

The 5-Methoxylation of Oxindole Derivatives

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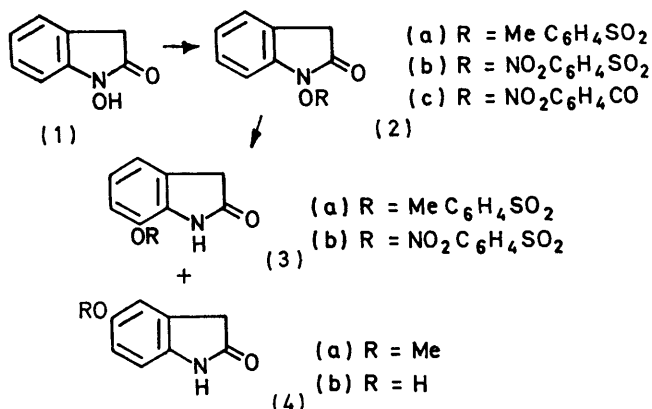
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Summary A two-step procedure is described for the conversion of 1-hydroxyoxindoles into 5-hydroxy- and 5-methoxy-oxindoles.

MEMBERS of a number of different families of indole alkaloids have been found to differ from each other only in the absence or presence of a 5-hydroxy- or 5-alkoxy-group.¹ Unfortunately, no simple method exists for the chemical interconversion of derivatives of either indoles or oxindoles into the corresponding 5-hydroxy- or 5-alkoxy-substituted indoles or oxindoles. We now report a simple two-step process for the conversion of 1-hydroxyoxindoles into 5-hydroxy- and 5-methoxy-oxindoles.

In principle, conversion of the hydroxy-group of 1-hydroxyoxindoles into a suitable leaving group should permit heterolytic cleavage of the N-O bond under solvo-

lytic conditions. Recent studies indicate that such a bond heterolysis should result in the formation of a partial positive charge on nitrogen.^{2,3} As previously noted,^{2,3} when a divalent electron-deficient nitrogen species (nitrenium ion) is generated adjacent to an aromatic ring, there occurs extensive delocalization of that charge into the ring. The carbonyl group of the oxindole should increase the degree of charge delocalization into the ring due to its inductive effect. However, a deleterious effect of the carbonyl group would be to inhibit the heterolytic cleavage of the N-O bond of the oxindole (**2**). This problem was clearly demonstrated in the methanolysis of the *p*-nitrobenzoate (**2c**). Although the *p*-nitrobenzoate anion is generally considered to be a good leaving group, it was not satisfactory for the generation of a nitrenium ion next to a carbonyl. Thus, the methanolysis of compound (**2**) merely resulted in



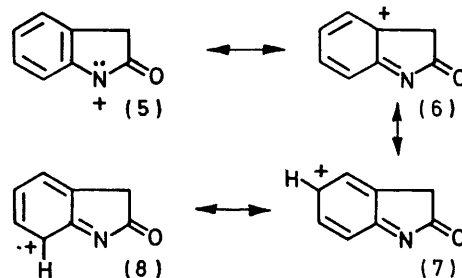
transesterification with the regeneration of the 1-hydroxy-compound (1) and the formation of methyl *p*-nitrobenzoate.

When compound (1)⁴ was allowed to react with toluene-*p*-sulphonyl chloride in tetrahydrofuran and triethylamine at -78° , the very unstable toluene-*p*-sulphonate (2a) was obtained. Attempts to isolate pure material were futile, since it spontaneously rearranged to the 7-substituted compound on warming to room temperature. Addition of methanol to the tetrahydrofuran solution of compound (2a) at -78° , followed by warming to room temperature, resulted in the formation of (3a) (34%) and 5-methoxyoxindole (4a) (42%), m.p. 153–154° (lit.,⁵ 153–154). The structure of compound (4a) was established by comparison of its i.r., u.v., and n.m.r. spectra with published data.⁵

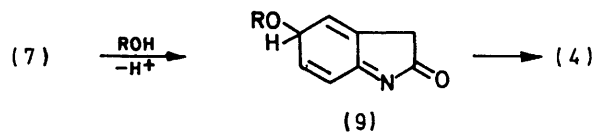
Addition of compound (2a) in tetrahydrofuran at -78° to dioxan-water (1:1) at 25° gave (3a) (29%) and 5-hydroxyoxindole (4b) (22%), m.p. 162–163° (lit.,⁶ 165–166). A comparison of spectral data with that reported⁶ confirmed the structure of compound (4b).

The dependence of yields on the efficiency of the leaving group was substantiated by the solvolytic behaviour of the *p*-nitrobenzenesulphonate (2b). Addition of methanol to

the ester (2b) in tetrahydrofuran at -78° followed by warming to room temperature resulted in the formation of (3b) (30%) and (4a) (52%).



By analogy with the generation of anilenium ions,^{2,3} the mechanism of the formation of compounds (4a) and (4b) may involve the initial heterolytic cleavage of the N–O bonds of the esters (2a) and (2b) to produce a delocalized nitrogen cation represented by the resonance structures (5)–(8). Nucleophilic attack of solvent on the ion (7), followed by loss of a proton from the solvent would produce the intermediate (9). Hydrogen migration from carbon to nitrogen and accompanying rearomatization would then yield the 5-substituted compound (4).



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¹ For recent reviews of indole alkaloid chemistry see W. I. Taylor, 'Indole Alkaloids', Pergamon Press, New York, 1966; R. Sundberg, 'The Chemistry of Indoles', Academic Press, New York, 1970.

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