Synthesis of Some New Derivatives of 4-Hydrazino-5*H*-pyridazino[4,5-*b*]indole

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This paper describes the synthesis of 1-chloro-4-hydrazino-5*H*-pyridazino[4,5-*b*]indole (**4**) and some of the triazoles (**6-8**), tetrazoles (**10-11**), triazolotetrazoles (**9**) and *bis*-tetrazoles (**12**) derived from it. All of these were previously unknown compounds.

Treating 1,4-dioxo-1,2,3,4-tetrahydro-5*H*-pyridazino[4,5-*b*]indole (**1**) with phosphorus oxychloride gave 1,4-dichloro-5*H*-pyridazino[4,5-*b*]indole (**2**), which reacts regioselectively with hydrazine to give compound **4**. The reactions of **4** with formic and acetic acids gave 6-chloro-11*H*-1,2,4-triazolo[4,3-*b*]pyridazino[4,5-*b*]indoles (**6a-6b**), respectively. Reaction of compound **6a** with hydrazine gave 6-hydrazino-11*H*-1,2,4-triazolo[4,3-*b*]-pyridazino[4,5,-*b*]indole (**8**). This with nitrous acid gave 6-azido-11*H*-1,2,4-triazolo[4,3-*b*]pyridazino[4,5-*b*]-indole (**9**). Compound **4** reacted with nitrous acid to give 6-chloro-11*H*-tetrazolo[4,5-*b*]pyridazino[4,5-*b*]-indole (**10**), which gave 1,4-diazydo-5*H*-pyridazino[4,5-*b*]indole (**12**), through successive reactions with hydrazine and nitrous acid. All compounds were characterized by elemental analysis, ir and ^{1}H-nmr spectra.

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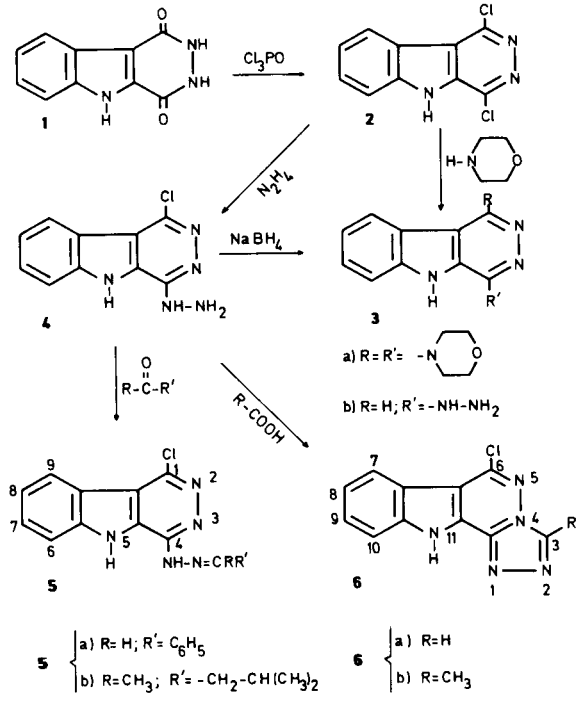
In a previous paper (1) we described the synthesis of 4-hydrazino-5*H*-pyridazino[4,5-*b*]indole, a structural analog of the well known antihypertensive agent Hydralazine (1-hydrazinophthalazine). This compound has shown some interesting antihypertensive properties as much in normotensive and hypertensive dogs (1), as in hypertensive rats (2). On the other hand, considerable attention has been drawn more recently to the synthesis of several condensed heterocyclic systems, especially those derived from triazole (3-7), tetrazole (3-9) and triazine (8,10-14). It is well known that the metabolism of Hydralazine is related to the formation of triazole derivatives (15,16). In this regard, we recently described the synthesis (3) of some triazole, tetrazole and triazine derivatives of the 4-hydrazino-5*H*-pyridazino[4,5-*b*]indole (3). This paper describes the synthesis of 1-chloro-4-hydrazino-5*H*-pyridazino[4,5-*b*]indole **4** and some of the triazoles (**6-8**), tetrazoles (**10,11**), triazolotetrazoles (**9**) and *bis*-tetrazoles (**12**) derived from it. All were previously unknown compounds.

