exclusion from moisture, 26 g (0.12 mol) of $(CF_3CO)_2O$. The resulting solution was stirred continuously in an ice bath for 1 h and then at room temperature overnight. The solvent and excess reagent were evaporated under reduced pressure. The residue was dissolved in 200 mL of Et_2O. A small amount of solid was removed by filtration and the filtrate was added to 500 mL of petroleum ether. The resulting solid was collected by filtration, washed with petroleum ether (2 × 20 mL), and dried to give 12.5 g of **12c**, mp 161–163 °C. An analytical sample was prepared by an additional reprecipitation from Et_2O and petroleum ether: mp 162–164 °C.

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Ergot Alkaloids. Synthesis of Nitrosourea Derivatives of Ergolines as Potential Anticancer Agents

A. Michael Crider, Catherine K. L. Lu, Heinz G. Floss, John M. Cassady,*

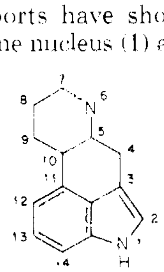
Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

and James A. Clemens

The Lilly Research Laboratories, Indianapolis, Indiana 46206. *Received February 6, 1978*

Nitrosourea derivatives of ergolines have been synthesized for the purpose of obtaining agents with both prolactin- and tumor-inhibitory activity. Two derivatives of 8-amino-6-methylergoline (**3**), 8-[3-(2-chloroethyl)-3-nitrosoureido]-1-nitroso-6-methylergoline (**5c**) and 8-[3-(2-chloroethyl)-3-nitrosoureido]-6-methylergoline (**5a**), have been prepared. In addition, nitroso (**7**) and chloroethylcarbamyl (**8**) derivatives of elymoclavine (**6**) are reported. Compounds **5a** and **5c** have activity against L1210 leukemia in mice but only moderate prolactin-inhibiting activity. The chloroethylcarbamyl derivative **8** of elymoclavine is a potent prolactin inhibitor.

A number of reports have shown that compounds containing the ergoline nucleus (**1**) are effective inhibitors



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of prolactin release.[1] Previously, we reported an attempt to prepare potential irreversible prolactin inhibitors by attaching alkylating groups at the 8 position of the ergoline skeleton.[2] As an extension of this work, an alkylating nitrosourea group has been incorporated into the ergoline system in an attempt to prepare compounds which are distributed in such a way that both prolactin and tumor inhibitory activity can be achieved with the same molecule.[3]

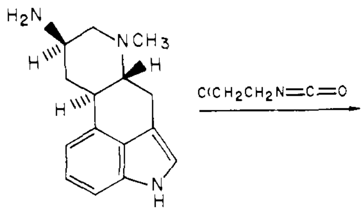
Ergolines appear to inhibit prolactin release from the anterior pituitary gland by interacting with the prolactin-inhibiting factor (PIF) receptor.[4] As an example, an ergolinylnitrosourea could possibly target a tumor located in the pituitary gland. Such a compound could be potentially useful in the treatment of Forbes–Albright Syndrome, a condition which is the result of a pituitary tumor in which excessive amounts of prolactin are produced leading to persistent lactation.

The N-(2-chloroethyl)-N-nitrosoureas **2** decompose (eq

$$\underset{\mathbf{2}}{RNH{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}\overset{\overset{\displaystyle N{=}O}{|}}{N}{-}CH_2CH_2Cl} \rightarrow RN{=}C{=}O + Y \qquad (1)$$

1) to yield an isocyanate and a variety of other reactive species (Y).[5] The interaction of one or more of these

Scheme I



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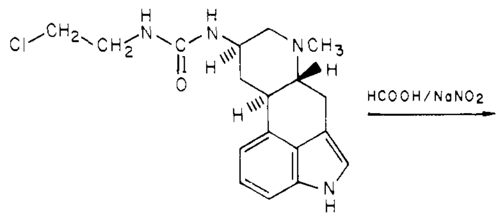

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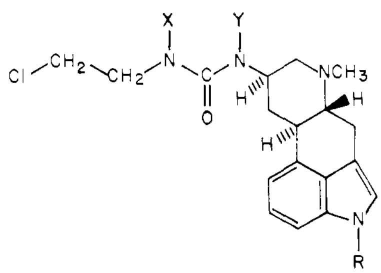


5a, R = H; X = NO; Y = H
b, R = H; X = H; Y = NO
c, R = NO; X = NO; Y = H

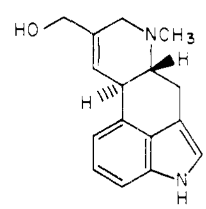
reactive moieties with biological macromolecules is thought to be responsible for the anticancer activity and the toxicity of the nitrosoureas.

