Absolute Configuration of the ·CH(OMe)·CHMe· System in the Phthiocerols

By **Kenneth Maskens** and **Nicholas Polgar,*** Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY

The absolute configuration of the ·CH(OMe)·CHMe· system in the phthiocerols. RCH(OMe)·CHMe·$[CH_2]_4$·CH(OH)·CH_2·CH(OH)·$[CH_2]_n$Me (R = Et or Me. n = 20 and 22), constituents of tuberculolipids, has been studied. By conversion of methoxyphthiocerane A. EtCH(OMe)·CHMe·$[CH_2]_{n+7}$Me. into the methyl-branched hydrocarbon EtCH_2·CHMe·$[CH_2]_{n+7}$Me having (−)-rotation it is shown that in the phthiocerols the asymmetric centre bearing the methyl branch has the *S*-configuration. In view of the *threo*-configuration of the adjacent asymmetric centres it follows that the centre bearing the methoxy-group has the *R*-configuration.

(+)- and (−)-*erythro*-3-Methoxy-2-methylbutyric acid. prepared in the course of the studies on the stereochemistry of the methoxyphthiocerane. are shown to have *S*- and *R*-configuration. respectively. at the asymmetric centre bearing the methyl branch.

In a previous paper [1] dealing with the stereochemistry of the phthiocerols A (I; R = Et) and B (I; R = Me), relative configurations have been assigned to the asymmetric centres bearing the methoxy-group and the methyl branch. The work now described concerns the absolute configurations of these centres.[2]

In the course of studies designed to demethylate the methoxyphthiocerane (II; R = Me and Et) [1] without affecting the adjoining asymmetric centre bearing the methyl branch, the procedure of Huffmann and Lott [3] involving heating with acetic anhydride in the presence of toluene-*p*-sulphonic acid was first investigated. This procedure, previously employed [4] for demethylating the phthiocerols, was in the present studies found by unidimensional multiple chromatography (u.m.c.) to give mixtures of acetoxy-compounds containing at least three components, thus indicating that some rearrangement may have occurred. Similar results were obtained by keeping the methoxyphthiocerane at room temperature with acetic anhydride containing boron trifluoride–ether complex. Attention was then turned to demethylations with hydrogen iodide and with hydrogen bromide in acetic anhydride and in acetic acid; benzene was added in order to increase the solubility of the methoxyphthiocerane. The resulting acetoxy-compounds appeared to be homogeneous. The proportion of acetoxy-compound in the product was greater when acetic acid rather than acetic anhydride was used, and was most favourable with hydrogen bromide in acetic acid and benzene; this procedure was, therefore, adopted.

A sample of methoxyphthiocerane consisting essentially of methoxyphthiocerane A (II; R = Et) gave on demethylation with hydrogen bromide in acetic acid and benzene the acetoxy-compound (III), here referred to as acetoxyphthiocerane A; the n.m.r. spectrum of the latter showed only one doublet for the protons of the methyl branch at τ 9·14 (J 7·0 Hz), and this, together with the clarity of the multiplet for the proton at C-3, indicated that only one diastereoisomer was present; its stereochemistry will be discussed later.

In addition to the acetoxy-compound a non-polar

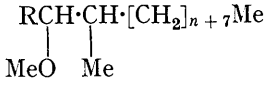
[1] K. Maskens and N. Polgar, *J.C.S. Perkin I*, 1973, 1117.
[2] Preliminary communication, K. Maskens and N. Polgar, *Chem. Comm.*, 1970, 340.
[3] M. N. Huffman and M. H. Lott, *J. Biol. Chem.*, 1948, **172**, 789.
[4] H. Demarteau-Ginsburg and E. Lederer, *Compt. rend.*, 1955, **240**, 815.

material was obtained which included a bromo-compound. Mass spectrometric and n.m.r. studies (see Experimental section) indicated that it has the structure (IV) (bromophthiocerane A).

