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STUDIES ON THE SYNTHESIS OF PENTACYCLIC *STRYCHNOS* INDOLE ALKALOIDS. PHOTOCYCLIZATION OF N-CHLOROACETYL-1,2,3,4,5,6-HEXAHYDRO-1,5-METHANOAZOCINO[4,3-b]INDOLE DERIVATIVES.[1]

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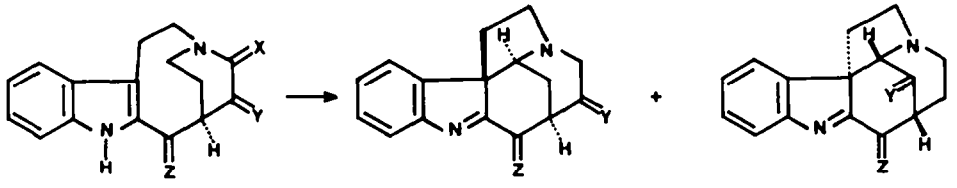
Abstract - Photocyclization of 2-chloroacetyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole (5) takes place at the indole 4-position to give a 1,2,3,4,5,6-hexahydro-2,11-ethano-1,5-methanoazocino[4,3-b]indole system. Consequently, the method appears to be unsuitable for constructing the pyrrolidine ring of pentacyclic *Strychnos* indole alkaloids.

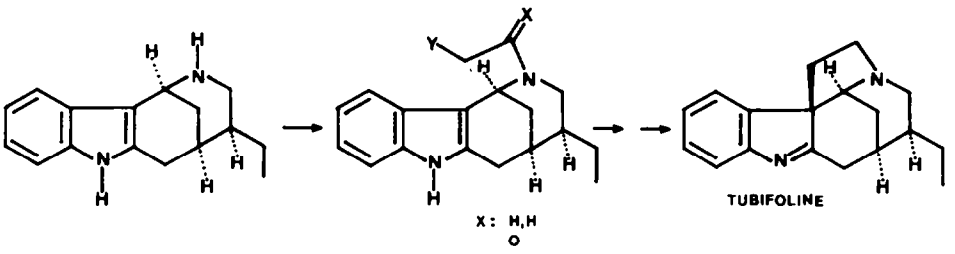
Although the synthesis of indole alkaloids, especially those related to *Corynanthe*, *Aspidosperma*, and *Iboga* structural types, has received considerable attention during recent years, a few synthetic routes to pentacyclic *Strychnos* indole alkaloids (tubifoline, condyfoline, condylocarpine, geissoschizoline, fluorocurarine, tubotaiwine) have been developed to date. Most of these syntheses converge to the tetracyclic ring skeleton of stemmadenine, which is further subjected to transanular cyclization by formation of the bond between the indole 3-position and one of the α-carbons of the piperidine ring.[2,3]



SCHEME 1

In the context of our studies directed to the synthesis of pentacyclic *Strychnos* indole alkaloids we planned to develop a new synthetic entry to these alkaloids consisting in the elaboration of the five membered E ring in the last synthetic steps from an appropriate tetracyclic 1,2,3,4,5,6-hexahydro-1,5-methanoazocino [4,3-b]indole system through introduction of a two-carbon unit on the piperidine

nitrogen atom followed by cyclization upon the indole 3-position. A conceptually similar route starting from a suitable octahydropyrido[3,2-c]carbazole system has successfully been employed for the synthesis of *Aspidosperma* alkaloids (minovine,[4] aspidospermidine,[5] kopsanone[6]) and related structures.[7]

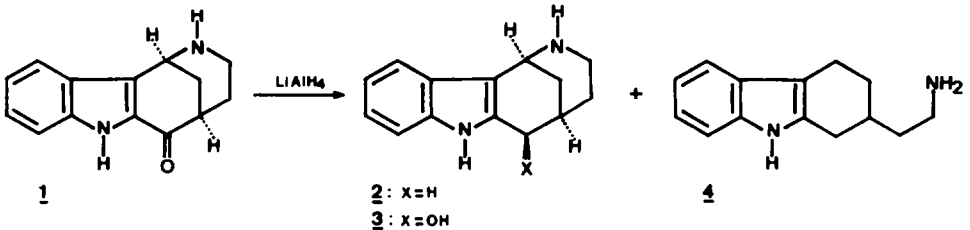


SCHEME 2

Among the several possibilities for constructing the E ring following the above methodology we selected that based on the photocyclization of an appropriate chloroacetamide. Photocyclization of chloroacetamides upon activated aromatic rings is a well known process,[8] which has been applied to the synthesis of indole alkaloids (tubifoline and condyfoline[2c]) and simplified analogues such as 20-deethylcatharanthine[9] and the tetracyclic ring skeletons of ngouniensine,[10] stemmadenine,[11] and quebrachamine-dihydrocleavamine.[12]

In order to evaluate the effectiveness of our proposal, since in a previous paper[13] we had reported a convenient synthesis of the tetracyclic secondary amine 1 (20-deethyl-4-demethyldasycarpidone[14]), we chose this simplified model structure lacking the C-20[14] two-carbon substituent characteristic of the majority of indole alkaloids as starting material.

As we reported before, attempts to reduce the carbonyl group of 1 under Wolff-Kishner conditions were unsuccessful, and 2,3-dihydro-1*H*-pyrrolo[2,3-*a*]carbazole was obtained as the only product.[15] For this reason we turned our attention to lithium aluminium hydride as a reducing agent for 2-acylindoles.[16] As expected, when ketone 1 was treated with an excess of lithium aluminium hydride in refluxing dioxane, the tetracyclic amine 2 was obtained in 53% yield. The corresponding alcohol 3, identical to that obtained by sodium borohydride reduction of ketone 1,[17] and the tetrahydrocarbazole 4 were obtained as by-products.



