Synthesis of (Heterocyclicamino)aminoalkylnaphthols and Reduced Tetrahydro Derivatives for Possible Antimalarial Activity

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Abstract □ New structures of (heterocyclicamino)aminoalkylnaphthols and reduced derivatives were synthesized in a rational attempt to introduce new compounds that may have antimalarial activity.

Keyphrases □ (Heterocyclicamino)aminoalkylnaphthols and reduced tetrahydro derivatives—synthesis as possible antimalarial agents □ Aminoalkylnaphthols (heterocyclicamino)—synthesis as possible antimalarial agents □ Antimalarial agents, potential—synthesis of (heterocyclicamino)aminoalkylnaphthols and reduced tetrahydro derivatives

Drugs of the aminoquinoline type have long been known for their sporontocidal and gametocidal action against all plasmodia of human malaria. The value of 4-aminoquinoline compounds rests on their activity against the asexual erythrocytic parasites of all species. Of this class of drugs, the most valuable are chloroquine (1) and amodiaquine (2); both are active for the treatment of acute malaria and for suppression of infection. However, they fail to act on the exoerythrocytic stages of malaria parasites and, therefore, do not prevent relapses of infection. Also, they have no sporontocidal action and, in particular, do not affect the gametocytes of the *falciparum* strain.

DISCUSSION

Another group of compounds which might be interpreted as antagonists of the K vitamins and have considerable antimalarial activity consists of 2-alkyl-3-hydroxy-1,4-naphthoquinone derivatives; they appear to act by inhibiting the respiration of plasmodia (3). Generally, naphthoquinone antimalarials are strong inhibitors of respiratory systems. There exists a close parallel relationship between antimalarial and antirespiratory activity for several quinones. Studies (4) revealed that a naphthoquinone must have a hydrophilic–lipophilic balance for maximal antimalarial activity. Hydroxylation of the side chain in these systems produced a hydrophilic shift; therefore, increasing the size of the hydrocarbon part of the chain would compensate for the loss in activity due to it.

Thus, the development of new agents that would structurally include systems of the naphthoquinone type, beside the nitrogen heterocyclic ones, might be useful for their possible application as antimalarials. The resistance of parasites to nitrogen heterocyclic compounds should not imply resistance to compounds of the quinonoid type, because both are probably acting through different mechanisms. Such agents that contain the structural features of both 4-aminoquinoline and hydroxynaphthalene derivatives might be expected to exhibit the antimalarial properties of both types.

These considerations suggested the synthesis of compounds including naphtholic Mannich bases or their tetrahydro forms, as side chains, attached to nitrogen heterocyclics of 4-aminoquinoline and 9-aminoacridine systems.

Both 4-amino-1-naphthol (5) and its reduced tetrahydro form (4-amino-1-hydroxy-5,6,7,8-tetrahydronaphthalene) (6) could undergo chemical oxidation to give the corresponding quinonoid forms.

Reaction of 4-nitro-1-naphthol (7) with formaldehyde and diethylamine or piperidine gave 2-diethylaminomethyl-4-nitro-1-naphthol (I*e*) and 2-piperidylmethyl-4-nitro-1-naphthol (I*f*).

Catalytic reduction of I*e* and I*f* gave the corresponding amines. Upon condensation of the amines with 4,7-dichloroquinoline, the products were I*a* and I*b*, respectively; with 6,9-dichloro-2-methoxyacridine, I*c* and I*d* were obtained.

Treatment of 4-acetamino-5,6,7,8-tetrahydro-1-naphthol (II*g*) (8) with paraformaldehyde and diethylamine or piperidine gave 4-acetamino-2-diethylaminomethyl-5,6,7,8-tetrahydro-1-naphthol (II*e*) and 4-acetamino-2-piperidylmethyl-5,6,7,8-tetrahydro-1-naphthol (II*f*) in fairly good yields. Hydrolysis of II*e* and II*f* and then condensation of the free amines with 4,7-dichloroquinoline gave II*a* and II*b*; with 6,9-dichloro-2-methoxyacridine, the products were II*c* and II*d*, respectively.

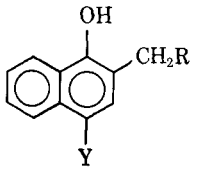
EXPERIMENTAL[1]

2-Diethylaminomethyl-4-nitro-1-naphthol (I*e*)—A mixture of 5.7 g. (0.03 mole) of 4-nitro-1-naphthol and 3 ml. (0.03 mole) of diethylamine in 20 ml. absolute ethanol was thoroughly shaken under cooling. To this mixture was added 2.4 ml. (0.03 mole) of formaldehyde solution (37%) with shaking for another few minutes. The formed yellow precipitate was filtered off and recrystallized from absolute ethanol (using charcoal) to give 6.6 g. (81% yield) of I*e* as orange crystals, m.p. 157–158°.

