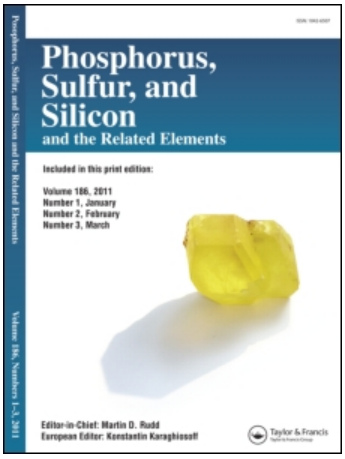

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Syntheses of Indigoid Dye Precursors and Bioactive Compounds Via Condensation of 1,2- and 1,4-Diones with Thiohydantoins

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SYNTHESES OF INDIGOID DYE PRECURSORS AND BIOACTIVE COMPOUNDS VIA CONDENSATION OF 1,2- AND 1,4-DIONES WITH THIOHYDANTOINS

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The condensation of 1,2- and 1,4-diketones with thiohydantoins to give tetrahydroquinodimethane and isatylidene derivatives respectively is described which may act as potential precursors for indigoid dyes as well as bioactive compounds. The synthesized compounds have been characterized by elemental analyses, spectral studies as well as by molecular modelling using PC WIN model. In addition, the newly synthesized products have been screened for antimicrobial activity.

Keywords: Antimicrobial activity; isatylidene and quinodimethane derivatives; semiempirical calculations; spectral characterization

INTRODUCTION

Indigoid compounds are important because of their application in textile dyeing. However the search for new indigoid derivatives from the structurally related chromophores can be used to produce compounds with shifted conjugation.[1] The chemistry of imidazolidine derivatives viz thiohydantoins (**Ia–b**) is of interest since many natural products possess its ring system and are useful in pharmacological activities.[2,3] Similarly indol-2,3-dione is well recognized for its wide spectrum of biological activities and its versatility toward a number of organic reactions has been reported.[4,5] Therefore coupling of these two antimicrobial agents would be expected to afford interesting series of

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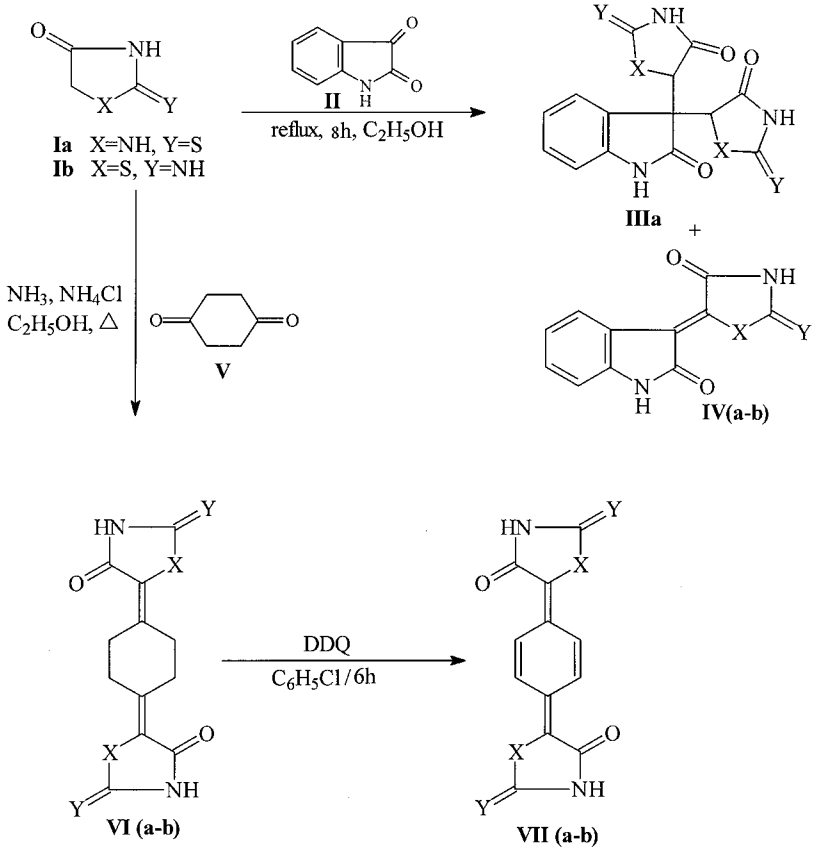
compounds having biological properties. In addition, our attention was drawn to the chemistry of the hydantions because it has been previously used to synthesize indigo types of dyes by reaction with cyclic ketones and their structure is similar to the chromophore of indigo.[6] The first *p*-quinodimethane derivative with donor-acceptor pattern of the indigo chromophore was reported by Iwatsuki et al.[7] However, we envisioned that the incorporation of D-A functional group into five membered ring should enhance the conjugation and make the chromophore system structurally similar to that of indigo.[8] Thus in continuation to our work on isatin derivatives with five membered heterocyclic compounds[9–11] and in support of the above assumptions we have succeeded in condensing various thiohydantoins with 1,4-dione (cyclohexan-1,4-dione) and 1,2-dione (indol-2,3-dione) and the results are presented below.

