

GABUNINE: A NATURAL DIMERIC INDOLE  
DERIVED FROM PERIVINE\*

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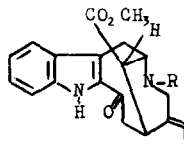
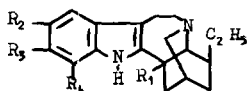
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AS the initial part of a complete chemical examination of Gabunia odoratissima Stapf (Apocynaceae), we previously described the isolation of several triterpenoids.<sup>1</sup> We now wish to report the isolation of nine indole alkaloids from this plant. One of these bases, gabunine, is of particular interest since it represents the first natural example of a perivine-derived dimeric indole alkaloid.<sup>2,3</sup>

Seven alkaloids of firmly established structure were isolated, all of which were identified by direct comparison with authentic samples: these were the iboga-type bases ibogamine (I),

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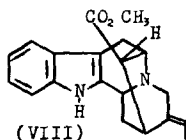
coronaridine (II), and isovoacangine (III),<sup>4</sup> the 2-acylindole bases vobasine (IV)<sup>2,5</sup> and perivine (V),<sup>5</sup> and the dimeric bases conoduramine (VI) and conodurine (VII)<sup>6</sup> which are chemically and perhaps also biogenetically derivable from vobasine (as vobasinol) and isovoacangine.



- |       |   |      |            |
|-------|---|------|------------|
| (I)   | $R_1 = R_2 = R_3 = R_4 = H$                                 |      |            |
| (II)  | $R_1 = CO_2 CH_3$ ; $R_2 = R_3 = R_4 = H$                   | (IV) | $R = CH_3$ |
| (III) | $R_1 = CO_2 CH_3$ ; $R_2 = R_4 = H$ ; $R_3 = OCH_3$         | (V)  | $R = H$    |
| (VI)  | $R_1 = CO_2 CH_3$ ; $R_2 = Vob$ ; $R_3 = OCH_3$ ; $R_4 = H$ |      |            |
| (VII) | $R_1 = CO_2 CH_3$ ; $R_2 = H$ ; $R_3 = OCH_3$ ; $R_4 = Vob$ |      |            |
| (IX)  | $R_1 = CO_2 CH_3$ ; $R_2 = H$ ; $R_3 = OCH_3$ ; $R_4 = Per$ |      |            |

The eighth alkaloid, present in very small amount, formed needles, m.p. 226-228° (dec.) from acetone. Spectral evidence led to the assumption that it probably possessed structure (VIII). Thus, an ultraviolet spectrum showed maxima at 226, 284 and 292 m $\mu$ , with intensities characteristic of a simple indole chromophore, while the infrared spectrum showed a carbonyl at 5.84  $\mu$  attributable to a carbomethoxy group. The NMR spectrum<sup>7</sup> of the alkaloid revealed an unsplit methyl at 3.13, suggestive of a carbomethoxy group shielded by the indole nucleus; other significant features observed were four aromatic protons in the region of 7.22, the

protons of an ethylidene group (doublet at 1.62,  $J = 7$  and quartet at 5.34,  $J = 7$ ) an indole NH at 8.55 (exchanged rapidly by  $D_2O$ ) and no additional methyl signal of any kind. At this point in the investigation, we learned that structure (VIII) had been independently assigned to pericyclivine, a new alkaloid isolated from Catharanthus lanceus,<sup>8</sup> and partially synthesized<sup>3</sup> by the acid-catalyzed cyclization of perivinol. Direct comparison established the identity of our base with pericyclivine (VIII).



The ninth alkaloid obtained from G. odoratissima was named gabunine. It crystallized from methanol or ethanol as needles, m.p. 244-246° (dec.),  $[\alpha]_D^{20} - 105^\circ$  (c, 0.62 in  $CHCl_3$ ) and analyzed as the dimeric composition  $C_{42}H_{50}N_4O_5$  (Calcd: C, 73.00; H, 7.25; N, 8.12; 3-OCH<sub>3</sub>, 13.48. Found: C, 73.09; H, 7.48; N, 7.93; 3-OCH<sub>3</sub>, 14.22). The ultraviolet spectrum of gabunine in ethanol indicated only indole or alkoxyindole chromophores:  $\lambda_{max}$  226 (log  $\epsilon$ , 4.83), 287 (4.24) and 295 (4.22); no spectral shift was observed in alkaline solution. Its infrared spectrum showed strong carbonyl absorption, attributable to ester carbonyl, around 5.78  $\mu$ ; two ester functions could be observed (peaks at 5.75  $\mu$  and 5.80  $\mu$ ) in the spectrum of gabunine hydrobromide (needles from acetone, m.p.

> 280°, dec.). The NMR spectrum of gabunine was particularly illuminating, especially when compared to those of conoduramine (VI) and conodurine (VII). Unlike conoduramine (which shows singlets for the 1,4-aromatic protons of its isovoacangine moiety<sup>6</sup>) but similar to conodurine, gabunine exhibits two aromatic ortho protons as an AB quartet (doublet centered at 6.83 and 7.28 $\tau$ ,  $J = 8.5$ ). Indeed, except for the conspicuous absence of an N<sub>10</sub> methyl peak around 2.49, the NMR spectrum of gabunine was virtually identical with that of conodurine (VII). It appeared likely, therefore, that gabunine might be N-desmethylconodurine. This was verified by conversion of gabunine to conodurine (identified by mixed m.p. and infrared spectral comparison) in good yield by mild reductive methylation in 50% aqueous dioxane using 38% aqueous formaldehyde, 10% palladium on charcoal and hydrogen as reagents. Gabunine thus has structure (IA), and is the first naturally occurring representative of a potentially large group of dimeric indole bases derived in part from perivine (via perivinol) rather than from the more common vobasine moiety.<sup>2</sup>

It is obviously of biogenetic interest that perivine, pericyclivine and gabunine were isolated from the same plant specimen, since the chemical interrelationships between these molecules are now well established. Nevertheless, the inadvertent synthesis of these molecules during the isolation and purification stage of our own as well as other reported investigations is by no means excluded.

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