QUINAZOLINOCARBOLINE ALKALOIDS CHEMISTRY: REACTIVITY OF EUXYLOPHORINES - Part I

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Abstract - The quinazolinocarboline alkaloids of type (1a) and (1b) showed a marked regioselectivity towards nucleophilic reagents, (1a) reacting at C_{13b}-N_{14} bond while (1b) cleaving the C_5-N_6 bond. The catalytic hydrogenation was also reported.

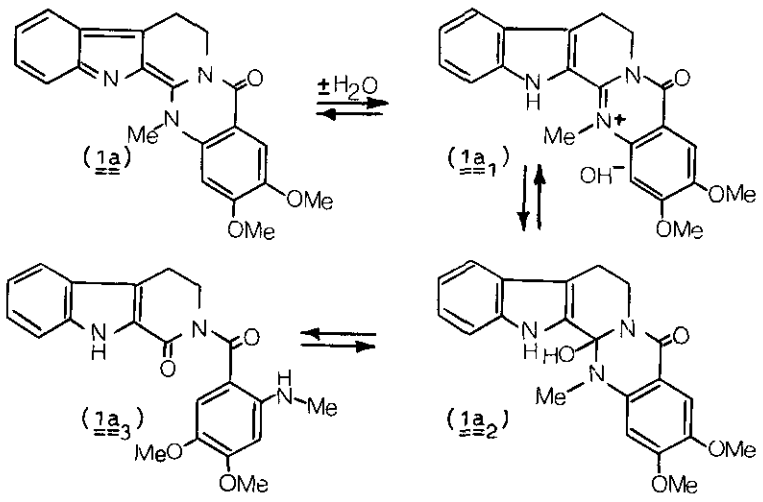
The structure determination and synthesis of several new quinazolinocarboline alkaloids, belonging to structural types designed (1a-d),(2a-f) and (3), were reported in previous papers on the Amazonian Rutacea Euxylophora paraensis Hub. (pao amarello, pao setin).[1]

We now wish to describe some interesting chemical behaviour of alkaloids of type (1), mainly (1a) and (1b), being unexceptional the reactivity of alkaloids of type (2). The spectral data disclosed for euxylophorine A (1a) the existence of a mixture of the orange-red anhydronium base[2] and the yellow "open-chain" form ($1a_3$) in dynamic equilibrium in solution. The yellow ($1a_3$), obtained by crystallisation from wet benzene, reverted to the red (1a) when heated in a suitable anhydrous solvent (e.g., benzene) or in crystalline state, having the same m.p. as (1a). ($1a_3$) exhibited ν_{max} (nujol) 3390,3230,1673,1650 cm^{-1} and ^{1}H-NMR (py-d_5+D_2O) δ2.95(3H,s,N-Me),3.35 and 4.35(each 2H,t,^3J 6.5Hz,C_4-H_2 and C_3-H_2),3.71 and 4.00(each 3H,s,OMe),6.42(1H,s,C_3,H) 7.30-8.20(4H,m,aromatic protons),7.56(1H,s,C_6,-H). The mass spectrum (EI,70eV,140°) showed no parent ion at m/e 379, but peaks at m/e 361($C_{21}H_{19}N_3O_3$,100%),359(59),346 ($C_{20}H_{16}N_3O_3$,36),180.5($C_{21}H_{19}N_3O_3^{2+}$,11),168($C_{11}H_8N_2$,22) characteristic of the anhydronium base (1a) were observed.

A solution of (1a) in aprotic solvents ($CHCl_3$,MeCN) gave relatively simple UV spectra with two maxima at 257 and 410 nm in $CHCl_3$ and at 253 and 402 nm in MeCN. Proof of structure (1a) came from IR spectrum (ν_{CO} at 1670 cm^{-1}, no evidence for NH group) and ^{1}H-NMR spectrum (py-d_5)(a strongly deshielded singlet at δ 5.23 for N-Me). On dilution of the MeCN solution with H_2O, the UV spectrum was altered with a new maximum at 382 nm due to the form ($1a_1$), as deduced from the similarity with that of the hydrochloride (λ_{max}389 nm) and tartrate (λ_{max} 383 nm) of (1a). Furthermore, immediately after dissolution of the "open-chain" form ($1a_3$) in anhydrous MeCN, a maximum at

309 nm was present. Later on the partial disappearance of this peak, a concerted increasing of the maximum at 402 nm, due to (1a)(isosbestic point at 338 nm), was observed. After 9 hr (25°) a 7:3 mixture of (1a) and ($1a_3$) was present and this distribution was similar to that observed when ($1a_3$) was allowed to stand in $CHCl_3$ (12 hr, r.t.)(isosbestic point at 343 nm).

