A New Glucoalkaloid from *Uncaria glabrata*

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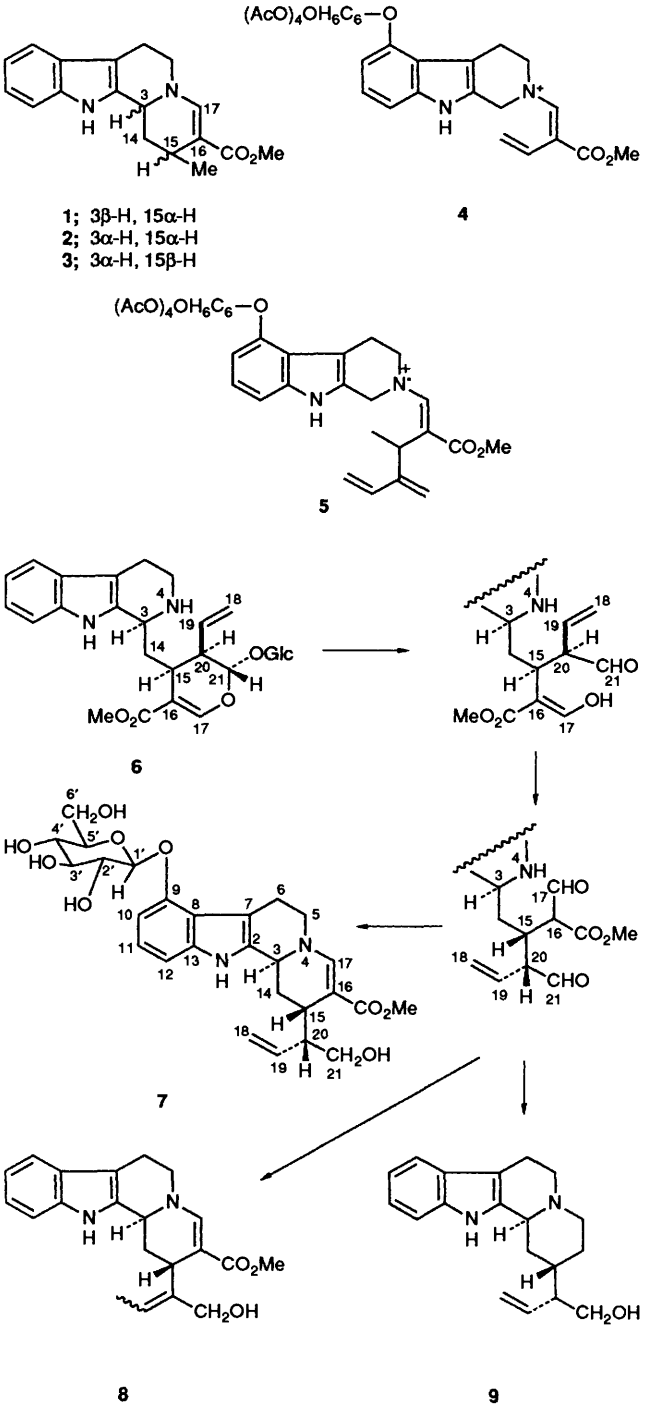
Extraction of the bark of *Uncaria glabrata* DC (Rubiaceae) has yielded an unusual indole monoterpenoid glucoalkaloid, glabratine, for which structure **7** is proposed on the grounds of its spectral data.

Uncaria glabrata DC (Rubiaceae), known in West Sumatra as 'akar kait' and used in traditional medicine as a remedy for food poisoning, is a woody climber attaining a height of > 30 m often with a trunk diam. of 10 cm. In continuation of our phytochemical survey of West Sumatra[1] it was observed that an extract of the bark of this plant gave a positive Mayer's test. The basic portion of the methanolic extract of the bark furnished a mixture of uncarines[2] whilst the neutral portion was a mixture of glycosides which after extensive chromatographic purification gave a glucoalkaloid, for which we suggest the trivial name glabratine, which formed needles (from ethanol), m.p. 263–265 °C.

