# STUDIES ON 4-(8-HYDROXY-5-QUINOLYLAZO)BENZENE-SULFONAMIDES AND THEIR METAL CHELATES AS POTENTIAL DRUGS

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Some new drugs containing both azo sulfonamide and 8-hydroxyquinoline moieties have been prepared. Some metal chelates with $Fe^{3+}$, $Co^{2+}$, $Cu^{2+}$, $Ni^{2+}$, and $Hg^{2+}$ ions have been synthesized and screened *in vitro* for their antibacterial activity.

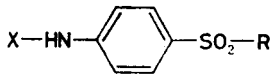
The first investigations on the sulfa drugs, done in Germany[1,2], resulted in the discovery of prontosil, a drug of high antibacterial activity[3-5]. Later on, sulfonamide derivatives have been found to be biologically versatile compounds of anticancer[6], antimalaria[7], antitubercular[8] and other diverse activities[9,10]. Observation on the antibacterial activity of prontosil ((2,4-diaminophenylazo)benzenesulfonamide) prompted us to synthesize compounds of the type *III* and examine their antibacterial activity.

The present communication describes the preparation and antimicrobial activity tests of twenty-eight compounds belonging to the azo sulfonamides series and their metal chelates. The compounds were prepared from 8-hydroxyquinoline and the sulfa drugs, synthesized for this purpose. The substituents in the sulfonamide moiety were chosen as to ensure widest possible variation in their size, electronegativity and chemical reactivity. The resulting compounds, on diazotization and coupling with 8-hydroxyquinoline, gave the corresponding substituted 4-(8-hydroxy-5-quinolylazo)-benzenesulfonamides *IIIa–n*.

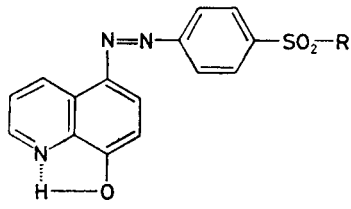
The interaction of *IIIa–n* with metal salts in solution afforded the corresponding metal chelates (metal : ligand ratio 1 : 2). The type of bonding in the metal chelates was deduced from their IR spectra. The presence of OH band at 3 260 $cm^{-1}$ in the spectra of compounds *III* and its disappearance in the spectra of metal chelates, as well as the shift of ν(C=N) to lower frequency, suggest coordination of the metal ions to the 8-hydroxyquinoline moiety. The presence of the sulfonamide group has been confirmed by a characteristic band in the vicinity of 1 325 $cm^{-1}$.

The prepared compounds possess both features of 8-hydroxyquinoline and azo--sulfonamide. So, the work described was carried out to extend the studies[11] on 8-hydroxyquinoline and their metal chelates which are of interest as potential pro-

-drugs. Synthesis of the new compounds involved the preparation of acetamidobenzenesulfonyl chloride and its reaction with compounds containing a nitrogen atom either attached to, or incorporated in, an aromatic or alicyclic ring to obtain compounds *Ia–n* as cited in the literature[12].



*Ia–n*, X = $CH_3CO$
*IIa–n*, X = H



*IIIa–n*

In formulae *I–III*:

*a*, R = anilino
*b*, R = *m*-toluidino
*c*, R = *m*-chloroanilino
*d*, R = *o*-chloroanilino
*e*, R = *m*-hydroxyanilio
*f*, R = *p*-hydroxyanilino
*g*, R = 2-aminopyridino
*h*, R = 3-aminopyridino
*i*, R = morpholino
*j*, R = piperidino
*k*, R = benzylamino
*l*, R = n-butylamino
*m*, R = dimethylamino
*n*, R = α-naphtylamino

The compounds *IIIa–n* showed variable antibacterial activity against a number of bacteria (Table I). Whereas compounds *IIIb* and *IIIk* have no effect on the used bacteria, compounds *IIIa*, *IIIl*, and *IIIm* are active (inhibition zones from 10–20 mm) against *Staphylococcus aureus*, *Escherichia coli*, and *Micrococcus luteus*. Furthermore, *IIIc*, *IIIf*, *IIIi*, and *IIIj* have inhibition zones ranging from 10–40 mm against *Escherichia coli*, *Micrococcus luteus*, and *Klebsiella pneumoniae*. Interestingly, compound *IIIn* exhibits an antibacterial activity against all the used bacteria.

For comparison, prontosil[2] was also tested against the mentioned bacteria under the same conditions. The results showed that prontosil has no effect on all the bacteria, except with *Staphylococcus aureus*, where the inhibition zone was 10 mm. So, it could be inferred that in most cases the activity of the prepared derivatives is higher than that of prontosil towards the bacteria used. Their antibacterial activity is enhanced on complexation with metals.

## EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a Perkin–Elmer 599 B spectrophotometer using the KBr disc technique. Acetamidobenzenesulfonamides *Ia–n* were

prepared as previously reported[12]. Sulfonamides *IIa—n* were obtained by hydrolysis of compounds *Ia—n* with 10% aqueous NaOH as described in the literature[12].

TABLE I

Biological screening of compounds *IIIa—n* and their metal complexes (inhibition zones in mm)

| Compound | Composition[a] | *Staphylococcus aureus* | *Escherichia coli* | *Micrococcus aureus* | *Klebsiella pneumoniae* |
|---|---|---|---|---|---|
| *IIIa* | $C_{21}H_{16}N_4O_3S$ | — | — | — | 10 |
| | $(C_{21}H_{15}N_4O_3S)_2FeNO_3$ | 10 | — | — | 20 |
| | $(C_{21}H_{15}N_4O_3S)_2Ni$ | 10 | 10 | — | 30 |
| | $(C_{21}H_{15}N_4O_3S)_2Cu$ | — | — | — | 20 |
| | $(C_{21}H_{15}N_4O_3S)_2Hg$ | 20 | 20 | 30 | 50 |
| *IIIb* | $C_{22}H_{18}N_4O_3S$ | — | — | — | — |
| | $(C_{22}H_{17}N_4O_3S)_2FeNO_3$ | — | 20 | — | 30 |
| *IIIc* | $C_{21}H_{15}N_4ClO_3S$ | — | 10 | 10 | 40 |
| | $(C_{21}H_{14}N_4ClO_3S)_2FeNO_3$ | 20 | 20 | 20 | 30 |
| *IIIf* | $C_{21}H_{16}N_4O_4S$ | — | — | 10 | 20 |
| | $(C_{21}H_{15}N_4O_4S)_2FeNO_3$ | 30 | 10 | 10 | 10 |
| *IIIg* | $C_{20}H_{15}N_5O_3S$ | 20 | 10 | — | 40 |
| | $(C_{20}H_{14}N_5O_3S)_2FeNO_3$ | 30 | 10 | 10 | 10 |
| *IIIi* | $C_{19}H_{18}N_4O_4S$ | — | — | 10 | 30 |
| | $(C_{19}H_{17}N_4O_4S)_2FeNO_3$ | 20 | 50 | 40 | 60 |
| *IIIj* | $C_{20}H_{20}N_4O_3S$ | 10 | — | 10 | 30 |
| | $(C_{20}H_{19}N_4O_3S)_2FeNO_3$ | 30 | 10 | 40 | 20 |
| *IIIk* | $C_{22}H_{18}N_4O_3S$ | — | — | — | — |
| | $(C_{22}H_{17}N_4O_3S)_2FeNO_3$ | — | — | — | 30 |
| *IIIl* | $C_{19}H_{20}N_4O_3S$ | — | — | — | 20 |
| | $(C_{19}H_{19}N_4O_3S)_2FeNO_3$ | — | 20 | — | 20 |
| | $(C_{19}H_{19}N_4O_3S)_2Hg$ | 50 | 60 | 30 | 10 |
| *IIIm* | $C_{17}H_{16}N_4O_3S$ | — | — | — | 20 |
| | $(C_{17}H_{15}N_4O_3S)_2FeNO_3$ | 10 | 10 | — | 20 |
| | $(C_{17}H_{15}N_4O_3S)_2Co$ | 20 | 10 | 40 | 10 |
| | $(C_{17}H_{15}N_4O_3S)_2Cu$ | 10 | 30 | 10 | 10 |
| *IIIn* | $C_{25}H_{18}N_4O_3S$ | 20 | 20 | 10 | 40 |
| | $(C_{25}H_{17}N_4O_3S)_2FeNO_3$ | 30 | 30 | 40 | 10 |

[a] All the compounds gave correct elemental analyses for S, N, and metal.

