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SESQUITERPENE ALCOHOLS FROM *ARTEMISIA PYGMAEA**

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Key Word Index—*Artemisia pygmaea*; Compositae; sesquiterpene alcohol; eudesmane; stereochemistry, mass spectral fragmentation; chemotaxonomy.

Abstract—*Artemisia pygmaea* Gray contains two sesquiterpene alcohols: the known cryptomeridiol (I) and pygmol (II), a new compound. No sesquiterpene lactones were found in the plant although other species of the section *Tridentatae* Rydb., with which *A. pygmaea* has been classified, are usually rich in lactones.

INTRODUCTION

EARLIER[1] and continuing studies of the sesquiterpene lactones of the North American members of the section *Seriphidium* Besser,[2] most of which are included in Beetle's section *Tridentatae*,[3] have shown that while there is a wide diversity in the chemical composition of these species, the lactones that characterize them are either closely related in structure or show relationships that can be accommodated within a rational hypothesis of their biosynthetic pathways.[4]

Artemisia pygmaea Gray is included in the section by some authors, but was regarded by Rydberg as excluded from this group and as forming a monotypic section *Pygmaea.*[5] Support for Rydberg's view was found by Holbo and Mozingo[6] on the basis of chromatographic studies (constituents not chemically identified), whose work disclosed the absence of species- and section-diagnostic spots on chromatograms of this species.

Artemisia pygmaea has now been examined for the presence of sesquiterpene lactones, and Holbo and Mozingo's conclusion is supported by the present results. No lactones were found in our specimen of the plant, but two sesquiterpene alcohols, whose structures bear a suggestive relationship to the lactones common to some members of the section, were isolated.

RESULTS AND DISCUSSION

Cryptomeridiol (I, selinane-4,11-diol) has been isolated from the gymnosperms *Widdringtonia dracomontana* Stapf.,[7] *Fokenia hodginsii* Henry and Thom.,[8] *Cryptomeria japonica*

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[1] GEISSMAN, T. A. and IRWIN, M. A. (1970) *Pure Appl. Chem.* **21,** 167.

[2] WARD, G. H. (1953) *Contr. Dudley Herbarium* **4,** 155.

[3] BEETLE, A. A. (1960) *Univ. Wyom. Agric. Exptl Sta. Bull.* No. 368.

[4] GEISSMAN, T. A. (1972) *Biosynthesis of Sesquiterpene Lactones of Compositae, Proc. XI Annual Symposium Phytochem. Soc. No. Amer., Monterrey, Mexico, October,* 1971, Academic Press, New York.

[5] RYDBERG, P. A. (1916) *N. Am. Flora* **34,** 224.

[6] HOLBO, H. R. and MOZINGO, H. N. (1965) *Am. J. Bot.* **52,** 970.

[7] ERDTMAN, H. and THOMAS, B. R. (1958) *Acta Chem. Scand.* **12,** 267.

[8] DOLEJŠ, L. and HEROUT, V. (1961) *Colln Czech. Chem. Commun.* **26,** 2045.

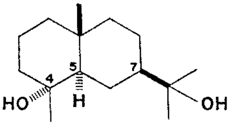
D. Don,[9] and *Callitris columellaris* F. Meull.[10] Its isolation from *A. pygmaea* represents its first known occurrence outside the Cupressaceae and Taxodiaceae. The compound agreed in composition and melting point ($C_{15}H_{28}O_2$, m.p. 134·5–135·5°) with the reported[7–9] values, and its spectral characteristics were in agreement with structure I. The MS did not show the molecular ion (*m/e* 240), but prominent fragment ions at M—18, M—18–18 and M—15–18–18 are accounted for by the presence of two hydroxyl groups. The base peak, *m/e* 59, is attributed to the ion $[(Me)_2COH]^+$, derived from the side chain at C-7.[11]

Table 1. NMR spectra of *A. pygmaea* sesquiterpenes

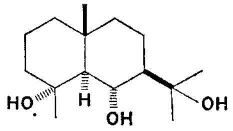
Compound	10-Me	4- and 11-Me	5-H	6-H	OH
I	0·86	1·11, 1·20, 1·20			1·72
II	0·87	1·20, 1·26, 1·34	1·42 (10·7)	4·18 (10·7/9·2)	5·2, 6·4; 5·65 (TFA)
III	0·89	1·20, 1·25, 1·49	2·35	—	3·48

Values are δ (*J* Hz), measured in $CDCl_3$.