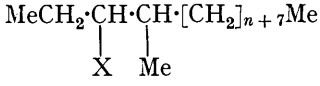
Reduction with lithium aluminium hydride converted acetoxyphthiocerane A (III) into the corresponding hydroxy-derivative (V), termed hydroxyphthiocerane A. Reaction of the latter with methanesulphonyl chloride gave the corresponding *O*-methylsulphonyl ester. Reduction of the product with lithium aluminium hydride, followed by catalytic hydrogenation (in order to reduce a trace of alkenes present) afforded the hydrocarbon (VI) (phthiocerane A) showing $[\alpha]_D$ −0·8°. Comparison of the sign of rotation of phthiocerane A with that of (−)-*R*-methyltritriacontane,[5] $[\alpha]_D$ −0·6°, enables assignment of the *R*-configuration to phthiocerane A; accordingly, in phthiocerol A the centre bearing the methyl branch has the *S*-configuration.

$$RCH(OMe)\cdot CHMe\cdot[CH_2]_4\cdot CH(OH)\cdot CH_2\cdot CH(OH)\cdot[CH_2]_nMe$$

(I) $n = 20$ and 22

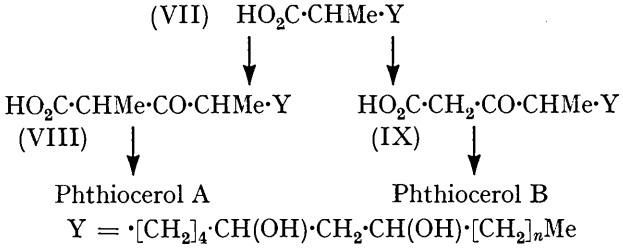


(II)



(III) X = OAc
(IV) X = Br
(V) X = OH
(VI) X = H

Phthiocerols A and B are presumably derived from a common precursor (VII) by incorporation of, respectively, one propionate or one acetate unit, followed by eventual decarboxylation of the ketones (VIII) and (IX), respectively.[6,7] Since the common precursor (VII) already contains the methyl branch present in both phthiocerols, the absolute configurations of the centre bearing the methyl branch are expected to be identical in phthiocerols A and B. From the *threo*-

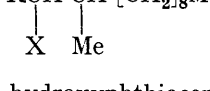


configuration [1] of the centres bearing the methoxy-group and the methyl branch it also follows that the centre bearing the methoxy-group has the *R*-configuration.

An attempt [8] has been made previously to assign the absolute configurations at C-3 and C-4 of phthiocerol A with the aid of the method of molecular-rotation differences, using calculations based upon Brewster's rules. From these calculations it was concluded that the absolute configurations at C-3 and C-4 were *S* and *R*, respectively, the opposite to those found in the present work.

Concerning the stereochemistry of acetoxyphthiocerane A (III) and its derivatives (IV) and (V) the following points are of interest. Cleavage by hydrogen bromide of mixed ethers containing primary and secondary alkyl groups occurs preferentially to give the primary alkyl bromide and secondary alcohol. With methyl secondary alkyl ethers the cleavage is entirely in this sense; for example, optically active 2-methoxybutane is cleaved to give butan-2-ol of the same configuration without racemisation, together with methyl bromide.[9] In the presence of an excess of hydrogen bromide the first-formed alcohol may undergo substitution to give a secondary alkyl bromide with inverted configuration.

During the demethylation of methoxyphthiocerane A with hydrogen bromide in acetic acid, cleavage of the primary C–O bond was considered to be followed by acetylation of the consequent secondary alcohol to give acetoxyphthiocerane A with retention of configuration at C-3. It was noticed in frequent analyses (t.l.c.) of the mixture during the course of demethylation that a small quantity of polar material was present, and that the quantity diminished towards the end of the reaction. In order to ascertain the relative configuration of the acetoxyphthiocerane a mixture of *threo*- and *erythro*-2-methoxy-3-methyldodecanes (X; X = OMe),[1] obtained by methylation of a mixture of the hydroxy-derivatives (X; X = OH) with the *erythro*-isomer predominating, was subjected to demethylation under the conditions used for methoxyphthiocerane A, and the resulting acetoxy-derivatives (X; X = OAc) were reduced with lithium aluminium hydride to the hydroxy-compounds (X; X = OH). The n.m.r. spectrum of the hydroxy-compounds used as starting material showed a pair of doublets (τ 8·85 and 8·88) for the methyl group attached to C-2 with the stronger signal at lower field, and the relative strengths of these signals in the n.m.r. spectrum of the hydroxy-compounds obtained after the above reaction cycle were unchanged. It is not expected that either the methylation or the reduction steps would lead to inversion of configuration, and it is, therefore, concluded that demethylation under these conditions takes place with retention of configuration. Since the methoxyphthioceranes have been shown [1] to have the *threo*-configuration, the acetoxyphthiocerane is assigned the *threo*-configuration.



