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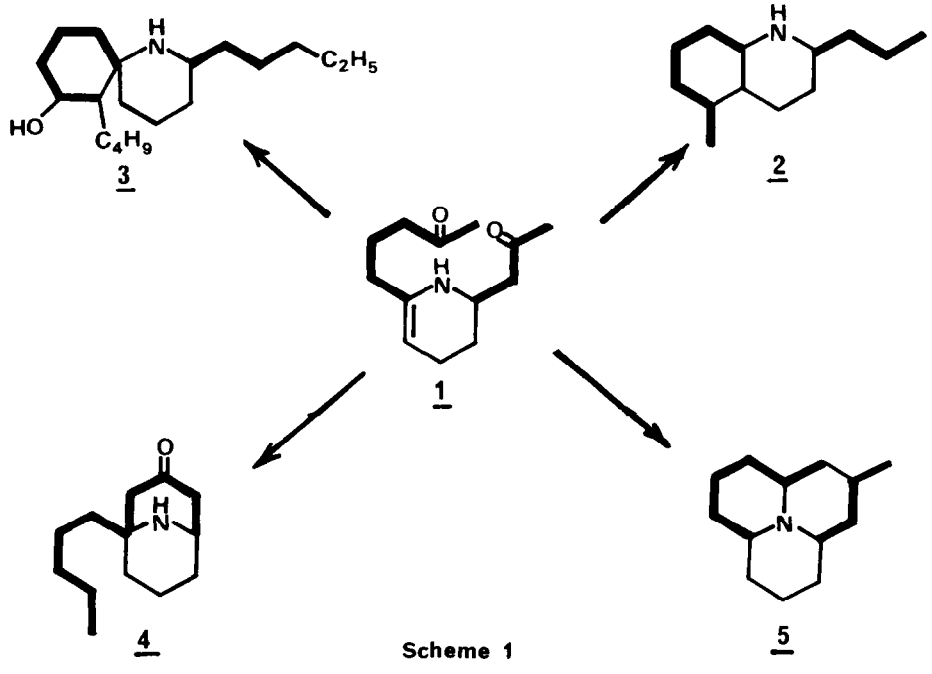
2-CYANO Δ^3 PIPERIDEINES X[1] :
BIOMIMETIC SYNTHESIS OF THE LADYBUG ALKALOIDS OF THE ADALINE SERIES

D.H. GNECCO MEDINA, D.S. GRIERSON and H.-P. HUSSON*

Institut de Chimie des Substances Naturelles du C.N.R.S., 91190 Gif s/Yvette (France)

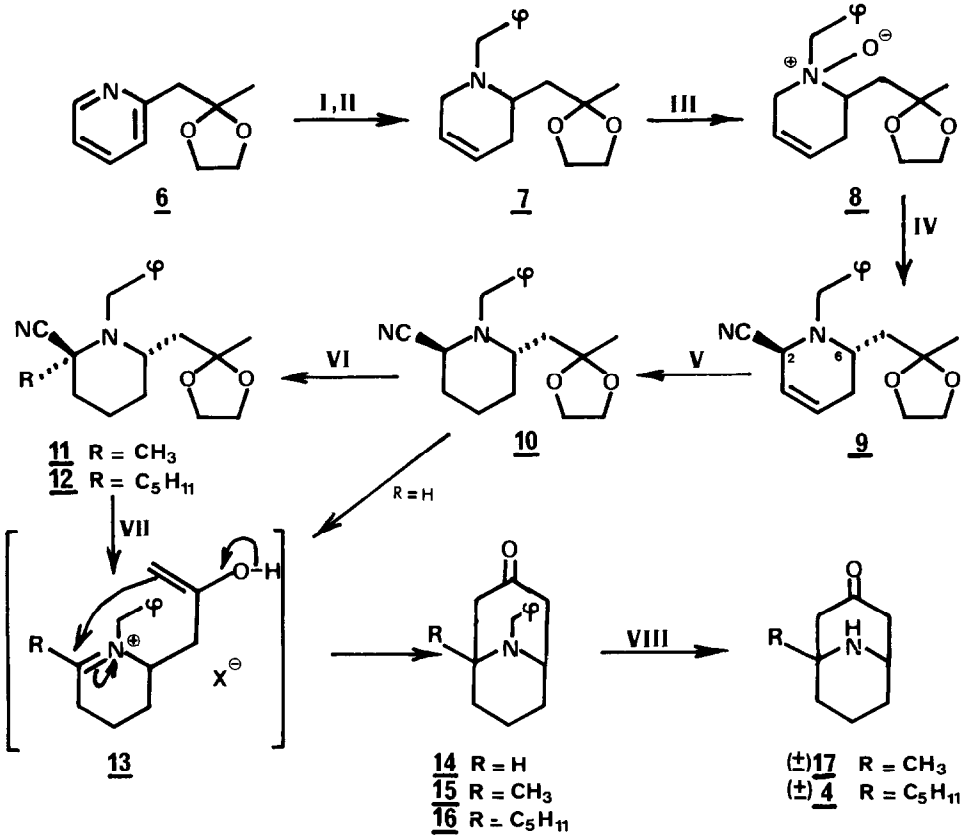
Summary : The ladybug alkaloids 4 and 17 of the adaline series were synthesized via intramolecular Mannich reaction of the intermediate iminium-enols 13, generated from the corresponding 2-cyano-2'-alkyl-6- (propan-2-one ethylene ketal) piperidines 11 and 12.