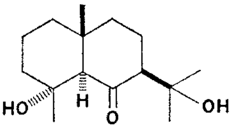
The NMR spectrum (Table 1) displays four 3-proton singlets for the methyl groups, and a sharp signal at δ 1·72 for the tertiary hydroxyl groups. No absorption below δ 2·0 was observed. These signals are completely in accord with the structure I and, coupled with the composition and melting point, establish the identity of the compound as cryptomeridiol.



(I) Cryptomeridiol

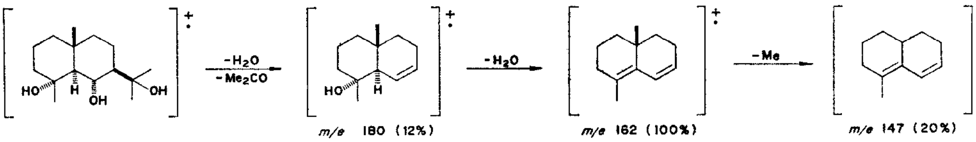


(II) Pygmol



(III)

Pygmol (II), $C_{15}H_{28}O_3$, m.p. 149–150·5°, showed IR absorption for hydrogen-bonded hydroxyl groups at 3320 cm^{-1}, and weak absorption at 3560 cm^{-1}. No MS molecular ion (*m/e* 256) was observed, but prominent fragment ions at M—15, M—18, M—15–18, M—18–18, M—15–18–18, M—18–18–18 and M—15–18–18–18 show that pygmol contains three hydroxyl groups. Other observed ions can be accounted for by the fragmentation shown in Scheme 1.



Scheme 1. MS fragmentation of pygmol.

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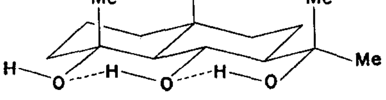
[9] Sumimoto, M., Ito, H., Hirai, H. and Wada, K. (1963) *Chem. & Ind.* 780.

[10] Rudman, P. (1964) *Chem. & Ind.* 808.

[11] Budzikiewicz, H., Djerassi, C. and Williams, D. H. (1964) *Structure Elucidation of Natural Products by Mass Spectrometry*, Holden-Day, San Francisco.

The NMR spectrum (Table 1) shows signals for the four methyl groups similar to those in the spectrum of cryptomeridiol; 3-proton singlets are seen at δ 0·87, 1·20, 1·26 and 1·34. The proton at C-6, coupled with H-5 (11 Hz) and H-7 (9 Hz), gave a quartet at δ 4·18, and was clearly *trans*-disposed to the 2 adjacent protons. The C-5 proton, spin-isolated from all protons except H-6, gave a doublet (11 Hz) at δ 1·42. The hydroxyl protons gave very broad peaks ($W_{1/2}$ = 30 Hz) at δ 5·2 (2 protons) and 6·4 (1 proton), which were altered to a single sharp peak at δ 5·65 on addition of a trace of trifluoroacetic acid. The low-field position and extreme breadth of these signals is strongly indicative of intramolecular hydrogen bonding.

It is noteworthy that the R_f (TLC) of pygmol, a triol, is higher than that of cryptomeridiol (0·30 vs. 0·15 on silica gel, acetone–$CHCl_3$, 3:7). This is consistent with the evidence from the NMR and IR spectra that the hydroxyl groups in pygmol are strongly hydrogen bonded. A probable conformation of pygmol is the following (IV):



(IV)

Chromic acid oxidation of pygmol (II) yielded a compound which was characterized by its IR and NMR spectra as the expected ketone (III). Its IR spectrum showed the carbonyl stretching frequency at the unusually low frequency of 1680 cm^{-1}, probably as a result of hydrogen bonding with one of the two tertiary hydroxyl groups. The OH stretching frequency showed this bonding, with strong absorption at 3520 cm^{-1} and a weak band at 3630 cm^{-1}. The NMR spectrum displayed the C-5 proton as a singlet at δ 2·35 and the hydroxyl protons as a broad band ($W_{1/2}$ = 18 Hz) at δ 3·5.

The above data establish the structure of pygmol as II. It is of special interest that *A. pygmaea*, a member of the section *Tridentatae*, has yielded no sesquiterpene lactones while other species within this section are notable for the quantity and structural variety of the lactone that they contain. It is also noteworthy that the nuclear C-6 hydroxyl group[12] appears at the position of the lactone ring closure in the typical lactones of the genus. Its presence cannot, of course, be regarded as an indication that conversion of a 7-isopropenylgermacradiene to a C-6/C-7 fused sesquiterpene lactone involves hydroxylation of C-6 as a step prior to oxidation of the isopropenyl group to the relevant carboxylic acid, but it does present the possibility. It will be recalled that the arbusculins,[13] present in *A. arbuscula* (section Tridentatae), represent a group of sesquiterpene lactones of relatively simple structure, being the lactones derived, in the simplest case, by lactone formation at C-6/C-7 in a precursor that could be pygmol.[14]

EXPERIMENTAL

Spectra were measured on: NMR, Varian A60-D; MS (70 eV, direct insertion), AEI-MS9; IR ($CHCl_3$) Perkin–Elmer 237.

