FORMATION OF A TEN-MEMBERED LACTAM BY CHLOROACETAMIDE PHOTOCYCLIZATION ON THE INDOLE 4-POSITION

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Abstract - Photocyclization of tricyclic chloroacetamide (**3**) occurs on the indole 4-position to give the ten-membered lactam (**4**), whose structure was confirmed by conversion to the tetracyclic amine (**6**). Some conformational aspects of lactam (**4**) and thiolactam (**5**), namely the observation of conformers by nmr as a consequence of a restricted inversion of the ten-membered ring, are discussed.

In the context of our studies[1] on the synthesis of akuammiline alkaloids (*i.e.* cathafoline, cabucraline)[2] by closure of the tryptamine bridge from tetracyclic 6,7-seco[3] derivatives, we decided to take advantage of the easy cleavage of the C-N_b bond in isogramine-type systems[4] to evaluate if the crucial quaternary C-7 center of these alkaloids could be generated by cyclization on the indole 3-position from a more flexible N-4 substituted tricyclic 3,4-seco compound (*i.e.* **3**, Scheme 1). The 3,4-seco skeleton is present in several structural variations of akuammiline alkaloids, for instance in 3,4-seco-3,14-dehydrocabucraline,[5] an alkaloid with an unusual skeleton that incorporates an eight-membered ring (Figure 1).

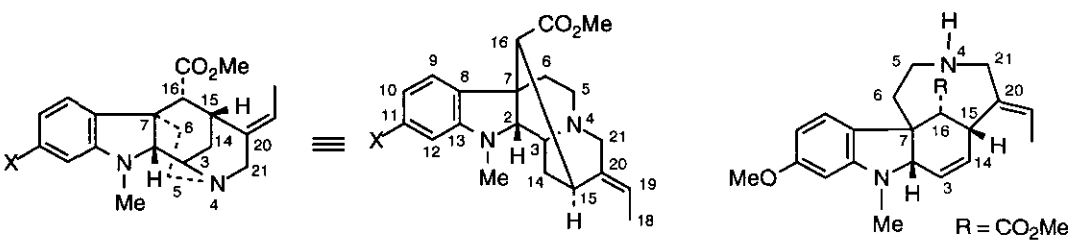
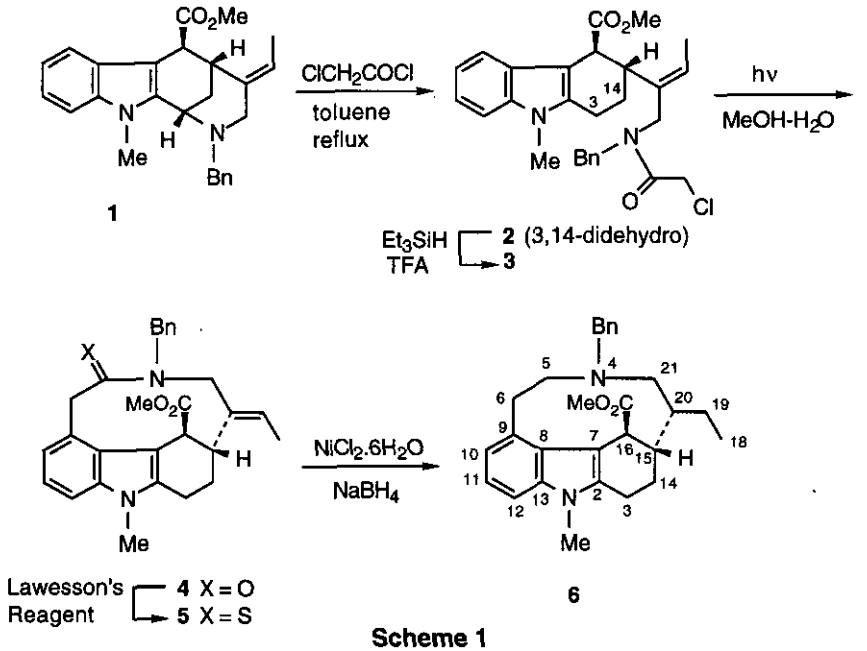


Figure 1

Since photocyclization of chloroacetamides on activated aromating rings is a good method of forming medium-sized lactams,[6] C-3 being the most reactive position of the indole nucleus in this reaction,[7] for our purpose we decided to test the photocyclization of the tricyclic 3,4-seco chloroacetamide (**3**).

