400. *Constituents of the Lipids of Tubercle Bacilli. Part VII.* Synthesis of (+)-2(L) : 4(L)-Dimethyldocosanoic Acid, an Oxidation Product of Mycolipenic Acid.†*

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(+)-2(*L*) : 4(*L*)-Dimethyldocosanoic acid † (X) has been synthesised with (+)-2(*L*) : 4(*L*)-dimethylhept-6-enoic acid (VII*a*) as intermediate, and the synthetic acid found to be identical with the dextrorotatory acid shown earlier to arise on oxidation of mycolipenic acid. The structure advanced previously for this oxidation product has thus been confirmed.

In previous studies mycolipenic acid was shown to afford on oxidation a dextrorotatory acid, $[\alpha]_D$ +7·1°, to which the structure of 2 : 4-dimethyldocosanoic acid (I) was assigned.[1,2] The present paper describes the synthesis of this dextrorotatory acid (a preliminary report [3] has been published).

The acid (I) has two asymmetric centres, and for the synthesis of the stereoisomer arising on oxidation of mycolipenic acid certain information on the stereochemical configuration of these asymmetric centres was needed. This was available from the investigations [1,2] already mentioned, which disclosed that the oxidation product (I) on further degradation affords a dextrorotatory acid, $[\alpha]_D$ about +7°, having the structure of 2-methyleicosanoic acid (II), the asymmetric centre at $C_{(2)}$ of the latter corresponding to

(I) $CH_3 \cdot [CH_2]_{17} \cdot CHMe \cdot CH_2 \cdot CHMe \cdot CO_2H$ $\quad$ $CH_3 \cdot [CH_2]_{17} \cdot CHMe \cdot CO_2H$ (II)

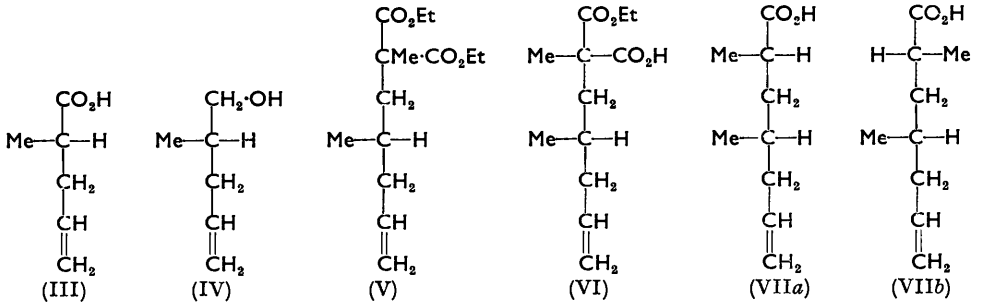
that at $C_{(4)}$ of the acid (I). Since the dextrorotatory forms of 2-methyl-substituted carboxylic acids are sterically related to L-(−)-glyceraldehyde ($CO_2H \equiv CHO$),[4] it follows that the oxidation product (I) has *L*-configuration in respect of $C_{(4)}$. Moreover, the dextrorotation of this oxidation product, itself a 2-methyl-carboxylic acid, also indicates *L*-configuration in respect of $C_{(2)}$. We are aware of the possible vicinal action between the asymmetric centres at $C_{(2)}$ and $C_{(4)}$ of this acid, but 4-methyl-carboxylic acids are known to have only small rotations and there is no significant difference between the rotations exhibited by the 2 : 4-dimethyl-substituted acid (I) and the 2-methyl-substituted acid (II). The stereoisomer arising on oxidation of mycolipenic acid is, therefore, regarded as 2(*L*) : 4(*L*)-dimethyldocosanoic acid.

