Teliglazine, a New Oxoaporphine Alkaloid from *Telitoxicum glaziovii*

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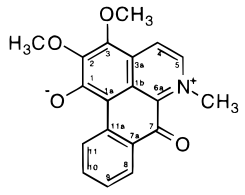
The structure of teliglazine (**1**), a new oxoaporphine alkaloid isolated from the basic fraction of *Telitoxicum glaziovii* Moldenke, was determined by spectral data and synthetic transformation from the known alkaloid, *O*-methylmoschatoline. Three other oxoaporphines, splendidine, imenine, *O*-methylmoschatoline; the azafluoranthene telitoxine, and the 4,5-dioxoaporphines, ouregidione and 4,5-dioxodehydroasimilobine, were also present in this plant.

The genus *Telitoxicum* belongs to the tribe Anomospermeae of the family Menispermaceae.[1] Three of the eight known species have been investigated and were found to contain interesting oxygenated aporphines.[2−4] In an earlier report,[2] we examined the nonphenolic fraction of the plant and found two oxoaporphinoids (*O*-methylmoschatoline and lysicamine) and two aporphines, telazoline and teladiazoline, each of which contains one free amino group. The three oxoaporphines [splendidine,[5] imenine,[6] and teliglazine (**1**)] currently found adds to the total number of aporphines from this species. The first azafluoranthene described in this genus was telitoxine,[7] which was isolated from the phenolic fraction, followed by ouregidione,[8] *O*-methylmoschatoline, and 4,5-dioxodehydroasimilobine,[9] which were obtained from the neutral fraction.

Teliglazine (**1**) was isolated from the nonphenolic basic fraction of this plant by chromatography and preparative TLC, followed by crystallization from $CHCl_3$ to give dark green crystals, mp 229−232 °C. In the IR spectrum there was a carbonyl absorption at 1619 cm^{-1}. The DCI−CH_4 mass spectrum of **1** revealed a molecular weight of 321 Da, and the DCI−ND_3 mass spectrum of **1** indicated that there were no exchangeable hydrogen atoms present. The molecular formula of **1**, which was determined to be $C_{19}H_{15}NO_4$ by HRDCIMS (CH_4 reagent gas), required 13 degrees of unsaturation. The EI and CI mass spectra of **1** consisted primarily of the molecular ion species with only minimal fragmentation, typical of the predominantly cyclic oxoaporphines.



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The appearance of the ^{1}H-NMR spectrum confirmed that **1** was indeed an oxoaporphine. There were six individual aromatic multiplets observed between δ 10.03 and 7.42 in the downfield region of the ^{1}H spectrum along with three methyl singlets at δ 4.87, 4.34, and 4.11. The two aromatic doublets and the methyl singlet at δ 4.87 were noticeably broader than the other signals. Homodecoupling experiments revealed the presence of an ABCD and an AB spin system. The four hydrogens of the former spin system were well defined and readily assignable to ring D positions H-8 through H-11 based on their similarities in chemical shift, multiplicity, and coupling constants with previously studied oxoaporphines. The two AB doublets that shared a 4.6-Hz coupling constant were typical of H-4 and H-5 on ring B.[3,4] Furthermore, the broadness of these doublets suggested that the nitrogen in ring B was quaternized. A broad methyl singlet at δ 4.87 was enhanced by NOE saturation of H-5. The δ 51.2 chemical shift of this methyl's carbon signal and long-range correlations shared between this methyl's hydrogens and adjacent carbons established that it was an *N*-methyl group.

Saturation of the δ 4.11 methoxyl singlet led to an NOE enhancement of the remaining ring B broad doublet, H-4, at δ 8.14, indicating that this methoxyl group was attached to C-3. Because saturation of the *N*-methyl and H-8 aromatic signals caused no enhancement of a ring C signal, **1** must be a 7-oxoaporphine. Likewise, saturation of the δ 4.34 methoxyl group caused no enhancement at H-11 in ring D, proving that it was not situated at C-1, and so it was positioned at C-2 by default.

Finally, placement of a phenolic group at position C-1 would have completed the assignment of structure **1**. However, the DCI−ND_3 mass spectrum had indicated there were no exchangeable hydrogens present, and the hydrogen count in the molecular formula was already expended. To conserve the molecule's neutrality, a negative oxide ion was placed at C-1 balancing the positive quaternary nitrogen charge. The ^{1}H assignments are summarized in the Experimental Section.

