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RESEARCH ARTICLE

SYNTHESIS OF 4-HYDROXY-2-PHENYL 6/7 SUBSTITUTED QUINOLINES AND ASSESMENT OF THEIR ANTIBACTERIAL ACTIVITY.

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Abstract

Industrial application of disperse dyes is based on numerous chromophore systems. Approximately 60 % of the available disperse dyes are azo based, and 25 % are anthraquinone based. Remainders of the dyes are quinaphthalene, methine, napthalimide, naphthaquinone and nitro based. The development in azo dyestuff chemistry is mainly to make in-roads into the traditional anthraquinone area. Development in azo disperse dyes over five decades have made it possible to produce a full range of colours with improved dyeing performance with better fastness properties, and also having therapeutic values. Synthesis and application of azo dyes derived from quinoline system have also been reported earlier. So this study is carried out to encourage the synthesis of some new azo disperse dyes like 4-hydroxy-2-phenyl 6/7 substituted quinolines along with their antibacterial activity.

Introduction:-

The versatility of azo class of dyes is due to the fact that azo compounds can be made and any dye azotized aromatic amine can be coupled with stable nucleophillic unsaturated system to give a colored azo product. Azo dyes have accounted for more than half of the total available disperse dyes, virtually covering a major part of the color spectrum. Heterocyclic diazo coupling components have played a prominent role in azo dye chemistry.

Heterocyclic coupling components give heterocyclic azo disperse dyes with color ranging from yellow to dark red. The compactness and extension of conjugation in the structures of heterocyclic compounds are important for the disperse dyes derived from them[7]. Over the past few decades, it has been found that only a few heterocyclic based coupling components attained the brilliance of the azo benzene dyes, as well as anthraquinone dyes with better therapeutic values[6].

Synthesis and application of disperse dyes derived from quinoline and quinolinoquinazoline moieties have been reported earlier[1, 2]. In a view of encouraging the reports of the technical application of heterocyclic dyes, it was thought necessary to undertake the synthesis and also study the antimicrobial property of mono azo disperse dyes based on 2-phenyl-4-hydroxy-6/7-substituted quinoline derivatives. The monoazo disperse dyes of the following types were prepared.

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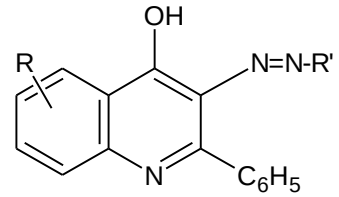
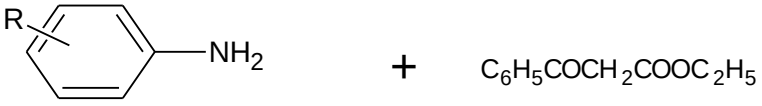


Where, R : 6-CH_3, 6-Cl, 6-OCH_3, 6-OC_2H_5,, 6-NO_2, 7-Cl
R' : Various diazo components

Azo compounds are known for their antibacterial properties. The synthesis of substituted 4-hydroxy-3-(substituted aryl azo)-2-phenyl quinolines were carried out to find whether they show an additional antibacterial effect or mutually imposing effect, or whether partial activity is retained[16]. The bacteria selected for the study of antibacterial activity by Disc Diffusion Technique[10] were *Escherichia coli, Salmonella paratyphi B, Bacillus subtilis* and *Staphylococcus aureus.* Disperse dyes gave the most satisfactory result due to their simple application methods[5, 15].

Materials and Methods:-

4-Hydroxy-2-phenyl-6/7- substituted quinoline can be synthesized by the following reaction.

