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1,5-Naphthyridines. Synthesis of 7-Chloro-4-(4-diethylamino-1-methylbutylamino)-2-methoxy-1,5-naphthyridine and Related Compounds (1)

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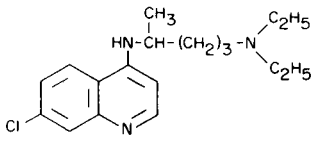
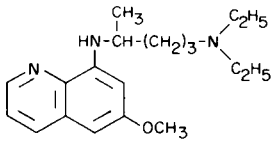
The synthesis of 7-chloro-4-(4-diethylamino-1-methylbutylamino)-2-methoxy-1,5-naphthyridine, a compound which incorporates the structure of both chloroquine (a schizontocidal drug) and pamaquine (a gametocytocidal drug), has been carried out. In addition, two structurally related derivatives, the "5-azachloroquine" and the "5-azapamaquine," have also been obtained by multi-step syntheses. "5-Azachloroquine" possesses good antimalarial activity against *Plasmodium berghei*. The compound was also found to be less toxic than the known 4-aminoquinoline and 8-aminoquinoline antimalarial drugs.

Among the known antimalarial drugs, chloroquine (I) and pamaquine (II) were found to act at different stages in the life cycle of malaria parasites. Chloroquine and other related 4-aminoquinoline derivatives are schizontocidal drugs which act at the asexual erythrocytic stage of the parasites, whereas pamaquine and related 8-aminoquinolines are gametocytocidal drugs which act against the secondary exo-erythrocytic stages and destroy sexual forms of human malaria parasites. The latter can also prevent or inhibit the development of oöcysts in mosquitoes (*i.e.* sporontocides) (2).

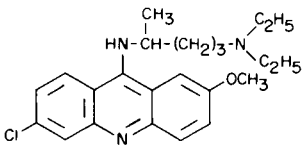


I

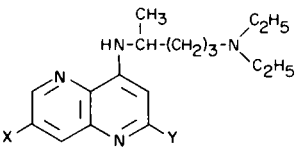


II

One of the many objectives of malaria chemotherapists is to search for an antimalarial drug that is both a schizontocide and a gametocytocide. As a part of our general program in the continued search for new antimalarial agents, an attempt was made to design and prepare such compounds, incorporating the structural features of both chloroquine and pamaquine. Although quinacrine [III, 6-chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxyacridine] possesses all the functional groups of chloroquine and pamaquine, it is actually a derivative of 4-aminoquinoline rather than a derivative of 8-aminoquinoline. Hence, compound III is only a schizontocidal drug (2). Therefore, the synthesis of 7-chloro-4-(4-diethylamino-1-methylbutylamino)-2-methoxy-1,5-naphthyridine (IVa) was contemplated. For comparison of antimalarial activity and further understanding of the mode of action of aminoquinoline derivatives, the syntheses of "5-azachloroquine" (IVb) and "5-azapamaquine" (IVc) were also carried out (3). It is interesting to note that antimalarial activity of a closely related compound, 4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (IVd), was found to be comparable to that of quinine (4).



III



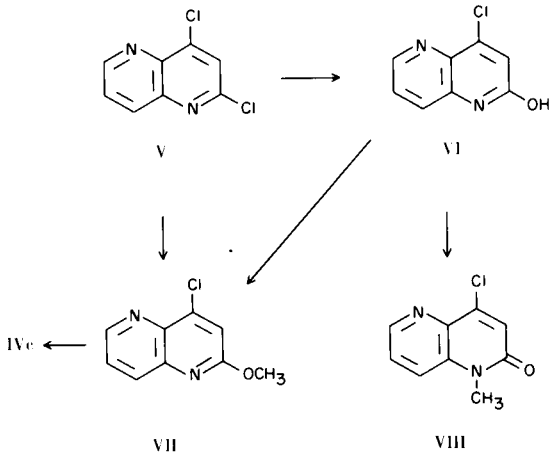
IVa: X = Cl, Y = OCH_3
b: X = Cl, Y = H
c: X = H, Y = OCH_3
d: X, Y = H

Our general synthetic approach required the preparation of substituted 4-chloro-1,5-naphthyridines and their aminolysis with novaldiamine. Thus for the synthesis of target compound IVc, 4-chloro-2-methoxy-1,5-naphthyridine (VII) was needed. Oakes and Rydon (5) had prepared 4-chloro-2-hydroxy-1,5-naphthyridine (VI) by the acid hydrolysis of 2,4-dichloro-1,5-naphthyridine (V).

Treatment of VI by diazomethane, with its known preference for *O*-methylation, should yield the deisred compound VII. However, a methanolic suspension of VI, when treated with ethereal diazomethane, gave a mixture from which was isolated, by a combination of fractional crystallization and sublimation, two products: A, m.p. 152-153° (52% yield) and B, m.p. 112-114° (32% yield). Both gave elemental analysis in agreement with the formula $C_9H_7ClN_2O$. The presence of a carbonyl absorption in the infrared absorption spectrum of compound A permitted a tentative identification of this substance as the product of *N*-methylation: 4-chloro-1-methyl-1,2-dihydro-1,5-naphthyridin-2-one (VIII). Compound B lacked a carbonyl band in the infrared spectrum and its ultraviolet spectrum resembled more closely that of 2,4-dichloro-1,5-naphthyridine (V, which possesses a fully aromatized ring system) than did that of compound A. Compound B was therefore assumed to be 4-chloro-2-methoxy-1,5-naphthyridine (VII). The tedious method of separating VII from its *N*-methylated isomer precluded the practical application of this procedure. Accordingly, preparation of VII by a different route was sought. It was reasoned that since the dichloronaphthyridine V underwent acid hydrolysis at the 2-position, methanolysis in the presence of acid catalyst might afford VII in an analogous manner. This proved to be the case: When compound V was refluxed with 5% methanolic hydrogen chloride for 6 hours, compound VII was obtained in 56% yield.