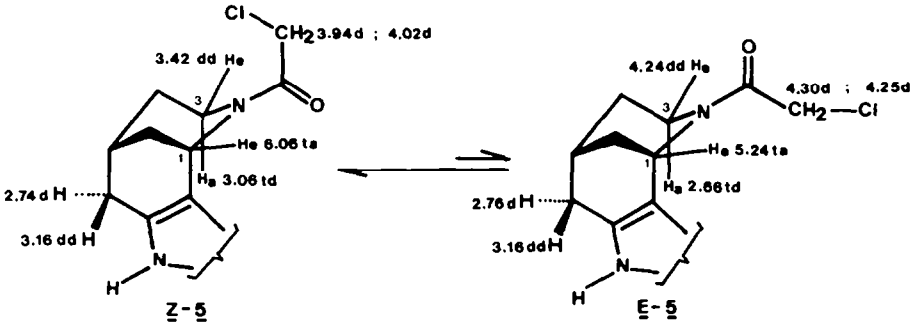
SCHEME 3

Formation of tetrahydrocarbazole 4 can be explained by considering the cleavage of the C_1-N_b bond of 2, a well known process in 3-aminomethylindoles,[18] followed by hydride addition to the resulting 3-alkylidene-3*H*-indole.

The ^{1}H-NMR spectrum of compound 2 showed, as the most significative signals, an apparent triplet at δ4.4 corresponding to the C-1 proton, as well as a doublet of

doublets at δ3.1 and a doublet at δ2.6 due to the pseudoaxial and pseudoequatorial protons of C-6 position, respectively.

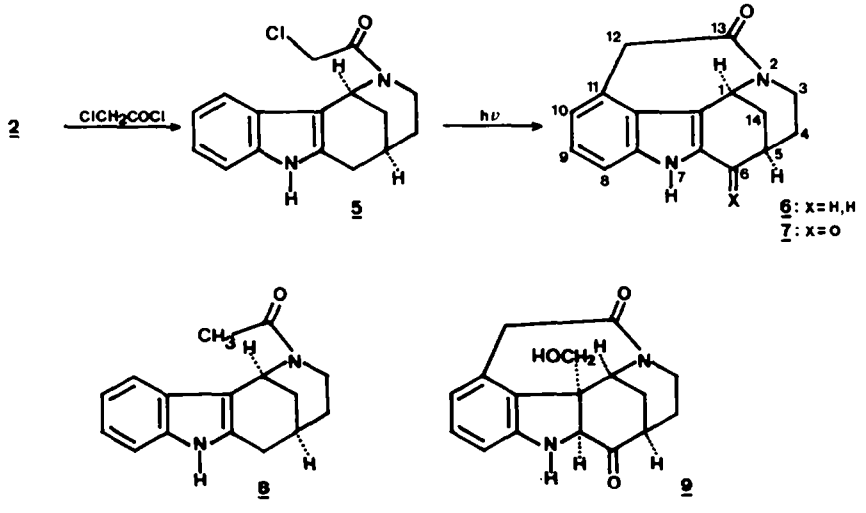
Treatment of amine 2 with chloroacetyl chloride under Schotten-Baumann conditions provided the chloroacetamide 5 in 65% yield as a mixture of rotamers due to restricted rotation of the chloroacetamide group.[19] Both rotamers, E and Z, were easily assignable in the ^{1}H-NMR spectrum on the basis of the multiplicity and chemical shift of signals corresponding to C-1, C-3, and diastereotopic methylene protons of the chloroacetamide group. The observed chemical shifts are showed in the following scheme.



SCHEME 4

As would be expected,[20] equatorial C-1 and C-3 protons appear more strongly deshielded in that rotamer in which they are located *cis* respect with the carbonyl group, whereas in the same situation the axial C-3 proton resonates at a higher magnetic field. The relative integration of the apparent triplets due to C-1 proton in both rotamers, two signals that do not overlap with any other in the spectrum, allows one to calculate a 78% population of rotamer Z, in which the bulkier substituent on amide nitrogen is located *cis* with respect to the carbonyl group.[21]

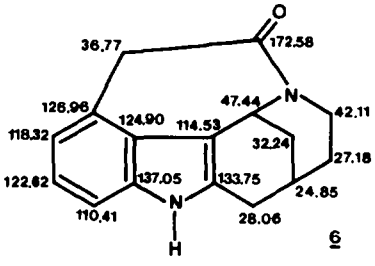
As mentioned above, photocyclization of chloroacetamide 5 at the indole 3-position should afford the pentacyclic ring system of *Strychnos* indole alkaloids. However, when compound 5 was subjected to photolysis for 45 minutes in methanolic solution containing potassium carbonate, instead of the desired system, the pentacyclic compound 6 coming from photocyclization of chloroacetamide at the indole 4-position was isolated in 40% yield. As by-product, 2-acylindole 7 was isolated in



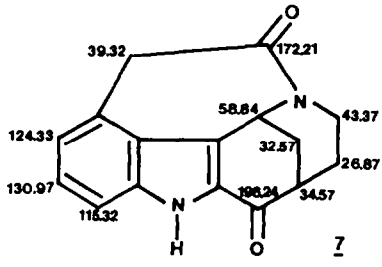
SCHEME 5

10% yield. When the irradiation time was increased to 3 hours 20 minutes, the yields of pentacyclic compounds 6 and 7 were 28% and 34%, respectively. Under these conditions acetamide 8 and alcohol 9 were also isolated as minor by-products (less than 6% yield).

