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NAPHTHOINDOLES.

8.* ELECTROPHILIC SUBSTITUTION REACTIONS OF 4,11-DIMETHOXYNAPHTHO[2,3-*f*]INDOLE-5,10-DIONE

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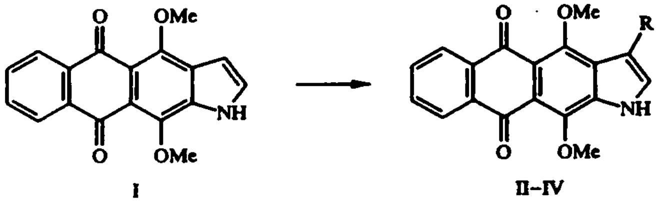
Some electrophilic substitution reactions characteristic of indole derivatives have been investigated for 4,11-dimethoxynaphtho[2,3-f]indole-5,10-dione. The corresponding 3 derivatives were obtained as a result of Vilsmeier, Mannich, and acylation reactions.

With the aim of studying the reactivity of 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione, synthesized previously [1], we have investigated certain electrophilic substitution reactions typical of indoles using weak electrophiles, as in the Vilsmeier, Mannich, and acylation reactions.

4,11-Dimethoxy-3-N,N-dimethylaminomethylnaphtho[2,3-*f*]indole-5,10-dione (II) was obtained in 70% yield by the reaction of 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (I) with dimethylamine and formaldehyde at 25°C by the method of [2] according to the Mannich reaction.



II R = CH_2NMe_2; III R = CHO; IV R = COMe

The use of a more efficient aminomethylating reagent, viz. N,N-dimethyl(methylene)ammonium chloride (crystalline Mannich reagent) [3], enabled compound (II) to be obtained chromatographically pure and requiring no further purification. Its yield was increased to 85%.

A comparison showed that the reactivities of unsubstituted naphtho[2,3-*f*]indole-5,10-dione [4] and of the naphthoindoledione (I) were practically identical in the aminomethylation reaction. The yields of Mannich bases were 88 and 85% respectively.

Formylation by the Vilsmeier–Haack method [5] is a convenient means of obtaining indole aldehydes. We varied reactant ratios and temperature when selecting optimum conditions for carrying out the Vilsmeier reaction for 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (I) with phosphorus oxychloride and N,N-dimethylformamide. The maximum yield (60%) of 3-formyl-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (III) was observed at 75°C and reactant ratios of 1:3:12. An increase in reaction temperature (as for a decrease) leads to a sharp reduction in the yield of aldehyde due to significant resinification of the reaction mass. The yield of formylation product from naphthoindoledione (I) in the Vilsmeier reaction proved to be less than the 3-formyl derivative of naphtho[2,3-*f*]indole-5,10-dione (68%) described in [4].

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*See [1] for Part 7.

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Friedel–Craft acylation [6] of compound (I) with acetic anhydride in the presence of $TiCl_4$ at 0-5°C gave 3-acetyl-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (IV) in lower yield (62%) than on acylation of the unsubstituted naphtho[2,3-*f*]indole-5,10-dione (79%). Replacement of $TiCl_4$ by $SnCl_4$ or $AlCl_3$ had practically no effect on the yield of 3-acetyl derivative (IV).

The PMR spectra of compounds (II)-(IV) confirmed the orientation of the electrophilic substitution at position 3 of the pyrrole ring. This was indicated by the absence of signals for the 3-H proton, the conversion of the 2-H proton signals from multiplets to doublets, and their displacement towards low field compared with the spectrum of the initial naphthoindoledione (I) by 0.81 [compound (II)], 1.4 [compound (III)], and 1.92 ppm [compound (IV)] respectively. In the PMR spectrum of Mannich base (II) singlet signals appeared for the protons of the methylene fragment at 4.3 and of the dimethylamino group at 2.41 ppm. In the PMR spectrum of aldehyde (III) a characteristic singlet signal appeared in the low field region for the aldehyde group at 10.49 ppm. In the high field region of the spectrum of the 3-acetyl derivative (IV) there was a singlet signal at 2.69 ppm for the acetyl group protons. In addition, displacement towards low field was observed in the PMR spectra of derivatives (II) and (III) for the broadened singlet signals of the N–H group protons compared with the N–H group signal of the initial naphthoindoledione (I) of 0.8 and 0.47 ppm respectively. The signals of the remaining protons in the spectra of compounds (II)-(IV) were displaced insignificantly.

Intense absorption bands were observed in the IR spectra of compounds (II)-(IV) at 1660-1670 and 3150-3350 cm^{-1} caused by the stretching vibrations of the C=O and N–H groups respectively. Additional absorption bands were displayed in the IR spectra of aldehyde (III) and 3-acetyl derivative (IV) at 1730 and 1690 cm^{-1} caused by the stretching vibrations of the C=O group of the aldehyde and acetyl fragments.

There were intense peaks in the mass spectra* of compounds (II)-(IV) for the molecular ions M^+ at 364, 335, and 349 which correspond to the calculated values.

