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1,6-Dihydro-3(2*H*)-pyridinones. IV.[1] Synthesis of (±)-Tabersonine and (±)-Cleavamine *via* a Common Intermediate, Ethyl 3-Ethyl-3-hydroxy-1,2,3,6-tetrahydropyridine-1-carboxylate[2]

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A formal synthesis of (±)-tabersonine (**1**) and a total synthesis of (±)-cleavamine (**2**) have been achieved *via* a common intermediate (**6**) derived from ethyl 1,6-dihydro-3(2*H*)-pyridinone-1-carboxylate (**5a**). The successful cyclization of the carboxylic acid (**20**) to the dioxocleavamine (**4**) is also discussed.

Keywords——dihydropyridinone; synthon; tabersonine; cleavamine; Claisen rearrangement; silver(I) oxide; polyphosphate ester; allylic rearrangement; total synthesis; indole alkaloid

Tabersonine (**1**), a representative Aspidosperma alkaloid, plays an important role as a biogenetic precursor of the Iboga and other Aspidosperma alkaloids.[3] On the other hand, cleavamine (**2**) is a degradation product of a bis indole-dihydroindole alkaloid, leurosine, formed by heating with concentrated hydrochloric acid in the presence of a reducing agent.[4] Cleavamine-type compounds have attracted much attention from a synthetic point of view because they constitute the indole portion of the bis indole-dihydroindole alkaloids represented by vinblastine, a clinically important antitumor agent. Among reports[5] on the synthesis of tabersonine (**1**), Ziegler *et al.*[5a] described a total synthesis of (±)-**1** *via* (±)-5,16-dioxo-14,15-dehydroquebrachamine (**3**). 5,16-Dioxocleavamine (**4**), the regioisomer of **3** at the ethyl group, would serve as a potential intermediate for cleavamine.[6]

In the previous papers,[1,7] we have demonstrated a convenient synthesis of *N*-substituted 1,6-dihydro-3(2*H*)-pyridinone (**5**) and shown that it is a very useful synthon for the syntheses of several kinds of alkaloids, *e.g.*, (±)-catharanthine, (±)-ibogamine, (±)-epiibogamine, and (±)-tecomanine. As a continuation of our studies on general synthesis of alkaloids starting from **5** as a common synthon, this paper describes a formal synthesis of (±)-tabersonine (**1**) and a total synthesis of (±)-cleavamine (**2**) *via* a common intermediate, ethyl 3-ethyl-3-hydroxy-1,2,3,6-tetrahydropyridine-1-carboxylate (**6**), derived from ethyl 1,6-dihydro-3(2*H*)-pyridinone-1-carboxylate (**5a**).

On reaction of **5a** with an excess of ethylmagnesium bromide in ether at −10°C, two products (**6** and **7**) were obtained in 41 and 11% yields, respectively. The structures of **6** and **7** were easily elucidated from spectral evidence. For example, the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **6** exhibited a broad singlet at 5.70 ppm due to the olefinic protons, while that of **7** showed no signal at lower field than 4.2 ppm. When the same reaction was carried out at lower temperature (−20°C), the yields of the products (**6** and **7**) were 52 and 22%, respectively. The reaction using ethyllithium instead of ethylmagnesium bromide, however, did not give a satisfactory result (Table I). The low yield of the products in the case of ethyllithium could be attributable to the attack of ethyllithium not only at the enone moiety but also at the urethane carbonyl.

Exposure of the 1,2-adduct (**6**) to 1% hydrochloric acid in boiling acetone effected an allylic rearrangement to give efficiently the isomerized allylic alcohol (**8**). Its ^{1}H-NMR spectrum exhibited the signals of an ethyl group attached to C-5 at 1.06 (3H, t, J=7 Hz) and

