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TWO NEW MORPHINANE ALKALOIDS FROM BEILSCHMIEDIA OREOPHILA SCHLECHTER (LAURACEAE)

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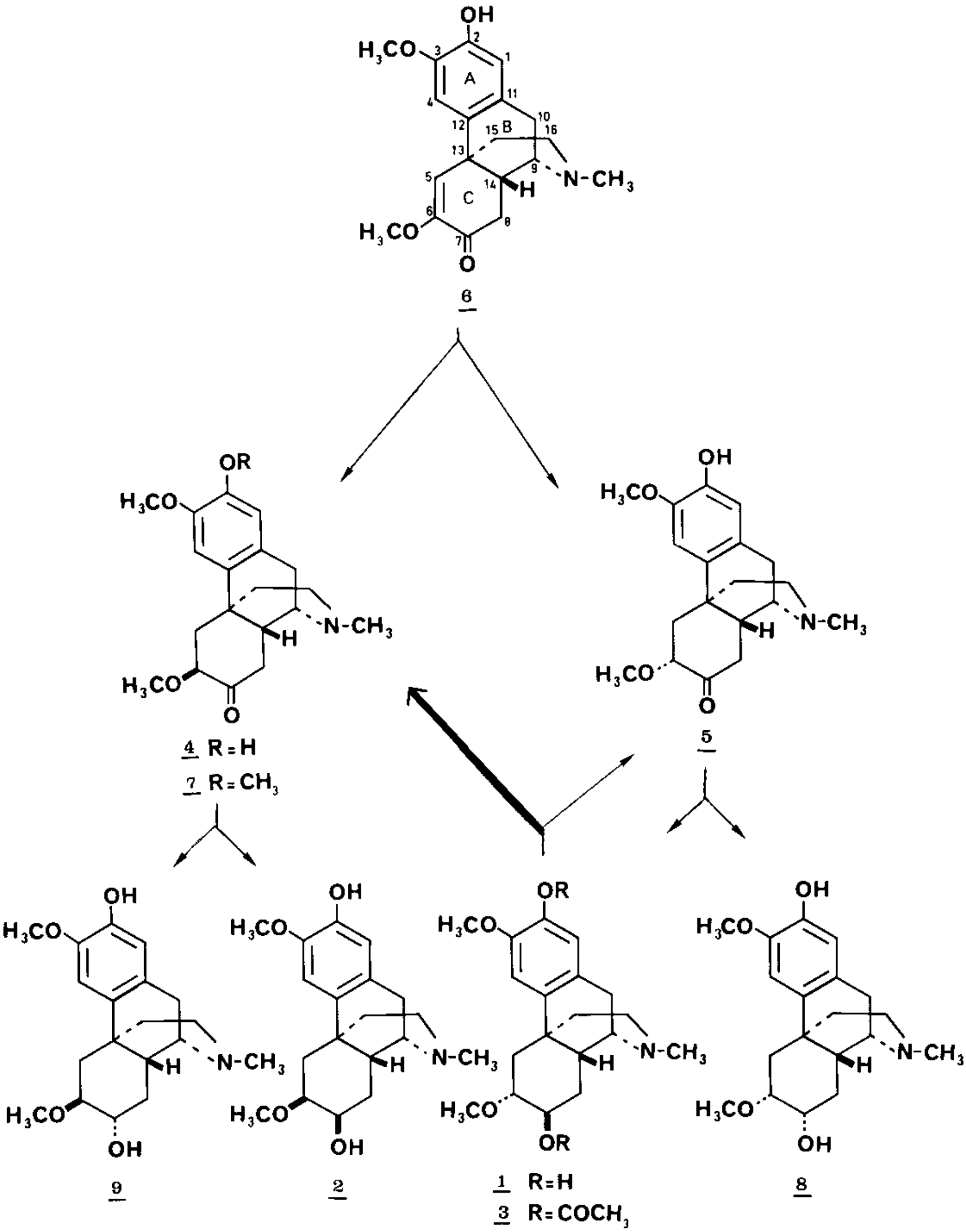
Abstract - Two new morphinane alkaloids, oreobeiline (1) and 6-epioreobeiline (2) have been isolated from the stem bark and wood of Beilschmiedia oreophila Schlechter. Their structures have been elucidated by spectroscopic studies and chemical correlations.

