Thermal and Photochemical Reaction of Isoxazolone with Indole-2,3-dione Derivatives

R. T. Pardasani* [a], P. Pardasani [a], S. Muktawat [a], R. Ghosh [a] and T. Mukherjee [b]

[a] Department of Chemistry, University of Rajasthan, Jaipur 302004, India
[b] Chemistry Division, Bhabha Atomic Research Centre, Mumbai 400085, India

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The reaction of indole-2,3-dione derivatives with five membered heterocycle, *viz* isoxazolone under thermal as well as photochemical conditions is described. While under refluxing ethanol these conditions afforded 2,3-dihydro-3-(5'-oxo-3'-phenylisoxazolidyl)indol-2-one **3** and a spiro product 2',3'-dihydro-3,7-diphenylspiro[diisoxazolo[4,5-*e*:4,5-*b*]pyran-8,3'-indol]-2'-one **4**, the uv light induced irradiation mainly produced 4,5-dioxo-3-phenylisoxazolo[5,4-*b*][1]benzazepine **5** and 3-phenylisoxazolo[5,4-*b*]quinoline-4-carboxylic acid **6**. The products have been characterised on the basis of spectral data and elemental analyses.

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In continuation of our work in the chemistry of indole-2,3-dione (isatin) derivatives, we have recently reported that the reaction of indole-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 indole-2,3-dione with other five membered heterocycles, *viz* isoxazolone. We were interested in these reactions as a wide spectrum of biological activities are associated with indole derivatives [3-5] and besides the isoxazolone [6-7] nucleus has also been shown to possess antibacterial and antitumour activity. Thus, introduction of an isoxazolone ring to the isatin system is expected to influence the biological activities significantly. Hence, it was thought desirable to synthesise a system having both ring systems, in order to evaluate the biological activities of the spiro/non-spiro products. In addition a survey of the literature revealed that although reactions of isoxazolone with 1,2-benzenediammine [8] and amino esters [9] are reported, no reaction with indole-2,3-dione derivatives has been mentioned. Thus we have investigated the reaction of indole-2,3-diones with 3-phenyl-5-isoxazolone under thermal conditions. Besides keeping in view the observations of Haucke *et al* [10] that under photochemical conditions, isatin may react through various intermediates and considering that isoxazolone may also exist in different tautomeric forms and can react in more than one manner as has been recently reported by Grandmont *et al* [11] on the basis of molecular modelling, we were prompted to explore this reaction under photochemical condition as well.

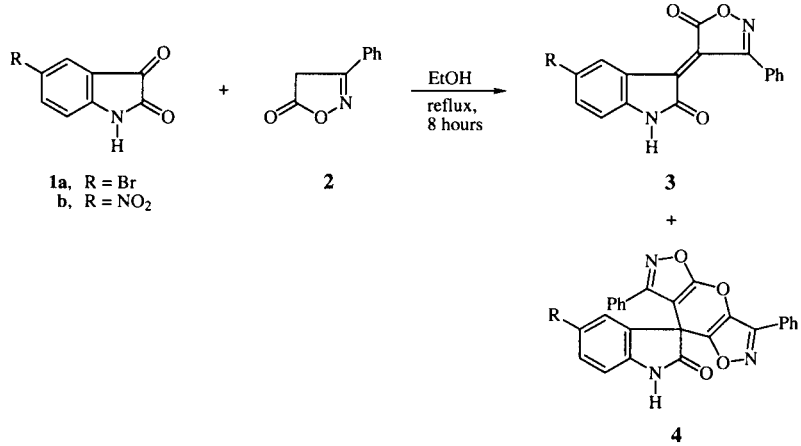
Results and Discussion.

The reaction of indole-2,3-diones **1a** and **1b** with 3-phenyl-5-isoxazolone **2** was carried out in a molar ratio of 1:2 in refluxing absolute ethanol for 8 hours (Scheme 1).