The molecular formula $C_{16}H_{16}N_2O$ was assigned to compound 6 on the basis of its elemental analysis and mass spectral data (M^+, 252). This clearly indicated that cyclization had occurred. However, the ^{1}H- and ^{13}C-NMR spectra established that indole 4-position, instead of 3-position, was the site of photocyclization. Thus, the most significant signals in the ^{1}H-NMR spectrum of 6 were: *i*) two doublets and one triplet in the aromatic region, corresponding to three protons in a vicinal relative position. This splitting pattern and coupling constants, along with the observation that 4-position is the only one of indole benzene ring available for cyclization, pointed out the structure 6 for this photocyclized product. *ii*) An apparent triplet at δ5.24 due to the methine proton between the aromatic ring and the nitrogen amide. This chemical shift, identical to that of the same proton in the *E* rotamer of the starting chloroacetamide 5, confirmed that cyclization had not occurred on the indole 3-position; a higher field shift would be expected for C-1 proton in this case as a consequence of the sp^3 character of indolenine 3-position. *iii*) A prominent AB-pattern corresponding to the diastereotopic methylene protons adjacent to the carbonyl group (δ3.48 and 4.78, *J*=14 Hz). The ^{13}C-NMR spectrum of 6 was in agreement with the proposed structure (see Scheme 6). The most significant datum was the presence of eight signals in the aromatic region, only three of them appearing as doublets in the off-resonance decoupled spectrum.



6



7

SCHEME 6

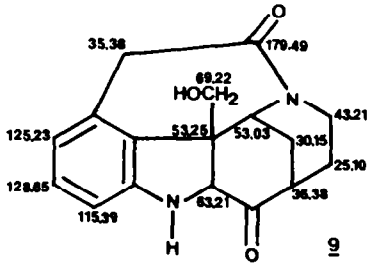
The fact that cyclization had proceeded on the indole 4-position would not be surprising, for though the indole 3-position is the one of highest reactivity towards chloroacetamide photocyclization, it has been demonstrated that the 4-position also possesses a high degree of reactivity.[22] In this context, it is worth commenting that the first example of chloroacetamide photocyclization upon an indole ring was that of chloroacetamide derived from tryptophan, and this cyclization took place at the indole 4-position to give an 8-membered lactam.[23]

On the basis of its mass spectrum (M^+, 266) and elemental analysis, the molecular formula $C_{16}H_{14}N_2O_2$ was assigned to compound 7. This revealed that an oxidation with respect to compound 6 had occurred. Also, the IR spectrum of 7 showed carbonyl absorptions at 1660 and 1615 cm^{-1}, indicative of a medium sized lactam and a 2-acylindole, respectively. These data, along with ^{1}H- and ^{13}C-NMR spectra, pointed out that the site of oxidation was the methylene contiguous to the indole nucleus. The most significant signals in the ^{1}H-NMR spectrum were: *i*) two doublets and a triplet in the aromatic region at a field lower than in compound 6, which is in agreement with the presence of an electron-withdrawing substituent attached to the indole ring; *ii*) a doublet at δ5.44 corresponding to the C-1 methine proton; *iii*) an AB system due to the diastereotopic methylene protons adjacent to the

amide carbonyl group. Finally, the assignment of structure 7 was confirmed by the ^{13}C-NMR data (see Scheme 6) : *i*) two signals, at δ172.2 and 196.2, due to amide and 2-acylindole carbonyl carbons, respectively; *ii*) three signals in the aromatic region appearing as doublets in the off-resonance spectrum; *iii*) six signals in the aliphatic region, corresponding to piperidine ring and benzylic methylene carbons.

The photooxidation of 2,3-dialkylindoles to the corresponding 2-acylindoles through 3-hydroperoxyindolenines as intermediates is a well known process.[24] In our experiments, though the irradiations were carried out under nitrogen, the presence of oxygen traces in the reaction medium cannot be absolutely excluded.

The structural assignment of minor product 9 was made from its spectroscopic data. The mass spectrum showed a molecular ion at m/e 298, 32 mass units more than in compound 7, and a base peak at m/e 267 corresponding to a loss of 31 mass units (CH_2OH) from the molecular ion. These data suggested a molecular formula $C_{17}H_{18}N_2O_3$ as well as the presence of an hydroxymethyl group. The ^{1}H-NMR spectrum exhibited, as in compounds 6 and 7, two doublets and a triplet in the aromatic region, and an AB system due to the diastereotopic methylene protons adjacent to amide carbonyl group. Although these data pointed out that cyclization had also taken place at the indole 4-position, the chemical shift (δ4.50) of the equatorial C-1 methine proton, at a field higher than in compounds 6 and 7, indicated the sp^3 character of the adjacent C-11b and therefore the presence of an indoline ring. The observation of a second AB system, at δ3.38 and 3.58, attributable to the diastereotopic methylene protons of the hydroxymethyl group is in agreement with the structure 9. The ^{13}C-NMR chemical shifts of 9 are given in the Scheme 7. The multiplicities in the off-resonance decoupled spectrum gave valuable information and confirmed the proposed structure: *i*) three doublets in the aromatic region; *ii*) a singlet at δ53.25 due to the quaternary carbon atom of the indoline 3-position,[25] which establishes that the addition of the hydroxymethyl group had occurred at this point; *iii*) three doublets in the aliphatic region, one more than in compounds 6 and 7, corresponding to methine of the indoline 2-position (C-6a) and bridgehead C-1 and C-5 positions; *iv*) signals due to five methylene carbons, one of them (δ69.22) attributable to that of hydroxymethyl substituent.