The starting point for the synthesis of this acid was *L*-(+)-2-methylpent-4-enoic acid [5] (III) which by reduction with lithium aluminium hydride gave *L*-(−)-2-methylpent-4-en-1-ol (IV). Condensation of the toluene-*p*-sulphonate of the latter or its iodo-derivative (obtained from the toluene-*p*-sulphonate by means of sodium iodide in acetone) with the sodio-derivative of ethyl methylmalonate, followed by hydrolysis of the intermediate malonic ester (V) and decarboxylation of the liberated acid, afforded 2 : 4(*L*)-dimethylhept-6-enoic acid (VII*a* and *b*) with the newly created asymmetric centre at $C_{(2)}$. Some earlier experiments in which the malonic ester (V), obtained by employing the toluene-*p*-sulphonyl ester of (IV) for the malonic ester condensation, was subjected to the subsequent stages without previous purification by distillation resulted in mixtures of the diastereoisomers (VII*a*) and (VII*b*) with specific rotations varying from +5·47° to +11·6°. Later, when the iodo-derivative from the alcohol (IV) was used for the condensation and the intermediate malonic ester (V) was distilled, the acid had $[\alpha]_D$ +12·5°. Comparative studies showed that the rotatory power of this acid was not affected by varying the rate of heating in the decarboxylation. Moreover, an experiment involving a partial hydrolysis of the

* Part VI, *J.*, 1955, 3971.
† The symbols *D* and *L* are used in the sense defined by Linstead *et al.* (*J.*, 1950, 3333).
[1] Polgar and Robinson, *Chem. and Ind.*, 1951, 685.
[2] Polgar, *J.*, 1954, 1008.
[3] Fray and Polgar, *Chem. and Ind.*, 1956, 22.
[4] Ställberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1947, **24**, *B*, No. 9.
[5] *Idem, ibid.*, 1946, **23**, *A*, No. 15.

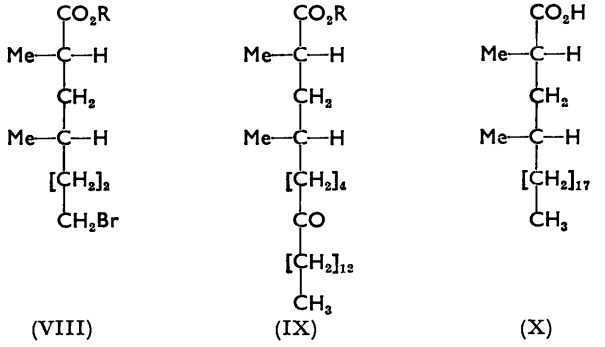
intermediate malonic ester and so giving rise to the half-ester (VI) (for brevity, only one diastereoisomer is shown), followed by decarboxylation of the latter and hydrolysis of the resulting ethyl ester, afforded an acid with similar rotation.

The magnitude of the dextrorotation of the acid resulting from the above procedures indicated a preponderance of one of the diastereoisomers, regarded as (+)-2(*L*) : 4(*L*)-dimethylhept-6-enoic acid (VII*a*) (see above), and attention was turned to its isolation. Various alkaloidal salts were prepared : the quinine salt proved satisfactory. After repeated crystallisation of this, the recovered acid exhibited $[\alpha]_D$ +19·9°. This on reaction



with hydrogen bromide with peroxide-catalysis [6] gave the bromo-acid (VIII; R = H), α_D +4·1° (homogeneous; *l*, 0·5), which probably contained a small proportion of the secondary bromide arising by the addition of hydrogen bromide according to Markownikoff's rule. In later experiments a sample of the bromo-acid, obtained by the same procedure from a mixture of the diastereoisomers (VII*a* and *b*), afforded, *via* the cinchonidine salt, a (+)-acid having α_D +5·30° (homogeneous; *l*, 0·5); the other diastereoisomer exhibiting α_D −3·86° was obtained through the quinine salt.

The bromo-acid (VIII; R = H) with diazomethane afforded the methyl ester (VIII; R = Me) which with sodium iodide in boiling acetone gave the corresponding iodo-deriv-



ative. Reaction of the latter with methyl 3-oxohexadecanoate [7] in the presence of potassium carbonate, followed by hydrolysis and ketonic cleavage, yielded the keto-acid (IX; R = H). This was converted into the corresponding methyl ester (IX; R = Me) which on Clemmensen reduction and subsequent hydrolysis gave an acid having $[\alpha]_D$ about +5°. The latter was found to be optically impure : presumably partial inversion in respect of $C_{(2)}$ had taken place in the later stages, probably during the Clemmensen reduction. After repeated crystallisation of the quinine salt, the recovered acid (X) had $[\alpha]_D$ +7·4° in agreement with the value (+7·1°) recorded [2] for the oxidation product of mycolipenic acid. The *X*-ray powder photograph of the *p*-bromophenacyl ester (m. p. 71°) of the synthetic acid was identical with that of the *p*-bromophenacyl ester (m. p. 69°) derived from the oxidation product; we are grateful to Mrs. D. M. Hodgkin, F.R.S., for these *X*-ray studies.

