SYNTHESIS OF OXOAPORPHINE BY PHOTOLYSIS: A TOTAL SYNTHESIS OF ATHEROLINE

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Two-step oxidation of 1-(3-benzyloxy-4-methoxybenzyl)-8-bromo-3,4-dihydro-6,7-dimethoxyisoquinoline (4), followed by debenzylation, addorded 8-bromo-1-(3-hydroxy-4-methoxybenzoyl)-6,7-dimethoxyisoquinoline (8), the irradiation of which yielded atheroline (1) and its positional isomer (3).

The structure of atheroline, isolated from Atherosperma moschatum,[1] was assigned to a phenolic oxoaporphine (1) by spectroscopic evidences and comparisons with synthetic O-ethylatheroline (2).[2] Cava and Noguchi confirmed the structure (1) by the total synthesis applying Pschorr reaction.[3] Oxoaporphines have recently drawn an attention from the pharmacological point of view.[4] Therefore we have been interested in an effective synthesis of oxoaporphine and now wish to report a synthesis of atheroline (1) by photolysis. By this procedure, a product (3), formed by coupling ortho to hydroxyl group, was also obtained.

A solution of 1-(3-benzyloxy-4-methoxybenzyl)-8-bromo-3,4-dihydro-6,7-dimethoxyisoquinoline (4)[5] in methanol was kept aside at room temperature for 6 days to give, in 65 % yield, 1-benzoyl-3,4-dihydroisoquinoline (5), mp 152 - 154° (from ethanol-chloroform), ν_{max} ($CHCl_3$): 1660 cm^{-1} (C=O), δ($CDCl_3$): 3.78, 3.87 and 3.90 (each 3H, each s, 3 x OMe), 5.16 (2H, s, $OC\underline{H}_2Ph$), and 6.73 ppm (1H, s, C_5 - H). During the above reaction, a small amount of 8-bromocorydaldine (6), mp 197 - 198° (from methanol-benzene), ν_{max} ($CHCl_3$): 1660 cm^{-1} (C=O), δ($CDCl_3$): 3.80 and 3.88 (each 3H, each s, 2 x OMe), and 6.69 ppm (1H, s, C_5 - H), also formed.

Refluxing 5 with sodium hydroxide in ethanol for 1 hr afforded, in 45 % yield, the 1-benzoylisoquinoline (7), mp 153 - 154° (from methanol) ν_{max} ($CHCl_3$): 1655 cm^{-1} (C=O), δ($CDCl_3$): 3.86 (6H, s, 2 x OMe), 3.97 (3H, s, OMe), 5.12 (2H, s, OCH_2Ph), 6.80 (1H, d, $\underline{J}$ 8 Hz, C_5, - H), 7.10 (1H, s, C_5 - H), 7.17 - 7.40 (6H, m, C_6, - H and 5 x ArH), 7.47 (1H, d, $\underline{J}$ 5.6 Hz, C_4 - H), 7.62 (1H, d, $\underline{J}$ 2 Hz, C_1, - H) and 8.35 ppm (1H, d, $\underline{J}$ 5.6 Hz, C_3 - H) and 8-bromocorydaldine (6) in a trace yield.

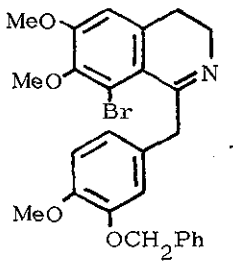
Debenzylation of the former 1-benzoylisoquinoline (7) by refluxing in a mixture (1 : 1 v/v) of methanol and concentrated hydrochloric acid afforded, in 70 % yield, the phenolic isoquinoline (8), mp 210 - 211° (decomp.) (from methanol), ν_{max} ($CHCl_3$): 3550 (OH) and 1660 cm^{-1} (C=O), δ (DMSO-d_6): 3.82 (6H, s, 2 x OMe), 4.02 (3H, s, OMe), 6.92 (1H, d, $\underline{J}$ 8 Hz, C_5, - H), 7.13 (1H, dd, $\underline{J}$ 8 and 2 Hz, C_6, - H), 7.25 (1H, d, $\underline{J}$ 2 Hz, C_2, - H), 7.63 (1H, s, C_5 - H), 7.87 (1H, d, $\underline{J}$ 5.6 Hz, C_4 - H) and 8.43 ppm (1H, d, $\underline{J}$ 5.6 Hz, C_3 - H).

