THIOSEMICARBAZONES OF 7-AZAISATIN DERIVATIVES

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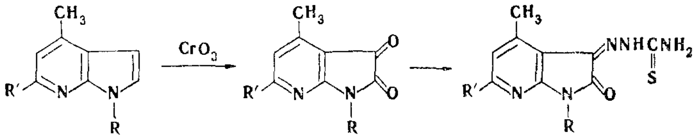
A number of derivatives of 7-azaisatin with various substituents in the pyridine and pyrrole rings were synthesized by oxidation of the corresponding 7-azaindoles with chromic acid in acetic acid. 4-Azaindole is not oxidized to 4-azaisatin under these conditions. The β-thiosemicarbazones of the 7-azaisatin derivatives were obtained.

The β-thiosemicarbazones of isatins have been studied extremely extensively in order to search for effective antivirus agents [1]. However, analogs of isatin with heteroatoms in the aromatic ring nevertheless remain difficult to obtain. Only 7-azaisatin [2], which was obtained by oxidation of 3-aminoazaoxindole with ferric chloride, and 4-methyl-6-chloro-7-azaisatin [3], which was synthesized by oxidation of 4-methyl-6-chloro-7-azaindole with chromic acid, have been described. However, in the latter case the product was obtained in only 8.2% yield.

We have established that in the oxidation of 4-methyl-6-chloro-7-azaindole with chromic acid a 15°C increase in the reaction temperature makes it possible to shorten the time from 7 h [3] to 3 h and to markedly raise the yield of 4-methyl-6-chloro-7-azaisatin. The same method made it possible in the oxidation of the corresponding 7-azaindoles (Ia-d) to obtain a number of previously undescribed 7-azaisatin derivatives (IIa-d).

An absorption band of C=O groups at 1740-1750 cm^{-1} is observed in the IR spectra of IIa-d.

The 7-azaisatins (IIa-d) obtained were converted to the corresponding β-thiosemicarbazones (IIIa-d).



Ia-d IIa-d IIIa-d

I–III a R=H, R'=Cl; b R=C_6H_5, R'=Cl; c R=$COCH_3$, R'=Cl; d R=4-$NO_2C_6H_4$, R'=H

It should be noted that the position of the nitrogen atom in the aromatic ring has a substantial effect on the oxidation of the azaindole; in particular, 4-azaindole is not oxidized by either chromic acid in acetic acid, by selenium dioxide in refluxing dioxane, or by Fieser or Sorette reagents.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with UR-20 and Specord 751R spectrometers. The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The melting points were determined with a Boetius apparatus and were not corrected. The individuality of all of the compounds obtained was confirmed by chromatography in a thin layer of Silufol with Erlich's reagent as the developer.

4-Methyl-6-chloro-7-azaisatin (IIa). A 2.7-ml sample of a 3 M solution of chromic acid was added at 80°C in the course of 3 h to a stirred solution of 1.0 g (5.1 mmole) of 4-methyl-6-chloro-7-azaindole [4] in 16 ml of acetic acid, after which the mixture was poured into

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TABLE 1. 7-Azaisatin Derivatives (IIa-d)

Compound	mp,* °C	IR spectrum, CO, cm^{-1}	PMR spectrum,† ppm				Found, %				Empirical formula	Calc., %				Yield, %
			4CH$_3$	5-H	6-H	R	C	H	Cl	N		C	H	Cl	N	
IIa	254—257	1740	2,55	6,0	—	—	48,6	2,5	18,5	14,1	$C_8H_5ClN_2O_2$	48,9	2,5	18,0	14,2	67
IIb	187	1750	2,4	6,7	—	7,1	61,7	3,4	12,7	10,3	$C_{14}H_9ClN_2O_2$	61,5	3,6	12,9	10,3	47
IIc	231—233	1750	2,4	6,7	—	2,75	50,2	2,7	14,8	11,9	$C_{10}H_7ClN_2O_3$	50,3	3,0	14,9	11,7	56
IId	155—157	1720, 1740	2,5	6,75	6,5	7,8 (Hortho) 7,5 (Hmeta)	59,3	4,3	—	14,7	$C_{14}H_9N_3O_4$	59,5	4,4	—	14,8	27

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*Compounds IIc, d were crystallized from alcohol, and IIb was crystallized from benzene.

