J. Chem. Tech. Biotechnol. 1982, **32**, 485–488

Synthesis of Some New Oxazoloquinolines and Stilbyloxazoloquinolines

A. S. Hammam*, A. S. Yanni, Z. H. Khalil and A. A. Abdel-Hafez

Chemistry Department, Assiut University, Assiut, Egypt

(*Paper received 26 June 1981 and accepted 10 November 1981*)

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

1. Introduction

It has been shown[1] (A. S. Hamman; A. S. Yanni; Z. H. Khalil; A. A. Abdel Hafez, unpublished work) that interaction of 5,7-diamino-8-hydroxyquinoline and 7-amino-8-hydroxyquinoline-5-sulphonic acid with aldehydes gave the corresponding 2-aryl(akyl)oxazolo[4,5-*h*]quinoline-5-Schiff's bases and 5-sulphonic acids respectively.

The biological and antibiotic activity of oxazoloquinoline compounds,[2–6] has led to an extension of this work with the aim to prepare a new series of the present 2-aryl(alkyl)oxazolo[4,5-*h*]quinolines and 2-stilbyloxazolo[4,5-*h*]quinolines which would possess interesting biological activity.

2. Experimental

I.r. spectra were determined with a Perkin–Elmer Infrared 137 B spectrophotometer.

2.1. Preparation of 7-nitroso-8-hydroxyquinoline-5-sulphonic acid (I)

A sample of (5.6 g, 0.025 mol) of 8-hydroxyquinoline-5-sulphonic[9] acid was dissolved in 100 cm^3 of a warm 2% (v/v) aqueous sodium hydroxide placed in a 0.5 dm^3 round-bottomed flask fitted with a mechanical stirrer and a separating funnel. The solution was cooled to 10°C and sodium nitrite (2.1g) was gradually added. The mixture was stirred and 5 cm^3 of conc. H_2SO_4 was added through the separating funnel over a period of 90 min while the temperature was kept at 0°C. About 200 g of crushed ice was added to the contents of the flask to keep the temperature constant during stirring. The reaction mixture was stirred for 1 h after introduction of H_2SO_4. The precipitated yellow solid was filtered off, washed with water and recrystallised from ethanol into dark yellow crystals of 7-nitroso-8-hydroxyquinoline-5-sulphonic acid (**I**; m.p. 308–310°C.)

Analysis for $C_9H_6O_5N_2S$ gave (%N,S): calculated N, 11.02; S, 12.60 and found N, 11.16; S, 12.80.

2.2. Preparation of 7-amino-8-hydroxyquinoline-5-sulphonic acid dihydrochloride (II)

A mixture of 7-nitroso-8-hydroxyquinoline-5-sulphonic acid (5 g, 0.022 mol), ethanol (20 cm^3), stannous chloride (8 g, 0.035 mol) and conc. HCl (25 cm^3) was heated under reflux for 6 h. The

*Present address: University of Riyadh, College of Education, Abha, Saudi Arabia.

0142–0356/82/0300–485 $02.00

resulting solution was concentrated to about half of its volume, cooled and the precipitated product was filtered off and crystallised from ethanol into fine yellow needles (**II**; m.p. 320°C, yield 80%). Analysis for $C_9H_{10}O_4N_2SCl_2$ gave (% N, S, Cl): calculated N, 8.95; S, 10.22; Cl, 22.68 and found N, 8.86; S, 10.33; Cl, 23.56.

2.3. Preparation of 7-amino-8-hydroxyquinoline hydrochloride (III)

A mixture of 7-amino-8-hydroxyquinoline-5-sulphonic acid (5 g, 0.022 mol), conc. HCl (6.6 cm^3) and water (100 cm^3) was heated under reflux for 6 h at 170°C. The reaction mixture was concentrated under reduced pressure and the precipitated solid was collected and recrystallised from ethanol into yellow needles (**III**; m.p. 290°C, yield 54%). Analysis for $C_9H_9ON_2Cl$ gave (% N, Cl): calculated N, 14.25; Cl, 18.07 and found N, 14.0; Cl, 18.25.

