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NEW BENZYNE APPROACH TO THE SYNTHESIS OF DEHYDROAPORPHINES, 4,5-DIOXOAPORPHINES AND ARISTOLACTAMS

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Abstract: A new strategy for the synthesis of some aporphinoid alkaloids is described. It is based on the intermolecular Diels-Alder cyclization between benzyne and an appropriate methylene isoquinoline derivative.

We have been interested during the past few years in the synthesis of isoquinoline alkaloids, particularly in aporphines and the highly oxidized members of this group[1]. An important feature easily recognizable in them is the presence of a phenanthrene (dehydroaporphines, 4,5-dioxoaporphines, aristolactams and aristolochic acids) or dihydrophenanthrene (aporphines) system.

We have now achieved a benzyne promoted synthesis of some oxidized members of the aporphine alkaloid group, including the first total synthesis of norcepharadione B and its N-methylated derivative as shown in Fig I. It is based on the intermolecular Diels-Alder reaction between a benzyne as dienophile and an adequately substituted methylene isoquinoline as diene.

Thus, to a refluxing DME solution of 1[2] containing a catalytic amount of trichloroacetic acid[3] an excess of both anthranilic acid and isoamylnitrite in DME were slowly and simultaneously added during 5 hrs. followed by 2 hrs. refluxing. A crude mixture was thus obtained, which after column chromatography afforded a 40% yield of N-acetyl-dehydronornuciferine 4[4]. Surprisingly the dihydroderivative of 4 could not be detected in the reaction mixture. This behaviour which is apparently a dehydrogenation of the initially formed dihydrophenanthrene by the benzyne had also been reported in other cases[5].

Having achieved the synthesis of dehydroaporphines such as 4 we have applied the same concept to the synthesis of 4,5-dioxoaporphines. Thus the required methylene derivative 2 was prepared through the sequence[6] shown in Fig II, starting from isoquinoline 7[7]. As 2 was found to be

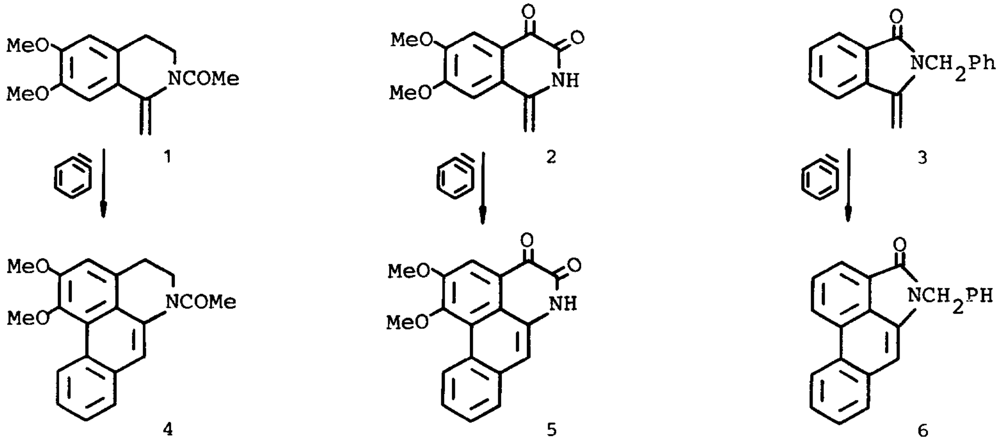

Fig I

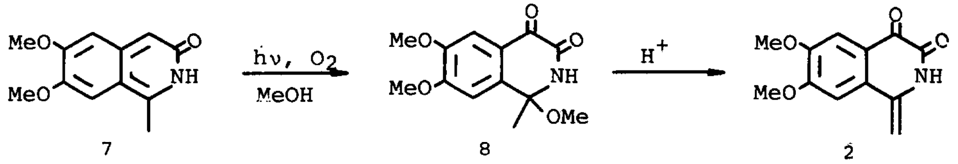

Fig II

unstable , we turned our attention to its precursor 8 which under acidic conditions slowly transforms into 2. As expected, the reaction of 8[4] with benzyne under the above mentioned conditions yielded norcepharadione B 5 in 40% yield. This compound was found to possess the same spectroscopic properties to the ones reported for the natural alkaloid[9]. Furthermore, its methylation (NaH, DMF, FSO_3Me) gave a 65% yield of cepharadione B totally identical to an authentic sample[8].

Finally we tested the possibility of synthesizing aristolactams such as 6.It was clear to us that the methylene phthalimidine 3 had a forced geometry which might effectively reduce the necessary overlapping of the extremes of the diene and dienophile. Our expectations were confirmed since we found that the reaction of benzyne,generated from anthranilic acid as above, and the methylene phthalimidine 3[10] directly produced the arislolactam 6[4] in only 22% yield.

In summary, a new convergent synthesis of some isoquinoline alkaloids is described.We believe its generality is evident although further synthetic tests will be necessary to prove its present importance.Another remarkable fact is that,in all cases, we were unable to detect the presence of any dihydrophenanthrene derivative.Further work in this area will also be needed to determine the full scope of this observation.

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4. All new compounds gave correct elemental analysis. 4 was obtained as prisms,mp, 94-6°C (ether-hexane),λ_{max}(EtOH):260,312(sh),322,351,369 nm;IR(KBr):1630 cm^{-1};NMR($CDCl_3$,δ)2.30(s,3H), 3.19(t,2H,J=5.6Hz),3.93(s,3H),4.02(s,3H),4.19(t,2H,J=5.6Hz),7.13(s,1H),7.29-7.76(m, 4H) , 9.54-9.56(m,1H) ppm;mass spectrum m/e (%): 321 (M^+, 35), 279 (15).
   8 crystallized from MeOH mp 150°C(d),λ_{max}(EtOH), 222, 247, 305, 341 nm;IR(KBr), 3200, 1700, 1690 cm^{-1};NMR($CDCl_3$,δ),1.86(s,3H),3.02(s,3H),3.96(s,3H),4.00(s,3H),6.90(s,1H),7.54(s,1H); mass spectrum m/e (%), 265 (M^+, 2), 235 (13), 234 (12),206 (35) , 31 (100).
   6 crystallized from EtOH, mp 174-6°C;λ_{max} (EtOH), 224, 233(sh), 246, 286, 298, 316(sh), 380 nm;IR(KBr), 1720, 1650 cm^{-1};NMR ($CDCl_3$,δ), 5.19(s,2H), 6.97(s,1H), 7.27-8.20(m, 10 H), 8.42-8.65 (m,2H);mass spectrum m/e (%), 309(M^+, 8), 218 (5), 191 (17), 91 (100).
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