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Iridoids from *Borreria verticillata*

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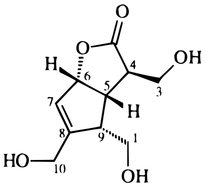
ABSTRACT



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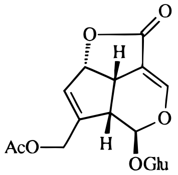

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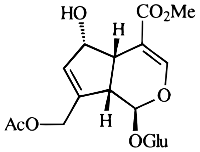

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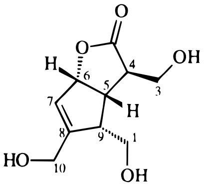
Borreria verticillata **contains the new iridoid aglycone borreriagenin (1), in addition to the known iridoids asperuloside (2) and daphylloside (3). The structure of borreriagenin (1) was elucidated by extensive NMR analysis.**

The family Rubiaceae has many pharmaceutically important plants. *Borreria verticillata* (L.) G. F. W. Mey is a species which occurs in the whole territory of Brazil and is commonly used in traditional medicine as an antipyretic and analgesic.

Previous phytochemical studies of this species showed the presence of terpenoid indole alkaloids of a special type.[1] In the present study we investigated the iridoids present in a specimen collected in Campos dos Goytacazes, Rio de Janeiro, Brazil. The new iridoid borreriagenin (**1**) and the known iridoids asperuloside (**2**) and daphylloside (**3**) were isolated from an MeOH extract of the flowers



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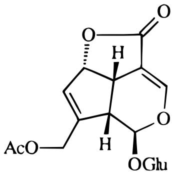

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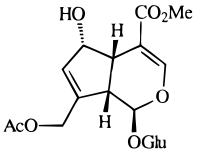

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The methanolic extract was submitted to flash chromatography using $CHCl_3$:MeOH mixtures. The fraction eluted with $CHCl_3$:MeOH (80:20 v/v) was submitted to chromatography on Sephadex LH-20 and yielded a crude iridoid mixture. This mixture was submitted to preparative HPLC. It yielded as the main component asperuloside (**2**), an iridoid very common within the Rubiaceae family and which has considerable taxonomic utility for the tribal classification within the family.[2] The genus *Borreria* belongs to the tribe Spermacoceae, within the subfamily Rubioideae. In this subfamily asperuloside (**2**) was found in nearly all species investigated, in contrast to the other subfamilies in which it was not found.[2]

In addition to asperuloside (**2**), a minor quantity of the iridoid daphylloside (**3**) was isolated, which is also quite common and is thought to be derived from asperuloside (**2**).[3] Besides these compounds a new nonglucosidic iridoid, named borreriagenin (**1**), was isolated. The UV spectrum of the compound had a maximum at λ 210 nm, showing that the compound had a different chromophore than asperuloside (**2**). The ^1H and ^{13}C NMR spectra of **1** (Table 1) revealed the absence of signals corresponding to a glucose moiety, with only 10 carbon signals in the ^{13}C NMR spectrum. An internal γ-lactone moiety was indicated by the carbonyl

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(1) Baldé, A. M.; Pieters, L. A.; Gergelv, A.; Wray, V.; Claeys, M.; Vlietinck, A. J. *Phytochemistry* **1991**, *30*, 997.

(2) Inouye, H.; Takeda, Y.; Nishimura, H.; Kanomi, A.; Okuda, T.; Puff, C. *Phytochemistry* **1988**, *27*, 2591.

(3) Inouye, H.; Okigawa, M.; Shimokawa, N. *Chem. Pharm. Bull.* **1969**, *17*, 1949.

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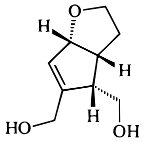
Table 1. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR Data of Borreriagenin (**1**) Obtained in D_2O as Solvent, Chemical Shifts (δ, Ppm), and Coupling Constants (J, Hz, in Parentheses)

atom	δ_C	δ_H
1	58.7	3.88, dd (11.7, 4.9) 3.76, dd (11.7, 4.1)
3	61.6	3.98, dd (11.3, 4.4) 3.88, dd (11.3, 4.1)
4	45.4	3.01, ddd (4.4, 4.4, 4.1)
5	42.3	3.30, ddd (8.7, 7.4, 4.4)
6	88.6	5.53, ddddd (7.4, 2.4, 1.7, 0.9, 0.7)
7	123.5	5.94, dddd (2.4, 1.8, 1.7, 1.5)
8	152.4	
9	47.8	3.15, ddddddd (8.7, 4.9, 4.1, 1.8, 1.1, 1.0, 0.7)
10	59.0	4.30, dddd (15.3, 1.5, 1.0, 0.9) 4.23, dddd (15.3, 1.7, 1.7, 1.1)
11	182.1	

