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SYNTHETIC STUDIES ON INDOLE ALKALOIDS. A STEREOCONTROLLED ENTRY TO THE CUANZINE STRUCTURAL UNIT [1]

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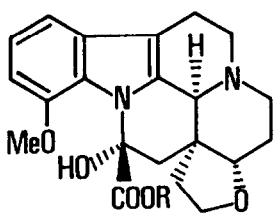
Abstract- An efficient synthesis of the cuanzine precursor 4d has been achieved beginning with 8-methoxy-dihydro-β-carboline 3b and utilizing as the key step the stereocontrolled alkylation of 16a (and/or 20a) followed by Hg(II)-induced heterocyclization.The structure and stereochemistry of 4d are thereby corroborated by chemical correlation with natural cuanzine 1a.

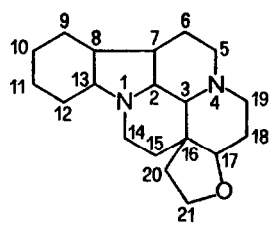
Cuanzine 1a [2] and decarbomethoxyapocuanzine 2 represent two hexacyclic indole alkaloids that first were isolated from Voacanga chalotiana (Apocynaceae), native to Angola, and whose structural assignments rest upon chemical transformations and spectroscopic analysis [3,4,5].

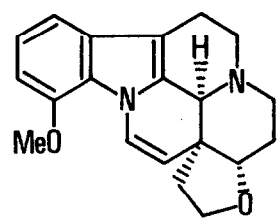
The most striking structural feature of the cuanzine alkaloids is the presence of the tetrahydrofuran ring angularly cis-fused to D-ring in the basic eburnane skeleton although this subunit is not unusual in biogenetically related Aspidosperma alkaloids.



1

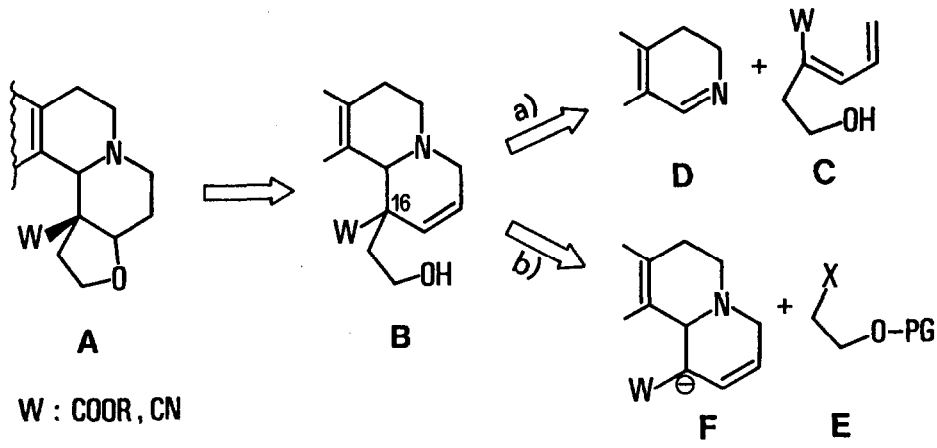
a) R: Me
b) R: H





2

The very promising vasodilating, antihypertensive and antiarrhythmic activity of 1a [6] led to initiation of synthetic studies and herein we report a detailed account of our investigation of A as an attractive precursor to 1a. The retro synthetic strategy relating the carbon skeleton of cuanzine to this intermediate is put forth in the Scheme below . Direct comparison of A with 1a shows several advantages: a) 19 of the 22 carbons necessary for the synthesis of 1a are present ; b) the relative stereochemistry at C-3, C-16 and C-17 is correct; c)the W group (CN,COOR) at C-16 will allow for the easy introduction of the E-ring at a later time ;d) stereochemical control of the C-14 would be likely afforded by the presence of the OMe group at C-12.



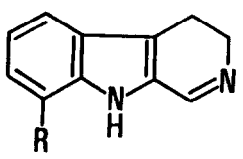
Encouraged by the ready accessibility of 3,4-dihydro-9H-pyrido[3,4-b]-indole 3a (dihydro- β-carboline) [7],we decided to test the viability of the first strategy for elaboration into 4a as a model study for construction of the cuanzine framework. Our initial approach involved the electrophile-initiated heterocyclisation [i.e., antarafacial attack of OH group on the (activated) π bond] of the tricyclic precursor 3a(⟶ 4a), clearly recognized as the product of an imino-Diels Alder cycloaddition between 3a and lactone 8a

Recently, the use of imino-Diels Alder reaction for the construction of alkaloids has received considerable attention due to the ability of this methodology to embody and control the stereochemistry of several stereogenic centers at one time [8]. Accordingly, the ability of C=N group to function as the 2π component in hetero-Diels Alder reaction is signaled by capture of both electron-deficient dienes (thermal) and electron-rich dienes (Lewis acid-catalyzed).Thus, reaction between 3a and the thermodynamically favoured (E)-lactone 8a woud be expected, in principle, to give 9a if reaction was to occur with exo-transition state.

Lactone 8a was prepared either from α-diphenylmethylsilyl-lactone 8b [9] by addition of the derived anion (LDA,THF,-78°C) to acrolein or by Wittig olefination of this compound with dihydro-3(triphenylphosphoranylidene) furan-2(3H)-one 8c [10] in refluxing benzene. On a large scale, the second procedure was more convenient and far superior (85% yield) leading predominantly (>10:1) to the desired (E)-geometry. When 3a was reacted with 8a in chlorobenzene at reflux and in the presence of bis-(3-tert-butyl-4-hydroxy- 5-methyl phenyl)-sulfide as a radical inhibitor, the spirolactone 10a was isolated in 53% yield. The 200-MHz proton NMR of 10a contained a ddd (J=10,4,2 Hz) at 5.98 ppm for H-19 and a dt (J=10,2 Hz) for H-18 whereas H-3 appeared as a broad s at 4.20 ppm. Although the spectral data were consistent with the required regiochemistry , the stereochemical assignment of the newly installed stereocenters C-3 and C-16 could not be achieved even by extensive decoupling experiments. In spite of considerable effort, we failed to obtain crystals of

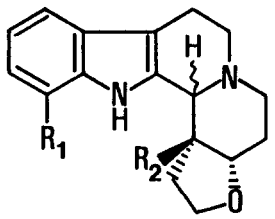
his compound amenable to X-ray crystallographic analysis.

Initial attempts directed at the construction of the tetrahydrofuran ring focused on a wo-step sequence of reduction-cyclisation of lactone 10a to 4a. Reduction of 10a as ccomplished by using $LiBH_4$ in THF at r.t. and afforded the diol 7b in 75% yield. One otable feature of the PMR spectrum of 7b was an AB system (J=11 Hz) at 3.70 ppm and 3.53 pm , characteristic of CH_2OH group proximal to the double bond. We were then faced with he problem of differentiating between the two OH groups of 7b , although electronic onsiderations and stereoelectronic constraints embodied in Baldwin's rules [11] for ring losure should favour formation of the five-membered ether (5-exo-trig) over alternate 4-, - and 6-endo modes [11]. In our case the double bond and the preexisting chiral center at -16 are in a ring so that the resulting tetrahydrofuran is generated with the required is-junction[12].



