611. *Synthetic Long-chain Aliphatic Compounds. Part V.** n-*Nonatricosanoic and* n-*Hexapentacosanoic Acids.*

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In continuation of attempts to ascend the homologous series of the straight-chain fatty acids, 18-ketononatricosanoic and 18-ketohexapentacosanoic acids † have been synthesised by our general method (Bowman, *J.*, 1950, 325) and have been reduced to the corresponding saturated acids.

In Part II (*J.*, 1950, 174), we reported the synthesis of *n*-tricosanoic acid by using the ester (I; $n = 7$, R = Et) as a means of extending the chain:

$$\underset{\text{(I.)}}{(RO_2C)_2CH\cdot[CH_2]_n\cdot CO_2R} \xrightarrow[\text{3CH}_2\text{Ph·OH}]{\text{Na–}} (CH_2Ph\cdot O_2C)_2CNa\cdot[CH_2]_n\cdot CO_2\cdot CH_2Ph$$

$$\xrightarrow[\text{(b) H}_2\text{–Pd; (c) –2CO}_2]{\text{(a) R'COCl (III.);}} \underset{\text{(IV.)}}{R'CO\cdot[CH_2]_{n+1}\cdot CO_2H} \longrightarrow \underset{\text{(V.)}}{R'\cdot[CH_2]_{n+2}\cdot CO_2H}$$

As it was clearly desirable to use a longer molecule for this purpose, we chose methyl hexadecane-1 : 1 : 16-tricarboxylate (I; $n = 15$, R = Me), which was prepared by two different routes from readily available starting materials.

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* Part IV, *J.*, 1951, 1087.

† Geneva notation ($CO_2H = 1$) is used throughout.

First, diethyl hexadecane-1 : 16-dicarboxylate (VI) (Swann, Oehler, and Pinkney, *Org. Synth.*, 1941, **21**, 48) was treated with ethyl oxalate in the presence of sodium ethoxide by a modification of Floyd and Miller's method (*J. Amer. Chem. Soc.*, 1947, **69**, 2354), to give mainly the mono-oxalo-derivative (VII) which, without further purification, was thermally degraded to the crude triester (VIII); hydrolysis then yielded a product from which the pure tricarboxylic acid (IX) was obtained, and this was esterified with methanol to the crystalline ester (I; $n = 15$, R = Me); a significant amount of the corresponding tetracarboxylic acid (X) was also obtained.

$$\underset{\text{(VI.)}}{\mathrm{EtO_2C{\cdot}[CH_2]_{15}{\cdot}CH_2{\cdot}CO_2Et}} \longrightarrow \underset{\text{(VII.)}}{\mathrm{EtO_2C{\cdot}[CH_2]_{15}{\cdot}CH(CO_2Et){\cdot}CO{\cdot}CO_2Et}} \longrightarrow$$

$$\underset{\text{(VIII.)}}{\mathrm{EtO_2C{\cdot}[CH_2]_{15}{\cdot}CH(CO_2Et)_2}} \longrightarrow \underset{\text{(IX.)}}{\mathrm{HO_2C{\cdot}[CH_2]_{15}{\cdot}CH(CO_2H)_2}} \longrightarrow (\mathrm{I};\ n = 15,\ \mathrm{R = Me})$$

$$\mathrm{(HO_2C)_2CH{\cdot}[CH_2]_{14}{\cdot}CH(CO_2H)_2}\quad \text{(X.)}$$

Alternatively, aleuritic acid (XI) was converted by Hunsdiecker's method (*Ber.*, 1943, **76**, *B*, 142) into the unsaturated acid (XII) which on catalytic hydrogenation and subsequent esterification furnished the ester (I; $n = 15$, R = Me) identical with the product obtained by the first route.

$$\underset{\text{(XI.)}}{\mathrm{HO{\cdot}[CH_2]_6{\cdot}CH(OH){\cdot}CH(OH){\cdot}[CH_2]_7{\cdot}CO_2H}} \xrightarrow[\text{(b) Zn–MeOH}]{\text{(a) HBr–HAc}} \mathrm{Br{\cdot}[CH_2]_6{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2Me}$$

$$\xrightarrow[\text{hydrolysis}]{\text{Malonation;}} \underset{\text{(XII.)}}{\mathrm{CH(CO_2H)_2{\cdot}[CH_2]_6{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H}} \xrightarrow[\text{MeOH}]{\mathrm{H^{\cdot}};} (\mathrm{I};\ n = 15,\ \mathrm{R = Me})$$

