26. *Methyl-substituted αβ-Unsaturated Acids. Part I.*

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In connection with investigations on the αβ-unsaturated acids of human tubercle bacilli the influence of an αβ-double bond on the rotation of optically active methyl-substituted acids has been studied by syntheses of model compounds from (+)-3 : 7-dimethyloctan-1-ol (dihydrocitronellol). Dehydrobromination of the α-bromo-substituted methyl ester derived from (−)-2 : 4 : 8-trimethylnonanoic acid * (VI) by means of alcoholic potassium hydroxide results in racemization of the product in respect of the asymmetric centre at C_γ, but pyridine dehydrobromination yields the optically active αβ-unsaturated ester (X; R = Me). Alkaline hydrolysis of the latter affords (−)-2 : 4 : 8-trimethylnon-2-enoic acid (X; R = H) which, although having the asymmetric centre adjacent to the αβ-double bond, exhibits a remarkable optical stability. This acid has a greatly increased rotation relative to the corresponding saturated acid, whereas there is no such increase if the asymmetric centre is removed further from the carboxyl group as exemplified by (−)-2 : 5 : 9-trimethyldec-2-enoic acid (XI; R = H). The relation of these findings to the structural features of the tubercle-bacilli acids is discussed.

Recent investigations in this laboratory have shown that the optically active acids of human tubercle bacilli are mixtures of saturated and unsaturated acids. The dextrorotatory fraction was found to contain αβ-unsaturated acids (Polgar, *Biochem. J.*, 1948, **42**, 206; Chanley and Polgar, *Nature*, 1950, **166**, 693) and it was noted that the rotation of these acids is greatly decreased on hydrogenation. This suggested the presence of an asymmetric centre near to the αβ-double bond and the object of the work now described has been to study optically active αβ-unsaturated acids with an asymmetric centre in the γ- and the δ-position, respectively. The work was undertaken concurrently with degradative studies which have already been reported in a preliminary note (Polgar and Robinson, *Chem. and Ind.*, 1951, 685).

The starting material chosen for the syntheses of the required optically active acids was (+)-3 : 7-dimethyloctan-1-ol (I), obtained by catalytic hydrogenation of (+)-citronellol. The main object was to prepare active 4 : 8-dimethylnonanoic * (III), 2 : 4 : 8-trimethylnonanoic (VI), and 2 : 5 : 9-trimethyldecanoic acid (IX), and to convert them into the corresponding αβ-unsaturated acids by α-bromination and subsequent dehydrobromination.

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* Geneva nomenclature (CO_2H = 1) is used throughout.

(−)-4 : 8-Dimethylnonanoic acid (III), $[\alpha]_D$ −1·0°, was obtained by converting (I) into the bromide (II) and carboxylating the derived Grignard complex.

(I) $CH_3{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}OH$ $CH_3{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CHMe{\cdot}CH_2{\cdot}CO_2H$ (IV)
(II) $CH_3{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}Br$ $CH_3{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CHMe{\cdot}CH_2Br$ (V)
(III) $CH_3{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}CO_2H$ $CH_3{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CHMe{\cdot}CH_2{\cdot}CHMe{\cdot}CO_2H$ (VI)

For the preparation of (−)-2 : 4 : 8-trimethylnonanoic acid (VI) the intermediate was (+)-3 : 7-dimethyloctanoic acid (IV). The latter, obtained previously by way of citronellic acid (Semmler, *Ber.*, 1893, **26**, 2254; Paal, *Chem. Zentr.*, 1917, II, 145) or *via* dihydrocitronellal (Sabetay and Bléger, *Bull. Soc. chim.*, 1928, **43**, 843; von Braun and Kaiser, *Ber.*, 1923, **56**, 2268), was more conveniently made from (I) by oxidation with chromic acid in acetone (cf. oxidation of 5-methyldecan-1-ol, Leese and Raphael, *J.*, 1950, 2728). The silver salt of the acid (IV) furnished, by the action of bromine in carbon tetrachloride (cf. Kleinberg, *Chem. Reviews*, 1947, **40**, 386), (−)-1-bromo-2 : 6-dimethylheptane (V) which by condensation with ethyl methylmalonate, followed by hydrolysis and decarboxylation of the product, afforded (−)-2 : 4 : 8-trimethylnonanoic acid (VI) having $[\alpha]_D$ −3·8°. [A new asymmetric centre at $C_{(2)}$ resulted from these processes.]