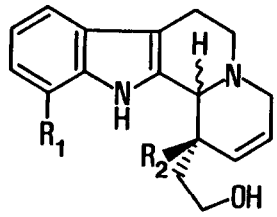
3

a) R : H
b) R : OMe



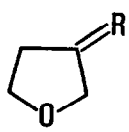
(**4**:3α-H ; **5**:3β-H)

a) R_1 : H ; R_2 : COOMe
b) R_1 : H ; R_2 : CH_2OH
c) R_1 : H ; R_2 : CH_2OAc
d) R_1 : OMe ; R_2 : CH_2OH



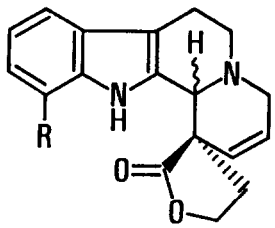
(**6**:3α-H ; **7**:3β-H)

a) R_1 : H ; R_2 : COOMe
b) R_1 : H ; R_2 : CH_2OH
c) R_1 : OMe ; R_2 : COOMe
d) R_1 : OMe ; R_2 : CH_2OH



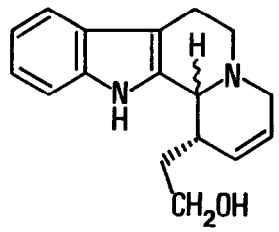
8

a) R : =CH-CH=CH_2
b) R : H, $SiPh_2Me$
c) R : PPh_3



(**9**:3α-H ; **10**:3β-H)

a) R : H
b) R : OMe



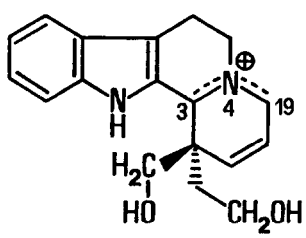
11

We initially chose to examine the chalcogenide-induced cyclisation of 7b through the agency of PhSeCl or PhSCl because the ensuing selenide or sulfide could be employed to advantage in subsequent steps. However, mild reaction conditions resulted in recovery of 7b, whereas more harsh conditions consumed the starting material but led to random electrophilic attack indole ring.

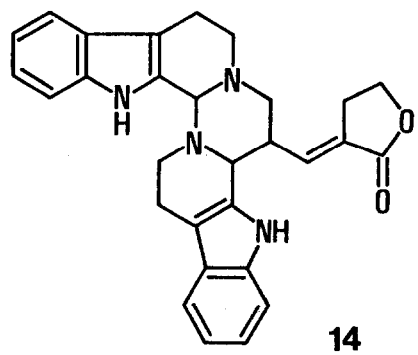
In 1980, Le Men and co-workers [13] reported that the related 17,18-didehydro- 14-epivincamine upon treatment with iodinating agent (followed by acidic workup) underwent a smooth heterocyclization to produce criocerine. We therefore considered the possibility of obtaining the required 4b in a similar fashion.In the event, treatment of 7b with iodine in the presence of KIO_3 in dioxane-water (12:1) at r.t. and subsequent hydrolytic treatment produced a mixture containing the starting material (35%) and the $\gamma\delta$-unsaturated alcohol 11 (42%)[m/z 268(M+.); 3.80(1H,dt, J=4.3,1.3 Hz;H-3)]. The formation of 11 could be initiated by a retro-Mannich reaction of the intermediate dieneiminium ion 12 (generated by one-electron oxidation) as has been previously observed by us in a related example [14]. The general result appeared to be that diol 7b reacted with electrophiles first exclusively at indole ring and/or bridgehead nitrogen atom and only afterward on the C(17)-C(18) double bond.

We therefore considered the cisoid dieneiminium ion 13 a potentially attractive precursor to 4b since the available evidence indicated that related systems undergo readily both intra- and intermolecular 1,4-addition with acceptable regiocontrol [15].The classical methods for accessing iminium ions (or their synthetic equivalents) appear to revolve around mercuric acetate oxidation of indoloquinolizidines [16], Mannich reaction [17], α-decarbonylation of amino acids [18] and direct treatment of N-oxides with suitable electrophiles (Polonovski-Potier-Husson reaction)[19].

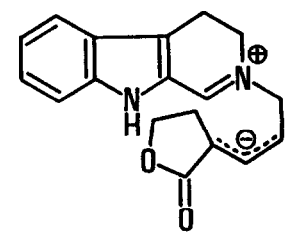
In order to arrive mildly at 13, recourse was made to the latter procedure. When 7b was allowed to react with 30% H_2O_2 in EtOH-$CHCl_3$ mixture (55 °C,48 h) the corresponding 7b-N-oxide [4.30 ppm(br s,H-3)] was obtained in 76% yield. Unfortunately, treatment of this compound with trifluoracetic anhydride in CH_2Cl_2 at 0 °C gave only unidentified products and all attempts in the presence of cyanide ions [15a,20] were likewise unsuccessful.



12: Δ^3
13: $\Delta^{4(19)}$



14



15

At this juncture, our attention became focused upon achieving dehydrogenation of 7b with $Hg(OAc)_2$. It is well-known that Hg(II) salt acts as oxidant towards tertiary amines through the intermediacy of an amino-mercuric complex which undergoes antiperiplanar elimination of AcOHg and an α-proton [21]. Our plan was based upon the expectation that the allylic H-19 would exhibit heightened acidity (vs H-3) [19b]. Thus, a solution of 7b was treated with a 5-fold excess of a 1:1 mixture of $Hg(OAc)_2$ and disodium edetate in deoxygenated $AcOH-H_2O$ (1:1) for 30 min at 80°C, followed by reductive work-up ($NaBH_4$ in 2M NaOH)[22]. Disappointingly, only a 37% yield of the requisite 5b and 25% of 11 were obtained, despite numerous variations of solvent, temperature, proportions of oxidant and demercuriation procedure.The EI-MS of 4b suggested that this was isomeric with diol 7b whereas its PMR showed the lack of the signals at 5.90-5.40 ppm (olefinic protons) but appeared exceedingly complex. Accordingly, in order to simplify the analysis, 5b was converted into a single monoacetate 5c but,to our dismay, it has been identified as having the 'wrong' trans,syn,cis-stereochemistry. Considering the presence of Bohlmann- Wenkert bands in IR spectrum it appeared reasonable that 5c possessed a C/D trans ring fusion and thence the lowfield singlet at 3.59 ppm belonged to H-3. The methine H-17 appeared at 4.22 ppm(dd,J=7.5,6.5 Hz) whereas the methylene protons at C-15(AB system, J=12.5 Hz).showed widely different chemical shifts (5.06 and 3.98 ppm) due to the location of one in the deshielding zone of the nearby indole ring. Irradiation of the H-3 signal resulted in enhancement of H-17(8%) in addition to enhancement (10%) of the H-5 signal. Additionally, a strong enhancement (21%) of the doublet at 5.06 ppm was obtained by irradiation of the NH signal (9.11 ppm) and only a 1,3-syn diaxial relationship between H-3 and H-17 in all chair- like conformation as in structure 5c can accomodate these n.O.e. results.

Thus, the imino-Diels Alder reaction of 3a with 8a proceeded with the exo-orientation to give, after synthetic manipulations, the 'uncorrect' configuration at C-3/C-16 .

