SYNTHESIS OF 2-PHENYLTHIENO[3,2-d]OXAZOLE AND 2-PHENYLTHIENO[3,2-d]THIAZOLE*

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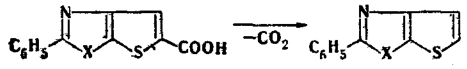
2-Phenylthieno[3,2-d]oxazole and 2-phenylthieno[3,2-d]thiazole were obtained by cyclization of the corresponding 2-phenyloxazole and 2-phenylthiazole derivatives. Their spectra and chemical properties were studied, and the pK$_a$ values of carboxylic acids with other two-ring systems with a condensed thiophene ring were also compared.

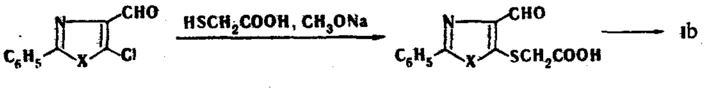
Heteroaromatic two-ring systems containing oxazole and thiazole rings condensed with thiophene were obtained by decarboxylation of the corresponding 5-carboxylic acids under previously used conditions [2].



Ia,b IIa,b

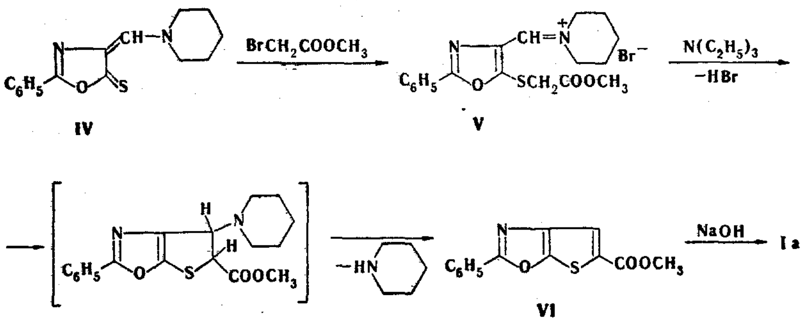
a X=O; б X=S

Compound Ib was synthesized in the same way as other analogous derivatives [2-4] from 2-phenyl-5-chloro-4-formylthiazole and thioglycolic acid in the presence of sodium methoxide.



IIIa,b

An attempt to obtain Ia in sufficiently high yield by this method was unsuccessful, since the readily formed sulfide IIIa [5] under these conditions undergoes mainly nucleophilic replacement of the thioglycolic acid residue by hydroxy and methoxy groups. The alkylation of 2-phenyl-4-piperidinomethyleneoxazole-5-thione (IV) with esters of bromo- or chloroacetic acids was used for the synthesis of Ia.



IV V VI

In contrast to the previously studied cyclization of aminomethylene derivatives of pyrazole-5-thione [4], in this case the reaction stops at the step involving the formation of alkylation product V, the hydrolysis of which leads to sulfide IIIa, which is identical to the compound previously described in [5]. The use of more severe conditions, for example,

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*See [1] for our preceding communications.

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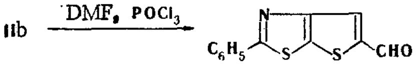
refluxing in toluene and xylene, promotes cleavage of the oxazole ring rather than cyclization. The reaction can be directed to favor cyclization and the formation of methyl 2-phenylthieno[3,2-d]oxazole-5-carboxylate (VI), the alkaline hydrolysis of which and acidification leads to Ia, only in the presence of bases (triethylamine and pyridine).

