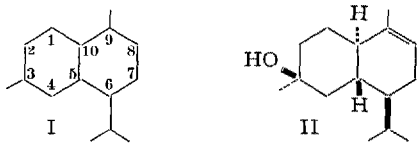
Sesquiterpenoids Minor Constituents of *Pinus parviflora*. On the Relationship between (−)-δ-Cadinol, (+)-δ-Cadinol, Sesquigoyol, Torreyol, and Brown Alga Cadinol[1-3]

The *Pinus parviflora* (var. *pentaphylla*) species is the common white pine endemic to the Japanese home islands as well as Taiwan[4]. The original investigation of the steam-distilled essential oil from this tree reported the presence of many common terpenes plus a sesquiterpene alcohol, sesquigoyol[5]. In a later structural study, sesquigoyol was formulated as 8-cadinen-3-ol[6-8]. A review article[9] on compounds possessing the cadinane skeleton (I)[10] commented on the similarity in physical properties between (−)-δ-cadinol (II) and (+)-sesquigoyol and concluded that these two compounds were mirror image forms of each other.



I II

The availability of *P. formosana*, a local variety of *P. parviflora* growing in Taiwan, prompted a reinvestigation of the constituents of this tree in the hope of reisolating sesquigoyol and comparing it with (−)-δ-cadinol. The milled wood[11] was extracted with hot petroleum ether and the organic phase was washed with aqueous base to remove the phenolic constituents. The resulting neutral extract was chromatographed over alumina (Brockman I, neutral). On gradually increasing the polarity of the eluent, the following compounds were isolated[12]: 1-docosanol (m.p. 70.5-71°C; phenylurethan, m.p. 85°C), sesquigoyol (m.p. 137–138°C; $[\alpha]_D^{27}$ + 101.96°C), β-sitosterol (m.p. 136–138°C) and 3,5-dimethoxystilbene[13] (m.p. 57.0–57.5°C; picrate, 121–122°C; trinitrobenzene adduct, 120–121°C; trinitroresorcinate, m.p. 148–149°C). It should be noted that the above naturally-occurring compounds were obtained only in very low yields. Intermediate chromatographic fractions were generally complex mixtures consisting of oils or waxes.

Sesquigoyol is considered to be the optical antipode of (−)-δ-cadinol on the basis of the following comparative data: the rotation was equal to and opposite in sign to that of (−)-δ-cadinol, the infrared spectra as determined in both a chloroform solution and in a potassium bromide pellet were indistinguishable with similar spectra from (−)-δ-cadinol, and identical chromatographic Rf values for the two alcohols were obtained by thin-layer chromatography using three totally different solvent systems. A mixed melting point determination gave a depressed melting point (126–130°C); however, such behavior between D- and L-compounds is not unusual.

Recently another sesquiterpene alcohol was isolated from the Siberian cedar[14] and subsequent work[15] ascribed to this substance the gross structure of (−)-δ-cadinol. The optical properties of the new compound, as well as the conversion of it to (+)-cadinene dihydrochloride[16,17], indicated that the substance was the mirror image isomer, or (+)-δ-cadinol. It was additionally postulated that torreyol[18,19] and sesquigoyol, on the basis of a comparison of earlier literature data, were identical with (+)-δ-cadinol[20]. These deductions for the optical relationships between (−)-δ-cadinol, (+)-δ-cadinol and sesquigoyol remain valid although the original[21] and subsequent molecular structures[22] for (−)-δ-cadinol have been replaced by a third formulation[1]. Further, it should be noted that some years ago the conclusion was drawn that sesquigoyol and torreyol were different compounds on the basis of a detailed comparison of considerable physical and chemical data[6]. Unfortunately, the original specimen of this alcohol is no longer available and this controversy can only be resolved by the reisolation and comparison of torreyol with the previously known cadinols[23].

A final comment on a fifth cadinol may be in order now. 'Brown alga cadinol' was obtained several years ago from

[1] Sesquiterpenoids II. For the previous paper in this series, see W. G. DAUBEN, B. WEINSTEIN, P. LIM, and A. B. ANDERSON, Tetrahedron *15*, 217 (1961).

[2] On leave of absence from the Department of Chemistry, National Taiwan University, Taipei, Taiwan, Republic of China.

[3] The National Council of Science, Republic of China, is thanked for the award of a fellowship for advanced study to one of us (K.-T.W.).

[4] N. T. MIROV, *Composition of Gum Turpentines of Pines* (U.S. Department of Agriculture, Technical Bulletin No. 1239, U.S. Government Printing Office, Washington 25, D.C. 1961), p. 40.

[5] Y. SEBE, J. chem. Soc. Japan *56*, 1137 (1935).

[6] Y. SEBE, J. chem. Soc. Japan *61*, 1269 (1940).