Aminolysis of VII with novaldiamine, the final step in the synthesis of IVc, gave some interesting results. Typical were those obtained using excess amine in dimethylformamide at 150° for 18 hours. The product, isolated as the free base by evaporative distillation, showed both *N*-methyl and *O*-methyl absorption in NMR. The infrared absorption also showed the presence of a pronounced carbonyl band, indicating an O → N shift of the methyl group during the reaction. The ratio of *N*-methylated to *O*-methylated compounds in the product was 4:3. Substantially the same results were obtained with reactions attempted at lower temperature (100°), for shorter periods (4 hours), with phenol, ethanol or excess amine as solvent. It was found that when the reaction was carried out in the presence of one molar equivalent of novaldiamine dihydrochloride, an increase in the amount of *N*-methylated product (based on carbonyl absorption intensity in the infrared spectrum) was noted.

Although no mechanistic interpretation could be offered, this observation suggested that the *O*-methyl to *N*-methyl transformation was acid catalyzed (6) and that suppression of amine hydrochloride formation by means of a proton scavenger might inhibit this undesirable transformation. Therefore the aminolysis was repeated using excess amine as solvent together with the addition of one



molar equivalent of potassium carbonate. A crude product was isolated which had essentially no carbonyl absorption. Purification of the product by column chromatography followed by evaporative distillation gave IVc in 49% yield.

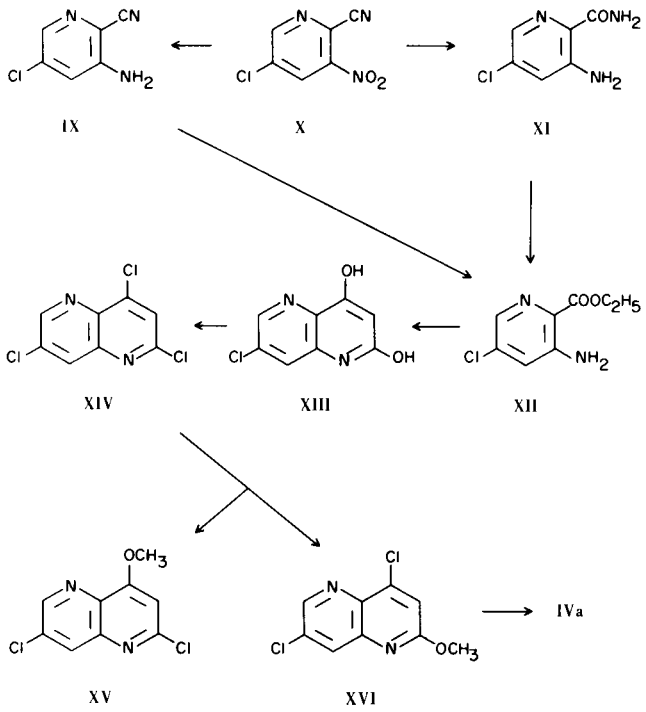
The synthesis of compound IVa followed a similar pattern. In this case the principal task involved the preparation of ethyl 3-amino-5-chloropicolinate (XII) and its conversion to the key intermediate 4,7-dichloro-2-methoxy-1,5-naphthyridine (XVI). Berrie, Newbold and Spring (7) reported the preparation of 3-amino-5-chloropicolinonitrile (IX) by iron-acetic acid reduction of the corresponding 3-nitro derivative X. In our hands the chemical reduction failed to give a good yield of IX except in small scale runs. However, it was found that reduction of the nitro compound proceeded smoothly with Raney nickel but the product isolated was invariably 3-amino-5-chloropicolinamide (XI) rather than the nitrile IX. Nevertheless, compound XI proved to be suitable for conversion to the desired ester XII. The latter was prepared in nearly quantitative yield from XI with ethanolic hydrogen chloride.

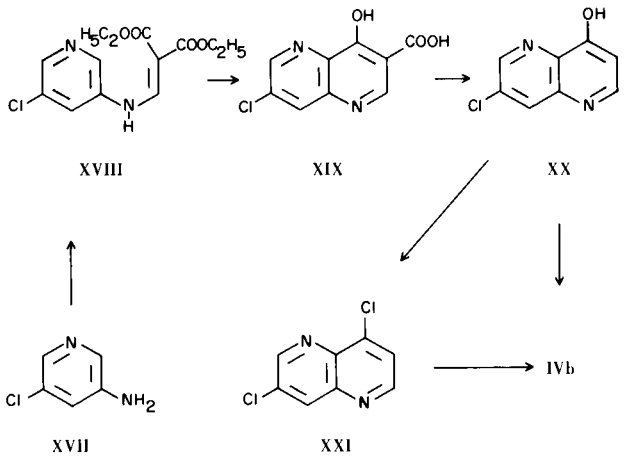
Condensation of XII with diethyl malonate followed by cyclization to give 7-chloro-2,4-dihydroxy-1,5-naphthyridine (XIII) and subsequent conversion to 2,4,7-trichloro-1,5-naphthyridine (XIV) were conducted in a manner similar to that described by Oakes and Rydon (5) for the preparation of V. Acid methanolysis of XIV, which was utilized for the preparation of 4-chloro-2-methoxy-1,5-naphthyridine (VII), was without effect for the conversion of the trichloro compound XIV to XVI. Treatment of XIV with one equivalent of sodium methoxide in methanol gave a crude reaction product, the NMR spectrum of which was consistent with the formation of a mixture of the two possible dichloromethoxy-1,5-naphthyridines XV and XVI. Thus, there were present two pairs of doublets at δ 8.14/8.77 and δ 8.04/8.69, corresponding to ring protons 6 and 8. The singlet absorp-

