38. *Synthetic Long-chain Aliphatic Compounds. Part I. Introduction. Myristic, Stearic, and Tricosanoic Acids.*

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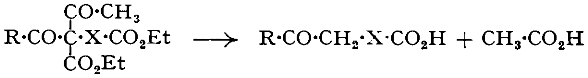
As a start in the systematic synthesis of long-chain, saturated and unsaturated acids, myristic, stearic, and *n*-tricosanoic acids have been prepared from the corresponding keto-acids by the ketone synthesis devised by Bowman (*J.*, in the press). A convenient method for the preparation of ω-bromoheptoic acid on a large scale has been devised.

Previous methods of synthesis of long-chain fatty acids may conveniently be classified into those using a β-keto-ester as intermediate and those using organo-metallic compounds. The most important of the first group is the well-known Robinson–Robinson synthesis (*J.*, 1925, **127**, 175; 1930, 745) in which an acylacetoacetic ester is submitted to graded hydrolysis to yield the keto-acid :



$$\mathrm{R{\cdot}CO{\cdot}}\overset{\mathrm{CO{\cdot}CH_3}}{\underset{\mathrm{CO_2Et}}{\mathrm{C}}}\mathrm{{\cdot}X{\cdot}CO_2Et} \longrightarrow \mathrm{R{\cdot}CO{\cdot}CH_2{\cdot}X{\cdot}CO_2H} + \mathrm{CH_3{\cdot}CO_2H}$$

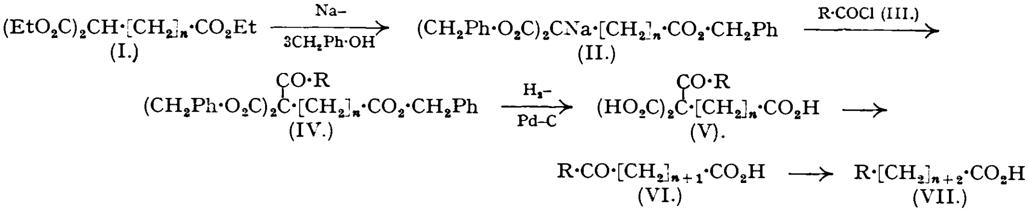
Though this synthesis gives good results in some cases it often suffers from the disadvantage of low yields and occasionally the separation of the products is difficult. This may be caused by hydrolysis in two directions with partial elimination of the " wrong " acyl group.

The second group, *viz.*, methods involving organo-metallic reagents, has been much used in recent years :

$$\mathrm{R_2M} + \mathrm{Cl{\cdot}CO{\cdot}[CH_2]_{\mathit{x}}{\cdot}CO_2Et} \longrightarrow \mathrm{R{\cdot}CO{\cdot}[CH_2]_{\mathit{x}}{\cdot}CO_2Et}$$

The most important of these reagents are the cadmium dialkyls (Cason, *Chem. Reviews*, 1947, **40**, 15) although the zinc alkyls have been shown to give excellent yields of keto-acids containing up to thirty-five carbon atoms (Jones, *J. Amer. Chem. Soc.*, 1947, **69**, 2350). The dialkylcadmium synthesis is probably the most convenient method for the preparation of straight-chain keto-acids up to C_{25} when the "chain-extender," *i.e.*, the acid chloride ester, is readily available and R is not too large. The disadvantages of this method are the difficulty of preparing the " chain-extender " (cf. Drake and Melamed, *J. Amer. Chem. Soc.*, 1948, **70**, 364) and the well-known tendency of the Wurtz reaction to become appreciable when Grignard reagents are prepared from the higher alkyl halides, with, often, difficulty in separating the resultant saturated paraffin R–R from the product (*inter al.*, Houston, *J. Amer. Chem. Soc.*, 1947, **69**, 517).

