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Synthesis of 8-[2-(amino-oxy) Ethylamino]-6-Methoxy Quinoline Hydrohalide and Related Compounds as Potential Antimalarials

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Some of 8-Aminoquinolines containing amino-oxy group have been prepared for the first time by hydrolysis of their precursor phthalimidoxy compounds and both the series screened for cardiovascular activity.

INTRODUCTION

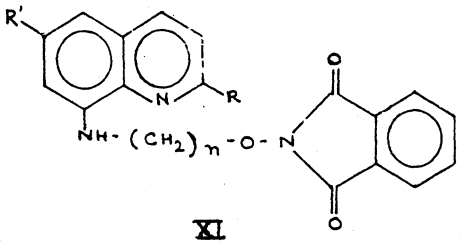
Malaria is the most widespread of all infections diseases, at least one-third of the earth's population is exposed to infection, with its disabling and lethal effects. Ceaseless efforts are being made by researchers to find out safer, more effective and economic drugs. The research in these fields is also necessitated by the fact that the malarial parasite (*Plasmodium*) become drug resistant over a period of time and the drug may become quite ineffective. A case in point is the resistance of *Plasmodium falsiparum* to chloroquin in several parts of the world.[1] A single drug may not be tolerated by all the people uniformly and different physical conditions may require different kinds of drug.

A small change in structure of the compound may either enhance or diminish the pharmacological activity, *e.g.*, in case of pamaquin, replacement of $—OCH_3$ by $—CH_3$ completely reduces the antimalarial activity.[2] Amino-oxy-containing compounds show diverse pharmacological activities[3, 4] as anticonvulsant, anti-inflammatory, analgesic, anorexigenic, antibacterial, antifungal, antibiotic, tuberculostatic, herbicidal, muscle relaxant, antimalarial and others. Many aminoquinoline derivatives are reported[5] to exhibit antimalarial activity.

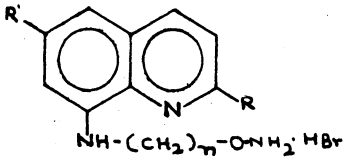
It was thought worthwhile to synthesize some compounds having —O—NH— group at the end of side chain instead of $—NH_2$ group in quinoline.

RESULTS AND DISCUSSION

This idea stimulated us to synthesize 8-[2-(amino-oxy) ethylamino]-6-methoxy quinoline and related compounds (XIIa–f) from its parental phthalimidoxy compounds (N-2[(6-methoxy-8-quinoly)amino]ethoxy)phthalimide and corresponding ones (XIa–f) as possible anti-malarials.



