188. *Synthetic Long-chain Aliphatic Compounds. Part IX.* Some Antituberculous Long-chain Amines.*

By D. E. Ames and R. E. Bowman.

(*With a Note by* G. A. H. Buttle and S. Squires.)

Several long-chain αω-tetramethyldiamines have been prepared by standard methods. The demonstration of antituberculous activity of 2-undecylpiperidines (Bowman and Fordham, *J.*, 1951, 2753) has led to a fuller examination of these bases, many of which have been prepared for biological test. All the isomeric *n*-dodecyl-piperidines and -pyrrolidines have also been made in an examination of the relation between structure and activity.†

Although long-chain primary αω-diamines and related compounds have been examined for antibacterial activity (King, Lourie, and Yorke, *Ann. Trop. Med. Parasit.*, 1938, **32**, 177; Fuller, *Biochem. J.*, 1942, **36**, 548), the corresponding αω-bisdimethylamines (I) have, so far as we are aware, escaped attention.

In the first instance, we examined the decamethylene compounds. Since decamethylenediamine and the di-*tert.*-amine (I; $n = 10$) were available from other work, it was only necessary to prepare the remaining bismethylamine (II) which was obtained from decamethylene dibromide as follows:

$$Me_2N\cdot[CH_2]_n\cdot NMe_2 \quad (I)$$

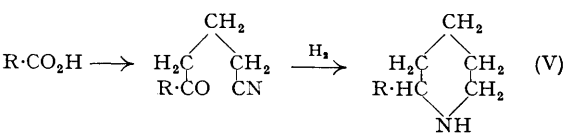
$$Br\cdot[CH_2]_{10}\cdot Br \longrightarrow CH_2Ph\cdot NMe\cdot[CH_2]_{10}\cdot NMe\cdot CH_2Ph \xrightarrow{H_2\text{–}Pd} NHMe\cdot[CH_2]_{10}\cdot NHMe \quad (II)$$

Next we prepared the di-*tert.*-amines (I; $n = 16$ and 18) by standard methods starting from hexadecane-1 : 16-dicarboxylic acid. Preliminary tests *in vitro* showed that, while the decamethylene derivatives were not particularly active, the compounds (I; $n = 16$ and 18) possessed considerable bacteriostatic activity against a number of micro-organisms including *Staphylococcus aureus* and *Mycobacterium tuberculosis*, the higher member being the more active. Two further amines (I; $n = 22$) and (III), the latter being prepared as indicated, were equally active.

$$CO_2H\cdot[CH_2]_{16}\cdot CO_2H \longrightarrow CH_3\cdot CO\cdot[CH_2]_{16}\cdot CO\cdot CH_3 \xrightarrow{Me_2NH\text{–}H_2} Me_2N\cdot CHMe\cdot[CH_2]_{16}\cdot CHMe\cdot NMe_2 \quad (III)$$

On the other hand, replacement of carbon atoms in the chain as in (IV) led to inactive material; the base was readily prepared by cyanoethylation of decamethylene glycol (Bruson and Riener, *J. Amer. Chem. Soc.*, 1943, **65**, **23**) followed by reduction and subsequent methylation of the resulting amine.

$$Me_2N\cdot[CH_2]_3\cdot O\cdot[CH_2]_{10}\cdot O\cdot[CH_2]_3\cdot NMe_2 \quad (IV)$$



However, owing to the high toxicity of the active compounds attention was directed to other classes of long-chain bases. At this time, 2-undecylpiperidine (V; $R = C_{11}H_{23}$) had been prepared in this laboratory (Bowman and Fordham, *loc. cit.*) by the route outlined above and was examined for antibacterial properties. Tests against *M. tuberculosis in vitro* revealed that, although somewhat less active than the straight-chain amines, it was much less toxic, and accordingly we prepared a series of long-chain-substituted piperidines and some related pyrrolidines.

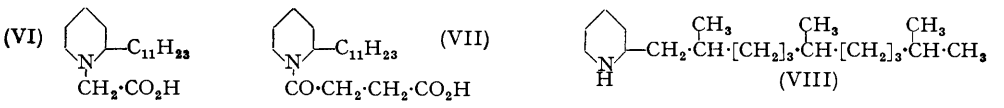
* Part VIII, *J.*, 1952, 677.

† Since this manuscript was prepared an announcement of similar work by Barry and his colleagues has appeared (*Nature*, 1951, **168**, 539).

The amine (V; R = $C_{11}H_{23}$) was first used for the preparation of several derivatives. Thus, 1-methyl-2-undecylpiperidine was obtained by methylation and was converted into the hydrochloride and methiodide. An impure sample of the carboxylic acid (VI) was prepared by condensation with ethyl chloroacetate and subsequent hydrolysis, and the amic acid (VII) was obtained, as an oil, by reaction with succinic anhydride.

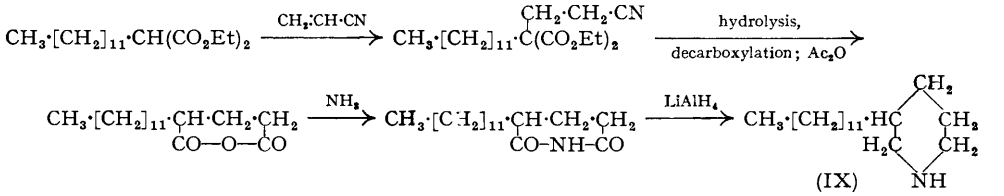
A series of 2-alkylpiperidines was then prepared, first, from the δ-keto-cyanides, and, secondly, by catalytic hydrogenation of the corresponding alkylpyridines. Satisfactory yields of 2-alkylpyridines were conveniently obtained by condensation of 2-picolyl-lithium with alkyl bromides (cf. Ziegler and Zeiser, *Annalen*, 1931, **485**, 179; for a review see Barkovsky, *Ann. Chim.*, 1944, **19**, 487). The maximum antibacterial activity in compounds (V) appeared to occur when the alkyl chain consisted of 12—15 carbon atoms.

The keto-cyanide method was also applied to the synthesis of the branched-chain amine (VIII), an oil, which furnished a hydrochloride of indefinite melting point, presumably



containing most or all of the possible isomers. Repeated recrystallisation of this material yielded a product of sharp melting point, which appeared to be a single isomer. This product had antituberculous activity similar to that of the straight-chain compounds.

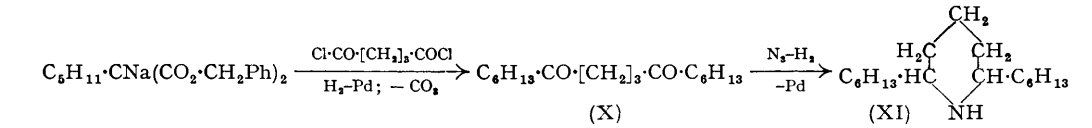
1-Dodecylpiperidine was readily obtained by hydrogenation of dodecylpyridinium bromide at normal temperature and pressure over Raney nickel W7 catalyst (Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 698) in the presence of diethylamine (cf. Barltrop and Taylor, *J.*, 1951, 108). 3-Dodecylpiperidine (IX) was prepared as in the annexed scheme. An analogous method for the synthesis of 4-dodecylpiperidine began by reduction



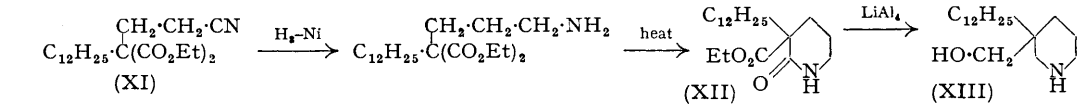
of ethyl dodecylmalonate with lithium aluminium hydride to 2-dodecylpropane-1 : 3-diol; however, repeated attempts to prepare the dibromide therefrom failed, and this route was abandoned. Reaction of 4-picolyl-lithium with dodecyl bromide yielded a complex mixture from which the required product could not be isolated. The alkylation of 4-picoline with undecyl chloride in the presence of sodamide, as described by Knight and Shaw (*loc. cit.*) and Barkovsky (*loc. cit.*), was readily effected, however. An attempt to hydrogenate the resulting 4-dodecylpyridine at normal pressure over Raney nickel W7 catalyst (as employed in the case of 2-alkylpyridines) was unsuccessful, but reduction with sodium and ethanol furnished 4-*n*-dodecylpiperidine which was isolated as its crystalline hydrochloride.

