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SYNTHESIS OF 1H-PYRROLO[2,3-*b*]PHENOXATHIIN-2,3-DIONE

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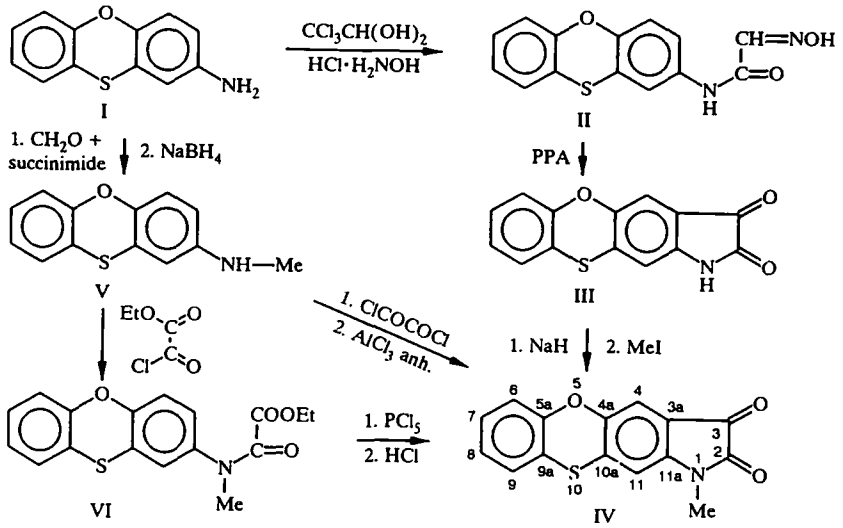
The title compound was obtained using the Sandmeyer reaction starting from 2-aminophenoxathiine. A new synthesis of N-methylpyrrolo[2,3-b]phenoxathiin-2,3-dione was also presented. Chemical and spectral data supporting the structure of the newly synthesized compounds were given. The isatin analogue, 1-methylpyrrolo-[2,3-b]phenoxathiin-2,3-dione-10,10-dioxide, could not be obtained.

Our interest in phenoxathiin [1-5] and isatin [6, 7] chemistry as well as the broad spectrum of biological activities for such compounds [8-10] prompted us to synthesize tetracyclic systems that contain both the above-mentioned rings.

Using the well-known Sandmeyer pattern [11] we carried out the transformation of 2-aminophenoxathiin (I) to isonitrosoanilide (II) and cyclization of the latter with PPA (20% yield) to the corresponding isatin (III). In our previous paper [6] we reported the synthesis of N-methyl derivative (IV) using Stolle cyclization [12] of 2-methylaminophenoxathiin (V). The same compound was now obtained from the sodium salt of (III) with methyliodide (Scheme 1).

Scheme 1



Another way to obtain compound IV in improved yield (because it avoids the formation of N,N′-bismethyl-N,N′-bisphenoxathiinyloxamide as by-product) is via the Baiocchi reaction [13]. Thus, the ethyl N-methyl-N-phenoxathiinyloxamate (VI) reacts at room temperature with phosphorus pentachloride and then the intermediate 3-chloro-3-ethoxyoxindole analogue gives the corresponding isatin IV by a mild acid hydrolysis (68% yield).

Using 2-aminophenoxathiin-10,10-dioxide (VII) in the Sandmeyer reaction we could not isolate the corresponding isonitrosoanilide (VIII).

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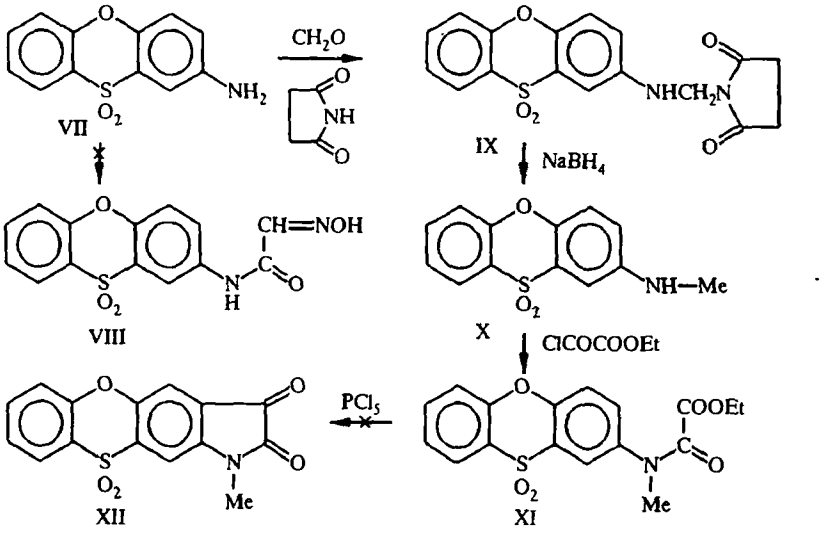
The reaction of dioxide VII with formaldehyde and succinimide (cf. [14]) followed by the action of $NaBH_4$ on the compound IX formed (see [15]) led to N-methyl-2-aminophenoxathiin-10,10-dioxide (X), which was then transformed to ethyl oxamate XI (Scheme 2).