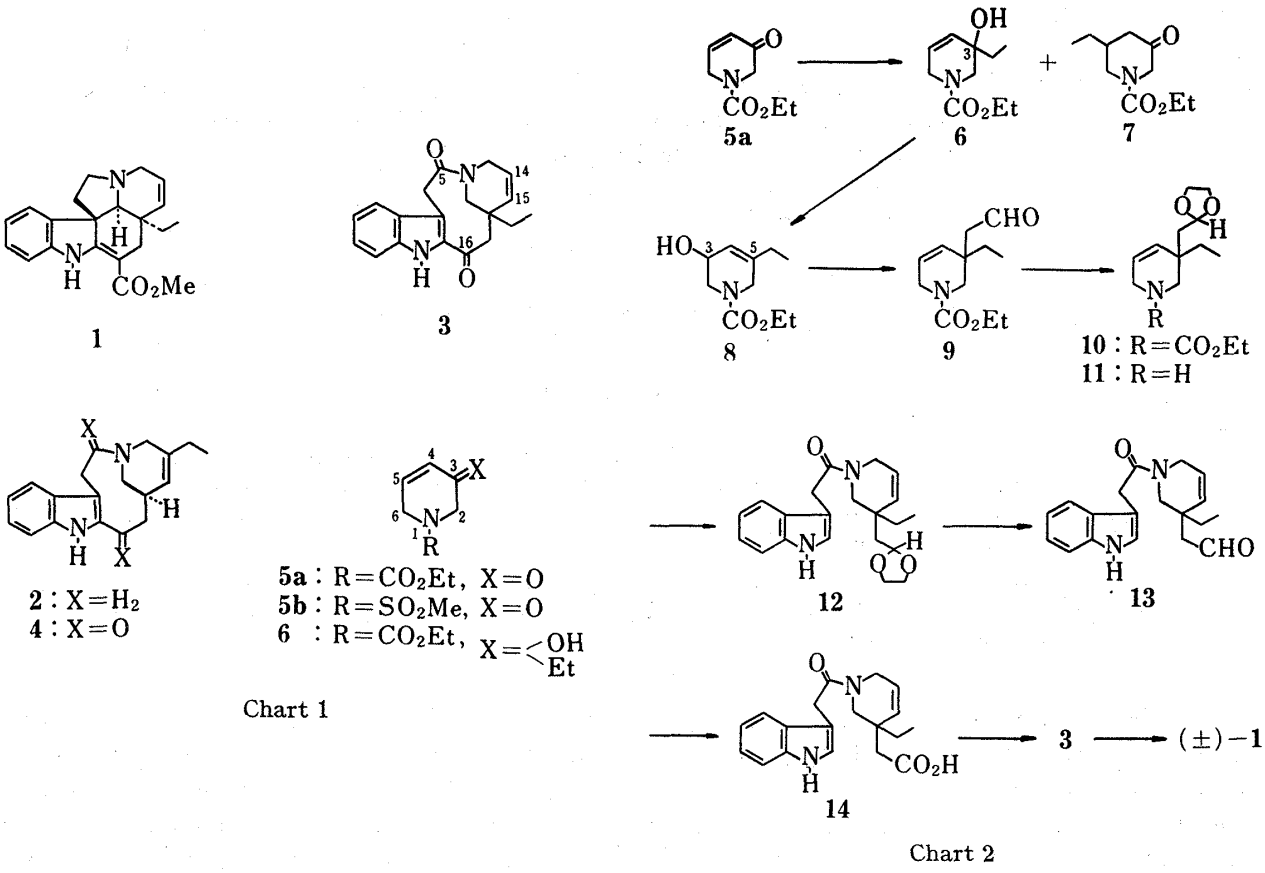

Chart 1

Chart 2

TABLE I. Reaction of the Dihydropyridinone (**5a**) with EtMgBr or EtLi

Reagent	Reaction temp. (°C)	Time (h)	Products (%)	
			6	**7**
EtMgBr	−10	1	41	11
EtMgBr	−20	1	52	22
EtLi	0	0.5	0	0
EtLi	−72	0.5	35	11

2.04 ppm (2H, q, J=7 Hz) and one olefinic proton signal at 5.62 ppm. On heating of a mixture of **8**, mercuric acetate, and ethyl vinyl ether[8] in a sealed tube at 205°C, Claisen rearrangement occurred smoothly to afford the labile aldehyde (**9**), which was acetalized to **10** in the usual manner. The mass spectrum of **10** showed a parent peak at m/e 269 and the ^{1}H-NMR spectrum exhibited a triplet (J=5 Hz) at 4.80 ppm due to the proton on the acetal carbon and a broad singlet at 5.60 ppm attributable to the olefinic protons. Basic hydrolysis of **10** with potassium hydroxide in aqueous ethanol under reflux for 72 h provided the desired amine (**11**) (37%; 80% yield based on the consumed starting material) along with the unchanged urethane (**10**; 59%). Condensation of **11** with β-indolylacetyl chloride[9] in the presence of potassium carbonate afforded the amide (**12**; 94%), which was subjected to mild acidic hydrolysis to give the aldehyde (**13**) in 86% yield. Oxidation of **13** to the carboxylic acid (**14**) was accomplished with silver(I) oxide[10] while several attempts to oxidize **13** with chromium trioxide were unsuccessful. Namely, treatment of **13** with silver nitrate and potassium hydroxide[11] in aqueous ethanol immediately afforded the carboxylic acid (**14**) in 68% yield. Finally, according to the procedure of Ziegler *et al.*,[5a] exposure of **14** to polyphosphoric acid (PPA) at 90°C yielded the cyclized product, (±)-5,16-dioxo-14,15-dehydroquebrachamine (**3**),

mp 225—226°C, in 37% yield. The synthetic product (**3**) was found to be identical with an authentic sample[5a] by means of ^{1}H-NMR comparison. Since Ziegler *et al.*[5a] had reported the successful conversion of **3** into (±)-tabersonine (**1**) in several steps, the present synthesis of **3** represents a formal synthesis of (±)-tabersonine (**1**).

Next, a total synthesis of (±)-cleavamine (**2**) was achieved as follows. The allylic alcohol (**6**) was subjected to the Claisen rearrangement under the conditions mentioned above to yield the aldehyde (**15**), which was treated with ethylene glycol in the presence of *p*-toluenesulfonic acid in boiling benzene to afford the acetal (**16**) in 66% overall yield from **6**. The ^{1}H-NMR spectrum of **16** exhibited a triplet (J=5 Hz) at 4.88 ppm and a multiplet at 5.40 ppm due to the proton on the acetal carbon and the olefinic proton, respectively. Deprotection of the *N*-substituent in **16** was carried out in the same manner as in the case of **10** to give the amine (**17**) and the unchanged starting material (**16**) in 59 and 36% yields, respectively. Reaction of **17** with *β*-indolylacetyl chloride gave the amide (**18**) and subsequent acidic hydrolysis provided the aldehyde (**19**), which was then oxidized with *in situ*-generated siliver(I) oxide to afford the carboxylic acid (**20**) in 67% yield from the amine (**17**).