The reaction of isatin **1a** (R = Br) with 3-phenyl-5-isoxazolone afforded **3a** in 63% yield and a spiro compound, 5'-bromo-2',3'-dihydro-3,7-diphenylspiro[diisoxazolo-[4,5-*e*:4,5-*b*]pyran-8,3'-indol]-2'-one **4a** in 10% yield. Isatin **1b** (R = NO_2) similarly gave compounds **3b** and **4b** in 78% and 15% yield, respectively.

The formation of compound **3** seems to occur by condensation of the carbonyl group at position 3 of isatin with the active methylene group of the isoxazolone, it is

Scheme 1



1a, R = Br
b, R = NO_2

2

3

4

in conformity with the recent observations of Zard *et al* [12] that the isoxazolone ring belongs to the "active methylene" class of compounds and can undergo a Knoevenagel type condensation with aldehydes and ketones [13]. Compound **4** may arise by condensation of isatin with enolic isoxazolone **2** in a molar ratio of 1:2 followed by cyclisation of the intermediate. Thus it is evident from these observations that under thermal conditions a) there is no decomposition of isatin to isatic acid (2-aminophenylglyoxalic acid) and b) there is no significant enolization of isoxazolone as is evident from the predominant formation of compound **3**.

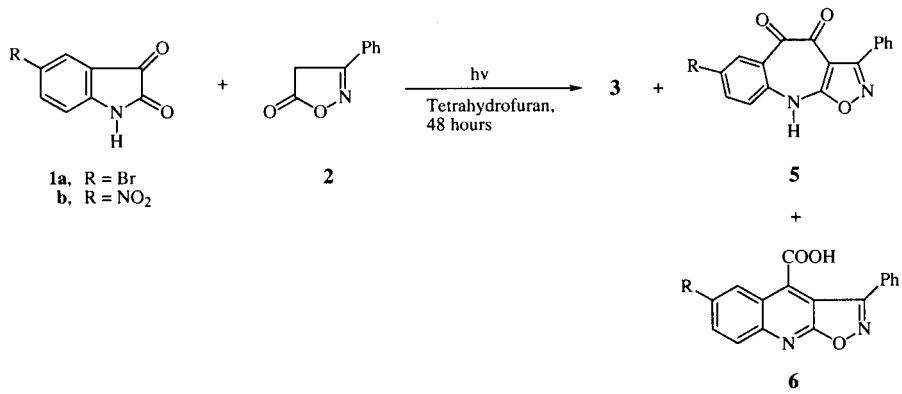
When the same reaction of isatin **1a** and **1b** with 3-phenyl-5-isoxazolone **2** was carried out under photochemical irradiation using a Hanovia medium pressure mercury arc lamp (~298-310 nm) for 48 hours, the thermal product **3** was obtained only in low yield, 11%, identified by comparision with an authentic sample obtained in the thermal reaction. However two new products, characterized as 7-bromo- or 7-nitro-4,5-dioxo-3-phenylisoxazolo[5,4-*b*][1]benzazepine **5** and 6-bromo- or 6-nitro-3-phenylisoxazolo[5,4-*b*]quinoline-4-carboxylic acid **6** were obtained in about 38% and 15% yield as shown in Scheme 2.

The structure of all products have been assigned from their spectral data (Table 2) as well as from literature data [14,15] for similar types of compounds.

In the ir spectrum of compound **3** characteristic absorption bands were observed at 1710 and 1680 cm^{-1}, assignable to two conjugated carbonyl groups. The exocyclic C=C absorption band was seen at 1620 cm^{-1}. Compound **4** displayed only one carbonyl absorption at 1678 cm^{-1} (-NHCO) along with -NH absorption in the region 3320-3160 cm^{-1} suggesting the involvement of the 3-carbonyl group of isatin in the reaction. The exocyclic C=C absorption band was not observed and instead the pyran-ether linkage was observed at 1180 cm^{-1}. In the ^1H nmr spectrum of products **3** and **4** signals corresponding to the active methylene protons of isoxazolone **2** [16-17] were absent in the region δ 3.8 ppm, whereas aromatic and imino protons were present in the required region, *i.e.* 6.7-8.2 ppm.

