Phytochemistry, 1970, Vol. 9, pp. 59 to 62. Pergamon Press. Printed in England.

SESQUITERPENE LACTONES. PSILOTROPIN FROM *PSILOSTROPHE COOPERI*

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(*Received* 16 *June* 1969)

Abstract—Psilotropin (I) is a sesquiterpene dilactone which differs from vermeerin (V) in the stereochemistry of the γ-lactone ring. The stereochemistry of the δ-lactone fusion is ambiguous, and that of the C-10 methyl group has not been established.

INTRODUCTION

IN FURTHER study of Compositae of the tribe Helenieae, the common south-western desert shrub *Psilostrophe cooperi* (Gray) Greene has been examined for the presence of constituents of the sesquiterpenoid lactone class. A compound, psilotropin, isolated from the plant and found by TLC examination of total extracts to be the principal constituent of this class of compounds present, has been found to be a dilactone, stereoiosmeric with vermeerin, a constituent of *Geigeria aspera* Harv.,[2] a member of the tribe *Inuleae*.

RESULTS AND DISCUSSION

Psilotropin, $C_{15}H_{20}O_4$, m.p. 144–145°, was isolated in 0·2 per cent yield from the above ground parts of *Psilostrophe cooperi*. Its i.r. and u.v. absorption (1767, 1734, 1645 cm^{-1}; 209, nm, $\log \epsilon$ 4·05) indicated its sesquiterpenoid lactonic character, a conclusion confirmed by the NMR spectrum. The latter showed the characteristic pair of doublets at δ 5·57 and 6·26 ($J = 3$ Hz) for the protons of the α-methylene-γ-lactone grouping common to this class of compounds. Signals for two methyl groups (3H each) at δ 1·08 (singlet) and 1·10 (doublet, $J = 6$ Hz) suggested the psilotropin was a pseudoguaianolide. The i.r. band at 1734 cm^{-1} is that of a δ-lactone of a kind different from that found in psilostachyin C.[3] Its structure was shown to be that depicted in I (Chart 1) by the character of the NMR signals for the protons at C-2 and C-4. The latter was seen as a sharp and symmetrical AB quartet at δ 3·82 and 4·12 ($J = 11$). Of the protons of the methylene group (C-2) adjacent to the carbonyl group, one was clearly discernible as a doublet of doublets ($J = 17$, 5 Hz) at δ 2·85; the other was obscured by signals in the region of δ 2·0–2·4. The lactonic (C*H*—O) proton was seen as an octet at δ 4·77, showing that the lactone was closed at C-8 rather than C-6. These observations are satisfactorily accommodated by structure I, which is that of a pseudoguaianolide that has been modified by an oxidative ring cleavage between C-3 and C-4.

Chemical confirmation of certain of these structural features was found in the following

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[1] Contribution No. 2420 from the Chemistry Department, UCLA.

[2] L. A. P. ANDERSON, W. T. DEKOCK, L. G. R. PACHLER and C. M. BRINK, *Tetrahedron* 23, 4153 (1967).

[3] H. B. KAGAN, H. E. MILLER, W. RENOLD, M. V. LASHMIKANTHAM, L. R. TETHER, W. HERZ and T. J. MABRY, *J. Org. Chem.* 31, 1629 (1966).

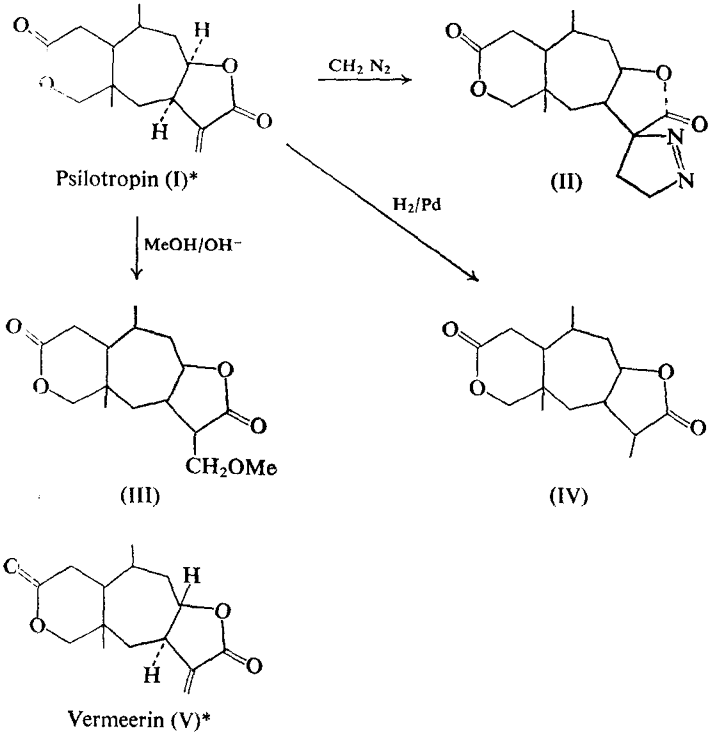

CHART 1.

