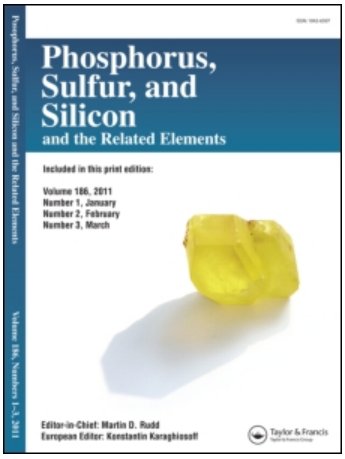

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REACTION OF 2-THIAZOLINE-2-THIOL WITH ISATIN DERIVATIVES

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The reaction of indol-2,3-dione derivatives with 2-thiazoline-2-thiol under thermal as well as photochemical conditions is described. Under refluxing ethanol it afforded 3,4'-dihydro-3-[2'-mercaptothiazolidine]indol-2-one. UV light-induced irradiation produced isomeric 2,4-dihydro-2-[2'-mercapto- thiazolidine]indol-3-one and 2-mercapto-thiazolo[5,4-b]quinoline-4-carboxylic acid. The synthesized compounds were characterized by elemental analyses and spectral studies and were screened for antimicrobial activity.

Keywords: Indol-2,3-dione; 2-thiazoline-2-thiol; 3,4'-dihydro-3-[2'-mercaptothiazolidine]indol-2- one; 2-mercaptothiazolo[5,4-b]quinoline-4-carboxylic acid; photochemical irradiation; IR; ^{1}HNMR analyses; antimicrobial activity

INTRODUCTION

In continuation to our work on the chemistry of indol-2,3-dione (isatin) derivatives, we have recently reported that the reaction of indol-2,3-diones with pyrazolone affords spiro as well as non-spiro compounds.[1,2] Prompted by these results, we have carried out the reaction of isatin with other five membered heterocycles *viz.* 2-thiazoline-2-thiol because a wide spectrum of pharmacological activities are associated with indole derivatives, and in addition, the thiazolidine[6,7] nucleus is well recognised for its antiinflammatory and antihypertensive activities. Thus a system incorporating these two moieties is likely to result in the formation of potent bioactive compounds. In addition, isatin has been reported to decompose into

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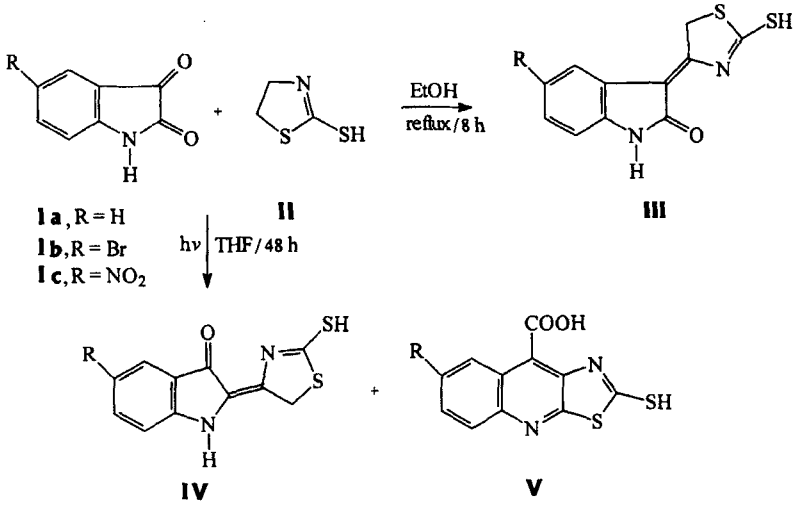
isatic acid under photochemical conditions.[8] Hence, we have investigated the reactions of indol-2,3-diones with 2-thiazoline-2-thiol separately under thermal as well as photochemical conditions.

RESULTS AND DISCUSSION

The reaction of indol-2,3-diones (**Ia-c**) and 2-thiazoline-2-thiol **II** was carried out in the molar ratio of 1:2 in refluxing absolute ethanol for 8 h (Scheme 1) whereby 3,4'-dihydro-3-[2'-mercaptothiazolidine]indol-2-one **III** was mainly produced in the moderate yield of 35–40%.