The ester (I; $n = 15$, R = Me) was used in preliminary experiments on the ascent of the series as follows. Purified behenic acid was converted by reaction with oxalyl chloride into its chloride (III; $\mathrm{R' = C_{21}H_{43}}$), and this was treated with the tribenzyl sodio-derivative of (IX). Debenzylation and decarboxylation in the usual manner then furnished 18-ketononatricosanoic acid (IV; $n = 15$, $\mathrm{R' = C_{21}H_{43}}$) in satisfactory yield and purity, and this was reduced by Huang-Minlon's method (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) to *n*-nonatricosanoic acid.

Repetition of the keto-acid synthesis, the $\mathrm{C_{39}}$ acid being used in place of behenic acid, gave crude 18-ketohexapentacosanoic acid (IV; $n = 15$, $\mathrm{R' = C_{38}H_{77}}$) (m. p. 117—118°) in 86% yield, and after some difficulty (see p. 2751) this was purified and had m. p. 119·2—120·2°. On reduction (see p. 2751), this afforded *n*-hexapentacosanoic acid, $\mathrm{C_{55}H_{111}{\cdot}CO_2H}$, in high yield.

We regard the foregoing work as exploratory in the handling of very long-chain compounds; and experiments are in progress to determine whether the rather wide melting-point ranges of the $\mathrm{C_{56}}$ derivatives are due to the length of chain or to impurity.

EXPERIMENTAL.

The methods of effecting the ketone synthesis were those already described (Bowman, *J.*, 1950, 325) except that the sodium ethoxide required for the preparation of the sodio-malonic esters was obtained by use of an aliquot portion of a standard solution of sodium ethoxide in pure absolute ethanol.

Ethyl Hexadecane-1 : 16-*dicarboxylate* (VI).—The ester was prepared according to the method described in *Org. Synth.* (*loc. cit.*) from potassium ethyl sebacate. The crude product, m. p. 41°, was separated by distillation *in vacuo* into two fractions, (*a*) b. p. 180°/1 mm., m. p. 46° (80%), and (*b*) b. p. 220°/1 mm., m. p. 64° (20%), consisting of substantially pure ethyl tetracosane-1 : 24-dicarboxylate. Fraction (*a*) was further purified by recrystallisation from light petroleum (b. p. 60—80°) to give material, m. p. 47° (constant). A sample of the latter was hydrolysed to the acid, m. p. 124·5° (lit., m. p. 124°), the solubility of which in acetone and ethylene dichloride at 20° was *ca.* 2% and 4%, respectively.

Hexadecane-1 : 1 : 16-*tricarboxylic Acid* (IX).—(*a*) Sodium (2·3 g., 0·1 mol.) was dissolved in dry ethanol (50 ml.) in a flask fitted with a short fractionating column suitable for use under reduced pressure, and the solution evaporated to dryness *in vacuo*. A solution of ethyl oxalate (14·6 g., 0·1 mol.) and ethyl hexadecane-1 : 16-dicarboxylate (38 g., 0·1 mol.) in toluene (200 ml.) was then added, and the mass kept at 45°/90 mm. for 12 hours, during which ethanol (3·7 g.), in the form of its azeotrope with toluene, was collected. The reaction mixture was then acidified at 0° with excess of hydrochloric acid, and the oxalo-derivatives extracted from the organic layer by shaking it with a solution of sodium hydroxide (2 g.) in water (125 ml.) and acetone (125 ml.) at 0°. The bulked acetone extracts were washed with fresh toluene and acidified at 0° in the presence of benzene (200 ml.). Evaporation of the benzene solution furnished the crude oxalo-derivatives (24 g.), and the bulked toluene solutions afforded unchanged ethyl hexadecane-1 : 1 : 16-tricarboxylate (21 g.).

