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STUDIES ON THE SYNTHESIS AND CHARACTERISATION OF SULPHONES DERIVED FROM ISATIN, TRIAZOLOINDOLE AND INDOPHENAZINES

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ABSTRACT

The synthesis of heteroaryl sulphones of the type Ar-SO_2 – Hetry[1] has been reported in which the hetry[1] part is represented by isatin, triazoloindole and indophenazine derivatives The key step in the synthesis of sulphones involve the rearrangement of the aryl sulphonyl derivatives to the corresponding sulphones. Structures of all the compounds were established on the basis of elemental and spectral analysis.

Key words: Isatin, Triazoloindole, Indophenazines.

INTRODUCTION

Chemotherapeutic importance of the sulphonamides, sulphones and amino sulphones is very well known.[1–3] Sulphuric acid has been known to cause the rearrangement or the hydrolysis of aryl sulphonanilides. Hydrolysis is reported to be the most common reaction for sulphonanilides and rearrangement predominates for N-alkyl or aryl substituted sulphonanilides leading to the formation of o-amino sulphone derivatives[4–12]. Concentration of the acid plays an important role in determining the nature of product which is formed in this reaction. Witt and Uermenyi[10] found that high acid concentration with sulphonanilides led primarily to the formation of the rearrangement products, the o–amino sulphones, rather than the expected hydrolytic products. Additional work by Witt and Truttwin[11] and later by Halberkanm[12] defined several of the parameters, which favoured the rearrangement reaction. When the N-alkyl aniline was either unsubstituted or possessed p-methyl, p-methoxy or p-chlorosubstituents then ortho rearrangement predominates.

A great variety of amino sulphones have been investigated in the past with regard to their anti-leprotic and antitubercular properties and a few have proved to be sufficiently

useful in the clinical treatment of leprosy at the acceptable levels of toxicity to deserve the designation of the chemotherapeutic agents.[2,3] Though the desired goal to produce such compounds, which are highly specific and have no or lesser deleterious toxic effects, has not been reached but the partial success obtained with certain amino-sulphones has stimulated manifold work in this direction. A survey of the literature reveals that the utilization of the above rearrangement technique as a synthetic route to difficultly accessible sulphones has received little attention only and therefore, the present study was undertaken with a view to expand its utility as a synthetic tool for the preparation of hetero aryl amino sulphones. For this purpose, the amines were selected instead of employing the sulphonanilides, in the present work, such that the amino nitrogen was incorporated in the heterocyclic ring.

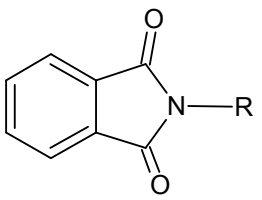
Physiological importance of indole is well documented in the literature. Indole nucleus is known to form an integral part of a large variety of pharmacologically important materials. Isatin provides a most convenient synthetic entry into the indole nucleus. Isatin is readily accessible from the aromatic anines by a simple two step process using the Sandmeyer's procedure.[13] The presence of the keto and lactam functions on the adjacent positions in the five membered ring of the isatin molecule provides tremendous potential in this molecule for the formation of the heterocyclic compounds.

This paper describes the synthesis of 1, 2, 4 – triazinoindole and indophenazine derivatives form N-aryl sulphonyl isatins and their rearrangement in a subsequent step to corresponding sulphone derivatives.

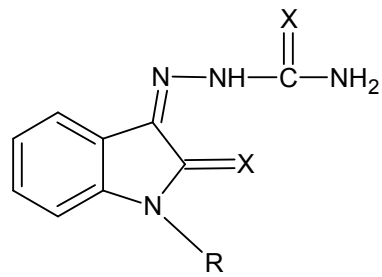
EXPERIMENTAL

Synthesis of 1, 2, 4 – triazino – [5, 6-b] indole derivatives from isatins - A large variety of isatins **(1 and 2)** have been reported to react with thiosemicarbazide to give isatin 0 3 – thiosemicarbazones **(3 and 4)**. These semicarbazones have been shown to exhibit significant antiviral properties. Treatment of isatin – 3 – thio semicarbazone[14, 17] **(3)** and N-methyl isatin – 3 – thio semicarbazone[14,16] **(4)** with mild alkali gave the corresponding 1, 2, 4 – triazine derivtives **7 and 8**, respectively (Fig. 1).

