Meisenheimer Rearrangement of Azetopyridoindoles. III.[1] Synthesis of 3,6-Epoxyhexahydroazocino[5,4-*b*]indoles

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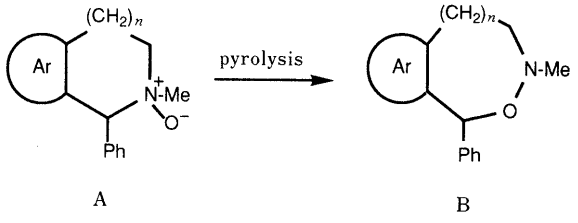
Oxidation of 2-ethylhexahydroazeto[1′,2′:1,2]pyrido[3,4-*b*]indole-1-carboxylate 9 with *m*-chloroperbenzoic acid in methylene dichloride at −5 °C gave the corresponding *cis*-N-oxide 10, which was spontaneously transformed in tetrahydrofuran to the 3,6-epoxy-1,2,3,4,5,6-hexahydroazocino[5,4-*b*]indole 11 (75%) *via* the [1,2]-Meisenheimer rearrangement, along with a formation of the isoxazolidinone 12 (6.4%) through Cope elimination. The structural assignment of azocinoindole 11 was accomplished, mainly based on the ^{1}H-NMR spectrum and also by chemical transformation of 11 to the azocinoindole 14.

Keywords Meisenheimer rearrangement; azetopyridoindole: epoxyazocinoindole; isoxazolidinone; azocinoindole; Cope elimination

The Meisenheimer rearrangement of nitrogen heterocycle N-oxides (A: $n=2$, 3, 4) has been extensively investigated for the preparation of 2,3-benzoxazepine,[3] 2,3-benzoxazocine,[4] and 2,3-benzoxazonine[4] derivatives (B: $n=2$, 3, 4). This thermal rearrangement, in the molten state and in solution, has been efficiently used to prepare various indolo-, thieno-, and benzothienoxazepines (B: $n=2$).[5] It was also reported that no such ring enlargement occurred on heating the N-oxides of fused bicyclic systems, such as benzo-quinolizines and benzo-indolizines.[5]

Previously, we reported[1b] that oxidation of 1,2-*cis*-1,2,4,5,10,10b-hexahydro-2-vinylazeto[1′,2′:1,2]pyrido-[3,4-*b*]indole-1-carboxylate **1** with *m*-chloroperbenzoic acid (MCPBA) in methylene dichloride (CH_2Cl_2) gave hexahydro[1′,2′]oxazepino[2′,3′:1,2]pyrido[3,4-*b*]indole-1-carboxylate **4**, which has a 12-carbaeudistomin skeleton,[6] in 81% yield *via* the [2,3]-Meisenheimer rearrangement of the corresponding *cis*-N-oxide **3**. On the other hand, peracid oxidation of the corresponding 1,2-*trans* derivative **2** gave the hexahydroisoxazolo[2′,3′:1,2]pyrido[3,4-*b*]indole **6** in 45% yield *via* the [1,2]-Meisenheimer rearrangement of the corresponding *cis*-N-oxide **5**. This paper presents a facile synthesis of 3,6-epoxyhexahydroazocino[5,4-*b*]indoles **11** and **18** by the Meisenheimer rearrangment of the 2-ethylazetopyridoindoles **9** and **16**, which were prepared from tetrahydro-β-carbolineacetate **7**.[1a]



A B

Chart 1

Aldol condensation of the ester **7** with propionaldehyde in the presence of lithium diisopropylamide (LDA) at −78 °C gave the alcohol **8**, as a mixture of diastereomers. This product was subjected to the same sequences (see Chart 3) as described for the preparation of the azetidine **1**.[7] The crude oil finally obtained was purified by silica gel (SiO_2) column chromatography to give the 2-ethylazeto-pyridoindole **9** (63% overall yield from **7**), as a single isomer, which was also alternatively obtained by catalytic hydrogenation (5% Pd–$BaSO_4$) of the azetidine **1** in 56% yield. The ^{1}H-NMR spectral data ($J_{1,2}=7.5$ Hz and $J_{1,10b}=2.0$ Hz) of **9** clearly showed that hydrogens on the

