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2-AMINOINDOLES

PREPARATION FROM 2-INDOLINETHIONES, TAUTOMERISM AND AUTOXIDATION

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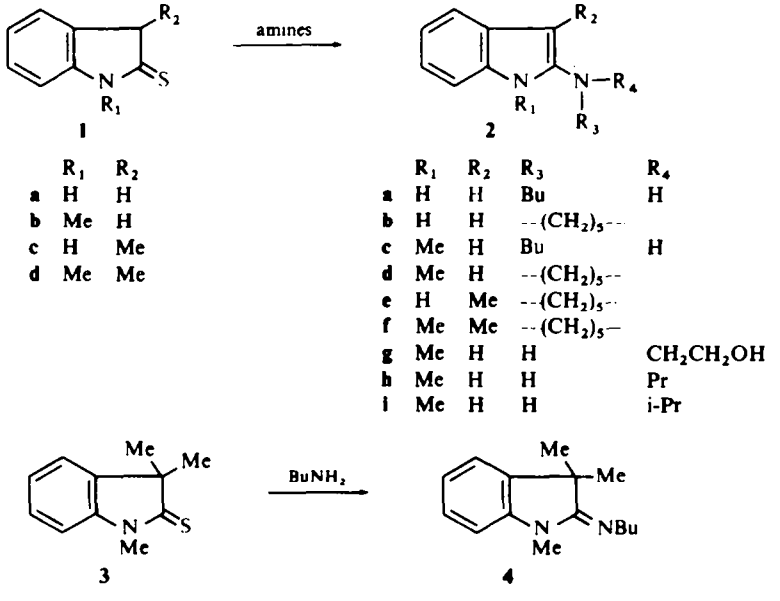
Abstract—2-Aminoindoles (**2** and **4**) have been prepared by the reaction of 2-indolinethiones (**1**) with primary and secondary aliphatic amines. The reaction of **1b** with ethyleneimine produced the S-alkylated product **5**, and with phenylhydrazine compound **9**. The reaction **1b** with aniline and **10** with piperidine failed to give an 2-aminoindole derivative or **12**. The UV and NMR spectra of the free base **2** shows the presence of a tautomeric mixture of **13** and **14** in bases **2c**, **2g**, **2h** and **2i**. The free base **2b** in $CDCl_3$ exists substantially in the indolenine form **15**. The free bases of **2b**, **2g**, **2h** and **2i** are susceptible to autoxidation to 3-oxo derivatives (**19**, **21**, **22** and **23**).

2-AMINOINDOLE and its methyl derivatives have been prepared from *o*-aminobenzylcyanide with ethoxide[1] and by the Curtius degradation of indole-2-carboxylic acid azide.[2] Ethyl 2-aminoindole-3-carboxylate has been prepared by the reduction of

CHART 1



1

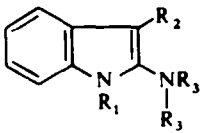
	R_1	R_2
a	H	H
b	Me	H
c	H	Me
d	Me	Me

2

	R_1	R_2	R_3	R_4
a	H	H	Bu	H
b	H	H	$-(CH_2)_5-$	
c	Me	H	Bu	H
d	Me	H	$-(CH_2)_5-$	
e	H	Me	$-(CH_2)_5-$	
f	Me	Me	$-(CH_2)_5-$	
g	Me	H	H	CH_2CH_2OH
h	Me	H	H	Pr
i	Me	H	H	i-Pr

3 4

TABLE 1. 2-AMINOINDOLES



2	R_1	R_2	R_3	R_4	Form	m.p.	Yield, %	Anal. Calcd. C	H	N	X	Anal. Found C	H	N	X
a	H	H	Bu	H	HBr	196–197°	40·5	53·53	6·37	10·41	29·69	53·99	5·92	10·32	28·99
b	H	H	—$(CH_2)_5$—		HBr	266–267°	82·8			ref. 8					
c	Me	H	Bu	H	HCl	187–188°	77·2	65·40	8·02	11·73		65·31	7·79	11·69	
d	Me	H	—$(CH_2)_5$—		free	73–75°	65·6	78·46	8·46	13·08		78·34	8·20	12·71	
e	H	Me	—$(CH_2)_5$—		HBr	187–188°	80			ref. 10					
f	Me	Me	—$(CH_2)_5$—		free	60–60·5°	25·5	78·90	8·83	12·27		78·63	8·75	12·55	
g	Me	H	H	CH_2CH_2OH	HCl	235–238°	38·6	58·28	6·67	12·36	15·63	57·50	6·70	12·58	15·74
h	Me	H	H	Pr	HBr	247–251·5°	30·9	53·54	6·36	10·41	29·69	53·73	6·37	10·09	29·68
i	Me	H	H	i-Pr	HBr	270°	44·1	53·54	6·36	10·41	29·69	53·99	6·39	10·33	29·53

TABLE 2. UV SPECTRA OF 2-AMINOINDOLES

Compound	UV λ_{max}^{EtOH} mμ (ε)	
	Salt form	Free base form
2a	257 (14,400), 280 (5,300)	270 (16,200), 278 (14,300), 305 (3,080)
2b	263 (16,600), 267 (16,400), 282 (8,410)	275 (19,200), 284 (18,300), 305^{sh} (5,840)
2c	264 (11,700), 280 (6,570)	235 (18,100), 271 (9,940), 283 (8,280), 300 (7,220)
2d	275 (12,600), 282 (10,900)	225 (24,900), 284 (10,300), 294 (9,500)
2f	278 (12,000), 283 (11,800), 292^{sh} (9,570)	230 (25,400), 290 (9,030), 296 (8,950)
2g	238^{sh} (8,380), 266 (11,600), 280^{sh} (7,380)	235 (20,000), 270 (11,960), 281 (9,500), 299 (7,940)
2h	238^{sh} (11,000), 264 (11,000), 280^{sh} (7,190), 302^{sh} (4,040)	235 (18,000), 270 (9,900), 283 (8,090), 301 (7,190)
2i	238^{sh} (10,000), 267 (10,400), 280^{sh} (7,310), 300^{sh} (4,040)	235 (18,300), 272 (9,420), 283 (8,460), 300 (7,690)