The new ketone synthesis described recently (*J.*, in the press) appears to be particularly well suited for the synthesis of long-chain aliphatic compounds. As applied to saturated fatty acids, it may be represented as follows :



$$\underset{\text{(I.)}}{\mathrm{(EtO_2C)_2CH{\cdot}[CH_2]_{\mathit{n}}{\cdot}CO_2Et}} \xrightarrow[\mathrm{3CH_2Ph{\cdot}OH}]{\mathrm{Na-}} \underset{\text{(II.)}}{\mathrm{(CH_2Ph{\cdot}O_2C)_2CNa{\cdot}[CH_2]_{\mathit{n}}{\cdot}CO_2{\cdot}CH_2Ph}} \xrightarrow{\mathrm{R{\cdot}COCl\ (III.)}}$$

$$\underset{\text{(IV.)}}{\mathrm{(CH_2Ph{\cdot}O_2C)_2}\overset{\mathrm{CO{\cdot}R}}{\mathrm{C}}\mathrm{{\cdot}[CH_2]_{\mathit{n}}{\cdot}CO_2{\cdot}CH_2Ph}} \xrightarrow[\mathrm{Pd\text{-}C}]{\mathrm{H_2-}} \underset{\text{(V.)}}{\mathrm{(HO_2C)_2}\overset{\mathrm{CO{\cdot}R}}{\mathrm{C}}\mathrm{{\cdot}[CH_2]_{\mathit{n}}{\cdot}CO_2H}} \longrightarrow$$

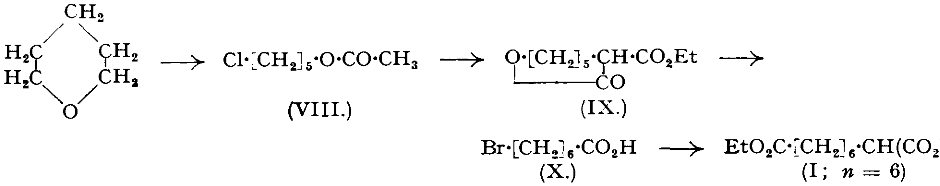
$$\underset{\text{(VI.)}}{\mathrm{R{\cdot}CO{\cdot}[CH_2]_{\mathit{n}+1}{\cdot}CO_2H}} \longrightarrow \underset{\text{(VII.)}}{\mathrm{R{\cdot}[CH_2]_{\mathit{n}+2}{\cdot}CO_2H}}$$

The advantages of the debenzylation synthesis are several. First, the yields are usually 70% or higher; secondly, the " chain-extender " is a malonic ester which may be obtained in several ways and may be purified through the crystalline triacid (cf. the β-keto-ester synthesis); thirdly, the intermediate reactant (IV) is rendered soluble by the three benzyl groups, so that subsequent reactions can be carried out in not too dilute solution.

One of the aims, therefore, of the present series of papers is to utilise this reaction for the preparation of fatty compounds of greater chain lengths than has hitherto been possible. Parallel researches are in hand on the synthesis of the higher unsaturated acids using the procedure already described in a preliminary note (Bowman, *Nature*, 1949, **163**, 95).

Before proceeding with the main objective we have examined two further applications of this synthesis and obtained thereby myristic and stearic acids.

For the synthesis of the former we chose the route employing hexanoyl chloride (III; R = C_5H_{11}) and ethyl heptane-1 : 1 : 7-tricarboxylate (I; $n = 6$). The latter has been previously obtained, in poor yield, by thermal degradation of the corresponding oxalo-ester obtained from ethyl azelaate (Zakutskaya and Gudovich, *J. Gen. Chem., Russia*, 1938, **8**, 216). Since it was required in considerable quantity for another investigation, we have examined a number of routes for its preparation and have developed a method based on tetrahydropyran which makes ω-bromoheptanoic acid readily accessible.



$$\longrightarrow Cl\cdot[CH_2]_5\cdot O\cdot CO\cdot CH_3 \longrightarrow \text{(IX)} \longrightarrow Br\cdot[CH_2]_6\cdot CO_2H \longrightarrow EtO_2C\cdot[CH_2]_6\cdot CH(CO_2Et)_2$$

Tetrahydropyran was converted into 5-chloroamyl acetate (VIII) by acetyl chloride in the presence of zinc chloride (Synerholm, *J. Amer. Chem. Soc.*, 1947, **69**, 2581), and the chloro-ester treated with sodiomalonic ester in alcohol to give the lactone ester (IX). Hydrobromic–acetic acids, followed by hydrobromic–sulphuric acids (Brown and Partridge, *J. Amer. Chem. Soc.*, 1944, **66**, 839), then furnished 7-bromoheptanoic acid * (X) in 60% overall yield. Finally the bromo-acid was azeotropically esterified in almost quantitative yield and treated with sodiomalonic ester in the usual manner to give the required triester (I; $n = 6$). Conversion of this into the corresponding tribenzyl sodio-ester and reaction of this material with *n*-hexanoyl chloride afforded a keto-ester (IV; $R = C_5H_{11}$; $n = 6$) which was debenzylated and decarboxylated to give 9-*ketotetradecanoic acid* * (VI; $R = C_5H_{11}$; $n = 6$). Wolff–Kishner reduction at atmospheric pressure (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) then furnished myristic acid.

