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2-CYANO Δ^3 PIPERIDEINES VIII[1] : BIOMIMETIC APPROACH TO THE SYNTHESIS OF THE DECAHYDROQUINOLINE RING SYSTEM OF POISON-DART FROG TOXINS

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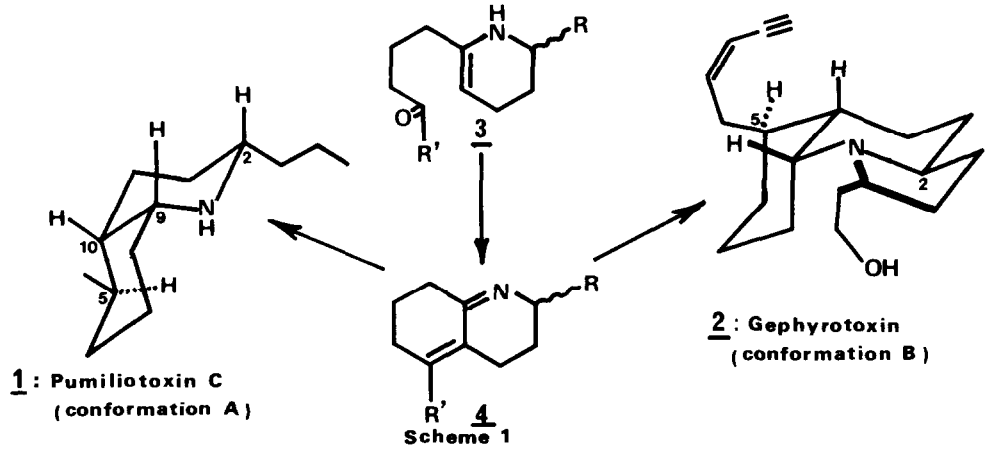
Summary : A biomimetic approach towards the synthesis of pumiliotoxin C has been developed. The key transformation of enamine equivalent 8 to 9 was catalyzed by contact with alumina. Cyclized intermediate 9 was then reduced stereospecifically to the trans decahydroquinoline 11 or stereoselectively to the cis compound 12.

Recent and intense interest has been directed towards the total synthesis of the poison-dart frog toxins pumiliotoxin-C[2] 1 and gephyrotoxin 2[3] due to their interesting pharmacological activities[4]. Both compounds 1 and 2 possess a cis-decahydroquinoline ring system with side chain substituents at the C-2 and C-5 positions[5] (the C-2 side chain of 2 being further attached at nitrogen, forming a third ring). The relative configurations of these substituents are not the same, however, with the consequence that the two natural compounds adopt opposite cis-fused conformations (conformations A and B)[6]. Any synthesis of these toxins has to take into account these structural features.

It has been proposed that the pumiliotoxin class and gephyrotoxin are formed biosynthetically by cyclization of a substituted piperidine enamine such as 3 (scheme 1)[7]. However, to our knowledge, no biomimetic approach to their synthesis has been reported, presumably due to the challenging problem of controlling the stereochemistry of the C-5, 9 and 10 centers during reduction of the essentially planar conjugated imine intermediate 4.

