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Synthesis and Biological Activities of Substituted 7-Chloroquinoline Derivatives, Part I

M.A. DAVE*, N.S. DESAI and A.V. NAIDU
K.J. Somaiya College of Science and Commerce, Vidyavihar, Mumbai-400 077, India

4-Hydroxy-7-chloroquinoline was treated with chloroacetic acid to get an acid, which on esterification gave ester. Subsequently hydrazide obtained was treated with aryl aldehydes to get hydrazones. 4,7-Dichloroquinoline was condensed with methylanthranilate and hydrazide was obtained using hydrazine hydrate. Hydrazones were synthesised using aryl aldehydes. 4-Amino-7-chloroquinoline was condensed with anhydrides having active hydrogen. Imides thus obtained were treated with aryldiazonium chloride to get hydrazone dyes.

7-Chloro-4-[4-methylidine-(aryl)-hydrazocarbonyl quinolinyloxy methane, 1-amino-(7-chloroquinoline)-2-[N-ethylidene-aryl] hydrazocarbonyl benzene, 7-chloro-4-[4-methylidene-(aryl)-hydrazocarbonylquinolinyloxy-methane, 1-amino-(7-chloroquinoline)-2-[N- methylidene-aryl]-hydrazocarbonyl benzene.

INTRODUCTION

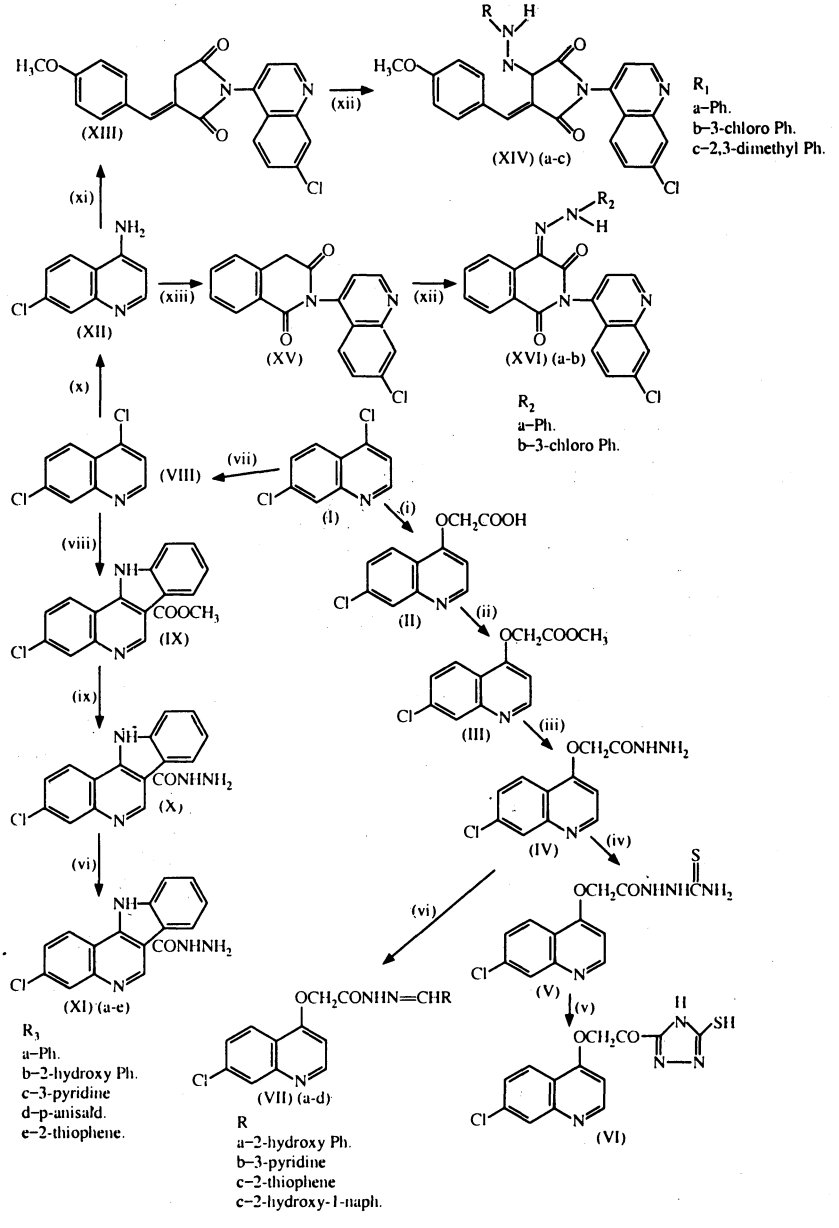
A large number of substituted hydrazides and their condensation products, including heterocyclic compounds having 5- or 6-membered rings known for various biological activities[1]. The present paper reports the synthesis of hydrazides and its condensation products from 4-hydroxy-7-chloroquinoline[2] **(I)** and 4,7-dichloroquinoline[2] **(VIII)**. With a view to synthesise the analogous compounds with possible antibacterial properties, the 7-chloro-4-quinolinyloxy acetic acid **(II)** from **I**, subsequently 7-chloro-4-quinolinyloxy methyl acetate **(III)** and 7-chloro-4-hydrazocarbonyl-quinolinyloxy methane **(IV)** were synthesised. Treatment of **IV** with potassium thiocyanate in dilute hydrochloric acid gave thiosemicarbazide derivative **(V)**. Refluxing of **V** with potassium hydroxide gave triazole derivative **(VI)**. Condensation of **IV** in ethanol with aldehydes (salicylaldehyde, pyridine-3-aldehyde, thiophene-2-aldehyde, 2-hydroxy-1-naphthaldehyde) gave the corresponding 7-chloro-4-[4-methylidine-(aryl)-hydrazocarbonyl quinolinyloxy methane **(VIIa–d)**.