9

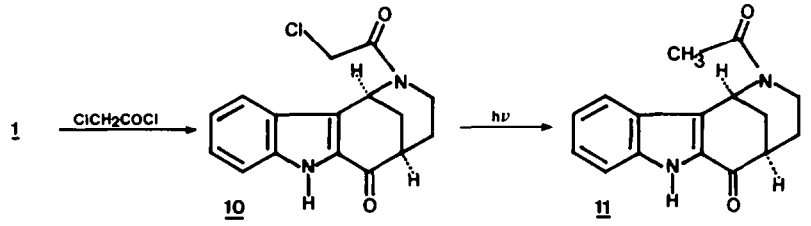
SCHEME 7

The formation of 9 can be accounted for by considering the conjugate photoaddition of methanol, solvent of reaction, upon the α,β-unsaturated ketone moiety of 7, a process which has been observed previously.[26]

The acetyl derivative 8 comes from dechlorination of the chloroacetyl group of compound 5. The reductive photodehalogenation of chloroacetamides is a well known process that involves an hydrogen abstraction from solvent.[27] Acetamide 8 was characterized by comparison with a sample unambiguously prepared by reaction of tetracyclic amine 4 with acethyl chloride. The most significant signals in the ^{1}H-NMR spectrum of 8 were two singlets (δ2.00 and 2.42) attributable to the acetamide me-

thyl group and two apparent triplets (δ5.20 and 6.16)due to the C-1 methine proton. The splitting of these signals indicated again the presence of rotamers.

In order to verify that oxidation of C-6 occurred after cyclization, chloroacetamide 10 was subjected to photocyclization conditions. It should be noted that, to our knowlwdge, there are no precedents of chloroacetamide photocyclizations on 2-acylindoles. Chloroacetamide 10 was prepared in excellent yield from aminoketone 1 by reaction with chloroacetyl chloride. Its ^{1}H-NMR spectrum also revealed the presence of rotamers, 93% of the Z rotational isomer being inferred from the relative integration of two apparent triplets due to C-1 methine proton. However, photolysis of chloroacetamide 10 under conditions similar to those used for compound 5 provided acetamide 11 in about 20% yield as the only isolable product. This result clearly establishes that oxidation takes place after cyclization of 5 and is in agreement with the observed increase in the proportion of 7 when the irradiation time of chloroacetamide 5 was prolonged. Acetamide 11 was identical (m.p., IR, NMR) to that prepared unambiguously by acetylation of amine 1.



SCHEME 8

The different behavior of chloroacetamides 5 and 10 under photolysis conditions probably reflects the deactivation towards photocyclization caused by the carbonyl group conjugated with the indole ring. Another factor that could explain the different reactivity of both chloroacetamides is that the ratio of rotamer E, having the required steric relationship for cyclization, in 10 is smaller than in 5.[21]

The results here reported make evident that photocyclization of 2-chloroacetyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole derivatives does not constitute a valid method for constructing the five-membered E ring of pentacyclic *Strychnos* indole alkaloids. Some factors could account for this failure: a) It is known that photocyclization of chloroacetamides on an aromatic nucleus is a good method of forming medium sized rings.[8c] In fact, compound 6 has a seven membered lactam, while photocyclization of 5 at an indole 3-position to give a pentacyclic *Strychnos* structure would imply closure of a five membered ring. b) As can be inferred from Dreiding stereomodels, in the boat piperidine conformation, that required for cyclization, the chloroacetyl group lies nearer to indole 4-position than to the indole 3-position. c) Finally, formation of pentacyclic *Strychnos* structures by photolysis of chloroacetamide 5 would imply the attack of the radical coming from chloroacetyl group upon a substituted indole 3-position, a process that to our knowledge has not been previously recorded.[28] In this context, it is worth commenting that the failure to obtain a pentacyclic *Aspidosperma* structure by chloroacetamide photocyclization on the substituted indole 3-position of an appropriate octahydropyrido[3,2-c]carbazole system has recently been reported.[5b]

EXPERIMENTAL

General. ^{1}H-NMR spectra were recorded with a Varian XL-200 (200 MHz) instrument or, where indicated, on a Perkin-Elmer R-24B (60 MHz) spectrometer using TMS as internal standart. ^{13}C-NMR spectra were determined on a Varian XL-200 spectrometer in $CDCl_3$-CD_3OD solution, unless indicated. Chemical shifts are reported in ppm downfield (δ) from TMS. IR spectra were taken with a Perkin-Elmer 1430 spectrophotometer, and only noteworthy absorptions (reciprocal centimeters) are listed. Mass spectra were obtained with a MS9-ZAB mass spectrometer. Melting points were determined with a Büchi capillary melting point apparatus and are uncorrected. Thin layer chromatography were done with Merck silica gel 60 F_{254}, aluminium pre-coated sheets. Routine column chromatographic purification of compounds was conducted using Merck silica gel 60 (catalog No. 7734) or Merck neutral aluminiumoxid 90 (aktiv I) (catalog No. 1077). Iodoplatinate reagent was used to locate the reaction components. Prior to concentration under reduced pressure, all organic extracts were dried over anhydrous sodium sulfate powder. Microanalyses were performed by the Instituto de Química Bio-Orgánica, Barcelona.