2.4. Synthesis of 2-aryloxazolo[4,5-h]quinoline (IV)

A mixture of **III** (0.0025 mol), aldehyde (0.004 mol) piperidine (0.5 cm^3) and ethanol (15 cm^3) was refluxed for 4–8 h. The reaction mixture was concentrated and cooled, whereby red-to-brown solids were separated, filtered, washed with petroleum ether (b.p. 40–60°C) and recrystallised from ethanol to give **IV**. The results are given in Table 1.

Table 1. 2-Aryl(alkyl)oxazolo[4,5-*h*]quinoline (**IVa–i**) and 2-stilbyloxazolo[4,5-*h*]quinoline (**VIa–i**)

Compound	M.p.(°C)	Solvent of crystallisation[a]	Yield (%)	Molecular formula	Analysis Found N	Found Cl	Required N	Required Cl
IVa	>350	E	43	$C_{18}H_{12}ON_2$	10.68	—	10.29	—
b	338–340	D	71	$C_{17}H_{12}O_2N_2$	9.67	—	10.14	—
c	350 (dec.)	E	45	$C_{16}H_{10}O_2N_2$	10.98	—	10.69	—
d	335 (dec.)	E	57	$C_{16}H_{10}O_2N_2$	10.98	—	10.69	—
e	210	D	57	$C_{18}H_{15}ON_3$	14.75	—	14.53	—
f	230	E	43	$C_{16}H_9ON_2Cl$	9.87	12.58	9.98	12.66
g	>350	D	57	$C_{16}H_9O_3N_3$	14.12	—	14.43	—
h	240 (dec.)	E	54	$C_{16}H_9O_3N_3$	14.12	—	14.43	—
i	320 (dec.)	D	63	$C_{11}H_8ON_2$	15.53	—	15.22	—
VIa	>350	E	57	$C_{18}H_{12}ON_2$	10.68	—	10.29	—
b	170 (dec.)	M	62	$C_{19}H_{14}O_2N_2$	9.00	—	9.27	—
c	175	E	62	$C_{19}H_{14}O_2N_2$	9.00	—	9.27	—
d	336–337	E	64	$C_{18}H_{12}O_2N_2$	9.32	—	9.72	—
e	340–342	E	64	$C_{18}H_{12}O_2N_2$	9.32	—	9.72	—
f	200	D	51	$C_{18}H_{11}ON_2Cl$	9.26	11.52	9.14	11.58
g	265	E	50	$C_{20}H_{14}ON_2$	8.97	—	9.40	—
h	>350	E	58	$C_{18}H_{11}O_3N_3$	13.70	—	13.25	—
i	>350	E	60	$C_{18}H_{11}O_3N_3$	13.70	—	13.25	—

[a] E, Ethanol; D, dioxane; M, methanol.

2.5. Synthesis of 8-hydroxyquinoline-7-Schiff's-base (V)

A mixture of **III** (0.0036 mol), acetylacetone (0.0072 mol), piperidine (1 cm^3) and ethanol (25 cm^3) was refluxed for 20 h. The reaction mixture was concentrated to 10 cm^3, the precipitated product was collected, washed with alcohol and crystallised from ethanol into fine yellow crystals (**V**; m.p. 328°C, yield 50%). The alcoholic solution of **V** gave a violet colour with ferric chloride solution. Analysis for $C_{14}H_{14}O_2N_2$ gave (% N): calculated N, 11.57 and found N, 11.96.

2.6. Synthesis of 2-methyloxazolo [4,5-h]quinoline (IVi)

A mixture of **III** (5 g), pyridine (20 cm^3) and acetic anhydride (40 cm^3) was refluxed for 20 h on a hot plate. The reaction mixture was diluted with ice-cold water whereby fine green-brown crystals

of **IVi** were separated, collected, washed with water and crystallised from dioxane into fine green-brown needles of **IVi** (m.p. 320°C, yield 63%). Analysis for $C_{11}H_8ON_2$ gave (% N): calculated N, 15.22 and found N, 15.53.

