Reaction of Isatin with Thiocarbohydrazide: a Correction

Reaktion von Isatin mit Thiocarbohydrazid: eine Berichtigung

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Heterocycles containing the indole ring system include some novel pharmacologically active compounds[1-3]. Isatin and its *N*-acetylisatin are extremely versatile intermediates in the construction of a variety of heterocyclic systems when reacted with thiosemicarbazide derivatives. Literature survey revealed various interesting reactions of thiocarbohydrazide with cyclic ketones[4], cyclic 1,2-diketones[5] and isatin[6-8].

Condensation of isatins **1** with thiocarbohydrazide (**2**) is reported to yield 2-oxo-1',2',4',5'-tetrahydro-spiro[3*H*-indole-3,3'-1,2,4,5-tetrazine]-6'-thiones **5** as a novel spiro system[9] rather than the expected thiocarbohydrazones **6**, tetrazipenes **3** or triazines **4** (Scheme 1). Structures **3** and **4** were excluded based on a C=O-band in the IR-spectra and by microanalyses. Structure **5** was solely based on interpretation of ^{1}H-NMR and mass spectra, which could be misleading as it is known that rearrangement and cyclization products rather than parent compounds may appear in mass spectra.

It was of interest to examine additional spectral and chemical evidences so proving the proposed structure **5**. Thus, the condensation product from **1** (R,X=H) and **2** was prepared as exactly described by *Joshi* et al.[9] and showed the same reported mp. and IR-spectrum. The product readily condenses with benzaldehyde to give the corresponding thiocarbohydrazone **7**. Compound **7** so obtained is identical with the product obtained by direct addition of isatin in ethanol to benzaldehyde monothiocarbohydrazone **8**. On the other hand, condensation of α-keto acids, namely, phenylpyruvic acid, *p*-chlorobenzylidenepyruvic acid and *p*-methoxybenzylidenepyruvic acid with *Joshi's*[9] product gave the corresponding α-keto acid hydrazones **9a-c**. Attempts to cyclize the latter compounds by heating under reflux in dimethylformamide led to decarboxylation to the hydrazones **10a-c**. Compounds **10a-c** were independently obtained by refluxing *Joshi's* compound with the appropriate aromatic aldehyde in ethanol. Heating isatin with *Joshi's* compound afforded the bis isatin thiocarbohydrazone **11**. UV-spectra of *Joshi's* compound and compounds **7** and **11** show two bands, the first is identical at λ max = 255 nm and log ε = 4.24, 4.37 and 4.47, respectively, the other band in the region 347-370. *Joshi's* compound shows this second band at λ max (log ε) = 347 (4.24) while the derivatives **7** and **11** show this band at λ max (log ε) = 370 (4.49; 4.88), respectively. The latter bathochromic and hyperchromic effect is attributable to the increased conjugation in compounds **7** and **11**. This rules out the spiro structure for this compound and favors the monothiocarbohydrazone structure **12**. Finally structure **12** was established by boiling its solution with fused sodium acetate and chloroacetic acid in ethanol to give compound **13**[10]. The structure of **13** was established based on elemental analyses and IR-spectral studies: its IR-spectrum displays the bands attributed to a NH_2 group. Thus, this investigation establishes that the structure of the reaction product of isatin **1** and thiocarbohydrazide (**2**) as thiocarbohydrazone **12** and not 2-oxo-1',2',4',5'-tetrahydrospiro[3*H*-indole-3,3'-1,2,4,5-tetrazine] -6'-thione **5** as reported recently[9] (Scheme 1).

Biological Activity

Compounds **7**, **9a**, **11**, **12**, and **13** were tested for two strains of *Gram*-positive and *Gram*-negative bacteria, yeast and fungi; the values of inhibition are indicated in Table 1.

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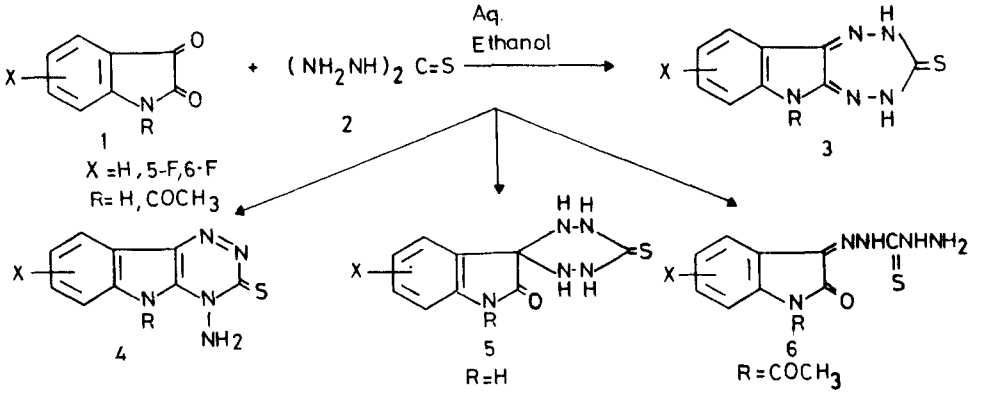

Scheme 1

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Table 1: Biological activity of **7**, **9a**, **11**, **12**, and **13**.

