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SPECTALINE AND ISO-6 CASSINE, TWO NEW PIPERIDIN 3-OL ALKALOIDS FROM THE LEAVES OF *CASSIA SPECTABILIS*

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Abstract—From the leaves of an african leguminosae: *Cassia spectabilis* DC, we have isolated two unprecedented piperidin 3-ol alkaloids. By spectral data, their structures were elucidated as follows: (+)Spectaline(**1**): 2(*S*)-methyl 6(*R*)-(13'-oxotetradecyl)piperidin 3(*S*)-ol and (−)iso-6-cassine(**2**): 2(*R*)-methyl 6(*R*)-(11'-oxodecyl) piperidin 3(*R*)-ol.

Some Cassia species (Leguminosae) like *Cassia excelsa* and *C. carnavalis* contain piperidinol alkaloids (cassine, carnavaline, prosopinone).[1,2] Several papers have been published on the stereochemistry and synthesis of these alkaloïds and their derivatives.[3,10] Many of these compounds possess pharmacological properties.[6]

Investigations on the alkaloïdal constituents of leaves of *C. spectabilis* DC have resulted in the isolation of two new piperidinol alkaloïds which we have named (+)spectaline(**1**) and (−)iso-6-cassine(**2**). Their stereostructure and absolute configuration have been elaborated on the basis of physical and chemical studies. Extracting a small quantity of seeds of the same plant has revealed by TLC the presence of four major alkaloïds, two of them having identical migrations as spectaline and iso-6-cassine. A fifth alkaloïd in much smaller quantity was also identified by TLC as cassine (**3**).

Spectaline hydrochloride m.p. = 155°, ν(KBr) = 3350(hydroxyl), 1715(ketone), 1570 cm^{-1} (NH_2^+); α_D^{25} (free base) = +8.0° and iso-6-cassine hydrochloride m.p. = 123°, ν(KBr) = 3350, 1715, 1570 cm^{-1}, α_D^{25} (free) = +3.3° analysed for the empirical formulae $C_{20}H_{39}NO_2 \cdot HCl$ and $C_{18}H_{35}NO_2 \cdot HCl$ in agreement with their mass spectra. Their acetyl derivatives established the presence of an OH group and a secondary amine group.

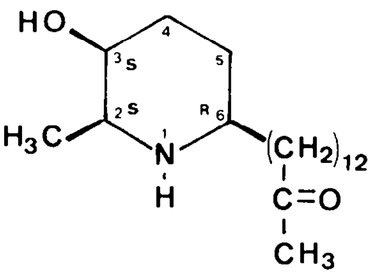
The fragmentations in the mass spectra of spectaline were very similar to those of cassine[10] except for two further methylene groups while the whole mass spectrum of iso-6-cassine was similar to that of cassine. The same observations were made on the diacetyl derivatives. Deuteration experiments[3] on spectaline and iso-6-cassine gave mass spectra of deuterio products consistent with the existence of a $-CH_2-CO-CH_3$ group. From all the above results, it was concluded that spectaline and iso-6-cassine are respectively higher homologues and a diastereoisomer of cassine.

The 100 MHz PMR spectra being fully in accord with PMR data of 2,6-dialkyl piperidin 3-ols[10] provided confirmatory evidence for the above conclusion. In the spectrum of spectaline, the 2-Me group appeared as a doublet at $\delta = 1.10$ ppm (J = 6.5 Hz) while the α-ketone methyl and methylene groups were respectively a singlet at $\delta = 2.13$ ppm and a triplet at $\delta = 2.42$ ppm (J = 6.5 Hz). The intense peak corresponding to the aliphatic methylene groups appeared at $\delta = 1.28$ ppm. Two unresolved multiplets were shown at approximately $\delta = 2.70$ and 2.90 ppm which were attributed to the methine hydrogens at C-6 and C-2. Double irradiation on the Me at C-2 left the signal at 2.9 as a doublet (J = 1.5 Hz). The carbinolic hydrogen at C-3 appeared as a broad singlet at $\delta = 3.55$ ppm with a width at half height of 6 Hz. The spectrum of iso-6-cassine differed only in the integrating area of the aliphatic methylene groups (10 instead of 12) and the height of the H-2 and H-3 signals. The hydrogen at C-2 was an octet at $\delta = 3.06$ ppm. Double irradiation on the Me at C-2 left the octet as a doublet ($J_{H^2-H^3} = 3$ Hz). The signal of the carbinolic hydrogen ($\delta = 3.66$ ppm) appeared as a quintet in which each of the inside three peaks were broadened by the coalescence of two peaks. Sub-spectral analysis of this multiplet gave $J_{H^3-H^{4'}} = 6.5$ Hz and $J_{H^3-H^{4'}} = 3.2$ Hz.

