Antifilarial and Antimalarial Agents. Basically Substituted 10-Aminobenzo[*b*][1,5]naphthyridines, 10-Aminobenzo[*b*][1,5]naphthyridine *N*-Oxides, and 8-Amino-1,5-naphthyridines (1,2)

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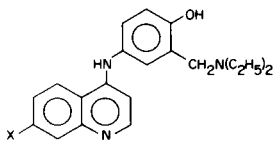
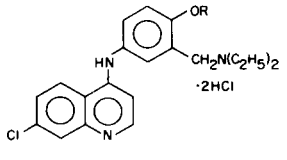
Various 2-alkoxy-7-chloro-10-[[(dialkylamino)alkyl]amino]benzo[*b*][1,5]naphthyridines (XI) and *N*-oxides (XV, XVII, XVIII, XXII), 4-[(2-alkoxy-7-chlorobenzo[*b*][1,5]naphthyridin-10-yl)-amino]-α-(diethylamino)-*o*-cresol derivatives (XII-XIV, XXI) and *N*-oxides (XIX, XX, XXV), 2-butoxy-8-[[(dialkylamino)alkyl]amino]-1,5-naphthyridines (XXVIa and b), and 2-butoxy-8-[[3-[(diethylamino)methyl]-*p*-anisidino]-1,5-naphthyridine (XXVII) were synthesized for antifilarial and antimalarial evaluation. The compounds were obtained in 13-91% yield by the condensation of 2-alkoxy-7,10-dichlorobenzo[*b*][1,5]naphthyridines, 2-alkoxy-7,10-dichlorobenzo[*b*][1,5]naphthyridine 5-oxides, and 2-butoxy-8-chloro-1,5-naphthyridine with the appropriate diamine in phenol, or by perbenzoic acid oxidation of the parent 10-amino-7-chlorobenzo-[*b*][1,5]naphthyridines in chloroform. Among them, eight compounds killed adult *Litomosoides carinii* in gerbils when administered in daily gavage doses of 25-400 mg./kg. for 5 days. Azacrine 5-oxide (XVII), the most active compound, was equipotent with amodiaquine (Ia), azacrine (IX), and quinacrine 10-oxide (VI). Twelve substances were active orally against *Plasmodium berghei* in mice at doses ranging from 3.8-155 mg./kg./day for 6 days. 7-Chloro-10-[3-[(diethylamino)-methyl]-*p*-anisidino]-2-methoxybenzo[*b*][1,5]naphthyridine 5-oxide dihydrochloride (XX) was approximately 12 times as potent as quinine against *P. berghei*, but was highly cross-resistant with chloroquine (IV). Structure-activity relationships are discussed.

In recent communications (1,3) it was reported that the antimalarial drugs amodiaquine dihydrochloride (Ia) (4,5), 4-[(7-bromo-4-quinolyl)amino]-α-(diethylamino)-*o*-cresol (Ib) (6), α-(diethylamino)-4-[(7-iodo-4-quinolyl)-amino]-*o*-cresol (Ic) (6), *O*-methylamodiaquine dihydrochloride (IIa) (7), *O*-ethylamodiaquine dihydrochloride (IIb) (5), *O*-methylamodiaquine 1-oxide (III) (8), and certain related 4-[(4-quinolyl)amino]-α-(dialkylamino)-*o*-cresols exhibit strong antifilarial activity against adult *Litomosoides carinii* in gerbils. In contradistinction, basically substituted aliphatic 4-aminoquinoline antimalarials such as chloroquine diphosphate (IV) (6) lacked appreciable antifilarial effects (1). However, additional studies in these laboratories showed that certain other basically substituted antimalarial agents including quinacrine dihydrochloride (Va) (6), 9-[[4-(diethylamino)-1-methylbutyl]amino]-6-iodo-2-methoxyacridine dihydrochloride (Vb) (9,10), quinacrine 10-oxide dihydrochloride (VI) (11), quinacrine N^{ω}-oxide dihydrochloride (VII)



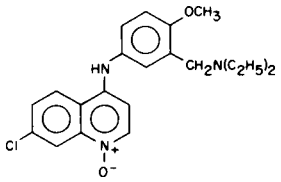
a, X = Cl·2HCl
b, X = Br
c, X = I

I

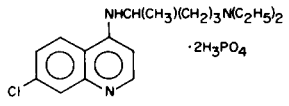


a, R = CH_3
b, R = C_2H_5

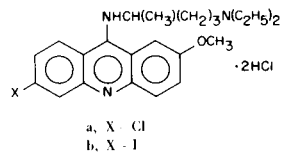
II



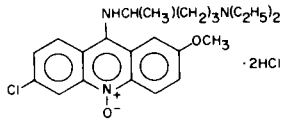
III



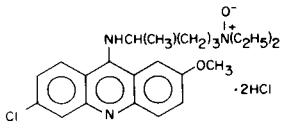
IV



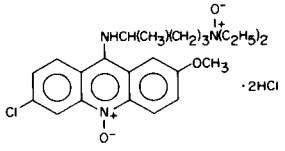
V



VI



VII



VIII

(11), quinacrine N^{ω},10-dioxide dihydrochloride (VIII) (11), and azacrine dihydrochloride (IX) (12), were lethal to adult *L. carinii* in gerbils at daily doses ranging from 25 to 200 mg./kg. for 5 days, although none was more potent than amodiaquine (1,3). It was therefore of interest to synthesize novel hybrids of compounds I-IX for antiparasitic evaluation. The present communication describes the preparation and properties of various basically substituted 10-aminobenzo[*b*][1,5]naphthyridines, 10-aminobenzo[*b*][1,5]naphthyridine *N*-oxides, and 8-amino-1,5-naphthyridines. Several of the compounds synthesized possessed marked antifilarial activity against *L. carinii* in gerbils and potent antimalarial effects against *Plasmodium berghei* in mice.

