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Mediterranean Journal of Chemistry **2011**, 1(3), 98-105

Study of the reaction of (*Z*)-5-bromo-3-(1-methylpyrrolidin-2-ylidene)-3*H*-indole with pentane-2,4-dione

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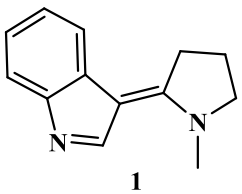
Abstract: The reaction of (Z)-5-bromo-3-(1-methylpyrrolidin-2-ylidene)-3*H*-indole with refluxing pentane-2,4-dione gave two compounds, the major product, 1-[(*E*)-4-(5-bromo-1*H*-indol-3-yl)-1-methyl-2,5,6,7-tetrahydro-1*H*-azepin-2-ylidene]propan-2-one being accompanied by 1-(7-(2-amino-5-bromophenyl)-1,4-dimethylindolin-5-yl)ethanone. Each product is believed to be derived from initial protonation of (Z)-5-bromo-3-(1-methylpyrrolidin-2-ylidene)-3*H*-indole by the diketone followed with nucleophilic diketone-C-3- addition at the C-2 of the 3*H*-indolium cation.

Keywords: (*Z*)-5-bromo-3-(1-methylpyrrolidin-2-ylidene)-3*H*-indole, pentane-2,4-dione; 1-[(*E*)-4-(5-bromo-1*H*-indol-3-yl)-1-methyl-2,5,6,7-tetrahydro-1*H*-azepin-2-ylidene]propan-2-one; 1-(7- (2-amino-5-bromophenyl)-1,4-dimethylindolin-5-yl) ethanone.

Introduction

The reaction of the complex formed from 1-methylpyrrolidin-2-one and $POCl_3$, with indole, gives rise to 3-(1-methylpyrrolidin-2-ylidene)-3*H*-indole **1**[1]. This compound contains an intriguing combination of enamine and imine (as part of a 3*H*-indole) groups in conjugation. Reaction with an electrophile at the imine nitrogen is particularly favored by delocalization of charge in the species, thus produced **1** [pK_a 10.6 by UV spectroscopic measurement in MeOH-H_2O (1:1)] [1, 2].



1

The UV absorption, NMR spectrum, and a crystallographic study of 3-(1-methylpyrrolidin-2-ylidene)-3*H*-indole **1** have been reported[3-7]. The chemistry of 3-

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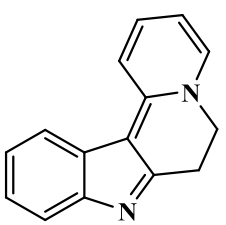
aminoalkylidene-3*H*-indoles such as **1** can be used for the construction of polycyclic indoles[7]. 6,7-Dihydroindolo[3,2-*a*]quinolizine **2** and 1,2,3,4,6,7-hexahydroindolo[3,2-*a*]quinolizine **3** can be obtained from cyclic allylamine-cyclic enamine isomerization by $(Ph_3P)_3RhCl$ catalysis.[7]



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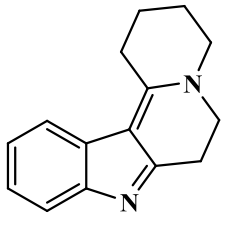
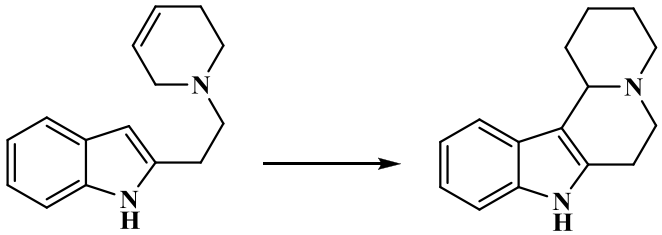


