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2-ETHOXY AND 2-ETHYLTHIOINDOLES. AUTOXIDATION AND NUCLEOPHILIC SUBSTITUTIONS[1]

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Abstract—2-Ethoxy-3-methyl-(**7**) and 2-ethoxy-1,3-dimethyl-(**11**) and 2-ethoxy-1,3,3-trimethyl-3H-indole (**14**) hydrofluoroborates have been prepared by a reaction of the corresponding oxindoles with Meerwein reagent. 2-Ethoxy-3-methylindole obtained upon basification of its fluoroboric acid salt (**17**) is unstable and autoxidizes to 2-ethoxy-3-methyl-3-hydroxy-3H-indole (**9**). 2-Ethylthioindole and 2-ethylthio-3-methylindole (**18**) have been prepared; **18** is stable enough to be isolated, but undergoes similar autoxidation in hexane or cyclohexane to afford quantitatively the hydroxy derivatives **19** and the sulfoxide **20** in 1:1 ratio.

The acid catalyzed hydrolysis of 2-ethoxy and 2-ethylthioindoles and nucleophilic displacement reactions of these compounds with amines have been studied.

PREVIOUS work[2] has shown that 3-methyl-2-piperidino-3H-indole hydrobromide (**2**) prepared by the catalytic hydrogenation of (3-methyl-2-indolyl)pyridinium bromide (**1**) autoxidized to **4** upon basification and the free base of **3** could not be isolated in the usual manner. In the present investigation a similar type of autoxidation was found in 2-ethoxy and 2-ethylthio-3-methylindoles.

2-Ethoxyindole (**5**) has been prepared from oxindole and triethyloxonium fluoborate (Meerwein reagent)[3, 4] and the indole-indolenine tautomerism was observed in its chloroform solution. When 3-methyloxindole was treated with Meerwein reagent under similar conditions, a compound **9**, m.p. 112–113·5°, was obtained. The structure of the compound was assigned as 2-ethoxy-3-hydroxy-3-methyl-3H-indole (**9**) instead of the expected **8** by means of spectroscopic studies as well as elemental analysis. The UV spectrum (λ_{max}^{EtOH} 262 mμ (ε, 5260)) shows an indolenine chromophore and the IR spectrum in chloroform solution exhibits the presence of an OH group (3580, 3400 cm^{-1}) and a conjugated C=N double bond (1590 cm^{-1}). The NMR spectrum in deuterochloroform shows a singlet for 3-Me at 1·58 ppm, a triplet and a multiplet for OEt group at 1·41 and 4·38 ppm. The mass spectrum shows an intense molecular ion peak at *m/e* 191 and main fragmentations are shown in Chart 2.

The structure of **9** was further confirmed by its hydrolysis to a known dioxindole **29**. The intermediate, fluoboric acid salt **7**, was isolated from the reaction mixture as colorless crystals, m.p. 130–131°, and its IR and NMR spectra (Experimental) show the presence of an H at 3-position and no OH group. The conversion of **7** to the hydroxylated compound **9** occurred during neutralization with 5N K_2CO_3 and extraction with a solvent. The NMR spectrum taken immediately after addition of a base exhibits the presence of the free base as an equilibrium mixture of **8a** and **8b**.

1,3-Dimethyloxindole **10** was treated with the Meerwein reagent to give the BF_4 salt **11**, m.p. 116–117°, which, upon basification, however, gave a stable free base **12**, b.p. 124–125°/2 mm. 1,3,3-Trimethyloxindole also gave the corresponding 2-ethoxyindolenine **14** on treatment with Meerwein reagent. On the other hand 2-ethoxyindole (**5**) has been reported to be autoxidized to indirubin upon long exposure to air.[5]

CHART 1

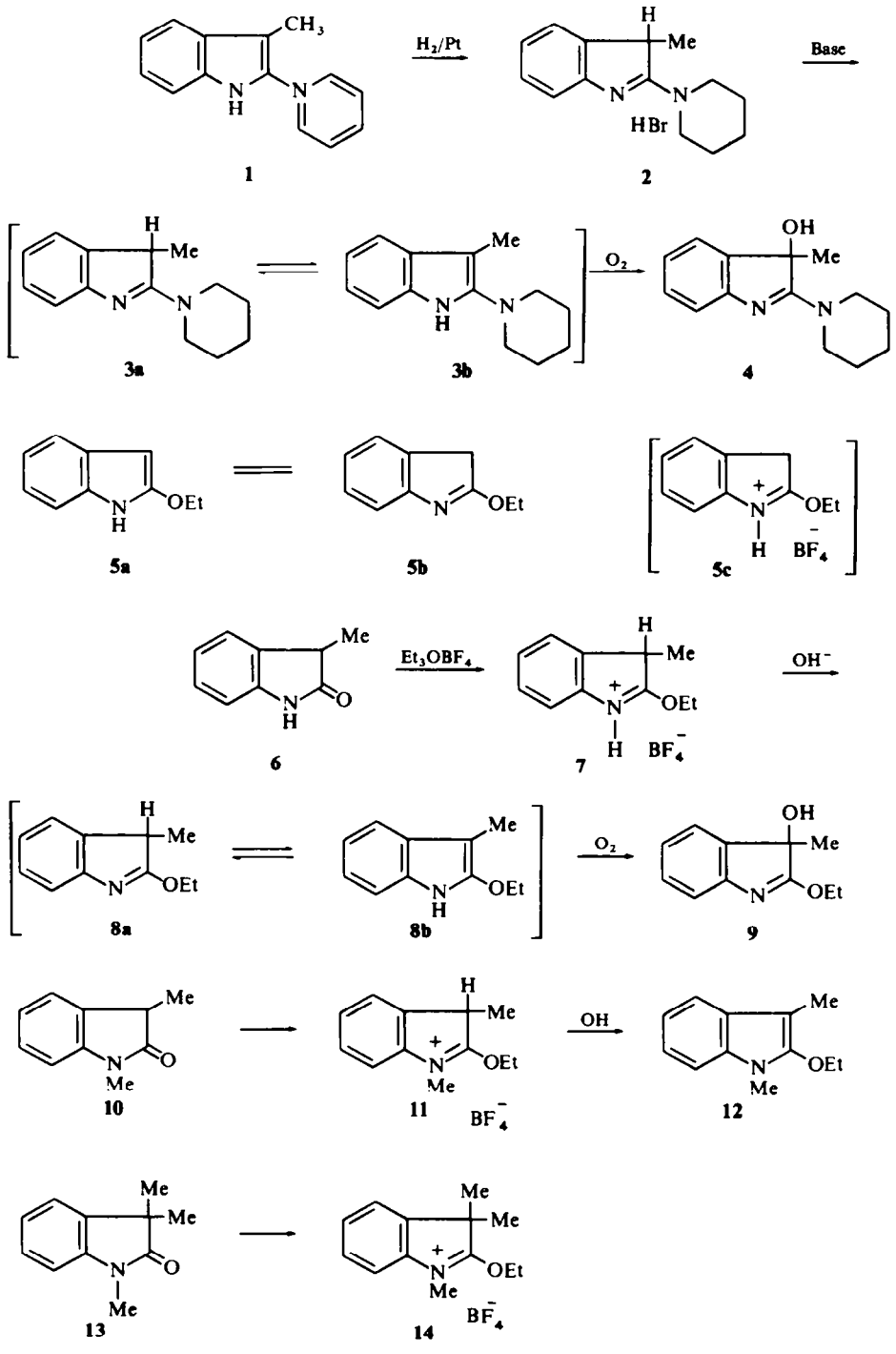

CH3
H2/Pt
H
Me
Base
HBr
1
2
3a
3b
O2
OH
4
OEt
5a
5b
5c
BF4
Et3OBF4
OH−
6
7
8a
8b
9
10
11
12
13
14
OH