CHEMISTRY

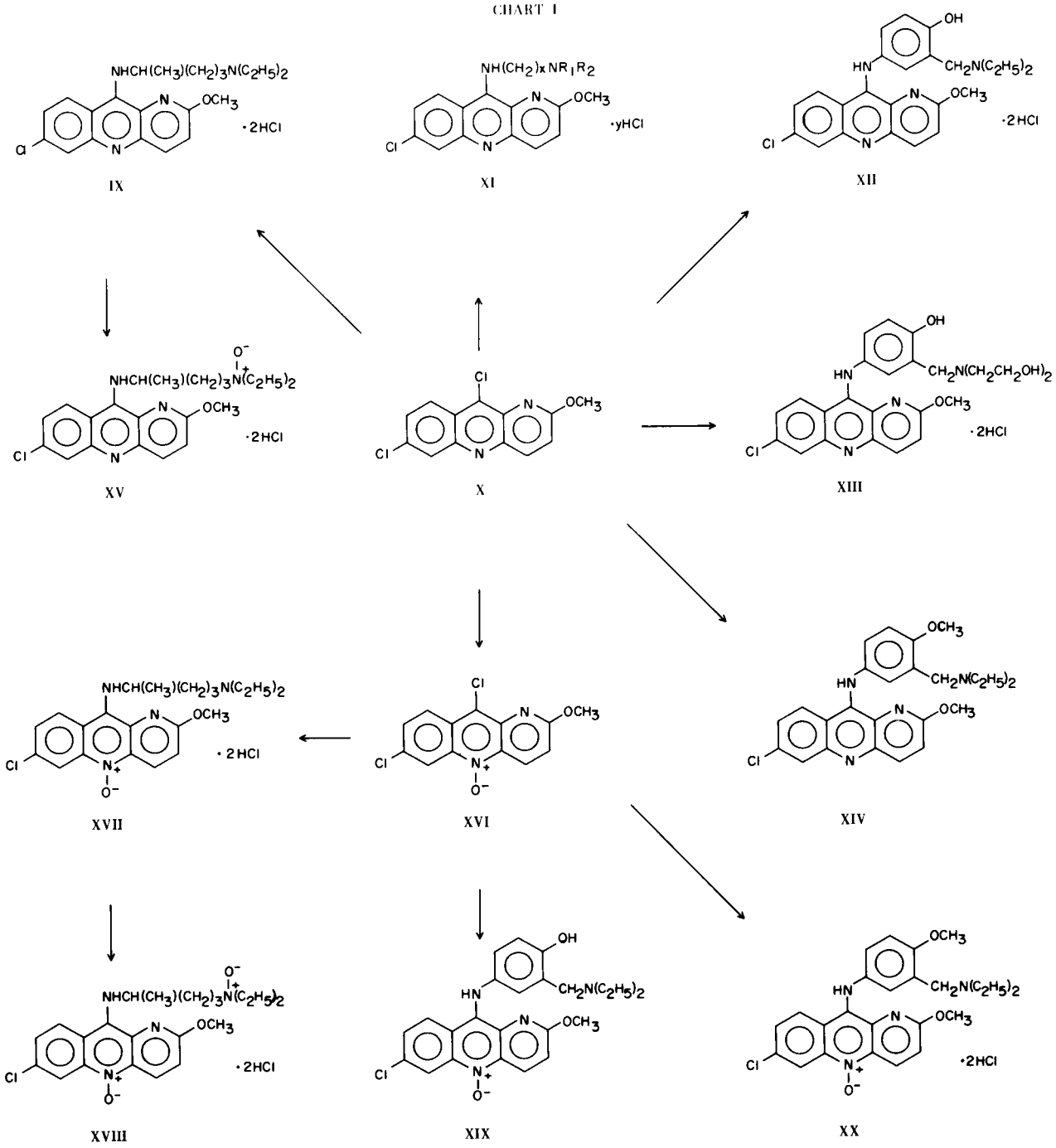
A group of 7-chloro-10-[[(dialkylamino)alkyl]amino]--2-methoxybenzo[*b*][1,5]naphthyridine analogs (XI, **1-5**, Table I) of azacrine (IX) were prepared in 65-91% yield by heating 7,10-dichloro-2-methoxybenzo[*b*][1,5]naphthyridine (X) (12) with 1-(2-aminoethyl)piperazine, 2,2′-[(3-aminopropyl)imino]diethanol, 1-(3-aminopropyl)-4-methylpiperazine, 4-(3-aminopropyl)-1-piperazineëthanol, and 2,2′-[[3-[(3-aminopropyl)amino]propyl]imino]diethanol in phenol on a steam bath for 3 hours. Three amodiaquine relatives of azacrine, namely 4-[(7-chloro-2-methoxybenzo[*b*][1,5]naphthyridin-10-yl)amino]-α-(diethylamino)-*o*-cresol dihydrochloride (XII) (37%), 2,2′-[[5-[(7-chloro-2-methoxybenzo[*b*][1,5]naphthyridin-10-yl)amino]salicyl]imino]diethanol dihydrochloride (XIII) (33%), and 7-chloro-10-[3-[(diethylamino)methyl]-*p*-anisidino]-2-methoxybenzo[*b*][1,5]naphthyridine (XIV) (13%), were obtained in a similar manner by the condensation of X with 4-amino-α-(diethylamino)-*o*-cresol dihydrochloride (5), 2,2′-(5-amino-2-hydroxybenzylimino)-diethanol dihydrochloride, and N^{α},N^{α}-diethyl-6-methoxytoluene-α,3-diamine dihydrochloride (5,8), respectively (Chart I).