The genus Beilschmiedia (Lauraceae) includes some 250 species of trees growing throughout Asia and the Pacific Islands. Two of them are new-caledonian endemic species : Beilschmiedia oreophila Schlechter[1] and Beilschmiedia neocaledonia Kostermans[2]. In a continuation of our series on the chemical constituents of plants from New Caledonia[3], we wish to report here the structural elucidation of two novel alkaloids isolated from the stem barks and wood of Beilschmiedia oreophila[4,5] and named oreobeiline and 6-epioreobeiline.

Oreobeiline (1) has been obtained as colourless prisms from chloroform, mp 116-118°C, $[\alpha]_D^{20} = +39°$ ($CHCl_3$, c=1). The empirical formula has been established by high resolution mass spectrometry as $C_{19}H_{27}NO_4$ (Found :333.1935 ; Calcd : 333.1940). The u v spectrum λ_{max}^{EtOH}nm (log ε) : 228 (3.61), 288 (3.53), 294 (sh., 3.48) is modified in alkaline medium $\lambda_{max}^{EtOH+KOH}$ nm (log ε) : 246 (3.73), 302 (3.64) and indicates the presence of a phenolic group. The general feature of the m s, m/z(%):333 (100), 318(9), 302(33), 288(9), 274(29), 260(20), 258(7), 244(18), 230(9), 196(88), 164(8), 122(14), 44(14) suggests the structure of a morphinane alkaloid with a saturated C ring[6]. The lack of substantial fragmentation at m/z = 59 (rel. int.



OH
H3CO
A
B
C
N-CH3
H
H3CO
O
6
OR
4 R=H
7 R=CH3
5
9
2
1 R=H
3 R=COCH3
8

< 2 %) is in favour of a B/C trans junction[7,8,9]. The n m r spectrum exhibits the two 1H-singlets at 6.67 and 6.60 ppm typical to H-1 and H-4 in a 2,3-disubstituted morphinane[10,11] and three 3H-singlets at 3.83 (ArOMe), 3.40 (ROMe) and 2.33 ppm (NMe). Two 1H-quartets at 3.47 (J = 3Hz) and 4.15 (J = 3Hz) ppm assigned to H-6 and H-7 are in good agreement with the presence of two axial oxygenated substituents at C-6 and C-7 on the cyclohexane moiety of the molecule. Acetylation of oreobeiline (1) (Ac_2O/C_5H_5N/20°C/48 h) leads in almost quantitative yield to a diacetyl derivative (3), $M^+ = 417$, which N.M.R. spectrum exhibits the signals of one ROAc (3H-singlet at 2.04 ppm) and one ArOAc (3H-singlet at 2.41 ppm).

Upon Oppenauer oxidation (Fluorenone/t-BuOK/C_6H_6/Rx./2 h), oreobeiline (1) gives rise to a 95:5 mixture of two isomeric ketones 4 ($M^+ = 331$; $[\alpha]_D^{20} = -37°$ ($CHCl_3$, c=1)) and 5 ($M^+ = 331$; $[\alpha]_D^{20} = -12°$ ($CHCl_3$; c=1)) in 80 % overall yield. Oppenauer oxidation at C-7 occurs with a simultaneous base-induced epimerization at C-6 and affords mainly the thermodynamically more stable isomer 4 bearing an equatorial 6-OMe group[8,9]. Evidence for this epimerization is given by the H-6 signal which appears as a double doublet with a large trans-diaxial coupling constant (J = 13 Hz, J' = 7 Hz) at 4.11 ppm on the n m r spectrum of 4. The absolute configuration at C-9, C-13 and C-14 and the nature of the substituents at C-2 (OH) and C-3 (OMe) of ketones 4 and 5 have been determined by chemical correlation. Catalytic reduction (H_2/1 atm./10 % Pd-C/EtOH/20°C/2 h) of pallidinine (6) of known absolute configuration[9] leads to a 50:50 mixture of ketones 4 and 5 in 60 % overall yield. Furthermore, methylation of ketone 4 (Me_2SO_4/t-BuOK/t-BuOH/40°C/3 h) gives quantitatively 5,6-dihydro-O-methylpallidinine 7 whose m s and n m r data are identical with those previously published[9] for this compound.

Finally, the structure and absolute stereochemistry of oreobeiline (1) have been confirmed by reduction ($NaBH_3CN$/AcOH/20°C/1 h/70 % overall yield) of ketone 5 bearing an axial 6-OMe group to a 50:50 mixture of two alcohols epimeric at C-7, 8 having an equatorial 7-OH group and 1 having an axial 7-OH group and identical with the natural product.