Treatment of **VIII** with methyl anthranilate gave 1-amino-(7-chloroquinoline)-2-carbmethoxybenzene **(IX)**; treatment of **IX** with hydrazine hydrate gave the corresponding 1-amino-(7-chloroquinoline)-2-hydrazocarbonylbenzene **(X)**. Condensation of **X** in ethanol with aldehydes (benzaldehyde, salicyaldehyde, pyridine-3-aldehyde, *p*-anisaldehyde, thiophene-2-aldehyde) gave the corresponding 1-amino-(7-chloroquinoline)-2-[N-methylidene-aryl]hydarzocarbonyl benzene **(XIa–e)**.

From the literature survey, it showed that reactions with 4-amino-7-chloroquinoline[3] **(XII)** were not much explored. Previous workers[3] had developed a general scheme for the hydrazone dyes, which involves fusion of anhydrides with secondary amines following diazotisation reaction to afforded

hydrazone dyes. In the present work 3-[4-methoxy benzylidine]-2,5-furandione and homophthalic anhydride were used to synthesise corresponding hydrazone dyes **(XVa–c)** and **(XVIa–b)**, after fusion with 4-amino-7-chloroquinoline.

Synthetic strategy has been outlined below,



(i) $ClCH_2COOH$ (ii) CH_3OH/H_2SO_4 (iii) $NH_2NH_2{\cdot}H_2O$ (iv) KSCN/dil. HCl (v) KOH (vi) R-CHO (vii) $POCl_3$ (viii) Methyl anthranilate (ix) $NH_2NH_2{\cdot}H_2O$ (x) Phenol, NH_3 (xi) M-2,5-furandione (xii) aryldiazo chloride (xiii) Homoph. anhyd.

EXPERIMENTAL

All melting points of the compounds synthesised are uncorrected. Micro analysis of the compounds was carried out on a Colemn instrument. IR spectra (KBr) were recorded on an AMX-500 Bruker Inst. (500 MHz) using TMS as the internal standard in measurement of PMR spectra. All the compounds gave satisfactory C, H and N analysis.

7-Chloro-4-quinolinyloxy acetic acid **(II)**: A mixture of I (1.8 g, 0.001 mol), chloroacetic acid (1 g, 0.01 mol) and sodium hydroxide solution (4.5 g in 25 mL water, 0.112 mol) was heated slowly till most of water has evaporated; solid separated out was crystallised from ethanol : DMSO (1 : 1).

7-Chloro-4-quinolinyloxy methyl acetate **(III)**: A mixture of **II** (1 g), methanol (10 mL) and concentrated sulphuric acid (1 mL) was refluxed for 4 h, the reaction mixture was cooled and the separated solid was crystallised from methanol.

7-Chloro-4-hydrazocarbonyl quinolinyloxymethane **(IV)**: A mixture of **III** (2.5 g, 0.01 mol) and hydrazine hydrate (98%, 1.5 mL., 0.03 mol.) in ethanol (25 mL) was refluxed for 4 h, the solid separated was crystallised from ethanol.

7-Chloro-4-thiosemicarbazidecarbonyl quinolinyloxy methane **(V)**: A mixture of **IV** (0.5 g, 0.002 mol), potassium thiocyanate (0.8 g, 0.0008 mol) in dilute hydrochloric acid (2 mL, in 10 mL water) was refluxed for 4 h. The solid separated was crystallised from ethanol.

