566. *Mycoceranic Acid. Part IV.*[1]

By N. Polgar and W. Smith.

The methyl esters of 2(*D*),4(*D*)-dimethylpentacosanoic,* 2(*D*),4(*D*),6(*D*)-trimethylhexacosanoic, and 2(*D'*),4(*D*),6(*D*),8(*D*)-tetramethyloctacosanoic acids have been synthesised from *L*-(+)-5-acetoxy-4-methylpentanoic acid by a route involving thiophen as a chain-extender. As already shown, the foregoing trimethyl- and tetramethyl-substituted acids represent major constituents of the lævorotatory acid fraction from the lipids of tubercle bacilli.

In connection with the studies described in Part III[1] we have synthesised methyl 2(*D*),4(*D*)-dimethylpentacosanoate * (VIII), 2(*D*),4(*D*),6(*D*)-trimethylhexacosanoate (XIV), and 2(*D'*),4(*D*),6(*D*),8(*D*)-tetramethyloctacosanoate (XVI). As already briefly reported,[3] *L*-(+)-5-acetoxy-4-methylpentanoic acid[4] (I) was chosen as a starting material, and we

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* The symbols *D* and *L* are used in the sense defined by Linstead *et al.*;[2] *D'* indicates a diastereoisomeric mixture with a preponderance of the *D*-form.

[1] Part III, Polgar and Smith, preceding paper.

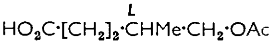
[2] Linstead, Lunt, and Weedon, *J.*, 1950, 3333.

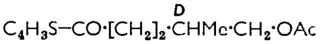
[3] Polgar and Smith, *Chem. and Ind.*, 1961, 1959.

[4] Bailey, Brice, Horne, and Polgar, *J.*, 1959, 661.

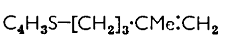
examined a route which involved the use of thiophen as a chain-extender;[5] the following are the details.

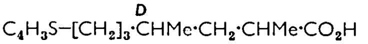
L-(+)-5-Acetoxy-4-methylpentanoic acid (I) was converted, by a Friedel–Crafts reaction involving the corresponding acid chloride and thiophen, into *D*-(+)-2-methyl-5-oxo-5-2′-thienylpentyl acetate (II), $[\alpha]_D$ +2·26° (the change of the prefix *L* to *D* is due to the conventional[2] change of the reference group). Reduction of this ketone by the Huang-Minlon modification[6] of the Wolff–Kishner procedure gave the alcohol (III; X = OH), $[\alpha]_D$ +24·6° (hydrolysis of the acetoxy-group having occurred during this procedure). Condensation of the corresponding iodide (III; X = I), obtained [together with a by-product, assumed to be the olefin (IV)] through the toluene-*p*-sulphonic ester, with the sodio-derivative of ethyl methylmalonate afforded by the usual successive stages (hydrolysis, decarboxylation) 2,4(*D*)-dimethyl-7-2′-thienylheptanoic acid (V) consisting of a mixture of the 2(*D*)- and 2(*L*)-diastereoisomers.

(I) 
$HO_2C{\cdot}[CH_2]_2{\cdot}\overset{L}{C}HMe{\cdot}CH_2{\cdot}OAc$

(II) 
$C_4H_3S{-}CO{\cdot}[CH_2]_2{\cdot}\overset{D}{C}HMe{\cdot}CH_2{\cdot}OAc$

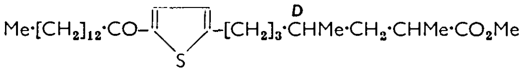

$C_4H_3S{-}[CH_2]_3{\cdot}\overset{D}{C}HMe{\cdot}CH_2{\cdot}X$ (III)

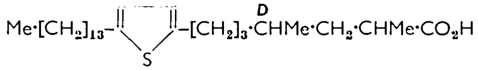
(IV) 
$C_4H_3S{-}[CH_2]_3{\cdot}CMe{:}CH_2$

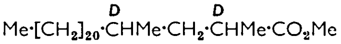

$C_4H_3S{-}[CH_2]_3{\cdot}\overset{D}{C}HMe{\cdot}CH_2{\cdot}CHMe{\cdot}CO_2H$ (V

C_4H_3S = 2-thienyl.

For the preparation of methyl 2(*D*),4(*D*)-dimethylpentacosanoate (VIII), the 2(*DL*),4(*D*)-acid (V) was converted by a Friedel–Crafts reaction involving its methyl ester and tetradecanoyl chloride into the thienyl ketone (VI) which was reduced by the Huang-Minlon method to yield the 2,5-disubstituted thiophen (VII). The latter resisted desulphurisation with nickel–aluminium alloy in aqueous ethanol, but prolonged heating with Raney nickel in refluxing ethanol (see Experimental section) gave satisfactory yields of 2(*DL*),4(*D*)-dimethylpentacosanoic acid. Chromatography of the corresponding methyl ester on alumina, followed by crystallisation of the lævorotatory eluates at low temperature, resulted in the isolation of the 2(*D*),4(*D*)-ester (VIII) with $[\alpha]_D$ −5·2°.