SCHEME 1

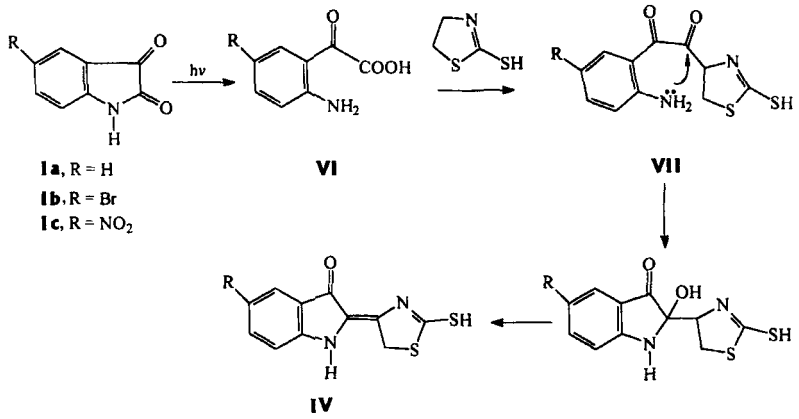
When the same reaction was carried out under photochemical irradiation using a medium pressure mercury lamp (~298–310 nm) for 48 h, instead of thermal product **III,** isomeric 2,4'-dihydro-2-[2'-mercaptothiazolidine]indol-3-one **IV** was characterized as the major compound in about 50% yield. A low yield (15-20%) of 2-mercaptothiazolo [5,4-**b**]quinoline-4-carboxylic acid **V** was also obtained.

While the formation of compound **III** seems to occur by condensation of carbonyl group at position 3 of isatin with methylene of 2-thiazo-

line-2-thiol, the formation of **IV** may be explained through the intermediacy of diketone **VII,** resulting from the condensation of isatic acid **VI** (obtained by the photochemical decomposition of isatin[8]) with 2-thiazoline-2-thiol. The intramolecular nucleophilic attack of the amino group on carbonyl carbon and subsequent elimination of a water molecule results in **IV** (Scheme 2). Similarly compound **V** may arise by the coupling of keto group of isatic acid **VI** with methylene of 2-thiazoline-2-thiol, followed by cyclisation. Such functionalized thiazolinoquinolines **V** may serve as useful synthons for the total synthesis of naturally occurring quinoline alkaloids.[9] The structure of the products have been ascertained by their spectral data and elemental analyses (Table I).

TABLE I Physical and Analytical Data of Compounds

Compound No.	*Physical State*	*Molecular formulae*	*MP °C*	*Yield %*	*Elemental analyses Calcd. (found)*		
					C	*H*	*N*
Thermal product							
IIIa	Red crystals	$C_{11}H_8N_2OS_2$	200	40	53.22 (53.18)	3.22 3.19	11.29 (11.22)
IIIb	Orange crystals	$C_{11}H_7BrN_2OS_2$	238	38	40.37 (40.32)	2.14 (2.11)	8.56 (8.48)
IIIc	Yellow Solid	$C_{11}H_7N_3O_3S_2$	265	35	45.05 45.00)	2.38 (2.32)	14.33 (14.26)
Photochemical products							
IVa	Orange Solid	$C_{11}H_8N_2OS_2$	190	50	53.22 (53.18)	3.22 (3.19)	11.29 (11.22)
IVb	Red solid	$C_{11}H_7BrN_2OS_2$	230	52	40.36 (40.32)	2.14 (2.11)	8.56 (8.48)
IVc	Yellow Solid	$C_{11}H_7N_3O_3S_2$	240	45	45.05 (45.00)	2.38 (2.32)	14.33 (14.26)
Va	Yellow solid	$C_{11}H_6N_2O_2S_2$	180	18	50.38 (50.32)	2.29 (2.23)	10.68 (10.68)
Vb	Red solid	$C_{11}H_5N_2O_2S_2$	210	15	38.72 (38.70)	1.46 (1.41)	8.21 (8.19)
Vc	Yellow solid	$C_{11}H_5N_3S_2O_4$	235	20	42.99 (42.94)	1.62 (1.57)	13.6 (13.4)



Ia, R = H
Ib, R = Br
Ic, R = NO_2

SCHEME 2

SPECTRAL STUDIES

The compound **III** displayed a characteristic carbonyl absorption band at 1682 cm^{-1} (>NHCO) alongwith >NH and methylene absorptions at 3310-3180 and 2900-2820 cm^{-1} respectively. In the IR spectra of compound **IV,** a characteristic absorption band due to carbonyl group was seen at 1700–1690 cm^{-1} and >NH absorption at 3320–3190 cm^{-1}. The absorption at 2910–2815cm^{-1} was due to methylene group. The IR spectrum of compound **V** exhibited carboxyl carbonyl absorption at 1690 cm^{-1} and absorption at 1610 cm^{-1} due νC=N. The peak at 2715 cm^{-1}corresponding to νSH group, was found in all products **III-V.** The asymmetric and symmetric vibrations of the nitro group were observed at 1575 and 1360 cm^{-1}. In the ^1H NMR spectra of products **III** and **IV** non appearance of methylene signals of 2-thiazoline-2-thiol in the region δ 3.70-4.00 and the appearance of additional resonance signals at δ 4.2-4.7 provide strong evidence for the formation of these compounds. Besides the presence of aromatic protons in the region δ 6.97-8.2, broad singlet at δ 8.50-9.30 for the NH proton and broad hump at δ 11.1 for the SH proton are also in harmony with the proposed structures. Compound **V** displayed signals for aromatic protons at δ 7.3–8.81, and the carboxylic proton was seen at δ 12.2-12.5.