An alternative route tried was from active 4 : 8-dimethylnon-7-en-2-ol (VII), obtainable from (+)-citronellal by reaction with methylmagnesium iodide (Rupe, Pfeiffer, and Splittgerber, *Ber.*, 1907, **40**, 2813). This was converted, on hydrogenation followed by treatment of the resulting (−)-4 : 8-dimethylnonan-2-ol with hydrobromic acid, into (−)-1 : 3 : 7-trimethyloctyl bromide (VIII) which by carboxylation of the derived Grignard compound afforded (VI) in low yields.

(VII) $CH_3{\cdot}CMe{:}CH{\cdot}[CH_2]_2{\cdot}CHMe{\cdot}CH_2{\cdot}CHMe{\cdot}OH$ $CH_3{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CHMe{\cdot}CH_2{\cdot}CHMeBr$ (VIII)

(−)-2 : 5 : 9-Trimethyldecanoic acid (IX), $[\alpha]_D$ −0·1°, was readily obtained by a malonic ester condensation employing the bromide (II) and ethyl methylmalonate.

(IX) $CH_3{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}CHMe{\cdot}CO_2H$

The acids were brominated in the presence of red phosphorus (Hell–Volhard–Zelinsky method), and the resulting α-brominated acid bromides converted into the methyl esters by the action of dry methanol. Dehydrobromination of these bromo-esters was then examined. In the case of the bromo-ester derived from (−)-2 : 4 : 8-trimethylnonanoic acid (VI) the action of alcoholic potassium hydroxide afforded an optically inactive material (light absorption : max., 2170 Å; log ε, 3·58) which, as will be shown in a later paper, is probably a mixture of unsaturated acids with an α-hydroxy-acid. However, refluxing the bromo-ester with anhydrous pyridine yielded methyl (−)-2 : 4 : 8-trimethylnon-2-enoate (X; R = Me), $[\alpha]_D$ −21·3°, exhibiting an absorption maximum at 2170 Å (log ε, 4·08). A similar dehydrobromination of the bromo-ester from (−)-2 : 5 : 9-trimethyldecanoic acid (IX) by means of pyridine furnished methyl (−)-2 : 5 : 9-trimethyldec-2-enoate (XI; R = Me), $[\alpha]_D$ −0·1°, having an absorption maximum at 2180 Å (log ε, 3·92). In a comparative experiment, pyridine dehydrobromination of methyl (+)-2-bromo-3 : 7-dimethyloctanoate (from IV) also readily yielded the αβ-unsaturated ester (log ε, 4·10 at 2190 Å). In contrast to the preceding examples, (−)-4 : 8-dimethylnonanoic acid (III) by an analogous dehydrobromination of its bromo-ester with pyridine gave only a tar which was insoluble in ether.

The main interest of the above results lies in the demonstration that the optical rotation of (−)-2 : 4 : 8-trimethylnonanoic acid (VI), with an asymmetric centre at C_γ, is greatly increased on introduction of an αβ-double bond, whereas there is no such increase on introducing the αβ-double bond into (−)-2 : 5 : 9-trimethyldecanoic acid (IX). If it is assumed that racemization did not take place in the latter case, the comparison already indicates that the decrease in the optical rotations of the αβ-unsaturated acids from tubercle bacilli on hydrogenation must be due to the presence of an asymmetric centre in the γ-position of these acids. The degradative studies already mentioned (Polgar and Robinson, *loc. cit.* and forthcoming publication) have confirmed this and also shown that one of these acids, termed mycolipenic acid-I, is 2 : 4 : 6-trimethyltetracos-2-enoic acid (XII). It thus contains the grouping $-CHMe\cdot CH\colon CMe\cdot CO_2H$ present in the synthetic acid (X; R = H). The synthesis of the latter, therefore, also indicates a possible route to the optically active natural substance.