To examine the effect of the introduction of an alkyl group at each of the α-positions of piperidine, the synthesis of 2 : 6-dihexylpiperidine (XI) was investigated; such amines appeared to be accessible by reduction of 1 : 5-diketones in the presence of ammonia. The debenzylation ketone synthesis (Bowman, *J.*, 1950, 325) provides two possible methods for the synthesis of symmetrical 1 : 5-diketones: first, condensation of an acid chloride with an alkylidenedimalonic ester and, secondly, condensation of glutaroyl dichloride with an alkylmalonic ester. Both methods were examined, but the former was unsuccessful as the attempted ester interchange between ethyl propylidenedimalonate and benzyl alcohol in the presence of sodium ethoxide evidently resulted in a retrograde Michael reaction (cf. Ingold and Powell, *J.*, 1921, **119**, 1976). Condensation of glutaroyl chloride with dibenzyl sodio-amylmalonate did, however, furnish the diketone (X) in small yield (25%). Catalytic hydrogenation of this in the presence of ammonia gave a heterogeneous

product, from which 2 : 6-dihexylpiperidine (XI) was isolated as the crystalline hydrochloride.

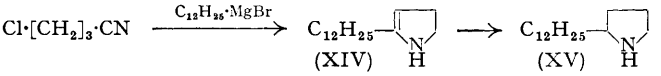


The synthesis of the 3 : 3-disubstituted piperidine (XIII), showing a further structural variation, was effected by the following route :

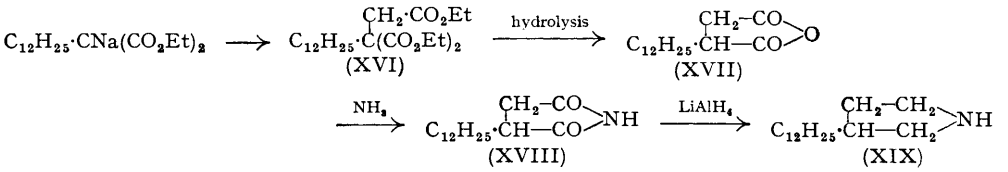


Catalytic hydrogenation of the acrylonitrile adduct (XI) of ethyl dodecylmalonate furnished the amine which, without isolation, was heated to give the carbethoxy-piperidone (XII). This was reduced with lithium aluminium hydride to 3-dodecyl-3-hydroxymethylpiperidine (XIII).

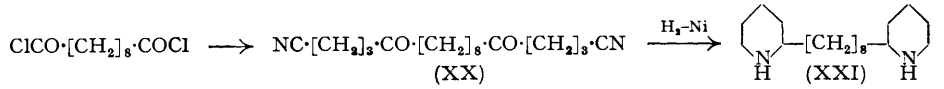
The three isomeric dodecylpyrrolidines were also prepared for comparison with the alkylpiperidines. 1-Dodecylpyrrolidine was obtained by alkylation of pyrrolidine by dodecyl bromide and anhydrous potassium carbonate. 2-Dodecylpyrrolidine (XV) appeared to be accessible from the alkylpyrroline (XIV). An impure sample of the latter was produced in small yield by reaction of dodecylmagnesium bromide with 3-chloropropyl cyanide, the method employed for the synthesis of shorter-chain compounds of this type by Craig, Bulbrook, and Hixon (*J. Amer. Chem. Soc.*, 1931, **53**, 1831). The alkylpyrroline could not be purified and the crude product was therefore hydrogenated, the resulting dodecylpyrrolidine being isolated as the crystalline hydrochloride. The



remaining isomer, 3-dodecylpyrrolidine, was prepared by a route analogous to that used for the synthesis of 3-dodecylpiperidine. Thus, ethyl sodiododecylmalonate was alkylated with ethyl chloroacetate and the product (XVI) converted into the anhydride (XVII). The corresponding imide (XVIII) was reduced with lithium aluminium hydride to the required 3-dodecylpyrrolidine (XIX).

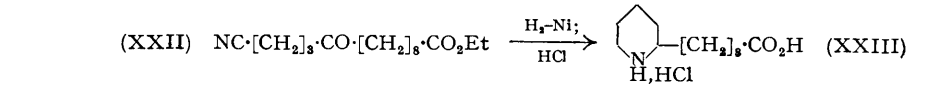


Finally, a base (XXI), incorporating both the long-chain αω-diamine and the α-alkylpiperidine structure, was synthesised. Use of sebacoyl chloride in the δ-keto-cyanide synthesis already mentioned gave a 33% yield of the diketo-dicyanide (XX), which was catalytically hydrogenated to 1 : 8-di-2′-piperidinyloctane (XXI) :



The acidic compounds separated during the isolation of (XX) were esterified with ethanol and the resulting esters, on fractional distillation, furnished a small yield (15%) of slightly impure ethyl 13-cyano-10-ketotridecanoate (XXII) evidently formed from the sebacoyl chloride by incomplete reaction. Catalytic hydrogenation of this product, followed

by hydrolysis of the ester group, gave 2-8′-carboxyoctylpiperidine (XXIII) isolated as its hydrochloride.



(XXII) $NC\cdot[CH_2]_3\cdot CO\cdot[CH_2]_8\cdot CO_2Et$ $\xrightarrow[HCl]{H_2\text{-}Ni;}$ $-[CH_2]_8\cdot CO_2H$ (XXIII)

Biological Results [by G. A. H. BUTTLE and S. SQUIRES].—The compounds described in the preceding section have all been tested against *Staphylococcus aureus* and *Mycobacterium tuberculosis*, the results being set out in the annexed table. Inspection of them

	Maximum dilution inhibiting : [1] *Staph. pyogenes* [2]	*Myc. tuberculosis* [3]	Toxicity, L.D. 50, Subcut.; mg./kg.
Diamines			
$NH_2\cdot[CH_2]_{10}\cdot NH_2$	1/1000	—	—
$Me\cdot NH\cdot[CH_2]_{10}\cdot NHMe$	1/1000	Inactive	—
$Me_2N\cdot[CH_2]_{10}\cdot NMe_2$	1/1000	—	—
$Me_2N\cdot[CH_2]_{16}\cdot NMe_2$	$1/10^6$	1/512 000	5
$Me_2N\cdot[CH_2]_{18}\cdot NMe_2$	$1/2 \times 10^6$	1/512 000	5
$Me_2N\cdot[CH_2]_{22}\cdot NMe_2$	$1/2 \times 10^6$	$1/10^6$	5
$Me_2N\cdot CHMe\cdot[CH_2]_{16}\cdot CHMe\cdot NMe_2$	$1/10^6$	1/512 000	—
$(Me_2N\cdot[CH_2]_3\cdot O\cdot[CH_2]_5\cdot)_2$	1/1000	Inactive	—
(XXI)	1/4000	1/4000	—
2-R-1-R′-Piperidines			
R / R′			
C_6H_{13} / H	Inactive	1/4000	—
C_9H_{19} / H	1/32 000	1/128 000	—
$C_{11}H_{23}$ / H	$1/2 \times 10^6$	1/256 000	400
$C_{11}H_{23}$ / CH_3	$1/2 \times 10^6$	1/512 000	—
$C_{11}H_{23}$ / $CH_2\cdot CO_2H$	1/128 000	1/64 000	—
$C_{11}H_{23}$ / $CO\cdot CH_2\cdot CH_2\cdot CO_2H$	1/128 000	1/100 000	—
$C_{12}H_{25}$ / H	1/512 000	1/128 000	—
$C_{13}H_{27}$ / H	$1/10^6$	1/128 000	800
$C_{15}H_{31}$ / H	$1/2 \times 10^6$	1/256 000	250
$C_{17}H_{35}$ / H	1/800 000	1/256 000	400
$C_{14}H_{29}$ / H (VIII)	1×10^6	1/128 000	250
$[CH_2]_8\cdot CO_2H$ / H	Inactive	1/1000	—
Pyrrolidines			
1-$C_{12}H_{25}$	1/256 000	1/64 000	—
2-$C_{12}H_{25}$	$1/10^6$	1/128 000	—
3-$C_{12}H_{25}$	$1/10^6$	1/256 000	—
Pyridines			
2-$C_{12}H_{25}$	1/512 000	1/32 000	—
4-$C_{12}H_{25}$	$1/2 \times 10^6$	1/64 000	—
Piperidines			
1-$C_{12}H_{25}$	1/128 000	1/128 000	—
2-$C_{12}H_{25}$	1/512 000	1/128 000	—
3-$C_{12}H_{25}$	$1/10^6$	1/256 000	—
4-$C_{12}H_{25}$	$1/10^6$	1/512 000	—
Miscellaneous			
2 : 6-Di-*n*-hexylpiperidine	1/64 000	1/32 000	—
1-Dodecyl-1-methylpiperidinium bromide	1/256 000	1/128 000	25
1-Dodecylpyridinium bromide	$1/2 \times 10^6$	1/128 000	—
1 : 1-Dimethyl-2-undecylpiperidinium iodide	1/512 000	1/256 000	—
2-Heptadecyl-1 : 1-dimethylpiperidinium iodide...	$1{\cdot}6 \times 10^6$	1/256 000	100
(XIII)	$1/2 \times 10^6$	1/512 000	100 *
Streptomycin	$1/10^6$	$1/10^6$	—