Scheme 2



However, the treatment of the ester XI with phosphorus pentachloride at room temperature followed by acid hydrolysis gave N-methyl-2-aminophenoxathiin-10,10-dioxide (X), instead of the desired cyclization product XII.

EXPERIMENTAL

IR Spectra were recorded in KBr pellets with a UR-20 spectrometer. Mass spectra were obtained on a Fisons MD 800 GC-MS spectrometer. Melting points were determined on a Boetius apparatus and are uncorrected.

Thin layer chromatography (TLC) was carried out on silicagel Merck plates using the unidimensional technique and the eluent was chloroform–tetrahydrofuran, 4:1, for I-V, and VII-X, and a toluene–petroleum ether–chloroform–ethyl acetate mixture, 8:3:3:1, for VI and XI. Visualization was done with iodine or UV lamp for phenoxathiin-10,10-dioxides and with concentrated sulfuric acid for phenoxathiin derivatives.

2-Aminophenoxathiin and 2-aminophenoxathiin-10,10-dioxide were obtained according to procedures published earlier [16].

N-[(α-Isonitroso)acetyl]-2-aminophenoxathiin (II). To a mixture of chloral hydrate (5 g, 0.03 mole), crystalline sodium sulfate (71 g, 0.5 mole), 2-aminophenoxathiin hydrochloride (7.54 g, 0.03 mole), and water (90 ml) a solution of hydroxylamine hydrochloride (7 g, 0,1 mole) in 30 ml water was added. The reaction mixture was refluxed for 1 h and the precipitate was filtered off. The α-iso-nitrosoanilide II (6,15 g, 72%), m.p. 176-178°C (ethanol–water, 1:1), was obtained as yellow crystals. R_f 0.52. IR spectrum: 3330, 3130, 3060, 3000, 2880, 1695, 1610, 1550, 1485, 1255, 1210, 1000, 820, 745, 720. ^{1}H NMR (60 MHz, DMSO-d_6): 6.46-7.43 (m, 7H, H_{arom}); 7.55 (bs, 1H, H_{oxime}); 10.32 (s, NH); 12.46 (bs, OH). Found, %: N 9.73; S 11.23. $C_{14}H_{10}N_2O_3S$. Calculated, %: N 9.79; S 11.18.

1H-Pyrrolo[2,3-*b*]phenoxathiin-2,3-dione (III). To isonitrosoanilide II (3 g, 0.01 mole), polyphosphoric acid (15 g) was added. The reaction mixture was kept at 56-60°C for 30 min, then it was poured into 200 ml water, and the dark-red precipitate was filtered off. The crude product was dissolved in 10 ml of 2 N sodium hydroxide, and after filtration the solution was acidified with concentrated hydrochloric acid to pH 7. A product (0.59 g, 21%) was obtained, whose recrystallization from acetone led to red crystals of isatin III, m.p. 259-261°C. R_f 0,38. IR spectrum: 3425, 3210, 1755, 1740, 1620, 1465, 1425, 1360, 1265, 1210, 1150, 820, 730. ^{1}H NMR spectrum (60 MHz, DMSO-d_6): 6.40-7.31 (m, 6H, H_{arom}); 10.8 (s, NH). Addition of D_2O caused the disappearance of the singlet at δ 10.8. Found, %: N 5.24; S 11.83. $C_{14}H_7NO_3S$. Calculated, %: N 5.20; S 11.89.

N-Methylpyrrolo[2,3-*b*]phenoxathiin-2,3-dione (IV). A. The mixture of compound III (0.54 g, 0.002 mole), 4 ml DMF, sodium hydride (0,1 g, 55% oil susp.), and methyliodide (0.3 g, 0.002 mole) was left overnight at ~20°C and then poured into 20 ml water. The precipitate was filtered off and, after recrystallization from acetone, red needles (0.42 g, 73.5%) with m.p. 242-244°C were obtained.

B. 1). To a solution of N-methyl-2-aminophenoxathiin (V, 2.29 g, 0.01 mole) and pyridine (0.8 ml, 0.01 mole) in 5 ml benzene, ethyl chloroglyoxalate (1.5 ml, 0.01 mole) was added dropwise with stirring. The reaction mixture was refluxed for 30 min, then poured into 20 ml water and ice. The organic phase was separated, while the water layer was extracted with 20 ml methylene chloride. After removing the organic layer and recrystallization from ethanol of crude ethyl N-methyl-N-phenoxathiinyloxamate (VI), 2.77 g with m.p. 113-115°C (84%), bright white crystals were obtained. R_f 0.31. Mass spectrum: *m/z* 329 (M^+, 100%). IR spectrum: 2975, 1740, 1670, 1495, 1470, 1270, 1220, 1120, 1020, 760, 720, 610. ^{1}H NMR (60 MHz, $CDCl_3$): 1.13 (t, 3H, CH_3, J = 7 Hz); 3.35 (s, 3H, NCH_3); 4.1 (q, 2H, CH_2, J = 7 Hz); 7.14-8.11 (m, 7H, H_{arom}). Found, %: S 9.65; N 4.19. $C_{17}H_{15}NO_4S$. Calculated, %: S 9.72; N 4.25.

