The Stereostructure of Bisabolene Trihydrochloride

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THE STEREOSTRUCTURE OF BISABOLENE TRIHYDROCHLORIDE

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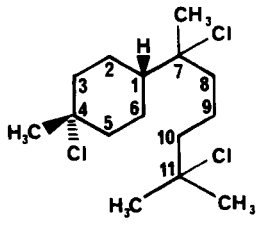
ABSTRACT.—The sterostructure of bisabolene trihydrochloride was established as **1** by spectral and X-ray methods.

Bisabolene trihydrochloride [**1**] is the characteristic crystalline derivative of the monocyclic sesquiterpenes, the bisabolenes, and the related alcohols, the bisabolols (1). These widely distributed natural products have been known for several decades and continue to be of synthetic and biological interest (2–6). Although bisabolene trihydrochloride has been used commonly as a key reference compound in the characterization of related terpenic substances, there has been no direct evidence for the location of the chlorine atom at C-7 in the gross structure of this central derivative, nor has the stereochemistry of this compound been described to date. The assignment in the literature of one of the chlorine atoms to C-7 (and not to C-1) was based on analogy and the assumption that C-1 was not involved in the formation of bisabolene trihydrochloride during treatment with HCl (7). The C-1 position, however, has been reported to undergo halogen addition in the case, for instance, of the cadalenic sesquiterpene ϵ-bulgarene (8).

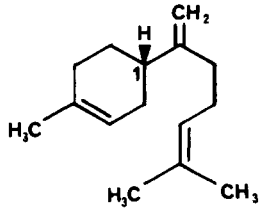
The present work includes the preparation of **1** from (−)-β-bisabolene [**2**] and represents the most recent phase of our continuing research in the determination of the total stereostructures of halogenated sesquiterpene derivatives (9,10). The spectral and X-ray data given below provide the first direct evidence for the location of the C-7 chlorine atom in **1**, confirming the gross structure of Ruzicka and Liguori (7), and these data establish for the first time for this compound the stereostructure that has the cyclohexane ring in the expected chair conformation with the organic substituents at C-1 and C-4 equatorial.

The ^{1}H-nmr spectrum (300 MHz) for **1** is consistent with a structure that has all of the four methyl groups attached to carbons bearing chlorine atoms. The ir spectrum showing absorption maxima for the tertiary carbon-chlorine bonds (T_{HHH}) supports the axial conformation of the chlorine at C-4 (11). The weak band observed at 642 cm^{-1}, due probably to the rotameric contributions of the side chain, would have been substantially stronger for an equatorial chlorine substituent (T_{CCH}) at C-4. The preferred stereochemistry of the chlorine atom on the ring (axial) is in agreement with our earlier findings (9,10). Based on these data the structure of bisabolene trihydrochloride is represented by **1**.

The conclusions regarding gross structure and stereochemistry are confirmed by X-ray data (Figure 1). The car-



1



2

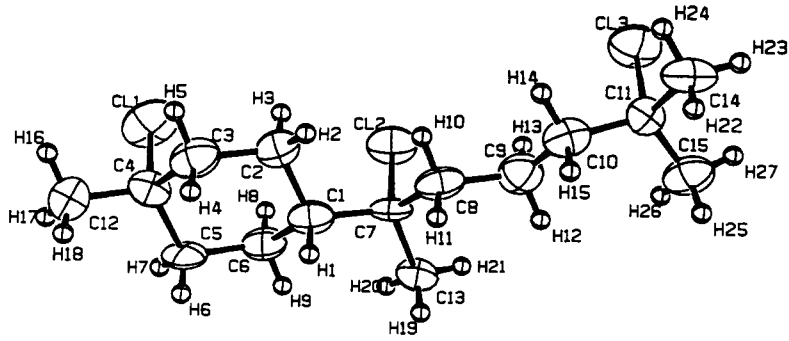


FIGURE 1. ORTEP representation of one of the enantiomers of bisabolene trihydrochloride [**1**].

bon-chlorine bond distances in **1** are consistent with reported values (9,10,12). The spreading of the bond angles is most pronounced in the side chain [C-7–C-8–C-9 = C-9–C-10–C-11 = 119(1)°]; the bond angles in the ring are increased to a lesser extent [C-2–C-3–C-4 = 115(1), C-4–C-5–C-6 = 112(1)°].