[1] In every instance half of the inhibitory concentration failed to prevent growth of test organism. [2] *Staphylococcus pyogenes*: N.C.T.C.6571; nutrient broth. [3] *Mycobacterium tuberculosis*: H.37 Rv.; Dubos medium.

* Intravenous, 25 mg./kg.; oral, 250 mg./kg. (no deaths).

suggests the following conclusions: (1) Maximum activity against both organisms in diamines (I) occurs when $n > 18$ and in piperidines (V) when $R > C_{11}$, and in both cases this activity is unaffected by branching of the chain. (2) The position of the chain in

the *n*-dodecyl-pyrrolidines and -piperidines has no marked effect on the activity against the *Staphylococcus* except in the case of the *tert.*-base where attachment of the alkyl substituent to the nitrogen atom lowers the activity; against *Myc. tuberculosis* the maximum activity is displayed in the isomer in which the long-chain is furthest from the nitrogen atom, *viz.*, 3-dodecylpyrrolidine and 4-dodecylpiperidine. (3) Although groupings containing the carboxylic acid function in the long-chain piperidines decrease the activity, introduction of a group containing a hydroxyl group (*e.g.*, XIII) is without effect and, indeed, it seems that future work in this direction with a view to a reduction of the toxicity of these compounds would be well worth while.

Tests were carried out *in vivo* with *n*-tridecylpiperidine but the results were disappointing: oral administration of 20 mg. daily to mice infected intravenously with *Myc. murine* (N.C.T.C. 5676) afforded no protection. [*Added*, 30.1.52]: Further tests made by Mr. S. R. M. Bushby revealed that after oral administration of 20 mg. of this substance the blood of mice showed no tuberculostatic activity and, although significant activity was found after the same dose given intraperitoneally, the compound proved too toxic, parentally for therapeutic use.

Experimental

General Procedures.—*δ-Keto-cyanides* (Bowman and Fordham, *loc. cit.*). The freshly distilled acid chloride (1·0 mol.) was added to a benzene solution of dibenzyl sodio-2-cyanoethylmalonate (1·05 mols.). The product was isolated in the usual manner, and hydrogenated in ethyl methyl ketone on palladised strontium carbonate (10% of Pd). Partial decarboxylation often interfered and was overcome by occasional evacuation and subsequent refilling with hydrogen. The solution was then boiled to complete decarboxylation, filtered, and evaporated, finally *in vacuo*. Acids were removed by washing the solution of the crude product in light petroleum (b. p. 60—80°)–ethyl acetate with excess of 0·1—0·5N-sodium hydroxide and then water. Evaporation of the dried ($MgSO_4$) solution furnished the keto-cyanide, which was purified by distillation or recrystallisation.

2-Alkylpyridines. An ethereal solution of ω-lithiopicoline (1·0 mol.) was prepared by Walter's method (*Org. Synth.*, **1934**, **23**, 83); alkyl bromide (0·85 mol.) was then added and the stirred solution was refluxed for 3 hours. After addition of dilute potassium hydroxide solution, the separated aqueous layer was extracted with light petroleum (b. p. 60—80°) and the combined organic layers were washed with water, dried ($MgSO_4$), and fractionally distilled. Unchanged alkyl bromide was rejected and the 2-alkylpyridine collected.

2-Alkylpiperidines. The δ-keto-cyanide (Method A) or 2-alkylpyridine (Method B) in ethanol was hydrogenated on Raney nickel W7 catalyst (Adkins and Billica, *loc. cit.*). Evaporation of the filtered solution furnished a gelatinous residue, apparently containing aluminium hydroxide. The product was isolated by distillation *in vacuo* or by addition of dilute sodium hydroxide solution followed by extraction with light petroleum (b. p. 60—80°).

1 : 10-*Bismethylaminodecane Dihydrochloride.*—A mixture of decamethylene dibromide (10 g.) and benzylmethylamine (30 g.) was heated at 110° for 6 hours, then cooled to room temperature and diluted with anhydrous ether (100 ml.). After removal of benzylmethylamine hydrobromide (14 g.), the filtrate was distilled, giving 1 : 10-*bisbenzylmethylaminodecane* as a viscous oil, b. p. 210°/0·2 mm. (11 g.) (Found: N, 6·8. $C_{26}H_{40}N_2$ requires N, 7·4%).

A solution of this in ethanol (150 ml.) was hydrogenated at normal pressure over 10% palladised charcoal (3 g.) until hydrogen uptake ceased (2 mols.). After removal of catalyst, the filtrate was made acid by addition of concentrated hydrochloric acid (10 ml.) and evaporated to dryness on the steam-bath. Crystallisation of the residue from ethanol (100 ml.) gave the *dihydrochloride* as prisms, m. p. 258° (Found: N, 9·9. $C_{12}H_{30}N_2Cl_2$ requires N, 10·3%); by concentration of the mother-liquors, more product was obtained (total yield, 6·5 g.).

1 : 16-*Diaminohexadecane Dihydrochloride.*—A mixture of hexadecane-1 : 16-dicarboxylic acid (4 g.), chloroform (200 ml.), and concentrated sulphuric acid (50 ml.) was heated to 50° with stirring, and sodium azide (5 g.) added during 2 hours. After a further 2 hours' stirring at the same temperature, the lower acid layer was separated and poured into water. The resulting suspension of base sulphate was treated with excess of sodium hydroxide (10N) at the b. p. until all solid had disappeared; the cooled solution was extracted with chloroform. Evaporation of the organic extract furnished the crude diamine which was isolated as its *dihydrochloride* (2·5 g.), needles (from ethanol), m. p. 340° (decomp.) (Found: N, 8·5. $C_{16}H_{38}N_2Cl_2$ requires N, 8·5%).

1 : 16-*Bisdimethylaminohexadecane Dihydrochloride*.—Sodium hydrogen carbonate (1·15 g.) was added in portions to formic acid (5 ml.; 98%) followed by the foregoing amine dihydrochloride (2·0 g.) and formaldehyde (3 ml. of 40%), and the mixture was heated under reflux in an oil-bath at 105° for 16 hours. The solution was evaporated to dryness and the residue dissolved in water and basified with sodium hydroxide solution. The base was isolated with benzene and, after removal of solvent, was converted directly into its *dihydrochloride* which separated from *n*-amyl alcohol (10 ml.)–ethyl methyl ketone (20 ml.) in thin plates, m. p. 234° (Found : N, 7·1. $C_{20}H_{46}N_2Cl_2$ requires N, 7·3%).

