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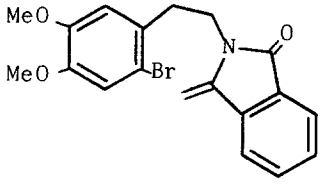
A NOVEL SYNTHESIS OF APORHOEADANES

Somsak Ruchirawat[1,2,3*], Werawat Lertwanawatana[1], Sunit Thianpatanagul[1]
Jesse L. Cashaw[2], and Virginia E. Davis[2,3]

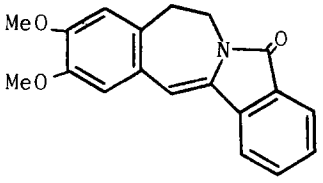
1 Department of Chemistry, Faculty of Science, Mahidol University, Rama VI Road, Bangkok 4, Thailand. 2 Neurochemistry and Addiction Research, Veterans Administration Medical Center, Houston, Texas 77211. 3 Department of Biochemistry, Baylor College of Medicine, Houston, Texas 77025

Abstract: A one-pot synthesis of aporhoeadanes from the reaction of 3,4-dihydroisoquinolines, 2-chloromethylbenzoyl chloride and sodium hydroxide, is described.

Aporhoeadane (I) has previously been synthesized by a multi-step sequence[1]. The key step was effected by irradiation of compound (II) in the presence of triethylamine to give aporhoeadane (I) in 20 % yield. Aporhoeadanes can also be obtained from further transformation of protoberberine derivatives[2] and phthalide-isoquinoline alkaloid[3].

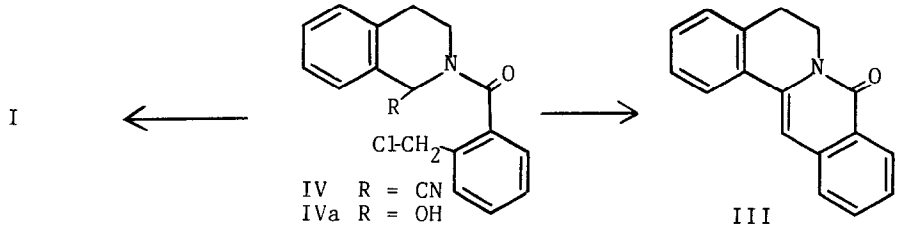


II

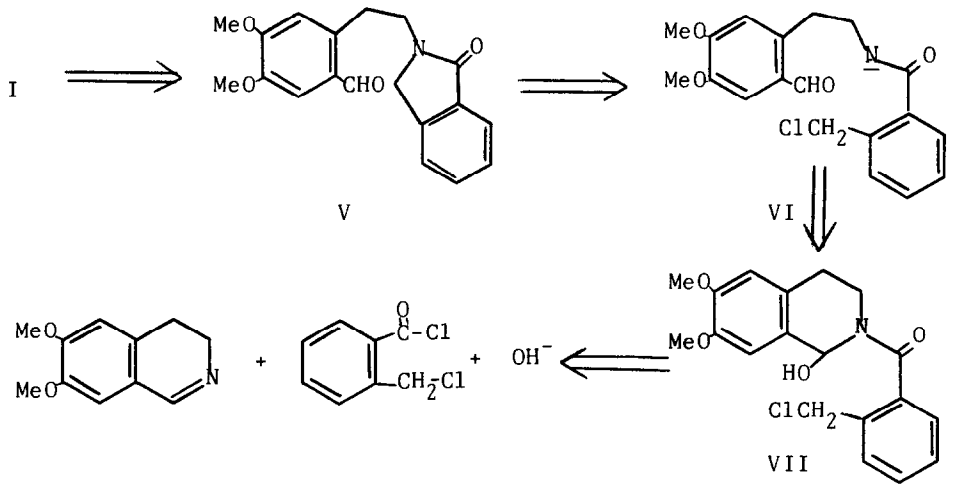


I

We have recently reported[4] the use of 3,4-dihydroisoquinoline and 2-chloromethylbenzoyl chloride to synthesize the 8-oxoprotoberberine (III) via the Reissert compound (IV). We report here a one-pot procedure for the synthesis[5] of aporhoeadanes from 3,4-dihydroisoquinolines and 2-chloromethylbenzoyl chloride via the pseudobase (IVa)



The synthetic approach was based on the retrosynthetic analysis of aporhoeadane skeleton and this is shown in scheme.



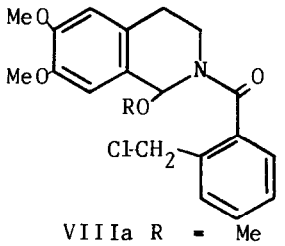
Breaking of carbon-carbon double bond of aporhoeadane (I) could lead to the aldehyde intermediate (V). Cleavage of carbon-nitrogen bond followed by condensation of amide anion (VI) with aldehyde group then gave the pseudobase (VII). Pseudobase (VII) could be formed by the reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline with 2-chloromethylbenzoyl chloride in the presence of hydroxide ion.