(2-nitrophenyl)cyanoacetic acid.[3] 2-(Benzenesulfonylamino)indoles have been prepared by the reaction of indoles with sulfonyl azide.[4] 2-Amino-3-hydroxy-3-aryl-3*H*-indoles have been prepared by the reaction of 3-phenyldioxindole with amines[5] or by the reaction of 2-aroyl-2,2-dichloroacetanilide with cyanide.[6] Recently tetrahydroazepino[2.3-*b*]indole has been prepared by the Beckmann rearrangement of tetrahydrocarbazole-1-one oxime.[7] None of these methods can serve as a general method for the preparation of 2-aminoindoles.

In a previous report,[8] 2-indolinethiones were synthesised. The reaction of 2-indolinethiones with amines has now been investigated with a view to obtaining the corresponding 2-aminoindoles which have not been described. The thioneamide is known to afford the amidine or N-substituted thioneamide on reaction with amines.[9]

When 2-indolinethione (**1a**) was refluxed with an excess of butylamine under a stream of nitrogen 2-aminoindole **2a** was obtained as the hydrobromide. Under similar conditions, the reaction of **1a** with piperidine provide **2b** as the hydrobromide and was identical with a sample prepared from 2-ethoxyindole and piperidine.[10] Methyl substituted 2-indolinethiones (**1b**, **c**, **d**) were converted to 2-aminoindoles (**2c–2f**) on treatment with piperidine or butylamine under similar conditions. (Table 1). The yield of **2f** was probably reduced due to the steric hindrance of two Me groups at the 1 and 3-positions. The steric effect of this reaction was further demonstrated in

