

OXIDATIVE FUNCTIONALIZATION
AT THE BENZYLIC CARBON OF α -SUBSTITUTED INDOLES
WITH BENZOYL PEROXIDE¹

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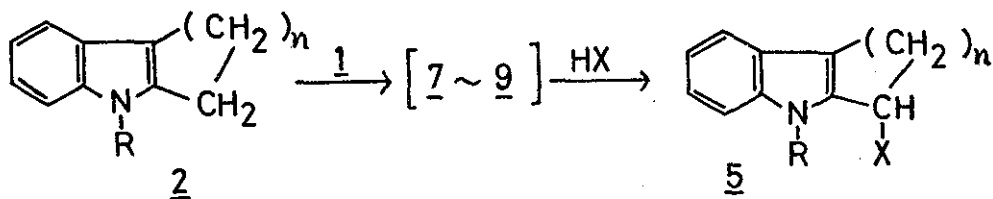
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On reaction with benzoyl peroxide 1 followed by treatment with a nucleophile, oxidative functionalization can be achieved at the benzylic carbon of α -substituted indoles 2.

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 heterocycles¹, we have previously reported that benzoyl peroxide 1, a typical radical reagent, converts N-methylindoles directly into indoxyl, oxindole and dioxindole O-benzoates². Further, it has been shown that 1 converts N-substituted pyrroles into 2-hydroxy- and 2,5-dihydroxypyrrole O-benzoates under mild conditions³. 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 4⁵. 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 = NHCH₂Ph, 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.

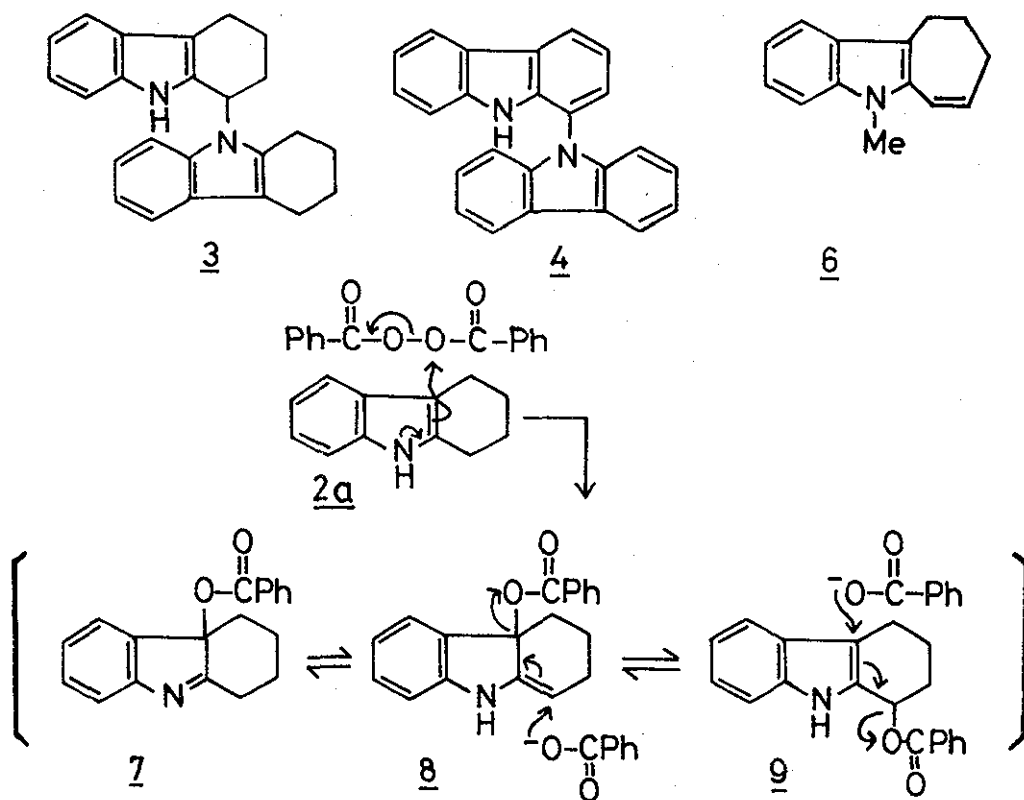


a : R = H, n = 3

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.



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 2a⁹ and cyclooctenindole¹⁰ are susceptible 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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