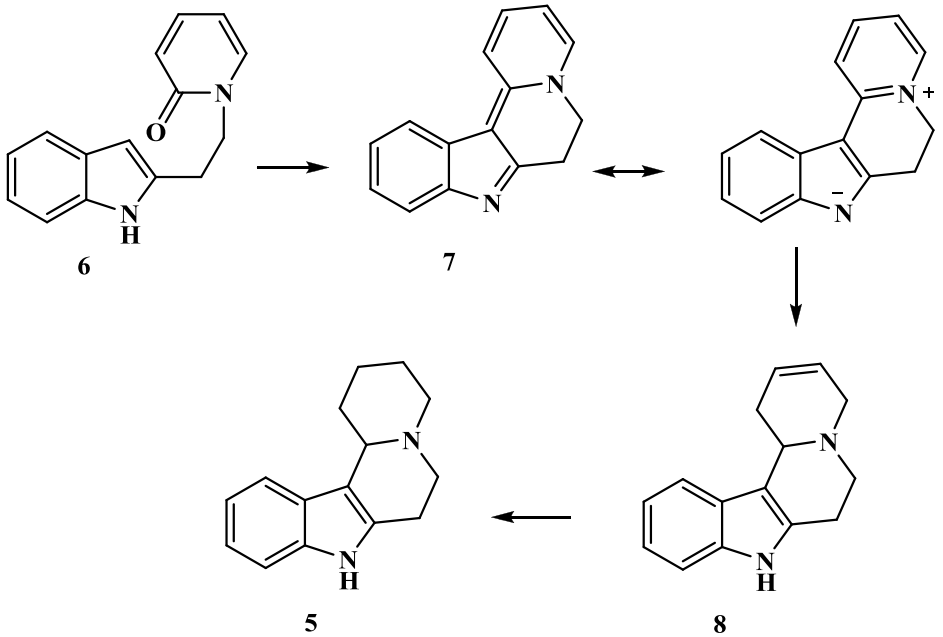
3

Treatment of allylamine **4** with $(Ph_3P)_3RhCl$ in aqueous acetonitrile at 100 °C produces tetracycle **5** in 48% yield[7].



4 **5**

Complimentarily, tetracycle **5** could be obtained via 3-aminoalkylidene-3*H*-indole chemistry. In the first step, cyclization of indole-N-substituent **6** using phosphorus oxychloride yielded the further conjugated 3-aminoalkylidene-3*H*-indole **7**. Sodium borohydride reduction of **7** produced **8**, which could be catalytically reduced to **5** (Scheme 1)[7].



6 **7**

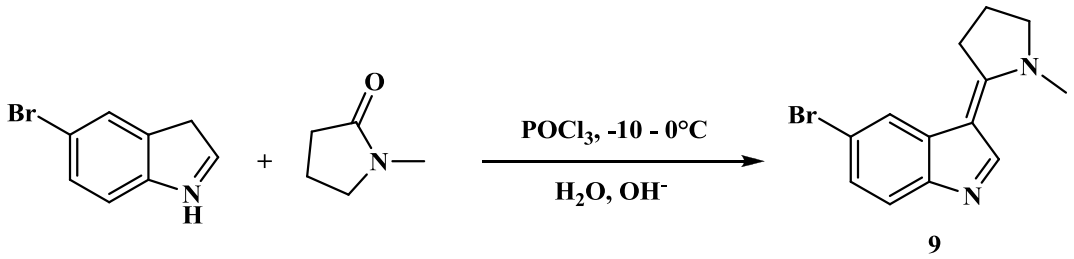
5 **8**

Scheme 1

We report here the synthesis and reaction of 5-bromo-3-(1-methylpyrrolidin-2-ylidene)-3*H*-indole **9** with pentane-2,4-dione which we believe is initiated by proton transfer from the weakly acidic 1,3-dicarbonyl component to the strongly basic nitrogen of **9**.