6-Epioreobeiline (2) has been obtained as colourless needles from methanol, mp 207-209°C, $[\alpha]_D^{20} = +59°$ ($CHCl_3$, c=1). The empirical formula has been established by high resolution mass spectrometry as $C_{19}H_{27}NO_4$ (Found : 333.1945 ; Calcd : 333.1940). The m s and u v spectrum were almost indistinguishable from those of oreobeiline (1). The n m r spectrum exhibits two 1H-singlets at 6.67 (H-1) and 6.62 (H-4) and three 3H-singlets at 3.82 (ArOMe), 3.45 (ROMe) and 2.31 ppm (NMe).

It differs significantly from that of oreobeiline by the H-6 signal which is a double double doublet with a large trans-diaxial coupling constant (J = 14.5 Hz, J' = 5 Hz; J" = 3 Hz) at 3.50 ppm. The H-7 signal is a quartet (J = 3 Hz) at 4.28 ppm very similar to that observed on the spectrum of oreobeiline. These elements are in favour of the structure of 6-epioreobeiline 2 for this second natural alkaloid. This structure has been ascertained and the absolute stereochemistry determined by chemical correlation. Reduction ($NaBH_3CN/AcOH$/20°C/1 h/70 % overall yield) of ketone 4 leads to a 50:50 mixture of two alcohols epimeric at C-7, 9 having an equatorial 7-OH group and 2 having an axial 7-OH group. This latter compound is identical with the natural product.

From a chemotaxonomic point of view, it is interesting to note the presence of a new type of morphinane alkaloids with a saturated C-ring in *Beilschmiedia oreophila*. Morphinane alkaloids had not been previously isolated from the related species *Beilschmiedia elliptica* White et Francis from Australia[12] and *Beilschmiedia podagrica* Kostermans from New Guinea[13]. Nevertheless, morphinanenones and morphinanedienones had been previously isolated from species belonging to the related genera *Ocotea* [8,9] and *Litsea*[14].

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REFERENCES AND NOTES

1. R. Schlechter, *Bot. Jahrb.*, 1906, **39**, 106.
2. A.J.G.H. Kostermans, in A. Aubréville and J.F. Leroy "Flore de la Nouvelle Calédonie et Dépendances". Muséum National d'Histoire Naturelle, Paris, 1974, **5**, pp. 3-12.
3. Part XCIII in the series "Plantes de Nouvelle Calédonie".
   Part XCII, see "Alcaloides de *Sarcomelicope leiocarpa*", G. Baudouin, F. Tillequin, M. Koch, M.E. Tran Huu Dau, J. Guilhem, J. Pusset and G. Chauvière, *J. Nat. Prod.*, 1985, **48**, in press.

4. The plant material has been collected at Yaté (New Caledonia) in july 1982. Herbarium samples (JPGC 346 and 382) are kept in the herbarium of the Muséum National d'Histoire Naturelle (Paris).
5. The leaves of Beilschmiedia oreophila Schlechter have yielded about 0.40 % of crude alkaloids by standard means. The main constituents have proven to be three known aporphine bases, thaliporphine, isoboldine and wilsonirine and one morphinanedienone, pallidine. The stem barks have yielded 3.60 % and the wood 0.35 % of qualitatively nearly identical crude alkaloids. The three major bases, pallidinine, orebeiline and 6-epioreobeiline belong to the morphinane series.
6. L.J. Haynes, G.E.M. Husbands and K.L. Stuarts, J. Chem. Soc. (C), 1968, 951.
7. A. Mandelbaum and D. Ginsburg, Tetrahedron Lett., 1965, 2479.
8. V. Vecchietti, C. Casagrande and G. Ferrari, Tetrehedron Lett., 1976, 1631.
9. V. Vecchietti, C. Casagrande, G. Ferrari, B. Danieli and G. Palmisano, J. Chem. Soc. Perkin Trans. I, 1981, 578.
10. W. Döpke, H. Flentje and P.W. Jeffs, Tetrahedron, 1968, **24**, 4459.
11. F. Roblot, R. Hocquemiller and A. Cavé, Bull. Soc. Chim. Fr. II, 1984, 139.
12. P.S. Clezy, E. Gellert, D.Y.K. Lau and A.W. Nichol, Aust. J. Chem., 1966, **19**, 135.
13. S.R. Johns, J.A. Lamberton, A.A. Sioumis and H.J. Tweeddale, Aust. J. Chem., 1969, **22**, 1277.
14. M. Sivakumaran and K.W. Gopinath, Ind. J. Chem., 1976, **14B**, 150.

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