Tetrahedron Letters,Vol.22,No.47,pp 4751-4754,1981 0040-4039/81/474751-04$02.00
Printed in Great Britain

FURTHER EXAMPLES OF PREFERRED TRANSITION STATE GEOMETRIES IN THE OXIDATIVE CYCLISATION OF INDOLE AND ISOQUINOLINE DERIVATIVES

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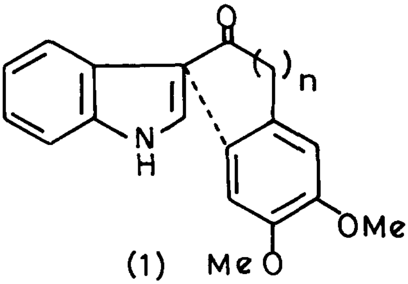
Summary: Electrochemical and chemical oxidative cyclisation reactions of some indole and isoquinoline derivatives appear to favour 6-membered transition states rather than the 5-membered counterparts. These results are analysed in terms of the Baldwin rules for ring-closure.

Sometime ago we drew attention[1] to the fact that the Baldwin rules for ring-closure[2] seemingly provide an explanation for the failure of the enaminoketone (1,n=1) to cyclise on electrochemical oxidation in acetonitrile solution containing sodium perchlorate, whereas its higher homologue (1,n=2) gives rise to a tetracyclic product (2). We argued that the transition state geometry required for the cyclisation of the first example might be regarded as a disfavoured 5-endo-trig arrangement, but that necessary for its homologue (dotted line in the formula) is of the favoured 6-endo-trig type.



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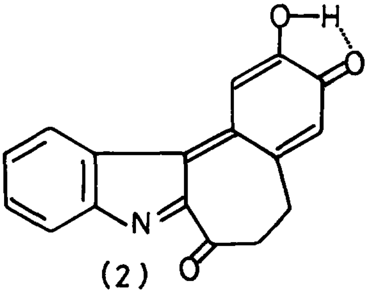
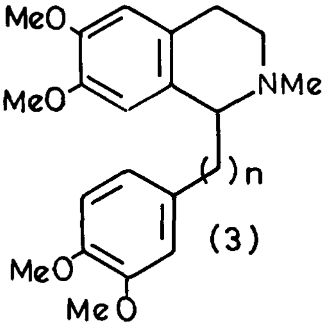


(2)

Here we provide some further examples which indicate the generality of this situation. Thus it is known that electrochemical oxidation of laudanosine (3,n=1) in non-acidic media yields O-methylflavinantine (4)[3] rather than the salt (5,n=1), but we note its higher homologue (3,n=2) affords the perchlorate (5, n=2) as the sole reaction product.[4] Similarly, the 4-benzyl-1,2,3,4-tetrahydroisoquinoline (6,n=1) gives the cation (7), whereas the phenethyl derivative (6, n=2) yields the isohomoaporphine (8,n=2). Should this reaction proceed directly it may be analysed in terms of a 7-endo-trig process, but it seems more probable that the initial product is the cation (9,n=2), or an equivalent, which then rearranges to the isohomoaporphine. The yield of this compound is poor and it is accompanied by intermolecular coupled products. However, these can be eliminated if the reaction is carried out in acidic media, or if thallium (III) trifluoroacetate and boron trifluoride etherate in acetonitrile and carbon tetrachloride[5] is employed as the oxidant.

Anodic oxidation of the 4-benzyltetrahydroisoquinolinium salt (10) effects stepwise dehydrogenation first to the 3,4-dihydroisoquinolinium cation (11) and then to the salt (12).[6] Interestingly vanadium oxytrifluoride oxidation of the free base (6,n=1) affords the isoaporphine (8,n=1)[7] and it may be that here direct cyclisation is accomplished through favourable transition state geometry without the need to postulate an intermediate (9,n=1).



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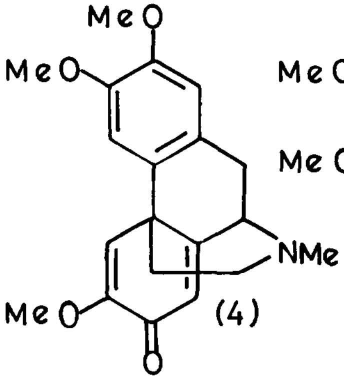

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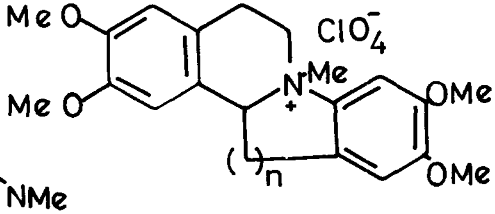

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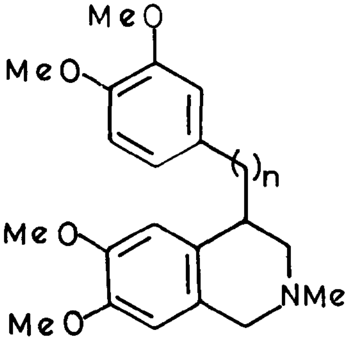

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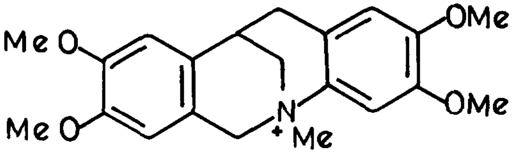