(VI) 

(VII) 

(VIII) 
$Me{\cdot}[CH_2]_{20}{\cdot}\overset{D}{C}HMe{\cdot}CH_2{\cdot}\overset{D}{C}HMe{\cdot}CO_2Me$

The separation of the diastereoisomeric forms of the acid (V) was then examined. A number of unsuccessful attempts, involving chromatography of the methyl ester derived from the acid (V) on alumina, and preparation of the camphorsulphonate and hydrogen phthalate of the corresponding alcohol, are described in the Experimental section. Various alkaloidal salts of the acid (V) were also prepared, and, ultimately, the cinchonidine salt proved satisfactory. Crystallisations of the latter from acetone afforded the 2(*D*)-diastereoisomer, $[\alpha]_D$ −6·7°, which was used for the syntheses of the esters (XIV) and (XVI) described below.

The 2(*D*)-form of the acid (V) was converted into its methyl ester and thence, by reduction with lithium aluminium hydride, into the 2(*D*),4(*D*)-alcohol (IX; X = OH). The corresponding iodide (IX; X = I) on condensation with ethyl methylsodiomalonate, followed by the usual successive stages, yielded 2,4(*D*),6(*D*)-trimethyl-9-2′-thienylnonanoic acid (X). Friedel–Crafts condensation of the corresponding methyl ester with

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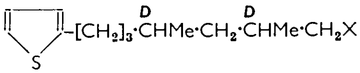
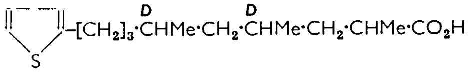
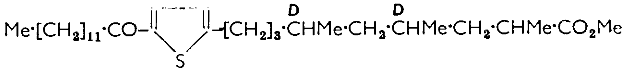
[5] Grey, McGhie, and Ross, *J.*, 1960, 1502.

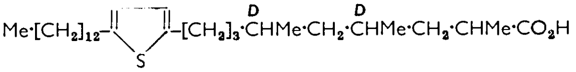
[6] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.

tridecanoyl chloride gave the thienyl ketone (XI) which by the Huang-Minlon reduction afforded 2,4(*D*),6(*D*)-trimethyl-9-(5-tridecyl-2-thienyl)nonanoic acid (XII). Desulphurisation of the latter with Raney nickel gave 2,4(*D*),6(*D*)-trimethylhexacosanoic acid (XIII). The crude acid showed a sulphur content indicating the presence of about 10% of the 2,5-disubstituted thiophen (XII). The latter could not be separated from the required acid by chromatography or by crystallisations, but it was eventually removed by heating the corresponding methyl esters with mercuric acetate in acetic acid, thus converting the disubstituted thiophen (XII) into the dimercuriacetate. The purified ester on repeated chromatography over alumina gave methyl 2(*D*),4(*D*),6(*D*)-trimethylhexacosanoate (XIV), $[\alpha]_D$ $-7{\cdot}25°$. Reduction of this ester with lithium aluminium hydride gave 2(*D*),4(*D*),6(*D*)-trimethylhexacosan-1-ol (XV; X = OH), $[\alpha]_D$ $+3{\cdot}15°$, which was converted into the corresponding iodide (XV; X = I). The latter was converted, by the malonic ester procedure already described, followed by esterification of the resulting tetramethyl-substituted acid, into methyl 2(*D'*),4(*D*),6(*D*),8(*D*)-tetramethyloctacosanoate (XVI), $[\alpha]_D$ $-5{\cdot}25°$. [Comparison of the rotatory power of this ester with the rotations given above for methyl 2(*D*),4(*D*)-dimethylpentacosanoate and 2(*D*),4(*D*),6(*D*)-trimethylhexacosanoate indicates the preponderance of the 2(*D*)-form.] The last-named product was obtained in yields too small to permit the isolation of the pure 2(*D*)-isomer.