ANTIMICROBIAL ACTIVITY

The synthesized heterocyclic compounds **(III-V)** were evaluated for their antimicrobial activities at a concentration of 100 μg/disk in agar media. The method adopted for activity is the Paper disk diffusion method of A.W. Bauer et al.[10] in which the compound is allowed to diffuse through a solid medium so that a gradient is established, the concentration being highest near the site of application of the compound and decreasing with distance. The test bacterium or fungus is seeded on the medium, and its sensitivity to the compound is determined from the inhibition of the growth. The reference compounds used for the antibacterial and antifungal activities were *Streptomycin* and *Mycostatin.* All compounds were found to be moderately active against *E. coli, S. facaelus* (bacteria), *R. solani, F. oxysporium,* and *F. solani* (fungus), and the results are summarised in Table II

TABLE II Antimicrobial Activity of the Title Compounds

Compound No.	*Zone of inhibition in mm (Activity Index)*				
	E. Coli	*S. faecilus*	*R. Solani*	*F. oxysporium*	*F. Solani*
IIIa	8.8 (0.88)	9.5 (0.95)	10.0 (1.00)	8.5 (0.85)	7.8 (0.76)
IIIb	11.2 (1.02)	9.8 (1.04)	12.2 (1.02)	9.8 (0.96)	10.8 (0.97)
IIIc	12.4 (1.02)	10.6 (0.98)	12.6 (1.06)	14.0 (1.20)	13.2 (0.98)
IVa	8.9 (0.88)	9.4 (0.95)	10.2 (1.02)	8.4 (0.84)	7.9 (0.78)
IVb	11.2 (1.12)	9.8 (1.02)	12.6 (1.04)	9.8 (0.92)	10.6 (1.06)
IVc	13.4 (1.10)	11.6 (1.12)	12.6 (1.02)	13.0 (1.13)	12.2 (1.12)
Va	10.0 (1.00)	9.1 (0.98)	9.8 (1.07)	12.2 (1.05)	11.0 (1.10)
Vb	10.5 (1.05)	9.8 (0.98)	10.0 (1.02)	12.0 (1.06)	12.6 (1.08)
Vc	11.5 (1.15)	10.5 (1.05)	11.4 (1.12)	12.5 (1.20)	13.5 (1.20)

Activity index =Inhibition zone of sample / Inhibition zone of the standard.

EXPERIMENTAL

Melting points were determined in open glass capillary and are uncorrected. The IR spectra were recorded on Nicolet Magna IR™ spectrometer model 550 in KBr pellets. The ^1H NMR spectra were obtained in DMSO-d_6 on a FX 90Q Jeol spectrophotometer at 89.55 MHz using TMS as internal standard. Microanalyses were obtained using a Perkin Elmer Series 11 C, H, N, S, O analyser-2400. Photochemical irradiation was conducted under nitrogen atmosphere by a Hanovia 1-litre photochemical reactor equipped with a medium pressure arc. The solvents were purified by standard procedures.[11,12]

A representative method for thermal and photochemical reactions is described below:

Thermal reaction

A mixture of isatin (**I**; 3.4 mmol) and 2-thiazoline-2-thiol (**II;** 6.7 mmol) in the molar ratio of 1 :2 was refluxed for 8 h in absolute alcohol (75ml). After completion of the reaction as monitored by TLC, the mixture was concentrated under vacuuo and then allowed to crystallize overnight (12 h) at 0 °C whereby yellow to red shiny crystals of **III** crystallized out (35-40%). The crystals were filtered and washed with petroleum-ether . Purity was confirmed by TLC. The product was characterized as 3,4'-dihydro-3-[2'-mercaptothiazolidine]indol-2-one.

Photochemical reaction

A mixture of isatin (**I;** 6.8 mmol) and 2-thiazolidine-2-thiol (**II;** 13.4 mmol) in the molar ratio of 1:2 in dried THF (190 ml) was subjected to UV irradiation using a Hanovia 1-litre medium pressure (~298-310 nm) lamp in an inert atmosphere for 48 h. The reaction was monitored to complete consumption of isatin. The mixture was then concentrated under vacuuo and subjected to column chromatography over silica-gel. Two major fractions were obtained. The first fraction from petroleum ether-chloroform (2:3) gave compound **IV** (50%) whereas another fraction from chloroform-ethyl acetate (9:1) afforded **V** as yellow crystalline solid (15-20%).

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