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PHENOXATHIIN CHEMISTRY. REMARKS CONCERNING THE BENZOYLATION REACTION OF PHENOXATHIIN

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Benzoylation of phenoxathiin leads to a mixture of 2- and 3-benzoylphenoxathiins. Starting from 3-phenoxathiincarbonyl chloride and benzene in the presence of anhydrous aluminum chloride, 2-benzoylphenoxathiin was obtained instead of the 3-substituted isomer. Treating 3-benzoylphenoxathiin with aluminum chloride and hydrogen chloride a rearrangement reaction took place, leading to 2-benzoylphenoxathiin.

It is known that phenoxathiin (I) acetylation in the presence of titanium tetrachloride leads to a mixture of 2- (II) and 3-acetylphenoxathiins (III) [1]. Continuing our study of the orientation of the electrophilic substitution in phenoxathiin system, we tried to isolate from the benzoylation mixture the 3-position isomer.

In this paper a rearrangement reaction from the 3- to 2-position in the phenoxathiin series is presented for the first time (see Scheme 1).

Scheme 1

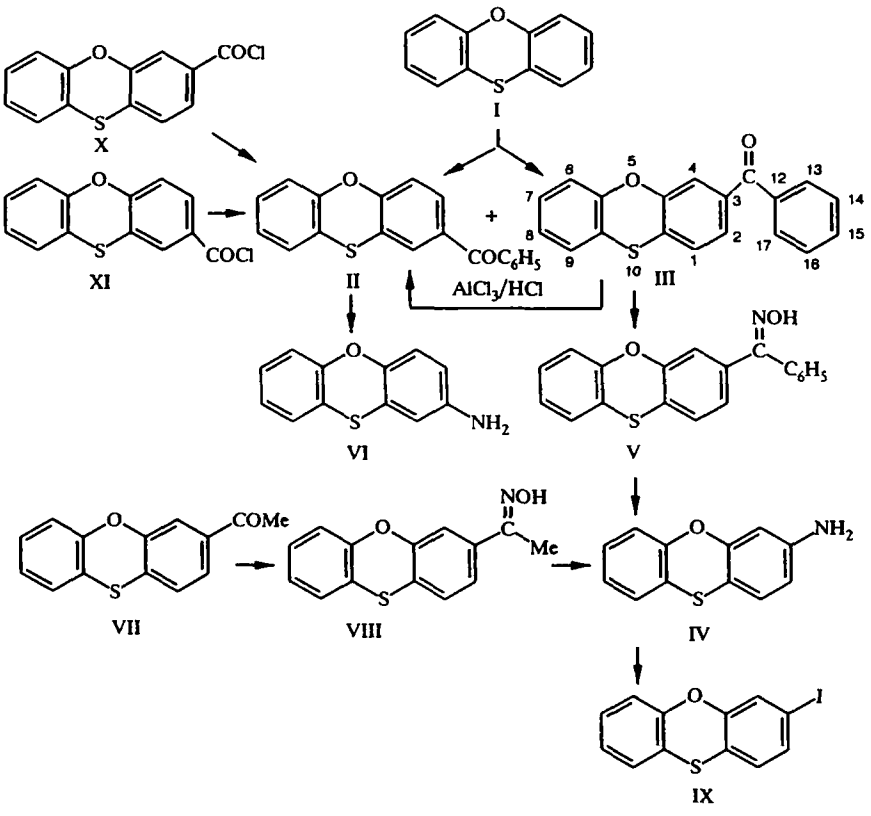

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TABLE 1. ^{13}C Chemical Shifts (ppm)