There was an insufficient amount of sample to obtain a useful ^{13}C-NMR spectrum of **1**. However, having already established the ^{1}H assignments, the ^{13}C assignments were determined for 18 of the 19 the carbon atoms present (all but C-1) through the more sensitive ^{1}H-detected inverse HMQC and HMBC correlation data. Not surprisingly, the C-1 resonance could not be identi-

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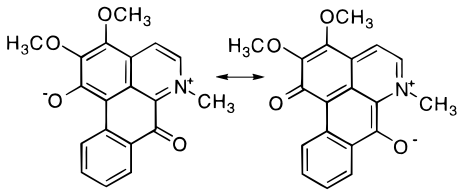

Figure 1. Tautomers of compound **1**.

fied because there were no protons close enough to correlate with it. This observation was consistent with the remote position of C-1 in the proposed structure. These ^{13}C assignments for **1** were consistent with those of other 7-oxoaporphines.[10] Especially revealing were the chemical shifts of the quaternary *N*-methyl carbon signal at δ 51.2 and the C-7 carbonyl at δ 177.0, which was identified by its three-bond correlation with H-8 at δ 8.48. The ^{13}C assignments are summarized in the Experimental Section.

Compound **1** was expected to tautomerize as shown in Figure 1. Two of the first quaternary 7-oxoaporphines, corunine (isolated from *Glaucium flavum*[11]) and alkaloid PO-3 (isolated from *Papaver orientale*[12]), exhibited the same tautomerism under basic conditions. The UV spectrum of **1** showed the extended conjugation of the chromophore. When exposed to acidic conditions, the C-1 phenoxide ion in compound **1** protonated to form the appropriate phenolic quaternary salt, and the color changed dramatically from green (neutral or basic) to pink (acidic).

If compound **1** were a salt with a phenolic group at C-1, then the 322-Da ion actually observed in the mass spectrum would be the true, positively charged parent ion rather than a neutral parent ion that had been protonated by the CH_4 gas in the mass spectrometer and would correspond to a $C_{19}H_{16}NO_4$ molecular formula. A strong negative CIMS was obtained for **1** with an odd electron molecular ion (*m*/*z* 321) that could only have been observed for a neutral compound. In addition, all attempts to methylate, silylate, or acetylate **1** failed, indicating that there was no phenolic hydroxyl group present.

A synthetic sample of teliglazine was prepared by treating *O*-methylmoschatoline with excess MeI in Me_2CO at room temperature for 18 h to give a dark green solution that, on purification by column chromatography, gave dark green crystals identical with **1** (76% yield) by co-TLC and spectral data. *T. glaziovii* is the first species of the South American Menispermaceae to give this zwitterion oxoaporphine.

Splendidine and imenine, both 4-substituted oxoaporphines, were only previously isolated from *Abuta refescens*/*splendida*. The presence of these two alkaloids in *Telitoxicum* is consistent with its relationship to *Abuta*. ^{13}C-NMR chemical shift assignments for these oxoaporphines are given in the Experimental Section. Ouregidione has been previously isolated from *Guatteria ouregou* and 4,5-dioxodehydroasimilobine from the genus *Aristolochia*, but this is the first report of these compounds from South American Menispermaceae.

Experimental Section

General Experimental Procedures. Melting points are uncorrected. IR spectra were recorded on a Mattson Genesis series FT-IR spectrophotometer and UV spectra on a Hewlett-Packard 5842 diode array UV/vis spectrophotometer. All homonuclear and heteronuclear 1D and 2D NMR data were recorded on a Bruker AMX-400 spectrometer in $CDCl_3$. DCIMS were obtained on a Finnigan model 4610 quadrupole mass spectrometer using CH_4, NH_3 and ND_3, as the CI reagent gases in both the positive and negative ion modes. ESIMS/MS were obtained in the positive ion mode on a SCIEX API 300 triple quadrupole mass spectrometer. The HRDCIMS were acquired on a VG-70SE using CH_4 as the CI reagent gas. Analytical and preparative TLC were carried out on precoated Si gel G (Kieselgel G254) plates. Reagent grade chemicals (Fisher) were used throughout.

Plant Material. Plant material was previously described by Menachery and Edgren.[2]

Extraction and Isolation. The extraction procedure for the plant material was previously described.[2] Teliglazine, imenine, and splendidine were isolated from the nonphenolic fraction by column chromatography and preparative TLC followed by crystallization. The hexane-insoluble neutral fraction (22.8 g) from the extraction of 7.0 kg of plant material collected from the State of Para, Brazil, by N. T. Silva (a voucher specimen identified by Dr. B. A. Krukoff was placed in the New York Botanical Garden herbarium) was chromatographed over Si gel-60 by elution with $CHCl_3$ and $CHCl_3$−MeOH mixtures. The alkaloids 4,5-dioxodehydroasimilobine, ouregidione, *O*-methylmoschatoline, and telikovinone were obtained in pure form from this fraction only after a second and/or third chromatographic separation and recrystallization.

