walker and Lumsden, J., 1901, **79**, 1191), so an extension of 11 or 12 carbon atoms in each cycle of operations is quite feasible.

It is hoped that this development will be described in subsequent communications, and in the present memoir the conversion of certain acids, $R{\cdot}CO_2H$, into γ-keto-acids, $R{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$, and the related alkylbutyrolactones is recorded.

Undecoic, undecenic and elaidic acids were converted into the chlorides and condensed with the sodium derivative of ethyl acetosuccinate in ethereal solution; the products were hydrolysed by means of dilute aqueous potassium hydroxide, at first in the cold and later on the steam-bath, and good yields of the keto-acids resulted.

By using benzoyl chloride, β-benzoylpropionic acid was obtained in about 41% yield, but β-*o*-nitrobenzoylpropionic acid could not be prepared by this method. This is in accord with anticipation

based on the theory already mentioned, and, from the same point of view, the failure to prepare a keto-dibasic acid by hydrolysing the ester $CO_2Et\cdot CH_2\cdot C(CO\cdot CH_3)(CO_2Et)\cdot CO\cdot[CH_2]_8\cdot CO_2Et$ is explicable. There is no further reference to these negative results in the experimental section.

The preparation of a diketo-acid succeeded, but, again, the keto-acids are stronger than the fatty acids and, as expected, the yield was poor. For this example, 10-*ketotridecoic acid* was synthesised by an application of the method of Parts I and II; its chloride and ethyl sodioacetosuccinate afforded an ester,

$$CH_3\cdot[CH_2]_2\cdot CO\cdot[CH_2]_8\cdot CO\cdot C(CO\cdot CH_3)(CO_2Et)\cdot CH_2\cdot CO_2Et,$$

which on hydrolysis gave 4 : 13-*diketopalmitic acid.* This acid is of interest in that, on reduction and dehydration, it should furnish an unsaturated palmitolactone,

$$CH_3\cdot[CH_2]_2\cdot CH{:}CH\cdot[CH_2]_7\cdot\overbrace{CH\cdot[CH_2]_2\cdot CO}^{O},$$

which, according to a recent patent (E.P. 292,962 of 1929), has been isolated from female secretory organs, and is claimed to be the physiologically active ovarian hormone.

These statements, in view of the recent remarkable work of Butenandt (compare *Chem.-Ztg.*, 1929, 938) on progynon, must await further confirmation; several authorities have, however, expressed the view that there exists more than one ovarian hormone.

5-*Ketopalmitic acid* has been obtained from lauryl chloride and ethyl sodio-α-acetoglutarate, followed by hydrolysis of the product; the opportunity is taken to describe the 7- and 8-*ketopalmitic acids*, which were obtained by applications of the method of Part I. These substances are the conceivable hydration products of palmitolic acid and have been prepared in connexion with an investigation of the course of that reaction.

EXPERIMENTAL.

4-*Ketomyristic Acid*, $CH_3\cdot[CH_2]_9\cdot CO\cdot[CH_2]_2\cdot CO_2H$.—Sodium (2·3 g.) was granulated under toluene, washed with ether, and suspended in anhydrous ether (120 c.c.), and ethyl acetosuccinate (21·6 g.) gradually added, the solution of the sodium being completed by heating on the steam-bath for 10 minutes. A solution of undecoyl chloride (obtained from 17·6 g. of the acid by the action of pure thionyl chloride and removal of the excess of the reagent in a vacuum) in ether (20 c.c.) was slowly added to the cooled mixture, which was kept for 12 hours and then refluxed for 10 minutes. The product was isolated and agitated for 4½ hours with aqueous potassium hydroxide (1200 c.c. of 4%). After acidification with acetic acid and isolation by means of ether, it was submitted to the action of boiling 5% sulphuric acid for 4 hours, and the hydrolysis

was completed by boiling with 8% sodium hydroxide solution for 1 hour. The product crystallised from light petroleum (b. p. 60—80°) in colourless plates (once crystallised; yield, 8·5 g. or 72%), m. p. 87° (Found : C, 69·7; H, 10·7. Calc. for $C_{14}H_{26}O_3$: C, 69·4; H, 10·7%) alone or mixed with the specimen previously prepared by another method (Robinson and Robinson, J., 1926, 2204).

