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Molecular Structure of a Reductive Dimer of Pulegone

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Synopsis. The molecular structure of "bishydropulegone," a reductive dimer of pulegone, was determined as (1*R*,3′a*R*,4*R*,6′*R*,7′a*S*)-7-′a-hydroxy-2′,2′,3′,3′,4,6′-hexamethylspiro[cyclohexane-1,1′-indan]-2-one by X-ray crystallographic analysis.

After "bishydropulegol" $C_{20}H_{36}O_2$ had been isolated by Pascual et al. as one of the dimeric products of the reduction of (*R*)-(+)-pulegone with sodium,[1] a systematic investigation of this reduction was carried out by the same group.[2–15] They isolated five hydroxy ketones and the diols as the reductive dimer and elucidated their structures by chemical degradation and spectral studies. Furthermore, many derivatives of these products were also synthesized for the structural elucidation of these dimers. Among their work, the most prominent results obtained were the classification of the five ketols into two groups acording to the orientation of the carbonyl group in the ring B[9] and a determination of the absolute configurations of the spiro-carbons of two hydroxy ketones ("bishydropulegone" and "isobishydropulegone") and the relative stereochemistries of the hydroxyl and carbonyl groups of these and other hydroxy ketones.[14] However, the stereochemistry at the C05 and C09 positions of these products has not yet been elucidated.

In this paper, we describe the molecular structure of bishydropulegone (Fig. 1) determined by an X-ray crystallographic analysis.

Experimental

Melting points were determined with a Mitamura melting point apparatus (No. 8209) and are uncorrected. IR spectra were recorded on a JEOL JIR 100 FT-IR spectrophotometer in CCl_4. ^1H NMR spectra were recorded on a JEOL FX-90Q (90 MHz) instrument in $CDCl_3$, unless otherwise stated. Coupling constants (*J*) are given in hertz.

(*R*)-(+)-pulegone was supplied by Takasago Perfumery Industrial Co., Ltd.: Bp 94—95 °C/10 mmHg (1 mmHg= 133.322 Pa); n_D^{20} 1.4875; d_4^{20} 0.9351; $[\alpha]_D^{20}$ +20.2° (*c* 1.01, $CHCl_3$).

Bishydropulegone was prepared through the oxidation of bishydropulegol, which was obtained by a modified Pascual procedure as follows.[1] Small pieces of Sodium (ca. 9 g) were gradually added to a solution of (*R*)-(+)-pulegone (10.4 g, 68.4 m mol) in ether (20 ml) in an ice bath. The whole mixture was stirred at room temperature for 24 h. Then, unreacted sodium pieces were removed and wet ether (50 ml) was added to the reaction mixture. Water (each 5 ml) was added three times over 3 d. The product was extracted with ether and the extract was washed with water and saturated brine and then dried (anhydrous sodium sulfate). The removal of the solvent left an oil (10.3 g), which was distilled to give a fraction (6.35 g, 61.5%) boiling at 90—144 °C (bath temperature/15—12 mmHg) and a residual oil (3.97 g, 38.5%). The residue was passed through a sillica-gel column by eluting with hexane–AcOEt (5:1) to give a soft mass (2.34 g). The mass was further purified using a sillica-gel column chromatography by eluting with hexane–AcOEt (10:1) to give bishydropulegol (1.20 g, 51.2% of the residue) as an amorphous soft mass. To a stirred solution of bishydropulegol (230 mg, 0.75 m mol) in acetic acid (1.6 ml) was added dropwise a 10% CrO_3–CH_3COOH solution (ca. 16 ml). After being stirred at room temperature for 24 h, the mixture was diluted with water (3.3 ml) and extracted with benzene. The extract was washed with water and saturated brine and dried (anhydrous sodium sulfate). The removal of the solvent affored an oil (214 mg), which was purified by sillica-gel column chromatography using hexane–AcOEt (10:1) as the solvent to give bishydropulegone (124 mg, 54.3%) as crystals, mp 100 °C, recrystallized from petroleum ether–EtOH (10:1); $[\alpha]_D^{19}$+72.1° (*c* 1.06, $CHCl_3$); IR (CCl_4) 3474 (intramolecularly hydrogen-bonded OH), 1678 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.86 (3H, d, *J*=6.4 Hz, Me), 1.01 (3H, d, *J*=6.4 Hz, Me), 0.87 (3H, s, Me), 0.98 (3H, s, Me), 1.09 (3H, s, Me), 1.25 (3H, s, Me), 4.97 (1H, d, *J*=2.1 Hz, OH). Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.37; H, 11.18%. Found: C, 78.64; H, 11.57%.