The oxalo-derivative was heated at 160—180° under 2 mm. pressure for 3 hours, giving 21 g. of crude residue, hydrolysis of which in the usual manner furnished an acid of m. p. 87—100° which was separated as follows. The crude product was dissolved in acetone (100 ml.), and the solution cooled to 10°, crude hexadecane-1 : 1 : 16-tricarboxylic acid, m. p. 117°, separating; dilution of the filtrate with an equal volume of water then precipitated the tricarboxylic acid, which was dissolved by heating and then allowed to cool, whereupon it (10·2 g.) separated; it had m. p. 90°. Evaporation of most of the acetone from the mother-liquor furnished crude hexadecane-1 : 1 : 16 : 16-tetracarboxylic acid (4 g.), which separated from aqueous acetone in clusters of prismatic needles, m. p. 138°, of the *hemihydrate* (Found : C, 58·2; H, 8·4. $C_{20}H_{34}O_8,\frac{1}{2}H_2O$ requires C, 58·4; H, 8·5%). Hexadecane-1 : 1 : 16-tricarboxylic acid was purified by crystallisation from aqueous acetone (5 vols.; 1 : 1) and then from ethylene dichloride, from which it separated in colourless laths as the *monohydrate*, m. p. 90·5° (Found : C, 60·5; H, 9·6. $C_{19}H_{34}O_6,H_2O$ requires C, 60·6; H, 9·6%).

Both the tri- and the tetra-carboxylic acid, when heated to 180°, furnished hexadecane-1 : 16-dicarboxylic acid, m. p. 124°.

(*b*) Hexadec-9-ene-1 : 1 : 16-tricarboxylic acid (XII) was prepared from aleuritic acid (120 g.) according to Hunsdiecker's procedures (*loc. cit.*; see Bloomquist and Holley, *J. Amer. Chem. Soc.*, 1948, **70**, 36), except that the crude 15-bromopentadec-9-enoic acid, m. p. 38—40°, was esterified with methanol by the method of Brown *et al.* (*J. Org. Chem.*, 1947, **12**, 160) by using chloroform (200 ml.), methanol (150 ml.), and sulphuric acid (2 ml.) to give the methyl ester as a yellow oil, b. p. 162—164°/0·1 mm. (Hunsdiecker gives b. p. 179°/2 mm.), which was treated with sodio-malonic ester as described. The unsaturated tricarboxylic acid (XII) (30 g.; m. p. 69—70°) was dissolved in ethyl acetate (300 ml.) and hydrogenated at atmospheric pressure by use of palladised charcoal (3% Pd). After removal of the catalyst, cooling of the filtrate to −5° deposited pure hexadecane-1 : 1 : 16-tricarboxylic acid, m. p. 90° (30 g.).

Methyl n-*Hexadecane*-1 : 1 : 16-*tricarboxylate*.—The free acid, prepared by either method, was esterified by dissolution in 10 times its weight of 1% methanolic hydrogen chloride; the solution was kept at 40° for 12 hours and then evaporated to dryness under reduced pressure. Two repetitions of this process and crystallisation of the residue from methanol (5 vols.) at 10° furnished the pure *ester* (90%) as colourless plates, m. p. 45° (Found : C, 65·8; H, 10·2. $C_{22}H_{40}O_6$ requires C, 66·0; H, 10·0%).

18-*Ketononatricosanoic Acid*.—A sample of behenic acid, obtained by hydrogenation of purified erucic acid, was crystallised in turn from ethanol (3 times), acetone, ethyl acetate, benzene, and dioxan to give material of f. p. 79·5°, m. p. 79·8°. The acid (8·5 g., 0·025 mol.) was dissolved in dry benzene (75 ml.), excess of oxalyl chloride (6 g.) added dropwise, and the solution refluxed for 0·5 hour. Excess of oxalyl chloride was then removed by distillation through a short Fenske column until the distillate was free from halogen. The resulting solution of behenoyl chloride was then added to a benzene solution (250 ml.) of tribenzyl sodio-hexadecane-1 : 1 : 16-tricarboxylate prepared in the usual manner from the methyl ester (10 g., 0·025 mol.), benzyl alcohol (8·1 g., 0·075 mol.), and sodium ethoxide (0·025 mol. as 7% solution in ethanol), and the mixture set aside at room temperature for 24 hours. After being worked up as usual, the keto-triester (23·8 g.) was hydrogenated in ethyl acetate solution (200 ml.) in the presence of palladised strontium carbonate (4 g.; 10% Pd) until the required volume of hydrogen had been absorbed. The reaction mixture was then warmed to 40° to dissolve some solid matter which had separated during the hydrogenation, and filtered, and the catalyst extracted with boiling ethyl acetate (100 ml.). The combined ethyl acetate solutions were boiled under reflux for 0·5 hour to effect decarboxylation and then cooled to room temperature; 18-*ketononatricosanoic acid* (10·1 g., 70%), m. p. 110°, separated and was crystallised from boiling toluene (150 ml.) several times, forming microscopic rhombohedra (9·6 g.), m. p. 110·3—110·6° (Found : C, 78·8; H, 12·7. $C_{39}H_{76}O_3$ requires C, 79·1; H, 12·8%).

