20. *Experiments relating to Phthiocerol. Part II.* Synthesis of (+)-6-Methoxy-6-methylnonanoic Acid.*

By J. W. Lewis and N. Polgar.

(+)-6-Methoxy-6-methylnonanoic acid has been synthesised, with (+)-2-methoxy-2-methylpentanoic and (+)-6-methoxy-6-methyl-5-oxononanoic acid as intermediates. The synthetic acid is not the enantiomer of the lævorotatory C_{11} methoxy-acid arising on oxidation of phthiocerol.

Earlier work [1] showed that phthiocerol, on oxidation with chromic acid, affords *n*-tetracosanoic acid together with a C_{11} methoxy-acid. The isolation of these oxidation products, together with other evidence which included the formation of a β-diketone by mild oxidation of phthiocerol, indicated that the latter is a tetratriacontane-9 : 11-diol containing a methyl and a methoxyl group, probably both attached at $C_{(4)}$ (cf. I). This suggested that the C_{11} oxidation product (found to be lævorotatory [2]) might be 6-methoxy-6-methylnonanoic acid (II), and it was of interest to prepare an optically active specimen of this acid for comparison. The present communication records the synthesis of its (+)-form.

(I) $CH_3 \cdot [CH_2]_{22} \cdot CH(OH) \cdot CH_2 \cdot CH(OH) \cdot [CH_2]_4 \cdot CMe(OMe) \cdot [CH_2]_2 \cdot CH_3$

(II) $CH_3 \cdot [CH_2]_2 \cdot CMe(OMe) \cdot [CH_2]_4 \cdot CO_2H$

The starting material was pentan-2-one which was converted, *via* its cyanohydrin (III), into methyl 2-hydroxy-2-methylpentanoate (IV); the latter was treated with methyl iodide–silver oxide. Only partial methylation occurred and after three repetitions of this procedure the product still contained unchanged hydroxy-ester. Pure 2-methoxy-2-methylpentanoic acid (V) was obtained from this mixture by hydrolysis, and treatment of the liberated acids with lead tetra-acetate: this left the α-methoxy-acid unchanged, but converted the α-hydroxy-acid into pentan-2-one. In further experiments it was found that the methoxy-acid can be readily separated from the hydroxy-acid by crystallisation of the quinine salts from acetone. Moreover, the quinine salt derived from the methoxy-acid also proved satisfactory for the resolution of the latter, affording the (+)-enantiomer, $[\alpha]_D$ +24·3°.

(III) $CH_3 \cdot [CH_2]_2 \cdot CMe(OH) \cdot CN$ $\quad$ $CH_3 \cdot [CH_2]_2 \cdot CMe(OH) \cdot CO_2Me$ (IV)

(V) $CH_3 \cdot [CH_2]_2 \cdot CMe(OMe) \cdot CO_2H$ $\quad$ $CH_3 \cdot [CH_2]_2 \cdot CMe(OMe) \cdot CH_2 \cdot OH$ (VI)

We then turned to the conversion of the (+)-enantiomer of 2-methoxy-2-methylpentanoic acid (V) into the higher homologue (II). The malonic ester method was examined first. In a model experiment the acid (V) was converted, by reduction with lithium aluminium hydride, into 2-methoxy-2-methylpentan-1-ol (VI), and this into its toluene-*p*-sulphonate. Condensation with ethyl sodiomalonate, followed by hydrolysis of the resulting substituted malonic ester, then gave only small amounts of acidic material; moreover, on attempted decarboxylation of the latter the product contained according to its infrared spectrum a γ-lactone and no methoxyl group.

Then (+)-2-methoxy-2-methylpentanoic acid (V) was converted into the acid chloride which, with ethyl sodio-acetoacetate, followed by sodium methoxide (cf. Ställberg-Stenhagen and Stenhagen [3]), afforded (+)-(methyl 4-methoxy-4-methyl-3-oxoheptanoate) (VII). The sodio-derivative of this ester, on reaction with ethyl β-iodopropionate under the conditions described by Ställberg-Stenhagen and Stenhagen,[3] followed by hydrolysis

* Part I, *J.*, 1955, 3971.