Compound	1	2	3	4	5	6
7	-	+	-	-	-	+
9a	++	+	-	-	-	-
11	-	-	++	++	+	-
12	++	++	+	+	-	+
13	++	+	++	++	+	-

*1: *Bacillus subtilis*, 2: *Staphylococus aureus*, 3: *Escherichia coli*, 4: *Pseudomonas aeruginosa*, 5: *Candida albicans*, 6: *Aspergillus niger*.

Experimental Part

Melting points: uncorrected. - IR spectra (KBr): Pye-Unicam SP-1100. - UV spectra (ethanol): Unicam SP 1720. - Microanalyses: Microanalytical Centre at Cairo University. Compounds prepared by different methods were checked by mixed mp. and identity of IR-spectra.

Isatin-β-thiocarbohydrazone (**12**)

The aqueous solution of thiocarbohydrazide (**2**) (0.01 mole) was stirred without further heating and treated dropwise over 15 min with isatin (0.01 mole) in 25 ml of ethanol. The product began to precipitate during the course of addition. The mixture was allowed to stand overnight, then it was filtered, washed with dilute ethanol and dried, **12** was recrystallized from ethanol (Table).

Benzaldehyde monothiocarbohydrazone (**8**)

A solution of thiocarbohydrazide (0.01 mole) and benzaldehyde (0.01 mole) in ethanol (20 ml) was heated under reflux for 30 min and then left for 2 h at room temp. The precipitate was crystallized from ethanol to give **8** (Table).

β-*Isatin benzaldehyde thiocarbohydrazone* (**7**)

(a) Compound **12** (0.01 mole) was refluxed with benzaldehyde (0.01 mole) and alcohol (15 ml) for 3 h. The solid was crystallized from DMF/ethanol as orange crystals of **7** in an almost quantitative yield (Table).

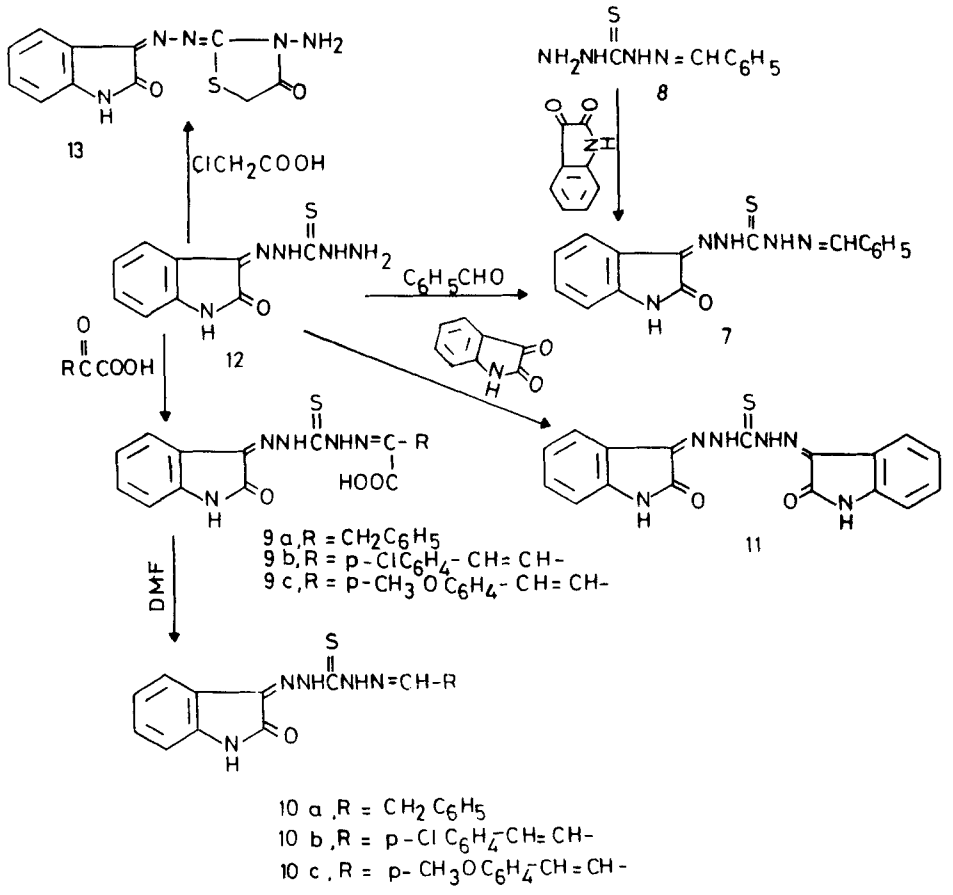
(b) From compound **8** and isatin as described for **12**.