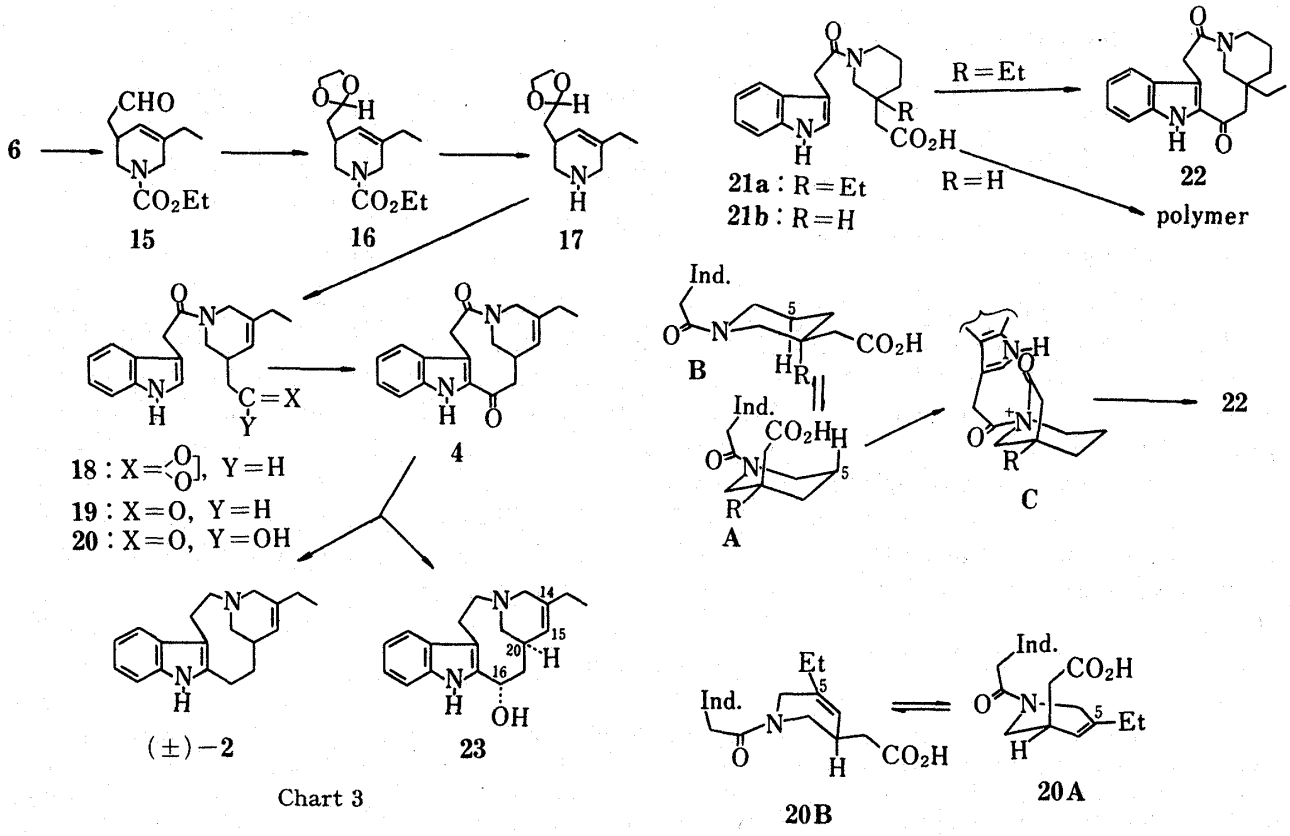

Chart 3

Chart 4

Ziegler and his co-workers[12] reported the reaction of the carboxylic acids (**21a** and **21b**) with PPA. The acid (**21a**) affords the cyclized product (**22**) in a good yield while only the polymerized product is obtained in the case of **21b**. The successful cyclization of **21a** or **14** can be well interpreted as follows. Compounds **21a** and **14** each exist in a *ca.* 1:1 mixture of two conformers **A** and **B** because of the equal steric magnitudes of the ethyl and acetic acid groups both attached to C-3 of the piperidine ring: one (**A**) has an axial acetic acid group and the other (**B**) an equatorial one. Only the axial conformer **A** could give the reactive intermediate (**C**)[13] which easily affords the cyclized product (**22** or **3**).[12] On the other hand, in the acid (**21b**) the acetic acid group exclusively occupies the equatorial position (conformer **B**) and therefore

only polymerized material is obtained.

Although the present carboxylic acid (**20**) bears only the acetic acid group at the C-3 position of the piperidine ring, the acetic acid group in **20** is expected to be situated in the axial position (**20A**), which is essential to the ring closure, because of the sp^2 character of the 1- and 5-positions of the ring. In fact, treatment of **20** with a large excess of PPA at 85°C for 40 min provided the desired product, (±)-5,16-dioxocleavamine (**4**), mp 199—200°C, though in a low yield (12%). The structure of **4** was determined from the following spectral evidence. The infrared (IR) spectrum showed a carbonyl band at 1650 cm^{-1} due to both the amido and ketonic carbonyl functions and the ^{1}H-NMR spectrum exhibited only four aromaitc proton signals at 6.90—7.38 (3H) and 7.65 ppm (1H). In order to improve the yield of the product (**4**), various reaction conditions were examined (Table II). As a result, polyphosphate ester[14] (PPE) was found to be somewhat more effective than PPA. Namely, when the reaction was carried out by heating the carboxylic acid (**21**) with PPE in chloroform for 2 h, the cyclized product (**4**) was isolated in 36% yield.

