SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF CERTAIN QUINOLINE DERIVATIVES

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Some aryl or heterocyclic mercaptans reacted with 8-quinolyl chloroacetate *II* or 8-quinolinoxyacetyl chloride *IV* to give the corresponding 8-quinolyl-α-mercaptoacetate *V* or 8-quinolyloxy thioacetate *VI*, respectively. The mercaptans *V* were oxidized to the corresponding sulfones *VII*. Some of these compounds were tested for their antimicrobial activities in comparison with tetracycline reference compound.

8-Hydroxyquinoline and its derivatives are reported as well known antimicrobial agents[1 - 4]. In many cases this antimicrobial activity has been attributed to chelating properties served by the 8-hydroxyl group and the quinoline ring nitrogen[5]. Some metal complexes of 8-hydroxyquinoline have been studied due to their established biological activities[6 - 10]. Furthermore some sulfur containing compounds are drugs of proven therapeutic importance used against a wide spectrum of bacterial ailments[11 - 16].

We report herein the preparation of some 8-quinolyl-α-mercaptoacetates *V*, 8-quinoloxy thioacetate derivatives *VI* and 8-quinolyl-α-sulfonylacetates *VII* (Scheme 1) with the aim to investigate their antimicrobial potency with reference to the starting 8-hydroxyquinoline. The effect of the side chain variation as ester and ether upon the antimicrobial action shall also be discussed.

EXPERIMENTAL

The time required for completion of the reaction was monitored by thin layer chromatography (TLC). Melting points were determined in open-glass capillaries and are uncorrected. IR Spectra were recorded on a Pye–Unicam SP 200-G IR Spectrophotometer. ^{1}H NMR spectra were measured in $(CD_3)_2SO$ or trifluoroacetic acid using TMS as internal standard on EM 360, 90 MHz NMR Spectrometer.

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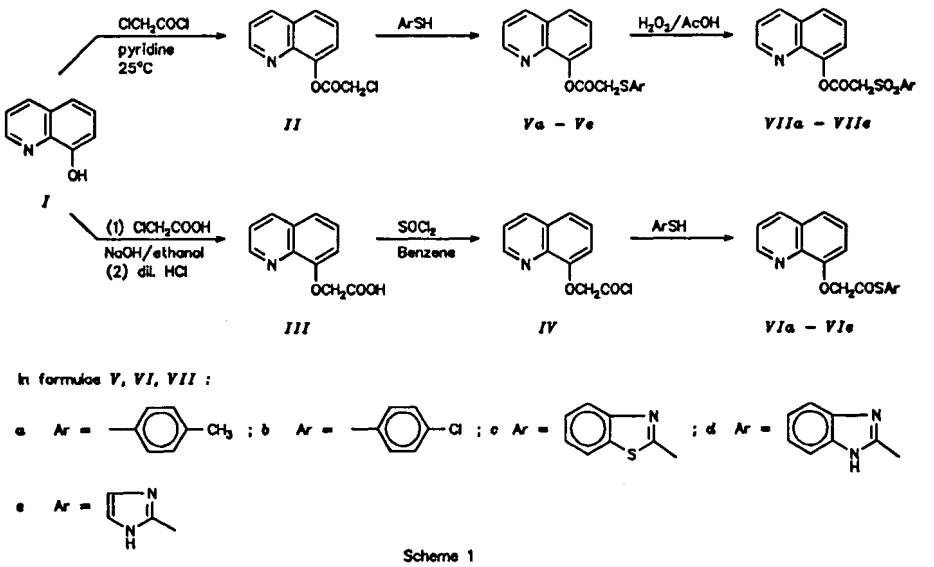

Scheme 1

8-Quinolyl-α-chloroacetate *II* (ref.[17])

In a two necked round bottomed flask (250 ml) fitted with a reflux condenser and a 50 ml dropping funnel, 5.8 g (0.04 mol) 8-hydroxyquinoline were dissolved in 100 ml dry pyridine. To the stirred solution there was added dropwise 2 ml (2.5 g, 0.022 mol) of freshly distilled chloroacetylchloride. The reaction mixture was then stirred for 2 h at room temperature and filtered. The golden yellow precipitate was crystallized from petroleum ether, m.p. 218 – 220 °C.