(X) R = Me
(XI) R = Et

The hydroxyphthiocerane (V) had $[\alpha]_D$ −4·9°, as

[5] S. Ställberg-Stenhagen and E. Stenhagen, *J. Biol. Chem.*, 1950, **183**, 223.
[6] M. Gastambide-Odier, J.-M. Delaumeny, and E. Lederer, *Chem. and Ind.*, 1963, 1285.
[7] D. E. Minnikin and N. Polgar, *Chem. Comm.*, 1965, 495.
[8] M. Welby-Gieusse and J. F. Tocanne, *Tetrahedron*, 1970, **26**, 2875.
[9] R. L. Burwell, jun., L. M. Elkin, and L. G. Maury, *J. Amer. Chem. Soc.*, 1951, **73**, 2428.

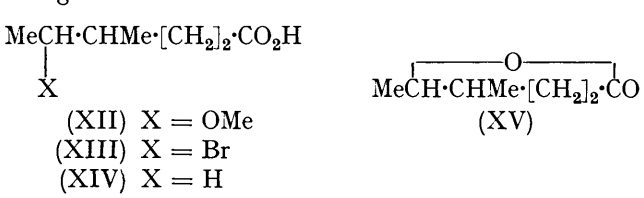
compared with $[\alpha]_D$ +1·8° for the acetoxy-compound (III). The change in sign of rotation without change of configuration for a secondary alcohol and its acetate is comparable with the similar change between octan-3-ol and the acetate of the same configuration.[10] Comparison of the n.m.r. spectrum of the hydroxyphthiocerane with that of a mixture of *threo*- and *erythro*-4-methyltridecan-3-ols (XI; X = OH) [1] containing an excess of the *erythro*-isomer showed, by inspection of the signals for the methyl branch and the hydrogen atom at C-3, that the hydroxyphthiocerane corresponded with the minor component of the mixture, and thus has the *threo*-configuration.

The bromo-compound (IV) could arise as a result of substitution by hydrogen bromide of either acetoxyphthiocerane, or the possible immediate demethylation product, hydroxyphthiocerane. Both of these have the *threo*-configuration, and it is to be expected that the single isomer produced would be formed with inversion of configuration; it is, therefore, assumed to be the *erythro*-isomer.

The following assignments of absolute configurations can thus be made:

	Asymmetric centre bearing the methyl branch	Adjoining asymmetric centre (bearing OMe OAc, or Br)	$[\alpha]_D$ (°)
Phthiocerol A	*S*	*R*	−4·5
Phthiocerol B	*S*	*R*	−8·2
Methoxyphthiocerane A	*S*	*R*	−0·5
Acetoxyphthiocerane A	*S*	*R*	+1·8
Bromophthiocerane A	*S*	*S*	−1·6
Hydroxyphthiocerane A	*S*	*R*	−4·9
Phthiocerane A	*R*		−0·8

During the present studies the methyl ester derived from the (+)-enantiomer of *erythro*-5-methoxy-4-methylhexanoic acid (XII),[11] obtained by chain elongation of (+)-*erythro*-3-methoxy-2-methylbutyric acid,[1] was demethylated with hydrogen bromide in benzene–acetic acid, to give 5-bromo-4-methylhexanoic acid (XIII). This product, formed under conditions not normally conducive to extensive transesterification and without the simultaneous formation of the 5-acetoxy-compound, could have arisen by substitution of an intermediate δ-lactone (XV) derived from the initial demethylation product. Hydrogenolysis of the methyl ester of (XIII) over palladium in methanolic potassium hydroxide gave 4-methylhexanoic acid (XIV) with (+)-rotation; the (+)-anteiso-acids have been shown to have the *S*-configuration.[12]



(XII) X = OMe
(XIII) X = Br
(XIV) X = H

(XV)

[10] Y. R. Naves, *Helv. Chim. Acta*, 1943, **26**, 1036.
[11] K. Maskens and N. Polgar, *J.C.S. Perkin I*, 1973, 109.
[12] W. Klyne, *Progr. Stereochem.*, 1954, **1**, 205.

EXPERIMENTAL

For general points see ref. 1.