TABLE II. Cyclization of the Carboxylic Acid (**20**)

Reagent	Solvent	Temp. (°C)	Time (min)	Products (%)	
				4	**20**
PPA	—	85	40	12	52
PPA	—	110	40	0	0
conc. H_2SO_4	$CHCl_3$	Reflux	400	0	0
PPE	CH_2Cl_2	Reflux	120	Trace	0
PPE	$CHCl_3$	Reflux	120	36	0

Finally, reduction of **4** with lithium aluminum hydride in dioxane furnished (±)-cleavamine (**2**) (±)-16-hydroxycleavamine (**23**) in 13 and 42% yields, respectively. In the ^{1}H-NMR spectrum of **23** the C_{16}-hydrogen appeared at a rather low field (5.20 ppm) owing to an anisotropy of the amino nitrogen, suggesting that the relative configuration of the C_{16}-hydroxy group and C_{20}-hydrogen is *cis*.[15] The synthetic product (**2**) was proved to be identical with (+)-cleavamine by means of IR and ^{1}H-NMR comparisons.

The dioxo- or hydroxycleavamine (**4** or **23**) readily obtained in the present work should be useful as a powerful synthetic intermediate for other cleavamine-type compounds, *e.g.*, velbanamine, 16-methoxycarbonylcleavamine, and dihydrocleavamines.

Experimental

All melting points are uncorrected. IR spectra were measured with a JASCO A-102 spectrometer. Mass spectra (MS) were taken with a Hitachi M-80 mass spectrometer (direct inlet, at 75 eV) and ultraviolet (UV) spectra with a Hitachi 323 spectrophotometer. ^{1}H-NMR spectra were recorded with a JEOL PMX-60 or FX-100 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad. All organic extracts were dried over anhydrous sodium sulfate. Column chromatography was carried out with Silica gel 60 (70—230 mesh, Merck) and Alumina 90 (70—230 mesh, Merck).

Ethyl 3-Ethyl-3-hydroxy-1,2,3,6-tetrahydropyridine-1-carboxylate (6) and Ethyl 5-Ethyl-3-oxopiperidine-1-carboxylate (7)——a) A solution of the dihydropyridinone (**5a**; 1.1 g) in dry ether (20 ml) was added dropwise to a stirred solution of EtMgBr in dry ether [prepared from Mg (650 mg) and EtBr (2.0 ml) in dry ether (20 ml)] over 20 min at −10°C, and stirring was continued for another 1 h at the same temperature. Sat. NH_4Cl solution (10 ml) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with ether (30 ml×2) and the combined ethereal layer was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on silica gel in $CHCl_3$. The first fraction afforded 142 mg (11%) of the 1,4-adduct (**7**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1685 (CO). ^{1}H-NMR δ: 0.94 (3H, t, J=7 Hz, C_5–$CH_2\underline{CH_3}$), 1.24 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 4.10 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$). MS *m/e* (%): 199 (36, M^+), 142 (100), 115 (22), 98 (31). High resolution MS *m/e*: Calcd for $C_{10}H_{17}NO_3$: 199.1208. Found: 199.1210. The second fraction afforded 510 mg (41%) of the 1,2-adduct

(**6**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3575 (OH), 1680 (CO), 1650 (C=C). ^{1}H-NMR δ: 0.97 (3H, t, J=8 Hz, C_3–$CH_2C\underline{H}_3$), 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.55 (2H, q, J=8 Hz, C_3–$C\underline{H}_2CH_3$), 2.91 (1H, s, OH), 3.43 (2H, s, C_2–H), 3.87 (2H, br s, C_6–H), 4.10 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.70 (2H, br s, C_4– and C_5–H). MS *m/e* (%): 199 (33, M^+), 142 (44), 102 (30), 98 (100). High resolution MS *m/e*: Calcd for $C_{10}H_{17}NO_3$: 199.1208. Found: 199.1213.

b) A solution of **5a** (840 mg) in dry ether (10 ml) was added dropwise to a stirred solution of EtMgBr in dry ether [prepared from Mg (400 mg) and EtBr (1.1 ml) in dry ether (10 ml)] over 30 min at −20°C, and stirring was continued for another 1 h. Work-up as usual afforded 220 mg (22%) of **7** and 515 mg (52%) of **6**.

c) A solution of **5a** (830 mg) in dry ether (10 ml) was added dropwise to a stirred solution of EtLi in dry ether [prepared from Li (330 mg) and EtBr (1.75 ml) in dry ether (10 ml)] over 30 min at −72°C, and stirring was continued for another 30 min at the same temperature. Work-up as usual afforded 103 mg (11%) of **7** and 330 mg (35%) of **6**.

