Intramolecular Diels–Alder Reactions. 5. Approaches to the Pyrrolo[3,4-*c*]carbazole and Pyrido[4,3-*c*]carbazole Systems[1]

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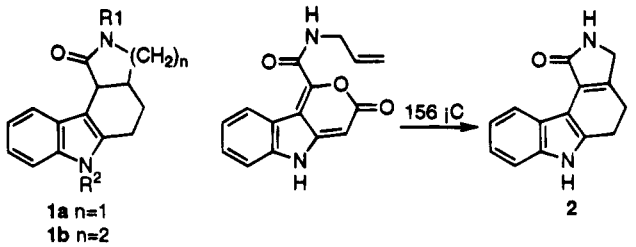
Two methods for the preparation of indole-2,3-quinodimethanes are reported. Treatment of 1,2-dimethyl-α-oxo-*N*-(phenylmethyl)-*N*-2-propenyl-1*H*-indole-3-acetamide (**3**) with sodium bis(trimethylsilyl)amide in refluxing THF gave 2-(phenylmethyl)-10c-hydroxy-6-methyl-3,3a,4,5,6,10c-hexahydropyrrolo[3,4-*c*]carbazol-1(2*H*)-one (**5**) in 18% yield by intramolecular Diels–Alder reaction of the intermediate enolate **4**. $LiBH_4$-reduction of amide **3** and thermolysis of the resulting α-hydroxyamide **8** at 190 °C gave a 63:37 mixture of the *cis* and *trans* isomers of 2-(phenylmethyl)-6-methyl-3,3a,4,5,6,10c-hexahydropyrrolo[3,4-*c*]carbazol-1(2*H*)-one (**9a** and **9b**) in 64% yield. The corresponding *N*-3-butenylamide **10** at 205 °C led to a 67:33 mixture of *cis*- and *trans*-7-methyl-2,3,4,4a,5,6,7,11c-octahydro-2-(phenylmethyl)-1*H*-pyrido[4,3-c]carbazol-1-one (**11a** and **11b**) in 53% yield. Thermolysis of 1,2-dimethyl-α-hydroxy-*N*-(phenylmethyl)-*N*-2-propynyl-1H-indole-3-acetamide (**15**) gave an equimolar mixture of lactam **9a** and the aromatized product, 3,6-dihydro-6-methyl-2-(phenylmethyl)pyrrolo[3,4-*c*]carbazol-1(2*H*)-one (**17**) in 80% yield by disproportionation of the intermediate lactam **16**. Reaction of 1,2-dimethyl-1*H*-indole-3-carboxaldehyde with methyl acrylate and sodium bis(trimethylsilyl)amide produced methyl 1,2-dihydro-9-methyl-9*H*-carbazole-3-carboxylate (**20**) in 26% yield, most likely by a sequence of Michael addition to the enolate of the aldehyde and intramolecular aldol condensation.

Introduction

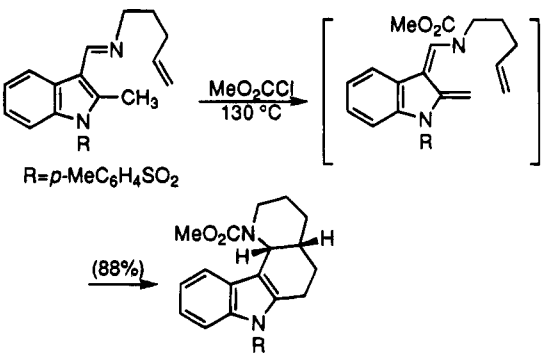
In their pioneering studies of the indole-2,3-quinodimethane system,[3,4] Magnus and co-workers observed that these reactive intermediates may be generated with remarkable ease. For instance, treatment of imines of 2-methyl-1*H*-indole-3-carboxaldehydes with acid chlorides or anhydrides gave rise to indole-2,3-quinodimethanes which in the example illustrated[5] were trapped as the intramolecular Diels–Alder adducts (Scheme 1).

In connection with a project directed at the preparation of novel agents for central nervous system diseases we have used an adaptation of this approach for a synthesis of the hexahydropyrrolo[3,4-*c*]carbazol-1-one system **1a** and the homologous octahydro-1*H*-pyrido[4,3-*c*]carbazol-1-one system **1b**. The latter appears to be new except



for more highly unsaturated analogs; derivatives of the former have been prepared previously by Fischer indole synthesis[6] or Diels–Alder reaction of 2-vinylindoles with maleimides.[7] The unsaturated lactam **2** has been prepared by intramolecular Diels–Alder reaction involving a 3-oxopyrano[4,3-*b*]indole as the substrate followed by extrusion of carbon dioxide and a 1,5-hydrogen shift.[8]

Scheme 1



Results and Discussion

Reaction of 1,2-dimethylindole with oxalyl chloride[9] followed by treatment of the 1,2-dimethyl-α-oxo-1*H*-indole-3-acetyl chloride so obtained with *N*-benzylallylamine gave the amide **3** in 76% yield. It could be distilled

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(1) Paper 4: Ciganek, E.; Wuonola, M. A.; Harlow, R. L. *J. Heterocycl. Chem.* **1994**, *31*, 1251.

(2) Current address: 121 Spring House Way, Kennett Square, PA 19348.

(3) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35.

(4) For other approaches, see: Pindur, U.; Erfanian-Abdoust, H. *Chem. Rev.* **1989**, *89*, 1681. Pindur, U.; Haber, M. *J. Prakt. Chem.* **1993**, *335*, 12. Fray, E. B.; Moody, C. J.; Shah, P. *Tetrahedron* **1993**, *49*, 439 and references cited therein.

(5) Gallagher, T.; Magnus, P. *Tetrahedron* **1981**, *37*, 3889.