The transformation of (1a) into ($1a_3$) could be represented as a four-fold equilibrium[3] taking place through the quaternary ammonium salt ($1a_1$),neutral covalent hydrate(carbinolamine,pseudobase)($1a_2$) and fission of the ring D.



A different behaviour was observed in polar protic (hydrogen-bonding) solvents (e.g., EtOH). Both (1a) and ($1a_3$) gave the same spectrum with maxima at 329 and 390 nm, pointing out that the abovementioned equilibrium was displaced towards the anhydronium base and/or ammonium salt form while increasing the polarity of the solvent. There was no evidence for the intermediacy of carbinolamine ($1a_2$) or its equivalent form.[4,5]

The UV properties of euxylophorine B (1b) were quite different from those of (1a), the solution in MeCN (λ_{max} 278 and 352 nm) and $CHCl_3$ (λ_{max} 263 and 360 nm) showing no change with time. Only a marked colour change was observed when the yellow-orange solution of (1b) in MeOH was allowed to stand at r.t. This solution faded to colourless and a single compound (5a) was isolated in quantitative yield, m.p. 269-71°(dec) λ_{max}(MeCN) 228,246,292 and 353 nm(lg ε 4.51,4.58,4.05 and 3.95); ν_{max}(nujol) 3490, 1712,1610 cm^{-1}; ^{1}H-NMR(py-d_5) δ 3.46(3H,s,NMe),3.53(3H,s,CO_2Me),3.70 and 3.80(each 3H,s,OMe),6.93(1H,s,C_6-H),7.39(1H,s,C_3-H),7.73 and 8.40(2H,AB pattern,^{3}J 5.0,C_3-H and C_4-H),10.25(1H,br s,NH). ^{1}H-NMR(CF_3CO_2H+20%$CDCl_3$,soon after dissolution) δ 3.85 (3H,s,NMe),3.90(3H,s,CO_2Me),4.10 and 4.18(each 3H,s,OMe),7.30-7.80(8H,m,aromatic protons);EI-MS(140°)m/e 391($M^{+\cdot}$,26%),362(7),359($M^{+\cdot}$-MeOH,13),344(10),332($M^{+\cdot}$-CO_2Me,100), 329.6(m^* for 391 → 359). (5a) was slowly converted in TFA-$CDCl_3$ solution (NMR tube,

$t_{1/2}$ ~ 13 days, r.t.) to the trifluoroacetate of (1b).

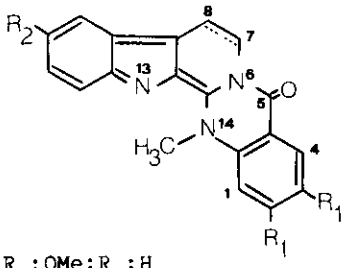
Thermolysis of (5a) at 280° (0.1 mm_{Hg}, 30 min) gave the benzodiazepine (6) in 35% yield, m.p. 204-6°(i-Pr_2O/$CHCl_3$); λ_{max}(MeOH) 249 and 347 nm(lg ε 4.63 and 3.82); ν_{max}(nujol) 1668, 1615, 1610 cm^{-1}; ^{1}H-NMR(DMSO-d_6) δ 3.46(3H, s, NMe), 3.81 and 3.92 (each 3H, s, OMe), 6.82(1H, s, C_4-H), 7.41(1H, s, C_1-H), 7.76 and 8.26(2H, AB pattern, ^{3}J 5.5, C_8-H and C_7-H), 8.71(1H, dd, ^{3}J 7.5, ^{4}J 1.5, C_{12}-H); EI-MS(165°) m/e 359($M^{+\cdot}$, 100%), 343(26) 327(26), 312(22), 168(30). The benzodiazepine (6) was also obtained by refluxing (1b) in dioxane containing 5% NEt_3 (15 hr) in 68% yield.[6]

(1b) dissolved in N NaOH undergoing a facile cleavage to give the colourless carboxylate (5b)[7] and this was reverted to yellow (1b) by acid treatment.[8]