EXPERIMENTAL

The PMR spectra were drawn on a Varian Unity 400 spectrometer, internal standard was TMS. The IR spectra were taken on a Perkin–Elmer 599 spectrometer in Nujol. Mass spectra were taken on a Varian MAT 112 chromato-mass spectrometer. A check on the progress of reactions and the purity of compounds was carried out by TLC on Silufol UV 254 plates. Preparative chromatography was effected on silica gel type L 40/100.

4,11-Dimethoxy-3-N,N-dimethylaminomethylnaphtho[2,3-*f*]indole-5,10-dione (II). N,N-Dimethyl(methylene)-ammonium chloride (0.2 g, 2.2 mmole) was added to a solution of 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (I) (0.2 g, 0.65 mmole) in DMF (20 ml). The mixture was heated for 3 h at 75-80°C, cooled to room temperature, and poured into water. A 20% $NaHCO_3$ solution (20 ml) was added to the mixture, which was then extracted with toluene (3 × 50 ml). The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuum. The compound was crystallized from heptane–methanol (3:1) and 4,11-dimethoxy-3-N,N-dimethylaminomethylnaphtho[2,3-*f*]indole-5,10-dione (II) (0.2 g, 85%) was obtained as yellow crystals of mp 143-144°C. PMR spectrum (in $CDCl_3$): 13.18 (1H, m, N–H); 8.22 (1H, d, 2-H); 7.71 (2H, m, 6-H, 9-H); 7.51 (2H, m, 7-H, 8-H); 4.30 (2H, s, CH_2); 4.10 (3H, s, OCH_3); 4.07 (3H, s, OCH_3); 2.41 ppm [6H, s, $N(CH_3)_2$]. IR spectrum: 3260 (N–H), 1670 cm^{-1} (C=O). Mass spectrum: 364 (100), 326 (70), 320 (50), 293 (45), 274 (64), 252 (47), 215 (39). Found, %: C 69.2; H 5.6; N 7.8. $C_{21}H_{20}N_2O_4$. Calculated, %: C 69.2; H 5.5; N 7.7. M^+ 364.

3-Formyl-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (III). Phosphorus oxychloride (0.1 ml, 1 mmole) was added with stirring to freshly distilled DMF (0.31 ml, 4 mmole) at −5°C. The mixture was stirred at room temperature for 1 h, cooled to −5°C, and a solution of 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (I) (0.1 g, 0.32 mmole) in DMF (5 ml) added. The reaction mixture was stirred for 1 h at 75°C. After cooling to room temperature the mixture was poured into water, 10% KOH solution was added to pH 7, the solid filtered off, washed with water, and dried. The solid was chromatographed (silica gel, ether–benzene 1:3). 3-Formyl-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (III) (0.13 g, 60%) was obtained as yellow crystals of mp 263-265°C (from dioxan). PMR spectrum (in DMSO-D_6): 12.85 (1H, m, N–H); 10.49 (1H, s, COH); 8.81 (1H, d, 2-H); 7.74 (2H, m, 6-H, 9-H); 7.54 (2H, m, 7-H, 8-H); 4.11 (3H, s, OCH_3); 4.08 ppm (3H, s, OCH_3). IR spectrum: 3320 (N–H), 1730, 1660 cm^{-1} (C=O). Mass spectrum: 335 (100), 320 (23), 305 (20), 288 (30), 248 (15), 193 (10). Found, %: C 68.0; H 3.9; N 4.1. $C_{19}H_{13}NO_5$. Calculated, %: C 68.0; H 3.9; N 4.2. M^+ 335.

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*Values of m/z are given for ion peaks, the relative intensities as % of the maximum are given in parentheses.

3-Acetyl-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (IV). Titanium tetrachloride (0.2 ml, 1.2 mmole) was added to acetic anhydride (2 ml) at 0°C and the mixture stirred for 10 min. A solution of 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (I) (0.1 g, 0.32 mmole) in dichloroethane (10 ml) was added at a temperature below 5°C. The reaction mixture was kept for 20 h at 0°C, stirring periodically. The mixture was then poured into water and extracted with ethyl acetate (3 × 50 ml). The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuum. The residue was chromatographed (silica gel, ether–benzene 1:1). 3-Acetyl-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (IV) (0.075 g, 62%) was obtained as yellow crystals of mp 278-279°C (from dioxan). PMR spectrum (in DMSO-D_6): 12.15 (1H, m, N–H); 8.23 (1H, d, 2-H); 7.97 (2H, m, 6-H, 9-H); 7.73 (2H, m, 7-H, 8-H); 4.10 (3H, s, OCH_3); 4.00 (3H, s, OCH_3), 2.69 ppm (3H, s, 3-Ac). IR spectrum: 3250 (N–H), 1690, 1660 cm^{-1} (C=O). Mass spectrum: 349 (100), 334 (21), 316 (18), 302 (27), 288 (18), 276 (20). Found, %: C 69.0; H 4.2; N 4.1. $C_{20}H_{15}NO_5$. Calculated, %: C 68.8; H 4.3; N 4.0. M^+ 349.

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