†In DMSO.

TABLE 2. β-Thiosemicarbazones of 7-Azaisatin Derivatives (IIIa-d)

Compound	mp, °C (from methanol)	IR spectrum, cm^{-1}		Found, %					Empirical formula	Calc., %					Yield, %
		NH	CO	C	H	Cl	N	S		C	H	Cl	N	S	
IIIa	327—330	3450	1720	40,1	3,1	13,1	25,9	11,6	$C_8H_8ClN_5OS$	40,2	3,0	13,2	26,0	11,9	87
IIIb	360 (dec.)	3430	1710	52,1	3,3	9,7	20,3	8,7	$C_{15}H_{12}ClN_5OS$	52,1	3,5	10,1	20,2	9,2	92
IIIc	300 (dec.)	3420	1715	42,5	3,5	11,2	22,2	10,6	$C_{11}H_{10}ClN_5OS$	42,4	3,2	11,4	22,2	10,3	85
IIId	244—246	3440	1730	50,8	3,9	—	23,7	13,9	$C_{15}H_{12}N_5O_3S$	50,5	3,6	—	23,6	13,7	91

water. The aqueous mixture was made alkaline with sodium bicarbonate solution and extracted with chloroform. The chloroform extracts were combined, dried with magnesium sulfate, and evaporated at reduced pressure. The residue was crystallized from benzene to give 0.7 g (67%) of IIa. Compounds IIb-d were obtained by a similar method (Table 1).

β-Thiosemicarbazones IIa-d. These compounds were obtained by the method in [1]. It is expedient to obtain them from thoroughly purified starting substances. The properties are presented in Table 2.

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DIINDOLYLS.

8.* SYNTHESIS OF DI(5-INDOLYL) OXIDE

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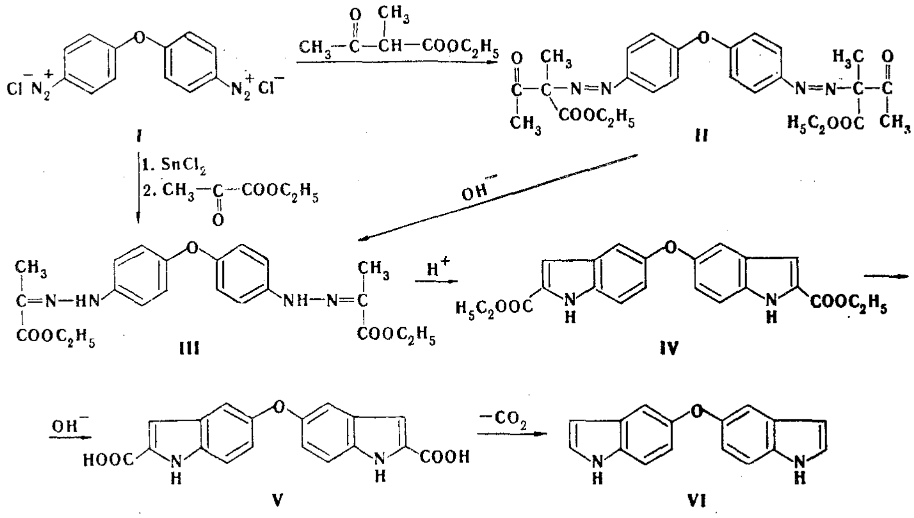
Bis(2-carbethoxy-5-indolyl) oxide was obtained by cyclization of ethyl pyruvate 4,4'-diphenyloxydihydrazone. 5-Phenoxy-2-carbethoxyindole was also isolated from the reaction products. Saponification of these esters gave the corresponding acids, the thermal decarboxylation of which yielded di(5-indolyl) oxide and 5-phenoxyindole.

We have previously reported the synthesis of some uncondensed diindolyls [1-3]. Continuing our research in this area we have obtained the parent compound of a new heterocyclic system, viz., di(5-indolyl) oxide, via the scheme



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*See [1] for Communication 7.

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