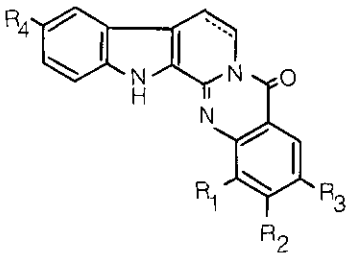
The behaviour of (1a) and (1b) towards reducing reagents was also very different. With $NaBH_4$ in MeOH (30 min, r.t.) (1a) gave in quantitative yield the colourless dihydroderivative (4a), m.p. 248°(n-hexane/$CHCl_3$); λ_{max}(MeOH) 268 and 290 nm(lg ε 4.11 and 3.90); ν_{max}($CHCl_3$) 3480, 1640 cm^{-1}; EI-MS(185°) m/e 363($M^{+\cdot}$, 100%), 362(42), 194(55), 193(36), 178(69), 169(18). Euxylophorine A (1a) was smoothly reduced by $LiAlH_4$ in refluxing THF (2 hr) to the desoxo derivative (4b) in 75% yield, m.p. 204°(benzene); λ_{max}(MeOH) 272(sh), 282 and 290 nm (lg ε 3.94 and 3.92); ^{1}H-NMR(py-d_5+D_2O) δ 2.78 (3H, s, NMe), 3.04(4H, m, C_7-H_2 + C_8-H_2), 3.82 and 3.84(each 3H, s, OMe), 3.77 and 3.92(2H, AB pattern, ^{2}J 10.0, C_5-$H_A$$H_B$), 4.94(1H, s, C_{13b}-H), 6.72(1H, s, C_1-H), 6.80(1H, s, C_4-H). The same product resulted when (4a) was reduced with $LiAlH_4$ (Et_2O, r.t.) under N_2. Attempted reduction of (1b) with excess $NaBH_4$ in MeOH at r.t. for 24 hr was unsuccessful; however, when (1b) was heated with $LiAlH_4$ in THF (2 hr) or with $NaBH_4$ in MeOH (9 hr) the C_5-N_6 bond was cleaved to give the alcohol (5c) in 50-75% yield, M.p. 130°($CHCl_3$); λ_{max}(MeOH) 244, 294 and 345 nm(lg ε 4.42, 3.94 and 3.77); ν_{max}(nujol) 3390, 3310, 1610, 1595 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 3.38(3H, s, NMe), 3.58 and 3.84(each 3H, s, OMe), 4.45(2H, s, CH_2OH) 5.44(1H, br s, OH), 6.66(1H, s, C_3-H), 7.21(1H, s, C_6-H), 9.35(1H, br s, NH); EI-MS(170°) m/e 363($M^{+\cdot}$, 100%), 332($M^{+\cdot}$-CH_3O, 23), 331(100), 169(23). Acetylation of (5c) gave the monoacetate (5d), m.p. 126°(n-hexane/$CHCl_3$); ν_{max}(nujol) 3350, 1730, 1630, 1610 cm^{-1}; EI-MS (180°) m/e 405($M^{+\cdot}$, 24%), 362($M^{+\cdot}$-C_2H_3O, 11), 333(44), 332($M^{+\cdot}$-$C_3H_5O_2$, 100).

Hydrogenation of (1a) as well as (1b) with PtO_2 in AcOH containing 1% $HClO_4$ resulted in the exclusive formation of (7)(80-85% isolated yield) rather than the expected derivative (4a).[9,10] (7): m.p. 195-7°(MeOH); λ_{max}(MeCN) 239, 252 and 376 nm(lg ε 4.00, 3.94 and 4.44); ν_{max}(nujol) 1698, 1610 cm^{-1}; ^{1}H-NMR(TFA+20% $CDCl_3$) δ 1.70-2.90(8H, m, ring A protons), 3.03 and 4.62(each 2H, t, ^{3}J 7.0, C_8-H_2 and C_7-H_2), 4.13(3H, s, NMe), 4.20 and 4.35(each 3H, s, OMe), 7.27(1H, s, C_1-H), 7.84(1H, s, C_4-H); EI-MS(180°) m/e 365($M^{+\cdot}$, 100%), 364(21), 337($M^{+\cdot}$-C_2H_4, 33), 182.5(M^{2+}, 4). The assignment of structure (7) was confirmed by its reduction with $NaBH_4$ in MeOH(30 min, r.t.) to give quantitatively (8), m.p. 195° (dec)(i-Pr_2O/benzene); ν_{max}(nujol) 3310, 1635, 1610 cm^{-1}; λ_{max}(MeOH) 233, 315 and 373 nm (lg ε 4.37, 3.57, 3.62); EI-MS (190°) m/e 367($M^{+\cdot}$, 100%), 366(87), 194(91), 193(20), 178(65), 174(30), 173(61).

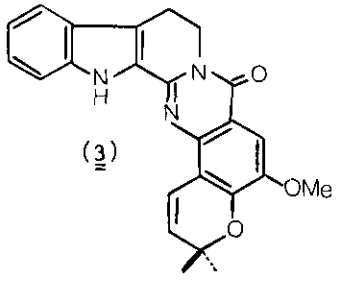
The regioselectivity observed in the above reactions depends upon the presence of C_7-C_8 double bond. We are investigating currently the thermal behaviour of several quinazolinocarboline bases of type (1) with different substituents at N_{14} and will report on these in a future paper.



