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

Tetsuji Kametani,* Hideo Nemoto, Mie Takeuchi, Mitsuhiro Takeshita, and Keiichiro Fukumoto

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

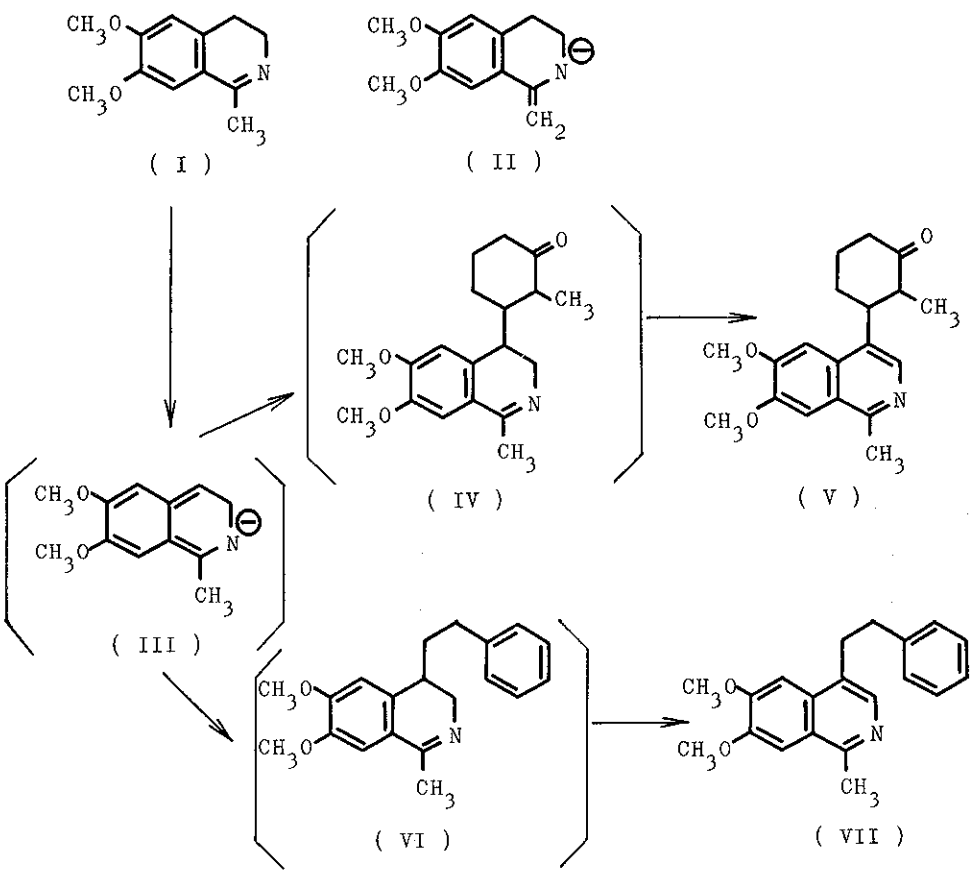
Alkylation of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (I) with 2-methylcyclohex-2-en-1-one and phenethyl bromide in the presence of sodium hydride and dimethyl sulphoxide gave 6,7-dimethoxy-1-methyl-4-(2-methyl-3-oxocyclohexyl)isoquinoline (V) and 6,7-dimethoxy-1-methyl-4-phenethylisoquinoline (VII), respectively. On the other hand, reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline (VIII) with 3,4-methylenedioxyphenethyl 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,[1-6] 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°; $\nu(CHCl_3)$ 1700 cm^{-1}; $\delta(CDCl_3)$ 0.88 (d, 3H, J 6 Hz, $CHC\underline{H}_3$), 2.88 (s, 3H, C_1-CH_3), 4.03 (s, 6H, 2 x 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 [λ_{max} (MeOH) 314 and 326 nm] and the position of substitution was easily determined by the presence of the signal of C_3-proton (δ 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, $\delta(CDCl_3)$ 2.83 (s, 3H, C_1-CH_3), 2.98 - 3.26 (m, 4H, $C\underline{H}_2C\underline{H}_2$), 3.91 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 7.0 - 7.33 (m, 7H, ArH), 8.06 (s, 1H, C_3-H); m/e 307 (M^+), λ(MeOH) 315 and 327 nm. In addition, microanalysis of its picrate [m.p. 210 - 211° (decomp.)] showed it to be

Chart 1

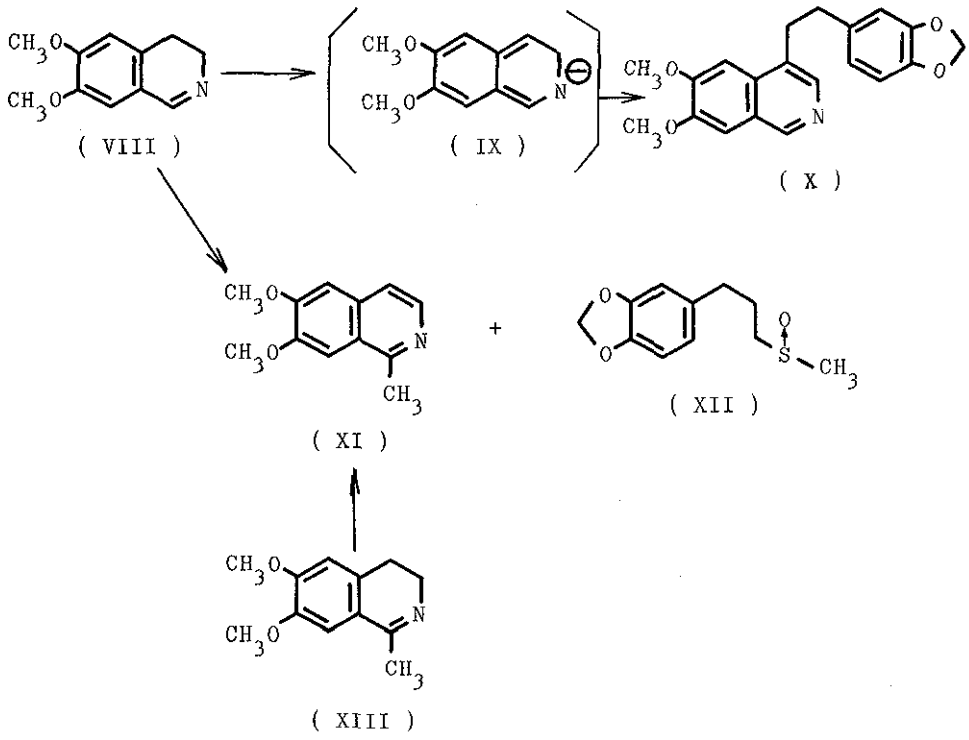


6,7-dimethoxy-1-methyl-4-phenethylisoquinoline (VII). By analogy to (IV), the formation of the compound (VII) can be rationalised *via* intermediate (VI).

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 ($CDCl_3$) 2.89 (s, 3H, C_1-CH_3), 4.0 (s, 6H, 2 x OCH_3), 6.9 - 7.5 (m, 3H, ArH), 8.2 (d, 1H, J 6 Hz, C_3-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 ($CDCl_3$) 2.55 (s, 3H, SO-CH_3), 5.93 (s, 2 H, OCH_2O); 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



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