76. *Experiments Relating to Phthiocerol. Part III.*[1] *Degradative Studies of a C_{11} Oxidation Product of Phthiocerol.*

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New degradative evidence shows that the C_{11} methoxy-acid arising on oxidation of phthiocerol [2] is 7-methoxy-6-methylnonanoic acid (III); this structure has been proved by conversion of the methoxy-acid into 6-methyl-7-oxononanoic acid (V). The latter was synthesised *via* 4-methylhept-6-en-3-one (VIII) by addition of hydrogen bromide catalysed by peroxide, followed by condensation of the resulting bromide (IX) with ethyl sodiomalonate.

These and earlier results [2] indicate that phthiocerol is essentially 3-methoxy-4-methyl-*n*-tetratriacontane-9 : 11-diol (VI).

The synthetical investigation reported in Part II [1] showed that the structure of the C_{11} methoxy-acid previously obtained [2] on oxidation of phthiocerol, and provisionally formulated as 6-methoxy-6-methylnonanoic acid (I), required revision. Degradative studies of the C_{11} methoxy-acid are now described.

In the earlier work, the C_{11} methoxy-acid was obtained in amounts which were insufficient for further studies. After various attempts to improve the isolation, the methyl ester of the C_{11} acid was obtained in reasonable yields by fractional distillation of the methyl esters of the crude mixture of acids resulting on oxidation of phthiocerol; the C_{11} acid is lævorotatory.

Demethylation of the C_{11} methoxy-acid with hot acetic anhydride–toluene-*p*-sulphonic acid (cf. Huffmann and Lott [3]) afforded a mixture of the corresponding acetoxy-acid and an unsaturated acid showing an infrared band at 966 cm.$^{-1}$ (*trans*-CH=CH). Under the same conditions, 6-methoxy-6-methylnonanoic acid [1] (I), possessing a tertiary methoxyl group, was demethylated to a product which did not absorb in the 966 cm.$^{-1}$ region; moreover, it contained no acetoxy-group. These comparative experiments indicated the presence of the grouping $\cdot CH_2\cdot CH(OMe)\cdot$ in the C_{11} oxidation product.

When the methyl ester of the C_{11} oxidation product was treated with acetic anhydride and toluene-*p*-sulphonic acid under less vigorous conditions, it was converted into the acetoxy-ester which was hydrolysed to the corresponding hydroxy-acid. This was esterified, and then oxidised with chromic acid: the product consisted of an oxo-ester, together with unoxidised material. Hence the hydroxyl group must have been secondary.

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

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

The provisional formula (I) already mentioned for the C_{11} oxidation product of phthiocerol was based upon the structure (II) earlier suggested [2] for phthiocerol with the methoxyl and the methyl group both at $C_{(4)}$. Among the evidence advanced for this structure was the formation of a halogen-free product on refluxing phthiocerol with a solution of hydrogen bromide in glacial acetic acid, followed by treatment of the resulting bromo-derivative with zinc and sodium iodide in acetone; this suggested that removal

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[1] Part II, Lewis and Polgar, *J.*, 1958, 102.

[2] Part I, Hall, Lewis, and Polgar, *J.*, 1955, 3971.

[3] Huffmann and Lott, *J. Biol. Chem.*, 1948, **172**, 789.

of the methoxyl group by the action of hydrogen bromide gave rise to an intermediate tertiary bromide which readily underwent elimination of the elements of hydrogen bromide during the above procedure. A tertiary bromide could also have arisen, however, by rearrangement during the demethylation according to the scheme

$$\cdot CHMe\cdot CH(OMe)\cdot \longrightarrow \cdot CMeBr\cdot CH_2\cdot$$

which is analogous to the known conversion of 1 : 2-dimethylpropyl alcohol by reaction with hydrogen chloride into 1 : 1-dimethylpropyl chloride.[4] On the basis of this interpretation, the earlier evidence [2] would also satisfy modifications of the structure (II) for phthiocerol in which the methoxyl group is placed at $C_{(3)}$ or $C_{(5)}$; the C_{11} oxidation product would then have structure (III) or (IV), respectively. A decision in favour of (III) was reached as follows:

(III) $CH_3\cdot CH_2\cdot CH(OMe)\cdot CHMe\cdot[CH_2]_4\cdot CO_2H$
(IV) $CH_3\cdot[CH_2]_2\cdot CHMe\cdot CH(OMe)\cdot[CH_2]_3\cdot CO_2H$

The oxo-ester obtained on oxidation of the demethylated product with chromic acid (see above) was hydrolysed, and the oxo-acid treated with acetic anhydride and sodium acetate under conditions known [5] to convert δ-oxo-acids into enol lactones; however, the infrared spectrum of the product showed the absence of enol-lactonic absorption, thus indicating that the acid was not a δ-oxo-acid. This argued against the presence of methoxyl in the δ-position of the parent-methoxy-acid as in formula (IV), and pointed to the alternative structure (III). The oxo-acid which resulted from the methoxy-acid by the procedures described is then 6-methyl-7-oxononanoic acid (V).

