(ECO CHEMIE, Utrecht, The Netherlands). The measurements were performed at a stationary hanging mercury drop electrode (Metrohm, 663 VA). The electrode types and fillings were the same as used in polarography. The solvent and the supporting electrolyte were also the same as used in polarography. Oxygen was expelled by bubbling CH_3CN-saturated nitrogen (Hoekloos, very pure) through for at least 5 min.

Coulometry was carried out with a Metrohm coulostat E524 and a Metrohm integrator E525. The coulostat was operated with a constant potential (potentiostatic coulometry). The electrode types and fillings were the same as used in polarography. The solvent and the supporting electrolyte were also the same as used in polarography and cyclic voltammetry. A mercury pool was used as cathode, and it was separated from the platinum counter-electrode by a salt bridge. Oxygen was expelled by bubbling CH_3CN-saturated nitrogen (Hoekloos, very pure) through for at least 10 min.

Calculations. Molecular mechanics calculations were performed with CHARMm and the graphical QUANTA interface.[28] Force-field parameters were taken from CHARMm. With molecular mechanics the steric energy minima of the complexes and of isolated guest molecules were determined by variation of all the relevant degrees of freedom: position and orientation of the guest and rotatable bonds in the substituent to the Schiff base moiety of the host.

Acknowledgment. The 500-MHz ^1H NMR spectra were recorded at the Dutch National HF-NMR facility (Nijmegen, The Netherlands, supported by SON). We are indebted to J. M. Visser and J. M. L. Vrielink for recording the NMR spectra, to T. W. Stevens for recording the mass spectra, to A. M. Montanaro-Christenhusz for performing the elemental analyses and Karl-Fischer titrations, to W. Lengton for daily assistance with the polarographic experiments, and to A. Spijkerman for solving a part of the crystal structure.

Supplementary Material Available: Tables of positional and thermal parameters of all non-hydrogen atoms, bond distances and angles, and dihydral angles of the **10b**·4-*tert*-butylpyridine complex, ^1H NMR spectra of the compounds **1**, **6a**, **6b**, **6c**, and **9b**, and drawings of the calculated structures of the pyridine, 4-methylpyridine, and 4-*tert*-butylpyridine complexes of **2**, **10a**, **10b**, and **11** (23 pages). Ordering information is given on any current masthead page.

Hexacyclic Indole Alkaloids. A Highly Convergent Total Synthesis of Cuanzine

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Received June 14, 1990

A novel route to the hexacyclic indole alkaloid cuanzine **1** has been developed. Key synthetic steps include the cyclocondensation of the imine **8** with the dihydrofuran **10** followed by homogeneous-catalyzed hydrogenation, wherein the COOMe group at C(20) serves as a diastereocontrol element in establishing the C(15) stereogenicity. In order to define local energy minima, the conformational space of some intermediates has been explored by empirical force field calculations (MM2).

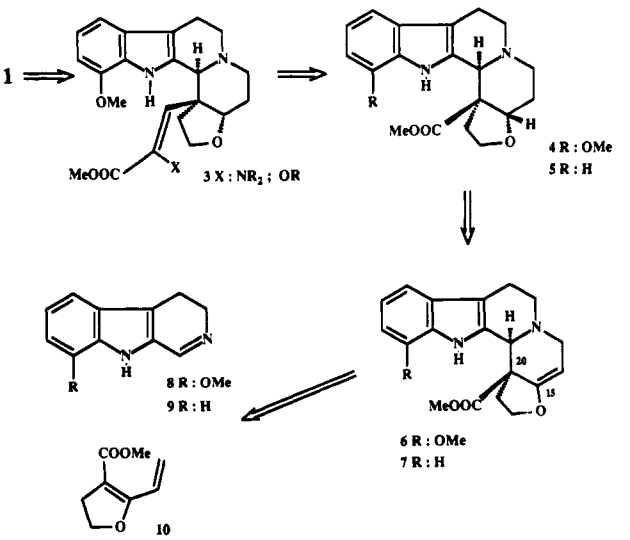
Cuanzine **1**, a representative hexacyclic indole alkaloid, was first isolated from the roots of *Voacanga chalotiana* (Apocynaceae) in the 1970s and intensively studied for its vasodilating, antihypertensive, and antiarrhythmic activities.[1] This compound belongs to a subgroup of eburnanes having an oxygen atom bridging C(15) to C(18) in a cis-fused D/F ring junction.[2]

Although the oxygenation at C(15) and/or C(18) in the conjectural biogenetic precursors does not occur in any of the eburnanes previously isolated, the occurrence of a tetrahydrofuran ring is very common amongst biogenetically related Aspidosperma alkaloids, viz. benenine, modestanine, hazuntine, vandrikine.[3]

Cuanzine was originally assigned the *R* configuration for C(16) of **2** on the basis of spectroscopic evidence. This assignment was later reversed to that of **1** by using MM2 empirical force field calculations, and this structure has been proven conclusively by single-crystal X-ray analysis of cuanzine hydrochloride.[4]

We recently reported a synthetic approach to the ABCDF pentacyclic framework of **1** that featured an intermolecular imino Diels–Alder reaction as pivotal step,[5] and in the meantime Langlois and co-workers have completed a conceptually similar entry to 12-demethoxycuanzine.[6] In this paper we describe an alternative approach which allows the stereoselective synthesis of **1** in a highly convergent manner and the essential elements of

Scheme I



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(1) (a) Bombardelli, E.; Bonati, A.; Gabetta, B.; Martinelli, E. M.; Mustich, G.; Danieli, B. *Tetrahedron* **1974**, *30*, 4141. (b) Bombardelli, E.; Bonati, A.; Danieli, B.; Gabetta, B.; Martinelli, E. M.; Mustich, B. *Experientia* **1974**, 979. (c) Inverni della Beffa S.p.A., Fr. Demande 2,303,544; *Chem. Abstr.* **1977**, *87*, 28999c.

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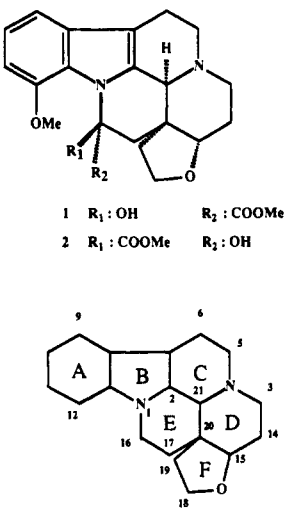
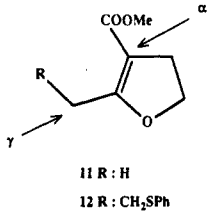


Figure 1. Ring numbering system of cuanzine skeleton.

our strategy are illustrated in a retrosynthetic format[7] (Scheme I).

