A NEW ALKYLATING METHOD
AT THE 4-POSITION OF ISOQUINOLINE DERIVATIVES

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Alkylation of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (I) with 2-methylcyclohex-2-en-1-one and phenethyl bromide in the presence of sodium hydride and dimethyl sulphoxide gave 6,7-dimethoxy-1-methyl-4-(2-methyl-3-oxocyclohexyl)isoquinoline (V) and 6,7-dimethoxy-1-methyl-4-phenethylisoquinoline (VII), respectively. On the other hand, reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline (VIII) with 3,4-methylene dioxyphenethyl bromide under the same conditions gave 6,7-dimethoxy-1-methylisoquinoline (XI) and methyl 3-(3,4-methylenedioxyphenyl)propyl sulphoxide (XII).

Alkylation and acylation at the 4 position of isoquinoline derivatives have been reported, but these methods have some defects in yield and general application. This stimulated us to explore new methods available for the synthesis of the 4-substituted isoquinoline derivatives from 3,4-dihydroisoquinolines.
Firstly we studied the enamine formation of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (I) under basic conditions to determine whether compound (II) or (III) was formed as the transient intermediate. For this purpose, isoquinoline (I) was heated in a mixture of sodium hydride and dimethyl sulphoxide and 2-methylcyclohex-2-en-1-one was added to the cooled reaction mixture in order to trap the enamine formed. Purification of the reaction mixture gave 6,7-dimethoxy-1-methyl-4-(2-methyl-3-oxocyclohexyl)-isoquinoline (V) in 25.7% yield, m.p. 183 - 184°; \( \nu (\text{CHCl}_3) 1700 \text{ cm}^{-1} \); \( \delta (\text{CDCl}_3) 0.88 (d, 3H, J = 6 \text{ Hz}, \text{CHCH}_3), 2.88 (s, 3H, C_1-\text{CH}_2), 4.03 (s, 6H, 2 \times \text{OCH}_3), 7.17 (s, 1H, ArH), 7.25 (s, 1H, ArH), 8.26 (s, 1H, C_3-H); m/e 313 (M^+)\). These data suggested that the cyclohexanone was attached to the isoquinoline ring [\( \lambda_{\text{max}} (\text{MeOH}) 314 \) and 326 nm] and the position of substitution was easily determined by the presence of the signal of C_3-proton (\( \delta 8.26, s \)). This was rationalised by the formation of enamine III, followed by Michael addition to 2-methylcyclohexenone and then dehydrogenation of the resulting IV. Having thus established that compound (I) formed the enamine (III) under basic conditions, we next examined its behavior on alkylation.

The 3,4-dihydroisoquinoline (I) was treated successively with sodium hydride in dimethyl sulphoxide and phenethyl bromide under the same conditions to give a colourless oil in 20.5% yield, \( \delta (\text{CDCl}_3) 2.83 (s, 3H, C_1-\text{CH}_2), 2.98 - 3.26 (m, 4H, \text{CH}_2\text{CH}_2), 3.91 (s, 3H, \text{OCH}_3), 3.96 (s, 3H, \text{OCH}_3), 7.0 - 7.33 (m, 7H, ArH), 8.06 (s, 1H, C_3-H); m/e 307 (M^+), \lambda (\text{MeOH}) 315\) and 327 nm. In addition, microanalysis of its picrate [m.p. 210 - 211° (decomp.)] showed it to be
6,7-dimethoxy-1-methyl-4-phenethylisoquinoline (VII). By analogy to (IV), the formation of the compound (VII) can be rationalised via intermediate (VI).

Secondly 3,4-dihydro-6,7-dimethoxyisoquinoline (VIII) was treated with 3,4-methylenedioxyphenethyl bromide in the presence of sodium hydride in dimethyl sulphoxide to give two compounds which were separated by silica gel column chromatography. The first compound (XI) (12.3 % yield) [δ (CDCl₃) 2.89 (s, 3H, C₁-CH₃), 4.0 (s, 6H, 2 x OCH₂), 6.9 - 7.5 (m, 3H, ArH), 8.2 (d, 1H, J 6 Hz, C₃-H); m/e 203 (M⁺), λ(MeOH) 312 and 325 nm] was identical in spectroscopic comparisons with an authentic sample prepared from 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (XIII). The second one (oil; 16 % yield) was assigned the structure XII by the following data, δ (CDCl₃) 2.55 (s, 3H, SO-CH₃), 5.93 (s, 2 H, OCH₂O); m/e 226 (M⁺). The expected compound X was not obtained differently from the case of I.

The reaction mechanism, limitations, and application of this new alkylation at the 4-position of 3,4-dihydroisoquinoline derivatives are now under investigation.
Chart 2

\[ \text{VIII} \rightarrow \text{IX} \rightarrow \text{X} \]

\[ \text{XI} + \text{XII} \]

\[ \text{XIII} \]
REFERENCES


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