Mycoceranic Acid. Part II.*

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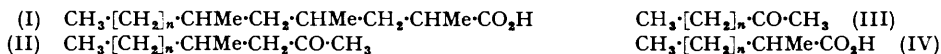
(+)-4-Methylhexacosan-2-one and several straight-chain ketones have been synthesised for comparison with two ketones resulting from the stepwise degradations of mycoceranic acid (cf. Part I *). The latter is now provisionally regarded as 2(D) : 4(D) : 6(D)-trimethyloctacosanoic acid,† and some preliminary studies in the synthesis of this acid are reported.
The synthesis of 2 : 4 : 6(D)-trimethyloctacosanoic acid is described.

MYCOCERANIC ACID, a lævorotatory acid isolated from the lipids of tubercle bacilli, has been shown, by a series of stepwise degradations, to have the structure (I) where n is probably 21 (Part I *). It remained, therefore, to confirm the length of the normal chain. The degradation products already described include the ketones (II) and (III), and the first aim of the present work was to identify these ketones by synthesis.

The ketone (II), containing an asymmetric carbon atom, resulted from the above degradative studies in amounts which were insufficient for determining its rotation. However, the configuration of the asymmetric carbon atom of this ketone may be fixed by reference to another degradation product of mycoceranic acid, namely, the 2-methyl-substituted lævorotatory acid (IV) (cf. Part I *) of which $C_{(2)}$ corresponds to $C_{(4)}$ of the ketone (II). The lævorotatory form of 2-methyl-substituted carboxylic acids has been sterically related to D-(+)-glyceric aldehyde † (Ställberg-Stenhagen and Stenhagen, *Arkiv Kemi, Min., Geol.*, 1947, **24**, B, No. 9). This relationship was based upon the correlation of (+)-methylsuccinic acid with (+)-malic acid, established by the method of " quasi-racemates " (Fredga, *ibid.*, 1942, **15**, B, No. 23), and recently confirmed by direct chemical correlation (Freudenberg and Hohmann, *Annalen*, 1953, **584**, 54). From these considerations, the above ketone (II) is assigned to the D-series.
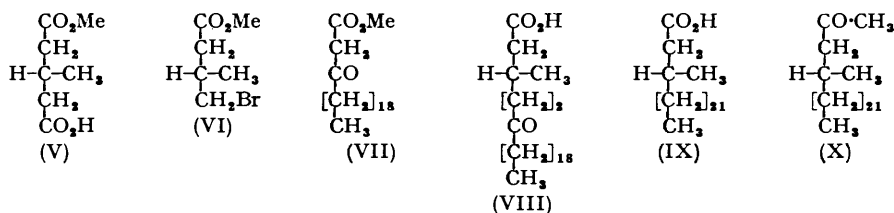
(I) $CH_3 \cdot [CH_2]_n \cdot CHMe \cdot CH_2 \cdot CHMe \cdot CH_2 \cdot CHMe \cdot CO_2H$ $CH_3 \cdot [CH_2]_n \cdot CO \cdot CH_3$ (III)

(II) $CH_3 \cdot [CH_2]_n \cdot CHMe \cdot CH_2 \cdot CO \cdot CH_3$ $CH_3 \cdot [CH_2]_n \cdot CHMe \cdot CO_2H$ (IV)

The D-form of 4-methylhexacosan-2-one (II; $n = 21$) was synthesised *via* D-3-methyl-pentacosanoic acid (IX). The starting point was L-(+)-methyl hydrogen 3-methyl-glutarate (V) (Ställberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1947, **25**, A, No. 10; Linstead, Lunt, and Weedon, *J.*, 1950, 3333). This (and its enantiomorph) has been converted earlier into various long-chain 3-methyl-carboxylic acids by methods involving reaction of the half-ester chloride with a β-keto-ester (Ställberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1948, **26**, A, No. 1; and later papers), or by the electrolysis of mixtures of the half ester and a fatty acid (Ställberg-Stenhagen, *Arkiv Kemi*, 1950, **2**, 95; Linstead, Lunt, and Weedon, *J.*, 1951, 1130). We found it advantageous to convert the half ester, by reaction of its silver salt with bromine (Hunsdiecker and Hunsdiecker, *Ber.*, 1942, **75**, 291) into (—)-(methyl D-4-bromo-3-methylbutanoate) (VI) (the change of prefix L to D is due to the conventional † alteration of the reference group), $[\alpha]_D$ —2·54°, which on refluxing with sodium iodide in acetone gave the corresponding iodo-ester. The latter, on reaction with the sodio-derivative of methyl 3-oxodocosanoate (VII) (obtained by the action of eicosanoyl chloride upon ethyl sodioacetoacetate), followed by hydrolysis and ketonic cleavage, afforded D-(+)-3-methyl-6-oxopentacosanoic acid (VIII), $[\alpha]_D$ +4·65°. This was converted by Clemmensen reduction into D-(+)-3-methylpentacosanoic acid (IX), $[\alpha]_D$ +3·76°, and thence, by reaction of the acid chloride with methylzinc iodide (Blaise, *Bull. Soc. chim. France*, 1911, **9**, pp. i—xxvi) into D-(+)-4-methylhexacosan-2-one (X), $[\alpha]_D$ +4·9°.

