

# Synthesis and Biological Activity of 2-Substituted-3-ethyl-*N*-alkyl/arylindoles

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Some new 2-substituted-*N*-(aminomethylaryl/aminoethylaryl)indole-3-ylglyoxylamides **3a-h** and their corresponding 2-substituted-3-ethyl-*N*-alkyl/aryl indoles **4a-d,f,g** were synthesized. These compounds were evaluated for their cardiovascular as well as antiparkinsonian activities.

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Several indole derivatives have been reported to possess cardiovascular (3) as well as antiparkinsonian activity (4). The substitution of heterocyclic moieties in the indole nucleus have a marked influence on the biological activities (5,6). This prompted the synthesis of 2-substituted-3-ethyl-*N*-alkyl/arylindoles with a view to study the effect of different functional variants on biological activity. The compounds were evaluated for their cardiovascular, behavioural and antiparkinsonian activity.

### Chemistry.

The indoles **1a-b** were prepared according to published procedures (7,8). The indoleglyoxyl chlorides **2a-b** were prepared by the reaction of the appropriate indole with oxalyl chloride which on condensation with different aryl

amines gave the 2-substituted-*N*-(aminomethylaryl/aminoethylaryl)indole-3-ylglyoxylamides **3a-h** (Table I). These were reduced with lithium aluminium hydride to yield the corresponding 2-substituted-3-ethyl-*N*-alkyl/arylindoles **4a-d,f,g** (Table II).

### Biological Studies.

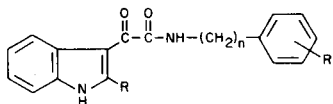
#### a) Cardiovascular Activity.

The effects of these compounds were studied on resting blood pressure and pressor responses evoked either by carotid occlusion (CO) or intravenous noradrenaline (NA 1-2 µg/kg) in chloralose (80 mg/kg iv) anaesthetized dogs.

Out of eight compounds, seven (**3a-g**) exhibited hypertension of varying degree (10-100 mm Hg) and duration. Compound **3h**, however, induced transient hypotension

Table I

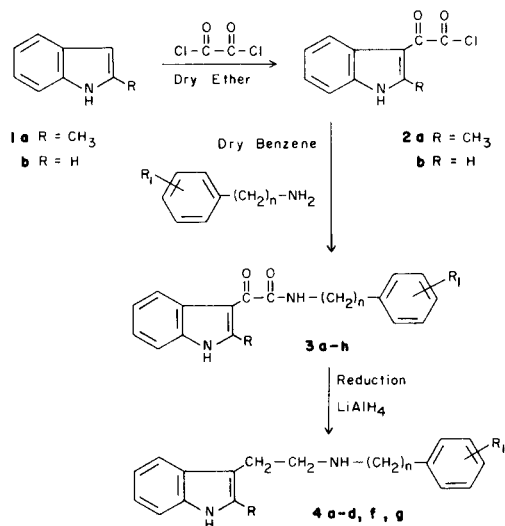
2-Substituted-*N*-(aminomethylaryl/aminoethylaryl)indole-3-yl-glyoxylamides (**3a-h**)



Compound No.	R	R <sub>1</sub>	(CH <sub>2</sub> ) <sub>n</sub>	Mp °C	Yield %	Purified Solvent (a)	Formula		Analysis % (b)		
							Calcd	Found	C	H	N
<b>3a</b>	CH <sub>3</sub>	4-CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>2</sub>	178	60	i	C <sub>20</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub>	Calcd	75.00	6.25	8.75
							Found	74.99	6.21	8.71	
<b>3b</b>	CH <sub>3</sub>	4-Cl	(CH <sub>2</sub> ) <sub>2</sub> C-CH <sub>2</sub>	184	70	ii/iii	C <sub>21</sub> H <sub>21</sub> ClN <sub>2</sub> O <sub>2</sub>	Calcd	68.38	5.69	7.59
							Found	68.35	5.66	7.52	
<b>3c</b>	CH <sub>3</sub>	3,4-(OCH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub>	204	65	ii/iii	C <sub>20</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub>	Calcd	68.18	5.68	7.95
							Found	68.14	5.64	7.97	
<b>3d</b>	CH <sub>3</sub>	4-Cl	(CH <sub>2</sub> ) <sub>2</sub>	166	75	iv	C <sub>19</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>2</sub>	Calcd	66.96	4.99	8.22
							Found	66.93	4.95	8.26	
<b>3e</b>	CH <sub>3</sub>	2,4-(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub>	187	60	ii/iii	C <sub>20</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub>	Calcd	75.00	6.25	8.75
							Found	74.98	6.22	8.78	
<b>3f</b>	H	4-Cl	(CH <sub>2</sub> ) <sub>2</sub>	90	80	ii/iii	C <sub>18</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>2</sub>	Calcd	66.15	4.59	8.57
							Found	66.12	4.56	8.53	
<b>3g</b>	H	4-CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>2</sub>	108	65	ii/iii	C <sub>19</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub>	Calcd	74.50	5.88	9.15
							Found	74.49	5.85	9.27	
<b>3h</b>	H	2,4-(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub>	124	68	ii/iii	C <sub>19</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub>	Calcd	74.50	5.88	9.15
							Found	74.48	5.86	9.23	

(a) i = Solvent ether; ii = ethanol; iii = water; iv = petroleum ether. (b) C, H and N agree with the theoretical value to within 0.4%.