1,2,3,4,5-Hexahydro-1,5-methanoazocino[4,3-b]indole (2). An excess of lithium aluminium hydride (4.2 g, 110 mmol) was slowly added under nitrogen to a solution of 1[15] (2.5 g, 11 mmol) in anhydrous dioxane (200 ml). After 17 h of refluxing,[29] the mixture was cooled in an ice bath and the excess of lithium aluminium hydride was decomposed with 8 ml of water. The dioxane solution was decanted and the aluminium salts were digested with chloroform (3×100 ml). The chloroform and dioxane solutions were combined, dried, and evaporated to give a pale yellow foam (2.4 g) which was chromatographed through silica gel. On continuous elution with 70:30:5 ether-acetone-diethylamine, compound 2, alcohol 3, and tetrahydrocarbazole 4 were isolated in the following order: *i*) *2-(2-aminoethyl)-1,2,3,4-tetrahydrocarbazole* (4): 0.52 g (22% yield); NMR (60 MHz, $CDCl_3$) 1.0-2.9 (complex signal, 13H, aliphatic and NH_2); 6.7-7.5 (m, 4H, indole); 8.1 (br s, 1H, indole NH); IR (NaCl) 3470 (indole NH), 3120-3440 (NH_2). The picrate melted at 196-198ºC (absolute ethanol). (Found: C,54.26; H, 4.56; N,15.79. Calcd. for $C_{20}H_{21}N_5O_7$: C,54.18; H,4.77; N,15.79). *ii*) 2: 1.20 g (53% yield); NMR ($CDCl_3$) 1.50-2.74 (complex signal, 8H, alicyclic and NH); 2.60 (d, J=18 Hz, 1H, H-6eq); 3.10 (dd, J=18, 7Hz, 1H, C-6ax); 4.44 (apparent t, 1H, H-1); 7.00-7.76 (m, 4H, indole); 8.10 (br s, 1H, indole NH); IR ($CHCl_3$) 3480 (indole NH); ^{13}C-NMR ($CDCl_3$) 25.57 (d, C-5); 28.70 (t, C-6); 32.02 (t, C-12); 32.19 (t, C-4); 36.83 (t, C-3); 44.38 (d, C-1); 108.38 (s, C-11b); 110.57 (d, C-8); 116.92 (d, C-11); 119.06 (d, C-9); 120.77 (d, C-10); 125.65 (s, C-11a); 135.97 (s, C-6a); 136.56 (s, C-7a). The picrate melted at 201-202ºC (absolute ethanol). (Found: C,54.78; H,4.31; N,15.53. Calcd. for $C_{20}H_{19}N_5O_7$: C,54.42; H,4.34; N,15.86). *iii*) *6-Hydroxy-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole* (3): 0.37 g (15% yield). A sample recrystallized from absolute methanol melted at 225-227ºC; NMR (60 MHz, DMSO-d_6) 1.4-2.5 (complex signal, 7H, alicyclic); 3.8 (br s, 2H, NH and OH); 4.1 (apparent t, 1H, H-1); 4.9 (d, 1H, J=6 Hz, H-6); 6.7-7.5 (m, 4H, indole); 11.3 (br s, 1H, indole NH); IR (KBr) 3400 (indole NH), 3000-3600 (OH and NH); MS, m/e (relative intensity) 228 (M^+, 27),211(13),181(26),180(27),168(54),167(100),158(15),156(14),143(21),130(21), 117(12),115(12),91(8),89(9). (Found: C,73.41; H,7.19; N,12.08. Calcd. for $C_{14}H_{16}N_2O$: C,73.66; H,7.06; N,12.27).

When the excess of lithium aluminium hydride was decomposed with ethyl acetate instead of water, *2-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole* was also isolated from the reaction mixture.[30] NMR (60 MHz, $CDCl_3$) 1.1 (t, 3H, CH_3); 1.3-3.3 (complex signal, 11H, aliphatic); 4.1 (apparent t, 1H, H-1); 6.7-7.5 (m, 4H, indole); 8.5 (br s, 1H, NH); IR (KBr) 3400 (NH). The hydrochloride melted at 232-235ºC (acetone). (Found: C,69.22; H,7.64; N,9.98; Cl,13.12. Calcd. for $C_{16}H_{21}ClN_2$: C,69.43; H,7.65; N,10.12; Cl,12.81).

2-Chloroacetyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole (5). A solution of chloroacetyl chloride (0.3 ml, 3.7 mmol) in methylene chloride (10 ml) was added dropwise under nitrogen to a stirred two phase mixture of amine 2 (400 mg, 1.9 mmol) in methylene chloride (20 ml) and 1N aqueous sodium hydroxide solution (14 ml) The resulting mixture was stirred for 5 h at room temperature and the organic layer was separated. The aqueous layer was extracted with methylene chloride (3×100 ml). The combined organic solutions were washed with brine, dried, and evaporated to give a solid residue which was chromatographed through alumina. On elution with 4:6 benzene-chloroform, pure chloroacetamide 5 was obtained (350 mg, 65% yield). A sample recrystallized from anhydrous acetone melted at 178-179ºC; NMR ($CDCl_3$-CD_3OD) 1.60-2.40 (m, 4H, H-4 and H-12); 2.52 (m, 1H, H-5); 2.74 and 2.76 (2d, J=17Hz, 1H, H-6eq); 2.66 and 3.06 (2td, J=14, 4Hz, 1H, H-3ax); 3.16 (dd, J=17, 7Hz, 1H, H-6ax); 3.42 and 4.24 (2dd, J=14, 6Hz, 1H, H-3eq); 3.94 and 4.02 (2d, J=12Hz, Z rotamer, $ClCH_2CO$); 4.30 and 4.25 (2d, J=12Hz, E rotamer, $ClCH_2CO$); 5.24 and 6.06 (2 apparent t, 1H, H-1); 7.00-7.20 (m, 2H, H-9 and H-10); 7.30 (d, J=8 Hz, H-8); 7.54 (d, J=8Hz, 1H, H-11); IR ($CHCl_3$) 3470 (NH), 1620 (C=O). (Found: C,66.92; H,5.96; N,9.88. Calcd. for $C_{16}H_{17}ClN_2O$: C,66.55; H,5.93; N,9.70).