(IX)


(X)


(XI)


(XII)


(XIII) $\mathrm{Me{\cdot}[CH_2]_{19}{\cdot}\overset{D}{C}HMe{\cdot}CH_2{\cdot}\overset{D}{C}HMe{\cdot}CH_2{\cdot}CHMe{\cdot}CO_2H}$

(XIV) $\mathrm{Me{\cdot}[CH_2]_{19}{\cdot}\overset{D}{C}HMe{\cdot}CH_2{\cdot}\overset{D}{C}HMe{\cdot}CH_2{\cdot}\overset{D}{C}HMe{\cdot}CO_2Me}$

(XV) $\mathrm{Me{\cdot}[CH_2]_{19}{\cdot}\overset{D}{C}HMe{\cdot}CH_2{\cdot}\overset{D}{C}HMe{\cdot}CH_2{\cdot}\overset{D}{C}HMe{\cdot}CH_2{\cdot}X}$

(XVI) $\mathrm{Me{\cdot}[CH_2]_{19}{\cdot}\overset{D}{C}HMe{\cdot}CH_2{\cdot}\overset{D}{C}HMe{\cdot}CH_2{\cdot}\overset{D}{C}HMe{\cdot}CH_2{\cdot}\overset{D'}{C}HMe{\cdot}CO_2Me}$

As already reported,[1,7] the methyl esters of the lævorotatory acid fraction from the lipids of tubercle bacilli contain a number of homologues of the above esters (XIV) and (XVI). The scheme described above may be readily adapted for the syntheses of these homologues by using, for the stages (X) ⟶ (XI), in place of tridecanoyl chloride, another acid chloride with the appropriate chain-length.

EXPERIMENTAL

Petrol refers to light petroleum of b. p. 40—60°. The alumina used for chromatography was standardised according to Brockmann and Schodder.[8] Optical rotations were measured in chloroform (l = I) unless otherwise stated.

D-(+)-2-*Methyl*-5-*oxo*-5-2'-*thienylpentyl Acetate* (II).—Purified *L*-(+)-5-acetoxy-4-methylpentanoic acid [9] (250 g.) was refluxed with thionyl chloride (467 g.) for 19 hr. Distillation of

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[7] C. Asselineau, J. Asselineau, Ryhage, Ställberg-Stenhagen, and Stenhagen, *Acta Chem. Scand.*, 1959, **13**, 822.

[8] Brockmann and Schodder, *Ber.*, 1941, **74**, 73.

[9] Brettle, Polgar, and Smith, *J.*, 1960, 2802.

the product gave the acid chloride as a liquid (217 g.), b. p. 113—117°/10 mm.; the corresponding *amide*, obtained with aqueous ammonia at 0°, was an oil, b. p. 150—152°/0·1 mm., n_D^{18} 1·4675 (Found: C, 54·8; H, 8·6; N, 8·0. $C_8H_{15}NO_3$ requires C, 54·6; H, 8·7; N, 8·1%).

Freshly distilled stannic chloride (300 g.) was added dropwise with stirring to a solution of the above acid chloride (217 g.) and thiophen (113 g.) in dry benzene (1200 ml.) at 0° during 2 hr. (cf. Grey *et al.*[5]). After a further 3 hours' stirring at room temperature the mixture was cooled (0°), and dilute hydrochloric acid added. The benzene layer was separated, and the aqueous layer extracted with ether. The combined extracts were washed with water, dried ($MgSO_4$), and distilled to give *D*-(+)-2-*methyl*-5-*oxo*-5-2′-*thienylpentyl acetate* (190·2 g., 70% yield), b. p. 126—136°/0·1—0·15 mm., $[\alpha]_D^{21}$ +2·26° (*c* 5·75) (Found: C, 59·6; H, 6·5; S, 13·2. $C_{12}H_{16}SO_3$ requires C, 60·0; H, 6·7; S, 13·3%). The 2,4-*dinitrophenylhydrazone* crystallised from ethanol as bright red needles, m. p. 175—176° (Found: C, 51·1; H, 4·7; N, 13·7; S, 7·5. $C_{18}H_{20}N_4O_6S$ requires C, 51·4; H, 4·8; N, 13·3; S, 7·6%).

D-(+)-2-*Methyl*-5-2′-*thienylpentan*-1-*ol* (III; X = OH).—The preceding thienyl ketone (190 g.) and 64% aqueous hydrazine (320 ml.) in diethylene glycol (1500 ml.) were heated at 110—120° with stirring for 1 hr. After the solution had cooled to 40°, potassium hydroxide (320 g.) in hot diethylene glycol (1 l.) was added, and the mixture heated with stirring at 150—160° for 2 hr. Next day the mixture was poured into dilute hydrochloric acid and extracted with ether. Distillation of the dried ($MgSO_4$) extract afforded the *alcohol* (III; X = OH) (121 g., 83%), b. p. 88—90°/0·1 mm., n_D^{16} 1·5245, $[\alpha]_D^{23}$ +24·6° (*c* 4·5) (Found: C, 65·0; H, 8·7; S, 17·6. $C_{10}H_{16}OS$ requires C, 65·1; H, 8·7; S, 17·4%). The α-*naphthylurethane* had m. p. 78·5—79° after crystallisation from light petroleum (b. p. 100—120°) (Found: C, 71·4; H, 6·6; N, 4·5; S, 8·9. $C_{21}H_{23}NO_2S$ requires C, 71·4; H, 6·6; N, 4·0; S, 9·0%).