In the hope that it would provide clues with regard to mechanistic subtleties, the major by-product 14, formed in a typical reaction of 3a with 8a, was isolated in 18% yield. On the basis of spectroscopic data, 14[m/z 464(M+.); 8.20 and 7.98 ppm(s,2 x NH),4.69(s, N-CH-N)] appeared to result from addition of a second molecule of 3a to 10a Thermal reversal of this reaction was indicated by the mass spectral behaviour of 14:the EI-MS obtained by direct insertion, gave fragments at m/z 295 and 294, corresponding to (10a+H)+ and (10a)+., as the highest significant ions. The transformation 10a ⟶ 14 might occur by easy reversible breakdown into the zwitterion 15 and its interception by the imine moiety of 3a to yield 14, a point verified by heating 10a alone with 3a at 120 C for 2 h and observing the formation of 14 (39% isolated yield). This result is not unprecedented since the participation of imines as the 2π component in [(2+2)+2] cycloadditions has been previously observed [23].

We could now turn our attention to the critical spirolactone forming reaction.Cyclo-addition of 3a with 8a seemed best formulated as a formal Diels Alder reaction, presumably occurring through a polarized transition state with dipolar character (e.g.,15) whose orientation depends upon the relative ability of the nitrogen atom of C=N moiety to add in

a terminal 1,6-sense to the activated butadiene 8a [24]. The exo-configuration at C-20 points to a six-centre TS with the carbomethoxy group in a pseudo-equatorial conformation.

Although 5b did not have the desired stereochemistry there was still the chance that C-3 could be inverted to give the 'correct' stereochemestry as in 4b. Attempts to perform this transformation by dehydrogenation [$Hg(OAc)_2$ or $Pb(OAc)_4$] followed by reduction with several reagents ($NaBH_4$,$LiAlH_4$,$NaBH_3CN$,Bu_3SnH) were unsuccessful.In each case, the overall reaction led to regeneration of 5b with complete retention of configuration at C-3.

These disappointing results can be attributed to stereoelectronic effects in which nucleophilic addition of hydride occurs to the most stable chair-like TS so as to maintain maximum orbital overlap between the incoming nucleophile and the developing lone electron pair orbital [25]. Moreover, all efforts to isomerize 5b to 4b directly in acid medium according to Gaskill and Joule proved unrewarding [26].

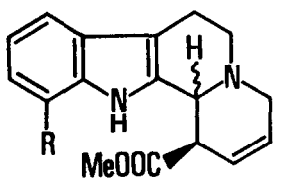
Our failure to assemble in a stereocontrolled manner both the D-ring and the quaternary center C-16 in a single step had eliminated one of the potential advantages of the route depicted in the Scheme.We envisaged that the anion F derived from the corresponding indoloquinolizidine , could coupled to a two-carbon fragment E which would eventually be used to elaborate the tetrahydrofuran E-ring by electrophile-induced heterocyclisation onto the double bond. (Scheme 1, route b)

In 1983 Y.Langlois and co-workers [27] extended the pioneering of Bohlmann on the thermal cycloaddition of simple imines with electron-poor dienes and cleverly adapted this methodology to the synthesis of some relevant indole alkaloids.

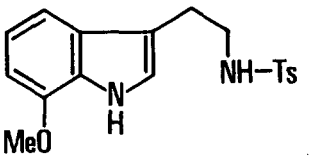
In the light of these specific results, it was expected that preparation of the tetracyclic intermediate 16a from 8-methoxy-dihydro-β-carboline 3b and methyl 2,4-pentadienoate, would provide a suitable precursor to 20a (or its synthetic equivalents). The imine 3b required in this approach was first prepared by adapting the method of Spath and Lederer [29] but , although quite direct, the yields of these reactions were fairly modest (<15%). In order to synthesize 3b by a better method, we prepared the protected tryptamine derivative 17 from 1-[(4-methyl-phenyl)sulfonyl]-2-methoxy-pyrrolidine 18[30] and 2-methoxyphenyl hydrazine [31] in refluxing AcOH. Conversion of 17 into 3b was achieved in satisfactory overall yield by intramolecular sulfonamidomethylation (1,3,5-trioxane,CH_2Cl_2, methanesulfonic acid) [32] followed by sequential deprotection (Red-Al®,THF,reflux)[33] of the resulting 19a(⟶ 19b) and chemoselective dehydrogenation with PhIO in CH_2Cl_2 at r.t.[34].

Good yields of the Diels Alder adduct were obtained when 3b and methyl pentadienoate were allowed to react in refluxing chlorobenzene for 6 h and this reaction was quite stereoselective , a nearly 1:1 mixture of the requisite 16a and its conjugated isomer 20a being obtained in 69 % yield.The key features in the PMR spectrum of 16a were the doublet (J=9.5 Hz) at 4.03 ppm for H-3 and the presence of two aliphatic methine carbons (48.6 and 56.7 ppm)in the DEPT CMR spectrum. In the PMR of 20a, the signal due to the bridgehead methine appeared as singlet at 5.08 ppm whereas only one olefinic proton signal was observed at 7.27 pm.

The conversion of 21 was carried out both on the mixture of 16a and 20a and on the separated isomers as well by the use of the method disclosed earlier by Y.Langlois [27]. Disappointingly, attempts to alkylate regioselectively the mixture of 16a/20a with 1-bromo-2(tetrahydropyran-2-yloxy)ethane in THF-HMPA at -78°C gave only low yields of the desired 21 owing to competing N-alkylation. However, slow addition of the bromide to a dark red suspension of the dipotassium dienolate (generated by KH in dry DMF at -25°C) effected cleanly the required alkylation to deliver the stereochemically homogeneous compound 21 (disregarding the anomeric center), whose deprotection furnished directly lactone 9b in 78 % overall yield. In the diastereoisomeric TS presented by the exocyclic dienolate, the geometric constraints imposed by stereoelectronic control elements appeared to be comparable. The steric bias imposed by the indole ring would direct the π-facial selection with alkylation at C-16 proceeding anti to the allylic substituent [35].The PMR (DMSO-d_6) confirmed the presence of two olefinic protons at 5.77 and 5.47 ppm (both broad doublets, J=10 Hz).and a singlet at 3.65 ppm for H-3. Operating under the assumption that



16
a) R : OMe
b) R : H



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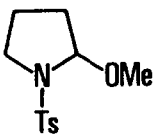

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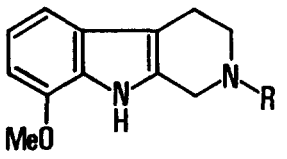
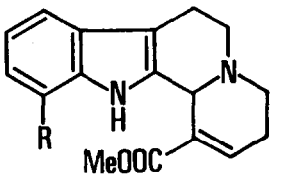
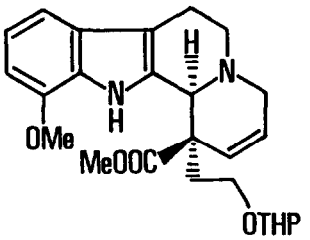