Anal.—Calc. for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.62; N, 10.22. Found: C, 65.46; H, 6.14; N, 10.19.

Catalytic Reduction of I*e*—A suspension of 2.7 g. (0.01 mole) of I*e* in 100 ml. of ethanol was shaken with 0.1 g. of 5% palladized charcoal at room temperature. Hydrogen was added at 3 atm. until the absorption of hydrogen ceased. The catalyst was removed and washed with 10 ml. of absolute ethanol, and the combined solvent was distilled. The residual amine was obtained as a brown mass, which could not be recrystallized in trials with different solvents.

The salts, hydrochloride and oxalate, were hygroscopic. This intermediate amine could be successfully condensed with the desired chloroheterocycles.



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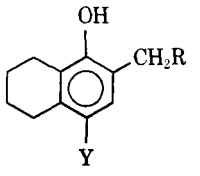

II

I*a*: Y = 7-chloro-4-quinolylamino, R = $N(C_2H_5)_2$
I*b*: Y = 7-chloro-4-quinolylamino, R = piperidyl
I*c*: Y = 6-chloro-2-methoxy-9-acridylamino, R = $N(C_2H_5)_2$
I*d*: Y = 6-chloro-2-methoxy-9-acridylamino, R = piperidyl
I*e*: Y = NO_2, R = $N(C_2H_5)_2$
I*f*: Y = NO_2, R = piperidyl
I*g*: Y = NH_2, R = piperidyl
II*a*: Y = 7-chloro-4-quinolylamino, R = $N(C_2H_5)_2$
II*b*: Y = 7-chloro-4-quinolylamino, R = piperidyl
II*c*: Y = 6-chloro-2-methoxy-9-acridylamino, R = $N(C_2H_5)_2$
II*d*: Y = 6-chloro-2-methoxy-9-acridylamino, R = piperidyl
II*e*: Y = $NHCOCH_3$, R = $N(C_2H_5)_2$
II*f*: Y = $NHCOCH_3$, R = piperidyl
II*g*: Y = $NHCOCH_3$, R = H
II*h*: Y = NH_2, R = $N(C_2H_5)_2$
II*i*: Y = NH_2, R = piperidyl

[1] All melting points were determined by the use of a Gallenkamp electric melting-point apparatus and are uncorrected. Microanalyses were performed by the microanalytical laboratory, National Research Center, Cairo, U.A.R., and Spang Microanalytical Laboratory, Ann Arbor, Mich.

4-(7-Chloro-4-quinolylamino)-2-diethylaminomethyl-1-naphthol (Ia)—A mixture of 6.4 g. (0.025 mole) of the free amine obtained through the reduction of Ie, 4.95 g. (0.025 mole) of 4,7-dichloroquinoline in 300 ml. absolute ethanol, and 6 ml. concentrated HCl was refluxed for 6 hr. on a steam bath. The mixture was cooled and neutralized with sodium carbonate solution (10%). The formed brown precipitate was filtered, washed with water, and dried to give 7.2 g. (72% yield) of Ig. This was analyzed in the form of its crystallizable picrate (from acetone), m.p. 234–236°.

Anal.—Calc. for $C_{30}H_{27}ClN_6O_8$: C, 56.72; H, 4.25; N, 13.24. Found: C, 56.53; H, 4.32; N, 13.56.

4-(6-Chloro-2-methoxy-9-acridylamino)-2-diethylaminomethyl-1-naphthol (Ic)—A mixture of 4.8 g. (0.08 mole) of the free amine obtained through the reduction of Ie, 4.2 g. (0.08 mole) of 6,9-dichloro-2-methoxyacridine in 400 ml. absolute ethanol, and a few drops of concentrated HCl was refluxed for 10 hr. over a steam bath. The ethyl alcohol was removed by distillation, and the residual hydrochloride of Ic was washed with ether. This was treated with charcoal and recrystallized from glacial acetic acid, giving 6.4 g. (76% yield) of Ic as yellow crystals, m.p. >300°.

Anal.—Calc. for $C_{29}H_{28}ClN_3O_2 \cdot HCl \cdot H_2O$: C, 64.50; H, 5.79; Cl, 13.13; N, 7.78. Found: C, 64.81; H, 5.55; Cl, 13.20; N, 7.48.

