QUINAZOLINOCARBOLINE ALKALOIDS CHEMISTRY: THERMAL REARRANGEMENT OF 14-ALKYLINDOLO[2',3':3,4]PYRIDO[2,1-b]QUINAZOLIN-5-ONE - PART II

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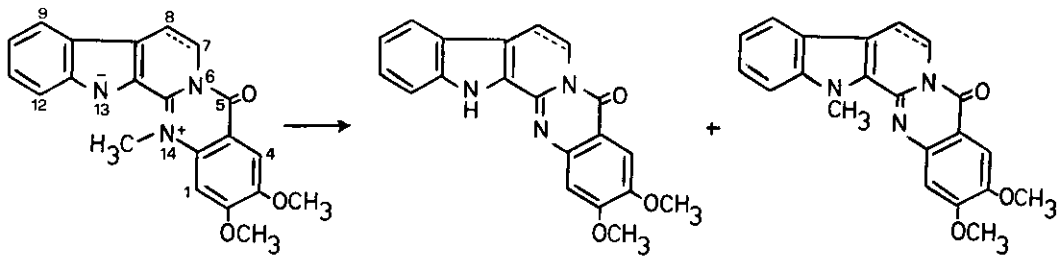
Abstract - The thermal rearrangement of 14-alkylindolo[2',3':3,4]pyrido[2,1-b]quinazolin-5-ones (1a-h) in boiling DMSO has been studied. (1a-d,f,g) give hydrogen migration products (2a,c,e,g,h) and alkyl migration products (2b,d,f,k,l) respectively, whereas (1e,h) give only (2g). Crossover experiments support the intramolecular character of these processes. The formation of hydrogen migration products is interpreted through an α-elimination induced by N_{13} atom and α-bond cleavage. A radical fragmentation-recombination mechanism is suggested for alkyl migration.

During our search for chemical characterization[1] of quinazolinocarboline alkaloids isolated from the bark of Euxylophora paraensis Hub. (Rutaceae) we have observed that 2,3-dimethoxy-14-methylindolo[2',3':3,4]pyrido[2,1-b]quinazolin-5(14H)-one (euxylophorine B)(1a) and 8,14-dihydro-2,3-dimethoxy-14-methylindolo[2',3':3,4]pyrido[2,1-b]quinazolin-5(7H)-one (euxylophorine A)(1b) underwent pyrolytic rearrangement when heated at their melting points in a sealed tube. Thus from (1a) the natural euxylophoricine B (2a) and the N_{13}-methyl derivative (2b)[2] were isolated in almost equal amounts and similarly, from (1b), euxylophoricine A (2c) and N_{13}-methyl euxylophoricine A (2d)[2] were obtained along with significant quantities of the corresponding 7,8-didehydro derivatives (2a) and (2b).



(1a,b) (2a,c) (2b,d)

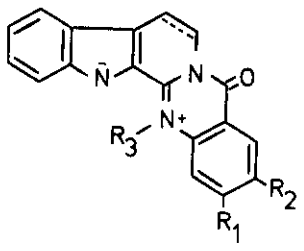
Under these conditions the conversion and the ratio of these products were erratic depending mainly upon heating rate. Heating the above alkaloids in suitable solvents made easier the control of the decomposition.

No reaction occurred at all and starting material was recovered unchanged when (1a) was boiled in benzene for 72 hr, whilst in toluene and xylene at their boiling points (2a) was the only detectable product (tlc) in ca. 28 and 36% yield. In the higher boiling solvents DMSO at 190° and diphenyl ether at 260°, the starting material disappeared after ca. 3 and 2 hr, and (2a) and (2b) were recovered after silica gel preparative tlc in ca. 40 and 35% respectively.

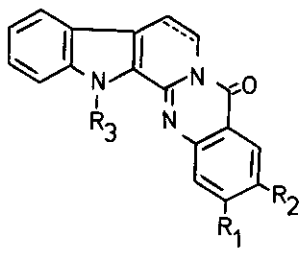
A similar study was extended to the synthetic carbolines (1e-h) in order to test the generality of this behaviour. The carbolines (1e),(1f),(1g) and (1h) were obtained as salts by condensation of the corresponding methyl N-ethylanthranilate, methyl N-allylanthranilate[3], methyl N-benzylanthranilate and methyl N-(2-phenylethyl)anthranilate[4] with 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-one (tetrahydronorharmanone) in the presence of $POCl_3$.