The semicarbazone of the ketone (X) had m. p. 101—102° which is some 9° higher than that reported (Part I, *loc. cit.*) for the semicarbazone of the degradation product (II) after only one crystallisation (owing to the small amounts of material available). The X-ray

diffraction powder photographs, kindly taken by Mrs. D. M. Crowfoot Hodgkin, were very similar, but in the region of 20 Å the synthetic product gave a line, and the semicarbazone of the degradation product a rather broad region of heavy scattering, thus indicating the presence of a contaminant in the degradation product. For similar reasons an attempt

$$
\begin{array}{cccccc}
CO_2Me & CO_2Me & CO_2Me & CO_2H & CO_2H & CO\cdot CH_3 \\
CH_2 & CH_2 & CH_2 & CH_2 & CH_2 & CH_2 \\
H\text{-}C\text{-}CH_3 & H\text{-}C\text{-}CH_3 & CO & H\text{-}C\text{-}CH_3 & H\text{-}C\text{-}CH_3 & H\text{-}C\text{-}CH_3 \\
CH_2 & CH_2Br & [CH_2]_{18} & [CH_2]_2 & [CH_2]_{21} & [CH_2]_{21} \\
CO_2H & (VI) & CH_3 & CO & CH_3 & CH_3 \\
(V) & & (VII) & [CH_2]_{18} & (IX) & (X) \\
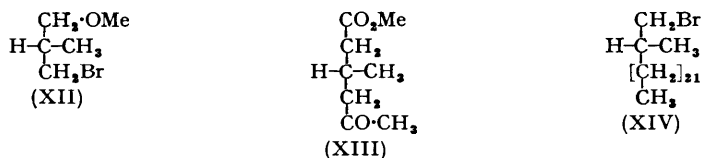& & & CH_3 & & \\
& & & (VIII) & &
\end{array}
$$

to identify the degradation product (III) (see above) by comparison of its semicarbazone with those of docosan-2-one, tricosan-2-one, and tetracosan-2-one (the preparations of these ketones are included in the Experimental section) has not so far been successful. A discussion on the question of the homogeneity of the lævorotatory acid employed for the degradative studies is reserved for a future communication. Meanwhile, mycoceranic acid is tentatively regarded as 2 : 4 : 6-trimethyloctacosanoic acid (I; $n = 21$).

In regard to the configurations of the asymmetric centres of mycoceranic acid it is of interest that mycoceranic acid, itself a 2-methyl-carboxylic acid, and also the 2-methyl-carboxylic acids (IV) (see above) and (XI) resulting from the stepwise degradations of mycoceranic acid (Part I, *loc. cit.*) are all lævorotatory. Although mycoceranic acid has additional asymmetric centres at $C_{(4)}$ and $C_{(6)}$ corresponding to $C_{(2)}$ of the acids (XI) and (IV), respectively, and the acid (XI) one additional centre of asymmetry at $C_{(4)}$, their rotatory powers, from comparison with optically active 2- and 4-methyl-carboxylic acids recorded in literature, appear to be largely due to the asymmetric centre at $C_{(2)}$. Since the lævorotatory form of 2-methyl-carboxylic acids has been assigned to the *D*-series (see above), it may be assumed that mycoceranic acid has *D*-configuration in respect of all three asymmetric centres.

$$(XI) \quad CH_3\cdot[CH_2]_n\cdot CHMe\cdot CH_2\cdot CHMe\cdot CO_2H$$

In the course of investigations into the synthesis of $2(D) : 4(D) : 6(D)$-trimethyl-octacosanoic acid we have devoted some attention to a route which involves the linking together, by a Grignard reaction, of two molecules each containing one optically active centre, *e.g.*, of (X) with (XII), or (XIII) with (XIV). Thus, condensation of the optically active ketone (X) with the Grignard derivative of the optically active bromide (XII), followed by dehydration of the resultant product, would give the ethylenic compounds (XV) which could be converted by catalytic hydrogenation into (XVI) with the newly created asymmetric centre at $C_{(4)}$. The latter, separated from each of the previously existing optically active centres at $C_{(2)}$ and $C_{(6)}$ by only one methylene group, may be expected to arise with a preponderance of one configuration, and it was of interest to study the direction and extent of this asymmetric synthesis. The isolation of the requisite diastereoisomer,
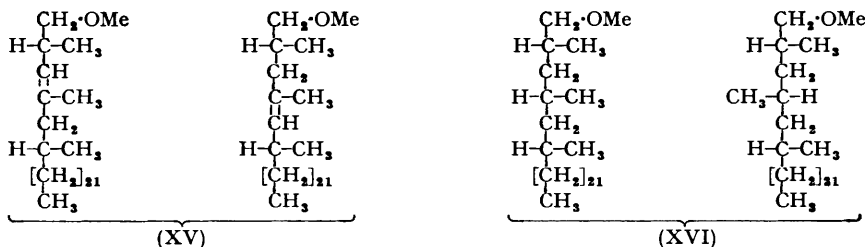
$$
\begin{array}{ccc}
CH_2\cdot OMe & CO_2Me & CH_2Br \\
H\text{-}C\text{-}CH_3 & CH_2 & H\text{-}C\text{-}CH_3 \\
CH_2Br & H\text{-}C\text{-}CH_3 & [CH_2]_{21} \\
(XII) & CH_2 & CH_3 \\
& CO\cdot CH_3 & (XIV) \\
& (XIII) &
\end{array}
$$