8-Quinoloxy Acetyl Chloride *IV* (ref.[18])

To solution of 2.46 g (0.044 mol) of potassium hydroxide in 100 ml absolute ethanol 3.1 g (0.022 mol) of 8-hydroxyquinoline was added. Then 2.5 g (0.022 mol) of chloroacetic acid was added portionwise. The solution was refluxed under stirring for 20 h. After cooling to room temperature, the reaction mixture was acidified by 5 ml of conc. HCl and filtered to remove the precipitated KCl. The ethanol was removed under reduced pressure to afford the corresponding acid which was converted to the acid chloride by treatment with 2.5 ml of thionyl chloride in 50 ml dry benzene and subsequent reflux for one hour. The solvent and excess thionyl chloride was removed by distillation under reduced pressure. The residual acid chloride was crystallized from petroleum ether and used for synthesis of the thioacetates derivatives *VIa – VIe*.

Reaction of 8-Chloroacetoxyquinoline or 8-Quinoloxyacetyl Chloride with Aryl(heterocyclic) Mercaptans

8-Chloroacetoxyquinoline *II* or 8-quinoloxyacetyl chloride *IV* (0.01 mol) was dissolved in 25 ml dry benzene. To this solution 0.01 mol of the aryl(heterocyclic) mercaptan was added portionwise and the

mixture was refluxed for 8 h. Benzene was removed under reduced pressure and the product was crystallized from the proper solvent (Table I).

Oxidation of 2'-Aryl(heterocyclic)mercapto-8-acetoxyquinoline (General Procedure)

2'-Aryl(heterocyclic)mercapto-8-acetoxyquinoline (0.01 mol) was dissolved in glacial acetic acid and the calculated volume of hydrogen peroxide was added dropwise. The reaction mixture was left to stand 3 days at room temperature, then decomposed with ice cool water. The combined solvents were removed and the products were crystallized from the proper solvents (Table II).

TABLE I
Physical properties, yields and elemental analyses of compounds *V* and *VII*

Compound	X	M. p., °C (Yield, %)	Formula (M. w.)	Calculated / Found			
				% C	% H	% N	% S
Va	S	220 – 222[a] (73)	$C_{18}H_{15}NO_2S$ (309)	69.90 69.50	4.85 4.80	4.53 4.30	10.35 10.50
Vb[e]	S	245[a] (72)	$C_{17}H_{12}ClNO_2S$ (332)	62.02 62.30	3.64 3.50	4.25 4.20	9.72 10.00
Vc	S	140 – 142[b] (65)	$C_{18}H_{12}N_2O_2S_2$ (352)	61.36 61.20	3.40 3.40	7.95 7.80	18.18 18.50
Vd	S	210 – 212[c] (72)	$C_{18}H_{13}N_3O_2S$ (334)	64.67 64.50	3.59 3.20	12.59 12.40	9.58 9.30
Ve	S	170[b] (63)	$C_{14}H_{11}N_3O_2S$ (285)	58.94 58.50	3.85 3.70	14.73 14.40	11.22 11.30
VIIa	SO_2	80 – 82[a] (70)	$C_{18}H_{15}NO_4S$ (341)	63.34 63.30	4.30 4.18	4.12 3.90	9.38 8.60
VIIb	SO_2	62 – 64[a] (73)	$C_{17}H_{12}NO_4S$ (361)	56.50 56.30	3.30 3.20	3.87 3.40	8.80 8.30
VIIc	SO_2	120 – 122[a] (73)	$C_{18}H_{12}N_2O_4S_2$ (384)	56.25 56.70	3.10 2.50	7.29 7.90	16.60 16.40
VIId	SO_2	60 – 63[a] (75)	$C_{18}H_{13}N_3O_4S$ (366)	59.01 58.50	3.24 3.10	11.47 11.20	8.70 8.21
VIIe	SO_2	115 – 117[d] (65)	$C_{14}H_{11}N_3O_4S$ (317)	52.95 52.20	3.40 3.10	13.20 12.99	10.09 9.70

Crystallized from: [a] ethanol/water; [b] ethanol; [c] methanol; [d] methanol/water. [e] Calculated: 10.6% Cl, found: 10.6% Cl.

RESULTS AND DISCUSSION

The IR spectra of the 8-quinolylacetate derivatives (*Va – Ve*) show a characteristic strong absorption band at 1 730 – 1 740 cm^{-1} corresponding to the stretching vibrations of C=O group in ester function. It was observed that the type of substituent on α-position of the side chain has no considerable influence on the frequency of this carbonyl function. Also when the α-positioned sulfur atom is oxidized to the corresponding sulfone (*VIIa – VIIe*) there is no observable change in the frequency of the carbonyl ester in comparison to the parent compounds. The α-sulfonyl derivatives are characterized furthermore by the appearance of a new band at ~1 410 cm^{-1} corresponding to the $-SO_2$ group. In the 8-quinolinoxythioacetate derivatives (*VIa – VIe*) the frequency of the carbonyl group is generally lowered to 1 700 – 1 690 cm^{-1} due to the presence of sulfur atom in ester moiety instead of oxygen.