1 : 18-*Bisdimethylamino-octadecane Dihydrochloride*.—(*a*) Octadecamethylene-1 : 18-diamine (Pfeiffer and Lübbe, *J. pr. Chem.*, **1933**, **136**, 321) was methylated as in the previous experiment, furnishing the *dihydrochloride* as clusters of plates (from *n*-propanol–ethyl methyl ketone), m. p. 234° (Found : N, 6·6; Cl, 17·6. $C_{22}H_{50}N_2Cl_2$ requires N, 6·8; Cl, 17·2%).

(*b*) Hexadecane-1 : 16-dicarboxylic acid (2·0 g.) was warmed at 50° with thionyl chloride (10 c.c.) for 2 hours and, after removal of the excess of thionyl halide, the acid chloride was dissolved in ether (50 c.c.). This solution was gradually added to an ethereal solution of dimethylamine (40 c.c.; 2M), and the mixture refluxed for 30 minutes and then evaporated *in vacuo*. The residual product was washed with potassium hydrogen carbonate solution and water; crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) (activated charcoal) furnished NNN'N'-*tetramethylhexadecane*-1 : 16-*dicarboxyamide* (1·3 g.) in large, lustrous plates, m. p. 98° (Found : N, 7·8. $C_{22}H_{44}O_2N_2$ requires N, 7·6%). This (0·95 g.) was added to a stirred solution of lithium aluminium hydride (0·2 g.) in ether (20 c.c.), and the mixture was boiled under reflux for 2 hours, the product being isolated with ethyl acetate in the usual manner. The resulting crude amine was treated with ethanolic hydrogen chloride to give the required dihydrochloride, m. p. 234—235° (0·8 g.).

1 : 22-*Bisdimethylaminodocosane Dihydrochloride*.—1 : 22-Dimethoxy-*n*-docosane (4·2 g.; m. p. 54°; obtained, as will be reported later, as a by-product during the preparation of 11-methoxyundecylmagnesium bromide), was dissolved in hydrogen bromide–acetic acid (50 ml.; 15% w/v), and concentrated sulphuric acid (7 ml.) was added. After being heated at 100° for 8 hours, the cooled mixture was poured into water, and the solid product (m. p. 56—60°) collected. After a further similar treatment with the same reagents, the crude 1 : 22-dibromodocosane had m. p. 68—70° and then crystallised from ethanol–ethyl acetate in plates, m. p. 71—71·5° (2·5 g.) (Signer and Sprecher, *Helv. Chim. Acta*, 1947, **30**, 1001, reported m. p. 71·5—72°). A solution in ethanolic dimethylamine (20 ml.; 30%) was set aside at room temperature for 10 days and then heated to 95° for 10 hours. The crude diamine obtained by evaporation of solvent was converted, in the usual manner, into its *dihydrochloride*, short prisms, m. p. 236°, from ethanol–ethyl methyl ketone (Found : N, 5·8. $C_{26}H_{58}N_2Cl_2$ requires N, 6·0%).

n-*Eicosane*-2 : 18-*dione*.—Hexadecane-1 : 16-dicarboxylic acid (10·5 g.) was converted into its dichloride with thionyl chloride (12 ml.) at 80° for 1 hour and volatile halides were removed under reduced pressure. The residue in benzene (50 ml.) was treated with ethoxymagnesiomalonic ester (0·15 mol.) and the product hydrolysed with propionic acid following the general instructions of Bowman (*J.*, 1950, 322), to give the *ketone* (crude yield, 7 g. after appreciable loss by accident), colourless prismatic needles (from ethyl acetate), m. p. 90·5—91° (Found : C, 77·4; H, 12·4. $C_{20}H_{38}O_2$ requires C, 77·2; H, 12·3%).

2 : 18-*Bisdimethylaminoeicosane Dihydrochloride*.—The foregoing ketone (3 g.) was hydrogenated at 45°/1 atm. in ethanol (130 ml.) containing dimethylamine (5 g.) over 5% palladised charcoal (2 g.) until absorption of gas was complete (2 mols.). After removal of catalyst, the filtrate was evaporated to dryness and the base isolated as its *dihydrochloride* (3·0 g.), tiny prisms (from ethanol–ethyl methyl ketone), m. p. 196° (Found : N, 6·5. $C_{24}H_{54}N_2Cl_2$ requires N, 6·4%).

1 : 10-*Di*-2'-*cyanoethoxydecane*.—Acrylonitrile (6·5 g.) was gradually added to a stirred mixture of decane-1 : 10-diol (10 g.), dioxan (30 c.c.; distilled over sodium), and potassium hydroxide solution (0·4 c.c.; 40%) at 25—30° (cf. Bruson and Riener, *loc. cit.*). The mixture was stirred for 6 hours, left overnight, then poured into dilute sulphuric acid, the product being isolated with ethyl acetate. Distillation yielded a material, b. p. 120—180°/0·1 mm.; which appeared to consist mainly of the mono-adduct, and then 1 : 10-di-2'-cyanoethoxydecane, b. p. 180—185°/0·1 mm., as a colourless oil (8 g.), which crystallised in clusters of prisms, f. p. 39—38° (thermometer in liquid). Reaction of the low-boiling material with acrylonitrile in the same manner yielded more product (4 g.; total yield, 75%).

1 : 10-*Di*-3'-*aminopropoxydecane*.—The foregoing dicyanide (12 g.) in ethanol (200 c.c.) was mixed with saturated ethanolic ammonia (100 c.c.) and hydrogenated on Raney nickel (W7) catalyst; absorption ceased when 3·9 l. had been taken up (calc., 3·8 l.). Distillation of the

filtered solution yielded material, b. p. 160—180°/0·2 mm., redistillation of which furnished 1 : 10-*di*-3′-*aminopropoxydecane* (9 g.) as a colourless oil, b. p. 160—163°/0·3 mm., which crystallised in clusters of prisms, f. p. 28—27° (Found: C, 66·7; H, 12·8. $C_{16}H_{36}O_2N_2$ requires C, 66·6; H, 12·6%). The derived *dihydrochloride* crystallised from ethanol–ethyl methyl ketone in plates, m. p. 205—206° (Found: Cl, 20·0. $C_{16}H_{38}O_2N_2Cl_2$ requires Cl, 19·6%).

1 : 10-*Di*-3′-*dimethylaminopropoxydecane*.—A mixture of the foregoing amine (7·5 g.), formic acid (25 c.c.; 98%), and aqueous formaldehyde (25 c.c.; 35%) was heated at 100° for 12 hours and then poured into excess of sodium hydroxide solution, the product being isolated with light petroleum (b. p. 60—80°). 1 : 10-*Di*-3′-*dimethylaminopropoxydecane* (7·5 g.) was distilled as a colourless oil, b. p. 157°/0·2 mm., n_D^{20} 1·4522 (Found: C, 69·8; H, 12·8. $C_{20}H_{44}O_2N_2$ requires C, 69·7; H, 12·9%). The *dihydrochloride* crystallised from ethyl methyl ketone–ethanol in plates, m. p. 176° (Found: Cl, 17·4. $C_{20}H_{46}O_2N_2Cl_2$ requires C, 17·0%).

δ-*Keto-cyanides*.—The general procedure was used for the preparation of the δ-*keto-cyanides* tabulated.

Keto-cyanides, R·CO·CH_2·CH_2·CH_2·CN.