Ethyl 5-Ethyl-3-hydroxy-1,2,3,6-tetrahydropyridine-1-carboxylate (**8**)——A solution of **6** (0.40 g) in purified acetone (10 ml) containing 1% HCl (3 ml) was refluxed with stirring for 3 h. The solvent was evaporated off and the residue was taken up in $CHCl_3$ (50 ml). The organic layer was washed with brine, dried and concentrated to leave an oily residue, which was chromatographed on alumina in $CHCl_3$. The first fraction afforded 50 mg of the unchanged starting material (**6**) and the second one afforded 290 mg (73%; 83% based on the consumed starting material) of the secondary alcohol (**8**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3575 (OH), 1680 (CO), 1660 (C=C). ^{1}H-NMR δ: 1.06 (3H, t, J=7 Hz, C_5–$CH_2C\underline{H}_3$), 1.28 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.04 (2H, q, J=7 Hz, C_5–$C\underline{H}_2CH_3$), 3.47 (1H, dd, J=13 and 4 Hz, C_2–H), 3.62 (1H, dd, J=13 and 4 Hz, C_2–H), 3.75 (1H, d, J=10 Hz, C_6–H), 3.95 (1H, d, J=10 Hz, C_6–H), 4.15 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.62 (1H, m, C_4–H). High resolution MS *m/e*: Calcd for $C_{10}H_{17}NO_3$: 199.1208. Found: 199.1243.

Ethyl 3-Ethyl-3-(2-oxoethyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (**9**)——A mixture of the alcohol (**8**; 730 mg), $Hg(OAc)_2$ (0.50 g), and ethyl vinyl ether (4 ml) was heated at 205°C in a sealed tube for 43 h. The solvent was removed *in vacuo* and the residue was taken up in C_6H_6 (100 ml). The C_6H_6 layer was washed with 10% HCl (5 ml×2) and water, dried, and concentrated to leave an oily residue (crude **9**), which was used for the next step without further purification. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2725 (CHO), 1710, 1685 (CO), 1650 (C=C). ^{1}H-NMR δ: 0.90 (3H, t, J=7 Hz, C_3–$CH_2C\underline{H}_3$), 1.32 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.37 (2H, d, J=3 Hz, $C\underline{H}_2CHO$), 4.12 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.70 (2H, br s, C_4– and C_5–H), 9.65 (1H, t, J=3 Hz, CHO).

Ethyl 3-Ethyl-3-(2-ethylenedioxyethyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (**10**)——A mixture of the crude aldehyde (**9**), ethylene glycol (1.0 ml), *p*-TsOH (trace), and C_6H_6 (70 ml) was refluxed with stirring for 3 h while the water formed was azeotropically removed using a Dean–Stark apparatus. After cooling, the reaction mixture was washed with sat. $NaHCO_3$ and brine, dried, and concentrated to leave an oily residue, which was chromatographed on alumina in C_6H_6 to afford 582 mg (59% from **8**) of the acetal (**10**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (CO), 1650 (C=C). ^{1}H-NMR δ: 0.87 (3H, t, J=7 Hz, C_3–$CH_2C\underline{H}_3$), 1.23(3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.70 (2H, d, J=5 Hz, $C\underline{H}_2C\langle{}^{O}_{O}\rangle$), 3.37 (2H, s, C_2–H), 4.17 (4H, s, OCH_2CH_2O), 4.10 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.80 (1H, t, J=5 Hz, $CH\langle{}^{O}_{O}\rangle$), 5.60 (2H, br s, C_4– and C_5–H). MS *m/e* (%): 269 (3, M^+), 181 (48), 73 (100). High resolution MS *m/e*: Calcd for $C_{14}H_{23}NO_4$: 269.1626. Found: 269.1637.

3-Ethyl-3-(2-ethylenedioxyethyl)-1,2,3,6-tetrahydropyridine (**11**)——A mixture of the urethane (**10**; 440 mg), KOH (0.40 g), EtOH (10 ml), and water (5 ml) was refluxed with stirring for 72 h. Ethanol was evaporated off *in vacuo* and the remainder was extracted with $CHCl_3$ (20 ml, 5 ml×3). The extract was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on alumina in $CHCl_3$. The first fraction afforded 235 mg (59%) of the unchanged starting material (**10**) and the second one afforded 120 mg (37%; 80% based on the consumed starting material) of the amine (**11**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 1635 (C=C). ^{1}H-NMR δ: 0.86 (3H, t, J=8 Hz, C_3–$CH_2C\underline{H}_3$), 1.41 (2H, q, J=8 Hz, C_3–$C\underline{H}_2CH_3$), 1.69 (2H, d, J=5 Hz, C_3–$C\underline{H}_2CH\langle{}^{O}_{O}\rangle$), 2.50 (1H, s, NH), 2.68 (1H, d, J=12 Hz, C_2–H), 2.83 (1H, d, J=12 Hz, C_2–H), 3.22 (2H, m, C_6–H), 3.68—4.20 (4H, m, OCH_2CH_2O), 4.90 (1H, t, J=5 Hz, $CH\langle{}^{O}_{O}\rangle$), 5.55 (1H, br d, J=10 Hz, C_4–H), 5.70 (1H, dt, J=10 and 3 Hz, C_5–H). MS *m/e*: 197 (M^+). The picrolonate: mp 234—235°C (from MeOH). *Anal.* Calcd for $C_{11}H_{19}NO_2 \cdot C_{10}H_8N_4O_5$: C, 54.65; H, 5.90; N, 15.18. Found: C, 54.94; H, 5.84; N, 15.12.