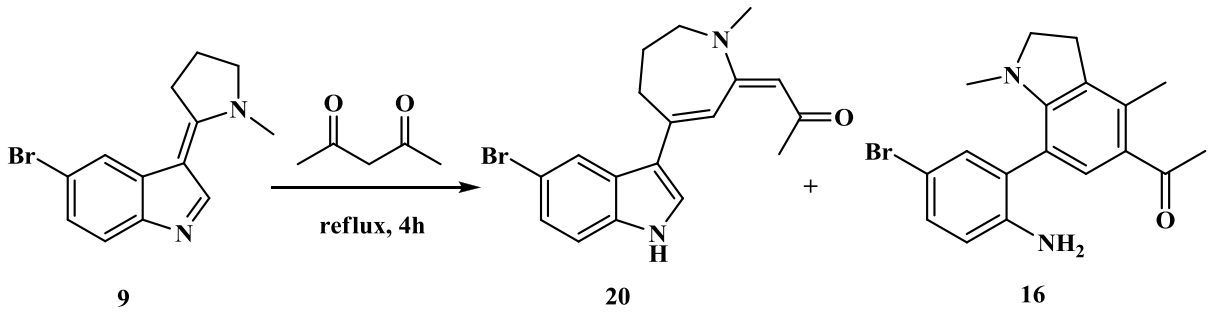
Results and Discussion

5-Bromo-3-(1-methylpyrrolidin-2-ylidene)-3*H*-indole **9** was 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 to 0 °C, white needle crystals of the indole derivative **9** were obtained after crystallization from *n*-hexane/acetone, in 95% yield (Scheme 2).



Scheme 2

When 5-bromo-3-(1-methylpyrrolidin-2-ylidene)-3*H*-indole **9** was treated with pentane-2,4-dione at reflux, two products were formed, and were identified as 1-[(*E*)-4-(5-bromo-1*H*-indol-3-yl)-1-methyl-2,5,6,7-tetrahydro-1*H*-azepin-2-ylidene]propan-2-one **20** in 78% yield and 1-(7-(2-amino-5-bromophenyl)-2,3-dihydro-1,4-dimethyl-1*H*-indol-5-yl)ethanone **16** in 4% yield (Scheme 3).



Scheme 3

The major yellow crystalline product **20** showed strong UV absorption at λ_{max} 350 nm. Its ^{1}H-NMR spectrum had a singlet at δ 11.12 ppm belonging to exchangeable N-H hydrogen. The exocyclic =CH proton was observed as a singlet at δ 5.19 ppm. The N-CH_3 and acetyl protons as two three-hydrogen singlets were observed at δ 3.14 and 2.18 ppm respectively. In the ^{13}C-NMR spectrum of compound **20**, 18 different signals were detected. The carbonyl stretching frequency at ν = 1611 cm^{-1} in its FT-IR spectrum indicated that the carbonyl group was conjugated.

We examined the crystal structure of the major product **20**, $C_{18}H_{19}BrN_2O$[8]. The seven-membered azepine ring adopts a twist-boat conformation. Bond distances and angles in **20** are in the normal range and are given in Tables 1 and 2; Table 3 contains selected torsion angles.

The planar 5-bromoindole bicycle is not coplanar with the enone in the seven-membered azepine ring. The dihedral angle between the enone double bond and the mean plane of the indole ring is 27.8°. The sum of the angles at the azepine nitrogen is 359.4°, indicating its conjugating interaction with the exocyclic enone and that therefore it is sp^2 hybridized. The exocyclic double bond has *E* geometry. An N—H···O hydrogen bond between the indole ring and the carbonyl group of the propan-2-one group links the molecules into chains along the b axis (Figures 1 and 2).

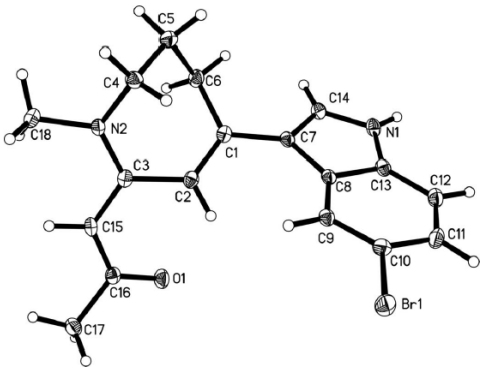


Figure 1. The structure of **20** with displacement ellipsoids for the non-hydrogen atoms drawn at the 50% probability level. The atom label numbers are those used in the Tables.

