Synthesis of Indole-2-carbaldehydes, 2-(2-Aminoethyl)- and 2-(2-Aminopropyl)-indoles

By **G. A. Bhat** and **S. Siddappa,*** Department of Chemistry, Karnatak University, Dharwar-3, S. India

Various substituted 2-hydroxymethylindoles have been prepared by lithium aluminium hydride reduction of corresponding 2-ethoxycarbonylindoles and oxidised with activated manganese dioxide to the respective indole-2-carbaldehydes. Some of the aldehydes have been prepared from the 2-ethoxycarbonylindoles by the McFadyen and Stevens procedure and the two methods are compared. The aldehydes were condensed with nitromethane and nitroethane and the condensation products reduced with lithium aluminium hydride to obtain 2-(2-aminoethyl)- and 2-(2-aminopropyl)-indoles.

A large number of structural analogues of serotonin have been synthesised and their biological activities evaluated in recent years. In continuation of previous work,[1] we report here the synthesis of various 2-(2-aminoethyl)-indoles and 2-(2-aminopropyl)indoles prepared for biological evaluation. While indole-3-carbaldehydes can be obtained in very high yields from corresponding indoles by the method of Smith,[2] indole-2-carbaldehydes required as intermediates for the synthesis of the title compounds are not easily accessible. Indole-2-carbaldehyde was prepared in poor yield by Taylor [3] by the oxidation of 2-hydroxymethylindole with potassium permanganate in acetone and by an improved method by Harley-Mason and Pavri [4] in which activated manganese dioxide was used to oxidise the alcohol. Dambal and Siddappa [5] reported the synthesis of some indole-2-carbaldehydes from 2-ethoxycarbonylindoles by the McFadyen and Stevens procedure. This method was now extended to the synthesis of other indole-2-carbaldehydes. Ethyl 5-methoxyindole-2-carboxylate (Ia) was converted almost quantitatively into the carbohydrazide (IIa); this was tosylated to obtain (IIIa) which upon reaction with anhydrous sodium carbonate in ethylene glycol yielded 5-methoxyindole-2-carbaldehyde (Va) (*ca.* 41%). Similarly, 5-methoxy-3-methylindole-2-carbaldehyde (Vb), 7-methoxy-3-methylindole-2-carbaldehyde (Vd), 5-methoxyindole-2-carbaldehyde (Vf), and 3-methyl-5-ethoxyindole-2-carbaldehyde (Vg) were prepared from the appropriate indole-2-carboxylates (Ia, b, d, f, and g). The aldehydes contained impurities which were removed by repeated chromatographic separation on alumina. Since the purification of the aldehydes obtained by this method was lengthy, we prepared the aldehydes by Harley-Mason's procedure to compare the two routes. The appropriate indole-2-carboxylic ester (I) was reduced with lithium aluminium hydride to give the indole-2-methanol (IV) which on oxidation with activated manganese dioxide yielded the indole-2-carbaldehyde (V). The oxidation reaction was followed by t.l.c. and was found to take *ca.* 20—30 hr. The latter route generally gave the indole-2-carbaldehydes in higher yields (60—70%) and in a purer form; further, they could be easily purified by crystallisation. The various aldehydes (Va—h) are described in Table 4. The indole-2-carbaldehydes condensed readily with nitromethane to give 2-(2-nitrovinyl)indoles (VIa—d and f—h) in 70—75% yields and on reduction with lithium aluminium hydride gave the required 2-(2-aminoethyl)-indoles (VIIa—d and f—h) in 60—65% yields. Similarly, condensation of the aldehydes (VIIa, b, f, and g) with nitroethane gave 2-(2-nitropropenyl)indoles in

---

[1] L. D. Basanagoudar and S. Siddappa, *J. Chem. Soc.* (*C*), 1967, 2599.

