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A CONVENIENT SYNTHESIS OF 3-INDOLYLTHIOL AND DERIVATIVES

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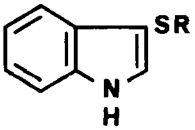
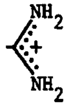
In a recent publication we have described a novel reaction in which the oxidation of thioureas in the presence of pyrroles with halogens gives S[pyrrolyl]isothiuronium salts.[1] In continuation of our studies we have found that the reaction may be extended to the indole series to give S[3-indolyl]isothiuronium salts. Thus, when an aqueous methanolic solution of indole and thiourea was treated with one equivalent of iodine-potassium iodide reagent at room temperature or below, the iodine was rapidly consumed, and concentration of the solvent in vacuo gave S[3-Indolyl]isothiuronium iodide (Ia) as a colourless crystalline solid, m.p. 214-216° dec. in 80-90% yield. The product was characterised by its elemental analysis and nmr spectrum (DMSO-d_6) which showed signals at δ7.1 - 7.8 (multiplet, 4 protons, aromatic CH), δ8.03 (doublet sharpening to singlet on deuteration, 1 proton, α-CH of indole), δ8.7 (Broad signal, 4 exchangeable protons, isothiuronium NH) and δ12.2 (broadened doublet, 1 exchangeable proton, indole NH).

Treatment of (Ia) with aqueous alkali at 80-100°C for 5-10 minutes under nitrogen followed by acidification gave 3-indolylthiol (Ib), pale cream plates, m.p. 100-101°C, in 90-95% yield. The nmr spectrum of the thiol ($CDCl_3$) showed signals at δ2.82 (doublet, 1 exchangeable proton, SH), δ7.05 - 7.35 (multiplet, 4 protons, aromatic CH), and δ7.55 - 8.25 (multiplet, 2 protons, 1 exchangeable, α-CH of indole and indole NH respectively). The mass spectrum showed a molecular ion at m/e 149 and fragment ions corresponding to the loss of H, S and HCN with appropriate metastable peaks. The thiol was very easily oxidized by air, hydrogen peroxide, iodine, ferric chloride and alkaline potassium ferricyanide to 3,3'-diindolyl disulphide (Ic), m.p. 218-220°c (lit.[2] 217-218°) identical in all respects with an authentic sample, thus establishing the position of attachment of the sulphur substituent in the indole ring.

Oddo and Mingoia[3] claimed to have synthesized 3-indolylthiol by reaction of indolemagnesium bromide with sulphur, benzoylation of the product and finally alkaline hydrolysis. Their product had m.p. 235°, was only sparingly soluble in hot alkali and did not oxidize with air or ferric chloride. A recent re-investigation[4] of their work showed the compound to be

3-benzoylindole. Attempts to prepare 3-indolylthiol by reduction of 3,3'-diindolyldisulphide with lithium aluminium hydride[2] were unsuccessful, although several derivatives of the thiol were prepared in situ. Very recently[4] reduction of the disulphide with glucose in alkaline solution has been reported to give 3-indolyl thiol in 66% yield; this appears to be the only previous successful synthesis of the thiol. The product obtained by this method had m.p. 99-100° and gave a benzoate, m.p. 142-144°C. Schotten-Baumann benzoylation of thiol prepared by alkaline hydrolysis of the thiuronium salt (Ia) also gave a benzoate (Id) of m.p. 142-143°C, establishing the identity of the thiols prepared by the two methods.



a R =  I^-

b R = H

c R = S-(3-indolyl)

d R = COPh

e R = 2,4-dinitrophenyl

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An investigation of the chemical properties of 3-indolylthiol has revealed that it behaves as a typical thiol, undergoing facile base-catalysed addition to propiolic acids, isocyanates and isothiocyanates to give indolylthioacrylic acids, thiocarbamates and dithiocarbamates respectively. S-alkylation and S-acylation were readily effected in alkaline solution, and reaction with 2,4-dinitrochlorobenzene and alkali gave 3-indolyl 2',4'-dinitrophenyl sulphide (Ic), m.p. 175° (lit.[2] 175-175.5°).

On storage 3-indolylthiol oxidizes slowly to the disulphide. However most reactions (acylation, alkylation and addition) may be conveniently carried out on the thiol generated in situ from the thiuronium salt and alkali. Indeed, isolation of the thiuronium salt was not always necessary, and good yields of S-alkyl derivatives were obtained in one step from indole.

References

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