Buchnerine and N-(Z)-p-Methoxycinnamoylbuchnerine, Two New Macrocyclic Alkaloids from Clerodendrum buchneri

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BUCHNERINE AND N^1-(*Z*)-*p*-METHOXYCINNAMOYL-BUCHNERINE, TWO NEW MACROCYCLIC ALKALOIDS FROM *CLERODENDRUM BUCHNERI*

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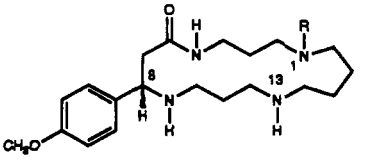
ABSTRACT.—Two new macrocyclic spermine alkaloids, buchnerine [**1**] and N^1-(*Z*)-*p*-methoxycinnamoylbuchnerine [**2**], have been isolated from *Clerodendrum buchneri* (Verbenaceae), and their structures established by a study of their spectral and chemical properties.

In a preceding communication, we described the isolation of two macrocyclic spermidine alkaloids, myricoidine and dihydromyricoidine, from *Clerodendrum myricoides* (Verbenaceae) (1). We now report the isolation and the structure determination of two new spermine alkaloids, buchnerine [**1**] and N^1-(*Z*)-*p*-methoxycinnamoylbuchnerine [**2**], from another *Clerodendrum* species: *Clerodendrum buchneri* Gürke.

RESULTS AND DISCUSSIONS

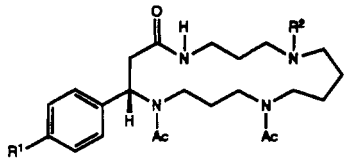
Buchnerine [**1**] [$C_{20}H_{34}N_4O_2$ by hrms, $[\alpha]^{22}D$ $-26°$ (c=0.5, MeOH)] and N^1-(*Z*)-*p*-methoxycinnamoylbuchnerine [**2**] [$C_{30}H_{42}N_4O_4$ by hrms, $[\alpha]^{22}D$ $-28°$ (c=1.2, MeOH)] were isolated in very minute amounts (ca. 1 ppm and 4 ppm, respectively, from the dried leaves) after repetitive countercurrent distributions and chromatographies.

Among the six unsaturations present in buchnerine [**1**], five are accounted for by the presence of the carbonyl group of a secondary amide and the benzene ring of *p*-methoxyphenyl group as evidenced by the ir and ^{1}H-nmr spectra. The ^{1}H-nmr spectrum of **1** also displayed a double doublet signal at 3.95 ppm attributable to a benzylic proton (H-8) on a carbon atom bearing a nitrogen atom and a methylene group (2), a frequently encountered environment in other polyamine alkaloids. Taken together, the above data are in agreement with a β-aminodihydro-*p*-methoxycinnamide subunit in the molecule. As there is no indication for the presence of a double bond, the sixth unsaturation is assignable to a cycle. There are neither *C*Me nor *N*Me groups in **1**; it is likely, therefore, that the remaining part of the molecule is incorporated in a spermine moiety, a common base in the polyamine alkaloids (3), although an isomeric structure cannot be ruled out at this stage. If these two structural subunits are connected, structure **1** incorporating a 17-membered ring is obtained, accounting for all the properties of buchnerine.



1 R= H
2 R= COCH=CHC$_6$H$_4$OMe (*Z*)

The spectroscopic properties of N^1-(*Z*)-*p*-methoxycinnamoylbuchnerine [**2**] established that this base is closely related to buchnerine [**1**]; the $C_{10}H_8O_2$ difference between the formulae of the two alkaloids and the presence in the ^{1}H- and ^{13}C-nmr spectra of **2** of supplementary signals assignable to a *p*-methoxyphenyl group and a conjugated C=C double bond suggested that **2** is a *p*-methoxycinnamoyl derivative of **1**. The chemical shifts of the olefinic protons and the magnitude of the coupling constant (12.5 Hz) are only compatible with a *Z* configuration for the double bond (4,5). In the ^{1}H-nmr spectrum of **2**, the signal of the benzylic proton H-8 appeared as a double doublet at 3.94 ppm and was shifted to 5.66 ppm in *N,N*-diacetyl-N^1-



3 R^1= OMe, R^2= $COCH{=}CHC_6H_4OMe(Z)$
4 R^1= OMe, R^2= $COCH_2CH_2C_6H_4OMe$
5 R^1= H, R^2= $COCH{=}CHC_6H_5$ (*E*)
6 R^1= H, R^2= $COCH_2CH_2C_6H_5$

(*Z*)-*p*-methoxycinnamoylbuchnerine [**3**], establishing the secondary nature of N-9 in **2**.