19
a) R : Ts
b) R : H



20
a) R : OMe
b) R : H



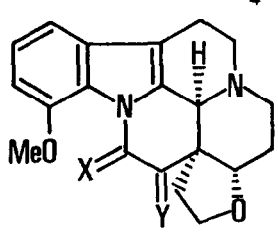
21

the correct stereoisomer had been produced,a point which we intended to check after carrying out the heterocyclisation reaction, 9b was reduced with $LiAlH_4$ in refluxing THF to provide diol 6d. In its PMR along with H-3 (3.87 ppm) and olefinic protons [5.90 ppm (dd,J=10,3.2 Hz;H-18) and 5.37 ppm(d,J=10 Hz,H-17)],the AB system (J=11 Hz) at 3.70 and 3.53 ppm for diastereotopic H-15 protons (vs 3.16 and 2.86 ppm in 11b) indicated the equatorial orientation of the homoallylic alcohol function in 6d. This compound was now elaborated under the conditions similar to those previously employed for preparation of 5b. Namely, diol 6d was treated with $Hg(OAc)_2$ in the presence of Na_2EDTA in THF-H_2O(1:1) at 80°C for 12 h, followed by in situ reduction with alkaline $NaBH_4$,to afford the target

compound 4d in 52 % overall yield. The formation of the five-membered oxacycle was indicated by NMR decoupling experiments since the two ddd due to the C-20 protons at 1.84 ppm (J=12,8.2,5.3 Hz) and 2.17 ppm (J=12,8.2,6 Hz) were coupled to two other protons whose chemical shifts(3.86 and 4.14 ppm) were indicative of the oxygenated carbon C-21. Furthermore, H-17 appeared as a broad t (J=2.3 Hz) at 3.91 ppm whilst C-15 methylene protons were easily recognised as an AB system (J=10.5 Hz) at 3.37 and 3.91 ppm. Furthermore, DEPT editing of the CMR spectra allowed identification of two aliphatic methines at 82.3 (C-17) and 63.9 ppm (C-3). This configurational assignment was inferred from the nuclear Overhauser measurements, where irradiation of H-17 (3.81 ppm)in the corresponding acetate resulted in a 8% increase of one of H-C(15).

For comparison purposes,a parallel sequence led from 3,4-dihydro-β-carboline 3a (via the known 16b and 20b)[27c] to the lactone 9a and then to the pentacyclic compound 4b in analogous fashion. Direct comparison by high-field proton NMR spectra of this compound and that obtained by the first approach (i.e. 4b) confirmed that these are different and that the 'right' diastereoisomer 4d had been generated.

Finally, to prove beyond any doubt the stereochemistry which has been drawn for 4d, a chemical correlation with natural cuanzine 1a has been performed through a reaction sequence that proceeded with maintenance of integrity of the three contiguous stereocenters in 1a. The initial transformation involved oxidative decarboxylation of cuanzinic acid 1b with Pb(IV) acetate in AcOH at r.t. to lactam 22a, followed by de-homologation with excision of C-14. Toward this end, 22a was subjected to nitrosation to 22b with t-BuONO in THF in the presence of t-BuOK [37] and chemoselective reduction (aq. $TiCl_3$ MeOH,r.t.)[38] at C-17 giving rise to 22c (41% overall). Subsequent exposure to $LiAlH_4$ in refluxing THF produced the carbinolamine 22a as a 7:3 diastereoisomeric mixture. Since we were unable to effect direct oxidative cleavage of the C(14)-C(15) bond in both 22c and 22d, we turned to a two-stage process involving reduction of the masked carbonyl function and oxidative fission as discrete steps. Thus, the mixture of 22a was reduced with KBH_4 in refluxing 1.7M KOH in MeOH [39] to the pentacyclic diol 23 which was immediately cleaved [$NaIO_4$, MeOH-H_2O(1:1),0 °C] to 24. Reduction of this aldehyde with



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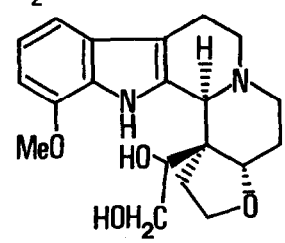
a) X:O ; Y:H_2
b) X:O ; Y:NOH
c) X:O ; Y:β-OH,α-H
d) X:OH ; Y:β-OH,α-H



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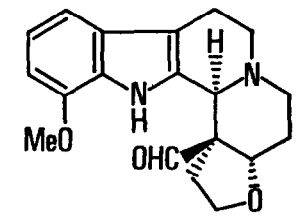

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$NaBH_4$ in i-PrOH at 0°C afforded the corresponding alcohol which was shown to be identical with 4d in a complete array of analytical procedures.

In conclusion, the alcohol 4d possesses most of the key structural features of the cuanzine ring system as well as displaying the correct stereochemical arrangement at several crucial points. Work is now underway to utilize this strategy in the total synthesis of (±)-cuanzine and related compounds.

EXPERIMENTAL PART

Melting points were recorded on a Buchi capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin Elmer 681 spectrophotometer and UV spectra on a Perkin Elmer 554 UV-vis spectrophotometer. PMR spectra were recorded on a Bruker WP-80 (80 MHz), Bruker ACE-250 (250 MHz) and Bruker CPX-300(300 MHz) instrument .CMR spectra were obtained on a Bruker ACE-250(62.86 MHz).Chemical shifts are expressed in ppm downfield from tetramethylsilane and coupling constants (J values) are given in Hz. EI-MS (70 eV), HR-MS (R=5000) and positive FAB-MS were recorded on a VG 70-70 EQ instrument. Compounds were detected on developed chromatograms by fluorescence quenching (254 or 365 nm) or visualised with cerium (IV) ammonium sulfate (CAS,1% in 85% H_3PO_4), R_f and colours(CAS spray on TLC of products are given)

Preparation of (E)-lactone 8a.- A mixture of freshly crystallized 8c (1.65 g,4.78 mmol) and acrolein (320 μl,4.78 mmol) in dry benzene (80 ml) was stirred at 60°C under nitrogen. After completion of the reaction (1.5 h) the mixture was cooled to r.t. and the resulting solid removed by filtration and the solvent evaporated in vacuo. The residue afforded the lactone 8a as a colourless thick oil after plug filtration (silica gel, 400 mesh, with CH_2Cl_2 as a solvent)(575 mg,97%);R_f ($CHCl_3$) 0.20; IR($CHCl_3$):1745 ; PMR(80MHz,$CDCl_3$): 6.43(1H,ddd,J=16.9, 11.3, 9.4;H-4);7.05(1H,dt,J=11.3,2.8;H-3);5.62(1H,d,J=9.4;H-5) ;4.40 (2H,t,J=6.6;H-2);2.96(2H,dt,J=6.6,2.8;H-1).

