# STUDIES OF POTENTIAL HETEROCYCLIC SULFONES AS ANTIMICROBIAL AGENTS

## SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NOVEL SUBSTITUTED ARYLSULFONYLBENZO[h]QUINOLINE DERIVATIVES

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Abstract - A series of substituted arylthiobenzo[h]quinoline (sulfides, Ia~If and IIa~IIc) synthesised earlier were oxidised (with 1% $KMnO_4$) to get their corresponding sulfones (IA~IF and IIA~IIC). All these compounds have been characterised by their elemental analysis, molecular weight determination (Rast Method) and spectral studies (IR and $^1H$ NMR). These compounds have been screened for antimicrobial activity against Gram positive Cocci and Gram negative Bacilli.

## INTRODUCTION

A perusal of literature revealed that no work has so far been reported on arylsulfonylbenzo[h]quinolines. As such the syntheses and structural studies of these sulfones, hitherto unknown, would be of considerable importance. In our earlier communication we have synthesised arylthiobenzo[h]quinoline[1]. However, the present communication describes the synthesis and structural elucidation of arylsulfonylbenzo[h]quinolines (sulfones).

Heterocyclic sulfones have been found to exhibit antimicrobial activity[2,3]. Besides this, sulfones have also been used as antimalarials[4,5] and antileprotic agents[6]. Realising the medicinal importance of sulfones and benzo[h]quinoline compounds, various arylsulfonylbenzo[h]quinoline compounds were successfully synthesised in this laboratory. These were tested for antimicrobial activity.

Inspite of the number of methods known for oxidation of sulfides to sulfones the one involving the oxidation (with 1% $KMnO_4$)[7] was found to be most elegant and convenient. Various arylthiobenzo[h]quinolines (Ia~If) and (IIa~IIc) were prepared and subsequently oxidised with 1% $KMnO_4$ to the corresponding arylsulfonylbenzo[h]quinolines (IA~IF and IIA~IIC). The structures of TLC pure sulfones (IA~IF and IIA~IIC) have been established through elemental analysis, molecular weight determination (Rast method, cf. Table I) and spectral studies (IR and $^1H$ NMR).

SPECTRAL STUDIES

The compounds showed characteristic absorption bands in Ir spectra in the vicinity of 1600-1450 $cm^{-1}$ along with characteristic absorptions bands at 1350 $cm^{-1}$, 1145 $cm^{-1}$, 1180-1070 $cm^{-1}$ (for sulfonyl groups) and at 655-610 $cm^{-1}$ (due to S-aryl vibration) were observed. This clearly indicates these compounds as aromatic heterocyclic sulfones.

By and large the presence of 10 protons were established in the aromatic range at $\delta$7.5 to $\delta$8.4. In the NMR spectra at $\delta$ 9.40 a broad signal for 1H was accounted for the presence of proton at C-10. The shifting of this signal to downfield with a broad appearance was due to its partial bonding characteristic with the angular nitrogen. In IA one more proton (i.e. 11 H) was observed in the range of $\delta$ 7.8 to $\delta$8.2 since there was no substituent in the aromatic ring of arylsulfonyl group. The presence of C-$CH_3$, O-$CH_3$ and $NH_2$ groups are further established in these compounds on the basis of their NMR spectra (cf. Table II).

ANTIBACTERIAL ACTIVITY

The antibacterial activity of nine compounds was studied against Gram positive Cocci i.e. Staphylococcus aureus 'a', Streptococcus faecalis 'b' and Gram negative Bacilli i.e. Escherichia coli 'c' Klebsiella pneumoniae 'd' and Pseudomonas aeruginosa 'e' in 200 ug/disc (cf. Table III).

After comparing the antimicrobial activity of the compounds with various bacteria the following conclusions were drawn:

1. The substitution of arylsulfonyl group at p-position to nitrogen favours the activity as the compounds having arylsulfonyl group at o-position to nitrogen.

2. In arylsulfonyl moiety the substitution does not favour the activity. IA and IIA are found to be most active against almost all bacteria.

