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LUXANDRINE, A QUATERNARY BENZYLISOQUINOLINE FROM *PSEUDOXANDRA SCLEROCARPA**

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Key Word Index—*Pseudoxandra sclerocarpa*; Annonaceae; trunk bark; quaternary benzylisoquinoline alkaloid.

Abstract—A new 6,7-dihydroxytetrahydrobenzylisoquinoline has been isolated and identified from the quaternary alkaloidal fraction of the bases of *Pseudoxandra sclerocarpa*.

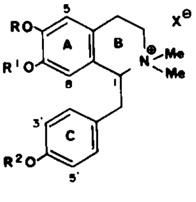
INTRODUCTION

In continuation of our investigations on the Annonaceae, we have studied the constituents of the trunk bark of *Pseudoxandra sclerocarpa* Maas, collected from the equatorial forest of Colombia. The non-quaternary alkaloidal fraction of the plant has been examined and several alkaloids have been isolated and identified [1–4]‡. The present work describes the isolation and identification of luxandrine (**1**) as the major component of the quaternary alkaloidal fraction of *P. sclerocarpa*. Luxandrine is a hitherto unknown isomer of magnocurarine (**2**) and contains a catechol unit in its structure.

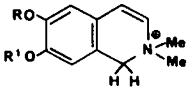
RESULTS AND DISCUSSION

The defatted trunk bark of *P. sclerocarpa* was basified with ammonia and the non-quaternary alkaloids were extracted with dichloromethane. The marc was extracted with methanol and the quaternary alkaloids were isolated as a mixture of iodomercurates. The latter were converted to chlorides by passage through Amberlite IRN-78, in the chloride form; the chlorides were separated on silica gel and the chloride of luxandrine (**1**) was isolated as the major product.

The UV spectrum of **1** clearly indicated a benzyltetrahydroisoquinoline. A pronounced bathochromic shift with alkali indicated phenolic hydroxyl groups. The mass spectrum of **1** obtained by chemical ionization indicated a simple benzyltetrahydroisoquinoline and a molecular weight of 314 for the cation of **1**. The molecular weight was consistent with the molecular formula $C_{19}H_{24}O_3N$. The mass spectruum of **1** obtained by electron impact showed a prominent fragment at *m/z* 192. This was assigned structure **7**, its formation following benzylic fission of **1** indicating the presence of two hydroxyl groups



1 $R = R^1 = H$; $R^2 = Me$; $X = OH$
2 $R^1 = R^2 = H$, $R = Me$; $X = OH$
3 $R = R^1 = R^2 = Me$, $X = I$
4 $R = R^1 = Ac$, $R^2 = Me$, $X = Cl$
5 $R = R^1 = R^2 = Ac$, $X = OH$
6 $R = R^1 = R^2 = H$; $X = OH$



7 $R = R^1 = H$
8 $R = H$, $R^1 = Me$; or $R = Me$, $R^1 = H$
9 $R = H$, $R^1 = Ac$, or $R = Ac$, $R^1 = H$

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*Part 67 in the series "Alkaloids of the Annonaceae". For Part 66 see Jossang, A., Leboeuf, M., Cavé, A. and Sevenet, T. (1986) *J. Nat. Prod.* (in press).

‡*Pseudoxandra sclerocarpa* now replaces *Pseudoxandra aff. lucida*, as used in preceding publications.

in the A-ring of **1**. The positions of the hydroxyl groups and the methoxyl group were assigned on ^{1}H NMR analysis of **1**. The proton at C-8 appeared at a characteristic high field of δ5.94, while the proton at C-5 appeared within the region of the signals of the A_2B_2 system of ring C.

The structure of **1** was confirmed by methylation as well as by acetylation. Methylation of phenolic hydroxyl groups was effected by conversion of the quaternary chloride to iodide followed by reaction with methyl iodide and methanolic potash [5]. The product, **3**, *O*,*O*-dimethyl luxandrine iodide, showed no bathochromic shift with alkali in its UV spectrum and gave a significant fragment ion at *m/z* 206. This was assigned structure **8**. Its formation could be explained by fission of a methoxyl group by iodide ion. The ^{1}H NMR spectrum of **3** gave evidence for five methyl groups. The diacetyl derivative **4** was obtained from the chloride of **1** by reaction with pyridine and acetic anhydride at room temperature. The UV spectrum of **4** showed no bathochromic shift with alkali. The mass spectrum of **4** obtained on electron impact showed extensive fragmentation. Structure **9** was assigned to the ion at *m/z* 234, formed by acetyl group fission following benzylic fission. The mass spectrum of **4** obtained on chemical ionization showed a molecular ion at *m/z* 398 corresponding to the cation of **4**. This spectrum also showed evidence of an accompanying molecular ion at *m/z* 426. We consider this ion to be the cation of **5**, which could have been formed on acetylation of the quaternary triphenolic benzylisoquinoline, *O*-demethylluxandrine (**6**), occurring in the plant. The ^{1}H NMR spectrum of **4** was in accord with the assigned structure. The positive specific rotation of **4** coupled with a descending tail in its CD curve gave evidence for the *R*-configuration at C-1 [6]. Luxandrine (**1**) is therefore in the same configurational series as magnocurarine (**2**).

Luxandrine (**1**) is the second example of a benzyltetrahydroisoquinoline with a catechol unit to be isolated from a plant source, higenamine, 6,7,4′-trihydroxy-1,2,3,4-tetrahydroisoquinoline being the first example [7]; both compounds have been isolated from the Annonaceae. A catecholic aporphine [8] and two catecholic berbines [9, 10] have also been reported from the Annonaceae.