The stereochemistry of 2,6-dialkylpiperidin 3-ol systems is reflected in the IR by the OH stretching frequency.[11,14] The IR spectrum of spectaline in CCl_4 solution showed a large bonded -OH at 3530 cm^{-1} and only a very small free -OH band at 3635 cm^{-1} ($\epsilon_b/\epsilon_f = 4$) as does the spectrum of cassine.[3,8] This is characteristic of the all *cis* systems in which the most favorable conformation possesses the OH group in the axial configuration favorable to intramolecular H-bonding with the N atom of the piperidine nucleus. The signal of the carbinol hydrogen in the PMR spectrum gave further confirmation: the width at half height ($\omega_{1/2} = 6$ Hz) is known to be characteristic of an equatorial hydrogen in the 3-piperidinol derivatives.[8,13,15] (An axial carbinol hydrogen as in iso-3-cassine[8] would have appeared as a very broad singlet ($\omega_{1/2} \cong 25$ Hz). Spectaline thus possesses the all *cis* configuration like cassine and the conformation shown in **4** exists predominantly in solution.

The IR spectrum of iso-6-cassine exhibits both free (3635 cm^{-1}) and bonded (3535 cm^{-1}) hydroxyls of approximately equal height ($\epsilon_b/\epsilon_f = 1$). This observation means that either the side chain, or the Me group is *trans* to the other two substituents.[11] In both cases, two conformations with and without intramolecular H-bond possibility are favorable. The weighted average coupling constants deduced from the PMR spectrum showed that the hydrogen at C-2 is *cis* with regard to the hydrogen at C-3.[15] We can then assign stereostructure **2** to iso-6-cassine. Rapid conformational inversion between the two conformers shown in **5** occurs in solution. Using the limiting values for coupling constants of H-2 axial -H-3 equatorial = 1.5 Hz (spectaline, azimine[14]) and H-2 equatorial-H-3 axial = 4.5 Hz (6-methylpiperidine 3-ol[16]), the mole fraction of each conformer was estimated as being 0.5.

Structure **2** for iso-6-cassine and relative stereochemi-



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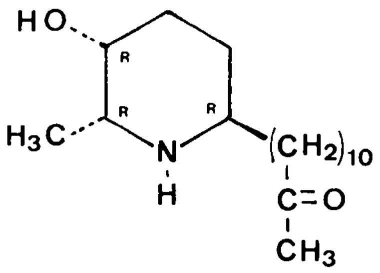

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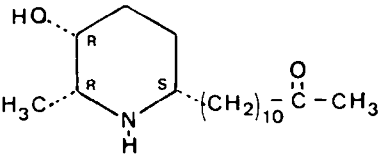

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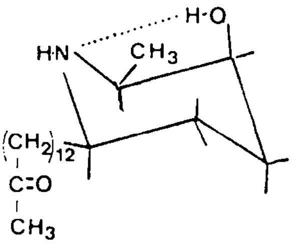

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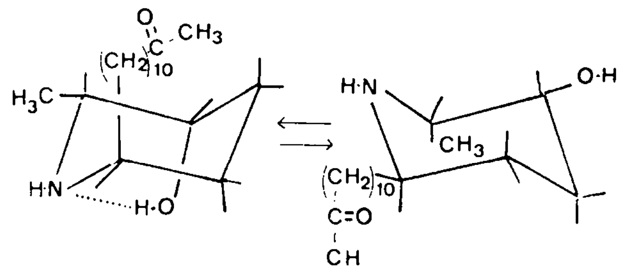

5.

cal assignments were confirmed by X-ray diffraction studies.[17]

Horeau's process[18,19] used successfully for establishing the absolute configuration of piperidinols alkaloïds[20] was applied to spectaline: deflection(−); optical yield 27%; 2(*S*), 3(*S*), 6(*R*) and iso-6-cassine: (+); 20%; 2(*R*), 3(*R*), 6(*R*).