(X) $CH_3\cdot CHMe\cdot[CH_2]_3\cdot CHMe\cdot CH\colon CMe\cdot CO_2R$ $CH_3\cdot CHMe\cdot[CH_2]_3\cdot CHMe\cdot CH_2\cdot CH\colon CMe\cdot CO_2R$ (XI)

$CH_3\cdot[CH_2]_{17}\cdot CHMe\cdot CH_2\cdot CHMe\cdot CH\colon CMe\cdot CO_2H$ (XII)

A feature of interest is the presence in the above acids (X) and (XII) of a three-carbon tautomeric system with an asymmetric centre adjacent to the αβ-double bond. It is evident that if at any time by tautomeric displacement of the double bond the corresponding βγ-unsaturated form were to be formed, racemization would necessarily result. When, however, methyl (—)-2 : 4 : 8-trimethylnon-2-enoate (X; R = Me) was hydrolysed by refluxing it for several hours with alcoholic potassium hydroxide, the acid was obtained with $[\alpha]_D$ —24·6° and there was no loss in rotatory power when it was further heated with an excess of alkali. This indicates much hindrance to the tautomeric mobility of the system $-CHMe\cdot CH\colon CMe\cdot CO_2H$. A similarly restricted tautomeric mobility has already been observed by Kon, Linstead, and their collaborators (*J.*, 1931, 1411; 1932, 2452, 2454) with αβ-dialkyl-substituted αβ- or βγ-unsaturated acids (*e.g.*, 2-ethyl-3-methylhex-2-enoic acid remains almost unchanged by prolonged boiling with an excess of aqueous potash).

It is of interest that ethyl (—)-2-carbethoxy-4 : 8-dimethylnonanoate (XIII), $[\alpha]_D$ —2·6°, obtained from (III) by way of the α-bromo- and the α-cyano-ester, on dehydrobromination of its α-bromo-derivative with pyridine gave an unsaturated product having a low extinction coefficient (log ε, 3·58 at 2190 Å) and no measurable rotation. This appears consistent with earlier findings that in such three-carbon tautomeric systems a γ-alkyl substituent favours the βγ-unsaturated form (Goldberg and Linstead, *J.*, 1928, 2343) and a second carbethoxyl grouping at the α-carbon atom, while favouring αβ-unsaturation, also tends to promote the tautomeric mobility of the system (Kon and Speight, *J.*, 1926, 2727).

During this work ethyl (—)-3-hydroxy-2 : 3 : 5 : 9-tetramethyldecanoate (XIV) has also been prepared by a Reformatsky reaction from (+)-4 : 8-dimethylnonan-2-one, the latter having been obtained from (—)-4 : 8-dimethylnonan-2-ol on oxidation with chromic acid. Dehydration of the hydroxy-ester (XIV) by phosphorus oxychloride (cf. Kon and Nargund, *J.*, 1932, 2461) gave an unsaturated ester containing only a small proportion of the αβ-unsaturated form (log ε, 3·45 at 2100 Å).

$CH_3\cdot CHMe\cdot[CH_2]_3\cdot CHMe\cdot CH_2\cdot CH(CO_2Et)_2$ (XIII)

$CH_3\cdot CHMe\cdot[CH_2]_3\cdot CHMe\cdot CH_2\cdot CMe(OH)\cdot CHMe\cdot CO_2Et$ (XIV)

EXPERIMENTAL

Ultra-violet absorption spectra were determined in methanol. We are indebted to Dr. F. B. Strauss for the measurements. Optical rotations were determined in 0·5-dm. tubes. M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss.

(+)-3 : 7-*Dimethyloctanoic Acid* (IV).—To a rapidly stirred solution of (+)-3 : 7-dimethyloctan-1-ol (I) (30 g.; $[\alpha]_D$ +3·5°, obtained by catalytic hydrogenation of commercial citronellol, $[\alpha]_D$ +3·7°) in acetone (100 c.c.) was added dropwise a solution of chromium trioxide (40 g.) in water (68 c.c.) and concentrated sulphuric acid (12 c.c.) during 75 minutes at such a rate that the temperature was maintained at 40—60°. The mixture was then diluted with water and extracted with ether from which the acidic fraction was removed by 10% sodium hydroxide solution. Acidification of the alkaline extract and isolation by means of ether afforded (+)-3 : 7-dimethyloctanoic acid (14·4 g., 44%), b. p. 139—141°/15 mm., d_4^{17} 0·880, $[\alpha]_D^{17}$ +4·2° (homog.) (Found: C, 70·0; H, 11·3. Calc. for $C_{10}H_{20}O_2$: C, 69·8; H, 11·6%). Three other runs, using the same quantities, were worked up together, yielding 54 g. (55%) of the acid.