Thermal cycloaddition of 3a with lactone 8a.- A degassed(three freeze-thaw cycles in vacuo) solution of 3a(1.12 g,6.58 mmol) and lactone 8a(815 mg,6.58 mmol) in dry chlorobenzene (50 ml) in a silylated resealable Carius tube was heated at 160 C for 6 h in the presence of bis-(3- tert-butyl-4-hydroxy-5-methylphenyl)sulfide (15 mg). After cooling to r.t.,the tube was opened and the excess solvent was removed under reduced pressure. Ethyl acetate (200 ml) was added to the dark brown residue and the mixture was extracted with 0.1N HCl (3 x 50 ml). The combined aqueous layers were basified with 1N NaOH and extracted with dichloromethane (3 x 50 ml) The residue was chromatographed eluting with CH_2Cl_2-MeOH (97:3). Evaporation of the solvent provided 10a(1.02 g,53%) followed by 16(550 mg,18%). Data for 10a: R_f (CH_2Cl_2-MeOH,97:3) 0.41 (yellow) ; IR($CHCl_3$):3440,2800,2750,1750; PMR(250 MHz,$CDCl_3$): 7.78(1H,s,NH),7.60-7.00(4H,m,aromatic protons), 5.98(1H,ddd, J=10, 2 ; H-18),5.85 (1H,dt,J=10,2;H-17),4.20(1H,br s,H-3),4.30 & 4.08(2H,m, H-21),2.30-2.00 (2H, m,H-20), 3.51 (1H,ddd,J=17,4,2;H-19),3.26(1H,dt,J=17,2;H-19),3.11(1H,ddd, J=10,4.5, 1.5; H-5),2.68 (1H,dt,J=10,3.5;H-5),2.96(1H,dddd,J=15,10,4.5,2;H-6),2.75(1H, ddt, J=15, 3.5, 1.5, 1.5; H-6);EI-MS: m/z 294(M+.),171,170,169,115. Data for 14: R_f (CH_2Cl_2-MeOH, 93:3): 0.14 (yellow) ;IR($CHCl_3$):3450,2830,2780,1740; PMR(80 MHz,$CDCl_3$): 8.20(1H,s,NH),7.98 (1H,s, NH) ,6.90-7.05 (9H,m,aromatic protons),4.69 (1H,br s,H-3); EI-MS: m/z 464(M+.),462, 295, 294,293,185.

Reduction of lactone 10a to diol 7b.- A suspension of $LiBH_4$ (630 mg,30 mmol) in THF (50 ml) was added to a solution of spirolactone 10a (870 mg,2.96 mmol) in THF (50 ml). After 8 h the solution was evaporated and the residue taken up in H_2O (100 ml) and extracted with CH_2Cl_2(5 x 20 ml).The combined extracts were dried ,filtered and concentrated to give pure diol 7b (661 mg, 75%) as a colourless foam, pure in TLC [R_f (EtOAc/propan-2-ol/ammonia, 47:3:1) 0.17(violet)]; PMR(250 MHz,DMSO-d_6): 10.75(1H,br s,NH),7.30-6.80(4H,m,aromatic protons),5.80(1H,br s,OH),5.87 (1H,dd,J=10,3;H-17),5.45(1H,br d,J=10;H-18),3.70 & 3.53(2H, AB syst,J=11;diastereotopic H-15) ,EI-MS:m/z 298(M+.,27%),170(100),169(80).

Hg(II)-mediated heterocyclization of 7b to 5b.- To a solution of mercuric acetate (1.33 g, 4.20 mmol) and Na_2EDTA bihydrate (1.74 g,4.20 mmol) in degassed AcOH-H_2O(1:1)(50 ml) was added the diol 7b (250 mg,0.89 mmol) and resulting mixture was heated at 80 °C under nitrogen for 2 h. The mixture was cooled and basified (pH 9) with 20% NaOH solution and poured onto a solution of $NaBH_4$ (500 mg) in MeOH (10 ml). The precipitate of Hg was filtered off and washed with MeOH(20 ml). The combined filtrate and washings were concentrated and extracted with CH_2Cl_2 (3 x 50 ml). The combined organic extracts were dried, filtered and evaporated. Purification by PLC (AcOEt/propan-2-ol/ammonia,96:4:2) provided the alcohol 11 (52 mg,25%) and 5b(90 mg,36%). Data for 11: R_f 0.44(yellow); PMR(80 MHz,$CDCl_3$): 7.70(1H,br s,NH),5.87(2H,m,H-17 & H-18),3.80 (1H,br s,H-3);EI-MS:m/z 268(M+.,36%),171(13),170(100),169(13). Data for 5b: R_f 0.25 (yellow- green) ; EI-MS: m/z 298(M+.,80%) ,297(100),281(18),198(15),197(97),185(46),184(57) ,170(81) ,169(91) ,156(47) .Treatment of 5b (85 mg,0.28 mmol) with Ac_2O(150 μl) in pyridine (5 ml) at r.t. for 3 h afforded,after the usual work-up, the pure acetate 5c(92 mg,95%),R_f (CH_2Cl_2-MeOH, 49:1) 0.30(yellow);IR($CHCl_3$):3350,2840,2800,2740,1715; PMR(300 MHz,$CDCl_3$):9.11(1H,br s,NH), 7.55-7.00(4H,m,aromatic protons),5.06 & 3.98(2H,AB syst,J=12.5;diastereotopic H-15),3.59 (1H, br s,H-3),3.99 & 3.75(2H,m,diastereotopic H-21),2.17 & 1.28(2H,m,diastereotopic H-20); FAB-MS(glycerol as matrix):341(MH+,11%),339(20),185(100),149(10).

Synthesis of N-tosyl-7-methoxy-tryptamine 17.- A solution of 2-methoxyphenylhydrazine (7.5 g, 54.3 mmol) and 18 (13.8 g,54 mmol) in glacial AcOH (100 ml) was heated at 100°C for 5 h under nitrogen atmosphere. The solvent was evaporated to dryness and the residue was filtered on silica gel employing $CHCl_3$-MeOH(4:1) as eluent to give pure 17(1.83 g,74%) as a glassy colourless solid; PMR(80 MHz,$CDCl_3$;indole numbering):8.23(1H,br s,NH),7.70-7.10 (4H,AA'XX' system, aromatic protons),6.61(1H,dd,J=5.8,3.8;H-6),4.50(1H,br t,J=5;SO_2NH), 3.92(3H,s,OMe), 3.20(2H,q, J=6;H-2),2.86(2H,t,J=6;H-1),2.40(3H,s,Me-Ar).

Synthesis of N-tosyl-8-methoxy-1,2,3,4-tetrahydro-β-carboline 19a.- A solution of sulfonamide 17 (870 mg,1.90 mmol) and s-trioxane (65 mg) in 1,2-dichloroethane (50 ml) containing methanesulfonic acid (2 ml) was kept at r.t. with stirring and under exclusion of moisture. After 30 min, the mixture was cooled at 0 °C and diluted with $CHCl_3$(50 ml). The organic layer was washed with 5% $NaHCO_3$ solution (3 x 50 ml) and water (100 ml),dried and evaporated. The crude compound was purified by flash chromatography ($CHCl_3$-MeOH,4:1)to afford pure 19a (625 mg,70%) as a colourless solid, R_f ($CHCl_3$-MeOH-ammonia,40:10:1) 0.77 (yellow); PMR(80 MHz,$CDCl_3$):8.00(1H,br s,NH),7.80- 7.20(4H,m,tosyl aromatic),7.05-6.95 (2H,m,H-5 & H-6),6.60(1H,dd,J=6.5,5;H-7),4.35(2H,br s,H-1),3.90(3H,s,OMe),3.45(2H,t,J=6, H-3) ,2.80(2H,br t,H-4),2.38(3H,s, Me-Ar); EI-MS: m/z 470(M+., 100%) ,171(86).