Irradiation of the phenolic 1-benzoylisoquinoline (8) through Vycor

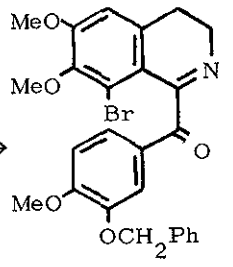
filter with a 450 W mercury lamp in the presence of sodium hydroxide in methanol for 2.6 hr, followed by purification of the crude product with silica gel column chromatography, yielded the compound A, mp 219 - 220° in 2.5 % yield and compound B, mp 250 - 251° in 24 % yield together with a small amount of the starting material (8). The structure of compound A was assigned 11-hydroxy-1,2,10-trimethoxy-7-oxoaporphine (3) on the basis of the following spectroscopic data, λ_{max} (MeOH): 271, 353, and 412 nm (log ε : 4.49, 3.94, and 3.97), ν_{max} ($CHCl_3$) 1666 cm^{-1} (C = O), δ($CDCl_3$) 3.90, 4.06 and 4.11 (each 3H, each s, 3 x OMe), 7.15 (1H, d, J 9 Hz, C_9 - H), 7.20 (1H, s, C_3 - H), 7.75 (1H, d, J 5.6 Hz, C_4 - H), 8.11 (1H, d, J 9 Hz, C_8 - H), 8.85 (1H, d, J 5.6 Hz, C_5 - H), and 9.29 ppm (1H, broad s, OH, disappeared with D_2O), m/e 337 (M^+). The formation of 3 by coupling ortho to hydroxyl group seemd to be intersting because an irradiation of phenolic 8-bromotetrahydroisoquinoline (9) had given selectively only (±)-N-methyllaurotetanine (10) by coupling para to the hydroxyl group.[5]

The uv and nmr spectra of the compound B were consistent with the reported data for atheroline (1)[3] and the structure was further confirmed by conversion of compound B into the O-acetate (11), mp 216 - 218° (decomp.) (lit.,[3] 216 - 218°), whose ir and nmr spectra were identical with the previously reported ones.[3]

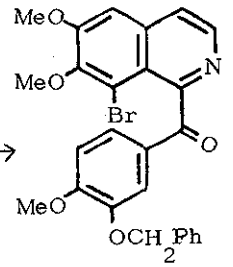
Thus, a total synthesis of atheroline has been accomplished and it is very intersting that two position isomers were formed by irradiation of phenolic 8-bromoisoquinoline.



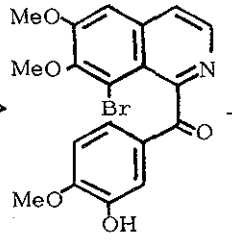
(4)



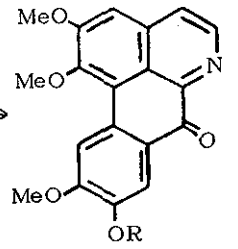
(5)



(7)

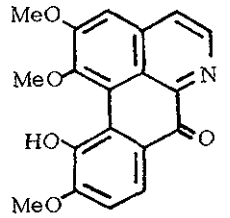


(8)

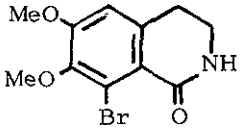


(1) R = H
(2) R = CH_2Me
(11) R = Ac

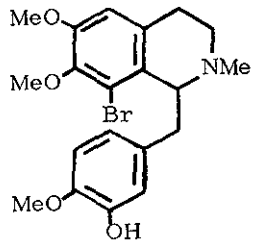
+



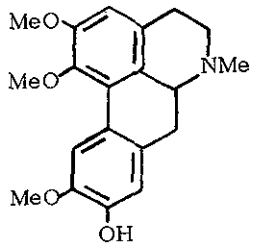
(3)



(6)



(9)



(10)

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