

Synthesis, Antiinflammatory and Antibacterial Activities of Substituted 10*H*-Indolo[3,2-*b*]quinoxalines

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A new series of fused quinoxalines as indoloquinoxalines were synthesized by condensing the appropriate isatin and *o*-phenylenediamine. *N*-Mannich bases of 10*H*-indoloquinoxalines (1–9) were synthesized by reacting formaldehyde and various secondary amines with indolo[3,2-*b*]quinoxaline. These compounds produced good antibacterial and anti-inflammatory activities.

Key Words: Synthesis, Indolo[3,2-*b*]quinoxaline, Mannich bases.

INTRODUCTION

Interactions of indoloquinoxalines with various B-forms of DNAs were also reported^{1–4} for the antitumour activity. Substituted indoloquinoxalines were reported to possess antiherpes virus⁵ and antimalarial⁶ activities. Recently, the synthesis of indoloquinoxalines⁷ has been reported. In the present communication, the synthesis of the Mannich bases of the indoloquinoxalines and their pharmacological properties like antiinflammatory and antibacterial activities has been reported.

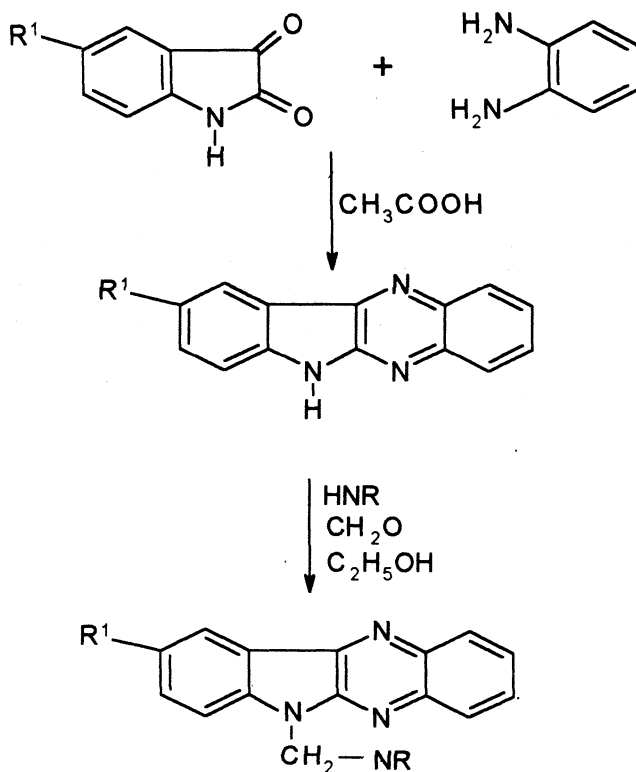
EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded (in KBr) on Bomem FT-IR spectrometer M.B. serial. ¹H NMR spectra were recorded on 300 MHz Bruker DPX 300. The chemical shifts are reported as parts per million downfield from tetramethylsilane. Microanalyses for C, H, N were performed on Heraeus CHN rapid analyzer. Analyses indicated by the symbols of the elements are within ±0.4% of the theoretical values. ¹H NMR and IR spectra were consistent with the assigned structures.

General method of synthesis of *N*-Mannich bases of 10*H*-indolo[3,2-*b*]quinoxaline (1–9)

N-Mannich bases of 10*H*-indolo[3,2-*b*]quinoxalines were prepared by reported method⁷. 7-Nitro/methoxy 10*H*-indolo[3,2-*b*]quinoxaline (0.005 M) in 10 mL of ethanol was added into a mixture of 0.005 M of *sec*-amine and formaldehyde (0.005 M) with continuous stirring for 1 h. Then the reaction mixture was refluxed for 20 min; on cooling, the product formed was filtered, dried in vacuum and recrystallized using ethylacetate. The purity was established by single spot on TLC plates. Their physical and spectral data are presented in Tables 1 and 2.