2-Piperidinomethyl-4-nitro-1-naphthol (If)—A mixture of 5.7 g. (0.03 mole) of 4-nitro-1-naphthol and 3 ml. (0.03 mole) of piperidine in 20 ml. absolute ethanol was thoroughly shaken under cooling for a few minutes. To this mixture was added 2.4 ml. (0.03 mole) of formaldehyde solution (37%) with good shaking. The formed yellow precipitate was filtered off and then recrystallized from ethanol after treatment with charcoal, giving 5.9 g. (69% yield) of If as orange crystals, m.p. 189–190°.

Anal.—Calc. for $C_{16}H_{18}N_2O_3$: C, 67.19; H, 6.35; N, 9.79. Found: C, 67.28; H, 6.50; N, 9.71.

2-Piperidinomethyl-4-amino-1-naphthol (Ig)—A mixture of 3.8 g. (0.01 mole) of If in 100 ml. of absolute ethanol was shaken with 0.1 g. of 5% palladized charcoal at ordinary temperature and 3 atm. pressure until the absorption of hydrogen ceased. The catalyst was removed and then washed with 10 ml. absolute alcohol. Dry hydrogen chloride gas was immediately passed into the combined alcoholic solution. The formed white precipitate was filtered off, washed with ether, and recrystallized from ethanol, giving 3 g. (78% yield) of Ig as dihydrochloride monohydrate, m.p. 246° dec.

Anal.—Calc. for $C_{16}H_{20}N_2O \cdot 2HCl \cdot H_2O$: C, 55.38; H, 6.98; N, 8.07. Found: C, 55.46; H, 6.82; N, 8.10.

4-(7-Chloro-4-quinolylamino)-2-piperidinomethyl-1-naphthol (Ib)—A mixture of 0.4 g. (0.025 mole) of Ig, 4.9 g. (0.025 mole) of 4,7-dichloroquinoline in 200 ml. ethanol, and a few drops of concentrated HCl was refluxed for 6 hr. on a steam bath. The solvent was removed by distillation. The dried residue was treated with ether and filtered. The hydrochloride product of Ib was then treated with charcoal and recrystallized from a methanol–benzene mixture, giving 4.2 g. (40% yield) of Ib, m.p. 270° dec.

Anal.—Calc. for $C_{25}H_{24}ClN_3O \cdot HCl \cdot H_2O$: Cl, 15.05; N, 8.92. Found: Cl, 15.14; N, 8.88.

4-(6-Chloro-2-methoxy-9-acridylamino)-2-piperidinomethyl-1-naphthol (Id)—A mixture of 2.6 g. (0.01 mole) of Ig and 2.8 g. (0.01 mole) of 6,9-dichloro-2-methoxyacridine was treated in the same way as described for the preparation of Ic. The hydrochloride salt of Id was collected and washed with ether. It weighed 2.2 g. (41% yield) and was recrystallized from ethanol after treatment with charcoal, m.p. > 360°.

Anal.—Calc. for $C_{30}H_{28}ClN_3O_2 \cdot HCl \cdot H_2O$: C, 65.28; H, 5.67; Cl, 12.85. Found: C, 65.34; H, 5.55; Cl, 12.65.

2-Diethylaminomethyl-4-acetamino-5,6,7,8-tetrahydro-1-naphthol (IIe)—A mixture of 4.7 g. (0.025 mole) of IIg, 2 g. (0.027 mole) of diethylamine, and 0.8 g. (0.008 mole) of paraformaldehyde in 100 ml. absolute ethanol was refluxed on a steam bath for 10 hr. The reaction mixture was filtered from the insoluble materials, concentrated, and allowed to cool. Upon dilution with water, a white precipitate formed. This was collected and recrystallized from aqueous ethanol to give 5.5 g. (72% yield) of IIe, m.p. 156–157°.

Anal.—Calc. for $C_{17}H_{26}N_2O_2$: C, 70.80; H, 8.96; N, 10.21. Found: C, 71.05; H, 9.13; N, 10.21.

2-Diethylaminomethyl-4-amino-5,6,7,8-tetrahydro-1-naphthol (IIh)—A solution of 5.5 g. (0.02 mole) of IIe and 25 ml. of concentrated HCl in 100 ml. absolute ethanol was refluxed on a steam bath for 10 hr. The solvent was distilled under suction, and the viscous residue was basified with ammonium hydroxide and extracted with ether. The ethereal layer was washed with water, dried over anhydrous magnesium sulfate, and then distilled. Trials to recrystallize the residual free amine, IIh, were unsuccessful; its hydrochloride and oxalate salts were hygroscopic. The amino compound was used without further treatment in the following steps.