Photolysis of chloroacetamide 5. A solution of chloroacetamide 5 (950 mg, 3.3 mmol) in methanol (300 ml) containing potassium carbonate (1 g, 7.2 mmol) was irradiated under nitrogen at room temperature for 3 h 20 min using a 125W medium-pressure mercury lamp in a quartz immersion well reactor. The reaction mixture was evaporated to dryness and the residue was repeatedly chromatographed through silica gel:

i) On elution with 8:2 benzene-chloroform, *13-oxo-1,2,3,4,5,6-hexahydro-2,11-ethano-1,5-methanoazocino[4,3-b]indole* (6) was obtained in 28% yield. A sample recrystallized from absolute methanol melted at 283-285ºC; UV(EtOH):λmax 269(logε=3.78) nm; NMR ($CDCl_3$-CD_3OD) 0.93 (tt, J=14, 5Hz, 1H, H-4ax); 1.88-2.04 (m, 1H, H-4eq); 2.02 (dd, J=14, 3.5Hz, 1H, H-14eq); 2.36 (d, J=14Hz, 1H, H-6eq); 2.32-2.64 (complex signal, 2H, H-5eq and H-14ax); 2.86-2.98 (m, 1H, H-6ax); 2.94 (td, J=14, 4Hz, 1H, H-3ax); 3.48 and 4.78 (2d, J=14Hz, 2H, H-12); 3.88 (ddd, J=14, 5, 2Hz, 1H, H-3eq); 5.24 (t, J=3.5Hz, 1H, H-1); 6.78 (d, J=8Hz, 1H, H-10); 6.96 (t, J=8Hz, 1H, H-9); 7.10 (d, J=8Hz, 1H, H-8); IR (KBr) 3120-3300 (NH), 1620 (C=O); MS, m/e (relative intensity) 253 (M^{+}+1, 14),252(M^{+}, 100),251(14),223(20),195(17),194(16),183(20),182 (50),181(51),180(82),169(21),168(39),167(52),166(20),154(53),152(23),127(21),115 (24),77(16),63(15),56(40). (Found: C,76.07; H,6.68; N,11.02. Calcd. for $C_{16}H_{16}N_2O$: C,76.16; H,6.39; N,11.10). *ii*) On elution with 9:1 benzene-chloroform, *2-acetyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole* (8) was obtained in less than 5% yield. Its spectroscopic data were coincident with those of compound prepared by acetylation of amine 2 with acetyl chloride. *iii*) On elution with 96:4 chloroform-methanol, *6,13-dioxo-1,2,3,4,5,6-hexahydro-2,11-ethano-1,5-methanoazocino[4,3-b]indole* (7) was isolated in 34% yield. A sample recrystallized from absolute methanol melted higher than 320ºC; UV(EtOH):λmax 323(logε=3.70),289(logε=3.74),281(logε=3.75) nm; NMR ($CDCl_3$-CD_3OD) 1.68-1.88 (m, 1H, H-4eq); 1.90-2.08 (m, 1H, H-4ax); 2.45 (dtd, J=12, 4.5, 2Hz, 1H, H-14eq); 2.82 (d, J=12Hz, 1H, H-14ax); 3.48 and 4.80 (2d, J=15 Hz, 2H, H-12); 3.50-3.62 (complex signal, 2H, H-5eq and H-3ax); 4.30 (ddd, J=14, 7, 2Hz, 1H, H-3eq); 5.44 (d, J=4.5Hz, 1H, H-1); 7.02 (dt, J=7, 1Hz, 1H, H-10); 7.18 (dt, J=9, 1Hz, 1H, H-8); 7.36 (dd, J=9, 7Hz, 1H, H-9); IR (KBr) 3320-3600 (NH), 1660 (C=O lactam), 1615 (C=O acylindole); MS, m/e (relative intensity)267(M^{+}+1,19),266 (M^{+},100),238(19),237(71),211(17),210(79),209(36). (Found: C,67.33; H,5.65; N,9.74. Calcd. for $C_{16}H_{14}N_2O_2.H_2O$: C,67.53; H,5.62, N,9.84). *iv*) Finally, on elution with 9:1 chloroform-methanol, *11b-hydroxymethyl-6,13-dioxo-1,2,3,4,5,6,6a,11b-octahydro-2,11-ethano-1,5-methanoazocino[4,3-b]indole* (9) was isolated in 6% yield, m.p. 275-280ºC; UV(EtOH):λmax 274(logε3.17)nm; NMR ($CDCl_3$-CD_3OD) 1.04-1.34 (m, 1H, H-4ax); 1.82-2.06 (m, 2H, H-14ax and H-4eq); 2.28 (d, J=13Hz, 1H, H-14eq); 2.82-3.10 (complex signal, 3H, H-3ax, H-6a and H-5eq); 3.20 and 3.42 (2d, J=13Hz, 2H, H-12); 3.48 and 3.58 (2d, J=11Hz, 2H, CH_2OH); 3.56 (dd, J=13, 6.5Hz, 1H, H-3eq); 4.5 (d, J=4Hz, 1H, H-1); 6.76 (d, J=8Hz, 1H, H-10); 6.94 (d, J=8Hz, 1H, H-8); 7.12 (t, J= 8Hz, 1H, H-9); IR ($CHCl_3$) 3300-3450 (NH and OH), 1630-1700 (C=O lactam and C=O); MS, m/e (relative intensity): 299(M^{+}+1, 8),298(M^{+},35),268(26),267(100),239(35),170 (18),115(18),83(15),82(18),55(15).

2-Acetyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole (8). Operaring as in the case of chloroacetamide 5, acetamide 8 (173 mg, 72% yield) was obtained from amine 2 (200 mg, 0.9 mmol) and acetyl chloride (0.15 ml, 1.9 mmol) in methylene chloride (21 ml) and 1N aqueous sodium hydroxide solution (5 ml). A sample recrystallized from anhydrous acetone melted at 195-197ºC; NMR ($CDCl_3$-CD_3OD) 1.56-2.16 (m, 4H, H-4 and H-12); 2.00 and 2.42 (2s, 3H, CH_3CO); 2.50 (m, 1H, H-5); 2.71 and 2.73 (2d, 1H, H-6eq); 2.61 and 3.03 (2td, J=14.5, 4Hz, 1H, H-3ax); 3.16 (dd, J=17, 7Hz, 1H, H-6ax); 3.42 and 4.36 (2dd, J=13.5, 5.5Hz, 1H, H-3eq); 5.20 and 6.16 2 apparent t, 1H, H-1); 7.00-7.42 (m, 3H, indole); 7.60 (d, 1H, H-11); 8.22 and 8.38 (2br s, 1H, NH); IR (KBr) 3120-3300 (NH), 1610 (C=O). (Found: C,75.86; H,7.23; N,11.17. Calcd. for $C_{16}H_{18}N_2O$: C,75.56; H,7.13; N,11.01).