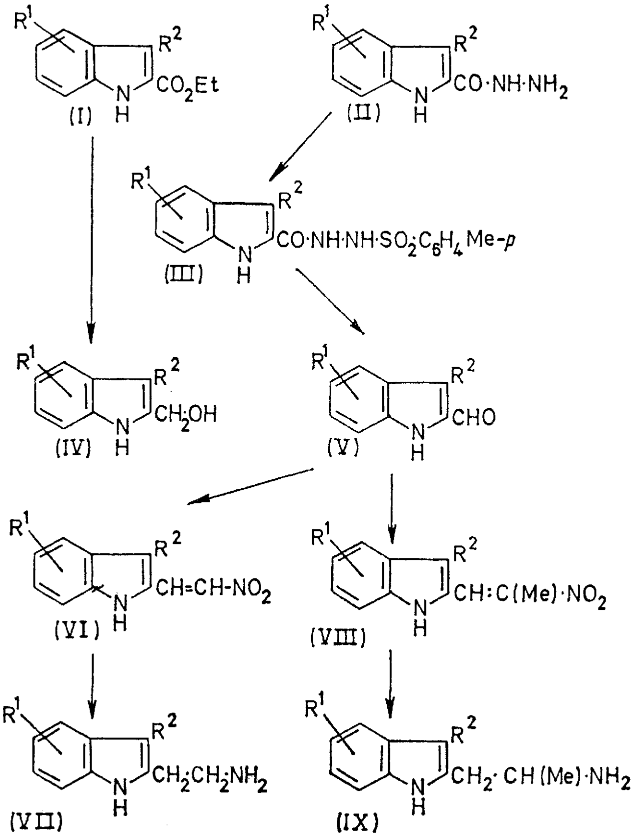
[2] G. F. Smith, *J. Chem. Soc.*, 1954, 3842.

[3] W. I. Taylor, *Helv. Chim. Acta*, 1950, **33**, 164.

[4] J. Harley-Mason and E. H. Pavri, *J. Chem. Soc.*, 1963, 2565.

[5] S. B. Dambal and S. Siddappa, *J. Indian Chem. Soc.*, 1965, **42**, 112.

70—75% yields and on subsequent reduction with lithium aluminium hydride gave the required 2-(2-aminopropyl)indoles (IXa, b, f, and g) in 65—70% yield.



	R^1	R^2
a;	5-OMe	H
b;	5-OMe	Me
c;	7-OMe	H
d;	7-OMe	Me
e;	6-OMe	H
f;	5-OEt	H
g;	5-OEt	Me
h;	7-OEt	H

The i.r. spectra of the alcohols (IVa—h) and the aldehydes (Va—h) have been recorded.

EXPERIMENTAL

The spectra were recorded on a Perkin-Elmer Infracord using potassium bromide discs.

Preparation of Starting Materials.—The following substituted ethyl indole-2-carboxylates were prepared by literature methods, *viz.*, 5-methoxy- (Ia),[6] 5-methoxy-3-methyl- (Ib),[7] 7-methoxy- (Ic),[7] 7-methoxy-3-methyl- (Id),[7] 6-methoxy- (Ie),[8] 5-ethoxy- (If),[6] and 5-ethoxy-3-methyl- (Ig).[9] Ethyl 7-ethoxyindole-2-carboxylate (Ih) was prepared from 3-ethoxy-2-nitrotoluene by Reissert method as described for (Ia).[7]

Preparation of Indole-2-carbohydrazides.—To ethyl 5-methoxyindole-2-carboxylate (5 g.) dissolved in absolute ethanol (50 ml.), was added hydrazine hydrate (100%, 10 ml.); the mixture was then heated under reflux on a water-bath for 5—6 hr. The colourless crystalline hydrazide that separated from the cool solution was filtered off, washed with ethanol, and crystallised from absolute ethanol. The various indole-2-carbohydrazides similarly prepared are described in Table 1.

TABLE 1

Indole-2-carbohydrazides (IIa, b, d, f, and g)

Compd.	M.p.*	Found N (%)	Molecular formula	Calculated N (%)
(IIa)	241°	20·25	$C_{10}H_{11}N_3O_2$	20·5
(IIb)	267	19·4	$C_{11}H_{13}N_3O_2$	19·2
(IId)	245	18·8	$C_{11}H_{13}N_3O_2$	19·2
(IIf)	261	18·95	$C_{11}H_{13}N_3O_2$	19·2
(IIg)	238	17·9	$C_{12}H_{15}N_3O_2$	18·02

* All decomposed at m.p.

