328. *Methyl-substituted Long-chain Acids. Part II.*

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In a previous communication (Polgar and Robinson, *J.*, 1945, 389), which is regarded as Part I of this series, it was shown that phthioic acid might be 2 : 12 : 18-trimethyltricosoic acid.* Since biological tests with the synthetic substance of this constitution indicated that, similarly to the natural acid, it produced lesions resembling those of tuberculosis, it became of interest to study the structural requirements for this effect.

The present paper reports syntheses of 2 : 12 : 18-*trimethyltricosa*-12 : 18-*dienic acid*, 2-*methyltricosoic acid*, and 2 : 12-*dimethyltricosoic acid*. It is found that 2 : 12 : 18-trimethyltricosa-12 : 18-dienoic acid also shows marked activity in producing these specific tissue reactions; 2 : 12-dimethyltricosoic acid, with the $C_{(18)}$-methyl of 2 : 12 : 18-trimethyltricosoic acid absent, is slightly active; whereas 2-methyltricosoic acid is inactive.

The preparation of 12 : 16-*dimethyltricosoic* and 12 : 15-*dimethyldocosoic acid* is also described.

Previous investigations (Polgar and Robinson, *loc. cit.*) indicated that phthioic acid is a methyl-substituted long-chain acid with three such branches, probably 2 : 12 : 18-trimethyltricosoic acid,* and this structure has been shown to be feasible by the synthesis of the substance.

* All the aliphatic acids mentioned in Part I (*J.*, 1945, 389) were numbered according to the Geneva system, $\overset{5}{C}\text{–}\overset{4}{C}\text{–}\overset{3}{C}\text{–}\overset{2}{C}\text{–}\overset{1}{CO_2H}$; undecanoic and higher acids were given the Geneva termination "anoic," but the "an" was omitted for decoic and lower acids. Nomenclature in the present and succeeding paper follows that more recently used in the Journal. The C of the CO_2H is not enumerated, numerals 1, 2, 3, etc. corresponding to α, β, γ, etc.; Greek letters are used with trivial names, numerals with names which embody a numerical root; alternatively, the hydrocarbon name terminated by a numeral and "carboxylic acid" may be used. Thus, *e.g.*, $CH_3{\cdot}CH_2{\cdot}CHBr{\cdot}CO_2H$ may be termed α-bromobutyric or 1-bromopropane-1-carboxylic acid, and $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CHBr{\cdot}CO_2H$ 1-bromohexoic or 1-bromopentane-1-carboxylic acid; the acid now termed 2 : 12 : 18-trimethyltricosoic acid was previously (*loc. cit.*) termed 3 : 13 : 19-trimethyltricosanoic acid.—Editor.

Further studies of the natural acid are in progress and have led to the conclusion that " phthioic acid " is not homogeneous. Hence our conclusions can only approximate to the truth. Meanwhile biological tests indicated that 2 : 12 : 18-trimethyltricosanoic acid exhibits activities similar to those obtained with the natural substance, whereas other methyl-substituted long-chain acids described in Part I, *e.g.*, 1 : 12-dimethylpentacosoic, 12 : 16 : 20-trimethyldocosoic, and 1 : 12 : 16 : 20-tetramethyldocosoic acid, were found to be inactive in this respect. This pointed to a high degree of structural specificity and it became necessary to study closely the effect of modifications in the structure of 2 : 12 : 18-trimethyltricosoic acid on the biological activity.

The introduction of ethylenic linkages, while otherwise retaining the structure of 2 : 12 : 18-trimethyltricosoic acid, seemed of interest in view of the possibility that dehydrogenation reactions may take place in the organism resulting in similar unsaturated intermediates. Esters of unsaturated acids with non-conjugated ethylenic linkages such as linoleic or linolenic acid are stated to be capable of producing certain tissue reactions owing to their transformation in the intercellular medium into insoluble semi-solid, amorphous substances which gradually acquire the property of retaining phenolised fuchsin with the same tenacity as do acid-fast bacilli (Hass, *Arch. Path.*, 1938, **26**, 956, 1183, 1196). Moreover, the caseation process occurring in tuberculous lesions has also been claimed earlier to be caused by the presence of unsaturated acids and it has been suggested that unsaturated fatty acids suppress the autolytic enzymes somewhat in proportion to their degree of unsaturation (Jobling and Petersen, *J. Exp. Med.*, 1914, **19**, 251, 459, and other papers). In this connexion a suggestion made by Robertson *et al.* (*J. Amer. Chem. Soc.*, 1944, **66**, 1894) is also of interest, namely, that unsaturated acids with non-conjugated ethylenic linkages are oxidation catalysts, oxidising, for example, sulphides to sulphoxides.

