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ORIENTATION EFFECTS IN PHENOXATHIIN ACETYLATION AND FORMYLATION

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In acetylation and formylation of phenoxathiin, besides 2-acyl-substituted main products, the 3-isomers form in ca. 10% yield. The structure of 3-acetylphenoxathiin isolated by fractional crystallization from the mixture resulted after acetylation was proved by means of physical and chemical methods.

Despite extensive research [1-13] carried out in the last decades to elucidate the contribution of sulfur or oxygen atoms to directing electrophilic substitution of phenoxathiin (I), the orientation effects have not yet been fully explained. It is known that phenoxathiin acetylation leads to a mixture of 2-acetyl-, 2,7- and 2,8-diacetylphenoxathiins, with composition depending on the reaction conditions [5-13]. Although upon the diacetylation of phenoxathiin, Coic et al. [12] obtained a mixture of 2-acetylphenoxathiin (II), unreacted phenoxathiin, 2,7- and 2,8-diacetylphenoxathiin, they did not succeed in finding evidence of the formation of 3-acetylphenoxathiin (III), which, together with 2-acetylphenoxathiin, could explain the formation of both 2,7- and 2,8-diacetylphenoxathiins.

In this paper the isolation of 3-acetylphenoxathiin from the mixture resulting upon acetylation is presented for the first time. It has been also found that besides the 2-isomer (IV) in the Rieche–Gross reaction of phenoxathiin, 3-formylphenoxathiin (V) forms (Scheme 1).

By purifying the crude mixture resulting upon phenoxathiin acetylation, we obtained 2-acetylphenoxathiin with mp 118-119°C. The melting points as referred to in the literature for 2-acetylphenoxathiin range between 108-118°C [5-11, 13]. The fact that recrystallization leads to a remarkable rise of melting point may suggest the formation of isomer mixture. Thus, it has been proved for the first time that up to 10% of the isomer substituted in position 3 is present in the acetylation product. In a similar way a mixture of 2- and 3-formylphenoxathiins is obtained during the formylation reaction of phenoxathiin.

The evidence for obtaining 3-isomers in the two reactions was obtained both by chemical and spectral methods. Detection of phenoxathiin derivatives, substituted in position 3, in the reaction mixture through physicochemical methods (IR, chromatography, ^{1}H NMR 60-80 MHz) is difficult due to the close values of constants for both isomers.

Although 2-acetylphenoxathiin (II) was prepared several decades ago, the separation of the isomer with acetyl group in position 3 has not been achieved yet, probably because its melting point is close to that of phenoxathiin and this isomer could be considered as unreacted starting material. The presence of 3-acetylphenoxathiin (III) was discovered by thin layer chromatography of the product resulting from evaporation of the recrystallization filtrates of 2-acetylphenoxathiin when 3-acetylphenoxathiin radical cation appeared red colored upon treatment with concentrated sulfuric acid, unlike the phenoxathiin radical cation, which was violet-blue.

3-Acetylphenoxathiin (III) structure was chemically proved by a series of transformations that lead to 3-formylphenoxathiin (V) (Scheme 1). 2-Hydroxymethyl- and 3-hydroxymethylphenoxathiin were prepared through a new way, by reducing corresponding acid chlorides with sodium borohydride in acetonitrile.