signal at δ_C 182.1 (C-8) and the oxygenated sp^3 carbon at δ_C 88.6 (CH-6). Three hydroxymethyl groupings were indicated by the carbon signals at δ_C 61.6, 59.0, and 58.7. Analysis of the HMBC spectrum led to the proposed structure and enabled the complete assignment of the ^{1}H and ^{13}C NMR spectra (Table 1). By analysis of the coupling constants (J) observed in the ^{1}H NMR of **1** and comparison with reported structures, the stereochemistry of the four chiral centers (CH-4, CH-5, CH-6, and CH-9) could be derived. The structure is closely related to asperuloside (**2**). In fact asperuloside (**2**) could be its biosynthetic precursor yielding borreriagenin (**1**) through deglucosylation and subsequent reduction. This means that the carbon atoms 5 and 9 should have the normal configurations (5*S* and 9*R* as shown in **1** and **2**). Furthermore, nearly all iridoids which have been found in nature have these configurations. Only a few exceptions are known, none of which occur within the Rubiaceae family. With the *R*-configuration for C-5 fixed, C-6 should have the *S*-configuration, with H-6 in the β-position because the fusion of the γ-lactone ring can only take place in the *cis*-fashion. A further confirmation of the derived configurations of CH-5, CH-6, and CH-9 is provided by comparison with the spectral data of ningpogenin (**4**), which was isolated from *Scrophularia ningpoensis*.[4] All coupling constants, including the long-range coupling constants, of the hydrogens attached to the ring containing these carbons are very similar to those found in borreriagenin (**1**).



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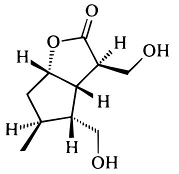

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Thus, the only chiral center to be resolved was CH-4. An indication for the *R*-configuration of C-4 was found in the literature: gelsemiol (**5**), an iridoid isolated from *Gelsemium serpervirens*,[5] has a nearly identical H-4/H-5 coupling constant (about 4.5 Hz in both cases). The stereochemistry based on the above-mentioned arguments (Figure 1) was checked by NOE difference spectroscopy. Thus, irradiation of H-7 (δ_H 5.94) resulted in a 4.7% enhancement of the H-6 (δ_H 5.53) signal and small enhancements of the signals of both H-10 hydrogens. Irradiation of H-6 gave a 6.2% enhancement of the H-7 signal and a 7.4% enhancement of the H-5 (δ_H 3.30) signal. Irradiation of H-5 yielded a 9.1% enhancement of the H-6 signal, a 1.4% enhancement of the H-9 (δ_H 3.15) signal, an enhancement of nearly 3% for the signals of both H-3 (δ_H 3.98 and 3.88) hydrogens, and a small enhancement of the signals of both H-1 (δ_H 3.80 and 3.76) hydrogens. The enhancement of the 2H-3 hydrogens and the absence of an enhancement of the H-4 hydrogen are strong arguments in favor of the 4*R*-configuration.

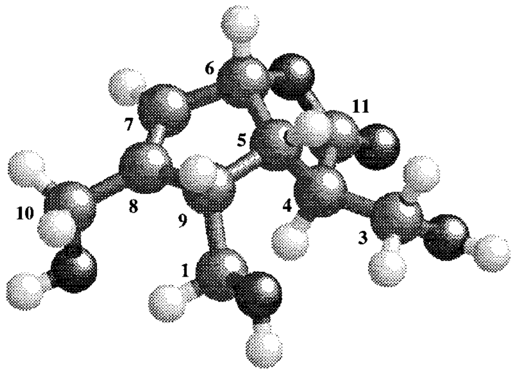
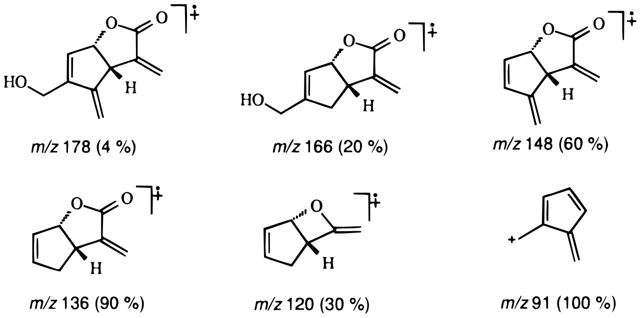


Figure 1. Stereochemical view of borreriagenin (**1**).

This configuration was further substantiated by the irradiation of H-4, which yielded enhancements of about 2% for the signals of all four of the H-3 and H-1 hydrogens, but no enhancement of the signal of H-5. Finally, irradiation of the H-9 hydrogen yielded an enhancement of the signals of H-5 (5.8%), both H-1 hydrogens (1.5 and 2.0%), and one of the 2H-10 hydrogens (2.1%).

Scheme 1. Explanation of the Fragmentation Pattern Observed



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(4) Qian, J.; Hunkler, D.; Rimpler, H. *Phytochemistry* **1992**, *31*, 905.

Iridoid aglycones are relatively rare and they are found in quite different families, such as Loganiaceae, Bignoniaceae, Apocynaceae, Scrophulariaceae, and Verbenaceae.[6] Their occurrence does not seem to have any chemosystematic value.

Finally, our attention was directed to the principal peaks registered in the mass spectrum of borreriagenin **1** (Scheme 1). A proposal for the fragmentation patterns justifying the principal peaks is described in Scheme 1.

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Supporting Information Available: Additional spectroscopic data of borreriagenin (^{1}H NMR in CD_3OD), asperuloside, and daphylloside (completely assigned ^{1}H NMR spectra). Experimental data of the extraction and isolation procedure, conditions for the HPLC separation. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Jensen, S. R.; Kirk, O.; Nielsen, B. J.; Norrestam, R. *Phytochemistry* **1987**, *26*, 1725.

(6) Boros, O. R.; Stermitz, F. R. *J. Nat. Prod.* **1991**, *54*, 1192.