2-*Toluene*-p-*sulphonhydrazidocarbonylindoles* (III).—Toluene-*p*-sulphonyl chloride (2·4 g.) was added in small portions with constant shaking to an ice-cold solution of 5-methoxyindole-2-carbohydrazide (2·5 g.), dissolved in freshly distilled pyridine (40 ml.). The reaction mixture was set aside in an ice-bath for 1 hr. and then for 1 hr. at room temperature. It was then poured on crushed ice containing conc. hydrochloric acid (35 ml.). The solid that separated was filtered off, washed with dilute hydrochloric acid and water, and crystallised from ethanol or dioxan. The 2-toluene-*p*-sulphonhydrazidocarbonylindoles are described in Table 2.

TABLE 2

2-Toluene-*p*-sulphonhydrazidocarbonylindoles
(IIIa, b, d, f, and g)

Compd.	M.p.*	Found N (%)	Molecular formula	Calculated N (%)
(IIIa)	249°	11·8	$C_{17}H_{17}N_3O_4S$	11·7
(IIIb)	241	10·95	$C_{18}H_{19}N_3O_4S$	11·25
(IIId)	222	11·1	$C_{18}H_{19}N_3O_4S$	11·25
(IIIf)	227	11·4	$C_{18}H_{19}N_3O_4S$	11·25
(IIIg)	230	11·15	$C_{19}H_{21}N_3O_4S$	10·85

* All decomposed at m.p.

Indole-2-carbaldehydes from Compound (III): *Method A*.—5-Methoxy-2-toluene-*p*-sulphonhydrazidoindole (2·5 g.) in ethylene glycol (25 ml.) was heated to 160° in an oil-bath and at the boiling solution anhydrous potassium carbonate (2·5 g.) was added. After 5 min. at this temperature the reaction mixture was poured on crushed ice (500 g.) and then set aside for 1 hr. The solid that separated was filtered off, dried, and chromatographed repeatedly on a neutral alumina column with benzene as eluant. The various indole-2-carbaldehydes prepared were identical with the aldehydes prepared by method B described below (no depression in mixed m.p.).

2-*Hydroxymethylindoles*.—A solution of the appropriate ethyl indole-2-carboxylate (5 g.) in dry ether (80 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (1·5 g.) in dry ether (50 ml.). After complete

---

[6] H. N. Rydon and S. Siddappa, *J. Chem. Soc.*, 1951, 2462.

[7] K. G. Blaikie and W. H. Perkin, jun., *J. Chem. Soc.*, 1924, **125**, 296.

[8] W. O. Karmerk, W. H. Perkin, and R. Robinson, *J. Chem. Soc.*, 1921, **119**, 1632.

[9] S. Keimatsu and S. Sugasawa, *J. Pharm. Soc., Japan*, 1928, **48**, 348.

TABLE 3

2-Hydroxymethylindoles (IVa—h)

Compd.	M.p.	Found (%)			Molecular formula	Calc. (%)			I.r. spectra (μ) *	
		C	H	N		C	H	N	$\nu_{OH/NH}$	ν_{CH}
(IVa)	82°	67·55	6·3	8·2	$C_{10}H_{11}NO_2$	67·8	6·2	7·9	3·14s	3·51ms
(IVb)	95—96	69·55	6·6	7·5	$C_{11}H_{13}NO_2$	69·1	6·8	7·35	3·02s	3·48s
(IVc)	83—84	67·6	6·1	8·1	$C_{10}H_{11}NO_2$	67·8	6·2	7·9	2·98s, 3·1s, doublet	3·47s
(IVd)	169—170	68·75	7·0	7·55	$C_{11}H_{13}NO_2$	69·1	6·8	7·35	2·8s, 3·04s, doublet	3·41s
(IVe)	111	68·15	5·9	8·2	$C_{10}H_{11}NO_2$	67·8	6·2	7·9	2·9s, 3·05s	3·41ms
(IVf)	84—85	68·9	6·9	7·45	$C_{11}H_{13}NO_2$	69·1	6·8	7·35	3·1s	3·42s
(IVg)	91—92	70·1	7·15	7·0	$C_{12}H_{15}NO_2$	70·25	7·3	6·85	3·0s, 3·14s	3·49s
(IVh)	99	68·95	6·8	7·55	$C_{11}H_{13}NO_2$	69·1	6·8	7·35	2·9s, 3·09s	3·42m

s = Strong; m = medium.