(6) Nagai, T.; Myokan, I.; Keishi, F.; Ohta, K.; Taya, N.; Miyabara, S.; Shibata, M.; Mikami, H.; Hori, T. Ger. Offen. DE 4,034,687 (1991); *Chem. Abstr.* **1991**, *115*, 279992m. Reed, G. W. B.; Cheng, P. T. W.; McLean, S. *Can. J. Chem.* **1982**, *60*, 419. Rashidyan, L. G.; Asratyan, S. N.; Karagezyan, K. S.; Mkrtchyan, A. R.; Sedrakyan, R. O.; Tatevosyan, G. T. *Arm. Khim. Zh.* **1968**, *21*, 793; *Chem. Abstr.* **1969**, *71*, 21972.

(7) Balasubramanian, T.; Balasubramanian, K. K. *J. Chem. Soc., Chem. Commun.* **1994**, 1237. Pindur, U.; Otto, C. *Tetrahedron* **1992**, *48*, 3515. Kleinschroth, J.; Hartenstein, J.; Schaechtele, C.; Rudolph, C.; Dooley, D. J.; Weinheimer, G. U.S. Patent 4,912,107 (1990); *Chem. Abstr.* **1990**, *113*, 191154n. Eitel, M.; Pindur, U. *J. Org. Chem.* **1990**, *55*, 5368. Eitel, M.; Pindur, U. *Heterocycles* **1988**, *27*, 2353. Pindur, U.; Eitel, M. *Helv. Chim. Acta* **1988**, *71*, 1060. Ziegler, F. E.; Spitzner, E. B.; Wilkins, C. K. *J. Org. Chem.* **1971**, *36*, 1759.

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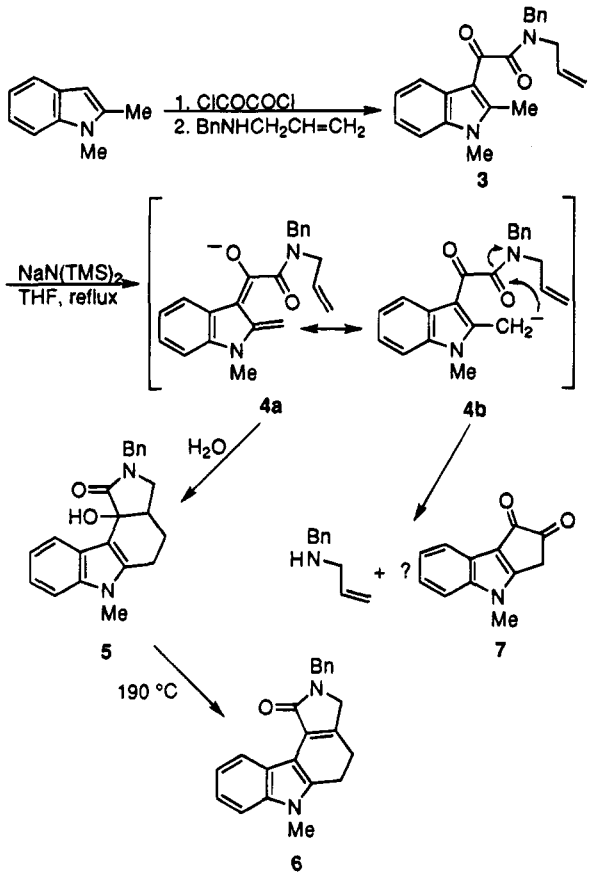
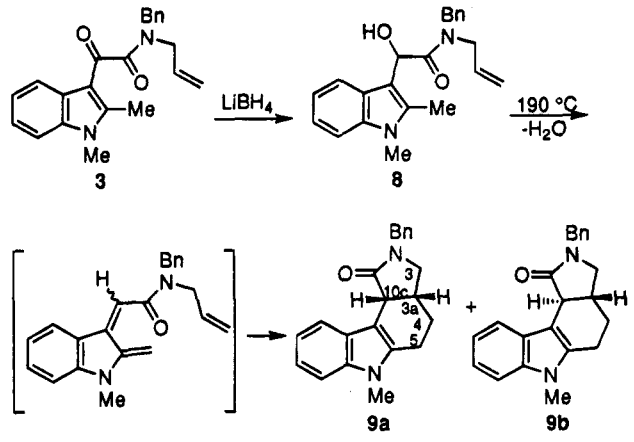
Scheme 2



under reduced pressure at 250 °C bath temperature without cyclization. However, treatment with sodium bis(trimethylsilyl)amide in refluxing THF gave, after aqueous workup, 2-(phenylmethyl)-10c-hydroxy-6-methyl-3,3a,4,5,6,10c-hexahydropyrrolo[3,4-*c*]carbazol-1(2*H*)-one (**5**) in 18% yield, presumably by intramolecular Diels–Alder reaction[10] of the intermediate enolate **4a** (Scheme 2).[11] The sterochemistry of lactam **5** was not determined but is assumed to be the more stable *cis* (see below). The main product was *N*-benzylallylamine, which made up 60% of the crude product mixture. It may have been formed by intramolecular cleavage of the mesomer **4b** as shown in Scheme 2; a compound having an NMR spectrum consistent with structure **7** was isolated in too small a quantity to permit complete characterization. The enolate **4** was formed at room temperature as shown by quenching with D_2O, but cyclization was slow at that temperature. Heating hydroxylactam **5** to 190 °C resulted in dehydration to the unsaturated lactam **6** (Scheme 2); a small amount (ca. 7%) of the aromatized product **17** (Scheme 4) was also

Scheme 3

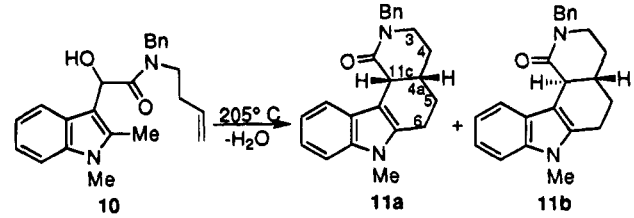


formed. The NMR spectrum of lactam **6** agreed well with that of the 2,6-unsubstituted analog **2**.[8]

Reaction of amide **3** with LDA in THF at room temperature gave a complex product mixture; unreacted starting material was isolated when it was heated with sodium acetate in acetic anhydride at 140 °C. When amide **3** was treated with sodium hydride in THF at room temperature, no reaction occurred. At reflux, amide **3** was cleaved between the two carbonyl groups to give *N*-allyl-*N*-benzylformamide in 37% yield; cyclization and dehydration to give the unsaturated lactam **6** occurred to the extent of 13%.