2.7. Synthesis of 2-stilbyloxazolo[4,5-*h*]quinoline (VI)

A mixture of 2-methyloxazolo[4,5-*h*]quinoline (**IVi**, 0.0027 mol), aromatic aldehyde (0.0027 mol) and piperidine (0.1 cm^3) and ethanol (20 cm^3) 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. The results are given in Table 1.

2.8. Biological screening for selected oxazoloquinoline (IV, VI)

The culture medium was nutrient agar (NA)[8] supplemented with yeast (1 g dm^{-3}); the bacterial suspension was prepared by adding 1 cm^3 of sterile distilled water to a 24 h-old culture of the test organism grown on a NA slant. Portions of (1 cm^3) bacterial suspension were added to Erlenmeyer flasks containing 150 cm^3 of NA and these were incubated for 24 h.

Petri dishes containing sterile modified NA were flooded with the bacterial suspension of the test organism (two plates for each organism). Two filter-paper discs (1 cm diameter) containing the selected compounds (**IVc, g**; **VId, f**) dissolved in ethylene glycol (10 mg dm^{-3}) were placed on each plate. The plates were incubated at 37°C for 24 h and the diameters of the inhibition zones were measured. The experiments were repeated three times and the results obtained were averaged. The results are given in Table 2.

Table 2. Results of antibacterial screening of selected compounds (expressed as diameter of inhibition zone in mm)

Compound tested	*Pseudomonas* sp. (−ve)	*Bacillus cereus* (+ve)	*Staphylococcus aureus* (+ve)	*Sarcina lutea* (+ve)
IVc	3	3	8	3
IVg	3	—	3	—
VId	—	3	—	—
VIf	—	—	3	—

3. Results and discussion

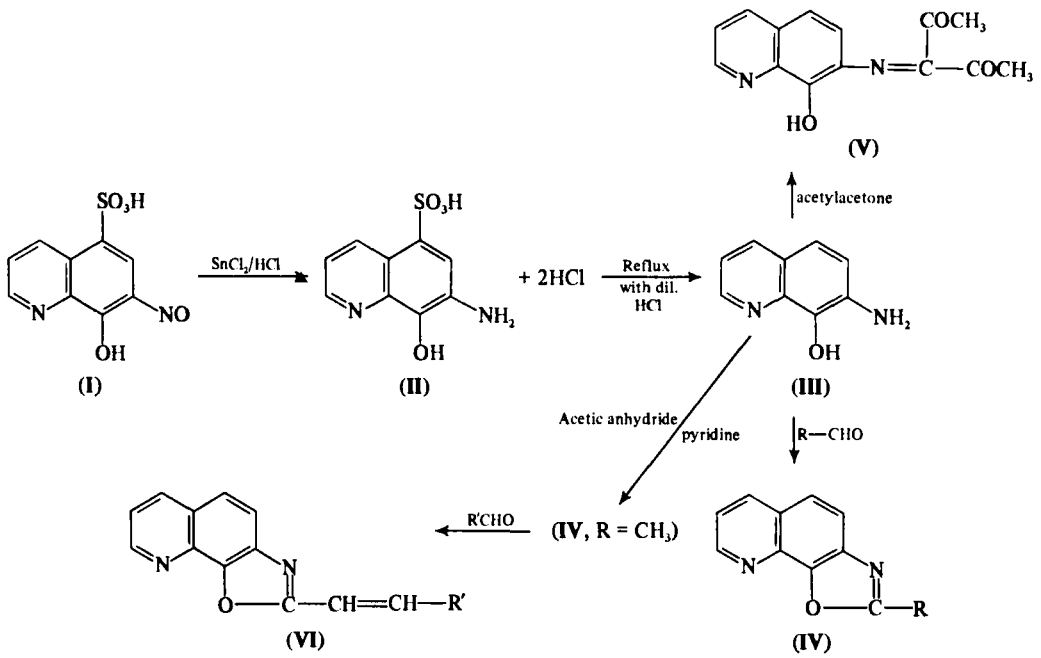
7-Amino-8-hydroxyquinoline-5-sulphonic acid (**II**)[9] was prepared previously via 7-azobenzene-8-hydroxyquinoline-5-sulphonic acid. **II** was synthesised by nitrosation of 8-hydroxyquinoline-5-sulphonic acid[9] followed by reduction with stannous chloride HCl to the 7-amino derivative (**II**). Elimination of the sulphonic acid group with dilute/HCl gave 7-amino-8-hydroxyquinoline (**III**).

