SYNTHESIS OF 5-(p-CHLOROPHENYLSULFONYL)INDOLE AND SOME OF ITS DERIVATIVES

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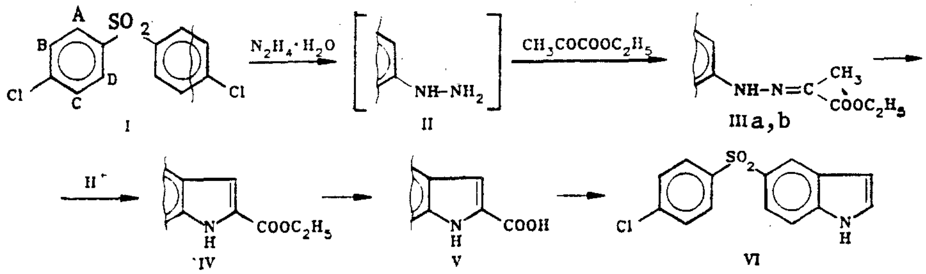
The synthesis of the previously unknown 5-(p-chlorophenylsulfonyl)indole with a free β-position is described. Derivatives of the new compound containing functional substituents at the 2-position of the indole ring were prepared.

The present work was carried out in order to synthesize 5-(p-chlorophenylsulfonyl)indole (VI) – a monosubstituted analog of the previously described bis(5-indolyl)sulfone [1]. Compound VI was obtained according to the following scheme:



As the starting compound, 4,4'-dichlorodiphenyl sulfone (I) was used, which on reaction with hydrazine hydrate in butanol gave 4-(p-chlorophenylsulfonyl)phenylhydrazine (II) in admixture with 4,4'-dihydrazinodiphenyl sulfone; thus, part of the starting dichlorophenyl sulfone remains unreacted. Because of its instability we were unable to separate the mixture. Its reaction with ethyl pyruvate [1] leads to the formation of a mixture of hydrazones, also including two geometrical isomers of 4-(p-chlorophenylsulfonyl)phenylhydrazone of ethyl pyruvate (IIIa, b), which could be separated into syn- (IIIa) and anti- (IIIb) forms.

In the PMR spectrum of the syn-isomer IIIa, a weak-field signal of the NH group proton is observed at 12.2 ppm, which indicates the presence of a fairly strong intramolecular hydrogen bond between the NH group proton and the carbonyl group. The signals of the NH group proton for the anti-form are in the stronger field (7.9 ppm) (Table 1).

A bathochromic shift of the longwave absorption maxima is observed in the UV spectrum of the syn-isomer IIIa (5-7 nm on the average), in comparison with the anti-isomer IIIb, due to the presence of an intramolecular hydrogen bond, as also confirmed by the IR spectral data. The absorption bands at 1690 (CO) and 3300 cm^{-1} (NH) in the IR spectrum of the anti-isomer IIIb are shifted in the spectrum of the syn-isomer (IIIa) to the lower frequencies region – to 1670 and 3270 cm^{-1}, respectively.

2-Ethoxycarbonyl-5-(p-chlorophenylsulfonyl)indole (IV) was obtained in a 10% yield by cyclization of hydrazone III by the action of polyphosphoric acid [2]. Saponification of ester IV leads to the formation of the corresponding acid, the thermal decarboxylation of which gives 5-(p-chlorophenylsulfonyl)indole (VI).

The assignment of the PMR signals (Table 2) of compounds IV-VI was based on the changes in the multiplicity of signals of the indole part of the molecule – the presence in the spectrum of the AB-system with SSCC 8 Hz characteristic for the ortho-protons.

An intense peak of the molecular ion with m/z 291.5 is observed in the mass spectrum of compound VI.

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TABLE 1. PMR Spectra of Compounds IIIa, b (in $CDCl_3$)

Compound	Chemical shifts, δ, ppm								SSCC, Hz
	2-H.d (6-H)	3-H.d (5-H)	7-H.d (11-H)	8-H.d (10-H)	CH_3, s	CH_2CH_3, q	CH_3CH_2, t	NH, br.s.	
IIIa	7,82	7,31	7,81	7,43	2,17	4,22	1,29	12,21	$J_{CH_2CH_3}=7{,}00$; $J_{23}=J_{56}=8{,}77$
IIIb	7,83	7,28	7,84	7,45	2,13	4,32	1,38	7,90	$J_{CH_2CH_3}=6{,}90$; $J_{23}=J_{56}=8{,}77$

TABLE 2. PMR Spectra of Compounds IV-VIII[*1]