The synthesis of 2 : 12 : 18-*trimethyltricosa*-12 : 18-*dienoic* acid was, therefore, undertaken and it was hoped that biological examination of this acid and comparison of its action with that of the corresponding saturated acid would also throw some light upon the nature of this action.

Its synthesis was achieved in the same general way as that of the corresponding saturated acid (Part I, *loc. cit.*). The required intermediate, 12 : 18-*dimethyldocosa*-1 : 12 : 18-*triene* (I), was obtained by reaction of 6-methyldec-6-enylmagnesium bromide with tridec-12-en-2-one. It was converted by hydrogen iodide into (II) and thence by condensation with ethyl sodionalonate into *ethyl* (1 : 11 : 17-*trimethylheneicosa*-11 : 17-*dienyl*)*malonate* [2 : 12 : 18-*trimethyldocosa*-12 : 18-*diene*-1 : 1-*dicarboxylate*] (III). Hydrolysis, followed by decarboxylation, afforded the dienoic acid (IV).

(I.) $CH_3{\cdot}[CH_2]_2{\cdot}CH{:}CMe{\cdot}[CH_2]_4{\cdot}CH{:}CMe{\cdot}[CH_2]_9{\cdot}CH{:}CH_2$

(II.) $CH_3{\cdot}[CH_2]_3{\cdot}CIMe{\cdot}[CH_2]_5{\cdot}CIMe{\cdot}[CH_2]_9{\cdot}CHIMe$

(III) $CH_3{\cdot}[CH_2]_2{\cdot}CH{:}CMe{\cdot}[CH_2]_4{\cdot}CH{\cdot}CMe{\cdot}[CH_2]_9{\cdot}CHMe{\cdot}CH(CO_2Et)_2$

(IV.) $CH_3{\cdot}[CH_2]_2{\cdot}CH{:}CMe{\cdot}[CH_2]_4{\cdot}CH{:}CMe{\cdot}[CH_2]_9{\cdot}CHMe{\cdot}CH_2{\cdot}CO_2H$

Respecting the above condensation of (II) with ethyl sodiomalonate it should be noted that the tertiary carbon atoms bearing iodine are attached on each side to a methylene group so that the elimination of hydrogen iodide would be expected to occur in each of the two possible directions. Hence we are not entitled to assume that the resulting dienoic acid is homogeneous.

The preparation of 2-*methyltricosoic acid* and 2 : 12-*dimethyltricosoic acid* was then considered, in order to study the influence of omission of one or more of the methyl branches present in 2 : 12 : 18-trimethyltricosoic acid on the biological activity.

For the preparation of 2-methyltricosoic acid *docos*-1-*en*-12-*one* (V), obtained by the action of *n*-undecoyl chloride on undec-10-enylzinc iodide, was converted by hydrogen iodide into (VI); condensation with ethyl sodiomalonate, followed by hydrolysis and decarboxylation, gave 12-*keto*-2-*methyltricosoic acid* (VII) which by Clemmensen reduction afforded 2-methyltricosoic acid (VIII).

(V.) $CH_3{\cdot}[CH_2]_9{\cdot}CO{\cdot}[CH_2]_9{\cdot}CH{:}CH_2$

(VI.) $CH_3{\cdot}[CH_2]_9{\cdot}CO{\cdot}[CH_2]_9{\cdot}CHIMe$

(VII.) $CH_3{\cdot}[CH_2]_9{\cdot}CO{\cdot}[CH_2]_9{\cdot}CHMe{\cdot}CH_2{\cdot}CO_2H$

(VIII.) $CH_3{\cdot}[CH_2]_{19}{\cdot}CHMe{\cdot}CH_2{\cdot}CO_2H$

2 : 12-Dimethyltricosoic acid was synthesised by interaction of tridec-12-en-2-one with a Grignard solution from *n*-decyl bromide, to give 12-*methyldocos*-1-*en*-12-*ol* (IX) which by treat-

ment with hydrogen iodide, followed by condensation with ethyl sodiomalonate, afforded *ethyl* (1 : 11-*dimethylheneicos*-11-*enyl*)*malonate* (X). This was transformed in the usual stages into the required acid (XI).

