Progress in Chemical and Biochemical Research **2019**, 2, 34-39

Progress in Chemical and Biochemical Research

Journal homepage: www.pcbiochemres.com

Tertiary cyclic amides in Vilsmeier type reaction with indoles

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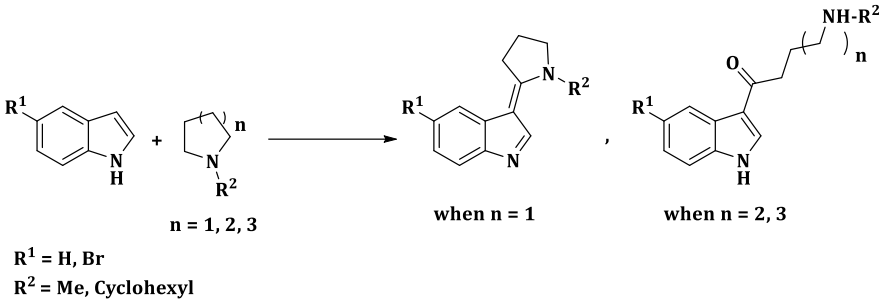
ARTICLE INFO

Article history:
Received: 10 January 2019
Accepted: 17 February 2019
Available online: 14 March 2019
Manuscript ID: PCBR-1810-1016

GRAPHICAL ABSTRACT



KEYWORDS

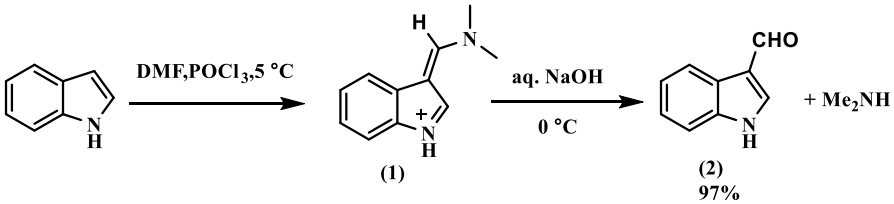
3-(1-Alkyl-pyrrolidine-2-ylidene)3*H*-indoles
Amino ketones
Indoles
Phosphorus oxy chloride
Vilsmeier reaction

ABSTRACT

The reaction of indoles with the complex formed from tertiary cyclic amides and phosphorus oxychloride, followed by basification using sodium hydroxide, was studied. In the case of five member amide rings, 3-(1-alkyl-pyrrolidine-2-ylidene)3*H*-indoles were obtained but in the case of six and seven member amide rings, ring opening was occurred and amino ketones were obtained.

1. Introduction

Vilsmeier–Haack reaction also called Vilsmeier reaction was first used for the formylation of an active arene, during which a mixture of phosphorus oxychloride and dimethylformamide (Vilsmeier reagent) was added to *N,N*-dimethyl aniline [1].The reaction of indole with the Vilsmeier reagent, followed by base, is the classic and very efficient method for the 3-formylation of indoles (Scheme 1) [2]. Before the alkaline hydrolysis step, the product which was a salt, 3-[(dimethylamino)methylene]-3*H*-indolium chloride (**1**), was followed by a basic workup affording dimethylamine and aldehyde. 3-Acylindoles can be obtained from Vilsmeier reaction of indole and tertiary amides in combination to phosphorus oxychloride [3].



Scheme 1. The reaction of indole with Vilsmeier reagent for the 3-formylation of indoles

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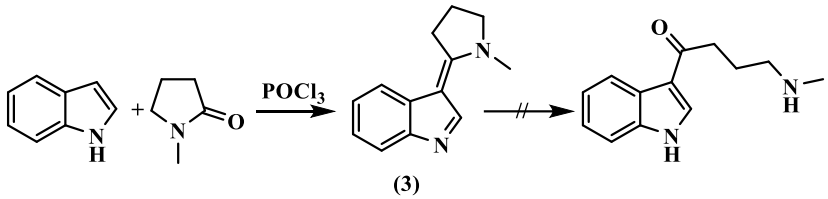
†Electronic Supplementary Information (ESI) available

However, when 1-methylpyrrolidine-2-one is used as the cyclic amide component, 3-(1-methylpyrrolidin-2-ylidene)-3*H*-indole (**3**) can be the product, without forming any amino ketone product [4].