[6] Smith, *Chem. and Ind.*, 1937, **15**, 833; 1938, **16**, 461.
[7] Ställberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1945, **20**, *A*, No. 19.

Experimental

α refers to homogeneous liquids ($l = 1$) unless otherwise stated.

(±)-2-*Methylpent*-4-*enoic Acid*.—Ethyl 2-ethoxycarbonyl-2-methylpent-4-enoate, b. p. 110—113°/15 mm., was obtained in 90% yield by a malonic ester condensation employing allyl chloride and ethyl methylmalonate (cf. ref. 5). This ester (380 g.) was refluxed with potassium hydroxide (280 g.) in water (2·8 l.) until a clear solution resulted (about 25 hr.). The solution was concentrated (to about 2 l.), acidified (to pH 2) with hydrochloric acid, and extracted with ether. Evaporation of the dried (Na_2SO_4) ethereal extract, followed by decarboxylation of the residue at 160—170° (bath), gave (±)-2-methylpent-4-enoic acid (164 g., 81%), b. p. 102—104°/20 mm. (Ställberg-Stenhagen [5] records b. p. *ca.* 104°/20 mm.).

L-(+)-2-*Methylpent*-4-*enoic Acid* (III).—The (±)-acid was resolved by the procedure given by Ställberg-Stenhagen [5] with slight modifications in detail. Quinine (390 g., 1 mol.) was added gradually to a solution of the (±)-acid (137 g., 1 mol.) in boiling acetone (2·3 l.); the resulting solution was filtered and left overnight. The quinine salt which separated as needles was recrystallised seven times from acetone, then dissolved in dilute hydrochloric acid, and the solution extracted with ether. Distillation gave *L*-(+)-2-methylpent-4-enoic acid (21 g., 31%), b. p. 97—98°/16 mm., n_D^{18} 1·4308, d_4^{19} 0·954, α_D^{19} +7·86°, $[\alpha]_D^{19}$ +8·24° [Ställberg-Stenhagen gives α_D^{16} +7·62° (ref. 5) and α_D^{20} +7·88° (ref. 8)] (Found: C, 62·8; H, 8·8. Calc. for $C_6H_{10}O_2$: C, 63·1; H, 8·8%).

Several batches of the (±)-acid were resolved in the same way and the mother-liquors resulting from the crystallisations combined and evaporated. From the regenerated acid (345 g.), α_D^{16} −0·53°, further amounts of the (+)-acid were obtained by the following procedure.

Resolution with quinine as described above gave 48 g. of the fully resolved (+)-acid; the mother-liquors from the first three crystallisations of the quinine salt yielded 225 g. of acid having α_D^{15} −4·41°, and those from the last five crystallisations afforded 46 g. of acid, α_D^{14} +5·02°. The foregoing (−)-acid was converted, by means of methanolic sulphuric acid, into the methyl ester, and the latter racemised [9] by refluxing it with ethanolic sodium ethoxide (from 39 g. of sodium in 400 c.c. of ethanol) for 4 hr. A solution of sodium hydroxide (30 g.) in water (400 c.c.) was then added and the mixture refluxed for 2 hr., then concentrated to about half its volume and acidified (hydrochloric acid). Ether-extraction and distillation afforded the acid (158 g.) with α_D^{15} −0·02°. This, combined with the above partially resolved (+)-acid, gave by repetition of the above resolution procedure 41 g. of the fully resolved acid.

L-(−)-2-*Methylpent*-4-*en*-1-*ol* (IV).—*L*-(+)-2-Methylpent-4-enoic acid (30 g.) was added dropwise with stirring to lithium aluminium hydride (11·2 g.) in ether (200 c.c.) during 1·5 hr. at such a rate that the solvent refluxed gently. After a further 0·5 hr., the excess of lithium aluminium hydride was decomposed by water. Ice-cold 10% sulphuric acid (1 l.) was then added and the ethereal layer separated; the aqueous phase was extracted with ether (3 times), and the combined ethereal extracts were shaken with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated. Distillation of the residue yielded L-(−)-2-*methylpent*-4-*en*-1-*ol* (22 g., 84%), b. p. 145—146°, n_D^{18} 1·4345, d_4^{18} 0·845, $[\alpha]_D^{18}$ −2·62° (Found: C, 71·7; H, 12·3. $C_6H_{12}O$ requires C, 71·9; H, 12·1%). The α-*naphthylurethane* crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 76·5° (Found: C, 76·0; H, 7·3; N, 5·0. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1; N, 5·2%).

