Phytochemistry, 1976, Vol. 15, pp. 543–544. Pergamon Press. Printed in England.

THE ALKALOIDS OF *ASPIDOSPERMA CUSPA*: 16-EPI-ISOSITSIRIKINE, A NEW INDOLE BASE

J. Couceiro Simões* and B. Gilbert†
Centro de Pesquisas de Produtos Naturais, Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, Brazil
and
W. J. Cretney, M. Hearn and J. P. Kutney†
Department of Chemistry, University of British Columbia, Vancouver, Canada

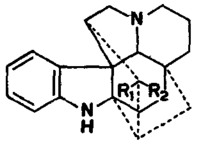
(*Revised Received* 14 *August* 1975)

Key Word Index—*Aspidosperma cuspa*; Apocynaceae; Aspidosperma alkaloid; 16-epi-isositsirikine; indole alkaloid.

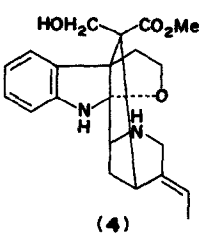
Abstract—*Aspidosperma cuspa* Blake contains kopsanone, epikopsanol, kopsanol, aspidodasycarpine and 16-epi-isositsirikine. Both chemical and botanical data support the allocation of this species to a unique series within the genus.

INTRODUCTION

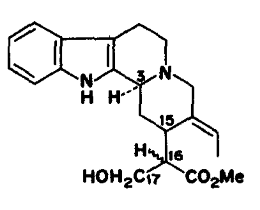
Based on chemical [1–5] and botanical [6,7] studies, the classical subdivision [8] of the genus *Aspidosperma* has been revised [6]. One species, however, *A. cuspa* did not botanically belong to any of the main subdivisions and was accordingly assigned to a unique series (A. P. Duarte, unpublished results). A chemical study was therefore of interest and the results now recorded support the separate classification of the species.



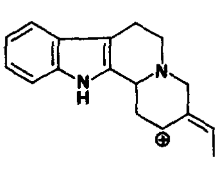
(1) $R_1, R_2 = O$
(2) $R_1 = OH$; $R_2 = H$
(3) $R_1 = H$; $R_2 = OH$



(4)



(5) 16β H; 16α—CH_2OH R
(6) 16α H; 16β—CH_2OH S
(7) 16,17 -double bond



a, *m/e* 251

Of the alkaloids isolated, kopsanone (1) and epikopsanol (2) (accompanied by kopsanol (3) for which chromatographic evidence was obtained) are characteristic of the Macrocarpa series [5,9]. Aspidodasycarpine (4), on the other hand is found in the very distinct Dasycarpa series [10]. The third main alkaloid, epi-isositsirikine (5), has probably been detected previously in *A. oblongum* A.DC [11], but is now characterized structurally for the first time. Its occurrence is in accord with the expected pattern for the Nitida subgroup to which *A. oblongum* belongs and from which related indolic alkaloids have been isolated [3–5].

16-Epi-isositsirikine exhibited many of the spectral features characteristic of isositsirikine [12], but in distinctly different positions. Thus the presence of the benzene unsubstituted indole nucleus, =CH–Me side chain, CH_2OH and CO_2Me could be deduced from the NMR spectrum. The latter two groups could probably be placed in a single side chain, since loss of $C_4H_7O_3$ was evidenced by the main fragmentation of the molecular ion (*m/e* 354) to *m/e* 251, to which structure **a** can be ascribed. Further fragmentation showed the β-carboline alkaloid characteristic peaks at *m/e* 156, 169, 170 and 184.

The Bohlmann bands in the infrared spectrum (2780 and 2835 cm^{-1}) favoured a 3α-H [13] and by general analogy with other corynantheol-type alkaloids, 15α-H could be expected. Since the *A. cuspa* alkaloid was different from isositsirikine (5) which has the *S* configuration at postiton 16, the 16-*R* epimeric structure (6) could be proposed for it. Sodium borohydride reduction of geissoschizine (7) [14,15] in fact yielded the two 16 epimers and these were separated by repeated preparative TLC, to give isositsirikine (5) and 16-epi-isositsirikine (6), the latter identical to the natural alkaloid of *A. cuspa*.

---

* Present address: Instituto de Química, Universidade Federal do Pará, Belém, Pará.
† To whom correspondence should be addressed.

EXPERIMENTAL

Mps are uncorrected.