Compound	Chemical shifts, δ, ppm							SSCC, Hz
	1-H, br.s	3-H	4-H	6-H	7-H	A—H (D—H)	B—H (C—H)	
IV[*2]	12,48	7,38 d	8,44 d	7,77 d.d	7,63 d.d	7,95 d	7,66 d	$J_{CH_2CH_3}=7{,}30$; $J_{13}=2{,}20$; $J_{46}=1{,}83$; $J_{47}=0{,}73$; $J_{AB}=8{,}40$
V	12,30	7,30 s	8,40 s	7,74 d	7,60 d	7,94 d	7,65 d	$J_{AB}=8{,}77$; $J_{67}=8{,}77$
VI[*3]	10,80	6,71 m	8,33 d	7,70 d.d	7,62 d.d	7,98 d	7,59 d	$J_{12}=2{,}56$; $J_{13}=2{,}19$; $J_{23}=2{,}93$; $J_{37}=J_{47}=0{,}73$; $J_{46}=1{,}46$; $J_{67}=8{,}04$; $J_{AB}=8{,}41$
VII[*4]	12,23	7,28 br.s	8,34 d	7,69 d.d	7,58 d	7,95 d	7,65 d	$J_{46}=J_{AC}=1{,}83$; $J_{AB}=8{,}77$; $J_{67}=8{,}78$
VIII	11,67	7,49 d.d	8,50 br.s	7,87 d.d	7,73 d	8,01 d.d	7,64 d.d	$J_{13}=2{,}19$; $J_{37}=1{,}10$; $J_{46}=1{,}83$; $J_{67}=9{,}13$; $J_{AB}=8{,}77$

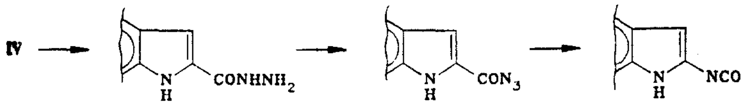
[*1] The spectra of compounds IV-VII were run in DMSO-D_6, and those of VIII in acetone-D_6.

[*2] 4.37 (q, CH_2CH_3); 1.36 ppm (t, CH_3CH_2).

[*3] COOH, a broad exchangeable signal; 7.56 ppm (d.d, 2-H).

[*4] 9.98 (s, NH); 4.56 ppm (s, NH_2).

To study the Curtius rearrangement for the synthesized systems, the azide of 5-(p-chlorophenylsulfonyl)indole-2-carboxylic acid (VIII) was prepared from the corresponding hydrazide VII. The latter was isolated by the reaction of ester IV with hydrazine hydrate in isopropanol [3]. Azide VIII was obtained in acetic acid by adding a sodium nitrite solution in water. The Curtius rearrangement was carried out by boiling azide VIII in absolute dioxane. The yield of the isocyanate IX was 87%.



VII VIII IX

EXPERIMENTAL

The course of the reaction and the purity of the compounds was monitored on Silufol UV-254 plates. The purification and the separation of the compounds were carried out on a column with silica gel 100/250 μm. The UV spectra were run on a Specord spectrophotometer in ethanol, and the IR spectra – on a UR-20 spectrophotometer in mineral oil. The mass spectrum was taken on a MX-1303 spectrometer, using an ionizing voltage of 50 eV. The PMR spectra were recorded on a CFT-20 Varian spectrometer (80 MHz), using TMS as internal standard.

The elemental analysis data for C, H, and N correspond to the calculated values.

5-(p-Chlorophenylsulfonyl)phenylhydrazone of Ethyl Pyruvate (IIIa, b, $C_{17}H_{17}ClN_2O_4S$). Triethylamine (2-3 drops) was added to a mixture of 28.7 g (100 mmoles) of 4,4'-dichlorophenyl sulfone and 75 ml of hydrazine hydrate in 50 ml of butanol, and the mixture was boiled for 10 h with continuous stirring. The solution obtained was cooled and diluted with 0.5 liter of water. The precipitate that separated out was filtered off, washed with water to a neutral reaction, dissolved in 25 ml of isopropanol, and 9 ml of ethyl pyruvate was added at room temperature. The stirring was continued for 1 h. The precipitate that separated out was filtered off, washed with ether, and dried. The separation into the syn- and anti-isomers was carried out on a column, using a benzene–ether (3:1) mixture as eluent.