Synthesis of 8-methoxy-1,2,3,4-tetrahydro-β-carboline 19b - A 3.4M solution of sodium bis-(2-methoxy- ethoxy)aluminum hydride in toluene (Red Al®)(3 ml) was added to a solution of 19a(2.1 g, 4.47 mmol) in dry THF (100 ml) and the mixture was heated at reflux for 5 h under nitrogen. After cooling, 1N aq NaOH (50 ml) was added with external cooling, whereupon two phases separated. From the upper layer, most of the tetrahydrofuran was removed by evaporation under reduced pressure. The lower layer was extracted with EtOAc (3 x 50 ml) and these extracts were combined with the residue from the upper layer. This mixture was washed with H_2O(3 x 50 ml), dried and evaporated to give a brown residue. Flash chromatography eluting with $CHCl_3$-MeOH-ammonia (40:10:1) afforded 19b (830 mg,92%) as a pale yellow solid; R_f 0.36(yellow); PMR (80 MHz,$CDCl_3$): 7.95 (1H,br s,NH),6.61(1H,dd, J=6.4, 2.2;H-7),4.00(2H,br t,J=1.6;H-1),3.92(3H,s,OMe),3.16(2H,br t,J=5.3;H-3),2.71(2H,br t,J=5.3;H-4),1.70[1H,br s,N(b)H].

Dehydrogenation of 19b to dihydro-β-carboline 3b. - 8-Methoxy-1,2,3,4-tetrahydro--carboline 19b (200 mg, 1.0 mmol) and PhIO (222 mg,1.0 mmol) were dissolved in dry CH_2Cl_2(40 ml) in a nitrogen-purged oven dried 50 ml-flask. The reaction was allowed to stir in the dark for 10 min at r.t. TLC analysis ($CHCl_3$-MeOH, 19:1) showed the complete disappearance of the starting material and the formation of a single more polar product. The reaction mixture was worked by diluting with dichloromethane (20 ml) and washing the organic phase with 0.1 M HCl (2 x 20 ml). The yellow aqueous layer was made basic (pH 8) with concd ammonia and two CH_2Cl_2 extractions (20 ml each) were carried out. The combined

extracts were washed with water,dried and the solvent removed in vacuo. The yellowish residue was then purified by flash chromatography eluting with $CHCl_3$-MeOH (19:1) providing 3b (1.582 g,80%) as a pale yellow foam;R_f ($CHCl_3$-MeOH-ammonia,40:10:1) 0.64(yellow); PMR (80 MHz,$CDCl_3$) : 9.00(1H,br s,NH),8.38(1H,t,J=1.8;H-1),6.70(1H,dd,J=9,3;H-7 ,3.91(2H,br t,J=6;H-3),3.90 (3H,s,OMe),2.88(2H,br t,J=6;NH); EI-MS: m/z 200(M+.,83%),199(100), 184(27), 173(10).

Thermal cycloaddition of 3b with methyl 2,4-pentadienoate.- A mixture of 3b(2.38 g,11.90 mmol) and methyl 2,4-pentadienoate (1.103 g, 14.28 mmol) was heated in dry chlorobenzene (70 ml) at 150°C for 6 h in a sealed Pyrex tube. Evaporation of the solvent yielded a dark residue which was chromatographed (CH_2Cl_2-MeOH,97:3) to give pure 16a (1.336 g,36%) and 20a (1.225 g,33%). Data for 16a: R_f 0.47(green-yellow); PMR(250 MHz,$CDCl_3$): 8.62(1H,br s, NH), 7.11(1H,br d,J=7.5;H-9), 7.02(1H,t,J=7.5;H-10),6.61(1H,dd,J=7.5,1.5;H-11), 5.97(1H, dddd J=10.3,5,2.5,1.8;H-18),5.82(1h,ddd,J=10.3,3.5,1.5;H-17),4.03(1H,br d,J=9.5 ;H-3),3.93 (3H, s,COOMe),3.88(3H,s,OMe),3.50(1H,m,H-5),3.21(1H,br d,J=16;H-19),3.14(1H,ddd, J=9.5, 3.5,1.8;H-6),2.99(1H,dddd,J=15.2,10,4.7,1.8;H-6),2.80-2.65 (2H,m,H-5 & H-6); CMR ($CDCl_3$):133.1(C-2),56.7(C-3),35.2(C-5),21.8(C-6),26.2(C-8),110.0(C-7),110.9(C-9), 119.6 (C-10),101.8(C-11),146.0(C-12),123.1(C-13),175.1(C-15),48.6(C-16),127.9(C-17),123.1 (C-18) 51.8(C-19),53.8 & 52.5(OMe);HR-MS: m/z 312.1477, calcd for $C_{18}H_{20}N_2O_3$ m/z 312.1474. Data for 20a: R_f :0.23(green yellow); PMR(250 MHz,$CDCl_3$): 8.80(1H,br s,NH),7.27(1H,br s,H-15), 7.12(1H,br d,J=7.3;H-9), 7.01(1H,t, J=7.3; H-10), 6.62(1H,br d,J=7.3;H-11), 5.08(1H,br s,H-3),3.94 & 3.92(2 s,2 x OMe),2.21 (1H,br d,J=17.5,4.5;H-18); CMR($CDCl_3$):132.3 (C-2), 55.1(C-3),51.2(C-5),17.1(C-6),106.9 (C-7),128.3(C-8) 110.8(C-9),119.5(C-10),101.6 (C-11), 146.0(C-12),125.6(C-13),168.3(C-14), 129.8(C-16),141.7(C-17),16.4(C-18),41.8(C-19),53.7 & 52.1(OMe).

Alkylation of 16a/20a to 21 - A flame-dried 100-ml three necked flask was equipped with a magnetic stirring bar, low-temperature thermometer, nitrogen inlet adaptor and rubber septum. The flask was flushed with nitrogen and charged with 1.716 g (14.7 mmol) of a 35% dispersion of KH in mineral oil.The potassium hydride was freed from oil by washing with three 30-ml of dry ether and withdrawing the supernatant solvent with a syringe, after which dry DMF (30 ml) was added. The mixture was stirred and cooled in a CCl_4-dry ice slush bath maintained at -25°C as the mixture of 16a/20a (1.53 g,4.90 mmol) in dry DMF (10 ml) was added. The resulting dark-red suspension was stirred for another 10 min after which 1-bromo-2(tetrahydropyran-2-yl-oxy)-ethane (1.04 g,5 mmol) in dry DMF(2 ml) was injected through the septum. The bath was removed and the mixture was stirred at r.t. for additional 30 min and then poured into saturated ammonium chloride solution (50 ml) and extracted with ether (3 x 20 ml). The combined ether layers were washed a with sat. $NaHCO_3$,dried and filtered. The solvent was evaporated and the residue chromatographed on silica gel (Et_2O-hexanes,3:1) to yield 21 (1.77 g,82%); R_f 0.18 (yellow); PMR(80 MHz, $CDCl_3$): 9.20(1H,br s,NH),7.02(1H,dd,J=7.2,1.8;H-9), 6.98(1H, J=7.2;H-10),6.26(1H,dt,J=7.2, 1.8;H-11),5.98(1H,ddd,J=11,4.8,2.4;H-18),5.30(1H,ddd,J=11.5,2.5;H-17),4.35(1H,m,O-CH-O),33 .96(3H,s,COOMe),3.20(3H,s,OMe): EI-MS: m/z 440(M+.,50%),355(45), 325(55),199(62),85(24).