if successful, would open the way to a synthesis of $2(D) : 4(D) : 6(D)$-trimethyloctacosanoic acid by a further extension involving known procedures. Similar considerations apply to the modification of this scheme involving a Grignard reaction between (XIII) and (XIV).

The above approach is still under investigation, but some preliminary experiments in the synthesis of the requisite optically active intermediates are described below.

It was thought that the optically active methoxy-bromide (XII) might be accessible from the *L*-form of methyl 4-bromo-3-methylbutanoate (see above) by conversion into the

methoxy-ester (XVII), followed by hydrolysis, and reaction of the silver salt of the resulting acid with bromine. However, in a model experiment employing the D-form (VI) of methyl 4-bromo-3-methylbutanoate, reaction with sodium methoxide in methanol gave a product

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   CH₂·OMe          CH₂·OMe          CH₂·OMe          CH₂·OMe
 H-C-CH₃          H-C-CH₃          H-C-CH₃          H-C-CH₃
   CH               CH₂              CH₂              CH₂
   C-CH₃            C-CH₃          H-C-CH₃          CH₃-C-H
   CH₂              CH               CH₂              CH₂
 H-C-CH₃          H-C-CH₃          H-C-CH₃          H-C-CH₃
  [CH₂]₂₁          [CH₂]₂₁          [CH₂]₂₁          [CH₂]₂₁
   CH₃              CH₃              CH₃              CH₃
 _____/      _____/
            (XV)                              (XVI)
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having $[\alpha]_D$ —85·4°, the analysis and high rotatory power of which indicated the structure of a *cyclo*propane derivative, arising by the elimination of hydrogen bromide.

In another experiment, reaction of the racemic form of methyl 4-bromo-3-methyl-butanoate with silver carbonate in methanol (cf. Ziegler, Weber, and Gellert, *Ber.*, 1942, **75**, 1715) also failed to furnish the required methoxy-ester. An alternative procedure tried involved the conversion of the bromo-ester, by means of potassium acetate in glacial acetic acid, into the corresponding acetoxy-ester which was subjected to the action of methanolic hydrogen chloride to produce the hydroxy-ester. Methylation of the product by means of methyl iodide and silver oxide (Purdie and Irvine, *J.*, 1899, **75**, 485) failed, however, to yield the pure methoxy-ester, and owing to the unsatisfactory yields this approach was not pursued further.

In further experiments, methyl 3-methyl-4-phenoxybutanoate (XVIII) was obtained in 17% yield by reaction of phenol with methyl 4-iodo-3-methylbutanoate in the presence of potassium carbonate and methyl propyl ketone. Attempts to improve the yield of the phenoxy-ester by increasing the molar ratio of phenol to the iodo-ester failed, but the yield was slightly increased (to 21%) by using, as a solvent, acetone in place of methyl propyl ketone. In an attempt to employ this phenoxy-ester instead of the methoxy-derivative (see above), the corresponding acid was converted into its silver salt, and the latter subjected to the action of bromine. The product was, however, a bromo-acid of the composition $C_{11}H_{13}O_3Br$, and not the expected bromide (XIX), presumably substitution of the benzene nucleus by bromine having taken place. An analogous result is that of Dauben and Tills (*J. Amer. Chem. Soc.*, 1950, **72**, 3185) who obtained 2-bromo-5-methoxybenzoic acid on reaction of the silver salt of *m*-methoxybenzoic acid with bromine.

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   CH₂·OMe                      MeO₂C·CH₂·CHMe·CH₂·OPh
 H-C-CH₃                                (XVIII)
   CH₂
   CO₂Me                        Br·CH₂·CHMe·CH₂·OPh
  (XVII)                                 (XIX)
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Concurrently with the above studies, we also examined the preparation of the optically active keto-ester (XIII). The corresponding acid, obtained by Ställberg-Stenhagen (*Arkiv Kemi, Min., Geol.*, 1948, **26**, A, No. 12) by a procedure involving reaction of the acid chloride derived from the half ester (V) with the sodio-derivative of methyl aceto-acetate, was stated to show rotations varying considerably from one preparation to the other. This was explained by the existence of keto-acid–hydroxy-lactone tautomerism, and it was reported that a specimen of the keto-acid having α_D —3·3° (homog., *l*, 1) yielded on Clemmensen reduction (+)-3-methylhexanoic acid with $[M]_D$ +3·9°, to be compared with a previously recorded value of 3·6° (Levene and Marker, *J. Biol. Chem.*, 1932, **98**, 1). We tried to obtain the above keto-ester (XIII) in one stage by the action of methylzinc iodide on the acid chloride of the half ester (V). The product had $]\alpha]_D$ —1·1°, and gave on Clemmensen reduction, followed by hydrolysis, an acid having $[\alpha]_D$ +11·05°, $[M]_D$ +14·4°, values which are considerably higher than those quoted above for (+)-3-methylhexanoic acid. The presence, in small amounts, of an unsaturated contaminant arising from the