2-Chloroacetyl-6-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole (10). To a solution of amine 1 (500 mg, 2.2 mmol) in chloroform (25 ml) containing potassium carbonate (700 mg) a solution of chloroacetyl chloride (0.23 ml, 3.3 mmol) in chloroform (10 ml) was added dropwise. The mixture was stirred at room temperature for 1 h 30 min. After addition of water (10 ml), stirring was maintained for 20 min. The chloroform layer was collected and the aqueous phase was extracted with chloroform (3×50 ml). The combined organic extracts were washed with brine, dried, and evaporated to give a solid which was chromatographed through silica gel. On elution with 2:8 benzene-chloroform, pure 10 (640 mg, 95% yield) was obtained. A sample recrystallized from anhydrous acetone melted at 193-195ºC; NMR ($CDCl_3$-CD_3OD) 1.96-2.44 (m, 3H, H-4 and H-12ax); 2.60 (dc, 1H, J=13, 6, 3Hz, 1H, H-12eq); 2.95 (m, 1H, H-5eq); 2.70 and 3.14 (2td, J=14, 4.5Hz,1H, H-3ax); 3.62 and 4.44 (2dd, J=14, 5Hz, 1H, H-3eq); 4.02 and 4.06 (2d, J=12Hz, Z rotamer, $ClCH_2CO$); 4.34 and 4.54 (2d, J=12Hz, E rotamer, $ClCH_2CO$); 5.50 and 6.34 (2 apparent t, 1H, H-1); 7.20 (t, J=8Hz, 1H, H-10); 7.36-7.54 (m, 2H, H-8 and H-9); 7.86 (d, J=8Hz, 1H, H-11); 9.31 and 9.54 (2br s, 1H, NH); IR (KBr) 3150-3500 (NH), 1610-1680 (C=O amide and 2-acylindole); ^{13}C-NMR ($CDCl_3$) 29.16 (t, C-4); 34.97 (t, $ClCH_2$); 39.26 (t, C-12); 41.29 (d, C-5); 41.39 (t, C-3); 41.76 (d, C-1); 112.85 (d, C-8); 121.51 (d, C-11); 122.40 (d, C-10); 124.33 (s, C-11b); 124.94 (s, C-11a); 127.77 (d, C-9); 133.24 (s, C-6a); 138.43 (s, C-7a); 165.65 (s, NCO); 192.60 (s, C-6). (Found: C, 63.27; H,5.47; Cl,11.03; N,8.08. Calcd. for $C_{16}H_{15}ClN_2O_2.1/2C_3H_6O$: C,63.35; H,5.46; Cl,10.68; N,8.44).

Photolysis of chloroacetamide 10. Irradiations of chloroacetamide 10 were carried out in the same conditions that in the case of 5, using methanol (3 h) or acetonitrile (9 h) as solvents. In all cases, acetamide 11 was the only product isolable in about 20% yield after purification by chromatography through silica gel (eluent: chloroform). A sample recrystallyzed from methanol-ether melted at 265ºC (dec.); NMR (60MHz, DMSO-d_6): 1.5-4.5 (complex signal, 7H alicyclic); 1.9

and 2.4 (2s, 3H, CH_3CO); 5.6 and 6.2 (2 apparent t, 1H, H-1); 6.8-7.8 (m, 4H, indole); IR (KBr) 3000-3400 (NH), 1660 (C=O acylindole), 1605 (C=O amide). (Found: C, 71.76; H,6.11; N,10.32. Calcd. for $C_{16}H_{16}N_2O_2$: C,71.62; H,6.01; N,10.44).

2-Acetyl-6-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole (11). Acetyl chloride (0.1 ml, 1.0 mmol) in methylene chloride (5 ml) was added dropwise to a two-phase solution of amine 1 (150 mg, 0.66 mmol) and potassium carbonate (250 mg) in methylene chloride (20 ml) and water (5 ml). The usual work-up afforded 152 mg (85% yield) of pure 11, identical to that above obtained.