2(*DL*),4(*D*)-*Dimethyl*-7-2′-*thienylheptanoic Acid* (V).—Toluene-*p*-sulphonyl chloride (46 g.) was added in small portions during 0·5 hr. to a solution of the above alcohol (23·5 g.) in dry pyridine (200 ml.) at 0°, the mixture being shaken. After a further 16 hr. at room temperature (*ca.* 20°), the mixture was poured into dilute hydrochloric acid, and extracted with ether. The extract was washed with dilute hydrochloric acid and then with water, dried over a mixture of sodium carbonate (to remove any residual acidic material) and magnesium sulphate, and evaporated. The resulting crude product (41·9 g.) (Found: C, 58·5; H, 6·6; S, 18·1. Calc. for $C_{17}H_{22}O_3S_2$: C, 60·3; H, 6·5; S, 18·9%) was refluxed, with stirring, with a solution of anhydrous sodium iodide (37 g.) in dry acetone (250 ml.) for 18 hr. The mixture was then poured into dilute hydrochloric acid and extracted with ether, and the extract washed, successively, with water, aqueous sodium hydrogen sulphite, and water, then dried ($MgSO_4$) and evaporated. The product was chromatographed in petrol on alumina (activity II). Petrol eluted an oil (33 g.) which was essentially the required iodide, but showed somewhat high carbon and low iodine values (Found: C, 41·9; H, 5·5; I, 42·1; S, 10·7. Calc. for $C_{10}H_{15}IS$: C, 40·9; H, 5·1; I, 43·2; S, 10·9%) owing to the presence of some olefinic material (see below). This iodide (32·5 g.), without further purification, was refluxed with ethyl methylsodiomalonate (from 2·9 g. of sodium, 30 g. of ethyl methylmalonate, and 200 ml. of ethanol) for 6 hr. After acidification with dilute hydrochloric acid, the product was isolated by means of ether, then refluxed with potassium hydroxide (30 g.) in water (90 ml.) and methanol (210 ml.) for 4·5 hr. Most of the methanol was then distilled off, and the residue poured into dilute hydrochloric acid. The product, isolated by extraction with ether, was decarboxylated by heating it at 180° for 1·25 hr.; it was then refluxed with aqueous-methanolic potassium hydroxide (as above), and the liberated acid again subjected to the decarboxylation procedure, affording the crude dimethyl-substituted acid (21·5 g.). Extraction of an ethereal solution of this acid with 5% aqueous potassium hydroxide, followed by acidification of the alkaline extract and ether-extraction gave the 2(*DL*),4(*D*)-*acid* (V), b. p. 153—156°/0·2 mm., n_D^{17} 1·5085 (Found: C, 65·1; H, 8·7; S, 13·4. $C_{13}H_{20}O_2S$ requires C, 65·0; H, 8·4; S, 13·3%). The *S*-*benzylthiouronium* salt crystallised from ethanol as plates, m. p. 129—130° (Found: C, 61·8; H, 7·2; N, 7·2; S, 16·2. $C_{21}H_{30}N_2O_2S_2$ requires C, 62·1; H, 7·4; N, 6·9; S, 15·8%).

The ethereal solution remaining after the above extraction with aqueous potassium hydroxide afforded on distillation an oil, b. p. 110—116°/10 mm., n_D^{21} 1·5150, regarded as 2-*methyl*-5-2′-*thienylpent*-1-*ene* (IV) (Found: C, 72·3; H, 8·3; S, 19·4. $C_{10}H_{14}S$ requires C, 72·2; H, 8·5; S, 19·3%); it rapidly decolorised bromine water and aqueous potassium permanganate, and showed in its infrared spectrum bands at 1639 (C=C) and 885 cm.$^{-1}$ (CRR′ = CH_2), but no bands characteristic of an ester or acid carbonyl.

(−)-*2(D),4(D)-Dimethyl-7-2′-thienylheptanoic Acid*.—In preliminary experiments the 2(*DL*),4(*D*)-acid (V) was converted, by means of 5% methanolic sulphuric acid, into the corresponding methyl ester, and attempts were made to separate the diastereoisomeric forms by chromatography over alumina. When the ester (6·5 g.) was chromatographed in petrol over alumina (activity II; 100 g.), none of the fractions eluted by petrol showed measurable rotation. On chromatography of a 5-g. sample over alumina (activity I; 110 g.) the first fractions eluted by petrol showed small negative rotations ($[\alpha]_D^{20}$ −1·0° and −0·6°, respectively); only about 70% of material was, however recovered, and the procedure appeared of little practical value. Some unsuccessful attempts to separate the diastereoisomeric forms of the corresponding alcohol are described later below [see section " 2(*DL*),4(*D*)-Dimethyl-7-2′-thienylheptan-1-ol "). In further experiments involving alkaloidal salts of the 2(*DL*),4(*D*)-acid (V) the quinine, brucine, and cinchonine salts failed to crystallise. Eventually, the cinchonidine salt was found suitable, and the following procedure was adopted.