Scheme



(-60 mm Hg).

Interestingly enough, all of the corresponding reduced (-C=O to -CH<sub>2</sub>-) compounds, **4a**, **4c**, **4d**, **4f** and **4g**, induced short lasting (less than 5 minutes) hypotension of varying magnitudes (50-80 mm Hg).

#### b) General Behaviour and Antiparkinsonian Activity (Table III).

The compounds were administered in mice and albino rats in a dose of 10 mg/kg ip in aqueous suspension with gum accacia and the effects were observed on general behaviour (awareness, neuromuscular system, motor system, sensory system, autonomic system) and antiparkinsonian

activity was tested against oxotremorine (0.5 mg/kg ip) induced tremor (**9**), reserpine induced rigidity (**10**) and catatonia (**11**). General behaviour was not affected by any compound. Four compounds, **3b**, **3c**, **4d** and **4f** have shown significant antitremor activity whereas seven compounds, **3c**, **3d**, **3g**, **3h**, **4a**, **4d** and **4f**, exhibited marked antirigidity activity. Potent anticatatonc activity was observed in compounds **3c**, **3d**, **3g**, **3h**, **4a** and **4d**.

ALD<sub>50</sub> values of the compounds (**12**) were > 1000 mg/kg ip (except compound **3d**) thereby indicating a good safety margin.

#### EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. Compounds were routinely checked for their homogeneity by tlc on silica gel G. Infrared spectra ( $\nu$  max in cm<sup>-1</sup>) were recorded on Perkin-Elmer Infracord 137 and nmr spectra were determined in deuteriochloroform on a Varian 90D instrument using TMS as the internal standard.

2-Methyl-*N-p*-(*p*-chlorophenyl)- $\alpha,\alpha$ -(dimethylethylamino)indole-3-ylglyoxyamides (**3b**), (**3a-h**) (Table I).

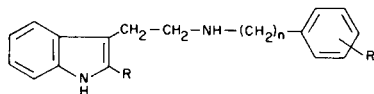
To 2-methylindoleglyoxylyl chloride (0.01 mole) in dry benzene (50 ml), *p*-(*p*-chlorophenyl)- $\alpha,\alpha$ -(dimethylethylamine) was added slowly. The reaction mixture was refluxed for eight hours. The solvent was distilled off and the residue thus obtained was washed with petroleum ether (40-60°) and recrystallized from ethanol/water, mp 184° dec; nmr (deuteriochloroform):  $\delta$  (ppm) 7.14 (s, 5H, aromatic), 7.00 (d, 1H, 7C), 6.92 (s, 2H, 3', 5', C, aromatic) 2.8 (d, 1H, N-H), 1.1 (s, 3H, 2-CH<sub>3</sub>), 1.3 (s, 6H, gem-dimethyl), 2.4 (d, 2H, methylene group), 2.62 (s, 1H, N-H) in chain.

Anal. Calcd. for C<sub>21</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>2</sub>: C, 68.38; H, 5.69; N, 7.59. Found: C, 68.35; H, 5.66; N, 7.52.

Compound **3a** in Table I showed characteristic -NH stretching bands at 3200 cm<sup>-1</sup> and C=O, a stretching vibration at 1600 cm<sup>-1</sup> in the infrared spectrum.

2-Methyl-3-3-*N-p*-(*p*-chlorophenyl)- $\alpha,\alpha$ -(dimethylethylamino)-ethylindoles (**4b**), (**4a-d,f,g**) (Table II).

Table II

.2-Substituted 3-ethyl-*N*-alkyl/arylindoles (**4a-d,f,g**)