The photoproduct **5** displayed characteristic infrared absorption bands at 3230, 1760 and 1740 cm^{-1} expected from an imino group and the carbonyl groups of an α-diketone respectively. In the ^1H nmr spectrum a multiplet was observed for aromatic protons in the region δ 7.2-7.3 ppm. A singlet at δ 10.2 ppm corresponded to associated imino protons. The ir spectrum of product **6** exhibited a carboxyl carbonyl absorption at 1695 cm^{-1} and a C=N absorption at 1610 cm^{-1}. The ^1H nmr spectrum displayed required signals at δ 6.97 (d, J = 7.0 Hz, H-8), 7.44 (m, 3-C_6H_5), 8.11 (dd, J = 7.0 Hz, J = 2.0 Hz, H-7), 8.2 (d, J = 2.0 Hz, H-5), 11.40 (s, 4-COOH). The structure of all these products were further established by elemental analyses (Table 3).

Scheme 2



1a, R = Br
b, R = NO_2

2

The formation of compound **5** may be explained by the condensation of isatic acid (5-bromo, or 5-nitro-2-aminophenylglyoxalic acid) resulting from the photochemical decomposition [10] of isatin **1a** or **1b** with the enolic form of isoxazolone. Similarly the isoxazoloquinoline derivative **6** may arise by reaction of isatic acid with the active methylene group of isoxazolone. Hence it may be suggested that there is greater decomposition of isatin to isatic acid under photochemical conditions. This fact has been further supported by molecular modelling using the PC PH4 programme. On the basis of the calculation of the heat of formation (Table 1) it may be suggested that isatic acid is thermodynamically more stable than the corresponding isatin.

Table 1

Heat of Formation of Indole-2,3-diones and the Corresponding Isatic Acids

Compound	5-Bromo-isatin	5-Bromo-isatic acid	5-nitro-isatin	5-nitro isatic acid
H_f (Kcal/mol)	+9.80	-35.52	+31.78	-10.19