This chloroacetamide (**3**), whose nmr spectra showed the presence of rotamers (3:1 ratio) due to the restricted rotation of the amide group,[8] was prepared in 70% overall yield by treatment of tetracycle (**1**)[1] with chloroacetyl chloride followed by reduction of the resulting dihydrocarbazole (**2**) with triethylsilane in the presence of trifluoroacetic acid (Scheme 1). However, when **3** was irradiated in methanol-water with a medium-pressure mercury lamp, the ten-membered ring lactam (**4**), coming from cyclization on the indole 4-position, was obtained (only isolable product; 35% yield) instead of the eight-membered lactam that would have resulted from cyclization on the indole 3-position. Tetracyclic lactam (**4**) showed duplicate signals in the ^{1}H- and ^{13}C-nmr spectra, thus indicating the existence of two conformational states in solution (1:1 ratio) with a high energy barrier to interconversion. On raising the temperature to 120 °C in DMSO-d_6, the duplicate signals in the ^{1}H-nmr spectrum coalesced into single peaks.



Scheme 1

In order to confirm the proposed structure, lactam (**4**) was elaborated into the corresponding tetracyclic amine (**6**) by reaction with Lawesson's reagent followed by desulfurization of the resulting thiolactam (**5**) with nickel boride.[9] The latter process takes place with concomitant reduction of the ethylidene double bond to give a C-20 ethyl substituent (undetermined relative stereochemistry). Whereas the nmr spectra

of thiolactam (**5**) again showed the existence of two conformational states (3:1 ratio), tetracyclic amine (**6**) exhibited clear ^{1}H- and ^{13}C-nmr spectra, thus allowing the unambiguous elucidation of the structure with the aid of 2D nmr techniques (^{1}H-^{1}H COSY, HMQC, and HMBC). An HMBC correlation of 6-H with C-9 and C-10, along with the absence of quaternary carbons in the aliphatic region of the ^{13}C-nmr spectrum, clearly established that photocyclization had occurred on the indole 4-position.

The nature of conformers present in **4** and **5** was the next point to study. Inspection of molecular models of lactam (**4**) indicated that, as occurs in other lactams of similar size,[10] both *cis*- and *trans*-arrangements around the C-N bond are possible. However, in the *trans* form the steric interactions between the bulky benzyl group and the indole ring would result in the disturbance of the planarity of the

Table 1. ^{1}H-Nmr Chemical Shifts of Thiolactam (**5**) and Amine (**6**).[a,b]

	5 (Major conformer **A**)	**5** (Minor conformer **B**)	**6**
3-H	2.80 (m)	2.80 (m)	2.66 (m) 2.78 (td, *J* = 12.5, 3 Hz)
6-H	4.40 (d, *J* = 20.5 Hz) 5.54 (d, *J* = 20.5 Hz)	4.82 (d, *J* = 15 Hz) 5.63 (d, *J* = 15 Hz)	2.66 (m) 3.25 (dd, *J* = 14.5, 6.5 Hz)
10-H	6.85 (d, J = 7 Hz)	6.80 (d, *J* = 7 Hz)	6.57 (d, *J* = 7 Hz)
11-H	*c*	*c*	6.92 (dd, *J* = 8.5, 7 Hz)
12-H	*c*	*c*	7.06 (d, *J* = 8.5 Hz)
14-H	1.52 (m) 2.33 (m)	1.15 (m) 2.33 (m)	0.72 (m) 2.05 (m)
15-H	3.93 (t, *J* = 7.5 Hz)	3.88 (t, *J* = 8 Hz)	3.06 (m)
16-H	4.79 (d, *J* = 1.5 Hz)	4.44 (s)	6.36 (s)
18-H	1.77 (d, *J* = 7 Hz)	1.76 (d, *J* = 7 Hz)	0.88 (t, *J* = 7 Hz)
19-H	5.43 (q, *J* = 7 Hz)	5.38 (q, *J* = 7 Hz)	1.00 (m) 1.16 (m)
20-H			1.86 (m)
21-H	2.92 (d, *J* = 15.2 Hz) 3.99 (d, *J* = 15.2 Hz)	4.40 (masked) 5.03 (d, *J* = 15 Hz)	1.96 (d, *J* = 13.5 Hz) 2.35 (dd, *J* = 13.5, 7.5 Hz)
$CH_2C_6H_5$	3.45 (d, *J* = 15 Hz) 5.23 (d, *J* = 15 Hz)	3.28 (d, *J* = 14 Hz) 5.19 (d, *J* = 14 Hz)	3.18 (d, *J* = 14 Hz) 3.88 (d, *J* = 14 Hz)
$CH_2C_6H_5$	*c*	*c*	7.19 (m) 7.29 (m) 7.36 (m)
NMe	3.72 (s)	3.65 (s)	3.62 (s)
OMe	3.53 (s)	3.58 (s)	3.51 (s)