Scheme 2. The reaction of indole with 1-methylpyrrolidine-2-one under Vilsmeier condition

This compound contains an intriguing combination of enamine and imine (as part of 3*H*-indole) groups in conjugation. Study of the reaction of (Z)-3-(1-methylpyrrolidin-2-ylidene)-3*H*-indole (**3**) has revealed some remarkable properties and transformations. For example, it was shown to be a remarkably strong base, pK_a 10.6, for an imine, as compared to that of 4a-methyl-1,2,3,4-tetrahydro-4a(i)*H*-carbazole with a pK_a of 3.6 [5]. The structure, reactions and crystallographic analysis of this compound have been discussed [5-9]. We have found that 5-bromo-3-(1-methylpyrrolidine)ylidene-3*H*-indole (**4**) is obtained from the reaction of 5-bromoindole with 1-methylpyrrolidine-2-one and phosphorus oxychloride in 95% yield [10]. The reaction of this compound with acidic organic compounds was studied with our group [9,11]. We have reported the reaction of indole with the combination of 1-cyclohexyl-2-pyrrolidinone and phosphorus oxychloride giving the hydrochloride of 3-(1-cyclohexylpyrrolidin-2-ylidene)-3*H*-indole. The free base could be obtained by a very careful neutralization of this salt using NaOH at -5°C. The crystal structure of the hydrochloride, as a dihydrate, was determined [12]. The 3-(2-pyrrolidineylidene)-3*H*-indoles are stable compounds and they resist the hydrolysis of the corresponding amino ketones.

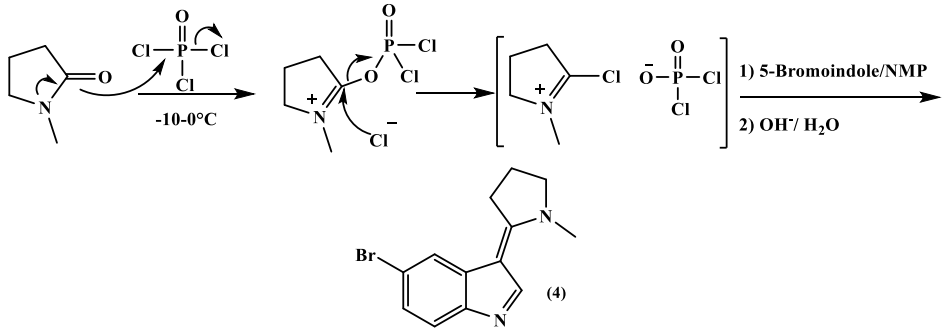
Our interest in these types of reactions promoted us to test the use of different tertiary cyclic amides in reaction with indoles under Vilsmeier condition.

2. Resultsand discussion

In order to further explore the products of tertiary cyclic amides reactions with indoles under Vilsmeier condition, a number of five and six member amides were studied. Thus, we came to use 1-methylpyrrolidine-2-one, 1-cyclohexyl-2-pyrrolidinone, 1-methylpiperidine-2-one and 1-methylazepan-2-one in reaction with phosphorus oxychloride and indole or 5-bromoindole.

When 1-methylpyrrolidine-2-one as a tertiary amide is subjected to Vilsmeier reaction with indole,the resulting product is 3-(1-methylpyrrolidine-2-ylidene)-3*H*-indole (**3**). This compound has a high level of basicity and reactivity. The overall synthesis pathway of this compound is similar to that of Youngdale and its colleagues [4], but we managed to achieve higher efficiencies by controlling the temperature, time and pHand which provide more complete spectral data [9].