3-Ethyl-3-(2-ethylenedioxyethyl)-1-(β-indolylacetyl)-1,2,3,6-tetrahydropyridine (**12**)——A solution of β-indolylacetyl chloride (155 mg) in CH_2Cl_2 (2 ml) was added to a stirred solution of the amine (**11**; 140 mg) in CH_2Cl_2 (4 ml) over 1 min and then a solution of K_2CO_3 (0.10 g) in water (2 ml) was added to the resulting mixture under ice cooling. After further stirring for 5 min under cooling, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (20 ml×2). The combined organic layer was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on alumina in $CHCl_3$ to afford 237 mg (94%) of the amide (**12**) as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (NH), 1650 (C=C), 1620

(CO). ^{1}H-NMR δ: 0.83 (3H, t, J=7 Hz, C_3–$CH_2C\underline{H}_3$), 1.45 (2H, q, J=7 Hz, C_3–$C\underline{H}_2CH_3$), 1.70 (2H, d, J=5 Hz, C_3–$C\underline{H}_2CH\langle^{O}_{O}$), 3.77 (4H, s, OCH_2CH_2O), 4.76 (1H, t, J=5 Hz, $CH\langle^{O}_{O}$), 5.60 (2H, br s, C_4- and C_5–H), 6.83—7.53 (5H, m, Ar–H), 8.60 (1H, m, NH). MS *m/e* (%): 354 (19, M^+), 130 (100).

3-Ethyl-1-(β-indolylacetyl)-3-(2-oxoethyl)-1,2,3,6-tetrahydropyridine (13)——A solution of **12** (0.050 g) in THF (10 ml) containing 10% HCl (0.5 ml) was refluxed with stirring for 8 h. After cooling, the reaction mixture was diluted with $CHCl_3$ (20 ml) and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (5 ml×2) and the combined organic layer was washed with brine. The dried organic layer was concentrated to leave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 38 mg (86%) of the aldehyde (**13**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (NH), 2725 (CHO), 1715 (CO), 1650 (C=C), 1625 (NCO). ^{1}H-NMR δ: 0.83 (3H, t, J=7 Hz, C_3–$CH_2C\underline{H}_3$), 5.63 (2H, br s, C_4– and C_5–H), 7.0—7.7 (5H, m, Ar–H), 8.50 (1H, m, NH), 9.50 (1H, m, CHO). MS *m/e* (%): 310 (38, M^+), 149 (40), 130 (100).

3-Ethyl-1-(β-indolylacetyl)-1,2,3,6-tetrahydropyridine-3-acetic Acid (14)——A solution of $AgNO_3$ (0.10 g) in distilled water (2 ml) was added to a stirred solution of the aldehyde (**13**; 0.10 g) in EtOH (4 ml) all at once under ice cooling, and immediately a solution of KOH (0.10 g) in water (2 ml) was added dropwise to the mixture over 2—3 min under ice cooling. After further stirring for 10 min, the inorganic substances were filtered off and washed thoroughly with water. The filtrate and washings were acidified to pH 1 with conc. HCl and extracted with $CHCl_3$ (10 ml×10). The extract was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on silica gel in $CHCl_3$–MeOH (9: 1) to afford 71 mg (68%) of the carboxylic acid (**14**) as a glassy solid. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (NH), 3600—2400 (COOH), 1705 (CO), 1650 (C=C), 1620 (NCO). ^{1}H-NMR δ (at 60°C): 0.86 (3H, t, J=8 Hz, C_3–$CH_2C\underline{H}_3$), 1.49 (2H, q, J=8 Hz, C_3–$C\underline{H}_2CH_3$), 2.26 (2H, s, $C\underline{H}_2COOH$), 3.88 (2H, s, C_2–H), 3.84 (1H, d, J=18 Hz, C_6–H), 4.08 (1H, d, J=18 Hz, C_6–H), 5.63 (2H, br s, C_4– and C_5–H), 7.0—7.6 (6H, m, Ar–H and COOH), 8.25 (1H, m, NH). MS *m/e* (%): 326 (9, M^+), 130 (100).

(±)-5,16-Dioxo-14,15-dehydroquebrachamine (3)——A powdered carboxylic acid (**14**; 32 mg) was added to 3 ml of PPA (*ca.* 118% H_3PO_4) and the mixture was heated at 90°C with stirring for 30 min. Ice water was added to the resulting mixture and the whole was extracted with $CHCl_3$ (10 ml×3). The extract was washed with sat. $NaHCO_3$ and brine, dried, and concentrated to leave a semi-solid, which was chromatographed on silica gel in $CHCl_3$ to afford 11 mg (37%) of the cyclized product (**3**) as colorless plates, mp 225—226°C (from acetone) (lit.[5a] mp 225—226°C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (NH), 1650 (C=C), 1630 (CO). ^{1}H-NMR δ: 0.97 (3H, t, J=8 Hz, C_{20}–$CH_2C\underline{H}_3$), 1.42 (2H, q, J=8 Hz, C_{20}–$C\underline{H}_2CH_3$), 2.76 (1H, d, J=12 Hz, C_{17}–H), 3.04 (1H, d, J=12 Hz, C_{17}–H), 3.22 (1H, d, J=14 Hz, C_{21}–H), 3.45 (1H, d, J=18 Hz, C_{13}–H), 4.16 (1H, d, J=14 Hz, C_{21}–H), 4.27 (2H, s, $ArCH_2$), 4.88 (1H, d, J=18 Hz, C_{13}–H), 5.76 (2H, br s, C_{14}– and C_{15}–H), 7.10—7.72 (4H, m, Ar–H), 9.06 (1H, s, NH). UV λ_{max}^{MeOH} nm (log ε): 243 (4.15), 319.5 (4.21). MS *m/e* (%): 308 (80, M^+), 108 (100). High resolution MS *m/e*: Calcd for $C_{19}H_{20}N_2O_2$: 308.1523. Found: 308.1571. The synthetic product was proved to be identical with an authentic sample of (±)-5,16-dioxo-14,15-dehydroquebrachamine (**3**) by means of ^{1}H-NMR comparison.