Compound	II	III	IV	VI	IX
C-1	130,34	128,17	112,83	127,37	127,97
C-2	133,93	126,12	144,87	115,59	133,44
C-3	128,84	137,10	114,31	146,70	90,70
C-4	117,40	118,97	118,30	104,95	127,64
C-6	117,88	117,86	117,72	117,77	117,92
C-7	126,80	126,38	127,64	126,82	127,81
C-8	125,09	124,85	124,10	124,36	124,88
C-9	127,99	126,72	126,77	127,31	127,91
C-4a	155,20	151,62	153,16	153,29	152,57
C-5a	151,14	151,45	152,79	152,27	151,71
C-9a	118,94	120,38	120,08	121,24	120,48
C-10a	120,37	133,96	120,83	107,74	119,46
C-11	194,64	194,90	—	—	—
C-12	137,48	137,37	—	—	—
C-13/C-17	129,77	129,74	—	—	—
C-14/C-16	128,38	128,24	—	—	—
C-15	132,40	132,36	—	—	—

TABLE 2. ^{1}H Chemical Shifts

Compound	δ_H (ppm), J (Hz)					
	H-1	H-2	H-3	H-4	H-6—H-9	others
II	7,57 (d, J_{13} = 2,0)	—	7,58 (d. d, J_{31} = 2,1; J_{34} = 8,9)	7,03 (d, J_{43} = 8,9)	6,98...7,17 (m, 4H)	7,46...7,73* (m, 5H, $H_{(13)}$—$H_{(17)}$)
III	7,47 (d, J_{12} = 8,4)	7,45 (d.d, J_{21} = 8,3; J_{24} = 2,3)	—	7,41 (d, J_{42} = 2,2)	7,01...7,15 (m, 4H)	7,42...7,72* (m, 5H, $H_{(13)}$—$H_{(17)}$)
IV	6,42 (d, J_{13} = 2,3)	—	6,42 (d. d, J_{34} = 9,3; J_{31} = 2,6)	6,81 (d, J_{43} = 9,2)	6,94...7,12 (m, 4H)	3,5 (s, NH_2)
VI	6,81 (d, J_{12} = 8,1)	6,36 (d.d, J_{21} = 8,1; J_{24} = 2,3)	—	6,40 (d, J_{42} = 2,3)	6,95...7,12 (m, 4H)	3,38 (s, NH_2)
IX	6,80 (d, J_{12} = 8,1)	7,31 (d.d, J_{21} = 8,1; J_{24} = 1,8)	—	7,35 (d, J_{42} = 1,9)	6,97...7,15 (m, 4H)	—

*Overlapped signals.

The presence of 3-benzoylphenoxathiin (III) was confirmed both by chemical and spectral methods (IR, NMR, GC/MS).

First of all, the presence of 3-benzoylphenoxathiin determined by recording the ^{13}C-NMR spectrum ($CDCl_3$, 300 MHz) of the mixture obtained in the benzoylation reaction when two near signals (194.64 and 194.91) for carbonyl carbon atoms were observed.

By purifying the crude mixture resulting from phenoxathiin benzoylation, we obtained 2-benzoylphenoxathiin (II) with mp 119-120°C. The melting point in the literature for 2-benzoylphenoxathiin ranges between 96-119°C [2-4].

Bright-yellow crystals with mp 83-92°C were obtained from the recrystallization filtrate, having in the mass spectrum a peak the molecular ion (M^+ = 304) corresponding to the molecular weight of benzoylphenoxathiin. After eight successive recrystallizations a product with mp 81-83°C was obtained, still having two signals in the ^{13}C NMR spectrum. For the main component of this specimen the structure of 3-benzoylphenoxathiin (III) was chemically proved by a series of transformations that leads to 3-aminophenoxathiin (IV), which was obtained by J. F. Nobis and N. W. Burske in another way [5]. By treating

the fraction with mp 81-83°C with hydroxylamine hydrochloride followed by Beckmann rearrangement of the oxime V, 3-aminophenoxathiin (IV) containing traces of 2-aminophenoxathiin (VI) traces was obtained. The presence of both 3- and 2-aminophenoxathiins was proved by thin layer chromatography (TLC), as the two amines have different R_f values, when the development was done with chloroform–tetrahydrofuran, 4:1 (R_{fVI} 0.38 and R_{fIV} 0.45).

3-Aminophenoxathiin (IV) was also synthesized from 3-acetylphenoxathiin (VII) via oxime VIII and subsequently transformed to 3-iodophenoxathiin (IX), known in the literature [5].