The 2(*DL*),4(*D*)-acid (156·7 g., 1 mol.) and cinchonidine (176 g., 1 mol.) were heated with acetone (1550 ml.) for 10 min.; the solution was allowed to cool to room temperature, filtered, and then set aside at −10°. The cinchonidine salt which crystallised as waxy crystals (a small second crop was obtained on concentration of the mother-liquors) was recrystallised repeatedly from acetone. The course of the separation of the diastereoisomers was followed by decomposing small quantities of the salt by adding a slight excess of dilute hydrochloric acid and isolating the liberated acid by ether-extraction. After three recrystallisations of the cinchonidine salt, the recovered acid had $[\alpha]_D^{20}$ −6·13° (*c* 13·4). After five recrystallisations the cinchonidine salt yielded an acid having $[\alpha]_D^{20}$ −6·5° (*c* 10·5), and, after seven recrystallisations, an acid having $[\alpha]_D^{20}$ −6·72° ± 0·15° (*c* 12·95). Further recrystallisations of the salt did not increase the rotation of the regained acid.

The mother-liquors from the first crystallisations on addition of dilute hydrochloric acid, followed by ether-extraction, afforded acid having $[\alpha]_D^{20}$ +3·0°. This (+)-acid (85 g.) was converted, by means of 5% methanolic sulphuric acid, into the methyl ester, and the latter refluxed with sodium methoxide (from 40 g. of sodium in 400 ml. of methanol) for 2 hr.; potassium hydroxide (40 g.) in water (100 ml.) was then added, and the mixture refluxed for 2 hr. The resultant acid (84·5 g.), isolated from the hydrolysis mixture in the usual way, had no measurable rotation. This material was used for the isolation (*via* the cinchonidine salt) of a further amount of the (−)-acid.

Four repetitions of the above procedures afforded eventually 33 g. of the (−)-acid, which on distillation gave the (−)-*2(D),4(D)-acid* as an oil (30 g.), b. p. 147—153°/0·06 mm., n_D^{17} 1·5092, $[\alpha]_D^{20}$ −6·73° ± 0·02° (homogeneous), d_4^{20} 1·050 (Found: C, 65·0; H, 8·4; S, 13·4. $C_{13}H_{20}O_2S$ requires C, 65·0; H, 8·4; S, 13·3%).

Methyl 2(*DL*),4(*D*)-*Dimethyl-7-(5-tetradecanoyl-2-thienyl)heptanoate* (VI).—Stannic chloride (27 g.) was added dropwise with stirring to a solution of tetradecanoyl chloride (26·5 g; prepared from tetradecanoic acid by means of thionyl chloride) and methyl 2(*DL*),4(*D*)-dimethyl-7-2′-thienylheptanoate (25·4 g.; obtained from the corresponding acid by the action of 5% methanolic sulphuric acid) in benzene (250 ml.) at <10° during 45 min.; the mixture was then stirred at room temperature for a further 1·5 hr. After addition of N-hydrochloric acid (150 ml.) with cooling and stirring, the benzene layer was separated, and the aqueous layer extracted with ether. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated. The product was purified by chromatography over a column containing silica gel (upper layer) and alumina (lower layer); petrol eluted the *thienyl ketone* (VI) as a pale yellow oil (40 g., 86%). A 1-g. sample distilled at 265—270°/0·1 mm. and had $n_D^{22\cdot5}$ 1·4970 (Found: C, 72·5; H, 10·6; S, 7·0. $C_{28}H_{48}O_3S$ requires C, 72·4; H, 10·4; S, 6·9%). The corresponding semicarbazone and 2,4-dinitrophenylhydrazone were obtained as oils; the *2,4-dinitrophenylsemicarbazone*, prepared by the usual procedure,[10] had m. p. 94—96° (Found: C, 61·6; H, 7·5; N, 10·2. $C_{35}H_{53}N_5O_7S$ requires C, 61·3; H, 7·7; N, 10·2%).

