Synthesis of some New Oxazoloquinolines and Stilbyloxazoloquinolines

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A new series of 2-aryl(alkyl)oxazoloquinolines (4) were prepared through the reaction of 7-amino-8-hydroxyquinoline with aromatic (or aliphatic) aldehydes in presence of piperidine as a catalyst. Interaction of 2-methyloxazolo[4,5-*h*]quinoline with aromatic aldehydes in presence of piperidine as a catalyst gave 2-stilbyloxazolo[4,5-*h*]quinolines. Structural configuration of the prepared compounds was determined by elemental and spectral analysis.

IN previous articles^{1,2} of this series, it was shown that interaction of 5,7-diamino-8-hydroxyquinoline and 7-amino-8-hydroxyquinoline-5-sulphonic acid with aldehydes gave the corresponding 2-aryl(alkyl)oxazolo[4,5-*h*]quinoline-5-Schiff bases and 5-sulphonic acids, respectively. The biological and antibiotic activity of the oxazoloquinoline compounds³⁻⁷, has led us to extend this work with the aim to prepare a new series of the parent 2-aryl(alkyl)oxazolo[4,5-*h*]quinolines and 2-stilbyloxazolo[4,5-*h*]quinolines which would possess some interesting biological activity.

Results and Discussion

7-Amino-8-hydroxyquinoline-5-sulphonic acid⁸ (2) was previously prepared *via* 7-azobenzene-8-hydroxyquinoline-5-sulphonic acid. In our method, 2 was synthesised in a simple route through nitrosation of 8-hydroxyquinoline-5-sulphonic acid⁹ followed by reduction with stannous chloride/hydrochloric acid to the 7-amino derivative (2). Elimination of the sulphonic acid group with dilute hydrochloric acid afforded 7-amino-8-hydroxyquinoline (3). Interaction of 3 with aromatic aldehydes in ethanol and piperidine as a catalyst gave 2-aryloxazolo[4,5-*h*]quinolines (4). The reaction was found to be also successful with aliphatic aldehyde, but needing more piperidine and a longer period of heating. The yield was somewhat lower than those with the aromatic aldehydes. The structure of the compounds was elucidated by elemental analysis and ir spectra which showed well defined bands characterising the oxazolo ring at 1580 cm⁻¹ (ν_{O-N}), 1185 cm⁻¹ (ν_{C-O-C})¹⁰, while absorptions due to OH and NH₂ groups in 3 disappeared. Interaction of 3 with acetylacetone under the same conditions gave 8-hydroxyquinoline-7-Schiff's base (5). The alcoholic solution of 5 gave a violet colour with ferric chloride, and the ir spectra showed the OH absorption at 3560 cm⁻¹. Acetylation of

3 with acetic anhydride—pyridine mixture (2:1) directly gave 2-methyloxazolo[4,5-*h*]quinoline¹¹ (4i). The identity of the compound with that obtained by the previous method described above was achieved by elemental analysis and mixed melting points. The reaction of 4i with aromatic aldehydes, in presence of ethanol and piperidine, gave 2-stilbyloxazolo[4,5-*h*]quinoline (6) (Scheme 1, Table 1). Infrared spectra showed well defined bands at 1690 cm⁻¹ attributable to $\nu_{C=O}$.

Scheme 1

The uv-visible spectra of saturated ethanolic (95%) solutions of 4a, b, g and the 2-stilbyl derivatives (6a, b, i) showed somewhat similar pattern of absorption spectra in the uv region, with slight differences in the visible side. They showed mainly

TABLE 1—2-ARYL(ALKYL)OXAZOLO[4,5-*h*]QUINOLINE (4a–i) AND 2-STILBYLOXAZOLO[4,5-*h*]QUINOLINE (6a–i)