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REFERENCES AND NOTES

1. This work was presented in a preliminary form at the XX Reunión Bienal de la Real Sociedad Española de Química, Castellón, Spain, 1984.
2. a) D. Schumann and H. Schmidt, *Helv. Chim. Acta*, 1963, *46*, 1996; b) J. Harley-Mason, *Pure Appl. Chem.*, 1975, *41*, 167 and references cited therein; c) A. Wu and V. Snieckus, *Tetrahedron Lett.*, 1975, 2057. d) Y. Ban, K. Yoshida, J. Goto, and T. Oishi, *J. Am. Chem. Soc.*, 1981, *103*, 6990. e) S. Takano, M. Hirama, and K. Ogasawara, *Tetrahedron Lett.*, 1982, *23*, 881. f) Y. Ban, K. Yoshida, J. Goto, T. Oishi, and E. Takeda, *Tetrahedron*, 1983, *39*, 3657.
3. A different approach was used in a synthesis of geissoschizoline, which constituted the first synthesis of a pentacyclic *Strychnos* indole alkaloid: E.E. Van Tamelen, L.J. Dolby, and R.G. Lawton, *Tetrahedron Lett.*, 1960, 30.
4. a) F.E. Ziegler and E.B. Spitzner, *J. Am. Chem. Soc.*, 1970, *92*, 3492; b) F.E. Ziegler and E.B. Spitzner, *J. Am. Chem. Soc.*, 1973, *95*, 7146.
5. a) T. Gallagher and P. Magnus, *J. Am. Chem. Soc.*, 1982, *104*, 1140; b) T. Gallagher, P. Magnus, and J.C. Huffman, *J. Am. Chem. Soc.*, 1983, *105*, 4750.
6. a) T. Gallagher and P. Magnus, *J. Am. Chem. Soc.*, 1983, *105*, 2086; b) P. Magnus, T. Gallagher, P. Brown, and J.C. Huffman, *J. Am. Chem. Soc.*, 1984, *106*, 2105.
7. a) H.-P. Husson, C. Thal, P. Potier, and E. Wenkert, *Chem. Comm.*, 1970, 480; b) M. Natsume and I. Utsunomiya, *Heterocycles*, 1982, *17*, 111; c) P. Magnus and P. Pappalardo, *J. Am. Chem. Soc.*, 1983, *105*, 6525; d) P. Magnus, T. Gallagher, P. Brown, and P. Pappalardo, *Acc. Chem. Res.*, 1984, *17*, 35.
8. a) J.D. Coyle, *Chem. Rev.*, 1978, *78*, 97; b) O. Yonemitsu, *Yakugaku Zasshi*, 1982, *102*, 716; c) R.J. Sundberg in "Organic Photochemistry", A, Padwa, ed., Marcell Dekker, 1983, Vol. 6, Chapter II.
9. a) R.J. Sundberg and J.D. Bloom, *Tetrahedron Lett.*, 1978, 5157; b) R.J. Sundberg and J.D. Bloom, *J. Org. Chem.*, 1980, *45*, 3382.
10. R.J. Sundberg and F.X. Smith, *J. Org. Chem.*, 1975, *40*, 2613.
11. K.S. Bhandari, J.A. Eekhoorn, A. Wu, and V. Snieckus, *Synthetic Comm.*, 1975, 5, 79.
12. a) R.J. Sundberg and R.L. Parton, *Tetrahedron Lett.*, 1976, 1163; b) R.J. Sundberg, J.G. Luis. R.L. Parton, S. Schreiber, P.C. Srinivasan, P. Lamb, P. Forcier, and R.F. Bryan, *J. Org. Chem.*, 1978, *43*, 4859.
13. M. Feliz, J. Bosch, D. Mauleón, M. Amat, and A. Domingo, *J. Org. Chem.*, 1982, *47*, 2435.
14. Numbering system based on a biogenetic interrelationship of indole alkaloids as proposed by: J. Le Men and W.I. Taylor, *Experientia*, 1965, *21*, 508.
15. J. Bosch, M. Amat, and A. Domingo, *Heterocycles*, 1984, *22*, 561.
16. L.J. Dolby and D.L. Booth, *J. Org. Chem.*, 1965, *30*, 1550.
17. J. Bosch and M. Amat, *An. Quim.*, in press.
18. a) B.G. Gower and E. Leete, *J. Am. Chem. Soc.*, 1963, *85*, 3683; b) see ref. 15 and references cited therein.
19. W.E. Stewart and T.H. Siddall, *Chem. Rev.*, 1970, *70*, 517.
20. a) L.A. La Planche and M.T. Rogers, *J. Am. Chem. Soc.*, 1963, *85*, 3728; b) H. Paulsen and K. Todt, *Angew. Chem. Int. Ed. Engl.*, 1966, 5, 899; c) R.A. Johnson, *J. Org. Chem.*, 1968, *33*, 3627.
21. T. Hamada, Y. Okuno, M. Ohmori, T. Nishi, and O. Yonemitsu, *Chem. Pharm. Bull.*, 1981, *29*, 128.
22. a) S. Naruto and O. Yonemitsu, *Tetrahedron Lett.*, 1975, 3399; b) S. Naruto and O. Yonemitsu, *Chem. Pharm. Bull.*, 1980, *28*, 900.
23. a) O. Yonemitsu, P. Cerutti, and B. Witkop, *J. Am. Chem. Soc.*, 1966, *88*, 3941; b) T. Kobayashi, T.F. Spande, H. Aogayi, and B. Witkop, *J. Med. Chem.*, 1969, *12*, 636.
24. T. Hino and M. Nakagawa, *Heterocycles*, 1977, *8*, 743 and references cited therein.
25. This chemical shift is similar to that reported for the quaternary carbon of β-indoline position in pentacyclic structures related to *Strychnos* indole alkaloids: a) E. Wenkert, H.T.A. Cheung, H.E. Gottlieb, M.C. Kock, A. Rabaron, and M.M. Plat, *J. Org. Chem.*, 1978, *43*, 1099; b) M. Shamma and D.M. Hindenlang, "Carbon-13 NMR shift Assignments of Amines and Alkaloids", Plenum Press, New York, 1979, p. 284.
26. a) M. Pfau, R. Dulou, and M. Vilkas, *Compt. Rend.*, 1962, 1817; b) P. de Mayo,

J.-P. Pete, and M. Tchir, *Can. J. Chem.*, 1968, *46*, 2535.
27. See ref. 10 and references cited therein.
28. However, see: O. Schindler, P. Niklaus, U. Stauss, and H.P. Härter, *Helv. Chim. Acta*, 1976, *59*, 2704.
29. When this reaction was effected for longer reaction times, increasing amounts of tetrahydrocarbazole 4 were obtained,whereas with shorter reaction times alcohol 3 became the major product.
30. Its formation can be accounted for by considering the aminolysis of ethyl acetate followed by hydride reduction of the resulting acetamide.