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19-ETHOXYCORONARIDINE, A NOVEL ALKALOID FROM *TABERNAEMONTANA GLANDULOSA**

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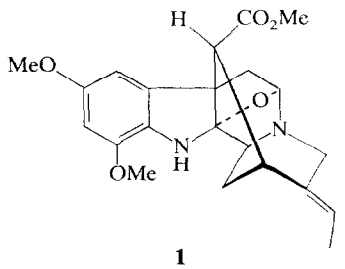
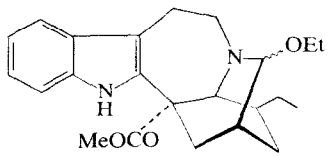
Key Word Index—*Tabernaemontana glandulosa*; Apocynaceae; ibogamine alkaloids; 19-ethoxycoronaridine.

In the course of our screening alkaloids from *Tabernaemontana* species, we investigated the constituents of *T. glandulosa* (syn. *Gabunia glandulosa*) collected in Ghana. From the MeOH extracts of the stems as well as of the leaves we isolated tabernulosine (**1**) as the main alkaloid [1], a new base of the picrinine type [2] with a substitution pattern of the benzene ring unusual for alkaloids. Besides **1** the plant extracts contained some minor alkaloids among them a compound which was mainly found in the extract from the stems and for which structure **2** was deduced.



1



2

The ^{1}H NMR spectrum shows triplets at δ 1.13 and 0.88 due to two Me groups; one of the corresponding CH_2 groups appears as a quartet at 3.32 and thus demonstrates the presence of an OEt group in **2**. The MS is characterized by a very easy loss of $^{\cdot}$Et from the M^+ ion. In acidic solution, in the presence of traces of water, **2** is rapidly decomposed to a more polar compound **3**, which was identified as 19-hydroxycoronaridine [3]. From the characteristic ^{1}H NMR signals of the hydrogen at C-19 [4] we must conclude, that the isolated alkaloid **2** is a 17:3 mixture of 19-epimers. CD measurements on **2** exhibit a positive Cotton effect at 245 nm and a negative effect at 285 nm, which indicates that **2** belongs to the (−)-ibogamine series [5, 6].

Reduction of **2** using $LiAlH_4$ yielded coronaridinol (**4**) [3], whereas $NaBH_4$ reduction of **3** gave coronaridine (**5**) (Scheme 1) [2]. **2** could be prepared from **5** by treatment with a C_6H_6–EtOH solution of iodine: after 12 hr at room temperature 45% of the starting material had been converted into the 19-ethoxy derivative **2**; a further 50% of the starting material could be recovered unchanged. All experiments to transform **5** into **2** by other methods [7, 8] failed.

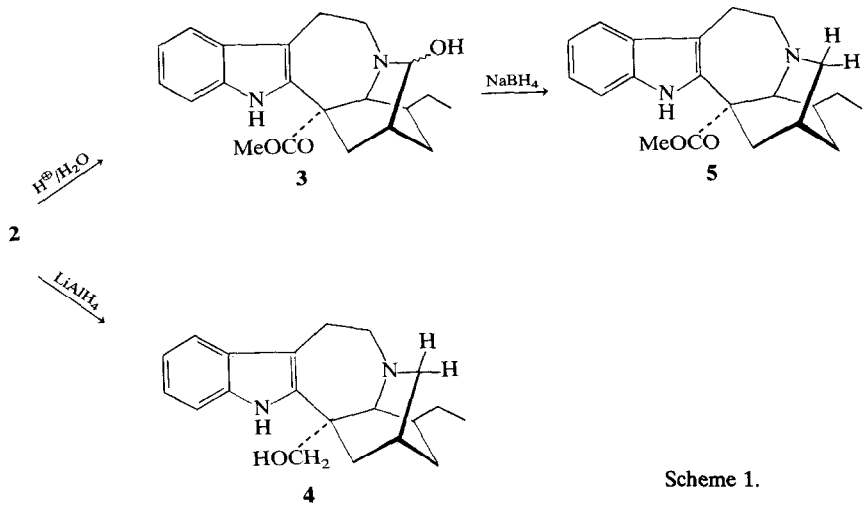
The carbinolamine group itself is comparatively rare in natural products; however, **2** has the very unique feature of being a naturally-occurring ethyl derivative of a carbinolamine. Particularly from a biogenetic point of view there arises the question whether **2** may be an artefact formed during the separation or isolation procedures. In our opinion 3 arguments provide evidence that **2** must be a genuine constituent of *T. glandulosa*. (1) **2** was isolated from different batches of air-dried plant material after work-up in different ways using only EtOH-free solvents. (2) In spite of the fact that large quantities of MeOH were used during work-up, we could not detect any 19-methoxycoronaridine. (3) The carbinolamine **3**, when kept in MeOH or EtOH solution neutral or HCl-acidic does not yield the corresponding α-alkoxyamine.

EXPERIMENTAL

Plant material. Stems and leaves of *T. glandulosa* Stapf (syn. *Gabunia glandulosa* Stapf) were collected in Ghana. A herbarium specimen was identified by Prof. Dr. D. Vogellehner, Botany Department, University of Freiburg, and is being stored in the herbarium.