Hydrolysis of the THP-derivative 21 to spirolactone 9b. - The ester 21 (440 mg,1.0 mmol) was dissolved in a 1:1 MeOH-H_2O mixture (50 ml) containing 2N HCl (5 ml) and stirred at r.t,.After 1 h, most of the solvent was evaporated and the residue made alkaline (pH 8) by addition of concd ammonoia. The mixture was extracted exhaustively with $CHCl_3$ (3 x 20 ml) and the combined organic layers were washed with brine,dried and filtered. Removal of solvent gave a colourless residue which was recrystallised from ether to afford 9b (308 mg,95%),m.p. 192°C; PMR(250 MHz,DMSO-d_6): 10.34(1H,br s,NH),6.92(1H,br d,J=7.5;H-9),6.84 (1H,t,J=7.5;H-10),6.57(1H,br d, J=7.5;H-11),5.87(1H,br d,J=10;H-18),5.57(1H,br d,J=10; H-17) ,4.19(2H,t ,J=7.5;H-21), 3.82(3H,s, COOMe), 3.75(1H,s,H-3);CMR (DMSO-d_6):131.6(C-2), 61.0(C-3),52.5(C-5),21.3(C-6),111.6(C-7),128.2(C-8),110.6(C-9),119.3(C-10),102.0(C-11), 146.0(C-12),126.5(C-13),175.4(C-15),48.1(C-16),127.3&127.7(C-17/C-18),49.5(C-19), 33.5 (C-20), 64.3(C-21),55.0(OMe); HR-MS:m/z 324.1472;calcd for $C_{18}H_{20}N_2O_3$: m/z 324.1477

Reduction of spirolactone 9b to diol 6d - A solution of 9b (650 mg,2.0 mmol) in dry THF (100 ml) was added dropwise to a suspension of $LiAlH_4$ (76 mg,2.0 mmol) in THF (5 ml) at 0° and the mixture was stirred under nitrogen for 2 h. Excess of $LiAlH_4$ was destroyed by careful addition of water at 0°C.The precipitated aluminum salts were dissolved in 6N NaOH

and the aqueous layer was decanted. The organic layer was diluted with EtOAc (50 ml) and thoroughly washed with H_2O . The organic extracts were dried and evaporated to give pure diol 6d (610 mg,93%) as an amorphous glass; R_f (CH_2Cl_2-MeOH,19:1) 0.26(green). PMR (250 MHz,DMSO-d_6):9.92(1H,br s,NH), 6.94(1H,br d,J=7.5,H-9),6.82(1H,t,J=7.5,H-10),6.52(1H,br d,J=7.5,H-11), 5.90(1H, dd,J=10, 3.2;H-18),5.55(1H,br s,C-15-OH),5.37(1H,dd,J=10;H-17), 5.34(1H,s,C-21-OH),3.87(1H,s,H-3),3.16 & 2.86(2H,AB syst,J=11,H-15),1.80(1H,ddd,J=16.5, 9.5,3.5;H-20),1.52(1H,ddd,J=16.5,5,1.5;H-20');CMR(DMSO-d_6):132.5(C-2),61.8(C-3),54.3(C-5), 21.7(C-6) ,110.9(C-7) ,128.0(C-8) ,110.5(C-9) ,119.3(C-10) ,101.7(C-11),154.6(C-12),126.0 (C-13) ,67.0(C-15),44.2(C-16),127.2(C-17),133.3(C-18),51.3(C-19),36.8(C-20),56.8(C-21).

Heterocyclization of 6d to 4d.- A solution of $Hg(OAc)_2$(845 mg,2.66 mmol) in distilled H_2O (50 ml) containing disodium edetate (990 mg,2.66 mmol) was added to a solution of 6d (175 mg,0.53 mmol) in THF (50 ml) and the mixture was heated at 90°C for 12 h while its colour changed from colourless to deep yellow. After cooling, the mixture was adjusted to pH 8 with 2N NaOH and $NaBH_4$ (100 mg) was added portionwise. The resulting black slurry was stirred at r.t. for 20 min. The precipitated was filtered off and the filtrate was concentrated. The residue was extracted with $CHCl_3$ (3 x 30 ml) and the extracts were washed with brine, dried and evaporated to leave a yellowish solid .Purification by flash chromatography ($CHCl_3$-MeOH,19:1) afforded pure 4d (97 mg,56%) as a nicely crystalline compound,m.p. 198°C(i-Pr_2O);R_f ($CHCl_3$-MeOH,19:1) 0.41(green); PMR (250 MHz,$CDCl_3$):7.86(1H, br s, NH),7.09(1H,dd,J=7.5,1.5;H-9) ,7.02(1H,t,J=7.5 ;H-10), 6.63 (1H,dd,J=7.5,1.5;H-11) ,4.14(1H,dt,J=9,5.3;H-21),3.93(3H,s,COOMe) ,3.91(1H ,t,J=2.3; H-17),3.86 (1H,dt,J=9,6; H-21'), 3.76(1H,m,H-3),3.37(1H,dd,J=10.5,1.5;H-15') ,2.17 (1H,ddd,J=12, 8.2,6;H-20) ,1.84 (1H,ddd,J=12,8.2,5.3;H-20'); CMR($CDCl_3$):130.9(C-2),63.9(C-3),53.8(C-5), 21.8(C-6),112.9 (C-7), 127.9 (C-8),111.0(C-9),120.1(C-10),102.2(C-11),145.6(C-12), 126.5(C-13),67.8 (C-15), 48.2 (C-16),82.3(C-17),27.8(C-18), 51.5(C-19),34.8(C-20),65.6(C-21),55.2(OMe); HR-MS: m/z 328.1784; calcd for $C_{19}H_{24}N_2O_3$, m/z 328.1787.

Oxidative decarboxylation of cuanzinic acid perchlorate 1b $HClO_4$ to 22a - A mixture of 1b.$HClO_4$ (560 mg,1.15 mmol)(obtained from alkaline hydrolysis of cuanzine and treatment with $HClO_4$) and Pb(IV) acetate (560 mg,1.26 mmol)in degassed AcOH (5 ml) was stirred at r.t. under nitrogen. After 2 h, H_2O(50 ml) and concd ammonia (5 ml) were added, and the mixture was extracted with CH_2Cl_2(2 x 50 ml). The organic extracts were evaporated and the yellow glassy residue of 22a (342 mg,88%) was used without further purification;R_f (benzene- EtOH-ammonia,89:10:1) 0.21(green-yellow);IR($CHCl_3$): 1720 ; UV(MeOH): 238 and 310 nm; PMR (80 MHz,$CDCl_3$):7.25(1H,t,J=7.7;H-10),7.01(1H,dd,J=7.7,1.5;H-9), 6.88(1H,dd,J=7.7, 1.5;H-11), 4.45(1H,br t,J=2.6;H-3),4.05(1H,dd, J=10.2,5.2;H-17),3.97(3H,s,OMe),3.59(1H,br t,J=8.5; H-21),3.05 & 2.67(2H, AB syst ,J=15.4;H-15).EI-MS : m/z 338 (M+.,100%), 337(65), 310(7), 282(11), 253(27), 236(11), 224(17), 210(50),195(7)