5-(7-Chloro-4-quinolinyloxymethane)-1,2,4-mercapto-S-triazole **(VI)**: A mixture of **V** (0.6 g, 0.002 mol) and potassium hydroxide (10%, 5 mL was heated on a steam bath for 3 h. After completion of reaction, the reaction mixture was neutralised with acetic acid and the solid separated out was crystallised from ethanol.

7-Chloro - 4-[4-methylidine - (aryl)] - hydrazocarbonyl quinolinoxymethane **(VIIa–d):** A mixture of **IV** (0.5 g, 0.002 mol) and corresponding aromatic aldehyde (0.002 mol) in ethanol was refluxed for 1 h. The solid separated out was crystallised from ethanol : DMSO (1 : 1) mixture.

1-Amino-(7-chloroquinoline)-2-carbmethoxybenzene **(IX)**: A mixture of **VIII** (2 g, 0.02 mol) and methylanthranilate (1.5 g, 0.02 mol) in ethanol (20 mL), was refluxed for 4 h. The solid separated was crystallised from ethanol.

1-Amino-(7-chloroquinoline)-2-hydrazocarbonylbenzene **(X)**: A mixture of **IX** (3 g, 0.01 mol) and hydrazine hydrate (98%, 1.5 mL, 0.03 mol) in ethanol (25 mL) was refluxed for 4 h on a steam bath. The reaction mixture was cooled to room temperature. The solid separated out was crystallised from ethanol.

1-Amino-(7-chloroquinoline)-2-[N-methylidine-aryl] hydrazocarbonylbenzene **(XIa–c)**: A mixture of **X** (0.3 g, 0.001 mol) and corresponding aromatic aldehyde (0.001 mol) in ethanol was refluxed for 1 h. The solid separated out was crystallised from ethanol : DMSO (1 : 1) mixture.

1-(7-Chloroquinoline)-3-(4-methoxybenzylidino)-pyrolidene-2,5-dione **(XIII):** A mixture of **XII** and 3-(4-methoxy benzylidiene)-2,5-furandione was heated to 180–200°C in an oil-bath for 2 h. The reaction mixture was cooled and the solid separated out was crystallised from methanol.

1-(7-Chloroquinoline-3-(4-methoxy bezylidino)-4-aryl hydarzono-pyrolidene-*2,5-dione* **(XIVa–c):** **XIII** (1 g, 0.001 mol) was dissolved in DMSO (20 mL) and the solution was cooled to 0°C. A solution of aryldiazonium chloride [corresponding aryl amine 0.002 mol, HCl (6 mL, 6 N), $NaNO_2$ (0.7 g, 0.01 mol)] at about 0–5°C was added dropwise to the solution of fused anhydride in DMSO. The solid separated out was stirred for additional 30 min and crystallised from xylene.

2-(7-Chloroquinoline)-1,3-(2H,4H)-isoquinolinedione **(XV):** A mixture of **XV** and homophthalic anhydride was heated to 180–200°C in an oil-bath for 2 h. The reaction mixture was cooled and the solid separated out was crystallised from methanol.

TABLE-1
PHYSICAL DATA OF THE PRODUCTS

Compound No.	m.p. (°C)	Colour	Yield (%)	m.f.
II	252–54	Colourless	95.00	$C_{11}H_8NO_3Cl$
III	184–85	Colourless	94.00	$C_{12}H_{10}NO_3Cl$
IV	266–67	Colourless	89.70	$C_{11}H_{10}N_3O_2Cl$
V	240–41	Light yellow	79.30	$C_{12}H_{11}N_4O_2SCl$
VI	260–62	Yellow	82.30	$C_{12}H_9N_4OSCl$
VIIa	> 280	Colourless	79.80	$C_{18}H_{14}N_3O_3Cl$
VIIb	228–29	Colourless	77.30	$C_{17}H_{13}N_4O_2Cl$
VIIc	210–12	Colourless	75.77	$C_{16}H_{12}N_3O_2SCl$
VIId	> 280	Colourless	72.36	$C_{22}H_{17}N_3O_3Cl$
IX	230–32	Colourless	81.30	$C_{17}H_{13}N_2O_2Cl$
X	218–20	Colourless	81.70	$C_{16}H_{13}N_4OCl$
XIa	282–83	Colourless	79.30	$C_{23}H_{17}N_4OCl$
XIb	259–60	Colourless	82.50	$C_{23}H_{17}N_4O_2Cl$
XIc	140–42	Colourless	74.30	$C_{22}H_{16}N_5OCl$
XId	144–45	Light yellow	82.47	$C_{23}H_{17}N_4O_2Cl$
XIe	232–33	Light yellow	75.77	$C_{21}H_{15}N_4OSCl$
XIII	223–24	Brownish red	68.32	$C_{21}H_{16}N_2O_3Cl$
XIVa	> 280d	Brownish red	58.36	$C_{27}H_{20}N_4O_3Cl$
XIVb	> 280d	Brownish red	52.12	$C_{27}H_{19_2}N_2O_2Cl$
XIVc	> 280d	Brownish red	59.22	$C_{29}H_{24}N_4O_3Cl$
XV	245–46	Brownish red	68.36	$C_{18}H_{10}N_2O_2Cl$
XVIa	256–60	Brownish red	53.58	$C_{24}H_{15}N_4O_2Cl$
XVIb	> 280d	Brownish red	55.70	$C_{24}H_{14}N_4O_2Cl_2$

