Azahomoaporphines: a New Heterocyclic Skeleton from Annonaceae[1]

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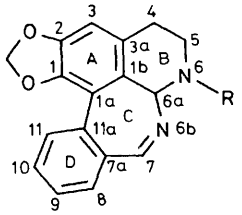
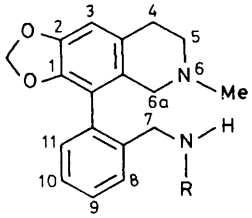
The structure elucidation of dragabine (**1**) and nordragabine (**2**), the first derivatives of the novel azahomoaporphine skeleton, isolated from *Guatteria sagotiana* and *Meiogyne virgata* (Annonaceae), is reported.

During the last decade a number of alkaloids with novel ring systems hypothetically derived from aporphines have been isolated, in particular from plants belonging to the Annonaceae,[2] Eupomatiaceae,[3] and Berberidaceae families.[4] The proposed biogenetic sequences generally involve ring scission, often followed by reclosure which may lead to the formation of an oxygen- or nitrogen-containing heterocycle. We now report the structure elucidation of dragabine (**1**) and nordragabine (**2**), the first examples of aporphinoids incorporating a second nitrogen atom, in ring c. For the sake of simplicity, the usual aporphine numbering system is retained for these



(**1**) R = Me
(**2**) R = H



(**3**) R = H
(**4**) R = MeCO

compounds and their derivatives in which ring c has been opened, designating the extra nitrogen atom as N-6b.

Dragabine (**1**) was isolated in small amounts (0.005 and 0.001% of the dried bark and leaves, respectively) from *Guatteria sagotiana* (Annonaceae) collected in French Guiana.† This substance could not be crystallised and gave an insignificant optical rotation.‡ Its u.v. spectrum was unchanged in basic solution; on adding acid, the u.v. spectrum displayed shoulders at 232 and 256 nm and maxima at 316 and 372 nm.‡ The base peak in the mass spectrum‡ corresponded to the loss of a hydrogen atom from the rather stable molecular ion, after which HCN was lost with ease; a fairly abundant fragment at *m/z* 249 suggested a retro-Diels–Alder extrusion of CH_2NCH_3 from the molecular ion, as is characteristically found for the aporphines; loss of HCN from this fragment then gave another intense peak at *m/z* 222. The i.r. spectrum showed a weak band at 1665 cm^{-1} attributable to an imine function which could explain the electron impact induced loss of HCN. A tertiary carbon in the ^{13}C n.m.r. spectrum at δ 161.7 was correspondingly observed in the *J*-modulated ^{13}C n.m.r. spectrum. The ^1H n.m.r. spectrum was strongly reminiscent of that of roemerine (1,2-methylenedioxyaporphine), but the signals assignable to 6a-H and 7-H diverged markedly from the patterns found for previously known aporphinoids; these protons constituted an AB system, resonating at δ 4.37 and 8.42 with a coupling constant of 2.5 Hz. A long-range *J*-correlated 2D ^1H n.m.r. experiment showed that the δ 8.42 hydrogen nucleus was also weakly coupled to the aromatic ring protons resonating at δ 7.55 and 7.96, indicating that dragabine must have structure (**1**).

The reduction of dragabine ($NaBH_4$, MeOH) led to an amorphous product (**3**),‡ the mass spectrum of which showed the unexpected incorporation of four hydrogen atoms into the original molecule and was dominated by the loss of NH_3 from the molecular ion and its M^+-H companion, after which CH_2NCH_3 was expelled. In the ^1H n.m.r. spectrum the ring A, B, and D protons appeared more shielded than in dragabine, the original 6a-H doublet was replaced by a geminal AB system at δ 2.98 and 3.17, and the 7-H doublet was replaced by a two-proton singlet at δ 3.64. A long-range COSY experiment showed that these two spin systems were no longer coupled to each other, but that the protons resonating at δ 3.64 still displayed a weak coupling to the aromatic ring protons resonating as multiplets at δ 7.16, 7.41, and 7.50. All these data point to the opening of ring c of dragabine upon reduction. The cleavage of one of the C–N bonds of an N–C–N chain with $NaBH_4$ has been observed on a number of occasions,[5] but the scope of this reaction is not known and deserves further study.

Acetylation of (**3**) (Ac_2O, MeOH) gave the monoacetyl derivative (**4**),‡ with a typical amide i.r. absorption and an *N*-acetyl signal in the ^1H n.m.r. spectrum, in which the singlet at δ 3.64 was replaced by the upfield components of an ABX system resonating at δ 4.17, 4.29, and 5.93; the latter broad peak slowly disappeared in the presence of D_2O with concomitant simplification of the δ 4.1—4.3 region of the spectrum as expected for a benzylamide group.

Nordragabine (**2**) was isolated in traces from the trunk bark of *Meiogyne virgata* (Annonaceae) from Borneo.† It could not be induced to crystallise, and underwent considerable decomposition on standing. Its u.v. spectrum was similar to (**1**) including a bathochromic shift in acid solution.§ The mass spectrum showed a very abundant molecular ion and fragmentations indicative of a close relationship to dragabine.§ The ^1H n.m.r. spectrum was very similar to that of dragabine except for the absence of an *N*-CH_3 signal.§ These data, in the light of the more complete study which was only possible with dragabine, led to the attribution of structure (**2**) to the substance from *M. virgata*.