[1] Hall, Lewis, and Polgar, *J.*, 1955, 3971.

[2] Drayson, Lewis, and Polgar, unpublished work.

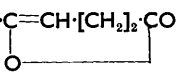
[3] Ställberg-Stenhagen and Stenhagen, *Arkiv Kemi, Min., Geol.*, 1944, **19**. *A*, No. 1; and later papers.

and ketonic cleavage, gave (+)-6-methoxy-6-methyl-5-oxononanoic acid (VIII), $[\alpha]_D$ +20·2°.

It remained to convert the keto-acid (VIII) into the deoxy-acid (II). An attempt to reduce the keto-acid by the Wolff–Kishner (Huang-Minlon) procedure cleaved the methoxyl group with the formation of unsaturated material (cf. the formation of olefins noted [4] on Wolff–Kishner reduction of α-ketols). Removal of the keto-group by preparation of a thioketal, followed by treatment with Raney nickel,[5] also failed owing to loss of the methoxyl group during the formation of the thioketal. Finally the enol lactone (IX), obtained from the (+)-form of the acid (VIII) by the action of acetic anhydride and sodium acetate,[7] passed on hydrogenation [6] into the acid (II), $[\alpha]_D$ +2·8°.

(VII) $CH_3\cdot[CH_2]_2\cdot CMe(OMe)\cdot CO\cdot CH_2\cdot CO_2Me$

(VIII) $CH_3\cdot[CH_2]_2\cdot CMe(OMe)\cdot CO\cdot[CH_2]_3\cdot CO_2H$

(IX) 

This acid and the C_{11} oxidation product of phthiocerol showed differences in their infrared absorption spectra, and in m. p. and *X*-ray powder photographs (kindly taken by Mrs. D. M. Hodgkin, F.R.S.) of their *S*-benzylthiuronium salts. A notable feature in the infrared spectra was a difference in the position of the bands attributable to the methoxyl group: the synthetic acid, possessing a tertiary methoxyl group, absorbed at 1075 cm.$^{-1}$, whereas the oxidation product showed a band at 1093 cm.$^{-1}$. It is noteworthy that this band corresponded to the position found in another investigation [8] for branched-chain aliphatic compounds with a secondary methoxyl group. Experiments designed to obtain further evidence by degradation of the C_{11} oxidation product will be described later.

Experimental

Optical rotations were determined for homogeneous liquids in a 0·5-dm. tube, and infrared spectra for natural films, unless otherwise stated.

Pentan-2-one Cyanohydrin (III).—Pentan-2-one (400 g.) was added to a solution of sodium pyrosulphite (750 g.) in water (400 c.c.), and the precipitated bisulphite compound collected. To an ice-cooled, stirred suspension of the latter in a little water a solution of potassium cyanide (700 g.) in water (800 c.c.) was gradually added, and stirring continued for 1 hr.; the upper layer was then separated. The aqueous mixture was extracted with ether, and the dried ($MgSO_4$) extract evaporated (before all the ether had been removed, 10 c.c. of sulphuric acid were added). Distillation of the combined liquids through a Vigreux column (20 c.c.) afforded, after a forerun (90 g.; mainly pentan-2-one), *n*-pentan-2-one cyanohydrin (410 g.; 78%), b. p. 102°/19 mm., n_D^{18} 1·4207. Ultée [9] gives b. p. 100°/21 mm. and n_D^{13} 1·42585.

Methyl 2-Hydroxy-2-methylpentanoate (IV).—A mixture of the above cyanohydrin (170 g., 1·5 mol.), dry methanol (56 g., 1·75 mol.), light petroleum (b. p. 40—60°; 100 c.c.), and dry ether (100 c.c.) was saturated with dry hydrogen chloride at 0°. The resulting homogeneous mixture was left overnight in a refrigerator; the imidoate hydrochloride crystallised. The crystals were collected, washed with light petroleum, and, without further purification, decomposed with water (300 c.c.). The crude product, isolated by ether-extraction, was distilled through a Vigreux column (30 c.c.) to give methyl 2-hydroxy-2-methylpentanoate (91 g.), b. p. 70—70·5°/19 mm., n_D^{20} 1·4193, and a higher-boiling fraction, b. p. 72—103°/19 mm. (45 g.; largely unchanged cyanohydrin); the latter, on repetition of the above methanolysis procedure, gave further amounts of the hydroxy-ester. Heilmann [10] gives b. p. 65—66°/15 mm. for methyl 2-hydroxy-2-methylpentanoate obtained by a different procedure.