TABLE 4

Indole-2-carbaldehydes (Va—h)

Compd.	M.p.	Yield (%)		Found (%)			Molecular formula	Calc. (%)			I.r. spectra (μ) *	
		Method A	Method B	C	H	N		C	H	N	$\nu_{C=O}$	ν_{NH}
(Va)	140—141°	41	61	68·2	5·4	8·1	$C_{10}H_9NO_2$	68·6	5·15	8·0	5·98s	3·12s
(Vb)	229—231	50	71	69·55	6·0	7·65	$C_{11}H_{11}NO_2$	69·85	5·8	7·41	6·15s	3·02m
(Vc)	114		66	68·8	5·6	8·0	$C_{10}H_9NO_2$	68·6	5·15	8·0	6·12s	3·2s
(Vd)	130	48	69	69·5	5·55	7·4	$C_{11}H_{11}NO_2$	69·85	5·8	7·41	6·1s	3·04s
(Ve)	157		62	68·9	5·3	7·8	$C_{10}H_9NO_2$	68·6	5·15	8·0	6·06s, 6·2s	3·05s
(Vf)	171	43	61	70·0	6·0	7·2	$C_{11}H_{11}NO_2$	69·85	5·8	7·41	6·1s	3·02s
(Vg)	231	49	70	70·65	6·1	7·1	$C_{12}H_{13}NO_2$	70·95	6·4	6·9	6·19s	3·02s
(Vh)	176		63	69·6	5·55	7·26	$C_{11}H_{11}NO_2$	69·85	5·8	7·41	6·04s	3·11s

s = Strong; m = medium.

TABLE 5

2-(2-Nitrovinyl)indoles (VIa—d and f—h)

Compd.	M.p.	Found (%)			Molecular formula	Calc. (%)		
		C	H	N		C	H	N
(VIa)	176° (decomp.)	60·25	4·3	12·6	$C_{11}H_{10}N_2O_3$	60·54	4·6	12·85
(VIb)	211	62·3	4·9	12·0	$C_{12}H_{12}N_2O_3$	62·07	5·15	12·05
(VIc)	182 (decomp.)	60·2	4·8	12·7	$C_{11}H_{10}N_2O_3$	60·54	4·6	12·85
(VId)	187	62·2	4·9	11·95	$C_{12}H_{12}N_2O_3$	62·07	5·15	12·05
(VIf)	166 (decomp.)	61·9	4·85	12·25	$C_{12}H_{12}N_2O_3$	62·07	5·15	12·05
(VIg)	222 (decomp.)	63·75	5·7	11·45	$C_{13}H_{14}N_2O_3$	63·42	6·0	11·4
(VIh)	179	61·95	5·0	12·2	$C_{12}H_{12}N_2O_3$	62·07	5·15	12·05

TABLE 6

2-(2-Aminoethyl)indoles (VIIa—d and f—h)

Compd.	M.p.	Found (%)			Molecular formula	Calc. (%)		
		C	H	N		C	H	N
Benzoyl derivatives of (VIIa)	185°	73·1	5·9	9·69	$C_{18}H_{18}N_2O_2$	73·5	6·1	9·5
(VIIb)	137	70·4	7·65	13·8	$C_{12}H_{16}N_2O$	70·6	7·85	13·75
(VIIc)	180	69·6	7·4	14·48	$C_{11}H_{14}N_2O$	69·45	7·35	14·75
Benzoyl derivative of (VIId)	61 (decomp.)	74·35	6·5	9·1	$C_{19}H_{20}N_2O_2$	74·0	6·5	9·1
Benzoyl derivative of (VIIf)	218	74·3	6·55	9·12	$C_{19}H_{20}N_2O_2$	74·0	6·5	9·1
(VIIg)	130	71·35	8·4	12·87	$C_{13}H_{18}N_2O$	71·55	8·25	12·85
(VIIh)	117	70·4	7·6	13·84	$C_{12}H_{16}N_2O$	70·6	7·85	13·75

TABLE 7

2-(2-Nitropropenyl)indoles (VIIIa, b, f, and g)