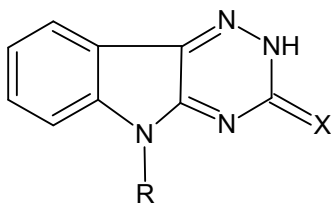
N – Methyl isatin – 3 – semicarbazone **(6)** was cyclised in a likewise manner to the oxo derivative **(9)**, but the cyclisation of the thiosemicarbazones **(4)** to **(8)** occurred much more easily.



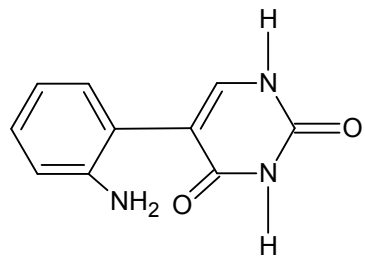
(1) R = H
(2) R = Me



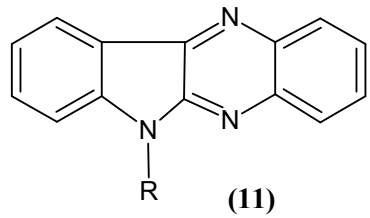
(3) X = S R = H
(4) X = S R = Me
(5) X = O R = H
(6) X = O R = Me



(7) X = S R = H
(8) X = S R = Me
(10) X = O R = Me



(9)