[4] Barton and Robinson, *J.*, 1954, 3045; and the literature quoted there.
[5] Wolfrom and Karabinos, *J. Amer. Chem. Soc.*, 1944, **66**, 909; Hauptmann, *ibid.*, 1947, **69**, 562.
[6] Cf. Jacobs and Scott, *J. Biol. Chem.*, 1930, **87**, 601; 1931, **93**, 139.
[7] Cf. Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223.
[8] Morgan and Polgar, unpublished work.
[9] Ultée, *Rec. Trav. chim.*, 1909, **28**, 1.
[10] Heilmann, *Bull. Soc. chim. France*, 1929, **45**, 412.

2-Methoxy-2-methylpentanoic Acid (V).—The preceding hydroxy-ester (32·5 g.) was refluxed with methyl iodide (50 c.c.) and silver oxide (78 g.; added in five portions during 7 hr.). The mixture was filtered while hot, and the silver salts, after being washed with ether, were extracted with hot chloroform. Removal of the solvents gave a product which showed a weak band at 1087 cm.$^{-1}$ (OMe) and strong hydroxyl absorption. After three further methylations by the above procedure the product was hydrolysed by refluxing it with aqueous-methanolic (1 : 5) potassium hydroxide (8%); the bulk of the methanol was then removed, and the liberated acid isolated by ether-extraction. A 13-g. portion of this product was dissolved in dry benzene (200 c.c.) and oxidised by lead tetra-acetate (11 g.; added in two portions) at 60° (bath) for 3 hr. The mixture was then acidified with hydrochloric acid, and the product isolated by separation of the benzene layer and extraction of the aqueous phase with ether. Distillation of the combined organic layers gave *2-methoxy-2-methylpentanoic acid* (6 g.), b. p. 117°/25 mm. (Found: C, 57·6; H, 10·0. $C_7H_{14}O_3$ requires C, 57·5; H, 9·7%).

Resolution of 2-Methoxy-2-methylpentanoic Acid.—In a preliminary experiment a 0·95-g. sample of the crude acid, resulting from two methylations of methyl 2-hydroxy-2-methylpentanoate and subsequent hydrolysis as described in the preceding section, was dissolved in hot acetone (10 c.c.), and quinine (2·2 g.) was gradually added; the resulting solution was filtered and left overnight. The quinine salt which separated as fine needles was recrystallised from acetone, then decomposed with dilute hydrochloric acid: the liberated acid was isolated by ether-extraction and distillation. Its infrared spectrum showed a strong methoxyl band, and no absorption due to the presence of hydroxyl.

The above procedure was used to prepare the quinine salt from a larger batch of the acid (160 g.). After seven recrystallisations of the quinine salt (261 g.) from acetone, the regained acid (12·2 g.) had α_D^{14} +12·09°. This was again converted into the quinine salt which after one recrystallisation from acetone gave acid (7·5 g.) having α_D^{14} +12·26°, $[\alpha]_D^{14}$ +24·04°. The mother-liquors of the last recrystallisation of the quinine salt yielded 3·8 g. of acid having α_D^{14} +11·3°. This was converted into the quinine salt which after two recrystallisations gave acid (0·92 g.) with $\alpha_D^{9·5}$ +12·80°, $\alpha_D^{11·5}$ +12·64°. A further formation and recrystallisation of the quinine salt gave on decomposition the (+)-acid (0·42 g.), $\alpha_D^{11·5}$ +12·65°, α_D^{15} +12·39°, $[\alpha]_D^{15}$ +24·30°.

