Synthesis of 2- and 4-Substituted 5,12-Dihydroxy-6,11-dioxo-1-azanaphthacenes from 2-Aminoquinizarine

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The reaction of 2-aminoquinizarine with α,β-unsaturated carbonyl compounds in presence of 10*N*-hydrochloric acid gives 2- and 4-substituted 5,12-dihydroxy-6,11-dioxo-1-azanaphthacenes.

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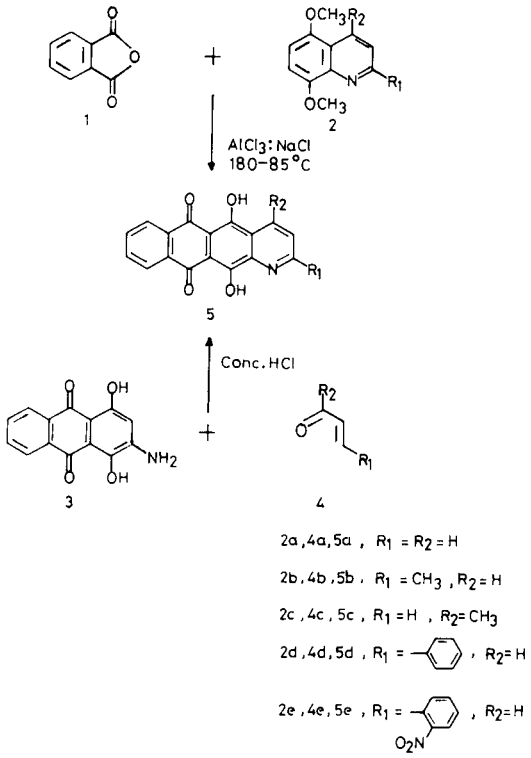
Recently, we have reported the synthesis of 5,12-dihydroxy-6,11-dioxo-1-azanaphthacenes [1], 5,12-dihydroxy-6,11-dioxo-1,2,3,4-tetrahydro-1-azanaphthacenes [2] and 6,11-dioxo-4,5,12-trihydroxy-1-azanaphthacenes [3] by the cyclocondensation of 5,8-dimethoxyquinolines **2**, 5,8-dimethoxy-1,2,3,4-tetrahydroquinolines and ethyl 5,8-dimethoxy-4-hydroxyquinoline-3-carboxylate respectively with phthalic anhydride, in the presence of sodium aluminium chloride melt. There is only one report regarding the synthesis of 1-azanaphthacene by reaction of 2-aminoquinizarine (**3**) with glycerol [4]. Here we wish to report the synthesis of different 2- and 4-substituted 5,12-dihydroxy-6,11-dioxo-1-azanaphthacenes **5b-5e** by the reaction of 2-aminoquinizarine (**3**) with different, α,β-unsaturated carbonyl compounds (Scheme I).

The required 2-aminoquinizarine (**3**) was prepared by modification of a known procedure [4]. The reaction of **3** with crotonaldehyde (**4b**) in the presence of 10N hydrochloric acid gave 5,12-dihydroxy-6,11-dioxo-2-methyl-1-azanaphthacene (**5b**) in 31% yield. The characteristic peaks at 453.0, 497.8 and 513.6 nm in visible spectrum (dichloromethane) of **5b** shows the presence of 5,12-dihydroxy-6,11-dioxo-1-azanaphthacene chromophore [1]. In the ^{1}H nmr spectrum, the presence of peaks for the protons in the A ring and the molecular ion peak in the mass spectrum confirms the structure of **5b** (see Experimental).

Similarly, the reaction of **3** with methyl vinyl ketone (**4c**) gave the 4-methyl-1-azanaphthacene **5c** in 39% yield. The reaction of cinnamaldehyde (**4d**) and 2-nitrocinnamaldehyde (**4e**) with **3** gave 5,12-dihydroxy-6,11-dioxo-2-phenyl-1-azanapthacene (**5d**) in 16% yield and 5,12-dihydroxy-6,11-dioxo-2-(2′-nitrophenyl)-1-azanaphthacene (**5e**) in 14% yield respectively. The structure of all the compounds were confirmed by different spectroscopic and analytical data.