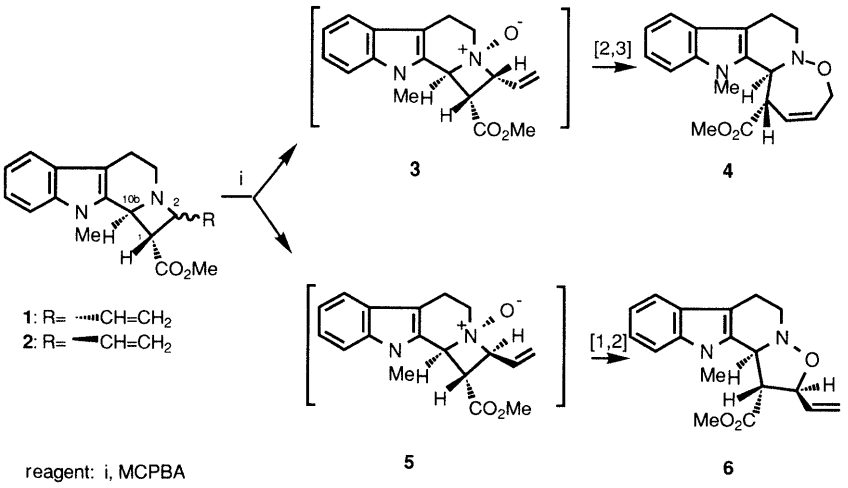
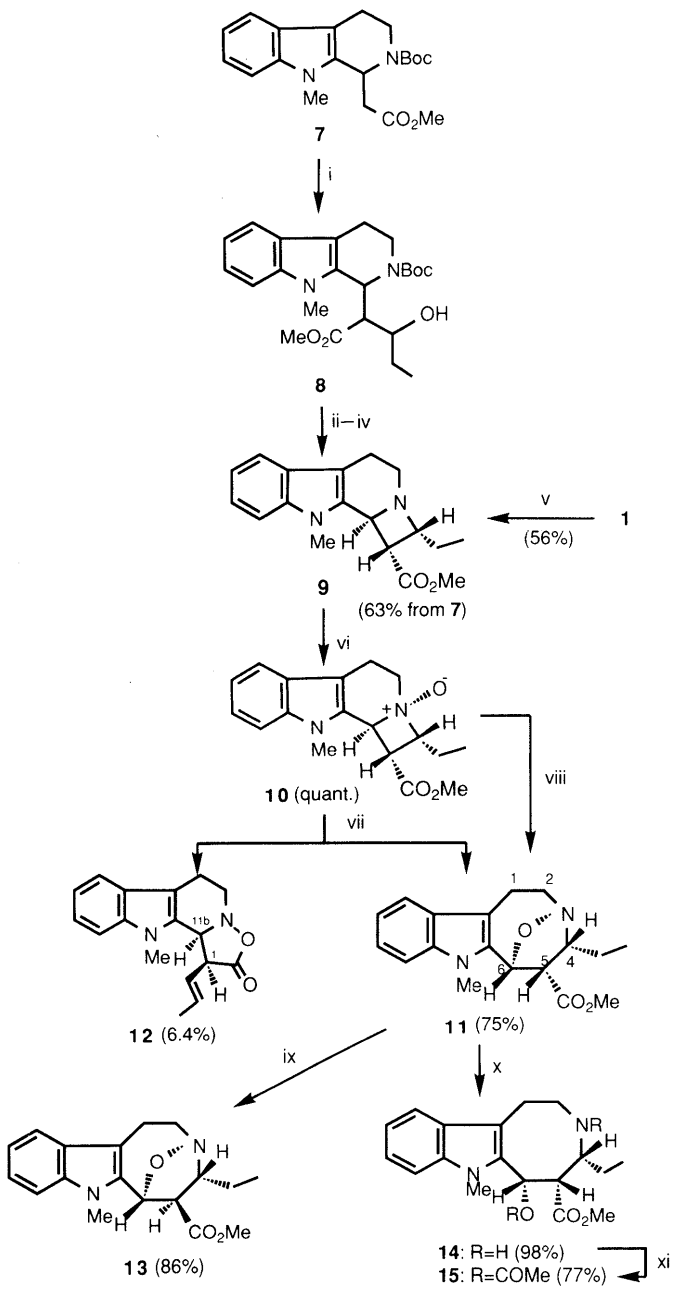


Chart 2



reagents:

i, $MeCH_2CHO$/LDA; ii, MsCl/Et_3N; iii, HCl/EtOAc; iv, DBU/DMSO/r.t.; v, 5% Pd-$BaSO_4$ / H_2; vi, MCPBA; vii, THF, r.t.; viii, 90% MeOH/reflux; ix, NaOMe in MeOH/reflux; x, 10% Pd-C/H_2; xi, Ac_2O

Chart 3

azetidine ring adopted a 1,2-*cis* and 1,10b-*trans* relationship, based on the general rule developed for azeto[2,1-*a*]-isoquinolines,[8] in which the vicinal coupling constants $^3J_{(H,H)}$*cis* (7–8 Hz) are larger than $^3J_{(H,H)}$*trans* (2–3 Hz).

Oxidation of the azetidine **9** with MCPBA (1.2 eq) in CH_2Cl_2 at −5 °C followed by prompt work-up at lower temperature than 20 °C afforded the N-oxide **10**,[9] which is thermally labile, in quantitative yield. The ^{1}H-NMR spectrum suggested it to be a single diastereomer and also showed a significant downfield shift of the signals of the methylene protons [δ 1.87, 2.60 (each 1H, each m)] of the ethyl group, from the position [δ 1.63 (2H, m)] in the spectrum of the amine **9**. This indicates that **10** is the *cis* N-oxide, in which the $C\underline{H}_2CH_3$ hydrogens are in close proximity to the N-oxide moiety. When the isolated N-oxide **10** was allowed to stand in CH_2Cl_2 at 25 °C, the reaction proceeded very slowly but exclusively to give the [1,2]-Meisenheimer rearrangement product **11** in 65% yield. On the other hand, in THF at room temperature, the reaction went to completion within 1 h to give **11** (75% yield), along with a small amount of *trans*-propenyl-substituted isoxazolidinone **12** (6.4% yield). The MS of **11** showed the same molecular formula ($C_{18}H_{22}N_2O_3$) as that of the N-oxide **10**. Its ^{1}H-NMR spectrum showed characteristic downfield shifts of the signal of 6-H at δ 5.84 (d, J = 4.0 Hz) and the signal of 5-H at δ 3.86 (dd, J = 9.0, 4.0 Hz). The latter signal was collapsed to a doublet (J = 9.0 Hz) by irradiation of the former signal. The assignments of 4-C, 5-C, and 6-C were accomplished by ^{1}H–^{13}C shift-correlated 2-D NMR spectroscopy. On the basis of these results, the structure of **11** was supposed to be a 3,6-epoxy-1,2,3,4,5,6-hexahydroazocino[5,4-*b*]indole derivative, having a new ring system.