The starting material, the 1,4-dioxo-1,2,3,4-tetrahydro-5*H*-pyridazino[4,5-*b*]indole **1**, was prepared through a slight modification of a previously reported (17) method. Treating this compound with phosphorus oxychloride in the usual way (1) gave a 90% yield of 1,4-dichloro-5*H*-pyridazino[4,5-*b*]indole **2**, which reacted with hydrazine regioselectively to give 1-chloro-4-hydrazino-5*H*-pyridazino[4,5-*b*]indole **4**. At present, all of our attempts to obtain the 1,4-dihydrazino derivative by treating compound **2** with hydrazine have been fruitless. This behaviour of compound **2** is in contrast to its reaction with morpholine to give (85%) the 1,4-dimorpholino-5*H*-pyridazino[4,5-*b*]-indole **3a**.

scheme 1



The structure of compound **4** was questionable on the basis of its analytical and spectral (^{1}H-nmr, ir) data, but when reduced with sodium borohydride in the presence of

sodium hydroxide, the chlorine atom was easily removed and compound **3b** was obtained. This compound had been prepared and unequivocally identified by us (1) by a different method. This compound was also characterized by two of its hydrazones **5a** and **5b**. Compound **4**, boiled with formic or acetic acids (3), gave the corresponding 1,2,4-triazolo[4,3-*b*]pyridazinoindole derivatives **6a** and **6b**, respectively (Scheme 1).

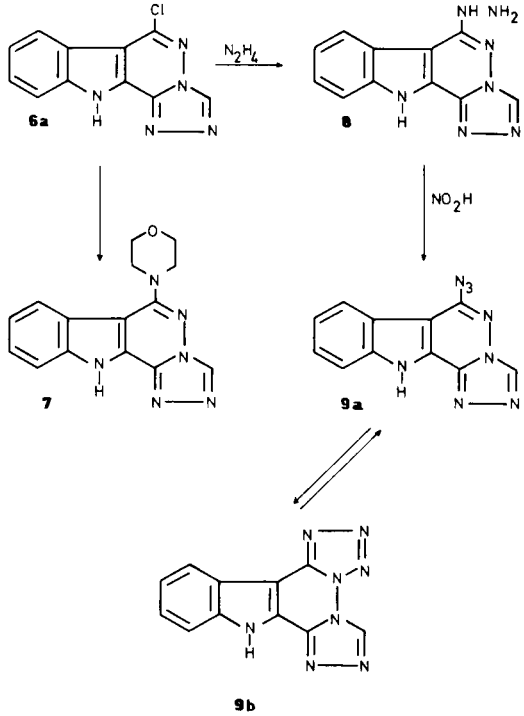
In contrast to the behaviour of compound **2**, when treating compound **6a** with hydrazine as well as morpholine, the 1-hydrazino derivative **8** and the 1-morpholino derivative **7** were obtained. Thus, the tetrazole system considerably increases the reactivity of the chlorine atom to displacement by nucleophilic reagent. This behaviour must be a consequence of the smaller electron donating effect of the tetrazole system, because of its stabilization by resonance, as compared with the chlorine atom or the hydrazino group. However, it is not as easy to explain the reactivity of compound **2** with morpholine. When compound **8** was treated with nitrous acid, the azide-triazole derivative **9** was obtained. The ir spectra of this compound shows bands at about 2120 (s) and at about 1280 (m) cm^{-1} assigned to the azido group. It seems to us that the structure **9a** would best describe the configuration of this compound in the solid state.

When compound **4** was treated with nitrous acid, compound **10** was obtained. This compound shows much slighter ir bands for the azido group than compound **9** and it seems that in the case of compound **10**, both forms, **10a** and **10b**, coexist in the solid state.

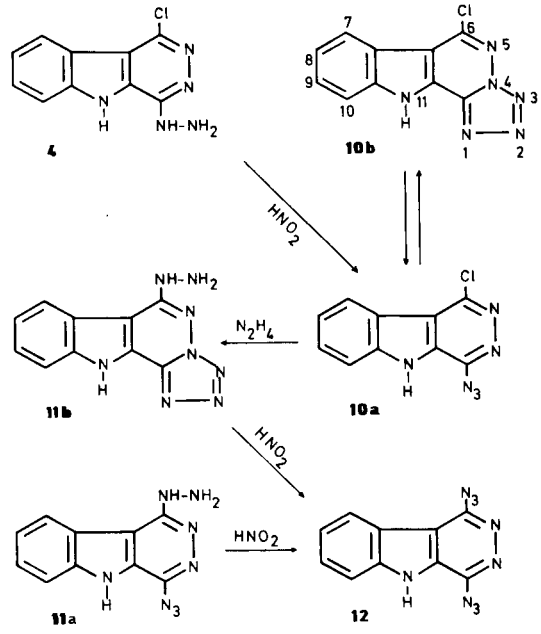
When compound **10b** was treated with hydrazine, compound **11** was obtained. This compound does not show any of the characteristic ir bands for the azido group, and so it seems that its structure in the solid state would be better represented by the formula **11b**.