To avoid these side reactions, amide **3** was reduced with lithium borohydride to the hydroxyamide **8** which on heating to 190 °C gave a 63:37 mixture of the *cis* and *trans* isomers of 2-(phenylmethyl)-6-methyl-3,3a,4,5,6,-10c-hexahydropyrrolo[3,4-*c*]carbazol-1(2*H*)-one (**9a** and **9b**) in 64% yield (Scheme 3). The structures were assigned by NOESY (strong cross peak between H_{3a} and H_{10c} in isomer **9a** only) and by the observation that the *trans* isomer **9b** was isomerized completely to the *cis* isomer **9a** on treatment with sodium bis(trimethylsilyl)-amide in THF at room temperature. Attempts to effect dehydration of amide **8** to the indole-2,3-quinodimethane with acids or thionyl chloride in pyridine led to decomposition.

Essentially identical results were obtained with the homologous amide **10** except that a somewhat higher temperature was required to effect dehydration and cyclization (205 °C as compared to 190 °C for amide **8**). The yield was 53% and the isomer ratio of **11a**:**11b** was 67:33. The stereochemistry was again determined by NOESY (strong cross peak between H_{4a} and H_{11c} in isomer **11a** only).



The stereochemical outcome of these two intramolecular Diels–Alder reactions differs from that of the imine cyclizations illustrated in Scheme 1 which without exception give exclusively the *cis*-fused adducts.[3] This was considered to be a consequence of steric interaction between the benzene ring and the bulky X substituent

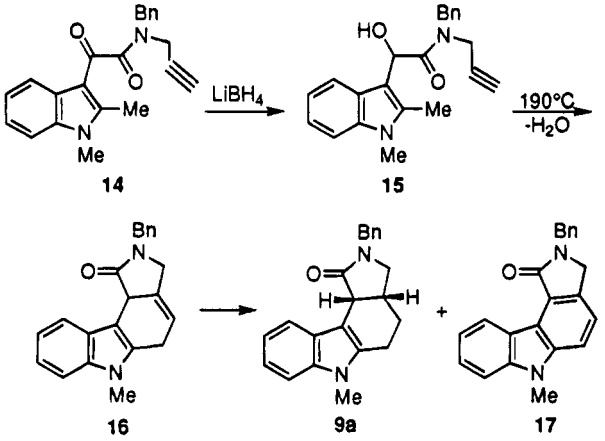
(8) Moody, C. J.; Rahimtoola, K. F.; Porter, B.; Ross, B. C. *J. Org. Chem.* **1992**, *57*, 2105.

(9) Speeter, M. E.; Anthony, W. C. *J. Am. Chem. Soc.* **1954**, *76*, 6208. The reaction was first reported by M. Giua (*Gazz. Chim. Ital.* **1924**, *54*, 593), who erroneously claimed acylation at the 2-position.

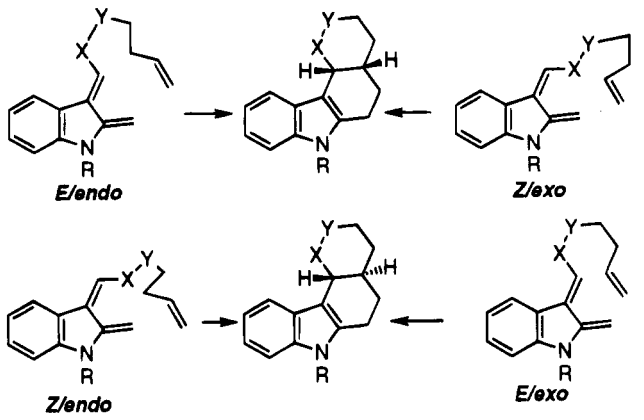
(10) Reviews: (a) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (b) Ciganek, E. *Org. React.* **1984**, *32*, 1. (c) Taber, D. F. *Intramolecular Diels–Alder and Alder Ene Reactions*, Springer, Berlin, 1984. (d) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (e) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187. (f) Roush, W. R. In *Advances in Cycloaddition;* Curran, D. P., Ed.; JAI, Greenwich, CT, 1990; Vol. 2, p 91. (g) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds. Pergamon Press: Oxford, 1991; Vol. 5, p 513.

(11) For an intramolecular Diels–Alder reaction involving the lithium salt of an amide as the diene, see: Peréz Meirás, D.; Guitián, E.; Castedo, L. *Tetrahedron Lett.* **1990**, *31*, 2331. Cf. also: Shea, K. J.; Wada, E. *Tetrahedron Lett.* **1982**, *23*, 1523.

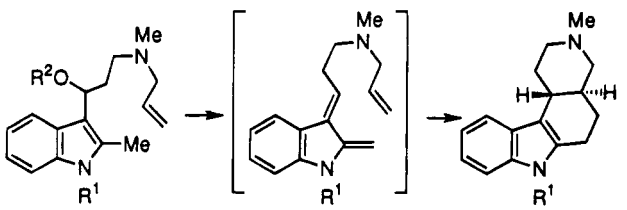
Scheme 4



(X = R¹CON; Y = CH_2) in the *E/exo* transition state (TS).[3] Models indicate that the *Z/endo* TS, which also leads to the *trans*-fused product, is very strained. In the present cases, the offending group X is the much smaller carbonyl group (Y = NBn) so that some *trans*-fused product is formed via the *E/exo* TS. The *cis*-fused product is most likely[3] formed via the *Z/exo* TS; the alternate *E/endo* TS suffers from serious steric interactions of the allyl CH_2 group with the benzene ring. By