Total Synthesis of Cuanzine

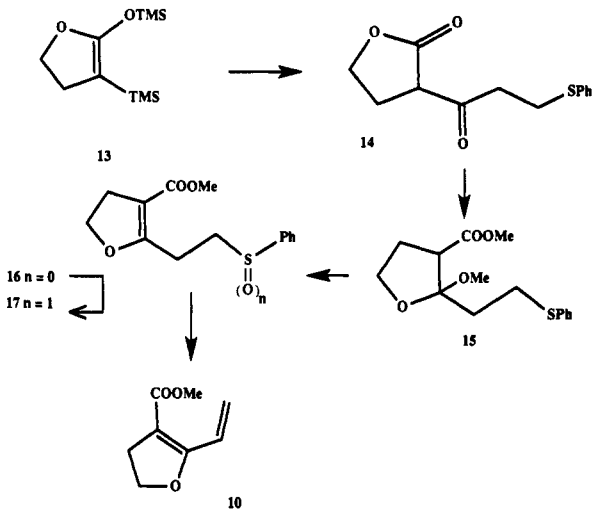
Smith and co-workers[8] reported that kinetic deprotonation of dihydrofuran **11** employing the LDA–HMPA complex followed by quenching with electrophiles led to a mixture of α- and γ-alkylated products, with the γ-adduct predominating 3:2 in each case. Unfortunately, all attempts to exploit this behavior for synthesis of **10**, through utilization of halomethylphenyl sulfide as electrophile (→**12**) followed by oxidative elimination, proved unsuccessful.



The greater facility with which ketones are known to undergo nucleophilic addition relative to ester carbonyls led to the prediction that the most efficient entry to **10** would involve the acid-catalyzed dehydration of an appropriately substituted 2-acylbutyrolactone **14** (acyllactone rearrangement).[9]

In Scheme II, the homoallylic sulfide system in **16** once again should be an excellent synthon for the exocyclic vinyl unit. Thus, the 2-position of butyrolactone was first acylated by 3-(phenylthio)propionyl chloride.[10] We explored several protocols for this transformation, including quenching of the lithio anion (generated by LDA or by LiICA[11]), or the bromozinc enolate (generated by 2-bromobutyrolactone and zinc–graphite[12]), or known 2-((trimethylsilyl)oxy)-3-(trimethylsilyl)-4,5-dihydrofuran (**13**).[13] The last procedure proved to be the best, affording **14** in 76% yield. The failure to effect the direct transformation of **14** to **16** with acids led us to examine a stepwise procedure. Conversion of **14** to the intermediate **15** as a probable mixture of diastereomers by treatment with MeOH in the presence of pyridinium *p*-toluenesulfonate (PPTS) and subsequent continuous removal of MeOH (camphorsulfonic acid, 4-Å molecular sieves, refluxing toluene) provided **16** in 74% overall yield. Unmasking of the vinyl moiety required chemoselective oxidation ($NaIO_4$, MeOH–H_2O) to **17** followed by thermolysis (refluxing cyclohexane in the presence of $CaCO_3$). The assigned structure **10** was entirely consistent with the spectral data, including the presence of three low-field mutually coupled protons (J = 17.6, 10.7, 2.1 Hz) at 5.51, 5.85, and 7.17 ppm due to the pendant vinyl unit.

Scheme II



The ability of a C=N group to act as the 2π component in a hetero-Diels–Alder reaction is signaled by capture of both electron-deficient dienes (thermal) and electron-rich dienes (Lewis acid catalyzed).[14]

However before investigating the intermolecular cycloaddition of **8** with **10** some experiments were conducted on a simpler heterodienophile. Thus, thermolysis of readily available **9**[15] in the presence of **10** in a variety of refluxing solvents (i.e., xylenes, chlorobenzene, mesitylene) provided no reactions or proved to be extremely sluggish leading to

(2) The numbering used within this paper is based on the biogenetic system used for indole alkaloids [Le Men, J.; Taylor, N. J. *Experientia* **1965**, *21*, 508] and is depicted in Figure 1. In order to facilitate comparisons between the compounds described herein, the same numbering system is retained in all formula embodying the indole ring although such a numbering does not follow Chemical Abstracts rules.

(3) For a review of the *Aspidosperma* alkaloids, see: Saxton, J. E. In *Heterocyclic Compounds. The Monoterpenoids Indole Alkaloids (The Aspidosperma Alkaloids)*; Saxton J. E., Ed.; Wiley: New York, 1983; Vol. 25, Part 4, pp 331–437. See also: Cordell, G. A. In *The Alkaloids (The Aspidosperma Alkaloids)*; Manske, R. H. F., Rodrigo, R. G., Eds.; Academic Press: New York, 1979; Vol. XVII, Chapter 4, pp 200–384.

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(9) This rearrangement has been reviewed by Korte and Buchel [Korte, F.; Buchel, K. M. *Angew. Chem.* **1959**, *71*, 709].

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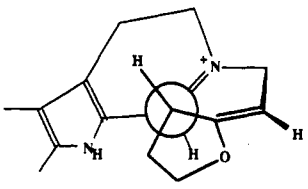
(15) MacLaren, J. A. *Aust. J. Chem.* **1987**, *40*, 1617.

a complex mixture of products. Even an attempt at promoting the above reaction through the use of Lewis acids (BF_3-Et_2O, TMSOTf, ZnI_2) went unrewarded. Fortunately, we discovered that heating (120 °C, sealed tube) of a degassed solution of **9** and **10** in *acetonitrile* in the presence of bis(3-*tert*-butyl-4-hydroxy-5-methylphenyl) sulfide as polymerization inhibitor for 6 h delivered the diastereomerically pure **7** in 64% isolated yield. This reaction was performed under relatively dilute conditions (~0.05 M) and stopped prior to consumption of **10** since prolonged heating generated products of cycloaddition of **10** with itself. Analysis of a 300-MHz ^1H NMR spectrum of **7** called attention to the fact that the COOMe group appears shielded (3.45 ppm). This, presumably, stems from adoption by **7** of a *trans*-quinolizidine $^4H_{21}$ conformation where diamagnetic shielding by the indole ring can operate only on the axially oriented COOMe group (see Molecular Mechanics Investigations).