An alternative keto-acid synthesis would utilise the reaction of an acid chloride ester with a benzyl alkylsodiomalonate, thus :

$$\underset{\text{(XI.)}}{EtO_2C\cdot[CH_2]_n\cdot COCl} + \underset{\text{(XII.)}}{Na\cdot CR(CO_2\cdot CH_2Ph)_2} \longrightarrow \underset{\text{(XIII.)}}{(CH_2Ph\cdot O_2C)_2CR\cdot CO\cdot[CH_2]_n\cdot CO_2Et}$$

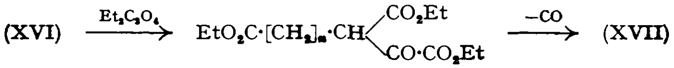
$$\xrightarrow[\text{Pd–C}]{H_2-} \underset{\text{(XIV.)}}{R\cdot CH_2\cdot CO\cdot[CH_2]_n\cdot CO_2H} \longrightarrow \underset{\text{(XV.)}}{R\cdot[CH_2]_{n+2}\cdot CO_2H}$$

Accordingly, to test this route, sebacic ester chloride (XI; $n = 8$) was condensed with benzyl *n*-heptylsodiomalonate (XII; $R = C_7H_{15}$) and the resulting keto-triester (XIII; $R = C_7H_{15}$, $n = 8$) submitted to the usual reactions to give the known 10-keto-octadecanoic acid (XIV; $R = C_7H_{15}$, $n = 8$), which was then reduced to stearic acid.

Our main objective being to ascend the fatty acids series as rapidly as possible, it will be necessary to prepare " chain-extenders " of the general formula (I) where n is as great as possible. Aliphatic αω-dicarboxylic esters are available by a number of routes and accordingly we have examined methods for their conversion into the corresponding malonic esters (I). The carbethoxylation technique of Wallingford *et al.* (*J. Amer. Chem. Soc.*, 1941, **63**, 2056) using ethyl carbonate appeared to be of interest since it is a one-stage process and has already been applied to sebacic ester (XVI; $n = 7$) by the same authors, to give a product formulated by them as

$$\underset{\text{(XVI.)}}{EtO_2C\cdot[CH_2]_n\cdot CH_2\cdot CO_2Et} \xrightarrow[\text{NaOEt}]{Et_2CO_3-} \underset{\text{(XVII.)}}{EtO_2C\cdot[CH_2]_n\cdot CH(CO_2Et)_2}$$

(XVII; $n = 7$). In our hands, however, this product, although similar, was impure as shown by a low saponification value and a wide boiling range; and the derived tricarboxylic acid had neither the required equivalent weight nor a sharp melting point. We therefore abandoned this method and investigated an alternative route by way of the oxalo-ester (XVIII).



$$\text{(XVI)} \xrightarrow{Et_2C_2O_4} EtO_2C\cdot[CH_2]_n\cdot CH\begin{cases}CO_2Et\\ CO\cdot CO_2Et\end{cases} \xrightarrow{-CO} \text{(XVII)}$$

(XVIII.)

After some preliminary experiments we obtained the required ethyl *n*-octane-1 : 1 : 8-tricarboxylate (XVII; $n = 7$) in good yield and in a high state of purity from ethyl sebacate,

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* Geneva numbering is used in this series of papers.—Ed.

without purification of the intermediate oxalo-ester (XVIII; $n = 7$) (cf. Zakutskaya, *J. Gen. Chem., Russia*, 1940, **10**, 1553). Myristoyl chloride was condensed with benzyl sodio-octane-1 : 1 : 8-tricarboxylate (II; $n = 7$), and the resulting keto-triester (IV; $R = C_{13}H_{27}$; $n = 7$) was debenzylated and decarboxylated by the general method. 10-*Ketotricosanoic acid* (VI; $R = C_{13}H_{27}$; $n = 7$) was thus obtained in exceptionally high yield (crude, 93%; pure, 85%) Reduction to the known *n*-tricosanoic acid, in quantitative yield, was carried out as above.

