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SYNTHESIS OF AAPTAMINE, A NOVEL MARINE ALKALOID

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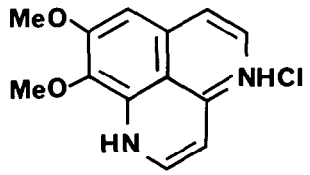
Summary: The novel sponge alkaloid aaptamine has been synthesized for the first time by an efficient route starting from 6-methoxy-7-hydroxy-3,4-dihydroisoquinoline.

The isolation and structure determination of the novel marine alkaloid aaptamine (1) was reported in 1982. Aaptamine, which occurs in the Okinawan sea sponge Aaptos aaptos, is of considerable interest both as a remarkable α-adrenoceptor blocking agent and as the first example of a new heterocyclic system, 1H-benzo[de]-1,6-naphthyridine.[1] We now report the first synthesis of aaptamine.

The readily available 6-methoxy-7-hydroxy-3,4-dihydroisoquinoline[2] (2) was nitrated regioselectively[3] to give (60%) the yellow 8-nitro derivative (3), mp 235-240°C.[4] When (3) was heated to 120°C with the monoethyl ester of malonic acid,



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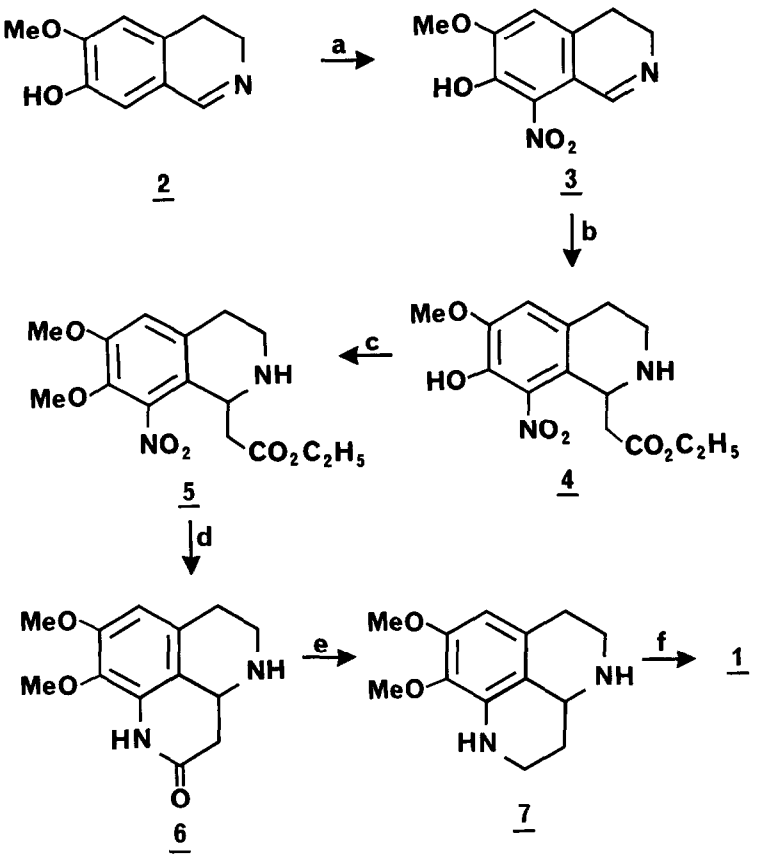
it was converted (70%) into the orange-red nitro ester (4), mp 158-159°C. Diazomethane methylation of (4) afforded (100%) the corresponding methyl ether (5), mp 97-99°C. Catalytic hydrogenation of (5) gave directly (65%) the δ-lactam (6), mp 162-164°C. Diborane reduction of (6) proceeded cleanly to give (95%) hexahydroaaptamine (7), mp 114-116°C. Palladium dehydrogenation of (7) afforded aaptamine (1), isolated as yellow needles of its chloride salt (60%), mp 107°C. All spectral characteristics of this chloride were identical with those reported for the natural product.[5]

The α-blocking activity of aaptamine strongly suggests the desirability of synthesizing more or less highly oxygenated analogs for pharmacological evaluation. Work is in progress in our laboratories on the synthesis of such analogs.



a) 40% HNO_3, $NaNO_2$ (cat.), 5°; b) $HO_2CCH_2CO_2Et$ (1.3 eq.), 120°;

c) CN_2N_2, Et_2O, CH_2Cl_2; d) H_2, Pd-C, 10% HCl; e) BH_3, THF;

f) 5% Pd-C, xylene, reflux.

References

1. H. Nakamura, J. Kobayashi, Y. Ohizumi, Y. Hirata, Tetrahedron Lett., 5555 (1982).
2. A. Brossi, J. O'Brien, S. Teitel, Org. Preps. and Procs., 2, 281 (1970).
3. C. Casagrande and L. Canonica, J. Chem. Soc. Perkin I, 1647 (1975).
4. All new compounds were characterized by ^1H NMR spectroscopy and elemental analysis.
5. 1: ^1N HMR (DMSO-d_6) δ 13.1 (1 H, d, J = 4.5 Hz), 12.3 (1 H, d, J = 5.3 Hz), 7.85 (1 H, dd, J = 6.6 Hz), 7.41 (1 H, dd, J = 7.0 Hz and J = 8.4), 7.13 (1 H, s), 6.88 (1 H, d, J = 7.1 Hz), 6.47 (1 H, d, J = 7.0 Hz), 3.98 (3 H, s), 3.82 (3 H, s); UV (H_2O) λ max 216 (ε = 10,800), 237 (ε = 11,600), 254 (ε = 12,700), 310 (ε = 4900), 348 (ε = 4200), 380 (4700).

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