Tetrahedron Letters,Vol.24,No.41,pp 4481-4484,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

RIBASIDINE, A NEW RIBASINE ALKALOID. STRUCTURE AND CHARACTERIZATION

J.M.Boente, M.J.Campello, L.Castedo*, D.Domínguez, J.M.Saá, R.Suau and M.C.Vidal

Departamento Química Orgánica de la Facultad de Química e Instituto de Productos Naturales Orgánicos (Sección de Alcaloides) del C.S.I.C. Santiago de Compostela (SPAIN)

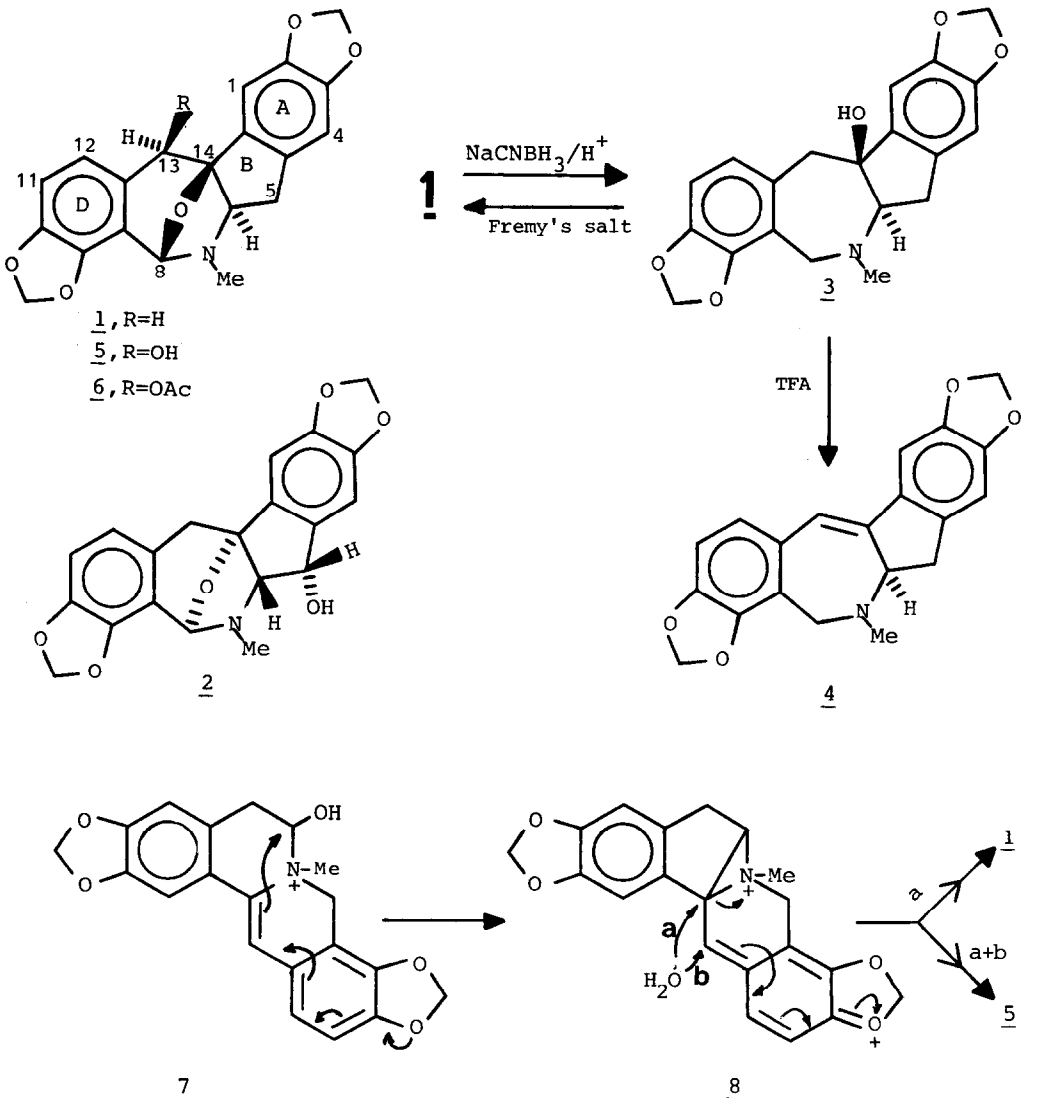
Abstract: Ribasidine (5), isolated from *Sarcocapnos enneaphylla* and *Corydalis claviculata*, has been proved to be a 13-β-hydroxyribasine alkaloid. Some chemical properties of the ribasine alkaloids are also described.