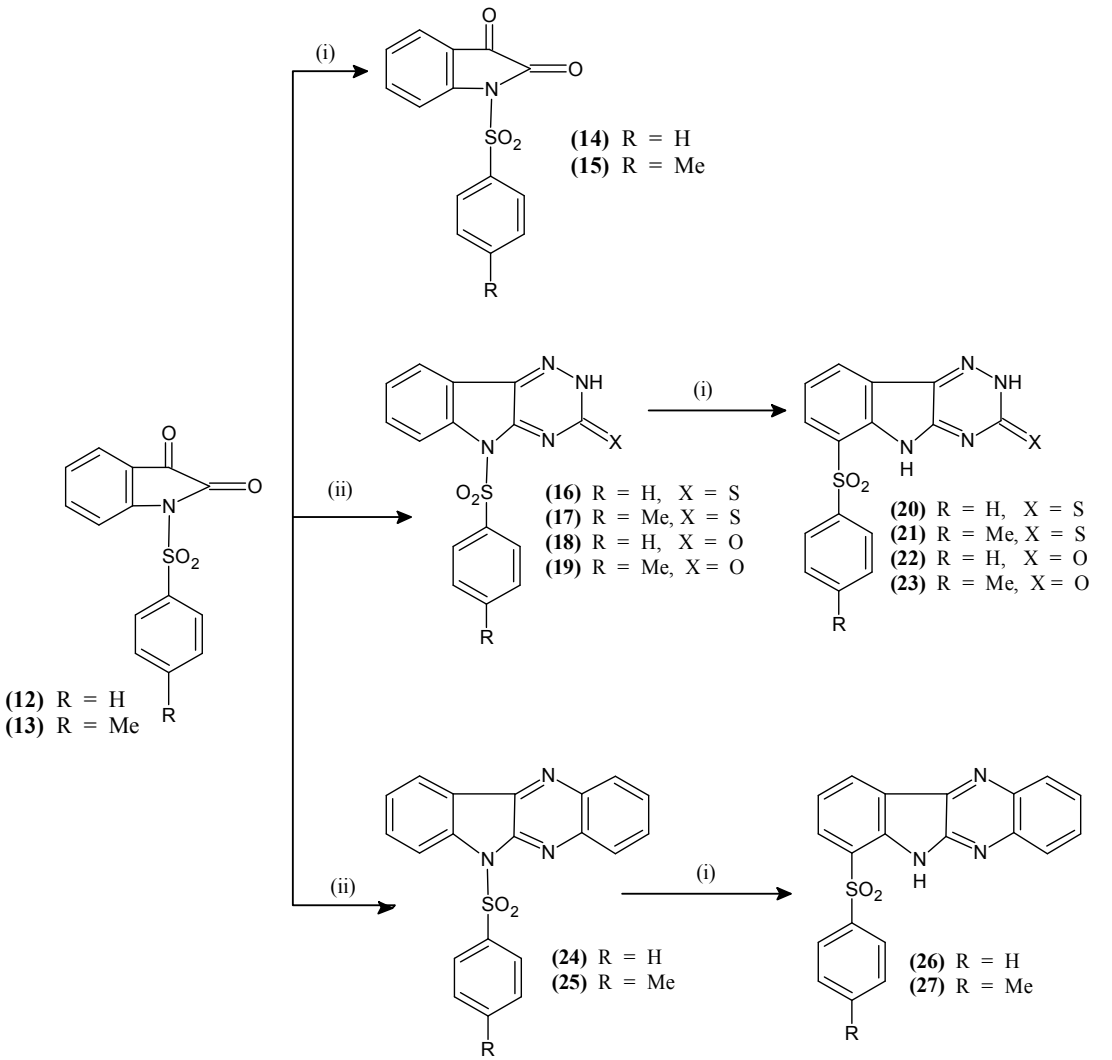


(11)

Fig. 1

Synthesis of indolo (2, 3-b) quinoxalines (indophenazines) from isatin: Reaction of a variety of substituted isatins with o-phenylenediamine has been reported to give indolo (2, 3-b) quinoxaline **(11),** Substituted o-phenylene diamines have also been used to give substituted **11**.[20, 21] The preparation of compound **11** is usually carried out by simply heating the o-phenylenediamine with isatin, however, polyphosphoric acid has also

been used in some cases.[22,23] A variety of the reactions of indophenazines have been studied. N – Substituted indophenazines have been shown to possess antimicrobial properties[24].



Scheme 1

Table 1. Physical data

Compound	Molecular formula	Molecular weight	M. P. (ºC)	Yield (%)	R_f Value*	Elemental analysis (%)			
						Nitrogen		Sulphur	
						Calculated	Found	Calculated	Found
12	$C_{14}H_9NO_4S$	287	186	79	0.63	5.054	5.016	11.552	11.332
13	$C_{15}H_{11}NO_4S$	301	205	78	0.52	3.482	3.271	7.960	7.616
16	$C_{15}H_{10}N_4O_2S_2$	342	270	80	0.48	16.374	16.172	18.713	18.699
17	$C_{16}H_{12}N_4O_2S_2$	356	279	90	0.54	15.730	15.590	17.977	17.702
18	$C_{15}H_{10}N_4O_3S$	326	272	88	0.61	17.177	17.013	9.815	9.697
19	$C_{16}H_{12}N_4O_3S$	340	261	85	0.59	16.470	16.201	9.411	9.398
24	$C_{20}H_{13}N_3O_2S$	359	142	82	0.68	11.699	11.443	8.913	8.718
25	$C_{21}H_{15}N_3O_2S$	373	146	87	0.70	11.260	11.019	8.579	8.368

* Solvent system : Benzene : Ethanol : Ammonia (7 : 2 : 1, v/v Upper layer) and absorbent : Silica gel G