3 : 7-*Dimethyloct-2-enoic Acid*.—To a mixture of (+)-3 : 7-dimethyloctanoic acid (50 g.) and red phosphorus (9·02 g.) was added dropwise dry bromine (182 g.) during 30 minutes while the mixture was stirred at 90° (bath-temp.). After a further 15 hours' heating at 90°, the mixture was cooled and dry methanol (60 c.c.) introduced during 1 hour. The product was kept at room

temperature for 1 hour, then refluxed for 2 hours. Dilution with water and extraction with ether afforded the crude bromo-ester. This ester (2 g.) and pyridine (4 c.c.) were refluxed for 10 hours. The mixture was then cooled and poured into dilute hydrochloric acid, and *methyl* 3 : 7-*dimethyloct*-2-*enoate* isolated, with ether, as an oil (0·6 g.), b. p. 115°/15 mm. (Found : C, 71·1; H, 10·9. $C_{11}H_{20}O_2$ requires C, 71·7; H, 10·9%). Light absorption : Max., 2190 Å; log ε, 4·10.

The foregoing ester (0·4 g.) was refluxed with potassium hydroxide (0·5 g.) in water (1 c.c.) and ethanol (4 c.c.) for 3 hours. Dilution with water, acidification, and isolation with ether afforded 3 : 7-*dimethyloct*-2-*enoic acid*, b. p. 140°/15 mm. Light absorption : Max., 2180 Å; log ε, 4·04. The S-*benzylthiuronium* salt crystallized from aqueous ethanol in leaflets, m. p. 149° (Found : C, 63·7; H, 8·3; N, 8·1. $C_{18}H_{28}O_2N_2S$ requires C, 64·3; H, 8·3; N, 8·3%).

(−)-1-*Bromo*-3 : 7-*dimethyloctane* (II).—(+)-3 : 7-Dimethyloctan-1-ol (117 g.) was refluxed with hydrobromic acid (48%; 277 c.c.) and concentrated sulphuric acid (55·5 c.c.) for 3·5 hours. The mixture was then poured into water and extracted with ether. Evaporation of the ether afforded the bromide, b. p. 102—107°/15 mm. (91 g.), d_4^{20} 1·05, $[\alpha]_D^{20}$ −4·6° (homog.).

(−)-4 : 8-*Dimethylnonanoic Acid* (III).—A Grignard reagent was prepared from the preceding bromide (25 g.) and magnesium (3 g.) in ether (50 c.c.) in the usual fashion. Solid carbon dioxide was added to the cooled solution, and the mixture set aside at room temperature for 2 hours. It was then poured into dilute hydrochloric acid, and the ethereal layer washed with water and extracted with 10% aqueous sodium hydroxide (4 × 25 c.c.). The product obtained on acidification of the alkaline extracts was isolated with ether and distilled, affording (−)-4 : 8-dimethylnonanoic acid (9·3 g.), b. p. 152°/12 mm., d_{24}^{24} 0·879, $[\alpha]_D^{17}$ −1·0° (homog.) (Found : C, 70·9; H, 12·1. Calc. for $C_{11}H_{22}O_2$: C, 71·0; H, 11·8%). Von Braun and Kaiser, *Ber.*, 1923, **56**, 2268, record $[\alpha]_D$ −0·58°.

Methyl (−)-2-*Bromo*-4 : 8-*dimethylnonanoate*.—The preceding acid (8 g.) was brominated as before (28 g. of bromine, 1·33 g. of red phosphorus). Reaction of the resulting acid bromide with dry methanol (10 c.c.) in the manner already described gave *methyl* (−)-2-*bromo*-4 : 8-*dimethylnonanoate* which distilled as an oil (10 g.), b. p. 135—138°/12 mm., d_4^{22} 1·125, $[\alpha]_D^{18}$ −6·5° (homog.) (Found : C, 51·65; H, 8·1; Br, 28·6. $C_{12}H_{23}O_2Br$ requires C, 51·6; H, 8·2; Br, 28·7%).