transformations. Psilotropin readily formed a pyrazoline (II) when treated with diazomethane; it added the elements of methanol at the 11,13-double bond to give the 13-methoxy-11,13-dihydro compound (III); and it was reduced to the 11,13-dihydro compound (IV) with hydrogen and palladium–charcoal. All of these compounds had spectral properties (i.r., u.v., NMR., MS) in complete accord with the structures shown in Chart 1.

Structure I is identical in its gross features with that of vermeerin (V).[2] Indeed, psilotropin and vermeerin have nearly the same melting point, and most of the details of the NMR spectra of the two compounds show a close correspondence. Significant differences between the compounds exist with respect to the optical rotations of the compounds and their derivatives, and the chemical shift of the lactonic proton at C-8. Psilotropin (I) and its derivatives (II and III) have positive optical rotations; vermeerin (V) and the corresponding derivatives have negative rotations. The NMR signal for the proton at C-8 in psilotropin is an octet at δ 4·77, while that in vermeerin is described[2] as an octet at δ 3·95.

That psilotropin (m.p. 144–145°) and vermeerin (m.p. 143–145°) are not identical was shown by direct comparison,[4] and studies of the circular dichroism of the two compounds at the $n \to \pi^*$ transition of the γ-lactone showed that they differ in the sterochemistry of the γ-lactone ring. Psilotropin shows a strong negative Cotton effect, showing that the C-7/C-8 lactone is *cis*. The circular dichroism curve of vermeerin was almost the mirror image of that of I, showing that the γ-lactone is *trans*-fused.[5]

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* Only the stereochemistry of the γ-lactone is explicit in these formulas.

[4] We thank Dr. deKock for a specimen of vermeerin.

[5] T. G. WADDELL, W. STÖCKLIN and T. A. GEISSMAN, *Tetrahedron Letters* 1313 (1969).

The dilactonic character of psilotropin, suggested by the i.r. absorption at 1734 cm^{-1}, by the features of the NMR spectrum described above, and by the absence of ketonic absorbtion in the u.v., was further demonstrated by titration: two equivalents of alkali were consumed. Moreover, the signals for the —CH$_2$O— and —CH$_2$CO— protons of psilotropin correspond in chemical shifts with those reported for δ-valerolactone (δ 4·09 and 2·27 respectively) and with the same groupings of vermeerin.[2]

The sterochemistry at C-1, C-5 and C-10 in psilotropin have not been established.[6] Biogenetic considerations would lead to the assumption that the C-5 methyl group is β-disposed and that C-1 H is α. Attempts to decide this question by examination of the circular, dichroism at the $n \rightarrow \pi^*$ transition of the δ-lactone gave results that were regarded as ambiguous, for the uncertainties in the conformation of the δ-lactone ring are such as to render such evidence inconclusive. In addition, attempts to establish the configuration at C-10 by oxidation of psilotropin to methylsuccinic acid were unsuccessful, for, while the vigorous oxidation of psilotropin yielded crude mixtures that could be shown (by TLC) to contain methylsuccinic acid, the pure acid could not be obtained in sufficient amount to establish its identity. Further studies on the stereochemistry of these positions will be pursued when additional material can be secured.

EXPERIMENTAL

M.ps were taken in capillaries and are corrected. Spectral measurements were made with Beckman IR4 (i.r.), Varian A60D (NMR) and AEI-MS9 (m.s.) instruments.