n-*Nonatricosanoic Acid*.—A mixture of the foregoing keto-acid (9·3 g.), potassium hydroxide (4 g.), hydrazine hydrate (5 ml.; 50%), and 2 : 2′-dihydroxydiethyl ether (100 ml.) was heated under reflux at 140° for 4 hours, whereafter the temperature of the mixture was raised to 200° by distillation and kept at that temperature for 7 hours. Water (10 ml.) was then added, and the solution refluxed for a further 3 hours. The cooled solution was diluted with water and acidified with excess of hydrochloric acid to give the almost pure acid, m. p. 101·2° (9 g., 99%). Crystallised to constant m. p. from toluene (3 × 150 ml.) and ethyl methyl ketone (3 × 200 ml.), the *acid* (8·4 g.) was obtained as microscopic plates, m. p. 101·3—102° (Found : C, 80·5; H, 13·2. $C_{39}H_{78}O_2$ requires C, 80·9; H, 13·5%).

A sample of the acid (0·5 g.) was treated with oxalyl chloride in benzene (10 ml.) at 50° for 4 hours, the solution evaporated to dryness, and the residual acid chloride refluxed with methanol (5 ml.) for 12 hours. Evaporation and crystallisation (4 times) from acetone–toluene furnished *methyl* n-*tricosanoate* as ill-defined plates, m. p. 82·1—82·5° (Found : C, 80·7; H, 13·3. $C_{40}H_{80}O_2$ requires C, 81·1; H, 13·5%).

18-*Ketohexapentacosanoic Acid*.—The foregoing acid (17·3 g.) was converted into its acid chloride with oxalyl chloride (10 g.) as previously described, and the product treated with tribenzyl sodio-hexadecane-1 : 1 : 16-tricarboxylate (0·033 mol.) as in the previous experiment. The resulting acylmalonic ester solidified on removal of solvent but dissolved in ethyl acetate (500 ml.) on warming to 50°. Palladised strontium carbonate (4 g.; 10% Pd) was added to the solution, which was then stirred in an atmosphere of hydrogen at 30°. Absorption of gas was slow after a rapid start probably because the product crystallised from the solution, coating the surface of the catalyst. Hydrogenation was carried out at 30° for 4 hours, then at 50° for a further 4 hours, whereafter no further gas absorption took place.

Removal of the solvent and decarboxylation was then effected by heating the mixture at 120° (oil-bath) until no further distillation took place. The residue was then boiled with toluene (2 × 500 ml.), and filtration carried out at the b. p. The combined filtrates, on cooling, deposited the crude keto-acid, which was filtered off and dried: the yield was 21·5 g. (86%), and the m. p. 117—118°. An attempted determination of its equivalent weight by titration in boiling aqueous 2 : 2′-dihydroxydiethyl ether with 0·1N-sodium hydroxide gave a value of 1670 (Calc.: 830), presumably owing to the separation of a highly insoluble sodium acid salt, $C_{38}H_{77}\cdot CO\cdot[CH_2]_{16}\cdot CO_2Na,C_{38}H_{77}\cdot CO\cdot[CH_2]_{16}\cdot CO_2H$. In alcoholic solution, lower values (*ca.* 1100) were obtained with difficulty.