Attempted Dehydrobromination of Methyl (−)-2-*Bromo*-4 : 8-*dimethylnonanoate*.—The preceding bromo-ester was refluxed with a large excess of anhydrous pyridine for 5 hours. On pouring of the solution into dilute hydrochloric acid a tar was obtained which was insoluble in ether; no ether-soluble product was found. The same result was obtained on refluxing the bromo-ester (2 g.) with pyridine (4 c.c.) for 30 minutes.

(−)-1-*Bromo*-2 : 6-*dimethylheptane* (V).—To a solution of (+)-3 : 7-dimethyloctanoic acid (27 g.) in a slight excess of aqueous ammonia was added a solution of silver nitrate (27·2 g.) in water (20 c.c.), and the mixture heated at 80° for 30 minutes. The precipitated silver salt was collected, and washed with aqueous ammonia, water, and finally repeatedly with acetone. It was dried at 100° for 30 minutes. A suspension of the salt in carbon tetrachloride (50 c.c.) was stirred and cooled with running water while bromine (8 c.c.) was added dropwise during 30 minutes; the mixture was then refluxed on the steam-bath for 1 hour. After filtration, the solution was evaporated, and the residue taken up in ether and extracted with 10% sodium hydroxide solution to remove unchanged acid (4 g.). Distillation of the ethereal solution afforded (−)-1-*bromo*-2 : 6-*dimethylheptane* (16·5 g., 55%), b. p. 82—85°/12 mm., d_4^{20} 1·065, $[\alpha]_D^{15}$ −0·4° (homog.) (Found : C, 51·7; H, 9·25; Br, 38·6. $C_9H_{19}Br$ requires C, 52·2; H, 9·2; Br, 38·65%).

(−)-4 : 8-*Dimethylnonan*-2-*ol*.—(−)-4 : 8-Dimethylnon-7-en-2-ol (VII) was prepared from (+)-citronellal, $[\alpha]_D^{15}$ +10·8°, according to the procedure of Rupe *et al.* (*loc. cit.*) except that the ethereal extract of the crude product was washed with a concentrated solution of sodium hydrogen sulphite to remove unchanged citronellal. Evaporation and distillation of the residual product afforded (−)-4 : 8-dimethylnon-7-en-2-ol, b. p. 130—135°/25 mm., $[\alpha]_D^{15}$ −0·8° (homog.) (Rupe *et al.*, starting from citronellal, $[\alpha]_D$ +12·3°, record $[\alpha]_D$ +0·55°). This was hydrogenated in ethanol (100 g. in 400 c.c.) in the presence of Raney nickel at 50°/50 atm., to give (−)-4 : 8-*dimethylnonan*-2-*ol*, $[\alpha]_D^{15}$ −4·7° (homog.) (Found : C, 76·7; H, 14·0. $C_{11}H_{24}O$ requires C, 76·8; H, 14·0%).

(−)-1 : 3 : 7-*Trimethyloctyl Bromide* (VIII).—The preceding alcohol (50 g.) was refluxed with hydrobromic acid (48%; 109 c.c.) and concentrated sulphuric acid (5 c.c.). After 1 hour a further quantity (5 c.c.) of concentrated sulphuric acid was added and refluxing continued for a further 3 hours. Dilution with water and isolation with ether afforded, in addition to an unsaturated fraction, b. p. 75—102°/15 mm. (23·5 g.), (−)-1 : 3 : 7-*trimethyloctyl bromide* (25·5 g.), b. p. 103—108°/15 mm., $[\alpha]_D^{15}$ −4·4° (homog.) (Found : Br, 33·2. $C_{11}H_{23}Br$ requires Br, 34·0%). The procedure is obviously unsatisfactory for the preparation of bromides from secondary alcohols.