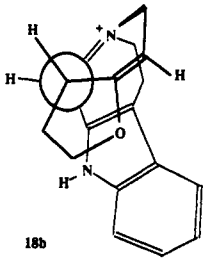
Additional spectral features lend further supports to this assignment: (a) the presence of strong Wenkert–Bohlmann bands (2730, 2800, and 2830 cm^{-1})[16] characteristic of an axial bridgehead hydrogen within a *trans*-quinolizidine; (b) H-21 resonates at 3.61 ppm (viz., upfield of 3.8 ppm) whereas chemical shifts downfield from 3.8 ppm reflect a *cis*-quinolizidine structure;[17] (c) a 1,3-syn relationship between H-21 and high-field H-19α was ascertained by analysis of NOEDS of **7**.[18]

The above results indicate that this reaction is strongly influenced by the polarity of reaction medium, suggesting a stepwise mechanism involving zwitterionic intermediate(s) (e.g., **18**) rather than a concerted [4 + 2] cycloaddition. The observed regiochemistry depends upon the relative ability of the nitrogen atom of C=N moiety to add in a 1,6-sense to the electron-deficient acceptor **10**.

At this point we were faced with a stereochemical question regarding the above cycloaddition. Two possible transition states **18a** and **18b** can be envisioned, but Dreiding models indicated that **18a** with the enol ether C=C bond "exo" should be favored over **18b**.



18a



18b

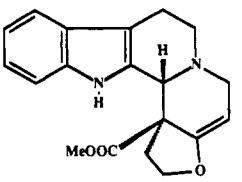
The MM2 force field finds the lowest energy conformation of the "right" isomer **7** to be 4.60 kcal/mol more stable than that of **19**. The singleness of the product formed in the above cyclocondensation could be explained either by the thermodynamic lability of **19** or by the energy differences in the transition states mirroring the energy differences of the ground-state conformations of **7** and **19**.

With **7** in hand, the next objective became the hydrogenation of enol double bond in a proximofacial manner, i.e. in a process occurring at the face of the molecule bearing the CO_2Me group as a reference group.[19]

Inspection of Dreiding models shows a very subtle difference between the two faces: the β-face (*Re,Re*) is partially hindered by the bulky CO_2Me group, whereas the opposite face possesses two axially disposed hydrogens (H-3β and H-2β). Moreover, the C(14)–C(15) double bond in **7** is highly pyramidalized toward the β-face of the molecule thereby favoring the proximofacial over distofacial attack.[20] All these factors can play conflicting roles in predicting the stereochemical outcome of hydrogenation of **7**.

Our initial efforts to effect hydrogenation of **7** under classical heterogeneous conditions (5% Pd/C, 5% Pd/$BaSO_4$, 10% Pt/C, 5% Rh/C) were on the whole disappointing.[21] In contrast to these results, the 1,2-syn relationship between CO_2Me and H–C(15) in the required **5** could be established by homogeneous hydrogenation of the enol double bond under guidance of CO_2Me group with iridium(I)-centered catalyst and recently published examples convincingly demonstrated a similar coordinative bias.[22] Thus, by hydrogenation (1 atm) of **7** in degassed CH_2Cl_2 at room temperature in the presence of 5% mol of $Ir(cod)py(PCy_3)PF_6$ (Crabtree's catalyst),[23] an extremely clean and rapid reaction (20 min) took place to give a single (>95% one diastereoisomer) ester **5** in 89% yield.

This compound exhibited characteristic signals in the ^1H NMR spectrum at 3.56 ppm for the bridgehead hydrogen H-21 (*trans*-quinolizidine) while the methine H-15 appeared as an apparent triplet ($J_{14\alpha,15} \sim J_{14\beta,15}$ = 3.0 Hz) at 4.01 ppm. A molecular mechanics model of the hypothetical isomer **20** indicates, according to the Haasnoot–Altona equation,[24] that $J_{14\beta,15}$ would be considerably larger than 3.0 Hz for this stereoisomer [11.5 Hz, H(14β)–H(15) dihedral angle ~−179°].



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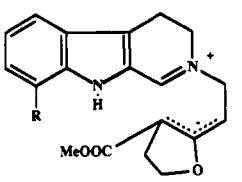

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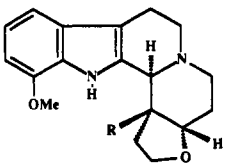
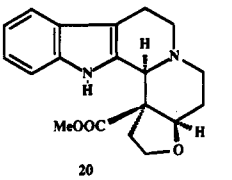


21 R: CHO

22 R: CH_2OH



20

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(18) By MM2 calculations the following nonbonding distances in the ground-state conformation of **7** and **19** were found: H-21/H-19α (2.44 Å) and H-21/-19β (3.44 Å) for **7**; H-21/H-19α (3.91 Å) and H-21/H-19β (3.86 Å) for **19**.

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(20) O(16) is bent down from the plane defined by C(14)–C(15)–C(20) by 7.0° and H(14) is similarly bent down from C(3)–C(14)–C(15) by 2.8°. This noncoplanarity would, in principle, cause the top faced in **7** to be more exposed to reactants. The preference for exo over endo addition in norbornene has been recently explained by a similar out-of-plane bending of vinylic hydrogen atoms (Ermer, O.; Bell, P.; Mason, S. A. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1239).

(21) The low or even moderate diastereofacial selectivity observed under heterogeneous hydrogenation of **7** accords perfectly with the faible haptofilicity of methoxycarbonyl group (see ref 19).

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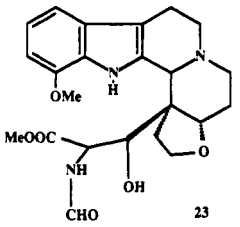
Table I. Relative Steric Energies (kcal/mol) and Selected Geometrical Features of Compounds 5, 17, 19, and 20

		C ring[a]			D ring[a]			F ring[a]		
	E	Q	ϕ_2	Θ	Q	ϕ_2	Θ	q_2	ϕ_2	τ (deg)[b]
$\mathbf{7A_t}$	0.00	0.49	319	128	0.53	318	52	0.37	338	+35
$\mathbf{7B_t}$	0.45	0.49	319	128	0.54	316	52	0.37	336	−150
$\mathbf{7C_t}$	1.48	0.49	320	129	0.53	315	52	0.29	354	−65
$\mathbf{7D_c}$	7.74	0.47	304	124	0.57	221	102	0.36	331	−121
$\mathbf{7E_c}$	6.90	0.47	307	125	0.55	218	105	0.36	335	+63
$\mathbf{7F_c}$	9.45	0.50	287	118	0.64	231	93	0.35	317	+4
$\mathbf{7G_c}$	5.70	0.45	160	48	0.45	301	54	0.37	338	−171
$\mathbf{7H_c}$	5.30	0.45	159	48	0.45	298	55	0.36	336	+5
$\mathbf{19A_t}$	4.60[c]	0.49	329	130	0.53	8	58	0.42	173	−48
$\mathbf{19B_t}$	5.46[c]	0.49	328	130	0.53	6	57	0.41	177	+122
$\mathbf{19C_c}$	8.35[c]	0.46	335	130	0.45	154	129	0.40	161	−42
$\mathbf{19D_c}$	9.18[c]	0.46	335	130	0.45	153	129	0.41	160	+144
$\mathbf{19E_c}$	6.08[c]	0.47	149	49	0.50	23	63	0.39	165	−42
$\mathbf{19F_c}$	6.86[c]	0.47	150	49	0.50	22	62	0.39	164	+139
$\mathbf{5A_t}$	0.00	0.49	337	131	0.53	33	11	0.40	222	+88
$\mathbf{5B_t}$	0.45	0.50	335	130	0.53	28	10	0.40	193	−125
$\mathbf{20A_t}$	2.03[d]	0.49	324	129	0.62	252	9	0.44	16	+155
$\mathbf{20B_t}$	2.99[d]	0.49	329	130	0.62	233	8	0.43	23	−48