(IX.) $CH_3 \cdot [CH_2]_9 \cdot C(OH)Me \cdot [CH_2]_9 \cdot CH{:}CH_2$

(X.) $CH_3 \cdot [CH_2]_8 \cdot CH{:}CMe \cdot [CH_2]_9 \cdot CHMe \cdot CH(CO_2Et)_2$

(XI.) $CH_3 \cdot [CH_2]_9 \cdot CHMe \cdot [CH_2]_9 \cdot CHMe \cdot CH_2 \cdot CO_2H$

Biological studies of the foregoing acids as well as those described in Part I were undertaken by Mr. C. E. Coulthard and Dr. L. Dickinson, of the Research Department of Boots Pure Drug Company, Ltd., and Dr. J. Ungar, of Glaxo Laboratories Ltd. Dr. Ungar states :

" The biological activity of these fatty acids has been studied in mice and guinea-pigs.

" In mice the acute toxicity has been controlled to determine the dose which can be safely injected without causing acute death. The substances have been injected in the form of homogeneous suspensions in 10% ethyl alcohol. In guinea-pigs the substances have been tested for their granuloma-producing properties. Different amounts of suspensions from 5 mg. to 200 mg. have been injected intraperitoneally into young guinea-pigs, and at regular intervals individual guinea-pigs were killed, and detailed *post-mortem* examinations performed. When the compounds were active we noticed after nine days the formation of small nodules, 2—3 mm. in diameter, on the omentum, and small similar nodules in the mesenterial glands and liver. After 14—18 days these nodules increased in number and size, and formed caseous lesions which greatly increased in size. After 4 weeks calcification of these nodules was already visible. In case of the more active compounds granuloma-like nodules were visible in the diaphragm and lungs. The histological sections showed pictures which resembled a specific granuloma, the primary cause of which seemed to be local necrosis. It started with a small cell infiltration with macrophages and development of epitheloid cells and giant cells of the Langerhans type." *

Of the substances described in this paper 2 : 12 : 18-trimethyltricosa-12 : 18-dienoic acid induces the above lesions when injected in a dose of 100 mg. 2 : 12-Dimethyltricosoic acid is slightly active in amounts of 50 mg. and 100 mg., and has some activity in a dose of 25 mg. 2-Methyltricosoic acid is inactive.

From these preliminary tests it is not yet possible to assess any differences in degree of activity and, in particular, further studies will be necessary to determine whether the ethylenic linkages in the above dienoic acid have any additional effect, as compared with the corresponding saturated acid.

The activity of 2 : 12-dimethyltricosoic acid seems to suggest that the $C_{(18)}$-methyl group of 2 : 12 : 18-trimethyltricosoic acid is not indispensable for the activity of the substance, but present evidence indicates that a third methyl branch, in addition to those at $C_{(2)}$ and $C_{(12)}$, is necessary in order to produce extensive lesions. Full discussion of this point must be reserved for a future communication.

The opportunity is taken to record in the Experimental section the preparations of 12 : 16-*dimethyltricosoic* and 12 : 15-*dimethyldocosoic acid*, the latter originally designed to serve as an intermediate for the preparation of its higher homologue, 13 : 16-dimethyltricosoic acid. These preparations were initiated in view of the high activity of a specimen of 12 : 15-dimethyltricosoic acid described in Part I. The work was discontinued when further investigations, to be described in a subsequent paper, indicated that this activity was probably due to the presence of a $C_{(2)}$-substituted isomer.

Experimental.