tions of ring proton 3 appeared at δ 6.87 and δ 7.14. The methoxyl protons were evident at δ 4.02 and δ 4.12. The absorption intensities of each set of peaks were in the required ratio of 1:1:1:3. The identity of the two components was deduced as follows: A comparison of the NMR spectra of XV, XVI, with that of VII revealed that the H-3 proton singlet of the major component (constituting 78% of the mixture) was only slightly shifted from that of VII (whose structure has already been established), whereas the corresponding peak of the minor component was markedly shifted up-field. It was reasoned that little change in charge density of carbon-3 would result from substitution of chlorine at carbon-7. Accordingly, the hydrogen-3 singlet of a compound with structure XVI should be shifted only slightly from that of VII. Hence, the major component in the reaction mixture was identified as 4,7-dichloro-2-methoxy-1,5-naphthyridine (XVI). This component proved to be readily separable from the isomer, XV, by recrystallization from methanol.

Aminolysis of the pure XVI with novaldiamine in the presence of potassium carbonate and purification of the crude product by column chromatography yielded the desired target compound IVa.

The use of ethoxymethylenemalonic ester by Price and Roberts (8) and by Adams *et al.* (9) for the synthesis of 3-carbethoxy-7-chloro-4-hydroxyquinoline and 3-carbethoxy-4-hydroxy-1,5-naphthyridine, respectively, was adapted for the synthesis of compound IVb. Accordingly, 5-chloronicotinic acid was prepared by a modification of the procedure reported by Bachman and Micucci (10) and, utilizing the method of Czuba (11), was converted to 3-amino-5-chloropyridine (XVII). Condensation of XVII with diethyl ethoxymethylenemalonate at 100° gave diethyl 5-chloro-3-pyridylaminomethylenemalonate (XVIII). A partial purification of XVIII was found to be necessary for a good yield in the subsequent cyclization reaction to 3-carboxy-7-chloro-4-hydroxy-1,5-naphthyridine (XIX). Decarboxylation of XIX was accomplished in boiling quinoline, and the resulting 7-chloro-4-hydroxy-1,5-naphthyridine (XX) was treated with phosphorus oxychloride (to yield XXI) followed by excess novaldiamine at 120° to give the desired 7-chloro-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (IVb) in 16% yield. A more direct and efficient route to IVb can be achieved by the aminolysis of the hydroxy compound XX with novaldiamine in the presence of novaldiamine dihydrochloride.





Preliminary antimalarial test results indicated that 7-chloro-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (IVb), the "5-azachloroquine" compound, possesses very good antimalarial activity against *Plasmodium berghei* in mice. Furthermore, the compound is much less toxic than the existing 4-aminoquinoline and 8-aminoquinoline drugs. For comparison, activity and toxicity of IVb and chloroquine diphosphate against *P. berghei* are listed in Table I. While testing is not yet complete, compound IVb also shows good activity against *P. gallinaceum* in chicks. The other two compounds, IVa and IVc, are less active than IVb against *P. berghei*. Compound IVc was found to inhibit the growth of *Streptococcus faecalis* at 10-99 γ/10 ml. This inhibitory activity was not reversed by 0.1 γ of folic acid.

TABLE I

Comparison of Antimalarial Activity of 5-Azachloroquine (IVb) and Chloroquine Diphosphate Against *Plasmodium berghei* in Mice (a,b)

Compound	Drug Dose (mg./kg.)	Results of Tests (Daily Mortality) (Day/Number of Deaths)						Mean Survival Time, Treated	Mean Survival Time, Control	Toxic Deaths
IVb	640	19/1	20/2	22/1	(1 cure)			20.3	6.1	0
	320	15/3	20/2					17.0	6.1	0
	160	12/1	13/1	15/1	16/1	19/1		15.0	6.1	0
	80	12/2	14/1	16/1	19/1			14.6	6.1	0
	40	7/1	8/2	11/2				9.0	6.1	0
	20	6/3	7/2					6.4	6.1	0
Chloroquine	640	3/10						3.0	6.9	10
diphosphate	320	3/10						3.0	6.9	10
	160	13/2	14/4	15/1	16/1	19/1	22/1	15.4	6.9	0
	80	12/2	13/3	14/1	15/2	20/1	22/1	14.9	6.9	0
	40	11/2	12/2	13/3	16/1	21/2		14.3	6.9	0
	20	10/3	12/3	14/1	16/1	19/1	20/1	13.5	6.9	0

(a) Test Results were obtained by Dr. Leo Rane, University of Miami School of Medicine (Contract DA-49-193-MD-2218) and provided by the Division of Medicinal Chemistry, Walter Reed Army Institute of Research. (b) Mice are infected with a lethal dose of *P. berghei* three days prior to administration of the chemical at each dose level. Five mice in each test group for compound IVb, ten mice per each group for chloroquine diphosphate.