2-Benzoylphenoxathiin (II) was obtained in high yield on our attempt to synthesize pure 3-benzoylphenoxathiin by treating 3-phenoxathiincarbonyl chloride (X) with benzene in the presence of aluminum chloride. 2-Benzoylphenoxathiin was also obtained from 2-phenoxathiincarbonyl chloride (XI) by means of the above-mentioned Friedel–Crafts reaction. Treating 3-benzoylphenoxathiin (fraction with mp 81-83°C) with anhydrous aluminum chloride and gaseous hydrogen chloride, 2-benzoylphenoxathiin was also obtained. These experimental results led us to the conclusion that a rearrangement reaction of 3-benzoylphenoxathiin to 2-benzoylphenoxathiin took place.

All attempts to reveal the rearrangement using polyphosphoric acid or titanium (IV) chloride in the Friedel–Crafts acylation of benzene with 2- and 3-phenoxathiincarbonyl chloride failed. Also no rearrangement reaction was observed by treating 3-benzoylphenoxathiin with trifluoroacetic acid or aluminum chloride (without gaseous hydrogen chloride).

Similar rearrangement reactions are known for the indole [6] or pyrolle [7] series. Work is in progress to propose a mechanism for this benzoylphenoxathiin rearrangement reaction.

The ^1H- and ^{13}C-chemical shifts are listed in Tables 1 and 2; the assignments of the proton and carbon resonances were based on comparison with phenoxathiin [8] for compounds II, IV, VI, and IX, and with 2-benzoylphenoxathiin for III. Coupling constants and two-dimensional experiments (H, H-COSY and C, H-COSY) were also used.

EXPERIMENTAL

IR spectra were recorded in KBr pellets with an UR-20 apparatus. NMR spectra were recorded on a Varian Gemini-300 spectrometer in $CDCl_3$. Mass spectra were obtained on a Fisons 800 GC-MS spectrometer. Melting points were determined on a Boetius apparatus and are uncorrected. Thin layer chromatography (TLC) was carried out on silica gel Merck plates using the unidimensional technique, and the development was done with chloroform–tetrahydrofuran, 4:1. Visualization was done with conc. sulfuric acid or UV lamp (254 nm).

2- and 3-Phenoxathiincarbonyl chlorides were obtained according to literature data [9, 10].

3-Benzoylphenoxathiin (III). To a mixture of phenoxathiin (50 g, 0.25 mole), dry methylene chloride (200 ml), and titanium (IV) chloride (32 ml, 0.29 mole) benzoyl chloride (32 ml, 0.27 mole) was added dropwise for 2 h. Stirring was continued for another 4 h at room temperature followed by heating to 35-40°C for 2 h. The reaction mixture was poured into 200 ml of water and ice. The organic phase was separated, and the aqueous phase was extracted with 50 ml methylene chloride. The combined organic phases were washed first with 50 ml 5% sodium carbonate solution, then with 2 × 50 ml water. After drying over anhydrous calcium chloride and removing methylene chloride, 72 g (93%) of crude benzoylphenoxathiin was obtained, which was then distilled under low pressure. The middle fraction (62 g) was dissolved in 150 ml of warm isopropyl alcohol with charcoal, the solution obtained after hot filtration was cooled to 60°C, and the precipitate was filtered off to give 56.5 g of benzoylphenoxathiin with mp 96-105°C. An additional amount (12 g) with mp 85-102°C was obtained from the filtrate by cooling at room temperature. The distillation head (8.1 g) was recrystallized in a similar way, leading to 5.4 g of benzoylphenoxathiin with mp 84-90°C.

The precipitates with close melting points resulting from successive recrystallizations and concentration of the filtrates were combined and recrystallized. After approximately eight such recrystallizations by the same technique as above, the two isomers were obtained: 2-benzoylphenoxathiin (II) with mp 119-120°C (40.7 g, 53.5% yield; mass spectrum, *m/z*: 304; M^+, 100%) and 3-benzoylphenoxathiin (III) with mp 81-83°C (8.2 g, 10.7% yield; mass spectrum, *m/z*: 304; M^+, 100%). IR spectrum: 680, 740, 970, 1280, 1440, 1470, 1590, 1640. Found, %: C 74.66; H 3.89; S 10.48. $C_{19}H_{12}O_2S$. Calculated, %: C 75.00; H 3.94; S 10.52.