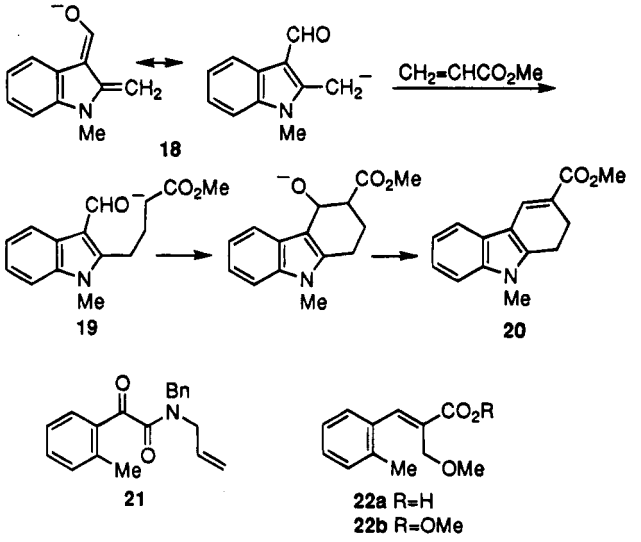
contrast, the indole-2,3-quinodimethane **13**, generated by Et_3N-induced elimination from ester **12**, gives predominantly the *trans*-fused product via the *E/exo* TS (*trans/cis* 95:5).[12] The alcohol precursor of ester **12** apparently could not be made to undergo dehydration.



12 R^1=*p*-$C_6H_4SO_2$
R^2=2,6-$Cl_2C_6H_3CO$

The *N*-propynyl analog **14** of amide **3** (Scheme 4) not unexpectedly failed to undergo cyclization on treatment with sodium bis(trimethylsilyl)amide since this would require the electronically unfavorable addition of an acetylide to an enolate. Formation of the dianion of amide **14** at room temperature was demonstrated by quenching

Scheme 5



with D_2O. Reduction of amide **14** followed by thermolytic dehydration of the amide **15** in degassed toluene at 190 °C resulted in disproportionation to give mostly a 1:1 mixture of lactam **9a** and the aromatized product **17** in 80% yield (Scheme 4). A small amount of what may have been the primary product **16** was detected in the NMR spectrum of the crude product mixture. The *trans* isomer **9b**, which is stable at that temperature, was absent within detectability by NMR spectroscopy, which indicates that the hydrogen transfer between two molecules of lactam **16** is either face-specific and concerted or any intermediate accepts the second hydrogen to give only the more stable *cis* isomer **9a**. When amide **15** was heated to 190 °C in air, only the aromatized product **17** was observed.

The observation that enolate **4** undergoes an intramolecular Diels–Alder reaction (Scheme 2) led us to examine briefly the behavior of the enolate **18** of 1,2-dimethyl-3-indolecarboxaldehyde in cycloadditions. Treatment of the aldehyde with sodium hydride and methyl acrylate in refluxing THF indeed produced the adduct **20** in 26% yield (Scheme 5). However, cyclopentene failed to add to enolate **18** under these conditions; also, reaction of *N*-methyl- and *N*-*t*-BOC-indole-2,3-quinodimethane with methyl acrylate is reported to give both regioisomeric adducts, the minor having the regiochemistry corresponding to that of adduct **20**.[13] The reaction thus most likely proceeds in two steps via the Michael adduct **19**. The transformation is reminiscent of the synthesis of 3-substituted 2*H*-1-benzopyrans by base-catalyzed reaction of salicylaldehydes with Michael acceptors.[14]

Extension of the reactions described above to the corresponding benzene derivatives was unsuccessful. Thus attempted cyclization of amide **21** with sodium bis(trimethylsilyl)amide in THF produced a complex mixture. Cyclization may succeed by photoenolization,[15] but this has not been investigated. Reaction of *o*-tolualdehyde with sodium hydride and methyl acrylate in THF proceeded without involvement of the methyl group and gave a mixture of the acid **22a** and the ester **22b**. Details of this reaction are given in a separate publication.[16]

(12) Hersloef, M.; Martin, A. R. *Tetrahedron Lett.* **1987**, *28*, 3423. The stereochemical assignments were made by ^{13}C NMR.

(13) Marinelli, E. R. *Tetrahedron Lett.* **1982**, *23*, 2745.

(14) Bachman, G. B.; Levine, H. A. *J. Am. Chem. Soc.* **1948**, *70*, 599. Deboer, C. D. U.S. Patent 3,796,727 (1974). René, L.; Royer, R. *Eur. J. Med. Chem.* **1975**, *10*, 72.

(15) Yang, N. C.; Rivas, C. *J. Am. Chem. Soc.* **1961**, *83*, 2213. Oppolzer, W.; Keller, K. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 728.

Experimental Section

General. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were determined in $CDCl_3$ unless otherwise specified. Melting points were measured in unsealed capillary tubes and are uncorrected. Mass spectra were obtained by chemical ionization (NH_3 or CH_4) or by electron ionization.

Materials. Starting materials were obtained from Janssen Chimica or Aldrich Chemical Co. The THF used was EM Science anhydrous grade (stored over 4A sieves). $MgSO_4$ was used throughout to dry solutions in organic solvents.

1,2-Dimethyl-α-oxo-1*H*-indole-3-acetyl Chloride. To a stirred suspension of 5.93 g (40.9 mmol) of 1,2-dimethylindole and 100 mL of ether was added slowly at 0 °C 5.8 g (45.6 mmol) of oxalyl chloride. The mixture was stirred in an ice bath for 30 min, and the solids were collected by filtration, washed twice with cold ether, and dried under vacuum at room temperature to give 6.13 g (64%) of the title compound. ^1H NMR δ 7.9 (m, 1 H), 7.4 (m, 3 H), 3.8 (s, 3 H), 2.8 (s, 3 H). This product was used without further purification. Concentration of the filtrates and washings at room temperature gave 3.02 g of a 3:1 mixture of the title compound and 1,2-dimethyl-1*H*-indole-3-carbonyl chloride. A sample was treated with methanol for conversion into the methyl esters and subjected to MS: found $(M + H)^+$ 232 (major component) and 204 (minor component).