[a] In $CDCl_3$ at 500 MHz. [b] Assignments were aided by ^{1}H-^{1}H COSY and HMQC. [c] Included in a multiplet at 7.04-7.35 ppm.

C-N bond, which is not compatible with the observed normal ir absorption (1630 cm^{-1}) of the amide carbonyl group of **4**.

A careful examination of the ^1H-nmr spectrum of thiolactam (**5**) with the aid of ^1H-^1H COSY and HMQC experiments allowed the complete assignment of all signals of the major conformer (**A**) as well as of the most important peaks of the minor one (**B**) (Table 1). Some pairs of signals strongly differ in chemical shift, in particular those due to 21-H, which appear more shielded in the major conformer. These conformers, both with a *cis* C-N bond, arise from a slow ring inversion caused by the restricted twisting of the thioamide bond.[11] The same phenomenon accounts for the observation of conformers in the nmr spectra of lactam (**4**) (Figure 2). For thiolactam (**5**), conformations (**A**) and (**B**) are supported by a NOESY correlation between 19-H and the benzylic methylene protons that would not exist in a *trans* thiolactam. In addition, in conformer (**A**) (C-21 down) there is a NOESY cross peak between 16-H and 6-H, whereas in conformer (**B**) (C-21 up) there are NOESY cross peaks between 6-H and 16-H, 6-H and 21-H, and 16-H and 21-H.

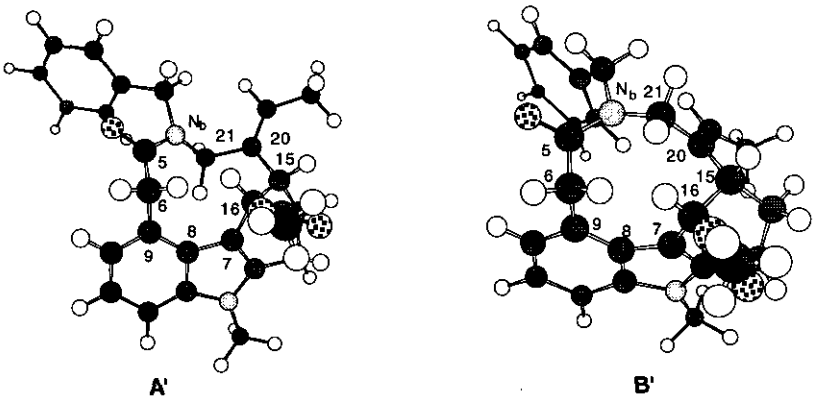


Figure 2. Graphical Representation of Conformers (**A'**) and (**B'**) of Lactam (**4**)[12]