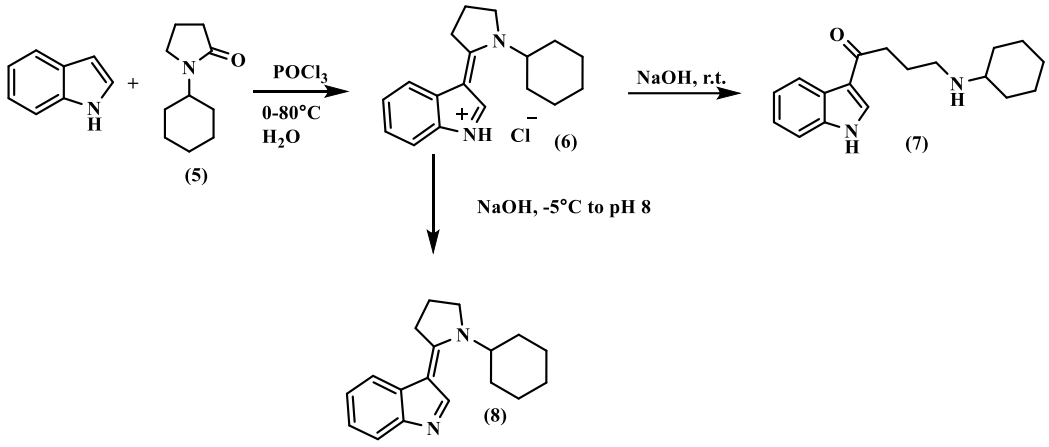
5-Bromo-3-(1-methylpyrrolidin-2-ylidene)-3*H*-indole (**4**) can be obtained from the reaction of 5-bromoindole with 1-methylpyrrolidin-2-one in the presence of $POCl_3$. We found that when the complex of $POCl_3$ and 1-methylpyrrolidin-2-one was produced at –10-0°C, the yield was improved and white needle crystals of 5-bromo-3-(1-methylpyrrolidin-2-ylidene)-3*H*-indole (**4**) was obtained after crystallization from n-hexane/acetone, in 95% yield (Scheme 3). This compound is a strong base, and reaction with an electrophile at the imine nitrogen is particularly favored by delocalization of charge in the species [10,11,13]. It was speculated that the reaction of (**4**) with active methylene compounds was initiated by proton transfer from the weak acid.



Scheme 3. The reaction of 5-bromoindole with 1-methylpyrrolidine-2-one under Vilsmeier condition

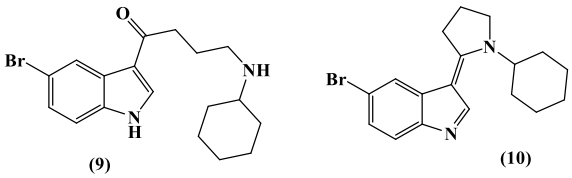
When 1-cyclohexyl-2-pyrrolidinone (**5**) was employed in a standard Vilsmeier process, as both solvent and reactant, and after diluting the final reaction mixture with water, a white precipitate was formed and filtered off (25% yield) leaving a clear aqueous solution. The solid proved to be the hydrochloride of 3-(1-cyclohexylpyrrolidin-2-ylidene)-3*H*-indole (6.HCl) as a dehydrate [12].

When the clear aqueous solution was made by the addition of sodium hydroxide at room temperature, a solid was formed, filtered off (68% yield) and purified. It proved to be the ketone (**7**) resulting from ring opening. The principal evidences for this were the conjugated carbonyl stretching at 1624 cm^{-1}, the ^{13}C-NMR signal for carbonyl carbon at d 201.4, the typical 3-acylindole UV absorption, and the observation of an indolic *N*-hydrogen ^{1}H-NMR signal at 10.25. The free 3-(1-cyclohexylpyrrolidin-2-ylidene)-3*H*-indole base (**8**) could be obtained by a very careful neutralization of its hydrochloride salt: this was achieved by dissolving the salt in water, cooling the solution to −5°C, slow addition of aqueous NaOH precooled to −5°C till the pH reached 8, vigorous stirring, rapid extraction with pre-cooled $CHCl_3$, drying of the extract and, finally, evaporation. The overall situation is summarized in Scheme 4.