Very recently we have described the isolation from *Sarcocapnos crassifolia* and *Corydalis claviculata* of ribasine (1),[1] the first example of a new class of alkaloids. Soon afterwards, Shamma et al.,[2] independently, reported the isolation from *Corydalis claviculata* of an amorphous alkaloid, which they named limogine, whose optical rotation and spectroscopic data are in full agreement with those of ribasine. The same relative configurational structure was assigned to both alkaloids. However, as the absolute configuration of ribasine was established by X-ray analysis[1] and that of limogine by CD[2], the absolute configuration of the latter is probably that we have described for ribasine (1).

As Shamma et al.[2] also reported the isolation of himalayamine (2),[3] a ring-B hydroxyribasine derivative, we wish now to disclose the isolation of ribasidine (5), the first ring-C hydroxyribasine, as well as some novel chemical properties of ribasine.

Ribasidine (5) was obtained from *Sarcocapnos enneaphylla* and *Corydalis claviculata* as white needles, mp 230°($CHCl_3$), $[\alpha]_D^{25}$= +120 (c: 0.04, EtOH). Its molecular formula, $C_{20}H_{17}NO_6$, was confirmed by MS (M^+, 31%, f:367.1056,c:367.1056), 366(11), 204(5), 192(100), 188(38), 176(34), 163(11), 149(7) and 146(6). Its UV spectrum showed λ_{max}(EtOH)(log ε): 211(4.48), 235sh(3.98) and 291(3.98) nm; upon addition of acid (HCl 5%) the shoulder became a defined band at λ_{max} 242(3.93)nm.[4] IR ν_{max}(BrK): 3580(-OH), 2860-3050, 1485, 1255 and 1030 cm^{-1}. In the aromatic region the pmr (200 MHz, $CDCl_3$) exhibited two one proton singlets at δ 7.35 and 6.64 (H-1 and H-4 respectivily, the latter having the same chemical shift as in ribasine (1))and an AB_q at δ 6.82 and 6.95 ppm (J_{AB}=7.9 Hz, H-11 and H-12 respectively, the former being close to that of ribasine (1)). In addition, two methylendioxy groups at δ 5.95 (s, 2H) and 5.99 and 5.95 (AB_q, J_{AB}=1.3 Hz, 2H), two singlets at 5.68 (H-8) and 4.39 (broad, H-13), three double doublets centered at 3.10 (1H, J_{gem}=16 and J_{cis}=8 Hz, H-5), 2.95 (1H, J_{gem}=16 and J_{trans}=3.1 Hz,

H-5) and 2.74 (1H, J_{cis}=8 and J_{trans}=3.1 Hz, H-6), and a singlet for an N-Me group at 2.23 ppm, were observed. The ^{13}C-NMR (20 MHz, $CDCl_3$+CD_3OD) showed signals for aliphatic carbons at 35.04 (q, N-Me), 36.04 (t, C-5), 66.88 (d, C-6), 71.64(d, C-13), 89.24 (d, C-8), 95.98 (s, C-14), 101.44 (t, OCH_2O) and 101.63 ppm (t, OCH_2O). In the aromatic region it exhibited four doublets (at 105.25, 107.48, 108.86 and 123.60 ppm), four singlets (at 113.75, 129.48, 132.02 and 137.77 ppm) and four quaternary carbons bound to oxygen (at 143.89, 146.86, 147.17 and 149.69 ppm).