γ-n-Decylbutyrolactone, $CH_3{\cdot}[CH_2]_9{\cdot}CH{\cdot}CH_2{\cdot}CH_2$.—A solution of 4-ketomyristic acid (4 g.) in anhydrous ethyl alcohol (90 g.) was gradually added to sodium (7·5 g.) contained in a flask heated at 150—160°. After 1½ hours, the alcohol was evaporated, and the residue mixed with dilute hydrochloric acid. The product was collected by means of ether, boiled for 30 minutes with 15% hydrochloric acid (120 c.c.) in order to ensure the formation of the *lactone* from the hydroxy-acid, washed in ethereal solution with aqueous sodium carbonate, freed from the solvent, and crystallised from light petroleum and later from methyl alcohol; it formed long slender needles, m. p. 30—31° (yield, 2·7 g. or 71%) (Found : C, 74·3; H, 11·3. $C_{14}H_{26}O_2$ requires C, 74·3; H, 11·5%).

5-Ketopalmitic Acid, $CH_3{\cdot}[CH_2]_{10}{\cdot}CO{\cdot}[CH_2]_3{\cdot}CO_2H$.—Ethyl sodioacetosuccinate dissolved in ether when prepared as described above, but ethyl sodio-α-acetylglutarate separated as a colourless powder and the solution of the sodium was thereby hindered.

The reaction in the present case was carried out in the usual manner, sodium (1·4 g.), ether (140 c.c.), ethyl α-acetylglutarate (13·9 g.), and lauryl chloride (13·0 g.) being used; finally, the mixture was refluxed for 1 hour and the product isolated and shaken with 3% sodium hydroxide solution (850 c.c.) for 12 hours. The mixture was then concentrated on the steam-bath for 1 hour and the *acid* obtained by addition to ice and hydrochloric acid was crystallised from light petroleum, methyl alcohol and benzene, forming colourless plates, m. p. 88° (Found : C, 71·2; H, 11·2. $C_{16}H_{30}O_3$ requires C, 71·1; H, 11·1%). On reduction by means of sodium and absolute ethyl alcohol, and treatment of the product with boiling 15% hydrochloric acid, 5-ketopalmitic acid furnished *δ-undecylvalerolactone*, which crystallised from light petroleum in plates, m. p. 29·5—30·0° (Found : C, 75·5; H, 11·8. $C_{16}H_{30}O_2$ requires C, 75·6; H, 11·8%).

7-Ketopalmitic Acid, $CH_3{\cdot}[CH_2]_8{\cdot}CO{\cdot}[CH_2]_5{\cdot}CO_2H$.—The condensation product from ethyl sodio-α-acetodecoate (16·5 g. of the ester) and 6-carbethoxyhexoyl chloride (13 g.), prepared in ethereal solution, was isolated and hydrolysed successively by agitation for 5 hours with 3% potassium hydroxide solution (700 c.c.), by boiling with 5% sulphuric acid (500 c.c.) for 24 hours, and, after steam-

distillation for the separation of methyl *n*-nonyl ketone, by boiling with 3½% potassium hydroxide solution for 6 hours. The *acid*, purified through its sparingly soluble sodium salt (4 g., or 22%) and then by crystallisation from light petroleum and from methyl alcohol, formed colourless plates, m. p. 78° (Found: C, 71·2; H, 11·0. $C_{16}H_{30}O_3$ requires C, 71·1; H, 11·1%).

8-*Ketopalmitic Acid*, $CH_3{\cdot}[CH_2]_7{\cdot}CO{\cdot}[CH_2]_6{\cdot}CO_2H$.—By an application of the method of Grün and Wirth (*Ber.*, 1922, **55**, 2207) for the preparation of ethyl hydrogen sebacate, ethyl suberate (96 g.) gave ethyl hydrogen suberate (49 g.), which furnished 7-carbethoxyheptoyl chloride, b. p. 182°/69 mm. (yield, 85%).