Acetoxyphthiocerane A (III).—A sample of methoxyphthiocerane consisting essentially of methoxyphthiocerane A (0·770 g), benzene (10 cm³), hydrogen bromide in acetic acid (45%; 5 cm³), and acetic acid (5 cm³) were stirred for 2 days at room temperature. The mixture was then poured into water and extracted with benzene. The extract was washed successively with dilute aqueous sodium hydroxide, water, and saturated aqueous sodium chloride, dried, and evaporated. The product (0·805 g) was subjected to preparative layer chromatography (p.l.c.) [petroleum–ether (98 : 2); 3 passes], and three bands were removed.

Band II gave *acetoxyphthiocerane A* (0·471 g), m.p. 59°, R_F 0·48 [petroleum–ether (95 : 5)], $[\alpha]_D^{20}$ +1·8°, τ 5·26 (m, ·C*H*·OAc), 7·95 (s, CH_3·CO), and 9·07—9·21 (methyls), *m/e* 490 (*M* − AcOH, 36%), 462 (*M′* − AcOH, 30%), 130 (McLafferty rearrangement, 35%), and 101 (α-cleavage, 80%).

Band I gave polar material (0·038 g) [t.l.c. in petroleum–ether (80 : 20), R_F 0·28 and 0·34].

Band III gave a mixture of products from which, by chromatography on neutral alumina (150 g; activity I), followed by p.l.c. (petroleum), *bromophthiocerane* (0·084 g) was isolated; m.p. 57°, R_F 0·65 (petroleum), $[\alpha]_D^{20}$ −1·6° (*c* 5·6), τ 5·95 (m, EtC*H*Br·CHMe·), 8·05 (m, ·CHBr·C*H*Me·CH_2·), 8·95 (t, *J* 7 Hz, CH_3·CH_2·CHBr·), 9·05 (d, *J* 6·5 Hz, Me branch), and 9·11 (terminal Me). The mass spectrum showed low intensity molecular ion peaks at *m/e* 572, 570, 544, and 542, intense peaks at *m/e* 80 and 82 (HBr) and peaks at *m/e* 490 and 491, and 462 and 463, corresponding to loss of hydrogen bromide and bromine, respectively.

Hydroxyphthiocerane A (V).—A solution of acetoxyphthiocerane A (0·431 g) in ether (10 cm³) was added during 15 min to a stirred, ice-cooled solution of lithium aluminium hydride (0·5 g) in ether (90 cm³). The solution was stirred at room temperature for 1 h, and the crude product isolated in the usual way. The product was chromatographed on silica gel (40 g; deactivated with 2·5% water). Elution with petroleum–ether (98 : 2) gave *hydroxyphthiocerane A*, m.p. 75° (from chloroform), $[\alpha]_D^{20}$ −4·9° (*c* 2·7), R_F 0·39 [petroleum–ether (80 : 20)], τ 6·63 (m, C*H*·OH), and 9·03 (t), 9·11 (t), and 9·12 (d) (methyls), *m/e* 508 (*M* − H_2O, 6%), 480 (*M′*, 4%), 479 (*M* − C_2H_5, 10%), 462 (*M′* − H_2O, 10%), 451 (*M′* − C_2H_5, 21%), 420 (*M′* − H_2O − 42, 8%), and 59 (EtCHOH⁺, 100%).

Phthiocerane A (VI).—A solution of hydroxyphthiocerane A (0·174 g, 0·00035 mol) in pyridine (5 cm³) and benzene (5 cm³) was stirred and cooled during the addition of a solution of methanesulphonyl chloride (0·080 g, 0·00070 mol) in pyridine (1 cm³). The solution was stirred at room temperature until t.l.c. indicated that the reaction was complete (0·5 h). A solution of the crude *O*-methanesulphonate (0·228 g), isolated in the usual manner, in ether (10 cm³) was added to a stirred solution of lithium aluminium hydride (0·20 g) in ether (40 cm³), and the solution was boiled and stirred for 12 h. The product, which contained some hydroxyphthiocerane, was subjected once more to methylsulphonation, followed by reduction with lithium aluminium hydride, to give, after chromatography on silica, material (0·114 g) having $[\alpha]_D^{22}$ −0·6° (*c* 11·4). A small amount of unsaturated material was present; the product was, therefore, hydrogenated in cyclohexane

(20 cm³) over platinic oxide (10 mg) for 6 h. (−)-*Phthiocerane A* (0·082 g), m.p. 60°, $[\alpha]_D^{20}$ −0·8° (*c* 4·1) was thus obtained; the n.m.r. spectrum showed the presence of methyl and methylene groups only.