The keto-acid was exceedingly insoluble in most of the common lower-boiling solvents but dissolved readily in boiling toluene and *cyclo*hexanone, separating on cooling in gelatinous form from which the high-boiling solvent was best removed by trituration with cold acetone and subsequent drying *in vacuo*. In attempts to purify this substance, a sample (5 g.) was dissolved in boiling toluene, the solution allowed to cool to $T°$, and the mixture filtered; the crop was dried as above, and its m. p. ($t_c°$) recorded. The filtrate was then evaporated to dryness under reduced pressure, and the residue weighed (w) and its m. p. ($t_r°$) taken:

No. of cryst.	Vol. of toluene, c.c.	T.	Crop : $t_c°$.	Residue : w (mg.).	$t_r°$.
1	110	19°	117°	28	89°
2	110	15	117	2	89
6	160	18	117·3	22	93
11	240	35	118	250	96
15	200	37	118	90	99
24	180	40°	119·4°	10	107°
27	180	55	119·7	190	119
28	190	55	119·7	200	119·5
29	160	53	119·7	100	119·7
30	200	30	119·7	trace	119·7

The m. p.s, t_e and t_r, were not as sharp, as indicated above, but represent the same stage of collapse in the capillary; it is perhaps significant that all the m. p.s of the C_{56} compounds were not nearly so sharp as those of the corresponding C_{39} materials. Guided by these results, we quickly purified the main bulk by crystallisation from boiling toluene, the acid separating at 50—55° being collected. n-18-*Ketohexapentacosanoic acid* was thus obtained as microscopic plates, m. p. 119·2—120·2° (Found: C, 80·7; H, 13·0. $C_{56}H_{110}O_3$ requires C, 81·0; H, 13·2%). The *ethyl* ester, prepared by the azeotropic method and crystallised from toluene, had m. p. 95·6—96·1° (Found: C, 80·8; H, 13·1. $C_{58}H_{114}O_3$ requires C, 81·1; H, 13·3%).

Wolff–Kishner Reduction of 18-*Ketohexapentacosanoic Acid*.—(*a*) The first experiment was carried out as in the case of the C_{39} keto-acid by using the foregoing keto-acid (1 g.), hydrazine hydrate (1 ml.; 50%), potassium hydroxide (1 g.), and 2 : 2′-dihydroxydiethyl ether (35 ml.). The product, however, had m. p. 117°, raised to 118° by admixture with the original keto-acid and was, presumably, only partly reduced (Found: C, 80·5; H, 13·1%).

(*b*) After several such failures, it seemed likely that the main difficulty was due to the use of a quantity of hydrazine which, although large in proportion to the keto-acid, was nevertheless small enough to be volatilised into the empty space of the flask and condenser under the conditions of reflux. Accordingly, conditions were modified, and a large excess of the base was used as follows: A mixture of the keto-acid (1 g.), potassium hydroxide (1 g.), hydrazine hydrate (7 ml.; 50%), and 2 : 2′-dihydroxydiethyl ether (50 ml.) was heated at 125° (bath-temp.) for 24 hours, then slowly (2 hours) raised to 200°, and kept at that temperature for a further 5 hours. The reaction mixture, which was homogeneous at the start of the final stage, separated into two phases later. A sample of the top phase was decomposed by boiling it with dilute hydrochloric acid to give a material of m. p. 114—115°, which, however, when boiled for 72 hours with a mixture of concentrated hydrochloric acid (5 ml.), acetic acid (5 ml.), and toluene (10 ml.), was slowly decomposed, giving a product whose m. p. slowly fell to 110°. Decomposition of this product, which may be an acid hydrazide, may also be accomplished by alkaline hydrolysis, since addition of water (7 ml.) to the main bulk of reduction mixture, followed by refluxing for 24 hours and subsequent acidification in the usual manner, gave, in almost quantitative yield, the substance of m. p. 110°.

n-*Hexapentacosanoic acid*, obtained in this manner, was readily purified by crystallisation from toluene and had m. p. 109·3—109·6° (Found: C, 82·0; H, 13·5. $C_{56}H_{112}O_2$ requires C, 82·3; H, 13·7%). It formed an *ethyl* ester, which crystallised from toluene or dioxan, and had m. p. 99·3—100·2° (Found: C, 82·1; H, 13·5. $C_{58}H_{116}O_2$ requires C, 82·4; H, 13·7%).

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