Although the stereochemistry of the epoxyazocinoindole **11** could not be resolved clearly by measurements of the nuclear Overhauser effects (NOE), the dihedral angles estimated by an inspection of the Dreiding model for 4-H and 5-H (ϕ = 0—5°) and 5-H and 6-H (ϕ = 110—120°) were well consistent with the observed J values. In order to obtain definitive evidence for the stereochemistry of **11**, a solution of **11** in MeOH in the presence of NaOMe (2 eq) was refluxed for 10 min to afford an epimer **13** in 86% yield, with recovery of the starting material **11** in 12% yield. In the ^{1}H-NMR spectrum of **13**, the coupling constant ($J_{5,6}$) of H-6 had a value (8.0 Hz) exceeding that (4.0 Hz) for the corresponding protons of its isomer **11**. The value (J = 8.0 Hz) is also well consistent with that estimated by an inspection of the Dreiding model for 5-H and 6-H (ϕ = 10—20°). Thus, it can be concluded that the protons at C-5 and C-6 are located *cis* in **11** and *trans* in **13**.

Structural elucidation of the isoxazolidinone **12** [MS *m/z*: 282 (M^+)] was performed mainly on the basis of spectral data. The IR spectrum showed a carbonyl absorption[10] band at 1765 cm^{-1} and the ^{1}H-NMR spectrum lacked signals of methoxy methyl protons. Although the stereochemistry of **12** could not be clarified from the coupling constant ($J_{1,11b}$ = 8.2 Hz), a positive NOE enhancement (5.7%) was observed in the ^{1}H resonance of 1-H when 11b-H was irradiated: compound **12** was therefore shown to have *cis*-stereochemistry. Since the N-oxide **10** has a *cis*-relationship between the N–O bond and the ethyl group, the mechanism of the formation of **12** could involve the Cope elimination product as an intermediate, followed by cyclization with elimination of MeOH (Chart 4).

It is believed that the [1,2]-Meisenheimer rearrangement proceeds *via* a homolytic dissociation–recombination mechanism.[3-5,11] Previously, Lorand reported[12] that the thermal Meisenheimer rearrangement of *N*-benzyl-*N*-methylaniline *N*-oxide to *N*-benzyloxy-*N*-methylaniline proceeds *via* a homolytic dissociation–recombination mechanism by a quantitative study using radical scavengers such as molecular oxygen, carbon tetrachloride, and a thiol. The azetidine N-oxide **10** might be susceptible to C_{10b}–N bond fission, since C_{10b} is in a benzylic position and the azetidine ring is highly strained. Thus, it seems reasonable to assume

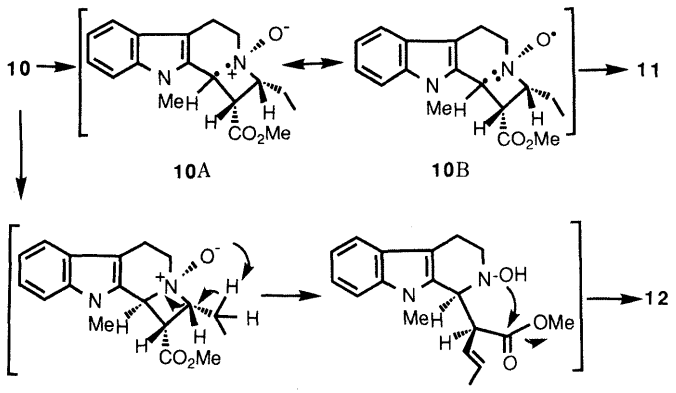
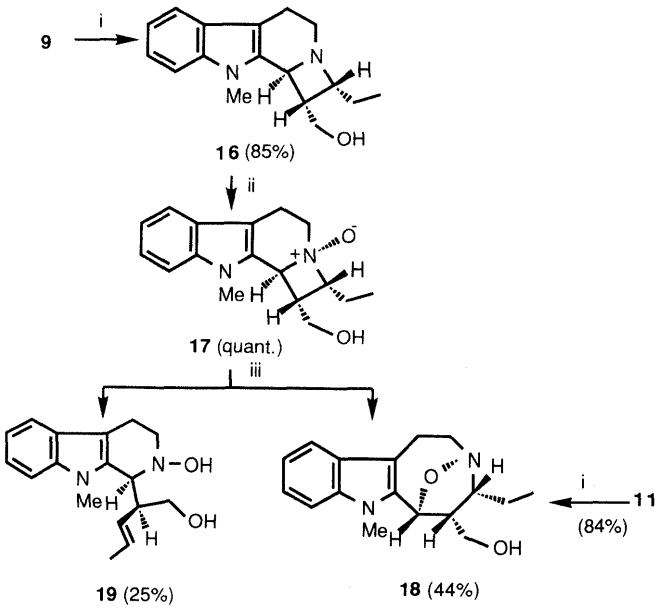