Finally, compound **12**, obtained by known procedures (3) from compound **11**, shows ir bands at about 2115 (s), 1240 (m) and 1215 (m) cm^{-1} and its structure thus appears to be in the form of the azido-tetrazolo tautomers as in compounds **9**, **10** and **11**.

scheme 2



scheme 3



EXPERIMENTAL

Melting points were determined in a Kofler apparatus and they are uncorrected. Elemental analyses were obtained from vacuum-dried samples (over phosphorus pentoxide at 1-3 mm Hg, 2-3 hours, at about 60-70°). Ir spectra were recorded on a Perkin-Elmer 237 apparatus in potassium bromide tablets, and the frequencies are expressed in cm^{-1}. ^{1}H-nmr spectra were obtained on a Perkin-Elmer R-24A (60 MHz) or R-32 (90 MHz) instrument in the indicated solvents. Chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units (s, d, t,... for singlet, doublet, triplet...; dd, double doublet; bs, broad signal).

1,4-Dioxo-1,2,3,4-tetrahydro-5*H*-pyridazino[4,5-*b*]indole (**1**).

To a solution of 10.0 g (43 mmoles) of dimethyl-2,3-indoledicarboxylate in a minimal amount of boiling ethanol, 98% hydrazine hydrate (10 ml) was added dropwise. Then, the reaction mixture was boiled for 10 hours. On cooling, a yellow, wool-like solid precipitated. After filtration, the solid was dissolved in warm (about 60°) 10% ammonium hydroxide and the product was reprecipitated by neutralization of the solution with 1*N* hydrochloric acid. After filtration, the solid was successively washed with 1*N* hydrochloric acid (5 × 20 ml), water (5 × 20 ml) and warm

ethanol (5 × 20 ml) and then dried, giving 6.5 g (75%) of white needles, mp 330°, (reported (17), mp 360°); ir: 2600-3300 (bs, NH), 1660 (s, C=O), 1630 (s, C=N), 1430 (s, C-N), 740 (s, aromatic 1,2-disubstituted); ^{1}H-nmr (DMSO-d_6): 7.30-7.90 (m, 3H, H-6, H-7, H-8), 8.15-8.30 (m, 1H, H-9), 10.45 (bs, 2H, CONH), 12.65 (s, 1H, NH indole).

1,4-Dichloro-5*H*-pyridazino[4,5-*b*]indole (**2**).

Compound **1** (2.0 g, 10 mmoles) was suspended in phosphorus oxychloride (40 ml) and the mixture was warmed to 90° for 4 hours. On cooling the compound precipitated. After filtration, the solid was washed successively with water (5 × 20 ml), ethanol (5 × 50 ml) and ether (5 × 50 ml) and dried giving 2.14 g (90%) of white solid, mp 250° (d); ir: 3060-3180 (bs, NH), 1620 (m), 1588 (m, C=N), 745 (s, aromatic 1,2-disubstituted), 660 (m, C-Cl); ^{1}H-nmr (DMSO-d_6): 7.40-7.85 (m, 3H, H-6, H-7, H-8), 8.30-8.45 (m, 1H-9), 13.60 (bs, 1H, NH indole).

Anal. Calcd. for $C_{10}H_5Cl_2N_3$: C, 50.42; H, 2.10, N, 17.64. Found: C, 50.74; H, 2.07; N, 17.41.

1,4-*bis*(*N*-Morpholino)-5*H*-pyridazino[4,5-*b*]indole (**3a**).

