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Importance of the Baldwin rules to the intramolecular anodic coupling of isoquinoline and indole derivatives

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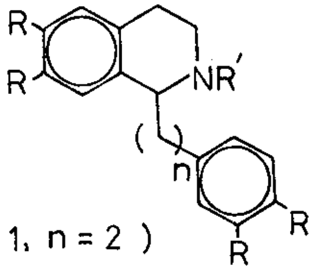
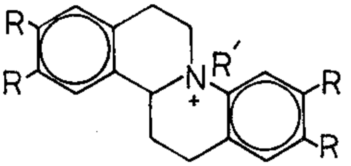
The coupling reactions of radical cations derived from certain isoquinolines and indoles is favoured only when six membered transition states are involved. In the case of 3-substituted indoles initial attack at position-3 occurs, followed by a selective bond breaking and rearrangement.

In a previous study[1] we noted that the anodic oxidation of the 1-phenethyltetrahydroisoquinoline (1) affords the tetracyclic structure (2), but despite several attempts the oxidation of the 1-benzyl analogue (3) yields only O-methylflavinanthine (4)[2], no other products were isolated. On this basis it seems that the question of the relative stabilities of five versus six membered transition states are very important in coupling reactions involving radical cations of this type.

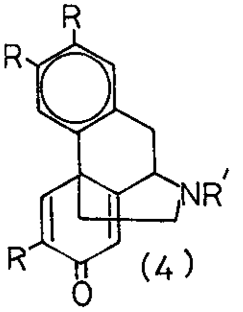


(1, n = 2)

(3, n = 1)



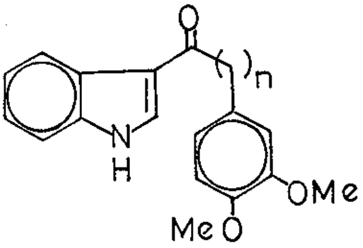
(2)



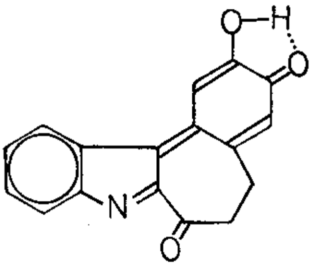
(4)

R = OMe: R′ = Me

Another related example is provided by the two indole derivatives (5) and (6). The first compound undergoes one electron oxidation at +1 3v (versus SCE) but is recovered unchanged in a preparative experiment at this potential. The higher homologue (6), however, is transformed at +1.35v almost quantitatively into the tetracyclic product (7)

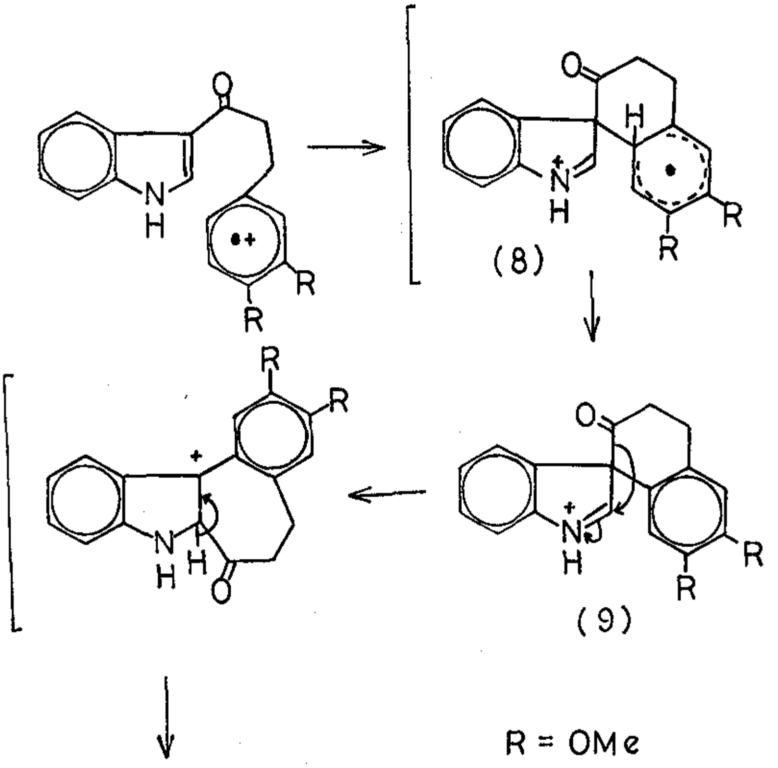


(5, n = 1)
(6, n = 2)



(7)

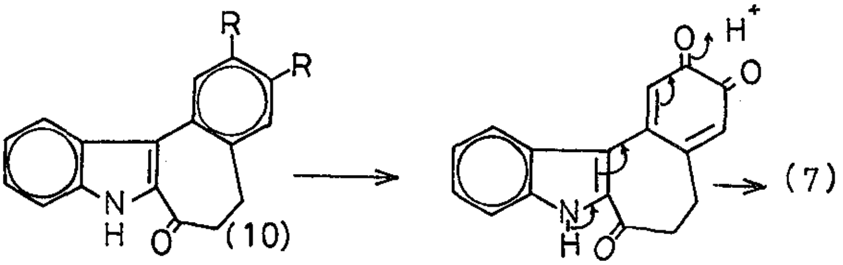
The formation of this last compound indicates that the initial radical cation formed from the dimethoxylated aryl ring system (the indole-3-formyl unit is not oxidized below +1.8v) attacks the indole unit at C-3 forming the species (8) which is further oxidized to the cation (9). The anticipated product (10) is then oxidized[4] onto a quinone species tautomeric with (7) We formulate structure (7) as shown since it fails to react with <u>ortho</u>-phenylene diamine and various dienophiles, and also shows a one proton singlet at the low field position of δ 12.6 ppm (removed by D_2O) in the ^1H nmr spectrum. Other resonances occur at δ 2.95 (4H, bs, CH_2CH_2), 6.56 (1H, s), 6.80 (1H, s) 7.27-7.72 (3H, m), 8.00 (1H, bd J = 8Hz). The compound is black in colour and has λ_{max} 241, 310, 350 nm; ν_{max} 3340s, 1670, 1658, 1640 cm^{-1}.



(8)

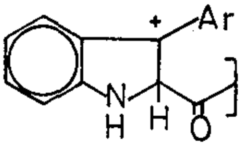
(9)

R = OMe

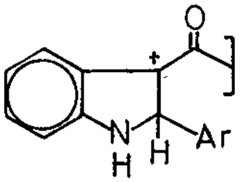


If the lower homologue (5) were to enter into a similar reaction then the necessary intermediate corresponding to (8) would contain a five membered ring system, presumably this is much less stable and thus intramolecular coupling is not observed in this case.

The formation of (7) is quite interesting since it illustrates the general rule that electrophilic attack at C-3 of the indole nucleus, followed by rearrangement, predominates over direct cyclisation at C-2. The reaction also provides an interesting comparison between the relative stabilities of the two alternative cations (11) and (12). As expected only product derived from (11) is observed since a developing positive centre next to a carbonyl group is strongly disfavoured.



(11)



(12)

Acknowledgment

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1. A.Najafi and M.Sainsbury, Heterocycles, 1977, 6, 459
2. L.L.Miller, F.R.Stermitz and J R.Falck, J.Amer Chem.Soc , 1973, 95, 2651.
3. J.E.Baldwin, Chem.Soc Chem.Commun., 1976, 734.
4. In the actual electrolysis six Faradays of current per mol of substrate were used.

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