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points are uncorrected and were determined on a Kofler hot stage micro block. Ir spectra were determined on Perkin-Elmer Model 710 and 337 spectrophotometers; nmr spectra were recorded in $CDCl_3$ (TMS internal standard) on Varian XL-200 and XL-300 instruments. Optical rotations were determined in $CHCl_3$ using a Perkin-Elmer 241MC Spectropolarimeter. Gc separations were carried out on an Aerograph Autoprep Model A-700 chromatograph, and gc-ms determinations were carried out on a Hewlett Packard Model 5985B instrument. X-ray crystallography was carried out by The Molecular Structure Corporation, 3200A Research Forest Drive, The Woodlands, Texas.

ISOLATION OF (−)-β-BISABOLENE [**2**].—(−)-β-Bisabolene was isolated from oil of bergamot (13), obtained from *Citrus aurantium* L. subsp. *bergamia* (Risso and Poit.) Wright and Arn. (Rutaceae), following a modification of the procedure described by Herout *et al.* (14). A neutral fraction was prepared by washing a pentane solution of the crude oil (J. Mannheimer Inc.) successively with 5% HCl, 5% $NaHCO_3$, 5% NaOH, and H_2O. The organic layer was dried over Na_2SO_4, and evaporation of the solvent through a fractionating column yielded 77% of neutralized material. A preliminary investigation of the latter by gc-ms (SE-30) indicated the presence of β-bisabolene [**2**] as one of the nine major constituents in the botanical source (15,16). Found for **2**: (70 eV) *m/e* (rel. int.) $[M]^+$ 204 (15), 161 (14), 135 (6), 119 (16), 109 (24), 93 (77), 79 (34), 69 (100), 55 (14). A high boiling fraction of the neutral oil (bp 89–91°, 2–3 mm) was obtained by distillation through a Vigreux column. This material in turn was chromatographed at a slow rate on neutral alumina (Brockmann Activity I) using a ratio of 16:1 of adsorbent to sample and a long column. The fractions which eluted with petroleum ether (20–40°, the hydrocarbon fractions) were combined, and a final separation of the latter into three major components was carried out by preparative gc (20 ft × ⅜ in. column at 200°, He rate 1.5 ml/sec). The two minor components which eluted first were tentatively identified (ms, ir) as the sesquiterpenes β-caryophyllene and α-bergamotene, which is consistent with the findings of Herout *et al.* (14). The main peak with retention time 2.8 h was identified as **2** (14,16): ir (CCl_4) 3060, 2965, 2910, 1640, 1440, 1380, 892 cm^{-1}; ^1H nmr (200 MHz) δ 1.71, 1.67, 1.63 (all singlets, 3H each), 4.77 (m, 2H), 5.43 and 5.42 (broad singlets, 1 H each); $[\alpha]_D$ −68.27°.

BISABOLENE TRIHYDROCHLORIDE [**1**].—A solution of a freshly isolated sample of **2** (0.087 g) in anhydrous Et_2O (1.0 ml) was saturated, under N_2, with dry HCl gas at −18° (ice and salt). The reaction mixture was stored at 5° for 72 h. After removal of the solvent, the semi-solid product was recrystallized (MeOH) to constant mp (79–80°) yielding pure **1** (14): ir (KBr) strong bands at 2950, 1440, 1355, 1300, 1138, 870, 768, 570, 542, 525 cm^{-1}; ^1H nmr (300 MHz) δ 1.53 (s, 3H), 1.59 (s, 6H), 1.62 (s, 3H); $[\alpha]_D$ 0°. X-ray analysis: $C_{15}H_{27}Cl_3$, MW 313.74 established the monoclinic space group *C2/c* with unit cell dimensions $a = 55.30$ (6), $b = 6.013$ (1) and $c = 10.404$ (3) Å; $\beta = 96.74$ (5)°; $V = 3435$ (6) $Å^3$; $\rho(calc) = 1.21$ g/cm^3 and $Z = 8$; Cu Kα radiation ($\lambda = 1.54178$ Å), $\mu = 46.84$ cm^{-1}, $F(000) = 1344$. The crystal dimensions were 0.20 × 0.15 × 0.10 mm, and the number of reflections measured was 2588 (total) and 2564

(unique). The X-ray structure was solved by direct methods (TEXAN software package) with hydrogen atoms included in calculated positions. Refinement was carried out by the full matrix least squares method; $R = 0.085$ ($R_w = 0.104$).[1]

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[1]Atomic coordinates for this compound have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, UK.