The first fraction is the syn-form IIIa, mp 189-190°C. IR spectrum: 3270 (NH), 1670 cm^{-1} (C=O). UV spectrum, λ_{max} nm (log ε): 208 (4.20), 215 (4.33), 223 (3.60), 235 (3.73), 251 (4.65), 257 (3.95). Yield 0.25 g (12%).

The second fraction is the anti-form IIIb, mp 203-204°C. IR spectrum: 3300 (NH), 1690 cm^{-1} (C=O). UV spectrum, λ_{max}, nm (log ε): 204 (4.18), 212 (4.54), 220 (3.69), 229 (3.60), 249 (4.46), 252 (4.59). Yield 1.4 g (70%).

2-Ethoxycarbonyl-5-(p-chlorophenylsulfonyl)indole (IV, $C_{17}H_{14}ClNSO_4$). A mixture of 3.82 g (10 mmoles) of hydrazone III and 40 g of polyphosphoric acid was heated to 120-125°C and stirred for 1 h, and then cooled and poured into water. The precipitate that separated out was filtered, washed with water, and dried, and purified on a column, using benzene as eluent, mp 177-178°C. IR spectrum: 3310 (NH), 1680 cm^{-1} (C=O). UV spectrum, λ_{max}, nm (log ε): 202 (4.16), 213 (4.34), 218 (4.22), 225 (4.55), 235 (3.83), 2.41 (4.01), 245 (4.00).

2-Hydroxycarbonyl-5-(p-chlorophenylsulfonyl)indole (V, $C_{15}H_{10}ClNSO_4$). A suspension of a 3.6 g (10 mmoles) of the cyclic ester IV and 100 ml of 6% NaOH solution was boiled with stirring for 4 h. The solution was cooled, the precipitate was filtered off, washed with water, and dried; mp 309-310°C. IR spectrum: 3380 (NH), 1690 cm^{-1} (C=O). UV spectrum, λ_{max}, nm (log ε): 207 (3.32), 218 (3.34), 225 (3.57), 234 (2.94), 249 (1.82). Yield 2.3 g (86%).

5-(p-Chlorophenylsulfonyl)indole (VI, $C_{14}H_{10}ClNSO_2$. A 1 g portion (2 mmoles) of acid V was held at 320°C for 10 min in an inert gas current. Compound VI was purified on a column, using benzene as eluent; mp 169-170°C. IR spectrum: 3300 (NH). UV spectrum, λ_{max}, nm (log ε): 205 (3.27), 212 (3.53), 218 (3.31), 223 (3.46), 235 (2.88). Yield 0.57 g (68%).

5-(p-Chlorophenylsulfonyl)indole-2-carboxylic Acid Hydrazide (VII, $C_{15}H_{12}ClN_3O_3S$). A mixture of 2 g (5 mmoles) of compound IV, 20 ml of hydrazine hydrate, and 25 ml of isopropanol was boiled for 8 h. After cooling, yellow crystals crystallized out and were filtered off. The filtrate was diluted with water to give additional hydrazide. After crystallization from ethanol, the product was in the form of pale-yellow crystals, mp 172-176°C. IR spectrum: 1650 (C=O), 3180 cm^{-1} (NH). UV spectrum, λ_{max}, nm (log ε): 209 (2.3), 226 (2.4), 238 (2.3), 261 (1.4), 285 (2.1), 303 (2.0), 312 (2.8). Yield 1.6 g (89%).

5-(p-Chlorophenylsulfonyl)indole-2-carboxylic Acid Azide (VIII). A solution of 1.6 g of $NaNO_2$ in 8 ml of water was added with stirring to a solution of 1.7 g (5 mmoles) of hydrazide VII in 80 ml of 50% acetic acid cooled to –5°C. The precipitate that separated out was filtered off, washed with water, and dried; mp 172°C (decomp.). IR spectrum: 1660 (C=O), 1450 (N≡N), 1400 cm^{-1} (N=N). UV spectrum, λ_{max}, nm (log ε): 266 (3.14), 207 (1.5), 217 (1.6), 226 (1.7), 238 (1.4), 245 (1.9), 263 (1.8). Yield 1.3 g (78%).

5-(p-Chlorophenylsulfonyl)indolyl 2-Isocyanate (IX, $C_{15}H_{19}ClN_2O_3S$). A solution of 1.5 g (5 mmoles) of azide VIII in 30 ml of absolute dioxane was heated for 5 h, and then dioxane was distilled in vacuo to give brown crystals, mp 174-176°C. IR spectrum: 1640 (C=O), 3200 cm^{-1} (NH). Yield 1 g (75%).

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