Although contrary to our synthetic interest, the above chloroacetamide photocyclization on the indole 4-position giving a ten-membered lactam is interesting in several respects:

a) It confirms that photocyclization of chloroacetamides on the indole 3-position is inhibited by the presence of a substituent at this position. Some reports have already shown the failure of chloroacetamide photocyclizations on the 3-position in 3-alkylindoles, although in these cases the failure was attributed to the conformational rigidity of the starting chloroacetamides, in which the nitrogen is

included in a fused or bridged polycyclic ring system.[13] Clearly this is not the case in chloroacetamide (**3**), where the nitrogen is in a freely rotating chain. In fact, to our knowledge, no examples of photocyclization of chloroacetamides on the 3-position of a 3-alkylindole have been reported.[14]

b) Photocyclization of chloroacetamides is a good method of forming medium-sized lactam rings, in particular seven-, eight-, and nine-membered rings.[6] The closure of a ten- (or higher) membered ring by this procedure is rare.[15]

c) Finally, it is worth mentioning that tetracycles (**4-6**) are [*c*,*d*]-fused indoles, a class of bridged systems usually displaying interesting biological activities. Serotobenine, indolactam V, lyngbyatoxin A, and teleocidins are examples of naturally occurring compounds[16] containing an eight- or nine-membered lactam ring bridging the indole 3- and 4-positions.

EXPERIMENTAL

General. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. Unless otherwise noted, ^{1}H and ^{13}C-nmr spectra were recorded in $CDCl_3$ solution on Varian Gemini 300 (300 and 74.5 MHz, respectively) or Varian XL-500 (500 MHz) instruments. Chemical shifts are expressed in parts per million (δ) relative to internal TMS. Ir spectra were recorded on a Nicolet 205 FT-IR spectrophotometer. Uv spectra were obtained using an Hitachi U-2000 apparatus. Mass spectra were determined on a Hewlett-Packard 5988A mass spectrometer or on a Autospec-VG (HRMS). Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04-0.06 mm). Drying of organic extracts during the work-up of reactions was performed over anhydrous sodium sulfate. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Centro de Investigación y Desarrollo (CSIC), Barcelona. The biogenetic numbering (see **6** in Scheme 1) is used to describe the nmr spectra of all compounds.

Methyl *trans*-3-(1-[*N*-Benzyl-*N*-(chloroacetyl)aminomethyl]-1-(*E*)-propenyl)-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate (3). Chloroacetyl chloride (0.32 ml, 4.12 mmol) was slowly added to a solution of tetracycle (**1**)[1] (150 mg, 0.37 mmol) in anhydrous toluene (10 ml), and the mixture was refluxed for 3 h. The reaction mixture was partitioned between aqueous 10% sodium carbonate solution and ether, and extracted with ether. The organic extracts were dried and evaporated to give a residue (crude **2**), which was dissolved in dichloromethane (5 ml). Triethylsilane (0.19 ml, 1.12 mmol) and TFA (0.15 ml, 1.87 mmol) were added to the resulting solution, and the mixture was refluxed for 1.5 h. The reaction mixture was poured into aqueous 10%

sodium carbonate solution and extracted with dichloromethane. The organic extracts were dried and evaporated, and the resulting residue was chromatographed (flash, ether) to give carbazole (**3**) (125 mg, 70%): mp 110-111 °C (ether-cyclohexane); ir (film) 1730, 1656 (CO); ^{1}H-nmr (300 MHz, major rotamer, assignments were aided by ^{1}H–^{1}H COSY and HMQC) 1.68 (d, *J* = 6.9 Hz, 3H, 18-H), 1.95 (m, 2H, 14-H), 2.85 (m, 2H, 3-H), 3.35 (m, 1H, 15-H), 3.61 (s, 3H, OCH_3), 3.73 (s, 3H, NCH_3), 3.86 (m, 2H, 16-H and 21-H), 4.11 (m, 3H, CH_2Cl and 21-H), 4.60 (m, 2H, $CH_2C_6H_5$), 5.40 (q, *J* = 6.9 Hz, 1H, 19-H), 7.00-7.40 (m, 9H, Ar); ^{13}C-nmr (74.5 MHz, major rotamer, assignments were aided by HMQC) 12.8 (C-18), 22.0 (C-3), 26.8 (C-14), 29.0 (NCH_3), 38.9 (C-15), 41.1 (CH_2Cl), 43.8 (C-16), 47.3 (C-21), 49.0 ($CH_2C_6H_5$), 51.8 (OCH_3), 105.8 (C-7), 108.8 (C-12), 117.4 (C-9), 119.3 (C-10), 120.3 (C-19), 121.0 (C-11), 125.4 (C-8), 127.5, 128.1, 128.6 (C_6H_5), 133.5 (C-2), 135.9, 136.7, 136.8 (C_6H_5, C-13, C-20), 167.6, 174.6 (CO); uv (MeOH, λ max) 283, 225, 207 nm; ms (m/z, relative intensity) 478 (M^+, 1); 446 (20), 263 (100). Anal. Calcd for $C_{28}H_{31}N_2O_3Cl$: C, 70.21; H, 6.52; N, 5.85; Cl, 7.40. Found: C, 70.28; H, 6.63; N, 5.79; Cl, 7.44.