The CIMS(NH_3) of the new alkaloid showed a weak MH^+ ion at *m/z* 531 which was more intense in the FABMS, which also showed a strong fragment ion at *m/z* 369 corresponding to the loss of a hexose ($C_6H_{10}O_5$) unit. The microanalytical data were in accord with the molecular formula $C_{27}H_{34}N_2O_9$. Acetylation of glabratine with acetic anhydride and pyridine supplied an amorphous pentaacetate which exhibited an MH^+ ion at *m/z* 741 in its FABMS, which suggested, if the hexose residue had undergone tetraacetylation, that the aglycone contained a hydroxy group which had also undergone acetylation.

The ^1H and ^{13}C NMR spectra (see Table 1) were highly informative and their analysis was aided by proton–proton decoupling, ^1H, ^{13}C heteronuclear correlation, and by the DEPT technique. The chemical shift and multiplicity of certain signals in the ^{13}C spectrum of the pentaacetate were very similar to those for the C-3, C-5, C-6, C-15, C-17[3] and the methoxycarbonyl group of the synthetic compounds **1**,[4] **2** and **3**[5] of the vallesiachotamine type.[6] The electronic spectrum of glabratine: λ_{max}(MeOH) 224 and 294 nm (ε 34 300 and 31 900 respectively), was also reminiscent of that of vallesiachotamine **8**.[6] The band at 294 nm was of enhanced intensity owing to the superposition of the β-aminoacrylate chromophore on the indole spectrum. In keeping with the presence of this chromophore the IR spectrum (KBr) of glabratine showed bands at 1655 (C=O) and 1580 (C=C) cm^{-1}.

The chemical shifts of the indolic carbon atoms in the ^{13}C NMR spectrum of the pentaacetate pointed to oxygenation at C-9[7] which was also supported by the observation of NOE interactions between the NH proton and an aromatic proton at C-12 (the only alternative location for oxygenation). The observed second-order aromatic ^1H NMR spectrum was computer simulated providing the chemical shifts and coupling constants shown in Table 1. In addition to the sugar residue, the ^{13}C NMR spectrum revealed the presence of a vinyl group, a methine carbon, and a methylene group attached to oxygen, and the ^1H NMR spectrum, with appropriate decoupling experiments, indicated their interrelationship as CH_2=CH–CH–CH_2O and their attachment at C-15 through the methine carbon atom.



Scheme 1

Table 1 NMR spectra of glabratine pentaacetate

Carbon no.	δ_C	δ_H, J/Hz
2	131.93	
3	48.17	4.57, br d, $J_{3,14\beta}$ 12.5
5	51.18	3.51, ddd, $J_{5\alpha,5\beta}$ 12.0, $J_{5\alpha,6\beta}$ 12.0, $J_{5\alpha,6\alpha}$ 3.5
		3.63, dd, $J_{5\beta,5\alpha}$ 12.0, $J_{5\beta,6\beta}$ 4.5
6	23.63	2.76, 6-βH
		3.05, br d, $J_{6\alpha,6\beta}$ 15.5
7	107.60	
8	116.69	
9	150.71	
10	103.08	6.59, X of ABX, $J_{10,11}$ 8.0, $J_{10,12}$ 1.2
11	122.23	7.03, AB of ABX, $J_{11,12}$ 9.7,
12	106.42	$J_{11,10}$ 8.0, $J_{12,10}$ 1.2
13	137.95	
14	32.26	1.62, ddd, $J_{14\beta,14\alpha}$ 12.5, $J_{14\beta,3}$ 12.5, $J_{14\beta,15\beta}$ 4.5
		2.42, m
15	31.34	2.93, ddd, $J_{15,20}$ 6.5, $J_{15,14\beta}$ 4.5, $J_{15,14\alpha}$ 1.5
16	94.56	
17	146.54	7.59, s
18	117.31	5.04, dd, $J_{18,19}$ 10.0, $J_{18,18}$ 1.5
		5.06, dd, $J_{18,19}$ 16.5, $J_{18,18}$ 1.5
19	138.48	5.79, ddd, $J_{19,18}$ 16.5, $J_{19,18}$ 10.0, $J_{19,20}$ 8.5
20	50.38	2.42, m
21	66.29	4.09, dd, $J_{21,21}$ 10.5, $J_{21,20}$ 8.0
		4.37, dd, $J_{21,21}$ 10.5, $J_{21,20}$ 3.5
CO_2Me	166.99	
OMe	50.60	3.66, s
NH	—	8.38, br s
1′	98.03	5.28, d, $J_{1',2'}$ 7.6
2′	71.00	5.40, dd, $J_{2',3'}$ 9.0, $J_{2',1'}$ 7.6
3′	72.99	5.33, dd, $J_{3',4'}$ 9.0, $J_{3',2'}$ 9.0
4′	68.44	5.20, dd, $J_{4',5'}$ 9.9, $J_{4',3'}$ 9.0
5′	71.96	3.94, ddd, $J_{5',4'}$ 9.9, $J_{5',6'}$ 5.5, $J_{5',6'}$ 2.4
6′	62.02	4.18, dd, $J_{6',6'}$ 12.9, $J_{6',5'}$ 2.4
		4.32, dd, $J_{6',6'}$ 12.9, $J_{6',5'}$ 5.5
$MeCO.O$	171.61, 170.62, 170.26, 169.50, 169.24	
$MeCO.O$	21.09, 20.70, 20.63, 20.58 (×2)	