EXPERIMENTAL

All melting points were taken on a Thomas-Hoover melting point apparatus. The ultraviolet absorption spectra were determined with a Beckman DK-2 spectrophotometer. The infrared spectra were taken with a Perkin-Elmer Infracord, and the NMR data were obtained with Varian A-60 High Resolution NMR spectrometer.

4-Chloro-2-methoxy-1,5-naphthyridine (VII).

A solution of 10 g. (0.05 mole) of 2,4-dichloro-1,5-naphthyridine (5) (V) in 100 ml. of 5% hydrogen chloride in methanol was refluxed for 6 hours. The solvent was removed *in vacuo* and the residue was cautiously made alkaline with aqueous ammonia in the presence of crushed ice. On filtration there was obtained 6.5 g. of the crude product. This was extracted with 300 ml. of boiling heptane. The residue (0.7 g., 8% yield) was identified as 4-chloro-2-hydroxy-1,5-naphthyridine (5) (VI), m.p. 263°, by its infrared spectrum. The volume of the filtrate was reduced to 50 ml. On cooling, 5.2 g. (56% yield) of 4-chloro-2-methoxy-1,5-naphthyridine (VII) was isolated as pinkish needles, m.p. 114-115°; λ max (ethanol), 251 mμ (ε, 4,000), 259 mμ (ε, 4,000), 268 mμ (ε, 3,000), 312 mμ (ε, 7,000) and 326 mμ (ε, 6,800); IR (nujol), 6.25 μ (aromatic ring), 8.10 and 8.30 μ (OCH_3); NMR (deuteriochloroform), δ 3.89 (3H, *s*, OCH_3), 6.92 (1H, *s*, ring H-3), 7.28 (1H, *q*, ring H-7), 7.78 (1H, *q*, H-8) and 8.80 (1H, *q*, ring H-6).

Anal. Calcd. for $C_9H_7ClN_2O$: C, 55.54; H, 3.63; N, 14.40. Found: C, 55.74; H, 3.50; N, 14.45.

4-Chloro-1-methyl-1,2-dihydro-1,5-naphthyridin-2-one (VIII).

To a suspension of 6.0 g. (0.033 mole) of 4-chloro-2-hydroxy-1,5-naphthyridine (5) (VI) in 500 ml. of methanol was added an ethereal solution of diazomethane to the point where further addition of the reagent did not produce effervescence. After standing overnight, solvents were removed *in vacuo* and the residue obtained was fractionally crystallized from heptane. After two recrystallizations, the head fraction afforded 2.6 g. of 4-chloro-1-methyl-1,2-dihydro-1,5-naphthyridin-2-one as buff needles, m.p. 152-153°; λ max (ethanol), 225 mμ (ε, 37,800), 326 mμ (ε, 9,000); IR (nujol), 6.08 μ (C = O); NMR (deuteriochloroform), δ 3.58 (3H, *s*, NCH_3), 6.88 (1H, *s*, ring H-3), 7.20-7.65 (2H, *m*, ring H-7 and H-8), 8.66 (1H, *q*, ring H-6).

Anal. Calcd. for $C_9H_7ClN_2O$: C, 55.54; H, 3.63; N, 14.40. Found: C, 55.80; H, 3.68; N, 14.45.

An additional 0.8 g. of the same compound, m.p. 150-152°, was obtained from the subsequent head fraction, total yield, 3.4 g. (52%).

All remaining material was combined and the solvent was removed. There was obtained 2.4 g. of yellowish solid, m.p. 106-112°. One-tenth of this material (240 mg.) was sublimed at 100° to give 229 mg. of white crystals, m.p. 107-111°. This material, when recrystallized from ether-hexane, afforded 210 mg. (32% yield) of 4-chloro-2-methoxy-1,5-naphthyridine as white needles, m.p. 112-114°. Its infrared spectrum was identical with that prepared by the aforementioned method.

4-(4-Diethylamino-1-methylbutylamino)-2-methoxy-1,5-naphthyridine (IVc).