Clemmensen reduction is a possibility, and the product clearly requires further examination. It should be noted, however, that according to previous reports (Ställberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1948, **26**, *A*, No. 12 ; Chase and Hey, *J.*, 1952, 553) the action of alkylcadmium on the acid chloride of optically active methyl hydrogen 3-methylglutarate at the requisite high temperatures leads to rearrangement of the half-ester chloride (involving interchange of the ester and acid chloride groups) and, hence, to racemisation. The present experiments appear to suggest that the danger of racemisation may be reduced, if not eliminated, by employing, instead of alkylcadmium, the more reactive alkylzinc halides which require milder reaction conditions.

Meanwhile 2 : 4 : 6(*D*)-trimethyloctacosanoic acid has been synthesised by the following procedure.

D-1-Bromo-2-methyltetracosane (XIV), obtained from *D*-(+)-3-methylpentacosanoic acid (IX) by reaction of its silver salt with bromine, gave by condensation with ethyl methylmalonate and the usual subsequent procedure 2 : 4(*D*)-dimethylhexacosanoic acid, characterised as its *p*-bromophenacyl ester, m. p. 67—73°. It is of interest that this melting point is close to the m. p. (68°) reported (Part I, *loc. cit.*) for the *p*-bromophenacyl ester of the degradation product (XI) mentioned earlier, now regarded as 2(*D*) : 4(*D*)-dimethylhexacosanoic acid. The above acid, by reduction with lithium aluminium hydride, followed by conversion of the resultant alcohol into the iodide, and condensation of the latter with ethyl methylmalonate, afforded 2 : 4 : 6(*D*)-trimethyloctacosanoic acid. This, representing a mixture of stereoisomers, differed in its m. p. (45°) and the m. p. of its *p*-bromophenacyl ester (62—67°) from those recorded (Chanley and Polgar, *J.*, 1954, 1003) for the naturally occurring acid and its derivative (30°, and 31·5° respectively), but the infrared spectra of the acids showed close agreement.

EXPERIMENTAL

Ketones.—Methyl iodide (5 g.) was added, according to the procedure of Blaise (*loc. cit.*), to a mixture of toluene (2·5 c.c.), ethyl acetate (1 g.), and zinc-copper couple (4·5 g. ; prepared by Howard's method, *J. Res. Nat. Bur. Stand.*, 1940, **24**, 677), and the mixture refluxed for 5 hr. It was then cooled with ice, and, after the addition of toluene (10 c.c.), the solution was decanted. A solution of the requisite acid chloride (about 1 g.) in toluene (15 c.c.) was introduced during 15 min. with cooling and stirring, and, after a further 5 min., the mixture was decomposed by pouring it on ice. The product, isolated in the known manner, was refluxed with 5% ethanolic potassium hydroxide (50 c.c.) for 0·5 hr. in order to hydrolyse any ester formed as a by-product. After acidification with dilute hydrochloric acid, the product was collected with ether, and the ethereal extract washed, successively, with aqueous potassium hydroxide and water, then dried (MgSO$_4$). Removal of the solvent gave the crude ketone.

The requisite acids were obtained from octadecan-1-ol, purified by distillation of its acetate through an 18-inch electrically heated column packed with wire-gauze rings, by standard homologation procedures. They were converted into the acid chlorides by means of thionyl chloride (purified by successive distillations from quinoline and linseed oil). The following ketones were obtained :

Docosan-2-one, after crystallisation from ethanol, had m. p. 64—65° (Found : C, 81·4; H, 13·5. C$_{22}$H$_{44}$O requires C, 81·5; H, 13·6%). It gave a *semicarbazone*, m. p. 128—129° (from ethanol) (Found : C,72·5; H, 12·2; N, 10·8. C$_{23}$H$_{47}$ON$_3$ requires C, 72·4; H, 12·3; N, 11·0%).

Tricosan-2-one, m. p. 66—67° (from ethanol) (Found : C, 81·9; H, 13·5. C$_{23}$H$_{46}$O requires C, 81·7; H, 13·6%), gave a *semicarbazone*, m. p. 129·5—130·5° after crystallisation from ethanol (Found : C, 73·0; H, 12·4; N, 10·4. C$_{24}$H$_{49}$ON$_3$ requires C, 72·9; H, 12·4; N, 10·6%).