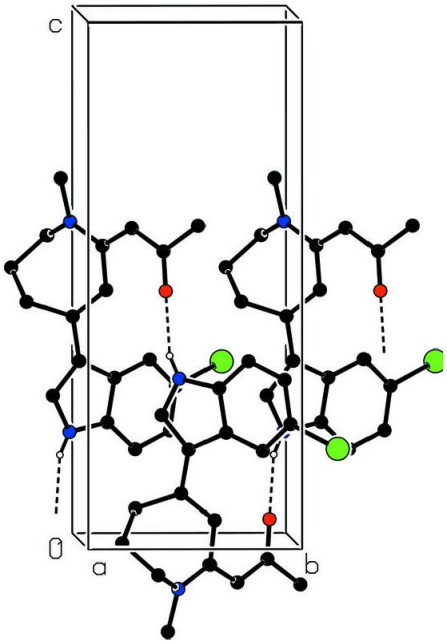


Figure 2. Packing arrangement of **20** viewed down axis *a*. Dashed lines indicate N—H···O hydrogen bonds between the indole ring and the carbonyl group extending from the propan-2-one group linking the molecules into chains along the *c* axis.

Table 1. Bond lengths in **20** (atom numbering is given in Figure 1)

Br1 C10 1.9073(17)	O1 C16 1.244(2)	N1 C14 1.358(2)
N1 C13 1.376(2)	N1 H1N 0.78(2)	N2 C3 1.362(2)
N2 C18 1.457(2)	N2 C4 1.469(2)	C1 C2 1.352(2)
C1 C7 1.465(2)	C1 C6 1.513(2)	C2 C3 1.466(2)
C2 H2 0.9500	C3 C15 1.393(2)	C4 C5 1.523(2)
C4 H4A 0.9900	C4 H4B 0.9900	C5 C6 1.540(3)
C5 H5A 0.9900	C5 H5B 0.9900	C6 H6A 0.9900
C6 H6B 0.9900	C7 C14 1.381(2)	C7 C8 1.444(2)
C8 C9 1.404(2)	C8 C13 1.416(2)	C9 C10 1.377(2)
C9 H9 0.9500	C10 C11 1.401(2)	C11 C12 1.381(3)
C11 H11 0.9500	C12 C13 1.395(2)	C12 H12 0.9500
C14 H14 0.9500	C15 C16 1.424(2)	C15 H15 0.9500
C16 C17 1.517(2)	C17 H17A 0.9800	C17 H17B 0.9800
C17 H17C 0.9800	C18 H18A 0.9800	C18 H18B 0.9800
C18 H18C 0.9800		

Table 2. Bond angles in **20** (atom numbering is given in Figure 1)

