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THE TOTAL STEREOSTRUCTURE OF (-)-MUUROLENE DIHYDROCHLORIDE

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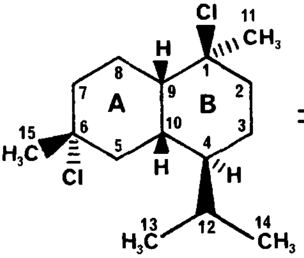
Abstract: The stereochemistry and absolute configuration of (-)-muurolene dihydrochloride were determined by X-ray crystallographic methods, providing the first direct evidence for the chiral identities of the related sesquiterpenoids.

Muurolene dihydrochloride is a characteristic, well-defined crystalline derivative of the natural muurolenes[1,2,3] and muurolols[3,4,5], and of the copaenes[2,6]. The determination of the gross structure and of the partial stereochemistry of muurolene dihydrochloride is due mainly to the classical work of Westfelt[2,3]. However, this work did not lead to any assignment of the stereochemistry at the halogenated centers, C_1 and C_6 (I)[7].

The recent publications by Gatilov et al.[8], and by Borg-Karlson et al.[9] of studies of the molecular structure of (-)-muurolene dihydrochloride by X-ray crystallography prompt us to report our results in a similar crystallographic investigation of the same substance. Our findings are in agreement with the published results[8,9] with regard to gross structure and relative stereochemistry, and they establish further for the first time by direct physical methods the absolute configuration as that shown below.



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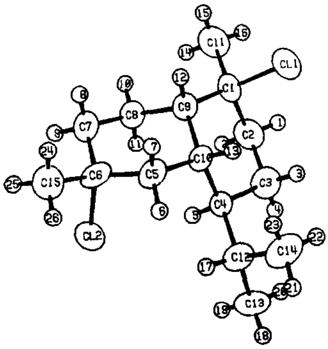

The absolute configurations of the natural substances in the muurolane and copaane series have been assigned previously on the basis of their chemical correlation[2,3,4,6,9] with sesquiterpenoid derivatives in the cadinane series[10,11], which in turn were assigned absolute configuration on the basis of either ORD

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†The ORTEP drawing is for one of the two crystallographically independent molecules of (-)-muurolene dihydrochloride (vide infra).

data or of a degradation to S-(+)-isopropylsuccinic acid[12]. The present work therefore establishes by crystallographic methods the chiral configurations of the natural muurolanes and copaanes, and also that of the widespread group of cadinanes.

The muurolene dihydrochloride used in the X-ray studies was prepared by the method described by Westfelt[3,14]. The crystals which formed as well-defined plates (m.p. 86-87°; $[\alpha]_D^{22}$ - 12°, c 0.107, $CHC\ell_3$) belonged to the monoclinic space group $P2_1$. The unit cell dimensions were $a = 9.836(2)$, $b = 11.650(4)$, $c = 13.674(5)$ Å; $\beta = 95.24(2)°$; $V = 1560.4$ Å^3; $\rho = 1.18$ g/cm^3; $Z = 4$. The X-ray structure was solved by direct methods and the refinement was carried out by the full matrix least-squares method, with hydrogen atoms included in calculated positions to an R_1 value of 0.0467 and R_2 value of 0.0557. In a refinement of both enantiomorphic possibilities a significantly lower R value was observed for the reported configuration (I).* This lower R value is a consequence of the anomalous scattering of chlorine. The reduction in the R value observed for the correct enantiomorph was significant at the 99.5% probability level by the Hamilton R factor ratio test. The data given below for the bond angles and the bond lengths (TABLES 1 and 2) are for two crystallographically independent molecules. The numbers in the parentheses are estimated standard deviations in terms of the least significant digits[15].

TABLE 1. Bond Angles in Degrees

C2-C1-Cℓ	107.7(6), 107.4(6)	C5-C6-C7	112.5(8), 110.0(8)
C9-C1-Cℓ	107.1(5), 105.1(6)	C5-C6-C15	110.8(8), 111.5(8)
C11-C1-Cℓ	105.4(6), 106.7(7)	C7-C6-C15	111.3(8), 112.0(7)
C2-C1-C9	110.9(7), 111.9(7)	C6-C7-C8	112.9(7), 113.1(6)
C2-C1-C11	112.0(8), 111.8(8)	C7-C8-C9	110.5(7), 109.8(8)
C9-C1-C11	113.3(7), 113.4(8)	C1-C9-C8	112.6(6), 112.3(7)
C1-C2-C3	112.9(7), 115.0(7)	C1-C9-C10	112.8(6), 112.7(7)
C2-C3-C4	112.4(7), 111.1(6)	C8-C9-C10	110.7(7), 108.2(7)
C3-C4-C10	109.8(7), 108.1(7)	C4-C10-C9	114.3(6), 113.5(6)
C3-C4-C12	112.5(7), 111.6(6)	C4-C10-C5	116.2(7), 116.9(8)
C10-C4-C12	112.7(7), 114.6(6)	C5-C10-C9	108.7(6), 108.6(6)
C6-C5-C10	116.7(7), 117.7(7)	C4-C12-C13	111.6(8), 112.9(7)
C5-C6-Cℓ	109.9(6), 110.4(6)	C4-C12-C14	115.9(8), 111.5(7)
C7-C6-Cℓ	106.7(7), 106.9(7)	C13-C12-C14	109.9(7), 111.3(7)
C15-C6-Cℓ	105.2(8), 105.8(8)		