Tetracosan-2-one, m. p. 67—68° (from ethanol) (Found : C, 81·5; H, 13·4. C$_{24}$H$_{48}$O requires C, 81·8; H, 13·6%), gave a *semicarbazone*, m. p. 131—131·5° (from ethanol) (Found : C, 73·1; H, 12·4; N, 10·0. C$_{25}$H$_{51}$ON$_3$ requires C, 73·4; H, 12·5; N, 10·3%).

(−)-(*Methyl* D-4-*bromo-3-methylbutanoate* (VI).—*L*-(+)-(Methyl hydrogen 3-methyl-glutarate) (V), α_D^{15} +0·72° (homog.; *l.* = 1), was obtained by Ställberg-Stenhagen's procedure (*Arkiv Kemi, Min., Geol.*, 1947, **25**, *A*, No. 10) with the modifications suggested by Linstead, Lunt, and Weedon (*loc. cit.*) [Ställberg-Stenhagen gives α_D^{22} +0·65° (homog.; *l* = 1); Linstead *et al.* give $\alpha_D^{17.7}$ +0·65° (homog.; *l* = 1)]. An aqueous solution of the sodium salt, prepared by neutralising the half ester (20 g.) with N-sodium hydroxide (phenolphthalein), was added

dropwise with stirring to a warm solution of silver nitrate (21·3 g.) in water (90 c.c.), and the precipitated silver salt collected, washed, successively, with water, acetone, and ether, then dried *in vacuo* over calcium chloride, finely ground, and finally dried *in vacuo* over phosphoric oxide. A suspension of the silver salt (30 g.) in dry carbon tetrachloride (100 c.c.) was stirred and cooled with water while bromine (18 g.) was added slowly during 1 hr.; the mixture was then refluxed on the steam-bath for 1 hr., and, after cooling, filtered through glass-wool. The silver bromide remaining on the filter was washed with ether, and the ethereal washings were added to the filtrate. The solution was evaporated and the residue taken up in ether, then washed, successively, with 5% aqueous potassium hydroxide (to remove any acid), and water, and dried ($MgSO_4$). Distillation afforded ($-$)-*(methyl D-4-bromo-3-methylbutanoate)* (12·85 g.; 60%) as a slightly yellow liquid, b. p. 94—96°/20 mm., $[\alpha]_D^{17\cdot5}$ $-2\cdot54°$ (homog.; *l*, 0·5), n_D^{19} 1·4602 (Found: C, 37·65, 37·05; H, 5·9, 6·15; Br, 40·3. $C_6H_{11}O_2Br$ requires C, 36·95; H, 5·65; Br, 41·0%).

Methyl 3-Oxodocosanoate (VII) (cf. Ställberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1945, **20**, *A*, No. 19).—(i) Benzene (250 c.c.) and ethyl acetoacetate (19·5 g.) were added to granulated sodium (3·3 g.), and the mixture was heated on a steam-bath with stirring for 3 hr. After the mixture had cooled to room temperature, eicosanoyl chloride (43·5 g.; obtained from eicosanoic acid, m. p. 75°, by means of thionyl chloride) in warm benzene was added dropwise, and the mixture refluxed with stirring for 15 min. The product was poured into dilute sulphuric acid, and, after the addition of ether, the organic layer separated, washed with water, and evaporated. The residue, dissolved in warm dry benzene (150 c.c.), was shaken with sodium methoxide in methanol (4·7 g. of sodium in 200 c.c. of methanol) for 20 hr. Acidification and ether-extraction, followed by removal of the solvents gave a product, m. p. 58—64° after successive crystallisations from ethanol and acetone (Found: C, 76·0; H, 12·4%). Titration of a 0·5-g. portion, dissolved in warm ethanol, with aqueous-ethanolic potassium hydroxide indicated the presence of about 30% of eicosanoic acid. The titrated solution deposited on cooling a mixture of potassium eicosanoate and methyl 3-oxodocosanoate. This was treated with hot light petroleum (b. p. 40—60°) in which the methyl ester was readily soluble and the potassium salt almost insoluble. Evaporation of the solution, followed by crystallisation of the residual product from ethanol, furnished methyl 3-oxodocosanoate, m. p. 62—62·5° (Found: C, 75·1; H, 11·9. Calc. for $C_{23}H_{44}O_3$: C, 75·0; H, 12·0%). Ställberg-Stenhagen (*loc. cit.*) records m. p. 62·6°.

(ii) The product resulting on reaction of eicosanoyl chloride (93 g.) with ethyl sodioaceto-acetate (from 45·5 g. of ethyl acetoacetate, and 7·5 g. of sodium), as described above, was dissolved in warm benzene (380 c.c.) and kept with sodium (12 g.) in methanol (450 c.c.) for 20 hr. with occasional warming and shaking. The product was acidified with dilute hydro-chloric acid, ether added, and the benzene–ether layer washed successively with water, 1% aqueous potassium hydroxide (to remove eicosanoic acid) (ethanol was added to break the resulting emulsion), and water, and dried ($MgSO_4$). Evaporation, followed by crystallisation of the residual product from ethanol, gave methyl 3-oxodocosanoate (30·5 g., 29%), m. p. 62—62·8° (Found: C, 75·0; H, 12·1%).