Isolation. Dried stems (1 kg), cut into pieces, were extracted with hot MeOH, the extract concd and the resulting soln made acidic with HOAc. This soln was then extracted with hexane and C_6H_6 to remove non-alkaloidal products. The remaining soln was basified with conc NH_4OH to pH 10 and extracted with $CHCl_3$ (EtOH-free). This extract on concn *in vacuo* yielded 3.5 g crude alkaloids (= A^1). Treatment of 300 g dried leaves in the same manner yielded 4 g crude alkaloids (= A^2). A^1 was chromatographed over 250 g Sephadex LH-20 with MeOH–$CHCl_3$ (7:3). 20×40 ml fractions were collected and monitored by UV (254 nm) and TLC assay; fractions 1–7 (= B^1) were combined as were 8–11 (= B^2) and 12–20 (= B^3). B^2 (2.5 g) was chromatographed over 250 g basic Al_2O_3 (activity II–III) with 1 l. $CHCl_3$; 1 l. $CHCl_3$–MeOH, 49:1; 1 l. $CHCl_3$–MeOH, 9:1. 140×25 ml

* Part 3 in the series "Constituents of West African Medicinal Plants" and Part 9 in the series "Alkaloids in *Tabernaemontana* Species". For Parts 2 and 8, respectively, see ref. [1].



Scheme 1.

fractions C were collected and monitored by UV (254 nm) and TLC. Fractions C 61–69 (550 mg) were combined and rechromatographed over 50 g OR-PVA 500 with MeOH–$CHCl_3$, 7:3. 20×10 ml fractions D were collected. After evapn to dryness of fractions D 10–12 we isolated 60 mg 19-ethoxycoronaridine (**2**) as a colourless oil, which was eventually purified (depending on batch of plant material and/or procedure of extraction, separation and isolation) from small amounts of 19-hydroxycoronaridine (**3**) by prep-TLC (Si gel; C_6H_6–EtOAc, 3:2, multiple development). In the same manner we isolated 2 mg of 19-ethoxycoronaridine from A^2. $C_{23}H_{30}N_2O_3$ (M^+, meas.: 382.2261, calc.: 382.2256). $[\alpha]_D^{20} - 59°$ ($c = 1$); Ce^{4+} [9]: bluish/grey. UV λ_{max} nm (log ε): 292 (3.88); 286 (3.92); 225 (4.51). IR (KBr) cm^{-1}: 3450 (NH), 1725 (C=O). CD: (*c* 0.084 mg/ml) λ (Δε) 285 (−3.03), 245 nm (2.68). ^1H NMR (90 MHz, $CDCl_3$, TMS): δ 7.9 ppm (1H, *s*, NH), 7.55–6.95 (4H), 4.33 (0.15H, *d*, $J = 7.5$ Hz) and 4.05 (0.85H, *d*, $J = 2$ Hz), 3.78–3.64 (*ca* 2H), 3.63 (3H, *s*, OMe), 3.32 (2H, *q*, $J = 7$ Hz), 3.15–1.3 (*ca* 11H), 1.13 (3H, *t*, $J = 7$ Hz), 0.88 (3H, *t* (*br*), $J = 7$ Hz). MS (70 eV): ***m/e*** (%) 382 (61, M^+), 381 (8), 354 (8), 353 (19), 362 (6), 339 (9), 338 (33), 337 (100), 336 (16), 326 (6), 325 (6), 323 (8), 307 (6), 305 (6), 293 (6), 277 (6), 253 (6), 252 (16), 240 (9), 229 (10), 228 (8), 221 (6), 214 (11), 209 (6), 208 (6), 206 (6), 196 (7), 195 (8), 194 (9), 193 (6), 182 (8), 181 (7), 180 (12), 170 (8), 169 (12), 168 (23), 167 (16), 166 (6), 156 (6), 155 (8), 154 (21), 145 (6), 144 (10), 143 (10), 136 (10), 135 (6), 130 (8), 128 (6), 127 (6), 124 (6), 122 (10).

Hydrolysis of **2** *to* 19-*hydroxycoronaridine* (**3**). After 2 hr at room temp. in 5 ml $CHCl_3$ and 0.1 ml 2 N HCl, **2** (2 mg) was completely converted into a more polar compound, identical in all spectral data and chromatographic properties with 19-hydroxycoronaridine (**3**) [3].

Reduction of **2** *to coronaridinol* (**4**). A soln of 2 mg **2** in THF was reduced at 0° with 100 mg $LiAlH_4$. The suspension was worked up in the usual manner. The product was purified by prep-TLC (Si gel) using $CHCl_3$–MeOH (9:1) and found to be identical (spectral data and chromatographic properties) with authentic coronaridinol (**4**) produced by reduction of coronaridine (**5**).

Partial synthesis of **2**. Coronaridine (**5**) (50 mg) was dissolved in 15 ml C_6H_6 and 15 ml EtOH. A soln of 50 mg I_2 in 15 ml C_6H_6 was added dropwise at 10° over 1 hr. After stirring for 12 hr at room temp. the soln was washed with aq. $NaHCO_3$ and $Na_2S_2O_3$ solns. The C_6H_6 layer was separated and the aq. layer extracted with $CHCl_3$. The combined organic layers were dried (Na_2SO_4) and evapd *in vacuo*. The oily residue was chromatographed over Si gel. Elution with C_6H_6–EtOAc (3:2) gave 27 mg unchanged coronaridine (**5**) and then 25 mg 19-ethoxycoronaridine (**2**).

Reduction of **3** (*from* **2**) *to coronaridine* (**5**). A soln of **3** (5 mg) in 5 ml MeOH was reduced at room temp. with 10 mg $NaBH_4$; the suspension was worked up in the usual manner and the only product separated from trace impurities by prep-TLC (Si gel) using C_6H_6–EtOAc, (3:2). It was found to be identical in every respect with authentic coronaridine (**5**).

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