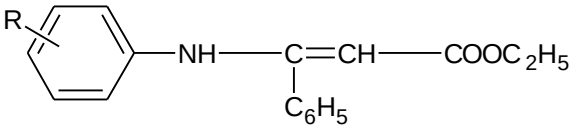


Aryl amine Ethyl benzoyl acetate

↓

A drop of concentrated HCl refluxed in boiling toluene for 8 hours

↓

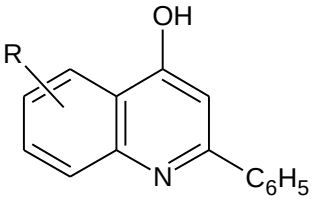


Anil-anilide

↓

Cyclised by PPA

↓



4-Hydroxy-2-phenyl-6/7- substituted quinoline
Where, R: 6-CH_3, 6-Cl, 6-OCH_3, 6-OC_2H_5,, 6-NO_2, 7-Cl

A mixture of aryl amine (based component) 0.04 Mole and ethyl benzoylacetate 0.02 Mole with a drop of concentrated HCl was refluxed in 30 ml of boiling toluene for 8 hours, and the solvent was evaporated living a residue which was directly cyclised by Poly Phosphoric Acid (PPA)[11].

Preparation of PPA:-

It is prepared by dissolving 30 grams Phosphorus pentoxide in 18 ml of ortho-phosphoric acid (d: 1.75). The mixture was heated at 95 - 100 °C for 30 minutes. The scum was removed, and the clear solution thus obtained was used for cyclisation experiment.

Cyclisation:-

The above crude anil-anilide was mixed with freshly prepare PPA and stirred well for some time with temperature raised to 120 °C. The mixture was kept in a dessicator over night. Next day, the temperature was slowly raised step

wise by 10 °C until it reached 155 °C for 90 minutes. This treatment helps in getting clean product with a high yield. The reaction mass was decomposed with crushed ice and neutralized with a mixed solution of Sodium and Ammonium hydroxide, maintaining it slightly on the acidic side. The product was filtered, washed with water, and dried. Different yields were obtained for different compounds have different melting points as shown in Table 1.

The product was purified by alkali and acid treatment, and crystallized using aqueous ethanol. These crystals exhibited different melting points. In case of 4-hydroxy-7-chloro-2-phenyl quinoline, the melting point (M.P.) range is large. So it is presumed to be a mixture of isomers. The isomers can be separated by heating 4 grams of the product with 80 ml alcohol. The hot solution is filtered, leaving a residue of 4-hydroxy-7-chloro-2-phenyl quinoline.

Antibacterial Activity:-

The antibacterial activity of the compounds was tested by the Standard Disc Diffusion Method developed by Bauer[10] using Muller Hintons Agar medium[4]. All the compounds were dissolved in Dimethyl formamide (DMF). Proper drug controls were used. 2-phenyl-4 hydroxy-6,7 substituted quinoline derivatives, and mono azo disperse dyes based on 2-phenyl- 4-hydroxy-6,7 substituted quinoline derivatives were taken at a concentration of 50 mg/ml for assessing their antibacterial activity. The compound diffused into the medium produced a concentration gradient. After a prefixed incubation period, the zone of inhibition was measured in mm. The test cultures used for the purpose are:

- ***Bacillus subtilis***
- ***Staphylococcus aureus***
- ***Escherichia coli***
- ***Salmonella paratyphi B***

The inoculum was standardized at 1.5 x 10^8 CFU/ml by comparing with turbidity standard (0.5 \Mac Farland tube).The plates were inoculated by dipping a sterile swab into the inoculum. Excess of the inoculum was removed by pressing and rotating the swab firmly against the side of the tube above the level of the liquid.

The swab was streaked all over the surface of the medium thrice rotating the plate through an angle of 60 degrees after each application. Finally, the swab was passed round the edge of the agar surface. The inoculum was dried for a few minutes at room temperature. The antibiotic discs were placed on the inoculated plates using a pair of sterile forceps. A sterile needle tip was used to place the antibiotic disc on the plate. The plates were then kept in an incubator maintained at 35 °C for 24 hours. Next day, the diameter of each zone of inhibition was measured and recorded in mm.