Finally, complete assignment of all CMR data could be made for spectaline and iso-6-cassine in analogy with published values for different stereoisomers of 2,6-dialkyl piperidin 3-ols.[20,22,23]

Alkaloïds derived from 2,6-dialkylpiperidinol seldom occur in nature. Only a few other plants contain such alkaloïds.[1,6] It is also worth while noting that the absolute configuration of the nucleus piperidine of spectaline and iso-6-cassine has not yet been found in natural alkaloïds.

EXPERIMENTAL

The plant material was gathered by C. Delaude in Kinshasa plateau (Zaïre) and identified by H. Breyne (Botanical department of Kinshasa University).

M.ps were taken on a Fisher-John apparatus and are uncorrected. IR spectra were examined on a Beckman IR-10 spectrometer or a Unicam SP 700 UV spectrometer for the near IR. The spectra were obtained as CCl_4 solns with a cell path length of 0.1 cm and as KBr pellets. The absorption bands are reported in wavenumbers (cm^{-1}) and are designated as strong (S), medium (M), weak (W), sharp (Sp) and broad (Bd). Only significant bands from these spectra are quoted. Optical rotation was measured on a spectropolarimeter ORD/UV.5. PMR spectra were obtained on a Varian HA-100 spectrometer using TMS as the internal standard. All spectra were recorded in the frequency sweep mode. The signal multiplicities are denoted as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qu), octuplet (oc) and multiplet (m). Occasionally signals are also designated as being broad (bd). CMR (broad-band decoupled and off-resonance) spectra were recorded by Mr. J. Denoël (Univ. Liège) on a multikern Bruker HFX-90 with TMS as internal standard. Mass spectra were run in an A.E.I.MS-902S mass spectrometer operating at 70 eV and using direct insertion probe. TLC experiments were carried on Merck Silicagel F_{254} plates using $CHCl_3$; EtOH; NH_4OH 25%: 9/1/0.5 mixture as developper and Draggendorf reagent as spray.

Isolation. Leaves of *C. spectabilis* DC (700 g) were extracted with 6 l. of 1% ethanolic tartaric acid at 50–60°. The extracts were filtered and concentrated under reduced pressure to 0.8 l., diluted with 1.5 l. of water and treated with 75 ml 2N H_2SO_4. The acid soln was washed with ether and made basic (p_H 10) with conc ammonia. This soln was extracted with chloroform and the organic layers distilled to dryness to leave 2.4 g.

This material was dissolved in 5 ml EtOH and made acid with 15 ml 2N HCl. The acid soln was extracted twice with benzene. The aqueous layer was made basic by 40% NaOHaq and extracted three times with chloroform; the extracts were washed with water and concentrated to dryness to leave a dark yellow oil (1.9 g). This was digested repeatedly with boiling hexane, leaving an insoluble residue of 0.85 g. The hexane soln was concentrated to dryness to yield 1.05 g (0.15%) of a clear yellow oil. This residue gave positive Draggendorf's and Mayer's tests and showed on TLC plate the presence of two major alkaloïds: *spectaline* (**1**) and *iso-6-cassine* (**2**) which were separated by preparative layer chromatography (0.5 mm) to give 0.325 g (0.046%) of **1** ($R_F = 0.65$) and 0.310 g (0.044%) of **2** ($R_F = 0.40$).