[a] Ring puckering parameters (Q, ϕ, Θ) defined according to Cremer and Pople (Cremer, D. Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354). [b] Torsional angle C(15)–C(20)–C(17)–O(22). [c,d] Indicate the steric energy relative to the ground state of **7** and **5**, respectively.

Having successfully tested this approach in the above model, we proceeded to apply it to methoxy analogue **8**[5] and in a closely related sequence the required **4** was obtained via **6** in 44%. Although the overall yield is modest, this highly convergent approach assembles in only two steps the central core of cuanzine with the correct stereochemistry and requisite functionality. The structure of target molecule **1** includes four stereogenic centers. In reality, we need only concern ourselves with the three contiguous, viz. C(15), C(20), and C(21), because the presence of C(12)-OMe group serves an essential role in controlling the installation of the isolated stereocenter at C(16).[25]

Hence, the methoxycarbonyl group in **4** was reduced (DIBAH, −20 °C) to the corresponding alcohol **22**, and subsequent oxidation according to Parikh and Doering[26] gave **21** in 69% yield. At this juncture, we intended to exploit the previously developed Schollkopf methodology for construction of the E ring.[6,27] Aldehyde **21** was coupled with methyl isocyanoacetate (*t*-BuOK, THF, −70 °C → room temperature) to give the α-formamido-β-hydroxy ester **23**[28] (70%) which was subjected to the sequence:



23

dehydration (*N,N'*-carbonyldiimidazole, TEA, MeCN)[29] and, without purification, hydrolysis (MeOH–HCl, reflux); preparative TLC then afforded (±)-cuanzine **1** (31% overall yield from **22**). The synthetic sample matches authentic (−)-cuanzine isolated from *Voacanga chalotiana* in spectroscopic and TLC values.

Molecular Mechanics Investigations

First of all we employed the EEF calculations for the search of conformational space for the pentacyclic compounds **7**/**19** and the energy minimizations were performed by Allinger's MM2(85) program.[30] In these adducts the indole moiety is almost rigidly planar while the conformational flexibility due to D–E rings led to a multiplicity of possible conformations. In effect, the degrees of freedom for these systems are further increased by inversion at the bridgehead nitrogen atom and by rotation of COOMe group at C(20). The investigation of the conformational space for **7**/**19** was undertaken according to the following strategy. Consideration of Dreiding molecular models led to a starting geometry having the C and D rings in $^4H_5$ and $^4H_{21}$ conformations, respectively, and then subjected to overall minimization. The resulting optimized geometry $\mathbf{7A_t}$ (where the subscript t designates a trans-C/D fusion; 0 kcal/mol) showed about the chosen conformations for C and D rings, whereas the E ring assumed a $^{20}T_{19}$ form. Driving of any dihedral angle by MM-2 torsional driver in C, D, and E rings did not furnish any new minima, while driving of the atom tetrad C(15)–C(20)–C(17)–O(22) by 15° incremental changes allowed the determination of two other minima $\mathbf{7B_t}$ and $\mathbf{7C_t}$ with a steric energy of 0.45 and 1.48 kcal/mol, respectively, above the global minimum.

A similar procedure was applied to the conformations having a cis-C/D fusion. A starting *cis*-quinolizidine geometry was optimized and the resulting compounds $\mathbf{7D_c}$ (7.74 kcal/mol) can be described as E_5 for C, intermediate between $^{3,20}B$ and $^3T_{15}$ for D, and E_{19} for the E ring. The application of the dihedral driver option for full range scan of C(15)–C(20)–C(17)–O(22) angle allowed the determination of all other minima corresponding to the rotation of COOMe group, i.e. $\mathbf{7E_c}$ (6.90 kcal/mol) and $\mathbf{7F_c}$ (9.45 kcal/mol). Driving of C(2)–C(21)–N(4)–C(5) from the value of −30° observed in $\mathbf{7D_c}$ toward positive values (by 5° incremental changes) furnished conformation $\mathbf{7G_c}$ (5.70 kcal/mol) having $^5H_4$–E_4, E_{21}, and E_{19}–$^{20}T_{19}$ geometry for C–E rings, respectively. Usual driving of the C(15)–C-

(25) The energy difference between cuanzine **1** and 16-epicuanzine **2** was found to be 1.3 kcal/mol, favoring the "exclusive" formation of the desired carbinolamine **1** (see ref 4).

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(28) The unexpected formation of **23** instead of 2-oxazolidine-4-carboxylate can be attributed to its hydrolysis in weakly basic medium (cf.: Hoppe, D.; Schollkopf, U. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 432. Schollkopf, U. *Ibid.* **1970**, *10*, 763).

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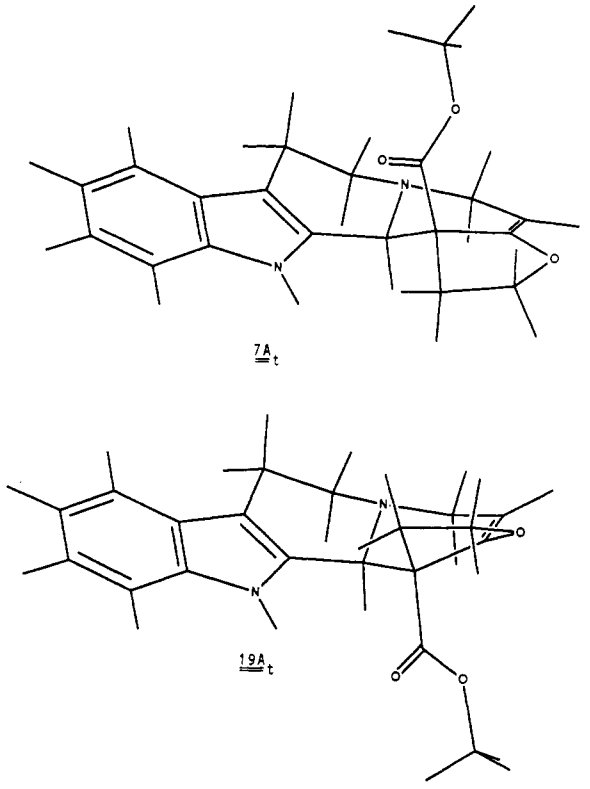

Figure 2. Representation of the MM2 calculated ground-state conformations $\mathbf{7A_t}$ and $\mathbf{19A_t}$ for compounds **7** and **19**, respectively.