A reasonable hypothesis to explain the origin of the azahomoaporphines would involve the oxidation of the C-6a/C-7 bond of classical aporphinoids following a route analogous to that postulated for the *seco*-bisbenzylisoquinolines and some simple isoquinolines.[6] Ammonia capture by the intermediate imino-aldehydes would then produce the characteristic azepine ring. The lack of optical activity in such a strained biphenyl system as is found in the azahomoaporphines raises the possibility that this final step may be non-enzymatic. To determine if it might have taken place during the extraction process, small samples of plant material were extracted in parallel, basifying with NH_4OH in one case

† *G. sagotiana* R. E. Fr., was collected in Cacao, French Guiana, in January, 1979, and identified by J.-J. de Granville and N. Hallé. Voucher specimens (HJ 2280) are deposited in the herbaria of the Centre ORSTOM, Cayenne, and in the Muséum National d'Histoire Naturelle, Paris. *M. virgata* (Bl.) Miq., was collected in Poring, Sabah, Borneo, in July, 1982, and identified by P. J. Maas. Voucher specimens (WS 58) are deposited in the herbaria of the Rijksuniversiteit, Utrecht, and in the Muséum National d'Histoire Naturelle, Paris.

‡ Dragabine (**1**): $C_{18}H_{16}N_2O_2$ (M^+ 292.1207, calc. 292.1212); $\lambda_{max.}$ (EtOH) (log ε) 228 (4.43), 260 sh (4.02), and 300 (3.78) nm; $\lambda_{max.}$ (EtOH + HCl) (log ε) 232 sh (4.35), 256 sh (4.13), 316 (3.81), and 372 (3.65) nm; $\nu_{max.}$ (film) 1665 cm^{-1}; *m/z* (electron impact, 70 eV) 292 (M^+) (86%), 291 (100), 265 (16), 264 (77), 263 (24), 262 (40), 249 (18), 222 (40); ^1H n.m.r. ($CDCl_3$, 500 MHz), δ 2.60 (3H, s, NMe), 2.72 (1H, dd, *J* 16.5, 3.5 Hz, 4e-H), 2.89 (1H, dd, *J* 11.0, 6.2 Hz, 5e-H), 3.15 (1H, ddd, *J* 16.5, 12.7, 6.2 Hz, 4a-H), 3.48 (1H, ddd, *J* 12.7, 11.0, 3.5 Hz, 5a-H), 4.37 (1H, d, *J* 2.5 Hz, 6a-H), 5.84 and 6.07 (1H each, 2d, *J* 1.5 Hz, 1-OCH_2O-2), 6.73 (1H, s, 3-H), 7.48 (1H, ddd, *J* 7.5, 7.5, 1.9 Hz, 9-H), 7.55 (1H, dd, *J* 7.5, 1.9 Hz, 8-H), 7.57 (1H, ddd, *J* 7.5, 7.5, 1.9 Hz, 10-H), 7.96 (1H, dd, *J* 7.5, 1.9 Hz, 11-H), and 8.42 (1H, d, *J* 2.5 Hz, 7-H); ^{13}C n.m.r. (CD_3OD, 125.8 MHz), δ 29.0 (t, C-4), 40.9 (q, NMe), 46.1 (t, C-5), 75.5 (d, C-6a), 102.4 (t, OCH_2O), 109.6 (d, C-3), 118.8 (s, C-1a), 127.5 (s, C-3a), 128.9 (d, C-8), 130.1 (s, C-1b), 130.5 (d, C-11), 130.9 (d, C-9), 131.3 (d, C-10), 133.9 (s, C-11a), 135.2 (s, C-7a), 145.1 (s, C-1), 148.6 (s, C-2), and 161.7 (d, C-7).

Tetrahydrodragabine (**3**): $C_{18}H_{20}N_2O_2$, *m/z* (electron impact, 70 eV) 296 (M^+) (1.2%), 295 (2.9), 294 (6.9), 293 (9.6), 280 (12), 279 (37), 278 (71), 264 (22), 263 (15), 237 (11), 236 (54), 235 (22), 85 (56), 83 (100); $\lambda_{max.}$ (EtOH) 222 and 294 nm; ^1H n.m.r. ($CDCl_3$, 500 MHz), δ 2.30 (3H, s, NMe), 2.57 (2H, br.s, D_2O exchangeable, NH_2), 2.57, 2.70, 2.88, and 2.92 (1H each, 4m, 4-H and 5-H), 2.98 and 3.17 (1H each, 2d, *J* 15.6 Hz, 6a-H), 3.64 (2H, s, 7-H), 5.83 and 5.87 (1H each, 2d, *J* 1.5 Hz, 1-OCH_2O-2), 6.63 (1H, s, 3-H), 7.16 (1H, dd, *J*, 7.8, 1.9 Hz, 8-H), 7.32 (1H, ddd, *J* 7.8, 7.8, 1.9 Hz, 9-H), 7.41 (1H, ddd, *J* 7.8, 7.8, 1.9 Hz, 10-H), 7.50 (1H, dd, *J* 7.8, 1.9 Hz, 11-H).