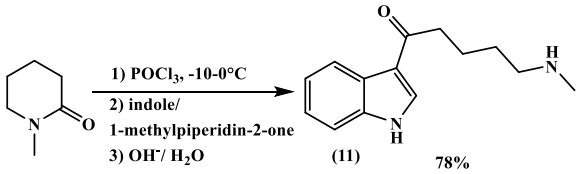


Scheme 4. The reaction of indole with 1-cyclohexyl-2-pyrrolidinone under Vilsmeier condition

1-(5-Bromo-1*H*-indol-3-yl)-4-(cyclohexylamino)butan-1-one (**9**) as ketone product and 5-bromo-3-(1-cyclohexylpyrrolidin-2-ylidene)-3*H*-indole (**10**) as free base were obtained from the reaction of 5-bromoindole with 1-cyclohexyl-2-pyrrolidinone in the presence of $POCl_3$.



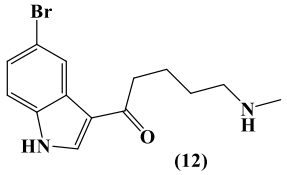
The reaction between 1-methylpiperidine-2-one as a six member ring type of tertiary amidewith indole in the presence of phosphorus oxychloride and low temperatures,takes a different path from 1-methylpyrrolidone.In this case, the product resulting from the opening of the 6-member ring (1-(1*H*-indol-3-yl)-5-(methylamino)pentan-1-one (**11**)) was obtained (Scheme 5).



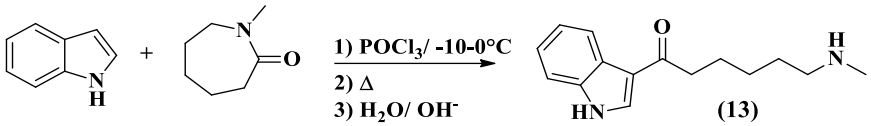
Scheme 5. The reaction of indole with 1-methylpiperidine-2-one under Vilsmeier condition

The ^{1}H-NMR spectrum of 1-(1*H*-indol-3-yl)-5-(methylamino) pentan-1-one (**11**) indicated the-NH indole peak at 11.85 ppm as a broad singlet.

The main product of the reaction between 1-methylpiperidine-2-one and 5-bromoindole in the presence of phosphorus oxychlorideat low temperatures is the product resulting from the opening of a six-membered ring or 1-(5-bromo-1*H*-indol-3-yl)-5-(methylamino)pentan-1-one (**12**). In the IR spectrum the conjugate C=O absorption appears at 1628.77 cm^{-1}.



When the activated complex of 1-methylazepan-2-one (as a seven-membered ring) with phosphorus oxychloride is reacted with indole at low temperatures under Vilsmeier conditions, 1-(1*H*-indol-3-yl)-6-(methylamino)hexan-1-one (**13**) as the product resulting from the opening of the azepan ring is obtained.



Scheme 6. The reaction of indole with 1-methylazepan-2-one under Vilsmeier condition

The reactivity of six and seven-membered heterocyclic structures was different from the five-membered structures in these reactions. It seems thatsix and seven-membered heterocyclic (2-ylidene)-3*H*-indole structures are unstable because of the ring strain in these structures, so the ring opening products were obtained.

3. Experimental details

Melting points were determined on a Philip Harris C4954718 apparatus. Infrared spectra were recorded on a Thermo Nicolet (Nexus 670) Fourier transform (FT) infrared spectrometer, using sodium chloride cells and measured in KBr pellets. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker 300 spectrometer in $CDCl_3$ using TMS as the internal reference. Mass spectra were recorded on Agilent 6890-N-Network-GC-system.Analytical thin-layer chromatography (TLC) was carried out with Merck silica gel 60 $F_{254\lambda}$ aluminum sheets and detection was made with the help of a UV lamp (λ 254 nm). The ultraviolet spectra are recorded with the Perkin Elmer Lambda 25 UV device. Microanalyses were performed on a Leco Analyzer 932.