2). To a solution of compound VI (1.65 g, 0.005 mole) and 3 ml carbon tetrachloride, phosphorus pentachloride (1 g, 0.005 mole) was added. The reaction mixture was stirred for 30 min at room temperature and $POCl_3$ and CCl_4 were removed by distillation under low pressure. The residue was treated at room temperature with 5 ml HCl 2 N for 1 h. The red precipitate was filtered off and, after recrystallization from acetone, 0.96 g (68%) of product IV, m.p. 242-244°C were obtained. Mass-spectrum: *m/z* 283 (M^+, 100%). IR Spectrum: 1725, 1620, 1465, 1425, 1360, 1270, 1220, 1060, 850, 747. ^{13}C NMR (100 MHz, DMSO-d_6): 21.10 (CH_3), 153.33 $C_{(2)}$, 176.28 $C_{(3)}$, 108.63 $C_{(4)}$, 112.75 $C_{(6)}$, 123.63 $C_{(7)}$, 119.88 $C_{(8)}$, 121.28 $C_{(9)}$, 102.27 $C_{(11)}$, 111.83 $C_{(3a)}$, 142.58 $C_{(4a)}$, 145.83 $C_{(5a)}$, 110.85 $C_{(9a)}$, 128.63 $C_{(10a)}$, 142.77 $C_{(11a)}$. ^{1}H NMR (400 MHz, DMSO-d_6): 3.25 (s, 3H, CH_3); 6.5 (s, 1H, 11-H); 7.17 (s, 1H, 4-H); 6.99-7.21 (m, 4H, four H_{arom}). Found, %: N 4.97; S 11.58. $C_{15}H_9NO_3S$. Calculated, %: N 4.94; S 11.3.

2-(Succinimidomethylamino)phenoxathiin-10,10-dioxide (IX). To a mixture of 2-amino-phenoxathiin-10,10-dioxide (2.47 g, 0.01 mole), 37% aqueous formaldehyde (0.75 ml, 0.01 mole) and 15 ml ethanol succinimide (1.2 g, 0.01 mole) were added. The reaction mixture was refluxed for 4 h and, after cooling, filtration, and drying, a precipitate of IX (2.1 g, 58.6%) was obtained. Recrystallization from ethanol–water, 4:1, led to yellow needles with m.p. 215-217°C. R_f 0.76. ^{1}H NMR (60 MHz, $CDCl_3$): 2.76 (s, 4H, $COCH_2CH_2CO$); 4.98 (s, 2H, NCH_2N); 6.56 (bs, 1H, NH), 7.12-8.23 (m, 7H, H_{arom}). Found, %: N 7.87; S 8.96. $C_{17}H_{14}N_2O_5S$. Calculated, %: N 7.82; S 8.93.

N-Methyl-2-aminophenoxathiin-10,10-dioxide (X). A warm solution of compound IX (3.58 g, 0.01 mole) in 20 ml acetonitrile was treated during 10 min with sodium borohydride (0.38 g, 0.01 mole). After heating on a steam bath for 45 min, the reaction mixture was poured into cold water and a white solid (2.23 g, 87.5%) crystallized. Recrystallization from ethanol–water, 4:1 gave white needles of product X with m.p. 141-143°C. Mass spectrum: *m/z* 261 (M^+, 100). ^{1}H NMR (60 MHz, $CDCl_3$): 2.87 (s, 3H, CH_3); 3.96 (bs, 1H, NH); 6.66-8.13 (m, 7H, H_{arom}). Addition of D_2O caused the disappearance of the singlet at δ 3.96. IR spectrum: 575, 770, 835, 910, 1150, 1225, 1280, 1445, 1470, 1515, 1620, 2890, 3395. Found, %: N 5.40; S 12.28. $C_{13}H_{11}NO_3S$. Calculated, %: N 5.36; S 12.26.

N-Ethoxyglyoxyl-N-methylphenoxathiin-10,10-dioxide (XI). To a mixture of compound X (2.61 g, 0.01 mole), 1.5 ml Py, and 10 ml benzene, ethyl chloroglyoxalate (1.5 ml, 0.01 mole) was added. The reaction mixture was refluxed for 1 h. The solvent was removed and 10 ml cold water was poured over the solid material. A product (1.1 g, 84.6%) was obtained, whose recrystallization from ethanol led to white crystals of XI. R_f 0.28. Mass spectrum: *m/z* 361 (M^+, 100%). ^{1}H NMR (60 MHz, $CDCl_3$): 1.19 (t, 3H, CH_3, J = 7 Hz); 3.4 (s, 3H, NCH_3); 4.06 (q, 2H, CH_2, J = 7 Hz); 7.2-8.1 (m, 7H, H_{arom}). IR spectrum: 560, 580, 760, 1015, 1160, 1245, 1275, 1290, 1440, 1470, 1495, 1675, 1725, 1990. Found, %: N 3.91; S 8.76. $C_{17}H_{15}NO_6S$. Calculated, %: N 3.87; S 8.86.

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