(1e): red-orange powder, m.p. 178° (dec); λ_{max}(EtOH) 282,292,315 and 365nm. It was obtained by careful azeotropic removal of water (refluxing benzene in the presence of molecular sieves) from the yellow hydrated "open-chain" form (3a), m.p. 178° (dec), λ_{max}(MeOH) 313 and 383nm; λ_{max}(MeOH + 1% $HClO_4$) 245 and 383nm; ν_{max}(nujol) 3410, 3240,1665cm^{-1}; EI-MS (115°, 70eV) m/e 333($C_{20}H_{19}N_3O_2^{+\cdot}$, 39%), 315($C_{20}H_{17}N_3O^{+\cdot}$, 55), 287(100), 286(90), 186(48), 147(100); m* at m/e 64.9 for 333→147; EI-MS (185°) m/e 333(1%), 315(53), 287(100), 286(65).

(1f): orange powder, m.p. 195° (dec); λ_{max}(EtOH) 282,290,315 and 365nm; ^{1}H-NMR ($CDCl_3$+ 20% TFA) δ 3.42(2H,t,^{3}J 7 Hz, C_8-H_2), 4.72(2H,t,^{3}J 7 Hz, C_7-H_2), 5.50(2H,m, $N_{14}C$-H_2), 5.64-6.80(3H, ABX pattern, olefinic protons), 8.00(1H,dd,^{3}J 2 Hz, C_1-H), 8.45(1H,dd ^{3}J 8 Hz,^{4}J 2 Hz, C_4-H), 9.44(1h,br s, NH). (1f) was obtained by gentle drying of the quaternary ammonium hydroxide (4), m.p. 195° (dec), intense yellow needles from benzene; λ_{max}(MeOH) 246 and 363nm, unchanged upon $HClO_4$ addition; ν_{max}(nujol) 1685 and 1612cm^{-1}; EI-MS (150°) m/e 327($C_{21}H_{17}N_3O^{+\cdot}$, 8%), 312(12), 287(100), 286(76); m* at



(1a) R_1,R_2:OMe; R_3:Me; Δ^7
(1b) R_1,R_2:OMe; R_3:Me
(1c) R_1,R_2:OMe; R_3:Me-d_3; Δ^7
(1d) R_1,R_2:H; R_3:Me; Δ^7
(1e) R_1,R_2:H; R_3:Et
(1f) R_1,R_2:H; R_3:allyl
(1g) R_1,R_2:H; R_3:benzyl
(1h) R_1,R_2:H; R_3:2-phenylethyl

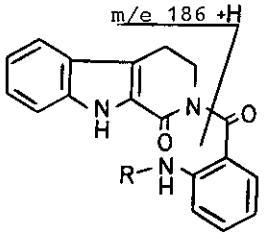


(2a) R_1,R_2:OMe; R_3:H; Δ^7
(2b) R_1,R_2:OMe; R_3:Me; Δ^7
(2c) R_1,R_2:OMe; R_3:H
(2d) R_1,R_2:OMe; R_3:Me
(2e) R_1,R_2:OMe; R_3:D; Δ^7
(2f) R_1,R_2:OMe; R_3:Me-d_3; Δ^7
(2g) R_1,R_2,R_3:H
(2h) R_1,R_2,R_3:H; Δ^7
(2i) R_1,R_2:H; R_3:Me; Δ^7
(2j) R_1,R_2:H; R_3:Et
(2k) R_1,R_2:H; R_3:allyl
(2l) R_1,R_2:H; R_3:benzyl
(2m) R_1,R_2:H; R_3:2-phenylethyl

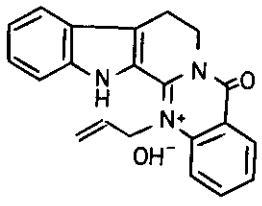
m/e 285.0 corresponding to the 287→286 transition.