Methyl *trans*-12-Benzyl-3,5-ethanoiminoethano-10(*E*)-ethylidene-9-methyl-13-oxo-1,2,3,4-tetrahydrocarbazole-4-carboxylate (4). A solution of chloroacetamide (**3**) (130 mg, 0.27 mmol) in methanol-water (1:1, 260 ml) containing sodium hydrogencarbonate (150 mg) was irradiated under argon at room temperature for 30 min using a 125 W medium-pressure mercury lamp in a quartz immersion well reactor. The reaction mixture was evaporated to dryness, and the residue was chromatographed (flash, 99:1 Cl_2CH_2-MeOH) to give tetracycle (**4**) (42 mg, 35%): mp 185-187 °C (ether-cyclohexane); ir (film) 1728, 1630 (CO); ^{1}H-nmr (300 MHz,) 1.25 (m, 1H, 14-H), 1.75 (m, 3H, 18-H), 2.40 (m, 1H, 14-H), 2.90 (m, 3H, 3-H, 21-H), 3.53 and 3.58 (2s, 3H, OCH_3), 3.65 and 3.71 (2s, 3H, NCH_3), 3.90 (m, 2H, 21-H, 15-H), 4.36 (d, *J* = 15.4 Hz, 1H, $CH_2C_6H_5$), 4.67 (m, 3H, 6-H, 16-H), 4.93 (d, *J* = 15.4 Hz, 1H, $CH_2C_6H_5$), 5.29 and 5.40 (2q, *J* = 6.7 Hz, 1H, 19-H), 6.62 (m, 1H, indole), 7.05-7.40 (m, 7H, Ar); ^{1}H-nmr (DMSO-d_6, 120 °C, most significant signals) 1.68 (d, *J* = 6.9 Hz, 3H, 18-H), 2.30 (m, 1H, 14-H), 2.70 (m, 1H, 3-H), 2.85 (m, 1H, 3-H), 3.51 (s, 3H, OCH_3), 3.67 (s, 3H, NCH_3), 4.50 (m, 4H, $CH_2C_6H_5$, 6-H), 5.35 (q, *J* = 6.9 Hz, 1H, 19-H), 6.85 (d, *J* = 7.5 Hz, 1H, 12-H), 7.05 (t, *J* = 7.5 Hz, 1H, 11-H), 7.30 (m, 6H, Ar); ^{13}C-nmr (74.5 MHz) 14.1 and 14.3 (C-18), 21.1 and 21.4 (C-3), 29.5 (NCH_3), 29.7 and 30.1 (C-14), 35.6 (C-15), 39.2 (C-16), 41.8 and 42.6 (C-6), 48.6 and 50.7 (C-21), 52.1 (OCH_3), 53.6 ($CH_2C_6H_5$), 107.9 and 108.6 (C-12), 120.4 (C-11), 120,6 (C-19), 122.2 (C-10), 124.9 (C-8), 135.7 (C-2), 136.8 (C-20), 137.4 (C-9), 142.0 (C-13), 174.3, 174.9 and 175.1 (CO); uv (MeOH, λ max) 292, 226 nm; ms (m/z, relative intensity) 442 (M^+, 32), 383 (63), 255 (100). Anal. Calcd for $C_{28}H_{30}N_2O_3.1/4\ H_2O$: C, 75.23; H, 6.87; N, 6.27. Found: C, 75.23; H, 6.91; N, 6.18.