CHART 2

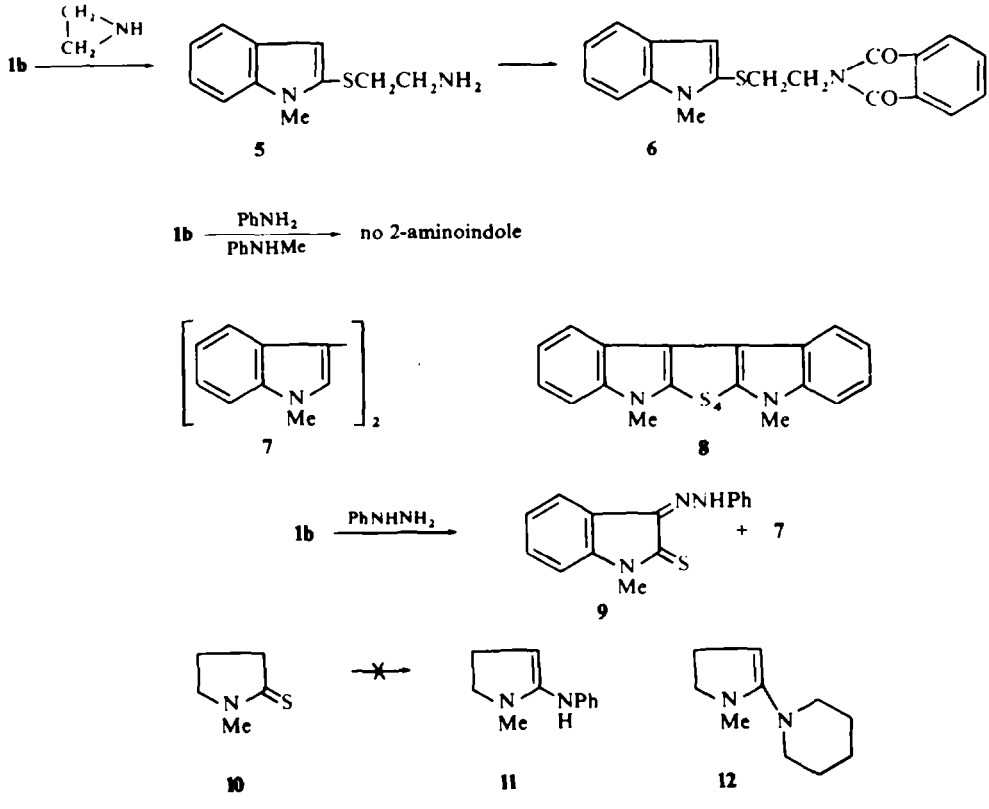


TABLE 3. NMR SPECTRA OF 2-AMINOINDOLES

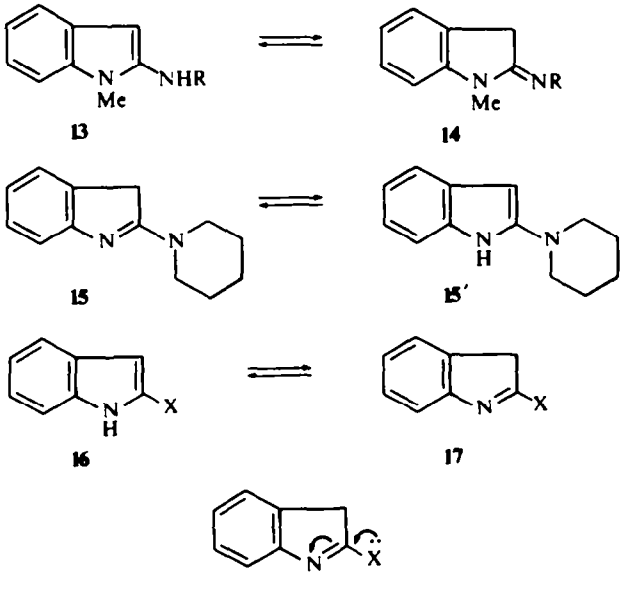
Compound	NMR (in $CDCl_3$, ppm from TMS)
2a.HBr	0·94 (t, CH_3), 1·35–1·97 (m, CH_2CH_2—), 3·78 (q, CH_2—N), 4·35 (s, 3-CH_2), 10·4 (s, NH)
2c.HCl	0·98 (t, CH_3), 1·47–1·91 (m, —CH_2CH_2—), 3·59 (q, CH_2- N), 3·92 (s, N-Me), 4·14 (s, 3-CH_2)
2d	1·67 (s, broad, β-, γ-H in piperidine), 2·67 (s, broad, α-H in piperidine), 3·57 (s, N—Me), 5·84 (s, 3-H)
2f	1·65 (s, broad, β-, γ-H in piperidine), 3·17 (s, broad, α-H in piperidine), 2·34 (s, 3-Me), 3·60 (s, N—Me)
2g.HCl	(in CF_3COOH): 3·62 (s, N—Me), 3·92 (t, CH_2—N), 4·25 (s, broad, 3-CH_2 and CH_2OH), 3·75 (s, broad, OH), 8·2 (s, broad, NH)
2h.HBr	1·00 (t, CH_3), 1·92 (m, C—CH_2—C), 3·50 (q, CH_2—N), 3·87 (s, N—Me), 4·07 (s, 3-CH_2), 11·23 (s, broad, NH)

the case of **3**. 2-Aminoindole **4** was isolated in poor yield even after a longer reaction time, and characterised as its picrate. The reactions of **1b** with propyl and isopropylamines were carried out in butanol since the reaction at the b.p. of the amines did not give a satisfactory yield. The reaction of **1b** with ethanolamine produced **2g**, but, when **1b** was heated with excess N-methylethanolamine, the expected salt of 2-aminoindole was not obtained in a crystalline form, though the UV spectrum of the crude product corresponded to 2-aminoindoles (**2**). In order to demonstrate the formation of a 2-aminoindole derivative, the crude product was hydrolysed with ethanolic HCl to afford 1-methyloxindole in 40% yield. This result suggests that the 2-aminoindole derivative was formed at least in 40% yield, since **1b** is stable to acid hydrolysis under a similar conditions.

The reaction with amine, however, was found not to be a general reaction. When **1b** was refluxed with an excess of ethyleneimine for 2·5 hr, S-alkylated compound **5** was obtained instead of a 2-aminoindole derivative. Its phthaloyl derivative **6** was identical with a sample prepared from **1b** by S-alkylation with N-(2-bromoethyl)-phthalimide.[11] 2-Indolinethione **1b** served as a nucleophile to cleave the aziridine ring.

The reaction of **1b** with aniline and with N-methylaniline was examined at the b.p. of the amine or in butanol, but no 2-aminoindole derivative was obtained. When **1b** was heated with phenylhydrazine in butanol under a stream of nitrogen, a small amount of red crystalline **9** was obtained in addition to **7**. The NMR spectrum of the red crystals shows a singlet at 3·62 ppm for N-Me and a singlet at 15·7 for NH. The substance has the molecular ion peak in mass spectrum at *m/e* 267 and shows λ_{max} 226, 290, 420 and 470^{sh} mμ. These spectral data support the structure **9** for the red crystals.

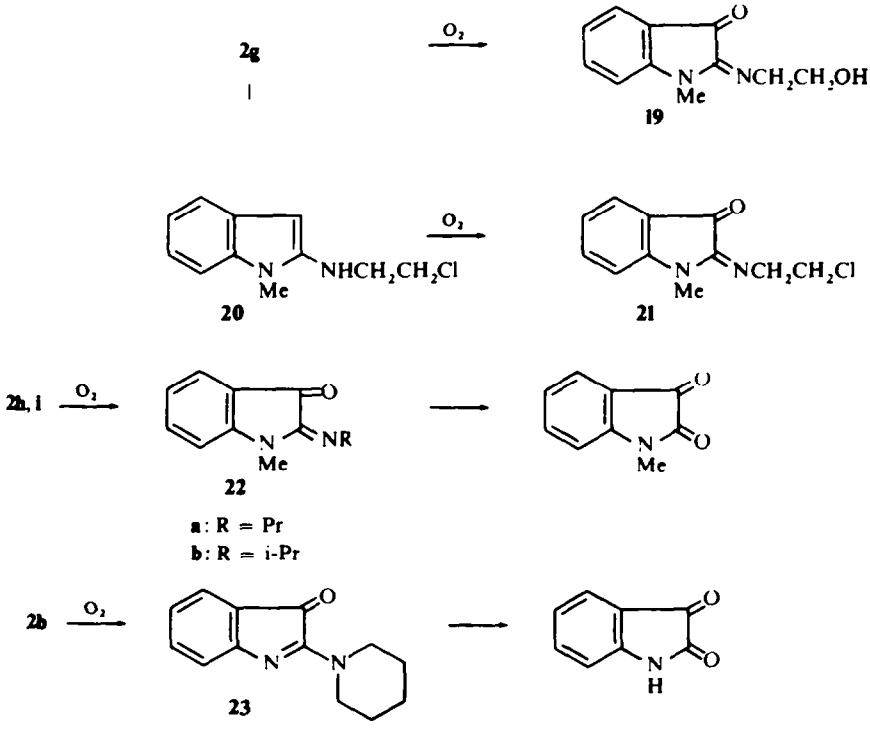
CHART 3



The reaction of a cyclic thioneamide, 1-methyl-2-pyrrolidinethione (**10**), with piperidine or aniline was carried out in order to compare the reactivity of **10** with that of the indolinethiones, but the expected **11** or **12** was not formed. 2-Indolinethiones could be good starting material for the preparation of 2-aminoindoles, though some limitation was observed. The UV and NMR spectra of **2** are shown in Tables 2 and 3.