(1g): orange needles, m.p. 183° (dec); λ_{max}(EtOH) 283,291,314 and 365nm; ^{1}H-NMR ($CDCl_3$ + 20% TFA) δ 3.43(2H,t,^{3}J 7 Hz, C_8-H$_2$), 4.76(2H,t,^{3}J 7 Hz, C_7-H$_2$), 6.06(2H, s, Ar-CH$_2$-N$^+$), 7.46-8.00(12H,m, aromatic protons), 8.50(1H,dd,^{3}J 8 Hz, C_4-H), 8.80 (1H,br s, NH). (1g) was obtained, like (1e) from the yellow "open-chain" form (3b), m.p. 183° (dec), λ_{max}(MeOH) 312 and 382nm; λ_{max}(MeOH + 1% $HClO_4$) 244 and 367nm; ν_{max} (nujol) 3382,3270,1676 and 1656cm^{-1}; EI-MS (110°) m/e 395($C_{25}H_{21}N_3O_2^{+\cdot}$,21%), 377($C_{25}H_{19}N_3O^{+\cdot}$, 55), 300(72), 287(78), 286(100), 209(72), 186(21), 182(28), 91(90); m* at m/e 238.7 for the 377→300 transition; EI-MS (180°) m/e 395(0.9%), 377(57), 300 (60), 287(100), 91(88).

(1h): orange needles, m.p. 180° (dec); λ_{max}(EtOH) 280,291,315 and 363nm; ^{1}H-NMR ($CDCl_3$ + 20% TFA) δ 2.83(2H,m, Ar-CH$_2$), 3.01(2H,m, C_8-H$_2$), 4.36(2H,m, C_7-H$_2$), 5.51 (2H,m, Ar-CH$_2$-CH$_2$), 6.35-8.18(13H,m, aromatic protons). (1h), like (1e) and (1g), was obtained from (3c), yellow needles from benzene,m.p. 180° (dec); λ_{max}(MeOH) 312 and 382nm; λ_{max}(MeOH + 1% $HClO_4$) 246 and 367nm; ν_{max}(KBr) 3410,3280,1665 and 1640 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.98(2H,m, Ar-CH$_2$), 3.18(2H,m, C_8-H$_2$), 3.50(2H,m, NH-CH$_2$), 4.20 (2H,m, C_7-H$_2$), 6.33-7.70(13H,m, aromatic protons), 10.05(1H,br s, NH); EI-MS (110°) m/e 409($C_{26}H_{23}N_3O_2^{+\cdot}$, 5%), 391($C_{26}H_{21}N_3O^{+\cdot}$, 6), 301(391-PhCH$_2^{\cdot}$, 26), 300(100), 287 (76), 186(51); EI-MS (180°) m/e 409(0.4%), 391(5), 285(100), 268(87).



(3a) R:Et
(3b) R:benzyl
(3c) R:2-phenylethyl



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Exposure of anhydro bases to moisture at r.t. brought about rehydration and they survived as salts only in the presence of strong acids. A correlation had been noted between the dependence on temperature of the equilibrium "hydrated" ⇄ "anhydronium" forms and the observed mass spectra of these carbolines under electron impact. In fact, the mass spectra of (3a), (3b) and (3c) at low temperature (~110°) exhibited ions at m/e 333, m/e 395, m/e 409 and ions at m/e 315, m/e 377, m/e 391, indicative of the "open-chain" forms and anhydro bases (1e), (1g), (1h) respectively, whereas that of (4) contained only ion at m/e 327 due to (1f). Furthermore, the low temperature-mass spectra of (3a), (3b), (3c) showed an intense ion at m/e 186 (see Formulae 3) attributable to tetrahydronorharman-1-one ion radical. At higher temperatures (~180°) we observed the almost complete disappearence of the ions at m/e 333, 395, 409 and at m/e 186, indicating the occurrence of thermal induced dehydration.

Thermal rearrangement of (1f) and (1g) in boiling DMSO (2.5 hr) gave a ca. 1:1 mixture (68% isolated yield) of rutaecarpine (2g) and N_{13}-allylrutaecarpine (2k)[2b] and a 45:55 mixture (75%) of (2g) and N_{13}-benzylrutaecarpine (2l)[2b] respectively. In both cases, traces (<3%) of 7,8-didehydro rutaecarpine (2h) (λ_{max}^{MeCN} 248,267,280 327,350, 368 and 389nm) and 7,8-didehydro N_{13}-alkylrutaecarpine [λ_{max}(MeCN)~ 256,275, 287, 337,360,360,380 and 404nm] were isolated and identified by UV and MS data. On the other hand, thermolysis of (1e) and (1h) under the same conditions furnished rutaecarpine (2g) (45 and 55%) along with 7,8-didehydro rutaecarpine (2h) (<3%) and no traces of N_{13}-ethylrutaecarpine (2j)[2b] and N_{13}-(2-phenylethyl)rutaecarpine (2m)[2b] were detected by tlc comparison.