Table 2. Physical data

Compound	Molecular formula	Molecular weight	M. P. (°C)	Yield (%)	R_f Value*	Elemental analysis (%)			
						Nitrogen		Sulphur	
						Calculated	Found	Calculated	Found
14	$C_{14}H_9NO_4S$	287	210	39	0.52	5.054	5.022	11.552	11.252
15	$C_{15}H_{11}NO_4S$	301	240	36	0.63	3.491	3.191	7.980	7.590
20	$C_{15}H_{10}N_4O_2S_2$	342	280	32	0.48	16.374	16.189	18.713	18.401
21	$C_{16}H_{12}N_2O_2S_2$	356	289	35	0.65	15.730	15.318	8.988	8.528
22	$C_{15}H_{10}N_4O_3S$	326	281	43	0.59	17.177	17.031	9.815	9.498
23	$C_{16}H_{12}N_4O_3S$	340	282	40	0.48	16.470	16.197	9.411	9.201
26	$C_{20}H_{13}N_3O_2S$	359	170	41	0.42	5.054	5.012	11.552	11.317
27	$C_{21}H_{15}N_3O_2S$	373	175	42	0.70	3.491	3.291	7.980	7.726

* Solvent system : Benzene : Ethanol : Ammonia (7 : 2 : 1, v/v Upper layer) and absorbent : Silica gel G

Table 3. ν_{max} (cm^{-1}) in IR spectra

Compound	Substituted aryl ring	C = S	C-N	C = N	NH	-NH- (Bend)	C = O	O=S=O
12	1290, 1150, 1025, 930, 860	-	-	-	-	-	1730, 1690	1170, 1330
13	1290, 1155, 1020, 930, 860	-	-	-	-	-	1720, 1685	1175, 1310
16	1280, 1150, 1020, 930, 960	1160	1585	1610	3190	1607	-	1175, 1320
17	1285, 1150, 1020, 935, 960	1150	1584	1620	3180	1603	-	1175, 1330
18	1280, 1155, 1020, 930, 960	-	1580	1605	3185	1601	1720, 1682	1170, 1310
19	1290, 1150, 1025, 930, 960	-	1581	1618	3180	1605	1715, 1680	1175, 1330
24	1285, 1155, 1020, 930, 960	-	-	-	-	-	-	1170, 1330
25	1290, 1155, 1025, 930, 960	-	-	-	-	-	-	-1175, 1330

Table 4. ν_{max} (cm^{-1}) in IR spectra

Compound	Substituted aryl ring	C = S	C-N	C=N	NH	-NH- (Bend)	C=O	O=S=O
14	1285, 1150, 1020, 930, 960	-	-	-	3182	1605	1170, 1680	1150, 1310
15	1285, 1150, 1020, 930, 960	-	-	-	3184	1604	1705, 1675	1149, 1320
20	1290, 1150, 1020, 930, 860	1160	1585	1610	3180	1601	-	1155, 1330
21	1290, 1150, 1020, 935, 860	1159	1580	1600	3185	1567	-	1150, 1330
22	1280, 1155, 1020, 930, 860	-	1582	1605	3175	1560	1710, 1671	1155, 1330
23	1285, 1150, 1020, 935, 960	-	1579	1615	3180	1620	1700, 1672	1145, 1310
26	1285, 1150, 1025, 930, 960	-	-	-	3190	1621	-	1155, 1330
27	1280, 1155, 1020, 930, 960	-	-	-	3195	1615	-	1150, 1320

Table 5. ^{1}H NMR spectral data for sulphones (chemical shifts are expressed in δ ppm)

Compound	Aromatic proton	CH_3 Proton	NH Proton (Exchanged with D_2O)
14	7.1-8.17 (m) 8H	-	2.12 (S) 1H
15	7.1-8.15 (m) 7H	1.81 (S) 3H	2.11 (S) 1H
20	6.90-8.10 (m) 9H (Ar.H, NH) (8H) (1H)	-	2.10 (S) 1H
21	7.11-8.16 (m) 8H (Ar.H, NH) (7H) (1H)	1.83 (S) 3H	2.09 (S) 1H
22	7.12-8.19 (m) 9H (Ar.H, NH) (8H) (1H)	-	2.08 (S) 1H
23	6.95-8.15 (m) 8H (Ar.H, NH) (7H) (1H)	1.78 (S) 3H	2.10 (S) – 1H
26	7.1-8.10 (m) 12H	-	2.07 (S) 1H
27	6.73-8.16 (m) 11H	1.77 (S) 3H	2.13 (S) 1H