Teliglazine (1): dark green needles (0.9 mg, $CHCl_3$), mp 229−232 °C; IR ($CHCl_3$) ν_{max} 1619, 1595, 1576, 1538, 1262, 1136 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 246 (sh, 3.24), 318 (3.43), 430 (2.53), 648 (2.55) nm; UV (EtOH + 0.1 M HCl) λ_{max} (log ϵ) 248 (3.31), 294 (3.29), 316 (sh, 3.06), 378 (2.59), 520 (2.47) nm; ^1H NMR ($CDCl_3$, 400 MHz) δ 10.03 (1H, dm, J = 8.3 Hz, H-11), 8.48 (1H, dd, J = 1.5, 8.3 Hz, H-8), 8.14 (1H, br d, J = 4.6 Hz, H-4), 7.88 (1H, br d, J = 4.6 Hz, H-5), 7.79 (1H, ddd, J = 1.5, 6.9, 8.3 Hz, H-10), 7.42 (1H, ddd, J = 1.5, 6.9, 8.3 Hz, H-9), 4.87 (3H, br s, NCH_3), 4.34 (3H, s, OCH_3-2), 4.11 (3H, s, OCH_3-3); ^{13}C NMR (from correlation data, $CDCl_3$, 100 MHz) δ 177.0 (s, C-7), 152.3 (s, C-2), 143.7 (s, C-3), 136.9 (s, C-11a), 135.1 (s, C-6a), 134.8 (d, C-5), 134.1 (d, C-10), 130.1 (s, C-7a), 126.6 (d, C-8), 126.5 (d, C-11), 124.8 (d, C-9), 124.5 (s, C-1b), 117.2 (d, C-4), 117.0 (s, C-3a), 105.6 (s, C-1a), 61.5 (q, OCH_3-3), 60.9 (q, OCH_3-2), 51.2 (q, NCH_3), C-1 not detected; LRESIMS/MS *m*/*z* 322 (16) $[M + H]^+$, 307 (9) $[322 - CH_3]^{\bullet+}$, 292 (17) $[322 - OCH_3 + H]^+$, 289 (100) $[307 - H_2O]^{\bullet+}$, 278 (31) $[322 - C_2H_6N]^{\bullet+}$, 261 (25) $[289 - CO]^{\bullet+}$; HRDCIMS 321.1004 (M^+, calcd for $C_{19}H_{15}NO_4$, 321.1001).

Identification of Known Compounds. Ouregidione (1.8 mg), imenine (0.7 mg), splendidine (1.2 mg), telitoxine (1.3 mg), *O*-methylmoschatoline (4.3 mg), 4,5-dioxodehydroasimilobine (4.5 mg), and telikovinone (16 mg) were identified by ^1H NMR, IR, UV, and MS. Co-TLC was also used for splendidine, imenine, telitoxine, telikovinone, and *O*-methylmoschatoline.

Splendidine: ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.7 (s, C-7), 155.9 (s, C-2), 152.3 (s, C-4), 152.1 (s, C-1), 139.2 (s, C-6a), 134.5 (s, C-11a), 133.9 (d, C-10), 132.3 (s, C-7a), 128.8 (d, C-8), 128.7 (d, C-9), 128.4 (d, C-11), 126.6 (d,

C-5), 125.5 (s, C-3a), 123.0 (s, C-1b), 119.8 (s, C-1a), 101.6 (d, C-3), 60.6 (q, OCH_3-1), 56.6 (q, OCH_3-4), 56.2 (q, OCH_3-2); LRCH_4CI/MS *m/z* 322 (100) $[M + H]^+$.

Imenine: ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.7 (s, C-7), 156.3 (s, C-1), 153.6 (s, C-4), 150.4 (s, C-3), 149.5 (s, C-2), 139.2 (s, C-6a), 134.6 (s, C-11a), 133.8 (d, C-10), 131.4 (s, C-7a), 128.5 (d, C-8), 128.1 (d, C-9), 127.9 (d, C-11), 127.7 (d, C-5), 124.3 (s, C-1b), 120.8 (s, C-3a), 116.2 (s, C-1a), 62.2 (q, OCH_3-3), 61.6 (q, OCH_3-2), 61.0 (q, OCH_3-1), 57.1 (q, OCH_3-4); LRCH_4CI/MS *m/z* 352 (100) $[M + H]^+$.

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