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The Influence of Acids on 4-Benzyl-1,2-dihydroisoquinoline Derivatives

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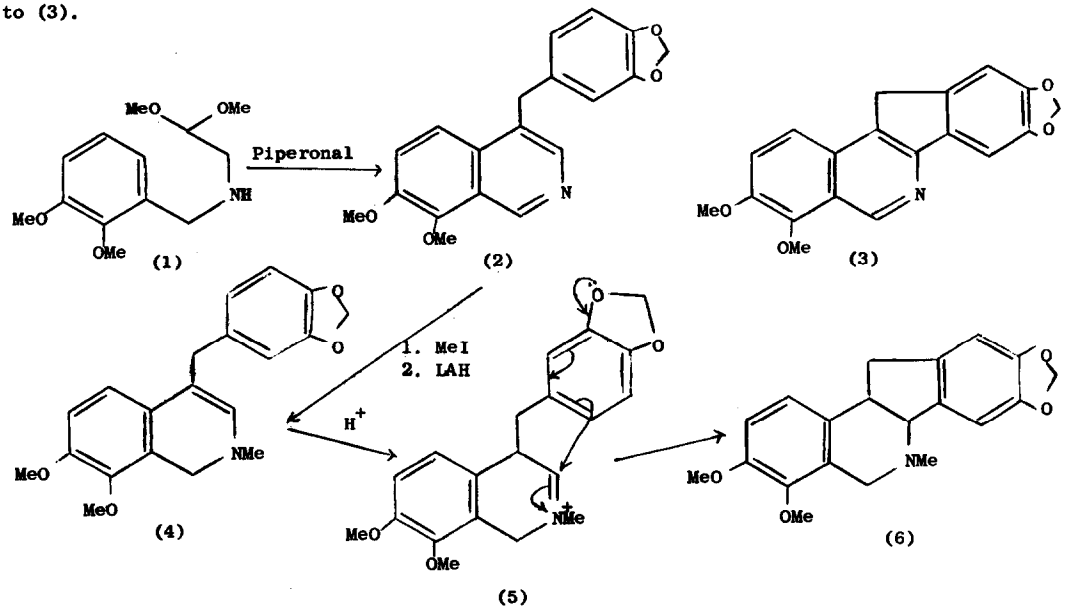
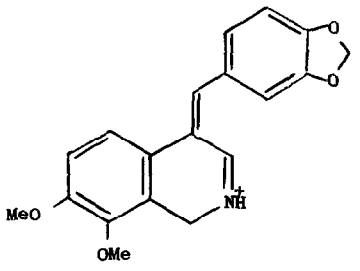
It has been shown[1,2] that aromatic aldehydes react with benzylaminoacetaldehyde dialkyl acetals, for example (1), in the presence of acids, to form 4-benzylisoquinoline derivatives. Recently Gensler et al[3] have reported the isolation of a small amount of the indenoisoquinoline (3) as well as (2), hydrochloride m.p. 100-102°, from the interaction of (1) with piperonal. They further claim that the 1,2-dihydroisoquinoline (4) obtained by reducing the methiodide of (3) with LAH cyclises when treated with an acetic acid-hydrochloric acid mixture to form (6) via the imminium ion (5). The structure for this product (an oil) was supported by the dehydrogenation of (6) with iodine to form a quaternary salt said to be identical with the methiodide of (3), m.p. 243-245°.

Our interest in indenoisoquinoline derivatives stems from our study[4] of some reactions of cryptopine and we have also reacted (1) with piperonal and have obtained (3) as described by Gensler et al, but the major product, hydrochloride m.p. 100-102° was found to be (7), which is easily isomerised to (2) when attempts are made to release the base from its hydrochloride. In our hands treatment of the 1,2-dihydroisoquinoline (4) with acetic-hydrochloric acid mixture as described by the previous workers, or with perchloric acid, led not to ring-closure but to disproportionation. The products of the reaction were conclusively shown to be the metho-salt of (2) and the 4-benzyl-1,2,3,4-tetrahydroisoquinoline (8). Some isomerisation of (4) to (10) was also observed. A similar disproportionation was observed in our previous attempts[2b] to cyclise (9). It is possible for ring-closure of (8) to occur during the dehydrogenation with iodine, so an authentic specimen of (6), m.p. 155-156° was prepared by reducing the methiodide of (3) m.p. 253-254° with $NaBH_4$. We were not surprised to find that quaternisation of (3) with methyl iodide was unsatisfactory; the reaction of the base with dimethyl sulphate, followed by KI, was a superior method. The product (6) was found not to be identical with the base produced by acid treatment of (4).

It is our contention that protonation of 4-substituted-1,2-dihydroisoquinolines such as (4) to form the imminium ion (5) necessary for cyclisation to (6) is inhibited by the C_4-substituent. Consistent with this view is our observation that reduction of 4-benzyl-isoquinolinium salts with $NaBH_4$ leads to the 1,2-dihydroisoquinoline and not to the expected 1,2,3,4-tetrahydroisoquinoline derivatives. The generally accepted mechanism[5] for this latter reduction (11) ⟶ (14) involves an imminium ion (13) as an intermediate. A different situation exists when an electron-donating group is attached to C_3 of a 4-substituted-1,2-dihydroisoquinoline; thus epicryptopirubin chloride (15) can[4] be protonated, and reduced by $NaBH_4$ and the methiodide of (3) behaves similarly. The formation of the indenoisoquinoline (3) during the reaction of (1) with piperonal is readily rationalised since the required imminium ion (18) is produced during the electrophilic attack of piperonal at C_4 of the 1,2-dihydroisoquinoline (16), formed from (1), and NOT by protonation of a 4-benzyl-1,2-dihydroisoquinoline. The product (18) may be precipitated as the hydrochloride from the reaction mixture or may cyclise to (19) which can be aerially oxidised to (3), or the cyclisation may occur in the intermediate (17) to form (20) which may then undergo dehydration to (19). A precedent exists[4] for the ready oxidation of (19) to (3).