It has been reported[1b] that 2-aminoindole is present as the 2-aminoindolenine form and 1-methyl-2-aminoindole as 2-iminoindoline form. The free bases **2d** and **2f** are present as the indolic form and their UV spectra correspond to the typical indolic absorption. The free bases, **2c**, **2g**, **2h** and **2i**, exhibit similar UV spectra (λ_{max} 270, 280 and 300 mμ) which differ from those of **2d** and **2f**. The UV spectrum of **4** shows the λ_{max} 275 mμ. Therefore, it is considered that these compounds must be present in EtOH as tautomeric mixtures of 2-aminoindole (**13**) and 2-iminoindoline (**14**). This was confirmed by the NMR spectra in $CDCl_3$ taken immediately after basification of the hydrohalides salts. The NMe signal of **2d** and **2f** appears at 3·57 and 3·60 ppm, respectively, and that of **4** appears at 3·13 ppm. The NMR spectra of the free bases, **2c**, **2g**, **2h** and **2i** show two NMe signals at around 3·60 and 3·15 ppm (Experimental). A comparison of the intensity of the both signals indicated that **2c**, **2h** and **2i** in $CDCl_3$ were predominantly present in the indolic form (**13**) and **2g** as the indoline tautomer (**14**). The NMR spectrum of **2b** taken immediately after the

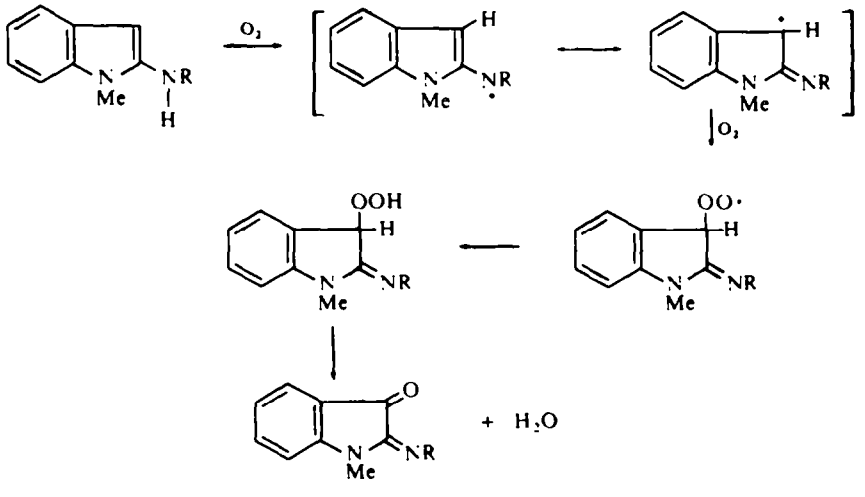
CHART 4



basification of its hydrobromide shows two broad singlets in the same intensity at 1·67 and 3·57 ppm. The former corresponds to the 6H due to β and γ-methylene of piperidine and the latter to the 6H due to α-methylene of piperidine and the methylene at 3-position of the indole,* and no signal for the indolic β-H and NH is present. This suggests that **2b** exist substantially in the indolenine form **15**. The presence of indole-indolenine tautomerism of the compound **16** (X = OEt) in the NMR spectra was first observed by Harley–Mason, indicating that the indolenine form predominates.[12] On the other hand, the compound **16** (X = SEt) exists only in the indolic form.[10] The stability of the indolenine form (**17**) seems to increase in the following order: X = SEt < OEt < N. This order is the same as the electron donating power of the substituent at 2-position which could increase the contribution of the zwitter ionic resonance form (**18**).

In our early report the autoxidation of **2e** to the 3-hydroxyindolenine was discussed.[13] We now found another type of auto-oxidation product of these 2-aminoindoles.[14] While free bases of **2d** and **2f** are stable towards autoxidation and can be purified, and free bases of the compounds **2a**, **2b**, **2c**, **2g**, **2h** and **2i** are very susceptible to air and discolour on standing or during purification. When the hydrochloride of **2g** was basified with $NaHCO_3$ and extracted with methylene chloride and left for 24 hr, a red crystalline substance **19** was obtained. The structure of **19** was confirmed by the following spectral data. The IR spectrum of **19** shows a CO band at 1710 and $\nu_{C=N}$ at 1650 cm^{-1}. The UV spectrum in EtOH is λ_{max} (ε); 232 (18,600), 257 (25,800), 263 (25,200), 300^{sh} (3,600), 477 (1,300). The NMR spectrum in $CDCl_3$ shows a singlet at 3·21 (3H, NMe), a triplet at 3·84 (2H, NCH_2), a triplet at 4·21 (2H, CH_2O). The mass spectrum shows a molecular ion peak at *m/e* 204. The compound **2g** was converted to **20**, and was also autoxidised to give red crystals (**21**).