Methyl *trans*-12-Benzyl-3,5-ethanoiminoethano-10-(*E*)-ethylidene-9-methyl-13-thiooxo-1,2,3,4-tetrahydrocarbazole-4-carboxylate (5). A solution of lactam (**4**) (125 mg, 0.28 mmol) and Lawesson's reagent (66 mg, 0.16 mmol) in toluene (30 ml) was refluxed for 3 h. The solvent was removed and the resulting residue was chromatographed (flash, 1:1 ether-hexane) to give thiolactam (**5**) (125 mg, 96%): mp 179-180°C (ether-acetone); ir (*film*) 1728 (CO), 1262 (C=S); ^{1}H-nmr, Table 1; ^{13}C-nmr (major rotamer, 74.5 MHz, assignments were aided by HMQC) 14.3 (C-18), 21.3 (C-3), 28.2 (C-14), 29.5 (NCH_3), 37.9 (C-15), 42.2 (C-16), 52.1 (OCH_3), 54.3 (C-6), 56.0 (C-21), 60.8 ($CH_2C_6H_5$), 108.0 (C-12), 108.5 (C-7), 120.8 (C-11), 124.6 (C-8), 126.9 (C-10), 127.5, 128.7 (C_6H_5), 129.4 (C-19), 134.6, 136.3, 137.6, 140.6 (C-2, C-9, C-13, C-20, C_6H_5), 175.2 (CO), 207.2 (C=S); ^{13}C-nmr (*minor* rotamer, most significant signals) 14.0 (C-18), 21.4 (C-3), 30.0 (C-14), 35.8 (C-15), 40.3 (C-16), 49.9 (C-21), 54.7 (C-6), 57.6 ($CH_2C_6H_5$), 108.5 (C-12), 120.5 (C-10), 130.7 (C-19); ms (m/z, relative intensity) 460 (M+2, 17), 458 (M^+, 100), 399 (74). Anal. Calcd for $C_{28}H_{30}N_2O_2S$: C, 73.34; H, 6.59; N, 6.11; S, 6.99. Found: C, 73.24; H, 6.58; N, 6.10%; S, 6.99.

Methyl *trans*-12-Benzyl-3,5-ethanoiminoethano-10-ethyl-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate (6). Sodium borohydride (118 mg, 3.12 mmol) was slowly added to a solution of thiolactam (**5**) (60 mg, 0.13 mmol) and nickel chloride hexahydrate (253 mg, 1.05 mmol) in MeOH-THF (1:1, 40ml) at -40 °C, and the resulting mixture was stirred at this temperature for 5 min. The suspension was filtered through Celite®, the solvent was removed, and the residue was chromatographed (flash, dichloromethane) to give **6** (20 mg, 35%) as an oil: Ir (film) 1727 (CO); ^{1}H-nmr, Table 1; ^{13}C-nmr (74.5 MHz, assignments were aided by HMQC and HMBC) 12.5 (C-18), 21.5 (C-3), 25.4 (C-19), 26.7 (C-14), 29.5 (NCH_3), 37.6 (C-6), 38.1 (C-15), 38.3 (C-16), 45.2 (C.20), 51.8 (OCH_3), 58.4 (C-21), 58.9 (C-5), 60.5 ($CH_2C_6H_5$), 107.0 (C-12), 108.9 (C-3), 119.9 (C-11), 120.1 (C-10), 124.3 (C-8), 126.8, 128.2, 128.9 (C_6H_5), 135.0 (C-9), 137.0 (C-13), 140.7 (C_6H_5), 142.5 (C-2), 176.9 (CO); uv (MeOH, λ max) 285, 227, 201 nm; ms (m/z, relative intensity) 430 (M^+, 14); 255 (100); HRms calcd for $C_{28}H_{34}N_2O_2$ 430.2612, found 430.2620.

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