2 : 12 : 18-*Trimethyltricosa*-12 : 18-*dienoic Acid*.—12 : 18-*Dimethyldocosa*-1 : 12 : 18-*triene* (I). Ethyl 5-methyldec-5-enoate (55 g.; b. p. 125—130°), obtained by a Grignard reaction from *n*-butyl bromide and ethyl 5-ketoheptoate and dehydration of the resulting carbinol (cf. Polgar and Robinson, *loc. cit.*), was reduced by sodium (33 g.) and butyl alcohol (540 c.c.), to give 6-methyldec-6-enol (31 g.; 70% yield), b. p. 127—130°/17 mm., $n_D^{17°}$ 1·4556. This was dissolved in toluene (55 c.c.), and phosphorus tribromide (18 g., 6·3 c.c.) in toluene (55 c.c.) then added during 3 hours, with vigorous stirring while cooling in an ice–salt bath. Next day the mixture was decomposed by ice, and the bromide isolated in the usual way as a colourless oil (21 g.), b. p. 127°/17 mm., $n_D^{17°}$ 1·4780.

A solution of tridec-12-en-2-one (23·5 g.; Polgar and Robinson, *loc. cit.*) in ether (40 c.c.) was added to a Grignard compound from the above bromide (27 g.), magnesium (3·3 g.), and ether (50 c.c.), kept under nitrogen. The resulting carbinol, isolated in the usual manner, was dehydrated over a trace of iodine (170°; 2 hours) and gave a mobile oil (19 g.), a sample of which boiled, over sodium, at 176—185° (bath)/0·2 mm. affording 12 : 18-*dimethyldocosa*-1 : 12 : 18-*triene*, $n_D^{19°}$ 1·4720 (Found : C, 86·5; H, 13·5. $C_{22}H_{44}$ requires C, 86·65; H, 13·25%).

* *Added in Proof.*—Cf. *Brit. J. Exp. Path.*, 1948, **29**, 322.

Ethyl (1 : 11 : 17-*trimethylheneicosa*-11 : 17-*dienyl*)*malonate* (III). A solution of the crude diene (17·7 g.) in benzene (40 c.c.) was saturated with hydrogen iodide with cooling in ice. Next day the solvent was removed under diminished pressure at 30—40° (bath), and the residual oil added with stirring to an excess of ethyl sodiomalonate (from 7·5 g. of sodium and 70 g. of ethyl malonate) in alcohol (110 c.c.), while heating the mixture. It was kept overnight under nitrogen and then boiled under reflux for 3 hours, and the product isolated in the usual manner. After removal of substances, b. p. <150° (bath temperature)/9 mm., a viscous oil (26 g.) remained, a sample of which, on distillation, afforded *ethyl* (1 : 11 : 17-*trimethylheneicosa*-11 : 17-*dienyl*)*malonate* as a colourless oil, b. p. 206°/0·15 mm., $n_D^{17°}$ 1·4681 (Found : C, 75·7; H, 11·2. $C_{31}H_{56}O_4$ requires C, 75·6; H, 11·3%).

2 : 12 : 18-*Trimethyltricosa*-12 : 18-*dienoic acid* (IV). A sample (1·75 g.) of the foregoing malonic ester was hydrolysed by boiling it under reflux for 3 hours under nitrogen with a solution of potassium hydroxide (1 g.) in alcohol (25 c.c.), and the free acid decarboxylated on distillation in a high vacuum. This furnished 2 : 12 : 18-*trimethyltricosa*-12 : 18-*dienoic acid* as a viscous oil (1·4 g.), b. p. 210°/0·06 mm., $n_D^{19°}$ 1·4740 (Found : C, 79·1; H, 12·2. $C_{26}H_{48}O_2$ requires C, 79·5; H, 12·2%).

On hydrogenation of a sample (2·8 g.) of the above malonic ester in alcohol (100 c.c.) in the presence of Raney nickel, the theoretical amount of hydrogen ($2H_2$) was absorbed. The saturated product, hydrolysed and decarboxylated as usual, afforded 2 : 12 : 18-trimethyltricosoic acid (0·7 g.), b. p. 204°/0·25 mm., $n_D^{18°}$ 1·4590 (Found : C, 78·5; H, 12·9. Calc. for $C_{26}H_{52}O_2$: C, 78·8; H, 13·1%).