2(*DL*),4(*D*)-*Dimethyl-7-(5-tetradecyl-2-thienyl)heptanoic Acid* (VII).—The preceding thienyl ketone (39 g.) and 64% aqueous hydrazine (65 ml.) in diethylene glycol (300 ml.) were heated at 130° with stirring for 1·5 hr. After the solution had cooled to 40°, potassium hydroxide (65 g.) in hot diethylene glycol (200 ml.) was added, and the mixture heated until the temperature reached 158°, then set aside at room temperature overnight. Next day the mixture was heated

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[10] McVeigh and Rose, *J.*, 1945, 713.

until its temperature reached 200°, and heating was continued at this temperature for a further 1·5 hr. The mixture was allowed to cool, then poured into dilute hydrochloric acid, and extracted with ether. Evaporation of the dried ($MgSO_4$) extract gave the crude *acid* as a liquid (36 g.) which was used without purification for the next stage. A 1-g. sample distilled at 270—280°/0·07 mm. as a pale yellow liquid, n_D^{15} 1·4932 (Found: C, 74·4; H, 11·2; S, 7·3. $C_{27}H_{48}O_2S$ requires C, 74·3; H, 11·0; S, 7·3%).

(−)-*Methyl* 2(*D*),4(*D*)-*Dimethylpentacosanoate* (VIII).—A solution of the preceding thienyl-acid (4·55 g.) in ethanol (500 ml.) was refluxed with Raney nickel (from 130 g. of nickel–aluminium alloy, prepared essentially as described [11] for Raney nickel W-5, except that the catalyst was washed, by decantation with twelve 500-ml. portions of water, and then with eight 100-ml. portions of ethanol, the washing procedure being completed in 45 min. and the resultant Raney nickel used immediately), with stirring for 69 hr. The nickel was then filtered off and dissolved in dilute hydrochloric acid, and the mixture was extracted with ether. The ethereal extract was combined with the ethanolic filtrate, and the whole evaporated. The product was chromatographed in petrol–ether (9 : 1) on silica gel; this eluted a pale yellow solid (4·2 g.) (Found: S, 0·5%) which after crystallisation from ethyl acetate gave 2(*DL*),4(*D*)-*dimethylpentacosanoic acid*, m. p. 48—52° (Found: C, 78·8; H, 13·1. $C_{27}H_{54}O_2$ requires C, 79·0; H, 13·2%).

When, in comparative experiments, the thienyl-acid was refluxed with Raney nickel (i) for 19 hr. and (ii) for 40 hr., the products, isolated as above, were found to contain 4·2% and 1·0% of sulphur, respectively. When the solvent ethanol was replaced by xylene (in order to reduce the time of the reaction by increasing the temperature) and the mixture was refluxed for 18 hr., the product (2·3 g.) which was adsorbed on the nickel catalyst (isolated by dissolving the nickel in hydrochloric acid, followed by ether-extraction) was found to contain 0·9% of sulphur; the material (2·05 g.) which remained in the solvent was a gum (Found: S, 2·1%). In a preliminary experiment which involved adding nickel–aluminium alloy (13·5 g.), with stirring, during 5·5 hr. to the thienyl-acid (1·5 g.) in refluxing 17% aqueous potassium hydroxide (200 ml.; the addition of the alloy caused the mixture to foam excessively), followed by a further 4 hours' refluxing, the product contained 2·3% of sulphur; on addition of nickel–aluminium alloy (20 g.) during 1 hr. to a refluxing solution of the thienyl-acid (2 g.) in 20% aqueous-ethanolic (1 : 1) potassium hydroxide (300 ml.), the resulting product was mainly the unchanged thienyl-acid (Found: S, 6·5%).

The above 2(*DL*),4(*D*)-acid (12·1 g.) was esterified with 5% methanolic sulphuric acid, and the ester chromatographed in petrol on alumina (activity II; 200 g.). Elution with petrol gave in the first fractions material having $[\alpha]_D^{20}$ −4·0° (*c* 11·5) which on crystallisation from a solution in petrol at −6° afforded *methyl* 2(*D*),4(*D*)-*dimethylpentacosanoate* (1 g.), m. p. 40—43°, $[\alpha]_D^{20}$ −5·20° (*c* 17·9) (Found: C, 79·3; H, 13·25. $C_{28}H_{56}O_2$ requires C, 79·1; H, 13·35%); further crystallisation from petrol failed to increase the rotatory power.

2(*DL*),4(*D*)-*Dimethyl*-7-2′-*thienylheptan*-1-*ol*.—The methyl ester of the 2(*DL*),4(*D*)-acid (V) (18·5 g.) in ether (150 ml.) was added to a stirred suspension of lithium aluminium hydride (9 g.) in ether (300 ml.) during 15 min. and the mixture refluxed for a further 10 min. The excess of lithium aluminium hydride was decomposed by an ethereal solution of ethyl acetate; water was then added, followed by dilute sulphuric acid. The aqueous phase was extracted with ether, and the combined ethereal solutions were washed with water, dried ($MgSO_4$), and evaporated. The residue (16·5 g.) gave on distillation the 2(*DL*),4(*D*)-*alcohol* having b. p. 106—108°/0·05 mm., n_D^{17} 1·5123 (Found: C, 69·2; H, 9·9. $C_{13}H_{22}OS$ requires C, 69·0; H, 9·8%). The camphorsulphonate, prepared by keeping the above alcohol (1 g.) and (+)-camphor-10-sulphonyl chloride (1 g.) in pyridine (30 ml.) at 20° for 16 hr., was an oil which failed to crystallise. The hydrogen phthalate, obtained by heating the alcohol (5·82 g.) and phthalic anhydride (3·9 g.) in pyridine (4 ml.) and benzene (10 ml.) on a steam-bath under reflux for 3·5 hr., followed by the addition of dilute hydrochloric acid and ether-extraction, was a resin; its brucine salt, prepared in acetone solution, gave the free base on attempted crystallisation from aqueous acetone.

