

THE STEREOCHEMISTRY OF (–)-PINIDINOL, A PIPERIDINE ALKALOID FROM *PICEA ENGELMANNII*

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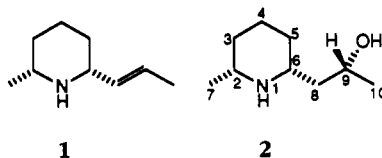
ABSTRACT.—A single crystal X-ray study on the 4-bromophenylthiocarbamate derivative of (–)-pinidinol hydrochloride established the stereostructure of this alkaloid from *Picea engelmannii* as (2*R*,6*R*)-2-methyl-6-[(2*R*)-2-hydroxypropyl]piperidine [2].

More than 30 years ago, the alkaloid (–)-pinidine [1] was reported (1) from several species of *Pinus* (Pinaceae), and its structure (2), absolute configuration (3), synthesis (4), and biosynthesis (5,6) were subsequently studied. No further alkaloids from conifers were reported until the recent discovery (7) of (–)-2-methyl-6-(2-hydroxypropyl)-piperidine, dubbed pinidinol, from needles and roots of *Picea engelmannii* Parry (Pinaceae) and its root parasite *Pedicularis bracteosa* (Scrophulariaceae). While spectral analysis allowed for assignment of the gross structure (7), both relative and absolute stereochemistry remained unelucidated, and this provided impetus for the present study.

A single crystal X-ray study of the 4-bromophenylthiocarbamate of the hydrochloride of (–)-pinidinol resulted in the structure of Figure 1, establishing the identity of (–)-pinidinol as 2, (2*R*,6*R*)-2-methyl-6-[(2*R*)-2-hydroxypropyl]piperidine.

In addition to its occurrence in Engelmann spruce, 2 has also now been found in Colorado blue spruce (*Picea pungens*),¹ Norway spruce (*Picea abies*),² and Sitka spruce (*Picea sitchensis*).³

Engelmann spruce contains α - and β -pinene as major terpene constituents (8), and hence the suggested (1) correlation



between lack of these terpenes and presence of alkaloids in the Pinaceae no longer holds. Because both Engelmann and Colorado blue spruce are attacked by spruce budworm, the previous statement (9) that “none of the hosts of spruce budworm contains alkaloids” is incorrect, and it will be of interest to determine what role, if any, this alkaloid may play in the resistance or susceptibility of spruce trees to budworm or other insects. In general, chemical studies of defensive substances in conifers have previously concentrated on terpenes.

EXPERIMENTAL

DERIVATIVE PREPARATION.—(–)-Pinidinol (7) (10 mg) was heated in a test tube with 30 mg of 4-bromophenylisothiocyanate over a small flame until the mixture liquified and then one additional minute. The tube was allowed to cool to 25° and then cooled in ice, whereupon the mixture solidified to a light tan solid. The solid was triturated twice with 0.5 ml hexane, and crystallization was attempted from EtOH/toluene. A solid was obtained whose mass spectrum was consistent with that expected for the 4-bromophenylthiocarbamate derivative of the alcohol function of pinidinol. A suitable crystal was not obtained. The solid was dissolved in EtOH, one drop of dilute aqueous HCl was added, the solution was evaporated, and the residue crystallized from EtOH/toluene to yield 1 mg of the 4-bromophenyl-

¹Schneider and Stanton, unpublished results.

²Stermitz and Tawara, unpublished results.

³Stermitz, unpublished results.

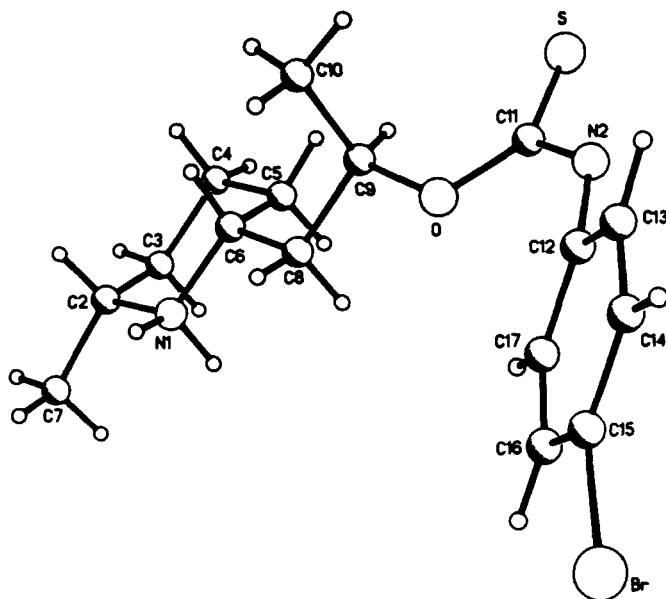


FIGURE 1. X-Ray structure of (2*R*,6*R*)-2-methyl-6-[(2*R*)-2-(4-bromophenylthiocarbamoyl)propyl]piperidine hydrochloride. The Cl⁻ was removed for clarity.

thiocarbamate derivative of pinidinol hydrochloride, mp 215–216°.

CRYSTAL DATA.—C₁₆H₂₄BrClN₂OS, 431.85 amu. Orthorhombic, clear colorless crystal. Space group *P*2₁2₁2₁, *a* = 7.451 (2) Å, *b* = 12.665 (3) Å, *c* = 19.781 (4) Å. MoKα radiation, *R* = 0.034 for 3141 unique reflections collected on a Nicolet R3m diffractometer. The intensities of the control reflections (200, 020, 002) monitored every 97 reflections showed no significant trend; Lorentz and polarization corrections were applied. The structure was solved by direct methods (program SOLV) (10). The refinements involved anisotropic thermal parameters for all non-hydrogen atoms. The hydrogen atoms were included in calculated positions. Refinement of a multiplicative factor on the imaginary components of the anomalous scattering terms indicated the correct enantiomorph. Further data and results, including tables of atomic coordinates, thermal parameters, and bond lengths and bond angles are in the Supplementary Material supplied to reviewers and available from FRS.⁴

⁴Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

ACKNOWLEDGMENTS

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