2 : 4(L)-*Dimethylhept*-6-*enoic Acid*.—Mixtures of the 2(*D*)- and the 2(*L*)-diastereoisomer with a preponderance of the latter resulted from the following procedures.

(i) Dry pyridine (30 g., 2·1 mol.) was gradually added with stirring to an ice-cold mixture of *L*-(−)-2-methylpent-4-en-1-ol (18 g., 1 mol.) and toluene-*p*-sulphonyl chloride (36 g., 1·05 mol.) during about 2 hr., and stirring continued for a further 2 hr. The product was acidified with dilute hydrochloric acid and extracted with ether, and the dried (K_2CO_3) extract was evaporated. After removal of the last traces of water azeotropically (benzene), the residual pale yellow oil (43 g.), α_D *ca.* +3·3°, consisting of the *toluene*-p-*sulphonate* (Found: C, 61·8; H, 7·1; S, 12·7. $C_{13}H_{18}O_3S$ requires C, 61·4; H, 7·1; S, 12·6%), was used without purification for the next stage. This was effected by refluxing the toluene-*p*-sulphonate (40 g.) with the sodio-derivative of ethyl methylmalonate (from 4 g. of sodium, 30 g. of ethyl methylmalonate, and 200 c.c. of ethanol) and some sodium iodide for 5 hr. After dilution with water and acidification (hydrochloric acid), the product was isolated with the aid of ether, then refluxed with a solution of potassium hydroxide (30 g.) in water (300 c.c.) for 24 hr. The resulting solution was acidified

[8] Ställberg-Stenhagen, *Arkiv Kemi*, 1950, **1**, No. 18.
[9] Kenyon and Young, *J.*, 1940, 216.

with hydrochloric acid and the product, isolated by ether-extraction, was decarboxylated at 150—160° (bath); it was then refluxed with 10% aqueous potassium hydroxide (50 c.c.) for 1 hr. Distillation of the liberated acid furnished a colourless liquid (10 g.), b. p. 138—140°/22 mm., n_D^{17} 1·4447, d_4^{16} 0·930, $[\alpha]_D^{16}$ +8·84° (Found: C, 69·0; H, 10·5. Calc. for $C_9H_{16}O_2$: C, 69·2; H, 10·3%). In two other experiments carried out in the same way the acid resulted with $[\alpha]_D^{17}$ +5·47° and $[\alpha]_D^{20}$ +11·6°, severally.

(ii) The above toluene-*p*-sulphonate (40 g.) was refluxed with a solution of anhydrous sodium iodide (50 g.) in dry acetone (500 c.c.) for 12 hr. The resulting iodo-derivative, isolated in the known manner, was refluxed with the sodio-derivative of ethyl methylmalonate (from 3·7 g. of sodium, 28 g. of ethyl methylmalonate, and 150 c.c. of ethanol) for 10 hr. After acidification with glacial acetic acid, the mixture was concentrated to half bulk and diluted with water, and the product isolated by ether-extraction. Distillation through a short Vigreux column gave a low-boiling fraction (*ca.* 10 g.), b. p. 135°/20 mm. (unchanged iodo-derivative and ethyl methylmalonate), followed by (+)-[*ethyl 2-ethoxycarbonyl-2* : 4(L)-*dimethylhept-6-enoate*] (V) (19 g.), b. p. 142—145°/20 mm., n_D^{16} 1·4427, d_4^{16} 0·984, $[\alpha]_D^{16}$ +2·62° (Found: C, 65·9; H, 9·2. $C_{14}H_{24}O_4$ requires C, 65·6; H, 9·4%). This ester (31 g.) was refluxed with potassium hydroxide (25 g.) in water (20 c.c.) and ethanol (100 c.c.) for 4 hr. The resulting solution was concentrated (to about 50 c.c.), acidified with hydrochloric acid, then extracted with ether, and the dried ($MgSO_4$) extract evaporated. Decarboxylation of the residue at 170—180° (bath), followed by refluxing of the product with 10% aqueous potassium hydroxide (80 c.c.) for 1 hr. and distillation of the liberated acid, afforded a liquid (16 g.), b. p. 128—130°/14 mm., n_D^{17} 1·4442, d_4^{17} 0·929, $[\alpha]_D^{14}$ +12·5°.

