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Preparation of Isatogens from 2-Substituted Indolines

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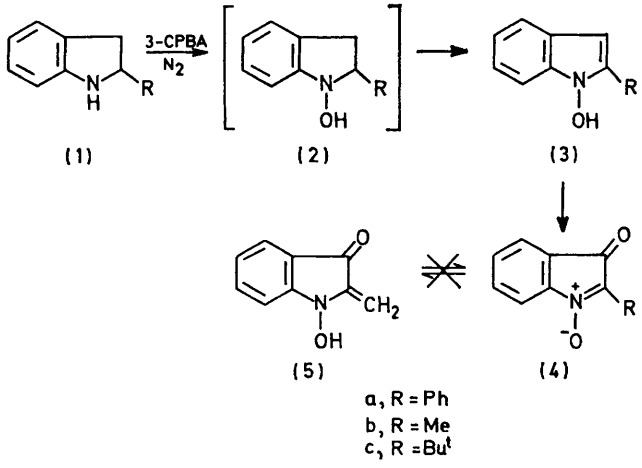
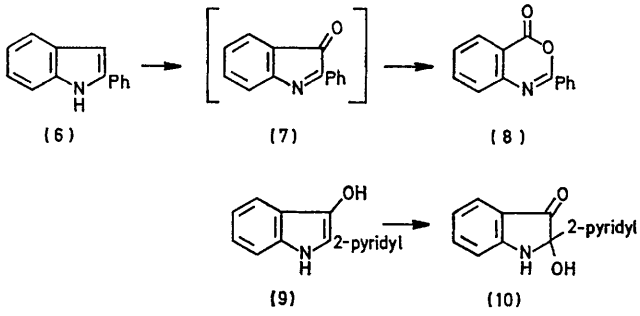
Summary The oxidation of indolines with 3-chloroperoxybenzoic acid provides a useful route for the preparation of isatogens and makes available the previously unknown 2-alkylisatogens.

Isatogens (**4**) have usually been prepared from acetylenic or stilbene intermediates. Oxidation of 1-hydroxy-2-substituted indoles (**3**) to isatogens with peroxybenzoic acids is the first general method reported for the preparation of isatogens from compounds containing an indole ring.[2] Isatogens with 2-alkyl substituents (**4**; R = alkyl) are unknown, although the tautomerism (**4**) ⇌ (**5**) of such compounds is a possibility.[3]



3-Chloroperoxybenzoic acid (3-CPBA) has been used for the *N*-hydroxylation of secondary aliphatic amines.[4] We have found that 2-substituted indolines (**1**) are readily oxidised to isatogens (**4**), in yields of 30 (**4b,c**) to 60% (**4a**), by 3-CPBA probably *via* the *N*-hydroxy-compounds (**2**) and (**3**). This method appears to be a general route to isatogens including the previously unknown 2-alkylisatogens (**4b,c**).



The indolines were obtained by reduction of the appropriate indole either by Zn–H_3PO_4 (**1a**)[5] or catalytically using PtO_2–EtOH–$FB(OH)_2$ (**1b,c**)[6] To a stirred solution of the indoline in $CHCl_3$ or Et_2O under nitrogen at room temperature, 3-CPBA (4 mol. equiv.) was added over 10—15 min. After a further 20—30 min stirring, washing ($NaHCO_3$ solution), and drying ($MgSO_4$) evaporation under reduced pressure (**4a,c**) or trituration of the residual oil with light petroleum (**4b**) gave the isatogens. The isatogen (**4a**) was identical with an authentic sample,[1] and (**4c**), gold plates, m.p. 104°, gave satisfactory analytical results, whilst (**4b**), yellow prisms, m.p. 115°, gave M^+ at 161·047 and showed metastable peaks consistent with this formulation. The i.r. spectra (Nujol) of (**4b,c**) showed no N–H or O–H absorptions, and strong carbonyl bands at 1700 (**4b**) and 1690 (**4c**), together with a sharp peak at *ca.* 1175 ($\geqslant N^+–O$)

cm^{-1};[1] τ ($CDCl_3$) (**4b**) 7·84 (3H, s), and 2·5 (4H, tightly coupled AB system); (**4c**) 8·55 (9H, s) 2·5 (4H, tightly coupled AB system).[1] On this evidence there is no detectable tautomerism (**4b**) $\rightleftharpoons$ (**5**) but this is being investigated.

The proposed mechanism was supported by the identification by t.l.c. of (**3a**) in the reaction of (**1a**) with $<$ 4 mol. equiv. of 3-CPBA and the failure to detect by t.l.c. any products which could arise from the oxidation of indole or indoxyl intermediates. These intermediates could theoretically arise by loss of water from the 1-hydroxyindolines (**2**) or by oxidation at C-3 of the indoline or indole ring. Under these conditions (**6**) gave the benzoxazine (**8**) (61%), presumably *via* the intermediate (**7**) which is known to be oxidised by peroxybenzoic acids to the benzoxazine.[7,8] The unstable nature of 2-phenylindoxyl led us to study the oxidation of the more stable 2-(2-pyridyl)indoxyl (**9**).[9] A further advantage in selecting this compound is the known stability of the adduct (**10**)[8,9] which would facilitate detection of the indolinone should it be formed. Under the above conditions the indoxyl (**9**) gave the adduct (**10**) (13%) and the reaction mixture had a strong carbonyl absorption at 1780 cm^{-1} characteristic of a benzoxazine, which was not, however, isolated from the reaction. These reactions strongly suggest that indoles are first attacked at the C-3 position by peroxy acids but that the indolines (**1**) preferentially undergo *N*-hydroxylation, (**1**) $\rightarrow$ (**2**), followed by oxidation of the indole ring, (**2**) $\rightarrow$ (**3**), and subsequent attack at C-3, (**3**) $\rightarrow$ (**4**).

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[1] C. C. Bond and M. Hooper, *J. Chem. Soc.* (*C*), 1969, 2453, and references cited therein.
[2] C. C. Bond and M. Hooper, *Synthesis*, in the press.
[3] M. Hooper and D. G. Wibberley, *J. Chem. Soc.* (*C*), 1966, 1596.
[4] A. H. Beckett, R. T. Coutts, and F. A. Ogunbona, *J. Pharm. Pharmacol.*, 1973, **25**, 190; *ibid.*, Suppl. 170P.
[5] W. A. Remers in 'Indoles—Part I,' ed. W. J. Houlihan, p. 166, Wiley-Interscience, 1972.
[6] A. Smith and J. H. P. Utley, *Chem. Comm.*, 1965, 427.
[7] R. J. Richmann and A. Hassner, *J. Org. Chem.*, 1968, **33**, 2548.
[8] H. S. Ch'ng, Ph.D. Thesis, University of London, 1971.
[9] D. A. Patterson and D. G. Wibberley, *J. Chem. Soc.*, 1965, 1706.