Synthesis of 7-phenyl (and – p- tolyl) isatinyl sulphones from isatins : It is evident from the results (Table 4) that substitution at the nitrogen atom in isatin is a requirement for the above cyclisations. In the related transformations, where acid or alkali was used in the reactions with isatin, it was observed that isatin was very prone to undergo ring cleavage reactions. In view of this fact, it appeared necessary to examine the stability of N-aryl sulphonyl isatins in strongly acidic medium as the rearrangement of this material and all the other related compounds prepared in the present study was to be done in concentrated sulphuric acid medium.

Isatin required in the present study was prepared in accordance with the Sandmeyer's procedure.[13] N-aryl sulphonyl derivatives of isatin (**12**, R = H, and **13**, R = Me) were obtained from isatin by treatment of the same with corresponding aryl sulphonyl chlorides. Sulphuric acid has been known to cause the rearrangement of sulphonamides to sulphones.[4–9] This technique was employed in the present work to convert sulphonamides to sulphones. Thus for effecting the desired rearrangement reaction, **(12)** and **(13),** was treated with concentrated sulphuric acid which formed the rearranged sulphones, the 7-aryl isatinyl sulphone (**14**, R=H and **(15)** R=CH_3) in good yield.

After having successfully established the formation of **(14)** and **(15)** from **(12)** and **(13)** by the above proton catalyzed rearrangement reaction, we turned our attention towards utilizing this rearrangement technique for the synthesis of difficultly accessible heteroaryl sulphones, by using the synthetic strategies outlined in **Scheme 1.**

Synthesis of 6-p- tolyl – 1,2,4 – triazino –3- thio – [5,6-b] indolyl sulphone : N-p- Tolyl sulphonyl isatin **(13)** was used as a starting material for the synthesis of **(20)**. **(13)** was obtained by the reaction of isatin with p-toluene sulphonyl chloride. Treatment of **(13)** with thiosemicarbazide in presence of a mild alkali gave the thiosemicarbazone whose presence in the reaction mixture was ascertained by comparison of the T.L.C. of the mixture with an authentic sample, but the same was not isolated. It underwent instantaneous cyclisation in presence of alkali used, to give 5-p-tolyl sulphonyl – 1, 2, 4 – trizaino (5, 6 – b) indole – 3- thione **(17),** 5-Phenyl sulphonyl – 1, 2, 4 – triazino – (5, 6-b) – indole – 3- thione **(16)** gave a similar reaction with N-phenyl sulphonyl isatin **(12)**.

In an identical reaction, N-p-tolyl isatin **(13)** was treated with semicarbazide to give the corresponding semicarbazone (whose formatiion in *situ was* established on the basis of the comparison of T. L. C. of the reaction mixture with an authentic sample) which in presence of alkali (present in the reaction mixture) underwent cyclisation quite readily to give 5-p-tolyl sulphonyl – 1, 2, 4 – triazino – [5, 6-b]-indole – 3 – one **(19).** A similar reaction with N-phenyl sulphonyl isatin **(12)** gave 5-phenyl sulphonyl – 1, 2, 4 –triazino [5, 6-b] indole – 3 – one **(18).**

Rearrangement of **(17)** with concentrated sulphuric acid afforded the corresponding sulphone 6-p-tolyl – 1, 2, 4 – triazino – 3- thio – [5, 6-b] indolyl sulphone **(21)**. A similar reaction with **(16), (18)** and **(19)** yielded the sulphone **(20), (21)** and **(22),** respectively (scheme 1).

Synthesis of 7-p-tolyl-indolo (2, 3-b) quinoxalinyl sulphone (or 7-p-tolyl indophenazine): Compound **(26)** was obtained from 6-p-tolyl-indolo-(2, 3-b) – quinoxaline **(24)**, by N-p-tolyl sulphonyl isatin and o-phenylenediamine in acetic acid. A similar reaction with N-phenyl sulphonyl isatin and o-phenylenediamine afforded the 6-phenyl sulphonyl – indolo – [2,3-b] quinoxaline **(23)**.