CHART 5



* The NMR spectrum of **2b** in $CDCl_3$ which was obtained by the basification of **2b**HBr with K_2CO_3 in D_2O showed two broad inglets at 1·67 and 3·57 ppm and because of the deuteration at 3-methylene of **15** the intensity ratio of these signals was 6:4.

In the autoxidation of **2h**·HBr and **2i**·HBr, about one mole of oxygen was absorbed during 20 min for **2h** and 80 min for **2i**, respectively. Both crude products show the 2-imino-3-oxo-indoline chromophor, but **22** could not be purified. The formation of **22*** was proved by acid hydrolysis of the crude product to give 1-methylisatin. These results indicate that 2-aminoindole derivatives having an NH group and no substituent at the 3-position easily autoxidise to 3-oxo derivatives. In an analogous autoxidation of 2b·HBr, the spectral data of crude product indicated the formation of **23**, but as the crude could not be purified, it was hydrolysed to isatin and piperidine. The prominent effect of a N atom at 2-position of **16** is interesting in comparison with 16 (X = OEt and SEt), which is fairly stable towards autoxidation,[10] though the compound **16** (X = OEt) was reported to be autoxidised to indirubin on long exposure to air.[15] The order of susceptibility of **16** towards oxygen was the same as that of the stability of the indolenine form in $CDCl_3$, and the indoles having a stronger electron donating group at 2-position are more susceptible to autoxidation. The possible reaction path of the autoxidation of 2-aminoindoles is outlined in Chart 5.

EXPERIMENTAL

M.ps are uncorrected. IR spectra were recorded on a JASCO-DS-301 model or a Hitachi G-3 model spectrophotometer. UV spectra were recorded on a Cary model 14 or a Hitachi EPS-3T spectrophotometer. NMR spectra were taken with a Varian HR-100 or JOEL JNM-4H-100 spectrometer.

2-Butylaminoindole (**2a**) *hydrobromide*. A soln of **1a**[8] (1·0 g) in butylamine (20 ml) was refluxed for 2 hr under a stream of N_2. The mixture was evaporated to a pale green powder (1·4 g). This was dissolved in EtOH and was with EtOH–HBr to give **2a**·HBr (730 mg, 40·3%), m.p. 190–193°, as colourless crystals. Recrystallisations from EtOH–Et_2O gave an analytical sample of **2a**·HBr, m.p. 196–197°; IR ν_{max}^{KBr} 1670 cm^{-1} (C=N).

2-Piperidinoindole (**2b**) *hydrobromide*. A soln of **1a** (700 mg) in piperidine (23 ml) was refluxed for 2 hr under a stream of N_2. The mixture was treated as above to give **2b**·HBr (1·09 g, 82·8%), which was recrystallised from EtOH to furnish **2b**·HBr, m.p. 266–271°, which was identical with the sample prepared from 2-ethoxyindole and piperidine.[10]

2-Butylamino-1-methylindole (**2c**) *hydrochloride*. A soln of **1b**[8] (1·0 g) in butylamine (23 ml) was refluxed for 9 hr under a stream of N_2. The mixture was evaporated *in vacuo* to leave a pale brown oil (1·2 g), to which EtOH–HCl was added and diluted with Et_2O to give **2c**·HCl (950 mg, 77·2%), m.p. 170°. From the mother liquor **1b** (200 mg) was recovered. Crude **2c**·HCl was recrystallized from EtOH–Et_2O to give **2c**·HCl, m.p. 187–188°, as colourless crystals; IR ν_{max}^{KBr} 1670 cm^{-1} (C=N). A soln of **2c**·HCl (50 mg) in D_2O (0·5 ml) was basified with NaOH and extracted with $CDCl_3$ (1 ml) and dried over Na_2SO_4. The NMR spectrum of the soln: 0·97 (t, CH_3—CH_2— in **13** and **14**), 1·55 (m, C—CH_2CH_2—C in **13** and **14**), 3·17 (s, NMe in **14**), 3·17 (t, CH_2N in **13** and **14**), 3·48 (s, NMe in **13**). The intensity of these signal disclose that **13** is predominant in the equilibrium mixture.

1-Methyl-2-piperidinoindole (**2d**). A soln of **1b** (500 mg) in piperidine (15 ml) was refluxed for 4 hr until **1b** had disappeared on TLC. The mixture was evaporated *in vacuo* to leave a dark green solid (800 mg). The solid was purified over silicic acid column to give **2d** (430 mg, 65·5%), m.p. 55–58°. Recrystallisation from hexane gave **2d**, m.p. 73–74°, as colourless crystals; IR ν_{max}^{KBr} 1550, 1470, 770, 750 cm^{-1} (indole ring); picrate, m.p. 147·5–149·5°. (Found: C, 54·26; H, 4·59; N, 15·92. $C_{14}H_8N_2 \cdot C_6H_3N_3O_7$ requires: C, 54·17; H, 4·77; N, 15·80%).

3-Methyl-2-piperidinoindole (**2e**) *hydrobromide*. A soln of **1c** (1·43 g) in piperidine (50 ml) was refluxed for 3 hr. The UV spectral change and TLC were employed to examine the end of the reaction. The residue obtained on evaporation of excess piperidine was immediately dissolved in the minimum amount of EtOH and HBr-saturated EtOH was added. Then excess EtOH was evaporated off to leave a residue which was recrystallised from H_2O to give **2e** HBr (1·9 g, 80%), m.p. 115–120°. Recrystallisation from H_2O and heating at 80° *in vacuo* gave **2e**·HBr, m.p. 188° (dec), as colourless pillars.[13]

* The appearance of $\nu_{C=O}$ band due to **22** during the autoxidation of **2h** and **2i** was followed by taking the IR spectra (cf Experimental).