Earlier work in these laboratories demonstrated that the antimalarial potency of amodiaquine (Ia), quinacrine (Va), oxychloroquine, and certain related 4-aminoquinolines and 9-aminoacridines could be markedly enhanced by *N*-oxidation (8,11). It was therefore of particular interest to synthesize representative *N*-oxides of azacrine (IX) (12) and azacrine congeners (Charts I and II). Oxidation of azacrine base with perbenzoic acid in chloroform (8,11) gave 7-chloro-10-[[4-(diethylamino)-1-methylbutyl]-amino]-2-methoxybenzo[*b*][1,5]naphthyridine N^{ω}-oxide dihydrochloride (azacrine N^{ω}-oxide dihydrochloride) (XV) in 52% yield. Treatment of 7,10-dichloro-2-methoxybenzo[*b*][1,5]naphthyridine (X) (12) with *m*-chloroperbenzoic acid in chloroform afforded 7,10-dichloro-2-methoxybenzo[*b*][1,5]naphthyridine 5-oxide (XVI) (63%), which was allowed to react with N^{1},N^{1}-diethyl-1,4-pentanediamine in phenol to give 7-chloro-10-[[4-(diethylamino)-1-methylbutyl]amino]-2-methoxybenzo[*b*]-[1,5]naphthyridine 5-oxide dihydrochloride (azacrine 5-oxide dihydrochloride) (XVII) (37%). Subsequent perbenzoic acid oxidation of azacrine 5-oxide (XVII) afforded 7-chloro-10-[[4-(diethylamino)-1-methylbutyl]amino]-2-methoxybenzo[*b*][1,5]naphthyridine N^{ω},5-dioxide dihydrochloride (azacrine N^{ω},5-dioxide dihydrochloride) (XVIII) (55%).

Several amodiaquine relatives of azacrine 5-oxide (XVII) were also prepared (Chart I). Thus the condensation of 7,10-dichloro-2-methoxybenzo[*b*][1,5]naphthyridine 5-oxide (XVI) with 4-amino-α-(diethylamino)-*o*-cresol dihydrochloride (5) and N^{α},N^{α}-diethyl-6-methoxytoluene-α,3-diamine dihydrochloride (5,8) in phenol gave 4-[(7-chloro-2-methoxybenzo[*b*][1,5]naphthyridin-10-yl)-amino]-α-(diethylamino)-*o*-cresol 5-oxide (XIX) and 7-chloro-10-[3-[(diethylamino)methyl]-*p*-anisidino]-2-methoxybenzo[*b*][1,5]naphthyridine 5-oxide dihydrochloride (XX) in 27 and 52% yield, respectively.

A report by Goldberg *et al.* (13) that 2-butoxy-8-[[4-(diethylamino)-1-methylbutyl]amino]-1,5-naphthyridine (XXVIa) displayed strong antimalarial effects against *Plasmodium gallinaceum* in chicks and *P. berghei* in mice stimulated the synthesis of hybrids of amodiaquine and azacrine having a butoxy substituent at position 2 of the benzo[*b*][1,5]naphthyridine ring (Chart II). Condensation of 2-butoxy-7,10-dichlorobenzo[*b*][1,5]naphthyridine (XXIII) (12) with N^{α},N^{α}-diethyl-6-methoxytoluene-α,3-diamine in phenol yielded 2-butoxy-7-chloro-10-[3-[(diethylamino)methyl]-*p*-anisidino]benzo[*b*][1,5]naphthyridine (XXI) (51%). Oxidation of XXIII with *m*-chloroperbenzoic acid in chloroform gave 2-butoxy-7,10-dichlorobenzo[*b*][1,5]naphthyridine 5-oxide (XXIV) (96%), which upon treatment with N^{1},N^{1}-diethyl-1,4-pentanediamine and N^{α},N^{α}-diethyl-6-methoxytoluene-α,3-diamine dihydrochloride in phenol afforded 2-butoxy-7-chloro-10-[[4-

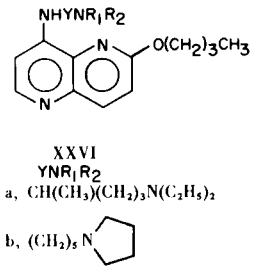
CHART I



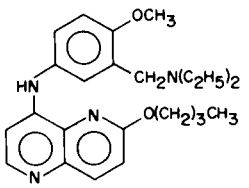
(diethylamino)-1-methylbutyl]amino]benzo[*b*][1,5]naphthyridine 5-oxide (XXII) (46%) and 2-butoxy-7-chloro-10-[[3-[(diethylamino)methyl]-*p*-anisidino]benzo[*b*][1,5]-naphthyridine 5-oxide (XXV) (59%), respectively.

Lastly, two new 1,5-naphthyridine analogs (XXVIb and XXVII) of 2-butoxy-8-[[4-(diethylamino)-1-methylbutyl]amino]-1,5-naphthyridine (XXVIa) (13) and amodiaquine (Ia) were synthesized for comparative antiparasitic evaluation. The fusion of 2-butoxy-8-chloro-1,5-naphthyridine (13) with 1-(5-aminopentyl)pyrrolidine at 180-190° gave 2-butoxy-8-[[5-(1-pyrrolidinyl)pentyl]amino]-1,5-naphthyridine (XXVIb) (53%), while the condensation with N^{α},N^{α}-diethyl-6-methoxytoluene-α,3-diamine afforded 2-butoxy-8-[[3-[(diethylamino)methyl]-*p*-anisidino]-1,5-naphthyridine (XXVII) (33%).