R	Yield, %		Formula	Found C, %	Found H, %	Required C, %	Required H, %
n-Hexyl	68	n_D^{20} 1·4519, b. p. 100—105°/0·1 mm.	$C_{11}H_{19}ON$	73·0	10·2	72·9	10·6
n-Nonyl	80	n_D^{20} 1·4510, b. p. 138—140°/0·5 mm.	$C_{14}H_{25}ON$	74·8	10·6	75·3	11·3
n-Tridecyl	75	Thin plates, m. p. 44°, from methanol; b. p. 160—165°/0·4 mm.	$C_{18}H_{33}ON$	77·4	11·9	77·4	11·9
n-Heptadecyl	85	Lustrous rectangular plates, m. p. 60—60·5°, from methanol	$C_{22}H_{41}ON$	(N, 4·4%)		(N, 4·2%)	
2 : 6 : 10-Trimethylundecyl [1]	70	n_D^{20} 1·4570, b. p. 165—170°/0·5 mm.	$C_{19}H_{35}ON$	77·5	11·2	77·8	12·0

[1] Prepared from 3 : 7 : 11-trimethyldodecanoyl chloride (Karrer, Favarger, Merz, and Milhaud, *Helv. Chim. Acta*, 1948, **31**, 1505).

These cyanides were characterised by hydrolysis with ethanolic potassium hydroxide to the tabulated δ-*keto-acids*.

Keto-acids, R·CO·CH_2·CH_2·CH_2·CO_2H.

R		Formula	Found C, %	Found H, %	Found Equiv.	Required C, %	Required H, %	Required Equiv.
n-Hexyl	Lustrous plates,[1, 2] m. p. 60—61°	—	—	—	—	—	—	—
n-Nonyl	Plates,[1] m. p. 80—81°	$C_{14}H_{26}O_3$	70·0	10·7	—	69·4	10·8	—
n-Tridecyl	Plates,[3, 4] m. p. 91—92°	$C_{18}H_{34}O_3$	72·2	11·4	301	72·4	11·5	298
n-Heptadecyl	Plates,[3] m. p. 98—99°	$C_{22}H_{42}O_3$	74·6	11·4	352	74·5	11·9	355

[1] From ethyl acetate–light petroleum (b. p. 40—60°). [2] Franke *et al.* (*Monatsh.*, 1936, **69**, 167) gave m. p. 60°. [3] From methanol. [4] Hirata and Nakanishi (*Bull. Chem. Soc., Japan*, 1949, **22**, 121) give m. p. 81·5° which seems unexpectedly low.

2-*Alkylpyridines*.—The procedure already described gave 2-dodecyl- (67%), b. p. 122—124°/0·4 mm., n_D^{20} 1·4813 (Barkovsky, *loc. cit.*, gave n_D^{14} 1·4858), and 2-pentadecyl-pyridine (25%), b. p. 158—162°/0·5 mm., f. p. 25° (Knight and Shaw, *loc. cit.*, record m. p. 29°).

2-*Dodecylpyridine Hydrochloride*.—Hydrogen chloride was passed into a solution of the base in light petroleum (b. p. 60—80°). The crystalline product was placed in a vacuum-desiccator over potassium hydroxide to remove excess of hydrogen chloride. The *hydrochloride* separated from light petroleum (b. p. 60—80°)–ethyl methyl ketone in microscopic plates, m. p. 63—64° (Found: Cl, 12·3. $C_{17}H_{30}NCl$ requires Cl, 12·5%).

2-*Alkylpiperidines*.—Reduction of the appropriate δ-keto-cyanide (Method A) or alkylpyridine (Method B) furnished the *amines* (V), and the *hydrochlorides* tabulated.

2-*Alkylpiperidines*.

Alkyl	Prep. (yield, %)	B. p./mm.	n_D^{20}	Formula	Found C, %	Found H, %	Required C, %	Required H, %
n-Hexyl	A (70)	57°/0·4	1·4569	$C_{11}H_{23}N$	78·1	13·5	78·0	13·7
n-Nonyl	A (80)	95—98°/0·5	1·4611	$C_{14}H_{29}N$	79·8	13·5	79·5	13·8
n-Dodecyl	B (90)	133—135°/0·7 (f. p. 18—17°)	1·4626	$C_{17}H_{35}N$	80·9	14·0	80·5	13·9
n-Tridecyl	A (71)	135—138°/0·4 (f. p. 16—15°)	1·4630	$C_{18}H_{37}N$	81·2	13·8	80·8	13·9
n-Pentadecyl	B (83)	154—157°/0·4 (f. p. 26—25°)	1·4646	$C_{20}H_{41}N$	80·6	14·1	81·3	14·0
n-Heptadecyl	A (80)	170—172°/0·3 (f. p. 29°)	—	$C_{22}H_{45}N$	81·4	14·0	81·6	14·0
2 : 6 : 10-Trimethylundecyl	A (70)	125—128°/0·4	1·4638	$C_{19}H_{39}N$	81·1	13·6	81·1	14·0

2-Alkylpiperidine Hydrochlorides.

Alkyl		M. p.	Formula	Found: Cl, %	Required: Cl, %
n-Hexyl	Large prismatic needles [1]	159°	$C_{11}H_{24}NCl$	17·6	17·2
n-Nonyl	Needles [1]	140	$C_{14}H_{30}NCl$	14·7	14·3
n-Dodecyl	Fine needles [2]	154—155	$C_{17}H_{36}NCl$	12·4	12·2
n-Tridecyl	,,	138	$C_{18}H_{38}NCl$	12·2	11·7
n-Pentadecyl	,,	138—139	$C_{20}H_{42}NCl$	10·8	10·7
n-Heptadecyl	Fine needles [1]	136—137	$C_{22}H_{46}NCl$	10·3	9·8
2 : 6 : 10-Trimethyl-undecyl	Small plates [3]	145—146	$C_{19}H_{40}NCl$	11·0	11·2

[1] From methyl ethyl ketone–ethanol. [2] From ethanol. [3] Separated from the mixture of isomers of indefinite m. p. by repeated crystallisation from ethyl methyl ketone.

1-*Methyl*-2-*undecylpiperidine*.—A mixture of 2-undecylpiperidine (1·5 g.; Bowman and Fordham, *loc. cit.*), formic acid (1·5 c.c.; 98%), and aqueous formaldehyde (1·5 c.c.; 35%) was heated at 100° for 12 hours. After addition of excess of dilute sodium hydroxide solution, 1-*methyl*-2-*undecylpiperidine* was isolated with light petroleum (b. p. 60—80°) and distilled as a colourless oil, b. p. 120°/0·4 mm., n_D^{20} 1·4626 (1·2 g.) (Found: C, 80·7; H, 14·1. $C_{17}H_{35}N$ requires C, 80·6; H, 13·9%). The *hydrochloride* crystallised from ethyl methyl ketone–light petroleum (b. p. 60—80°) in tiny prisms, m. p. 115—116° (Found: Cl, 12·8. $C_{17}H_{36}NCl$ requires Cl, 12·2%). The *methiodide* separated from ethanol in tiny prisms, m. p. 188° (Found: I, 31·9. $C_{18}H_{38}NI$ requires I, 32·1%).

Ethyl 2-*Undecylpiperidinoacetate*.—2-Undecylpiperidine (2·5 g.), ethyl chloroacetate (1·8 g.), and anhydrous potassium carbonate (2 g.) were heated at 110—115° for 4 hours and the mixture was then diluted with water, the product being extracted with ethyl acetate. Distillation yielded the *ester* as a colourless oil, b. p. 145—148°/0·1 mm., n_D^{20} 1·4638 (2·1 g.) (Found: C, 73·7; H, 12·1. $C_{20}H_{39}O_2N$ requires C, 73·8; H, 12·1%).

The ester (2·0 g.) was refluxed with concentrated hydrochloric acid (15 c.c.) and water (15 c.c.) for 8 hours and the solution was then evaporated to dryness. The residue was stirred with ether, and aniline added dropwise until no further precipitation occurred. The filtered solution was evaporated to dryness giving a viscous oil, which only partly crystallised on storage. Attempts to purify this acid by crystallisation and by distillation were unsuccessful.