1,3-*Dimethyl-2-piperidinoindole* (**2f**). A soln of **1d** (570 mg) in piperidine (15 ml) was refluxed for 27 hr under a stream of N_2. The mixture was evaporated *in vacuo* to leave a brown oil (600 mg). This was dissolved in CH_2Cl_2 and extracted with 10% HCl. The acidic layer was basified with NaOH aq with cooling and extracted with CH_2Cl_2. The CH_2Cl_2 soln was evaporated *in vacuo* after drying to leave a solid (crude **2f**, 187 mg, 25·5%), m.p. 53–56°, which was purified over a silicic acid column and recrystallised from aq EtOH to give **2f**, m.p. 60–60·5°, as colourless crystals; IR ν_{max}^{KBr} 1585, 1570, 1470, 740 cm^{-1} (indole ring).

1,3,3-*Trimethyl-2-butyliminoindole* (**4**). A soln of **3** (1·97 g) in butylamine (30 ml) was refluxed for 30 hr. The UV spectrum of the mixture still showed the presence of unreacted **3**. The mixture was evaporated *in vacuo* to leave an oil (2·08 g). This oil was dissolved in CH_2Cl_2 and extracted with 10% HCl. The CH_2Cl_2 layer was evaporated to leave a brown oil (1·86 g) from which **3** (1·6 g) was recovered after silicic acid chromatographic purification. The acidic layer was basified with NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 soln was evaporated *in vacuo* to leave an oil (110 mg) which could not be induced to crystallise; UV λ_{max}^{EtOH} 275 mμ; NMR (ppm from TMS in $CDCl_3$); 0·94 (t, 3H, CH_3—C), 1·54 (singlet overlapped with small multiplets, 3-CH_3 and CH_2CH_2—C), 3·13 (s, NMe), 3·69 (t, N—CH_2), 6·53–7·25 (m, aromatic H). The picrate was recrystallised from EtOH to afford yellow crystals, m.p. 132–133°. (Found: C, 54·63; H, 5·36; N, 15·18. $C_{21}H_{25}N_5O_7$ requires: C, 54·90; H, 5·48; N, 15·14%).

2-(2-*Hydroxyethylamino*)-1-*methylindole* (**2g**) *hydrochloride*

A soln of **1b** (8·72 g) in ethanolamine (90 ml) was heated at 120–140° (bath temp) for 4 hr with stirring under a stream of N_2. The UV absorption of the mixture showed λ_{max} 315 mμ at the beginning and then changed to λ_{max} 270 mμ. The mixture was evaporated *in vacuo* to remove an excess ethanolamine. The residue was dissolved in a small amount of EtOH and EtOH–HCl was added. A pale yellow ppt was collected and washed with CH_2Cl_2. The solid was recrystallised from EtOH–Et_2O twice to give **2g**·HCl (4·94 g, 38·6%), m.p. 230–235°. Further recrystallisation from the same solvent gave an analytical sample of **2g**·HCl, m.p. 235–238°; Mass; *m/e* (relative abundance, %); 191 (M^+, 10), 190 (57), 159 (100), 146 (39), 131 (76), 118 (66). IR ν_{max}^{KBr} cm^{-1} 3310, 3260 (OH), 1662 (C=N), 1615, 1470, 760 (indole ring). The NMR spectrum of **2g** taken immediately after the basification of **2g**·HCl in $CDCl_3$ showed a mixture of **13** and **14**; 3·18 (s, NMe in **14**), 3·3 (broad, NCH_2 in **13** and **14**), 3·50 (s, NMe in **13**), 3·53 (s, 3-CH_2 in **14**), 3·82 (m, C—CH_2O in **13** and **14**), 5·50 (s, 3-H in **13**). Intensities of these signals showed **14** to be predominant. The NMR spectrum taken by the addition of NaOD–D_2O to a suspension of **2g** HCl in $CDCl_3$ showed better figure of two singlets of NMe of **13** and **14** due to the deuteration of 3-CH_2 in **14** and 3-H in **13**.

Reaction of **1b** *with* N-*methylethanolamine*. A mixture of **1b** (1·09 g) in N-methylethanolamine (10 ml) was refluxed for 6 hr under a stream of N_2. The mixture was evaporated *in vacuo* to leave a dark brown oil. The crude products showed λ_{max} at 294 mμ in EtOH and 274 and 282 mμ in EtOH–HCl which were similar to those of the crude product of **2g**, but various attempts to isolate a salt were not successful. The crude mixture was dissolved in EtOH (100 ml) and 10% HCl (30 ml) and refluxed for 30 min. The UV spectrum of the mixture changed to the oxindole type (λ_{max} 250 mμ). The mixture was evaporated *in vacuo* and the residue was extracted with ether. The solvent was evaporated and the residue was chromatographed over silicic acid. A fraction eluted with CH_2Cl_2 gave 1-methyloxindole (467 mg, 47·6% based on **1b**). Recrystallisation from hexane gave 1-methyloxindole, m.p. 86–89° (326 mg, 33%), which was identical with the authentic sample.