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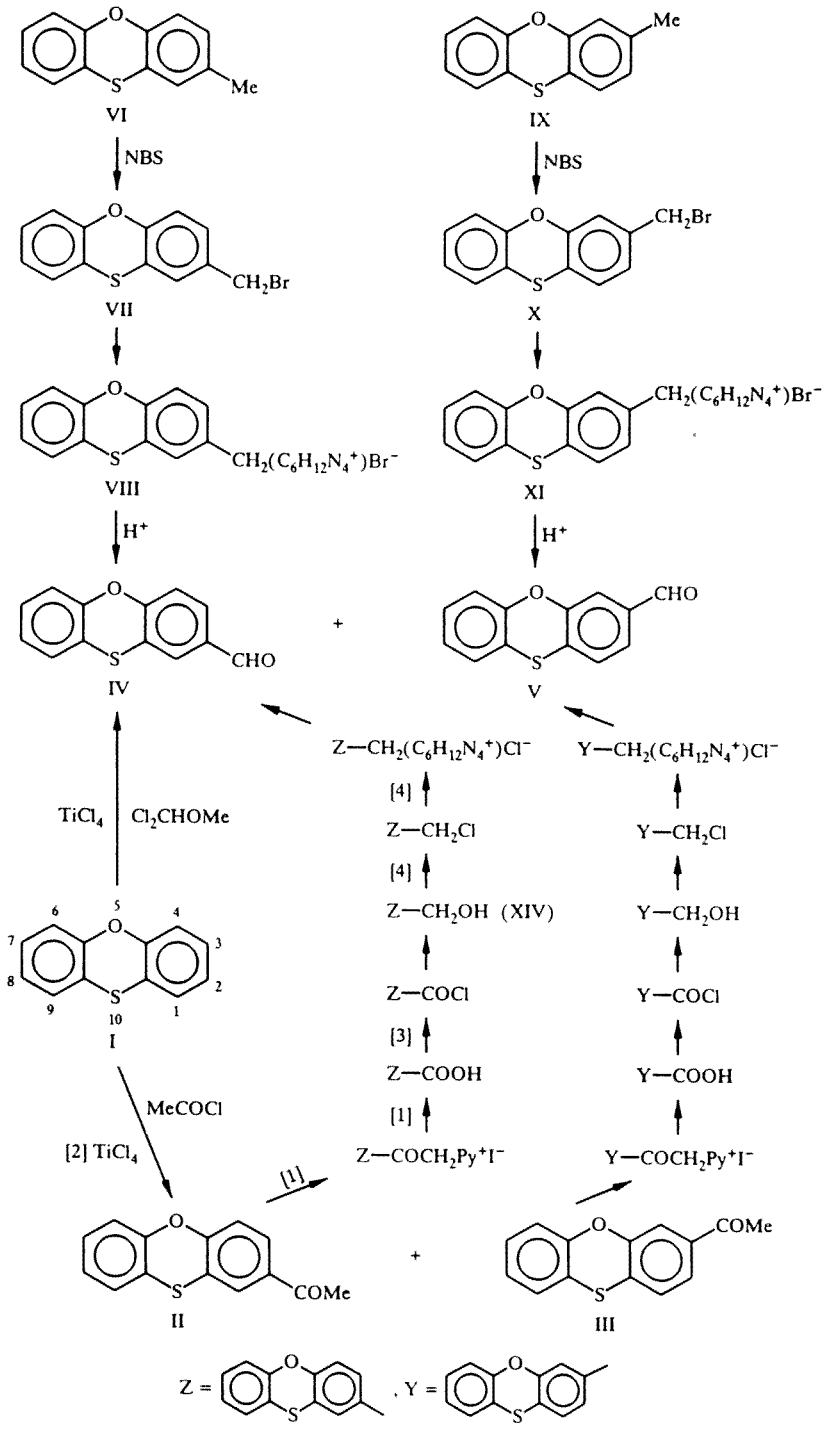
Scheme 1

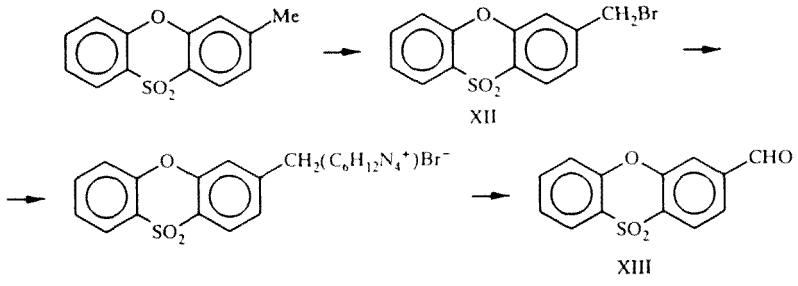

VI
IX
NBS
VII
X
VIII
XI
H+
IV
V
Z—CH2(C6H12N4+)Cl−
Y—CH2(C6H12N4+)Cl−
[4]
Z—CH2Cl
Y—CH2Cl
Z—CH2OH (XIV)
Y—CH2OH
Z—COCl
Y—COCl
[3]
Z—COOH
Y—COOH
[1]
Z—COCH2Py+I−
Y—COCH2Py+I−
TiCl4
Cl2CHOMe
MeCOCl
[2] TiCl4
I
II
III
Z =
Y =

Unambiguous samples of aldehydes IV and V were synthesized from 2- and 3-methylphenoxathiins through the Wohl–Ziegler bromination reaction followed by the Sommelet reaction (paths VI → VII → VIII → IV and IX → XI → V).

