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A CONVENIENT SYNTHESIS OF 8-OXOPROTOBERBERINE DERIVATIVES[1]

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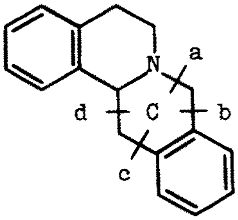
Summary: The annulation of isoquinoline derivatives to form the 8-oxoprotoberberine derivatives is described. The key step of the reaction involves intramolecular alkylation of the Reissert compounds.

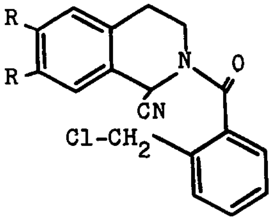
Many synthetic routes[2] have been reported for the synthesis of protoberberine alkaloids. The approaches for the construction of ring C of these alkaloids can be classified into four main approaches i.e. intramolecular Mannich reaction, thermolysis reaction of benzocyclobutene derivatives, variants of the Bischler-Napieralski reaction, photochemical reaction and other miscellaneous reactions. Analysis of various approaches for the construction of ring C from isoquinoline derivatives in term of the carbon-carbon bond formation is illustrated in structure (I)



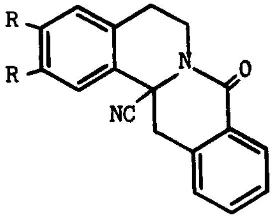
(I)

Simultaneous formation of bonds a and b can be accomplished by intramolecular Mannich reaction. Prominent among other reactions, thermolysis or N-alkylation can be used to form bond a, while bond b and bond c can be formed by photochemical reaction. Bond c formation can also be effected by benzyne reaction.

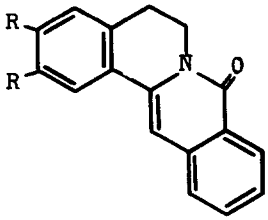
We report here another new approach based on the formation of bond d[3]. Our approach is illustrated in scheme.



(II)



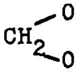
(III)



(IV)

a) R = OMe

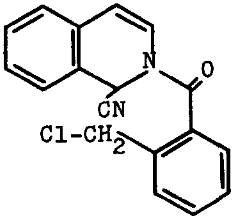
b) R = H

c) R = 

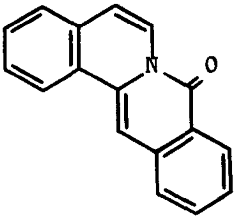
$CH_2\langle^{O}_{O}$

The alkylation of the carbanion of the Reissert compounds with various alkyl halides has been exploited successfully for the synthesis of various isoquinoline derivatives[4]. We reason that the intramolecular alkylation in compound (II) would be much more facilitated and by starting with the Reissert compound (II), compound (III) would be formed which on elimination of HCN could lead to the 8-oxoprotoberberine (IV). To test the above idea, the Reissert compounds (IIa-c) were synthesized. All the Reissert compounds were synthesized by our developed-method[5], i.e. the reaction of 3,4-dihydroisoquinoline with acid chloride and trimethylsilyl cyanide in methylene chloride. Reaction of 6,7-dimethoxy 3,4-dihydroisoquinoline with 2-chloromethylbenzoyl chloride and trimethylsilyl cyanide in methylene chloride gave 2-chloromethylbenzoyl-6,7-dimethoxy-1,2,3,4-tetrahydro isoquinaldonitrile (IIa), mp 175-177°C(EtOH) in 81% yield. Similarly the Reissert compounds[6] (IIb), mp 143-145°C (MeOH) and (IIc), mp 137.5-139 °C (MeOH) were synthesized in 86, 81 % yields respectively. Reactions of the Reissert compounds (IIa-c) with sodium hydride in dimethylformamide at room temperature for o.5 h. led directly to 8-oxoprotoberberine derivatives (IVa[7]), mp 187-190 °C (MeOH), (IVb[8]), mp 98-99 °C (t-butanol) and (IVc) mp 183-184 °C (EtOH) in 92, 87 and 84 % yields respectively. Interestingly, the loss of HCN was very facile and the cyano intermediate (III) could not be isolated from the above reaction.

The reaction could be extended successfully to the synthesis of dehydro-8-oxoprotoberberine derivatives. For example, reaction of isoquinoline with 2-chloromethylbenzoyl chloride, trimethylsilyl cyanide together with a catalytic amount of anhydrous aluminium chloride in methylene chloride gave 2-chloromethylbenzoyl 1,2-dihydroisoquinaldonitrile (V), mp 140-142 °C (MeOH) in 86 % yield. When treated with sodium hydride in dimethylformamide for 0.5 h., the Reissert compound (V) was converted to 5,6,13,14-dehydro-8-oxoprotoberberine (VI), mp 143-145 °C (MeOH) in 87 % yield.