β-*Isatin (substituted glyoxylic acid) thiocarbohydrazones* **9a-c**

General Procedure

Compound **12** (0.01 mole) in ethanol (25 ml, 80%) and the appropriate α-keto acid (0.01 mole) were heated under reflux for 6 h. The precipitate was crystallized from DMF/ethanol (Table 2).

Comp.	Mp.	Mol.	% Analysis			Calcd. Found	
	(°C)	Formula	C	H	N	S	Cl
12	300	$C_9H_9N_5SO$	45.9	3.8	29.8	13.6	
		(235.3)	45.6	3.7	30.0	13.7	
8	196	$C_8H_{10}N_4S$	49.5	5.2	28.8	16.5	
		(194.3)	49.0	5.5	28.4	16.1	
7	247	$C_{16}H_{13}N_5SO$	59.4	4.1	21.6	9.9	
		(323.4)	59.0	4.5	21.1	9.6	
9a	254	$C_{18}H_{15}N_5SO_3$	56.7	4.0	18.4	8.4	
		(381.4)	56.3	3.5	18.0	8.1	
9b	225	$C_{19}H_{14}N_5SO_3Cl$	53.3	3.3	16.4	7.5	8.3
		(427.9)	53.0	3.7	16.1	7.0	8.6
9c	235	$C_{20}H_{17}N_5SO_4$	56.7	4.1	16.5	7.6	
		(423.5)	56.2	4.4	16.1	7.0	
10a	250	$C_{17}H_{15}N_5SO$	60.5	4.9	20.7	9.5	
		(337.4)	60.1	4.2	20.3	9.0	
10b	235	$C_{18}H_{14}N_5SOCl$	56.3	3.7	18.2	8.4	9.2
		(383.9)	56.0	3.3	18.5	8.6	8.8
11	285	$C_{17}H_{12}N_6SO_2$	56.0	3.3	23.1	8.8	
		(364.4)	56.4	3.0	22.7	8.8	
13	275	$C_{11}H_9N_5SO_2$	48.0	3.3	25.4	11.6	
		(275.3)	47.5	3.0	25.7	11.2	



Scheme 2

β-Isatin hydrazonethiocarbohydrazones **10a,b**

General Procedure

(a) A solution of compound **9a** (0.5 g) in DMF (10 ml) was heated under reflux for 3 h, cooled and then diluted with water. The precipitate was collected and recrystallized from DMF/ethanol (Table 2).

(b) A solution of compound **12** (0.01 mole) and of the appropriate aldehyde (0.01 mole) in ethanol (15 ml) was heated under reflux for 15 min. The solid was crystallized from DMF/ethanol and proved to be **10** (mixed mp).

Bis-β-isatinthiocarbohydrazones (**11**)

From compound **12** and isatin as described for **12**. The precipitate was recrystallized from DMF/ethanol (Table 2).

β-Isatin-(4-aminothiazoline-3,5-dione-5)azine (**13**)

A mixture of compound **12** (0.5 g) and fused sodium acetate (0.5 g) in ethanol (30 ml) was heated under reflux for 10 min, then chloroacetic acid (0.5 g) was added whereupon immediately NaCl began to separate. The mixture was again refluxed for 1 h, filtered while hot, then cooled. The precipitate was recrystallized to give compound **13** (Table 2).

Biological Activity test

Biological activity was determined according to the cup-plate method[11] adopted with some modification. Whatman No. 2 filter paper disks (0.5 cm) were impregnated with 200 µg of the test compound. The disk was placed on the surface of the cold solid medium in petridishes, inoculated with the microorganisms, and incubated at 5°C for 1 h to permit good diffusion and then transferred to an incubator at 28°C for 24 h. The sensitivity of microorganisms to the compounds is identified in the following manners

+++ = Highly sensitive (inhibition zone ≤ 15 mm)
++ = Fairly sensitive (inhibition zone ≤ 12 mm)
+ = Slightly sensitive (inhibition zone ≤ 9 mm)
– = Not sensitive

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