3-Formylphenoxathiin obtained as a by-product in the formylation of phenoxathiin with α,α-dichloromethyl methyl ether was detected by thin layer chromatography. The structure of 2-formylphenoxathiin from the reaction mixture resulting by formylation was also confirmed by synthesis of this compound starting from 2-acetylphenoxathiin.

The Whol–Ziegler and Sommelet reactions were successively applied also to 3-methylphenoxathiin-10,10-dioxide leading to compounds XII, XIII (Scheme 2).

Scheme 2



EXPERIMENTAL

Melting points were determined in an open capillary and are uncorrected.

IR spectra were recorded in KBr pellets with a UR-20 apparatus.

^{1}H NMR spectra were recorded on a Brucker apparatus (250 MHz) in DMSO-D_6, those for the compounds II-V, XIII were already published by us, as were the IR spectra for the compound III [14, 15].

Mass-spectra were obtained on a Trio 1000 GC-MS spectrometer.

Thin layer chromatography (TLC) was carried out on silica gel Merck plates using a unidimensional technique and the development was done with petroleum ether–ethyl ether–methylene chloride–ethyl acetate mixture, 7.5:1:2:1. Visualization was done with iodine for phenoxathiin-10,10-dioxides or with conc. sulfuric acid for phenoxathiins (colored spots of phenoxathiin radical cations).

3-Acetylphenoxathiin (III). To a mixture of phenoxathiin (200 g, 1 mole), anhydrous methylene chloride (630 ml) and titanium (IV) chloride (120 ml, 1.09 mole) cooled in an ice bath, acetyl chloride (80 ml, 1.12 mole) was added dropwise for 2 h. Stirring was continued for another 4.5 h at room temperature, followed by heating to 35-37°C for 2 h. The reaction mixture was poured into 1000 ml of water and ice. The organic phase was separated, while the water phase was extracted with 2 × 50 ml methylene chloride. The combined organic phases were washed first with 2 × 50 ml 10% sodium carbonate solution, then with 2 × 100 ml water. After drying over anhydrous calcium chloride and removing methylene chloride 218 g (90%) of crude acetylphenoxathiin were obtained, which were subsequently distilled under low pressure.

The distillation head was collected up to 210°C (18 g, 666-799 Pa) with mp 57-70°C, while the distillation middle was collected up to 238°C (168 g, 666-799 Pa).

The middle fraction was dissolved in 600 ml of warm isopropanol (charcoal), the solution obtained after hot filtration, was cooled to 40°C and the precipitate was filtered off to give 146 g of acetylphenoxathiin, mp 109-112°C. An additional amount (17.5 g) with mp 53-58°C (a mixture of phenoxathiin and 3-acetylphenoxathiin) was obtained from the filtrate by cooling at room temperature. Second recrystallization of 146 g of acetylphenoxathiin by the same procedure as above gave 89.5 g of 2-acetylphenoxathiin (II) with mp 118-119°C. From the filtrate of the latter, by cooling at room temperature an additional 32.5 g of a product with mp 113-117°C were obtained and 11 g of a product with mp 52-59°C were crystallized overnight.

The distillation head was recrystallized in a similar way, leading to 11 g of acetylphenoxathiin with mp 72-80°C.

The precipitates with close melting point resulting from successive recrystallizations, and concentrations of the filtrates were combined and recrystallized. After approximately twelve such recrystallizations by the same technique as above, the two isomers were obtained: 2-acetylphenoxathiin (146 g), mp 118-119°C (60.5%), R_f 0.80 (constants according to [2]) and 3-acetylphenoxathiin (22.75 g), mp 62-63°C (9.4%), R_f 0.82. Mass spectrum: *m/z* 242 (M^+, 100%). Found, %: C 69.52; H 4.45; S 13.34. $C_{14}H_{10}O_2S$. Calculated, %: C 69.40; H 4.16; S 13.23.

