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SYNTHESIS OF 3,3-DISUBSTITUTED 2-THIOPHTHALIDES

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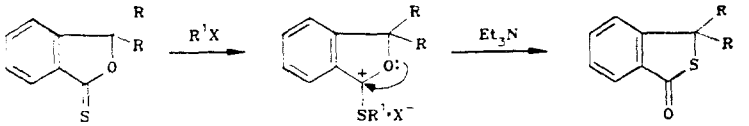
The alkylation of 1-thiophthalides followed by treatment of the reaction mixture with triethylamine constitutes a convenient method of preparing 3,3-disubstituted 2-thiophthalides.

2-Thiophthalides are used as starting materials in the preparation of a number of useful thiophthalane derivatives, some of which are used as antidepressants [1], dyes [2, 3], and analytical reagents [4]. A general synthetic route to 2-thiophthalides is the mercuric acetate oxidation of the corresponding 1,2-dithiophthalides [5]. However, the starting dithiophthalides, especially the 3,3-disubstituted ones, are not easily available. Other reported methods for the preparation of 2-thiophthalides lack specificity and have only limited applicability [6-9]. The isomerization of the unsubstituted 1-thiophthalide in the presence of amines under relatively harsh reaction conditions (high temperature and pressure) has been reported [10, 11]. Since 3,3-disubstituted 1-thiophthalides are easily available, we investigated their isomerization in more detail in order to broaden the synthetic scope of this reaction.

As a starting material, we used 1-thiophthalides I, containing aromatic or aliphatic substituents at the 3-position of the heterocycle. We found that the recyclization of the phthalane ring with the formation of the isomeric 2-thiophthalides III can be carried out under relatively mild conditions by alkylation of the 1-thiophthalides I, followed by treatment of the reaction mixture with triethylamine:



Ia, b IIa, b IIIa, b

I—III a R=Ph; b R=Me, R'X=MeI, Me_2SO_4, $Et_3O^+ \cdot BF_4^-$, $2\text{-}O_2NC_6H_4SO_3Me$

As alkylating reagents we used successfully methyl iodide, triethyloxonium tetrafluoroborate, a mixture of triethyl orthoformate and boron trifluoride etherate, dimethyl sulfate, and methyl o-nitrobenzenesulfonate. The yields of the target compounds were in the range 60-80% and were practically independent of both the alkylating reagent used and the $C_{(3)}$ substituents in the starting 1-thiophthalides.

Solutions of 1-thiophthalides I in polar and high-boiling solvents (chloroform, acetonitrile, toluene, o-dichlorobenzene) are stable to prolonged heating in the absence of alkylating reagents. The addition of triethylamine to these solutions also does not result in the isomerization of these compounds. The formation of 1-alkyl-thio-substituted phthalilium salts II is therefore a necessary condition for the recyclization of 1-thiophthalides.

The salts II proved to be unstable and we were not able to isolate any of them. This instability is probably due to a low basicity of the thiocarbonyl function of II, similar to that reported for phthalilium and thiophthalilium salts with alkoxy groups [12]. The formation of phthalilium salts is indicated by the precipitation of phthalilium-tetrafluoroborates upon addition of dry ether to the reaction mixtures, but these salts proved to be very hygroscopic

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and hydrolyzed already during filtration. The main hydrolysis product obtained by treatment of thiophthalide Ia with $Et_3O^+BF_4^-$ was found to be 3,3-diphenylphthalide. Its formation follows the general pathway of hydrolysis of 1-alkoxy- and alkylthio-substituted phthalilium and thiophthalilium salts [13]: a nucleophilic attack of H_2O at the α-carbon of the cation with the formation of unstable oxy compounds, which are stabilized by the elimination of an alcohol or thiol. The use of insufficiently dry solvents resulted in decreased yields of 2-thiophthalides III and increased formation of the corresponding phthalides due to the hydrolysis of the salts II.

Alkylation and protonation of phthalides and dithiophthalides takes place at the (thio)carbonyl function [12]. We proved the protonation of 1-thiophthalides I by comparing the electron spectra of Ia in different solvents. As expected, its longwave absorption maximum was bathochromically shifted on going from alcohol as the solvent to concentrated H_2SO_4 ($\Delta\lambda$ = 18 nm).

Our results indicate that the isomerization of 1-thiophthalides can take place only when the exocyclic C—S bond is polarized. This polarization leads to a delocalization of the electron density at the heteroatom of the ring, and thereby to a weakening of the $O_{(2)}$—$C_{(3)}$ bond. The opening of the lactone ring and the isomerization are assisted by the presence of a base.

We observed that even water can act as a base. Thus, the hydrolysis of the tetrafluoroborate IIa leads to the formation of 2-thiophthalide IIIa as a by-product. Furthermore, the oxidation of 1-thiophthalide Ia with mercuric acetate followed by treatment of the reaction mixture with H_2O leads to the formation of thiophthalide IIIa in 27% yield along with the expected 3,3-diphenylphthalide. This can be explained by the known ability of 1-thiophthalides to form phthalilium salts when treated with Hg(II) salts [10, 14].

