Tetrahedron Letters,Vol.25,No.26,pp 2767-2770, 1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

GUETTARDINE, A POSSIBLE BIOGENETIC INTERMEDIATE IN THE FORMATION OF CORYNANTHE-CINCHONA ALKALOIDS

M.H. Brillanceau, C. Kan-Fan, S.K. Kan and H.-P. Husson *

Institut de Chimie des Substances Naturelles, CNRS, 91190 Gif s/Yvette (France) and

Institut d'Electronique Fondamentale, Université de Paris-Sud 91405 Orsay (France)

Abstract :

The structure of guettardine 1, an indole alkaloid isolated from the bark of Guettarda heterosepala (Rubiaceae), was determined from an analysis of its MS, ^{1}H and ^{13}C NMR spectral data, and by a chemical correlation with dihydrocorynantheol 7. Guettardine 1 can be considered to be an intermediate between the Corynanthé and the cinchonamine groups of alkaloids which are precursors of quinine and its derivatives.

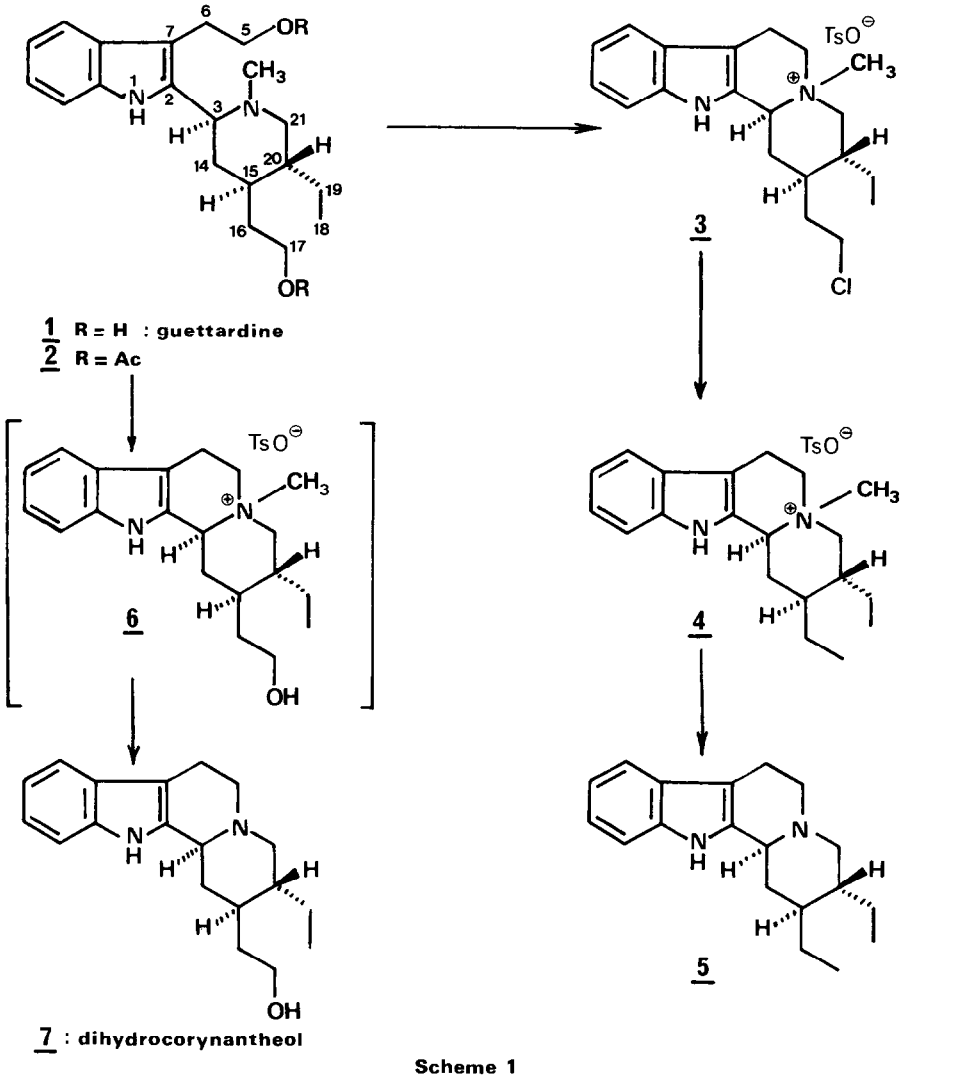
Further work in the studies of the alkaloids of the genus Guettarda (Rubiaceae)[2-3] has resulted in the isolation of guettardine 1 (scheme 1) from the bark of G. heterosepala. Following a classical extraction and purification method, guettardine 1 was isolated as an amorphous solid : $[\alpha]_D^{20}$ -10° (EtOH, C : 1%), Y 0.25 g/kg, 80% of the total alkaloids, whose molecular formula $C_{20}H_{30}O_2N_2$ was determined from its microanalysis and high resolution MS (exact mass $M^{+\cdot}$ 330.2324, calcd 330.2298)[4]. The UV : $\lambda_{max.}^{EtOH}$, nm (log ε) 226 (4.54), 277 (3.89), 284 (3.91), 292 (3.85) and ^{1}H NMR spectra (broad signal at 9 ppm, exchangeable with D_2O) indicated the presence of an indole chromophore with a free $N_{(a)}H$. Resonances were also observed in the proton spectrum for a N(4)-CH_3 group (s, 3H, 1.95 ppm) and an ethyl side chain (t, 3H, 0.85ppm ; m, 1H, 1.1 ppm and m, 1H, 1.55 ppm).