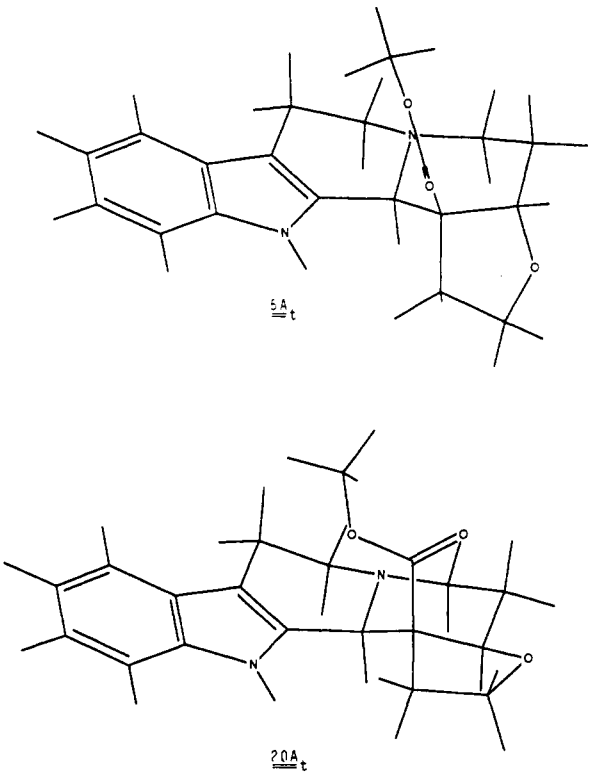

Figure 3. Representation of the MM2 calculated ground-state conformations $\mathbf{5A_t}$ and $\mathbf{20A_t}$ for compounds **5** and **20**, respectively.

(20)–C(17)–O(22) angle gave only conformer $\mathbf{7H_c}$ (5.30 kcal/mol).

These calculations allowed to conclude that the *trans*-quinolizidine C/D fusion is largely preferred for **7**, thereby implying that only conformations $\mathbf{7A_t}$–$\mathbf{7C_t}$ significantly contribute to the Boltzmann distribution of **7**: these conformations showed the same geometry for the pentacyclic framework while the O(22)Me group occupies positions above the D ring (in $\mathbf{7A_t}$), above the E ring (in $\mathbf{7C_t}$), or folded toward the indole moiety (in $\mathbf{7B_t}$).

The same overall strategy above illustrated for **7**, when applied to compound **19**, gave conformations **19A**–**19F** (Table I). The most populated conformations are $\mathbf{19A_t}$ and $\mathbf{19B_t}$ having C, D, and E rings in $^4H_5$, $^4H_3$–^4E, and $^{15}T_{20}$–E_{20} geometries, respectively, but a not negligible amount of *cis*-quinolizidines $\mathbf{19E_c}$ and $\mathbf{19F_c}$ could contribute to the overall population.

To map the conformational space of **5** and **20** we adopted a simplified strategy with respect to that used for the conformational analysis of **7** and **19**. Thus, two hydrogen atoms were added in two different ways ($\alpha\alpha$ and $\beta\beta$) to the enol double bond in the ground-state conformation $\mathbf{7A_t}$. The resulting two starting geometries were minimized yielding $\mathbf{20A_t}$ and $\mathbf{5A_t}$, respectively. A full-range scan of COOMe rotation allowed us to determine the other minima $\mathbf{20B_t}$ and $\mathbf{5B_t}$; the energies and the geometries of these conformations are reported in Table I. All the ^{1}H NMR vicinal coupling constants calculated from the corresponding dihedral angles of conformations $\mathbf{5A_t}$–$\mathbf{5B_t}$ are in close agreement with the experimental values of compound **5**.

Experimental Section

Melting points are uncorrected and were determined in open-ended capillaries. IR were obtained on a Perkin-Elmer 681 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WP-80 (80 MHz) and Bruker CXP-300 (300 MHz) in $CDCl_3$. Chemical shifts are expressed in part per million downfield from internal Me_4Si and coupling constants (J values) are expressed in hertz. EIMS and FAB$^+$-MS (glycerol as matrix) were recorded on a VG 70/70 EQ-HF instrument. TLC were performed on 0.25-mm thick layers of silica gel GF_{254} (Merck) on glass plates. Compounds were detected on developed chromatograms by fluorescence quenching with λ 254 or 365 nm and later visualized with cerium(IV) ammonium sulfate (CAS, 1% in 85% phosphoric acid) or alkaline potassium permanganate. R_f and color (spray on TLC) of products are given. Preparative-layer chromatography (PLC) was performed with silica gel G-60 (Merck) on glass plates (20 × 20 cm; thickness 1 mm) and activated at 120 °C for 30 min prior to use. Silica gel flash chromatography (FC) refers to the method of Still.[31]

Preparation of Acyl Lactone 14. Triethylamine (1.39 mL, 0.01 mol) dissolved in dry THF (5 mL) was added dropwise to a stirred mixture of 2-((trimethylsilyl)oxy)-3-(trimethylsilyl)-4,5-dihydrofuran (**13**)[13] (2.30 g, 0.01 mol) and 3-(phenylthio)-propionyl chloride[10] (2.00 g, 0.01 mol) in THF (25 mL) at 0 °C. The reaction mixture was stirred for 2 h at room temperature, and then the white solid was filtered off and thoroughly washed with EtOAc, and the organic phase was concentrated in vacuo. The resulting reddish oil was purified by FC ($CHCl_3$) to afford the lactone **14** (1.90 g, 76%) as an oil: IR 1720, 1675 cm^{-1}; ^{1}H NMR (80 MHz) 7.40–7.10 (5 H, m, aromatic protons), 4.30 (2 H, m), 3.60 (1 H, dd, J = 12.5, 9.5); EIMS m/z 250 ($M^{\cdot+}$, 44), 182 (30), 141 (52), 123 (100), 120 (83).