Isolation of cryptomeridiol (I) *and pygmol* (II). A 4·67-kg sample of the dried and ground aerial part of

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[12] The hydroxyl groups at C-4 and C-11 can be considered as arising by the reaction with water of carbonium ion centers generated in the cyclization steps.

[13] IRWIN, M. A. and GEISSMAN, T. A. (1969) *Phytochem.* **8**, 2411.

[14] For additional comment, see GEISSMAN, Ref. 4.

A. pygmaea[15] was extracted with $CHCl_3$. The residue remaining after removal of the solvent was partitioned between 3 l. of 75% aq. MeOH and 3 l. of hexane. The hexane phase was reextracted with 75% MeOH, and the combined MeOH phases were washed with hexane and concentrated to a gummy residue. This was chromatographed over a column of silica gel (8 × 45 cm), with benzene—$CHCl_3$ (1 : 1) containing increasing amounts of acetone. Twenty-nine 500-ml fractions were collected. Fractions 3–9 yielded a mixture of flavonoid compounds, which are under examination.[16] Fractions 12–19 were evaporated and the residue taken up in $CHCl_3$ and washed with aq. sodium carbonate. Chromatography of the $CHCl_3$ solution yielded 4·8 g of pygmol (II). Fractions 20–23 yielded 1·16 g of cryptomeridiol (I).

Cryptomeridiol, purified by sublimation as very fine needles, had m.p. 134·5–135·5°, $[\alpha]_D^{24}$ $-25{\cdot}8°$ (reported,[7] m.p. 137–138°, $[\alpha]_D$ $-24°$; reported,[8] m.p. 137·5°, $[\alpha]_D$ $-21{\cdot}7°$; reported,[9] m.p. 134·5–135·5°, $[\alpha]_D$ $-33{\cdot}3°$). Its IR spectrum showed bands at 3565 and 3400 cm^{-1}. The MS showed ions at *m/e* (rel. int.) 222 (3·0, M−18), 204 (26), 189 (32) and others including 59 (100). The NMR spectrum has been described above (*Anal.* Calc. for $C_{15}H_{28}O_2$: C, 74·95; H, 11·74. Found: C, 74·89; H, 11·71%).

Pygmol, crystallized as colorless granules (from Et_2O), had m.p. 149–150·5°. The IR spectrum showed bands at 3560 and 3320 cm^{-1}, and the MS showed ions at *m/e* (rel. int.) 241 (0·65, M−15), 238 (2·2), 223 (11), 220 (3·0), 205 (6·7), 202 (2·3), 187 (5·7), 180 (12), 177 (3·3), 165 (13), 163 (16), 162 (100), 147 (20), 137 (12), 122 (49), 109 (32), 95 (72), 93 (24), 85 (28), 59 (48), 43 (50) and 41 (24). The NMR spectrum has been described above (*Anal.* Calc. for $C_{15}H_{28}O_3$: C, 70·27; H, 11·01. Found: C, 70·32; H, 10·82%).

Dehydropygmol (III). Pygmol (350 mg) was treated with a solution of 130 mg of CrO_3 in 10 ml of HOAc. The $CHCl_3$ extract of the H_2O-diluted solution was chromatographed on silica gel, and the fractions containing III (TLC) were collected and the solvent removed. The IR spectrum showed absorption at 3630, 3520 and 1860 cm^{-1}. The NMR spectrum is described above. The compound, which could not be crystallized, was unstable and decomposed on keeping.

Acknowledgements—This study was supported by a research grant CM-14240 from the U.S. Public Health Service. Analyses are by Miss Heather King, U.C.L.A.

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[15] Collected by Mr. R. J. BARR (Voucher No. RJB-81568-APG) near Fredonia, Conconino Co., Arizona (August, 1968).

[16] RODRÍGUEZ, E., CARMAN, N. J., VANDER VELDE, G., MCREYNOLDS, J. H., MABRY, T. J., IRWIN, M. A. and GEISSMAN, T. A. (1972) *Phytochem.* **11**, 3509.