2-Ethoxyindoles and 2-Ethylthioindoles: their Autoxidation and Reactions with Piperidine

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3-METHYL-2-PIPERIDINO-3*H*-INDOLE (I; R=H) has been shown to be susceptible to aerial oxidation to afford the 3-hydroxy-compound (I; R=OH).[1] Direct hydroxylation at the 3-position of the indole ring by oxygen had not been observed in other 2,3-disubstituted indole derivatives, where 3-hydroperoxides were isolated as intermediates of the autoxidation and further rearranged to afford 2-acylindole derivatives or keto-amides.[2]

We now find that 2-ethoxy- and 2-ethylthio-3-methylindoles (II; X=O and S) undergo similar autoxidation. When 3-methyloxindole was treated with the Meerwein reagent following Harley-Mason's method[3] for the preparation of 2-ethoxyindole, colourless needles, m.p. 112—113·5°, were obtained. The structure of the compound was proved to be (IV) instead of the expected (II; X=O) by spectral data as well as elemental analysis; $\lambda_{\max}$ (EtOH) [mμ (ϵ)] 262 (5300), 275 (3700), 295 (2100); $\nu_{\max}$ ($CHCl_3$) (cm.$^{-1}$) 3580, 3400 (OH), 1590 (C=N); n.m.r. (p.p.m.) 1·41 (triplet, CH_3 in ethyl group), 1·58 (singlet, CH_3 at 3-position), 4·38 (multiplet, O·CH_2); *m/e* 191 (M^+).

The initial intermediate of the reaction, the HBF$_4$ salt of (II; X=O), m.p. 126—128°, n.m.r. (p.p.m.) 1·63 (doublet), 4·19 (quartet) ($CH_3\cdot CH\cdot$), was isolated in good yield. However, (II; X=O) obtained upon basification of the HBF$_4$ salt was very sensitive to aerial oxidation and was immediately converted into (IV), quantitatively, though the presence of (II; X=O) was confirmed by the n.m.r. spectrum which indicated the indolenine tautomer was predominant.

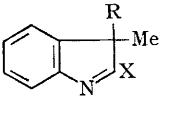
On the other hand, 2-ethoxy-1,3-dimethylindole (V), b.p. 124—125/2 mm. Hg (HBF$_4$ salt, m.p. 116—117°), which was prepared from 1,3-dimethyloxindole with the Meerwein reagent, was stable towards autoxidation. Considering the fact that 2-ethoxyindole prepared by us was fairly stable towards autoxidation, but colourless crystals became discoloured on standing,[4] the ready autoxidation of (II; X=O) might be due to the presence of NH and 3-methyl groups.

2-Ethylthioindole (VI), m.p. 32·5—33·5°, was prepared from indoline-2-thione.[5] In contrast with 2-ethoxyindole,[3] (VI) was present as an indolic form in chloroform solution as in the case of 2-methylthioindole;[5] compound (VI) was fairly stable towards autoxidation.

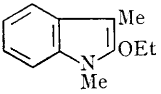
2-Ethylthio-3-methylindole (II; X=S), m.p. 33—33·5°, was obtained from 3-methylindoline-2-thione with ethyl iodide or by the reaction of skatole with ethanesulphenyl chloride,[6] and exhibited an indolic form in chloroform solution. The compound (II; X=S) was stable enough to be purified by column chromatography over silica gel or careful recrystallization from petrol. However, when a hexane solution of (II; X=S) was stirred at room temperature for 24 hr. in an open vessel, colourless crystals separated and were shown to consist of two components by thin-layer chromatography and n.m.r. spectroscopy. Separation of the components on a silica gel column afforded (VII) and (VIII) in nearly equal amounts. The first compound eluted, m.p. 117—117·5°, was (VII), λ_{max} (EtOH) [mμ (ϵ)] 228 (16,200), 284 (8000), 294 (8700), 305 (8500); n.m.r. (p.p.m.) 1·42 (triplet, CH_3 in ethyl group), 1·54 (singlet, CH_3 at 3-position), 2·69 (singlet, broad, OH), 3·23 (quartet, S·CH_2·)·, m/e 207 $(M)^+$.

The second compound eluted, m.p. 136—137° (decomp.), was (VIII), λ_{max} (EtOH) [mμ (ϵ)] 222 (25,600), 284 (14,800); ν_{max} (KBr) (cm.$^{-1}$) 3110 (bonded NH), 1005 (SO); n.m.r. (p.p.m.) 1·15 (triplet, CH_3 in ethyl group), 2·47 (singlet, CH_3 at 3-position), 3·29 (multiplet, SO·CH_2·), 11·01 (singlet, broad, hydrogen-bonded NH); m/e 207 (M^+).

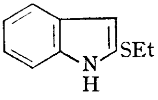
The fact that compound (VI) was fairly stable, and that no sulphoxide was obtained under similar conditions, indicated that direct autoxidation of the thioether of (II; X=S) with air did not take place. Thus a plausible mechanism of autoxidation of these compounds could be that shown in the chart. 3-Hydroperoxides (or hydroperoxy-radicals) of (II) may initially be formed as in the case of 2,3-disubstituted indoles. The hydroperoxide (III; X=O) could not rearrange to afford a 2-acylindole or keto-amide as in the case of 2,3-dialkylindoles due to the presence of the 2-ethoxy-group, but gave the 3-hydroxy-compound (IV). However, the hydroperoxide (III; X=S) may oxidize the thioether of the starting material (II; X=S) to form (VII) and (VIII).[7] These results indicate that the autoxidation of 2,3-disubstituted indoles proceeds *via* the hydroperoxide (or hydroperoxy-radical), but the products may differ due to the nature of the substituent at the 2-position.



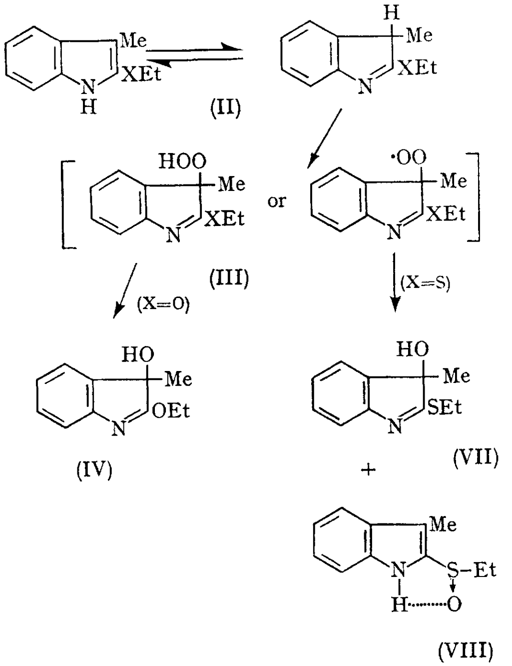
(I) (X=1-piperidino)



(V)



(VI)



When 2-ethoxyindole was heated under reflux with an excess of piperidine under nitrogen, 2-piperidino-3*H*-indole was obtained in good yield and characterised as the hydrobromide, m.p. 265—267°. The compound (VI), however, did not give the piperidino-derivative under the same reaction conditions. Similarly the HBF_4 salt of (II; X=O) reacted with piperidine to afford (I; R=H), but the compounds (II; X=S) and (V) did not react with piperidine under the same conditions. These difference may be explained by the presence of indolenine tautomer in the case of the 2-ethoxy-derivatives. However, the fact that the compound (IV) reacted with piperidine to afford (I; R=OH), but the compound (VII) did not react under the same conditions, indicating the indolenine structure was not the essential factor. Investigation of other properties of these compounds is in progress.

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