The presence or absence of the *N*-oxide group on the

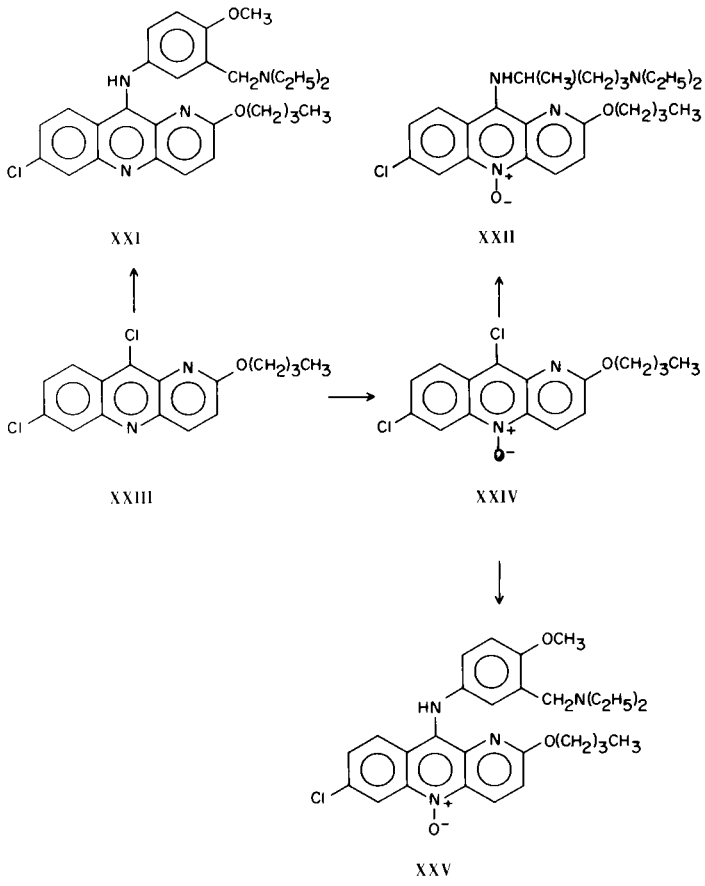


XXVI
YNR_1R_2
a, $CH(CH_3)(CH_2)_3N(C_2H_5)_2$
b, $(CH_2)_5N$



XXVII

CHART II



XXI XXII XXIII XXIV XXV

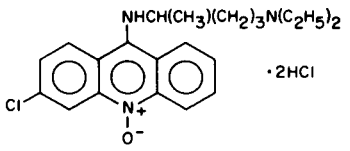
ring or side chain nitrogen of the 10-amino-7-chlorobenzo-[*b*][1,5]naphthyridines could be discerned by several means (Table II). First, the presence of the oxygen lowered the pK'_a 2 to 4 units from the values obtained for the corresponding unoxidized parent compounds. Secondly, the presence of the oxygen attached to the ring nitrogen atom caused a shift to longer wavelengths in the UV absorption spectra. This was especially large when measured in alkaline solution (Table II), but has also been observed in acid solution (8,11) in other heterocyclic systems. Finally, in comparing the NMR curves from IX, XV, XVII, and XVIII, it is apparent that the attachment of the oxygen to the side chain nitrogen caused a downfield shift not only for the signal from the protons on the methylene groups adjacent to the nitrogen atom, but also of the triplet due to the methyl group adjacent to the methylene group. A comparison of quinacrine (Va) and the quinacrine *N*-oxides VI-VIII (11) showed a similar pattern (Table II).

BIOLOGICAL RESULTS

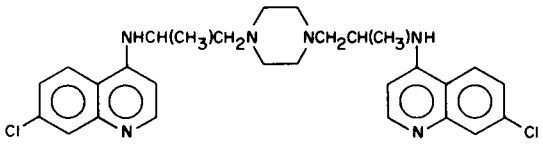
The 10-amino-7-chlorobenzo[*b*][1,5]naphthyridines (XII-XIV, XXI), 10-amino-7-chlorobenzo[*b*][1,5]naphthyridine *N*-oxides (XV, XVII-XX, XXII, and XXV), and 8-amino-2-butoxy-1,5-naphthyridines (XXVIa and b, XXVII) were supplied to Dr. Paul E. Thompson and coworkers of these laboratories for evaluation against *Plasmodium berghei* in mice (16). As in previous work the drugs were administered continuously in the diet for 6 days to mice infected with a normal drug-sensitive strain of *P. berghei*. Results (Table III) are expressed both in terms of the SD_{90} (daily dose required for 90% suppression of the parasitemia) and the quinine equivalent Q (the ratio of the SD_{90} of quinine hydrochloride to the SD_{90} of the test substance under comparable experimental conditions). Consistent with earlier results in the 4-aminoquinoline and 9-aminoacridine series (8,11), the antimalarial potency of azacrine dihydrochloride (IX) (SD_{90} = 14.7 mg./kg./day, Q = 5.1) was markedly enhanced by the introduction of the N^{ω}-oxide (XV) (SD_{90} = 5.9 mg./kg./day, Q = 12.6) or the 5-oxide (XVII) (SD_{90} = 3.8 mg./kg./day, Q = 19.6) and maintained in the N^{ω},5-dioxide (XVIII) (SD_{90} = 11.2 mg./kg./day, Q = 6.7). Similarly, the activity of the amodiaquine analog of azacrine (XII) (SD_{90} = 19.8 mg./kg./day, Q = 3.8) and the *O*-methylamodiaquine analog of azacrine (XIV) (SD_{90} = 14.3 mg./kg./day, Q = 5.2) was enhanced by the introduction of a 5-oxide function (XIX, SD_{90} = 6.2 mg./kg./day, Q = 12.0 and XX, SD_{90} = 6.3 mg./kg./day, Q = 11.8, respectively). However, the potency of the corresponding 2-butoxy derivative (XXI, SD_{90} = 22.0 mg./kg./day, Q = 3.4) was not enhanced by the formation of the 5-oxide (XXV, SD_{90} = 18.5 mg./kg./day, Q = 4.0). The three 8-amino-2-butoxy-1,5-naphthyridines (XXVIa and b, XXVII) were 0.5 to 1.4 times as potent as quinine, but did not approach azacrine and the azacrine congeners in potency.