(V)



(VI)

The NMR spectra of the dihydro-Reissert compounds (IIa-c) and the Reissert compound (V) show the characteristic AB quartet due to the geminal coupling of benzylic protons in the benzyl chloride moiety. In the case of the Reissert compound (V), the pattern of the AB quartet is clearly recognized, however, the pattern is less apparent in the dihydro-Reissert compounds.

In conclusion, we have developed a highly efficient synthetic method for the construction of 8-oxoprotoberberine and dehydro -8-oxoprotoberberine nuclei. Since both 8-oxoprotoberberine[9] and dehydro-8-oxoprotoberberine[10] could be converted to the corresponding protoberberine alkaloids, our method could serve for the synthesis of such compounds. Apart from the application to the synthesis of oxygenated 8-oxoprotoberberine derivatives, our method has a distinct advantage for the synthesis of non-oxygenated 8-oxoprotoberberine which can not be obtained conveniently by other previously reported methods. Such methods normally require some activating group for the cyclization either in the final steps or in the synthesis of starting materials.

References and Notes

1) This work was taken in part from M. Sc. thesis of W. Lertwanawatana, Mahidol University 1978.

2) For reviews, see a) M. Shamma, 'The Isoquinoline Alkaloids', Academic Press New York (1972) p. 268; b) M. Shamma and J. L. Moniot, 'Isoquinoline Research' 1972-1977, Plenum Press, New York and London (1978) p. 209; c) T. Kametani, M. Ihara, and T. Honda, Heterocycles, 4, 483 (1976); d) Y. Kondo, Heterocycles, 4, 197 (1976); e) B. R. Pai, K. Nagarajan, S. Suguna, and S. Nagarajan, Heterocycles, 6, 1377 (1977).

3) Recently a different approach for the formation of bond d was reported, see T. Shono, K. Yoshida, K. Ando, Y. Usui, and H. Hamaguchi, Tetrahedron Lett., 4819 (1978).

4) For a review, see F. D. Popp, Heterocycles, 1, 165, (1973).

5) S. Ruchirawat, N. Phadungkul, M. Chuankamnerdkarn, and C. Thebtaranonth, Heterocycles, 6, 43 (1977).

6) All new compounds have been fully characterized and the characteristic ir and nmr absorptions of the Reissert compounds and the 8-oxoprotoberberine derivatives are as follows, compound (IIa) ir 1650 cm^{-1}, nmr δ 6.55 (s, $C\underline{H}$-CN), 4.58, 4.86 (dd, J = 12 Hz, $-C\underline{H}_2Cl$); compound (IIb) ir 1640 cm^{-1}, nmr δ 6.57 (s, $C\underline{H}$-CN), 4.58, 4.84 (dd, J = 12 Hz, $-C\underline{H}_2Cl$); compound (IIc) ir 1650 cm^{-1}, nmr δ 6.59 ($C\underline{H}$-CN), 4.54, 4.83 (dd, J = 12 Hz, $-C\underline{H}_2Cl$); compound (V) ir 1665, 1625 cm^{-1}, nmr δ 6.69 ($C\underline{H}$-CN), 4.48, 4.92 (dd, J = 12 Hz, $-C\underline{H}_2Cl$); compound (IVa) ir 1640, 1615 cm^{-1}, nmr δ 2.94 (t, J = 7 Hz, $-C\underline{H}_2Ar$), 4.39 (t, J = 7 Hz, $-C\underline{H}_2N$), 7.32 (s, C-13 $\underline{H}C=$); compound (IVb) ir 1630, 1610 cm^{-1}, nmr δ 2.98 (t, J = 7 Hz, $-C\underline{H}_2Ar$), 4.28 (t, J = 7 Hz, $-C\underline{H}_2N$), 7.35 (s, C-13 $\underline{H}C=$); compound (IVc) ir 1640, 1615 cm^{-1}, nmr δ 2.9 (t, J = 7 Hz, $-C\underline{H}_2Ar$), 4.35 (t, J = 7 Hz, $-C\underline{H}_2N$), 7.28 (s, C-13 $\underline{H}C=$); compound (VI) ir 1660, 1615 cm^{-1}, nmr δ 6.71 (dd, J = 8 Hz, C-5 $\underline{H}C=$), 7.43 (s, C-13 $\underline{H}C=$), 8.62 (dd, J = 8 Hz, C-6 $=C\underline{H}-N$).

7)Lit mp 189-190 (EtOH), D. W. Brown and S. F. Dyke, Tetrahedron, 22, 2429 (1966).

8)Lit mp 93-94 (ether-hexane), N. C. Yang, A. Shani, and G. R. Lenz, J. Amer. Chem. Soc. 88. 5369 (1966).

9) T. Kametani, T. Honda, T. Sugai, and K. Fukumoto, Heterocycles, 4, 927 (1976).

10) D. W. Brown, S. F. Dyke, M. Sainsbury, and G. Hardy, J. Chem. Soc., 3219 (1971).

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