RESULTS AND DISCUSSIONS

The reaction of thiohydantoin **Ia** and indol-2,3-dione **II** was carried out in the molar ratio of 2:1 in refluxing absolute ethanol for 5 h whereby 3′,5-[bis(4-imidazolidinone-2-thioxo)]indol-2′-one **IIIa** was mainly produced in 60% yield along with 2′,3′-dihydro-3-(4-imidazolidinone-2-thioxo)indol-2′-one **IVa** in 10% yield. Similar reaction with pseudothiohydantoin **Ib** afforded only 2′,3′-dihydro-3-(4-imidazolidinone-2-thioxo)indol-2′-one **IVb** in 45% yield. When the reaction of thiohydantoin (**Ia–b**) was carried out with cyclohexan-1,4-dione **V** in the molar ratio of 2:1 in inert atmosphere in the presence of hot saturated solution of NH_4Cl at 80°C for 2 h (Scheme 1), tetrahydroquinodimethane derivative (**VIa–b**) was produced in moderate yield of 35–45%. While the formation of oxindole **III** derivatives and isatylidene **IV** derivatives may be explained by Knoevenagel condensation of active methylene of thiohydantoin with 3-carbonyl of indol-2,3-dione as observed by Johnson[12] as well as Zard et al.[13] in case of piperidine and isoxazolone, the formation of tetrahydroquinodimethane derivative **VI** may simply take place by condensation of cyclohexan-1,4-dione with active methylene of thiohydantoin. The dehydrogenation of **VIa** to dark violet quinodimethane **VIIa** was accomplished with an excess of 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) in refluxing chlorobenzene. The UV absorption spectrum of **VIIa** [λ_{max} (ethanol) = 400 nm broad] had a wavelength about 150 nm greater than **VIa**. The insertion of one or two double bonds into the quinodimethane system **VIIa** thus causes a bathochromic shift which is typical of the indigoid system upon extension of the central π electron system.



SCHEME 1

SPECTRAL STUDIES

In the IR spectrum of compound **III** characteristic absorption bands were observed at 1720, 1680, 1670 (for three NHCO) along with >NH absorption at 3300–3150 cm^{-1}. Compound **IV** displayed carbonyl absorption at 1710 and 1678 cm^{-1} assignable to two conjugated carbonyl groups. The exocyclic C=C absorption band was seen at 1620 cm^{-1}. In the ^1H NMR spectrum of products of **III** and **IV** signals corresponding to the active methylene protons were absent in the region δ 3.8 ppm whereas aromatic protons were present in the required region, that is, δ 6.85–8.45 and imino protons were observed at δ 11.0 and 11.2. The ^{13}C NMR spectrum of **IIIa** displayed peaks for C=O at δ 178.1 and 169.5, C=S at 165.4, benzenoid carbons at 147.3–121.8, quarternary carbon

at 110.1 and the tertiary carbon at 107.9 and 96.0. The ^{13}C NMR of **IVa** showed signals at δ 187.8 and 184.2 for C=O, 176.59 for C=S, 142.8–124.9 for benzenoid carbons and at 120.4 and 109.7 ppm for olefinic carbons. Additional evidence was obtained from the mass spectra. Mass spectrum of **IIIa** gave molecular ion peak at m/z 361 while for **IVa** calculated mass is 245 and the measured mass is 245.025. The UV absorption spectra of compound **VIa** [λ_{max} (ethanol) = 250 nm] and **VIIa** [λ_{max} (ethanol) = 400 nm broad] showed that quinodimethane derivative has longer wavelength which is typical of indigoid system. The IR spectrum of tetrahydroquinodimethane product **VI** displayed characteristic absorption bands at 3400–3100, 1710, 1620, and 1200 cm^{-1} expected from an imino groups, carbonyl group and C=S group respectively. In the ^{1}H NMR spectrum a singlet was observed at δ 2.5 and 3.8 for methylene protons, singlets at δ 9.8 and 11.6 corresponded to imino protons. In the ^{1}H NMR spectrum of **VIIa**, quinonoid protons were observed in the region δ 6.72–7.3 whereas imino protons appeared at δ 9.2 and 10.5 ppm. The ^{13}C NMR of **VIa** displayed C=O at δ 180.0, C=S at 162.3, C=C at 121.7, and 97.4 and methylene carbons at 47.35 ppm respectively whereas in the ^{13}C NMR spectrum of **VIIa**, C=O was seen at δ 179.2, C=S at 170.0 and the quinonoid carbons appeared in the region of 137.5–152.5 ppm respectively. Mass spectrum of **VIIa** gave molecular ion peak at m/z 304. The structures of all these products were further established by elemental analyses (Table I).