Virtually all chloroquine-resistant strains of *P. berghei* studied to date have proved to be uniformly cross-resistant to an array of 4-aminoquinoline and 9-aminoacridine derivatives, including amodiaquine (Ia) (17), amopyroquin (17), quinacrine (Va) (17), 3-chloro-9-[[4-(diethylamino)-1-methylbutyl]amino]acridine 10-oxide dihydrochloride (XXVIII) (11,17), 4,4′-[1,4-piperazinediylbis(1-methyl-

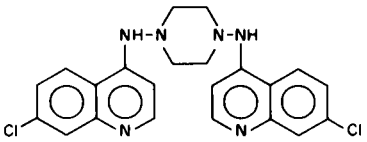
ethyleneimino)]bis[7-chloroquinoline] (XXIX) (18), and 4,4′-(1,4-piperazinediyldiimino)bis[7-chloroquinoline] (XXX) (19),



XXVIII



XXIX

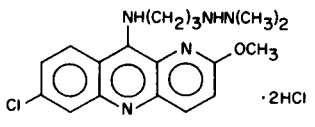


XXX

and miscellaneous 4-aminoquinolines (18,20). Nevertheless, it was of interest to test a representative 10-amino-7-chlorobenzo[*b*][1,5]naphthyridine against a chloroquine-resistant line of *P. berghei* in the remote possibility that the 1,5-naphthyridine moiety might confer substantially broader action against chloroquine-resistant lines. In a parallel study 7-chloro-10-[[3-[(diethylamino)methyl]-*p*-anisidino]-2-methoxybenzo[*b*][1,5]naphthyridine 5-oxide dihydrochloride (XX) was administered at drug-diet levels of 0.156, 0.004, and 0.001% for 6 days both to mice infected with the normal drug-susceptible strain of *P. berghei* and a strain made highly resistant (77-fold) to chloroquine (16). Compound XX produced only a 37% reduction of the parasitemia in the chloroquine-resistant line at the highest dose level employed, namely 0.156% (18 mg./kg.). In contradistinction, the drug caused a comparable reduction of the parasitemia in the parent drug-susceptible strain at a dose of approximately 2 mg./kg./day. These data indicate a strong degree of cross-resistance (>9-fold) between 7-chloro-10-[[3-[(diethylamino)methyl]-*p*-anisidino]-2-methoxybenzo[*b*][1,5]naphthyridine 5-oxide dihydrochloride (XX) and chloroquine, and discourage further interests in the antimalarial properties of this and related benzo[*b*][1,5]naphthyridines.

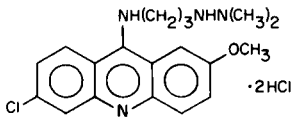
Representative 10-amino-7-chlorobenzo[*b*][1,5]naphthyridines (XII, XXI), benzo[*b*][1,5]naphthyridine *N*-oxides (XV, XVII-XX, XXV), and 8-amino-2-butoxy-1,5-naphthyridines (XXVIa, XXVII) described in the present communication were also supplied to Dr. P. E. Thompson and co-workers of these laboratories for evaluation as potential antifilarial agents against *Litomosoides carinii* in gerbils. As in previous work (1,3), drugs were administered twice daily by gavage as solutions or suspensions in aqueous 1% (hydroxyethyl) cellulose and 0.1% Tween 80 (volumes of 5 ml./kg.). Doses are expressed in terms of the free base equivalent. Examinations for microfilariae were made in Giemsa-stained thick films of blood drawn from the retro-ocular sinus. These parasite counts were started early in patency and were continued at 1 to 4 day intervals until the animals were examined for adult worms (1,3). Surviving animals were sacrificed and examined for adult worms on day 15 after the first drug dose by searching the pleural and peritoneal cavities. The numbers of live and dead worms at autopsy were scored relative to untreated infections in control gerbils (1,3). Eight compounds (XII, XV, XVII, XVIII, XX, XXI, XXVIa, and XXVII) killed a few to many adult *L. carinii* in gerbils when administered in daily 25-400 mg./kg. gavage doses for 5 days. Azacrine 5-oxide dihydrochloride (XVII), the most active compound tested, was lethal to adult *L. carinii* at daily doses of 25 or 50 mg./kg. and was roughly comparable in potency with amodiaquine (Ia), azacrine (IX), quinacrine (Va), and quinacrine 10-oxide (VI). None of the compounds showed direct action against the circulating microfilariae.

Previous studies in these laboratories have shown that the substitution of a hydrazine or hydroxylamine moiety for an amine function at the proximal or distal position of azacrine or quinacrine analogs has a deleterious effect on antimalarial activity (19,21). In this regard it is noteworthy that three such derivatives, namely 7-chloro-10-[[3-(2,2-dimethylhydrazino)propyl]amino]-2-methoxybenzo[*b*][1,5]naphthyridine dihydrochloride (XXXI) (21), 6-chloro-9-[[3-(2,2-dimethylhydrazino)propyl]amino]-

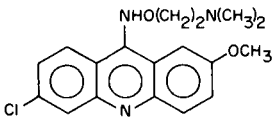


XXXI

2-methoxyacridine dihydrochloride (XXXII) (21), and 6-chloro-9-[[2-(dimethylamino)ethoxy]amino]-2-methoxyacridine (XXXIII) (19), lacked appreciable antifilarial



XXXII



XXXIII

effects against *L. carinii* in gerbils at daily gavage doses ranging from 50-200 mg./kg.

Expanded studies with quinacrine 10-oxide dihydrochloride (VI) demonstrated that the drug was inactive against adult *L. carinii in vitro* at drug concentrations ranging from 1.3 to 21.3 μg./ml. (3b). This observation suggests that metabolites of quinacrine 10-oxide and allied substances may be wholly or partly responsible for their antifilarial properties. Quinacrine 10-oxide dihydrochloride also lacked appreciable effects against *Dirofilaria immitis* adults or microfilaria in dogs at a dose of 5 mg./kg. twice daily for 5 days (3b).

EXPERIMENTAL (22)

7-Chloro-10-[[(dialkylamino)alkyl]amino]-2-methoxybenzo[*b*][1,5]naphthyridines (XI) (**1-5**, Table I).

A mixture of 27.9 g. (0.1 mole) of 7,10-dichloro-2-methoxybenzo[*b*][1,5]naphthyridine (X) (12), 20.2 g. (0.108 mole) of 4-(3-aminopropyl)-1-piperazineëthanol, and 65 g. of phenol was stirred and heated on a steam bath for 3 hours. The reaction mixture was diluted with 200 ml. of ethanol and poured with vigorous stirring into a mixture of 25 ml. of concentrated hydrochloric acid and 2 l. of acetone. The yellow solid that precipitated was collected by filtration and washed with acetone. Crystallization from an ethanol-acetone mixture containing an excess of concentrated hydrochloric acid gave 54.2 g. (91%) of 4-[3-[(7-chloro-2-methoxybenzo[*b*][1,5]naphthyridin-10-yl)amino]propyl]-1-piperazineëthanol trihydrochloride hydrate (**4**, Table I) as yellow crystals, m.p. 242-243°.

