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1,2-DIHYDROISOQUINOLINE REARRANGEMENTS

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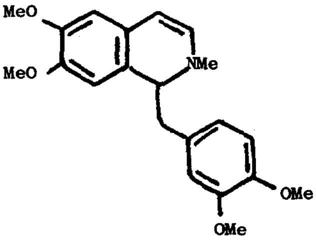
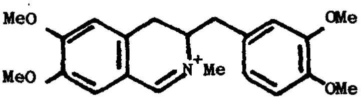
Knabe and Kubitz have shown recently[1,2] that mild acid treatment of 2-methyl-1,2-dihydropapaverine (1) results in the formation, in 70% yield, of the 2-methyl-3-(3',4'-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinolinium salt (2).



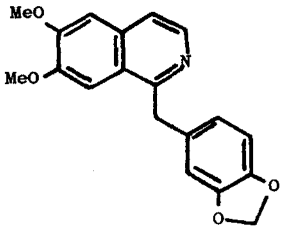
(1)



(2)

It became of interest to us to study the action of dilute acids on a 1-benzylisoquinoline derivative, whose aromatic rings were unsymmetrically substituted.

1-(3',4'-methylenedioxybenzyl)-6,7-dimethoxyisoquinoline (3), (m.p. 123°, lit.[3] 123°) was synthesised by the standard[4] Bischler-Napieralski ring-closure of the corresponding amide, followed by dehydrogenation of the intermediate 3,4—dihydroisoquinoline[5] (m.p. 108°).



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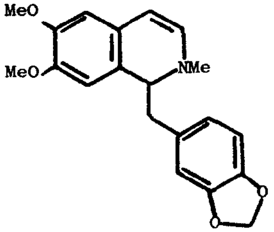
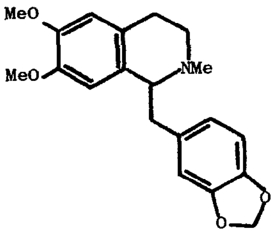


(4)

The methiodide of (3) (m.p. 232°) was reduced, in tetrahydrofuran solution, with lithium aluminium hydride, essentially as described previously[6]; the resulting 1,2-dihydroisoquinoline (4) ($\lambda_{max.}$ at 215, 255, 290 and 335 mμ) was, without delay, warmed with 2N hydrochloric acid as described by Knabe and Kubitz[2,7]. An intense red-violet colour developed, which very quickly faded to yellow. Basification and extraction with chloroform then yielded an oil ($\lambda_{max.}$ at 214, 245, 290, 315 and 368 mμ), which was reduced immediately with sodium borohydride in ethanol. The product (m.p. 170°, methiodide monohydrate 155-158° dec.) was different from authentic[8] 1-(3',4'-methylenedioxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5) (m.p. 122°, methiodidemonohydrate m.p. 215-216°), and was shown to be 2-methyl-3-(3',4'-methylenedioxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoli (6) by Hofmann degradation.



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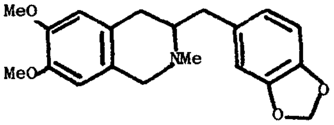
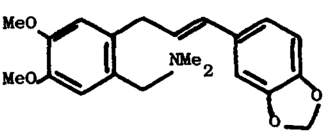


(6)

From the ozonolysis of the styrenoid methine base (7) ($\lambda_{max.}$ at 271 and 292 mμ) piperonal (80%) was isolated. The nitrogen-containing fragment (8) was very unstable, presumably due to cyclisation to, and decomposition of the 1,2-dihydroisoquinoline (9).



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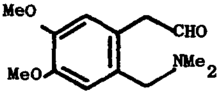
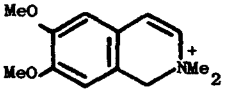
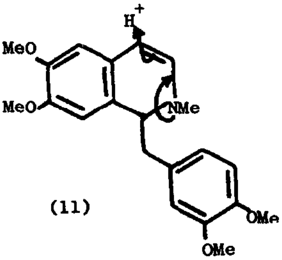


(8)



(9)

It is remarkable that of the β-hydrogen atoms available in the transition state of the Hofmann degradation of (6), it is one of those of the exocyclic benzyl group which is preferred. The generally accepted mechanism for the conversion of 2-methyl-1,2-dihydropapaverine (11) to N-methylpavine[6,9], which is brought about by concentrated acids, involves the protonated form (12) of (11). This is then susceptible to nucleophilic attack as shown.



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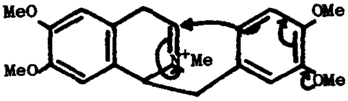

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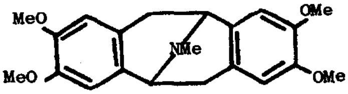

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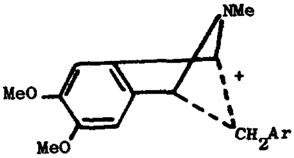
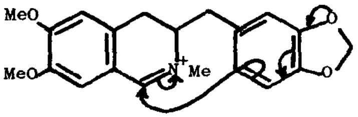


(14)

In the benzyl-migration reaction it is possible that the intermediate of type (12) reacts as (14), and the reaction may therefore be reversible. However treatme of the 3-benzyl derivative (15) with dilute mineral acids led only to recovered starting material. It is also possible that a pavine-like structure (16) could arise from (15), but once again only starting material was recovered when (15) was heated with a mixture of formic and phosphoric acids under the conditions[9] whereby (11) was converted into (13).



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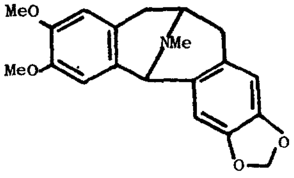

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