A mixture of 3.0 g. (0.015 mole) of 4-chloro-2-methoxy-1,5-naphthyridine (VII), 2.1 g. (0.015 mole) of potassium carbonate and 25 ml. of novaldiamine (2-amino-4-diethylaminopentane) was heated at 140° for 18 hours. After cooling, the inorganic salts were removed by filtration and the excess amine distilled from the filtrate at 0.1 mm. The residue was dissolved in 5% hydrochloric acid (50 ml.) and the solution extracted with ether (3 x 50 ml.). The ether extract was dried and evaporated to give 0.7 g. of solid, m.p. 107-112°, identified as 4-chloro-2-methoxy-1,5-naphthyridine by infrared spectrum (36% recovery). The aqueous phase was made basic with 30% sodium hydroxide and extracted with ether (3 x 50 ml.). The ether extract was dried and solvent removed *in vacuo*. The residual oil, after heating at 100° under vacuum (0.05 mm.) to remove traces of amine, was dissolved in ether (10 ml.) and absorbed on a 20 x 3 cm. column of basic alumina (Grade 1). Elution with ether (1 liter) and 0.5% methanol-ether (300 ml.) afforded, after evaporation of solvents, 3.1 g. of light yellow oil. This was evaporatively distilled at 80-100° at 0.05 mm. to give 2.3 g. (49% yield) 4-(4-diethylamino-1-methylbutylamino)-2-methoxy-1,5-naphthyridine (IVc) as a clear liquid with a faint yellow tinge, n_D^{20} 1.5629. Ultraviolet absorption at λ max (*p*H 1), 231 mμ (ε, 16,000), 296 mμ (ε, 9,500) and 320 mμ (ε, 11,400); λ max (*p*H 11), 229 mμ (ε, 13,000), 255 mμ (ε, 19,600) and 324 mμ (ε, 6,300); IR (liquid film), 3.00 μ (NH), 6.22 and 6.32 μ (aromatic ring), 6.40 μ (NH), 8.30 μ (OCH_3); NMR (deuteriochloroform), δ 0.80-2.65 (19H, *m*, side chain $-CH_2-$ and $-CH_3$), 3.96 (3H, *s*, OCH_3), 5.93 (1H, *s*, ring H-3), 6.32 (1H, broad *d*, N–H), 7.27 (1H, *q*, ring H-7), 7.87 (1H, *q*, ring H-8), 8.38 (1H, *q*, ring H-6).

Anal. Calcd. for $C_{18}H_{28}N_4O$: C, 68.32; H, 8.92; N, 17.71. Found: C, 68.30; H, 9.01; N, 17.44.

A dipicrate was prepared and recrystallized from ethanol, m.p. 138-139°.

Anal. Calcd. for $C_{30}H_{34}N_{10}O_{15}$: C, 46.51; H, 4.41; N, 18.08. Found: C, 46.20: H, 4.28; N, 17.90.

3-Amino-5-chloropicolinamide (XI).

Raney nickel (20 g., approximately two teaspoonsful) was washed successively with 200 ml. of water, 200 ml. of 5% acetic acid, 200 ml. of water, and three 200 ml. portions of 95% ethanol. This was added to a solution of 10.5 g. (0.056 mole) of 5-chloro-3-nitropicolinonitrile (X) in 200 ml. of 95% ethanol. The mixture was then hydrogenated on a Parr hydrogenator at 45 psig for 1 hour. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo* to give 8.5 g. (87% yield) of 3-amino-5-chloropicolinamide as a tan powder, m.p. 158-162°. An analytical sample was obtained by recrystallization from a mixture of methanol and water, m.p. 165-166°. The infrared spectrum of this material showed NH absorption at 2.95 μ, 3.1 μ, and 3.2 μ. The amide carbonyl was present at 6.0 μ. An absorption at 6.32 μ is assigned to NH bending. This product was found to be identical to that obtained (m.p. 168°) from 3-amino-5-chloropicolinonitrile (7).

Anal. Calcd. for $C_6H_6ClN_3O$: C, 42.00; H, 3.53; N, 24.49. Found: C, 42.01; H, 3.78; N, 24.24.

Ethyl 3-Amino-5-chloropicolinate (XII).

Method A.

A solution of 3 g. (0.02 mole) of 3-amino-5-chloropicolinonitrile (7) in 200 ml. of absolute ethanol was saturated with dry hydrogen chloride. The mixture was refluxed for 5 hours and then evaporated to dryness *in vacuo*. The residual solid was redissolved in 200 ml. of absolute ethanol, saturated again with hydrogen chloride, and refluxed for 18 hours. After removal of ethanol *in vacuo*, cold saturated aqueous sodium bicarbonate solution was added to the residue. The resulting crude solid product was collected by filtration, dried, and recrystallized from benzene to give 3.4 g. (85% yield) of XII, m.p. 146-148°. An analytical sample was prepared by recrystallization from benzene, m.p. 149-150°. The infrared spectrum showed absorption at 2.90 μ, 3.05 μ, and 3.15 μ in the N–H region. A carbonyl absorption was noted at 5.95 μ.

Anal. Calcd. for $C_8H_9ClN_2O_2$: C, 47.89; H, 4.52; N, 13.96. Found: C, 48.48; H, 4.34; N, 14.26.

Method B.

A solution of 8.5 g. (0.05 mole) of 3-amino-5-chloropicolinamide (XI) in 800 ml. of absolute ethanol was saturated with hydrogen chloride. The resulting solution was refluxed for 18 hours, cooled, and the solvent removed *in vacuo*. Cold, saturated aqueous sodium bicarbonate was added to the residual hydrochloride. After being filtered and dried the free amine ester was extracted with 250 ml. of boiling heptane. The extract was then concentrated and chilled to give 9.6 g. (97% yield) of ethyl 3-amino-5-chloropicolinate, m.p. 144-148°. An analytically pure sample was obtained by recrystallization of the product from methanol, m.p. 148-150°. The melting point was not depressed on admixture with an analytical sample (m.p. 149-150°) prepared by Method A. The infrared spectra of both products were also identical.

N,N'-Bis(5-chloro-2-ethoxycarbonyl-3-pyridyl)malonamide and 7-Chloro-2,4-dihydroxy-1,5-naphthyridine (XIII).