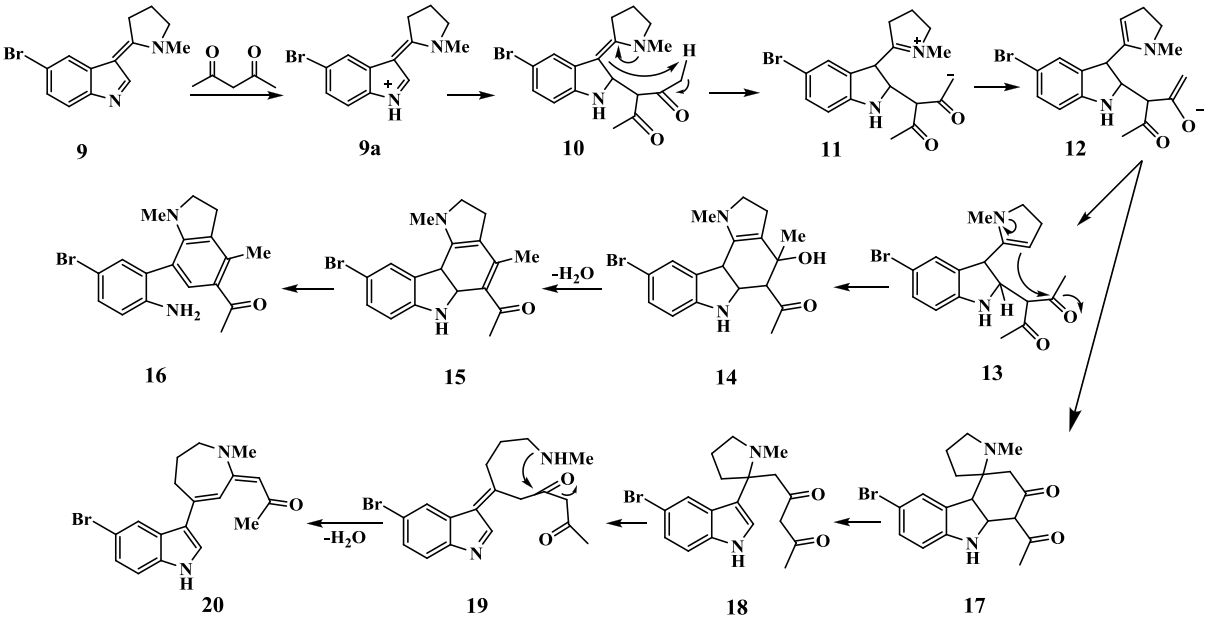
C14 N1 C13 109.16(15)	C14 N1 H1N 128.0(17)	C13 N1 H1N 122.8(17)
C3 N2 C18 121.71(14)	C3 N2 C4 120.60(14)	C18 N2 C4 117.12(14)
C2 C1 C7 121.26(15)	C2 C1 C6 120.54(15)	C7 C1 C6 118.15(15)
C1 C2 C3 124.97(16)	C1 C2 H2 117.5	C3 C2 H2 117.5
N2 C3 C15 120.71(15)	N2 C3 C2 117.31(15)	C15 C3 C2 121.94(15)
N2 C4 C5 112.73(15)	N2 C4 H4A 109.0	C5 C4 H4A 109.0
N2 C4 H4B 109.0	C5 C4 H4B 109.0	H4A C4 H4B 107.8
C4 C5 C6 110.69(14)	C4 C5 H5A 109.5	C6 C5 H5A 109.5
C4 C5 H5B 109.5	C6 C5 H5B 109.5	H5A C5 H5B 108.1
C1 C6 C5 112.85(15)	C1 C6 H6A 109.0	C5 C6 H6A 109.0
C1 C6 H6B 109.0	C5 C6 H6B 109.0	H6A C6 H6B 107.8
C14 C7 C8 105.58(15)	C14 C7 C1 125.92(16)	C8 C7 C1 128.47(15)
C9 C8 C13 118.31(15)	C9 C8 C7 134.56(16)	C13 C8 C7 106.97(15)
C10 C9 C8 117.91(15)	C10 C9 H9 121.0	C8 C9 H9 121.0
C9 C10 C11 123.34(16)	C9 C10 Br1 118.64(13)	C11 C10 Br1 117.95(13)
C12 C11 C10 119.71(16)	C12 C11 H11 120.1	C10 C11 H11 120.1
C11 C12 C13 117.54(17)	C11 C12 H12 121.2	C13 C12 H12 121.2
N1 C13 C12 129.44(16)	N1 C13 C8 107.56(15)	C12 C13 C8 123.00(16)
N1 C14 C7 110.71(16)	N1 C14 H14 124.6	C7 C14 H14 124.6
C3 C15 C16 125.26(16)	C3 C15 H15 117.4	C16 C15 H15 117.4
O1 C16 C15 125.42(16)	O1 C16 C17 117.02(15)	C15 C16 C17 117.55(15)
C16 C17 H17A 109.5	C16 C17 H17B 109.5	H17A C17 H17B 109.5
C16 C17 H17C 109.5	H17A C17 H17C 109.5	H17B C17 H17C 109.5
N2 C18 H18A 109.5	N2 C18 H18B 109.5	H18A C18 H18B 109.5
N2 C18 H18C 109.5	H18A C18 H18C 109.5	H18B C18 H18C 109.5

Table 3. Torsion angles in **20** (atom numbering is given in Figure 1)