Compd. no.	M p. ^a °C	Yield %	Molecular formula	Analysis % : Found/(Calcd.)	
				N	Cl
4a	350 ^a	43	C ₁₈ H ₁₂ ON ₂	10.68 (10.29)	—
4b	338–340 ^b	71	C ₁₇ H ₁₂ O ₂ N ₂	9.67 (10.14)	—
4c	350d ^a	45	C ₁₈ H ₁₀ O ₂ N ₂	10.98 (10.69)	—
4d	335d ^a	57	C ₁₈ H ₁₀ O ₂ N ₂	10.98 (10.69)	—
4e	210 ^b	57	C ₁₈ H ₁₂ ON ₂	14.75 (14.53)	—
4f	230 ^a	43	C ₁₆ H ₈ ON ₂ Cl	9.87 (9.98)	12.58 (12.66)
4g	>350 ^b	57	C ₁₈ H ₈ O ₃ N ₂	14.12 (14.43)	—
4h	240d ^a	54	C ₁₈ H ₈ O ₃ N ₂	14.12 (14.43)	—
4i	320d ^b	63	C ₁₁ H ₈ ON ₂	15.53 (15.22)	—
6a	>350 ^a	57	C ₁₈ H ₁₂ ON ₂	10.68 (10.29)	—
6b	170d ^a	62	C ₁₈ H ₁₄ O ₂ N ₂	9.00 (9.27)	—
6c	175 ^a	62	C ₁₈ H ₁₄ O ₂ N ₂	9.00 (9.27)	—
6d	335–337 ^a	64	C ₁₈ H ₁₂ O ₂ N ₂	9.32 (9.72)	—
6e	340–342 ^a	64	C ₁₈ H ₁₂ O ₂ N ₂	9.32 (9.72)	—
6f	200 ^b	51	C ₁₈ H ₁₁ ON ₂ Cl	9.26 (9.14)	11.52 (11.58)
6g	265 ^a	50	C ₂₀ H ₁₄ ON ₂	8.97 (9.40)	—
6h	>350 ^a	58	C ₁₈ H ₁₁ O ₃ N ₂	13.70 (13.25)	—
6i	>350 ^a	60	C ₁₈ H ₁₁ O ₃ N ₂	13.70 (13.25)	—

^aSolvent of crystallisation : ^aethanol, ^bdioxane, ^cmethanol.

three bands in the uv region 250–320 nm, assigned to electronic transitions $\pi-\pi^*$ in benzenoid and oxazoloquinoline nucleus. The fourth band appearing in the visible region, is influenced by the type of substituent and may be attributed to intramolecular charge transfer (C.T.) from nitrogen of the oxazole to that of quinoline nucleus. Thus introducing of electron-deactivating group (e.g. NO₂ group, 4g) causes a blue-shift by 30 nm relative to 4a (λ_{max} 400 nm), while the corresponding *p*-nitrostilbyloxazolo[4,5-*h*]quinoline (6) is red-shifted by 10 nm due to the increase of conjugation in the molecule by a $-\text{CH}=\text{CH}-$ group.

Biological testing of these compounds showed a remarkable activity towards both gram-positive (e.g. *Bacillus cereus*, *Staphylococcus aureus*, and *Sarcina lutea*) and gram-negative bacteria (e.g. *Pseudomonas* sp.). It was also found that the activity decreases with the stilbyl derivatives (5). The 5-sulphonic acid derivatives of 4 which had been shown in previous work were more potent than the corresponding desulphonated derivatives.

Experimental

The ir spectra were determined with a Perkin-Elmer 137B spectrophotometer. Uv spectra were

recorded on a Carl-Zeiss Vs. 2-P spectrophotometer using 1 cm matched silica cells. Melting points were not corrected.

7-Nitroso-8-hydroxyquinoline-5-sulphonic acid (1) : 8-Hydroxyquinoline-5-sulphonic acid^a (5.6 g, 0.025 mol) was dissolved in warm 2% aqueous sodium hydroxide solution (100 ml) placed in a 500 ml round bottomed flask fitted with a mechanical stirrer and a separating funnel. The solution was cooled to 10° in an ice-bath and sodium nitrite (2.1 g 0.03 mol) was gradually added. The mixture was stirred and concentrated sulphuric acid (5 ml) was added through the separating funnel over a period of 90 min at 0°. Crushed ice (~200 g) was added to the contents of the flask to keep the temperature constant during stirring. The reaction mixture was stirred for an additional 1 h after all sulphuric acid was introduced. The precipitated yellow solid was filtered off, washed with water and recrystallised from ethanol dark yellow crystals of 7-nitroso-3-hydroxyquinoline-5-sulphonic acid (2), m.p., 308–10° d (Found : N, 11.16 ; S, 12.80. C₉H₆O₈N₂S calcd. for : N, 11.02 ; S, 12.60%).

