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OXIDATIVE FUNCTIONALIZATION AT THE BENZYLIC CARBON OF α-SUBSTITUTED INDOLES WITH BENZOYL PEROXIDE[1]

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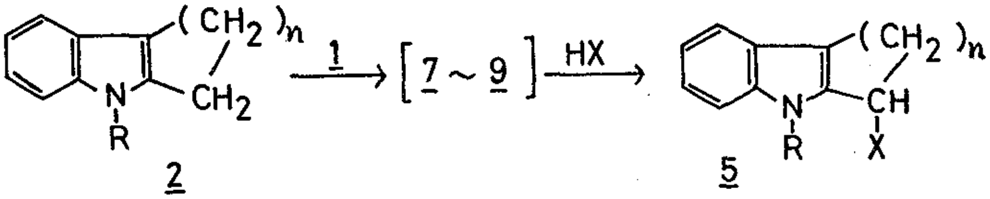
On reaction with benzoyl peroxide 1 followed by treatment with a nucleophile, oxidative functionalization can be achieved at the benzylic carbon of α-substituted indoles 2.

Oxidative transformation of the indole ring involves both the 2 and 3 positions leading to oxindoles and indoxyls. In the course of our study on the homolytic reactions of heterocycles[1], we have previously reported that benzoyl peroxide 1, a typical radical reagent, converts N-methylindoles directly into indoxyl, oxindole and dioxindole O-benzoates[2]. Further, it has been shown that 1 converts N-substituted pyrroles into 2-hydroxy- and 2,5-dihydroxypyrrole O-benzoates under mild conditions[3]. We have now extended these reactions to tricyclic indole derivatives in which the size of the isocyclic ring C are 6 and 7 members.

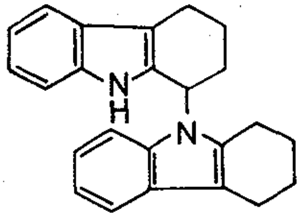
When a mixture of tetrahydrocarbazole 2a and 1 in benzene was allowed to react at room temperature, none of definite products were isolated although 1 was rapidly consumed within 1.5 hr. However, similar reaction (2a : 1 = 2 : 1) in pyridine afforded a dimeric product 3 (mp 223-225°(decomp))[4] in 50 % yield.

The structure 3 was assigned by comparing the mps of the dehydrogenated derivative obtained by heating 3 with chloranil and its picrate with those of 1,9-dicarbazyl 4.[5] This result suggests that the above reaction generates an intermediate activated at the 1-position of 2a, which subsequently reacts with the second 2a ultimately to form 3. To test this possibility, an equimolar mixture of 2b and 1 in benzene was similarly reacted. Since possible intermediates were not isolated, the reaction mixture was subsequently treated *in situ* with excess of methanol. As expected, 1-methoxy-9-methyltetrahydrocarbazole 5b (X = OMe ; mp 58-59°) was obtained in 33 % yield. When treated with a methanol solution of benzylamine, 5b (X = $NHCH_2Ph$, picrate mp 185-188°; 29 %) and 5b (X = OMe ; 21 %) were isolated after preparative TLC. Likewise, 2c on treatment with 1 followed by adding ethanol gave 5c (X = OEt, oil ; 31 %) together with 6(picrate dark red prisms,mp 105-6°;10%)which apparently arises from the elimination reaction of the former. The structure of 5c (X = OEt) was supported also by its conversion into the picrate of 6 on treatment with picric acid.



a : R = H, n = 3 b : R = Me, n = 3 c : R = Me, n = 4

A mechanistic pathway for the formation of 5 (and 3) can be formulated in terms of the following sequence. The unusual ease with which 1 reacts with the indoles strongly suggests that ionic character must at least in part be involved in these reactions.[2,3] Thus by analogy with the established pattern of electrophilic substitution of indoles,[6] benzoyloxylation occurs first in the 11-position to form indolenine 7 and is followed by tautomeric shift[7,8] to yield enamine 8 which may be attacked by benzoate giving 1-benzoate 9. The reaction solutions may thus contain the equilibrium mixture 7-9, among which probably 8 would accept the nucleophiles (in place of benzoate) ultimately to yield 5.



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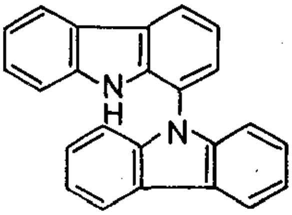

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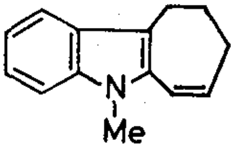

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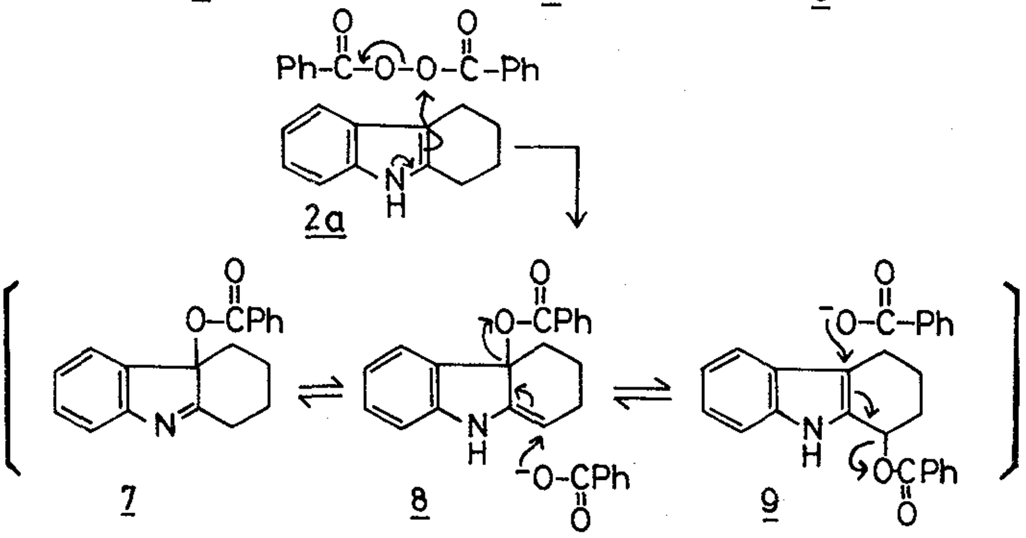

The synthetic usefulness is obvious if it is possible to achieve chemical selectivity by imposing orientation on some otherwise unselective functionalization reactions. Although the α-benzylic carbon of some indoles such as **2a**[9] and cyclooctenoindole[10] are succeptible to oxidation, the usually isolable products are ketones from which further reactions must start to introduce appropriate functional groups. The benzoyl peroxide-induced oxidative functionalization here described indicates that certain nucleophiles can be introduced in one step at the benzylic carbon of α-substituted indoles. Examples of the synthetic application of this method will be reported in a forthcoming paper.

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