All these data clearly show that ribasidine (5) must be a 13-hydroxy derivative of ribasine (1). Since the NMR data of the lower part of ribasidine (5) is very similar to that of ribasine (1) it can be assumed that both compounds have a trans B-C fusion. In addition, molecular models show that the alternative cis fusion is geometrically impossible due to the presence of the ether bridge. At this point it only remained to establish the relative configuration at C-13. To this end some relevant data are the downfield shifts observed at protons H-1 (+0.48 ppm) and H-12 (+0.31 ppm) in ribasidine (5) as compared to ribasine (1). Molecular models of both epimers at C-13 strongly suggest the β-configuration for the hydroxy group in ribasidine since with this orientation it is closer to both the affected protons (H-1 as H-12). This assignement is also corroborated by the downfield shift observed in H-13α (+1.68 ppm with respect to H-13α in ribasine) which is very close to the value (+1.66) observed by Shamma[2] for the geminal proton at C-5 when comparing limogine and himalayamine(2).This relative stereochemistry was finally proved by an NMR nuclear Overhauser enhancement difference spectroscopy (NOEDS) of ribasidine (5). Irradiation at H-6 led to a 6.8% NOE of H-13α.On the other hand, irradiation of H-13α gave enhancement of H-6 (8.0%) H-12(9.0%) and H-1 (5.5%).

Further proof of the structure of ribasidine (5) was obtained upon acetylation (Ac_2O/Py) giving (6)[5,9]as white needles, mp 198°(MeOH), the most important feature of its NMR being the upfield shift of H-1 (-0.41 ppm with respect to H-1 in ribasidine (5)) as would be expected for an acetoxy group in the β-position. On treatment with MeI ribasidine gave the corresponding quaternary salt.[6,9]

All the above data strongly suggest the structure of ribasidine to be that depicted in (5).[7] Due to lack of material a chemical correlation between ribasine (1) and ribasidine (5) has not yet been possible.

Concerning the chemical properties of this new class of alkaloids, resistance to the reductive opening of the ether bridge in limogine was observed [2]. We have found that treatment of ribasine (1) with $NaCNBH_3$ in an acidic methanolic solution afforded in 90% yield the hydroxycompound (3)[8,9] which upon treatment with TFA in CH_2Cl_2 at room temperature easily dehydrates to give the stilbene derivative (4)[10]. Finally, a very interesting result was observed when dihydroribasine(3) was treated with Fremy's salt[11] (py/Na_2CO_3 5%,RT) which gave a 80% yield of optically pure ribasine (1).This oxidation can be envisaged as proceeding via an iminium salt which is subsequently trapped by the hydroxy group at C-14[12].

Apart from protopine[1,2], a possible biogenetic precursor of this class of alkaloids might be stylopine, which on further oxidation would give the intermediate (7), a compound which has been recognized as a precursor in the biogenesis of benzophenanthridines[13]. Further rearrangement of (7) via an aziridinium cation (8) could afford both (1) and (5) as shown in Scheme 1.

ACKNOWLEDGEMENTS.We thank the Comisión Asesora(Spain) for its financial support.We are grateful to Dr.Alvaro Fernández(Depto.Q.Orgánica,Universidad Salamanca(Spain)for the NOEDS experiments(Bruker WP-200 SY).