Compound **2** (1.50 g, 6 mmoles) was boiled with morpholine (40 ml) for 4 hours. On cooling, the product precipitated. After filtration, the white solid was washed successively with water (5 × 25 ml) and ethanol (5 × 25 ml) and recrystallized in DMI giving 1.72 g (85%) of white needles, mp 320°; ir: 3220 (bs, NH), 1625 (m, C=N), 760 (s, aromatic 1,2-disubstituted); ^{1}H-nmr (DMSO-d_6): 3.30-3.60 (m, l8H, CH_2-N morpholine), 3.80-4.10 (m, 8H, CH_2-O morpholine), 7.30-7.82 (m, 3H, H-6, H-7, H-8), 7.90 -8.10 (m, 1H-9), 13.10 (s, 1H, NH indole).

Anal. Calcd. for $C_{18}H_{21}N_5O_2$: C, 63.71; H, 6.19; N, 20.64. Found: C, 63.71; H, 6.39; N, 20.35.

1-Chloro-4-hydrazino-5*H*-pyridazino[4,5-*b*]indole (**4**).

A mixture of compound **2** (2.40 g, 10 mmoles) and 98% hydrazine hydrate (40 ml) was boiled for 6 hours. On cooling, the product precipitated, and after filtration, it was washed successively with water (5 × 20 ml), ethanol (5 × 20 ml) and ether (5 × 20 ml) and dried. This compound was not further purified (1.98 g, 85%), mp 235° dec; Ir: 3100-3350 (bs, NH), 1630-1620 (m, C=N), 740 (m, aromatic 1,2-disubstituted); ^{1}H-nmr (DMSO-d_6, at about 125°): 4.00-6.00 (bs, 3H, NH-NH_2), 7.30-7.90 (m, 3H, H-6, H-7, H-8), 8.15-8.60 (m, 1H-9), 12.90 (s, 1H, NH indole).

Anal. Cacld for $C_{10}H_8ClN_5$: C, 51.39; H, 3.43; N, 28.35. Found: C, 50.94; H, 3.61; N, 28.10.

4-Hydrazino-5*H*-pyridazino[4,5-*b*]indole (**3b**).

To a stirred suspension of compound **4** (0.5 g, 2.5 mmoles) in a mixture of dioxane (15 ml), 10% sodium hydroxide (5 ml) and sodium borohydride (0.70 g) was added in small amounts. Stirring was then maintained at room temperature for 10 hours, after which the solid material was filtered off and recrystallized from dried ethanol/hydrogen chloride. We obtained 0.4 g (51%) of the trihydrochloride of the compound **3b**, mp 252-254° dec. The mp, ir and ^{1}H-nmr spectra were the same as those reported (3) previously for this compound.

4-(N^2-Benzylidenehydrazino)-5*H*-pyridazino[4,5-*b*]indole (**5a**).

A mixture of compound **4** (2.40 g, 10 mmoles), benzaldehyde (8.0 ml) and dioxane (50 ml) was boiled for one hour. On cooling, a brown solid precipitate formed which was filtered and washed with warm ethanol (5 × 30 ml), giving 2.73 g (85%), of brown needles, mp 280°; ir: 3400 (s, -NH), 1610 (s)-1590 (s, C=N), 760 (s)-690 (s, aromatic monosubstituted), 740 (s, aromatic 1,2-disubstituted); ^{1}H-nmr (DMSO-d_6): 7.45 (s, 1H, CH=N), 7.30-7.60 (m, 4H), 7.80-8.35 (m, 3H), 8.35-8.55 (m, 2H for C_6H_5 and H-6, H-7, H-8, H-9), 12.45 (s, 1H, NH indole).

Anal. Calcd. for $C_{17}H_{12}ClN_4$: C, 63.45; H, 3.73; N, 21.77. Found: C, 63.14; H, 3.87; N, 21.98.

4-(N^2-1,3-Dimethylbutylidenehydrazino)-5*H*-pyridazino[4,5-*b*]indole (**5b**).

A mixture of compound **4** (2.0 g, 8.5 mmoles) and methylsilobutylketone (50 ml) was boiled for 2 hours. The solvent was removed in vacuo and the residual solid recrystallized from ethanol-water, giving 1.83 g (70%) of fine brown crystals, mp 150-175° dec; ir: 2700-3400 (bs, NH), 1680 (s, C=N), 1590 (s, C=N), 750 (s, aromatic 1,2-disubustituted); ^{1}H-nmr (DMSO-d_6): 1.00 (d, 6H, $2CH_3$), 1.50-1.70 (m, 1H, CH), 2.10-2.30 (m, 5H, CH_3-C=, CH_2), 7.30-8.10 (m, 3H, H-6, H-7, H-8), 8.20-8.40 (m, 1H, H-9).