(+)-2(*D*),4(*D*)-*Dimethyl*-7-2′-*thienylheptan*-1-*ol* (IX; X = OH).—The 2(*D*)-form of the acid (V) (30 g.) was converted, by means of 5% methanolic sulphuric acid, into its methyl ester; reduction of the latter with lithium aluminium hydride, as described above for the 2(*DL*)-alcohol, gave on evaporation of the ethereal extract 2(*D*),4(*D*)-*dimethyl*-7-2′-*thienylheptan*-1-*ol*

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[11] Horning, *Org. Synth.*, Coll. Vol. III, 1955, p. 180.

(26·7 g., 97%), n_D^{17} 1·5123, $[\alpha]_D^{20}$ +13·5° (*c* 11·2) (Found: C, 69·3; H, 10·0; S, 13·8. $C_{13}H_{22}OS$ requires C, 69·0; H, 9·8; S, 14·1%).

2,4(*D*),6(*D*)-*Trimethyl*-9-2′-*thienylnonanic Acid* (X).—Toluene-*p*-sulphonyl chloride (44 g.) was added slowly to an ice-cooled solution of the above 2(*D*),4(*D*)-alcohol (26·5 g.) in dry pyridine (220 ml.), the mixture being shaken frequently; it was then kept at 0° for 46 hr. The crude toluene-*p*-sulphonate was isolated in the usual way, and then purified by chromatography over a column containing silica gel (upper layer) and alumina (activity IV; lower layer). Petrol–ether (1 : 1) eluted the *toluene-*p*-sulphonate* as a liquid (45 g., quantitative yield) (Found: C, 62·8; H, 7·4; S, 17·1. $C_{20}H_{28}O_3S_2$ requires C, 63·1; H, 7·4; S, 16·9%). This product (44·5 g.) was refluxed, with stirring, with sodium iodide (45 g.) and acetone (400 ml.) for 19 hr., and the resulting iodide (37·5 g.), isolated as already described for a similar case, refluxed with ethyl methylsodiomalonate (from 3 g. of sodium, 30 g. of ethyl methylmalonate, and 150 ml. of ethanol) for 5·5 hr. The resulting disubstituted malonic ester, isolated in the usual way, was hydrolysed by refluxing 10% aqueous–methanolic (3 : 7) potassium hydroxide (300 ml.; 15 hr.), and the liberated acid decarboxylated by heating it at 180° for 1 hr., then subjected to a repetition of the foregoing hydrolysis and decarboxylation procedure. The product was chromatographed over silica gel; petrol–ether (9 : 1) eluted the purified acid (27·8 g.) which was taken up in ether. Extraction of the ethereal solution with 5% aqueous potassium hydroxide, followed by acidification of the alkaline extract and ether-extraction gave the 2,4(*D*),6(*D*)-*acid* as an oil (24·9 g.) (Found: C, 68·4; H, 9·3; S, 11·0. $C_{16}H_{26}O_2S$ requires C, 68·3; H, 9·2; S, 11·3%).

Methyl 2,4(*D*),6(*D*)-*Trimethyl*-9-(5-*tridecanoyl*-2-*thienyl*)*nonanoate* (XI).—The preceding acid was converted by means of 5% methanolic sulphuric acid into its methyl ester, and the latter (25·5 g.) subjected to Friedel–Crafts condensation with tridecanoyl chloride (21·7 g.; prepared from tridecanoic acid, Eastman Kodak Company, by the action of thionyl chloride) in benzene (250 ml.) in the presence of stannic chloride (25·5 g.) as already described for similar cases. The resulting crude product was purified by chromatography over a column containing silica gel (upper layer) and alumina (lower layer). Petrol–ether (9 : 1) eluted the thienyl ketone as a yellow oil (42·9 g.); its 2,4-*dinitrophenylsemicarbazone* had m. p. 93—94° (Found: C, 62·1; H, 8·1; N, 9·4; S, 4·9. $C_{37}H_{57}N_5O_7S$ requires C, 62·1; H, 8·0; N, 9·7; S, 4·5%).