Substituted 4-(8-Hydroxy-5-quinolylazo)benzenesulfonamides *IIIa—n*

These compounds were prepared by diazotization of the free *p*-aminobenzenesulfonamides *IIa—n* (10 mmol) in acetic acid (20 ml), at 0°C and coupling with molar equivalent of 8-hydroxyquinoline in sodium hydroxide. The reactions were accompanied with a change in colour from pale to

TABLE II

Physico-chemical characteristics of compounds *IIIa—n*

| Compound | M.p., °C | Formula (M.w.) | Calculated/found | | | | |
|---|---|---|---|---|---|---|---|
| | | | % C | % H | % N | % S | % Cl |
| *IIIa* | 185 | $C_{21}H_{16}N_4O_3S$ | 62·36 | 3·99 | 13·85 | 7·92 | — |
| | | (404·4) | 62·30 | 3·91 | 13·91 | 8·01 | — |
| *IIIb* | 138—140 | $C_{22}H_{18}N_4O_3S$ | 63·14 | 4·33 | 13·39 | 7·66 | — |
| | | (418·5) | 63·22 | 4·29 | 13·33 | 7·72 | — |
| *IIIc* | 195 | $C_{21}H_{15}ClN_4O_3S$ | 57·47 | 3·44 | 12·77 | 7·30 | 8·07 |
| | | (438·9) | 57·38 | 3·47 | 12·82 | 7·38 | 7·91 |
| *IIId* | 157—159 | $C_{21}H_{15}ClN_4O_3S$ | 57·47 | 3·44 | 12·77 | 7·30 | 8·07 |
| | | (438·9) | 57·52 | 3·39 | 12·83 | 7·41 | 7·88 |
| *IIIe* | 245 | $C_{21}H_{16}N_4O_4S$ | 60·00 | 3·83 | 13·33 | 7·63 | — |
| | | (420·4) | 59·96 | 3·76 | 13·41 | 7·71 | — |
| *IIIf* | 210 | $C_{21}H_{16}N_4O_4S$ | 60·00 | 3·83 | 13·33 | 7·63 | — |
| | | (420·4) | 60·02 | 3·78 | 13·42 | 7·69 | — |
| *IIIg* | 235 | $C_{20}H_{15}N_5O_3S$ | 59·25 | 3·73 | 17·27 | 7·90 | |
| | | (405·4) | 59·31 | 3·66 | 17·19 | 7·81 | — |
| *IIIh* | 255 | $C_{20}H_{15}N_5O_3S$ | 59·25 | 3·73 | 17·27 | 7·90 | — |
| | | (405·4) | 59·21 | 3·73 | 17·31 | 7·82 | — |
| *IIIi* | 310—312 | $C_{19}H_{18}N_4O_4S$ | 57·25 | 4·55 | 14·06 | 8·05 | — |
| | | (398·4) | 57·32 | 4·30 | 14·00 | 7·96 | |
| *IIIj* | 215 | $C_{20}H_{20}N_4O_3S$ | 60·59 | 5·08 | 14·13 | 8·08 | — |
| | | (396·5) | 60·70 | 5·00 | 14·21 | 8·01 | — |
| *IIIk* | 283 | $C_{22}H_{18}N_4O_3S$ | 63·14 | 4·33 | 13·39 | 7·66 | — |
| | | (418·5) | 63·09 | 4·24 | 13·31 | 7·59 | — |
| *IIIl* | 199 | $C_{19}H_{20}N_4O_3S$ | 59·36 | 5·24 | 14·57 | 8·34 | — |
| | | (384·5) | 59·44 | 5·12 | 14·16 | 8·41 | — |
| *IIIm* | 203 | $C_{17}H_{16}N_4O_3S$ | 57·29 | 4·52 | 15·72 | 8·99 | — |
| | | (356·4) | 57·23 | 4·51 | 15·81 | 8·90 | — |
| *IIIn* | 219 | $C_{25}H_{18}N_4O_3S$ | 66·07 | 3·99 | 12·33 | 7·05 | — |
| | | (545·5) | 66·51 | 3·93 | 12·29 | 7·11 | — |

deep red. The dye precipitated after stirring for one to three days. The products were crystallized from ethanol and their physical and analytical data are given in Table II.

### Preparation of the Complexes

A hot solution of the ligand (6 mmol) in ethanol (20 ml) was added dropwise under stirring to a solution of the given metal salt (3 mmol) (ferric nitrate, cobalt chloride, nickel chloride, copper acetate or mercuric chloride) in ethanol (20 ml). The mixture was stirred for one hour and the precipitated complex was filtered, washed with ethanol, and dried over $P_4O_{10}$.

### Screening for Antibacterial Activity

The bacteriostatic activity against *Staphylococcus aureus*, *Escherichia coli*, *Micrococcus luteus*, and *Klebsiella pneumoniae* were tested by the usual cup plate agar diffusion technique[13,14]; 1% solutions of the chelates were prepared. The dishes were allowed to stand in a refrigerator at 4–8°C for 0·5 h to allow diffusion of the solutions and were then incubated at 37 ± 1°C for 48 h. The inhibition zones were measured with the callipers.

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