Ethyl 5-Ethyl-3-(2-ethylenedioxyethyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (16)——A mixture of the alcohol (**6**; 978 mg), $Hg(OAc)_2$ (0.60 g), and ethyl vinyl ether (10 ml) was heated at 200°C in a sealed tube for 48 h. The solvent was evaporated off and the residue was taken up in C_6H_6 (70 ml). The organic layer was washed with water, 10% HCl, and then water and dried. The organic layer containing the crude aldehyde (**15**) was used for the next step without further purification.

The above solution containing **15** was concentrated to 2/3 of the original volume under reduced pressure, then ethylene glycol (2.0 ml) and *p*-TsOH (trace) were added to the residue. The resulting mixture was refluxed with stirring for 2 h while the water formed was azeotropically removed using a Dean–Stark apparatus. Work-up as usual gave an oily residue, which was chromatographed on alumina in C_6H_6 to afford 871 mg (66% from **6**) of the acetal (**16**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (CO). ^{1}H-NMR δ: 1.00 (3H, t, J=7.5 Hz, C_5–$CH_2C\underline{H}_3$), 1.23 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.67—4.00 (4H, m, OCH_2CH_2O), 4.09 (2H, q, J=7 Hz, $OCH_2C\underline{H}_3$), 4.88 (1H, t, J=5 Hz, $CH\langle^{O}_{O}$), 5.40 (1H, m, C_4–H). High resolution MS *m/e*: Calcd for $C_{14}H_{23}NO_4$: 269.1626. Found: 269.1623.

5-Ethyl-3-(2-ethylenedioxyethyl)-1,2,3,6-tetrahydropyridine (17)——A mixture of the urethane (**16**; 290 mg), KOH (10% aqueous solution; 5 ml), and EtOH (25 ml) was refluxed with stirring for 72 h. Work-up as usual gave an oily residue, which was chromatographed on alumina in C_6H_6. The first fraction afforded the unchanged starting material (**16**; 103 mg) and the second one afforded 126 mg (59%; 92% based on the consumed starting material) of the amine (**17**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3320 (NH), 1660 (C=C). ^{1}H-NMR δ: 0.98 (3H, t, J=7 Hz, C_5–$CH_2C\underline{H}_3$), 1.65 (2H, dd, J=6 and 4.5 Hz, C_3–CH_2), 1.90 (2H, q, J=7 Hz, C_5–$CH_2C\underline{H}_3$), 2.02 (1H, s, NH), 3.83 (4H, m, OCH_2CH_2O), 4.84 (1H, t, J=4.5 Hz, $CH\langle^{O}_{O}$), 5.33 (1H, m, C_4–H). High resolution MS *m/e*: Calcd for $C_{11}H_{19}NO_2$: 197.1414. Found: 197.1393.

5-Ethyl-3-(2-ethylenedioxyethyl)-1-(β-indolylacetyl)-1,2,3,6-tetrahydropyridine (18)——A solution of β-indolylacetyl chloride (0.50 g) in CH_2Cl_2 (10 ml) was added to a stirred solution of th amine (**17**; 472 mg) in CH_2Cl_2 (15 ml) over 1 min under ice cooling and then a solution of K_2CO_3 (0.50 g) in water (8 ml) was added

to the mixture. After further stirring for 5 min under ice cooling, work-up as usual gave an oily residue, which was chromatographed on Silica gel in $CHCl_3$ to afford 965 mg (quantitative yield) of the amide (**18**) as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (NH), 1625 (NCO). MS *m/e* (%): 354 (10, M^+), 130 (100).

5-Ethyl-1-(β-indolylacetyl)-3-(2-oxoethyl)-1,2,3,6-tetrahydropyridine (**19**)——A mixture of the acetal (**18**; 1.04 g), 10% HCl (1.0 ml), THF (50 ml), and water (2.5 ml) was refluxed with stirring for 2 h. The organic solvent was carefully evaporated off at room temperature *in vacuo* and the remainder was extracted with $CHCl_3$ (25 ml×3). The extract was washed with sat. $NaHCO_3$ and brine, dried, and concentrated to leave an oily residue (**19**, 929 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3475 (NH), 2730 (CHO), 1720 (CO), 1630 (NCO). ^{1}H-NMR δ: 0.95 (3H, t, J=7 Hz, C_5–$CH_2C\underline{H}_3$), 1.93 (2H, q, J=7 Hz, C_5–$C\underline{H}_2CH_3$), 5.35 (1H, m, C_4–H), 6.9—7.3 (4H, m, Ar H), 7.60 (1H, m, Ar–H), 8.03 (1H, m, NH), 9.56 (1H, s, CHO). The crude product of **19** was used for the next step without further purification.