2-Methoxy-2-methylpentan-1-ol (VI).—2-Methoxy-2-methylpentanoic acid (5·3 g.) in ether (50 c.c.) was added slowly to a solution of lithium aluminium hydride (3·2 g.) in ether (150 c.c.). The mixture was kept at the room temperature for 1·5 hr., then refluxed for 1 hr. The excess of lithium aluminium hydride was decomposed by ethyl acetate (10 c.c.), and water (10 c.c.) and dilute hydrochloric acid (50 c.c.) were added. The ether layer was separated, and the aqueous layer was extracted with ether. The combined ethereal solutions were washed with 5% aqueous potassium hydroxide, and then with water, dried ($MgSO_4$), and distilled, to give *2-methoxy-2-methylpentan-1-ol* (4 g.), b. p. 95—98°/45 mm. (Found: C, 63·6; H, 12·4. $C_7H_{16}O_2$ requires C, 63·6; H, 12·1%).

Attempted Malonic Ester Condensation.—Dry pyridine (4·8 g.) was added with stirring under exclusion of moisture to an ice-cold mixture of 2-methoxy-2-methylpentan-1-ol (3·8 g.) and toluene-*p*-sulphonyl chloride (6·1 g.) during 0·5 hr., and stirring continued for a further hour. After acidification with dilute hydrochloric acid, the mixture was extracted with ether, and the product resulting on evaporation of the extract dried azeotropically (benzene), giving crude 2-methoxy-2-methylpentyl toluene-*p*-sulphonate (7·9 g.) (Found: S, 11·2. $C_{14}H_{22}O_4S$ requires S, 11·2%). This ester (6 g.) was refluxed with ethyl sodiomalonate (from 0·52 g. of sodium, 4·4 g. of ethyl malonate, and 40 c.c. of ethanol) and sodium iodide (5 g.) for 20 hr. After acidification with dilute hydrochloric acid, the product was isolated with the aid of ether, then refluxed with 25% aqueous-methanolic (1 : 1) potassium hydroxide for 4 hr. The solution was acidified and extracted with ether, and the acid fraction (1·3 g.) removed from the ethereal solution with 10% aqueous potassium hydroxide. Decarboxylation of the liberated acid at 150—170° (bath), followed by distillation, yielded a product which showed in its infrared spectrum a band at 1761 cm.$^{-1}$ (γ-lactone), but no bands due to a carboxyl or methoxyl group.

Methyl 4-Methoxy-4-methyl-3-oxoheptanoate (VII).—Thionyl chloride (10·75 g.) in benzene (40 c.c.) was added to an ice-cold mixture of 2-methoxy-2-methylpentanoic acid (10·15 g.) with pyridine (8·8 g.) and benzene (20 c.c.), and the solution was set aside for 1 hr. The solvent and excess of thionyl chloride were removed under reduced pressure at 50° (bath); more benzene was added and, after decantation of the benzene solution from the residue, the process was repeated. The resulting acid chloride in benzene (20 c.c.) was then refluxed for 1 hr. with

ethyl sodioacetoacetate (obtained by refluxing 10·4 g. of ethyl acetoacetate, 1·7 g. of granulated sodium, and 120 c.c. of benzene for 3 hr.). The product was poured into ice-cold dilute sulphuric acid, and the benzene layer separated; the aqueous phase was extracted with ether, and the combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated. The residue (13·5 g.) was kept with sodium (2·1 g.) in dry methanol (75 c.c.) at the room temperature for 6 hr. Acidification and ether-extraction, followed by distillation, gave *methyl 4-methoxy-4-methyl-3-oxoheptanoate* (7·2 g.), b. p. 123—125°/24 mm., n_D^{17} 1·4363 (Found: C, 59·6; H, 8·7. $C_{10}H_{18}O_4$ requires C, 59·4; H, 8·9%).

(+)-2-Methoxy-2-methylpentanoic acid (7·5 g.; α_D^{14} +12·26°) gave by the above procedure the (+)-keto-ester (5·38 g.), α_D^{20} +16·57°.

