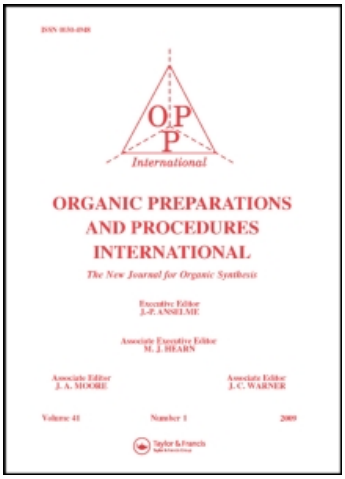

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USE OF 5,8-DIMETHOXYQUINOLINES IN THE SYNTHESIS OF NOVEL 5,12-DIHYDROXY-6,11-DIOXO-1-AZANAPHTHACENES

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USE OF 5,8-DIMETHOXYQUINOLINES IN THE SYNTHESIS OF NOVEL 5,12-DIHYDROXY-6,11-DIOXO-1-AZANAPHTHACENES

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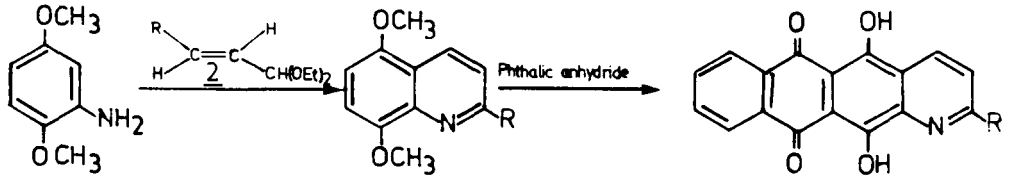
The naphthacene nucleus is present in tetracycline[1] and anthracycline[2] antibiotics. The replacement of one methine group by nitrogen at positions 1, 2, or 5 gives the corresponding azanaphthacene[3]. The synthesis of 1-azanaphthacene is less common as compared to the synthesis of 2- and 5-azanaphthacenes. We now report a convenient synthesis of new 5,12-dihydroxy-6,11-dioxo-1-azanaphthacenes starting from 5,8-dimethoxyquinolines. The required



1 3 4

a) R = H b) R = CH_3

5,8-dimethoxyquinolines (3a and 3b) were prepared by a modified Skraup reaction[4] of 2,5-dimethoxyaniline (1) with acrolein diethylacetal (2a) or crotonaldehyde diethylacetal (2b) in the presence of arsenic pentoxide/phosphoric acid.

The condensation of quinolinic anhydride with 1,4-dihydroxynaphthalene is the only reported[5] method for the synthesis of 6,11-dihydroxy-5,12-dioxo-1-azanaphthacene. The cyclo-condensation of phthalic anhydride with 5,8-dimethoxyquinolines (3a and 3b) in $AlCl_3$/NaCl (2:1) melt at 180-85°C gives the 5,12-dihydroxy-6,11-dioxo-1-azana- phthacenes (4a and 4b) in 35% and 38% yields respectively. The structure of the title compounds (4a and 5b) have been confirmed by various spectroscopic and analytical data.

EXPERIMENTAL SECTION

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Ultraviolet-visible spectra were recorded on a Shimadzu-UV 260 spectro-photometer. Infrared spectra were determined on a Perkin-Elmer FTIR-1710 spectro-photometer. Nuclear magnetic resonance spectra were determined on a Joel FX-200 (200 MHz) Fourier transform instrument and a Perkin-Elmer R 32 (90 MHz) instrument using TMS as the internal reference. Mass spectra were determined on a Jeol JMS-D-300 mass spectrometer.

General Procedure for the Preparation of 5,8-Dimethoxyquinolines (3).- A mixture of 2,5-dimethoxyaniline (1) (19 mmol), arsenic pentoxide (20 mmol) and phosphoric acid (25 ml)

was heated in an oil bath to 75-80°C and 2 (23 mmol) was added drop by drop to the mixture with stirring. Following the addition, the mixture was stirred an additional hour at the same temperature. Then it was cooled and poured into cold water (100 ml). The aqueous solution was made alkaline (pH8) with ammonium hydroxide. The precipitated solid was collected, dried and extracted with cyclohexane using a Soxhlet apparatus. The resulting product was purified by column chromatography on silica gel using benzene as the eluent followed by recrystallization from petroleum ether.

5,8-Dimethoxyquinoline (3a), yield 16%, mp. 74-75°, lit.[6] mp. 75-76°. IR (Nujol): 1616, 1590, 1260, 1230, 1140, 1100, 1090, cm^{-1}; NMR ($CDCl_3$): δ 3.90 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 6.72 (d, 1H, J = 8Hz, H-7), 6.90 (d, 1H, J = 8Hz, H-6), 7.40 (m, 1H, H-3), 8.56 (d, 1H, J = 8Hz, H-4), 8.95 (d, 1H, J = 8Hz, H-2).