Compounds **1-3** and **5** (Table I) were prepared in a similar manner from 7,10-dichloro-2-methoxybenzo[*b*][1,5]naphthyridine (X) (12) and the appropriate polyamine in phenol.

4-[(7-Chloro-2-methoxybenzo[*b*][1,5]naphthyridin-10-yl)amino]-α-(diethylamino)-*o*-cresol Dihydrochloride (XII).

7,10-Dichloro-2-methoxybenzo[*b*][1,5]naphthyridine (X) (12) (27.9 g., 0.1 mole), 4-amino-α-(diethylamino)-*o*-cresol dihydrochloride (5) (26.7 g., 0.1 mole), and 75 g. of phenol was stirred and heated on a steam bath for 3 hours. The reaction mixture was cooled and poured into 3 l. of acetone containing excess concentrated hydrochloric acid. The solid that precipitated was collected by filtration, washed with acetone, and dried. The product was dissolved in water, made alkaline with sodium hydroxide, and extracted with chloroform. The combined chloroform extracts were washed successively with dilute aqueous sodium hydroxide and water, and the chloroform was removed *in vacuo*. The residue was treated with excess concentrated hydrochloric acid and diluted with acetone. The precipitate was collected, washed with acetone, dried *in vacuo* at 50°, and equilibrated in the air prior to analysis. The reddish-brown product weighed 20.0 g. (37%), m.p. 263° dec.

Anal. Calcd. for $C_{24}H_{25}ClN_4O_2 \cdot 2HCl \cdot 1.33H_2O$: C, 54.00; H, 5.60; N, 10.50; H_2O, 4.50. Found: C, 53.98; H, 5.41; N, 10.60; H_2O, 4.60.

2,2′-[[[5-[(7-Chloro-2-methoxybenzo[*b*][1,5]naphthyridin-10-yl)amino]salicyl]imino]diethanol Dihydrochloride (XIII).

Utilizing the procedure described above for the preparation of 4-[(7-chloro-2-methoxybenzo[*b*][1,5]naphthyridin-10-yl)amino]-α-(diethylamino)-*o*-cresol dihydrochloride (XII), the condensation of 55.8 g. (0.2 mole) of 7,10-dichloro-2-methoxybenzo[*b*][1,5]-naphthyridine (X) (12) with 59.8 g. (0.2 mole) of 2,2′-(5-amino-2-hydroxybenzylimino)diethanol dihydrochloride (15) in 75 g. of phenol afforded 37.0 g. (33%) of product as orange crystals from ethanol-acetone, m.p. 240° dec.

Anal. Calcd. for $C_{24}H_{25}ClN_4O_4 \cdot 2HCl \cdot H_2O$: C, 51.48; H, 5.22; N, 10.00; H_2O, 3.22. Found: C, 51.63; H, 5,28; N, 10.28; H_2O, 2.71.

7-Chloro-10-[[3-[(diethylamino)methyl]-*p*-anisidino]-2-methoxybenzo[*b*][1,5]naphthyridine (XIV).

Condensation of 5.0 g. (0.018 mole) of N^{α},N^{α}-diethyl-6-methoxytoluene-α,3-diamine dihydrochloride (5,8) with 5.0 g. (0.018 mole) of 7,10-dichloro-2-methoxybenzo[*b*][1,5]naphthyridine (12) in phenol according to the procedure described for the preparation of 7-chloro-10-[[3-[(diethylamino)methyl]-*p*-anisidino]-2-methoxybenzo[*b*][1,5]naphthyridine 5-oxide dihydrochloride (XX) gave 3.3 g. of the crude hydrochloride. The salt was converted to the base and recrystallized once from petroleum ether (b.p. 30-60°) and twice from acetonitrile to give 1.1 g. (13%) of pure base as orange crystals, m.p. 109-111°.

Anal. Calcd. for $C_{25}H_{27}ClN_4O_2$: C, 66.58; H, 6.04; N, 12.42. Found: C, 66.33; H, 5.99; N, 12.39.

7-Chloro-10-[[4-(diethylamino)-1-methylbutyl]amino]-2-methoxybenzo[*b*][1,5]naphthyridine N^{ω}-Oxide Dihydrochloride. Azacrine N^{ω}-Oxide Dihydrochloride (XV).

An aqueous solution of 20.0 g. (0.042 mole) of 7-chloro-10-[[4-(diethylamino)-1-methylbutyl]amino]-2-methoxybenzo[*b*][1,5]naphthyridine dihydrochloride (azacrine) (IX) (12) was made alkaline with aqueous sodium hydroxide and the base was extracted with chloroform. The combined chloroform extracts were washed with water and dried over anhydrous potassium carbonate. A solution of 6.9 g. (0.05 mole) of perbenzoic acid (23) in 100 ml. of chloroform was added portionwise over 5 minutes. The temperature rose to 30° and the reaction mixture turned dark red. After 3 days, the mixture was washed successively with two 50 ml. portions of 10% aqueous sodium carbonate and water, and the chloroform solution was dried over anhydrous potassium carbonate. The chloroform was removed *in vacuo* and the residue was treated with 500 ml. of 2-propanol and 2.5 equivalents of a 2-propanol-hydrogen chloride mixture. The 2-propanol mixture was concentrated to 250 ml., diluted with acetone, and cooled. The product was collected by filtration and recrystallized from 2-propanol-acetone to give 11.0 g. (52%) of yellow crystals, m.p. 202-204°.

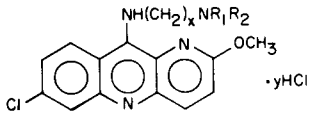
Anal. Calcd. for $C_{22}H_{29}ClN_4O_2 \cdot 2HCl \cdot 0.5H_2O$: C, 52.96; H, 6.47; N, 11.23; Cl, 21.32; H_2O, 1.81. Found: C, 52.65; H, 6.05; N, 11.07; Cl, 21.47; H_2O, 1.94.