On treatment of 3,4-dihydro-6,7-dimethoxyisoquinoline with 2-chloromethylbenzoyl chloride in the presence of sodium hydroxide in benzene solution at room temperature for 0.5 h., two products were isolated by preparative layer chromatography. These two products were identified to be the rather unstable pseudobase (VII)in 35 % yield, ir ($CHCl_3$) 1635 cm^{-1}, nmr ($CDCl_3$) δ 6.67 (HO-C<u>H</u>-N) and aldehyde intermediate (V, 25 % yield), mp (EtOH) 148-150 ^{o}C, ir ($CHCl_3$) 1670, 1685 (shoulder) cm^{-1}, nmr ($CDCl_3$) δ 3.39 (apparent t, J = 8 Hz, C<u>H</u>$_2$-Ar), 3.82, 3.91 (2s, 2xOC<u>H</u>$_3$), 4.32 (s, Ar-C<u>H</u>$_2$-N), 6.82 (s, Ar<u>H</u>), 7.32-8.00 (m,, 5xAr<u>H</u>), 10.32 (s, C<u>H</u>O), ms m/e 325 (M^+), 105 (100%).

Pseudobase (VII) could be smoothly transformed to the aporhoeadane (I) by sodium hydroxide in methanol (1h., room temperature, 59 % yield). As expected, the aldehyde intermediate (V) was similarly transformed to the aporhoeadane (I) in 87 % yield, mp (MeOH) 190-192 ^{o}C., (Lit[1] mp 195-196 ^{o}C).

It is interesting to note that when the condensation was carried out by using benzene as the solvent (heterogeneous condition), no aporhoeadane (I) could be isolated. We reason this is due to the low solubility of sodium hydroxide in benzene and thus further condensation was prevented. However, in such a condition the hydration of the benzoyl iminium intermediate to the corresponding pseudobase was very facile.

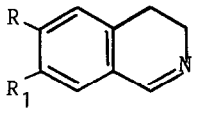
Condensation of 3,4-dihydro-6,7-dimethoxyisoquinoline with 2-chloromethylbenzoyl chloride in benzene solution followed by crystallization in methanol or ethanol gave the expected addition products, (VIIIa) mp 115-116 °C and (VIIIb) mp 120-122 °C in 63 % and 50 %yields respectively.

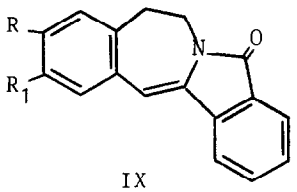


VIIIa R = Me
b R = Et

With the above experimental facts in mind, we have successfully devised a very efficient one-pot synthesis of aporhoeadane (I). The reaction was carried out by condensing 3,4-dihydro-6,7-dimethoxyisoquinoline with 2-chloromethylbenzoyl chloride in the presence of sodium hydroxide in benzene solution for 0.5 h., benzene was then removed from the reaction mixture followed by addition of methanol to the mixture. By the above procedure, moderate yield of aporhoeadane (I) was isolated. Three runs were carried out and the average yield was 59 % after purification by preparative layer chromatography.

The reaction of 2-chloromethylbenzoyl chloride with other 3,4-dihydroisoquinolines in the presence of sodium hydroxide was also investigated in an effort to effect a one-pot synthesis of other aporhoeadanes. For example, reaction of 3,4-dihydro-6-methoxyisoquinoline with 2-chloromethylbenzoyl chloride and sodium hydroxide as in the above procedure gave the aporhoeadane (IXa) in 32 % yield, mp (MeOH) 133-134 °C, ir (nujol) 1685, 1645 cm^{-1}, nmr ($CDCl_3$) 3.03 (t, J=4.5 Hz, Ar$\underline{CH}_2$), 3.78 (s, O$\underline{CH}_3$), 4.1 (t, J=4.5 Hz, $\underline{CH}_2$-N), 6.52 (s, $\underline{CH}$=), 6.7 (s, Ar$\underline{H}$), 6.82-7.92 (m, 5xAr$\underline{H}$), ms m/e 277 (M^+ and base peak). Similarly, 3,4-dihydro-6,7-methylenedioxyisoquinoline gave the aporhoeadane (IXb) mp (MeOH) 213.5-214.5 °C in 27 % yield[6].





IX

a R = OMe R_1 = H

b R + R_1 = -O-CH_2-O-

Our investigation showed that for the success of the synthesis, oxygen at the 6^{th} position of isoquinoline is required and the counterion of the hydroxide group is crucial in the above rearrangement[7].

References and Notes

1) H.O. Bernhard and V. Snieckus, Tetrahedron Lett., 4867 (1971)

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3) a. S. Teitel, W. Klotzer, J. Borgese, and A. Brossi, Can. J. Chem., 50, 2022 (1972), b. J. Trojanek, Z. Vesely, V. Suchan, and J. Holubek, Coll. Czech. Chem. Comm., 40, 681 (1975)

4) S. Ruchirawat, W. Lertwanawatana, and P. Thepchumrune, Tetrahedron Lett., 189 (1980)

5) For a related approach for the synthesis of rhoeadane, see M. Shamma and L. Toke, Tetrahedron, 31, 1991 (1975)

6) All new compounds have been fully characterized.

7) The details of this investigation will be the subject of our future communication.

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