Diethyl malonate (150 ml.) was heated to 170-180°. To this was added, in portions, with stirring, 20 g. (0.1 mole) of ethyl 3-amino-5-chloropicolinate (XII). The ethanol produced (6 ml.) during the reaction was removed through a Dean-Stark trap. After the addition of ester was completed, the reaction mixture was cooled to 80° and the excess diethyl malonate removed by distillation *in vacuo*. The residue was triturated with 100 ml. of anhydrous ether and filtered. The solid was extracted with three 100-ml. portions of boiling anhydrous ether. The residual solid thus obtained was recrystallized from aqueous acetic acid with charcoal treatment to give 8.2 g. (35% yield) of *N,N'*-bis(5-chloro-2-ethoxycarbonyl-3-pyridyl)malonamide m.p. 235-238°. An analytical sample was prepared by recrystallization from aqueous acetic acid, m.p. 236-238°.

Anal. Calcd. for $C_{19}H_{18}Cl_2N_4O_6$: C, 48.63; H, 3.87; N, 11.94. Found: C, 48.63; H, 3.72; N, 11.95.

The ethereal filtrates from the above reaction were combined and treated with 3.5 g. of sodium (0.15 g.-atom) dissolved in 50 ml. of absolute ethanol. A precipitate formed immediately. The reaction mixture was stirred under reflux for 5 hours, cooled and the solid removed by filtration. This was added to 60 ml. of 25% aqueous sodium hydroxide and the mixture heated cautiously until effervescence ceased and for an additional 3 hours thereafter at the boiling point. Boiling water (300 ml.) was then added, the solution filtered and the filtrate acidified with glacial acetic acid. The resulting suspension was digested at the boiling point for 1 hour, cooled and filtered to give 11 g. (56% yield) of 7-chloro-2,4-dihydroxy-1,5-naphthyridine as light tan needles, m.p. 329-332° dec. An analytical sample was prepared by recrystallization from aqueous acetic acid, m.p. 337-338° dec. The ultraviolet spectrum showed λ max (*p*H 1), 320 mμ (ε, 11,000) and λ max

(*p*H 11), 314 mμ (ε, 13,000).

Anal. Calcd. for $C_8H_5ClN_2O_2$: C, 48.88; H, 2.56; N, 14.25. Found: C, 48.64; H, 2.64; N, 14.08.

2,4,7-Trichloro-1,5-naphthyridine (XIV).

A mixture of 13 g. (0.67 mole) of 7-chloro-2,4-dihydroxy-1,5-naphthyridine (XIII) and 150 ml. of phosphorus oxychloride was heated under reflux for 3 hours. After cooling, the excess phosphorus oxychloride was removed *in vacuo*. The residue was chilled and treated with ice and concentrated ammonium hydroxide. The resulting solid was removed by filtration, dried and extracted with 300 ml. of boiling heptane. Evaporation of the solvent and chilling yielded 10 g. (63% yield) of 2,4,7-trichloro-1,5-naphthyridine as orange brown needles, m.p. 190-193°. An analytical sample was obtained by recrystallization from hexane, m.p. 194-195°.

Anal. Calcd. for $C_8H_3Cl_3N_2$: C, 41.15; H, 1.30; N, 12.00. Found: C, 41.18; H, 1.25; N, 12.27.

4,7-Dichloro-2-methoxy-1,5-naphthyridine (XVI).

A 5 ml. solution of sodium methoxide in methanol [prepared by dissolving 2.3 g. (0.1 g.-atom) of sodium in 100 ml. of methanol] was diluted with 25 ml. of methanol and added, with stirring, to a solution of 1.2 g. (0.005 mole) of 2,4,7-trichloro-1,5-naphthyridine (XIV) in 200 ml. of methanol over a period of 1 hour. After stirring overnight at room temperature, the solvent was removed *in vacuo* and the residue was dissolved in boiling benzene. The insoluble material was removed by filtration and the filtrate was evaporated *in vacuo*. There was obtained 1.1 g. of white solid, m.p. 113-132°. An NMR spectrum of this material (in deuteriochloroform) indicated that it consisted of a mixture of 1 part of 2,7-dichloro-4-methoxy-1,5-naphthyridine (XV) and 3.5 parts of 4,7-dichloro-2-methoxy-1,5-naphthyridine (XVI). The solid was dissolved in 100 ml. of boiling methanol. On cooling, there was deposited 0.55 g. of 4,7-dichloro-2-methoxy-1,5-naphthyridine (XVI) as long, white needles, m.p. 139-140°. An additional portion (0.15 g.) of the same compound, m.p. 139-140°, was obtained when the volume of the mother liquor was reduced to one-half, giving a total yield of 0.70 g. (69% yield). A portion of this material was recrystallized from hexane to give an analytical sample, m.p. 140-141°; λ max (ethanol), 316 mμ (ε, 9,400), 330 mμ (ε, 9,900); IR (nujol), 6.28 μ (aromatic ring), 8.30 μ (OCH_3); NMR (deuteriochloroform), δ 4.02 (3H, *s*, OCH_3), 7.14 (1H, *s*, ring H-3), 8.04 (1H, *d*, ring H-8), 8.69 (1H, *d*, ring H-6). The peaks in the NMR spectrum of the pure product were superimposable upon those of the major component of the crude reaction product.

Anal. Calcd. for $C_9H_6Cl_2N_2O$: C, 47.19; H, 2.64; N, 12.23. Found: C, 47.30; H, 2.94; N, 12.11.