4 - (Arylhydrazono) - 2 - (7-chloroquinoline) - 1,3-(2H,4H) - isoquinolinedione **(XVIa–b):** **XV** (1 g, 0.001 mol) was dissolved in acetone (20 mL) and the solution was cooled to 0°C. A solution of aryldiazonium chloride [corresponding

aryl amine 0.002 mol, HCl (6 mL, 6 N), $NaNO_2$ (0.7 g, 0.01 mol)] at about 0–5°C was added dropwise to the solution of fused anhydride in acetone. The solid separated out was stirred for additional 30 min. and crystallised from xylene.

RESULTS AND DISCUSSION

The IR spectrum of 7-chloro-4-quinolinyloxy acetic acid **(II)** showed the absorption band in the region of 1730–1700 cm^{-1} due to carbonyl group. The IR spectra of ester **(III)** showed the absorption band of 1750–1730 cm^{-1} due to ester carbonyl group. The IR spectra of hydrazide **(IV)** showed the absorption band in the region of 3350–3200 cm^{-1} due to —NH stretching. The amido carbonyl group showed the absorption band in the region of 1660–1640 cm^{-1}.

The IR spectra of thiosemicarbazide derivative **(V)** showed the absorption band in the region of 3300–3280 cm^{-1} due to —NH stretching frequency. The amido carbonyl group showed the absorption band in the region of 1700–1680 cm^{-1}. The IR spectra of mercapto-S-triazole derivative **(VI)** showed the absorption in the region of 3250–3230 cm^{-1} due to —NH stretching. The absence of absorption in the region of 1700–1610 cm^{-1} due to carbonyl group, which was present in the starting material **V**, confirms that cyclisation has taken place.

The IR spectra of hydrazones **VIIa–d** showed the absorption band in the region of 3230–3220 cm^{-1} due to —NH stretching frequency. A moderately strong band at 1690–1660 cm^{-1} in the spectra of all hydrazones was attributed to the stretching frequency of —C=O group. Hydrazones exibit —C=N stretching frequency at 1620–1600 cm^{-1}. The NMR spectra showed a sharp singlet in the region of δ 3.5–4.0 ppm of two protons (—OCH_2) group. The multiplet in the region of δ 7.2–7.6 ppm was due to aromatic protons. A sharp singlet was observed at δ 8.0–8.3 ppm, attributed to one methylidene proton and a singlet at δ 8.8–8.9 ppm., attributed to the amido carbonyl group (—CONH—).

The IR spectra of **X** showed the absorption band in the region of 3200–3180 cm^{-1} due to —NH stretching. The cyclic carbonyl group showed absorption band in the region of 1680–1670 cm^{-1}. The IR spectra of hydrazones **XI**(a–e) showed the absorption band in the region of 3250–3220 cm^{-1} due to —NH stretching frequency. A moderately strong band at 1660–1640 cm^{-1} in the spectra of all hydrazones was attributed to the stretching frquency of —C=O group. Hydrazones exibit —C=N stretching frequency at 1620–1600 cm^{-1}. The NMR spectra showed multiplet in the region of δ 7.0–7.9 ppm. was due to the aromatic proton. Sharp singlets at δ 8.1 ppm and at δ 8.3 ppm were attributed to =CH proton and —CONH group.

The IR spectra of hydrazone dyes **XV**a–c and **XVIa–b** showed absorption band in the region of 3240–3220 cm^{-1} due to —NH stretching frequency. The cyclic carbonyl groups of —CO—N—CO— linkage showed absorption band in the region of 1730–1700 cm^{-1} and 1660–1630 cm^{-1}. The NMR spectra showed multiplet for aromatic protons in the region of δ 7.0–8.2 ppm. The singlets at δ 8.3 ppm. and δ 10.7 ppm. were attributed to methylidene proton and amino group proton respectively.

All the compounds were subjected to MIC (Minimum Inhibitory Concentration) Test. The stains of the following bacteria were used. *Staphylococcus aureus*, *Escheriachia coli*, *Salmonella typhi* and *Klebsiella pneumoniae*, and none of them showed any significant antibacterial activity.

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