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TABLE-1
PHYSICAL PARAMETERS OF N-MANNICH BASES OF
10H-INDOLO[3,2-B]QUINOXALINES

Compd. No.	NR	R ¹	m.f.	m.p. (°C)	Yield (%)	Solvent for recrystallization
1	Diethylamine	NO ₂	C ₁₉ H ₁₉ N ₅ O ₂	285	55	DMSO-ethylacetate (1 : 1)
2	4-Ethyl-piperazine	NO ₂	C ₂₁ H ₂₁ N ₆ O ₂	268	42	DMF
3	Diphenylamine	OCH ₃	C ₂₈ H ₂₂ N ₄ O	261	44	DMSO-ethylacetate (1 : 1)
4	Diethanolamine	OCH ₃	C ₂₀ H ₂₂ N ₄ O ₃	225	66	DMSO-benzene
5	Piperidine	OCH ₃	C ₂₁ H ₂₂ N ₄ O	241	53	DMSO
6	Piperazine	OCH ₃	C ₂₀ H ₂₁ N ₅ O	250	65	DMSO
7	Diethylamine	OCH ₃	C ₂₀ H ₂₂ N ₄ O	248	74	DMSO-ethylacetate (1 : 1)
8	4-Ethyl-piperazine	OCH ₃	C ₂₂ H ₂₅ N ₅ O	212	48	Ethylacetate
9	Morpholine	OCH ₃	C ₂₀ H ₂₀ N ₄ O ₂	230	64	Benzene

Antiinflammatory activity

The activity was performed by following the procedure of Winter *et al.*⁸ on groups of six animals each. Edema was induced in the rats by injecting carrageenan (0.05 mL, 1% w/v in 0.9% saline) into the subplantar tissue of the

right hind paw. One group was kept as control and treated with propylene glycol. The animals of standard drug and drug treated groups were pretreated with standard drug and test compounds given orally 1 h before the carrageenan injection, respectively. The paw volume (mL) was measured before carrageenan injection and 0, 1, 2 and 3 h thereafter, using plethysmometer. The percentage antiinflammatory activity was calculated according to formula given below:

% Antiinflammatory activity = $(1 - V_t/V_c) \times 100$ (where V_t and V_c are the volumes of edema in drug treated and the control groups, respectively). The results are tabulated in Table-3.

TABLE-2
THE SPECTRAL AND ELEMENTAL ANALYSES OF N-MANNICH BASES OF
10*H*-INDOLO[3,2-*B*]QUINOXALINES

Compd. No.	IR (KBr) (cm ⁻¹)	¹ H-NMR (DMSO-d ₆) δ : ppm	Carbon (%)		Nitrogen (%)	
			Calcd.	Found	Calcd.	Found
1	1665 ν(C=N), 1081 ν(>N—)	7.44–7.59 (m, 7H, Ar—H), 4.52–4.66 (s, 2H, —CH ₂ —), 1.65–1.81 (s, 10H, (C ₂ H ₅) ₂)	65.32	65.02	20.05	20.36
2	1643 ν(C=N), 1069 ν(>N—)	7.27–7.38 (m, 7H, Ar—H), 4.14–4.28 (s, 2H, —CH ₂ —), 2.4–2.57 (m, 8H, 2', 3', 5', 6'—CH ₂), 2.13–2.21 (s, 5H, C ₂ H ₅)	64.78	64.47	21.59	21.84
3	1645 ν(C=N), 1078 ν(>N—)	7.22–7.37 (m, 7H, Ar—H), 6.12–6.25 (s, 10H, (C ₆ H ₅) ₂), 4.18–4.31 (s, 2H, —CH ₂ —), 3.17–3.3 (s, 3H, —OCH ₃)	78.13	78.46	13.02	13.35
4	1637 ν(C=N), 1065 ν(>N—)	7.31–7.44 (m, 7H, Ar—H), 4.3–4.44 (s, 2H, —CH ₂ —), 3.24–3.36 (s, 2H, (—OH) ₂), 3.03–3.17 (s, 3H, OCH ₃), 2.27–2.41 (m, 8H, (C ₂ H ₄) ₂)	65.57	65.25	15.30	15.62
5	1647 ν(C=N), 1054 ν(>N—)	7.12–7.25 (m, 7H, Ar—H), 4.38–4.52 (s, 2H, —CH ₂ —), 3.14–3.25 (s, 3H, —OCH ₃), 2.77–2.92 (m, 10H, 2', 3', 4', 5', 6', —CH ₂)	72.83	72.55	16.18	16.42
6	1654 ν(C=N), 1087 ν(>N—)	7.22–7.37 (m, 7H, Ar—H), 4.42–4.56 (s, 1H, —NH), 4.18–4.29 (s, 2H, —CH ₂ —), 3.35–3.66 (s, 3H, —OCH ₃), 2.69–2.85 (m, 10H, 2', 3', 4', 5', 6', —CH ₂)	69.16	69.49	20.15	20.42
7	1643 ν(C=N), 1056 ν(>N—)	7.33–7.48 (m, 7H, Ar—H), 4.28–4.42 (s, 2H, —CH ₂ —), 3.14–3.32 (s, 3H, —OCH ₃), 1.7–1.84 (s, 10H, (C ₂ H ₅) ₂)	71.85	71.53	16.76	16.39
8	1656 ν(C=N), 1087 ν(>N—)	7.22–7.4 (m, 7H, Ar—H), 4.35–4.5 (s, 2H, —CH ₂ —), 3.3–3.45 (s, 3H, —OCH ₃), 2.33–2.47 (m, 8H, 2', 3', 5', 6', —CH ₂), 2.12–2.25 (s, 5H, (C ₂ H ₅) ₂)	70.4	70.72	18.66	18.37
9	1656 ν(C=N), 1062 ν(>N—)	7.26–7.35 (m, 7H, Ar—H), 4.38–4.52 (s, 2H, —CH ₂ —), 3.28–3.4 (s, 3H, —OCH ₃), 2.55–2.71 (m, 8H, 2', 3', 5', 6', —CH ₂)	68.96	68.65	16.09	16.38