References and Footnotes

1. J.M.Boente,L.Castedo,R.Cuadros,J.M.Saá,R.Suau,A.Perales,M.Martínez-Ripoll and J. Fayos,Tetrahedron Lett.,2029 (1983).
2. D.P.Allais,H.Guinaudeau,A.J.Freyer,M.Shamma,N.C.Gaugnli,B.Talapatra and S. K. Talapatra, Tetrahedron Lett.2445 (1983).
3. CD studies made by Shamma et al.[2] led them to propose identical chirality for both limogine and himalayamine(2).As limogine is identical to ribasine(1),the absolute configuration of himalayamine should be the enantiomer of expression (2).
4. This effect appears to be a characteristic of this class of alkaloids.
5. Ribasidine acetate(6),λ_{max}(EtOH)212,233(sh)and 290nm;λ_{max}(EtOH/H^+)212,243 and 292 nm;IR(KBr)2980-2880,1745,1485,1230 and 1040cm^{-1};MS,m/e 409(M^+,12),408(52),407(16), 365(32),349(100),319(36),192(40),188(72);NMR($CDCl_3$,80MHz)δ6.94(s,1H,H-1),6.99 and 6.74(AB_q,J_{AB}:8Hz,2H,H-12 and H-11),6.61(s,1H,H-4),5.91(m,5H,2xOCH_2O and H-13),5.74 (s,1H,H-8),2.81-3.11(m,3H,H-5 and H-6),2.25(s,3H,NMe) and 2.20(s,3H,-OAc);$(CD_3)_2CO$ δ6.90(s,1H,H-1),6.94 and 6.80(AB_q,J_{AB}:8Hz,2H,H-12 and H-11),6.68(s,1H,H-4),5.97-6.04(m,4H,2xOCH_2O),5.83(s,1H,H-13),5.58(s,1H,H-8),2.79-3.15(m,3H,H-5 and H-6),2.18 (s,3H,NMe) and 2.16 (s, 3H, -OAc).
6. Ribasidine methiodide,NMR($CD_3)_2CO$,80MHz)δ7.28(s,1H,H-1),7.21 and 7.08(AB_q,J_{AB}:8Hz, 2H,H-11 and H-12),6.82(s,1H,H-8),6.63(s,1H,H-4),6.23 and 6.17(AB_q,J_{AB}:1Hz,2H,OCH_2O), 6.04(m,2H,OCH_2O),4.80(m,1H,H-13),4.50(m,H-6),3.63(m,2H,H-5),3.51 and 3.30(s each, 6H, -N^+-Me_2).
7. We did in fact try to get an X-Ray analysis of ribasidine.Although we got a crude structure,the crystals lability did not allow an acceptable refinement.Personal communication from A.Perales(Instituto Rocasolano,Madrid).
8. Dihydroribasine(3),mp 139-141°(MeOH),$[\alpha]_D^{25}$ -303 (c,0.12,$CHCl_3$);λ_{max}(EtOH)(log ε) 210(4.43),238(3.90)and 296(4.06)nm;IR(KBr)3520,2940,1550,1480,1300,1085 and 1055 cm^{-1};MS,m/e 353(M^+,3),335(18),334(14),304(11),178(32),176(18)and 148(100);NNR ($CDCl_3$,80MHz)δ 6,94(s,1H,H-1),6.73(s,1H,H-4),6.78 and 6.65(AB_q,J_{AB}:8Hz,2H,H-11 and H-12),5.93(m,4H,2xOCH_2O),4.11 and 3.27(AB_q,J_{AB}:14.1,2H,H-8),3.44 and 3.02(AB_q , J_{AB}:14.6,2H,H-13),2.88-2.85(m,3H,H-6 and H-5) and 2.59 (s,3H,-NMe).
9. All new compounds gave satisfactory elemental analyses or high resolution MS.
10. Compound(4),mp 198-200°(MeOH),$[\alpha]_D^{25}$ -182(c,0.055,$CHCl_3$);λ_{max}(EtOH)(log ε)216 (4.48),230(sh,4.36),296(4.11)and 354(4.43)nm;IR(KBr) 3025-2820,1490,1450,1260, 1240 and 1050 cm^{-1};MS,m/e 335(M^+,100),334(80),320(7),304(10),176(15);NMR($CDCl_3$, 80MHz) δ6.95(s,1H,H-1),6.76(s,1H,H-4),6.80 and 6.70(AB_q,J:8.7Hz,2H,H-11and H-12), 6.68(s,1H,H-13),5.94(m,4H,2xOCH_2O),3.98(s,2H,H-8),3.80(m,1H,H-6),2.86-3.08(m,2H, H-5) and 2.42(s,3H,-NMe).
11. H.Zimmer,D.C.Lankin and S.W.Horgan,Chem.Rev.,71, 229 (1971).
12. We have carried out a similar reaction in the benzophenanthridine alkaloids,L. Castedo,D.Domínguez,A.Puga,J.M.Saá and R.Suau,Heterocycles,in press.
13. A.R.Battersby,J.Staunton,H.R.Wiltshire,R.J.Francis and R.Southgate,J.Chem.Soc. Perkin I, 1147 (1975).

(Received in UK 18 August 1983)