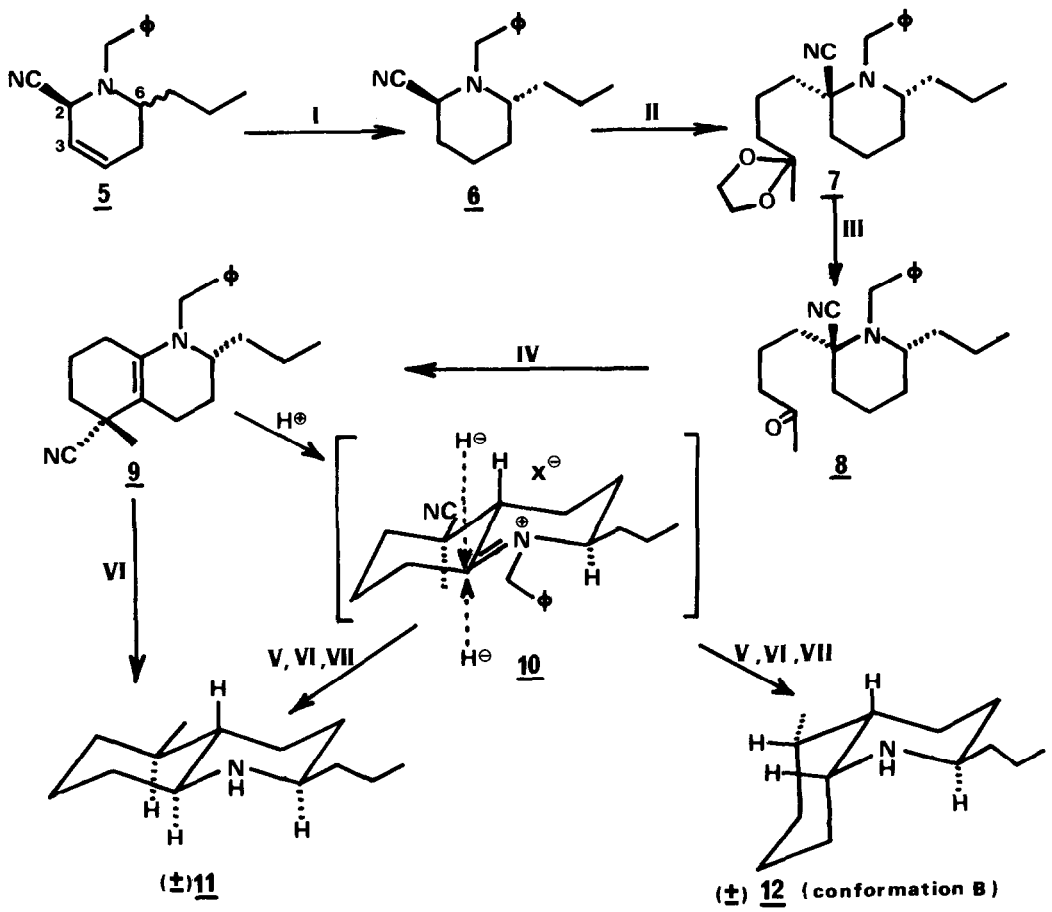


Scheme 1

Our experience with the chemistry of 2-cyano-Δ^3 piperideines[8,9] suggested that an aminonitrile equivalent 8 of the enamine precursor 3 could be readily prepared (scheme 2). We were thus tempted to examine the cyclization of 8 with the objective of developing a

convenient entry to the pumiliotoxin class of frog toxins. Our preliminary results are presented in this communication.

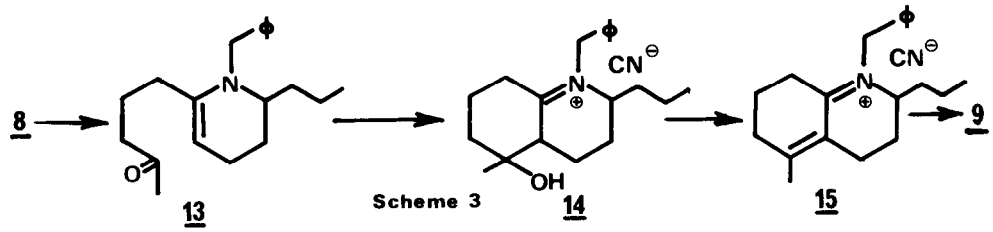
2-cyano Δ^3 piperideine 5 (a 3:2 mixture of epimers) was prepared from the corresponding pyridinium salt according to our procedure[8]. A single product 6[10] (Y = 85 %) was obtained on selective hydrogenation (Pd/C, H_2, EtOH) of the $\Delta^{3,4}$ double bond of 5[9]. Preparation of the anion of 6 (LDA, THF, - 30°) and its reaction with 5-chloro-2-pentanone ethylene ketal at room temperature led to the formation of 7[11] (Y = 55 %). Subsequent liberation of the ketone functionality (HCl/MeOH, rt, Y = ∿ 98 %) gave the desired enamine equivalent 8[11].



Reagents : I, H_2, C/Pd 10 %, EtOH, 12h ; II, LDA, THF, - 30°, $Cl(CH_2)_3$ C-CH_3, rt, 1.5h ; III : MeOH-HCl N (50:50), rt, 1h ; IV : Al_2O_3 act. II-III,  CH_2Cl_2, rt, 1h ; V : $NaBH_4$, CH_3OH, rt, 20h or $NaBH_3CN$, THF - H^+pH4, rt, 2h ; VI, NH_3/Na, THF, - 78°, 1h ; VII, H_2, C/Pd 10 %, MeOH, H^+, 12 h.

SCHEME 2

An efficient method for the cyclization of 8 was discovered when the crude product mixture from the ketal hydrolysis was column chromatographed on alumina[12]. On contact of 8 with alumina (Merck, Art. 1097) elimination of CN^-, cyclization, dehydration and, finally, 1,4-reintroduction of CN^- onto the resultant conjugated iminium 15 occurred successively, giving the cyano enamine 9[13] as a mixture of two epimers (9 : 1) in > 75 % yield (scheme 3).



Scheme 3

The major isomer, isolated pure after further chromatography was used in all subsequent experiments. The gross structure of this compound was deduced from the spectral data. However the configuration at C-5 was assigned on the basis of stereoelectronic arguments, ie. axial attack of CN^- on the conjugated iminium 15 whose C-2 propyl side chain is axial due to $A^{1,2}$ strain.