(−)-2 : 4 : 8-*Trimethylnonanoic Acid* (VI).—(a) *From* (−)-1-*bromo*-2 : 6-*dimethylheptane*. To an ethanolic solution of sodium ethoxide, obtained from sodium (3·2 g., 1·8 mols.) and ethanol (100 c.c.), were added ethyl methylmalonate (26·9 g., 2 mols.; Blatt, *Org. Synth.*, Coll. Vol. II, 1943, pp. 272, 279) and some sodium iodide, and the mixture was heated to boiling under reflux. 1-Bromo-2 : 6-dimethylheptane (16 g.) was then introduced dropwise during 15 minutes and refluxing continued for 6 hours. The bulk of the ethanol was evaporated, a solution of sodium hydroxide (24 g.) in water (30 c.c.) added to the residue, and the mixture refluxed for 6 hours. Decarboxylation (150—170°, 30 minutes) of the liberated acid furnished (−)-2 : 4 : 8-*trimethylnonanoic acid* (9 g.), b. p. 160°/15 mm., d_4^{22} 0·879, $[\alpha]_D^{15}$ −3·8° (homog.), n_D^{24} 1·4393 (Found : C, 71·5; H, 12·1. $C_{12}H_{24}O_2$ requires C, 72·0; H, 12·0%).

(b) *From* (−)-1 : 3 : 7-*trimethyloctyl bromide*. A Grignard reagent from this bromide (20 g.) and magnesium (2·2 g.) in ether (75 c.c.) was carboxylated by a large excess of solid carbon dioxide and the mixture kept for 2 hours. The Grignard complex was then decomposed by means of dilute hydrochloric acid, and the ether layer extracted with 10% aqueous sodium hydroxide. Acidification of the alkaline extract and isolation with ether, followed by distillation, gave (−)-2 : 4 : 8-trimethylnonanoic acid (3·5 g.), b. p. 160°/15 mm., $[\alpha]_D^{15}$ −3·5° (*c* 25 in Et_2O), n_D^{24} 1·4385 (Found : C, 72·35; H, 12·15%).

(−)-2 : 4 : 8-*Trimethylnon*-2-*enoic Acid* (X; R = H).—(−)-2 : 4 : 8-Trimethylnonanoic acid (9 g.) was heated with bromine (30 g.) in the presence of red phosphorus (1·35 g.) at 90° for 10 hours in the manner already described. Dry methanol (15 c.c.) was then slowly added and, after 2 hours' refluxing of the mixture, the resulting methyl ester was isolated with ether. The bromo-ester (7 g.) was refluxed with anhydrous pyridine (15 c.c.) for 15 hours. Dilution with water, extraction with ether, and distillation furnished *methyl* (−)-2 : 4 : 8-*trimethylnon*-2-*enoate* (X; R = Me) (4·1 g.), b. p. 113—116°/10 mm., d_4^{22} 0·873, $[\alpha]_D^{14}$ −21·3° (homog.), n_D^{19} 1·4452 (Found : C, 73·1; H, 11·3. $C_{13}H_{24}O_2$ requires C, 73·6; H, 11·3%). Light absorption : Max., 2170 Å; log ε, 4·08.

The foregoing methyl ester (1 g.) was refluxed with a solution of potassium hydroxide (0·75 g.) in ethanol (13 c.c.) and water (2 c.c.) for 5 hours. Extraction of the acidified mixture with ether and distillation gave (−)-2 : 4 : 8-*trimethylnon*-2-*enoic acid* (X; R = H) as an oil (0·8 g.), $[\alpha]_D^{13}$ −24·6° (*c*, 10 in Et_2O) (Found : C, 72·7; H, 11·1. $C_{12}H_{22}O_2$ requires C, 72·7; H, 11·1%). Light absorption : Max., 2170 Å; log ε, 4·05. No change in the optical rotation was observed on heating the acid with 10% alcoholic potassium hydroxide for 5 hours. The S-*benzylthiuronium* salt crystallized from aqueous ethanol in needles, m. p. 132—133° (Found : C, 65·7; H, 9·0; N, 7·6. $C_{20}H_{32}O_2N_2S$ requires C, 65·9; H, 8·8; N, 7·7%).

On refluxing of the above bromo-ester (2 g.) with a solution of potassium hydroxide (2 g.) in ethanol (9 c.c.) and water (1 c.c.) for 3 hours the resulting acid (Light absorption : Max., 2170 Å; log ε, 3·58) exhibited no measurable rotation.