Ground seeds of *C. spectabilis* DC (5 g) were extracted with 25 ml 5% HCl for 12 hr. The soln was filtered and made basic with 5 ml 7 N ammonia. The basic soln was stirred with 25 ml ether-chloroform 2/1 mixture for 24 hr and the organic acid layer was extracted several times with 5 ml 5% HCl. TLC of the concentrated extracts gave four major spots: $R_f = 0.65$ (a); 0.51 (b); 0.40 (c); 0.23 (d) and a few spots much weaker in intensity. One of them was identified by TLC as cassine ($R_f = 0.60$) with a standard sample obtained from *C. excelsia* Shrad.[3,5] Migration of spots (a) and (c) was identical with that of spectaline and 6-iso-cassine in several solvents systems.

Spectaline (**1**). The hydrochloride recrystallized from EtOAc, m.p. 155°. (Found: C, 65.98; H. 11.21; N, 3.96. $C_{20}H_{39}NO_2{\cdot}HCl$ requires: C, 66.39; H, 11.06; N, 3.87%). IR (KBr): 3350 (S, Bd), 2820(S), 2860(M), 1715(S, Sp), 1570(M), 1467(M), 1370(M), 720(W,Bd) cm^{-1}. Free base: $\alpha_D{}^{25} = +8.0°$; $\alpha^{25}_{550} = +9.5°$; (*c*, 0.27 $CHCl_3$); IR (CCl_4): 3530(S, Bd); 3635(W); MS: m/e = 326(1.4)(M + 1), 310(0.7), 282(0.5), 268(2.6), 266(0.6), 254(0.5), 240(0.4), 226(0.3), 212(0.5), 198(0.3), 184(0.3), 170(0.4), 156(0.5), 142(0.45), 128(0.3), 114(100), 96(7 rel.%). PMR($CDCl_3$): 1.10(d, 3H, J = 6.5 Hz); 1.28(s, 22H); 2.13(s, 3H); 2.42(t, 2H, J = 6.5 Hz); 2.70(m, 1H, bd); 2.90(m, 1H, bd); 3.55(s, 1H, bd, $\omega_{1/2} = 6$ Hz). CMR($CDCl_3$): 206.4(s, C-13′), 67.6(d, C-3), 57.0(d, C-2), 55.7(d, C-6), 43.7(t, C-12′), 37.1(t, C-1′), 32.3(t, C-4), 30.0(C-2′ → C-10′), 26.5(t, C-5), 26.0(q, C-14′), 24.0(t, C-11′), 19.0(q, $-CH_3$).

Diacetyl spectaline. IR(CCl_4): 2860(S), 2820(M), 1740(S, Sh), 1715(S, Sh), 1645(S, Sp), 1245(S) cm^{-1}.MS: m/e = 409(0.5), 394(0.6), 366(1.4), 352(3.5), 349(2.9), 338(0.7), 329(0.5), 310(0.5), 296(0.7), 292(0.9), 280(1.2), 268(0.8), 198(100), 156(51), 138(21), 96(35 rel.%).

Pentadeuterio spectaline. MS = 330(0.5)(M^+); 312(0.4)(M^+-CD_3); 284(0.9)(M^+-COCD_3); 268(2.1)($M^+-CD_2COCD_3$); 114(100); 96(11).

Iso-6-cassine (**2**). The hydrochloride from EtOAc, m.p. 123°. (Found: C, 64.35; H, 11.02; N, 4.26. $C_{18}H_{35}NO_2{\cdot}HCl$ requires: C, 64.76; H, 10.79; N, 4.19%); IR (KBr): 3350(S, Bd); 2860(S); 2820(S); 1715(S, Sp); 1570(W); 1467(M); 1370(M); 720(W) cm^{-1}. Free base: $\alpha_D{}^{25} = +3.3°$; $\alpha^{25}_{550} = +4.2°$ (C 0.26 $CHCl_3$); IR (CCl_4): 3535(S, Bd); 3635(S, Bd); MS: m/e = 298(1.8)(M + 1) 282(0.5), 254(0.9), 240(3.0), 238(0.8), 226(0.5), 212(0.7), 198(0.6), 184(0.5), 170(0.6), 156(0.7), 142(0.55), 128(0.4), 114(100), 96(8 rel.%). PMR($CDCl_3$): 1.08(d, 3H, J = 6.5 Hz), 1.28(s, 18H), 2.10(s, 3H), 2.42(t, 2H, J = 6.5 Hz), 2.80(m, 1H), 3.06(oc, 1H), 3.66(qu, 1H). CMR($CDCl_3$): 206.4(s, C-11′), 68.9(d, C-3), 50.4(d, C-2), 49.5(d, C-6), 43.7(t, C-10′), 34.0(t, C-1′), 30.0(C-2′ → C-8′), 28.7(t, C-4 and C-5), 26.9(q, C-12′), 24.3(t, C-9′), 15.7(q, $-CH_3$).