(iii) A 5·8-g. portion of (+)-[ethyl 2-ethoxycarbonyl-2 : 4(*L*)-dimethylhept-6-enoate] was worked up as described in the preceding experiment except that on hydrolysis of the ester the mixture was refluxed for 15 hr. and the product obtained on decarboxylation of the liberated acid was taken up in ether, then the acid fraction was removed from the ethereal solution with 20% aqueous potassium hydroxide. Acidification of the alkaline extract and isolation by means of ether afforded the acid (3 g.) having $[\alpha]_D^{16}$ +12·1° (*c* 30·0 in $COMe_2$).

(iv) When the above malonic ester (11 g.) was kept overnight with a solution of potassium hydroxide (5 g.) in water (5 c.c.) and ethanol (95 c.c.), the potassium salt of the half-ester separated as needles. The mixture was acidified with glacial acetic acid, then diluted with water and, after saturation with potassium chloride, extracted with ether. Re-extraction of the ethereal solution with 20% aqueous potassium hydroxide, followed by acidification of the alkaline extract, decarboxylation, and elimination of acidic material from the product by shaking of its ethereal solution with aqueous potassium hydroxide, gave (+)-[*ethyl* 2 : 4(L)-*dimethylhept-6-enoate*] [with a preponderance of the 2(*L*)-diastereoisomer] (4·3 g.), b. p. 87—88°/14 mm., n_D^{16} 1·4304, $[\alpha]_D^{16}$ +9·4° (*c* 30·2 in $COMe_2$) (Found: C, 72·0; H, 10·9. $C_{11}H_{20}O_2$ requires C, 71·7; H, 10·9%). This ester (4 g.) on hydrolysis with potassium hydroxide (3 g.) in boiling water (10 c.c.) and ethanol (20 c.c.) for 2 hr. afforded the corresponding acid having $[\alpha]_D^{16}$ +11·9° (*c* 31·5 in $COMe_2$).

(+)-2(L) : 4(L)-*Dimethylhept-6-enoic Acid* (VII*a*).—Preliminary experiments showed that the brucine salt of the acid described in the preceding section did not crystallise. In attempts to crystallise the strychnine or cinchonine salts the free bases separated from the solutions. Experiments employing cinchonidine seemed initially encouraging; the cinchonidine salt crystallised from acetone as needles, but on recrystallisation from the same solvent dissociation occurred, the free base separating. On recovery of the acid from the initially crystallised cinchonidine salt, the cinchonidine salt being then re-formed and allowed to crystallise from acetone, and this whole procedure being repeated several times, the most dextrorotatory acid obtained (starting from a specimen with $[\alpha]_D^{17}$ +5·47°) had $[\alpha]_D^{15}$ +10·8° (*c* 15·8 in $COMe_2$). Crystallisation of the cinchonidine methosalt, obtained by dissolving the acid in an aqueous solution of cinchonidine methohydroxide [10] and evaporating the solution, failed to increase the specific rotation of the acid. In further experiments the quinine salt (which in earlier attempts was an oil) was obtained as needles on crystallisation from aqueous acetone and, finally, the following procedure was adopted.