7-Chloro-4-(4-diethylamino-1-methylbutylamino)-2-methoxy-1,5-naphthyridine (IVa).

A mixture of 1.15 g. (0.005 mole) of 4,7-dichloro-2-methoxy-1,5-naphthyridine (XVI), 0.7 g. (0.005 mole) of potassium carbonate and 25 ml. of 2-amino-5-diethylaminopentane was heated with stirring at 140° for 20 hours. The excess amine was removed *in vacuo* and the residue dissolved in 50 ml. of 5% hydrochloric acid. The solution was extracted with 2 x 50 ml. portions of ether and the ether extract discarded. The aqueous phase was then made basic with 50% of aqueous sodium hydroxide and extracted with 3 x 50 ml. portions of ether. The ether extract was dried over sodium sulfate and the solvent removed *in vacuo*. The resulting residue was taken up in anhydrous ether and placed on a 20 x 3 cm. column of Woelm basic alumina (Grade I). Elution of the column with 200 ml. of anhydrous ether gave, on evaporation of solvent, a yellow oil which was purified by evaporative distillation at 0.05 mm. (80-100°). There was obtained 1.4 g. (79% yield) of IVa as a clear, light yellow oil, n_D^{20} 1.5663; λ max (*p*H 1), 304 mμ (ε, 13,000), 326 mμ (ε, 12,700); λ max (*p*H 11), 262 mμ (ε, 17,200), 318 mμ (ε, 7,000); IR (liquid film), 3.00 μ (NH), 6.25 and 6.30 μ (aromatic ring), 6.41 μ (NH), 8.30 μ (OCH_3); NMR (deuteriochloroform), δ 0.75-2.70 (19H, *m*, side chain $-CH_2-$ and $-CH_3$), 4.00 (3H, *s*, OCH_3), 5.98 (1H, *s*, ring H-3), 6.35 (1H, *d*, NH), 7.95 (1H, *d*, ring H-8), 8.42 (1H, *d*, ring H-6).

Anal. Calcd. for $C_{18}H_{27}ClN_4O$: C, 61.61; H, 7.76; N, 15.97. Found: C, 61.49; H, 7.98; N, 15.92.

A dipicrate was prepared and recrystallized from ethanol, m.p. 181-183°.

Anal. Calcd. for $C_{30}H_{33}ClN_{10}O_{15}$: C, 44.53; H, 4.11; N, 17.31. Found: C, 44.61; H, 4.03; N, 17.29.

3-Carboxy-7-chloro-4-hydroxy-1,5-naphthyridine (XIX).

A mixture of 6.4 g. (0.05 mole) of 3-amino-5-chloropyridine (10) (XVII) and 10.8 g. (0.05 mole) of diethyl ethoxymethylenemalonate were heated at 100° for 30 minutes. On cooling, the reaction mixture afforded a waxy solid, which was dissolved in 100 ml. of methanol. The solution was heated to 50° and an equal volume of water added. The product was induced to crystallize by cooling and scratching. After being chilled in ice, the product was collected by filtration and dried. The partially purified diethyl 5-chloro-3-pyridylaminomethylenemalonate (XVIII, 14 g., 95% yield) thus obtained was submitted to cyclization without further treatment.

To 200 ml. of refluxing diphenyl ether there was added cautiously, in portions, 15 g. (0.05 mole) of diethyl 5-chloro-3-pyridylaminomethylenemalonate (XVIII). The mixture was heated under reflux for an additional 10 minutes, cooled, diluted with 700 ml. hexane and filtered. Crude 3-carbethoxy-7-chloro-4-hydroxy-1,5-naphthyridine (12 g., 95% yield) was obtained as a brown powder, m.p. 310° dec. This product was refluxed with 150 ml. of 10% sodium hydroxide for 30 minutes. At the end of this period the ester had largely dissolved. The reaction was continued for an additional 30 minutes as a solid began to precipitate. This was dissolved by the addition of 300-400 ml. of boiling water. The solution was treated with charcoal and filtered. The filtrate was acidified with glacial acetic acid, cooled, and filtered. There was obtained 10 g. of 3-carboxy-7-chloro-4-hydroxy-1,5-naphthyridine as a tan powder, m.p. 265° dec. An analytical sample was prepared by recrystallization from a mixture of ethylene glycol monomethyl ether and water as lustrous plates, m.p. $>320°$.

Anal. Calcd. for $C_9H_5ClN_2O_3$: C, 48.12; H, 2.24; N, 12.48. Found: C, 48.08; H, 2.48; N, 12.59.

7-Chloro-4-hydroxy-1,5-naphthyridine (XX).

To 100 ml. of boiling quinoline there was added, in small portions, 2.2 g. (0.01 mole) of 3-carboxy-7-chloro-4-hydroxy-1,5-naphthyridine (XIX). After a few minutes the initially vigorous effervescence subsided and the mixture was heated at reflux temperature with stirring for an additional hour. The reaction mixture was cooled and to it was added three volumes of acetone. The resulting solid was collected by filtration. There was obtained 2.0 g. of crude 7-chloro-4-hydroxy-1,5-naphthyridine as a brown powder, Recrystallization from boiling water gave 1.2 g. (67% yield) of pure XX as white needles, which sublimed without melting when heated above 360°. An analytical sample was prepared by sublimation.

Anal. Calcd. for $C_8H_5ClN_2O$: C, 53.20; H, 2.79; N, 15.51. Found: C, 53.13; H, 2.59; N, 15.31.