(−)-2 : 5 : 9-*Trimethyldecanoic Acid* (IX).—(−)-1-Bromo-3 : 7-dimethyloctane (91 g.) was added to the sodio-derivative of ethyl methylmalonate, obtained from sodium (13·3 g., 1·4 mols.), ethanol (500 c.c.), and ethyl methylmalonate (108 g., 1·5 mols.), during 45 minutes while the mixture was refluxed; heating was then continued for 15 hours. *Ethyl* (−)-2-*carbethoxy*-2 : 5 : 9-*trimethyldecanoate*, isolated in the known manner, distilled as an oil (72 g.), b. p. 189—190°/15 mm., $[\alpha]_D^{20}$ −1·16° (homog.) (Found : C, 69·3; H, 10·9. $C_{18}H_{34}O_4$ requires C, 68·8; H, 10·8%). Hydrolysis with ethanolic potassium hydroxide (33 g., in 20 c.c. of water and 100 c.c. of ethanol), followed by acidification and decarboxylation (160—170°, 2 hours), furnished (−)-2 : 5 : 9-*trimethyldecanoic acid*, b. p. 177—178°/20 mm., as a pale yellow oil (45 g.), $[\alpha]_D^{23}$ −0·1° (homog.) (Found : C, 73·3; H, 12·4. $C_{13}H_{26}O_2$ requires C, 72·9; H, 12·15%).

(−)-2 : 5 : 9-*Trimethyldec*-2-*enoic Acid* (XI; R = H).—The preceding acid (20 g.) was heated with bromine (58 g.) in the presence of red phosphorus (3 g.) for 20 hours, as already described for similar cases, and the resulting crude acid bromide (24·8 g.) converted into the methyl ester by means of methanol (30 c.c.). A 15-g. portion of this ester was refluxed with anhydrous pyridine (30 c.c.) for 15 hours. *Methyl* (−)-2 : 5 : 9-*trimethyldec*-2-*enoate* (XI; R = Me), isolated as before, was an oil (7·8 g.), b. p. 137—139°/18 mm., $[\alpha]_D^{15}$ −0·1° (homog.) (Found : C, 74·8; H, 11·7. $C_{14}H_{26}O_2$ requires C, 74·3; H, 11·5%). Light absorption : Max., 2180 Å; log ε, 3·92.

The corresponding *acid*, obtained by hydrolysis with alcoholic potassium hydroxide, had

b. p. 172°/15 mm. (Found : C, 73·3; H, 11·6. $C_{13}H_{24}O_2$ requires C, 73·6; H, 11·3%). The acid had no measurable rotation in ether (*c*, 40). Its S-*benzylthiuronium* salt crystallized from aqueous ethanol in needles, m. p. 126° (Found : C, 67·2; H, 9·2; N, 7·7. $C_{21}H_{34}O_2N_2S$ requires C, 66·7; H, 9·0; N, 7·4%).

Ethyl (–)-2-*Carbethoxy*-4 : 8-*dimethylnonanoate* (XIII).—Methyl (–)-2-bromo-4 : 8-dimethylnonanoate (6 g.) was heated under reflux on a steam-bath with a solution of potassium cyanide (3·5 g.) in ethanol (25 c.c.) and water (5 c.c.) for 2 hours. Acidification with hydrochloric acid and extraction of the product with ether afforded the crude cyano-acid (4·8 g.) as a dark oil. This was heated under reflux with ethanol (20 c.c.) and concentrated sulphuric acid (7 c.c.) for 15 hours. After dilution with water the product was collected with ether and distilled. *Ethyl* (–)-2-*carbethoxy*-4 : 8-*dimethylnonanoate* was obtained as an oil (3·2 g.), b. p. 175—180°/18 mm., $[\alpha]_D^{18}$ –2·6° (homog.) (Found : C, 67·6; H, 10·65. $C_{16}H_{30}O_4$ requires C, 67·1; H, 10·5%).