The product from the interaction of ethyl sodio-2-acetononoate (22·8 g. of the ester) and 7-carbethoxyheptoyl chloride (22·2 g.) in dry ether was hydrolysed successively by shaking with 5% potassium hydroxide solution (400 c.c.) for 20 hours, by boiling with 5% sulphuric acid (400 c.c.) for 24 hours, and, after steam distillation, by boiling with 5% sodium hydroxide solution (250 c.c.) for 24 hours. The sodium salt, which separated on cooling, was decomposed; the *acid* crystallised from methyl alcohol (yield, 5 g. or 18%) in plates, m. p. 77—78° (Found: C, 70·8; H, 11·2. $C_{16}H_{30}O_3$ requires C, 71·1; H, 11·1%). The oily oxime was converted by sulphuric acid into an amide, m. p. 58°.

The hydration of palmitolic acid should yield a mixture of 7- and 8-ketopalmitic acids in which the latter should preponderate, for the reasons explained in Part II (J., 1926, 2205).

The action of sulphuric acid, followed by that of water, on palmitolic acid has been studied by Bodenstein (*Ber.*, 1894, **27**, 3400), who obtained a ketopalmitic acid, m. p. 74°, the oily oxime of which yielded, on transposition, an amide, m. p. 57·5—58°.

The freezing points of mixtures of 8-ketopalmitic acid and 7-ketopalmitic acid have been determined, and will be published in detail in connexion with a record of experiments on the hydration of palmitolic acid. It may be mentioned, however, that the freezing point of a mixture containing 30% of 7-ketopalmitic acid is about 6° lower than that of pure 8-ketopalmitic acid. Since it is certain that the 8-ketopalmitic acid is the major product of the hydration of palmitolic acid, it is apparent that the acid obtained by Bodenstein contained at most 30%, and may have contained as little as 10—20%, of the isomeride.

4-*Keto*-Δ^{13}-*tetradecenoic Acid*, $CH_2{:}CH{\cdot}[CH_2]_8{\cdot}CO{\cdot}[CH_2]_2{\cdot}CO_2H$.—The condensation product from ethyl sodioacetosuccinate (21 g. of the ester) and undecenoyl chloride (19·2 g.) was isolated and hydrolysed successively by agitation with 5% potassium hydroxide solution (1000 c.c.) for 8 hours, by boiling with 5% sulphuric acid

(700 c.c.) for 7 hours, and by boiling with 4½% potassium hydroxide solution for 4 hours. The mixture was acidified and steam-distilled in order to remove a little unchanged undecenoic acid; the residual *acid* crystallised from light petroleum in colourless plates, m. p. 79·5° (yield, 14·8 g. or 55%) (Found: C, 69·6; H, 9·7. $C_{14}H_{24}O_3$ requires C, 70·0; H, 10·0%).

γ-Δ⁹-Decenylbutyrolactone was obtained in 89% yield by reducing the acid (6 g.) in anhydrous alcohol (150 g.) with sodium (10 g.) under the usual conditions and subsequent treatment with boiling 15% hydrochloric acid. The lactone crystallised from light petroleum in needles, m. p. 26—27° (Found: C, 74·8; H, 10·7. $C_{14}H_{24}O_2$ requires C, 75·0; H, 10·7%). A solution in chloroform absorbed bromine, and this lactone is quite different from the decylbutyrolactone previously described.

trans-4-*Keto*-Δ¹²-*heneicosenoic Acid*,

$$CH_3{\cdot}[CH_2]_7{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO{\cdot}[CH_2]_2{\cdot}CO_2H.$$—Elaidyl chloride (30·2 g.) and ethyl sodioacetosuccinate (from 21·6 g. of the ester) were brought into reaction in ethereal solution (200 c.c.) in the usual manner and after 12 hours the mixture was boiled for 20 minutes. The product was agitated with 3% potassium hydroxide solution (1000 c.c.) for 8 hours and, after the addition of 30% aqueous potassium hydroxide (25 c.c.), the mixture was boiled for 2 hours. The solid obtained on acidification was crystallised from light petroleum (b. p. 40—60°); after further purification through the sparingly soluble sodium salt and by crystallisation from light petroleum and then from methyl alcohol, the *acid* formed lustrous plates, m. p. 82·5° (yield, 49%) (Found: C, 74·4; H, 11·1. $C_{21}H_{38}O_3$ requires C, 74·6; H, 11·2%).