Scheme 1



1 2 5 3 4

2a,4a,5a, $R_1 = R_2 = H$

2b,4b,5b, $R_1 = CH_3$, $R_2 = H$

2c,4c,5c, $R_1 = H$, $R_2 = CH_3$

2d,4d,5d, R_1 = , $R_2 = H$

2e,4e,5e, R_1 = , $R_2 = H$

EXPERIMENTAL

General Information.

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 spectrophotometer. Infrared spectra were determined on a Perkin Elmer FT IR-1710 spectrophotometer. Proton magnetic resonance spectra were determined on Jeol FX-200(200 MHz) Fourier transform instrument and a Perkin Elmer R-32(90 MHz) using TMS as an internal reference. Mass spectra were determined on a Jeol JMS D-300 mass spectrometer (70 eV).

2-Aminoquinizarine (**3**).

To an aqueous solution (600 ml) of quinizarine (5.75 g, 0.022 mole) and hydroxylamine hydrochloride (5 g, 0.07 mole), aqueous sodium hydroxide (40%, 14 ml) and added. The reaction mixture was heated for 10 hours at 95-100°. The reaction mixture was cooled to room temperature and acidified with hydrochloric acid to give 2-aminoquinizarine (**3**). The solid was filtered and recrystallized from nitrobenzene, yield 54%, mp 309° lit [4] mp 312°; uv-visible (acetonitrile): λ max (ε max m*M*) 235 (34.5), 262.4 (41.10), 502.6 (14.4); ir (potassium bromide): 3425, 3345, 3190, 1640, 1622, 1590, 1350, 1260, 1210, 820; ^{1}H nmr (DMSO-d_6): δ 6.28 (s, 1H, H-3), 7.12 (br, 2H, NH_2), 7.80 (m, 2H, H-6 and H-7), 8.20 (m, 2H, H-5 and H-8), 13.63 (br, 1H, -OH-1), 14.08 (s, 1H,

-OH-4); ms: m/z (relative intensity): 255 (M^+, 100.0), 256 ($M^+ + 1$, 40), 254 (16.25), 227 (6.25), 199 (2.5), 198 (3.75), 171 (2.5), 170 (5.0), 142 (3.75).

General Procedure for the Synthesis of 5,12-Dihydroxy-6,11-dioxo-1-azanaphthacenes **5b-5e**.

To a stirred solution of 2-aminoquinizarine (0.5 g) in concentrated hydrochloric acid (15 ml), α,β-unsaturated carbonyl compound (**4b**, **4c**, 10x molar excess, **4d**, **4e**, 2x molar excess) was added dropwise at 70-80° and the reaction mixture was refluxed for two hours with stirring. After cooling the mixture to room temperature, poured into cold water (200 ml). The solid separated was collected and washed with water, dried and subjected to column chromatography on silica gel. On eluting the column with petroleum ether:benzene (1:1), the unreacted 2-aminoquinizarine was obtained and on further elution of column with benzene or chloroform gave 1-azanaphthacenes **5b-5e** which were further purified by crystallization.

5,12-Dihydroxy-6,11-dioxo-2-methyl-1-azanaphthacene (**5b**).

This compound was obtained in a yield of 31%, mp 289-290° lit [1] mp 290°; uv-visible (dichloromethane): λ max (ε max m*M*) 261.0 (59.6), 453.0 (13.5), 497.8 (18.7), 513.6 (14.5); ir (potassium bromide): 1619, 1584, 1561, 1415, 1385, 1342, 1041, 1019 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.84 (s, 3H, $-CH_3$), 7.48 (d, 2H, J = 8.0 Hz, H-3), 7.88 (m, 2H, H-8 and H-9), 8.48 (m, 2H, H-7 and H-10), 8.72 (d, 1H, J = 8.0 Hz, H-4), 14.88 (s, 1H, OH-5), 15.0 (s, 1H, OH-12); ms: 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 (2.1).