Conversion of (+)-erythro-5-*Methoxy*-4-*methylhexanoic Acid into* (+)-4-*Methylhexanoic Acid.*—(+)-*erythro*-5-Methoxy-4-methylhexanoic acid (XII) (6·28 g; $[\alpha]_D^{20}$ +7·1°) [prepared from (+)-3-methoxy-2-methylbutyric acid [7] as described [1] for the (−)-enantiomer] was esterified with diazomethane. Distillation of the product gave the (+)-*methyl ester*, b.p. 102° at 23 mmHg, n_D^{24} 1·4250, $[\alpha]_D^{20}$ +7·4° (*c* 3·2) (Found: C, 62·3; H, 10·2. $C_9H_{18}O_3$ requires C, 62·0; H, 10·4%), τ 6·29 (3H, s, $\cdot CO_2 \cdot CH_3$), 6·65 (3H, s, $CH_3 \cdot CH \cdot O \cdot CH_3$), 6·77 (H, dq, *J* 6·2 and 3·8 Hz, $CH_3 \cdot CH \cdot O \cdot CH_3$), 7·62 (2H, m, $\cdot CH_2 \cdot CO_2Me$), 8·91 (3H, d, *J* 6·1 Hz, terminal Me), and 9·11 (3H, d, *J* 6·3 Hz, Me branch), *m/e* 174 (*M*, 2%), 159 (*M* − 15, 8%), and 59 ($CH_3 \cdot CHOMe^+$, 100%). This ester (1 g) was added to a cooled stirred mixture of benzene (8 cm³), acetic acid (4 cm³), and hydrogen bromide in acetic acid (45%; 4 cm³). The mixture was stirred at room temperature for 24 h, then poured into water, and extracted with ether. The ethereal solution was washed with water, then with saturated aqueous sodium chloride, dried, and evaporated. The crude product was esterified with diazomethane (much transesterification had occurred) before chromatography on silica gel (30 g). Elution with petroleum–ether (98 : 2; 200 cm³) gave the *ester* of the *bromo-acid* (XIII) (0·465 g), n_D^{24} 1·4662, $[\alpha]_D^{20}$ +18·8° (*c* 4·6) (Found: C, 43·3; H, 6·9; Br, 36·1. $C_8H_{15}BrO_2$ requires C, 43·2; H, 6·8; Br, 35·8%), τ 5·78 (1H, dq, *J* 7·0 and 3·9 Hz, $CH_3 \cdot CHBr$), 6·29 (3H, s, $\cdot CO_2 \cdot CH_3$), 7·64 (2H, m, $\cdot CH_2 \cdot CO_2Me$), 8·32 (d, *J* 7·0 Hz, terminal Me), and 8·97 (3H, d, *J* 6·5 Hz, Me branch), *m/e* 142 (*M* − HBr, 40%), 110 (142 − MeOH, 40%), 96 and 94 (CH_3Br^+, 36 and 38%), 74 (McLafferty rearrangement, 74%), and 71 (base peak).

The bromo-ester (0·92 g) in methanol (10 cm³) containing potassium hydroxide (1·2 g) was hydrogenated over palladised charcoal (5% Pd; 30 mg) during 6 h. The solution was boiled for 1 h, then filtered, and most of the methanol was evaporated from the filtrate. The residue was acidified with dilute hydrochloric acid and extracted with ether. Evaporation of the dried extract gave (+)-4-*methylhexanoic acid* (0·536 g), $[\alpha]_D^{20}$ +7·4° (*c* 3·3) (Found: C, 64·9; H, 11·0. $C_7H_{14}O_2$ requires C, 64·6; H, 10·8%), τ 7·63 (2H, t, *J* 7 Hz, $\cdot CH_2 \cdot CO_2H$) (5H, methylene and methine), and 9·11 and 9·12 (6H, Me branch and terminal Me), *m/e* 101 (*M* − 29, 20%), 60 [$CH_2{:}C(OH)_2^+$, 30%], 74 [$CH_3 \cdot CH{:}C(OH)_2^+$, 38%], and 43, 57, and 71 (hydrocarbon peaks; 71, base peak).

[3/739 *Received, 9th April,* 1973]