Quinine (58 g., 1 mol.) was gradually added to a solution of (+)-2 : 4(*L*)-dimethylhept-6-enoic acid (28 g., 1 mol.; representing a mixture of diastereoisomers, $[\alpha]_D^{16}$ +9·06°, resulting by combining several of the above preparations) in boiling acetone (75 c.c.); the solution was filtered and the filtrate cooled to room temperature. Water was added until turbidity resulted,

[10] Brettle and Polgar, *J.*, 1956, 1620.

and then acetone to give a clear solution. The quinine salt gradually separated as needles which were collected (after several hours, or next day) and recrystallised five times from aqueous acetone according to the procedure employed for the previous crystallisation. Decomposition of the resulting salt with dilute hydrochloric acid, followed by ether-extraction and distillation, gave acid (8·9 g.) with α_D^{14} +8·09° (*l* 0·5). This was again converted into the quinine salt which after one crystallisation gave acid (5·7 g.) having α_D^{16} +8·58° (*l* 0·5); on repetition of this procedure the regained acid (3 g.) showed α_D^{16} +8·98° (*l* 0·5). This material was combined with another batch (1·6 g.) of acid obtained by a similar procedure and having α_D^{16} +9·06° (*l* 0·5), and the whole reconverted into the quinine salt which after one crystallisation gave acid (3 g.) of α_D^{16} +9·22°, α_D^{19} +9·10° (*l* 0·5). A further formation and crystallisation of the quinine salt gave on decomposition as above the 2(L) : 4(L)-*diastereoisomer* (2 g.), b. p. 146—147°/37 mm., n_D^{14} 1·4439, d_4^{16} 0·928, α_D^{19} +9·23°, $[\alpha]_D^{19}$ +19·9° (*l* 0·5) (Found: C, 69·0; H, 10·5. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%); the rotation remained constant, within the limits of experimental error, on further crystallisation of the quinine salt. The S-*benzylthiuronium salt* crystallised from aqueous ethanol (1 : 1) as plates, m. p. 124° (Found: C, 63·4; H, 7·9; N, 8·5. $C_{17}H_{26}O_2N_2S$ requires C, 63·3; H, 8·1; N, 8·7%).

Mixtures of the diastereoisomers which were recovered with low dextrorotation from various residual mother-liquors of the above crystallisations of the quinine salts underwent partial inversion when their methyl esters were refluxed with 10% ethanolic sodium ethoxide, and the acid resulting on subsequent hydrolysis showed an increased rotatory power. Thus, a sample with $[\alpha]_D^{17}$ +0·52° gave by the foregoing procedure acid having $[\alpha]_D^{20}$ +7·57°. The quinine salt could also be prepared from ethereal solution and recrystallised from the same solvent.

(+)-7-*Bromo*-2(L) : 4(L)-*dimethylheptanoic Acid* (VIII; R = H).—(i) Hydrogen bromide was passed during 1 hr. into an ice-cold solution of the preceding 2(*L*) : 4(*L*)-diastereoisomer (2·5 g.) in light petroleum (b. p. 100—120°, purified by refluxing over potassium permanganate; 10 c.c.) in the presence of monoperphthalic acid (3·4% ethereal solution; 1 c.c.), air being allowed to enter the delivery tube at intervals; a heavy yellow oil separated. After addition of water, the mixture was extracted with ether, and the ethereal extract washed with water, dried ($MgSO_4$), and evaporated. A portion of the resulting crude *bromo-acid* (3·6 g.) was distilled, thus affording a colourless oil, b. p. 139—140°/1 mm., n_D^{16} 1·4773, α_D^{18} +4·1° (*l* 0·5) (Found: C, 45·7; H, 7·4; Br, 33·3. $C_9H_{17}O_2Br$ requires C, 45·6; H, 7·2; Br, 33·7%).

(ii) In later experiments samples of 2 : 4(*L*)-dimethylhept-6-enoic acid (mixtures of diastereoisomers resulting from the work described above) having $[\alpha]_D^{18}$ +7·1°, +11·1°, and +14·9°, severally, were converted into the bromo-derivative by the foregoing procedure. The products showed α_D (determined for the crude specimens; *l* 0·5) *ca.* −1·4°, +0·6°, and +1·7°, respectively.

Cinchonidine (23·5 g.) was added gradually to a boiling solution of the preceding bromo-acid having α_D +0·6° (19 g.) in acetone–ethanol (10 : 1; 440 c.c.); after filtration, the solution was allowed to cool to room temperature. Water was added until turbidity resulted, and then acetone to give a clear solution which was set aside overnight. The cinchonidine salt separated as needles which were recrystallised five times from aqueous acetone. Decomposition of the resulting salt in the usual manner gave the 2(L) : 4(L)-*diastereoisomer* (1·6 g.), b. p. 144—145°/2 mm., n_D^{18} 1·4764, α_D^{18} +5·3° (*l* 0·5), $[\alpha]_D^{20}$ +10·5° (*c* 12·8 in $COMe_2$) (Found: C, 46·0; H, 7·4; Br, 33·5%); the rotation was not increased by a further crystallisation of the cinchonidine salt.