2-*Methyltricosoic Acid.*—*Docos*-1-*en*-12-*one* (V). Undec-10-enyl iodide (71 g.; b. p. 92°/0·24 mm., $n_D^{19°}$ 1·4960, obtained from undec-10-enol *via* the chloride by boiling the latter under reflux with sodium iodide in dry acetone) was added, according to the procedure of Blaise (*Bull. Soc. chim.*, 1911, [iv], **9**, pp. i—xxvi), to a mixture of toluene (41 c.c.), ethyl acetate (20 c.c.), and zinc–copper couple (37 g.), and the mixture heated under reflux for 5 hours. The mixture was then cooled with ice, and the solution decanted. A solution of undecoyl chloride (41 g.; obtained from *n*-undecoic acid by means of thionyl chloride) in toluene (25 c.c.) was introduced during 10 minutes with cooling and stirring, and the mixture decomposed by pouring it on ice. The *ketone*, isolated in the usual manner, distilled as a colourless liquid (23 g.), b. p. 190°/0·3 mm., which quickly solidified. After crystallisation from alcohol it had m. p. 53° (Found : C, 82·0; H, 13·1. $C_{22}H_{42}O$ requires C, 82·0; H, 13·1%).

Ethyl (11-*keto*-1-*methylheneicosyl*)*malonate*. The above ketone (21 g.) in benzene solution (60 c.c.) was treated in the usual way with hydrogen iodide, and the product condensed with ethyl sodiomalonate (from 3 g. of sodium, 27 c.c. of ethyl malonate, and 50 c.c. of alcohol), the mixture being heated under reflux for 5 hours. Next day the product was worked up and substances, b. p. <140°/20 mm., were removed by distillation. A portion (13·5 g.) of the residue was then distilled, affording *ethyl* (11-*keto*-1-*methylheneicosyl*)*malonate* (5 g.) as a viscous oil, b. p. 247°/0·1 mm. (Found : C, 71·9; H, 10·8. $C_{29}H_{54}O_5$ requires C, 72·2; H, 11·2%).

12-*Keto*-2-*methyltricosoic acid* (VII). This *acid* was obtained from the foregoing malonic ester by the usual successive stages (hydrolysis, decarboxylation) as a viscous oil (3·2 g.), b. p. 224°/0·1 mm., which quickly crystallised and had m. p. 64° after crystallisation from ethanol (Found : C, 75·4; H, 11·7. $C_{24}H_{46}O_3$ requires C, 75·4; H, 12·0%).

2-*Methyltricosoic acid* (VIII). To an alcoholic solution (57 c.c.) of the above keto-acid (3·1 g.) which had been saturated with hydrogen chloride was added amalgamated zinc (29 g.), and the mixture boiled under reflux for 20 hours. Further quantities of amalgamated zinc (20 g.) were then added, and the mixture was boiled under reflux for a further 24 hours, while repeatedly passing hydrogen chloride into the solution until saturation. After the excess of zinc had been removed by treatment with concentrated hydrochloric acid (50 c.c.), the mixture was poured into water and extracted with ether. On hydrolysis 2-*methyltricosoic acid* was obtained as a colourless crystalline solid, m. p. 63·5° after recrystallisation from methanol–ether (Found : C, 78·2; H, 13·1. $C_{24}H_{48}O_2$ requires C, 78·3; H, 13·1%). Its acetol ester, obtained by boiling the sodium salt with chloroacetone in alcoholic solution, furnished a *semicarbazone* (cf. Polgar, *Biochem. J.*, 1948, **42**, 207) which separated from alcohol as a white crystalline powder, m. p. 90° (Found : C, 70·2; H, 11·5; N, 8·5. $C_{28}H_{55}O_3N_3$ requires C, 69·85; H, 11·4; N, 8·7%).

2 : 12-*Dimethyltricosoic Acid.*—12-*Methyldocos*-1-*en*-12-*ol* (IX). Dodec-10-enoic acid, m. p. 18° (6 g.; obtained by reaction of a Grignard solution from undec-10-enyl iodide with solid carbon dioxide), was converted by thionyl chloride into its chloride, b.p. 150°/20 mm., which (6·4 g.) with methylzinc iodide afforded tridec-12-en-2-one (5 g.), b p. 150°/23 mm., $n_D^{22°}$ 1·4440 (another preparation of this ketone, from undec-10-enyl cyanide and methylmagnesium iodide, was described in Part I, *loc. cit.*). This ketone (7 g.) in ethereal solution (15 c.c.) was caused to react in the usual manner with a Grignard solution, prepared from *n*-decyl bromide (20 g.) and magnesium (2·7 g.) in ether (35 c.c.). The resulting *carbinol* distilled as a colourless viscous oil (8 g.), b. p. 160°/0·1 mm., $n_D^{20°}$ 1·4625 (Found : C, 81·9; H, 13·2. $C_{23}H_{46}O$ requires C, 81·7; H, 13·6%).