The work so far described (completed in 1956 [6]) indicated, therefore, that the formula (II) for phthiocerol requires a modification by moving the methoxyl group from $C_{(4)}$ to $C_{(3)}$; hence phthiocerol is 3-methoxy-4-methyltetratriacontane-9 : 11-diol (VI).

(V) $CH_3\cdot CH_2\cdot CO\cdot CHMe\cdot[CH_2]_4\cdot CO_2H$
(VI) $CH_3\cdot[CH_2]_{22}\cdot CH(OH)\cdot CH_2\cdot CH(OH)\cdot[CH_2]_4\cdot CHMe\cdot CH(OMe)\cdot CH_2\cdot CH_3$

In further experiments the oxo-ester, isolated with the aid of Girard's P reagent, was found to have $[\alpha]_D$ +2·2°, and to yield on alkaline hydrolysis optically inactive oxo-acid; evidently racemisation has taken place owing to the presence of the asymmetric centre adjacent to the oxo-group. Structure (V) was eventually confirmed by comparison of the oxo-acid and its ethyl ester 2 : 4-dinitrophenylhydrazone with synthetic specimens. 6-Methyl-7-oxononanoic acid (V) was synthesised as follows:

The acid chloride from 2-methylpent-4-enoic acid [7] (VII) with ethylzinc iodide gave 4-methylhept-6-en-3-one (VIII). This ketone, by addition of hydrogen bromide in presence of peroxide as catalyst, followed by treatment of the crude bromide (IX) with ethyl sodiomalonate, gave ethyl 2-ethoxycarbonyl-6-methyl-7-oxononanoate (X). Hydrolysis of the latter, followed by decarboxylation of the liberated acid, afforded 6-methyl-7-oxononanoic acid (V).

(VII) $HO_2C\cdot CHMe\cdot CH_2\cdot CH{=}CH_2$
(VIII) $CH_3\cdot CH_2\cdot CO\cdot CHMe\cdot CH_2\cdot CH{=}CH_2$
(IX) $CH_3\cdot CH_2\cdot CO\cdot CHMe\cdot[CH_2]_3\cdot Br$
(X) $CH_3\cdot CH_2\cdot CO\cdot CHMe\cdot[CH_2]_3\cdot CH(CO_2Et)_2$

Ryhage, Stenhagen, and von Sydow [8] have proposed structure (XI) for phthiocerol from mass spectrometric studies, whereas Demarteau-Ginsburg,[9] referring to the studies

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[4] Whitmore and Johnston, *J. Amer. Chem. Soc.*, 1938, **60**, 2265.

[5] Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223; see also ref. 1.

[6] Lewis, D.Phil. Thesis, Oxford, 1956.

[7] Ställberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1946, **23**, *A*, No. 15; Fray and Polgar, *J.*, 1956, 2036.

[8] Ryhage, Stenhagen, and von Sydow, *Acta Chem. Scand.*, 1957, **11**, 180.

[9] Demarteau-Ginsburg, *Compt. rend.*, 1956, **243**, 2169.

of the Swedish investigators, suggests that phthiocerol is an approximately equimolecular mixture of compounds (VI) and (XI). These suggestions are not compatible with the formation of the C_{11} methoxy-acid as an oxidation product, and its conversion into 6-methyl-7-oxononanoic acid as shown above.

(XI) $CH_3{\cdot}[CH_2]_{20}{\cdot}CH(OH){\cdot}CH_2{\cdot}CH(OH){\cdot}[CH_2]_6{\cdot}CHMe{\cdot}CH(OMe){\cdot}CH_2{\cdot}CH_3$

EXPERIMENTAL

Infrared spectra were determined on liquid films except where otherwise stated. Optical rotations were measured in a 0·5-dm. tube.