TABLE 2. Bond Lengths in Angstroms

C1-Cℓ	1.827 (8), 1.844 (9)	C5-C6	1.511(12), 1.510(11)
C6-Cℓ	1.859(10), 1.843(10)	C5-C10	1.546(11), 1.553(11)
C1-C2	1.534(12), 1.510(12)	C6-C7	1.507(12), 1.553(12)
C1-C9	1.534(11), 1.551(12)	C6-C15	1.537(13), 1.499(12)
C1-C11	1.521(11), 1.508(13)	C7-C8	1.527(12), 1.503(12)
C2-C3	1.529(13), 1.521(12)	C8-C9	1.531(10), 1.553(12)
C3-C4	1.534(11), 1.522(11)	C9-C10	1.539(11), 1.547(11)
C4-C10	1.523(11), 1.529(11)	C12-C13	1.537(13), 1.530(13)
C4-C12	1.546(11), 1.569(10)	C12-C14	1.487(14), 1.504(11)

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*Refinement for the opposite enantiomorph yielded $R_1 = 0.0480$ and $R_2 = 0.0575$.

Our results confirm the observation of appreciable deviations from the normal carbon-chlorine bond lengths and from the normal bond angles which were reported by Gatilov et al.[8], but which were not observed by Borg-Karlson et al. who reported that these features appeared to be normal[9]. The spreading[8] of the C_6-C_5-C_{10} bond angle and the relative ease of rearrangement[9] to cadinene dihydrochloride were attributed to a 1,3-diaxial interaction[16] between the C_4-carbon atom and the chlorine atom at C_6 in muurolene dihydrochloride. The observation that muurolene dihydrobromide, in which these effects would be expected to be more pronounced, cannot be prepared in the usual fashion from a typical muurolene, the reaction[17] yielding only cadinene dihydrobromide which has no bulky 1,3-diaxial substituents, is a further example of the same effect.

The infrared spectrum of muurolene dihydrochloride shows absorption maxima (KBr pellet) for the carbon-chlorine bonds at 540 (strong), and 610, 635, and 660 cm^{-1} (all medium). The bands at 540 and 610 cm^{-1} can be assigned to tertiary carbon-chlorine bonds of the type T_{HHH} (at C_6) and T_{CHH} (at C_1), respectively[18], and suggest the presence of chlorine atoms in the two possible axial environments in this compound. The bands at the higher frequencies, however, fall in the range reported for tertiary carbon-chlorine bonds of the type T_{CCH}, and are suggestive of chlorine atoms which are in an equatorial environment[18,19]. On the basis of the infrared spectrum alone it is not possible to assign the stereochemistry of these halogenated centers. The data would suggest that at least one of the chlorine atoms is in an axial position and would rule out a structure with both chlorine atoms in equatorial positions Since both chlorines are now demonstrated by X-ray crystallography to be formally axial, the appearance of the absorption bands at the higher frequencies may be attributed to the distortion discussed above which causes the bonds located at C_5 and C_7 in the positions which are anti to the C_6-$C\ell$ bond[18] to be appreciably deflected (cf. ref. 16) from their normal coplanar relationship.

References and Footnotes

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13. The attribution by Mani (*cf.* ref. 10, p. 104) to Hanic (*cf.* ref. 11) of an independent determination of the absolute configuration of cadinene dihydrobromide is not in accord with the literature (*cf.* ref. 12).
14. We are greatly indebted to Professor V. Herout for supplying us with a sample of natural muurolenes[1]. We would also like to thank Dr. Lars Westfelt for a sample of (-)-muurolene dihydrochloride used for purposes of comparison[2,3].
15. The complete crystal data including tables of atomic coordinates, thermal parameters, bond distances and bond angles all with standard deviations are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lenfield Road, Cambridge, CB2 1EW, England.
16. Gatilov *et al.*[8] reported a particularly high value for the C_6-C_5-C_{10} bond angle (120, 119°); our corresponding values (TABLE 1) are 116.7, 117.7°. As would be expected, the C_4-C_{10}-C_5 angle is similarly increased: 116.2, 116.9° (reported[8], 115, 116°). The extent of the 1,3-diaxial spreading with respect to the C_6-$C\ell$ and the C_4-C_{10} bonds is indicated by our observed 26-degree deviation from parallelism in this structural feature. The ring A chair system is accordingly flattened and the gross non-planarity of the *cis*-decalin framework is somewhat reduced.
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