4-(7-Chloro-4-quinolylamino)-2-diethylaminomethyl-5,6,7,8-tetrahydro-1-naphthol (IIa)—A mixture of 2.9 g. (0.01 mole) of IIh, 2 g. (0.01 mole) of 4,7-dichloroquinoline, and a few drops of concentrated HCl in 25 ml. absolute ethanol was refluxed for 10 hr. The reaction mixture was cooled; its volume was doubled with water and then poured portionwise over a cold solution of aqueous ammonia under strong stirring. The formed buff precipitate was filtered, washed with water, and dried to give 4.5 g. (90% yield) of IIa upon recrystallization from cyclohexane, m.p. 214–215°.

Anal.—Calc. for $C_{24}H_{28}ClN_3O$: C, 70.32; H, 6.83; Cl, 8.66; N, 10.27. Found: C, 70.24; H, 7.15; Cl, 8.25; N, 10.06.

4-(6-Chloro-2-methoxy-9-acridylamino)-2-diethylaminomethyl-5,6,7,8-tetrahydro-1-naphthol (IIc)—A mixture of 4.8 g. (0.08 mole) of IIe, 4.2 g. (0.08 mole) of 6,9-dichloro-2-methoxyacridine in 300 ml. absolute ethanol, and a few drops of concentrated HCl was refluxed for 10 hr. Upon cooling, a yellow precipitate formed; this was filtered off, washed with alcohol, and recrystallized from ethanol, giving 6.4 g. (76% yield) of the hydrochloride of IIc, m.p. > 300°.

Anal.—Calc. for $C_{29}H_{32}ClN_3O_2 \cdot HCl \cdot H_2O$: C, 64.01; H, 6.49; Cl, 13.03; N, 7.72. Found: C, 64.04; H, 6.32; Cl, 13.37; N, 7.55.

2-Piperidinomethyl-4-acetamino-5,6,7,8-tetrahydro-1-naphthol (IIf)—The same procedure as described for IIe was applied using piperidine. The formed white precipitate was filtered and dried to give IIf (67% yield). It was recrystallized from an ethanol–hexane mixture, m.p. 164–166°.

Anal.—Calc. for $C_{18}H_{20}N_2O_2$: C, 71.51; H, 8.69; N, 9.27. Found: C, 71.44; H, 8.80; N, 8.80.

2-Piperidinomethyl-4-amino-5,6,7,8-tetrahydro-1-naphthol (IIi)—This was obtained through hydrolysis of IIf, similar to the procedure described for the preparation of IIh. This intermediate amine was used without further treatment for condensation reactions in the next steps.

4-(7-Chloro-4-quinolylamino)-2-piperidinomethyl-5,6,7,8-tetrahydro-1-naphthol (IIb)—A mixture of 4.9 g. (0.025 mole) of 4,7-dichloroquinoline, 6.5 g. (0.025 mole) of IIi in 200 ml. ethanol, and a few drops of concentrated HCl was refluxed for 10 hr. The solvent was distilled under suction until dry. The residue was treated with *n*-hexane, filtered, and washed with ether. The white residue obtained was recrystallized from methanol–ethyl acetate to give 4.4 g. of the hydrochloride of IIb (42% yield), m.p. 233° dec.

Anal.—Calc. for $C_{25}H_{28}ClN_3O \cdot HCl \cdot H_2O$: Cl, 14.91; N, 8.83. Found: Cl, 14.62; N, 8.88.

4-(6-Chloro-2-methoxy-9-acridylamino)-2-piperidinomethyl-5,6,7,8-tetrahydro-1-naphthol (IId)—A mixture of 1.3 g. (0.005 mole) of IIi, 1.4 g. (0.005 mole) of 6,9-dichloro-2-methoxyacridine in 20 ml. absolute ethanol, and a few drops of concentrated HCl was refluxed for 10 hr. Upon cooling, the formed yellow precipitate was filtered off, washed with alcohol, and recrystallized from ethanol to give 1.2 g. of the hydrochloride of IId (47% yield), m.p. > 300° dec.

Anal.—Calc. for $C_{30}H_{32}ClN_3O_2 \cdot HCl \cdot H_2O$: C, 64.81; H, 6.35; Cl, 12.75; N, 7.56. Found: C, 64.81; H, 6.55; Cl, 12.75; N, 7.48.