3-(Methoxycarbonyl)-2-(2-(phenylthio)ethyl)-4,5-dihydrofuran (16). To a solution of **14** (1.54 g, 6.16 mmol) in absolute methanol (50 mL) was added pyridinium *p*-toluenesulfonate[32] (500 mg) in small portions at room temperature. After the mixture was stirred overnight at room temperature the solvent was evaporated to give a residue which was extracted with ether. The extract was washed with saturated $NaHCO_3$, water, and brine and dried over $MgSO_4$. The product was chromatographed (hexanes–ether, 1:1) to afford the oily **15** (1.51 g, 83%) (probably as a diastereomeric mixture): R_f ($CHCl_3$) 0.43; IR 1740 cm^{-1}; ^{1}H NMR (80 MHz) 7.40–7.00 (5 H, m, aromatic protons), 3.90 (1 H,

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m, H-3), 3.57 (3 H, s, COOMe), 3.10 (3 H, s, OMe); EIMS m/z 296 ($M^{\bullet+}$, 13), 265 (21), 264 (18), 233 (63), 159 (75), 155 (100).

Lactol **15** (1.36 g, 4.59 mmol) and camphorsulfonic acid (100 mg) in dry toluene (50 mL) were placed in a flask fitted with a Dean–Stark trap containing 4-Å molecular sieves and heated to reflux for 6 h. The solution was diluted with ether, washed with saturated $NaHCO_3$, and worked up. The oily residue was chromatographed (hexanes–ether, 1:1) to afford the dihydrofuran **16** (1.08 g, 89%) as a colorless oil: R_f ($CHCl_3$) 0.53; IR 1690, 1640 cm^{-1}; ^1H NMR (80 MHz) 7.40–7.00 (5 H, m, aromatic protons), 4.30 (2 H, t, J = 9.6, H-5), 3.57 (3 H, s, COOMe), 2.90 (2 H, t, J = 9.6, H-4); EIMS m/z 264 ($M^{\bullet+}$, 20), 155 (66), 123 (100).

3-(Methoxycarbonyl)-2-vinyl-4,5-dihydrofuran (10). A solution of sodium metaperiodate (856 mg, 3.98 mmol) in water (20 mL) was added to a solution of thioether **16** (1.05 g, 3.98 mmol) in methanol (50 mL) at 0 °C within 10 min. After stirring at room temperature for 5 h, the reaction mixture was concentrated to one-forth of its original volume under reduced pressure and extracted with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$), and concentrated to afford an oil (1.03 g, 93%) that was homogeneous on TLC: R_f 0.13 (19:1 $CHCl_3$–AcOEt); ^1H NMR (80 MHz) 7.70–7.30 (5 H, m, aromatic protons), 4.30 (2 H, t, J = 9.6, H-5), 3.57 (3 H, s, COOMe), 2.90 (2 H, t, J = 9.6, H-4); FAB$^+$-MS m/z 281 (MH^+, 100). The sulfoxide **17** was used in the next step without further purification.

Calcium carbonate (343 mg, 3.43 mmol) was added to a solution of **17** (960 mg, 3.43 mmol) in cyclohexane (20 mL). The reaction mixture was heated at reflux under nitrogen and then cooled and filtered. The filtrate was concentrated in vacuo, and the residue was subjected to column chromatography. Elution with 1:1 hexane–ether gave the pure vinyl compound **10** (380 mg, 72%) as an oil: R_f 0.40 (19:1 $CHCl_3$–AcOEt); ^1H NMR (300 MHz) 7.17 (1 H, dd, J = 17.6, 10.7, H-1′), 5.85 (1 H, ddt, J = 17.6, 2.1, 0.8, H-2′), 5.51 (1 H, ddt, J = 10.7, 2.1, 0.8, H-2′), 4.45 (2 H, br t, J = 9.6, H-5), 3.60 (3 H, s, COOMe), 2.95 (2 H, br t, J = 9.6 H-4); EIMS m/z 154 ($M^{\bullet+}$, 45), 123 (34), 122 (25), 95 (25), 55 (100).

Cyclocondensation of β-Carboline 9 with 10 to 7. A dry Pyrex tube (3 × 20 cm) pretreated with hexamethyldisilazane was charged with **9**[15] (104 mg, 0.61 mmol), **10** (160 mg, 0.606 mmol), and dry MeCN (30 mL) in the presence of bis(3-*tert*-butyl-4-hydroxy-5-methylphenyl) sulfide (5 mg). The glass tube, cooled in an acetone–dry ice bath, was sealed under argon and then immersed in an oil bath maintained at 120–125 °C. After 6 h of heating, the tube was cooled and opened. The solvent was evaporated under reduced pressure. The syrupy residue was flash chromatographed, eluting with CH_2Cl_2–MeOH, 49:1, to afford **7** (125 mg, 64%) as colorless glass: R_f 0.20 (yellow); IR 3500, 2830, 2800, 2730, 1720 cm^{-1}; ^1H NMR (300 MHz) 7.77 (1 H, br s, NH), 7.45 (1 H, br d, J = 8, H-9), 7.31 (1 H, br dd, J = 8, 1, H-12), 7.10–7.02 (2 H, m, H-10 and H-11), 4.99 (1 H, t, J = 3, H-14), 4.27 (1 H, m, H-18α), 4.01 (1 H, m, H-18β), 3.61 (1 H, br s, H-21), 3.60 (1 H, dd, J = 16.5, 3, H-3β), 3.45 (3 H, s, COOMe), 3.14 (1 H, ddd, J = 11, 5, 1.5, H-5β), 3.09 (1 H, dd, J = 16.5, 3, H-3α), 2.84 (1 H, dddd, J = 15, 11, 5, 2, H-6β), 2.68 (1 H, ddt, J = 15, 4, 1.5, H-6α), 2.59 (1 H, dt, J = 11, 4, H-5α); FAB$^+$-MS m/z 325 (MH^+, 96), 324 (62), 323 (74), 170 (62), 123 (100).