Compd.	M.p.	Found (%)			Molecular formula	Calc. (%)		
		C	H	N		C	H	N
(VIIIa)	207° (decomp.)	61·65	5·0	11·9	$C_{12}H_{12}N_2O_3$	62·05	5·15	12·05
(VIIIb)	211 (decomp.)	63·2	5·6	11·55	$C_{13}H_{14}N_2O_3$	63·4	6·0	11·4
(VIIIf)	138	63·85	5·8	11·5	$C_{13}H_{14}N_2O_3$	63·4	6·0	11·4
(VIIIg)	176	64·8	6·3	10·85	$C_{14}H_{16}N_2O_3$	64·6	6·15	10·75

addition, it was stirred for a further hour. Excess of lithium aluminium hydride was decomposed by addition of water (1·5 ml.), sodium hydroxide (1·5 ml.; 15%), and finally water (3 ml.). The white precipitate was filtered off and washed several times with a little ether; the combined filtrates were washed with water, dried ($MgSO_4$), and evaporated to dryness; the residue was crystallised from the appropriate solvent. The 2-hydroxymethylindoles thus prepared are described in Table 3.

Indole-2-*carbaldehydes: Method B*.—The 2-hydroxymethylindole (4 g.) was dissolved in dichloromethane (250 ml.). Activated manganese dioxide (10 g.) was then added and the mixture was stirred at room temperature for 20—30 hr. The reaction was followed by t.l.c., the end-point being marked by the disappearance of the spot due to the 2-hydroxymethylindole. Whenever necessary, fresh quantity of manganese dioxide (2—3 g.) was added. The reaction mixture was filtered and the residual manganese dioxide was washed repeatedly with a little fresh dichloromethane. The combined filtrate was evaporated to dryness to give the crude indole-2-carbaldehyde as a pale yellow solid; this was crystallised. The indole-2-carbaldehydes thus prepared are described in Table 4.

TABLE 8

2-(2-Aminopropyl)indoles (IXa, b, f, and g)

Compd.	M.p.	Found (%) C	Found (%) H	Found (%) N	Molecular formula	Calc. (%) C	Calc. (%) H	Calc. (%) N
Bz deriv. of (IXa)	110°	74·35	6·25	9·3	$C_{19}H_{20}N_2O_2$	74·0	6·5	9·1
(IXb)	105	71·8	8·1	13·0	$C_{13}H_{18}N_2O$	71·55	8·25	12·85
(IXf)	98	71·95	8·5	12·65	$C_{13}H_{18}N_2O$	71·55	8·25	12·85
(IXg)	115	72·7	8·6	12·1	$C_{14}H_{20}N_2O$	72·4	8·6	12·05

2-(2-*Nitrovinyl*)*indoles*.—The indole-2-carbaldehyde (5 g.), nitromethane (8 ml.), and ammonium acetate (1 g.) were heated under reflux for ½ hr. The reaction mixture was cooled and the dark red crystals that separated were collected, washed thoroughly with water, dried, and crystallised from ethanol. The nitrovinylindoles prepared are described in Table 5.

2-(2-*Aminoethyl*)*indoles*.—A solution of the nitrovinylindole (1 g.) in tetrahydrofuran (25 ml.) was added dropwise to a stirred slurry of lithium aluminium hydride (1·5 g.) in dry ether (100 ml.). The mixture was gently heated under reflux for 10 hr. Excess of lithium aluminium hydride was decomposed by dropwise addition of water, sodium hydroxide (15%), and water. The white precipitate was filtered off and washed several times with a little ether. The combined filtrates were washed with water, dried ($MgSO_4$), and solvent was evaporated off; the residue if solid, was crystallised twice from suitable solvent, if liquid, it was converted into its benzoyl derivative which was chromatographed over neutral alumina. The aminoethylindoles prepared are described in Table 6.

2-(2-*Nitropropenyl*)*indoles*.—To a solution of the indole-2-carbaldehyde (1 g.) in nitroethane (0·5 ml.) was added four drops of benzylamine; the mixture heated under reflux for 1 hr. The cool reaction mixture deposited dark red crystals which were collected, washed with a little ether, dried, and crystallised from ethanol. The nitropropenylindoles prepared are described in Table 7.

2-(2-*Aminopropyl*)*indoles*.—2-(2-Nitropropenyl)indoles (1 g.) were reduced with lithium aluminium hydride as described for (VII). The solid products were crystallised and the liquids were characterised as benzoyl derivatives. The aminopropylindoles prepared are described in Table 8.

We thank Messrs V. A. Desai and G. S. Gadaginmath for the microanalyses.

[0/1186 *Received, July* 13*th*, 1970]