Phytochemistry, 1974, Vol. 13, pp. 611 to 613. Pergamon Press. Printed in England.

PICRIDIN AND DIHYDROPICRIDIN: REVISED STRUCTURES*

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(*Received* 31 *July* 1973. *Accepted* 10 *September* 1973)

Key Word Index—*Picridium cristallinum*; Compositae; sesquiterpene lactones; picridin; dihydropicridin; desacetylmatricarin; ψ-taraxasterol.

Abstract—The structures of dihydropicridin and picridin, two sesquiterpene lactones isolated from *Picridium cristallinum* Sch. Bip., are revised. Desacetylmatricarin and ψ-taraxasterol were also obtained from the same plant.

INTRODUCTION

IN A previous communication[1] we gave provisional structures to picridin and dihydropicridin, two new sesquiterpene lactones from *Picridium cristallinum* Sch. Bip., a Composite endemic to the Canary Isles. The present work, based on chemical and spectroscopic evidence, shows that these compounds are not eudesmanolides but guaianolides and correspond to the formulae **2** and **1**a, respectively.

RESULTS AND DISCUSSION

The less polar chromatographic fractions of the plant extract gave only ψ-taraxasterol. From the more polar ones we obtained dihydropicridin (**1**a), picridin (**2**) and desacetylmatricarin, the last compound being identified by spectral data[2] and conversion to matricarin.[3]

Dihydropicridin (**1**a), $C_{15}H_{20}O_4$, shows IR bands of OH, γ-lactone, α,β-unsaturated ketone and double bonds (3400, 1780, 1695 and 1615 cm^{-1}). The last one, very strong, is characteristic of enones with cisoid configuration.[4] In the UV it absorbs at 255 nm (ε 10^4). Its NMR spectrum displays a doublet centred at τ 8·75 corresponding to the Me–C_{11} and a singlet at 7·65 assigned to the Me–C_{10}. Another singlet at τ 7·55, which disappears on adding D_2O, must correspond to an OH function. The proton at C_6 appears as a triplet at τ 6·25 superimposed to a complex signal. In the acetate **1**b the latter signal is deshielded by 0·5 ppm which indicates that **1**a has a primary OH group. This is confirmed by the presence of a fragment $[M^+ - 31]$ in the MS of dihydropicridin. The nature of the skeleton was determined by dehydrogenation of **1**a with Se, obtaining chamazulene which was characterized by its TNB adduct.

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* Part XXIV in the series "Constituents of Compositae". For Part XXIII see GONZÁLEZ, A. G., BERMEJO, J., BRETÓN, J. L., MASSANET, G. M. and TRIANA, J. (1974) *Phytochemistry* **13**, in press.

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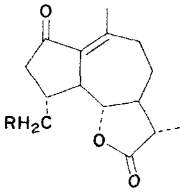
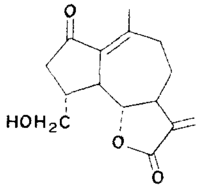
In order to relate **1a** to a substance of known structure and stereochemistry, the following reaction sequence was carried out: treatment of **1a** with TsCl gave **1c** which was refluxed with NaI in HOAc to yield **1d**. This compound gave a positive Beilstein test for halogen and in the UV absorbs at 255 nm (ϵ 11000); its NMR spectrum shows a signal at τ 6·32 attributed to $-CH_2I$. Reduction of **1d** with Zn in HOAc afforded **1e**, $C_{15}H_{20}O_3$, which still has a UV band at 255 nm but in the NMR spectrum, instead of the $-CH_2I$ signal, there appears a doublet at τ 8·80 corresponding to the Me–C_4.[5,6] Elimination of the carbonyl via the thioketal followed by Raney Ni desulfurization gave guai-1(10)-en-6,12-olide as an oil which was identified by direct comparison with an authentic sample.[7] Hence, **1a** must have the structure of 15-hydroxy-2-oxo-guai-1(10)-en-6,12-olide.

Picridin (**2**), separated from **1a** and desacetylmatricarin by preparative TLC, was obtained in very small quantity as an oil, whose UV spectrum reveals the presence of the same chromophore as in dihydropicridin. Its NMR data are very similar to those of **1a**, only that instead of the doublet at τ 8·75 appear two at 3·90 and 4·92 (*J* 3 Hz) attributable to an exocyclic $=CH_2$ conjugated with a lactone. Hydrogenation of **2** over PtO_2 yielded **3**, which was also obtained from **1a** under identical conditions. These findings prove that **2** is the 11(13)-dehydro derivative of **1a** and must have the structure 15-hydroxy-2-oxo-guai-1(10),11(13)-dien-6,12-olide.