CHART 2

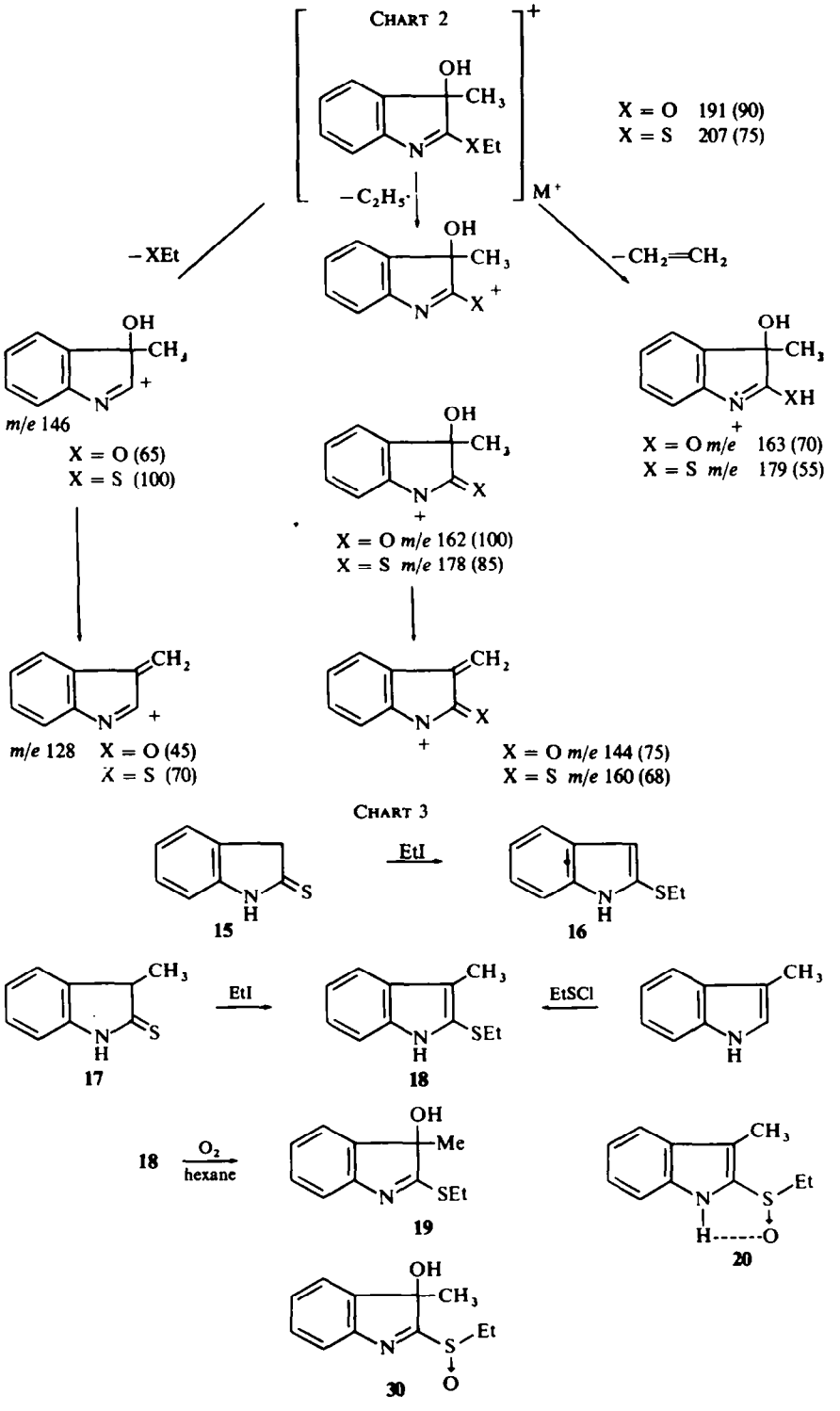


CHART 3

These results indicate that the presence of an NH and an alkyl substituent such as a Me group at 3-position of indole are essential for the rapid autoxidation of 2-ethoxyindoles to the corresponding 3-hydroxyindolenines.

Next the 2-ethylthioindoles, in which the O atom is replaced by S, were prepared. 2-Indolinethione[6] (**15**) gave 2-ethylthioindole (**16**) quantitatively by the reaction with ethyl iodide and potassium carbonate. 2-Ethylthio-3-methylindole (**18**) m.p. 33–33·5° was obtained under similar conditions. An alternate synthesis of **18** was via the reaction of skatole with ethanesulfenyl chloride.[7]

In contrast with 2-ethoxyindole, spectroscopic studies (NMR, UV) show that **16** and **18** are present in the indolic form in solvents such as chloroform and ethanol. 2-Ethylthioindole (**16**) was fairly stable towards autoxidation. 2-Ethylthio-3-methylindole (**18**) could be purified by column chromatography over silica gel or recrystallized from light petroleum. Repeated crystallizations from light petroleum or hexane raised the m.p. to 71–72°, whose NMR spectrum shows two new Me peaks in addition to that of **18** and other complicated signals. Moreover, it shows two spots more polar than that of **18**.

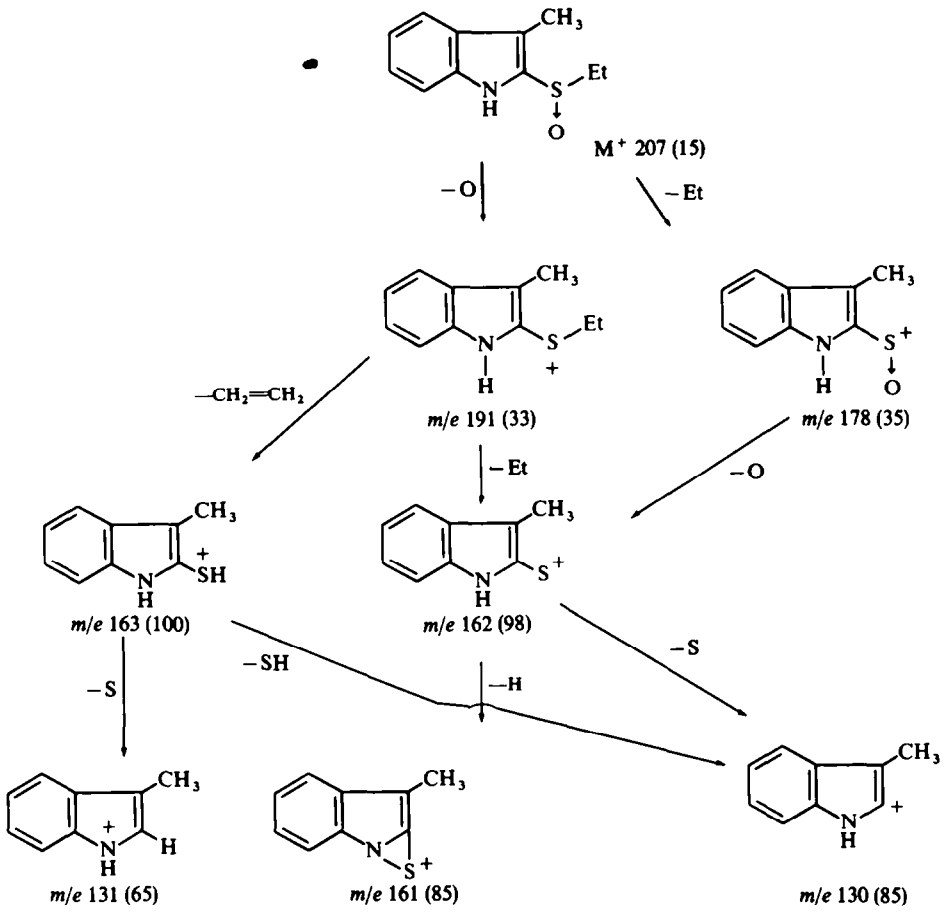
A hexane solution of purified **18** was stirred in an open vessel for 3 days and the resultant colorless crystalline precipitates, were shown to consist of two components (TLC and NMR spectrum). Separation of the crystals on a silica gel column afforded nearly equal amounts of **19**, m.p. 116–117° and **20**,* m.p. 136–137°. The analytical data of **19** and **20**, and their molecular ion peaks at *m/e* 207 corresponded to the formula $C_{11}H_{13}NOS$ with one O atom more than the starting material **18**, therefore, suggesting that **19** and **20** are the oxidation products, presumably formed by reaction with molecular oxygen. Their NMR spectra were compatible with the structures of **19** and **20**, respectively. The NMR spectrum of the first compound **19** eluted in $CDCl_3$ shows a singlet at 1·54 ppm for 3-Me, a triplet centered at 1·42 ppm for the Me in the ethylthio group, a singlet at 2·69 for an OH and a quartet at 3·23 for the methylene in the ethylthio group. In addition, the OH absorption band at 3300 cm^{-1} in the IR spectrum provided further confirmation. The NMR spectrum of the second compound eluted in $CDCl_3$ exhibited a triplet at 1·15 ppm for the Me in the Et group, a singlet at 2·47 ppm for the 3-Me, a multiplet at 3·29 for the methylene adjacent to the S-oxide, and a broad singlet at 11·01 for the H-bonded NH. Furthermore, the strong S—O stretching absorption of **20** appeared at 1005 cm^{-1}. The main fragmentations of the mass spectra of **19** and **20** are shown in Charts 2 and 4.