Results and Discussion:-

Table 1:- Synthesis of 4-Hydroxy-2-phenyl-6/7- Substituted Quinolines using different Aryl amine based components

Sr.	Name of the Compound	Anil-anilide Formed	Aryl Amine based component	Percentage Product Yield After Cyclisation	Melting Point °C
1	4-hydroxy-6-methyl-2-phenyl quinoline	β-p-toluidinocinnamo-p-toluidide	p-toluidine	76	294 – 295
2	4-hydroxy-6-chloro-2-phenyl quinoline	β-p-chloronilinocinnamo-p-chloroanilide	6-chloro aniline	70	350 – 351
3	4-hydroxy-6-methoxy-2-phenyl quinoline	β-p-methoxyanilinocinnamo-p-methoxyanilide	p-anisidine	85	288
4	4-hydroxy-6-ethoxy-2-phenyl quinoline	β-p-ethoxyanilinocinnamo-p-ethoxyanilide	P-phenetidine	78	284
5	4-hydroxy-6-nitro-2-phenyl quinoline	β-p-nitroanilinocinnamo-p-nitroanilide	4-nitro aniline	50	328 – 329
6	4-hydroxy-7-chloro-2-phenyl quinoline	β-m-chloroanilinocinnamo-m-chloroanilide	m-chloro aniline	80	245 – 268

The newly synthesised compounds with different yields as well as varying melting points can be further characterized using Infra red spectroscopy and NMR. The same was studied on 2-chloro-6-methyl-quinoline hydrazone derivatives[3].

Table 2:- Antibacterial Activity of 4-Hydroxy-2-phenyl-6/7- Substituted Quinolines.

Sr #	Name of the Compound	Zone of Inhibition, in mm			
		Bacillus subtilis	***Staphylococcus aureus***	***Escherichia coli***	***Salmonella paratyphi B***
	DMF Solvent (Control)	Nil	Nil	Nil	Nil
1	4-hydroxy-6-methyl-2-phenyl quinoline	Nil	Nil	12	12
2	4-hydroxy-6-chloro-2-phenyl quinoline	Nil	Nil	Nil	Nil
3	4-hydroxy-6-methoxy-2-phenyl quinoline	09	10	10	13
4	4-hydroxy-6-ethoxy-2-phenyl quinoline	Nil	11	09	Nil
5	4-hydroxy-6-nitro-2-phenyl quinoline	Nil	25	Nil	Nil
6	4-hydroxy-7-chloro-2-phenyl quinoline	09	12	Nil	Nil

Each compound synthesized had its specific maximum and minimum bacteriostatic potential depending upon the specific species. Similar results as those obtained were also found in the compound 2,4-dihydroxy-6-methyl quinoline. The antibacterial effect was equivalent to the current study[13, 14]. The quinoline moiety with a methoxy substituent at position 6 was found to be the most effective[8].

The results of the antibacterial activity of different compounds are summarized as follows:

1. 4-hydroxy-6-methoxy-2-phenyl quinoline (Sr# 3) was active against both Gram positive and Gram negative bacteria used as test organisms. Maximum antibacterial activity was shown by this compound.
2. 4-hydroxy-6-chloro-2-phenyl quinoline (Sr# 2) did not exhibit any antibacterial activity against both Gram positive and Gram negative bacteria.
3. 4-hydroxy-6-methyl-2-phenyl quinoline (Sr# 1), 4-hydroxy-6-ethoxy-2-phenyl quinoline (Sr# 4) and 4-hydroxy-7-chloro-2-phenyl quinoline (Sr# 6) exhibited moderate to good antibacterial activity against both Gram positive and Gram negative bacteria.
4. 4-hydroxy-6-nitro-2-phenyl quinoline (Sr# 5) exhibited highest antibacterial activity against only one Gram positive bacteria *Staphylococcus aureus*; whereas the same compound did not have any antibacterial effect on other Gram positive and Gram negative bacteria.

This implies that each compound acts differently over specific species of bacteria as far as its bacteriostatic potential and effect is concerned. These compounds can be subjected to evaluate their free radical scavenging activity by DPPH model in another study[7, 13]. These compounds need to be checked for their Anti-HIV properties, Analgesic activity, Antirheumatoid and Antitubercle activity[9, 12, 17].

Conclusion:-

From the above results it can be concluded that 4-hydroxy-6-methoxy-2-phenyl quinoline (Sr# 3), if coupled with other coupling components, would exhibit better antibacterial properties than the rest of the compounds synthesized.

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