C7 C1 C2 C3 179.45(15)	C6 C1 C2 C3 -3.2(3)	C18 N2 C3 C15 -9.5(2)
C4 N2 C3 C15 161.62(16)	C18 N2 C3 C2 173.07(15)	C4 N2 C3 C2 -15.8(2)
C1 C2 C3 N2 -38.6(2)	C1 C2 C3 C15 144.00(18)	C3 N2 C4 C5 83.4(2)
C18 N2 C4 C5 -105.10(17)	N2 C4 C5 C6 -44.4(2)	C2 C1 C6 C5 70.7(2)
C7 C1 C6 C5 -111.84(17)	C4 C5 C6 C1 -40.5(2)	C2 C1 C7 C14 150.24(18)
C6 C1 C7 C14 -27.2(2)	C2 C1 C7 C8 -27.8(3)	C6 C1 C7 C8 154.82(17)
C14 C7 C8 C9 173.91(19)	C1 C7 C8 C9 -7.8(3)	C14 C7 C8 C13 -1.33(18)
C1 C7 C8 C13 176.99(16)	C13 C8 C9 C10 -1.1(2)	C7 C8 C9 C10 -175.93(18)
C8 C9 C10 C11 -2.6(3)	C8 C9 C10 Br1 174.36(12)	C9 C10 C11 C12 3.2(3)
Br1 C10 C11 C12 -173.73(14)	C10 C11 C12 C13 0.0(3)	C14 N1 C13 C12 -179.52(18)
C14 N1 C13 C8 0.26(19)	C11 C12 C13 N1 176.04(18)	C11 C12 C13 C8 -3.7(3)
C9 C8 C13 N1 -175.47(15)	C7 C8 C13 N1 0.68(19)	C9 C8 C13 C12 4.3(3)
C7 C8 C13 C12 -179.53(16)	C13 N1 C14 C7 -1.2(2)	C8 C7 C14 N1 1.53(19)
C1 C7 C14 N1 -176.84(15)	N2 C3 C15 C16 172.13(16)	C2 C3 C15 C16 -10.5(3)
C3 C15 C16 O1 -10.6(3)	C3 C15 C16 C17 168.01(16)	

The mechanism which we believe represents the reaction of 5-bromo-3-(1-methylpyrrolidin-2-ylidene)-3*H*-indole (**9**) with pentane 2,4-dione is shown in Scheme 4. The best rationalization for the formation of the two products involves a common intermediate (**10**) resulting from diketone-C-3-enolate addition to the salt **9a** at the indole 2-position. Tautomerism of the enamine from the exocyclic to the endocyclic position [→ **12**] *via* a protonation–deprotonation sequence mediated either intramolecularly or by intramolecular protonation by an apposite methyl group proton, producing **11** transiently, would be followed by intramolecular enamine alkylation in **13**. This would generate intermediate tetracycle **(14)** which could produce **16** *via* the loss of water and 1, 2-elimination.

The major product **20** would be formed from the spirocycle **17** by 1, 2-elimination of diketone enolate, to give **18**, followed by a gramine type elimination of the basic nitrogen to give **19**. Subsequently, **20** would be simply formed by intramolecular interaction between secondary amine and ketone carbonyl and then loss of a molecule of water, enamine formation, and tautomerism to the aromatic indole (Scheme 4).



Scheme 4

Experimental Section

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. The routine purification of reagents and solutions was carried out by standard laboratory procedures (Armarego and Perrin, 1997). Analytical thin-layer chromatography (TLC) was carried out with Merck silica gel 60 $F_{254\lambda}$ aluminum sheets. Microanalyses were performed on a Leco Analyzer 932.