3-Acetylphenoxathiin Oxime (VIII). To a solution of 3-acetylphenoxathiin (24.2 g, 0.1 mole), 65 ml pyridine, and 65 ml ethanol, hydroxylamine hydrochloride (6.95 g, 0.1 mole) was added and the mixture was refluxed for 3 h. After addition of crushed ice, the precipitate was filtered off (24 g, 94.2% yield). On recrystallization from ethanol:water, 4:1 white crystals (22.7 g, 86.3%) of 3-acetylphenoxathiin oxime, mp 157-158°C were obtained. Found, %: N 5.41; S 12.40. $C_{14}H_{11}NO_2S$.

Calculated, %: N 5.44; S 12.45. Similarly we obtained 3-benzoylphenoxathiin oxime (V) (81% yield) with mp 148-150°C. Found, %: N 4.41; S 10.07. $C_{19}H_{13}NO_2S$. Calculated, %: N 4.38; S 10.03.

3-Aminophenoxathiin (IV). To an ice-cooled suspension of oxime VIII (25.7 g, 0.1 mole) in 500 ml dry benzene, finely powdered phosphorus pentachloride (20 g, 0.1 mole) was added in small portions with shaking, and the mixture was stirred at 40-45°C for a further 1 h. Then it was poured into 200 ml water and the organic layer was steam distilled; the residue on recrystallization from benzene gave needles of 3-acetamidophenoxathiin (19 g, 73.8%), mp 177-179°C. Found, %: N 5.39; S 12.50. $C_{14}H_{11}NO_2S$. Calculated, %: N 5.44; S 12.45. Similarly we obtained 3-benzamidophenoxathiin (73.2% yield), mp 159-161°C. Found, %: N 4.34; S 9.98. $C_{19}H_{13}NO_2S$. Calculated, %: N 4.38; S 10.03. Hydrolysis of both amides with hydrochloric acid:water (1:1) gave 3-aminophenoxathiin hydrochloride, mp 182-184°C, which with ammonium hydroxide afforded the base IV, mp 87-88°C. Found, %: N 6.10; S 13.82. $C_{12}H_9NOS$. Calculated, %: N 6.06; S 13.85.

3-Iodophenoxathiin (IX), mp 69-71°C (lit. mp 70-72°C) was obtained according to literature [5]. Found, %: S 9.77. $C_{12}H_7IOS$. Calculated, %: S 9.81.

Rearrangement of 3-Benzoylphenoxathiin into Its 2-Isomer. A. To a solution of chloride X (2.6 g, 0.01 mole) in 15 ml dry benzene, anhydrous aluminum chloride (1.4 g, 0.01 mole) was added in small portions, and the mixture was heated to 50°C for 5 h. The reaction mixture was poured into 10 ml water and ice and the organic layer was washed with 2 × 15 ml 10% sodium carbonate and then with water. The product was taken up in chloroform and the chloroform layer was dried over anhydrous Na_2SO_4. After removing the solvent and recrystallization from *i*-PrOH, 1.72 g (56.5%) of 2-benzoylphenoxathiin, mp 119-120°C, was obtained (instead of 3-benzoylphenoxathiin). Mass spectrum: *m/z* 304 (M^+, 100%).

B. Through a solution of 3-benzoylphenoxathiin (0.65 g, 0.0025 mole) and anhydrous aluminum chloride (0.35 g, 0.0026 mole) in 5 ml dry benzene dry gaseous hydrogen chloride was bubbled at 50°C for 5 h. The reaction mixture was then worked up as above and 2-benzoylphenoxathiin (0.38 g, 58% yield) with mp 119-120°C was obtained. Mass spectrum: *m/z* 304 (M^+, 100%).

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