Chart 4

that the epoxyazocine **11** arose by homolytic fission of the C_{10b}–N bond of **10** at room temperature, giving a diradical intermediate (**10B**), followed by intramolecular C–O bond formation (Chart 4). Interestingly, the N-oxide **10** was found to be very stable in 90% aqueous MeOH because of hydrogen bond formation. When a solution of **10** in 90% aqueous MeOH was refluxed for 15 h, the [1,2]-rearrangement product **11** was isolated in 43% yield after purification by column chromatography. It should be noted that the Cope elimination product **12** was not detected on TLC. This may be due to the reduction of nucleophilicity of the N-oxy anion by strong hydrogen bonding. In order to elucidate the diradical intermediate, the rearrangement of **10** in the presence of *tert*-dodecanethiol as a carbon radical scavenger was carried out in refluxing 90% aqueous MeOH for 15 h. The scavenger did not, however, reduce the yield of the epoxyazocine **11**. This may be because the intramolecular recombination of the diradical **10B** is very fast. However, although it seems less likely, an intramolecular cyclic process (*SNi*-process)[13] cannot be excluded as an alternative pathway.

Reductive cleavage of the N–O bond has been used to characterize the ring systems obtained through the [1,2]-Meisenheimer rearrangement, the 1,2-oxaza ring being converted to a secondary amino alcohol.[5] In confirmation of the structural assignment of epoxyazocines, reductive cleavage of the N–O bond in **11** by catalytic reduction[14] over 10% Pd–C was successfully achieved in a mixture of MeOH–EtOAc (1 : 1) to give the secondary amino alcohol **14**, which was then N- and O-acetylated to give the crystalline diacetate **15** in high yield (Chart 3). This route may provide a convenient method for the preparation of the azocino[5,4-*b*]indoles, which have the eight-membered ring.

In our experience,[15] MCPBA oxidation of a corresponding 1-hydroxymethyl derivative of the ester **1** afforded a mixture of products *via* competitive [2,3]- and [1,2]-Meisenheimer rearrangements, in contrast to the result for the ester **1** (see Chart 2). Thus, the effect of the methoxycarbonyl group on the azetidine ring was investigated. Reduction of the ester **9** with lithium aluminum hydride ($LiAlH_4$) gave the alcohol **16**, which was then oxidized with MCPBA in CH_2Cl_2 at room temperature to give the N-oxide **17** (thermally rather stable) as a crystalline material. By examination of the ^{1}H-NMR spectrum as described for **10**, it was readily clarified that the N-oxide **17** has a *cis*-ring



reagents: i, $LiAlH_4$; ii, MCPBA; iii, THF/ 50°C

Chart 5

juncture. Heating of a solution of **17** in THF at 50 °C for 3 h gave a mixture of the Meisenheimer rearrangement product **18** (44%) and the *N*-hydroxytetrahydro-β-carboline **19** (25%), of which the latter resulted from the Cope elimination. The isolation of **19** substantiated the mechanism for the formation of the isoxazolidinone **12**. The structural assignment of **18** was accomplished on the basis of spectroscopic data as well as a direct comparison with the alcohol **18** prepared by $LiAlH_4$ reduction of ester **11**.

In conclusion, we have described a facile synthesis of 3,6-epoxyhexahydroazocino[5,4-*b*]indole derivatives and a novel route to eight-membered nitrogen heterocycles, which are generally the most difficult to prepare by using cyclization methods,[16] through the [1,2]-Meisenheimer rearrangement of the N-oxides of azetopyrido[3,4-*b*]indoles under mild conditions.

Experimental

Melting points were determined on a Yanagimoto apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were determined with a Varian Gemini-200 spectrometer in $CDCl_3$, and MS with a Hitachi M-80 instrument. All reactions were carried out under a nitrogen atmosphere. For column chromatography, SiO_2 (Merck Art 9385) was used.

Methyl 2-(2-*tert*-Butoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-β-carbolin-1-yl)-3-hydroxypentanoate (8) A solution of **7** (3.58 g, 10 mmol) in THF (25 ml) was added dropwise to a solution of LDA [prepared from diisopropylamine (1.7 ml, 12 mmol) and *n*-BuLi (15% *n*-hexane solution, 7.6 ml, 12 mmol)] at −78 °C, and the mixture was stirred at this temperature for 20 min. Then, freshly distilled propionaldehyde (0.9 ml, 13 mmol) was added at once to this solution, and the whole was stirred at −78 °C for 20 min. The reaction was quenched with water, and THF was removed by evaporation. The residue was extracted with benzene–EtOAc (1 : 1), and the extract was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography [benzene–EtOAc (5 : 1)] to give **8** (3.82 g, 92%) as an oil. IR ($CHCl_3$) cm^{-1}: 3450 (OH), 1710, 1650 (CO). The ^{1}H-NMR spectrum was not sufficiently well resolved to permit assignment of all the signals, because a mixture of diastereoisomers was present. Selected signals were as follows: ^{1}H-NMR δ: 1.00 (3H, t, J=7.6 Hz, CH_2Me), 1.46 (9H, s, *tert*-Bu), 3.25 (3H, s, NMe), 3.66 (3H, s, CO_2Me), 5.76 (1H, d, J=4.6 Hz, NCH),