The stable cyanoenamine 9 can be considered as a γ-aminonitrile equivalent of the proposed biogenetic intermediate 4. To complete the synthesis of the cis-decahydroquinoline system of 1 from this key intermediate it thus remained to control the reduction of the $\Delta^{9,10}$ enamine double bond and the reductive removal of the cyano group (cleavage of the N-benzyl group being a trivial operation).

We first investigated borohydride reduction of the enamine system. Reaction of 9 with $NaBH_4$ in MeOH led to the formation of two inseparable isomeric products (Y = 97 %) in a 85 : 15 ratio as determined by measuring peak heights in the ^{13}C NMR spectrum. The same two products were also obtained using $NaBH_3CN$ in THF/HCl at pH 4.0, however the reaction was less selective (Y = 75 % : 45/55). The subsequent reaction of these mixtures with sodium in NH_3 liq. at - 78° for 1 h. produced the two corresponding decyano products in nearly quantitative yield without altering the isomer ratio. Finally, hydrogenolytic cleavage of the N-benzyl group (Pd/C, H_2, MeOH-HCl) then gave the two decahydroquinolines 11 and 12 which were readily separated by preparative layer chromatography on alumina (CH_2Cl_2/MeOH 2 %) (Y = 85 %)[14].

TLC and GC (20 % SE-30, 3 m, 185°/2 atm., N_2) comparison of products 11 and 12 with an authentic sample of pumiliotoxin-C showed that they were isomeric with the natural material.

The major component from $NaBH_4$ reduction of 9 corresponds to structure 12 where the cis fused ring adopts the conformation B so as to place both side chains in equatorial positions. The cis nature of the ring junction was deduced from the characteristic position for the H-2 (δ 2.69) and H-9 (δ 2.84) signals in the ^1H NMR spectrum[15], and from the large $J_{9,8ax}$ = 12 Hz coupling constant. The large coupling constant $J_{5,6ax}$ = 12 Hz was consistent with an equatorial orientation of the C-5 methyl group as were the ^{13}C NMR signals for an equatorial orientation of the C-2 propyl side chain.

The assignment of the trans diequatorial structure of 11 to the minor component was based upon the comparison of its ^{13}C NMR spectrum with published values[16].

It is important to note that the relative configurations of the methyl and propyl side chains of 11 and 12 are different. This we believe is a result of an isomerization of the C-5 center during decyanation of the intermediate leading to 11 (to be discussed in more detail later).

In a different approach, the cyclized cyanoenamine 9 was treated directly with Na/NH_3 liq. (1h, -78°). Vinylogous β-elimination of the benzyl group and reduction of the resultant conjugated imine 4 occurred on reductive decyanation leading in a single operation to the trans product 11 in high yield (⩾ 75 %). Also catalytic hydrogenation of the $\Delta^{9,10}$ double bond of 9 was studied. At atmospheric pressure (Pd/C, Ru/Al_2O_3) catalysts) the sterically crowded double bond was unreactive, and at higher pressures concomitant reduction of the nitrile group was observed.

In summary, the conversion of 8 to the cyclized aminonitrile 9 catalyzed by contact with alumina mimics very effectively the proposed biosynthetic transformation of enamine 3 to the conjugated imine 4. This key intermediate was in a short and high yielding fashion,

converted stereospecifically to the trans decahydroquinoline 11 (as yet found in but a few natural products), and stereoselectively (85 : 15) to the cis compound 12 possessing both the correct ring conformation and C-2 side chain configuration of gephyrotoxin 2. Pumiliotoxin-C 1 was not obtained using the methods studied for reduction of 9. However, these results will serve as a guideline to further and hopefully successful experimentation towards this natural system.

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REFERENCES AND NOTES :

1 - Part VII : F. GUIBE, D. S. GRIERSON and H.-P. HUSSON, Tetrahedron Lett., 1982, 23, 5055.

2 - For the most recent synthesis of pumiliotoxin C see : K. HATTORI, Y. MATSUMURA, T. MIYAZAKI, K. MARUOKA and H. YAMAMOTO, J. Am. Chem. Soc., 1981, 103, 7368.

3 - For the synthesis of gephyrotoxin see : R. FUJIMOTO, Y. KISHI and J.-F. BLOUNT, J. Am. Chem. Soc., 1980, 102, 7154.

4 - B. WITKOP, Experientia,1971, 27, 1121 ; M. MENSAH-DWUMAH and J. W. DALY, Toxicon, 1978, 16, 189.

5 - The pumiliotoxin C numbering is used for both structures.

6 - J. W. DALY, B. WITKOP, T. TOKUYAMA, T. NISHIKAWA and I. L. KARLE, Helv. Chim. Acta, 1977, 60, 1128.