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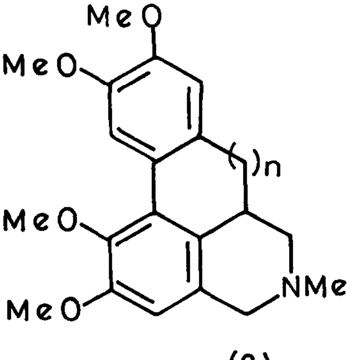

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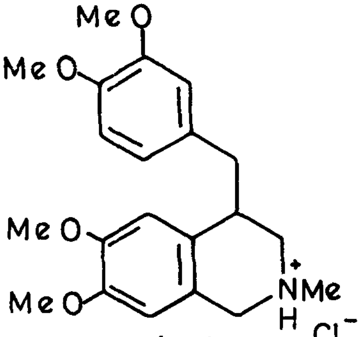

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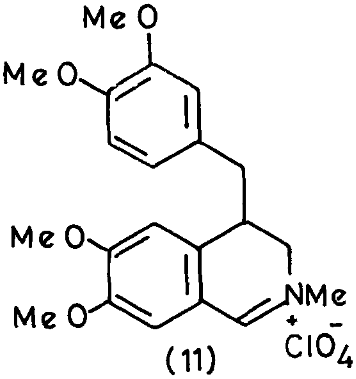

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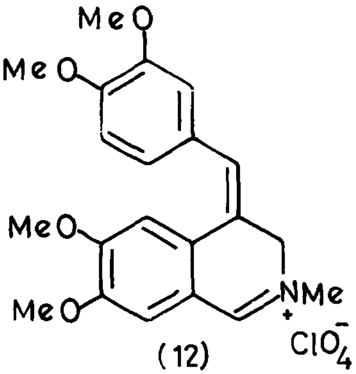
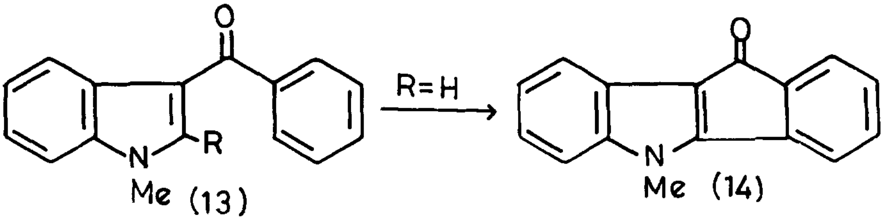
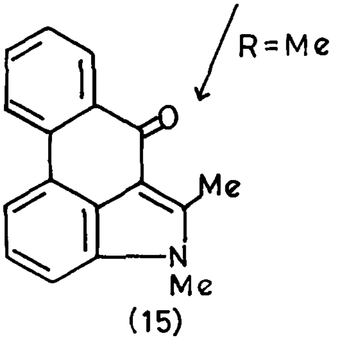
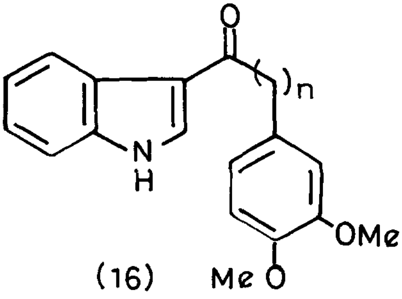


(12)

Itahara has shown[8] that the vinylogous amide (13,R=H) is cyclised to the tetracycle (14) by the action of palladium (II) acetate. Here it is assumed that either the aryl ring of the benzoyl group or the heterocycle is palladated prior to ring-closure and that carbon-carbon bond formation then occurs within the complex.[9] Our conclusions concerning the geometry of the transition states are now altered and we thought it would be instructive to examine the oxidation of the homologues (16,n=1) and (16,n=2) with this reagent, but neither afforded products analogous to (14) giving instead multicomponent mixtures. Originally it was suggested that only when the 2-position of the 3-benzoylindole is blocked does palladium (II acetate afford structures of the type (15), but we now find that this appears to be the primary reaction course, whether the 2-position is alkylated or not. However, should the 1-position be free as in the example (16,n=0) some N-benzoylation occurs leading to 1,3-dibenzoylindole (18) as well as the tetracyclic product (17).







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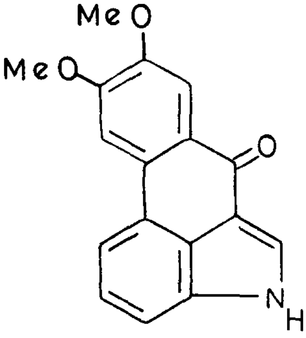

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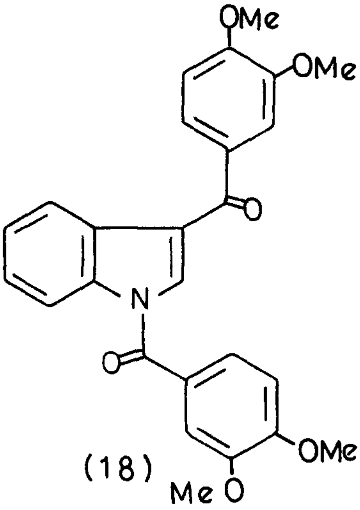

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Acknowledgement: The authors thank the Science Research Council for a grant awarded to Mark Powell.

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(Received in UK 7 September 1981)