It has often proven fruitful to take into account the biogenesis of complex natural products when planning their synthesis. The ladybug alkaloids adaline 4 and coccinelline 5 possess structural similarities which suggest that they are derived from a common biosynthetic precursor, Δ^2 piperideine 1 (scheme 1). In fact, it has been demonstrated that the biosynthesis of coccinelline 5, and its derivatives involves the polyacetate pathway, and the formation of 1 (in its imine form)[2].



Scheme 1

Similarly, it has recently been proposed[3] that the poison-dart frog toxins pumiliotoxin-C 2 and histrionicotoxin (depicted as its perhydroderivative 3) are also derived from a Δ^2 piperideine of type 1. Thus despite the diverse origins of these groups of compounds a common element, a 2,6-disubstituted Δ^2 piperideine, is involved in their respective biogenesis. It is this element which in turn suggests a common approach to their syntheses.



Reagents : I, $BrCH_2$-φ ; II, $NaBH_4$, CH_3OH ; III, mCPBA, CH_2Cl_2, rt, 10 m ; IV, $(CF_3CO)_2O$, CH_2Cl_2, -10°, 20 m — KCN, H^+ pH 4, rt, 1h. ; V, H_2, C/Pd 10 %, EtOH, 3 h. ; VI, LDA, THF, -20°, 20 m — RX, 2 h. ; VII, CH_3OH, HCl 10N (10 %) ; VIII, H_2, C/Pd 10%, EtOH, HCl, 3 h.

SCHEME 2

In two recent communications we have shown that aminonitrile equivalents of the enamine system of 1 could be prepared and used to construct the spirocyclic system of 3[4] and the decahydroquinoline ring system of 2[5] . In continuation of our work on the chemistry of 2-cyano Δ^3 piperideines we have extended the above theme to include construction of the azabicyclo[3,3,1] nonane system (ABN) of the ladybug defence alkaloids 4 and 17[6,19]. This represents the first biomimetic based synthesis of adaline 4[7] .

The key step of our synthetic route was an intramolecular Mannich reaction of the intermediate iminium-enol 13 derived from the enamine equivalents, aminonitriles 10-12 (Scheme 2)

2-Cyano Δ^3 piperideine 9 was obtained from the corresponding pyridine 6 via the sequence 6[8,9] → 7[10] → 8 → 9[11] according to established procedure[12] (overall yield 20 %). The trans stereochemistry between the C-2 and C-6 substituents of 9 was inferred from the observation of a AB resonance system in the ^{1}H NMR for the benzyl methylene protons[13,14]. Selective hydrogenation of the Δ^3 double bond of 9 (Pd/C - H_2) led to 10 in excellent yield (95 %)[15]. Alkylation of the anion derived from 10 (LDA, THF, -20°) respectively with methyl iodide and pentyl bromide afforded the 2,6-disubstituted compound 11 (highly unstable) and 12 (Y : 50 %)[16].