7 - J. W. DALY, G. B. BROWN, M. MENSAH-DWUMAH and C. W. MEYERS, Toxicon, 1978, 16, 163.

8 - D. S. GRIERSON, M. HARRIS and H.-P. HUSSON, J. Am. Chem. Soc., 1980, 102, 1064.

9 - M. BONIN, J. ROMERO, D. S. GRIERSON and H.-P. HUSSON, Tetrahedron Lett., 1981, 23, 3369.

10 - 6 : oil ; MS, m/e : 242 ($M^{+\cdot}$, 18) 199 (37), 172 (9), 91 (100) ; IR (neat) : 2200 and 1600 cm^{-1} ; ^1H MNR ($CDCl_3$, 60 MHz) : 2.55 (m, H-6), 3.60 (m, H-2), 3.15 and 4.18 (2d, J_{AB} = 14 Hz, $NCH_2\emptyset$) ; ^{13}C NMR ($CDCl_3$) : 14.6, 17.4, 21.1, 28.5, 30.7, 35.7, 51.5, 54.8, 57.3, 117.3, 127.4, 128.6, 128.8, 137.9.

11 - 7 : oil ; MS m/e : 370 ($M^{+\cdot}$, 5), 355 (10), 343 (30), 327 (53), 300 (48), 91 (100) ; IR (neat) : 2200 and 1600 cm^{-1} ; ^1H NMR ($CDCl_3$, 60 MHz) : 1.2 (s, CH_3-C(=O)-O), 2.5 (m, H-6), 3.8-3.85 (m, $O(CH_2)_2$-O-+ $NCH_2\emptyset$) ^{13}C NMR ($CDCl_3$) : 14.0, 18.5, 19.1, 20.8, 23.6, 31.1, 34.5, 37.4, 38.5, 39.3, 55.3, 61.1, 64.2, 64.4, 109.1, 119.8, 126, 127, 141.
8 : oil ; IR (neat) : 2200, 1720 and 1600 cm^{-1} ; ^1H NMR ($CDCl_3$, 60 MHz) : 1.95 (s, CO-CH_3), 2.5 (m, H-6), 3.7 (m, $NCH_2\emptyset$).

12 - F. REIS, K. BANNAI and H.-P. HUSSON, Tetrahedron Lett., 1976, 1085.

13 - 9 : major : oil ; MS m/e : 308 ($M^{+\cdot}$, 30), 293 (45), 265 (40), 91 (100) ; IR (CH_2Cl_2) : 2210 and 1610 cm^{-1} ; UV (λ_{max}^{EtOH}) : 252 nm ; ^1H NMR ($CDCl_3$, 80 MHz) ; 1.40 (s, C-CH_3), 3.0 (m, H-2), 4.0 and 4.20 (2d, J_{AB} = 16 Hz, $NCH_2\emptyset$) ; ^{13}C NMR ($CDCl_3$) : 14.2, 19.3, 19.6, 20.2, 23.6, 26.0, 26.6, 32.6, 36.4, 37.5, 52.9, 55.5, 99.5, 126.8, 126.9, 128.2, 128.5, 128.7, 137.5, 140.7

14 - 11 : HCl (ether-methanol) : mp 230°-240° (d) microanalysis : $C_{13}H_{25}N$, HCl ; ^{13}C NMR ($CDCl_3$) : 13.5, 18.8, 24.1, 27.2, 28.1, 30.0, 34.2 , 35.1, 36.6, 44.6, 58.3, 61.7 ; Base, m/e ; 195 ($M^{+\cdot}$, 8), 152(100) ; ^1H NMR ($CDCl_3$, 400 MHz) : 0.85 (d, $CH\,CH_3$) 1.97(m, H-10), 2.20 (m, H-9), 2.53 (m, H-2) ; 12 : HCl (ether-methanol) : mp 232°-233° ; microanalysis : $C_{13}H_{25}N$, HCl ; ^{13}C NMR ($CDCl_3$) : 13.9, 17.0, 18.7, 18.9, 22.0, 24.6, 27.9, 28.2, 34.2, 35.4, 37.5, 51.1, 55.8 ; Base, MS m/e : 195 ($M^{+\cdot}$, 5), 152 (100) ; ^1H NMR ($CDCl_3$, 400 MHz) : 0.80 (d, CH-CH_3), 1.83 (dq, J = 4 and 12 Hz, H-10), 2.69 (m, H-2), 2.84 (dt, J = 4 and 12Hz, H-9).

15 - E.L. ELIEL and F.W. WIERHAPPER, J. Org. Chem., 1979, 44, 1081 and references therein.

16 - G. HABERMEHL, H. ANDRES, K. MIYAHARA, B. WITKOP and J. W. DALY, Liebigs Ann. Chem., 1976, 1577.

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