The 2(D) : 4(L)-*diastereoisomer* was obtained from bromo-acid of α_D −1·4° (see above; 12 g.) *via* the quinine salt. Crystallisation of the latter from aqueous acetone at −10°, followed by three recrystallisations from the same solvent at room temperature, gave (−)-acid (2 g.), α_D^{16} −3·86° (*l* 0·5), $[\alpha]_D^{21}$ −8·0° (*c* 10·3 in $COMe_2$) (Found: C, 45·9; H, 7·2; Br, 33·9%); the rotation remained unchanged on a further crystallisation of the quinine salt.

(+)-[*Methyl* 7-*Bromo*-2(L) : 4(L)-*dimethylheptanoate*] (VIII; R = Me).—An ethereal solution of diazomethane was added to a solution of the above bromo-acid (1·4 g.; $[\alpha]_D$ +10·5°) in ether until a yellow colour persisted. The solution was then filtered and distilled, to give the *methyl* ester (1·3 g.), b. p. 150—151°/32 mm., n_D^{19} 1·4621, α_D^{20} +6·09° (*l* 0·5), $[\alpha]_D^{20}$ +10·9° (*c* 10·3 in $COMe_2$) (Found: C, 48·2; H, 7·6; Br, 31·5. $C_{10}H_{19}O_2Br$ requires C, 47·8; H, 7·6; Br, 31·8%).

The bromo-acid of α_D^{18} +4·1° (*l* 0·5) (see preceding section) gave a methyl ester, b. p. 136—138°/19 mm., n_D^{16} 1·4637, α_D^{19} +5·29° (*l* 0·5).

Methyl 3-*Oxohexadecanoate* (cf. ref. 7).—Granulated sodium (6·9 g., 1·1 mol.), ethyl acetoacetate (41 g., 1·5 mol.), and benzene (500 c.c.) were refluxed for 4 hr. To the mixture, cooled to room temperature, myristoyl chloride (67 g., 1 mol.; obtained from myristic acid, m. p. 55°, by means of thionyl chloride) in benzene (100 c.c.) was added gradually, and the whole refluxed for 1 hr., then poured into dilute sulphuric acid and ice. Ether was added and the organic

layer separated, washed with water, dried ($MgSO_4$), and evaporated. The residue was dissolved in warm benzene (150 c.c.) and kept with sodium (10 g.) in methanol (300 c.c.) overnight, then poured into dilute sulphuric acid and ice, and the mixture extracted with ether. The extract was washed, successively, with water, 1% aqueous potassium hydroxide (ethanol was added to break the resulting emulsion), and water, dried ($MgSO_4$), and evaporated. The residue was taken up in ether, then filtered (omitting this filtration resulted in a product with an unsharp m. p.); removal of the ether, followed by crystallisation of the product from ethanol, afforded methyl 3-oxohexadecanoate (24 g.) as plates, m. p. 40·5—41°, raised to 41—41·5° by two further crystallisations from the same solvent (Found : C, 71·6; H, 11·3. Calc. for $C_{17}H_{32}O_3$: C, 71·8; H, 11·3%) (Ställberg-Stenhagen [7] records m. p. 40·1°).