1-*Methyl-2-propylaminoindole* (**2h**) *hydrobromide*. To a boiling soln of **1b** (6·52 g) and propylamine (10 ml) in BuOH (210 ml) more propylamine (20 ml) was added dropwise under a stream of N_2 during 4 hr. The mixture was evaporated *in vacuo* and the residue dissolved in a small amount of EtOH and added to EtOH–HBr to give yellow ppt (**2h**·HBr, 3·13 g, 30·7%), m.p. 241–244°. Recrystallisation from EtOH gave **2h**·HBr, m.p. 247–251·5°, as colourless crystals; IR ν_{max}^{KBr} 1660 cm^{-1} (C=N). From the mother liquor **8** (460 mg), m.p. 246°, was obtained after one recrystallisation from benzene–hexane, and this sample was identical with the authentic sample[8] on TLC and IR spectra. The hydrochloride (**2h**·HCl), had m.p. 209–211° (from EtOH, dry at 100° *in vacuo*). (Found: C, 64·13; H, 7·56; N, 12·63; Cl, 15·93. $C_{14}H_{16}N_2$·HCl requires: C, 64·13; H, 7·62; N, 12·47; Cl, 15·78%).

The NMR spectrum of **2h** obtained by the addition of NaOD–D_2O in a $CDCl_3$ soln of **2h**·HBr showed two singlets at 3·16 and 3·47 ppm. The latter corresponded to the chemical shift of the NMe of **13** and was more intense than that of the former.

2-*Isopropylamino*-1-*methylindole* (**2i**) *hydrochloride*. To a boiling soln of **1b** (1·65 g) and isopropylamine (5 ml) in BuOH (50 ml) more isopropylamine (29 ml) was added dropwise during 6·5 hr under a stream of

N_2. The mixture was evaporated and the residue was treated as in the case of **2b** to afford crude **2i**·HBr (1·19 g, 44%), m.p. 255°. Recrystallisation from EtOH gave an analytical sample of **2i**·HBr, m.p. 267° (dec); IR ν_{max}^{KBr} 1665 cm^{-1} (C=N). The NMR spectrum of **2i** taken immediately after basification of **2i**·HBr showed a signal pattern of a mixture of **13** and **14**. Signals for **13**: 1·27 (d, Me in i-Pr), 3·50 (s, NMe), 5·52 (s, 3-H). Signals for **14**; 1·17 (d, Me in i-Pr), 3·17 (s, NMe). The integrated intensity showed the ratio of **13** to **14** was about 3:1. Broad signals for methylene at 3-position of **14** and methine of i-Pr group were observed at 3·2 and 3·6 ppm.

Reaction of **1b** *with ethyleneimine*

Formation of 2-(*2-aminoethyl-thio*-1-*methylindole* (**5**). A soln of **1b** (650 mg) in ethyleneimine (6 ml) was refluxed for 2·5 hr. The mixture was evaporated *in vacuo* to leave a brown oil (crude **5**, 800 mg), which did not crystallise. The UV spectrum of the crude mixture showed λ_{max}^{EtOH} 287 and 293^{sh} mμ; NMR (ppm from TMS in $CDCl_3$); 1·40 (s, NH_2), 2·80 (s, NCH_2CH_2S), 3·80 (s, NMe), 6·68 (s, 3-H). The crude product (**5**, 2·6 mg) was heated with phthalic anhydride (150 mg) in AcOH (5 ml) for 1 hr. The mixture was poured into water and the ppt was filtered off and recrystallised from benzene to give **6** (115 mg), m.p. 160–163°. Recrystallisation from benzene gave **6**, m.p. 161–163°, which was identical with the sample prepared by the alkylation[11] (mixed m.p. and IR spectra).

Reaction of **1b** *with phenylhydrazine*

Formation of **9**. A soln of **1b** (326 mg) and phenylhydrazine (216 mg) in BuOH (10 ml) was refluxed for 7 hr under a stream of N_2. The mixture was evaporated *in vacuo* and the residue was chromatographed over silicic acid column. A fraction eluted with benzene–hexane (1:2) gave a red semisolid (108 mg), which was recrystallised from hexane to give **9**, m.p. 123–124·5°, as red crystals. The sodium fusion test revealed the presence of S in the red crystal; Mass: *m/e* (relative abundance %); 269 (M + 2, 12), 267 (M^+, 100), 238 (13), 234 (26), 190 (12), 175 (15), 162 (13), 128 (13), 118 (12). The next fraction eluted with benzene–hexane gave 7 (110 mg), which was identical with the authentic sample in TLC and NMR spectra. The same red crystals (**9**) were also obtained by the above reaction when ten fold phenylhydrazine was used.

Reaction of **1b** *with aniline*

A mixture of **1b** (815 mg) in aniline (10 ml) was refluxed for 3·5 hr under a stream of N_2. The mixture became reddish orange. Excess of aniline was evaporated *in vacuo*. The residue was dissolved in benzene and extracted with 5% HCl. The benzene soln was washed with H_2O, dried and evaporated to leave an orange oil (440 mg), which was crystallised from benzene to give **7** (100 mg). Recrystallisation from the same solvent gave **7**, m.p. 179–182°, which showed no depression on mixed m.p. with an authentic sample. The aqueous layer was basified under cooling and extracted with benzene. The benzene extracts were evaporated *in vacuo* to leave a trace of red oil.

A reaction of **1b** with aniline in BuOH gave a mixture of unidentified products in addition to a small amount of **7** and **8** which were detected by TLC.