It was expected that treatment of aminonitriles 10-12 with acid would generate the iminium ion by elimination of the cyano group and liberate the ketone function thus permitting cyclization of the resultant intermediate 13 to occur. Indeed, refluxing a solution of 10 in methanol containing 10 % of HCl conc. for 4 hr led to the formation of 9-benzyl-3-one ABN 14[17] isolated as a crystalline product in 90 % yield. Similarly, cyclization of 12 under the same conditions (Δ, 48 hr) gave 9-benzyl adaline 16[20] in 90 % yield. Cyclization of 11 afforded 15[18] in only 10 % yield (after chromatography) however. The low yield obtained in this case undoubtedly reflects the instability of the aminonitrile 11. Subsequent debenzylation of 15 and 16 led to the natural products (±) 17[19] and (±) 4 respectively in nearly quantitative yields.

In conclusion, the facile formation of the azabicyclo[3.3.1] nonane ring system under Mannich reaction conditions is a good argument for the possible occurrence of such a step during the biosynthesis of the related alkaloids.

Aknowledgments : The authors would like to thank Dr Edda GÖSSINGER, Institut für Organische Chemie der Universität Wien, for copies of the ^{1}H NMR and IR spectra of (±) adaline.

References and Notes

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8 - 6 : prepared by ketalisation of 2-acetyl picoline[9] : oil ; MS m/e : 179 ($M^{+\cdot}$, 5), 164 (44), 92 (78), 87 (100). ^{1}H NMR ($CDCl_3$, 60 MHz, TMS δ = 0) : 1.25 (s, $C\underline{H}_3$), 3.10 (s, $C\underline{H}_2$), 3.90 (m, O-$C\underline{H}_2$-$C\underline{H}_2$-O).

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10 - 7 : oil : MS (high resolution) m/e : 273 ($C_{17}H_{23}NO_2$, 18), 230 (19), 182 (17), 172 (95), 91 (100), 87 (44) ; ^{1}H NMR ($CDCl_3$, 60 MHz, TMS δ = 0) : 1.25 (s, $C\underline{H}_3$), 3.05 (m, N-$C\underline{H}_2$-), 3.9 (m, O-$C\underline{H}_2$-$C\underline{H}_2$-O), 5.6 (m, $C\underline{H}$ = $C\underline{H}$).

11 - 9 : oil ; MS m/e : 298 (1), 271 (3), 230 (38), 197 (8), 172 (20), 91 (100) ; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS δ = 0) : 1.28 (s, $C\underline{H}_3$), 3.23 and 4.11 (d, J_{AB} = 14 Hz, N-$C\underline{H}_2$-), 3.60 (m, $\underline{H}$-C-CN), 5.35 (m, H-3), 5.86 (m, H-4).

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15 - 10 : oil ; MS (high resolution) m/e : 300 ($C_{18}H_{24}N_2O_2$, 0.5), 273 (1.2), 257 (2.4), 255 (1.4), 199 (25.5), 91 (100).

16 - 12 : oil ; MS m/e : 370 (1), 343 (3), 299 (10), 269 (10), 199 (20), 174 (37), 91 (100), 43 (32). Stereochemistry inferred from previous results[14].

17 - G.F. BOEHRINGER, Belgian Patent (1963). Chem. Abstr., 1964, 60, 13285h.

18 - 15 : oil ; MS m/e : 243 (97), 200 (44), 186 (49), 172 (32), 91 (100), 43 (47) ; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS δ = 0) : 1.65 (s, $C\underline{H}_3$), 1.5-2.2 (m, 6H), 2.36-2.5 (2 dd, 4H), 3.3 (m, 1H), 3.8 and 4.08 (d, J_{AB} = 14 Hz, N-$C\underline{H}_2$-), 7.2-7.5 (m, 5H).

19 - This alkaloid has been isolated for the first time from Euphorbia atoto : N.K. HART, S.R. JOHNS and J.A. LAMBERTON, Aust. J. Chem., 1967, 20, 561.

20 - All known compounds have been fully characterized and their spectral data are in accord with the literature values.

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