The configuration of the products **VII(a–b)** appears to be *anti*, probably due to less steric hindrance between two bulky sulphur atoms, on the basis of calculation of heat of formation (Table II) by molecular modelling using MOPAC 6 programme on AM1 scale. From the table it may also be noted that *anti* product of **VIIb** is more stable than that of **VIIa** by 14.81 Kcal/mol. This can be explained by the fact that in comparison to nitrogen, sulphur atom can readily donate its lone pair to extend the π conjugation, thereby stabilizing the system. On the other hand, product **VIIb**-*syn* is highly unstable because two large *syn* sulphur atoms disrupt the planarity of the molecule, essential for extended π conjugation. The optimized geometries of **VII (a–b)** *syn/anti* products are given in Figures 1 and 2.

ANTIMICROBIAL ACTIVITY

The synthesized products **III**, **IV**, **VI**, and **VII** were screened for their antibacterial and antifungal activities at the concentration of 100μ g/disc using *Streptomycin* and *Mycostanin* respectively as the reference compounds. The test organisms used included *Escherichia*

TABLE I Physical and Analytical Data of Compounds

Compound no.	Physical state	Molecular formula	m.p. (°C)	Yield (%)	Elemental analyses calcd. (found) C	H	N
IIIa	Dark brown solid	$C_{14}H_{11}N_5O_3S_2$	210	60	46.53 (46.68)	3.04 (3.09)	19.39 (19.52)
IVa	Buff colored solid	$C_{11}H_7N_3O_2S$	190	10	53.88 (54.10)	2.86 (3.00)	17.14 (18.10)
IVb	Pale brown solid	$C_{11}H_7N_3O_2S$	155	45	53.88 (54.25)	2.86 (3.05)	17.14 (18.0)
VIa	Dark brown solid	$C_{12}H_{12}N_4O_2S_2$	>290	62	46.75 (46.89)	3.89 (3.75)	18.18 (18.25)
VIb	Brown solid	$C_{12}H_{12}N_4O_2S_2$	>280	45	46.75 (47.02)	3.89 (4.01)	18.18 (18.32)
VIIa	Dark violet solid	$C_{12}H_8N_4O_2S_2$	260 dec	50	47.37 (47.21)	2.63 (2.70)	18.42 (18.38)

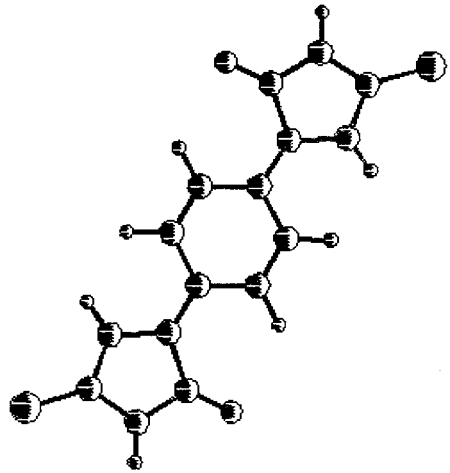
coli (gram negative bacterium), *Staphylococcus aureus* (gram positive bacterium), *Aspergillus flavus*, *Aspergillus niger* (fungi). Disc diffusion method of Varma et al.[14] was followed. Results obtained have been tabulated (Table III) in the form of inhibition zone and activity indices. Although all the compounds showed moderate to fairly good activities, a close look on the activity indices reveals that compound **IIIa** and **VIa** displayed pronounced activities against the two chosen bacteria.

EXPERIMENTAL

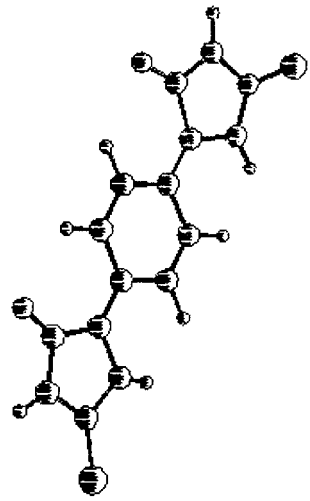
All the operations were carried out under nitrogen atmosphere. Melting points were determined in open glass capillary and are uncorrected. The solvents were purified by standard procedures.[15,16] The IR spectra were recorded on Nicolet Magna IR™ model 550 in KBr pellets. The ^1H and ^{13}C NMR spectra were obtained on Jeol FX-90Q and Bruker WM-400 (400 MHz FT NMR) model at 90 and 200 MHz respectively using TMS as internal standard. Chemical shifts are given in δ ppm. The mass