These results reveal that the S atom at the 2-position of skatole facilitates the hydroxylation at the 3-position such as oxygen and nitrogen, but the rate of oxidation is much slower than that of 2-ethoxy and 2-amino derivatives. The fact that compound **16** is fairly stable and that no sulfoxide was obtained under similar conditions indicates that direct autoxidation of thioether of **16** by molecular oxygen did not take place.

Therefore, it is necessary for 2-ethylthioindoles as well as 2-ethoxyindoles to have an alkyl substituent such as a Me group at 3-position to be autoxidized to the corresponding 3-hydroxy compounds. It is possible that the alkyl group at 3-position and 2-heteroatoms direct as well as facilitate the course of autoxidation.

* After our communication had been published, the compound **20** was prepared by Wieland *et al.*[8] from **18** by oxidation with hydrogen peroxide.

CHART 4



The general features of the oxidation of 2,3-dialkyl-substituted indole derivatives has been investigated.[9-12]* The initial product in many cases was the 3-hydroperoxyindolenine, which could often be isolated. The corresponding ketoamides were produced from hydroperoxides, indicating that oxidative cleavage of the 2–3 bond of indole had occurred. In some cases hydroperoxides rearranged to 2-acylindoles. However, 3-hydroxyindolenine derivatives are usually not obtained as the direct air oxidation product, but can be obtained by a catalytic or sodium borohydride reduction of the 3-hydroperoxyindolenine.

The autoxidation reaction observed in 2-heteroatom substituted indoles is most likely a free radical chain process, and may proceed via the hydroperoxide **23** as outlined in Chart 5. A study of the reaction mechanism is in progress.

The striking catalytic effect of 2-heteroatoms such as N, O and S may be attributed to their ability to induce intramolecular homolytic fission of the hydroperoxide to produce the corresponding 3-hydroxylated compounds.

* The chemiluminescence of indole derivatives is also related to autoxidation.[16]

CHART 5

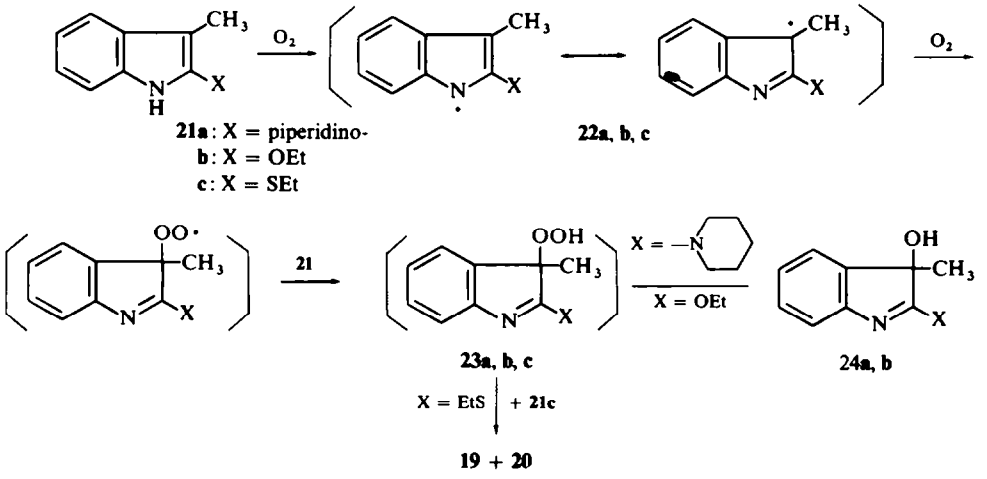
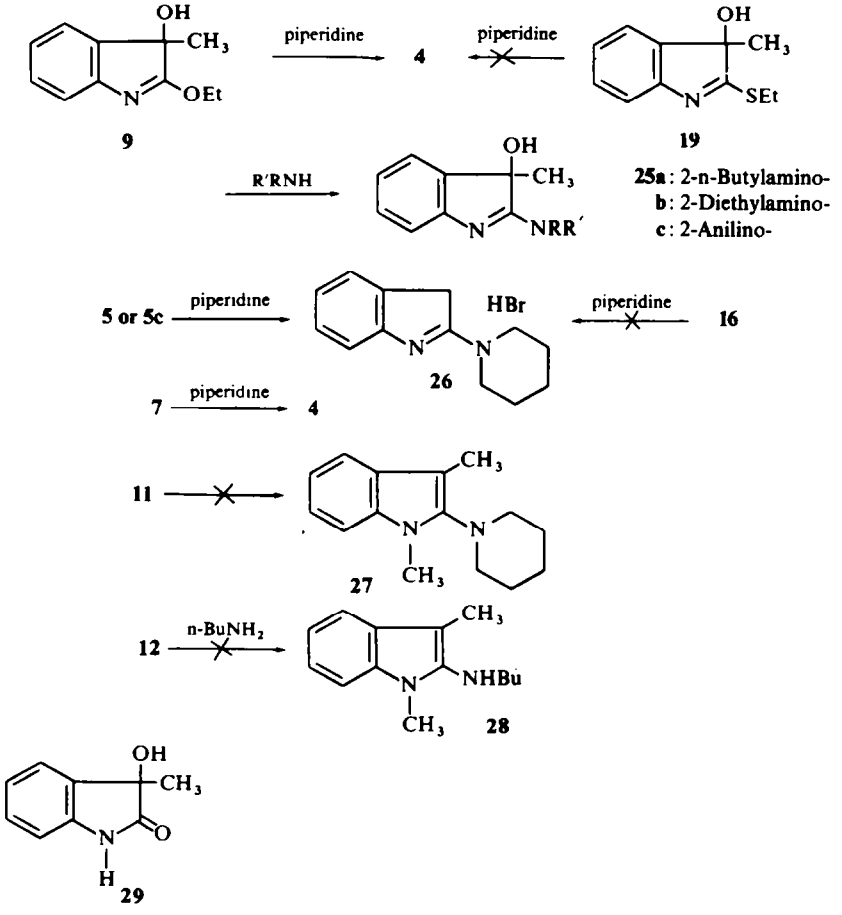