Chemistry. 6-Methyl-8-aminoergoline (3) was prepared by a series of conversions starting from methyl dihydrolysergate I.[2] Reaction of the amine 3 with 2-chloroethyl isocyanate gave the (2-chloroethyl)urea 4 (Scheme I) in moderate yield. Nitrosation of unsymmetrical 1,3-disubstituted ureas can theoretically give two isomeric nitrosoureas. However, Montgomery and coworkers[6] have shown that a nitrosating medium of anhydrous formic acid and steric factors can exert some degree of control over the position of nitrosation. Therefore, nitrosation of 8-[3-(2-chloroethyl)ureido]-6-methylergoline (4) with 99% HCOOH and dry sodium nitrite powder (Scheme I) would be expected to yield predominantly the nitrosourea **5a**. Isomeric purity of a nitrosourea has been shown by Montgomery et al.[6] to be most clearly established by NMR spectroscopy. The spectral asymmetry of the $N(NO)CONHCH_2CH_2Cl$ (A_2B_2X system) group due to the NH coupling of the adjacent methylene group can be clearly distinguished from the spectral symmetry of the $NHCON(NO)CH_2CH_2Cl$ (A_2B_2 system) group.

Nitrosation of the urea 4 gave two products with strikingly different mobilities on TLC (R_f values of 0.17 and 0.29, respectively). The two compounds were separated by column chromatography using silica gel as the adsorbent. Initially, the two products were thought to be the isomeric nitrosoureas **5a** and **5b**. However, the structural assignments of the two compounds were based on further analysis of their IR, NMR, UV, and mass spectra. The IR spectrum of the compound with the higher R_f value showed a band at 1490 cm^{-1}, indicating the presence of a nitroso group. Furthermore, the sharp absorption at 1710 cm^{-1} was characteristic of the shift to a higher wavenumber of the carbonyl absorption caused by nitrosation of the ureido function.[7] The presence of two distinct triplets (A_2B_2 system) centered at δ 3.54 and 4.22 in the NMR spectrum was strong evidence that the nitroso group was attached to the same nitrogen as the chloroethyl group ($NNOCH_2CH_2Cl$). The downfield shift in the aromatic region of the NMR spectrum along with the apparent absence of the indole NH proton led to the supposition that a N=O group was attached to the indole nitrogen. The UV spectrum of the compound showed two maxima at 264 and 330 nm. The spectrum resembles that of 3-methyl-1-nitrosoindole (maxima at 264 and 329–334 nm) reported by Smith and Hodson[8] and that of N_1-nitrosotryptophans (maxima at 269, 274, and 335 nm).[9] The mass spectrum of the postulated dinitroso compound showed a peak at *m/e* 266 corresponding to the losses of ($NO + ClCH_2CH_2N{=}NOH$) from the parent. High-resolution mass spectrometry ($M^+ - C_2H_5ClN_3O_2$) and elemental analysis of the product were in accord with the molecular formula ($C_{18}H_{21}ClN_6O_3$) of a dinitroso compound. Thus, the compound with the higher R_f value was assigned structure **5c**.

The IR spectrum of the compound with the lower R_f value exhibited IR absorptions of 3360 cm^{-1} attributed to the indole N–H stretching mode and at 1495 cm^{-1} due to the N=O group. Examination of the NMR spectrum of the compound showed an upfield triplet at δ 3.55 and a downfield triplet at δ 4.22 due to the $NNOCH_2CH_2Cl$ system. The indole NH was present at δ 7.96. The UV spectrum had absorption maxima at 292, 280, 272, and 222 nm similar to that of the urea 4 and lacked the absorption maximum at 330 nm associated with the 1-nitroso group in **5c**. The mass spectrum of the postulated mononitroso compound gave a peak at *m/e* 267, pointing to the loss of $ClCH_2CH_2N{=}NOH$ from the parent compound, which, taken together with other evidence, suggests a molecular formula $C_{18}H_{22}ClN_5O_2$.[10] The compound with the lower R_f value was, therefore, assigned the structure **5a**.