(1a) R_1:OMe;R_2:H
(1b) R_1:OMe;R_2:H; Δ^7
(1c) R_1,R_2:OMe
(1d) R_1,R_2:OMe; Δ^7
(7) 9,10,11,12-tetrahydro (1a)



(2a) R_1:OH;R_2,R_3,R_4:H
(2b) R_1,R_4:H;R_2,R_3:OMe
(2c) R_1,R_4:H;R_2,R_3:OMe; Δ^7
(2d) R_1:H;R_2,R_3,R_4:OMe
(2e) R_1:H;R_2,R_3,R_4:OMe; Δ^7
(2f) R_1,R_4:H;R_2:OH;R_3:OMe



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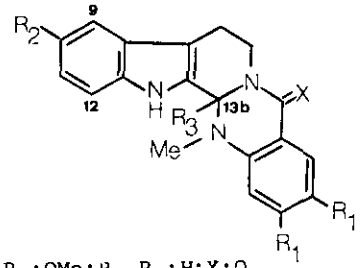
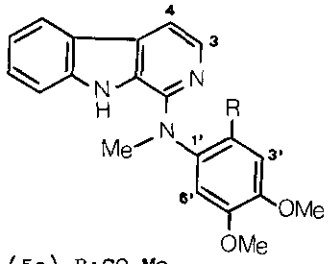
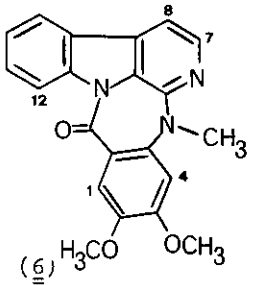


(4a) R_1:OMe;R_2,R_3:H;X:O
(4b) R_1:OMe;R_2,R_3:H;X:H_2
(4c) R_1,R_2,R_3:H;X:O
(4d) R_1,R_3:H;R_2:OMe;X:O
(4e) R_1:H;R_2:OMe;R_3:OEt;X:O
(8) 9,10,11,12-tetrahydro (4a)



(5a) R:CO_2Me
(5b) R:CO_2^- Na^+
(5c) R:CH_2OH
(5d) R:CH_2OAc



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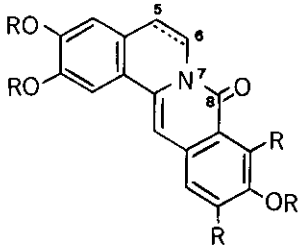

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REFERENCES AND NOTES

1. L.Canonica,B.Danieli,P.Manitto,G.Russo,and G.Ferrari,Tetrahedron Lett., 1968,4865,B.Danieli,P.Manitto,F.Ronchetti,G.Russo,and G.Ferrari,Experientia,1972,28,249;B.Danieli,P.Manitto,F.Ronchetti,G.Russo,and G.Ferrari,Phytochemistry,1972,11,1833;B.Danieli,G.Palmisano,G.Russo,and G.Ferrari,ibid., 1973,12,2521;B.Danieli,G.Palmisano,G.Raimoldi,and G.Russo,ibid.,1974,13, 1603;B.Danieli,C.Farachi,and G.Palmisano,ibid.,1976,15,1095.
2. For a review on the chemistry of carbolines,see R.A.Abramovitch and I.D. Spenser,"Advances in Heterocyclic Chemistry" ed. by A.R.Katritzky,Academic Press,New York and London,1964,vol. 3,p.79.
3. For a general discussion on pseudobases,see D.Beke,ibid.,1963,vol.1,p.167.
4. The transient existence of a 13b-ethoxydihydrohortiamine (4e) has been postulated by Pachter et al.(J.Amer.Chem.Soc.,1960,82,5187).
5. For an example of a stable carbinolamine in related heterocycles,see M.Rothe,T.Tòth,and D.Jacob,Angew.Chem.,1971,113.
6. Recently Shamma reported that the N_7-C_8 bond of protoberberine derivatives (9) was susceptible to cleavage with alkali only in the presence of 5-6 double bond(M.Shamma and L.A.Smeltz,Tetrahedron Lett.,1976,1415).
7. The cleavage of (1b) with 1 equiv NaOH in HMPT and Excess MeI at r.T. gave (5a) in almost quantitative yield(Cf.J.E.Shaw and D.C.Kunerth,J.Org.Chem., 1974,39,1968.
8. A comparable behaviour for 11H-pyrido 2,1-b quinazolin-11-one has been encountered by S.Carboni, Atti Soc. Toscana Sci. Nat.,1955,62,261 (C.A.,1956, 50,16767b).
9. Under the same conditions dehydroevodiamine (1;R_1,R_2:H) and hortiamine (1; R_1:H,R_2:OMe) gave the respective dihydroderivatives (4c) and (4d);I.J.Pachter and G.Suld,J.Org.Chem., 1960,25,1680 and Ref.4.
10. Hydrogenation of anhydronium bases with a similar course has been reported (see Ref. 2,pp.102-3).

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