*3-(1-methyl-2-pyrrolidinylidene)-3H-indole (**3**) [9].* To 1-methyl-2-pyrrolidinone (4 mL, 0.04 mol) cooled in an ice bath was added phosphorous oxychloride (4.08 g, 0.026 mol) with stirring time of 30 min. The temperature was maintained at –10-0°C. The mixture was then stirred again for an additional 10 min, and then a solution of indole (2.80 g, 0.024 mol) in 1-methyl-2-pyrrolidinone (4 mL, 0.04 mol) was slowly added during 1 h. The temperature rose to 45°C and a solid separated. The mixture was heated at 80°C for 3 h, and then mixed with water (100 mL). The clear solution was made basic by the addition of NaOH (6 g) in water (30 mL) causing a solid to separate. The solid was filtered off and washed with water. Recrystallization from ethanol-water afforded the desired product (4.21 g, 90%), mp 119-120°C. ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.20(2H, qn, *J* = 7.8Hz, $CH_2CH_2CH_2$), 3.37 (3H, s, CH_3N), 3.42 (2H, t, *J* = 8Hz, CH_2C=C), 3.77 (2H, t, *J* = 7.8Hz, CH_2N), 7.20 (2H, m, Ar), 7.53 (1H, m, indol-7-yl-H), 7.76 (1H, m, indol-4-yl-H), 8.34 (1H, s, α-3H-indolyl-H).^{13}C-NMR ($CDCl_3$) δ (ppm) 20.39, 35.08, 38.37, 58.03, 106.28, 119.23, 119.70, 121.87, 122.19, 130.77, 149.87, 151.33, 162.90. FT-IR (KBr, cm^{-1}) ν_{max} 2933, 1602, 1558, 1496, 1421, 1298, 1205, 1004, 765, 734.UV (EtOH, nm) λ_{max} 210, 252, 271, 344.

*5-Bromo-3-(1-methyl-2-pyrrolidinylidene)-3H-indole (**4**) [10].*The above procedure repeated with 5-bromoindole. Crystallization from *n*-hexane-acetone afforded the desired product (6.29 g, 95%), mp 208-210°C. ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.11 (2H, qn, *J* = 7.2Hz, $CH_2\underline{CH_2}CH_2$), 3.21 (3H, s, CH_3N overlapping with 2H of CH_2C=C), 3.70 (2H, t, *J* = 7.2 Hz, CH_2N), 7.27-7.61 (3H, m, Ar), 8.23 (1H, s, HC=N). ^{13}C-NMR δ (ppm) 20.16, 35.19, 38.46, 58.31, 105.77, 115.42, 120.89, 121.92, 124.82, 132.62, 149.94, 150.18, 163.55.FT-IR (KBr, cm^{-1}) ν_{max}3408, 2962, 1597, 1496, 1200, 806.UV (EtOH, nm) λ_{max}217, 278, 349.Found C, 56.41; H, 4.62; N, 9.93. $C_{13}H_{13}BrN_2$ requires C, 56.32; H, 4.73; N, 10.11.

*3-(1-Cyclohexylpyrrolidin-2-ylidene)-3H-indolium hydrochloride dehydrate (6.HCl.2H2O) [12].*To 1-cyclohexyl-2-pyrrolidinone (6.69 mL, 0.04 mol) cooled in an ice bath was added phosphorus oxychloride (2.40 mL, 0.026 mol) with stirring for 30 min and the temperature being kept at –10 to 0°C. The mixture was stirred for an additional 10 min and, then, a solution of indole (2.81 g, 0.024 mol) in 1-cyclohexyl-2-pyrrolidinone (6.69 mL, 0.04 mol) was slowly added while being stirred for 2 h. The temperature rose to 45°C and the mixture was kept at this temperature for 1 h, then heated at 80°C for 3 h and a solid separated. The mixture was cooled and then mixed with cold water (100 mL). A small amount of white solid was obtained besides the clear solution. The solid was filtered off and washed with cold water. Recrystallization from $PhMe/CH_2Cl_2$ gave 3-(1-cyclohexylpyrrolidin-2-ylidene)-3*H*-indolium hydrochloride dehydrate (**6**.HCl.$2H_2O$) (1.2 g, 25%), mp 90-92°C. ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.28-1.71 (6H, m, $3CH_2$), 1.92-2.40 (6H, m, $3CH_2$), 3.69 (2H, m, CH_2-C=), 4.09 (2H, m, CH_2-N), 4.28 (1H, m, CH-N), 7.23-7.81 (4H, m, Ar), 7.98 (1H, s, HC=N), 14.09 (1H, s, NH^+). ^{13}C-NMR ($CDCl_3$) δ (ppm) 16.3, 19.9, 20.0, 24.8, 30.3, 38.5, 53.2, 60.3, 61.8, 103.4, 114.9, 119.9, 123.6, 124.4, 125.8, 135.7, 137.4, 173.5. FT-IR (KBr, cm^{-1}) ν_{max}