Acetyltetrahydrodragabine (**4**): $C_{20}H_{22}N_2O_3$, ^1H n.m.r. ($CDCl_3$, 500 MHz), δ 1.93 (3H, s, NCOMe), 2.32 (3H, s, NMe), 2.60, 2.72, 2.89, and 2.93 (1H each, 4m, 4-H and 5-H), 3.00 and 3.18 (1H each, 2d, *J* 15.3 Hz, 6a-H), 4.17 and 4.29 (1H each, 2dd, *J* 14.5, 5.2 Hz, 7-H), 5.84 and 5.90 (1H each, 2d, *J* 1.5 Hz, 1-OCH_2O-2), 6.64 (1H, s, 3-H), 7.17 (1H, dd, *J* 7.5, 1.5 Hz, 8-H), 7.37 (1H, ddd, *J* 7.5, 7.5, 1.5 Hz, 9-H), 7.39 (1H, ddd, *J* 7.5, 7.5, 1.5 Hz, 10-H), and 7.50 (1H, dd, *J* 7.5, 1.5 Hz, H-11).

§ Nordragabine (**2**): $C_{17}H_{14}N_2O_2$, $\lambda_{max.}$ (EtOH) (log ε) 228 (4.36), 264 sh (3.92), and 297 (3.70) nm; $\lambda_{max.}$ (EtOH + HCl) (log ε) 228 (4.29), 318 (3.66), and 375 (3.32) nm; $\nu_{max.}$ (film) 1665 cm^{-1}; *m/z* (electron impact, 70 eV) 278 (M^+) (97%), 277 (100), 251 (11), 250 (81), 249 (42), 248 (53), 222 (23); ^1H n.m.r. ($CDCl_3$, 60 MHz), δ 2.72, 2.83, 3.08, and 3.33 (1H each, 4m, 4-H and 5-H), 3.58 (br.s, D_2O exchangeable, NH), 4.60 (1H, d, *J* 2.5 Hz, 6a-H), 5.81 and 6.06 (1H each, 2d, *J* 1.5 Hz, 1-OCH_2O-2), 6.72 (1H, s, 3-H), 7.48 and 7.52 (3H, m, 8-H, 9-H, 10-H), 7.93 (1H, m, 11-H), and 8.31 (1H, d, *J* 2.5 Hz, 7-H).

and with Na_2CO_3 in the other. The crude alkaloids obtained by both procedures were found to be indistinguishable by t.l.c., with weak Dragendorff-positive spots well aligned with an azahomoaporphine standard, indicating that these substances are not artefacts.

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References

1 For part 70 in the series 'Alcaloïdes des Annonacées,' see, A. Cavé, S. Rasamizafy, R. Hocquemiller, J. R. Deverre, and A. H. A. Hadi, *Plantes Méd. Phytothér.*, in the press.
2 M. Leboeuf, D. Cortes, R. Hocquemiller, and A. Cavé, *Planta Med.*, 1983, **48**, 234; A. Cavé, M. Leboeuf, and P. G. Waterman, in 'Alkaloids: Chemical and Biological Perspectives,' ed. S. W. Pelletier, Wiley-Interscience, New York, 1986, vol. 4; D. Tadić, B. K. Cassels, M. Leboeuf, and A. Cavé, *Phytochemistry*, 1986, **25**, in the press.
3 W. C. Taylor, *Aust. J. Chem.*, 1984, **37**, 1095.
4 M. Shamma, H.-Y. Lan, A. J. Freyer, J. E. Leet, A. Urzúa, and V. Fajardo, *J. Chem. Soc., Chem. Commun.*, 1983, 799; E. Valencia, A. Patra, A. J. Freyer, M. Shamma, and V. Fajardo, *Tetrahedron Lett.*, 1984, **25**, 3163; I. Weiss, A. J. Freyer, M. Shamma, and A. Urzua, *J. Chem. Soc., Chem. Commun.*, 1985, 3; I. Weiss, E. Valencia, A. J. Freyer, M. Shamma, V. Fajardo, and A. Urzúa, *Heterocycles*, 1985, **23**, 301.
5 J. C. Keresztesy and K. O. Donaldson, *Biochem. Biophys. Res. Commun.*, 1961, **5**, 286; J. Szmuszkovicz, E. Cerda, M. F. Grostic, and J. F. Zieserl, Jr., *Tetrahedron Lett.*, 1967, 3969; J. Szmuszkovicz, D. J. Duchamp, E. Cerda, and C. G. Chidester, *ibid.*, 1969, 1309; K. Shimizu, K. Ito, and M. Sekiya, *Chem. Pharm. Bull.*, 1974, **22**, 1256; G. Moad and S. J. Benkovic, *J. Am. Chem. Soc.*, 1978, **100**, 5495.
6 J. E. Leet, V. Elango, S. F. Hussain, and M. Shamma, *Heterocycles*, 1983, **20**, 425.