Table 2

NMR and IR Data of Compounds **3-6**

Compound	^{1}H NMR parameters (δ ppm)	IR parameters (ν cm^{-1})
3a	6.96 (d, J = 6.0 Hz, H-7), 7.35 (m, 3'-C_6H_5), 8.0 (dd, J_1 = 6.5 Hz, J_2 = 1.5 Hz, H-6), 8.15 (d, J = 1.5 Hz, H-4), 9.8 (s, -NH-)	3320 (-NH-), 1710, 1680 (conj C=O), 1620 (exo C=C)
3b	7.0 (d, J = 7.0 Hz, H-7), 7.30 (m, 3'-C_6H_5), 8.1 (dd, J_1 = 7.0 Hz, J_2 = 2.0 Hz, H-6), 8.24 (d, J = 2.0 Hz, H-4), 9.85 (s, -NH-)	3310 (-NH-), 1710, 1690 (conj C=O), 1615 (exo C=C)
4a	6.8 (d, J = 6.0 Hz, H-7), 7.3-7.6 (m, 3',6'-2 x C_6H_5), 8.0 (dd, J_1 = 7.0 Hz, J_2 = 2.0 Hz, H-6), 8.1 (d, J = 2.0 Hz, H-4), 9.82 (s, -NH-)	3320-3160 (-NH-), 1678 (-NHCO), 1180 (C-O-C)
4b	6.9 (d, J = 6.5 Hz, H-7), 7.38 (m, 3',6'-2 x C_6H_5), 7.9 (dd, J_1 = 6.5 Hz, J_2 = 2.0 Hz, H-6), 8.2 (d, J = 2.0 Hz, H-4), 9.85 (s, -NH-)	3310-3160 (-NH-), 1670 (-NHCO), 1170 (C-O-C)
5a	7.0 (d, J = 6 Hz, H-9), 7.3-7.4 (m, 3-C_6H_5), 8.1 (dd, J_1 = 7.0 Hz, J_2 = 2.5 Hz, H-8), 8.23 (d, J = 2.5 Hz, H-6), 9.8 (s, -NH-)	3230 (-NH-), 1760, 1740 (α-diketone)
5b	6.8 (d, J = 6.0 Hz, H-9), 7.4-7.45 (m, 3-C_6H_5), 8.15 (dd, J_1 = 7.0 Hz, J_2 = 2.5 Hz, H-8), 8.20 (d, J = 2.5 Hz, H-6), 9.9 (s, -NH-)	3228 (-NH-), 1758, 1740 (α-diketone)
6a	6.97 (d, J = 7.0 Hz, H-8), 7.44 (m, 3-C_6H_5), 8.11 (dd, J = 7.0 Hz, J_2 = 2.0 Hz, H-7), 8.2 (d, J = 2.0 Hz, H-5), 11.40 (s, 4-COOH)	1690 (C=O in COOH), 1610 (C=N)
6b	6.99 (d, J_1 = 6.5 Hz, H-8), 7.34-7.45 (m, 3-C_6H_5), 8.20 (dd, J_1 = 6.5 Hz, J_2 = 2.0 Hz, H-7), 8.25 (d, J = 2.0 Hz, H-5), 11.35 (s, 4-COOH)	1700 (C=O in COOH), 1610 (C=N)

Table 3

Physical and Analytical Data of Compounds **3-6**

Compound	Physical state	Yield %	Mp °C	Analysis Calcd./found C	H	N
Thermal Products						
3a	Buff Solid	63	155	55.28	2.43	7.58
				55.24	2.40	7.54
3b	Greyish	78	192-193	60.89	2.68	12.53
	Pellets			60.87	2.66	12.49
4a	Brownish	10	205-207	62.90	2.73	8.20
	Solid			62.87	2.70	8.18
4b	Violet	15	124-126	65.27	2.92	11.71
	Solid			65.25	2.89	11.68
Photochemical Products						
5a	Violet	35	180	55.28	2.43	7.58
	Solid			55.26	2.40	7.57
5b	Brick red	28	190	60.89	2.68	12.53
	Solid			60.85	2.64	12.49
6a	Brown	14	199	55.28	2.43	7.58
	Solid			55.25	2.40	7.56
6b	Yellowish	18	110	60.89	2.68	12.53
	Solid			60.87	2.64	12.53

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 potassium bromide pellets. The ^{1}H and ^{13}C nmr spectra were recorded on Jeol FX-90Q model at 89.55 MHz with tetramethylsilane as the internal standard, chemical shifts are given in δ ppm. Elemental analyses were performed with a Perkin Elmer Series 11 C, H, N, S, O Analyser-2400. Photochemical irradiation was conducted under a nitrogen atmosphere using a Hanovia 1 litre photochemical reactor equipped with a medium pressure arc. The solvents were purified by standard procedures [18,19]. A representative method for thermal and photochemical reactions is described below.

Thermal Reaction.

5-Bromo-2,3-dihydro-3-(5'-oxo-3'-phenylisoxazolidyl)indole-2-one (**3a**).

A mixture of 5-bromoisatin (0.81 g, 3.3 mmoles) and 3-phenyl-5-isoxazolone (1.07 g, 6.6 mmoles) in a molar ratio of 1:2 was refluxed for 8 hours in absolute alcohol (100 ml). After completion of reaction as monitored by tlc, the reaction mixture

was concentrated *in vacuo* and about half the solvent (*i.e.* ethanol) was removed. The concentrated reaction mixture was then allowed to crystallize overnight (18 hours) at 0° whereby a buff solid **3a** crystallized out. It was filtered, washed with petroleum ether (60-80) to yield 1.18 g (63%) of **3a**, mp 155°.