3411, 2929, 1591, 1429, 1229, 753.UV (EtOH, nm) λ_{max} 215, 252, 271, 336. MS (EI, 70 ev): *m/z* 184.93, 214.33, 254.40, 267.13.

4-(Cyclohexylamino)-1-(1H-indol-3-yl)butan-1-one ***(7)*** *[12].* When the clear solution, from the above procedure, was made basic by the addition of NaOH (6 g) in water (30 mL), a solid was separated. The solid was filtered off and washed with water. Recrystallization from *n*-hexane gave 4-(cyclohexylamino)-1-(1*H*-indol-3-yl)butan-1-one (**7**) (4.63 g, 68%), mp 112-113°C. ^{1}H-NMR (CDCl3) δ (ppm) 1.02-1.32 (4H, m, 2 CH_2 overlapping with 1H of NH), 1.60-1.80 (4H, m, 2 CH_2), 1.89-2.02 (4H, m, 2CH_2), 2.44-2.51 (1H, m, CH), 2.78 (2H, t, *J* 7.2Hz, CH_2-N**)**, 2.90 (2H, t, *J* 7.2Hz, CH_2-C=O), 7.20-7.41 (5H, m, Ar), 10.25 (1H, bs, indole NH). ^{13}C-NMR (CDCl3) δ (ppm) 20.7, 25.1, 25.8, 26.1, 30.2, 33.5, 49.8, 56.7, 58.5, 111.7, 119.4, 119.7, 121.9, 122.1, 123.2, 131.0, 149.0, 201.4. FT-IR (KBr, cm^{-1}) ν_{max} 3431, 3163, 2926, 1624, 1439, 1140, 750.UV (EtOH, nm) λ_{max} 211, 241, 261, 297. MS (EI, 70 ev): *m/z* 185.93, 261.13, 267.20, 284.80. Found C, 76.24; H, 8.47; N, 9.78. $C_{18}H_{24}N_2O$ requires C, 76.02; H, 8.51; N, 9.85.

3-(1-Cyclohexylpyrrolidin-2-ylidene)-3H-indole ***(8)*** *[12].*3-(1-Cyclohexylpyrrolidin-2-ylidene)-3*H*-indolium hydrochloride (**6**.HCl) was dissolved in water at 30-40°C with stirring, then the solution was cooled to -5°C then very slowly, with efficient stirring, treated with pre-cooled sodium hydroxide at -5°C (until pH=8). The mixture was shaken vigorously with pre-cooled chloroform and the layers rapidly separated. The chloroform layer was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was crystallized from *n*-hexane to give 3-(1-cyclohexylpyrrolidin-2-ylidene)-3*H*-indole (**8**), mp 85-86°C. ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.06-1.61 (6H, m, 3CH_2), 1.89-2.10 (6H, m, 3CH_2), 3.35 (2H, t, *J* 7.5Hz, CH_2-C=), 3.64 (2H, t, *J* 7.2Hz, CH_2-N), 4.24 (1H, m, CH-N), 7.16-7.74 (4H, m, Ar), 8.18 (1H, s, HC=N). ^{13}C-NMR ($CDCl_3$) δ (ppm) 20.7, 25.3, 30.2, 33.6, 35.7, 46.6, 49.8, 56.7, 58.5, 105.0, 119.5, 119.6, 121.8, 122.0, 131.0, 149.0, 151.1, 163.3.FT-IR (KBr, cm^{-1}) ν_{max} 3166, 2926, 1624, 1439, 1138, 748.UV (EtOH, nm) λ_{max} 218, 251, 283, 335.Found C, 81.22; H, 8.39; N, 10.61. $C_{18}H_{22}N_2$ requires C, 81.16; H, 8.32; N, 10.52.