The 2-thiophthalides III and the 3,3-diphenyl- and dimethylphthalides obtained in this work were characterized by comparison of their melting points, R_f values, and IR and UV spectra with that of samples prepared by known methods [5, 13, 15, 16].

EXPERIMENTAL

IR spectra were recorded in CCl_4 on a Specord-75 IR spectrophotometer, and UV spectra in ethanol on a Specord UV-vis. Reactions were followed by TLC on Silufol UV-254 plates. Preparative chromatography was carried out on silica gel L100/400 μ, using a 1:3 ether/hexane mixture.

Satisfactory elemental analysis data for C, H, and S were obtained for thiophthalides I.

3,3-Diphenyl-1-thiophthalide (Ia, $C_{20}H_{14}OS$). A mixture of 3 g (0.01 mole) 3,3-diphenylphthalide and 4.7 g (0.012 mole) 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) [17] was refluxed in 65 ml of toluene for 4 h. After removal of the solvent, the residual oil was dissolved in 25 ml of hot ethanol. The yellow solid formed on cooling was filtered off and recrystallized from ethanol. Yield 2.62 g (83%), mp 117-119°C, R_f 0.45. UV spectrum, λ_{max}, nm ($\log\varepsilon$): 223 (4.25), 300 (4.18). IR spectrum: 1271 cm^{-1} (C=S).

3,3-Dimethyl-1-thiophthalide (Ib, $C_{10}H_{10}OS$). This compound was prepared similarly, but the reaction mixture was refluxed for 2.5 h. The product Ib was purified by column chromatography. mp 30-33°C, R_f 0.35. UV spectrum, λ_{max}, nm ($\log\varepsilon$): 222 (4.01), 247 (3.83), 294 (4.15) (shoulder), 306 (4.18). IR spectrum: 1375, 1359 [C—H in gem-$C(CH_3)_3$], 1259 cm^{-1} (C=S). Yield 56%.

3,3-Diphenyl-2-thiophthalide (IIIa, $C_{20}H_{14}OS$). To a solution of 0.3 g (1 mmole) of thione Ia in 5 ml of dry 1,2-dichloroethane was added a solution of 0.29 g (1.5 mmoles) of triethyloxonium tetrafluoroborate in 3 ml of dichloroethane. The mixture was kept at room temperature for 3 h, then 0.28 ml (2 mmoles) of triethylamine was added, and the reaction mixture refluxed for 1 h. The solvent was removed and the product recrystallized from ethanol to afford 0.25 g (83%) of IIIa as colorless crystals melting at 160-161°C, which is in agreement with literature data [5]. IR spectrum: 1681 cm^{-1} (C=O). The alkylations of Ia with methyl iodide (in dichloroethane), Me_2SO_4 (in benzene), and with a mixture of $HC(OEt)_3$ + $BF_3 \cdot Et_2O$ [18] (in chloroform) were carried out analogously, whereas for alkylation with o-$O_2NC_6H_4SO_3Me$ equimolar amounts of the reagents were melted together at 130°C for 1 h, followed by the addition of absolute ethanol to the reaction mixture.

3,3-Dimethyl-2-thiophthalide (IIIb, $C_{10}H_{10}OS$). The isomerization of 1-thiophthalide Ib was performed analogously. The product was obtained as colorless crystals in 64-77% yield, mp 47-49°C (from pentane; literature, 46-48°C [13]). IR spectrum: 1678 cm^{-1} (C=O).

Hydrolysis of Tetrafluoroborate IIa. Thiophthalide Ia was treated with $Et_3O^+ \cdot BF_4^-$ as described above, and the reaction mixture diluted with 15 ml of dichloroethane and washed with 3 × 5 ml portions of 5% aqueous $NaHCO_3$. The organic layer was then washed with water (3 × 5 ml) and dried over Na_2SO_4. After removal of the solvent and purification of the residue by column chromatography, 0.07 g (23%) of IIIa and 0.16 g (56%) of 3,3-diphenylphthalide were obtained. The latter had mp 114-116°C after recrystallization from ethanol (the literature

gives 115°C [15]). IR spectrum of the phthalide: 1768 cm^{-1} (C=O).

Oxidation of 1-Thiophthalide Ia. A 0.8-g (2.5 mmoles) portion of $Hg(CH_3COO)_2$ was added to a solution of 0.2 g (0.66 mmole) of thiophthalide Ia in 20 ml of glacial CH_3COOH and the mixture was stirred at 50°C for 40 min. The mixture was then filtered, and the filtrate diluted with 50 ml of H_2O and extracted with 3 × 10 ml portions of ether. The ether extracts were washed with aqueous $NaHCO_3$, H_2O, and dried over Na_2SO_4. After removal of the solvent and column chromatography, 0.054 g (27%) of 2-thiophthalide IIIa and 0.12 g (63%) of 3,3-diphenylphthalide were obtained.

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