Ethyl-1-(β-indolylacetyl)-1,2,3,6-tetrahydropyridine-3-acetic Acid (**20**)——A solution of $AgNO_3$ (540 mg) in distilled water (10 ml) was added to a stirre solution of the aldehyde (**19**; 929 mg) in EtOH (20 ml) all at once under ice cooling and then 5% aq. NaOH solution (5 ml) was added to the mixture over 2—3 min under ice cooling. After further stirring for 10 min, work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 662 mg (67% from **18**) of the carboxylic acid (**20**) as a yellow foam. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (NH), 3400—2400 (COOH), 1705 (CO), 1620 (NCO). ^{1}H-NMR δ: 0.94 (3H, t, J=7 Hz, C_5–$CH_2C\underline{H}_3$), 1.92 (2H, br q, J=7 Hz, C_5–$C\underline{H}_2CH_3$), 5.36 (1H, m, C_4–H), 6.9—7.4 (4H, m, Ar–H), 7.54 (1H, m, Ar–H), 8.15 (1H, m, NH). MS *m/e* (%): 326 (22, M^+), 130 (100).

(±)-5,16-Dioxocleavamine (**4**)——a) The carboxylic acid (**20**; 784 mg) was added to PPA (*ca.* 118% H_3PO_4; 60 ml) and the mixture was stirred at 85°C for 40 min. Ice water was added and the resulting mixture was extracted with $CHCl_3$ (20 ml×4). The extract was washed with sat. $NaHCO_3$ and brine, dried, and concentrated to leave a brown residue, which was chromatographed on silica gel in $CHCl_3$. The first fraction afforded 96 mg (12%) of the cyclized product (**4**) as pale yellow plates, mp 199—200°C (from AcOEt). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470 (NH), 1650 (C=C, NCO). ^{1}H-NMR δ: 1.02 (3H, t, J=7 Hz, C_{14}–$CH_2C\underline{H}_3$), 1.98 (2H, q, J=7 Hz, C_{14}–$C\underline{H}_2CH_3$), 3.39 (1H, d, J=17 Hz, C_{13}–H), 4.85 (1H, d, J=17 Hz, C_{13}–H), 5.63 (1H, m, C_{15}–H), 6.90—7.38 (3H, m, Ar–H), 7.65 (1H, m, Ar–H), 9.09 (1H, m, NH). UV λ_{max}^{MeOH} nm (log ε): 244.5 (4.12), 321.5 (4.19). High resolution MS *m/e*: Calcd for $C_{19}H_{20}N_2O_2$: 308.1523. Found: 308.1517. The second fraction afforded the unchanged starting material (**20**; 409 mg). The yield of the dioxocleavamine (**4**) based on the consumed starting material was 26%.

b) A mixture of the carboxylic acid (**20**; 476 mg), PPE (1.5 ml) and dry $CHCl_3$ (100 ml) was refluxed with stirring for 2 h. The reaction mixture was washed with water, sat. $NaHCO_3$, and then water. The dried organic layer was concentrated to leave an oily residue, which was subjected to column chromatography (silica gel in $CHCl_3$) to afford 154 mg (36%) of **4**, which was identical with the sample obtained in a).

(±)-Cleavamine (**2**) **and (±)-16-Hydroxycleavamine** (**23**)——A mixture of **4** (162 mg), $LiAlH_4$ (576 mg), and dry dioxane (30 ml) was heated with stirring at 90°C for 2 h. Excess $LiAlH_4$ was decomposed with AcOEt and aqueous sat. Rochelle salt solution was added to the mixture. The inorganic substances were filtered off and the filtrate was dried and concentrated to leave a residue, which was chromatographed on alumina in C_6H_6. The first fraction afforded 19 mg (13%) of (±)-cleavamine (**2**) as colorless crystals, mp 113—114.5°C (from MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (NH), 1620 (C=C). ^{1}H-NMR δ: 1.06 (3H, t, J=7 Hz, C_{14}–$CH_2C\underline{H}_3$), 2.00 (2H, q, J=7 Hz, C_{14}–$C\underline{H}_2CH_3$), 5.25 (1H, m, C_{15}–H), 6.88—7.32 (3H, m, Ar–H), 7.42 (1H, m, Ar–H), 7.72 (1H, s, NH). UV λ_{max}^{MeOH} nm (log ε): 229.5 (4.40), 285.5 (3.76), 292.5 (3.72). High resolution MS *m/e*: Calcd for $C_{19}H_{24}N_2$: 280.1937. Found: 280.1931. The second fraction afforded 650 mg (42%) of (±)-16-hydroxycleavamine (**23**) as pale yellow crystals, mp 173—174°C (from ether). IR ν_{max}^{KBr} cm^{-1}: 3200 (NH, OH), 1615 (C=C). ^{1}H-NMR δ: 0.99 (3H, t, J=7 Hz, C_{14}–$CH_2C\underline{H}_3$), 1.96 (2H, q, J=7 Hz, C_{14}–$C\underline{H}_2CH_3$), 5.20 (1H, d d, J=11 and 5 Hz, C_{16}–H), 5.42 (1H, m, C_{15}–H), 6.84—7.28 (3H, m, Ar–H), 7.46 (1H, m, Ar–H), 8.34 (1H, s, NH), 8.65 (1H, d, J=11 Hz, OH). High resolution MS *m/e*: Calcd for $C_{19}H_{24}N_2O$: 296.1887. Found: 296.1896. The synthetic (±)-cleavamine (**2**) was proved to be identical with (+)-cleavamine by means of TLC, IR, and ^{1}H-NMR comparisons.

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