[7] SEBE actually postulated sesquigoyol to be 6-cadinen-3-ol based on the then current and accepted structure for cadinene dihydrochloride (3,6-dichlorocadinane). Subsequently, other workers showed this arrangement of chlorines to be incorrect and a revised scheme (3,9-dichlorocadinane) is now used for this basic cornerstone molecule in the sesquiterpene field. We have altered SEBE's original assignment for sesquigoyol to 8-cadinen-3-ol to conform to the modern cadinene dihydrochloride structure. Thus, his earlier elucidation work should be viewed in the light of this change.

[8] An interesting historical review of this whole area is given by J. SIMMONSEN and D. H. R. BARTON, *The Terpenes*, vol. III, 2nd Ed. (Cambridge University Press, Cambridge 1952).

[9] V. HEROUT and V. SÝKORA, Tetrahedron *4*, 246 (1958).

[10] The numbering of the cadinane nucleus here is that normally used for a steroid.

[11] We wish to thank both Mr. J. C. LIAO, Department of Forestry, National Taiwan University, for the botanical identification of the tree, and Professor Y. T. LIN, Department of Chemistry, National Taiwan University, for use of the extraction facilities in his laboratory.

[12] The optical rotation measurement was carried out in ethanol, and satisfactory elemental analyses were obtained for each substance. With the exception of sesquigoyol, the components isolated were compared with authentic specimens by using mixed melting points and spectroscopic methods (UV, IR, and NMR).

[13] We wish to thank Dr. H. ALBRECHT, Arizona Chemical Company, Panama City, Florida, for a sample of 3,5-dimethoxystilbene and its TNB adduct.

[14] V. A. PENTEGOVA, O. MOTL, and V. HEROUT, Coll. Czech. Chem. Comm. *26*, 1362 (1961).

[15] V. A. PENTEGOVA, O. MOTL, and V. HEROUT, Dokl. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk *138*, 850 (1961).

[16] The absolute configuration of (−)-cadinene dihydrobromide was established by V. SÝKORA, V. HEROUT, and F. SORM, Coll. Czech. Chem. Comm. *23*, 2181 (1958).

[17] A new chemical correlation between ε-cadinene and (−)-cryptone has confirmed the assignment of configuration in this series. See M. D. SOFFER, G. E. GUNDY, O. KORMAN, and M. A. ADAMS, Tetrahedron Letters 389 (1963).

[18] K. NISHIDA and H. UOTA, J. Soc. Chem. Ind. Japan, Suppl. bind. *43*, 64 (1940).

[19] K. NISHIDA and H. UOTA, J. Soc. Chem. Ind. Japan, Suppl. bind. *44*, 119 (1941).

[20] We wish to thank Dr. O. MOTL for sending us recently a sample of (+)-δ-cadinol. This material was shown to be identical with sesquigoyol through use of mixed melting point and infrared spectral methods. A depressed melting point was observed with (+)-δ-cadinol.

[21] O. MOTL, V. SÝKORA, V. HEROUT, and F. SORM, Coll. Czech. Chem. Comm. *23*, 1297 (1958).

[22] F. ALDERWEIRELDT, G. CHIURDOGLU, R. R. SMOLDERS, A. SOQUET, and M. VERZELE, Bull. Soc. Chim. Belg. *70*, 470 (1961).

[23] K. NISHIDA, personal communication.

Dictyopteris divaricata[24]. The reported physical properties (rotation and melting point) of both the alcohol and the related acetate were identical to the literature values for (−)-δ-cadinol and its acetate. A recent comparison between the 'alga cadinol' and (−)-δ-cadinol showed that these two alcohols were one and the same compound[25]. This same possibility was considered in the previously cited review article[9].

Zusammenfassung. 1-Dokosanol, Sesquigoyol, β-Sitosterin und 3,5-Dimethoxystilben wurden aus *P. formosana* isoliert. Es konnte gezeigt werden, dass Sesquigoyol der optische Antipode von (−)-δ-Cadinol ist.

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Department of Chemistry, Stanford University, Stanford (California, U.S.A.), June 13, 1963.

[24] M. TAKASKA and Y. ANDO, J. Chem. Soc. Japan, Pure Chem. Sect. *72*, 999 (1951).
[25] T. IRIE, personal communication.

Sur les équilibres d'épimérisation des *cis*- et *trans*-4-tertiobutylcyclohexanols

Les isomères *cis* et *trans* du 4-tertiobutylcyclohexanol constituent des composés conformationnellement homogènes particulièrement utiles pour l'étude de la stéréochimie des dérivés cyclohexaniques monocycliques.