Comparison of the ^{13}C NMR spectra of 1 [4] with its O-diacetyl derivative 2 [5] (Ac_2O/pyridine) indicated that two hydroxyl groups were present in the molecule at the terminal end of two ethyl side chains(α effect shift ≃ + 2 ppm and β ≃ - 4 ppm)[6].

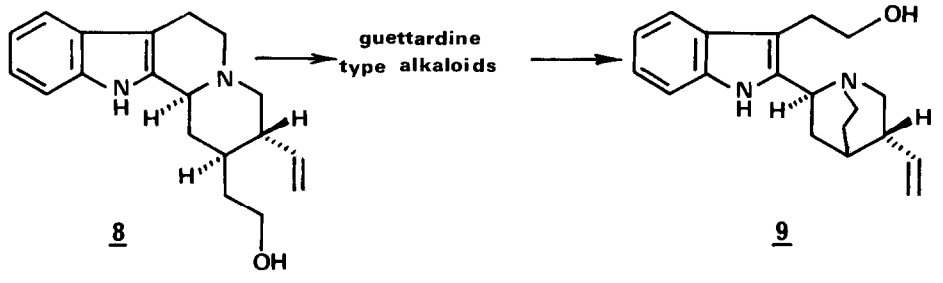
In addition, the signal at δ 3.3 ppm (dd, 1H) in the ^{1}H NMR spectrum of 1 remained unchanged after acetylation and was thus assigned to the tertiary proton at C-3, characteristic of the Corynanthé alkaloids.

Taken together, these spectral features suggested that guettardine was related to dihydro derivatives of corynantheol 8 or cinchonamine 9 (scheme 2) bearing, in addition a primary alcohol function.

The structure 1 was thus tentatively proposed for this new alkaloid.



Scheme 1



Scheme 2

Definitive proof for the structure 1 was obtained by a chemical correlation with dihydrocorynantheol 7. Firstly 1 was converted into 3 [8] (colourless crystals, Y : 60 %, $C_{27}H_{35}N_2O_3S$ Cl) by reaction of 1 with excess TsCl/pyridine followed by refluxing of the crude extract in DMF for 1 h. The structure 3 was assigned on the bases of its spectral data (FAB mass spectrometry and ^{13}C NMR [8]). The formation of this compound indicated that a bis tosylate was initialy produced which underwent both an intramolecular displacement of the C-5 tosyl group by the tertiary amine and an intramolecular substitution at C-17 by Cl^-. On partial reduction of 3 with $LiAlH_4$ (THF, Δ, 3h), compound 4 was obtained. Further treatment of 4 with $LiAlH_4$ (THF, Δ, 24 h) afforded dihydrocorynantheane 5. Unfortunately we did not have an authentic sample of 5 and since its spectral data were incomplete [11] we searched for a transformation of 1 into a known compound with which a proper comparison could be made.

Selective tosylation of the primary alcohol at C-5 was achieved by intramolecular base catalysed tosylation [12] of 1 (TsCl, 1 eq, CH_2Cl_2, 0°C, 12 h). By complete removal of the solvent and refluxing in DMF (1 h) the tosylate 6 was obtained. The crude product was converted without purification into dihydrocorynantheol 7 on treatment with $LiAlH_4$ in refluxing THF for 24 h. (Y : 40 % + 50 % of recovered 1).

The formation of dihydrocorynantheol 7 from guettardine 1 definitely established the relative and absolute configurations of the new alkaloid.

The isolation of guettardine in plants producing Cinchona alkaloids [13] is interesting from the biogenetic view-point. Although cinchonamine 9 or the corresponding aldehyde have been regarded as key intermediates in the biosynthesis of quinine from corynantheine [14, 15], the intermediates in the sequence 8 → 9 are unknown.

The isolation of guettardine 1 could indicate that cleavage of the β-carboline system of corynantheine precedes the formation of the quinuclidine ring. Guettardine 1 thus closely resembles the true biogenetic intermediate.

REFERENCES AND NOTES

1 - Plants from New Caledonia 89 for 88, see Ref. 16.

2 - C. Kan-Fan and H.-P. Husson, J.C.S. Chem. Comm., 1978, 618.