1-(5-Bromo-1H-indol-3-yl)-4-(cyclohexylamino)butan-1-one ***(9)****.* The above reaction condition was repeated with 5-bromo indole. When the clear solution was made basic by the addition of NaOH (6 g) in water (30 mL), a white solid separated. The solid was filtered off and washed with water. Recrystallization from n-hexane gave 1-(5-bromo-1*H*-indol-3-yl)-4-(cyclohexylamino)butan-1-one (**9**) (4.22 g, 62%), mp 108-109°C.^{1}H-NMR ($CDCl_3$) δ (ppm) 1.12-1.49 (4H, m, 2 CH_2), 1.51-1.87 (4H, m, 2 CH_2), 1.89-2.33 (4H, m, 2 CH_2), 3.18-3.34 (1H, m, CH), 3.48 (2H, t, *J* = 7.2Hz, CH_2-N), 3.79 (2H, t, *J* = 7.5Hz, CH_2-C=O), 3.94 (1H, bs, NH), 7.30-8.19 (4H, m, Ar), 10.37 (1H, bs, indole NH).^{13}C-NMR ($CDCl_3$) δ (ppm) 18.12, 25.18, 25.62, 26.04, 30.25, 31.62, 42.86, 50.15, 58.65, 104.61, 115.48, 120.83, 122.09, 124.74, 125.88, 127.38, 132.72, 195.66. FT-IR (KBr, cm^{-1}) ν_{max}3155, 2927, 1624, 1440, 1238, 750.UV (EtOH, nm) λ_{max}215, 249, 281, 289.

5-bromo-3-(1-cyclohexylpyrrolidin-2-ylidene)-3H-indole ***(10)****.* 5-Bromo-3-(1-cyclohexylpyrrolidin-2-ylidene)-3*H*-indolium hydrochloride was dissolved in water at 30-40°C with stirring, then the solution was cooled to -5°C then very slowly, with efficient stirring, treated with pre-cooled sodium hydroxide at -5°C (until pH=8). The mixture was shaken vigorously with pre-cooled chloroform and the layers rapidly separated. The chloroform layer was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was crystallized from n-hexane to give 5-bromo-3-(1-cyclohexylpyrrolidin-2-ylidene)-3*H*-indole (**10**), mp 209-210°C. ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.20-1.66 (6H, m, 3CH_2), 1.92-2.22 (6H, m, 3CH_2), 3.39 (2H, t, *J* = 7.5Hz, CH_2-C=), 3.74 (2H, t, *J* = 7.2Hz, CH_2-N), 4.26 (1H, m, CH-N), 7.25-7.60 (3H, m, Ar), 8.14 (1H, s, HC=N). ^{13}C-NMR ($CDCl_3$) δ (ppm) 19.08, 20.59, 22.73, 25.20, 30.22, 35.89, 46.12, 50.11, 58.67, 104.61, 115.50, 120.86, 122.10, 124.76, 132.69, 138.14, 149.31, 163.88.FT-IR (KBr, cm^{-1}) ν_{max} 3212, 2933, 1628, 1566, 1451, 1115, 878, 821.UV (EtOH, nm) λ_{max}215, 258, 279, 330.