The ms fragmentation pattern of **3** and its dihydroderivative **4** were very similar to those of acetylverbascenine [**5**] and acetyldihydroverbascenine [**6**] (6). A shift of 30 and 60 daltons was observed between most of the fragment ions in the spectra of compounds **3** and **5** on the one hand and **4** and **6** on the other hand, but a characteristic peak triad at *m/z* 242, 256, and 268 was present in the four spectra. This peak triade was consistent with the presence of a spermine moiety and indicated that the supplementary *p*-methoxycinnamoyl group in **2** is on N-1 (7,8).

The above data lead to the attribution of structural formula **1** and **2** to buchnerine and N^1-(*Z*)-*p*-methoxycinnamoylbuchnerine, respectively. This conclusion has been entirely confirmed by an unambiguous synthesis of the two alkaloids, which also established the absolute configuration 8*S* as depicted in **1** and **2** (9).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Ir spectra were determined on a Perkin-Elmer 237 or on a Brucker IFS 25 spectrometer. Eims data were obtained on a Micromass 7070F spectrometer. The nmr spectra were recorded on a Bruker WM 250 apparatus, in $CDCl_3$ with TMS as internal standard. Signal assignment in the ^{13}C-nmr spectra was aided by the DEPT pulse sequence. Optical rotations were measured on a Perkin-Elmer 141 polarimeter.

PLANT MATERIAL.—*C. buchneri* was collected in meridional Shaba (Zaïre) and identified by Professor F. Malaisse. A voucher specimen was deposited at the herbarium of the National Botanical Garden of Belgium (Meise).

EXTRACTION AND ISOLATION OF THE ALKALOIDS.—Dried and ground leaves of *C. buchneri* (6 kg) were extracted for 48 h with boiling MeOH in a Soxhlet apparatus. After filtration, the solution was evaporated under reduced pressure and the residue was dissolved in 0.2 N HCl; the filtered solution was basified with aqueous NaOH, extracted with $CHCl_3$, and evaporated; the residue was distributed between $CHCl_3$ and aqueous citric acid pH 2.2. Basification of the aqueous solution and extraction with $CHCl_3$ yielded the crude alkaloids as a brown residue (2.9 g).

The crude alkaloids were subjected to a countercurrent distribution ($CHCl_3$/McIlvaine buffer pH 6.3; 23 transfers). The residue from tubes 3–16 furnished homogeneous N^1-(*Z*)-*p*-methoxycinnamoylbuchnerine (27 mg) after chromatography on alumina [$CHCl_3$-MeOH (99:1)]. The residue from tubes 17–22 was chromatographed on alumina [$CHCl_3$-MeOH-NH_4OH (88:10:2)] and then was submitted to a further countercurrent distribution ($CHCl_3$/McIlvaine buffer pH 9.3). From tubes 9–19, homogeneous buchnerine (6 mg) was obtained.

Buchnerine [**1**].—Colorless oil: $[\alpha]^{22}D$ −26° (*c*=0.5, MeOH); ir (neat) 1645–1610, 1250, 834 cm^{-1}; eims *m/z* $[M]^+$ 362 (5%) ($C_{20}H_{34}N_4O_2$, found 362.2682, calcd 362.2680), 319 (22), 288 (41), 176 (29), 161 (33) ($C_{10}H_9O_2$, found 161.0602, calcd 161.0602), 134 (46), 121 (43), 98 (37), 84 (100); ^{1}H nmr δ 8.35 (m, 1H, NH-CO), 7.20 and 6.86 (AA′BB′ system, *J*=9 Hz, 4H), 3.95 (dd, *J*=4 and 9 Hz, 1H), 3.79 (s, 3H).