Anal. Calcd. for $C_{16}H_{18}ClN_5$: C, 60.85; H, 5.70; N, 22.18. Found: C, 60.48; H, 6.03; N, 21.80.

6-Chloro-11*H*-1,2,4-triazolo[4,3-*b*]pyridazino[4,5-*b*]indole (**6a**).

A mixture of compound **4** (2.50 g, 10 mmoles) and formic acid (50 ml) was boiled for 4 hours. The solvent was removed *in vacuo* and the residual solid suspended in ethanol (40 ml), filtered off, washed with water (5 × 10 ml) and finally recrystallized from DMF giving 2.19 g (90%) of fine white needles, mp 300°; ir: 2600-3100 (bs, NH), 1650 (m), 1620 (m, C=N), 750 (s, aromatic 1,2-disubstituted), 650 (m, C-Cl); ^{1}H-nmr (DMSO-d_6, at about 150°): 7.40-7.60 (m, 3H, H-8, H-9, H-10), 8.20-8.60 (m, 1H, H-7), 9.60 (s, 1H, H-3).

Anal. Calcd. for $C_{11}H_6ClN_5$: C, 53.97; H, 2.51; N, 28.27. Found: C, 54.14; H, 2.21; N, 28.32.

3-Methyl-6-chloro-11*H*-1,2,4-triazolo[4,3-*b*]pyridazino[4,5-*b*]indole (**6b**).

A mixture of compound **4** (2.50 g, 10 mmoles) and glacial acetic acid (40 ml) was boiled for 3 hours. The reaction mixture was poured onto crushed ice (200 g) and the precipitate collected by filtration, washed with water (5 × 25 ml) dried and recrystallized from DMF giving 2.31 g (90%) of fine white needles, mp 300°; ir: 2500-3100 (bs, NH), 1640 (m, C=N), 750 (s, aromatic 1,2-disubstituted), 625 (m, C-Cl). ^{1}H-nmr (trifluoroacetic acid): 3.15 (s, 3H, Ch_3), 7.40-7.90 (m, 3H, H-8, H-9, H-10), 8.20-8.45 (m, 1H, H-7).

Anal. Calcd. for $C_{12}H_8ClN_5$: C, 55.92; H, 3.10; N, 27.18. Found: C, 55.74; H, 2.96; N, 26.98.

6-(*N*-Morpholino)-11*H*-1,2,4-triazolo[4,3-*b*]pyridazino[4,5-*b*]indole (**7**).

A mixture of compound **6a** (2.40 g, 10 mmoles) and morpholine (50 ml) was boiled for 3 hours. The solvent was removed *in vacuo* and the residual solid disaggregated with ethanol (25 ml), collected by filtration, washed with warm dimethylformamide (5 × 15 ml) and ethanol (5 × 20 ml) and dried giving 2.5 g (85%) of white needles, mp 300°. This compound is insoluable in the usual solvents; ir: 2600-3100 (bs, NH), 1645 (m, C=N), 760 (m, aromatic 1,2-disubstituted); ^{1}H-nmr (DMSO-d_6, at about 150°): 3.30-3.60 (m, 4H, CH_2-N), 3.90-4.10 (m, 4H, CH_2-O), 7.40-7.90 (m, 3H, H-8, H-9, H-10), 7.90-8.15 (m, 1H, H-7), 9.30 (s, 1H, H-3).

Anal. Calcd. for $C_{15}H_{14}N_6O$: C, 61.22; H, 4.76; N, 28.57. Found: C, 61.49; H, 4.70; N, 28.40.

6-Hydrazino-11*H*-1,2,4-triazolo[4,3-*b*]pyridazino[4,5-*b*]indole (**8**).

A mixture of compound **6a** (1.0 g, 4 mmoles) and 98% hydrazine hydrate (25 ml) was boiled for 8 hours. On cooling, a white solid precipitated, which was collected by filtration and then washed with water (5 × 20 ml) and ethanol (5 × 20 ml) giving 0.86 g (90%), of brown solid mp 288°; ir: 2500-3330 (bs, NH), 1640 (m), 1620 (m, C=N), 750 (s, aromatic 1,2-disubstituted); ^{1}H-nmr (DMSO-d_6), at about 150°): 7.30-8.00 (m, 3H, H-8, H-9, H-10), 8.20-8.60 (m, 1H, H-7), 9.20 (s, 1H, H-3).