2-Hydroxymethylphenoxathiin (XIV). To sodium borohydride (4.25 g, 0.11 mole) in 135 ml of acetonitrile, 2-phenoxathiincarbonyl chloride (8 g, 0.03 mole) was added under cooling, waiting for a disappearance of the yellow color of the reaction mixture after each portion. The reaction mixture was maintained in the ice bath for 1 h more, then 10% sulfuric acid was added up to pH 4-5. Then 100 ml of methylene chloride were added, the organic phase was separated and the water phase was extracted with 50 ml of methylene chloride. The combined organic phases were washed with a 5% sodium carbonate solution, 50 ml distilled water, dried with anhydrous magnesium sulfate and the solvent was removed. 2-Hydroxymethylphenoxathiin (4.9 g, 66.6%), mp 86-88°C (*n*-heptane) was obtained [4], mp 87-88°C.

3-Formylphenoxathiin (V). A. To sodium borohydride (0.25 g, 0.006 mole) in 10 ml of acetonitrile, 3-phenoxathiincarbonyl chloride (0.45 g, 0.001 mole) was added in portions under stirring and cooling. The reaction mixture was maintained on an ice bath for 30 min more, then 10% sulfuric acid was added up to pH 4-5 and 5 ml of methylene chloride were added, and the precipitate was filtered off. The organic phase was concentrated, then 20 ml of 3% sodium carbonate solution and 15 ml of methylene chloride were added. The organic layer was separated, dried with anhydrous magnesium sulfate and evaporated. Residue was treated with anhydrous benzene (3 ml) and thionyl chloride (1 ml). The reaction mixture was heated on a steam bath for 20 min, the solvent was removed in a rotary evaporator and 5 mL of acetone and 0.25 g of hexamethylenetetramine were added to the oily residue. After 10 min refluxing the hexamine salt was separated and hydrolyzed with 5 ml of 50% acetic acid brought up to pH 3-3.5 with sodium hydroxide. After 2 h refluxing, the reaction mixture was extracted with 10 ml of methylene chloride, concentrated to a volume of 0.5 ml and chromatographed on SiO_2. Eluent: petroleum ether-ethyl ether-methylene chloride, 7.5:1:1.5. Extraction from silicagel of 3-formylphenoxathiin was done with methylene chloride. After removing the solvent, 50 mg (12%) of aldehyde V as yellow crystals with mp 73-75°C were obtained.

B. To an ice-cooled solution of phenoxathiin (20 g, 0.1 mole) and titanium (IV) chloride (75 ml, 0.38 mole) in 100 ml anhydrous methylene chloride, α,α-dichloromethyl methyl ether (12 ml, 0.13 mole) dissolved in 15 ml of anhydrous methylene chloride were added by dropping and stirring during 30 min. Stirring was continued for 3 h, reaction being monitored through TLC. The reaction mixture was poured into 200 ml of water acidified with 5 ml of conc. hydrochloric acid. The organic phase was separated, while the water phase was extracted with 2 × 25 ml of methylene chloride. The combined organic layers were washed with 3 × 50 ml water, dried with anhydrous calcium chloride and concentrated on rotary evaporator. The dark-yellow oily product thus obtained was extracted with 5 × 100 ml of isooctane, at each extraction the product was heated up to boiling point then isoocatane was decanted from the oil product. By cooling, we obtained 2-formylphenoxathiin (1.25 g) with mp 78-81°C, 7 g of product with mp 53-57°C and 4.34 g with mp 62-67°C, second and third fractions being mixtures of 2-formyl-, 3-formylphenoxathiin and unreacted starting material. 2-Formylphenoxathiin (IV, 5.25 g) was obtained by recrystallizing second and third fraction from isooctane. The yield of 2-formylphenoxathiin obtained by repeated recrystallization was found to be 20-30%, mp 80-81°C, R_f 0.83 (constants according to [4]). The 3-isomer V could be detected only by TLC (fluorescence at 360 nm). Unlike 3-acetylphenoxathiin 3-formylphenoxathiin could not be isolated by fractional crystallization in pure state.