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Determination of Nifurpipone in Urine

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Abstract □ Nifurpipone (5-nitrofuraldehyde-*N'*-methylpiperazinoacetylhydrazone) in urine was selectively adsorbed and eluted from cationic resin with methanolic ammonium hydroxide solution. The drug in the eluate was determined colorimetrically or spectrophotometrically.

Keyphrases □ Nifurpipone—isolation from urine, analysis □ 5-Nitrofuraldehyde-*N'*-methylpiperazinoacetylhydrazone—isolation from urine, analysis □ Ion-exchange chromatography—analysis of nifurpipone in urine

5-Nitrofuraldehyde-*N'*-methylpiperazinoacetylhydrazone (nifurpipone, I), a nitrofuran derivative, was synthesized and shown to be a useful antibacterial agent in urinary tract infections (1–3). An analytical procedure is needed to analyze this drug in the urine for studying the urinary excretion of the drug. Conklin and Hollifield (4, 5) used nitromethane to extract nitrofurantoin (or furazolidone), without extraction of its metabolite(s), from urine and alkalized the extract to produce a visible color. Chloroform was shown to be the more effective solvent for extraction of nifurpipone, but all attempts to obtain satisfactory recoveries from urines containing usual clinical amounts of the drug were unsuccessful.

The colorimetric method proposed by Buzard *et al.* (6) for determination of nitrofurans in plasma was based on the formation and colorimetric estimation of 5-nitro-2-furaldehyde phenylhydrazone. To overcome the interference in the assay of nitrofurantoin in urine, Bender *et al.* (7) placed urine samples on an activated clay[1]–diatomaceous earth[2] mixture to separate the drug from interfering pigments and then applied the colorimetric method of Buzard *et al.* (6). This technique required selected and standardized adsorption material, especially the activated clay. Furthermore, during our work the columns ran so slowly that they had to be discarded frequently.

It was found that because of the aminic characteristics of nifurpipone, it could be adsorbed on a cation-exchange resin and could be eluted from the resin with diluted aqueous methanolic ammonium hydroxide solution. The present paper describes a procedure for analysis of nifurpipone added to urine and from urine collected from subjects following a single oral administration of 100 mg. of the drug.

I

EXPERIMENTAL

Materials—Nifurpipone is a yellow powder which melts with decomposition at 167–168°. It is very soluble in methanol and chloroform; soluble in ethanol, acetone, and benzene; and insoluble in ethyl ether. Its solubility in water is 0.2%. The UV spectrum of nifurpipone in water shows two maximum peaks at 360 and 253 nm. The resin selected[3] was chromatographic grade. All other chemicals and reagents used were analytical or reagent grade.

Methods—A glass chromatographic column (20 × 1.5 cm.) was filled with 2.5 ml. of the resin and washed with 100 ml. of water.

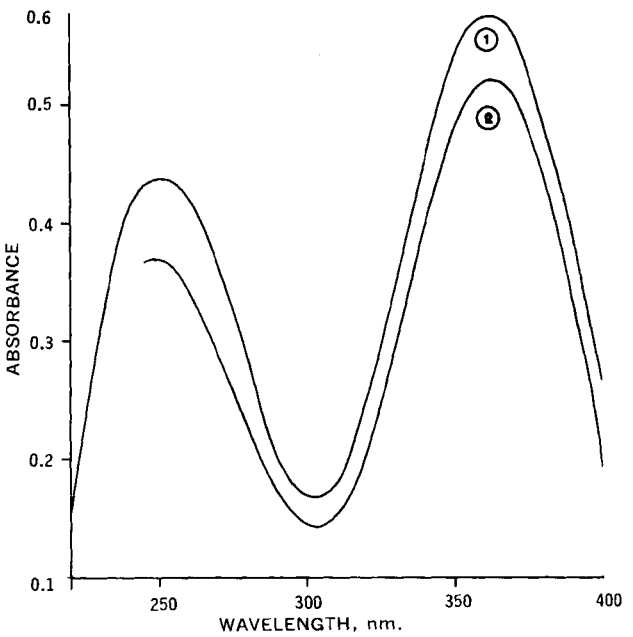

Figure 1—*Spectrophotometric curves. Key: 1, pure nifurpipone (10 mg./l.); and 2, nifurpipone from a urine sample.*

[1] Filtrol.
[2] Celite.

[3] Amberlite GC 50 (H^+), type I (100–120 mesh), Rohm and Haas Co.