The synthesized carboxylic acids Ia, b are colorless substances with a decomposition temperature above 200°C. Two absorption maxima at 245 and 310 nm are observed in their electronic spectra measured in ethanol. In the IR spectra the absorption band of the carbonyl group is found at 1670 cm^{-1}. A comparison of the pK_a values of Ia, b and of 1-phenylthieno[3,2-d]imidazole-5-carboxylic acid [1] measured in 50% aqueous dioxane with the pK_a values for carboxylic acids of two-ring systems containing a condensed thiophene ring annelated with five-membered heterorings with one heteroatom [3] shows that the transition to the correpsonding 1,3-azole derivatives is accompanied by an increase of ~0.3-0.5 pK_a units in the acid properties. In contrast to the 1-phenylimidazole ring, annelated oxazole and thiazole rings have an electron-acceptor effect.

2-Phenyl[3,2-d]oxazole (Ia) and 2-phenyl[3,2-d]thiazole (IIb), which are obtained from Ia, b when they are heated somewhat above their melting points, are colorless crystalline substances that are readily soluble in most organic solvents. Two absorption bands are also observed in their electronic spectra. The introduction of a condensed thiophene ring in place of a benzene ring (λ_{max} of 2-phenylbenzoxazole in ethanol is 299 nm [6]) leads to a hypsochromic shift of 4 nm. Thiazole-containing IIb is more deeply colored than the corresponding osazole derivative. The usual position of the signals of the α, β protons of the thiophene ring [3] at 7.57 and 6.88 ppm for IIa and 7.4-7.6 ppm for IIb and an appreciable splitting of the signals of the protons of the phenyl ring, which indicates strong coupling of the phenyl ring with the two-ring system because of the decrease in the angle between them [7], are observed in the PMR spectra. A comparison of the data from the PMR spectra for IIa, b and 1-phenylthieno[3,2-d]imidazole [1] confirms the conclusion drawn above that in the first two compounds the thiophene ring is an electron donor whereas in the latter compound it is an electron acceptor. This in turn indicates the ease with which these compounds undergo electrophilic substitution — formylation. Thus, whereas the formylation of 1-phenylthieno[3,2-d]imidazole took place at 60°C in 3-4 h, the reaction with IIb required more severe conditions and the use of excess formylating agent.



VII

The formyl group enters the α position of the thiophene ring of 2-phenylthieno[3,2-d]thiazole, which was confirmed by its oxidation to the corresponding carboxylic acid and identification of the latter from its spectral characteristics and a mixed-melting-point determination with an available sample.

EXPERIMENTAL

2-Phenylthieno[3,2-d]oxazole-5-carboxylic Acid (Ia). A) A 2.7-g (0.01 mole) sample of 2-phenyl-4-piperidinomethyleneoxazole-5-thione (IV) [5] was dissolved in 50 ml of benzene, 3.06 g (0.02 mole) of methyl bromoacetate was added, and the mixture was heated to 70°C and maintained at this temperature for 2 h. It was then cooled to 40°C, 1.34 ml (0.01 mole) of triethylamine was added, and the mixture was stirred for 9 h. The precipitated triethylamine hydrobromide was removed by filtration, the solvent was removed from the filtrate by distillation, the resinous residue was treated with water and ethanol, and the solid material was removed by filtration. The yield was 1.25 g (50%). Methyl 2-phenylthieno[3,2-d]oxazole-5-carboxylate (VI) had mp 188-190°C (from ethanol). IR spectrum (KBr): 1715 cm^{-1} (C=O). UV spectrum (in ethanol), λ_{max} (log ε): 243 (4.02) and 300 nm (3.56). Found: N 5.4; S 12.2% $C_{13}H_9NO_3S$. Calculated: N 5.4; S 12.4%.

B) A 1.23-g (0.005 mole) sample of ester VI was dissolved in 300 ml of an aqueous ethanol solution of potassium hydroxide [2 ml of water and 0.8 g (0.014 mole) of potassium hydroxide]. The mixture was maintained at room temperature for 20 h, after which the solvent was removed by distillation, and the residue was dissolved in hot water. The solution was filtered, and the filtrate was acidified with dilute hydrochloric acid. The resulting precipitate was removed by filtration, washed with water, and dried to give 0.8 g (67%) of a product with mp 259-260°C (dec., from aqueous ethanol). IR spectrum (in KBr): 1667 cm^{-1} (CO).