X-Ray diffraction analysis of bishydropulegone. For the X-ray experiments, a single crystal (0.4×0.4×0.4 mm) was mounted on a Rigaku automatic four-circle diffractometer AFC-6B using graphite monoclomated Mo *Kα* radiation (λ=0.71069 Å). Crystal data: Orthorhombic; space group $P2_12_12_1$; *a*=11.765(3), *b*=14.392(4), *c*=10.833(3) Å; *U*=1834.3 Å^3; D_x=1.110 g cm^{-3} for *Z*=4; μ(Mo *Kα*)=0.745 cm^{-1}.

Intensity data with a range $2° < 2\theta < 50°$ were collected by the ω scan method at a rate of 4° min^{-1}. The data were corrected for Lorentz, polarization factors and background effects, but not corrected for the absorption. The independent reflections (1729) were observed under the criterion $|F| > 6\sigma_F$ and were used in subsequent calculations.

The crystal structure was solved by a direct method using the program MULTAN.[16] Refinements of the structure were performed by block-diagonal least-squares calculations with anisotropic thermal parameters for non-hydrogen atoms. The hydrogen atoms were located on a difference map and included only structure-factor calculations which assumed the isotropic thermal parameters of the binding non-hydrogen atoms. The final refinement yielded an *R* value of 0.089 and an R_W of 0.103 (used unit weight).

The atomic scattering factors used were those from the literature.[17]

The absolute configuration was elucidated in the relation with (*R*)-(+)-pulegone[18] used as the reactant.

All crystallographic calculations were performed on the PANAFACOM U-1400 computer in Tokushima Bunri University (RASA and X-STANP program package) and at the computer center in Tokushima University (MULTAN program package).

Results and Discussion

The molecule is depicted in Fig. 2 (drawn by ORTEP).[19] The absolute configuration of the spirocarbon atom of bishydropulegone was unequivocally established as *R*.[14] The configuration of the 4-methyl

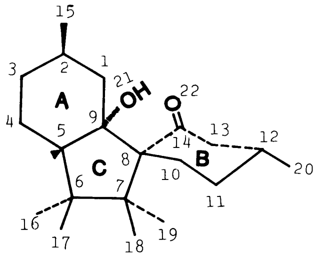

Fig. 1.

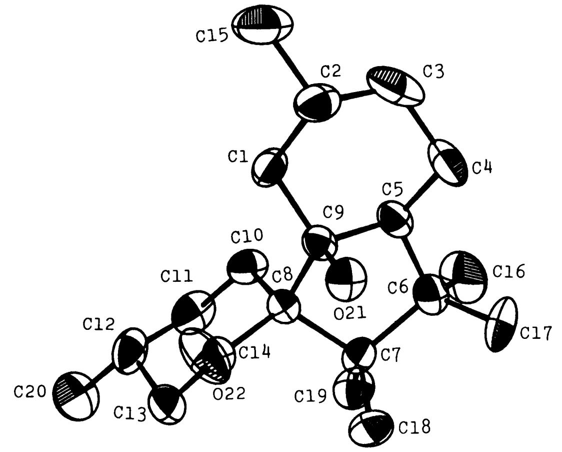

Fig. 2. ORTEP drawing of the molecular structure of bishydropulegone. Hydrogen atoms are omitted for clarity.

group relative to C06 and C07 is syn; also, the carbonyl group is syn with respect to the hydroxyl group. There is an intramolecular hydrogen bond between the hydroxyl group 021-H and the ketone 022 as shown by the short contact 2.635(8) Å[021⋯022]. This was also confirmed by measurements of the IR spectra with an FT-IR spectrometer in highly diluted solutions (2.5×10^{-3} mol dm^{-3}) of bishydropulegone (3474 and 1678 cm^{-1}).

The above results were completely the same as the conclusions obtained by Pascual et al.[14] As a new result, we showed that the ring fusion in perhydroindene is trans.

As a characteristic structural feature of bishydropulegone, the bond distances C06 and C07 [1.629 Å (11)] and C08 and C07 [1.615 Å (10)] were unusually extended. This may be due to four bulky tertiary methyl groups at C06 and C07.

In conclusion, the whole stereochemistry of bishydropulegone was determined to be (1*R*,3′a*R*,4*R*,6′*R*,7′a*S*)-7′a-hydroxy-2′,2′,3′,3′,4,6′-hexamethylspiro[cyclohexane-1,1′-indan]-2-one.

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The list of the structure factor, table of atomic parameters, bond distances, bond angles and torsion angles data has been deposited as Document No. 8649 at the Office of the Editor of Bull. Chem. Soc. Jpn.

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