7.03—7.32 (3H, m, ArH), 7.48 (1H, d, J=8.1 Hz, ArH). MS m/z: 416 (M^+). HRMS Calcd for $C_{23}H_{32}N_2O_5$: 416.2309. Found: 416.2309.

Methyl 2-Ethyl-10-methyl-1,2,4,5,10,10b-hexahydroazeto[1′,2′:1,2]-pyrido[3,4-*b*]indole-1-carboxylate (9) Method A: A solution of methanesulfonyl chloride (1.2 ml, 15 mmol) in CH_2Cl_2 (3 ml) was added dropwise to a solution of crude **8**, prepared from **7** (3.58 g, 10 mmol) as described above, and triethyl amine (4.2 ml, 30 mmol) in CH_2Cl_2 (30 ml) under ice-cooling, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with water, and the mixture was extracted with $CHCl_3$. The extract was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was, without purification, dissolved in 2.3 N HCl in EtOAc (60 ml) and the solution was stirred at room temperature for 2.5 h. After removal of the solvent by evaporation *in vacuo*, the residue was dissolved in DMSO (11 ml) containing 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) (3.13 g, 20 mmol). This solution was allowed to stand for 2.5 h, diluted with water (200 ml), and then extracted with EtOAc. The extract was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed [EtOAc–*n*-hexane (2:3)] to give **9** (1.88 g, 63% overall yield from **7**) as an oil. IR (film) cm^{-1}: 1740 (CO). ^{1}H-NMR δ: 0.91 (3H, t, J=7.5 Hz, CH_2Me), 1.63 (2H, quint, J=7.5 Hz, C$\underline{H}_2$Me), 2.64—2.80 (3H, m, NC$\underline{H}$HC$\underline{H}_2$), 3.06 (1H, dd, J=7.5, 2.0 Hz, 1-H), 3.10 (1H, m, NCH$\underline{H}$), 3.53 (3H, s, NMe), 3.75 (1H, q, J=7.5 Hz, 2-H), 3.82 (3H, s, CO_2Me), 5.09 (1H, d, J=2.0 Hz, 10b-H), 7.04—7.32 (3H, m, ArH), 7.55 (1H, d, J=7.5 Hz, ArH). ^{13}C-NMR δ: 10.53 (q), 16.16 (t), 26.2 (t), 29.52 (q), 43.30 (t), 46.67 (d), 52.06 (q), 53.56 (d), 60.97 (d), 107.62 (s), 108.80 (d), 118.33 (d), 119.11 (d), 121.63 (d), 126.66 (s), 133.89 (s), 137.07 (s), 172.25 (s). MS m/z: 298 (M^+). HRMS Calcd for $C_{18}H_{22}N_2O_2$: 298.1680. Found: 298.1680.

Method B: A solution of **1** (100 mg, 0.34 mmol) in THF (5 ml) was hydrogenated under atmospheric pressure with 5% Pd–$BaSO_4$ (34 mg) for 7 h. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was chromatographed [EtOAc–*n*-hexane (3:2)] to give **9** (56 mg, 56%). This was identical with the sample of **9** obtained by method A, based on comparison of their IR and ^{1}H-NMR spectra.

Oxidation of the Azetidine (9) with MCPBA A solution of MCPBA (80% purity) (90 mg, 0.4 mmol) in CH_2Cl_2 (3 ml) was added dropwise to a solution of **9** (100 mg, 0.33 mmol) in CH_2Cl_2 (5 ml) at 0—5 °C. After being stirred for 15 min at this temperature, the reaction mixture was diluted with cold CH_2Cl_2 (10 ml). The cold solution was then washed with cold 5% aqueous sodium carbonate, dried over Na_2SO_4, and concentrated under reduced pressure at below 20 °C, to give an amorphous product. The ^{1}H-NMR spectrum of this product clearly showed it to be the *cis*-N-oxide **10**; ^{1}H-NMR δ: 1.09 (3H, t, J=7.5 Hz, CH_2Me), 1.87, 2.60 (each 1H, each m, C$\underline{H}_2$Me), 3.35—3.80 (5H, m, NCH_2CH_2, 1-H), 3.52 (3H, s, NMe), 3.85 (3H, s, CO_2Me), 4.19 (1H, q, J=8.0 Hz, 2-H), 5.52 (1H,d, J=8.0 Hz, 10b-H), 7.07—7.30 (3H, m, ArH), 7.55 (1H, d, J=7.5 Hz, ArH). A solution of the N-oxide **10** thus obtained in THF (10 ml) was stirred at room temperature for 1 h and concentrated *in vacuo*. The residue was chromatographed [EtOAc–*n*-hexane (1:9)] to give **11** (78 mg, 75%) from the first fraction and **12** (6.0 mg, 6.4%) from the second fraction.