Bromination of Ethyl (–)-2-*Carbethoxy*-4 : 8-*dimethylnonanoate and Dehydrobromination of the* α-*Bromo-ester.*—Bromine (1·85 g.) in carbon tetrachloride (5 c.c.) was slowly added during 30 minutes to a boiling solution of ethyl (–)-2-carbethoxy-4 : 8-dimethylnonanoate (3·1 g.) in carbon tetrachloride (10 c.c.). The solution was refluxed for a further 6 hours; the carbon tetrachloride and excess of bromine were then distilled off under reduced pressure. The residual pale oil (3·9 g.) was refluxed in anhydrous pyridine (10 c.c.) for 15 hours. The mixture was then poured into dilute hydrochloric acid and the product isolated with ether. The resulting unsaturated *ester* distilled as a pale yellow oil (0·9 g.), b. p. 175°/18 mm. (Found : C, 67·1; H, 10·2. $C_{16}H_{28}O_4$ requires C, 67·6; H, 9·9%). Light absorption : Max., 2190 Å; log ε, 3·58. The product had no measurable rotation (c = 10 in Et_2O).

(+)-4 : 8-*Dimethylnonan*-2-*one*.—(–)-4 : 8-Dimethylnonan-2-ol (50 g.) was added with stirring during 1 hour to a solution of sodium dichromate (28·5 g.) in water (190 c.c.) and concentrated sulphuric acid (21 c.c.). The temperature was then raised to 90° and stirring continued for a further 2 hours. The mixture was then diluted with water and the product isolated by means of ether. Distillation gave (+)-4 : 8-*dimethylnonan*-2-*one* (45 g.), b. p. 87—92°/10 mm., $[\alpha]_D^{15}$ +2·1° (homog.) (Found : C, 77·9; H, 12·9. $C_{11}H_{22}O$ requires C, 77·7; H, 12·9%). Its *semicarbazone* crystallized from methanol in needles, m. p. 98° (Found : C, 63·2; H, 10·7; N, 19·0. $C_{12}H_{25}ON_3$ requires C, 63·45; H, 11·0; N, 18·5%).

Ethyl (–)-3-*Hydroxy*-2 : 3 : 5 : 9-*tetramethyldecanoate* (XIV).—A mixture of (+)-4 : 8-dimethylnonan-2-one (20 g.) and ethyl 2-bromopropionate (42·6 g.) in benzene (250 c.c.) was added dropwise during 2 hours to a suspension of zinc dust (16 g.) in benzene (50 c.c.) with stirring and heating under reflux. After a further 2 hours' refluxing the product was poured into dilute hydrochloric acid and worked up in the usual manner. On distillation *ethyl* (–)-3-*hydroxy*-2 : 3 : 5 : 9-*tetramethyldecanoate* (12·9 g.) was obtained, b. p. 168—172°/25 mm., $[\alpha]_D^{15}$ –0·8° (homog.) (Found : C, 70·4; H, 11·8. $C_{16}H_{32}O_3$ requires C, 70·6; H, 11·8%).

Dehydration of Ethyl (–)-3-*Hydroxy*-2 : 3 : 5 : 9-*tetramethyldecanoate*.—A solution of the preceding ester (12·8 g.) in benzene (45 c.c.) was refluxed with phosphorus oxychloride (7·7 g.) for 1·5 hours. The mixture was poured into water and the benzene layer washed repeatedly with dilute aqueous sodium hydroxide. Distillation gave the unsaturated *ester* (8·2 g.), b. p. 139—144°/12 mm., $[\alpha]_D^{17}$ –2·1° (homog.) (Found : C, 76·1; H, 11·9. $C_{16}H_{30}O_2$ requires C, 75·6; H, 11·8%). Light absorption : Max., 2100 A; log ε, 3·45. The corresponding *acid*, obtained by refluxing of the ester (2·9 g.) with potassium hydroxide (5 g.) in water (5 c.c.) and ethanol (25 c.c.) for 5 hours, had $[\alpha]_D^{17}$ –4·2° (c = 24 in Et_2O) (Found : C, 74·4; H, 11·7. $C_{14}H_{26}O_2$ requires C, 74·3; H, 11·5%). Light absorption : Max., 2100 Å; log ε, 3·43. Its S-*benzylthiuronium* salt crystallized from aqueous ethanol in leaflets, m. p. 113—114° (Found : C, 67·9; H, 9·05; N, 7·0. $C_{22}H_{36}O_2N_2S$ requires C, 67·35; H, 9·2; N, 7·1%).

The authors thank Professor Sir Robert Robinson, O.M., F.R.S., for his interest, and the Department of Scientific and Industrial Research for a Maintenance Allowance awarded to one of them (P. C. J.).

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