TABLE I

| Compound | Name of the Compound | Yield in % | m.p. °C | Rf | Analysis Calcd. | Found | M.W. (Rast Method) | $-SO_2$ absorptions |
|---|---|---|---|---|---|---|---|---|
| IA | 2-(Benzenesulfonyl)-4-methylbenzo[h]quinoline. | 77 | 140 | 0.69 | S=9.60<br>N=4.20<br>For $C_{20}H_{15}O_2NS$ | 9.42<br>4.04 | 328.5 | 1350, 1145 |
| IB | 2-(o-Carboxyl-benzenesulfonyl)-4-methylbenzo[h]quinoline. | 79 | 170 | 0.76 | S=8.44<br>N=3.71<br>For $C_{21}H_{15}O_4NS$ | 8.00<br>3.40 | 371.5 | 1350, 1140 |
| IC | 2-(o-Amino-benzenesulfonyl)-4-methylbenzo[h]quinoline. | 75 | 184 | 0.58 | S=9.19<br>N=8.04<br>For $C_{20}H_{16}O_2N_2S$ | 9.10<br>8.00 | 342.2 | 1350 1145 |
| ID | 2-(o-Nitro-benzenesulfonyl)-4-methylbenzo[h]quinoline. | 78 | 192 | 0.59 | S=8.46<br>N=7.40<br>For $C_{20}H_{14}O_4N_2S$ | 8.20<br>7.10 | 372.7 | 1360, 1140 |
| IE | 2-(p-Methylbenzenesulfonyl)-4-methylbenzo[h]quinoline. | 72 | 122 | 0.60 | S=9.22<br>N=4.03<br>For $C_{21}H_{17}O_2NS$ | 9.00<br>4.00 | 342.5 | 1360, 1145 |
| IF | 2-(p-Methoxybenzenesulfonyl)-4-methylbenzo[h]quinoline. | 76 | 146 | 0.62 | S=8.81<br>N=3.85<br>For $C_{21}H_{17}O_3NS$ | 8.60<br>3.60 | 368.5 | 1360 1150 |
| IIA | 4-(Benzenesulfonyl)-2-methylbenzo[h] quinoline. | 78 | 144 | 0.68 | S=9.60<br>N=4.20<br>For $C_{20}H_{15}O_2NS$ | 9.50<br>4.00 | 329.2 | 1350 1145 |
| IIB | 4-(o-Carboxylbenzenesulfonyl)-2-methylbenzo[h]quinoline. | 76 | 168 | 0.73 | S=8.44<br>N=3.71<br>For $C_{21}H_{15}O_4NS$ | 8.00<br>3.40 | 372.1 | 1350, 1140 |
| IIC | 4-(o-Aminobenzenesulfonyl)-2-methylbenzo[h]quinoline. | 73 | 172 | 0.59 | S=9.19<br>N=8.04<br>for $C_{20}H_{16}O_2N_2S$ | 9.10<br>8.80 | 343.2 | 1350, 1145 |

TABLE II

(NMR; $CDCl_3$; Chemical shifts in $\delta$ values)

| No. | Aromatic Protons | $-C-CH_3$ | $Ar-CH_3$ | $Ar-OCH_3$ | $Ar-NH_2$ |
|---|---|---|---|---|---|
| IA | 7.8-8.2(m)-11H<br>9.40(bs)-1H | 2.85(s)-3H | - | - | - |
| IB | 7.90-8.3(m)-10H<br>9.40(bs)-1H | 2.85(s)-3H | - | - | - |
| IC | 7.7-8.2(m)-10H<br>9.40(bs)-1H | 2.80(s)-3H | - | - | 4.5(s)-2H |
| ID | 7.90-8.4(m)-10H<br>9.40(bs)-1H | 2.90(s)-3H | - | - | - |
| IE | 7.7-8.4(m)-10H<br>9.40(bs)-1H | 2.80(s)-3H | 2.50(s)-3H | - | - |
| IF | 7.5-8.3(m)-10H<br>9.40(bs)-1H | 2.80(s)-3H | - | 3.85(s)-3H | - |
| IIA | 7.8-8.2(m)-11H<br>9.40(bs)-1H | 2.85(s)-3H | - | - | - |
| IIB | 7.90-8.30(m)-10H<br>9.40(bs)-1H | 2.85(s)-3H | - | - | - |
| IIC | 7.7-8.2(m)-10H<br>9.40(bs)-1H | 2.80(s)-3H | - | - | 4.5(s)-2H |

m = multiplet, bs = broad singlet; s = singlet.

3. The substitution of $-NO_2$ group decreases the activity to minimum.

4. The activity is in the following order:

IIA, IA > IIB > IIC, IC > IB, IE, IF > ID

5. The substitution of COOH group and $NH_2$ group decreases the activity but still the activity is more than the compounds having $-CH_3$ and $-OCH_3$ groups.

The summary of the results are given in Table IV.