7-Chloro-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (IVb).

Method A.

A mixture of 1.0 g. (0.0055 mole) of 7-chloro-4-hydroxy-1,5-naphthyridine (XX), 1.2 g. (0.05 mole) of 2-amino-5-diethylaminopentane dihydrochloride and 25 ml. of 2-amino-5-diethylaminopentane was heated at 150° with stirring. Within 5 hours all suspended solid had dissolved and heating and stirring were continued for an additional 12 hours. Excess amine was then removed *in vacuo* and the residual oil partitioned between 50 ml. of 10% aqueous sodium hydroxide and 100 ml. of ether. The ether extract was dried over anhydrous potassium carbonate, filtered, and evaporated. Any remaining free amine was removed from the residue under high vacuum. The residue was taken up in ether and chromatographed on a column of Woelm basic alumina (Grade I). Elution with ether (30 ml.) gave an amber colored oil which, upon evaporative distillation at 80-100° and 0.05 mm., afforded 0.7 g. (40% yield) of 7-chloro-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine as an orange oil, n_D^{20} 1.5636; λ max (*p*H 1), 242 mμ (ε, 15,400), 254 mμ (ε, 15,300), 292 mμ (ε, 3,200), 304 mμ (ε, 4,500), 344 mμ (ε, 13,100); λ max (*p*H 11), 240 mμ (ε, 13,800), 262 mμ (ε, 19,900), 350 mμ (ε, 7,300); IR (liquid film), 3.00 μ (NH), 6.32 μ (aromatic ring), 6.46 μ (NH); NMR (deuteriochloroform), δ 0.80-2.89 (19H, *m*, side chain $-CH_2-$ and $-CH_3$), 6.38 (1H, *d*, ring H-3), 6.45 (1H, broad *d*, deuterium oxide exchangeable, NH), 8.07 (1H, *d*, ring H-8), 8.37-8.40 (2H, overlapping *d*, ring H-2 and H-6).

Anal. Calcd. for $C_{17}H_{25}ClN_4$: C, 63.63; H, 7.85; N, 17.46. Found: C, 63.74; H, 8.05; N, 17.13.

A picrate was prepared and recrystallized from ethanol, m.p. 214-216°.

Anal. Calcd. for $C_{29}H_{31}ClN_{10}O_{14}$: C, 44.70; H, 4.01; N, 17.98. Found: C, 45.00; H, 3.74; N, 17.81.

Method B.

A mixture of 1.0 g. (0.0055 mole) of 7-chloro-4-hydroxy-1,5-naphthyridine (XX) and 25 ml. of phosphorus oxychloride was refluxed for 18 hours. Excess reagent was removed *in vacuo* and the residue was poured, with stirring, onto crushed ice; the mixture was neutralized with concentrated aqueous ammonia. The resulting solid was collected by filtration, dried and extracted with 50 ml. of boiling heptane. The volume of the extract was reduced to one-half and the solution chilled. The precipitated solid was collected by filtration. There was obtained 800 mg. (80% yield) of 4,7-dichloro-1,5-naphthyridine (XXI) as off-white needles, m.p. 176-179°. The product was then added to 25 ml. of 2-amino-5-diethylaminopentane and the resulting solution was heated at 120° for 18 hours. Excess amine was removed *in vacuo* and the residual oil partitioned between 50 ml. of 10% aqueous sodium hydroxide and 100 ml. of ether. The ether extract was dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified as described in Method A to give an overall 16% yield of an orange oil. The infrared spectrum and other physical properties of this material were identical with those of the product prepared by Method A.

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REFERENCES

(1) This investigation was supported by Contract No. DA-49-193-MD-2749 with the U. S. Army Medical Research and Development Command. This paper is Contribution No. 741 from the Army Research Program on malaria.

(2) C. A. Alvarado and L. J. Bruce-Chwatt, *Sci. Am.*, 206, 86 (1962); cf. "Terminology of Malaria and of Malaria Eradication," World Health Organization, Geneva, 1963, p. 67.

(3) A. A. Goldberg, R. S. Theobald and W. Williamson, *J. Chem. Soc.*, 2357 (1954), proposed the synthesis (not successful) of an isomer of IVc, 4-(4-diethylamino-1-methylbutylamino)-6-methoxy-1,5-naphthyridine.

(4) F. Y. Wiselogie, "A Survey of Antimalarial Drugs," J. W. Edwards, Ann Arbor, Michigan, 1946, Vol. II, part 2, p. 1365.

(5) V. Oakes and H. N. Rydon, *J. Chem. Soc.*, 204 (1958).

(6) It is of interest to note that thermal rearrangement of substituted 2- and 4-alkoxypyrimidines are accelerated mildly in the presence of organic bases. See D. J. Brown and T.-C. Lee, *Aust. J. Chem.*, 21, 243 (1968).

(7) A. H. Berrie, G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 2590 (1951).

(8) C. C. Price and R. M. Roberts, *J. Am. Chem. Soc.*, 68, 1204 (1946).

(9) J. T. Adams, C. K. Bradsher, D. S. Breslow, S. T. Amore and C. R. Hauser, *ibid.*, 68, 1317 (1946).

(10) G. B. Bachman and D. D. Micucci, *ibid.*, 70, 2381 (1948).

(11) W. Czuba, *Rocz. Chem.*, 34, 905 (1960).

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