CHART 6



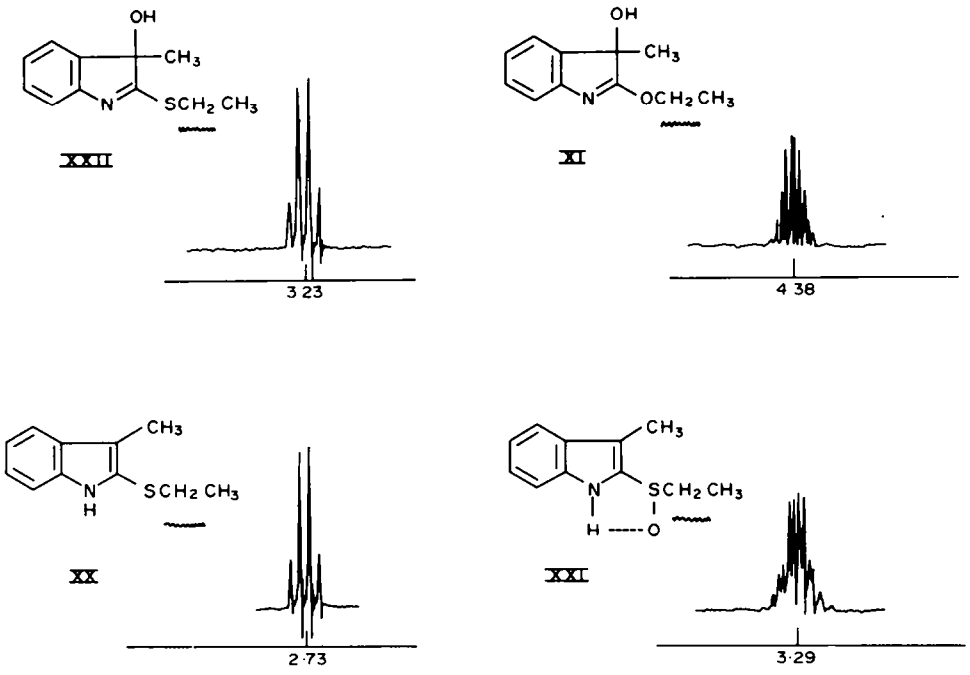


FIG. 1

On the other hand, 3-aminoindoles[13] and an azepinoindole derivative[14] are known to give 2-hydroxylated derivatives, respectively, under similar conditions. In some ibogaine type alkaloids,[15] direct 3-hydroxylated products have been isolated.

It has been shown that hydroperoxides oxidize allylsulfides to the corresponding sulfoxides.[17, 18] Another possible oxidation product of **18**, 3-hydroxy-2-ethylsulfoxy-3-methyl-3H-indole (**30**) which could be formed by the intramolecular oxidation of **23c** has not been isolated.

Further treatment of **19** and **20** in hexane has been attempted, but in each case only the starting material was recovered. The sulfoxide group at 2-position may prevent the further oxidation by forming a strong H-bond with the indole NH, so that the abstraction of hydrogen can not initiate the reaction.

The autoxidation of this type of indole will provide an interesting subject in the biochemical field.[19]

Characteristic features in the NMR spectra of these compounds, show that signals for the methylene adjacent to oxygen of **9** appear as a multiplet at 4·38 ppm, but a simple quartet is seen at 3·23 for the methylene adjacent to sulfur in **19**. This may be due to the non-equivalent methylene in **9** by the restricted rotation between C—O bond caused by two substituents at 3-position. The steric interaction of substituents at 3-position to C—S bond in **19** diminished, due to the bulky S atom and the methylene in **19** became equivalent protons. The methylene adjacent to sulfoxide in **20** shows multiplet signals because of the asymmetric center, while the methylene in **18** shows a simple quartet. These features are shown in Fig 1.

The general conditions most useful for the preparation of 3-hydroxy-2-aminoindoles from 2-ethoxyindole derivative **9** consist in refluxing a mixture of **9** and excess amines without solvent for several hours under a stream of nitrogen. The reaction of **9** with piperidine gave **4** which was identical with the specimen obtained by the previous method.[2] The reaction of **9** with other amines such as diethyl amine, buthylamine, and aniline provided the corresponding 2-amino derivatives, respectively. Remarkable differences between O and S was observed in the reaction of **19** with piperidine. The compound **19** did not give the piperidino derivative under similar conditions. Similarly 2-ethoxyindole **5** or its BF_4 salt **5c** furnished the corresponding 2-aminoindoles **26**, isolated as the hydrobromide, when refluxed with excess piperidine, while 2-ethylthioindole **16** did not react. Under an atmosphere of nitrogen **7** was converted into **4** on refluxing with piperidine. However, N-methylated derivative **11** did not react with piperidine, but gave the free base **12** and **12** was also recovered unchanged after refluxing with n-butylamine. Neither of the compounds **18** and **20** reacted with piperidine.

This means that the reaction of 2-heteroatom substituted indoles **21** with amines is likely to occur in compounds which form indole-indolenine structures under the reaction conditions. However, a compound like **19** having the indolenine structure is an exception, indicating that there are other factors to influence the reaction beside an indole-indolenine tautomerism.

The compound **4** having an amidine moiety, was stable towards nucleoohilic reagents such as ethoxide or ethyl mercaptide, but very susceptible to base catalyzed hydrolysis. When 2-ethoxy-3-methyl-3-hydroxyindolenine (**9**) having an iminoether moiety was treated with excess ethylmercaptan, only an acid catalyzed hydrolysis product, 3-methyldioxindole (**29**), was formed and 2-ethyl thioindole derivative **19** was not produced. Refluxing **11** with excess EtSH also did not give the corresponding 2-ethylthio-1,3-dimethylindole.

Acid hydrolysis of these compounds have also been examined. The hydroxyindolenine **9** and **19** were easily hydrolyzed to the 3-methyldioxindole **29** by treatment with ethanolic hydrochloric acid, while the compound **4** resisted acid hydrolysis even on refluxing with conc hydrochloric acid. 3-Methyl-2-ethoxy-3H-indole (**8**) was very susceptible towards acid and base catalyzed hydrolysis. Refluxing **18** and **20** with ethanolic hydrochloric acid furnished the hydrolyzed product **6**. Further extension of these studies is under investigation.

EXPERIMENTAL

M.ps and b.ps are uncorrected. IR spectra were recorded on JASCO-DS-301 model and JASCO-IR-S-II model spectrophotometers. UV spectra were recorded in 95% EtOH soln unless otherwise specified, on a Cary Model 14 or Perkin–Elmer 202 spectrometers. NMR spectra were determined in $CDCl_3$ with a Varian HR-100 spectrometer with TMS as internal standard. The chemical shifts were expressed by the δ-value in ppm. Gas chromatography was performed with a Hitachi F6D instrument, using XE-60 column.