In an effort to investigate the generality of the nitrosation reaction with ergolines, elymoclavine (6), available from submerged cultures of *Claviceps* strain SD58,[11] was nitrosated with sodium nitrite in formic acid (eq 2) The



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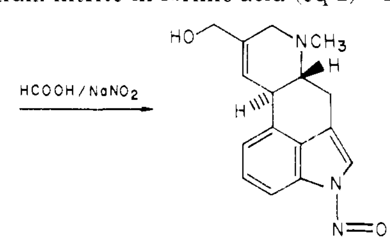

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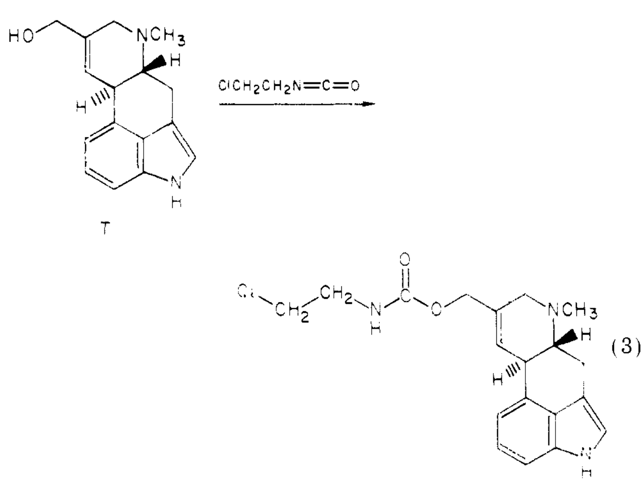
(2)

yellow reaction product was characterized by analysis of its IR, NMR, UV, and MS. The UV spectrum gave the characteristic absorption maximum at 330 nm of *N*-nitrosoindoles consistent with assignment of structure **7**.

Reaction of 2-chloroethyl isocyanate with elymoclavine (6) (eq 3) gave urethane 8 in excellent yield. Nitrosation of the urethane gave two products which were not fully characterized due to their instability.

Biological Activity. The compounds listed in Table I were evaluated for prolactin-inhibiting activity in the rat. The results of these tests are listed in the table. In most runs, ergocornine or lergotrile was included as a reference point and these values are given. Examination of the data in Table I shows that 3 is a relatively good prolactin inhibitor. However, the urea 4 and the dinitrosourea **5c** are devoid of any significant prolactin-inhibiting activity. The loss of prolactin inhibitory activity in the urea 4 and the



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dinitrosourea **5c** and the low potency of **5a** seem to be consistent with other derivatives in the 8β-aminoergoline series.[2] Apparently, a nitrogen in the 8β position carrying bulky substituents inhibits binding of the ergoline at the PIF receptor. However, in contrast to the 8β-aminoergoline series, several 8α-aminoergoline derivatives are good inhibitors of prolactin release.[12]

The urethane **8** (a C-17 derivative of elymoclavine) is, on the other hand, a very potent prolactin inhibitor, further indicating that, in the 8-ergolene series, bulky polar substituents at C-17 are conducive to significant prolactin inhibition.[13]

The nitrosoureas **5a** and **5c** were evaluated for antileukemic activity, and the results are shown in Table II. In these tests, N-(2-chloroethyl)-N'-(*trans*-4-methylcyclohexyl)-N-nitrosourea (MeCCNU, semustine)[14] was used as the reference compound. The dinitrosourea **5c** showed a modest level of activity in the P-388 system and relatively good activity in the L1210 test system. However, **5c** showed activity against L1210 only at high doses, 400 (T/C = 289) and 200 mg/kg (T/C = 164). At the higher dosage level, **5c** did exhibit one cure in a group of six mice; however, some toxicity (weight loss in excess of 4 g) was also evident at the higher doses. Perhaps one reason for the low potency of **5c** is its lack of significant solubility in the suspending medium.

The nitrosourea **5a** was tested only against L1210. The compound appears to be quite active over a fairly wide dosage range. In fact, at 200 mg/kg the compound exhibits a T/C of 383, with three cures in a group of six mice. However, again some toxicity is seen at higher doses. MeCCNU appears to be more potent than **5a** in the L1210 system, since activity does not fall off as rapidly at lower dosage levels.

Presently, further work is in progress on the synthesis of nitrosoureas in the ergoline series which have both potent antiprolactin and antitumor activity.