5'-Bromo-2',3'-dihydro-3,7-diphenylspiro[diisoxazolo-[4,5-*e*:4,5-*b*]pyran-8,3'-indole]-2'-one (**4a**).

The above filtrate was concentrated *in vacuo* and subjected to column chromatography over silica gel using solvents of increasing polarity. Ethyl acetate (100%) fraction afforded product **4a** as brownish solid 0.19 g (10%), mp 205-207°.

5-Nitro-2,3-dihydro-3-(5'-oxo-3'-phenylisoxazolidyl)indol-2-one (**3b**).

A Similar reaction was carried out with 5-nitroisatin (0.64 g, 3.3 mmoles) and 3-phenyl-5-isoxazolone (1.07 g, 6.6 mmoles) in a molar ratio of 1:2 in refluxing ethanol (100 ml) for 8 hours whereby greyish pellets, **3b**, 1.3 g mp 192-193° crystallized out.

5'-Bromo-2',3'-dihydro-3,7-diphenylspiro[diisoxazolo[4,5-*e*:4,5-*b*]pyran-8,3'-indol]-2'-one (**4b**).

Column chromatography of the above filtrate provided **4b** from chloroform-ethyl acetate (1:9) fraction as violet solid, 0.26 g (15%) mp 124-126°.

Photochemical Reaction.

7-Bromo-4,5-dioxo-3-phenylisoxazolo[5,4-*b*][1]benzazepine (**5a**).

A mixture of 5-bromoisatin (0.81 g, 3.3 mmoles) and 3-phenyl-5-isoxazolone (1.07 g, 6.6 mmoles) in a molar ratio of 1:2 in dried tetrahydrofuran (190 ml) was subjected to uv irradiation using a Hanovia 1 litre medium pressure (298-310 nm) lamp in an inert atmosphere for 48 hours. The reaction was monitored by tlc until complete consumption of the isatin. It was then concentrated *in vacuo* and subjected to column chromatography over silica gel. Three major fractions were obtained. The first fraction from the petroleum ether-chloroform (1:3) afforded compound **5a** as a dark violet solid, 0.66 g (35%), mp 180°.

Another fraction from ethyl acetate-methanol (9:1) was identified as compound **3a**, 0.20 g (11%) by comparison with the thermal product.

6-Bromo-3-phenylisoxazolo[5,4-*b*]quinoline-4-carboxylic Acid (**6a**).

Finally the fraction ethyl acetate-methanol (1:1) gave **6a** as a light brown solid, 0.26 g (14%), mp 199°.

Similarly a mixture of 5-nitroisatin (0.64 g, 3.3 mmoles) and 3-phenyl-5-isoxazolone (1.07 g, 6.6 mmoles) in a molar ratio of 1:2 in dry tetrahydrofuran (190 ml) was subjected to uv irradiation using a Hanovia 1 litre medium pressure (298-310 nm) lamp in an inert atmosphere for 48 hours. After the usual work up and purification by column chromatography, three fractions were obtained.

7-Nitro-4,5-dioxo-3-phenylisoxazolo[5,4-*b*]benzazepine (**5b**).

The first fraction from petroleum ether-chloroform (1:4) afforded compound **5b** as a brick red solid, 0.48 (28%), mp 190°.

The second fraction obtained from ethyl acetate-methanol (9:1) was characterised as **3b**, 0.20 (12%) as compared with the authentic sample obtained from the thermal reaction.

6-Nitro-3-phenylisoxazolo[5,4-*b*]quinoline-4-carboxylic Acid (**6b**).

The fraction from ethyl acetate-methanol (3:1) gave **6b** as a yellowish solid 0.30 g (18%), mp 110°.

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