EXPERIMENTAL.

The Vigreux column used in this work was of the usual type, 22 cm. in length. The Fenske column, the techniques used for conversion of malonic esters into the benzyl sodio-esters, the reactions of the latter with the acid chlorides, and debenzylations and decarboxylations were as described previously (Bowman, *loc. cit.*).

5-*Chloroamyl Acetate* (VIII).—This material was prepared from tetrahydropyran as described by Synerholm (*loc. cit.*) except that the quantity of anhydrous zinc chloride was reduced (5 g. per 2·5 mols. of acetyl chloride) and the product was distilled directly from the reaction mixture through the Vigreux column.

7-*Bromoheptanoic Acid* (X).—The foregoing chloro-compound (434 g., 2·63 mols.) was treated with sodiomalonic ester (3·2 mols.) in absolute ethanol (500 ml.) in the presence of sodium iodide (20 g.) at 110° for 6 hours. After removal of most of the ethanol and ethyl acetate by distillation, the cooled reaction mixture was added to dilute sulphuric acid, and the product, after saturation of the aqueous layer with ammonium sulphate, isolated with benzene (2 × 400 ml.). The solvent-free oil thus obtained was mixed with glacial acetic acid (500 ml.) and constant-boiling hydrobromic acid (500 ml.), and the resulting mixture slowly distilled through a Vigreux column, ethyl acetate (400 ml.) containing some ethyl bromide being collected during 4 hours; during this last phase decarboxylation had already started and was completed by further refluxing for 1 hour after the addition of sulphuric acid (50 ml.; 20N.). The cooled solution was then mixed with a further portion of constant-boiling hydrobromic acid (500 ml.) and concentrated sulphuric acid (150 ml.), and the mass heated at 110° (internal temperature) for 4 hours. After cooling to room temperature, the reaction mass was diluted with water, and the lower layer of bromo-acid separated; further product was obtained by extraction of the aqueous layer, previously saturated with ammonium sulphate, with ether (3 × 400 ml.). The combined organic extracts were then washed with water, dried (Na_2SO_4), and treated with active charcoal to remove most of the colour, and the solvent removed by distillation. The residue was found to contain some water and, accordingly, was mixed with benzene (1 l.), and the mixture refluxed with a phase-separator (Dean and Stark) until dry. After removal of solvent and a small fore-run, 7-bromoheptanoic acid was obtained as an almost colourless oil, b. p. 140—142°/1·5 mm. (378 g.; 60%, calc. on the tetrahydropyran), which solidified and had m. p. 28—29° (thermometer in liquid). The bromo-acid was characterised by conversion in the usual manner into the corresponding phenoxy-acid which separated from light petroleum (b. p. 40—60°) in needles, m. p. 56° (von Braun, *Ber.*, 1906, **39**, 4362, gave m. p. 56—57°).

Ethyl 7-*Bromoheptanoate*.—A mixture of the bromo-acid (376 g.), benzene (700 ml.), ethanol (300 ml.) and AnalaR concentrated sulphuric acid (3 ml.) was distilled through the Fenske column fitted with a phase-separator until no further phase-separation took place. The cooled solution was washed with water, sodium hydrogen carbonate solution, and again water, dried (Na_2SO_4), and distilled to give, after rejection of a fore-run (10 g.), the ethyl ester as a colourless liquid, b. p. 112°/5 mm., n_D^{20} 1·4608 (397 g., 93%).

Ethyl n-*Heptane*-1 : 1 : 7-*tricarboxylate* (I; n = 6).—The foregoing ester (237 g.; 1 mol.) was treated with sodiomalonic ester (1·75 mols.) in dry ethanol (700 ml.) in the presence of sodium iodide (10 g.) at 90—105° for 10 hours. After removal of solvent by distillation, the cooled mixture was treated with excess of dilute sulphuric acid and isolated in the usual manner to give the triester as a colourless oil, b. p. 146—147°/0·5 mm., n_D^{20} 1·4411 (263 g., 83%).