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. UV spectra were recorded on a Cary Model 17 spectrophotometer and are reported in wavelength (nm) followed by molar extinction coefficient (ε). IR spectra were recorded as KBr pellets with a Beckman IR-33 spectrophotometer. Mass spectra (MS) were obtained on a Hitachi RMU-6 low-resolution, a DuPont 21-492B double-focusing low-resolution, and a CEC 21-110 high-resolution mass spectrometer; *m/e* values are reported with relative intensity. NMR spectra (60 or 100 MHz) were recorded in $CDCl_3$, unless otherwise specified, with either a Varian Associates EM-360 or a JEOL PFT-100 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (1%) as the internal standard. Analytical data were obtained from the Microanalysis Laboratory, Department of Chemistry, Purdue University, or from Micro-Analysis Inc., Wilmington, Del. Where analyses are represented only by symbols of the elements, analytical results obtained for these elements were within ±0.4 of the theoretical value. TLC was performed on precoated Al_2O_3 or silica gel plastic sheets (Macherey-Nagel). Solvent systems used in developing the TLC plates were: A, $CHCl_3$–MeOH (95:5); B, $CHCl_3$–MeOH (9:1); C, $CHCl_3$–MeOH (98:2); D, $CHCl_3$–MeOH (8:2). Column chromatography was carried out using as the adsorbents MN-Kieselgel (70–325 mesh) and Al_2O_3 (Merck, basic, activity I). Preparative-layer chromatography was performed on Brinkmann silica gel plates (20 cm × 20 cm × 2.0 mm).

Determination of Prolactin-Inhibiting Ability. The prolactin-inhibiting ability of the ergolines was determined by the method previously described.[2]

8-[3-(2-Chloroethyl)ureido]-6-methylergoline (4). 8-Amino-6-methylergoline (3) (240 mg, 0.994 mmol) was dissolved in spectrAR grade $CHCl_3$ (20 mL), and 2-chloroethyl isocyanate (Eastman Kodak) (105 mg, 0.994 mmol) was added via syringe. After stirring for 23 h under N_2, the solvent was evaporated to give a yellow solid. Chromatography of the solid on a 30 × 2.5 cm column using Al_2O_3 (50 g) as the adsorbent and solvent system A as the eluent gave, after evaporation of the solvents, 157 mg (46%) of **4**, R_f 0.27 (Al_2O_3, solvent system D). An analytical sample was obtained by recrystallization of a small amount of **4** from CH_3CN to afford a white powder: mp 283–285 °C (dec); IR (KBr) 3340 (indole NH), 1630 (C=O), 1550 cm^{-1} (CNH, amide II); UV (MeOH) 292 nm (ε 9300), 281 (11 800), 274 (11 700), 222 (46 200); NMR (100 MHz) δ 2.08–4.28 (m, 13 H), 2.54 (s, 3 H, NCH_3), 5.00 (br s, 2 H, NHCONH), 6.86–7.21 (m, 4 H, Ar), 7.94 (br s, 1 H, indole NH); MS (low resolution) *m/e* 225 (5), 224 (M^+ – $NHCONHCH_2CH_2Cl$ + H, 88), 167 (100). Anal. ($C_{18}H_{23}ClN_4O$) H, N, C: calcd, 62.32; found, 61.33.