1,2-Dimethyl-α-oxo-*N*-(phenylmethyl)-*N*-2-propenyl-1*H*-indole-3-acetamide (3). To 3.2 g (22 mmol) of *N*-benzylallylamine, 30 mL of 15% aqueous NaOH, and 30 mL of CH_2Cl_2 was added slowly at 10–15 °C 4.72 g (20 mmol) of 1,2-dimethyl-α-oxo-1*H*-indole-3-acetyl chloride, and the mixture was stirred at rt overnight. Toluene (100 mL) was added, the layers were separated, and the toluene layer was washed sequentially with 10% aqueous HCl, 10% aqueous Na_2CO_3, and concentrated aqueous NaCl and dried. Removal of the solvent gave 7.00 g (101%) of the title compound as a solid containing a small amount of toluene. ^1H NMR δ 8.0 and 7.9 (m + d, J = 7 Hz, 1 H), 7.2–7.4 (m, 8 H), 5.4–6.0 (2 m, 1 H), 5.1–5.3 (m, 2 H), 4.8 and 4.4 (2 s, 2 H), 4.1 and 3.6 (2 d, J = 6 Hz, 2 H), 3.7 (2 s, 3 H), 2.8 and 2.7 (2 s, 3 H); the rotamer ratio was ca. 1:1. Crystallization of 0.43 g of crude amide **3** from EtOAc gave 0.31 g (73%) of an analytical sample, mp 127–128 °C. Anal. Calcd. for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.28; H, 6.36; N, 8.10.

The following amides were prepared in an analogous manner using the appropriate substituted benzylamine.

1,2-Dimethyl-α-oxo-*N*-(phenylmethyl)-*N*-3-butenyl-1*H*-indole-3-acetamide. Yield: 26% from 1,2-dimethylindole, mp 143–144 °C (MeCN). ^1H NMR δ 8.1 and 7,9 (m + d, J = 7 Hz, 1 H), 7.2–7.5 (m, 8 H), 5.6 and 5.8 (2 m, 1 H), 5.2–4.9 (m, 2 H), 5.2 and 4.5 (2 s, 2 H), 3.7 (2 s, 3 H), 3.5 and 3.3 (2 t, J = 7 Hz, 2 H), 2.8 and 2.7 (2 s, 3 H), 2.3–2.4 (2 m, 2 H); the ratio of rotamers was 88:12. Anal. Calcd. for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.22; H, 6.61; N, 7.69.

1,2-Dimethyl-α-oxo-*N*-(phenylmethyl)-*N*-2-propynyl-1*H*-indole-3-acetamide (14). Yield: 83% from the acid chloride, mp 155–156 °C (MeCN). ^1H NMR δ 8.0 (m, 1 H), 7.2–7.5 (m, 8 H), 4.9 and 4.6 (2 s, 2 H), 4.2 and 4.0 (2 d, J = 2 Hz, 2 H), 3.6 (2 s, 3 H), 2.7 and 2.6 (2 s, 3 H), 2.4 and 2.2 (2 t, J = 2 Hz, 1 H); the rotamer ratio was 7:3. Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.52; H, 5.80; N, 8.18.

2-(Phenylmethyl)-10c-hydroxy-6-methyl-3,3a,4,5,6,10c-hexahydropyrrolo[3,4-*c*]carbazol-1(2*H*)-one (5). To a solution of 1.04 g (3.0 mmol) of amide **3** in 8 mL of THF was added 6 mL of 1 M $NaN(TMS)_2$ in THF (6 mmol). The mixture was heated under reflux for 30 min and quenched with H_2O. Extraction with EtOAc and removal of the solvent from the dried extracts gave 0.93 g of a 60:40 (molar) mixture of *N*-benzylallylamine and product **5**.[17] Crystallization from EtOAc gave 0.19 g (18%) of the title compound, mp 174–175 °C (decomp). ^1H NMR δ 8.2 (d/d, J = 7/2 Hz, 1 H), 7.1–7.3 (m, 8 H); 4.7 (d, J = 15 Hz, 1 H); 4.1 (d, J = 15 Hz, 1 H), 3.6 (s, 3 H), 3.4 (s, 1 H), 3.2 (t, J = 9 Hz, 1 H), 3.0 (t, J = 10 Hz, 1 H), 2.6–2.8 (m, 3 H), 2.3 (m, 1 H), 2.0 (m, 1 H). ^{13}C NMR δ 17.9, 19.4, 29.1, 40.9, 44.3, 46.7, 74.0, 106.7, 108.5, 120.0, 121.1, 121.5, 125.2, 127.4, 127.9, 128.6, 136.0, 136.6, 137.3, 174.4. IR (KBr) 3400 (sharp, m-s), 1690 cm^{-1} (vs) among others. Anal. Calcd. for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 75.90; H, 6.35; N, 8.27. The mother liquor was concentrated, and the residue was stirred with 10 mL each of CH_2Cl_2 and 10% aqueous HCl and filtered to remove 6 mg of a yellow solid, possibly 3,4-dihydro-4-methylcyclopent[*b*]-1,2-dione **7**. ^1H NMR (in DMSO-d_6) δ 7.9 (d, J = 7 Hz, 1 H), 7.6 (d, J = 7 Hz, 1 H), 7.2–7.4 (m, 2 H), 4.5 (s, 2 H), 3.7 (s, 3 H). Removal of the solvent from the dried CH_2Cl_2 solution gave 0.08 g of an oil with a complex ^1H NMR. MS: $(M + H)^+$ 200 (base peak); calcd for $(C_{12}H_{10}NO_2)^+$(compound **7**): 200.

In a separate, identical experiment, samples of the reaction mixture quenched with D_2O after 10 min and 60 min at 25 °C led to products with identical NMR spectra except that the 60-min sample showed the presence of ca. 3% of cyclized product **5**. The two singlets of the 2-Me group in amide **3** were almost completely replaced by two triplets and the integration corresponded to 2 H. MS (relative intensity): $(M + H)^+$ 347 (33), 348 (100), 349 (41), 350 (10), 351 (1). MS of undeuteriated **3**: 347 (100), 348 (25), 349 (4).