XI

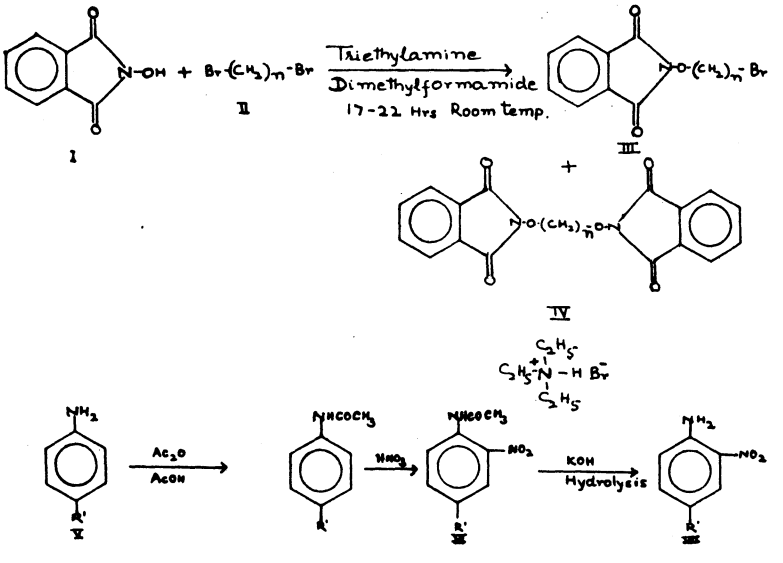


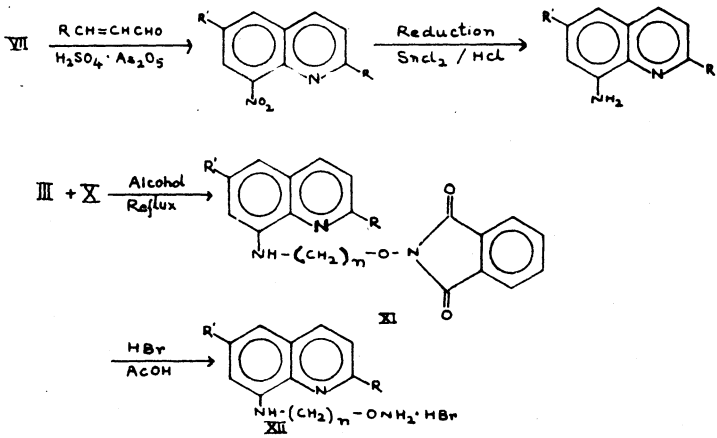
XII

where

R^1	R	n	
—OCH_3	H	2	—a
—OCH_3	H	3	—b
—OCH_3	H	4	—c
—OCH_3	CH_3	2	—d
—OCH_3	CH_3	3	—e
—OCH_3	CH_3	4	—f
—Cl	H	2	—g
—Cl	H	4	—h
—Cl	CH_3	2	—i

Following reaction sequences were used to synthesize the above said compounds:





Phthalimidoxy-alkyl bromides (III) were prepared from N-hydroxy phthalimide(I) and dibromoalkanes (II) by using method of Bauer and Suresh.[6] Bis phthalimidoxyalkanes (IV) was also obtained as byeproduct.

2-Nitro substituted anilines were prepared by procedure of Lothrop.[7] Substituted 8-nitroquinoline derivatives were prepared[8] by treating corresponding aniline compound with unsaturated aldehydes namely acrolein and crotonaldehyde. Hydrolysis of acetyl compound was carried out in Claisen alkali. Reduction of nitro group in (IX) was carried out with tin chloride and hydrochloric acid or in some cases with Fe powder in dil. acetic acid by the procedure described.[9]

Condensation of 8-amino quinolines with ω-phthalimidoxy bromides to give (XIa–f) was carried out by refluxing in absolute alcohol for variable time in presence of anhydrous potassium carbonate.

Hydrolysis of phthalimidoxy compound with aminoquinoline was achieved by boiling in an equal mixture (by volume) of acetic acid and hydrobromic acid. Cold mixture was filtered to remove phthalic acid. The filtrate was evaporated under reduced pressure. Residue was washed with petroleum ether and crystallised from methanol-chloroform mixture.

All the compounds were tested for antimalarial activity. Out of these 8 - [2 - (amino - oxy)butyl]amino - 2 - methyl - 6 - methoxy quinoline monohydrobromide was found to possess significant activity.[10]

Infrared spectra

Peak at 3175 cm^{-1} is due to ν(NH) stretch of —NH_2 which is supported by the corresponding —NH_2 deformation absorption at 1600 cm^{-1}.

Intense broad peak in the region 3000–2700 cm^{-1} shows the characteristic aliphatic ν(C—H) vibration of CH_3 (2960 cm^{-1}) and CH_2 (2950 cm^{-1}) typical of the compounds having structure and is merged with the —N stretching mode in this region.

The absorption in the region 1600–1530 cm^{-1} and 1500–1430 cm^{-1} clearly indicates the presence of the heterocyclic ring. The strong band at 1450 cm^{-1} is the characteristic of symmetrical CH_3 umbrella deformation of —OCH_3. Four

adjacent hydrogen of aromatic substituted system is obvious at 750 cm^{-1} while two adjacent hydrogen of unsymmetical trisubstituted aromatic is shown by the peak of 840 cm^{-1}.

EXPERIMENTAL

All the melting points are uncorrected; purity of compounds was tested by TLC and other usual methods.

Preparation of phthalimidoxy alkyl bromides

Method of Bauer and Suresh[6] has been used.