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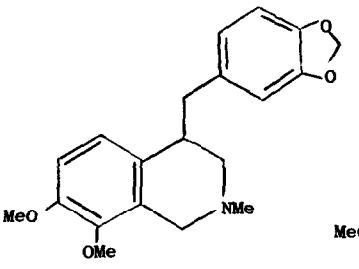

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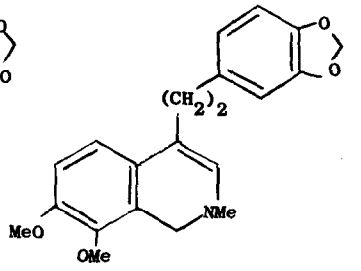

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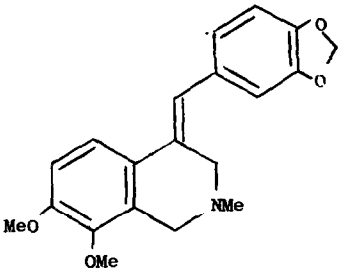

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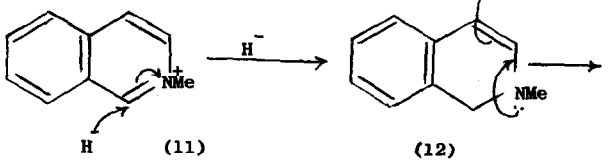

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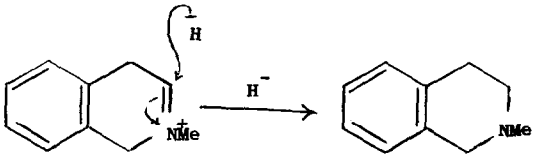

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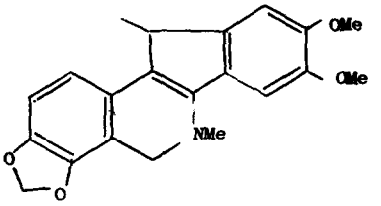

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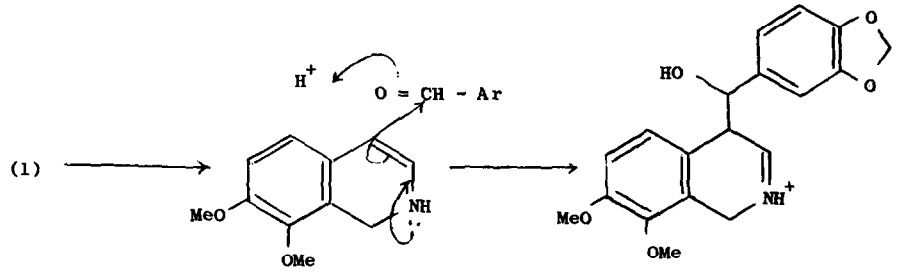
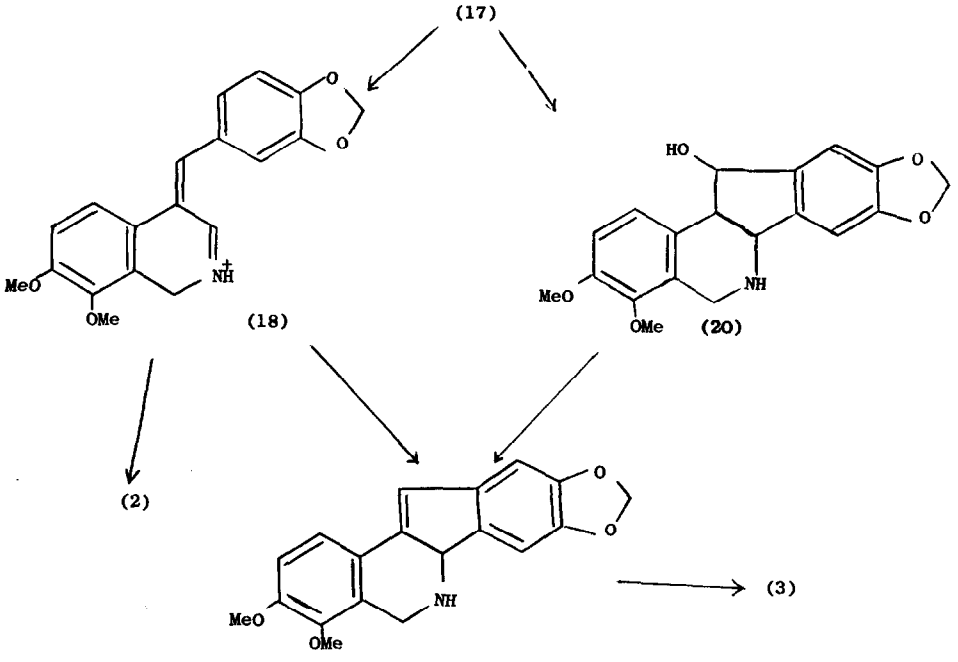


(16) (17)

(18) (20)



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