6-Methyl-2-(phenylmethyl)-3,4,5,6-tetrahydropyrrolo-[3,4-*c*]carbazol-1(2*H*)-one (6). Hydroxylactam **5** (0.17 g) was placed in a sublimator which was then evacuated to 0.005 mmHg, N_2 was added, and the procedure was repeated twice. The sublimator was then immersed in a 190 °C oil bath for 5 min, and the product was sublimed at 190 °C bath temperature/0.005 mmHg to give 0.15 g of sublimate consisting of 93% of lactam **6** and 7% of aromatized product **17** (87% and 7% yield, respectively). Crystallization from EtOAc gave a sample, mp 186–188 °C still containing 5% of **17**. ^1H NMR δ 8.6 (m, 1 H), 7.1–7.4 (m, 8 H), 4.6 (s, 2 H), 3.8 (s, 2 H), 3.6 (s, 3 H), 2.9 (t, J = 10 Hz, 2 H), 2.6 (t, J = 10 Hz, 2 H). ^{13}C NMR δ 20.1, 23.0, 29.4, 46.0, 52.1, 104.6, 108.4, 120.2, 120.7, 122.7, 123.8, 127.3, 128.1, 128.6, 129.7, 135.9, 137.0, 137.9, 140.0, 169.7. Anal. Calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.15; N, 8.53. Found: C, 80.14; H, 6.14; N, 8.46.

Reaction of 1,2-Dimethyl-α-oxo-*N*-(phenylmethyl)-*N*-2-propenyl-1*H*-indole-3-acetamide (3) with Sodium Hydride. Amide **3** (0.42 g, 1.2 mmol) was added to a mixture of 0.16 g of 60% sodium hydride in oil (4 mmol; previously washed with hexanes) and 5 mL of THF, and the mixture was heated under reflux for 3 h. Isolation with H_2O/EtOAc gave 0.37 g of product which by ^1H NMR was a mixture of 50% of unreacted **3**, 13% of unsaturated lactam **6**, and 37% of *N*-(phenylmethyl)-*N*-2-propenylformamide. The latter was isolated by short-path distillation at 160 °C bath temperature/0.005 mmHg and shown to be identical by ^1H NMR to an authentic sample (see below).

***N*-(Phenylmethyl)-*N*-2-propenylformamide.** A mixture of 3.0 g of *N*-benzylallylamine and 10 mL of formic acid was heated under reflux for 10 h and concentrated under vacuum. The residue was taken up in 50 mL of toluene, and the solution was washed sequentially with 10% aqueous HCl, water, and 10% aqueous Na_2CO_3. Removal of the solvent from the dried extracts and short-path distillation of the residue at 120–140 °C bath temperature/0.005 mmHg gave 2.01 g (56%[18]) of the title compound. ^1H NMR δ 8.3 and 8.2 (2 s, 1 H), 7.2–7.5 (m, 5 H), 5.6–5.8 (m, 1 H), 5.1–5.3 (m, 2 H), 4.5 and 4.4 (2 s, 3 H), 3.9 and 3.7 (2 d, J = 6 Hz, 2 H); the ratio of rotamers was 1:1. Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.02; H, 7.41; N, 8.00.

Reaction of 1,2-Dimethyl-α-oxo-*N*-(phenylmethyl)-*N*-2-propynyl-1*H*-indole-3-acetamide (14) with $NaN(TMS)_2$. To a solution of 0.34 g (1 mmol) of amide **14** in 3 mL of THF was added, with ice cooling, 3 mL of 1 M $NaN(TMS)_2$ in THF (3 mmol). A small sample was quenched with D_2O and extracted into CH_2Cl_2 after stirring at rt for 30 min. The ^1H NMR showded the two s at δ 2.7 and 2.6 mostly replaced by 2

(16) Ciganek, E. *J. Org. Chem.* **1995**, *60*, in press.

(17) Attempts at this point to remove the amine by extraction into aqueous HCl led to destruction of product **5**.

(18) The yield can probably be increased significantly by extending the reflux time.

t with an integration of 2 H; the two t at δ 2.4 and 2.2 due to the propynyl H were gone, and the two propargyl CH_2 were now singlets. Heating the rest of the solution at reflux resulted in slow disappearance of the starting material; the products had a broad ^1H NMR.

1,2-Dimethyl-α-hydroxy-*N*-(phenylmethyl)-*N*-2-propenyl-1*H*-indole-3-acetamide (8). To a solution of 3.40 g (9.83 mmol) of amide **3** in 30 mL of THF was added under N_2 with ice cooling 10 mL of 2M $LiBH_4$[19] (20 mmol). The mixture was stirred in an ice bath for 15 min and at rt for 1 h. Isolation with EtOAc/H_2O gave 3.33 g (97%) of the title compound, which was used in the next step without further purification. ^1H NMR δ 7.6 (t, J = 7 Hz, probably 2 d, 1 H), 7.0–7.3 (m, 7 H), 6.8 (d, J = 7 Hz, 1 H), 5.7 and 5.3 (2 m, 1 H), 5.5 (s, 1 H), 4.9–5.1 (m, ca. 3.5 H, contains one of the four benzyl doublets), 4.4 (2 d, J = 15 and 17 Hz, 1 H), 4.2 (d/d, J = 11/6 Hz, ca 0.5 H, one of the four allyl CH_2 d/d), 4.1 (d, J = 17 Hz, ca. 0.5 H), 3.4–3.9 (3 d/d, ca 1.5 H), 3.5 and 3.6 (2s, 3 H), 2.3 and 2.4 (2 s, 3 H). LRMS: 331 [(M + H − H_2O)$^+$].

The following α-hydroxyamides were prepared by the same method.