D-(+)-3-*Methyl-6-oxopentacosanoic Acid* (VIII).—Methyl D-4-iodo-3-methylbutanoate (9 g.; obtained from the corresponding bromo-derivative by refluxing it with sodium iodide in acetone) was refluxed with methyl 3-oxodocosanoate (13·6 g.) in methyl propyl ketone (152 c.c.), and dry potassium carbonate (30 g.) for 20 hr. (cf. Ställberg-Stenhagen and Stenhagen, *Arkiv Kemi, Min., Geol.*, 1944, **19**, *A*, No. 1). Water and ether were then added, the organic layer was washed with water and dried ($MgSO_4$), and the solvents were removed by distillation. The residue, taken up in warm benzene (44 c.c.), was kept with a solution of potassium hydroxide (34·6 g.) in water (34·6 c.c.) and methanol (520 c.c.) at 50° for 20 hr. The mixture was then acidified (dilute hydrochloric acid) and extracted with warm benzene, and the benzene extract was washed with warm water and evaporated. The residue, after successive crystallisations from acetone and light petroleum (b. p. 60—80°), gave D-(+)-3-*methyl-6-oxopentacosanoic acid* (7·5 g., 50%), m. p. 74·5—75·5°, $[\alpha]_D^{17}$ +4·65° (*c*, 7·95 in $CHCl_3$; *l*, 1) (Found: C, 75·6; H, 12·1. $C_{26}H_{50}O_3$ requires C, 76·1; H, 12·2%).

D-(+)-3-*Methylpentacosanoic Acid* (IX).—Amalgamated zinc (180 g.) was added to a solution of the above keto-acid (7·1 g.) in ethanol (180 c.c.), and a current of hydrogen chloride passed into the solution until saturation. After refluxing for several hours, the solution was again saturated with hydrogen chloride, and this process repeated 3 times with 4—6 hr. intervals. The viscous mixture was then cooled, water added, and the product collected with ether. After evaporation of the ethereal solution, the residue was subjected to a repetition of the above reduction procedure. Hydrolysis of the reduced ester with ethanolic potassium hydroxide, followed by crystallisation of the resulting crude acid from light petroleum (b. p. 60—80°),

afforded D-(+)-3-*methylpentacosanoic acid* (5·65 g., 83%), m. p. 67—68·5°, $[\alpha]_D^{17}$ +3·76° (*c*, 4·52 in CHCl₃; *l*, 1) (Found : C, 78·5; H, 13·0. $C_{26}H_{52}O_2$ requires C, 78·8; H, 13·1%).

D-(+)-4-*Methylhexacosan-2-one* (X).—The preceding acid (1·8 g.) was converted, by means of thionyl chloride, into the acid chloride which, by reaction with methylzinc iodide in the manner already described afforded D-(+)-4-*methylhexacosan-2-one* (0·7 g.), m. p. 52·5—53·5° (from ethanol), $[\alpha]_D^{22}$ +4·9° (*c*, 6·31 in CHCl₃; *l*, 1) (Found : C, 81·7; H, 13·5. $C_{27}H_{54}O$ requires C, 82·2; H, 13·7%). Its *semicarbazone* had m. p. 101—102° after crystallisation from ethanol (Found : C, 74·4; H, 12·3; N, 9·2. $C_{28}H_{57}ON_3$ requires C, 74·5; H, 12·6; N, 9·3%).

Reaction of (—)-(*Methyl* D-4-*Bromo-3-methylbutanoate*) *with Sodium Methoxide.*—The bromo-ester (12 g,) was refluxed with methanolic sodium methoxide (35 c.c.; equiv. to 1·8 g. of sodium) for 4 hr. The solution was concentrated to a smaller volume, acidified (dilute hydrochloric acid), and extracted with ether. Distillation furnished a colourless liquid (3·8 g.), b. p. 62°/85 mm., $[\alpha]_D^{17}$ —85·4° (*c*, 13·09 in Et₂O; *l*, 1). The analytical results (Found : C, 62·8, 62·9; H, 8·8, 8·6. Calc. for $C_6H_{10}O_2$: C, 63·15; H, 8·8%) suggest that elimination of hydrogen bromide has occurred, giving rise to a *cyclo*propane derivative.

Attempted Preparation of Methyl 4-Methoxy-3-methylbutanoate.—(i) Methyl 4-iodo-3-methyl-butanoate (5·3 g.; obtained by the procedure already described for the optically active ester) was refluxed with methanol (20 c.c.) in the presence of silver carbonate (13·7 g.) for 11 hr. Ether was then added, and the solution filtered, and, after being washed with water, dried (MgSO₄). Distillation afforded the fractions, (a) b. p. 80—86° (Found : C, 55·0; H, 7·9. Calc. for $C_7H_{14}O_3$: C, 57·5; H, 9·6%), and (b) b. p. 140° (Found : C, 58·6; H, 9·6%).