A solution of **10** in CH_2Cl_2 was allowed to stand at room temperature for 43 h followed by usual work-up, giving only **11** in 65% yield.

Methyl 5,6-*cis*-3,6-Epoxy-4-ethyl-7-methyl-1,2,3,4,5,6-hexahydroazocino[5,4-*b*]indole-5-carboxylate (11) mp 127—129 °C (from EtOH). IR ($CHCl_3$) cm^{-1}: 1735 (CO). ^{1}H-NMR δ: 1.02 (3H, t, J=7.5 Hz, CH_2Me), 1.30 and 1.58 (qch 1H, each m, C$\underline{H}_2$Me), 2.97 (2H, m $NCH_2C\underline{H}_2$), 3.07 (1H, q, J=9.0 Hz, NC$\underline{H}$H), 3.60 (1H, m, 4-H), 3.67 (3H, s, NMe), 3.75 (3H, s, CO_2Me), 3.80 (1H, m, NCH$\underline{H}$), 3.86 (1H, dd, J=9.0, 4.0 Hz, 5-H), 5.84 (1H, d, J=4.0 Hz, 6-H), 7.02—7.28 (3H, m, ArH), 7.46 (1H, d, J=7.5 Hz, ArH). ^{13}C-NMR δ: 12.06 (q), 21.31 (t), 24.00 (t), 29.88 (q), 52.19 (q), 59.00 (t), 60.68 (d), 70.86 (d), 77.74 (d), 109.32 (d), 112.19 (s), 118.05 (d), 119.38 (d), 121.41 (d), 126.89 (s), 136.19 (s), 140.38 (s), 171.21 (s). MS m/z: 314 (M^+). *Anal.* Calcd for $C_{18}H_{22}N_2O_3$: C, 68.76; H, 7.04; N, 8.88. Found: C, 68.77; H, 7.05; N, 8.91.

11-Methyl-2-oxo-1-(1-propen-1-yl)-1,2,5,6,11,11b-hexahydroisoxazolo-[2′,3′:1,2]pyrido[3,4-*b*]indole (12) Obtained as an oil. IR ($CHCl_3$) cm^{-1}: 1765 (CO). ^{1}H-NMR δ: 1.56 (3H, dd, J=6.6, 2.4 Hz, =CHMe), 2.89, 3.07, 3.35, and 3.69 (each 1H, each m, NCH_2CH_2), 3.56 (3H, s, NMe), 3.93 (1H, t, J=8.2 Hz, 1-H), 5.17 (1H, ddd, J=16.5, 8.2, 2.4 Hz, MeCH=C$\underline{H}$), 5.29 (1H, d, J=8.2 Hz, 11b-H), 5.90 (1H, qd, J=16.5, 6.6 Hz, MeC$\underline{H}$=), 7.10—7.34 (3H, m, ArH), 7.54 (1H, d, J=7.5 Hz, ArH). ^{13}C-NMR δ: 18.18 (q), 18.28 (t), 30.88 (q), 49.54 (d), 51.93 (t), 61.34 (d), 109.22 (d), 109.61 (s), 118.64 (d), 119.62 (d), 122.26 (d), 122.74 (d), 126.07 (s), 128.67 (s), 133.69 (d), 138.08 (s), 175.93 (s). MS m/z: 282 (M^+). HRMS Calcd for $C_{17}H_{18}N_2O_2$: 282.1367. Found: 282.1370.

Refluxing of a solution of the N-oxide **10** in 90% aqueous MeOH for 15 h followed by usual work-up gave only **11** in 43% yield.

Methyl 5,6-*trans*-3,6-Epoxy-4-ethyl-7-methyl-1,2,3,4,5,6-hexahydroazocino[5,4-*b*]indole-5-carboxylate (13) A solution of **11** (103 mg, 0.33 mmol) in dry MeOH (10 ml) containing NaOMe (37 mg, 0.66 mmol) was refluxed for 10 min. After evaporation of the solvent, the residue was neutralized with 5% aqueous acetic acid, and then extracted with EtOAc. The extract was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography to give **11** (12 mg, 12%) from the first fraction eluted with 20% EtOAc in hexane. The second fraction eluted with 40% EtOAc in hexane gave **13** (89 mg, 86%), mp 97—98 °C (from EtOH). IR ($CHCl_3$) cm^{-1}: 1730 (CO). ^{1}H-NMR δ: 1.02 (3H, t, J=7.3 Hz, CH_2Me), 1.71 (2H, m, J=7.3 Hz, C$\underline{H}_2$Me), 2.79—2.93 (1H, m, $NCH_2C\underline{H}$H), 3.16—3.29 (1H, m, $NCH_2CH\underline{H}$), 3.25 (3H, s, CO_2Me), 3.33—3.48 (1H, m, NC$\underline{H}$H), 3.70 (3H, s, NMe), 3.71 (1H, dd, J=8.0, 5.7 Hz, 5-H), 3.76 (1H, m, NCH$\underline{H}$), 3.91 (1H, td, J=7.3, 5.7 Hz, 4-H), 5.61 (1H, d, J=8.0 Hz, 6-H), 7.01—7.25 (3H, m, ArH), 7.44 (1H, d, J=7.6 Hz, ArH). ^{13}C-NMR δ: 11.68 (q), 21.29 (t), 29.56 (q), 30.19 (t), 51.83 (q), 50.75 (t), 62.81 (d), 63.97 (d), 76.51 (d), 109.11 (d), 112.28 (s), 118.78 (d), 119.17 (d), 121.75 (d), 127.00 (s), 136.42 (s), 137.03 (s), 169.29 (s). MS m/z: 314 (M^+). *Anal.* Calcd for $C_{18}H_{22}N_2O_3$: C, 68.56; H, 7.07; N, 8.95. Found: C, 68.77; H, 7.05; N, 8.91.