Cyclocondensation of 8 with 10 to 6. The methoxy analogue **6** was prepared as described above but using 8-methoxy-β-carboline **8**.[5] The crude reaction mixture was purified by PLC ($CHCl_3$) to yield **6** (52%) as a colorless needles from diisopropyl ether–CH_2Cl_2: mp 184 °C; R_f ($CHCl_3$) 0.10 (yellow); IR 3500, 2830, 2800, 2725, 1720; ^1H NMR (300 MHz) 7.83 (1 H, br s, NH), 7.10 (1 H, dd, J = 7.5, 1.5, H-9), 7.00 (1 H, t, J = 7.5 H-10), 6.62 (1 H, dd, J = 7.5, 1.5, H-11), 5.00, 3.63, and 3.11 (ABX system, J = 15, 3, 3; H_2-14 and H-3), 4.30 (1 H, t, J = 9, H-18), 4.04 (1 H, ddd, J = 11.5, 9, 6, H-18), 3.94 (3 H, s, OMe), 3.62 (1 H, br s, H-21), 3.47 (3 H, s, COOMe), 3.15 (1 H, ddd, J = 11, 5, 1.5, H-5β), 2.83 (1 H, dd, J = 11.5, 6, H-19), 2.61 (1 H, dt, J = 11, 3, H-5α), 2.33 (1 H, dt, J = 11.5, 9, H-19); FAB$^+$-MS (thioglycerol) m/z 355 (MH^+ 36), 353 (35), 293 (22), 277 (100).

Homogeneous Hydrogenation of 7 to 5. In a 100-mL round-bottom flask was placed a solution of **7** (202 mg, 0.623 mmol) in calcium hydride–distilled dichloromethane (25 mL) to produce a 0.025 M solution. The flask was cooled at −78 °C, evacuated, and filled with dry nitrogen. After addition of solid [Ir(cod)PCy_3(py)]PF_6[33] (26 mg, 0.032 mmol) the system was evacuated, hydrogen was introduced, and stirring commenced immediately. After 20 min, the solvent was evaporated and the catalyst was removed by filtration through a short column of silica gel (1:1 chloroform–EtOAc). The eluate was evaporated and purified by PLC (9:1 Et_2O–diethylamine) to afford **5** (181 mg, 89%) as a colorless foam: R_f (24:1 Et_2O–DEA) 0.23 (yellow); IR 3550, 2840, 2825, 2770, 1730 cm^{-1}; ^1H NMR 7.86 (1 H, br s, NH), 7.44 (1 H, dd, J = 8, 1, H-9), 7.31 (1 H, dd, J = 8, 1, H-12), 7.13 (1 H, dt, J = 8, 1, H-11), 7.06 (1 H, dt, J = 8, 1, H-10), 4.01 (1 H, t, J = 3, H-15), 4.16 (1 H, m, H-18), 3.96 (1 H, m, H-18), 3.56 (1 H, br s, H-21), 3.17 (1 H, ddd, J = 11, 5, 1.5, H-5β), 2.98 (1 H, dddd, J = 15, 11, 5, 2, H-6β), 2.91 (1 H, m, H-19), 2.68 (1 H, ddt, J = 15, 4, 1.5, 1.5, H-6α), 2.60 (1 H, dt, J = 11, 4, H-5α); FAB$^+$-MS m/z 327 (MH^+, 72), 326 (34), 325 (100).

Homogeneous Hydrogenation of 6 to 4. The methoxy analogue **4** was prepared as described above but using **6**. After removal of catalyst the crude mixture was purified by FC (CH_2Cl_2–EtOAc, 1:1) to give the pure ester **4** (85%) as colorless glass: R_f (Et_2O–diethylamine, 24:1) 0.32 (yellow); IR 3480, 2850, 2820, 2770, 1725 cm^{-1}; ^1H NMR (300 MHz) 8.00 (1 H, br s, NH), 7.07 (1 H, dd, J = 7.5, 1.5, H-9), 7.03 (1 H, t, J = 7.5, H-10), 6.61 (1 H, dd, J = 7.5, 1.5, H-11), 4.16 (1 H, ddd, J = 8.5, 8.5, 6, H-18), 4.01 (1 H, br t, J = 3, H-15), 3.96 (1 H, ddd, J = 8.5, 8.5, 6, H-18), 3.95 (3 H, s, OMe), 3.56 (1 H, br s, H-21), 3.47 (3 H, s, COOMe), 3.16 (1 H, br dd, J = 10.5, 5.5, H-5), 2.92 (1 H, ddd, J = 13, 8.5, 6, H-19), 2.58 (1 H, ddd, J = 10.5, 10.5, 4, H-5), 2.57–2.47 (1 H, m, H-19); EIMS m/z 356 ($M^{\bullet+}$, 89), 355 (100), 227 (38), 214 (15), 200 (45).

Conversion of 4 into Aldehyde 21. To a solution of **4** (150 mg, 0.42 mmol) in anhydrous CH_2Cl_2 (15 mL) at −78 °C under nitrogen was added a 1 M solution of diisobutylaluminum hydride–hexane (1.5 mL) over a 10-min period. After 3 h at −78 °C, the mixture was warmed to −20 °C and stirred for an additional 2 h, at which point it was quenched with MeOH (2 mL). The solution was then allowed to warm to room temperature, washed with brine, dried ($MgSO_4$), and evaporated. The resulting crude solid was purified by flash chromatography eluting with $CHCl_3$–MeOH (19:1) to give **22** (119 mg, 86%) as a white solid: mp 198 °C (diisopropylether); R_f (19:1 $CHCl_3$–MeOH) 0.41 (green), identical by MS, TLC, and ^1H NMR with that previously reported.[5]

To a solution of the above alcohol **22** (150 mg, 0.457 mmol) in dry DMSO (3 mL) were added triethylamine (0.38 mL, 2.74 mmol) and a solution of sulfur trioxide–pyridine complex (218 mg, 1.37 mmol) in DMSO (2 mL). After being stirred for 40 h at room temperature, the mixture was added to CH_2Cl_2, basified with 10% $NaHCO_3$ solution and washed with water. The residue obtained after the usual workup was purified by PLC (20:1 AcOEt–DEA) to afford the aldehyde **21** (113 mg, 76%) as colorless foam: R_f (10:1 AcOEt–DEA) 0.67 (yellow), identical in all respects with that previously reported.[5]

Condensation of Aldehyde 21 with Methyl Isocyanoacetate to 23. Potassium enolate of methyl isocyanoacetate was prepared by the addition of freshly sublimed potassium *tert*-butoxide (103 mg, 0.920 mmol) to a solution of methyl isocyanoacetate (55 μL, 0.612 mmol) in dry THF (10 mL) at 10 °C. After 10 min at 10 °C the mixture was cooled to −70 °C and a solution of aldehyde **21** (100 mg, 0.306 mmol) in THF (5 mL) was added. After 10 min at −70 °C the mixture was warmed slowly to room temperature (1 h). The reaction mixture was quenched at 0 °C with 5% NH_4Cl solution, diluted with dichloromethane, and washed with brine. Evaporation of the dried organic phase gave a crude residue, which was purified by PLC (AcOEt) to give **23** (98 mg, 70%) as colorless solid: R_f 49:1, AcOEt–DEA) 0.16 (blue); IR 3380, 2845, 2820, 2775, 1730, 1665 cm^{-1}; ^1H NMR (300 MHz) 7.90 (1 H, br s, NH), 7.06 (1 H, t, J = 6, H-10), 6.70 (1 H, s, CHO), 6.66 (1 H, dd, J = 6, 2.5, H-11), 5.60 (1 H, br d, J = 8, NHCO), 4.37 (1 H, br d, J = 8, H-16), 4.18 (1 H, br s, H-17), 3.96 (1 H, br s, H-21), 3.94 (3 H, s, OMe), 3.86 (1 H, br t, J = 3, H-15), 3.63 (3 H, s, OMe); EIMS m/z 443 (M^+, 20), 425 (30), 366 (28), 327 (100), 297 (17), 227 (100).