1-β-*Carboxypropionyl*-2-*undecylpiperidine*.—Succinic anhydride (0·6 g.) in benzene (15 c.c.) was refluxed with 2-undecylpiperidine (1·5 g.) for 15 minutes and the solution was then evaporated. The residual gum did not crystallise and was therefore dissolved in benzene (20 c.c.) and shaken with 0·5N-sodium hydroxide (50 c.c.). The separated aqueous layer was acidified and extracted repeatedly with benzene, the extracts being washed with water and evaporated. Removal of the last traces of solvent at 100°/0·5 mm. furnished 1-β-*carboxypropionyl*-2-*undecylpiperidine* as an almost colourless gum (Found: C, 70·4; H, 11·1. $C_{22}H_{44}O_3N$ requires C, 70·7; H, 11·0%).

2-*Heptadecyl*-1-*methylpiperidine*.—The foregoing amine (10 g.) was methylated by the same procedure as 2-undecylpiperidine. 2-*Heptadecyl*-1-*methylpiperidine* (8·5 g.) was distilled as a colourless oil, b. p. 166°/0·4 mm., which solidified on cooling and had f. p. 23° (thermometer in liquid) (Found: C, 82·2; H, 13·8. $C_{23}H_{47}N$ requires C, 81·8; H, 14·0%). The *hydrochloride* crystallised from ethyl methyl ketone–light petroleum (b. p. 60—80°) in colourless plates, m. p. 116—117° (Found: Cl, 9·7. $C_{23}H_{48}NCl$ requires Cl, 9·5%), and the *methiodide* from ethanol in microscopic plates, m. p. 218° (Found: I, 27·0. $C_{24}H_{50}NI$ requires I, 26·5%).

1-*Dodecylpyridinium Bromide*.—Dodecyl bromide (25 g.) was heated with pyridine (8 g.) at 150° for 1 hour and, on cooling, the mass crystallised. Recrystallisation from ethyl methyl ketone yielded large, colourless needles of 1-*dodecylpyridinium bromide monohydrate*, m. p. 74—75° (Found: C, 58·9; H, 9·1; Br, 22·9. $C_{17}H_{30}NBr,H_2O$ requires C, 58·9; H, 9·3; Br, 23·1%). Knight and Shaw (*J.*, 1938, 682) gave m. p. I, 89—90°, II, 125°, for the anhydrous substance. The water of crystallisation could not be removed *in vacuo* at 20° or 60°, and heating at 100°/0·5 mm. caused partial decomposition and some pyridine was produced. Addition of a solution of the hydrate in a minimum of ethanol to ether, as employed by Knight and Shaw, regenerated the unchanged hydrate.

1-*Dodecylpiperidine*.—The foregoing bromide (13 g.) in ethanol (150 c.c.) was hydrogenated at 20° and normal pressure in the presence of diethylamine (10 c.c.) and Raney nickel W7 catalyst (*ca.* 5 g.). Absorption was rapid (2·0 l. in 16 minutes) and eventually ceased when 2·6 l. had been taken up (calc., 2·7 l.). The filtered solution was evaporated and the residue dissolved in ethyl acetate; the solution was washed with 0·2N-sodium hydroxide solution and

then water, dried ($MgSO_4$), and distilled. 1-Dodecylpiperidine (8 g., 80%) was obtained as a colourless oil, b. p. 114—116°/0·4 mm., n_D^{20} 1·4578. Stross and Evans (*J. Amer. Chem. Soc.*, 1942, **64**, 2511) gave n_D^{20} 1·4588. The hydrochloride crystallised from ethyl methyl ketone in colourless needles, m. p. 187—188°. Karrer, Kahnt, Epstein, Jaffé, and Ishii (*Helv. Chim. Acta*, 1938, **21**, 223) reported m. p. 188—189°. The *methiodide* separated from light petroleum (b. p. 60—80°) in lustrous plates, m. p. 140° (Found : I, 31·6. $C_{18}H_{38}NI$ requires I, 32·1%).

α-*Dodecylglutaric Anhydride*.—Sodium (0·5 g.) was dissolved in ethyl dodecylmalonate (66 g., 0·2 mol.) at 100° and acrylonitrile (21 g., 0·4 mol.) was gradually added to the stirred mixture, which was then heated at 80—90° for 1 hour. After being heated under reflux with ethylene glycol (150 c.c.) and 10N-potassium hydroxide (100 c.c.) until evolution of ammonia ceased (12 hours), the solution was poured into 2N-sulphuric acid (750 c.c.), and the product isolated with ethyl acetate. Removal of the solvent yielded the crude triacid, which was decarboxylated at 200° (30 minutes); acetic anhydride (100 c.c.) was added and the mixture was refluxed for 2 hours and then distilled, to give the *anhydride* (37 g., 65%) as a colourless oil, b. p. 196—198°/0·5 mm., which rapidly crystallised and separated from light petroleum (b. p. 60—80°) in colourless plates, m. p. 57—58° (Found : C, 72·1; H, 10·6. $C_{17}H_{30}O_3$ requires C, 72·3; H, 10·7%).

A mixture of the anhydride (15 g.), aqueous ammonia (40 c.c.; *d* 0·88), and ethanol (10 c.c.) was distilled until the temperature reached 250° (bath) and kept at 240—250° for 20 minutes; on cooling, the product crystallised. α-*Dodecylglutarimide* (10 g., 65%) separated from light petroleum (b. p. 60—80°)–ethyl acetate (charcoal) in lustrous plates, m. p. 106—107° (Found : N, 5·3. $C_{17}H_{31}O_2N$ requires N, 5·0%).

3-*Dodecylpiperidine*.—The foregoing imide (6 g.) in a Soxhlet apparatus was extracted by refluxing a stirred solution of lithium aluminium hydride (3 g.) in ether (250 c.c.). After 4 hours' refluxing, N-potassium hydroxide (400 c.c.) was added and the product isolated with ethyl acetate. 3-*Dodecylpiperidine* (4 g.) distilled as a colourless oil, b. p. 136—138°/0·4 mm., n_D^{20} 1·4636 (Found : C, 81·0; H, 13·7. $C_{17}H_{35}N$ requires C, 80·5; H, 13·9%). The *hydrochloride* crystallised from ethyl methyl ketone–ethanol in clusters of prismatic needles, m. p. 137—138° (Found : Cl, 12·0. $C_{17}H_{36}NCl$ requires Cl, 12·2%).

2-*Dodecylpropane*-1 : 3-*diol*.—Ethyl dodecylmalonate (25 g.) was added during 30 minutes to a stirred solution of lithium aluminium hydride (6 g.) in ether (200 c.c.), and the mixture was then refluxed for 1 hour. The products were isolated with ether in the usual manner, distillation furnishing the *diol* as a colourless oil, b. p. 160—163°/0·5 mm., f. p. 69° (16·5 g., 89%), which separated from ethyl methyl ketone in lustrous, prismatic needles, m. p. 71—71·5° (Found : C, 73·7; H, 13·1. $C_{15}H_{32}O_2$ requires C, 73·7; H, 13·2%).

4-*Dodecylpyridine*.—4-Picoline (purified through the crystalline oxalate; Lidstone, *J.*, 1940, 241) was heated for 1 hour at 100° with powdered, commercial sodamide (5 g.); undecyl chloride (18 g.) was added and the mixture kept at 100° for 18 hours. After addition of water, the products were isolated with light petroleum (b. p. 60—80°) and fractionally distilled. 4-Dodecylpyridine (7 g.) was obtained as a colourless oil, b. p. 133—134°/0·3 mm., n_D^{20} 1·4834 (Barkovsky, *loc. cit.*, gave n_D^{14} 1·4856).