2,4(*D*),6(*D*)-*Trimethyl*-9-(5-*tridecyl*-2-*thienyl*)*nonanoic Acid* (XII).—The preceding thienyl ketone (42·3 g.) was reduced by the Huang-Minlon procedure [6] as described above for the preparation of the acid (VII). The crude product (38·4 g.) was purified by chromatography over silica gel; petrol–ether (9 : 1) eluted the reduced acid as a yellow oil (36·3 g.) which was used for the next stage. Distillation of a small sample afforded the *thienyl-acid*, b. p. 250—251°/0·05 mm., $n_D^{16\cdot5}$ 1·4910 (Found: C, 75·1; H, 11·5; S, 6·8. $C_{29}H_{52}O_2S$ requires C, 75·0; H, 11·3; S, 6·9%).

(−)-*Methyl* 2(*D*),4(*D*),6(*D*)-*Trimethylhexacosanoate* (XIV).—The thienyl-acid (XII) (13·8 g.) was desulphurised, as described for an earlier example, by heating it with Raney nickel (from 450 g. of nickel–aluminium alloy) in ethanol (1 l.) for 137 hr. The product, isolated as before, was chromatographed over silica gel; petrol–ether (9 : 1) eluted a wax (13·07 g.) (Found: S, 0·8%). This material (attempts to purify it by crystallisation from ethyl acetate or petrol were unsuccessful) was converted by means of 5% methanolic sulphuric acid into its methyl ester, and the latter (12·4 g.) heated with mercuric acetate (25 g.) in glacial acetic acid (250 ml.) for 4 hr. (during this procedure crystals of the dimercuriacetate of the thienyl-ester were deposited from the solution). The solution was filtered and, after addition of water (2 l.), extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$), and evaporated, and the product was chromatographed over a column containing silica (upper layer) and alumina (activity IV; lower layer). Elution with petrol–ether (23 : 2) gave the 2,4(*D*),6(*D*)-*ester* as a wax (11·9 g.), $[\alpha]_D^{22}$ −2·1° (*c* 12·07) (Found: C, 79·3; H, 13·7. $C_{29}H_{58}O_2$ requires C, 79·4; H, 13·6%). Chromatography of this ester in petrol on alumina (activity I—II), followed by rechromatography of the earlier petrol eluates (the first fractions, yielding an oil, being rejected each time), afforded *methyl* 2(*D*),4(*D*),6(*D*)-*trimethylhexacosanoate*, m. p. 25—25·5°, b. p. 234—236°/0·1 mm., $[\alpha]_D^{22}$ −7·25° (*c* 12·60) (Found: C, 80·0; H, 13·3. $C_{30}H_{60}O_2$ requires C, 79·6; H, 13·3%).

(+)-2(*D*),4(*D*),6(*D*)-*Trimethylhexacosan*-1-*ol* (XV; X = OH).—The preceding 2(*D*),4(*D*),6(*D*)-ester (1·9 g.) was reduced with lithium aluminium hydride as described for previous examples. The resulting crude alcohol was chromatographed over alumina (activity III; 80 g.). Petrol

(500 ml.) eluted a small amount of unchanged ester (0·094 g.); further elution with petrol–ether (9 : 1) afforded 2(*D*),4(*D*),6(*D*)-*trimethylhexacosan*-1-*ol* (1·64 g.), m. p. 40—41°, $[\alpha]_D^{22}$ +3·15° (*c* 12·75) (Found: C, 81·5; H, 13·9. $C_{29}H_{60}O$ requires C, 81·9; H, 14·1%).

(—)-*Methyl* 2(*D'*),4(*D*),6(*D*),8(*D*)-*Tetramethyloctacosanoate* (XVI).—The alcohol (XV; X = OH) (1·61 g.) was converted, through the toluene-*p*-sulphonate, into the corresponding iodide, as described for similar cases, and the iodide refluxed with ethyl methylsodiomalonate (from 1·55 g. of ethyl methylmalonate, 0·103 g. of sodium, and 25 ml. of ethanol) for 19 hr. After the usual successive stages (hydrolysis, decarboxylation), the product (1·255 g.) was chromatographed on alumina (activity II—III, 30 g.). The fractions eluted by petrol–ether (1 : 1) were rejected; ether–acetic acid (98 : 2) eluted the tetramethyl acid (0·598 g.). The latter was esterified with ethereal diazomethane, and the methyl ester chromatographed on alumina (activity II, 10 g.). Elution with petrol gave the 2(*D'*),4(*D*),6(*D*),8(*D*)-*ester* as an oil (0·53 g.), n_D^{24} 1·4550, $[\alpha]_D^{24}$ −5·25° (*c* 7·25) (Found: C, 80·2; H, 13·5. $C_{33}H_{66}O_2$ requires C, 80·1; H, 13·5%).

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