2-Ethoxy-3-methyl-3H-indolenine HBF_4 *salt* (**7**)

A soln of 2·5 g (0·017 mole) 3-methyloxindole and 2·8 g (0·017 mole) triethyloxonium fluoborate (Meerwein reagent[20]) in 15 ml of CH_2Cl_2 was refluxed for 24 hr. Evaporation of CH_2Cl_2 gave a solid, to which 10 ml dry benzene was added and left for 20 hr. The benzene layer was decanted to leave 2·9 g (65%) pale yellowish solid, m.p. 95–100°, 1 g of which was recrystallized 3 times from CH_2Cl_2–benzene to give 700 mg colorless needles, m.p. 126–128°. Further recrystallizations from this solvent gave m.p. 130–131°; UV λ_{max} mμ (ε) 276 (5300), 228 (19,240), λ_{min} 250 (3590); IR ν_{max}^{nujol} cm^{-1} 1640 ($C{=}\overset{+}{N}$), 1080, 1000 (BF_4^-, C-··O--C); NMR, 1·59

(t, CH_3 in Et), 1·63 (d, CH_3), 4·19 (q, CH at 3-position), 4·84 (q, CH_2 in Et), 10·00 (s, NH). (Found: C, 49·97; H, 5·32; N, 5·63. $C_{11}H_4NOBF_4$ requires: C, 50·22; H, 5·36; N, 5·33%). When neutralized with a base, **7** was converted into **9**.

2-Ethoxy-3-hydroxy-3-methyl-3H-indole (**9**)

A mixture of 7·4 g (0·05 mole) 3-methyloxindole and 8·2 g (0·05 mole) triethyloxonium fluoborate in 150 ml anhyd CH_2Cl_2 was refluxed for 15 hr and the solvent was evaporated to dryness to leave a residue, to which benzene was added and left overnight. Decantation of benzene gave a solid, which was neutralized with 5N K_2CO_3 at 0° and extracted with CH_2Cl_2, washed, and dried. The crystalline solid (5·85 g, 66·8%) obtained on evaporation of the solvent, was recrystallized from hexane–benzene to give colorless needles, m.p. 112–113·5°, UV λ_{max} mμ (ε) 262 (5300), 275 (3700), 295 (2100), IR ν_{max} ($CHCl_3$) cm^{-1} 3580, 3400 (OH), 1590 (C=N); NMR, 1·41 (t, CH_3 in Et), 1·58 (s, CH_3 at 3-position), 4·38 (m, OCH_2); mass, 191 M^+, see Chart 2. (Found: C, 69·20; H, 6·55; N, 7·54. $C_{11}H_{13}NO_2$ requires: C, 69·09; H, 6·85; N, 7·33%). The above benzene layer was evaporated to dryness to leave 3·32 g residue which was dissolved in 50 ml dry CH_2Cl_2 and refluxed for another 15 hr. The mixture was diluted with CH_2Cl_2 and neutralized with $NaHCO_3$ aq at 0°. The extracts were washed, dried, and evaporated to give 2·17 g residue, which was column chromatographed on 25 g silica gel prepared in hexane–benzene (1 : 1). The elution with benzene furnished 1·44 g solid, which on crystallization from EtOH gave pale yellow needles of **6**, m.p. 115–118°. Its IR, UV, and NMR spectral data were identical with those of an authentic specimen. The elution with CH_2Cl_2–CH_3CO_2Et gave 445 mg solid, which was recrystallized from acetone to give colorless needles of **29**, m.p. 156–158° (lit.[21] m.p. 161·5–162·5°). It was shown to be identical on TLC, and by comparison of its UV, IR, NMR, and mass spectra with the product prepared by the reaction of isatin with MeMgI.

2-Ethoxy-1,3-dimethyl-3H-indole HBF_4 *salt* (**11**)

A soln of 2 g (0·012 mole) 1,3-dimethyloxindole and 2·2 g (0·013 mole) $Et_3\overset{\oplus}{O}\overset{\ominus}{BF_4}$ in 10 ml anhyd CH_2Cl_2 was refluxed for 15 hr. The oily residue, after evaporation of CH_2Cl_2, was covered with dry benzene and left for 48 hr at 4–5°. The crystals were collected, 3·5 g, m.p. 100–102°. Further recrystallizations from CH_2Cl_2-benzene gave an analytical sample as colorless pillars, m.p. 116–117; UV λ_{max} mμ (ε) 292 (6460), 283 (7250), 228 (30,000); λ_{min} 250 (2650); IR ν_{max}^{nujol} cm^{-1} 1630 ($C=\overset{+}{N}$), 1000–1100 (BF_4^-, C—O—C); NMR, 1·64 (t, CH_3 in Et), 1·68 (d, CH_3 at 3-position), 3·61 (s, CH_3N), 4·66 (d, CH at 3-position), 5·01 (q, OCH_2), 7·26–7·41 (aromatic protons). (Found: C, 51·82; H, 5·77; N, 5·04. $C_{12}H_{16}NOBF_4$ requires: C, 52·01; H, 5·82; N, 5·06%). On treatment with an alkali, **11** readily decomposes to **12**.

1,3-*Dimethyl-2-ethoxyindole* (**12**)

A soln of 6·44 g (0·04 mole) 1,3-dimethyloxindole and 7·3 g (0·044 mole) Meerwein reagent in 10 ml anhyd CH_2Cl_2 was refluxed for 15 hr. The mixture was diluted with CH_2Cl_2 and neutralized with 5N K_2CO_3. The organic layer was washed, dried, and evaporated to leave 6·6 g residue, which was shown to consist of 1,3-dimethyl-2-ethoxyindole and unreacted **10** in 1 : 1 ratio by gas chromatography. The residue 6·6 g was chromatographed on 40 g silica gel prepared in hexane–benzene (1 : 1). The elution with hexane–benzene (1 : 1) provided 3·3 g oil which on distillation gave 3 g of **12** as a colorless liquid, b.p. 124–125°/2 mm; UV λ_{max} mμ (ε), 292 (7200), 284 (8120), 228 (34,000); λ_{min} 251 (2570); NMR, 1·30 (t, CH_3 in Et), 2·16 (s, CH_3 at 3-position), 3·4 (s, NMe), 4·05 (q, OCH_2), 7·05–7·42 (aromatic proton); mass, *m/e* (relative abundance) 189 (75, M^+), 174 (35, M—CH_3), 161 (90, M—CH_2=CH_2), 160 (100, M—Et). (Found: C, 75·88; H, 7·66; N, 7·20. $C_{12}H_{15}NO$: requires: C, 76·15; H, 7·99; N, 7·40%). The elution with CH_2Cl_2 gave 2·53 g unreacted **10** which was identified with its IR and UV spectra as well as gas chromatography and TLC.

2-Ethoxy-1,3,3-trimethyl-3H-indole HBF_4 *salt* **14**

A soln of 1·8 g (0·01 mole) 1,3,3-trimethyloxindole and 1·7 g (0·01 mole) $Et_3\overset{\oplus}{O}\overset{\ominus}{BF_4}$ in 10 ml anhyd CH_2Cl_2 was refluxed for 20 hr. The solvent was evaporated to leave a red oily substance, to which dry benzene was added to obtain a crystalline solid, 2·05 g (70%), m.p. 80–90°. Recrystallizations from CH_2Cl_2–benzene gave m.p. 133–134° (dec); IR ν_{max}^{nujol} cm^{-1} 1625, 1610, 1600 ($C=\overset{+}{N}$), 1100–1000 (BF_4^-, C—O—C); NMR, 1·67 (t, CH_3 in Et), 1·79 (s, CH_3), 3·70 (s, CH_3N), 5·17 (q, OCH_2). (Found: C, 53·22; H, 6·06; N, 4·93. $C_{13}H_{18}NOBF_4$ requires: C, 53·64; H, 6·23; N, 4·81%). When treated with H_2O or an alkali, **14** readily decomposes to **13**. Its UV spectrum in EtOH gave only oxindolic absorption.