***N*-3-Butenyl-1,2-dimethyl-α-hydroxy-*N*-(phenylmethyl)-1*H*-indole-3-acetamide (10).** Yield of crude material: 100%. ^1H NMR δ 7.6 (2 d, J = 7 Hz, 1 H), 7.0–7.4 (m, 7 H), 6.8 (d, J = 7 Hz, 1 H), 5.7 and 5.4, 2 m, 1 H), 5.4 and 5.6 (2 d, J = 6 Hz, 1 H), 4.8–5.0 (m, 2 H), 4.1–4.8 (4 d, J = 16 Hz, 2 H), 3.5 and 3.6 (2 s, 3 H), 2.3 and 2.4 (2 s, 3 H), 2.0–3.6 (m, 4 H).

1,2-Dimethyl-α-hydroxy-*N*-(phenylmethyl)-*N*-2-propynyl-1*H*-indole-3-acetamide (15). Yield of crude product: 100%. ^1H NMR δ 7.6 (2 d, J = 7 Hz, 1 H), 7.0–7.3 (m, 7 H), 6.7 (d, J = 7 Hz, 1 H), 5.7 and 5.5 (2 d, J = 5 Hz, 1 H), 5.1 (d, J = 15 Hz, ca 0.5 H), 4.2–4.6 (3 d, J = 15 Hz and 2 d, J = 5 Hz, ca 2.5 H), 4.0 (2 d, J = 2 Hz, 1 H), 3.6 and 3.5 (2 s, 3 H), 2.5 and 2.3 (2 s, 3 H), 2.0–2.4 (m, 2 H).

***Cis*- and *trans*-2-(Phenylmethyl)-6-methyl-3,3a,4,5,6,-10c-hexahydropyrrolo[3,4-*c*]carbazol-1(2*H*)-one (9a and 9b).** A solution of 1.56 g of amide **8** in 10 mL of toluene was placed in a Carius tube which was sealed under 0.005 mmHg vacuum after two freeze–thaw cycles[20] and heated fully submerged in a 190 °C oil bath for 2.5 h. The ^1H NMR of the crude product (1.58 g) showed a ratio of **9a**:**9b** = 63:37. Chromatography on silica gel and elution with hexanes/EtOAc 4:1 and 3:1 gave a total 0.94 g (64%) of the two isomers, the *trans* isomer **9b** being eluted first. Crystallization of the appropriate fractions from MeCN gave 0.23 g of **9b** and 0.51 g of **9a.** Isomer **9a**: mp 150–152 °C. ^1H NMR δ 8.0 (d/d, J = 7/1.5 Hz, 1 H), 7.1–7.4 (m, 8 H), 4.4 (s, 2 H), 3.9 (d, J = 8 Hz, 1 H; H_{10c}), 3.6 (s, 3 H), 3.5 (d/d, J = 7/10 Hz, 1 H; H_3), 3.0 (d/d, J = 10/4 Hz, 1 H; H_3), 2.6–2.8 (m, 3 H; $H_{3a,5}$), 1.8–2.0 (m, 2 H; H_4). The NOESY showed a strong cross peak between H_{10c} and H_{3a}. ^{13}C NMR δ 19.6, 25.1, 29.0, 31.2, 41.3, 46.6, 49.7, 104.6, 108.3, 119.3, 120.4, 121.0, 127.1, 127.4, 128.2, 128.5, 135.3, 136.8, 137.2, 174.2. IR (KBr) 1680 cm^{-1} (vs). Anal. Calcd. for $C_{22}H_{22}NO$; C, 79.97; H, 6.71; N, 8.49. Found: C, 79.76; H, 6.64; N, 8.44. Isomer **9b**: mp 145–151 °C. ^1H NMR δ 8.5 (d/d, J = 6/1 Hz, 1 H), 7.1–7.4 (m, 8 H), 4.7 (d, J = 15 Hz, 1 H), 4.4 (d, J = 15 Hz, 1 H), 3.6 (s, 3 H), 3.5 (d, J = 13 Hz, split further, 1 H; H_{10c}); 3.3 (d/d, J = 6.5/9 Hz, 1 H; H_3), 3.2 (d, J = 9 Hz, 1 H; H_3), 2.8–3.0 (m, 2 H; H_5), 2.4 (m, 1 H; H_{3a}), 2.2 (m, 1 H; H_4), 1.8 (m, 1 H; H_4). The NOESY exhibited cross peaks between H_{10c} and one each of H_3 and H_4 but not between H_{10c} and H_{3a}. ^{13}C NMR δ 22.5, 24.7, 29.2, 40.8, 46.5, 46.6, 50.1, 107.3, 108.1, 119.3, 120.7, 122.4, 125.5, 127.4, 128.1, 128.6, 135.1, 136.6, 137.2, 173.9. IR (KBr) 1692 cm^{-1} (vs). Anal. Calcd. for $C_{22}H_{22}NO$: C, 79.97; H, 6.71; N, 8.49. Found: C, 79.67; H, 6.60; N, 8.49.

Isomerization of 9b to 9a. To a solution of 0.20 g (0.63 mmol) of the crude mixture of isomers **9a** and **9b** (ratio 63:37) in 3 mL of THF was added at rt 0.4 mL of 1 M $NaN(TMS)_2$ in THF (0.4 mmol). TLC after 25 min (silica gel, 2:1 hexanes/EtOAc) showed the absence of isomer **9b** (R_f = 0.49; **9a**, R_f = 0.37). The ^1H NMR of the product isolated (H_2O, CH_2Cl_2; 0.19 g) after 30 min was mostly that of isomer **9a**; isomer **9b** was absent.