1.1. 5-Bromo-3-(1-methyl-2-pyrrolidinylidene)-3*H*-indole 9. To 1-methyl-2-pyrrolidinone (4 mL, 0.04 mol) cooled in an ice bath was added of phosphorous oxychloride (4.08 g, 0.026 mol) with stirring during 30 min. The temperature was maintained at –10 to 0 °C. The mixture was stirred an additional 10 min. and then a solution of 5-bromoindole (4.68 g, 0.024 mol) in of 1-methyl-2-pyrrolidinone (4 mL, 0.04 mol) was added slowly during 1 h. The temperature rose to 45 °C and a solid separated. The mixture was heated at 80 °C for 3 h 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 *n*-hexane-acetone afforded the desired product **(9)** (6.29 g, 95%), m.p. 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. ν_{max} 3408, 2962, 1597, 1496, 1200, 806. cm^{-1}. λ_{max} (EtOH) 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.

1.2. Reaction of 5-bromo-3-(1-methyl-2-pyrrolidinylidene)-3*H*-indole 9 with pentane-2,4-dione.

5-Bromo-3-(1-methylpyrrolidin-2-ylidene)-3*H*-indole **(9)** (0.5 g, 1.8 mmol) was heated in refluxing pentane-2,4-dione (11 ml) for 4 h. The excess 1,3-diketone was removed by distillation under reduced pressure to give a yellow solid which was recrystallized in *n*-hexane/ethanol to give yellow crystals of 1-[(*E*)-4-(5-bromo-1*H*-indol-3-yl)-1-methyl-2,5,6,7-tetrahydro-1*H*-azepin-2-ylidene]propan-2-one (**20**) (0.48 g, 78%), mp 186-188 °C.

1-(7-(2-amino-5-bromophenyl)-1,4-dimethylindolin-5-yl)ethanone (**16**) was obtained as an oil by preparative plate chromatography of the filtrate of (**20**), using toluene/ethyl acetate (5:2), in 4% yield.

1.2.1. 1-[(*E*)-4-(5-bromo-1*H*-indol-3-yl)-1-methyl-2,5,6,7-tetrahydro-1*H*-azepin-2-ylidene]propan-2-one 20. ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.0 (2H, qn, *J* = 6.6 Hz, azepin-6-yl-H_2), 2.18 (3H, s, MeCO overlying 2H, m, azepin-5-yl-H_2), 3.14 (3H, s, MeN), 3.41 (2H, t, *J* = 6.3 Hz, azepin-7-yl-H_2), 5.19 (1H, s, exocyclic =CH), 6.35 (1H, s, azepin-3-yl-H), 7.0 (1H, d, *J* = 8.7 Hz, ArH), 7.13 (1H, d, *J* = 8.7 Hz, ArH), 7.23 (1H, s, indol-4-yl-H), 7.93 (1H, s, indol-2-yl-H), 11.12 (1H, bs, NH). ^{13}C-NMR ($CDCl_3$) δ 28.8, 31.1, 31.4, 39.7, 52.2, 94.6, 113.4, 113.6, 119.6, 122.4, 124.2, 126.4, 127.1, 134.5, 141.3, 163.9, 193.4. ν_{max} 2915, 1611, 1506, 1340, 1189, 972, 787cm^{-1}. λ_{max} (EtOH) 236, 261, 350 nm.

1.2.2. 1-(7-(2-amino-5-bromophenyl)-1,4-dimethylindolin-5-yl)ethanone 16. ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.22-2.28 (4H, m, CH_2CH_2), 2.47 and 2.65 (6H and 3H, CH_3CO, CH_3N, CH_3Ar), 6.55-6.66 (4H, m, Ar), 12.69 (2H, bs, NH_2). ^{13}C-NMR ($CDCl_3$) δ 21.53, 23.12, 24.63, 29.68, 33.23, 102.31, 106.58, 110.95, 116.17, 116.71, 119.09, 124.46, 128.80, 139.40, 146.09, 163.54, 175.28, 205.40. ν_{max} 3382, 2925, 1624, 1265, 837 cm^{-1}. λ_{max} (EtOH) 228, 258, 302, 343 nm. MS: *m/z*: 223.53, 266.93, 358.87 (M^+), 360.73 (M^++2). Found C, 60.38; H, 5.21; N, 7.93. $C_{18}H_{19}BrN_2O$ requires C, 60.18; H, 5.33; N, 7.80.

Acknowledgements
The authors are grateful to the University of Urmia for financially supporting this work.

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