Anal. Calcd. for $C_{18}H_{11}NO_4$: C, 70.81; H, 3.64; N, 4.591. Found: C, 70.87; H, 3.6; N, 4.60.

5,12-Dihydroxy-6,11-dioxo-4-methyl-1-azanaphthacene (**5c**).

This compound was obtained in a yield of 39%; mp > 300°; uv-visible (dichloromethane): λ max (ε max m*M*) 263.2 (45.7), 460.2 (11.0), 480.6 (15.5), 521.0 (12.7); ir (potassium bromide): 1618, 1583, 1508, 1410, 1380, 1255, 1085, 1070, 1055; ^1H nmr (deuteriochloroform): δ 3.08 (s, 3H, CH_3), 7.50 (d, 1H, J = 5.0 Hz, H-3), 7.89 (m, 2H, H-8 and H-9), 8.51 (m, 2H, H-7 and H-10), 8.98 (d, 1H, J = 5.0 Hz, H-2), 15.05 (1H, 5-OH), 15.88 (1H, 12-OH); ms: m/z (relative intensity): 305.0 (100.0), 306 (42.0), 277 (8.6), 276.0 (5.0), 248.0 (4.0), 220.0 (3.0), 193.0 (11.0), 192.0 (8.0), 165.0 (8.0).

Anal. Calcd. for $C_{18}H_{11}NO_4$: C, 70.81; H, 3.64; N, 4.59. Found: C, 70.71; H, 3.74; N, 4.54.

5,12-Dihydroxy-6,11-dioxo-2-phenyl-1-azanaphthacene (**5d**).

This compound was obtained in a yield of 16%, mp 264-265° (benzene): uv-visible (dichloromethane): λ max (ε max m*M*): 284.2 (33.9), 322.6 (29.7), 448.0 (14.3), 484.2 (19.4), 517.2 (15.3); ir (potassium bromide): 1618, 1580, 1545, 3120, 840, 725 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.50 (m, 2H, H-3′ and H-5′), 7.80 (m, 2H, H-8 and H-9), 8.12 (d, 1H, J = 8.0 Hz, H-3), 8.24 (m, 3H, H-2′, H-4′ and H-6′), 8.44 (m, 2H, H-7 and H-8), 8.86 (d, 1H, J = 8.0 Hz, H-4), 14.87 (1H, OH-5), 14.92 (s, 1H, OH-12); ms: m/z (relative intensity): 367.0 (M^+, 100.0), 368.0 ($M^+ + 1$, 33.3), 339.0 (8.66), 311.0 (1.25), 310.0 (2.5), 283.0 (1.25), 282.0 (1.25), 255.0 (6.29), 254.0 (7.65).

Anal. Calcd. for $C_{23}H_{13}NO_4$: C, 75.19; H, 3.56; N, 3.81. Found: C, 74.95; H, 3.90; N, 3.32.

5,12-Dihydroxy-6,11-dioxo-2(2′-nitrophenyl)-1-azanaphthacene (**5e**).

This compound was obtained in a yield of 14%, mp > 300° (chloroform); uv-visible (dichloromethane): λ max (ε max m*M*) 263.6 (8.92), 454.0 (2.47), 481.2 (3.10), 514.8 (2.38); ir (potassium bromide): 1635, 1595, 1560, 1520, 1344, 853, 773 cm^{-1}, ^1H nmr (deuteriochloroform): δ 7.60-7.80 (m, 3H, aromatic), 7.82 (d, 1H, H-3), 7.90 (m, 2H, H-8 and H-9), 8.10 (m, 1H, aromatic), 8.50 (m, 2H, H-7 and H-10), 8.92 (d, 1H, H-4); ms: m/z (relative intensity): 412.0 (M^+, 100.0), 413.0 ($M^+ + 1$, 27.1), 382.0 (31.7), 366.0 (7.7).

Anal. Calcd. for $C_{23}H_{12}N_2O_6$: C, 66.99; H, 2.93; N, 6.78. Found: C, 66.60; H, 2.98; N, 6.69.

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