TABLE III

Sensitivity of Staphylococcus aureus (a), Streptococcus faecales (b), Escherichia coli (c), Klebsiella pneumoniae (d), Pseudomonas aeruginosa (e) against different substituted arylsulfonylbenzo h quinoline.

| Compounds | Concentration of different compound used was 200ug/disc | | | | |
|---|---|---|---|---|---|
| | a | b | c | d | e |
| IA | ++ | +++ | ++ | ++ | +++ |
| IB | + | + | + | +++ | ++ |
| IC | +++ | + | ++ | + | ++ |
| ID | + | + | + | + | + |
| IE | +++ | ++ | + | + | + |
| IF | + | + | +++ | ++ | ++ |
| IIA | +++ | ++ | ++ | ++ | +++ |
| IIB | + | +++ | ++ | ++ | ++ |
| IIC | +++ | +++ | +++ | + | + |

6-8 mm (+); 9-12 mm (++), 13-16 mm (+++)

TABLE IV

| Name of Bacteria | Maximum activity | Average activity | Least activity |
|---|---|---|---|
| a | IC, IE, IIA, IIC | IA | IB, ID, IF, IIB |
| b | IA, IIB, IIC | IE, IIA | IB, IC, ID, IF |
| c | IF, IIC | IA, IC, IIA, IIB | IA, IB, IE |
| d | IB | IA, IF, IIA, IIB | IC, ID, IE, IIC |
| e | IIA | IA, IB, IC, IF, IIB | ID, IE, IIC |

The plates of culture medium were uniformly seeded with 18 hr broth culture of the bacterium to be tested. Small (6 mm) sterile discs of standard

filter papers, impregnated with standard solutions of test compounds in one strength (vide supra), were placed on plates of culture medium at proper spacing. One disc impregnated with solvent (used for the preparation of solutions) was also placed on culture plates as control. These culture plates were kept for 18-20 hr in an incubator at 37°C. The zone of inhibition of growth of bacteria produced by the diffusion of compounds from the disc into the surrounding medium was measured. Each test compound in one concentration was tested with ten strains of each organism.

EXPERIMENTAL

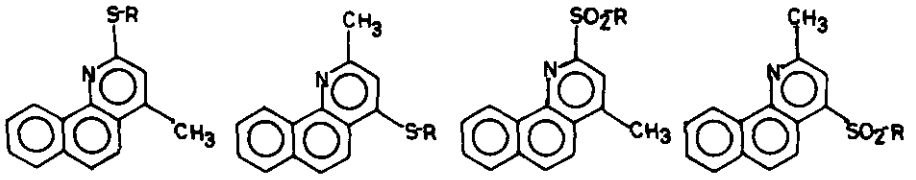
The melting points are uncorrected. The purity of compounds was checked by TLC using silica gel 'G' as stationary phase and benzene-ethanol-ammonia (7:2:1; v/v, upper layer) as mobile phase. Compounds were characterised by elemental analysis (sulfur and nitrogen) and spectral (IR and NMR) studies. IR spectra were recorded on Perkin Elmer-Infracord spectrometer in KBr pellets. NMR spectra were recorded on Varian-A-60 $MH_3$ spectrometer using $CDCl_3$ as solvent and TMS as an internal reference. The chemical shifts were expressed in $\delta$ values.

Substituted arylthiobenzo[h]quinoline derivatives (Ia~If and IIa~IIc) were synthesised by the method described earlier[1].

2-(Benzenesulfonyl)-4-methylbenzo[h]quinoline (IA)

To 1.50 g (0.005M) of 2-thiophenyl-4-methylbenzo[h]quinoline (Ia) dissolved in glacial acetic acid (15-20 ml), 1% $KMnO_4$ solution was added with occasional shaking as rapidly as decolorisation occurred. Excess of $KMnO_4$ solution was added with shaking followed by the addition of ethanol (ca. 50 ml). The reaction mixture was allowed to stand till the colour of $KMnO_4$ disappeared. The mixture was poured into ice cold water and filtered. The crude residue was exhaustively extracted with hot acetone and the solvent was evaporated off. The residue was crystallized from petroleum ether (bp 40-60°), when colourless shining crystals of IA were obtained.

On similar lines IB~IF and IIA~IIC were also synthesised from their corresponding sulfides (Ib~If and IIa~IIc) (cf. Chart I).



Ic~If IIa~IIc IA~IF IIA~IIC

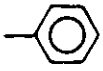
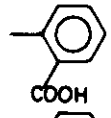
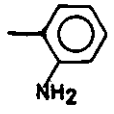
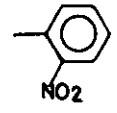
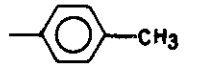
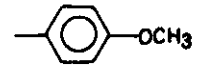
| R | SULFIDES | | SULFONES | |
|---|---|---|---|---|
| | I-SERIES | II-SERIES | I-SERIES | II-SERIES |
|  | Ia | IIa | IA | IIA |
|  | Ib | IIb | IB | IIB |
|  | Ic | IIc | IC | IIC |
|  | Id | – | ID | – |
|  | Ie | – | IE | – |
|  | If | – | IF | – |

CHART-1

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