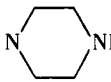
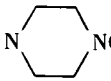
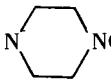
7,10-Dichloro-2-methoxybenzo[*b*][1,5]naphthyridine 5-Oxide (XVI).

A solution of 11.0 g. (0.04 mole) of 7,10-dichloro-2-methoxybenzo[*b*][1,5]naphthyridine (X) (12) in 600 ml. of chloroform was treated with a solution of 8.5 g. (0.044 mole) of *m*-chloroperbenzoic acid (80%) in 200 ml. of chloroform and the mixture

TABLE I

7-Chloro-10-[[(dialkylamino)alkyl]amino]-2-methoxybenzo[*b*][1,5]naphthyridines (a)

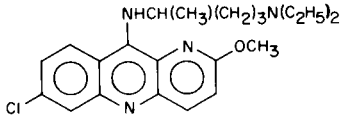
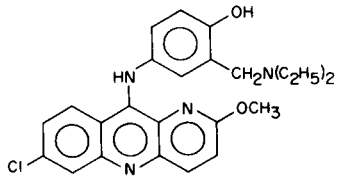
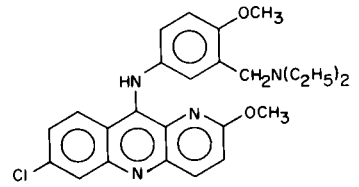
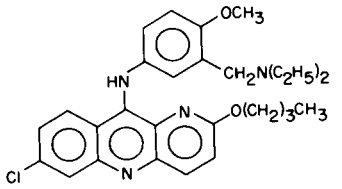
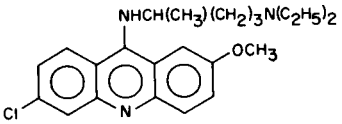


Compound No.	x	NR_1R_2	M.p., °C	Yield Purified, %	Formula		Carbon, %	Hydrogen, %	Nitrogen, %	Water, %
1	2		243-244	84	$C_{19}H_{22}ClN_5O{\cdot}3HCl{\cdot}2.5H_2O$	Calcd.:	43.36	5.75	13.31	8.56
						Found:	43.39	5.71	13.24	8.77
2	3	$N(CH_2CH_2OH)_2$	244-246 dec	65	$C_{20}H_{25}ClN_4O_3{\cdot}2HCl{\cdot}H_2O$	Calcd.:	48.44	5.89	11.30	3.63
						Found:	48.42	5.67	11.35	3.40
3	3		244-245	88	$C_{21}H_{26}ClN_5O{\cdot}3HCl{\cdot}2.33H_2O$	Calcd.:	45.75	6.16	12.70	7.62
						Found:	45.45	6.12	12.61	7.50
4	3		242-243	91	$C_{22}H_{28}ClN_5O_2{\cdot}3HCl{\cdot}2.9H_2O$	Calcd.:	44.67	6.27	11.84	8.83
						Found:	44.40	6.14	12.18	8.46
5	3	$NH(CH_2)_3N(CH_2CH_2OH)_2$	207-209	85	$C_{23}H_{32}ClN_5O_3{\cdot}3HCl{\cdot}1.75H_2O$	Calcd.:	45.82	6.44	11.62	5.23
						Found:	45.67	6.66	11.37	5.39

(a) Compounds were crystallized from ethanol-acetone.

TABLE II

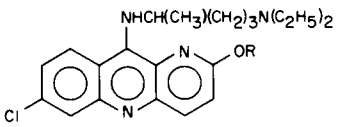
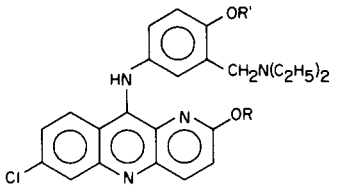
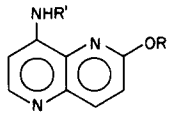
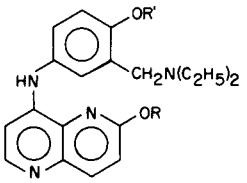
Physical Properties of Representative 10-Amino-7-chloro-2-methoxybenzo[*b*][1,5]naphthyridines, Benzo[*b*][1,5]naphthyridine *N*-Oxides, and 8-Amino-2-butoxy-1,5-naphthyridines

Basic Structure	Substituent	Compound No.	pK'_a (a) Chain	pK'_a (a) Ring	UV Absorption (b)	NMR Signals (c) NCH_2CH_3	NMR Signals (c) NCH_2CH_3
	None	IX	9.0	6.5	432 408	2.4	0.94 (t)
	N^{ω}-Oxide	XV	4.9	6.9	425 402	3.0	1.17 (t)
	5-Oxide	XVII	9.0	3.7	484	2.4	0.94 (t)
	N^{ω},5-Dioxide	XVIII	5.5	3.5	484	3.1	1.23 (t)
	None	XII	7.3	5.5	428		
	5-Oxide	XIX	7.4	3.0	520		
	None	XIV	8.6	5.8	430	2.48 (q)	0.90 (t)
	5-Oxide	XX	9.0	2.8	508	2.46 (q)	0.88 (t)
	None	XXI	7.8	5.3	428	2.46 (q)	0.90 (t)
	5-Oxide	XXV	8.3	3.0	505	2.45 (q)	0.88 (t)
	None	Va	9.0	7.2	414	2.4	0.90 (t)
	N^{ω}-Oxide	VII	5.4	7.6	418	3.0	1.14 (t)
	10-Oxide	VI	9.1	4.0	482		
	N^{ω},10-Dioxide	VIII	5.6	3.6	480	3.1	1.20 (t)

(a) Measured in 50% methanol. (b) Longest wavelength (mμ) maximum; measured in methanol containing excess potassium hydroxide. (c) Solvent: deuteriochloroform; t, triplet, q, quadruplet.