Compound No.	R	R <sub>1</sub>	(CH <sub>2</sub> ) <sub>n</sub>	Mp °C	Yield %	Purified Solvent (a)	Formula	Analysis % (b)			
								C	H	N	
<b>4a</b>	CH <sub>3</sub>	4-CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>2</sub>	192	25	i/ii	C <sub>20</sub> H <sub>24</sub> N <sub>2</sub>	Calcd	82.19	8.21	9.58
								Found	82.08	8.16	9.53
<b>4b</b>	CH <sub>3</sub>	4-Cl	(CH <sub>2</sub> ) <sub>2</sub> -C-CH <sub>2</sub>	194	35	i/ii	C <sub>21</sub> H <sub>25</sub> ClN <sub>2</sub>	Calcd	74.00	7.34	8.22
								Found	74.24	7.12	8.50
<b>4c</b>	CH <sub>3</sub>	3,4-(OCH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub>	216	50	i/ii	C <sub>20</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub>	Calcd	74.07	7.40	8.64
								Found	74.27	7.29	8.61
<b>4d</b>	CH <sub>3</sub>	4-Cl	(CH <sub>2</sub> ) <sub>2</sub>	78	55	i/ii	C <sub>19</sub> H <sub>21</sub> ClN <sub>2</sub>	Calcd	72.96	6.72	8.96
								Found	72.85	6.71	8.92
<b>4f</b>	H	4-Cl	(CH <sub>2</sub> ) <sub>2</sub>	260	50	i/ii	C <sub>18</sub> H <sub>19</sub> ClN <sub>2</sub>	Calcd	72.36	6.36	9.38
								Found	72.26	6.31	9.41
<b>4g</b>	H	4-CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>2</sub>	94	30	iii	C <sub>19</sub> H <sub>22</sub> N <sub>2</sub>	Calcd	82.01	7.91	10.07
								Found	82.11	7.96	10.17

(a) i = DMF; ii = water; iii = acetone. (b) C, H and N agree with the theoretical value to within 0.4%.

Table III

Compound No.	Cardiovascular Activity activity at 5 mg/kg iv		Antiparkinsonian Activity at 10 mg/kg ip			ALD <sub>50</sub> mg/kg ip
	Effect on Blood Pressure mg Hg	Effect in NA and CO	Tremor Index Mean ± S E	Rigidity %	Catatonias Scores Mean ± S E	
3a	+80	No effect	3.0 ± 0	100	3.0 ± 0	-
3b	+30	No effect	2.4 ± 0.21 (b)	80	2.8 ± 0.35	1000
3c	+10	No effect	2.0 ± 0.28 (b)	40	2.0 ± 0.24 (b)	1000
3d	+25	No effect	3.0 ± 0	40	2.3 ± 0.26 (b)	1000
3e	+25	No effect	3.0 ± 0	100	3.0 ± 0	-
3f	+100 (c)	Inhibited (d)	3.0 ± 0	100	3.0 ± 0	-
3g	+100 (c)	Inhibited (d)	3.0 ± 0	60	2.0 ± 0.28 (b)	1000
3h	-60	No effect	2.8 ± 0.17	40	2.1 ± 0.21 (b)	1000
4a	-50	No effect	3.0 ± 0	40	2.4 ± 0.24 (b)	1000
4b	(a)	(a)	3.0 ± 0	100	3.0 ± 0	-
4c	-60	No effect	2.6 ± 0.21	100	2.8 ± 0.17	1000
4d	-80	No effect	2.2 ± 0.19 (b)	40	2.4 ± 0.24 (b)	1000
4f	-75	No effect	2.4 ± 0.21 (b)	60	2.6 ± 0.31	1000
4g	-70	No effect	3 ± 0	80	3.0 ± 0	-

(a) Indicates drugs were not tested. (b) Significant difference ( $P < 0.05$ ) from control values. (c) Hypertensive response of 20 minutes duration. (d) Could be due to the marked hypertension.

To a stirred mixture of lithium aluminium hydride (1 g) in dry ether (50 ml) was added 2-methyl-*N-p*-(*p*-chlorophenyl)- $\alpha,\alpha$ -(dimethylethylamino)indole-3-ylglyoxylamide (0.005 mole) in small portions. The reaction mixture was refluxed for 12 hours and then the complex was decomposed. The precipitate salts were filtered off. On removal of the solvent from the filtrate, a solid was obtained which was recrystallized from DMF/water, mp 194° dec; nmr (deuteriochloroform);  $\delta$  (ppm) 7.1 (s, 5H, Ar), 7.0 (s, 2-H, 3', 5', Ar-C), 4.1 (q, 1H, N-H), 3.7 (q, 1-H, N-H), 2.9 (q, 2-H, 5'-CH<sub>2</sub>), 2.5 (s, 2-H, 6'-CH<sub>2</sub>), 2.25 (6-H, *gem*-dimethyl), 1.9 (s, 3H, 2-CH<sub>3</sub>), 1.2 (s, 2H, 2'-CH<sub>2</sub>), 6.9 (s, 7-C, 1H, Ar).

Anal. Calcd. for C<sub>12</sub>H<sub>25</sub>ClN<sub>2</sub>: C, 74.00; H, 7.34; N, 8.22. Found: C, 74.24; H, 7.12; N, 8.50.

Compound 4c in Table II showed characteristic bands of the -NH stretching vibration (3300 cm<sup>-1</sup>) in the infrared spectrum while the C=O stretching band was completely absent.

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