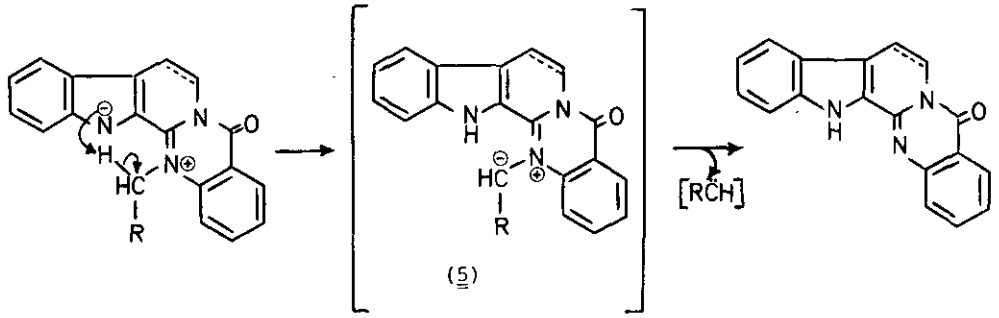
The mechanism for the formation of these products could be, in principle, either inter- or intramolecular. In order to help elucidate this behaviour, we synthesized (1c) by quaternization of (2a) with [$^2H_3$]-methyl iodide (>99%d) and subsequent treatment with Et_3N. When a 0.12M solution of a 1:1 mixture (molar ratio) of (1c) and (1d)[5] in anhydrous DMSO was heated at 190°±3° for 2.5 hr in an evacuated ampoule, frozen-thawed twice before being sealed, about 90% of the starting materials were consumed giving rise to a complex mixture of products. The resolution of the mixture into its components was allowed by careful plc. In addition to the starting materials, four components with R_f and UV fluorescence under Wood light identical to those of euxylophoricine B, 7,8-didehydro rutaecarpine, N_{13}-methyleuxylophoricine B and 7,8-didehydro N_{13}-methylrutaecarpine were isolated[6,7].

Intramolecular mechanism predicts the exclusive formation of deuteriated euxylophoricine B (2e) and N_{13}methyleuxylophoricine B (2f), and non-deuteriated (2h)and (2i). On the other hand, statistical intermolecular mechanism would lead to scrambling of deuterium.

The four components were analyzed by low-voltage mass spectrometry (12eV) for deuterium location. The mass spectra of euxylophoricine B and its N_{13}-methyl derivative exibited intense molecular peaks at m/e 346 and 362 respectively, indicating that one and three deuterium atoms had been incorporated giving rise to (2e) and (2f). The spectra of 7,8-didehydro rutaecarpine and its N_{13}-methyl derivative showed intense molecular ions at m/e 287 and 301 respectively and were identical in all respects to those of authentic samples of (2h) and (2i). The absence of any appreciable deuterium mixing (at least <5%) was in agreement with an intramolecular reaction mechanism.

Intramolecular hydrogen migration could occur by the formation of an ylide (5) (α-elimination induced by N_{13}) and α-bond cleavage to give rutaecarpine with subsequent ejection of a carbenoid specie, according to well-known behaviour of cycloimmonium ylides[8]. In the case of (1e) and (1h), an E_2 mechanism could be favored by the strongly electron attracting centre N_{14} with the removal of the β-hydrogen, according to a classical Hofmann elimination. However, the pyrolysis of (1h) in VPC-MS at 195° failed to give any traces of styrene, ethylbenzene being the only detectable product.

As regards the intramolecular alkyl migration, the carbolines (1a-h) are unable to rearrange to the corresponding N_{13}-alkylrutaecarpines by a S_Ni mechanism (6), since the endocyclic[9] nucleophilic displacement is stereo-electronically forbidden.