(ii) Methyl 4-bromo-3-methylbutanoate (31·4 g.; prepared as shown for the optically active form) was added to a solution of potassium acetate in glacial acetic acid (obtained by heating gently 55 g. of dry potassium acetate in 220 c.c. of glacial acetic acid until 110 c.c. of the latter had distilled), and the solution refluxed with stirring for 12 hr. Dilution with water, and ether-extraction furnished *methyl 4-acetoxy-3-methylbutanoate* (16 g., 58%) as a colourless liquid, b. p. 112—113°/20 mm., n_D^{18} 1·4266 (Found : C, 54·95; H, 8·0. $C_8H_{14}O_4$ requires C, 55·2; H, 8·1%). This was dissolved in dry methanol (100 c.c) containing 2·5% of hydrogen chloride, and the solution distilled slowly from a flask fitted with a fractionating column at such a rate that after 20 hr. approximately two-thirds of the solvent had distilled. Evaporation of the remaining solution under reduced pressure, followed by refluxing the residue with methyl iodide (170 g.), anhydrous calcium sulphate (20 g.), and silver oxide (35 g.; added in 4 portions) for 24 hr., gave on addition of ether and distillation of the filtered solution a colourless liquid, b. p. 84—90°/18 mm. (Found : C, 58·8; H, 8·1%).

Methyl 3-Methyl-4-phenoxybutanoate (XVIII).—(i) Potassium carbonate (29 g.) was added to a solution of phenol (3·4 g.) and methyl 4-iodo-3-methylbutanoate (8·7 g.) in methyl propyl ketone (140 c.c.), and the mixture refluxed for 14 hr. Ether was then added, and, after filtration, the ethereal solution washed successively with water, aqueous potassium hydroxide, and water, then dried (MgSO₄), and distilled, affording *methyl 3-methyl-4-phenoxybutanoate* (1·3 g., 17%) as a colourless oil, b. p. 146°/16 mm. (Found: C, 68·9; H, 7·7. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%). On employing acetone as the solvent instead of methyl propyl ketone the yield was increased to 21%.

(ii) A mixture of powdered sodium (0·8 g.), phenol (6·6 g.), and toluene (20 c.c.) was heated under reflux, with stirring, until all the sodium had reacted. Methyl 4-iodo-3-methylbutanoate (6 g.) was then added, and the mixture refluxed for 1 hr. After dilution with water, and ether-extraction, the ethereal solution was washed with 5% aqueous potassium hydroxide, and water, and dried (MgSO₄). Distillation afforded only a few drops of a colourless oil, b. p. 133°/7 mm., presumably the desired phenoxy-ester.

3-Methyl-4-phenoxybutanoic Acid.—Hydrolysis of the preceding ester with 20% aqueous potassium hydroxide gave the *acid* as a viscous liquid, b. p. 180°/20 mm. (Found : C, 67·5; 67·4; H, 6·8, 7·2. $C_{11}H_{14}O_3$ requires C, 68·1; H, 7·2%).

Attempted Preparation of 1-*Bromo-2-methyl-3-phenoxypropane* (XIX).—The above phenoxy-acid (2·3 g.) was converted into the ammonium salt by the addition of a slight excess of concentrated aqueous ammonia. Water (27 c.c.) was then added, the solution boiled for a short time to remove the excess of ammonia, and silver nitrate (2·3 g.) in water (10 c.c.) added. The precipitated silver salt was washed, dried, and caused to react with bromine (2 g.) in the presence of carbon tetrachloride (15 c.c.) as described for a previous case. The ethereal extract of the product, after being washed with 5% aqueous potassium hydroxide, yielded on evaporation practically no residue. The alkaline washings on acidification, followed by ether-extraction, and distillation, afforded a product (2·45 g.), b. p. 187°/0·1 mm., which after crystallisation

from light petroleum (b. p. 40—60°) had m. p. 79·5—80°, and appeared to be a bromo-derivative of 3-methyl-4-phenoxybutanoic acid (Found : C, 48·1; H, 4·8; Br, 29·0. Calc. for $C_{11}H_{13}O_3Br$: C, 48·4; H, 4·8; Br, 29·3%).

(—)-*Methyl 3-Methyl-5-oxohexanoate* (XIII).—Oxalyl chloride (6·4 g.) was added to L-(+)-methyl hydrogen 3-methylglutarate (6 g.) in benzene (30 c.c.), and the solution kept at 30° for 3 hr. The solvent and excess of oxalyl chloride were removed under reduced pressure at 40° (bath) ; more benzene was added, and the process repeated. The resulting acid chloride was then dissolved in toluene (8 c.c.), and caused to react with a solution of methylzinc iodide (from 16·2 g. of methyl iodide, 8 c.c. of toluene, 3·3 g. of ethyl acetate, and 14·7 g. of zinc-copper couple) in the manner already described. Distillation afforded a product, b. p. 98—100°/13 mm., which on redistillation yielded (—)-*methyl 3-methyl-5-oxohexanoate* as a colourless oil (3·8 g., 65%), b. p. 99°/13 mm., $[\alpha]_D^{16}$ —1·1° (c, 35·60 in Et_2O; l, 0·5), n_D^{17} 1·4290 (Found : C, 60·3; H, 8·7. $C_8H_{14}O_3$ requires C, 60·75; H, 8·9%).