γ-Δ⁸-Heptadecenylbutyrolactone,

$$CH_3{\cdot}[CH_2]_7{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}\overset{\overset{\Large O}{\frown}}{CH}{\cdot}CH_2{\cdot}CH_2{\cdot}CO.$$—The foregoing acid (9·8 g.), dissolved in absolute alcohol (200 g.), was added in the course of 15 minutes to sodium (15 g.) heated in an oil-bath at 140—150°. The sodium disappeared after 1 hour, and the product was isolated and boiled for 1 hour with 15% hydrochloric acid (180 c.c.). After being washed in ethereal solution with aqueous sodium carbonate, the crude *lactone* was washed with a little light petroleum; it then crystallised from this solvent (b. p. 40—60°) in colourless plates, m. p. 42° (yield, 6·1 g. or 65%) (Found: C, 78·4; H, 11·9. $C_{21}H_{38}O_2$ requires C, 78·3; H, 11·8%). The unsaturated nature of this substance was confirmed by noting its absorption of bromine in chloroform solution.

10-*Ketotridecoic Acid*, $CH_3{\cdot}[CH_2]_2{\cdot}CO{\cdot}[CH_2]_8{\cdot}CO_2H$.—Ethyl sodio-2-acetobutyrate (from 31·6 g. of the ester) was prepared in dry ether

(250 c.c.), and 9-carbethoxynonoyl chloride (46 g.) gradually added to the solution, which was kept for 12 hours and then refluxed for 20 minutes. The product was hydrolysed in the usual manner with cold 4% potassium hydroxide solution, boiling 6% sulphuric acid, and finally boiling 4% potassium hydroxide solution. The *keto-acid* was separated from sebacic acid by crystallisation from light petroleum, but this was a tedious operation and the yield was poor. The white plates had m. p. 63° (Found : C, 68·6; H, 10·4. $C_{13}H_{24}O_3$ requires C, 68·4; H, 10·5%).

4 : 13-*Diketopalmitic Acid*,

$$CH_3{\cdot}[CH_2]_2{\cdot}CO{\cdot}[CH_2]_8{\cdot}CO{\cdot}[CH_2]_2{\cdot}CO_2H.$$

10-Ketotridecoic acid (4 g.) was converted into its chloride by the action of thionyl chloride at 60°; decomposition occurred if the temperature was raised; the excess of reagent was removed in a vacuum. The interaction of the chloride with ethyl sodioaceto-succinate (4 g. of the ester) was carried out in the usual manner in dry ethereal solution, and the product was hydrolysed by shaking it for 12 hours with 3% aqueous potassium hydroxide (400 c.c.) and then concentrating the solution on the steam-bath for 1 hour. The *acid* precipitated on acidification crystallised from light petroleum, and then from ethyl acetate, in plates, m. p. 101° (Found : C, 67·7; H, 9·8. $C_{16}H_{28}O_4$ requires C, 67·6; H, 9·9%).

β-*Benzoylpropionic Acid.*—The applicability of the general method was further confirmed by the preparation of this acid by the usual procedure. The product from ethyl sodioacetosuccinate (12·5 g. of the ester) and benzoyl chloride (8·8 g.) was hydrolysed by cold 1½% aqueous potassium hydroxide (1200 c.c.) for 24 hours, and the solution concentrated on the steam-bath to about 100 c.c. The mixed acids were regenerated and collected and benzoic acid was removed by sublimation at 100°. The residue (4 g.), crystallised from benzene, had m. p. 116°, alone or mixed with a specimen prepared by the action of aluminium chloride on a mixture of benzene and succinic anhydride.

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