Anal. Calcd. for $C_{11}H_9N_7$: C, 55.23; H, 3.76; N, 41.00. Found: C, 55.14; H, 3.74; N, 41.39.

6-Azido-11*H*-1,2,4-triazolo[4,3-*b*]pyridazino[4,5-*b*]indole (**9**).

To a stirred solution of compound **8** (0.5 g, 2 mmoles) in 1*N* hydrochloric acid (40 ml), sodium nitrite (1.40 g, 2 mmoles) was added in small portions. Stirring was then maintained for 24 hours at room temperature, after which, a brown, solid precipitate was collected by filtration and washed successively with water (5 × 20 ml) and ethanol (5 × 20 ml), giving 0.4 g (80%) of brown needles, mp 300°; ir: 2500-3800 (bs, NH), 2120 (s, N_3), 1670 (s, C=N), 1285 (m), 1275 (m, N_3), 750 (s, aromatic 1,2-disubstituted); ^{1}H-nmr (DMSO-d_6, at about 150°): 7.50-8.00 (m, 3H, H-8, H-9, H-10), 8.20-8.80 (m, 1H, H-7), 9.50 (s, 1H, H-3).

Anal. Calcd. for $C_{11}H_6N_8$: C, 52.80; H, 2.40; N, 44.80. Found: C, 52.59;

H, 2.26; N, 44.40.

6-Chloro-11*H*-tetrazolo[4,5-*b*]pyridazino[4,5-*b*]indole (**10**).

To a well ground mixture of compound **4** (1.20 g, 5 mmoles) and sodium nitrite (2.0 g, 2.90 mmoles), 1*N* hydrochloric acid (100 ml) was added with constant stirring. This mixture was then continuously stirred for 2 hours at room temperature, after which, a solid material was collected by filtration and washed with water (10 × 25 ml). Following recrystallization in dimethylformamide-ethanol, 0.97 g (80%) of a brown colored solid was isolated, mp 250° dec; ir: 2600-3200 (bs, NH), 2120 (m)-1220 (w)-1252 (w) (N_3), 750 (s, aromatic 1,2-disubstituted); ^{1}H-nmr (DMSO-d_6 at about 35°): 7.30-8.10 (m, 3H, H-8, H-9, H-10), 8.15-8.50 (m, 1H, H-7).

Anal. Calcd. for $C_{10}H_5ClN_6$: C, 49.07: H, 2.04; N, 34.35. Found: C, 49.10; H, 1.81; N, 34.36.

6-Hydrazino-11*H*-tetrazolo[4,5-*b*]pyridazino[4,5-*b*]indole (**11**).

A mixture of compound **10** (1.20 g, 5 mmoles) and 98% hydrazine hydrate (50 ml) was boiled for 6 hours. The product, which crystallized on cooling, was collected by filtration and washed with water (10 × 30 ml) and ethanol (5 × 25 ml) and recrystallized in dimethyl formamide giving 0.84 g (70%) of brown solid, mp 282-285° dec; ir: 2600-3600 (bs, NH), 1630 (s, C=N), 740 (s, aromatic 1,2-disubstituted); ^{1}H-nmr (DMSO-d_6): 7.20-8.10 (m, 3H, H-8, H-9, H-10), 8.20-8.60 (m, 1H, H-7).

Anal. Calcd. for $C_{10}H_8N_8$: C, 50.00; H, 3.33; N, 46.66. Found: C, 49.83; H, 3.41; N, 46.90.

1,4-Diazido-5*H*-pyridazino[4,5-*b*]indole (**12**).

Compound **12** was synthetized from **11** in a manner similar to the preparation of **10**, and was obtained as a clear brown colored solid in 70% yield, mp 300°; ir: 2600-3200 (bs, NH), 2115 (s, N_3), 1650 (m)-1620 (m) (C=N), 1240 (m), 1215 (m, N_3), 740 (s, aromatic 1,2-disubstituted); ^{1}H-nmr (DMSO-d_6): 7.35-7.90 (m, 3H, H-8, H-9, H-10), 7.90-8.40 (m, 1H, H-7), 13.90 (s, 1H, NH indole).

Anal. Calcd. for $C_{10}H_5N_9$: C, 47.80; H, 1.99; N, 50.19. Found: C, 47.50; H, 2.05; N, 49.60.

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