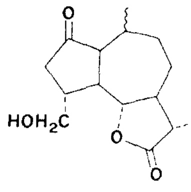


(1a) R = OH
(1b) R = OAc
(1c) R = OTs
(1d) R = I
(1e) R = H

(1)



(2)



(3)

EXPERIMENTAL

M.ps, determined on a Kofler block, are uncorrected. Solvent used for recrystallizing compounds was petrol.–EtOAc. Optical activities were measured in $CHCl_3$, UV spectra in EtOH and NMR spectra in $CDCl_3$ with TMS as internal reference. Column and dry column chromatography was realized on silica gel 0·2–0·5 and 0·063–0·20 mm, respectively. The spray reagent for TLC was H_2SO_4–HOAc–H_2O (1:20:4). Acetates were prepared with Ac_2O in pyridine at room temp for 24 hr.

Extraction and separation of the compounds. The air-dried finely cut aerial part of the plant (11·0 kg), collected near Puertito de Güimar (Tenerife), was extracted with EtOH in a Soxhlet. After concentrating, the residue was dissolved in hot EtOH (1 l.). $Pb(OAc)_2$ (50 g) in hot H_2O (1 l.) was added and the soln left overnight. It was filtered, concentrated till the EtOH was eliminated and extracted with EtOAc. Evaporation of the solvent gave a residue (60 g) which was chromatographed on silica gel (1 kg). C_6H_6–EtOAc (19:1) eluted ψ-taraxasterol, C_6H_6–EtOAc (4:1) desacetylmatricarin and finally C_6H_6–EtOAc (7:3) a mixture of desacetylmatricarin, dihydropicridin (**1a**) and picridin (**2**), from which **1a** was separated by dry column chromatography (C_6H_6–EtOAc, 4:1) and **2** by preparative TLC (C_6H_6–EtOAc, 1:1, double elution).

ψ-Taraxasterol (0·2 g), m.p. 190–193°, $[\alpha]_D$ 50° (*c* 0·30). Identified by direct comparison with an authentic sample (m.m.p., TLC, IR, NMR spectra superimposable).

Desacetylmatricarin (0·2 g), m.p. 130–132°, $[\alpha]_D$ 26° (*c* 0·40). Acetylation gave matricarin, m.p. 190–192°, $[\alpha]_D$ 30° (*c* 0·20). The physical and spectral data of both compounds are identical to those cited.[2,3]

Dihydropicridin (**1a**) (3·0 g), m.p. 175–177°, $[\alpha]_D$ −26° (*c* 4·00) (Found: C, 68·42; H, 7·82. $C_{15}H_{20}O_4$ requires: C, 68·16; H, 7·63%). λ_{max} 255 nm (ϵ 10^4). ν_{max}^{Nujol} 3400 (OH), 1780 (γ-lactone), 1695 (·CO·C=C, 5-membered ring), 1615 cm^{-1} (double bond). τ 6·25 (1H, *t*, *J* 9·5 Hz, H-C_6), 6·23 (2H, complex, $-C\underline{H}_2OH$), 7·55 (1H, *s*, OH), 7·65 (3H, *s*, Me–C_{10}), 8·75 (3H, *d*, *J* 7 Hz, Me–C_{11}). *m/e* (%) 264 (M^+, 12), 246 (6), 233 (7), 191 (100). *Acetate* **1b**, m.p.

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145–147°, $[\alpha]_D$ −19° (*c* 3·04) (Found: C, 66·89; H, 7·37. $C_{17}H_{22}O_5$ requires: C, 66·60; H, 7·10%). λ_{max} 255 nm (ϵ 11 000). $\nu_{max}^{CHCl_3}$ 1775 (γ-lactone), 1745 (OAc), 1700 (·CO·C=C, 5-membered ring), 1615 cm^{-1} (double bond). τ 5·75 (2H, *d*, *J* 6 Hz, $-C\underline{H}_2OAc$), 6·30 (1H, *t*, *J* 9 Hz, H-C_6), 7·62 (3H, *s*, Me–C_{10}), 7·95 (3H, *s*, OAc), 8·75 (3H, *d*, *J*, 7 Hz, Me–C_{11}).

Picridin **2** (15 mg), oil which failed to give satisfactory elemental analysis. λ_{max} 255 nm (ϵ 10^4). $\nu_{max}^{CHCl_3}$ 3450 (OH), 1765 (γ-lactone), 1700 (·CO·C=C, 5-membered ring), 1615 cm^{-1} (double bond). τ 3·90 and 4·92 (each 1H, *d*, *J* 3 Hz, $=CH_2$), 6·25 (1H, *t*, *J* 9 Hz, H–C_6), 6·30 (2H, complex, $-C\underline{H}_2OH$), 7·68 (3H, *s*, Me–C_{10}).

Dehydrogenation of dihydropicridin. **1a** (500 mg) was heated to 300° with Se (4 g) for 10 min under N_2. It was extracted with petrol., concentrated and chromatographed on Al_2O_3 (act. II–III) eluting with petrol. The residue of the first fractions, of intense blue colour, was dissolved in EtOH and treated with a satd soln of TNB, obtaining the TNB adduct of chamazulene, m.p. 129°, which was identified by comparison with an authentic sample.