The ^{13}C and ^1H NMR spectra of the sugar residue in both the alkaloid and its pentaacetate revealed that it was glucose and the magnitude of the coupling constant of the anomeric proton, in the ^1H NMR spectrum of the pentaacetate, with its neighbour ($J_{1',2'}$ 7.6 Hz) established the β-configuration of the glucoside linkage.[8]

The attachment of the glucose residue to the benzene ring was revealed by the mass spectra of both the alkaloid and its pentaacetate. The EIMS of the pentaacetate did not show a molecular ion but a base peak at m/z 627 and a weak ion at m/z 680 which were shown by high resolution to have the compositions $C_{31}H_{35}N_2O_{12}$ and $C_{35}H_{40}N_2O_{12}$ respectively, which correspond to the ions **4** and **5**, resulting from the elision of the side chain attached at C-15 in one case and the elimination of acetic acid in the other. In the FABMS of glabratine there was also an ion at m/z 459 resulting from the loss of the side chain attached at C-15. This evidence pointed to the attachment of the glucose residue at C-9 which was confirmed by the observation of a 13% NOE at the 10-H when the frequency of the anomeric proton was irradiated in the ^1H NMR spectrum of the pentaacetate.

This evidence allows structure **7** to be advanced without specification of stereochemistry.

The biosynthesis of the complex array of monoterpenoid indole alkaloids involves the key intermediate strictosidine **6** and commences with glycolysis. Glabratine would thus be derived from an oxygenated strictosidine (see Scheme 1) by glycolysis, rotation about the 14,15-bond, reduction of the aldehyde at C-21, and cyclization linking C-17 to N-4. Such a transposition requires a change from the normal 15α-H configuration found in secologanin to a 15β-H configuration. If the 15β-H stereochemistry is assumed then it follows from the proton coupling constants for 15-H, 14-H and 3-H that 3-H is in the expected α-configuration. The stereochemistry of C-20 is also assumed on the grounds of the probable biogenesis. The circular dichroism for glabratine is complicated by the superposition of the β-aminoacrylate chromophore on the indole chromophore so that it is hazardous to draw stereochemical conclusions from the sign of the Cotton effect near 290 nm.[10]

Glabratine **7** is thus a close relative of vallesiachotamine **8**[6] and antirhine **9**[11] in which strictosidine has undergone simple modifications. It, however, is highly unusual among indole monoterpenoid alkaloids in bearing a glucose residue on the benzenoid ring. Further work on the glucoalkaloids of this plant is in progress.

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