Isolation of the C_{11} *Methoxy-acid and its Methyl Ester.*—In the earlier work the following procedure was employed: chromium trioxide (6 g.) in water (6 c.c.) and glacial acetic acid (20 c.c.) was gradually added to phthiocerol (5 g.) in glacial acetic acid (40 c.c.), and the mixture heated on a steam-bath for 1 hr.; ethanol (10 c.c.) was then added to the cooled mixture. Most of the acetic acid was removed by distillation under reduced pressure, and the residue, after addition of dilute hydrochloric acid, was extracted with ether. Evaporation of the extract, followed by distillation of the product in steam, and isolation of the steam-volatile material by ether-extraction, gave the C_{11} methoxy-acid (0·31 g.), b. p. 190—200° (bath)/20 mm., n_D^{21} 1·4432, $[\alpha]_D^{17}$ −3·2° (*c* 4·22 in ether), −2·95° (*c* 9·50 in ether) (Found: C, 65·0; H, 10·5. Calc. for $C_{11}H_{22}O_3$: C, 65·3; H, 11·0%); infrared absorption: band at 1093 cm.$^{-1}$ (alkyl ether). More (0·2 g.) of the acid was obtained on distillation of the residue from the steam-distillation under reduced pressure.

Later the procedure was modified as follows: Phthiocerol (5 g.) in glacial acetic acid (200 c.c.) was heated on a steam-bath with chromium trioxide (6·2 g.) in water (75 c.c.) and acetic acid (75 c.c.) for 2 hr. The mixture was then poured into water and extracted with ether. After removal of the solvent and most of the acetic acid, the residue was esterified (with ethereal diazomethane or 3% methanolic sulphuric acid). Distillation gave the *methyl ester* of the C_{11} methoxy-acid (1·2 g., 61·5%), b. p. 118°/15 mm., n_D^{19} 1·4351 (Found: C, 66·5; H, 11·0. $C_{12}H_{24}O_3$ requires C, 66·7; H, 11·1%).

Demethylation of the C_{11} *Methoxy-acid.*—The methoxy-acid (0·32 g.) was heated on a steam-bath with acetic anhydride (10 c.c.) and toluene-*p*-sulphonic acid (0·12 g.) for 0·5 hr.; the mixture was then poured into water, and the whole heated on the steam-bath for 10 min. Ether-extraction followed by distillation gave a liquid (0·18 g.), b. p. 170—190° (bath)/20 mm. (Found: C, 67·3; H, 10·0. Calc. for $C_{12}H_{22}O_4$: C, 62·6; H, 9·6. Calc. for $C_{10}H_{18}O_2$: C, 70·6; H, 10·6%). The infrared spectrum showed bands at 966 (*trans*-CH=CH) and 1709 cm.$^{-1}$ (CO_2H), with a shoulder at 1739 cm.$^{-1}$ (OAc).

A specimen of 6-methoxy-6-methylnonanoic acid [1] similarly treated gave a liquid (Found: C, 71·1; H, 11·2%) whose infrared spectrum did not show bands due to methoxyl, acetoxyl, or *trans*-CH=CH groups.

Conversion of the C_{11} *Methoxy-acid into an Oxo-acid.*—The methyl ester (2·5 g.) of the C_{11} methoxy-acid was kept with acetic anhydride (200 c.c.) and toluene-*p*-sulphonic acid (0·65 g.) at room temperature for 40 hr., then poured into water. The resulting acetoxy-ester, isolated by ether-extraction, was hydrolysed by 1 hour's refluxing with potassium hydroxide solution (2 g. in 20 c.c. of water and 5 c.c. of ethanol). Acidification (hydrochloric acid) followed by ether-extraction gave the corresponding hydroxy-acid (the infrared spectrum of a distilled sample did not show a band corresponding to lactonic carbonyl) which was converted, by means of ethereal diazomethane, into the methyl ester, b. p. 120—150° (bath)/10 mm., showing a strong band at 3390 cm.$^{-1}$ (OH). This ester (2 g.) in glacial acetic acid (20 c.c.) was kept with a solution of chromium trioxide (1 g.) in a little water and acetic acid (10 c.c.) at room temperature for 40 hr., then poured into water. An ethereal extract was washed with aqueous sodium carbonate and water, dried ($MgSO_4$), and evaporated. The resulting ketonic product was then separated with Girard-P reagent from non-ketonic material (containing, according to its infrared spectrum, unoxidised hydroxy-ester). The ketone fraction, obtained from the Girard-P extract by decomposition with 1N-sulphuric acid, followed by ether-extraction, had $[\alpha]_D^{18}$ +2·2° (*c* 12·2 in ether): its infrared spectrum showed carbonyl bands at 1715 (ketone) and 1739 cm.$^{-1}$ (ester). Hydrolysis of this oxo-ester by refluxing 5% aqueous-ethanolic potassium hydroxide for 0·5 hr., followed by acidification and ether extraction, gave the oxo-acid, b. p.