9-*Ketotetradecanoic Acid* (VI; $R = C_5H_{11}$; $n = 6$).—Ethyl *n*-heptane-1 : 1 : 7-tricarboxylate (31·6 g., 0·1 mol.) was converted into the corresponding tribenzyl sodio-ester by means of sodium (2·3 g., 0·1 mol.), benzyl alcohol (32·5 g., 0·3 mol.) in benzene (300 ml.), and the product treated with hexanoyl chloride (b. p. 94°/120 mm.; 13·5 g., 0·1 mol.) according to the general procedure. The product was hydrogenated in ethanol (160 ml.) containing ethyl acetate (20 ml.), palladised charcoal (5 g.; 10%), and palladised strontium carbonate (5 g. of 10%). The catalyst was removed by filtration, the filtrate refluxed for 0·5 hour to bring about decarboxylation, and the solvent removed at atmospheric pressure and finally *in vacuo*. The residue was boiled with acetic acid (75 ml.) containing sulphuric acid (2·5 ml. of 20N.) for 0·5 hour to bring about ketone hydrolysis of any residual β-keto-ester, and the product was isolated by dilution with water and filtration; yield, 17 g. (70%); m. p. 59—61°. On crystallisation from light petroleum (b. p. 40—60°) 9-*ketotetradecanoic acid* separated in rosettes of needles, m. p. 66° (Found: C, 69·4; H, 10·7. $C_{14}H_{26}O_3$ requires C, 69·4; H, 10·7%). The p-*bromophenacyl* ester crystallised from 96% ethanol (norite) in needles, m. p. 78° (Found: C, 60·7; H, 6·9. $C_{22}H_{31}O_4Br$ requires C, 60·1; H, 7·3%).

A sample of the keto-acid was reduced with hydrazine and sodium hydroxide in 2 : 2′-dihydroxydiethyl ether, following exactly the procedure of Huang-Minlon (*loc. cit.*), to give myristic acid (80%) which separated from light petroleum (b. p. 40—60°) at −20° in plates, m. p. 53·5—54° (capillary) undepressed by admixture with authentic material.

10-*Keto-octadecanoic Acid* (XIV; $R = C_7H_{15}$; $n = 8$).—*n*-Heptylmalonic ester (b. p. 118—119°/1·5 mm.; 18·1 g., 0·07 mol.) was converted by sodium (1·61 g., 0·07 mol.) in benzene (300 ml.) into the sodium salt of its enolic form and treated with benzyl alcohol (15·5 g., 0·14 mol.) in the usual manner, to give benzyl sodio-*n*-heptylmalonate. This was then treated with sebacic ethyl ester chloride (17·4 g., 0·07 mol.), and the product debenzylated and decarboxylated as usual to give the crude product which was hydrolysed and isolated as in the previous experiment. The mixed acids, so obtained, were converted into their ethyl esters by azeotropic esterification and unchanged materials removed by distillation up to 190° (bath)/1 mm. The residual crude ethyl ester was hydrolysed with alkali and the keto-acid obtained in the usual manner, collected, and dried; yield, 14·9 g. (71%); m. p. 79—82°. 10-Keto-octadecanoic acid crystallised from light petroleum (b. p. 80—100°) in plates, m. p. 83°, and was characterised by conversion into the oily oxime and thence into the derived amide, plates (from methanol), m. p. 80° (cf. Robinson and Robinson, *J.*, 1926, 2207).

Ethyl n-*Octane*-1 : 1 : 8-*tricarboxylate* (XVII; *n* = 7).—Ethyl oxalate (73 g., 0·5 mol.) was added to a stirred suspension of ethanol-free sodium ethoxide (from 11·5 g. of sodium; 0·5 mol.) in dry benzene (400 ml.), followed by ethyl sebacate (XVI) (161 g., 0·62 mol.). The resulting homogeneous solution was kept at room temperature for 24 hours and extracted with ice-water (1 l.).* The organic layer was then extracted with aqueous sodium hydroxide (1 l.; 0·5N.) at 0°, and the combined aqueous extracts were washed with fresh benzene (200 ml.). Acidification of the combined aqueous extracts was effected in the presence of benzene (200 ml.) and ice with hydrochloric acid (250 ml.; 5N.). After the washing with water, the benzene solution was evaporated to dryness *in vacuo*, to give the crude oxalo-ester (XVIII; *n* = 7) (126 g.). The combined benzene extracts of neutral materials furnished, on distillation and fractionation, recovered ethyl sebacate (66 g.).