8-[3-(2-Chloroethyl)-3-nitrosoureido]-1-nitroso-6-methylergoline (5c) and 8-[3-(2-Chloroethyl)-3-nitrosoureido]-6-methylergoline (5a). A solution of 8-[(2-chloroethyl)ureido]-6-methylergoline (225 mg, 0.65 mmol) in 99% HCOOH (5 mL) was cooled to 0–5 °C and treated with $NaNO_2$ (135 mg, 1.95 mmol) in small portions. The dark orange solution was stirred for 0.5 h at 0–5 °C, diluted with H_2O (5 mL), and stirred for an additional 0.5 h at 0–5 °C. The reaction mixture was poured into an ice–H_2O mixture (30 mL), basified with 4 N NH_4OH, and extracted with $CHCl_3$ (2 × 150 mL). The combined $CHCl_3$ extracts were washed with H_2O (1 × 100 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to afford 248 mg of an orange solid. TLC of the solid on a silica gel plate using solvent system C indicated that the solid consisted of two components. Column chromatography on silica gel (30 g) using solvent system C eluted 118 mg (45%) of **5c**, R_f 0.29. Recrystallization of the solid from CH_3COCH_3 gave an analytical sample: mp 158–160 °C; IR (KBr) 3360 (NH), 1710 (C=O), 1530 (CNH, amide II), 1490 cm^{-1} (N=O); UV (MeOH) 330 nm (ε 4700), 262 (19 000); NMR (100 MHz) δ 2.06–4.40 (m, 10 H), 2.52 (s, 3 H, NCH_3), 3.54 (t, J = 7 Hz, 2 H, upfield half of A_2B_2 system due to $NNOCH_2CH_2Cl$), 4.22 (t, J = 7 Hz, 2 H, downfield half of A_2B_2 system due to $NNOCH_2CH_2Cl$), 6.84 (d, 1 H, NHCO), 7.16–8.20 (m, 4 H, Ar); MS (low resolution) *m/e* (rel intensity) 266 (10), 196 (13), 154 (20), 153 (20), 63 (25), 43 (43), 30 (60); MS (high resolution) calcd for $C_{16}H_{16}N_3O$ (M^+ – $ClCH_2CH_2N{=}NOH$ + NO), 266.129; found, 266.222. Anal. ($C_{18}H_{23}ClN_6O_3$) C, H, Cl, N: calcd, 20.77; found, 20.25.

Further elution of the column gave 52 mg (21%) of **5a**, R_f 0.17. In an attempt to prepare an analytical sample, a small portion of **5a** was rechromatographed on a silica gel column using solvent system C. Trituration of the solid with MeOH gave a light-yellow amorphous solid (**5a**), mp 165–167 °C. Repeated attempts to recrystallize this solid were unsuccessful, as were attempts to prepare a crystalline salt. Due to the small amount of sample and the instability of **5a**, a satisfactory analysis was not obtained: IR (KBr) 3360 (indole NH), 1730 (C=O), 1530 (CNH, amide II), 1495 (NO); UV (MeOH) 292 nm (ε 4700), 280 (6500), 272 (7000), 222 (31 600); NMR (100 MHz) δ 2.05–4.47 (m, 10 H), 2.56 (s, 3 H, NCH_3), 3.55 (t, J = 7 Hz, 2 H, upfield half of A_2B_2 system due to $NNOCH_2CH_2Cl$), 4.22 (t, J = 7 Hz, 2 H, downfield half of A_2B_2

Table I. Prolactin-Inhibiting Ability of 8-Ergolenes and 8-Aminoergolines[a]

compd no.	prolactin control value	prolactin value after treatment	inhib, %	level of signif[b]	inhib of ergocornine or lergotrile,[c] %
3	26.5 ± 3.6	11.3 ± 2.1	57	$P < 0.01$	
4	27.0 ± 3.3	26.2 ± 2.3		NS	(71)
5a	37.7 ± 3.9	26.5 ± 3.4	28	$P < 0.05$	
5c	27.0 ± 3.3	22.4 ± 3.2	17	NS	(71)
6	32.54 ± 0.9	9.39 ± 0.3	71	$P < 0.001$	(75)
7	37.7 ± 3.9	24.1 ± 5.3	36	$T = 2.0407$	
8	53.91 ± 4.72	7.21 ± 0.89	87	$P < 0.01$	88

[a] All compounds were tested at 10 μg per animal. Values are means plus or minus standard errors. [b] The level of significance was obtained according to Student's *t* test. [c] Lergotrile values are in parentheses.

Table II. Antileukemic Activity of Ergoline Nitrosoureas[a]

tumor	compd	dose, mg/kg	toxicity, day survivors	animal wt diff, T − C	% T/C (cures)
P388	**5c**	100	6/6	−1.8	201 (1)
		50	6/6	0.0	166
		25	6/6	−0.4	137
L1210	**5c**	400	5/5	−6.4	289 (1)
		200	5/5	−5.2	164
		100	5/5	−3.4	144
		50	5/5	−2.2	121
		25	5/5	−1.8	117
		12.5	5/5	−1.2	105
L1210	**5a**	400	5/5	−7.6	toxic
		200	5/5	−6.0	390 (3)
		100	5/5	−4.0	248 (1)
		50	5/5	−2.8	154
		25	5/5	−1.4	137
		12.5	5/5	−1.2	119
L1210	MeCCNU	100	4/6	−6.6	toxic
		50	6/6	−4.8	327 (3)
		25	6/6	−3.4	301 (3)
		12.5	6/6	−0.2	256 (2)
		6.25	6/6	+0.4	187 (1)