Preparation of substituted quinoline derivatives

2-Nitro-4-methoxy aniline was prepared by method of Horning (Organic Synthesis, Collective Volume III, p. 661). 2-Methyl-6-methoxy-8-nitroquinoline was prepared by method of Mathur and Robinson[11]. Nitroquinoline derivatives were reduced to corresponding amino derivatives by method of Smith.

Preparation of phthalimidoxy derivatives of substituted quinolines

ω-Phthalimidoxy alkyl bromide (0.01 mol) and substitued 8-aminoquinolines (0.01 mol) were dissolved in absolute alcohol (varying volume) and refluxed on a water bath for $\frac{1}{2}$ h. Potassium carbonate (0.01 mol) was added slowly in approx. 10 min. It was then refluxed for 9 to 30 h. Mixture was filtered hot. Curdy white precipitate was obtained on cooling the solution in ice. Product was recrystallised in different solvents. Time for reflux is shown in Table-1.

TABLE-1
ANALYTICAL AND PHYSICAL DATA OF SYNTHESISED COMPOUNDS (XIa–i)

S.No.	Mol. formula	Mol. Wt.	Solvent refluxed	Reflux time (h)	Solvent cryst.	m.p. (°C)	Yield (%)
XIa	$C_{20}H_{17}N_3O_4$	363	Ethanol	9	EtOH	255–56	69
XIb	$C_{21}H_{19}N_3O_4$	377	Alcohol	6	EtOH+ MeOH	248–49	66
XIc	$C_{22}H_{21}N_3O_4$	391	Abs. Alc.	15	EtOH+ MeOH	259–60	75
XId	$C_{21}H_{19}N_3O_4$	377	Dry Alc.	6.5	C_6H_6	219–20	42
XIe	$C_{22}H_{21}N_3O_4$	391	Dry Alc.	5.5	C_6H_6	209–11	53
XIf	$C_{23}H_{23}N_3O_4$	405	Abs. Alc.	26	C_6H_6	240–41	57
XIg	$C_{19}H_{14}N_3O_3Cl$	367.5	Abs. Alc.	21	EtOH	191–92	29
XIh	$C_{21}H_{18}N_3O_3Cl$	395.5	Abs. Alc.	18	i-PrOH	201–203	36
XIi	$C_{20}H_{16}N_3O_3Cl$	381.5	Dry Alc.	7	MeOH	222	22

TABLE-2
ANALYTICAL AND PHYSICAL DATA OF SYNTHESISED COMPOUNDS (XIa–i)

S. No.	Mol. Formula	Mol. wt.	Solvent cryst.	m.p. (°C)	Yield (%)
XIIa	$C_{12}H_{16}N_3O_2Br$	313	MeOH + $CHCl_3$	225–27	41
XIIb	$C_{13}H_{18}N_3O_2Br$	327	MeOH + $CHCl_3$	231–32	62
XIIc	$C_{14}H_{20}N_3O_2Br$	341	Hot water	237–38	65
XIId	$C_{13}H_{18}N_3O_2Br$	327	MeOH + H_2O	246–48	42
XIIe	$C_{14}H_{20}N_3O_2Br$	341	MeOH	236	39
XIIf	$C_{15}H_{22}N_3O_2Br$	355	MeOH	227–30	36
XIIg	$C_{11}H_{13}N_3OClBr$	317.5	Hot water	251–53	49
XIIh	$C_{13}H_{17}N_3OClBr$	345.5	Hot water	255–56	33
XIIi	$C_{12}H_{15}N_3OClBr$	331.5	MeOH + $CHCl_3$	265–66	25

Percentage composition have been confirmed by elemental analysis.

Hydrolysis of phthalimidoxy quinolyl derivatives

Above compound (0.02 mol) was boiled in a mixture of 47% HBr (25 mL) and glacial acetic acid (25 mL) for 5 min. On cooling, the phthalic acid obtained was filtered. The filtrate on evaporation *in vacuo* yielded a dirty white solid. Solvent of recrystallisation and the physical and analytical data of compounds are presented in Table-2.

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