Autoxidation of **2g**

Formation of 2-(*2-hydroxyethylimino*)-1-*methyl*-3-*oxo-indoline* (**19**). A suspension of **2g**·HCl (1·09 g) in CH_2Cl_2 was neutralised with $NaHCO_3$ and the CH_2Cl_2 soln was washed with H_2O and dried over K_2CO_3 for 24 hr. The CH_2Cl_2 soln was evaporated to leave a dark red solid (230 mg). Recrystallisation from benzene–hexane gave **19**, m.p. 98–99°, as orange-red crystals. (Found: C, 64·76; H, 5·84; N, 13·72. $C_{11}H_{12}N_2O_2$ requires: C, 64·69; H, 5·84; N, 13·72%); Mass *m/e* (relative abundance %); 204 (M^+, 44), 186 (M—H_2O, 96), 173 (M—CH_2OH,100), 161 (18), 158 (15), 146 (28), 145 (20), 132 (99), 117 (26), 105 (55), 104 (56), 77 (44). When **19** was mixed with alumina and eluted with benzene–CH_2Cl_2, **19** was hydrolysed to 1-methylisatin, which was identical with an authentic sample by mixed m.p. and IR spectra.

2-(*2-Chloroethylamino*)-1-*methylindole* (**20**). A mixture of **2g**·HCl (4·8 g) and $POCl_3$ (130 ml) was refluxed for 2 hr. The mixture was evaporated *in vacuo* to leave a brown semisolid which was crystallised on the addition of benzene. One recrystallisation from EtOH–Et_2O afforded **20**·HCl (3·96 g, 75·8%), m.p. 170–205°. Further recrystallisation from benzene–EtOH gave an analytical sample of **20**·HCl, m.p. 220–221° (dec), as colourless crystals. (Found: C, 53·99; H, 5·72; N, 11·50; Cl, 28·79. $C_{11}H_{19}N_2Cl$·HCl requires: C, 53·99; H, 5·75; N, 11·42; Cl, 28·93%); UV λ_{max}^{EtOH} mμ (ε); 247 (7,100), 266 (11,900), 280^{sh} (8,000); IR ν_{max}^{KBr} 1665 cm^{-1} (C=N); NMR (ppm from TMS in CF_3COOH); 3·63 (s, 3H, NMe), 3·91 (m, 4H, —CH_2CH_2—),

4·25 (s, 3-CH_2), 8·22 (s, 1H, NH); Mass *m/e* (relative abundance %); 210 (M + 2, 10), 208 (M^+, 24), 159 (M—CH_2Cl, 56), 146 (44), 131 (64), 118 (100), 91 (40).

Autoxidation of **20**

Formation of 2-(2-*chloroethylamino*)-1-*methyl*-3-*oxo-indoline* (**21**). When **20**·HCl (1·0 g) was treated as in the case of **2g**, a dark red solid (760 mg) was obtained. Recrystallisation from benzene–hexane gave **21**, m.p. 111–112°, as red crystals; IR ν_{max}^{KBr} 1710 (C=O), 1650 (C=N), 1610, 1480, 748 cm^{-1} (indole ring); UV λ_{max}^{EtOH} mμ (ε); 232 (28,000), 257 (28,500), 263 (28,700), 300^{sh} (3,000), 477 (1,500). Mass *m/e* (relative abundance %); 224 (M + 2, 4), 222 (M^+, 11), 187 (M—Cl, 100), 173 (M—CH_2Cl, 12), 160 (46), 132 (32), 105 (40), 104 (49), 77 (45).

Autoxidation of **2h**

To a suspension of **2h**·HBr (134 mg) in dichloroethane (10 ml) triethylamine (0·5 ml) was added under an atmosphere of O_2. About 12·6 ml of O_2 (*ca* 1 mole) was absorbed during 20 min. The soln was evaporated *in vacuo* to leave a dark red oil (crude **22a**), whose UV spectrum showed λ_{max} 233, 258, 264, 301^{sh}, and 470 mμ, but it could not be crystallised. A trial to purify **22a** as a hydrobromide resulted in the formation of 1-methylisatin (61 mg, 76% based on **2h**·HBr), whose IR spectrum was identical with that of an authentic specimen; mixed m.p. gave no depression.

Autoxidation of **2i**

When **2i**·HBr (134 mg) was treated as in the case of **2h**·HBr, about 10 ml of O_2 was absorbed during 1·5 hr. The mixture was evaporated to leave a dark red oil which showed the same UV spectrum as that of **22a**. The crude oil was hydrolysed with EtOH–HCl to give 1-methylisatin (40 mg, 56%).

A suspension of **2h**·HBr or **2i**·HBr (20 mg each) in $CDCl_3$ (0·3 ml) was basified with 10% NaOH and the $CDCl_3$ layer was dried over K_2CO_3. The IR spectral change of the $CDCl_3$ soln was followed during 24 hr. A band at 1665 cm^{-1} due to $\nu_{C=N}$ of **2h** or **2i** was at first the only absorption between 1650 and 1750 cm^{-1}, but after 6 hr a small new band appeared at 1710 cm^{-1} due to $\nu_{C=O}$ of **22**. After 24 hr the intensity of the band at 1710 cm^{-1} was increased and another band at 1650 cm^{-1} due to $\nu_{C=N}$ in **22** was also observed.

Autoxidation of **2b**

To a soln of **2b**·HBr (142 mg) in dichloroethane (10 ml) triethylamine (0·6 ml) was added under O_2. About one mole of O_2 was absorbed during 24 hr. The soln was evaporated *in vacuo* to leave a dark purple solid (230 mg), which showed λ_{max}^{EtOH} 262, 267, 280^{sh}, and 522 mμ. The residue was extracted with CH_2Cl_2 and washed with H_2O. The CH_2Cl_2 extracts were evaporated to leave a residue (IR ν_{max} cm^{-1}; 1720 (C=O), 1570 (C=N, conj.)), which was hydrolysed by refluxing with EtOH–HCl for 3 hr. The solvent was evaporated and the residue (117 mg) was chromatographed on a thick layer plate. Isatin (28 mg, 46·7%) and piperidine HCl (27 mg) were isolated and identified with authentic samples, respectively.

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