***cis*- and *trans*-7-Methyl-2,3,4,4a,5,6,7,11c-octahydro-2-(phenylmethyl)-1*H*-pyrido[4,3-*c*]carbazol-1-one (11a and 11b).** *N*-3-Butenyl-1,2-dimethyl-α-hydroxy-*N*-(phenylmethyl)-1*H*-indole-3-acetamide (**10**, 1.00 g) in 10 mL of toluene was degassed as described above and heated in a 205 °C oil bath for 4 h. The crude product (0.96 g, **11a**:**11b** = 67:33) was chromatographed on silica gel and eluted with hexanes/EtOAc 3:1 to give 0.17 g (18%) of isomer **11b**, which was not obtained in completely pure form, and 0.33 g (35%) of isomer **11a**, which was obtained as an oil: ^1H NMR δ 8.0 (d/d, J = 6/1 Hz, 1 H), 7.0–7.3 (m, 8 H), 4.6 (ABq, J = 15 Hz, 2 H), 3.8 (d, J = 5 Hz, 1 H, H_{11c}), 3.6 (s, 3 H), 3.1–3.3 (m, 2H), 2.6–2.8 (m, 2 H), 2.3 (m, 1 H, H_{4a}), 2.0 (m, 1 H), 1.8–1.9 (m, 3H). There was a strong NOE interaction between H_{11c} and H_{4a}. ^{13}C NMR δ 21.3, 25.6, 27.4, 29.0, 32.8, 41.0, 44.2, 50.1, 107.6, 108.3, 119.2, 120.6, 120.7, 127.2, 128.0, 128.1, 128.5, 135.2, 137.2, 137.5, 171.0. HRMS calcd for $C_{23}H_{25}N_2O$ [(M + H)$^+$], 345.196689; found, 345.195751. Isomer **11b**: oil. ^1H NMR δ 8.0 (d/d, J = 7/2 Hz, 1 H), 7.0–7.4 (m, 8 H), 4.9 (d, J =15 Hz, 1 H), 4.4 (d, J =15 Hz, 1 H), 3.6 (s, 3 H), 3.5 (d, J =11 Hz, 1 H), 3.4 (m, 1 H), 3.3 (m, 1 H), 2.7 (m, 2 H), 2.0–2.1 (m, 3 H), 1.5–1.7 (m, 2 H). ^{13}C NMR δ 22.1, 29.0, 29.3, 29.8, 36.4, 44.5, 44.7, 50.0, 106.3, 108.2, 118.9, 120.6, 122.5, 127.2, 127.4, 128.2, 128.5, 136.4, 137.3, 137.9, 171.7. HRMS calcd for $C_{23}H_{25}N_2O$ [(M + H)$^+$], 345.196689; found, 345.196281.

Thermolysis of 1,2-Dimethyl-α-hydroxy-*N*-(phenylmethyl)-*N*-2-propynyl-1*H*-indole-3-acetamide (15). A solution of 0.86 g of amide **15** in 10 mL of toluene was degassed as described above and heated in a 190 °C oil bath for 2.5 h to give 0.86 g of crude product containing ca. 40% each of lactams **9a** and **17** as determined by ^1H NMR. A third product having a 1 H d at δ 8.4 may have been lactam **16**. LRMS: (M + H)$^+$ 327 (**17**), 329 (**16**?), 331 (**9a**). Chromatography on silica gel and elution with hexanes/EtOAc 4:1 was complicated by the low solubility of lactam **17** in the solvent mixture. Appropriate fractions, all containing some lactam **9a** in addition to lactam **17** were triturated with MeCN and then crystallized from DMF to give 3,6-dihydro-6-methyl-2-(phenylmethyl)pyrrolo[3,4-*c*]-carbazol-1-(2*H*)-one (**17**), mp 199–200 °C still containing ca. 1% DMF which could not be removed by pulverizing the crystals and drying at 120 °C/0.005 mmHg. ^1H NMR δ 9.4 (d/d, J = 9/1 Hz, 1 H), 7.3–7.6 (m, 10 H), 4.9 (s, 2 H), 4.4 (s, 2 H), 3.9 (s, 3 H). ^{13}C NMR δ 29.2, 46.4, 50.0, 108.0, 111.3, 118.8, 119.4, 121.5, 126.5, 126.6, 126.7, 127.5, 128.2, 128.7, 133.1, 137.5, 140.7, 141.3, 169.4. Anal. Calcd. for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.57; N, 8.58. Found: C, 80.24; H, 5.63; N, 8.63. HRMS calcd for $C_{22}H_{19}N_2O$ [(M + H)$^+$], 327.149738; found, 327.151096.

Methyl 1,2-Dihydro-9-methyl-9*H*-carbazole-3-carboxylate (20). To a suspension of 0.20 g of prewashed NaH/oil (0.10 g, 4.2 mmol) in 5 mL of THF was added 0.55 g (3.2 mmol) of 1,2-dimethyl-1*H*-indole-3-carboxaldehyde,[21] and the mixture was stirred at rt for 30 min. Methyl acrylate (1 mL, 0.96 g, 11.2 mmol) was added, and the mixture was heated under reflux for 5 h. Isolation with H_2O/EtOAc gave 0.95 g of crude product which on crystallization from EtOAc furnished 0.20 g (26%) of the title compound, mp 112–113 °C. ^1H NMR δ 7.9 (t, J = 1 Hz, 1 H), 7.8 (d/d, J = 6/2 Hz, 1 H), 7.1–7.3 (m, 3 H), 3.8 (s, 3 H), 3.7 (s, 3 H), 2.8–3.0 (symmetrical A_2B_2 pattern, 4 H); the spectrum also showed the presence of ca. 3% of what is considered to be methyl 9-methyl-9*H*-carbazole-3-carboxylate, which must have been formed by dehydrogenation of ester **20** during crystallization since it was not present in the crude product: δ 8.8 (s, 1 H), 4.0 (s, 3 H), 3.9 (s, 3 H) among others. ^{13}C NMR of **20**: δ 20.7, 22.7, 29.5, 51.3, 109.4, 109.6, 117.4, 117.6, 120.8, 121.5, 125.1, 131.5, 137.8, 141.1, 168.3. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.46; H, 6.16; N, 5.71.

(19) Because of the poor solubility of amide **3** in EtOH, reduction with $NaBH_4$ was very slow.

(20) See reference 10b, p 97.

(21) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104. Canoira, L.; Gonzalo, R. J.; Subirata, J. B.; Escario, J. A.; Jimenez, I.; Martinez-Fernandez, A. R. *Eur. J. Med. Chem.* **1989**, *24*, 39.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **11a** and **11b** for which elemental analyses were not obtained (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be obtained from the ACS; see any current masthead page for ordering information.

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