Ethyl (1 : 11-*dimethylheneicos*-11-*enyl*)*malonate* (X). The above carbinol (8 g.) was treated with hydrogen iodide in the manner already described, and the product condensed with ethyl sodiomalonate (from 21 c.c. of ethyl malonate and 2·2 g. of sodium in 40 c.c. of alcohol). *Ethyl* (1 : 11-*dimethylheneicos*-11-*enyl*)*malonate* was obtained as a colourless liquid (6·8 g.), b. p. 229°/0·1 mm., $n_D^{22°}$ 1·4612 (Found : C, 75·4; H, 11·6. $C_{30}H_{56}O_4$ requires C, 75·0; H, 11·7%).

2 : 12-*Dimethyltricosoic acid* (XI). The foregoing malonic ester (16·7 g.) was hydrogenated in alcoholic solution (34 c.c.) in the presence of palladised barium sulphate at room temperature and normal pressure. The saturated product afforded, by hydrolysis and decarboxylation of the free acid in the usual way, 2 : 12-*dimethyltricosoic acid* as a colourless oil (4·2 g.), b. p. 212—218°/0·7 mm. (Found : C, 79·0; H, 12·9. $C_{25}H_{50}O_2$ requires C, 78·5; H, 13·1%). The 2 : 4-*dinitrophenylsemicarbazone* of its acetol ester crystallised from a mixture of benzene and alcohol as a pale yellow powder, m. p. 125—127° (Found : N, 10·8. $C_{35}H_{59}O_7N_5$ requires N, 10·6%).

12 : 15-*Dimethyldocosoic Acid.*—11 : 14-*Dimethyleicos*-1-*en*-11-*ol*. Ethyl 1-methylheptylidenecyanoacetate [1-cyano-2-methylnon-1-enoate] [72 g.; obtained from methyl hexyl ketone and ethyl cyanoacetate in 88% yield by the method of Cope *et al.* (*J. Amer. Chem. Soc.*, 1941, **63**, 3452)], b. p. 159—

160°/12 mm., was hydrogenated (alcoholic solution, palladised strontium carbonate), and the reduced product hydrolysed as described previously (cf. Part I, section 5-Methyldecoic Acid, p. 393). Decarboxylation of the free acid afforded 2-methylnonoic acid (43 g.), b. p. 140°/12 mm., $n_D^{16°}$ 1·4362 (Found : C, 69·6; H, 11·6. Calc. for $C_{10}H_{20}O_2$: C, 69·8; H, 11·6%). The butyl ester (56 g.) of this acid on reduction with sodium and butyl alcohol gave 3-methylnonanol (28 g.), b. p. 110—117°/13 mm., which was converted into its bromide (29 g.), b. p. 110°/27 mm. The Grignard solution, prepared from this bromide (29 g.) and magnesium (3·5 g.) in ether (85 c.c.) was then brought to reaction with dodec-11-en-2-one (30 g.) in ether (50 c.c.) in the usual way, yielding 11 : 14-*dimethyleicos*-1-*en*-11-*ol* (18 g.) as a viscous oil, b. p. 175°/0·2 mm., $n_D^{22°}$ 1·4590 (Found : C, 81·0; H, 13·3. $C_{22}H_{44}O$ requires C, 81·5; H, 13·6%).