190—220° (bath)/9 mm., n_D^{18} 1·4530, which showed no measurable rotation. The infrared spectrum was in close agreement with that of a synthetic specimen of 6-methyl-7-oxononanoic acid. The 2 : 4-*dinitrophenylhydrazone* of the corresponding ethyl ester formed orange plates (from ethanol), m. p. 78° (Found: C, 54·7; H, 6·6; N, 14·2. $C_{18}H_{26}O_6N_4$ requires C, 54·8; H, 6·6; N, 14·2%) undepressed on admixture with ethyl 6-methyl-7-oxononanoate 2 : 4-dinitrophenylhydrazone.

In a small-scale experiment the oxo-acid (50 mg.) was refluxed with acetic anhydride (5 c.c.) and sodium acetate (50 mg.) for 20 hr. The infrared spectrum (in carbon disulphide) of the product showed a band at 1712 cm.$^{-1}$ (CO, CO_2H), but no band corresponding to a δ-enol lactone (1754 cm.$^{-1}$).

4-*Methylhept*-6-*en*-3-*one* (VIII).—A solution of oxalyl chloride (35 g.) and 2-methylpent-4-enoic acid[7] (27 g.) in benzene (50 c.c.), was kept at 35° for 3 hr.; the solvent and excess of oxalyl chloride were then removed under reduced pressure. The resulting acid chloride was caused to react, according to Blaise's method,[10] with a solution of ethylzinc iodide (from 150 g. of ethyl iodide, 100 c.c. of toluene, 25 g. of ethyl acetate, and 125 g. of zinc–copper couple), and the mixture worked up as described earlier for analogous cases.[11] Distillation gave 4-*methylhept*-6-*en*-3-*one* (19 g., 64%), b. p. 152°, n_D^{15} 1·4322 (Found: C, 76·4; H, 11·0. $C_8H_{14}O$ requires C, 76·2; H, 11·1%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol as orange prisms, m. p. 57° (Found: C, 54·7; H, 5·7; N, 18·2. $C_{14}H_{18}O_4N_4$ requires C, 54·9; H, 5·9; N, 18·3%).

Ethyl 2-*Ethoxycarbonyl*-6-*methyl*-7-*oxononanoate* (X).—Hydrogen bromide was passed during 3 hr. into a solution of the preceding ketone (19 g.) in benzene (350 c.c.) in the presence of benzoyl peroxide (0·2 g.) and a few drops of water. The mixture was then washed with water, and the washings were extracted with ether; the combined organic liquids were dried ($MgSO_4$) and evaporated, to give the crude bromide (III). This was added to an ice-cold solution of ethyl sodiomalonate (from 25 g. of ethyl malonate, 3·7 g. of sodium, and 100 c.c. of ethanol), and the mixture was then refluxed for 0·5 hr. The product was poured into water, extracted with ether, and the extract washed, successively, with aqueous potassium carbonate, aqueous sodium thiosulphate, and water, then dried ($MgSO_4$), and evaporated. Distillation of the residue gave *ethyl* 2-*ethoxycarbonyl*-6-*methyl*-7-*oxononanoate* (16·7 g.), b. p. 179°/8 mm., n_D^{18} 1·4432 (Found: C, 62·7; H, 9·1. $C_{15}H_{26}O_5$ requires C, 62·9; H, 9·1%).

6-*Methyl*-7-*oxononanoic Acid* (V).—The malonic ester (16·7 g.) was refluxed with potassium hydroxide (10 g.) in water (200 c.c.) and ethanol (20 c.c.) for 2 hr. The resulting solution was acidified (hydrochloric acid), and the product, isolated by ether-extraction, decarboxylated at 170° (bath). The product was taken up in ether from which the acid was removed with 10% aqueous potassium hydroxide. The alkaline washings were then acidified (hydrochloric acid) and extracted with ether, and the dried ($MgSO_4$) extract evaporated. Distillation of the residue furnished 6-*methyl*-7-*oxononanoic acid* (6·5 g.), b. p. 190—192°/16 mm., n_D^{18} 1·4534 (Found: C, 64·2; H, 9·5. $C_{10}H_{18}O_3$ requires C, 64·5; H, 9·7%). Treatment of the acid with Brady's reagent gave *ethyl* 6-*methyl*-7-*oxononanoate* 2 : 4-*dinitrophenylhydrazone*, m. p. 78—79° (from ethanol) (Found: C, 54·7; H, 6·8; N, 14·2. $C_{18}H_{26}O_6N_4$ requires C, 54·8; H, 6·6; N, 14·2%). This product was also obtained through the *ethyl ester*, n_D^{23} 1·4357 (Found: C, 66·9; H, 10·2. $C_{12}H_{22}O_3$ requires C, 67·3; H, 10·3%), prepared from the acid by means of 10% ethanolic sulphuric acid.

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[10] Blaise, *Bull. Soc. chim. France*, 1911, **9**, i—xxvi.

[11] Marks and Polgar, *J.*, 1955, 3851.