Isolation of the alkaloids. Aspidosperma cuspa was collected at the base of the Serra do Cabral em Várzea da Palma (Fazenda Belgo Mineira), Pirapora, Minas Gerais, Brazil. The thin bark was removed, sun dried (dry wt 16 kg) ground and extracted with EtOH to give after evaporation a viscous concentrate (735 g). This was stirred with 10% HOAc, filtered and the filtrate subjected to successive extraction (residue wt in parentheses) with hexane (trace), C_6H_6 (4·6 g) and $CHCl_3$ (27·3 g), then extracted further with $CHCl_3$ at pH 7 (14·5 g), pH 9 (6·9 g) and pH 11 (2·8 g). The acid $CHCl_3$ extract yielded after chromatographic purification and recrystallization kopsanone (**1**, 0·24 g) and epikopsanol (**2**, 0·19 g) identical in all respects with samples from *A. ducke* [9]. A trace of kopsanol (**3**) was isolated and identified with an authentic sample by Rf and Ce^{IV} colour on TLC. Repeated C_6H_6 extraction of the pH 9 and pH 11 $CHCl_3$ extracts gave crude crystalline alkaloid (4·5 g) which on recrystallization from C_5H_6 and then Et_2O gave aspidodasycarpine (**4**), mp 208-209°, identical with an authentic sample by IR, UV, NMR, MS, mp and TLC comparison. The pH 7 $CHCl_3$ extract (7 g) was chromatographed on Si gel (60 g) and gave 16-epi-isositsirikine (0·48 g), mp 184–187° raised by recrystallization to 186–187°, $[\alpha]_D^{28}$ $-205°$ (*c*, 0·2 in $CHCl_3$); IR ν_{max}^{KBr} cm^{-1}: 2837, 2780, 1735, 1467, 1450, 1437, 1163, 825, 742; UV λ_{max}^{EtOH} nm (log ϵ): 226, 285, 293 (4·50, 3·90, 3·80), only slightly displaced by acid and alkali; NMR (100 MHz, $CDCl_3$); δ 1·58 (3H, *d*, *J* 7 Hz, $=CH-C\underline{H}_3$), 2·16 (2H, *t*, *J* 6 Hz), 3·5 (3H, *s*, $CO_2C\underline{H}_3$), 3·82 (4H, *d*, *J* 4·5 Hz superimposed on other absorption, $C\underline{H}_2OH$), 5·45 (1H, *q*, *J* 7 Hz, $=C\underline{H}-Me$), 6·96–7·50 (4H, *m*, aromatic H) and 8·28 (1H *br s*, indole $N\underline{H}$); MS (MS9, 70eV) *m/e* (rel. int.): 354 (M^+, 74%), 353 (M-1, 100), 336 (8), 323 ($M-CH_2OH$, 24), 295 ($M-CO_2Me$, 5), 251 ($M-CH(CH_2OH)CO_2Me$, 60), 249 (18), 237 (14), 186 (14), 170 (21), 169 (30), 156 (18). (Found: C, 71·32; H, 7·29; O, 13·43; N, 7·70. $C_{21}H_{26}O_3N_2$ requires: C, 71·16; H, 7·39; O, 13·54; N, 7·90%).

16-*Epi-isositsirikine from Geissoschizine.* Geissoschizine (34·1 mg) in dry MeOH (10 ml) was treated with $NaBH_4$ (5 mole-equiv.) at −30° during 30 min. After 1 hr at 20° 2N-HCl (5 ml) and then saturated Na_2CO_3 (10 ml) were added, the soln concentrated, extracted with $CHCl_3$ (3 × 25 ml) and the $CHCl_3$ evaporated. The resulting residue was separated by preparative TLC on neutral alumina (Woehlm grade III, EtOAc–MeOH 5:1) into geissoschizine (12·2 mg, 36%) and the two 16-epimers of isositsirikine (18·5 mg). Repeated TLC (EtOAc–*iso*-PrOH) gave 16-epi-isositsirikine (4·3 mg) as a yellow oil purified by further chromatography and finally crystallized from C_6H_6 under N_2, when it was identical to the natural alkaloid by IR comparison and in mp, mmp and TLC.

Acknowledgements—We thank Dr. T. Nishida for some NMR spectra and Dr. Alan Duffield for MS (Stanford University). Plant collection and botanical identification were made by Dr. Apparicio P. Duarte (Rio de Janeiro Botanical Garden). Supported by Banco Nacional de Desenvolvimento Econômico (Funtec Contract 47), the Conselho Nacional de Pesquisas, CAPES, Conselho de Pesquisas da UFRJ, and the National Research Council of Canada.

REFERENCES

1. Gilbert, B., Duarte, A. P., Nakagawa, Y., Joule J. A., Flores, S. E., Aguayo Brissolese, J., Campello, J., Carrazzoni, E. P., Owellen, R. J., Blossey, E. C., Brown, Jr. K. S. and Djerassi, C. (1965) *Tetrahedron* **21**, 1141.
2. Arndt, R. R., Brown, S. H., Ling, N. C., Roller, P., Djerassi, C., Ferreira, J. M., Gilbert, B., Miranda, E. C., Flores, S. E., Duarte, A. P. and Carrazzoni, E. P. (1967) *Phytochemistry* **6**, 1653.
3. Gilbert, B. (1965) *The Alkaloids*, Vol. **8** (Manske, R. H. Ed.), Academic Press, New York.
4. Gilbert, B. (1968) *The Alkaloids*, Vol. **11** (Manske, R. H. Ed.), Academic Press, New York.
5. Gilbert, B. (1966) *Anais Acad. Brasil. Ciênc.* **38**, Supl. 315.
6. Duarte, A. P. (1968) *Bol. Mus. Hist. Nat. Univ. Fed. Minas Gerais* (*Belo Horizonte*) **1**, 1.
7. Duarte, A. P. (1970) *An. Acad. Brasil. Ciênc.* **42**, Supl. 289.
8. Woodson, R. E. (1951) *Ann. Missouri Bot. Gard.* **38**, 119.
9. Ferreira, J. M., Gilbert, B., Kitagawa, M., Paes Leme, L. A. and Durham, L. (1966) *J. Chem. Soc.* C, 1260.
10. Joule, J. A., Ohashi, M., Gilbert, B. and Djerassi, C. (1965) *Tetrahedron* **21**, 1717.
11. Spiteller, G. and Spiteller-Friedmann, M. (1963) *Monatsh. Chem.* **94**, 779.
12. Kutney, J. P. and Brown, R. T. (1966) *Tetrahedron* **22**, 321.
13. Rosen, W. E. (1961) *Tetrahedron Letters* 481.
14. Bertho, A., Koll, M. and Ishak Ferosie, M. (1958) *Chem. Ber.* **91**, 2581.
15. Rapoport, H., Windgassen, R. J. Hughes, N. A. and Onak, T. P. (1959) *J. Am. Chem. Soc.* **81**, 3166.