[a] Testing was carried out through the cooperation of the National Cancer Institute, National Institutes of Health. For standard screening protocols, see R. I. Geran, N. H. Greenberg, M. M. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, 3(**2**), 1 (1972).

system due to $NNOCH_2CH_2Cl$), 6.74–7.96 (m, including br s, at 6.80, NHCO, and br s at 7.96, indole NH, 6 H); MS (low resolution) *m/e* rel intensity) 267 (6), 197 (2), 154 (4), 153 (3), 64 (33), 63 (24), 62 (100), 48 (40), 30 (54); MS (high resolution) calcd for $C_{16}H_{17}N_3O$ ($M^+ - ClCH_2CH_2N{=}NOH$), 267.137; found 267.147. Anal. ($C_{18}H_{22}ClN_5O_2$) C: calcd, 57.51; found, 55.10; H, N.

1-Nitroso-6-methyl-8-hydroxymethyl-8-ergolene (7). Elymoclavine (**6**) (1104 mg, 4.35 mmol) was dissolved in 99% HCOOH (15 mL), and the solution was cooled to 0–5 °C in an ice bath. The solution was treated with $NaNO_2$ (900 mg, 13.1 mmol) in small portions. The mixture was stirred for 0.5 h at 0–5 °C, diluted with H_2O (15 mL), and stirred for an additional 0.5 h at 0–5 °C. The mixture was basified (pH 8) with 8 N NH_4OH and extracted with $CHCl_3$ (4 × 50 mL). The combined $CHCl_3$ extracts were dried (Na_2SO_4), filtered, and evaporated under reduced pressure to afford a brown oil. The oil was dissolved in $CHCl_3$ and chromatographed on silica gel (50 g). The column was eluted with $CHCl_3$ (2 × 200 mL) and solvent system A (1 × 200 mL) followed by elution with solvent system B (3 × 200 mL), which after evaporation of the solvents gave 248 mg (20%) of **7**. An analytical sample was prepared by recrystallization (two times) from EtOAc to yield pure **7**: mp 149–150.5 °C; IR (KBr) 1420 cm^{-1} (NO); UV (MeOH) 330 nm (ε 6600), 262 (17 500); NMR (Me_2SO-d_6) 2.50 (s, 3 H, NCH_3), 2.77–3.83 (m, 6 H), 4.07 (s, 2 H, CH_2OH), 4.73 (br s, 1 H, OH), 6.33 (s, 1 H, vinyl), 7.33–8.30 (m, 4 H, Ar-H); MS (low resolution) *m/e* 283 (M^+, 8), 253 ($M^+ - NO$, 51), 223 (100), 167 (60), 154 (72), 124 (67). Anal. ($C_{16}H_{17}N_3O_2$) C, H, N.

8-[*N*-(2-Chloroethyl)carbamylmethyl]-6-methyl-8-ergolene (8). Elymoclavine (**6**) (508 mg, 2.0 mmol) was dissolved in dry THF (100 mL) and treated with 2-chloroethyl isocyanate (422 mg, 4.0 mmol) via syringe. The reaction mixture was refluxed for 65 h and filtered, and the solvent was evaporated to afford a dark-brown oil. The oil was dissolved in CH_2Cl_2 (100 mL) and washed with H_2O (5 × 50 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure to afford 639 mg (89%) of **8** as a light-brown solid foam, R_f 0.46 (silica gel, solvent system D). An analytical sample was obtained by preparative layer chromatography developing with solvent system B. The chromatographed compound was dissolved in $CHCl_3$, treated with charcoal, dried (Na_2SO_4), and filtered. Removal of the solvent gave crystalline **8**: mp 84 °C (dec); IR (KBr) 3400 and 3360 (NH), 1715 cm^{-1} (C=O); UV (MeOH) 294 nm (ε 5100), 283 (6100), 274 (5800), 222 (26 300); NMR (60 MHz) δ 2.05–3.96 (m, 10 H), 2.51 (s, 3 H, NCH_3), 4.62 (s, 2 H, CH_2OCONH), 5.20 (br s, 1 H, CONH), 6.54 (s, 1 H, vinyl), 6.84–7.30 (m, 4 H, Ar), 8.14 (br s, 1 H, indole NH). Anal. ($C_{19}H_{22}ClN_3O_2$) H, N, Cl, C: calcd, 63.42; found, 62.99.

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