6-Methoxy-6-methyl-5-oxononanoic Acid (VIII).—Methyl 4-methoxy-4-methyl-3-oxoheptanoate (7·07 g.) was refluxed with ethyl β-iodopropionate (7·95 g.), anhydrous potassium carbonate (10 g.), and dry pentan-2-one (70 c.c.) for 18 hr. After addition of water, the mixture was extracted with ether, and the extract washed with water, and dried ($MgSO_4$); the solvents were then removed under reduced pressure. The residue was kept at room temperature with a solution of potassium hydroxide (10 g.) in water (20 c.c.) and methanol (200 c.c.) for 18 hr. Removal of the bulk of the methanol, followed by acidification, ether-extraction, and distillation gave *6-methoxy-6-methyl-5-oxononanoic acid* (3·12 g.), b. p. 185—190°/23 mm., n_D^{20} 1·4525 (Found: C, 61·0; H, 9·5; OMe, 14·35. $C_{11}H_{20}O_4$ requires C, 61·1; H, 9·2; OMe, 14·35%).

The (+)-form of methyl 4-methoxy-4-methyl-3-oxoheptanoate gave by the same procedure (+)-6-methoxy-6-methyl-5-oxononanoic acid, b. p. 138—139°/0·9 mm., $[\alpha]_D^{19\cdot5}$ +20·2° (*c* 10·07 in Et_2O).

Attempted Reduction of the Keto-acid.—(i) The keto-acid (1·3 g.), when heated with potassium hydroxide (1 g., 85%) hydrazine hydrate (4 g.), and triethylene glycol (20 c.c.) according to the Huang-Minlon procedure,[11] gave on acidification and distillation of the product unsaturated material (Found: C, 69·9; H, 10·5. Calc. for $C_{10}H_{18}O_2$: C, 70·6; H, 10·6%).

(ii) The keto-acid (0·5 g.) was kept with ethanethiol (0·9 g.), freshly fused zinc chloride (0·5 g.), anhydrous magnesium sulphate (2 g.), and benzene (10 c.c.) at the room temperature for 3 hr.; the mixture was then poured into water, and the product isolated by ether-extraction. It showed no methoxyl band in the infrared spectrum.

3 : 4-Dihydro-6-(1-methoxy-1-methylbutyl)-2-pyrone (IX).—A partially active sample of 6-methoxy-6-methyl-5-oxononanoic acid (2 g.; $\alpha_D^{19\cdot5}$ +6·55°, obtained by the procedure described from incompletely resolved starting material) was refluxed with acetic anhydride (30 c.c.) and anhydrous sodium acetate (3 g.) for 18 hr., then poured into water, and extracted with ether; the extract was washed with aqueous sodium carbonate, then with water, dried ($MgSO_4$), and evaporated. Distillation of the residue gave the partially active *enol-lactone* (1·4 g.), b. p. 145—147°/14 mm., $n_D^{19\cdot5}$ 1·4691, α_D^{16} +5·35° (Found: C, 66·2; H, 9·0. $C_{11}H_{18}O_3$ requires C, 66·7; H, 9·1%).

(+)-6-Methoxy-6-methyl-5-oxononanoic acid gave by the same procedure the (+)-enol-lactone with $[\alpha]_D^{19}$ +19·5° (*c* 9·25 in Et_2O).

6-Methoxy-6-methylnonanoic Acid (II).—The above (+)-enol-lactone gave, on hydrogenation in ethanol at atmospheric pressure and room temperature in the presence of platinic oxide, *(+)-6-methoxy-6-methylnonanoic acid*, b. p. 190—200° (bath)/15 mm., $n_D^{22\cdot5}$ 1·4428, $[\alpha]_D^{20\cdot5}$ +2·8° (*c* 6·38 in Et_2O) (Found: C, 65·1; H, 11·0. $C_{11}H_{22}O_3$ requires C, 65·3; H, 10·9%). Its *S-benzylthiuronium salt* crystallised from ethanol–water (1 : 2) as colourless needles, m. p. 135° (Found: C, 62·3; H, 8·6; N, 7·4. $C_{19}H_{32}O_3N_2S$ requires C, 62·0; H, 8·7; N, 7·6%). On admixture with the *S*-benzylthiuronium salt (m. p. 137—139°) of the C_{11} oxidation product of phthiocerol, the m. p. was 131—133°.

We thank Mrs. D. M. Hodgkin, F.R.S., for the *X*-ray studies, and the Department of Scientific and Industrial Research for a maintenance award (to J. W. L.).

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, August 27th*, 1957.]

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