C. To 3-bromomethylphenoxathiin X (5 g, 0.017 mole) in 50 ml of acetone, hexamethylenetetramine (2.5 g, 0.017 mole) was added. The reaction mixture was refluxed 30 min and the precipitate was filtered off. Hexamine salt (7.25 g, 98.2%) mp 173-175°C (ethanol) was obtained as white crystals. 7 g of the salt were hydrolyzed with 90 ml of 50% acetic acid, brought to pH 3-3.5 with sodium hydroxide and refluxed for 3 h. A product (2.5 g, 67.5%) was obtained whose recrystallization from *n*-heptane led to yellow crystals of 3-formylphenoxathiin (V) mp 72-74°C. R_f 0.86. Mass spectrum: *m/z* 228 (M^+, 100%). IR spectrum: 1680 (CO), 1225 (C−O−C), 760 (4CH), 820 (2CH). Found, %: C 68.53; H 3.62; S 14.21. $C_{13}H_8O_2S$. Calculated, %: C 68.40; H 3.53; S 14.04.

3-Bromomethylphenoxathiin (X). 3-Methylphenoxathiin IX (6 g, 0.028 mole) was refluxed with N-bromosuccinimide (5.5 g, 0.03 mole) and 0.01 g of bisazoizobutyronitrile in 80 ml of anhydrous carbon tetrachloride for 7 h. The reaction flask was illuminated by a lamp of 200 W. Succinimide was filtered off, the filtrate was concentrated on a rotary evaporator until the emergence of yellowish-brown oil, 15 ml of anhydrous acetone was added and light-yellow crystals were formed. 3-Bromomethylphenoxathiin X (5 g, 60.9%) was obtained. After preparative chromatography, crystals with mp 124-126°C (*n*-heptane) were obtained. Eluent: *n*-heptane−ethyl ether−methylene chloride−ethyl acetate, 7.5:1:2:1. R_f 0.91. ^1H NMR spectrum: 4.65 (s, $-CH_2-$), 7-7.5 (m, CH arom.). Found, %: C 53.48; H 3.15; S 11.09. $C_{13}H_9BrOS$. Calculated, %: C 53.25; H 3.09; S 10.93.

3-Bromomethylphenoxathiin-10,10-dioxide (XII). 3-Methylphenoxathiin-10,10-dioxide (9 g, 0.036 mole) was refluxed with N-bromosuccinimide (8 g, 0.044 mole) and 0.01 g of bisazoizobutyronitrile in 180 ml of anhydrous carbon tetrachloride

for 2 h. The reaction flask was illuminated by a lamp of 200 W. Succinimide was filtered off and the filtrate was concentrated on rotary evaporator until 10.3 g (86.6%) of crude precipitate was obtained, mp 152-153°C (isopropanol), R_f 0.60. Mass spectrum: *m/z* 325 (M^+, 100%). ^1H NMR spectrum: 4.82 (s, $-CH_2-$), 7.52-8.09 (m, CH arom.). Found, %: C 48.20; H 2.95; S 9.97. $C_{13}H_9BrO_3S$. Calculated, %: C 48.01; H 2.78; S 9.85.

3-Formylphenoxathiin-10,10-dioxide (XIII). 3-Bromomethylphenoxathiin-10,10-dioxide (1 g, 0.004 mole) was refluxed with hexamethylenetetramine (0.56 g, 0.004 mole) in 20 ml of anhydrous acetone for 10 min. The reaction mixture was maintained overnight at room temperature. Hexamine salt (1.5 g, 96.1%) with mp 197-198°C was obtained, which was hydrolyzed with 50 ml of 50% acetic acid, brought to pH 3-3.5 with 10% sodium hydroxide. 3-Formylphenoxathiin-10,10-dioxide (0.35 g, 32.4%) with mp 191-193°C (contraction 178-180°C) was obtained, which after recrystallization from isopropanol led to light-yellow crystals with mp 190-194°C, R_f 0.75. Mass spectrum: *m/z* 260 (M^+, 100%). IR spectrum: 1700 (CO), 1232 (C−O−C), 770 (4 CH), 840 (2 CH), 555, 1160, 1335 (SO_2). Found, %: C 60.22; H 3.23; S 12.50. $C_{13}H_8O_4S$. Calculated, %: C 59.99; H 3.09; S 12.31.

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