On a procédé à l'épimérisation du 4-tertiobutylcyclohexanol par action de 1,2 équivalents d'un métal alcalin dans le benzène au reflux. Les conditions opératoires et la méthode de dosage sont décrites antérieurement[1,2]. D'autre part, en se basant sur les données de la littérature[3–6], on a réduit la 4-tertiobutylcyclohexanone par transfert catalytique d'hydrogène. Ainsi, 1 g de 4-tertiobutylcyclohexanone, 1 g de nickel de Raney et 3 ml de butanol secondaire sont chauffés au reflux pendant 80 h dans 30 ml de benzène sous agitation. Le mélange réactionnel est isolé avec une rendement global de 95%. Il est constitué des isomères *cis* et *trans* du 4-tertiobutylcyclohexanol dont les proportions sont analysées par spectrométrie infrarouge comme décrit précédemment[1]. Les résultats sont consignés dans le Tableau.

Epimérisation des *cis*- et *trans*-4-tertiobutylcyclohexanols

Agent épimérisant	Conditions	Rendement	% *trans*	Référence
Lithium/benzène	80°; 48 h	90%	84,5 ± 1	ce travail
Sodium/benzène	80°; 48 h	90%	83,0 ± 1	1
Potassium/benzène	80°; 48 h	90%	92,0 ± 1	2
Rubidium/benzene	80°; 48 h	90%	91,5 ± 1	ce travail
Caesium/benzène	80°; 48 h	90%	89,5 ± 1	ce travail
Nickel de Raney/H_2 cyclohexane	110°; 10 h	95%	66,0 ± 2	1
Nickel de Raney butanol-2/benzène	80°; 80 h	95%	63,0 ± 1	ce travail

L'on constate que les proportions en isomères *cis* et *trans* obtenus par épimérisation catalytique au nickel de Raney en présence d'hydrogène de même que par réduction par transfert catalytique d'hydrogène correspondent à l'équilibre thermodynamique des isomères *cis* et *trans* du 4-tertiobutylcyclohexanol[1,2,7,8]. En d'autres termes, la différence d'énergie libre déterminée par la relation $\Delta F = RT\ ln\ K$ vaut approximativement 0,4 Kcal/mole.

L'épimérisation par les alcoolates fournit des valeurs différentes pour les proportions de dérivé *cis* et *trans*. Il a été établi antérieurement[2], que pour ce type d'équilibrations, le titre en isomère *trans* de l'épimérisat est défini par:

$$X^{exp}_{trans} = X^{[B=0]}_{A_e,\text{ équilibre}} + (X^{[A=0]}_{B_e,\text{ équilibre}} - X^{[B=0]}_{A_e,\text{ équilibre}})\ [B]/C_A$$

(X: titre molaire; A_e et A_a: alcools équatoriaux et axiaux; B_e et B_a: complexes alcoolates correspondants; C_A: concentration totale en cyclanol).

Pour les métaux alcalins et dans les conditions expérimentales appliquées ici on a: $[B]/C_A = 1$ et $[A] = 0$. Dès lors,

$$X^{[B=0]}_{A_e,\text{ équilibre}} = 0 \quad \text{et} \quad X^{exp}_{trans} = X^{[A=0]}_{Be,\text{ équilibre}}.$$

En conclusion, l'équilibre mesuré correspond à l'équilibre conformationnel des complexes du type alcoolate des isomères *cis* et *trans* du 4-tertiobutylcyclohexanol. Il diffère de l'équilibre entre les alcools stéréoisomères libres et dépend du métal. Ainsi, la nature du métal employé semble jouer un rôle dans le compromis des interactions intramoléculaires attractives et répulsives déterminant l'équilibre entre les stéréoisomères envisagés. L'influence du métal dans les épimérisations intervient probablement en partie dans l'explication de la stéréochimie des réductions des cyclanones par les borohydures[9]. La stéréochimie des produits de réduction des cyclanones par des métaux dans l'ammoniac liquide dépend d'autre part egalement du métal employé[10].

Summary. In contrast with the catalytic isomerization of *cis* and *trans*-4-tertiobutylcyclohexanols, epimerization of this alcohol by a slight excess of an alkaline metal does not afford a correct measure of the relative stability of the two stereoisomers. The equilibrium which is reached depends on the metal which is used for the epimerization.

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[2] G. CHIURDOGLU, H. GONZE et W. MASSCHELEIN, Bull. Soc. Chim. Belg. *71*, 484 (1962).
[3] D. PAPA, E. SCHWENK et B. WHITMAN, J. org. Chem. *7*, 586 (1942).
[4] C. H. MILLIGAN et E. E. REID, J. Amer. chem. Soc. *44*, 202 (1922).
[5] R. MOZINGO, C. SPENCER et K. FOLKERS, J. Amer. chem. Soc. *66*, 1859 (1944).
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[9] W. M. JONES et H. E. WISE, J. Amer. chem. Soc. *84*, 997 (1962).
[10] G. OURISSON et A. RASSAT, Tetrahedron Letters *21*, 16 (1960).