Interaction of **III** with aromatic aldehydes in ethanol with piperidine as a catalyst gave 2-aryloxazolo[4,5-*h*]quinolines (**IV**). The reaction was also found to be successful with aliphatic aldehydes, but needed more piperidine and a longer period of heating. The yield was somewhat lower than those with aromatic aldehydes. The structure of the synthesised compounds was elucidated by elemental analysis and i.r. spectra which showed well defined bands characterising the oxazolo ring at 1580 cm^{-1} (νC=N), 1185 cm^{-1} (ν—C—O—C-cyclic group),[10] while absorptions due to —OH and $-NH_2$ groups in **III** disappeared.

Interaction of **III** with acetylacetone under the same conditions gave the 8-hydroxyquinoline-7-Schiff base (**V**). The alcoholic solution of **V** gave a violet colour with ferric chloride and the i.r. spectra showed the —OH absorption band at 3560 cm^{-1}.

Acetylation of **III** with acetic anhydride/pyridine (2:1) mixture gave 2-methyloxazolo[4,5-*h*]-quinoline (**IVi**) directly.[11] The identity of this compound with that obtained by the previous method described above was achieved by elemental analysis and mixed melting points.

The reaction of **IVi** with aromatic aldehydes, in the presence of ethanol and piperidine gave 2-stilbyloxazolo[4,5-*h*]quinoline (**VI**) (cf. scheme 1, Table 1). I.r. spectra showed well defined bands at 1690 cm^{-1} attributable to $\nu C{=}C$.



VIa, R′	$=C_6H_5-$
b	$=C_6H_4$—*p*-OCH_3
c	$=C_6H_4$—*o*-OCH_3
d	$=C_6H_4$—*p*-OH
e	$=C_6H_4$—*o*-OH
f	$=C_6H_4$—*p*-Cl
g	$=C_6H_4-CH{=}CH-$
h	$=C_6H_4$—*p*-NO_2
i	$=C_6H_4$—*o*-NO_2

IVa, R	$=C_6H_5-$
b	$=C_6H_4$—*p*-OCH_3
c	$=C_6H_4$—*p*-OH
d	$=C_6H_4$—*o*-OH
e	$=C_6H_4$—*p*-$N(CH_3)_2$
f	$=C_6H_4$—*p*-Cl
g	$=C_6H_4$—*p*-NO_2
h	$=C_6H_4$—*o*-NO_2
i	$=CH_3$

Scheme 1

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

References

1. Osman, A. M.; Khalil, Z. H.; Yanni, A. S. *J. appl. Chem. Biotechnol.* 1977, **27**, 206.
2. Rinehart, K. L.: Leadbetter, G.; Larson, R. A.; Forbis, R. M. *J. Am. Chem. Soc.* 1970,**92**, 927, 6994.
3. Staskur, B. *J. Org. Chem.* 1966, **31**, 2674.
4. Ikeda, M.; Tomiji, O. Japan Patent 6902219 (1969).
5. Wittmann, H.; Wohlkoenig, A.; Sterk, H.; Zieglar, E. *Monatsh. Chem.* 1970, **101**, 383.
6. Franck, R. W.; Gilligan, J. M. *J. Org.* 1971, **36**, 222.
7. *Beilstein Handbuch Der Organischer Chemie* Verlag Von Julius Springer, Berlin, 1935, XXII, Syst. No. 3380, 407.
8. Knudsen, E. T.; Rolinson, G. N. *Lancet* 1959, **i**, 1105.
9. Matsumara, K. *J. Am. Chem. Soc.* 1927, **49**, 810.
10. Somayajula, V. V.; Suba, N. V. *Curr. Sci. (India)* 1957, **25**, 25, 36.
11. Fraser, J.; Tittensor, E. *J. Chem. Soc.* 1956, 1781.