TABLE II Heat of Formation (ΔH_f) (Kcal/mol) of *Syn* and *Anti* Isomers

Compound	*Syn*	*Anti*
VIIa	71.09	70.61
VIIb	162.77	55.80



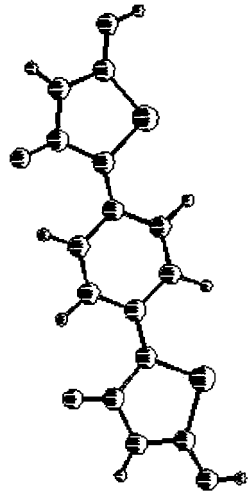
VIIa$_{syn}$



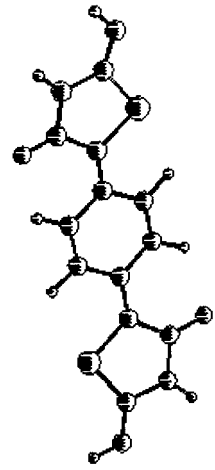
VIIa$_{anti}$

FIGURE 1 Optimized geometries of **VIIa** *syn/anti* isomers.

spectra were recorded on Jeol D-300 spectrometer at CDRI, Lucknow and Accurate Mass EI/CI Peak Match was obtained from National Mass Spectrometry Centre, University of Wales, Swansea, UK. Elemental analyses were performed by Perkin Elmer series C, H, N and S



VIIb$_{syn}$



VIIb$_{anti}$

FIGURE 2 Optimized geometries of **VIIb** *syn*/*anti* isomers.

analyser-2400. Molecular modelling were performed on PC WIN model on PCL-Pentium P1 computer using MOPAC 6.0 program.

A representative method for the reaction of thiohydantoin **Ia** with indol-2,3-dione **II** and cyclohexan-1,4-dione **V** is described below.

TABLE III Antimicrobial Activity of the Title Compounds

Compound no.	Zone of inhibition in mm (activity index)			
	E. coli	*S. aureus*	*A. niger*	*A. flavus*
III	10.2 (1.13)	8.0 (1.14)	6.0 (0.74)	9.4 (1.0)
IVa	9.5 (1.05)	7.0 (1.00)	7.8 (0.96)	9.2 (0.97)
IVb	6.8 (0.89)	7.2 (1.02)	8.0 (0.98)	9.6 (1.02)
VIa	10.4 (1.15)	8.3 (1.18)	8.5 (1.06)	9.95 (1.05)
VIb	9.8 (1.08)	7.1 (1.01)	6.0 (0.74)	9.4 (1.0)
IIa	10.1 (1.12)	7.7 (1.10)	8.2 (1.01)	9.3 (0.99)

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

A mixture of 2-thiohydantoin (**Ia**; 0.464 g; 4 mmol) and indol-2,3-dione (**II**; 0.294 g; 2 mmol) in the molar ratio 2:1 was refluxed under nitrogen atmosphere for 5 h in absolute ethanol. After completion of the reaction as monitored by TLC, the mixture was concentrated under vaccuo and then allowed to crystallize overnight (12 h) at 0°C whereby dark brown crystals of **IIIa** crystallized out (0.433 g; 60%), m.p. 210°C. It was filtered, washed with petroleum ether (60–80°C), was characterized as 3′,5-[bis-(4-imidazolinone-2-thioxo)]indol-2′-one.

The filtrate was concentrated in vaccuo and upon further crystallization from ethanol afforded product **IVa** as buff coloured solid (0.075 g; 10%), m.p. 190°C, characterized as 2′,3′-dihydro-3-(4-imidazolinone-2-thioxo) indol-2′-one.

A mixture of 2-thiohydantoin (**Ia**; 0.580 g; 5 mmol) and cyclohexan-1,4-dione (**V**; 0.280 g; 2.5 mmol) in the molar ratio 2:1 was refluxed under nitrogen atmosphere for 2 h in absolute ethanol to which were added first 3.5 ml of concentrated aqueous ammonia and then a hot solution of 3.5 gm of ammonium chloride in 6.0 ml water. The precipitate was filtered off and from the residual dark brown filtrate tetrahydroquinodimethane derivative **VIa** was crystallized as dark brown powder (0.519 g; 62%), m.p. $\geq$ 290°C.

A mixture of tetrahydroquinodimethane derivative (**VIa**; 0.400 g; 1.3 mmol) and DDQ (2.065 g; 9.1 mmol) in the molar ratio of 1:7 was refluxed under nitrogen atmosphere for 6 h in chlorobenzene. After completion of reaction as monitored by TLC the solvent was removed azeotropically whereby **VIIa** collected out as dark violet solid. It was

dried under vaccuo and was purified by recrystallization from toluene as dark violet crystals (0.197 g; 50%), m.p. 260°C (dec.).

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