* IR spectrum taken in KBr tablet showed a strong carbonyl absorption due to decomposition.

2-Ethylthioindole (**16**)

To a mixture of 1 g (0·0067 mole) 2-indolinethione and 2·5 g (0·018 mole) anhyd K_2CO_3 in 20 ml anhyd acetone was added with stirring 3·15 g (0·02 mole) EtI at room temp. The mixture was stirred for 4 hr at room temp and then filtered. The filtrate was evaporated to dryness to leave 1·3 g residue, which was chromatographed on 20 g silica gel prepared in benzene–hexane (1 : 1) to give 1·2 g (*ca* 100%) pale yellowish oil, which solidified upon standing. Recrystallizations from light petroleum gave m.p. 36–37·5°; UV λ_{max} mμ (ε) 298 (6740), 290 (8290), 282 (8030), 218 (20,480); λ_{min} 285 (7890), 253 (2040); IR ν_{max}^{nujol} cm^{-1} 3400 (NH), 750 (o-disubstituted benzene); NMR, 1·26 (t, CH_3 in Et), 2·83 (q, CH_2 in Et), 6·64 (s, β-H), 7·03–7·60 (m, aromatic protons), 7·99 (NH); mass, *m/e* (relative abundance) 177 (100, M^+), 149 (90, $M-C_2H_4$), 148 (95, $M-C_2H_5$), 116 (15, $M-C_2H_5S$). (Found: C, 67·94; H, 6·51; N, 8·04; S, 17·82. $C_{10}H_{11}NS$ requires: C, 67·78; H, 6·26; N, 7·91; S, 18·06%).

2-Ethylthio-3-methylindole (**18**)

(1) To a mixture of 407 mg (0·0025 mole) 3-methyl-2-indolinethione and 690 mg anhyd K_2CO_3 in 10 ml anhyd acetone was added 780 mg (0·005 mole) EtI with stirring at room temp and the stirring was continued for 4 hr under a stream of N_2. The mixture was filtered. The filtrate was evaporated to dryness and chromatographed on 8 g silica gel prepared in hexane–benzene (4 : 1) to give 473 mg (quantitative yield) of **18** as a sole product, a slightly colored oil, which crystallized upon standing. Careful rechromatography on silica gel prepared in light petroleum twice and crystallization from light petroleum gave analytically pure colorless needles, m.p. 33–33·5°; UV λ_{max} mμ (ε) 300 (10,250), 292 (12,230), 285 (11,080), 225 (27,370); λ_{min} 258 (2890); IR $\nu_{max}^{liquid\ film}$ 3420 (NH), 750 (*o*-disubstituted benzene); NMR, 1·21 (t, CH_3 in Et), 2·38 (s, CH_3 at 3-position), 2·73 (q, CH_2 in Et), 7·00–7·55 (m, aromatic protons), 7·87 (s, broad, NH); mass, *m/e* (relative aboundance), 191 (96, M^+), 176 (35, $M-CH_3$), 162 (100, M—Et), 130 (60, M—SEt). (Found: C, 69·06; H, 6·50; N, 7·25. $C_{11}H_{13}NS$ requires: C, 69·06; H, 6·85; N, 7·32%).

(2) To a soln of 54 g (0·412 mole) skatole in 400 ml abs ether was added dropwise 41 g (0·412 mole) freshly prepared C_2H_5SCl[22] in 200 ml dry CH_2Cl_2 at below 0°, and the mixture was stirred for 2 hr at 0°, then stirred for 15 hr at room temp under a stream of N_2. The mixture was diluted with CH_2Cl_2, neutralized with $NaHCO_3$ aq, washed, and dried. The residue, after evaporation of the solvent, was chromatographed on 230 g silica gel prepared in benzene to give 76·7 g (*ca* 100%) of **18**, whose IR, UV, and NMR spectra were identical with those of the specimen prepared by the previous method (**1**). GLC and TLC analysis also confirmed its identity.

Autoxidation of **18**: *Formation of* **19** *and* **20**

A soln of 500 mg (0·0025 mole) of **18** in hexane was stirred for 72 hr in an open air at room temp. The colorless ppts (360 mg) were collected. The mother liquor was stirred for another 24 hr and was evaporated to dryness to give 137 mg residue. The ppts and the residue were column chromatographed on 15 g silica gel prepared in CH_2Cl_2. Elution with this solvent furnished 230 mg crystalline solid, m.p. 85–87° (**19**), which was recrystallized from benzene–light petroleum to give colorless needles, m.p. 116·5–117·5°; UV λ_{max} mμ (ε) 305 (8530), 294 (8680), 284 (7990), 228 (16,240); λ_{min} 247 (3450), 287 (7800), 298 (8200); IR ν_{max}^{chf} cm^{-1} 3400 (OH); ν_{max}^{KBr} cm^{-1} 3300 (OH), 1610, 1500 (phenyl), 1190, 1120, 1095, 1065, 755 (*o*-disubstituted benzene); NMR, 1·42 (t, CH_3 in Et), 1·54 (s, CH_3 at 3-position), 2·69 (s, broad, OH)—this peak disappeared on treatment with D_2O, 3·23 (q, SCH_2); mass, Chart 2. (Found: C, 63·69; H, 6·28; N, 6·58. $C_{11}H_{13}NO$ requires: C, 63·75; H, 6·32; N, 6·76%).

The elution with 5% MeOH in CH_2Cl_2 yielded 243 mg of **20**, which on recrystallization from benzene–light petroleum gave m.p. 136–137°; total yield, 473 mg, 91%; UV λ_{max} mμ (ε) 284 (14,760), 228 (25,580); λ_{min} 253 (2790); IR ν_{max}^{KBr} cm^{-1} 3100 (NH), 1005 (SO), 750 (*o*-disubstituted benzene); NMR, 1·15 (t, CH_3 in Et), 2·47 (s, CH_3 at 3-position), 3·29 (m, $SOCH_2$), 11·01 (s, broad, H-bonded NH); mass, Chart 4. (Found: C, 63·99; H, 6·32; N, 6·80. $C_{11}H_{13}NO$ requires: C, 63·75; H, 6·32; N, 6·80%).

Preparation of 2-amino-3-hydroxyindoles from **9**

(1) *3-Hydroxy-3-methyl-2-piperidino-*3H*-indole* (**4**). A soln of 215 mg (0·011 mole) of **9** in 5 ml piperidine was refluxed for 4 hr and the excess piperidine was evaporated to leave a residue which was crystallized from acetone to give 260 mg, m.p. 204–205° (quantitative yield) of **4**, which was shown to be identical by comparison of its NMR, IR, UV spectra with the product prepared by previous method.[2]

(2) *2-n-Butylamino-3-hydroxy-3-methyl-*3H*-indole* (**25a**). A soln of 525 mg (0·03 mole) of **9** in 5 ml n-butylamine was refluxed for 3 hr. Removal of excess amine left a crystalline residue, 610 mg (93%), m.p. 145–155°.

Recrystallizations from acetone gave colorless needles, m.p. 165–166°; UV λ_{max} mμ (ε) 308 (3450), 283 sh (9070), 274 (10,640), 217 (19,440); λ_{min} 295 (3140), 243 (12,290); IR ν_{max}^{chf} cm^{-1} 3650, 3395 (OH, NH), 1580 (C=N), 1050 (C—O); NMR, 0·93 (t, CH_3), 1·47 (s, broad, CH_3 at 3-position and $—CH_2CH_2—$), 2·55–3·44 (m, CH_2 next to NH), 4·42 (s, broad, NH, OH)—this peak disappeared on treatment with D_2O, 6·82–7·27 (m, aromatic H); mass, *m/e* (relative abundance), 218 (100, M^+), 203 (30, M—CH_3), 200 (70, M—H_2O), 175 (70, M—C_3H_7), 146 (60, M—C_4H_9NH). (Found: C, 71·75; H, 8·46; N, 12·80. $C_{13}H_{18}N_2O$ requires: C, 71·52; H, 8·31; N, 12·84%).