12 : 15-*Dimethyldocosoic acid.* The foregoing carbinol was dehydrated over iodine, as described in previous preparations, to the diene (16·2 g.), b. p. 164°/0·1 mm. Treatment with hydrogen bromide in the presence of benzoyl peroxide (0·1 g.) in toluene solution (160 c.c.), followed by condensation with ethyl sodiomalonate and the usual successive stages, afforded the unsaturated *acid* (8 g.), b. p. 202°/0·05 mm., $n_D^{18°}$ 1·4642 (Found : C, 78·4; H, 12·6. $C_{24}H_{46}O_2$ requires C, 78·6; H, 12·5%). This was esterified by heating it under reflux with methanol (100 c.c.) and acetyl chloride (5 c.c.; cf. Jakob and Freudenberg, *Ber.*, 1941, **74**, 1001), and the resulting methyl ester (7·9 g.), b. p. 197°/0·3 mm., hydrogenated in alcoholic solution (34 c.c.) in the presence of palladised barium sulphate. Hydrolysis gave the saturated acid, which was purified by converting it into its acetol ester and thence into the *semicarbazone*. This derivative was obtained as a white crystalline powder (3·2 g.), m. p. 70° after recrystallisation from alcohol (Found : C, 69·6; H, 11·4. $C_{28}H_{55}O_3N_3$ requires C, 69·7; H, 11·6%). The semicarbazone was then boiled under reflux with alcoholic potassium hydroxide, and the acidified product isolated by means of ether. Removal of the solvent gave 12 : 15-*dimethyldocosoic acid* which crystallised from methanol in long needles, m. p. 43° (Found : C, 78·8; H, 13·2. $C_{24}H_{48}O_2$ requires C, 78·3; H, 13·0%).

The portion of the above semicarbazone which remained in the mother-liquor from the crystallisation of the crude product was isolated by adding water and collecting the separated oil with ether. The free acid, obtained on hydrolysis, distilled as a viscous liquid (1·6 g.), b. p. 208°/0·6 mm. (Found : C, 77·4; H, 12·6%), which probably is mainly 2 : 11 : 14-trimethylheneicosoic acid, expected to arise by addition of hydrogen bromide to the diene in the previous stage, if it proceeds in accordance with Markownikow's rule.

12 : 16-*Dimethyltricosoic Acid.*—4-*Methyldecanol.* 3-Methyldecoic acid (Part I, *loc. cit.*) was converted into its *methyl* ester by boiling the acid (17·7 g.) under reflux with dry methanol (100 c.c.) and acetyl chloride (5 c.c.) for 6 hours. The isolated product (16 g., or 84%) had b. p. 111°/13 mm., $n_D^{13°}$ 1·4326 (Found : C, 72·0; H, 12·05. $C_{12}H_{24}O_2$ requires C, 72·0; H, 12·0%). Reduction of the ester by means of sodium and butanol afforded 4-*methyldecanol* (11 g.), b. p. 115°/9 mm., $n_D^{17°}$ 1·4420 (Found : C, 76·2; H, 14·0. $C_{11}H_{24}O$ requires C, 76·7; H, 14·0%).

Dimethylheneicos-1-*en*-11-*ol.* The above alcohol was converted into its bromide, b. p. 122°/14 mm., and a Grignard solution from the latter (11 g.) brought to reaction in the usual manner with dodec-11-en-2-one (10 g.). 11 : 15-*Dimethylheneicos*-1-*en*-11-*ol* was obtained as a viscous oil (4 g.), b. p. 170—173°/0·2 mm. (Found : C, 81·2; H, 13·5. $C_{23}H_{46}O$ requires C, 81·6; H, 13·6%).

12 : 16-*Dimethyltricosoic acid.* The foregoing carbinol was dehydrated over iodine (190°; 2 hours), and the crude diene then subjected to the treatment with hydrogen bromide in the presence of benzoyl peroxide, followed by condensation with ethyl sodiomalonate and the usual successive stages. The resulting unsaturated acid (2 g.), b. p. 200°/0·06 mm., furnished on hydrogenation (alcohol solution, palladised barium sulphate) 12 : 16-*dimethyltricosoic acid*, b. p. 202°/0·2 mm., $n_D^{18°}$ 1·4620 (Found : C, 78·0; H, 12·9. $C_{25}H_{50}O_2$ requires C, 78·5; H, 13·1%). The acetol ester of this acid gave on treatment with semicarbazide acetate an oil; it furnished a 2 : 4-*dinitrophenylsemicarbazone* as a pale yellow crystalline product, m. p. 130° after crystallisation from alcohol (Found : C, 63·5; H, 8·9. $C_{35}H_{59}O_7N_5$ requires C, 63·2; H, 8·5%).

Side-chain methyl determination of the acid by the Kuhn–Roth method gave 1·8 molecules of acetic acid; however, by analogy with the preceding preparation the acid probably contains a $C_{(2)}$-substituted isomer. The amount obtained was insufficient for further examination.

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