Rearrangement of **(23)** with concentrated sulphuric acid afforded the 7-p-tolyl indolo [2, 3-b] quinoxalinyl sulphone **(26)** and the same reaction with **(14)** yielded the 7-phenyl-indolo – [2, 3-b] quinoxalinyl sulphone **(26)** in moderate yield.

Yield of all the aryl sulphonyl derivatives: Yields of (12), (13), (16), (17), (18), (19), (24) and **(25)** (Table 1) were found to be generally very good (i.e. in the range of 78-90%) but the yield of the corresponding sulphones viz. **(22), (23), (24)** and **(25)** were found to be only moderately good (i.e. above 40%), and that of **(14), (15), (20)** and **(21)** were very low i.e. below 40% (in the range of only 32 to 39%). One reason for this observed trend of the large variation in yield of sulphones from sulphonamides may be attributed to the formation of highly water soluble sulphonated products from sulphonamides in hot concentrated sulphuric acid, leading to the net loss in the concentration of sulphonamides undergoing the actual rearrangement reaction. However, some loss due to the simultaneous hydrolysis of aryl sulphonyl moiety from sulphonamides in the acidic medium employed in this reaction, can not be ruled out.

Structure of compounds (12-27): The progress of all the above reactions and the purity of all the synthetic materials was checked by T. L. C. The structure of all the compounds **(12)-(27)** were established on the basis of elemental analyses, IR and ^{1}H NMR spectral data. Physical data for all the compounds presented in the Table 1–5 were found to be consistent to the structures assigned to these molecules.

The structures of all the aryl sulphonyl derivatives viz. **(12), (13), (16), (17), (18), (19), (24),** and **(25)** were established on the basis of elemental analyses and IR spectra data and of the final products, the sulphones. **(14), (15), (20), (21), (22), (23), (26),** and **(27)** on the basis of elemental analyses, IR and ^{1}H NMR spectral data. The ^{1}H NMR spectral data confirmed the structure of all the sulphones and provided strong evidence in the favour of the structures assigned to the sulphonamides too, from which the sulphones were formed.

The IR spectra of all the above compounds exhibited bands in the region of 1175-1170 cm^{-1} and 1330-1310 cm^{-1} which were attributed to the presence of SO_2 group in the molecule. Compounds **(12)-(15)** showed two strong absorptions in the region of 1730-1705 cm^1 and 1685-1660 cm^{-1} and compounds **(18), (19), (22)** and **(23)** single absorption in the region of 1720-1700 cm^{-1} for the C=O group. All the compounds **(16), (23), (26)** and **(27)** showed absorption in the region of 3200 - 3175 cm^{-1} and 1600-1500 cm^{-1} for the NH group stretching and NH bending, respectively.

All the compounds showed absorptions for the aromatic ring at the appropriate region in the IR spectrum (Tables 3 and 4)

The ^{1}H NMR spectral data of only one of the final products **(15)** which is one of representative member of all the compounds synthesized has been discussed and the same

discussing way be applied for the elucidation of the structures of other compounds of this series using the ^{1}H NMR data presented in Table 5.

The ^{1}H NMR spectrum of **(14)** besides showing a broad singlet centered around at δ 2.11 ppm (exchanged with D_2O) for the presence of NH proton displayed a singlet at δ 1.80 ppm for the three protons of methyl group and a multiplet in the region of δ 7.1-8.1 ppm for seven protons of the aromatic rings, which confirmed the structure assigned to **(14)**. The above IR and ^{1}H NMR spectral data provided the conclusive evidences for the conversion of the sulphonamide **(13)** to sulphone **(15)** as it established clearly the presence of isatin NH in **(15)** and its absence in **(17)**. Had the rearrangement of **(13)** to sulphone **(15)** not taken place, one would have expected no singal for the NH proton and a multiplet for eight aromatic protons in **(15)** (at the place of seven protons only) as shown by its ^{1}H NMR spectrum.

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