A 1·8-g. portion of this keto-ester gave on Clemmensen reduction as described for a previous example, followed by hydrolysis of the reduced ester with 15% aqueous potassium hydroxide, (+)-3-methylhexanoic acid as a colourless oil (0·5 g.), b. p. 170° (bath)/80 mm., $[\alpha]_D^{18}$ +11·05° (c, 6·69 in C_6H_6; l, 0·5), $[M]_D^{18}$ +14·4°, n_D^{18} 1·4308 (Found : C, 65·0; H, 10·5. Calc. for $C_7H_{14}O_2$: C, 64·6; H, 10·8%). Levene and Marker (*J. Biol. Chem.*, 1931, **91**, 77) record $[\alpha]_D^{29}$ —3·1° (in C_6H_6), n_D^{25} 1·4214, for the (—)-form.

D-1-*Bromo-2-methyltetracosane* (XIV).—Reaction of the silver salt of D-(+)-3-methyl-pentacosanoic acid (4·72 g.; obtained by precipitation of an ethanolic solution of the potassium salt with ethanolic silver nitrate, followed by washing of the precipitate, successively, with warm water, ethanol, and ether, and drying over phosphoric oxide in a desiccator, then in vacuo at 100°) with bromine (1·5 g.) in carbon tetrachloride (30 c.c.) by the procedure previously described gave D-1-*bromo-2-methyltetracosane* (1·3 g.), m. p. 40—41° after crystallisation from acetone (Found : Br, 19·25. $C_{25}H_{51}Br$ requires Br, 18·55%).

2 : 4(D)-*Dimethylhexacosanoic Acid*.—The above bromide (2 g.) was added to the sodio-derivative of ethyl methylmalonate, prepared from sodium (0·22 g.), ethanol (6 c.c.), and ethyl methylmalonate (3·3 g.), and the mixture refluxed for 10 hr. After acidification with dilute hydrochloric acid, the resulting alkylated malonic ester was collected with the aid of ether. Hydrolysis and decarboxylation in the usual manner gave a product which distilled at 190° (bath)/0·01 mm., and, after crystallisation from light petroleum (b. p. 40—60°), afforded 2 : 4(D)-*dimethylhexacosanoic acid* (0·8 g.), m. p. 54—55° (Found : C, 79·2; H, 13·1. $C_{28}H_{56}O_2$ requires C, 79·2; H, 13·2%), showing no measurable rotation (c, 7·65 in $CHCl_3$; l, 1). Its p-*bromophenacyl ester* had m. p. 67—73° (from ethanol) (Found : C, 69·6; H, 9·8. $C_{36}H_{61}O_3Br$ requires C, 69·6; H, 9·8%).

2 : 4(D)-*Dimethylhexacosan-1-ol*.—The preceding acid (1 g.) in ether (8 c.c.) was added to a solution of lithium aluminium hydride (0·3 g.) in ether (10 c.c.), and the mixture refluxed, with stirring, for 3 hr. Next day the excess of lithium aluminium hydride was decomposed by the addition of ethyl acetate; water was then added, followed by the addition of dilute sulphuric acid. After removal of the ethereal layer, the aqueous phase was extracted with ether, and the combined ethereal solutions were washed with 5% aqueous potassium hydroxide, water, and dried ($MgSO_4$). Distillation afforded 2 : 4(D)-*dimethylhexacosan-1-ol* (0·82 g.), b. p. 215° (bath)/0·01 mm., m. p. 52—55° (Found : C, 81·6; H, 13·9. $C_{28}H_{58}O$ requires C, 81·9; C, 14·1%).

2 : 4 : 6(D)-*Trimethyloctacosanoic Acid*.—The above alcohol was converted into the iodide by heating it (0·73 g.) with red phosphorus (0·03 g.) and iodine (0·35 g.) at 180° (bath) for 3 hr. The iodide, b. p. 210—225°(bath)/0·01 mm., isolated in the known manner, on condensation with the sodio-derivative of ethyl methylmalonate (from 0·083 g. of sodium, 2 c.c. of ethanol, and 1·25 g. of ethyl methylmalonate), followed by the usual successive stages (hydrolysis, decarboxylation), gave a product which distilled at 220—240°(bath)/0·01 mm., and, after crystallisation from light petroleum (b. p. 40—60°) at 0°, afforded the required acid, m. p. 45° (Found : C, 80·2; H, 13·2. $C_{31}H_{62}O_2$ requires C, 79·8; H, 13·3%) ; the p-*bromophenacyl ester* had m. p. 62—67° (from ethanol) (Found : C, 70·9; H, 10·2; Br, 11·9. $C_{39}H_{67}O_3Br$ requires C, 70·6; H, 10·1; Br, 12·05%).