EXPERIMENTAL

UV spectra were obtained in EtOH. ^{1}H NMR spectra were run at 60 or 90 MHz; chemical shifts are in δ units, with TMS as internal standard. EIMS were recorded at 70 eV and CIMS were recorded with NH_3 as reagent gas. CD were obtained in MeOH.

Plant material. The trunk bark of *P. sclerocarpa* was collected at San Luis (Antioquia), Colombia in July 1982. Herbarium specimens have been deposited at the University of Antioquia, the Museum of Natural History in Paris and at the State University of Utrecht. The identification and description of this new species were recently finalized by Professor P. J. M. Maas of the State University of Utrecht [11].

Extraction and isolation. The mixture of quaternary iodomercurates (4.82 g) isolated from the trunk bark of *P. sclerocarpa* was dissolved in Me_2CO–MeOH–H_2O (6:3:1), passed through Amberlite IRN-78 (Cl^-) (300 ml) and a mixture of quaternary chlorides (1.9 g) was obtained. TLC examination of this mixture showed the presence of a highly polar major product. The chloride mixture was separated on a column of silica gel (Merck Art. 7736, 60 g) in CH_2Cl_2–MeOH–NH_4OH (14:4:1). Luxandrine (**1**) (1.35 g) isolated as the chloride was purified by prep. TLC on silica gel (Merck Art. 7730) in the same CH_2Cl_2–MeOH–NH_4OH system.

Luxandrine chloride (**1**). Pale brown amorphous solid, decomposing in solution; $[\alpha]_D + 27°$ ($CHCl_3$–MeOH, 10:1; *c* 0.24); UV λ_{max}^{EtOH} nm (log ε): 210 (4.47), 231 (4.22), 283 (3.75); EtOH + N NaOH: 251 (4.10), 310 (3.63), CIMS (NH_3) *m/z* (rel. int.): 314 $[M]^+$ (100); EIMS *m/z* (rel. int.): 313 $[M-H]^+$ (3), 192 [**7**] (29), 58 $[C_3H_8N]^+$ (100); ^{1}H NMR (90 MHz, CD_3OD): δ3.13 (3H, *s*, $^+$NMe), 3.37 (3H, *s*, $^+$NMe), 3.87 (3H, *s*, 4′-OMe), 5.94 (1H, *s*, H-8), 6.77 and 6.86 (4H, *dd*, *J* = 9Hz, H-2′, 3′, 5′, 6′), 6.82 (1H, *s*, H-5).

O,O-*Dimethylluxandrine iodide* (**3**). Luxandrine chloride (100 mg) was dissolved in H_2O (1.5 ml) and passed through Amberlite IRN-78 $[OH^-]$. The alkaline soln was neutralized with a few drops of HI and evaporated to dryness. The residue was refluxed for 1 hr with 0.5 N methanolic KOH (5 ml) and MeI (5 ml). The soln was evaporated to dryness and the residue taken up in CH_2Cl_2. Evaporation of solvent gave **3** (107 mg) as a pale yellow solid, $[\alpha]_D + 4°$ ($CHCl_3$–MeOH, 1:1; *c* 0.40); UV λ_{max}^{EtOH} nm (log ε): 221 (4.52), 281 (3.90), unchanged on addition of N NaOH; EIMS *m/z* (rel. int.): 341 $[M-H]^+$ (2), 206 [**8**] (15), 128 $[HI]^+$ (100), 127 $[I]^+$ (66); ^{1}H NMR (60 MHz, C_5D_5N): δ 3.37 (3H, *s*, $^-$NMe), 3.65 (6H, *s*, $^+$NMe and 7-OMe), 3.77 (3H, *s*, 4′-OMe), 3.93 (3H, *s*, 6-OMe).

O,O-*Diacetylluxandrine chloride* (**4**). Luxandrine chloride (55 mg) was allowed to react overnight at room temp. with dry pyridine (1.5 ml) and Ac_2O (1.5 ml). Evaporation to dryness gave **4** as a colourless amorphous solid, $[\alpha]_D + 27°$ ($CHCl_3$, few drops MeOH; *c* 0.22); UV λ_{max}^{EtOH} nm (log ε): 224 (4.37), 270 (3.18), unchanged on addition of N NaOH; CIMS (NH_3) *m/z* (rel. int.): 426 $[M]^-$ of **5** (4), 398 $[M]^+$ of **4** (10), 384 (100); EIMS *m/z* (rel. int.): 234 [**9**] (60), 192 [**7**] (16), 58 $[C_3H_8N]$ (100); ^{1}H NMR (90 MHz, CD_3OD): δ2.10 (3H, *s*, 7-OAc), 2.20 (3H, *s*, 6-OAc), 3.13 (3H, *s*, $^+$NMe), 3.49 (3H, *s*, $^+$NMe), 3.73 (3H, *s*, 4′-OMe), 5.70 (1H, *s*, H-8), 6.83 and 6.97 (4H, *dd*, *J* = 8 Hz, H-2′, 3′, 5′, 6′); ^{1}H NMR (60 MHz, CD_3OD): δ2.17 (3H, *s*, 7-OAc), 2.28 (3H, *s*, 6-OAc), 3.18 (3H, *s*, $^+$NMe), 3.48 (3H, *s*, $^+$NMe), 3.82 (3H, *s*, 4′-OMe), 5.87 (1H, *s*, H-8), 6.47 (1H, *s*, H-5); CD (MeOH; $c = 8.53 \times 10^{-4}$), $\Delta\varepsilon$ (nm): 0 (282), −0.5 (270), 0 (260), +5.3 (233), 0 (217).

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