(+)-[*Methyl* 2(L) : 4(L)-*Dimethyl*-9-*oxodocosanoate*] (IX; R = Me).—Hunsdiecker's procedure [11] with the modifications suggested by Ställberg-Stenhagen [12] was followed. (+)-[Methyl 7-bromo-2(*L*) : 4(*L*)-dimethylheptanoate] (1·3 g.; $[\alpha]_D$ +10·9°), sodium iodide (1·7 g.), and dry acetone (6 c.c.) were refluxed for 9 hr., and the crude iodo-ester was isolated in the known manner. This ester (1·6 g.) was refluxed with methyl 3-oxohexadecanoate (1·6 g.), anhydrous potassium carbonate (3 g.), and dry pentan-2-one (15 c.c.) for 20 hr. After addition of water, the mixture was extracted with ether, and the ethereal extract dried ($MgSO_4$) and evaporated. The residue (2·4 g.) was dissolved in warm benzene (10 c.c.) and added to a solution of potassium hydroxide (5 g.) in water (5 c.c.) and methanol (75 c.c.). From the mixture at 40—45° (20 hr.) needles were gradually deposited. The whole was then acidified with dilute hydrochloric acid and extracted with ether, and the ethereal layer washed with water, dried ($MgSO_4$), and evaporated, to give the crude keto-acid (2 g.). This was refluxed with methanol (15 c.c.) and concentrated sulphuric acid (0·75 g.) for 5·5 hr.; the mixture was then poured into water and the product isolated by ether-extraction. Distillation gave, after a fore-run (0·4 g.), b. p. 110—120°/1 mm. (essentially methyl myristate), (+)-[*methyl* 2(L) : 4(L)-*dimethyl*-9-*oxodocosanoate*] as a yellow liquid (1·5 g.; 73%, calc. on the bromo-ester), b. p. 182—185°/0·25 mm., n_D^{21} 1·4550, $[\alpha]_D^{22}$ +8·0° (*c* 9·97 in Et_2O) (Found : C, 75·9; H, 12·1. $C_{25}H_{48}O_3$ requires C, 75·7; H, 12·2%).

The bromo-ester (2·6 g.) with α_D^{19} +5·29° (see above) gave by the same procedure keto-ester (2·9 g.) of n_D^{21} 1·4549, $[\alpha]_D^{17}$ +7·5° (*c* 10·2 in Et_2O).

(+)-2(L) : 4(L)-*Dimethyldocosanoic Acid* (X).—Amalgamated zinc (40 g.) was added to a solution of the above keto-ester of $[\alpha]_D$ +8·0° in ethanol (40 c.c.), and a current of hydrogen chloride passed into the solution until saturation. After 4 hours' refluxing the solution was again saturated with hydrogen chloride, and this process was repeated three times at 4-hr. intervals. After addition of water, the mixture was extracted with ether; the dried ($MgSO_4$) extract was evaporated, and the residue subjected to a second such reduction. The product, isolated as before, was refluxed with potassium hydroxide (1 g.) in water (1 c.c.) and ethanol (7 c.c.) for 2 hr. Acidification and isolation of the product with the aid of ether gave a wax (1·3 g.), b. p. 220—230° (bath)/0·15 mm., m. p. 39—40°; after crystallisation from light petroleum (b. p. 40—60°) at −5° the product was obtained as rosettes, m. p. 41·5—42·5°, $[\alpha]_D^{23}$ +4·9° (*c* 5·3 in Et_2O) (Found : C, 78·7; H, 13·1. $C_{24}H_{48}O_2$ requires C, 78·3; H, 13·1%). This *acid*, in acetone, was converted into the quinine salt in the manner already described and the solution filtered; water was then added to the warm filtrate until a slight turbidity resulted. Cooling and shaking gave the gelatinous quinine salt. The mixture was warmed to effect solution, then a little acetone added, and the solution set aside overnight. The quinine salt separated as rosettes which after three recrystallisations by the procedure employed for the previous crystallisation, followed by decomposition of the salt with dilute hydrochloric acid and ether-extraction, afforded the 2(L) : 4(L)-*diastereoisomer* (0·3 g.) with $[\alpha]_D^{24}$ +7·0° (*c* 5·45 in Et_2O); after a further formation and crystallisation of the quinine salt, the regained acid had $[\alpha]_D^{25}$ +7·4° (*c* 3·76 in Et_2O). The *p*-bromophenacyl ester crystallised from ethanol as plates, m. p. 71° (Found : C, 68·2; H, 9·3; Br, 13·8. Calc. for $C_{32}H_{53}O_3Br$: C, 67·9; H, 9·4; Br, 14·1%); on admixture with the *p*-bromophenacyl ester derived from the oxidation product of mycolipenic acid (m. p. 69°; in the previous communication [2] m. p. 68° was recorded) the m. p. was 69·5—70·5°.

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[11] Hunsdiecker, *Ber.*, 1942, **75**, 1190.
[12] Ställberg-Stenhagen and Stenhagen, *Arkiv Kemi Min., Geol.*, 1944, **19**, *A*, No. 1.