Oximation of 22a to 22b.- To a stirred suspension of lactam 22a (200 mg,0.592 mmol) in dry DMF (25 ml) in the presence of t-BuONO (0.5 ml,5.92 mmol) was added under nitrogen, t-BuOK (158 mg, 1.52 mmol) at 0°C. After being stirred 10 min the resulting mixture was quenched with saturated soln.and extracted with CH_2Cl_2(2 x 20 ml). The organic phase was washed with brine, dried and evaporated to give pure oxime 22b (124 mg,57%),R_f (benzene- EtOH-concd ammonia,89:10:1) 0.21(yellow);IR(KBr);3440,1725 ; PMR(80 MHz,$CDCl_3$):12.00(1H,s,OH), 7.42 (1H,t,J=7.7;H-10) ,7.10(1H,dd,J=7.7,1.7;H-11),4.57(1H,br s,H-3),3.98-3.82(1H,m,H-17), 3.92 (3H,s,OMe), 3.60(1H,br t,J=8.5;H-21); EI-MS : m/z 367(M+.,65%), 350(15), 337(20), 322(37), 265(100), 250(20), 235(23)

Ti(III)-reduction of 22b to hydroxylactam 22c - Titanium (III) chloride (15 wt % solution in 20 wt % HCl)(1.5 ml) was added dropwise to a suspension of oxime 22b (100 mg,0.272 mmol) in MeOH-H_2O(1:1)(20 ml) until the violet colour of the solution persisted. After 1 h the reaction mixture was diluted with H_2O (50 ml), made alkaline (pH 8) with 5% $NaHCO_3$ solution and extracted with dichloromethane (2 x 25 ml). The organic phase was washed with brine, dried and evaporated to give pure 22c (84 mg,87%) as an amorphous colourless solid; R_f (benzene-EtOH-ammonia,89:10:1) 0.17(green-yellow); PMR(80 MHz,$CDCl_3$):7.28 (1H,t, J=7.7; H-10),7.02 (1H,dd,J=7.5,1.5;H-9),6.89(1H,dd,J=7.7,1.5;H-11),4.57 & 3.63(2H,AB syst, J=6.8; H-15 & OH), 4.43(1H,br t,J=2;H-3),4.08(1H,dd,J=10.2,5.2;H-17),3.98 (3H,s,OMe),3.70 (1H,br t,J=7.7; H-21); EI-MS :m/z 354(M+.,100%),326(40),268(19),253(17), 239(16),198(15) .

Reduction of 22c to carbinolamine 22d - Hydroxylactam 22c (171 mg,0.483 mmol) was added with stirring to a refluxing suspension of $LiAlH_4$ (18 mg,0.483 mmol) in dry THF (50 ml). The mixture was refluxed for 1 h, cooled to r.t. and then quenched by successive addition of EtOAc(2 ml) and saturated Rochelle salt solution (20 ml). The mixture was further stirred at r.t. for 15 min and extracted with CH_2Cl_2 (3 x 20 ml). Work-up as usual gave the carbinolamine 22d(163 mg, 95%) as a 7:3 mixture of diastereomers; R_f(AcOEt-$NHEt_2$,19:1) 0.26 & 0.20(yellow); PMR(80 MHz,$CDCl_3$) for the major epimer (14β -OH):7.15-7.10(2H,m,H-10 & H-9),6.73(1H,dd,J=6.7,1.5;H-11),6.93 & 6.23(2H,AB syst,J=4.5,H-14 eq & H-15 ax), 4.74 (1H,br t, J=9;H-17),3.99(3H,s,OMe); PMR for the minor epimer (14α -OH):7.20-7.00 (2H,m,H-10 & H-9),6.67(1H,dd,J=6.7,1.5;H-11),5.70 & 3.84(AB syst,J=6.7;H-14 ax & H-15ax), 4.03(3H,s,OMe)

Reductive cleavage of 22d to 23 - The foregoing compound 22d (75 mg,0.21 mmol) was dissolved in 1.7M KOH in MeOH (10 ml) and treated with KBH_4 (11 mg,0.21 mmol) and the mixture was refluxed for 1.5 h under nitrogen. The solvent was evaporated to dryness, and the residue partitioned between H_2O (50 ml) and $CHCl_3$(50 ml). The organic layer was washed with brine, H_2O(50 ml) and evaporated to yield the diol 23(58 mg,77%) as a colourless foam, pure in TLC (AcOEt-$NHEt_2$,9:1) 0.21(blue); EI-MS: m/z 358(M+.,83%), 357(100), 327(38), 227(96), 215(60),200(78),186(26).

Oxidative cleavage of 23 to aldehyde 24 -To a solution of 23(180 mg,0.50 mmol) in MeOH-H_2O(1:1) (20 ml) was added $NaIO_4$(106 mg,0.50 mmol) and the initially clear solution was stirred at 0°C for 10 min, eventually producing a voluminous white precipitate. This suspension was saturated with NaCl and extracted with EtOAc (3 x 20 ml). The combined extracts were dried, filtered and concentrated to furnish pure 24 (143 mg,88%);R_f (AcOEt-$NHEt_2$,10:1) 0.67(yellow); PMR(200 MHz,$CDCl_3$):9.70(1H,s,CHO),7.73(1H,s,NH),7.9(1H,dd,J=7.5, 1.5;H-10),7.00(1H,t,J=7.5;H-10),6.62(1H,dd,J=7.5,1.5;H-11),4.20(1H,ddd,J=10,10,6;H-21), 4.00(1H,ddd,J=14,10,6;H-21'),3.92(3H,s,)Me),3.80(1H,br t,J=4;H-17),3.67(1H,br s,H-3),2.23 (1H,ddd,J=14,9,6;H-20),2.12(1H,dq,J=17,4; H-18),1.95(1H,dddd,J=17,12,6,4;H-18'); HR-MS:m/z 326.1632; calcd for $C_{19}H_{22}N_2O_3$: m/z 326.1630.

Reduction of aldehyde 24 to 4d - To a solution of 24 (18 mg,0.055 mmol) in i-PrOH(2 ml) was added $NaBH_4$(2 mg).The stirred solution was allowed to stand at 0°C for 30 min, diluted with H_2O(10 ml) and extracted with CH_2Cl_2 (2 x 5 ml). Work-up as usual afforded pure 4d (17 mg, 95%). The alcohol so produced was identical by MS,TLC and 200-MHz PMR spectroscopy with that obtained from heterocyclization of 6d.

REFERENCES AND NOTES

[1] This work was partially disclosed by G.P.at the 17th Convegno Nazionale di Chimica Organica(Divisione di Chimica Organica della S.C.I.) held at Fiuggi, Sept 13-17,1987

[2] The atoms of all structures presented have been numbered on the basis of the full cuanzine skeleton [(3α,14α,16α,17α)-17,21-epoxy- 14,15-dihydro-12-methoxy-eburnamenine 14-carboxylic acid methyl ester].

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