(3) 2-*Diethylamino*-3-*hydroxy*-3-*methyl*-3H-*indole* (**25b**). A soln of 525 mg (0·03 mole) of **9** in 5 ml diethylamine was refluxed for 46 hr. The excess amine was distilled and the residue was crystallized from acetone to give 275 mg (42%), m.p. 110–124°. Recrystallizations from acetone gave m.p. 137–138·5°; UV λ_{max} mμ (ε) 320 (2100), 290 (5800), 278 (6560), 267 (5700), 215 (25,680); λ_{min} 245 (3300); IR ν_{max}^{chf} cm^{-1} 3590, 3380 (OH), 1590, 1560 (C=N), 1100, 1057, 1025 (C—O); NMR, 1·19 (t, CH), 1·60 (s, CH_3 at 3-position), 3·42, 3·52, 3·59 (m, 5H, OH and CH_2 in Et_2N), 6·75–7·27 (m, aromatic proton); mass, *m/e* (relative abundance), 218 (100, M^+), 203 (20, M—CH_3), 201 (25, M—H_2O), 189 (70, M—C_2H_5), 146 (70, M—$C_4H_{10}N$). (Found: C, 71·54; H, 8·18; N, 12·52. $C_{13}H_{18}N_2O$ requires: C, 71·52; H, 8·31; N, 12·84%).

(4) 2-*Anilino*-3-*hydroxy*-3-*methyl*-3H-*indole* (**25c**). A soln of 515 mg (0·03 mole) of **9** in 5 ml anhyd aniline was heated at 120° for 7 hr under a stream of N_2 and a mixture of benzene–hexane was added to obtain 260 mg (36·4%), m.p. 202–204·5°, of crystalline solid. Recrystallizations from acetone gave an analysis sample, m.p. 205·5–206·5° colorless prisms; UV λ_{max} mμ (ε) 315 (12,100), 293 (12,840), 283 (13,170); $\lambda_{max}^{EtOH—HCl}$ mμ (ε) 298 (8·630), 274 (8280), 218 (17,500); λ_{min} 287 (7460), 250 (5070), 205 (15,000); IR ν_{max}^{KBr} cm^{-1} 3300, 3050 (OH, NH), 1675 (C=N), 1618, 1595 (phenyl), 1197, 1142, 1102 (C—O); NMR, 1·68 (s, CH_3 at 3-position), 4·28 (s, broad, OH or NH), 6·97–7·36 (m, aromatic proton); mass, *m/e* (relative abundance) 238 (100, M^+), 223 (30, M—CH_3), 135 (80, M—$C_6H_5N{\equiv}C$), 146 (30, M—C_6H_5NH). (Found: C, 75·59; H, 6·31; N, 11·64. $C_{15}H_{14}N_2O$ requires: C, 75·60; H, 5·92; N, 11·76%). Compound **12** was refluxed in n-butylamine for 28 hr and recovered unchanged; **19** and **18** did not react with piperidine at refluxing temp.

Reaction of **7** *with piperidine*

Formation of **4**. A mixture of 500 mg (0·002 mole) of **7** and 5 ml anhyd piperidine was heated at 100–110° for 2 hr. The residue obtained on evaporation of excess piperidine was left overnight and then ether was added. The ethereal layer was concentrated to obtain 86 mg of **4**, m.p. 204–205°. The mother liquor was evaporated to dryness to give 240 mg oil which was crystallized from acetone to give 150 mg colorless needles, m.p. 205–206°, m.m.p. 205–206° with an authentic specimen. IR and UV spectra were identical with those of the specimen.

1,3-Dimethyloxindole **10** was obtained when the salt **11** was refluxed in piperidine and the corresponding 2-piperidino derivative was not obtained.

2-*Piperidino*-3H-*indole hydrobromide* (**26**)

(1) A soln of 1 g (0·0062 mole) 2-ethoxyindole in 5 ml piperidine was refluxed for 30 hr under a stream of N_2. The residue, after evaporation of piperidine, was dissolved in EtOH and saturated with HBr gas. Addition of ether to this soln afforded 1·4 g (80%) needles, m.p. 260–263°. Recrystallizations from EtOH gave colorless needles, m.p. 269–270°; UV λ_{max} mμ (ε) 272 (13,400), 212 (16,500); λ_{min} 235 (2300); IR ν_{max}^{KBr} cm^{-1} 1670 (C=N), 775 (*o*-disubstituted benzene); 3410, 1105, 1015 due to crystalline EtOH; NMR, 1·25 (t, 3H, CH_3 due to crystalline EtOH), 1·77 (s, broad, 6H, β,γ-methylenes in piperidine), 4·07, 4·19 (m, 4H, α-methylene in piperidine), 7·00–7·64 (m, aromatic protons), 9·75 (NH); mass, *m/e* (relative abundance) 200 (100, M^+), 199 (70, M—1), 172 (50, M—$CH_2{=}CH_2$), 116 (40, M—$C_5H_{10}N$). (Found: C, 55·31; H, 6·88; N, 8·67. $C_{13}H_{16}N_2{\cdot}C_2H_5OH{\cdot}HBr$ requires: C, 55·05; H, 7·08; N, 8·56%).

(2) A mixture of 500 mg (0·002 mole) of **5c** and 5 ml piperidine was refluxed for 3·5 hr. The residue obtained on evaporation of piperidine was dissolved in CH_2Cl_2 and washed with water, and dried. Removal of CH_2Cl_2 left a residue which was dissolved in EtOH–ether and saturated with HBr gas to give 430 mg crystals, m.p. 220–230°. Recrystallization from EtOH gave 300 mg colorless needles, m.p. 262–264°, whose IR, UV, and NMR spectra were identical with those of the sample made by the previous method (1) and a m.m.p. gave no depression.

In contrast with **5**, **16** was recovered unchanged after 20 hr refluxing in piperidine.

Acid hydrolysis of **9** *to* **29**

A soln of 350 mg (0·002 mole) of **9** in 5 ml EtOH containing 0·5 ml 10% HCl was stirred for 1 hr. The

reaction was followed by its UV spectral change to oxindole and the disappearance of **9** by gas chromatography. The residue, after removal of EtOH, was dissolved in CH_2Cl_2, washed, dried. Evaporation of the solvant left 270 mg (83%) crystalline solid, m.p. 145–150°. Recrystallization from acetone gave (**29**), m.p. 154–155°. M.m.p. and a comparison of the IR, UV, NMR spectra with an authentic specimen confirmed its identity.

Acid hydrolysis of **12** *to* **10**

A soln of 379 mg (0·002 mole) of **12** in a mixture of 5 ml EtOH containing 0·5 ml 10% HCl was stirred for 4 hr at room temp until the spot of **12** had disappeared on TLC and in the UV spectrum. The solvent was removed and the residue was dissolved in CH_2Cl_2 and neutralized with $NaHCO_3$ aq, washed, and dried. The evaporation of CH_2Cl_2 left 310 mg (96%) crystalline residue, m.p. 25–29°. Recrystallization from light petroleum gave m.p. 45–47°, whose IR and UV, NMR spectra, and its R_f value were identical with those of an authentic sample.