N^1-(Z)-p-*Methoxycinnamoylbuchnerine* [**2**].—Colorless oil: $[\alpha]^{22}D$ −28° (*c*=1.2, MeOH); ir (neat) 1640–1580, 1245, 825 cm^{-1}; eims *m/z* $[M]^+$ 522 (3%) ($C_{30}H_{42}N_4O_4$, found 522.3206, calcd 522.3204), 479 (4), 361 (6) ($C_{20}H_{33}N_4O_2$, found 361.2603, calcd 361.2603), 176 (15), 161 (100) ($C_{10}H_9O_2$, found 161.0602, calcd 161.0602), 133 (19), 127 (11), 121 (24), 112 (12), 98 (14); ^{1}H nmr δ 8.11 and 7.45 (2 m, 1H), 7.3–6.8 (m, 8H), 3.94 (dd, *J*=5 and 8 Hz, 1H), 3.79 (2 s, 6H); ^{13}C nmr (mixture of conformers) δ 172.5, 172.3, and 170.1 (C=O), 160.4, 159.5, 135.5, 135.3, and 128.9 (aromatic quaternary C), 133.6, 122.2, and 122.1 (vinylic C-H), 130.7, 128.3, 128.1, 114.8, 114.7 and 114.6 (arom. C-H), 59.7 (C-8), 55.9 (2-OMe), 50.3, 49.2, 48.9, 47.8, 46.8, 46.3, 44.6, 44.1, 38.0, and 37.3 (C-2, C-4, C-7, C-10, C-12, C-14, and C-17), 30.4, 30.0, 29.0, 27.6, 27.2, 27.0, 25.5 (C-3, C-11, C-15, and C-16).

N,N-*Diacetyl*-N^1-(Z)-p-*methoxycinnamoylbuchnerine* [**3**].—N^1-(*Z*)-*p*-Methoxycinnamoylbuchnerine [**2**] (5 mg) was dissolved in Ac_2O/pyridine (1:1) (0.1 ml). After standing for one night at room temperature, EtOH and $CHCl_3$

were added and the solution was evaporated to dryness. The residue was dissolved in $CHCl_3$, and the solution was washed with dilute NH_4OH, dried, and evaporated to give homogeneous (tlc) *N,N*-diacetyl-N^1-(*Z*)-*p*-methoxycinnamoylbuchnerine [**3**] (6 mg): $[\alpha]^{22}D$ −60° (*c*=0.6, MeOH); ms $[M]^+$ 606 (11%), 564 (20), 563 (54), 446 (3), 445 (8), 403 (9), 385 (5), 345 (3), 268 (7), 256 (1), 242 (1), 218 (3), 216 (3), 176 (6), 162 (13), 161 (100); ^1H nmr δ 5.66 (m, 1H, H-8), 3.80 (6H).

N,N-*Diacetyldihydro*-N^1-(Z)-p-*methoxycinnamoylbuchnerine* [**4**].—*N,N*-Diacetyl-N^1-(*Z*)-*p*-methoxycinnamoylbuchnerine [**3**] (6 mg) was hydrogenated (3 kg/cm^2) in MeOH (3 ml) over Pd/C for 3 h. After filtration and evaporation of the MeOH, *N,N*-diacetyldihydro-N^1-(*Z*)-*p*-methoxycinnamoylbuchnerine [**4**] was obtained quantitatively: eims *m/z* $[M]^+$ 608 (19%), 567 (8), 566 (37), 565 (100), 447 (10), 445 (14), 269 (8), 268 (26), 257 (8), 256 (15), 242 (7), 239 (9), 220 (7), 218 (10), 216 (9), 213 (8), 211 (8), 199 (7), 197 (7), 190 (7), 185 (9), 183 (7), 176 (20), 169 (12), 162 (19), 161 (83), 157 (10), 155 (19), 143 (12), 134 (54), 121 (94), 109 (34), 97 (50), 95 (48), 84 (68).

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