TABLE-3
ANTI-INFLAMMATORY ACTIVITY OF N-MANNICH BASES OF 10H-INDOLO
[3,2-B]QUINOXALINES

Compd. No.	mg kg ⁻¹ p.o.	% Inhibition of edema	Compd. No.	mg kg ⁻¹ p.o.	% Inhibition of edema
1	25	15.2*	6	25	24.8*
	50	31.1†		50	48.4‡
2	25	11.8*	7	25	19.0*
	50	22.5*		50	38.8†
3	25	16.6*	8	25	24.8†
	50	32.9*		50	39.5*
4	25	13.0*	9	25	29.2†
	50	24.5*		50	58.2*
5	25	14.6†			
	50	28.8*			

*P < 0.05, †P < 0.01, ‡P < 0.001

Antibacterial activity

All the compounds were screened *in-vitro* for their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus pumillus*, *Salmonella typhi*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* by agar dilution method⁹ at 100 µg/mL concentration using DMSO as solvent control. After 24 h of incubation at 37°C, the MIC was measured. The results are tabulated in Table-4.

TABLE-4
ANTIBACTERIAL ACTIVITY OF N-MANNICH BASES OF 10H-INDOLO
[3,2-B]QUINOXALINES (AGAR DILUTION METHOD)

Compd. No.	Minimum inhibitory concentration (drug concentrations in µg/mL)					
	<i>S. aureus</i>	<i>B. pumillus</i>	<i>S. typhi</i>	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>Ps. aeruginosa</i>
1	50	50	100	100	50	100
2	50	50	12.5	100	50	50
3	100	25	50	50	25	25
4	25	50	50	100	50	50
5	25	12.5	12.5	50	25	12.5
6	12.5	25	25	100	25	25
7	25	25	50	50	50	25
8	25	50	25	100	100	50
9	50	25	50	100	12.5	25

RESULTS AND DISCUSSION

All the synthesized compounds were evaluated for the antiinflammatory and antibacterial activities. In both the evaluations, compounds with the methoxy substitutions at R¹ produced better activity than the nitro substitutions. In the antiinflammatory study compounds with piperazine, diethylamino, 4-ethyl piperazino and morpholino substitutions (**6**, **7**, **8** and **9**) at NR position produced good antiinflammatory activity whereas other compounds were moderately active at the dose level of 50 mg/kg. In the antibacterial evaluation compounds with piperidine, piperazine and diethylamino substitutions (**5**, **6** and **7**) at NR position produced good antibacterial activity while other compounds were moderately active.

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