Triacetyl iso-6-cassine. IR(CCl_4): 2860(S), 2820(M); 1740(S, Sh); 1715(S, Sh); 1645(S, Sh); 1245(S) cm^{-1}; MS: m/e = 381(0.7); 338(0.8); 324(4); 321(2.9), 264(1.7); 198(100); 156(52); 138(20); 96(34 rel.%).

Pentadeuterio-iso-6-cassine. MS: m/e = 302(0.95)(M^+); 284(0.7)(M^+-CD_3); 256(0.6)(M^+-COCD_3); 240(2.6)($M^+-CD_2COCD_3$); 114(100); 96(10.5 rel.%).

REFERENCES

[1] J. B. Harborne, D. Boulter and B. L. Turner, *Chemotaxonomy of the Leguminosae*, Academic Press, New York (1971).

[2] D. Lythgoe, A. Busch, N. Schrazberg and M. Vernengo, *Chem. Abstr.* **77**, 164901K (1972).

[3] R. Highet, *J. Org. Chem.* **29**, (2), 471 (1964).

[4] R. Highet and P. Highet, *Ibid.* **31**, 1275 (1966).

[5] W. Rice and J. Coke, *Ibid.* **30**, 3420 (1965).

[6] E. Brown and R. Dhal, *Bull. Soc. Chim. Fr.* **11**, 4292 (1972).

[7] E. Brown, R. Dahl and J. Lavoue, *Tetrahedron Letters* **16**, 1055 (1971).

[8] E. Brown and A. Bonte, *Ibid.* **33**, 2881 (1975).

[9] E. Brown, J. Lavoue and R. Dhal, *Tetrahedron* **29**, 456 (1973).

[10] D. Lythgoe and M. Vernengo, *Tetrahedron Letters* **12**, 1133 (1967).

[11] M. Tichy and J. Sicher, *Ibid.* **12**, 511 (1962).

[12] J. Sicher and M. Tichy, *Ibid.* **12**, 6 (1959).

[13] E. Brown, R. Dhal and P. F. Casals, *Tetrahedron* **28**, 5607 (1972).

[14] S. Vasickova, A. Vitek and M. Tichy, *Coll. Czech. Chem. Comm.* **38**(6) 1791 (1973).

[15] R. Lyle, D. McMamon, W. Krueger and C. Spicer, *J. Org. Chem.* **31**, 4164 (1966).

[16] B. Belleau and Yum-Kin Au-Young, *J. Am. Chem. Soc.* **85**, 64 (1963).

[17] O. Dideberg, L. Dupont and I. Christofidis, *Crist. Struct. Comm.* **31**, **5**, 377 (1976).

[18] A. Horeau, *Tetrahedron Letters* **15**, 506 (1961).

[19] A. Horeau, *Ibid.* **21**, 965 (1962).

[20] Q. Khuong-Huu, E. Ratle, X. Monseur and R. Goutarel, *Bull. Soc. Chim. Belges* **81**, 425, 443 (1972).

[21] I. Morishima, K. Okada, T. Yonezawa and K. Goto, *J. Am. Chem. Soc.* **93**, 3922 (1971).

[22] H. Both and V. Griffiths, *J. Chem. Soc.* **2**, (6)842 (1973).

[23] L. F. Johnson and W. C. Jankowsky, *Carbon*-13 *NMR Spectra*, Wiley, Interscience (1972).