Methyl 4-Ethyl-6-hydroxy-7-methyl-1,2,3,4,5,6-hexahydroazocino[5,4-*b*]indole-5-carboxylate (14) A solution of **11** (800 mg, 2.5 mmol) in a mixture of EtOAc–MeOH (1:1) (30 ml) in the presence of 10% Pd–C (450 mg) was hydrogenated using a Skita apparatus under an initial pressure of 1 kg/cm^2 for 60 h. After being filtered through a Celite pad, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography [$CHCl_3$–MeOH (25:1)] to give the amino alcohol **14** (790 mg, 98%) as crystals, mp 164—165 °C (from EtOH–*n*-hexane). IR (KBr) cm^{-1}: 3370 (OH) and 1725 (CO). ^{1}H-NMR δ: 0.77 (3H, t, J=7.0 Hz, CH_2Me), 1.31—1.80 (2H, m, C$\underline{H}_2$Me), 2.44—2.57 (1H, m, 4-H), 2.63 (1H, t, J=4.0 Hz, 5-H), 2.68—3.44 (4H, m, NCH_2CH_2), 3.70 and 3.81 (each 3H, each s, CO_2Me and/or NMe), 5.56 (1H, d, J=4.0 Hz, 6-H), 7.08—7.35 (3H, m, ArH), 7.56 (1H, d, J=7.5 Hz, ArH). ^{13}C-NMR δ: 10.8 (q), 25.9 (t), 27.6 (t), 29.7 (q), 51.5 (t), 51.8 (q), 53.0 (d), 61.2 (d), 70.5 (d), 109.0 (d), 111.1 (s), 118.0 (d), 119.0 (d), 121.4 (d), 127.6 (s), 136.0 (s), 136.2 (s), 171.9 (s). MS m/z: 316 (M^+). *Anal.* Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.17; H, 7.68; N, 8.69.

Methyl 6-Acetoxy-3-acetyl-4-ethyl-7-methyl-1,2,3,4,5,6-hexahydroazocino[5,4-*b*]indole-5-carboxylate (15) A solution of the amino alcohol **14** (40 mg, 0.13 mmol) in acetic anhydride (0.5 ml) in the presence of a drop of pyridine was allowed to stand overnight. The reaction was quenched with ice-water, and the mixture was made alkaline with saturated sodium bicarbonate solution, and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated. The residual solid was recrystallized from a mixture of EtOH–*n*-hexane to give **15** (39 mg, 77%), mp 200—202 °C. IR (KBr) cm^{-1}: 1730, 1620 (CO). ^{1}H-NMR δ: 0.99 (3H, t, J=7.5 Hz, CH_2Me), 1.44 (3H, s, NCOMe), 1.59—1.85 (1H, m, C$\underline{H}$HMe), 2.05 (3H, s, OCOMe), 2.12—2.41 (1H, m, CH$\underline{H}$Me), 2.96—3.51 (4H, m, NCH_2CH_2), 3.70 (1H, m, 5-H), 3.75 and 3.80 (each 3H, each s, CO_2Me and/or NMe), 4.96 (1H, m, 4-H), 6.70 (1H, br s, 6-H), 7.0—7.31 (3H, m, ArH), 7.47 (1H, d, J=8.0 Hz, ArH). ^{13}C-NMR δ: 13.8 (q), 20.8 (q), 21.9 (t), 22.95 (q), 22.95 (t), 29.8 (q), 44.5 (t), 49.1 (d), 52.4 (q), 56.7 (d), 66.8 (d), 108.5 (s), 109.8 (d), 117.1 (d), 119.6 (d), 122.0 (d), 126.9 (s), 134.4 (s), 136.3 (s), 169.4 (s), 171.7 (s), 172.4 (s). MS m/z: 400 (M^+). *Anal.* Calcd for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.05; N, 7.00. Found: C, 65.78; H, 7.05; N, 6.89.