Psilotropin (I)

Psilostrophe cooperi (Gray) Greene was collected in May, 1968, at Chuckawalla Bench, Colorado Desert, Arizona.[7] The dried plant (1·75 kg) was ground in a Wiley mill and exhaustively extracted with CHCl$_3$. Removal of the solvent left a tar (63 g) which was dissolved in 500 ml of hot ethanol, to which was added 1500 ml of hot water. After separation from a tarry precipitate and clarification by filtration, the aqueous solution was extracted with CHCl$_3$ to give 14 g of a brown-green oil that showed several components on TLC, the principal one being psilotropin. Chromatography of the oil on silica gel (1 kg) and elution with solvents ranging from benzene–CHCl$_3$ to CHCl$_3$–acetone mixtures resulted in the separation, in benzene–CHCl$_3$ (1 : 9), and CHCl$_3$ eluates, of 3·6 g of psilotropin. Crystallized from ethyl acetate–petroleum ether, it formed colorless rosettes, m.p. 144–145°; $[\alpha]_D^{25}$ +63·8° (*c.* 0·46, ethanol); u.v. max 209 nm, ϵ 11,200; i.r. (CHCl$_3$), 1767, 1734, 1645 cm^{-1}. The mass spectrum showed the molecular ion of *m/e* 264. The NMR spectrum has been described above. (Found: C, 68·14; H, 7·69. Calc. for C$_{15}$H$_{20}$O$_4$: C, 68·14; H, 7·63%.)

Pyrazoline Derivatives of Psilotropin (II)

Treatment of a cold methanol solution of psilotropin with an excess of CH$_2$N$_2$ (in ether) yielded the pyrazoline; colorless leaflets from methanol–ether, m.p. 131–132°; $[\alpha]_D^{25}$ +229°; Mass spectrum, *m/e* 306 (M$^+$). (Found: C, 62·69; H, 7·22. Calc. for C$_{16}$H$_{22}$O$_4$N$_2$: C, 62·72; H, 7·24%.)

11,13-*Dihydro*-13-*methoxypsilotropin (III)*

A solution of 108 mg of psilotropin in 5 ml of methanol containing a trace of NaOMe was heated for 1 hour, acidified, diluted with water and extracted with CHCl$_3$. Evaporation of the CHCl$_3$ left a solid residue which crystallized from CHCl$_3$–petroleum ether as colorless needles, m.p. 153–155°; $[\alpha]_D^{25}$ +53·8°; M$^+$, *m/e* 296. The i.r. spectrum showed the γ-lactone at 1775 and the δ-lactone at 1734 cm^{-1}. (Found: C, 64·82; H, 8·16. Calc. for C$_{16}$H$_{24}$O$_5$: C, 64·82; H, 8·16%.)

11,13-*Dihydropsilotropin (IV)*

Reduction of psilotropin in ethanol with Pd-C in the usual way gave the dihydro compound; colorless needles (from acetone), m.p. 218°. The mass spectrum showed the molecular ion at *m/e* 266, but a small peak at *m/e* 264 showed that a trace of unreduced compound remained. The NMR spectrum, however, showed no vinyl proton and no vinyl methyl group signals. The i.r. spectrum showed peaks at 1750 and 1725 cm^{-1}, and the NMR spectrum contained the following signals: δ 4·60 (1H, C-8 H); δ 3·80 (center of AB quartet of —CH$_2$O—, J=11 Hz); δ 1·00 (3H, methyl at C-5); δ 1·00 (6H, d, J=8 Hz, methyls at C-10, C-11). (Found: C, 67·47; H, 8·19. Calc. for C$_{15}$H$_{22}$O$_4$: C, 67·64; H, 8·33%.)

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[6] The C-7/C-11 bond is assumed to be β, as in all other known lactones of the class.

[7] Collected by Mr. R. J. Barr, Voucher number RJB-68271.

Comparison of Psilotropin and Vermeerin

A specimen pf vermeerin (reported[2] m.p. 147°) had m.p. 143–145° (to a gel which decomposed at about 290°). A mixture of this with psilotropin, which melted sharply at 144–145°, melted over the range 137–185°. Upon TLC comparison of vermeerin and psilotropin in four solvent systems, the two compounds were in every case clearly separated by about 0·1–0·2 R_f units. In the i.r. spectrum reported for vermeerin[2] ($CHCl_3$) the two lactone carbonyl bands appeared at 1745 and 1730 cm^{-1}, while in our spectrum of psilotropin ($CHCl_3$) these absorptions were seen at 1767 and 1734 cm^{-1}. The differences in the NMR spectra (particularly in the signals for the protons at C-8) have been discussed above.

Acknowledgements—One of us (L.B.S.) is grateful for a Fulbright Research Scholarship. Part of the costs of this study were provided under a research grant, GM-14240-03, from the U.S. Public Health Service. Analyses are by Miss Heather King. We thank Mr. T. G. Waddell for carrying out the circular dichroism measurements.