3 - C. Kan-Fan and H.-P. Husson, J.C.S. Chem. Comm., 1979, 1015.

4 - 1 : MS m/e (relative intensity) : 330 ($M^{+\cdot}$, 57.5), 315 (7.5), 312 (12.5), 300 (22), 299 (5), 285 (5), 269 (12), 268 (17), 267 (17.3), 254 (5), 214 (25.5), 187 (26), 183 (30), 170 (65.6), 156 (100), 142 (50), 44 (50) ; ^{13}C NMR ($CDCl_3$, 22.6 MHz, Me_4Si δ = 0) : 10.8 C-18, 23.2 C-19, 27.7 C-6, 34.9 C-16, 36.7 C-15, 38.8 C-14, 41.7 C-20, 43.8 N-CH_3, 59.4 C-17, 61.1 C-3, 61.5 C-21, 62.6 C-5, 108.9 C-7, 111.1 C-12, 118.3 C-9, 119.1 C-11, 121.6 C-10, 128 C-8, 135.6 C-2, 136.5 C-13.

5 - 2 : amorphous, MS : 414 ($M^{+\cdot}$, 10) ; IR (neat) : 1740cm^{-1} ; ^{13}C NMR : 64.6 C-5, 23.6 C-6, 62.2 C-17, 31.2 C-16 ; ^1H NMR ($CDCl_3$, 400 MHz, Me_4Si, δ = 0) : 2.02 (s, 3H), 2.04 (s, 3H).

6 - The ^{13}C assignments were supported by OR experiments and by comparison with the values for 7 [7] and tryptophol (biogenetic numbering system of indole alkaloids) : 28.5 C-6, 62.5 C-5, 111.3 C-12, 111.9 C-7, 118.7 C-9, 119.2 C-11, 121.9 C-10, 122.6 C-2, 127.4 C-8, 136.4 C-13.

7 - G.M. Tamba Robert, Thèse de Doctorat d'Etat ès-Sciences, Université de Paris-Sud, Centre d'Orsay, 1982.

8 - 3 : mp 256° ($CHCl_3$); $C_{27}H_{35}N_2O_3SCl$ (microanalysis) ; MS (FAB, Xe, glycerol) m/e : 837,835, 833 ($2M^+$, TsO^-), 665, 663, 661 ($2M^+ - 1$), 333 and 331 (M^+ including Cl), 295 (M^+-HCl). ^{13}C NMR ($CDCl_3$-CD_3OD) : 10 C-18, 18.5 C-6, 23 C-19, 35 C-16, 35.8 C-15, 36.4 C-14, 36.6 C-20, 42.5 C-17, 53.1 N-CH_3, 53.3 C-5, 66.2 C-3, 69.3 C-21.

9 - 4 : mp 242° ($CHCl_3$) ; MS (FAB, Xe, glycerol) m/e : 765 ($2M^+$, TsO^-), 593 ($2M^+$-1), 591, 297 (M^+), 281 ($M^+ - 1 - CH_3$). ^1H NMR ($CDCl_3$, CD_3OD, 400 MHz, Me_4Si, δ = 0) : 0.85 (t, 3H CH_3-18), 0.95 (t, 3H, CH_3-17), 2.38 (s, 3H, CH_3-N) 3.2 (s, N-CH_3), 4.95 (dd, H-3).

10 - 5 : amorphous $[\alpha]_D^{20}$ - 30° (c : 0.3, EtOH), MS : 282 ($M^{+\cdot}$ 82), 281 (100), 253 (20), 225 (25), 170 (25), 156 (15). ^1H NMR (CD_3OD) : 1.07 (t, 3H) 1.12 (t, 3H), ^{13}C NMR (CD_3OD) : 10.9 and 11.2 C-17,C-18 ; 22.2 C-6, 24.3 C-19, 26.1 C-16, 34.9 C-14, 42 C-20, 42.3 C-15, 54.4 C-5, 61.1 C-3, 62 C-21.

11 - E.E. van Tamelen, P.E. Aldrich and T.J. Katz, Chem. Ind. (London) 1956, 793.

12 - H.-P. Husson, P. Potier et J. Le Men, Bull. Soc. Chim. Fr., 1966, 2256.

13 - Unpublished results from our laboratory.

14 - E. Leete, Accounts Chem. Res., 1969, 2, 59.

15 - A.R. Battersby and R.J. Parry, J.C.S. Chem. Comm., 1971, 30 ; ibid, 1971, 31.

16 - D. Guillaume, A.M. Morfaux, B. Richard, G. Massiot, L. Le Men-Olivier, J. Pusset and T. Sevenet, to be published.

AKNOWLEDGMENTS

We express our thanks to MM. Th. Sévenet and J. Pusset for collecting the plant material and Mlle C. Poupat and M. A. Ahond for the gift of a sample of dihydrocorynantheol.

(Received in France 30 January 1984)