2-Ethyl-1-hydroxymethyl-10-methyl-1,4,5,10b-tetrahydro-2*H*-azeto-[1′,2′:1,2]pyrido[3,4-*b*]indole (16) A solution of **9** (188 mg, 6.3 mmol) in THF (30 ml) was added dropwise to a suspension of $LiAlH_4$ (24 mg, 6.3 mmol) in THF (10 ml) under ice-cooling. After being stirred at room temperature for 1 h, the reaction mixture was quenched with 15% sodium hydroxide (0.24 ml) and water (5 ml), then filtered through a Celite pad. The filtrate was concentrated to a small volume and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated. The resulting solid was agitated with a mixture of EtOH–*n*-hexane (1:1) and collected by filtration to give **16** (145 mg, 85%), mp 155—156 °C (from EtOH–*n*-hexane). IR ($CHCl_3$) cm^{-1}: 3320 (OH). ^{1}H-NMR δ: 0.90 (3H, t, J=7.5 Hz, CH_2Me), 1.50—1.75 (2H, m, C$\underline{H}_2$Me), 2.32—2.46 (1H, m, 1-H), 2.63—3.22 (4H, m, NCH_2CH_2), 3.37 (1H, s, OH), 3.62 (3H, s, NMe), 3.63 (1H, q, J=8.0 Hz, 2-H), 4.03 (1H, dd, J=11.0, 5.0 Hz, C$\underline{H}$HOH), 4.24 (1H, dd, J=11.0, 9.6 Hz, CH$\underline{H}$OH), 4.69 (1H, br s, 10b-H), 7.05—7.33

(3H, m, ArH), 7.54 (1H, d, J=7.5 Hz, ArH). MS m/z: 270 (M^+). *Anal.* calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.43; H, 8.25; N, 10.33.

Oxidation of the Alcohol (16) with MCPBA A solution of **16** (200 mg, 0.74 mmol) was treated with MCPBA (192 mg, 0.89 mmol) in CH_2Cl_2 as described for the reaction of **9** with MCPBA to give the *cis*-N-oxide **17** [^{1}H-NMR δ: 1.00 (3H, t, J=7.5 Hz, CH_2Me), 1.85 (1H, m, CHHMe), 2.29 (1H, m, CHHMe), 2.65 (1H, br d, J=7.5 Hz, 1-H), 2.83—3.62 (4H, m, NCH_2CH_2), 3.58 (3H, s, NMe), 3.96 (2H, d, J=2.0 Hz, CH_2OH), 4.44 (1H, q, J=7.5 Hz, 2-H), 5.23 (1H, br s, 10b-H), 7.11—7.36 (3H, m, ArH), 7.53 (1H, d, J=7.5 Hz, ArH)] as crystals. The N-oxide **17** was hygroscopic, and was subjected to the following pyrolysis without purification. A solution of **17** thus obtained in THF (8 ml) was heated at 50 °C for 3 h. After evaporation of the solvent, the residue was chromatographed [EtOAc–*n*-hexane (3 : 2)] to give **19** (27 mg, 25%) from the first fraction and **18** (92 mg, 44%) from the second fraction.

3,6-Epoxy-4-ethyl-5-hydroxymethyl-7-methyl-1,2,3,4,5,6-hexahydroazocino[5,4-*b*]indole (18) mp 159—160 °C (from EtOH–*n*-hexane). IR ($CHCl_3$) cm^{-1}: 3350 (OH). ^{1}H-NMR δ: 0.97 (3H, t, J=7.0 Hz, CH_2Me), 1.40—1.63 (2H, m, CH_2Me), 2.04 (1H, br s, OH), 2.80—2.94 (1H, m, 5-H), 3.00—3.40 (4H, m, NCHHCH_2 and 4-H), 3.68 (3H, s, NMe), 3.71—3.97 (3H, m, NCHHCH_2, CH_2OH), 5.43 (1H, br s, 6-H), 7.02—7.29 (3H, m, ArH), 7.46 (1H, d, J=7.5 Hz, ArH). MS m/z: 286 (M^+). *Anal.* Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.12; H, 7.82; N, 9.77. This was alternatively synthesized as follows: A solution of **11** (174 mg, 0.56 mmol) in THF (3 ml) was added dropwise to a suspension of $LiAlH_4$ (21 mg, 0.56 mmol) in THF (5 ml) under ice-cooling. After being stirred for 20 min, the reaction was quenched with 15% sodium hydroxide (0.1 ml) and water (2 ml), and the mixture was filtered through a Celite pad. The filtrate was concentrated to a small volume, and extracted with EtOAc. After evaporation of the solvent, the resulting solid was recrystallized from EtOH–*n*-hexane to give **18** (134 mg, 84%), which was identical with an authentic sample of **18**, based on comparison of their ^{1}H-NMR spectra.

2-(2-Hydroxy-9-methyl-1,2,3,4-tetrahydro-β-carbolin-1-yl)-2-(1-propen-1-yl)ethanol (19) mp 115—116 °C (from ligroin–EtOAc). IR ($CHCl_3$) cm^{-1}: 3290 (OH). ^{1}H-NMR δ: 1.50 (3H, d, J=4.4 Hz, =CHMe), 2.65—3.50 (5H, m, NCH_2CH_2, CHCH_2OH), 3.62 (3H, s, NMe), 3.99 (2H, m, CH_2OH), 4.60 (1H, d, J=5.0 Hz, 1-H), 5.26—5.38 (2H, m, CH=CH), 7.06—7.33 (3H, m, ArH), 7.52 (1H, d, J=7.5 Hz, ArH). MS m/z: 286 (M^+). *Anal.* Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.49; H, 7.81; N, 9.81.

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References and Notes

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