7-Amino-8-hydroxyquinoline-5-sulphonic acid dihydrochloride (2) : A mixture of 7-nitroso-8-hydroxyquinoline-5-sulphonic acid (5 g), 0.022 mol, ethanol

(20 ml), stannous chloride (8 g, 0.035 mol) and concentrated hydrochloric acid (25 ml) was heated under reflux for 6 h. The resulting solution was concentrated to about half of its volume, cooled and the precipitated product was filtered off, and crystallised from ethanol to fine yellow needles of **2** (80%), m.p. 320°d (Found: N, 8.86; S, 10.33; Cl, 23.56. $C_9H_{10}O_4N_2S$ calcd. for: N, 8.95; S, 10.22; Cl, 22.68%).

7-Amino-8-hydroxyquinoline hydrochloride (3): A mixture of 7-amino-8-hydroxyquinoline-5-sulphonic acid (5 g, 0.022 mol), concentrated hydrochloric acid (6.6 ml) and water (100 ml) was heated under reflux for 6 h at 170°. The reaction mixture was concentrated under reduced pressure, and the precipitated solid was collected and recrystallised from ethanol into yellow needles of **3** (54%), m.p. 290° (Found: N, 14.0; Cl, 18.05. $C_9H_8ON_2Cl$ calcd for: N, 14.25; Cl, 18.07%).

2-Aryloxazolo[4,5-h]quinolines (4): A mixture of **3** (0.0025 mol), aldehyde (0.004 mol), piperidine (0.5 ml) and absolute ethanol (15 ml) was refluxed for 4–8 h. The reaction mixture was concentrated and cooled, whereby red to brown solids were separated, which were filtered off, washed with petroleum ether (b.p. 40–60°) and recrystallised from the proper solvent to give **4**. The results are given in Table 1.

8-Hydroxyquinoline-7-Schiff's base (5): A mixture of **3** (0.0076 mol), acetylacetone (0.0072 mol), piperidine (1 ml), and absolute ethanol (25 ml) was refluxed for 20 h. The reaction mixture was concentrated to 10 ml, and the precipitated product was collected, washed with alcohol and crystallised from ethanol to fine yellow crystals of **5** (50%), m.p. 328° (Found: N, 10.96. $C_{14}H_{14}O_2N_2$ calcd. for: N, 11.57%). The alcoholic solution of **5** gave violet colour with ferric chloride solution.

2-Methyloxazolo[4,5-h]quinoline (4i): A mixture of **3** (5 g), pyridine (20 ml), and acetic anhydride (40 ml) was refluxed for 20 h on a hot-plate. The reaction mixture was diluted with ice cold water whereby fine greenish brown crystals of **4i** separated, which were collected, washed with water and crystallised from dioxane, (63%), m.p. 320°d (Found: N, 15.53. $C_{11}H_8ON_2$ calcd. for: N, 15.22%).

2-Stilbyloxazolo[4,5-h]quinoline (6): A mixture of 2-methyloxazolo[4,5-h]quinoline (**4i**; 0.0027 mol), aromatic aldehyde (0.0027 mol) and piperidine (0.1 ml) and absolute ethanol (20 ml) was heated under reflux for 6–14 h. The reaction mixture was concentrated, cooled and the separated solid was collected and recrystallised from the appropriate solvent (Table 1).

Biological screening for selected oxazoloquinoline (4, 6): The culture medium was normal nutrient agar (N.A.) medium¹² supplemented with 1 g yeast/litre. The bacterial suspension was prepared by adding 1 ml of sterile distilled water to a 24 h old culture of the test organism grown on N.A. slant. Aliquots (1 ml) of bacterial suspension were added to Erlenmeyer flask containing 150 ml of N.A. and the flasks were incubated for 24 h.

Petri dishes containing sterile modified N.A. were flooded with the bacterial suspension of the test organisms (2 plates for each organism). Two filter paper discs (1 cm dia) containing the selected compounds (**4c**, **g**; **6d**, **f**) dissolved in ethylene glycol (10 mg dm⁻³) were placed on each plate. The plates were incubated at 37° for 24 h and the diameter of the inhibition zone was measured. The experiments were repeated 3 times and the results obtained were averaged. The results are given in Table 2.

TABLE 2—ANTIBACTERIAL SCREENING DATA* OF SELECTED COMPOUNDS

Compd. no.	<i>P. sp.</i> (-ve)	<i>B. cereus</i> (+ve)	<i>S. aureus</i> (+ve)	<i>S. lutea</i> (+ve)
4c	3	3	8	3
4g	3	—	3	—
6d	—	3	—	—
6f	—	—	3	—

*Expressed as diameter of inhibition zone in mm.

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