UV spectrum (in ethanol), λ (log ε): 240 (4.15) and 310 nm (4.35). The pK_a value in 50% aqueous dioxane at 20°C was 4.77 ± 0.03. Found: N 5.6; S 12.9%. $C_{12}H_7NO_3S$. Calculated: N 5.7; S 13.1%.

2-Phenylthieno[3,2-d]thiazole-5-carboxylic Acid (Ib). A 0.41-g (0.004 mole) sample of thioglycolic acid was added to a solution of sodium methoxide (0.26 g of sodium in 10 ml of methanol), 0.5 g (0.002 mole) of 2-phenyl-4-formyl-5-chlorothiazole [8] was added, and the mixture was allowed to stand at room temperature for 10 h. It was then refluxed for 1.5 h, after which the solvent was removed by distillation, and the residue was dissolved in water. The solution was filtered, and the filtrate was acidified with dilute hydrochloric acid to pH 3. The resulting precipitate was removed by filtration and washed with water. The yield of product with mp 269-271°C (dec., from acetic acid) was 60%. IR spectrum (in KBr): 1680 cm^{-1} (C=O). UV spectrum (in ethanol), λ_{max} (log ε): 264 (4.67) and 316 nm (4.51). The pK_a value in aqueous dioxane was 4.72 ± 0.03. Found: N 5.3; S 24.6%. $C_{12}H_7NO_2S_2$. Calculated: N 5.4; S 24.5%.

2-Phenylthieno[3,2-d]oxazole (IIa). A 0.3-g sample of Ia was heated in a sublimation apparatus at 275-280°C for 2-3 min until CO_2 evolution of sodium carbonate. The undissolved material was removed by filtration, washed with water, and dried. Compound IIa was extracted from it with hot heptane. The yield of product with mp 106-107°C (from n-heptane) was 30%. UV spectrum (in ethanol), λ_{max} (log ε): 225 (4.15), 277 shoulder (3.60), and 295 shoulder nm (3.57). PMR spectrum (in $CDCl_3$): 7.53 (5-H), 6.88 (4-H), and 7.6-8.1 (C_6H_5). Found: N 6.8; S 15.7%. $C_{11}H_7NOS$. Calculated: N 6.9; S 15.9%.

2-Phenylthieno[3,2-d]thiazole (IIb). This compound was similarly obtained by heating acid Ib to 290°C in a sublimation apparatus. The yield of product with mp 150-151°C (from n-heptane) was 65%. UV spectrum (in ethanol), λ_{max} (log ε): 240 (4.21) and 317 nm (4.00). PMR spectrum (in $CDCl_3$): 7.40-7.60 (5-H, 4-H) and 7.5-8.1 (C_6H_5). Found: N 6.3; S 29.3%. $C_{11}H_7NS_2$. Calculated: N 6.4; S 29.5%.

2-Phenyl-5-formylthieno[3,2-d]thiazole (VII). A freshly distilled 1.38-g (9 mmole) sample of phosphorus oxychloride was added dropwise at 0°C with stirring to 0.66 g (0.009 mmole) of IIb, after which cooling was discontinued, and the mixture was allowed to warm up spontaneously to 30-35°C. It was then heated to 70°C and stirred at this temperature for 10 h, after which it was cooled and poured over ice. The aqueous mixture was neutralized with sodium hydroxide solution to pH 2-3. The resulting precipitate was removed by filtration, washed with water, and dried to give 0.7 g (60%) of a product with mp 174-175°C (from ethanol). IR spectrum (in $CHCl_3$): 1670 cm^{-1} (C=O). UV spectrum (in ethanol), λ_{max} (log ε): 225 (3.94), 275 (4.53), and 320 nm (4.31). Found: N 5.9; S 26.2%. $C_{12}H_7NOS_1$. Calculated: N 5.7; S 25.9%.

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