^1H NMR spectra were taken in trifluoroacetic acid for some of the synthesized compounds. The general feature for all derivatives is the presence of the singlet corresponding to 2 H in the range between δ 3.9 – 3.5 ppm. The aromatic protons appear as a complex system in the range between δ 7.8 – 9.3 ppm. Some of the signals could be identified as that of δ 9.4 ppm (1 H) with characteristic *ortho*-coupling (~5 Hz). This signal was assigned to H-2 of the quinoline ring. Its downfield shift with respect to the other protons is due to the ring nitrogen. The triplet at δ 9.2 ppm integrated for 2 H will be assigned to H-3 and H-6 of the quinoline nucleus. The splitting pattern of this signal is attributed to the two *ortho* protons H-2/H-4 and/or H-5/H-7. The other aromatic protons of the side chain substituent appear in the range between 7.2 – 8.0 ppm.

TABLE II
Physical properties, yields and elemental analysis of compounds *VIa – VIe*

Compound	X	M. p., °C (Yield, %)	Formula (M. w.)	Calculated / Found			
				% C	% H	% N	% S
VIa	S	215 – 217[a] (83)	$C_{18}H_{15}NO_2S$ (309)	69.90 69.61	4.85 4.70	4.53 4.41	10.35 10.20
VIb[c]	S	230 – 232[a] (73)	$C_{17}H_{12}ClNO_2S$ (329)	62.02 62.50	3.64 3.40	4.25 4.25	9.72 9.50
VIc	S	280 – 282[a] (65)	$C_{18}H_{12}N_2O_2S_2$ (352)	61.36 61.10	3.40 3.21	7.95 7.70	18.18 18.20
VId	S	190 – 192[a] (72)	$C_{18}H_{12}N_3O_2S$ (334)	64.67 64.30	3.59 3.30	12.57 12.30	9.58 9.20
VIe	S	160 – 161[b] (63)	$C_{14}H_{11}N_3O_2S$ (285)	58.94 58.60	3.85 3.60	14.73 14.00	11.22 11.10

Crystallized from: [a] ethanol/water; [b] ethanol. [c] Calculated: 10.6% Cl, found: 10.7% Cl.

Antimicrobial Activity

The synthesized compounds *Va – Ve, VIa – VIe* and *VIIIa – VIIIe* were tested for their antimicrobial activity using agar cup diffusion techniques[19]. Their minimum inhibitory concentration (MIC) was calculated (μg ml^{-1}) against *Staphylococcus aureus* and *Escherichia coli*. This method depends on the diffusion of the drug tested from cylinders or from wells placed on the surface of seeded agar. As the plate is incubated, the drug diffuses into the medium giving zones of progressively lower concentration. The test organism can grow up to the zone on minimum inhibitory concentration but not inside it.

For determination of MIC of the tested compounds five different concentrations of each compound in $(CH_3)_2SO$ (5, 2.5, 1.25, 0.625, 0.31 μg ml^{-1}) were prepared under sterile conditions and transferred to the appropriate wells in the preinoculated agar plates. Five equivalent concentrations of 8-hydroxyquinoline were also prepared and tested against the same microorganism. After incubation of the petri dishes at 37 °C for 48 h the diameter of inhibition zones for each concentration of the considered compound was measured.

Table III gives the calculated MIC values for the tested compounds with their corresponding correlation coefficients.

TABLE III
Calculated MIC values for compounds under test

Compound	MIC[a] (correlation coefficient)	
	E. coli	*S. aureus*
Va	10.7 (0.98)	18.2 (0.991)
Vb	3.1 (0.966)	10.5 (0.986)
Vc	3.7 (0.989)	2.7 (0.945)
Vd	1.4 (0.930)	1.9 (0.997)
Ve	1.4 (0.98)	1.9 (0.99)
III	4.6 (0.673)	4.1 (0.614)
I	9.6 (0.959)	4.0 (0.992)
VIa	4.4 (0.978)	2.1 (0.981)
VIb	3.1 (0.945)	2.8 (0.981)
VIc	inactive	inactive
VId	3.8 (0.989)	4.3 (0.999)
VIe	3.9 (0.991)	3.4 (0.974)
Tetracycline	3.6 (0.99)	4.1 (0.99)

[a] In μg l^{-1}.

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