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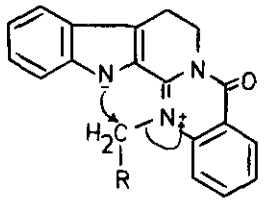
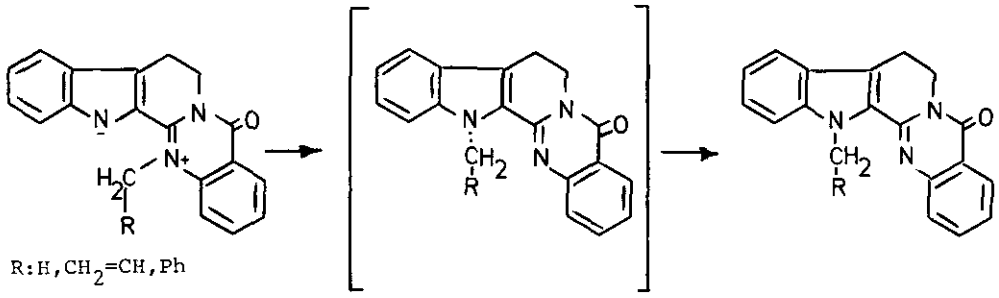


(6)

A formally allowed [1,4]sigmatropic shift is also ruled out because the N^{+}-alkyl group cannot adopt a conformation suitable for development of good bonding in the transition state and the inherent character of this process results in a relatively high activation energy.

The marked temperature dependence and the reluctance of (1e)[10] and (1h) to give alkyl migration under the above conditions, suggested the intervention of radical species in this process. *Since* free-radical scavengers (e.g., acrylamide and p-benzoquinone) were ineffective, the homolytic cleavage of the N_{14}-alkyl bond should give a tight radical pair which recombinated to form the N_{13}-alkyl bond, as shown in the following scheme.



R:H,CH_2=CH,Ph

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2. a) B.Danieli and G.Palmisano, Gazz. Chim. Ital., 1975, 105, 45; b) B.Danieli and G.Palmisano, J. Heterocyclic Chem., 1977, 14, 839.
3. Pale yellow oil, obtained by alkylation of anthranilic acid methyl ester with allyl bromide in K_2CO_3/acetone; ν_{max}(neat) 3380 and 1680cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.81(3H,s, OMe + 2H,br s, ^3J 5 Hz, NH-CH_2), 5.12(1H,ddt, ^3J 10 Hz, ^2J 2 Hz, ^4J 2 Hz, $\frac{H}{H}\!>\!C\!=\!C\!<^{H}$), 5.25(1H,ddt, ^3J 19 Hz, ^2J 2 Hz, ^4J 2 Hz, $\frac{H}{H}\!>\!C\!=\!C\!<^{H}$), 5.90 (1H,ddt, ^3J 19 Hz, ^3J 10 Hz, ^3J 5 Hz, $\frac{H}{H}\!>\!C\!=\!C\!<^{H}$), 6.5.-6.70(2H,m, aromatic protons), 7.31(1H ,ddd, ^3J 9 Hz, ^3J 7 Hz, ^4J 2 Hz, C_4-H), 7.90(1H,dd, ^3J 8 Hz, ^4J 2 Hz, C_6-H).
4. Yellowish oil, ν_{max}(neat) 3375 and 1683cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.95(2H,t, ^3J 7 Hz, Ph-CH_2), 3.47(2H,t, ^3J 7 Hz, NH-CH_2), 3.81(3H,s, OMe), 6.40-7.50(8H,m, aromatic protons), 7.92(1H,dd, ^3J 8 Hz, ^4J 2 Hz, C_6-H).
5. (1d) was obtained by dehydrogenation of dehydroevodiamine with DDQ in refluxing benzene; EI-MS (90°) m/e 299($M^{+\cdot}$, 22%), 298(100), 270($M^{+\cdot}$-CO-H, 45), 149.5(M^{2+}, 13).
6. Products isolated from thermolysis of (1a) in [$^2H_6$]-DMSO did not incorporate deuterium.
7. Preparative tlc on silica gel plates (layers 150mμ thick) using hexane-$CHCl_3$-Et_2NH, 5/4/1, gave euxylophoricine B (18%, R_f 0.23), 7,8-didehydro rutaecarpine (13%, R_f 0.46), N_{13}-methyleuxylophoricine B (21%, R_f 0.67) and 7,8-didehydro N_{13}-methylrutaecarpine (15%, R_f 0.75).
8. For a review, see G.Surpateanu, J.P.Catteau, P.Karafiloglou, and A.Lablanche-Combier, Tetrahedron, 1976, 32, 2647.
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