5,8-Dimethoxy-2-methylquinoline (3b), yield 22%; mp. 84°, lit.[7] mp. 84-85° IR (Nujol): 1610, 1595, 1260, 1220, 1140, 1100, 1090 cm^{-1}, NMR ($CDCl_3$): δ 2.72 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.67 (d, 1H, J = 8Hz, H-7), 6.90 (d, 1H, J = 8Hz, H-6), 7.28 (d, 1H, J = 8Hz, H-3), 8.45 (d, 1H, J = 8Hz, H-4).

General Procedure for the Synthesis for 1-Azanaphthacenes (4).- Phthalic anhydride (2 mmol) and 3 (1 mmol) were added to a melt of sodium chloride (10 mmol) and aluminium chloride (23 mmol) kept at 180-85°C and heated for 5 min under a nitrogen atmosphere. The reaction mixture was cooled to 0-5°C and treated with a saturated solution of oxalic acid (75 ml) added drop-wise over 15 min with stirring. Following the addition, the mixture was stirred 3 hrs at room temperature, then extracted with chloroform (3 X 100 ml). The extract was dried (Na_2SO_4) and purified by column chromatogaphy on silica gel using chloroform as the eluent followed by recrystallization from chloroform.

5,12-Dihydroxy-6,11-dioxo-1-azanaphthacene (4a), yield 33%; mp. >300°; UV-visible (CH_2Cl_2): 260.2 (e 48,850), 452.0 (e 11,200), 479.2 (e 16,280), 512.0 (e 12,340); IR (KBr): 1625, 1570, 1415, 1360, 1240, 1040 cm^{-1}; NMR ($CDCl_3$): δ 7.76 (m, 1H, H-3), 7.90 (m, 2H, H-8 & H-9), 8.50 (m, 2H, H-7 & H-10), 8.86 (d, 1H, H-4), 9.20 (m, 1H, H-2), 14.90 (s, 2H, OH-12 & OH-5); EIMS, m/z (relative intensity): 291.0 (M^+, 100.0), 292.0 (19.8), 263.0 (7.9), 179.0 (9.4), 178.0 (6.7), 76.0 (4.5).

Anal. Calcd. for $C_{17}H_9NO_4$: C, 70.09; H, 3.12; N, 4.59. Found: C, 70.22; H, 3.15; N, 4.77

5,12-Dihydroxy-6,11-dioxo-2-methyl-1-azanaphthacene (4b), yield 38%; mp. 290°, UV-\visible (CH_2Cl_2): 261.0 (ε 59,620), 453.0 (ε 13,500), 497.8 (ε 18,710), 513.6 (ε 14,500); IR (KBr): 1619, 1584, 1561, 1415, 1385, 1342, 1264, 1041, 1019 cm^{-1}, NMR ($CDCl_3$): δ 2.84 (s, 3H, 2-Me), 7.48 (d, 1H, J = 8.0 Hz, H-3), 7.88 (m, 2H, H-8 & H-9), 8.48 (m, 2H, H-7 & H-10), 8.72 (d, 1H, J = 8.0 Hz, H-4), 14.88 (s, 1H, OH-5), 15.00 (s, 1H, OH-12); EIMS, m/z (relative intensity): 305.0 (M^+, 100.0), 306.0 (22.3), 277.0 (8.6), 193.0 (7.7), 192.0 (3.6), 165.0 (3.1), 139.0 (2.9).

Anal. Calcd for $C_{18}H_{11}NO_4$: C, 70.81; H, 3.64; N, 4.59 Found: C,70.87; H, 3.65; N, 4.60

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A CONVENIENT SYNTHESIS OF POLYFLUORINATED α, ω-DIAMINES

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Recent reports of the synthesis of fluorinated diamines[1,2] coupled with their particular interest as non-invasive tumor imaging agents[2] prompt us to communicate our own convenient preparation of symmetrically fluorinated putrescine (4a) and cadaverine (4b) analogs as well as some of their bisamide and bisurea derivatives, 5 and 6, respectively.

In the evaluation of synthetic methodology toward the preparation of 4, three pathways were considered: 1) hydride reduction of perfluorosuccinamide and perfluoroglutaramide, 2) reduction of the corresponding perfluoro-α, ω-dinitriles, and 3) reduction of the dia- zides 3. Although the lithium aluminum hydride (LAH) reduction of perfluoroglutar- amide[3,4] has been reported to yield 4b, explosions have occurred using this procedure.[5] Use of borane-THF apparently cirvuments this hazard, although low yields of 4a were reported for the reduction of