4-*Dodecylpiperidine Hydrochloride*.—Sodium (25 g.) was added in two portions to the foregoing amine (6 g.) in ethanol (100 c.c.); the mixture was then heated (bath, 120°) for 1 hour. More ethanol was added to dissolve the remaining sodium and, after removal of the alcohol by steam-distillation, the products were isolated with light petroleum (b. p. 60—80°). The crude product was dissolved in ethyl methyl ketone (40 c.c.), and concentrated hydrochloric acid (2 c.c.) added; a first crop (1·6 g.) of crystals separated at 20° and a second (1·3 g.) at 0°. Recrystallisation of the combined products from ethyl methyl ketone furnished fine needles of 4-*dodecylpiperidine hydrochloride*, m. p. 165° (Found : C, 69·9; H, 12·2; Cl, 12·4. $C_{17}H_{36}NCl$ requires C, 70·4; H, 12·5; Cl, 12·2%).

Attempted Synthesis of 12-*Ethyltricosane*-10 : 14-*dione*.—Propylidenemalonic ester (Cope, Hofmann, Wyckoff, and Hardenbergh, *J. Amer. Chem. Soc.*, 1941, **63**, 3452) was treated with ethyl sodiomalonate as described by Goss, Ingold, and Thorpe (*J.*, 1923, **123**, 3353). Ethyl 2-ethylpropane-1 : 1 : 3 : 3-tetracarboxylate, b. p. 150—160°/0·4 mm., was thus obtained in 61% yield.

This (60 g.), sodium (7·7 g.), and benzyl alcohol (72 g.) in benzene were subjected to ester-interchange in the usual manner, and decanoyl chloride (61 g.) was then added. The products were isolated and debenzylated by the general procedure, the resulting solution being boiled, filtered, and evaporated. Light petroleum (b. p. 60—80°; 300 c.c.) and water (800 c.c.) were

added to the residual oil and the mixture was basified with 2N-sodium hydroxide solution (160 c.c.). The aqueous layer was extracted with light petroleum, and the combined organic layers were washed with 0·5N-sodium hydroxide and then water, dried ($MgSO_4$), and evaporated. Repeated fractional distillation of the product yielded undecan-2-one, b. p. 57°/0·3 mm., f. p. 10° (thermometer in liquid), n_D^{20} 1·4319 (semicarbazone, m. p. 122—123°), and *benzyl decanoate*, b. p. 140—145°/0·2 mm., n_D^{20} 1·4909 (Found : C, 77·5; H, 10·3. $C_{17}H_{26}O_2$ requires C, 77·8; H, 10·0%).

Glutaroyl Dichloride.—A mixture of glutaric acid (50 g.) and thionyl chloride (80 c.c.) was kept at room temperature for 5 hours and then warmed at 50° for ½ hour. After removal of excess of thionyl chloride by distillation *in vacuo*, the dichloride (45 g.) was distilled as a colourless oil, b. p. 88°/5 mm.

Heptadecane-7 : 11-dione.—The sodio-benzyl ester (0·4 mol.), prepared in the usual manner from sodium (9·2 g.), benzyl alcohol (86·5 g.), and ethyl amylmalonate (92 g.) in benzene, was treated with glutaroyl dichloride (32 g., 0·19 mol.), and the product isolated, debenzylated, and decarboxylated according to the general procedure. The crude product was shaken with light petroleum (b. p. 60—80°; 300 c.c.), ethyl acetate (50 c.c.), and water (500 c.c.), and the mixture basified with N-sodium hydroxide (100 c.c.). The separated aqueous layer was extracted twice with ethyl acetate–light petroleum (b. p. 60—80°), and the combined organic layers were washed with 0·5N-sodium hydroxide solution (200 c.c.) and then water (three times), dried ($MgSO_4$), and evaporated under reduced pressure. Crystallisation of the residue from light petroleum (b. p. 60—80°)–ethyl acetate (activated charcoal) and then from methanol yielded colourless plates of *heptadecane-7 : 11-dione* (12·5 g., 25%), m. p. 80—81° (Found : C, 75·5; H, 11·9. $C_{17}H_{32}O_2$ requires C, 76·1; H, 12·0%).

2 : 6-Dihexylpiperidine Hydrochloride.—The foregoing diketone (8 g.) in ethanol (200 c.c.), and ethanol (50 c.c.) saturated with ammonia, was hydrogenated at 25° in the presence of palladised charcoal (1 g.; 5% of Pd) and palladised strontium carbonate (3 × 3 g.; 10% of Pd). Absorption ceased when 1 l. had been taken up (calc., 1·4 l.), and the filtered solution was distilled, to give the impure amine, b. p. 100—106°/0·3 mm., n_D^{20} 1·4702 (6 g.) (Found : C, 81·6; H, 12·6. Calc. for $C_{17}H_{35}N$: C, 80·6; H, 13·9%). Concentrated hydrochloric acid (3·5 c.c.) was added to a solution of the crude product in hot ethanol (50 c.c.), and *2 : 6-dihexylpiperidine hydrochloride* (2·2 g.), which separated on cooling, was recrystallised from ethanol, forming short rods, m. p. 147° (Found : C, 70·4; H, 12·5; Cl, 12·1. $C_{17}H_{36}NCl$ requires C, 70·4; H, 12·5; Cl, 12·2%). Evaporation of the mother-liquor furnished a viscous, brown oil, which was not investigated further.

Ethyl 2-Cyanoethyldodecylmalonate.—Sodium (0·2 g.) was dissolved in ethyl dodecylmalonate (26 g.) at 100° (1½ hours), and freshly distilled acrylonitrile (8 g.) was then added. After 1 hour's heating (bath, 110°), glacial acetic acid (3 g.) and water (200 c.c.) were added, the product being isolated with light petroleum (b. p. 40—60°). Ethyl 2-cyanoethyldodecylmalonate (20 g., 65%) distilled as a colourless oil, b. p. 198—203°/1 mm., n_D^{20} 1·4509.

Ethyl 3-Dodecyl-2-ketopiperidine-3-carboxylate.—The foregoing cyano-diester (3·3 g.) in ethanol was hydrogenated, on Raney nickel W7 catalyst, until absorption ceased. After evaporation of the filtered solution the residue was heated (bath, 150°) for 10 minutes and, on cooling, the product crystallised. The *ester* (2·2 g.) separated from light petroleum (b. p. 40—60°) in plates, m. p. 71—72° (Found : C, 71·2; H, 10·9. $C_{20}H_{37}O_3N$ requires C, 70·7; H, 11·0%).

In another experiment, an attempt was made to distil the crude reduction product; considerable decomposition resulted and only a small amount (15%) of a colourless oil, b. p. 205—210°/0·9 mm., was collected. This material rapidly solidified and recrystallisation from light petroleum (b. p. 40—60°) furnished fine needles of *3-dodecylpiperid-2-one*, m. p. 79—80° (Found : C, 76·4; H, 12·0. $C_{17}H_{33}ON$ requires C, 76·3; H, 12·4%). The latter was probably formed by partial hydrolysis of the ester by the alkali present in the catalyst and decarboxylation on distillation. A mixture of this product with the ester (m. p. 71—72°) melted at about 61°.

3-Dodecyl-3-hydroxymethylpiperidine.—The foregoing ester (1·3 g.) was added to a stirred solution of lithium aluminium hydride (1·5 g.) in ether (120 c.c.). After 2 hours' refluxing, 2N-sodium hydroxide (200 c.c.) was added and the product isolated with benzene. The resulting oil could not be induced to crystallise, nor could the derived hydrochloride, and the product was therefore distilled. *3-Dodecyl-3-hydroxymethylpiperidine* (0·6 g.) was obtained having b. p. 175—180°/0·5 mm., n_D^{20} 1·4793 (Found : C, 75·9; H, 12·7. $C_{18}H_{37}ON$ requires C, 76·3; H, 13·2%).