The crude oxalo-ester was heated at 160—180°/5 mm. in the presence of powdered glass for 3 hours, whereafter no further gas evolution took place. Distillation of the residue through a fractionating column (15 × 1·2 cm. containing 3-mm. Fenske helices) furnished ethyl *n*-octane-1 : 1 : 8-tricarboxylate as a colourless oil, b. p. 160°/1 mm., n_D^{20} 1·4436, d_4^{20} 1·015 (Found : C, 61·5; H, 9·0; sap. val., 110. Calc. for $C_{17}H_{30}O_6$: C, 61·8; H, 9·1%; sap. equiv., 110). The yield of this material was 88 g. (72% based on unrecovered ethyl sebacate). Lower- (sap. equiv., 120) and higher-boiling fractions (sap. val., 105) were rejected.

A sample of the triester was hydrolysed with aqueous-alcoholic sodium hydroxide, and the n-*octane*-1 : 1 : 8-*tricarboxylic acid*, obtained by addition of *excess* of sulphuric acid, crystallised from ethylene dichloride–ethyl acetate whence it separated in rosettes of colourless needles, m. p. 108—109° (Found : C, 53·0; H, 6·9; equiv., 82. $C_{11}H_{18}O_6$ requires C, 53·7; H, 7·3%; equiv., 82). On heating at 160—180° it was converted into sebacic acid, leaflets (from water), m. p. and mixed m. p. 133°.

10-*Ketotricosanoic Acid* (VI; R = $C_{13}H_{27}$; *n* = 7).—Benzyl sodio-*n*-octane-1 : 1 : 8-tricarboxylate (0·1 mol.) was prepared in the usual manner from the foregoing triester (33·0 g., 0·1 mol.), sodium (2·3 g., 0·1 mol.), and benzyl alcohol (33·4 g., 0·3 mol.) in benzene solution and treated with myristoyl chloride [24·65 g., 0·1 mol.; b. p. 134°/2·5 mm. from acid, m. p. 53·6° (thermometer in liquid)]. The next stages, *i.e.*, hydrogenation, decarboxylation, and working up were carried out as for 9-ketotetradecanoic acid. The yield of crude material, m. p. 86°, was 36·2 g. (93%). The product contained some ester and was hydrolysed. Thus, 10·0 g. of crude acid were boiled with sodium hydroxide (100 ml.; N.) for 1 hour and acidified at the b. p., with shaking. 10-*Ketotricosanoic acid* was crystallised once from benzene (30 ml.) and then twice from acetone (100 ml. each time), from which it (8·7 g.) separated in colourless plates, m. p. 93·5° (constant) (Found : C, 74·7; H, 11·9. $C_{23}H_{44}O_3$ requires C, 75·0; H, 11·9%). The solubility of the keto-acid in acetone at 15° is *ca.* 0·2 g. per 100 ml.

It formed an *oxime* which crystallised from light petroleum (b. p. 40—60°) at 0° in plates, m. p. 43° (Found : N, 3·55. $C_{23}H_{45}O_3N$ requires N, 3·65%).

n-*Tricosanoic Acid.*—The foregoing keto-acid (20·2 g.) was reduced in the same manner as before using 2 : 2′-dihydroxydiethyl ether (150 ml.), hydrazine hydrate (14 ml.; 50%), and potassium hydroxide (12 g.) under reflux for 1·5 hours and then at 195° for 6 hours. The acid (19·4 g.; 100%) had m. p. 79° and was practically pure. It was crystallised from benzene (50 ml.) to give material, m. p. 79·1°, and then twice from acetone (70 ml., each time) from which it separated in colourless plates (17·9 g., m. p. 79·2° (constant). The solubility of *n*-tricosanoic acid in benzene at 15° is *ca.* 0·5 g. per 100 ml. and in acetone at 15° *ca.* 1 g. per 100 ml.

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