Conversion of 23 into Cuanzine 1. *N,N′*-Carbonyldiimidazole (42 mg, 0.26 mmol) was added to a solution of **23** (60 mg, 0.13

(33) The catalyst was prepared by Dr. F. Porta (Dipartimento di Chimica Inorganica e Metallorganica, Milano) according to ref 22d.

mmol) and dry triethylamine (40 μL, 0.30 mmol) in dry THF (5 mL), and the mixture was stirred at room temperature for 15 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane. The solution was washed sequentially with water and brine, dried ($MgSO_4$), and concentrated. The residue was taken up in dry methanol–hydrochloric acid [prepared by addition of acetyl chloride (50 μL) in anhydrous MeOH (5 mL)] and was refluxed under nitrogen for 1 h. The reaction medium was diluted with chloroform, and washed with 1% $NaHCO_3$, water, and brine. Evaporation of the dried organic phase gave a yellowish residue which was purified by PLC (benzene–EtOH–concentrated ammonia, 40:10:1) to give 1 (54 mg, 58%) as a colorless amorphous powder, identical with natural cuanzine on comparison of spectroscopic ^1H NMR, UV, MS, and TLC data.

Registry No. (±)-1, 132015-34-0; (±)-4, 131905-75-4; (±)-5, 131905-76-5; (±)-6, 131905-77-6; (±)-7, 131905-78-7; 8, 122835-08-9; 9, 4894-26-2; 10, 131905-79-8; 13, 65946-60-3; (±)-14, 131905-81-2; (±)-*cis*-15, 131905-80-1; (±)-*trans*-15, 131905-82-3; 16, 131905-83-4; (±)-17, 131905-84-5; (±)-19, 132015-35-1; (±)-20, 131932-50-8; (±)-21, 125160-81-8; (±)-22, 125160-62-5; (±)-23, 131905-85-6; $ClCO(CH_2)_2SPh$, 51849-21-9; methyl isocyanoacetate, 39687-95-1.

Supplementary Material Available: NMR spectra for compounds 4–7, 10, 14, 16, 21, and 23 (9 pages). Ordering information is given on any current masthead page.

Regioselective Oxidation of Piperidine-3 Derivatives: A Synthetic Route to 2,5-Substituted Piperidines

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Received June 12, 1990

Mercuric acetate oxidation of 1-benzyl-3,3-(ethylenedioxy)piperidine (1) and of 3-CO_2Et- and 3-CH_2OH-substituted piperidines 7–9 was shown to occur regioselectively at the 6-position. Trapping of the resulting 6-iminium ions with cyanide yielded the corresponding 5-substituted 2-piperidinecarbonitriles 5, 10, and 11. However, the 2-iminium ion was formed in the reaction of the *N*-oxide of 1 with trifluoroacetic anydride; with cyanide this afforded the regioisomeric 3,3-(ethylenedioxy)-2-piperidinecarbonitrile (2). Plausible mechanisms are advanced to explain this contrasting behavior. 1-Benzyl-5,5-(ethylenedioxy)-2-piperidinecarbonitrile (5) was transformed into other piperidine-2,5 derivatives by reaction of the α-amino nitrile anion with electrophoresis, followed by reductive decyanation.

The piperidine ring forms an integral feature of many alkaloid structures. Efforts in drug synthesis have been directed at simplifying the complex substitution pattern of piperidine rings in morphine (1,2,3,4-substituted), reserpine (1,2,4,5-substituted), and LSD (1,2,3,5-substituted). These efforts eventually resulted in the preparation of many highly efficient drugs characterized by nonchiral 1,4-substituted piperidine and piperazine structures.[1] The selectivity required in binding to the asymmetric receptor site calls for chiral and flexible guest molecules. Therefore, we became interested in the synthesis of 2,5-substituted piperidines, which share a regioisomeric substitution pattern but not the conformational rigidity with the polycyclic alkaloids. Flexibility in fitting the receptor site is a property common to both 1,4- and 2,5-substituted piperidines. General methods for the synthesis of the latter compounds are not available.[2] In this context we investigated a route consisting of selective oxidation at the 6-position of 3-substituted piperidines and trapping of the resulting iminium ions with cyanide.[3]

The ethylenedioxy-protected derivative 1 of 1-benzyl-3-piperidinone was chosen as the first substrate since the electronic and steric effects of the acetal group were expected to direct the course of oxidation in a regioselective way. However, transformation of 1 to the *N*-oxide, trifluoroacetylation, and trapping of the resulting iminium ion with cyanide exclusively yielded (70%) the 2,3-functionalized piperidine 2. This structure assignment is based on a singlet absorption at 3.52 ppm for H-2 in the ^1H NMR spectrum and a doublet absorption for the CN group in the ^1H-coupled ^{13}C spectrum (Table I). Probably, regioselectivity is governed by the higher acidity of protons H-2 versus H-6. In the analogous reactions of 3-alkyl-substituted piperidines [R = Et, $CH_2CH_2CO_2Me$, $CH(OCH_2CH_2O)$, etc.], invariably mixtures of the 2- and 6-regioisomers were obtained.[4] An E_2 type mechanism (vis.3) is generally accepted[5] for this Polonovski-Potier reaction.[6] Our result would imply the development, at an early stage of the reaction, of a partial negative charge on the C-2 atom stabilized both by the positively charged N-atom and the inductive effect of the acetal O-atoms.

Mercuric acetate oxidation of 1,3-dialkylpiperidines in aqueous acetic acid was reported to give nonregioselective oxidation at both the 2- and 6-position.[7] Upon alkaline extraction, the resulting 2-iminium products were converted to the 3-substituted enamines, whereas the 6-iminium products reacted to form the (enamine + iminium) dimers. This dimerization problem could be avoided by further oxidation to the lactam using a mercuric ace-

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0022-3263/91/1956-2386$02.50/0