Dihydropicridin tosylate (**1c**). To a soln of **1a** (150 mg) in dry pyridine (1 ml) TsCl (100 mg) was added and the mixture kept at 0° for 16 hr. After adding H_2O it was extracted with EtOAc, the extract washed with 2 N HCl, H_2O, 5% $NaHCO_3$ and H_2O and dried over Na_2SO_4. Dry column chromatography (C_6H_6–EtOAc, 4:1) of the residue gave **1c** (120 mg), m.p. 146–147°, $[\alpha]_D$ −30° (*c* 4·5). $\nu_{max}^{CHCl_3}$ 1780 (γ-lactone), 1700 (·CO·C=C, 5-membered ring), 1170 (S=O), 850 cm^{-1} (C–S).

15-*Iododihydropicridin* (**1d**). **1c** (100 mg) in HOAc (10 ml) was refluxed with NaI (500 mg) for 1 hr. The soln was poured in H_2O, extracted with EtOAc and the extract washed with H_2O, 5% $NaHCO_3$, H_2O, 5% $Na_2S_2O_3$ and H_2O. Purification of the residue by dry column chromatography (C_6H_6–EtOAc, 9:1) gave **1d** (50 mg), m.p. 151–153°, $[\alpha]_D$ −75° (*c* 0·20). λ_{max} 255 nm (ϵ 11 000). $\nu_{max}^{CHCl_3}$ 1770 (γ-lactone), 1700 (·CO·C=C, 5-membered ring), 1610 cm^{-1} (double bond). τ 6·30 (1H, *t*, *J* 9 Hz, H–C_6), 6·32 (2H, complex, $-CH_2I$), 7·60 (3H, *s*, Me–C_{10}), 8·70 (3H, *d*, *J* 7 Hz, Me–C_{11}).

15-*Desoxydihydropicridin* (**1e**). A soln of **1d** (50 mg) in HOAc (100 ml) was refluxed over Zn powder (200 mg) for 0·5 hr. After adding H_2O, it was extracted with EtOAc, the extract washed with 2 N HCl, H_2O, 5% $NaHCO_3$ and H_2O, dried and concentrated obtaining **1e** (50 mg), m.p. 145–147°, $[\alpha]_D$ −25° (*c* 1·32) (Found: C, 72·62; H, 8·35. $C_{15}H_{20}O_3$ requires: C, 72·55; H, 8·10%). λ_{max} 255 nm (ϵ 11 000). $\nu_{max}^{CHCl_3}$ 1785 (γ-lactone), 1700 (·CO·C=C, 5-membered ring), 1615 cm^{-1} (double bond). τ 6·33 (1H, *t*, *J* 9·5 Hz, H–C_6), 7·65 (3H, *s*, Me–C_{10}), 8·75 (3H, *d*, *J* 7·5 Hz, Me–C_{11}), 8·80 (3H, *d*, *J* 7 Hz, Me–C_4). *m/e* (%) 248 (M^+, 100), 175 (100), 137 (50), 133 (30).

Guai-1(10)-*en*-6,12-*olide*. A mixture of **1e** (45 mg), ethanedithiol (0·3 ml) and BF_3 etherate (0·5 ml) was kept at room temp for 3 hr. It was poured into $CHCl_3$, washed with satd $NaHCO_3$ and concentrated, giving a semi-solid residue which was dissolved in abs. EtOH (15 ml) and refluxed over Raney Ni (100 mg) for 2 hr. It was poured in H_2O, extracted with EtOAc and the residue chromatographed on a dry column (C_6H_6), obtaining guai-1(10)-en-6,12-olide as a colourless oil which would not crystallize and was identified by comparison with an authentic sample (TLC, IR, NMR spectra superimposable).

Tetrahydropicridin **3** *from* **1a**. **1a** (30 mg) in HOAc (2 ml) and EtOAc (2 ml) was hydrogenated over PtO_2 (100 mg) at room temp and atm pres till H_2 uptake ceased. This gave **3** (mixture of isomers) as an oil; ν_{max}^{Nujol} 3610, 3500 (OH), 1770 (γ-lactone), 1735 cm^{-1} (cyclopentanone), τ 6·35 (1H, *t*, *J* 9 Hz, H–C_6), 6·30 (2H, complex, $-C\underline{H}_2OH$), 8·78 (3H, *d*, *J* 7 Hz, Me–C_{11}), 9·05 (3H, *d*, *J* 7 Hz, Me–C_{10}).

3 *from* **2**. Treatment of **2** under the same hydrogenation conditions as above gave **3** which was shown to be identical with the product obtained from **1a** (TLC, IR, NMR spectra superimposable).

Acknowledgements—We thank Professor F. Šorm (Czechoslovak Academy of Science, Prague) for a sample of guai-1(10)-en-6,12-olide and Dr. C. Pascual (Universität Basel) for the MS. Two of us (G.M.M. and J.T.) thank the Ministerio de Educación y Ciencia for a fellowship "Formación de Personal Investigador". This work was performed within the Programme of Chemistry 1971 conceded by the Foundation "Juan March".