1 : 16-Dicyanohexadecane-4 : 13-dione.—Sebacoyl chloride (27·5 g., 0·115 mol.) was condensed

with dibenzyl sodio-2-cyanoethylmalonate (0·25 mol.) and the product debenzylated, decarboxylated, and isolated by the general procedure. Repeated crystallisation of the product from methanol furnished colourless plates of 1 : 16-*dicyanohexadecane*-4 : 13-*dione*, m. p. 72—73° (11 g., 33%) (Found : N, 9·2. $C_{18}H_{28}O_2N_2$ requires N, 9·2%). Hydrolysis with aqueous-ethanolic sodium hydroxide in the usual manner furnished 4 : 13-*diketohexadecane*-1 : 16-*dicarboxylic acid*, plates, m. p. 142—143°, from ethyl acetate (Found : C, 63·3; H, 9·0. $C_{18}H_{30}O_6$ requires C, 63·1; H, 8·8%).

This acid (5 g.) was reduced by the modified Wolff–Kishner method (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) with sodium hydroxide (5 g.) in water (5 c.c.), hydrazine hydrate (7 c.c.; 60%), and 2 : 2′-dihydroxydiethyl ether (80 c.c.). After the reaction mixture had been poured into excess of dilute sulphuric acid, the product was isolated with ethyl acetate, yielding hexadecane-1 : 16-dicarboxylic acid (3·8 g.), m. p. 123—124°, after crystallisation from ethanol.

1 : 8-*Di*-2′-*piperidyloctane*.—Hydrogenation of 1 : 16-dicyanohexadecane-4 : 13-dione (7 g.), as previously, furnished a yellow oil (4·5 g.), b. p. 163—166°/0·3 mm., redistillation of which yielded the *diamine*, b. p. 158—160°/0·2 mm., crystallising in prismatic needles, f. p. 37—36° (thermometer in liquid) (Found : C, 77·1; H, 12·3. $C_{18}H_{36}N_2$ requires C, 77·1; H, 12·9%). The derived *dihydrochloride* crystallised from ethanol–ethyl methyl ketone (charcoal) and then aqueous dioxan in microscopic plates, m. p. 229° (Found : Cl, 20·4. $C_{18}H_{38}N_2Cl_2$ requires Cl, 20·1%).

9-2′-*Piperidylnonanoic Acid Hydrochloride*.—The alkaline aqueous layer obtained during the synthesis of 1 : 16-dicyanohexadecane-4 : 13-dione was acidified with sulphuric acid (20 c.c.; 20N), and the oily product taken up in ethyl acetate (100 c.c.). The organic layer was washed with water, dried ($MgSO_4$), and evaporated, the residue being esterified azeotropically with ethanol (80 c.c.), benzene (100 c.c.), and concentrated sulphuric acid (0·5 c.c.). Fractional distillation of the resulting esters furnished crude *ethyl* 13-*cyano*-10-*ketotridecanoate*, b. p. 178°/0·2 mm., f. p. 41—40° (thermometer in liquid) (Found : C, 67·2; H, 9·5. $C_{16}H_{27}ON_3$ requires C, 68·3; H, 9·7%). This, without further purification, was hydrogenated, as before, and the resulting oily product was refluxed with concentrated hydrochloric acid (10 c.c.) and water (10 c.c.) for 8 hours. Evaporation of the solution and crystallisation of the residual solid from aqueous dioxan yielded plates of the *amino-acid hydrochloride*, m. p. 170° (2·5 g.) (Found : N, 5·0. $C_{14}H_{28}O_2NCl$ requires N, 5·0%).

1-*Dodecylpyrrolidine*.—Dodecyl bromide (10 g.) and pyrrolidine (6 g.) were heated with anhydrous potassium carbonate (4 g.) at 100—110° for 2 hours and then at 150° for ½ hour. After addition of water, the product was isolated with ethyl acetate and distilled, b. p. 108—112°/0·5 mm. (8 g.). 1-*Dodecylpyrrolidine*, purified by regeneration from the crystalline hydrochloride, had b. p. 108—110°/0·4 mm., n_D^{20} 1·4559, f. p. −6° to −7° (Found : C, 80·8; H, 13·9. $C_{16}H_{33}N$ requires C, 80·3; H, 13·9%). The *hydrochloride* separated from chloroform–light petroleum (b. p. 60—80°) in microscopic plates, m. p. 159—160° (Found : Cl, 12·8. $C_{16}H_{34}NCl$ requires Cl, 12·9%).

2-*Dodecylpyrrolidine Hydrochloride*.—3-Chloropropyl cyanide (10 g.) was added to a stirred ethereal solution of the Grignard reagent prepared from magnesium (5·0 g.) and dodecyl bromide (50 g.). After the mixture had been refluxed for 2 hours, ammonium chloride solution (250 c.c.; 20%) was added and the separated aqueous layer was extracted with benzene. The combined organic layers were washed with 2N-sodium hydroxide and then water, dried (K_2CO_3), and evaporated. The fraction, b. p. 120—140°/0·2 mm. (14 g.), which was separated from higher- and lower-boiling products by fractional distillation, was evidently not homogeneous and partly crystallised. This crude product was hydrogenated in ethanol on Raney nickel W7 catalyst (1·3 l. absorbed). The filtered solution was evaporated and 0·5N-sodium hydroxide solution (250 c.c.) added to the residue, the oily product being taken up in light petroleum (b. p. 40—60°). The dried (K_2CO_3) petroleum solution was saturated with hydrogen chloride and then cooled at 0°. 2-*Dodecylpyrrolidine hydrochloride* (1·1 g.), which separated, was recrystallised from light petroleum (b. p. 40—60°)–ethyl methyl ketone, forming lustrous plates, m. p. 83—84° (Found : C, 69·7; H, 12·3; Cl, 12·6. $C_{16}H_{34}NCl$ requires C, 69·7; H, 12·4; Cl, 12·9%).

Dodecylsuccinic Anhydride..—Sodium (2·3 g.) was dissolved in ethanol (100 c.c.) and, after successive addition of ethyl dodecylmalonate (33 g.) and ethyl chloroacetate (16 g.), the mixture was refluxed for 5 hours. Diethylene glycol (150 c.c.) and 10N-potassium hydroxide (60 c.c.) were added, ethanol was removed by distillation, and the residue was refluxed for 5 hours and then poured into excess of dilute sulphuric acid. The crude tricarboxylic acid, isolated with

ethyl acetate, was decarboxylated at 210—220° (½ hour) and then refluxed with acetic anhydride (100 c.c.) for 2 hours. Distillation furnished dodecylsuccinic anhydride (14 g.), b. p. 172—175°/0·5 mm., which rapidly crystallised and separated from light petroleum (b. p. 60—80°) in fine needles, m. p. 71—72° (Barry and Twomey, *Proc. Roy. Irish Acad.*, 1947, **51**, *B*, 137, give m. p. 69—70·5°).

α-*Dodecylsuccinimide.*—The foregoing anhydride (8·2 g.) and aqueous ammonia (25 c.c.; *d* 0·88) were distilled until the bath-temp. reached 260° and then heated at 260° for ½ hour. α-*Dodecylsuccinimide*, which crystallised on cooling, was recrystallised from ethyl acetate–light petroleum (b. p. 60—80°) in microscopic plates, m. p. 94—95° (5·6 g.) (Found : C, 71·7; H, 10·5. $C_{16}H_{29}O_2N$ requires C, 71·8; H, 10·9%).

3-*Dodecylpyrrolidine.*—To a solution of lithium aluminium hydride (3 g.) in ether (100 c.c.) was added the foregoing imide (5·4 g.), and the mixture was stirred under reflux for 8 hours. Dilute potassium hydroxide solution was added and the product isolated with ethyl acetate; distillation yielded 3-*dodecylpyrrolidine* (2·4 g.) as a colourless oil, b. p. 134—138°/0·8 mm., n_D^{20} 1·4631 (Found : C, 80·4; H, 13·8. $C_{16}H_{33}N$ requires C, 80·3; H, 13·9%). The derived *hydrochloride* separated from light petroleum (b. p. 60—80°) in lustrous plates, m. p. 81° (Found : Cl, 12·4. $C_{16}H_{34}NCl$ requires Cl, 12·9%).

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