1-(1H-indol-3-yl)-5-(methylamino)pentan-1-one ***(11)****.* To 1-methylpiperidine-2-one (4.56 mL, 0.04 mol, 4.52 g) cooled in an ice bath was added phosphorous oxychloride (4.08 g, 0.026 mol) with stirring during 30 min. The temperature was maintained at –10-0°C. The mixture was stirred an additional 10 min, and then a solution of indole (2.80 g, 0.024 mol) in 1-methylpiperidine-2-one (4.56 mL, 0.04 mol, 4.52 g) was added slowly during 2 h. The mixture was heated at 80°C for 3 h, and then mixed with water (100 mL). In this case pH = 1.4. The clear solution was made basic by the addition of NaOH (6 g) in water (30 mL) (pH=8∼9) causing a solid to separate. The solid was filtered off and washed with water. Recrystallization from n-hexane/acetone and a few drops of ethanol afford the desired product (4.30 g, 78%), mp 142-144°C.^{1}H-NMR (DMSO) δ (ppm)1.55-1.69 (4H, m, 2CH_2 overlapping with 1H of NH), 2.41 (3H, s, CH_3N), 2.74 (2H, t, *J* = 6.9Hz, CH_2N), 2.86 (2H, t, *J* = 6.9Hz, CH_2C=O), 7.13-8.32 (5H, m, Ar), 11.85 (1H, bs, indole NH). ^{13}C-NMR (DMSO) δ (ppm) 19.80, 22.54, 23.76, 38.71, 51.49, 112.25, 121.48, 121.79, 122.04, 123.12, 125.84, 134.26, 137.09, 195.52. FT-IR (KBr, cm^{-1}) ν_{max} 3374, 3168, 2939, 1619, 1522, 1437, 1137, 784, 635.UV (EtOH, nm) λ_{max}210, 241, 261, 297, 340.MS (EI, 70ev): *m/z* 199.73, 212.87, 230.93.

*1-(5-Bromo-1H-indol-3-yl)-5-(methylamino)pentan-1-one (**12**).* The above procedure repeated with 5-bromoindole.Recrystallization from n-hexane/acetone gave the desired product (5.98 g, 81%), mp132-134°C. ^{1}H-NMR (DMSO) δ (ppm)1.45 (2H, qn, *J* = 7.5Hz, CH_2)**,** 1.59 (2H, qn, *J* = 7.5Hz, CH_2), 2.21 (3H, s, CH_3N)**,** 2.43 (2H, m, CH_2-N overlapping with 1H of NH), 2.80 (2H, t, *J* = 7.5Hz, CH_2-C=O), 7.29-8.32 (4H, m, Ar), 11.66 (1H, s, indole NH). ^{13}C-NMR (DMSO) δ (ppm) 22.98, 28.74, 35.86, 40.94, 51.20, 114.70, 114.97, 116.16, 123.85, 125.82, 127.49, 135.50, 135.82, 196.66.FT-IR (KBr, cm^{-1}) ν_{max} 3154, 2935, 1628, 1521, 1431, 1108, 886.UV (EtOH, nm) λ_{max}218.47, 245.48, 296.71. MS (EI, 70ev): *m/z* 223.93, 279.87, 308.33, 310.67.

*1-(1H-indol-3-yl)-6-(methylamino)hexan-1-one (**13**).* To 1-methylazepan-2-one (5.13 mL, 5.09 g, 0.04 mol) cooled in an ice bath was added phosphorous oxychloride (4.08 g, 0.026 mol) while being stirred for 30 min. The temperature was maintained at –10-0 °C. The mixture was stirred for an additional 10 min, and then a solution of indole (2.80 g, 0.024 mol) in 1-methyl-2-pyrrolidinone (5.13 mL, 5.09 g, 0.04 mol) was slowly added during 2 h. The temperature rose to 45 °C and a solid separated. The mixture was heated at 80°C for 3 h, and then mixed with water (100 mL). The clear solution was made basic by the addition of NaOH (6 g) in water (30 mL) causing a solid to separate. The solid was filtered off and washed with water. Recrystallization from ethanol-water afford 1-(1*H*-indol-3-yl)-6-(methylamino)hexan-1-one (5.21 g, 89%),mp 150-152°C. ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.42-1.81(6H, m, 3CH_2overlapping with 1H of NH), 2.45(3H, s, CH_3N), 2.61(2H, t, J = 6.9Hz, CH_2-N), 2.83(2H, t, J = 7.2Hz, CH_2C=O), 7.39-8.39 (4H, m, Ar), 9.75(1H, bs, indole NH). ^{13}C-NMR ($CDCl_3$) δ (ppm) 25.03, 26.55, 27.68, 36.59, 39.51, 50.25, 111.45, 122.28, 122.38, 122.50, 123.53, 125.58, 131.32, 136.48, 196.37.FT-IR (KBr, cm^{-1}) ν_{max} 3286, 2929, 1630, 1506, 1152, 934, 743.UV (EtOH, nm) λ_{max}209, 241, 296.

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