Acid hydrolysis of **5** *to oxindole*

A soln of 170 mg (0·001 mole) 5 in 0·5 ml 10% HCl and 9·5 ml EtOH was refluxed for 8 hr until the UV spectrum confirmed the presence of an oxindole.

The residue obtained on evaporation of EtOH was taken up in CH_2Cl_2 and neutralized with $NaHCO_3$, washed, and dried. Removal of CH_2Cl_2 left 120 mg (90%) crystalline residue, which was recrystallized from benzene–hexane to give colorless needles, m.p. 123–124·5°. A m.m.p. with an authentic sample gave no depression. The IR, UV spectra and ist R_f value were identical with those of an authentic specimen.

Acid hydrolysis of **16** *to oxindole*

A soln of 200 mg (0·001 mole) of **16** in 0·5 ml 10% HCl and 4·5 ml EtOH was refluxed for 11 hr until its UV spectrum showed the presence of oxindole. On working up, a crystalline residue, 130 mg (89%), m.p. 80–83°, was obtained. Recrystallizations from hexane–benzene gave m.p. 123–125° with no depression with an authentic specimen.

Acid hydrolysis of **18** *to* **6**

To a soln of 500 mg (0·002 mole) **18** and 4·5 ml EtOH and 0·5 ml 10% HCl was refluxed for 30 hr until the UV spectrum showed the presence of oxindole. The solvent was removed and the residue was taken up with CH_2Cl_2, neutralized, washed, and dried. The evaporation of the solvent gave 380 mg (99%) crystalline residue, which was shown to be identical to 3-methyloxindole by comparison of IR, UV, NMR spectra and R_f value on alumina TLC and gas chromatography.

Acid hydrolysis of **19** *to* **29**

A soln of 30 mg of **19** in 3 ml HCl–EtOH (1:9) 10% HCl:EtOH) was refluxed for 10 min to complete hydrolysis. On working up, a crystalline residue (20 mg) was obtained, which was shown to be identical to **29** by comparison of IR, UV, NMR spectra and R_f value on TLC.

Acid hydrolysis of **20** *to* **6**

A soln of 50 mg of **20** in 5 ml HCl–EtOH ((1:9) 10% HCl:EtOH) was refluxed for 8 hr to give 3-methyloxindole after working up in usual manner.

Reaction of **9** *with* EtSH

Formation of 3*-methyldioxindole* (**29**). A soln of 500 mg (0·0025 mole) of **9** in freshly distilled EtSH was refluxed for 6 hr while colorless crystals were precipitated—102 mg, m.p. 150–152°. These were identified as **29** by IR, TLC, and a m.m.p. with an authentic sample. The mother liquor was evaporated to dryness to give 450 mg of a mixture of starting material and **29** by TLC and NMR spectrum.

Reaction of **11** *with* EtSH

A mixture of 120 mg (0·43 mole) of **11** and 5 ml EtSH was heated at reflux for 50 hr and excess EtSH was removed. The residue dissolved in CH_2Cl_2 was treated with 5N K_2CO_3, washed with H_2O, dried, and evaporated to give 58 mg (84%) of 1,3-dimethyloxindole. The presence of 1,3-dimethyl-2-ethylthioindole could not be detected by TLC analysis and NMR spectrum. When a soln of **9** in anhyd MeOH was saturated with dry H_2S at room temp and then at boiling temp, **29** was obtained and 3-hydroxy-3-methyl-2-indolinethione was not formed. **9** was not produced after refluxing a soln of **4** in EtOH–EtONa for 72 hr.

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REFERENCES

[1] Part of the work has been published as a communication. T. Hino, M. Nakagawa and S. Akaboshi, *Chem. Commun.* 656 (1967)
[2] T. Hino, M. Nakagawa, T. Wakatsuki, K. Ogawa and S. Yamada, *Tetrahedron* **23**, 1441 (1967)
[3] J. Harley-Mason and T. J. Leeney, *Proc. Chem. Soc.* 368 (1964)
[4] H. Plieninger and H. Bauer, *Angew. Chem.* **73**, 433 (1961)
[5] H. Plieninger, U. Lerch and D. Wild, *Ibid.* **77**, 505 (1965); H. Plieninger and D. Wild, *Chem. Ber.* **99**, 3063 (1966)
[6] T. Hino, K. Yamada and S. Akaboshi, *Chem. & Ind.* 275 (1967); T. Hino, K. Tsuneoka, M. Nakagawa and S. Akaboshi, *Chem. Pharm. Bull.* **17**, 550 (1969)
[7] T. Wieland and D. Grim, *Chem. Ber.* **98**, 1727 (1965)
[8] H. Faulstich, T. Wieland and C. Jochum, *Liebigs Ann.* **713**, 186 (1968)
[9] R. J. S. Beer, L. McGrath, A. Robertson and A. B. Woodier, *Nature, Lond.* **164**, 362 (1949); R. J. S. Beer, L. McGrath and A. Robertson, *J. Chem. Soc.* 2118, 3283 (1950); R. J. S. Beer, T. Broadhurst, A. Robertson, *Ibid.* 4351, 4946 (1952); 2440 (1953); R. J. S. Beer, T. Donavanik and A. Robertson, *Ibid.* 4139 (1954)
[10] B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.* **73**, 2188, 2196 (1951); **74**, 3855 (1952); B. Witkop, J. B. Patrick and M. Rosenblum, *Ibid.* **73**, 2641 (1951)
[11] E. Leete, *Ibid.* **83**, 3645 (1961); F. Y-H. Chen and E. Leete, *Tetrahedron Letters* 2013 (1963)
[12] H. H. Wasserman and M. B. Floyd, *Ibid.* 2009 (1963)
[13] C. W. Bird, *J. Chem. Soc.* 3490 (1965)
[14] J. B. Hester, Jr., *J. Org. Chem.* **32**, 3804 (1967)
[15] G. B. Guise, E. Ritchie and W. C. Taylor, *Austr. J. Chem.* **18**, 1278 (1965); D. W. Thomas and K. Bieman, *Tetrahedron* **24**, 4223 (1968); H. K. Schnos, D. W. Thomas, R. Aksornvitaya, W. R. Schleigh and S. M. Kupchan, *J. Org. Chem.* **33**, 1225 (1968); B. Hwang, J. A. Weisbach, B. Douglas and R. Raffauf, *Ibid.* **34**, 412 (1969)
[16] G. E. Philbrook, J. B. Ayers, J. F. Garst and J. R. Totter, *Photochem. Photobiol.* **4**, 869 (1965); F. McCapra, D. G. Richardson and Y. C. Young, *Ibid.* **4**, 1111 (1965); F. McCapra and Y. C. Young, *Chem. Commun.* 522 (1966)
[17] L. Bateman and F. W. Shipley, *J. Org. Chem.* 1996 (1955)
[18] A. A. Oswald, *Ibid.* **24**, 443 (1959)
[19] T. Hino and M. Nakagawa, *J. Am. Chem. Soc.* **91**, 4598 (1969)
[20] H. Meerwein, E. Battenberg, H. Gold, E. Pfeil and G. Willfang, *J. Prakt. Chem.* **154**, 83 (1939); H. Meerwein, *Org. Syn.* **46**, 120 (1965)
[21] M. Kohn and A. Ostersetzer, *Monatsh.* **32**, 905 (1911); E. Giovannini and J. Rosales, *Helv. Chem. Acta* **46**, 1338 (1963); H. H. Wasserman and M. B. Floyd, *Tetrahedron Letters* 2009 (1963)
[22] R. V. Jardine and R. K. Brown, *Canad. J. Chem.* **43**, 1293 (1965)