TABLE III

Antimalarial Effects of 10-Amino-7-chlorobenzo[*b*][1,5]naphthyridines, 10-Amino-7-chlorobenzo[*b*][1,5]naphthyridine *N*-Oxides, and 8-Amino-2-butoxy-1,5-naphthyridines Against *Plasmodium berghei* in Mice

Structure	R	R′	Other Substituent	Compound No.	No. of Mice	SD_{90} (a), mg./kg./day	Q (b)
	CH_3	---	None	IX	14	14.7	5.1
	CH_3	---	N^{ω}-Oxide	XV	28	5.9	12.6
	CH_3	---	5-Oxide	XVII	28	3.8	19.6
	CH_3	---	N^{ω},5-Dioxide	XVIII	14	11.2	6.7
	CH_3	H	None	XII	14	19.8	3.8
	CH_3	H	5-Oxide	XIX	14	6.2	12.0
	CH_3	CH_3	None	XIV	14	14.3	5.2
	CH_3	CH_3	5-Oxide	XX	28	6.3	11.8
	$(CH_2)_3CH_3$	CH_3	None	XXI	14	22.0	3.4
	$(CH_2)_3CH_3$	CH_3	5-Oxide	XXV	14	18.5	4.0
	$(CH_2)_3CH_3$	$CH(CH_3)(CH_2)_3N(C_2H_5)_2$	None	XXVIa	21	53	1.4
	$(CH_2)_3CH_3$	$(CH_2)_5N(CH_2)_4$	None	XXVIb	14	155	0.5
	$(CH_2)_3CH_3$	CH_3	None	XXVII	14	117	0.6

(a) SD_{90} represents the daily dose (mg./kg.) required for 90% suppression of the parasitemia in treated mice relative to control mice. The SD_{90} was estimated graphically using semi-logarithmic paper. (b) The quinine equivalent Q is the ratio of the SD_{90} of quinine hydrochloride (74.5 mg. base/kg./day) to the SD_{90} of the test substance under comparable experimental conditions. Drug amounts are expressed as free base.

was allowed to stand at room temperature for 48 hours. The yellow-green chloroform solution, which was highly fluorescent, was washed successively with dilute aqueous potassium carbonate and water and dried over anhydrous potassium carbonate. The dried chloroform solution was concentrated to 200 ml. and chilled. The product was collected by filtration and recrystallized from chloroform to give 7.5 g. (63%) of yellow crystals, m.p. 238-242°.

Anal. Calcd. for $C_{13}H_8Cl_2N_2O_2$: C, 52.90; H, 2.73; N, 9.49. Found: C, 52.53; H, 2.52; N, 9.23.

7-Chloro-10-[[4-(diethylamino)-1-methylbutyl]amino]-2-methoxybenzo[*b*][1,5]naphthyridine 5-Oxide Dihydrochloride. Azacrine 5-Oxide Dihydrochloride (XVII).

N^1,N^1-Diethyl-1,4-pentanediamine (5.0 g., 0.03 mole) and 7,10-dichloro-2-methoxybenzo[*b*][1,5]naphthyridine 5-oxide (XVI) (9.0 g., 0.03 mole) were allowed to react in phenol for 2.5 hours, and the reaction mixture was worked up according to the procedure described for the preparation of 4-[[3-[(7-chloro-2-methoxybenzo[*b*][1,5]naphthyridin-10-yl)amino]propyl]-1-piperazineëthanol trihydrochloride (4). The product (5.5 g., 37%) was obtained as bright yellow crystals from 2-propanol, m.p. 197-198° dec.

Anal. Calcd. for $C_{22}H_{29}ClN_4O_2 \cdot 2HCl$: C, 53.94; H, 6.38; N, 11.44. Found: C, 53.46; H, 6.66; N, 11.48.

7-Chloro-10-[[4-(diethylamino)-1-methylbutyl]amino]-2-methoxybenzo[*b*][1,5]naphthyridine N^{ω},5-Dioxide Dihydrochloride. Azacrine N^{ω},5-Dioxide Dihydrochloride (XVIII).

7-Chloro-10-[[4-(diethylamino)-1-methylbutyl]amino]-2-methoxybenzo[*b*][1,5]naphthyridine 5-oxide dihydrochloride (XVII) (6.0 g., 0.012 mole) was converted to the base, dissolved in chloroform, and treated with 1.66 g. (0.012 mole) of perbenzoic acid in 25 ml. of chloroform according to the procedure described for the preparation of 7-chloro-10-[[4-(diethylamino)-1-methylbutyl]-amino]-2-methoxybenzo[*b*][1,5]naphthyridine N^{ω}-oxide dihydrochloride (XV). The hydrochloric acid salt of the product (3.4 g., 55%) was obtained as yellow crystals from 2-propanol, m.p. 208-210° dec.

Anal. Calcd. for $C_{22}H_{29}ClN_4O_3 \cdot 2HCl \cdot 0.5H_2O$: C, 51.32; H, 6.27; N, 10.88. Found: C, 51.21; H, 6.12; N, 10.74.

4-[(7-Chloro-2-methoxybenzo[*b*][1,5]naphthyridin-10-yl)amino]-α-(diethylamino)-*o*-cresol 5-Oxide (XIX).

7,10-Dichloro-2-methoxybenzo[*b*][1,5]naphthyridine 5-oxide (XVI) (5.0 g., 0.017 mole) and 4-amino-α-(diethylamino)-*o*-cresol dihydrochloride (5) (4.6 g., 0.0175 mole) were condensed in phenol according to the procedure described for the preparation of 4-[(7-chloro-2-methoxybenzo[*b*][1,5]naphthyridin-10-yl)-amino]-α-(diethylamino)-*o*-cresol dihydrochloride (XII). The crude hydrochloride was converted to the base which was crystallized from chloroform-petroleum ether (b.p. 30-60°) to give 2.1 g. (27%) of maroon crystals, m.p. 205-206°.

Anal. Calcd. for $C_{24}H_{25}ClN_4O_3$: C, 63.64; H, 5.56; N, 12.37. Found: C, 63.19; H, 5.45; N, 12.04.

7-Chloro-10-[[3-[(diethylamino)methyl]-*p*-anisidino]-2-methoxybenzo[*b*][1,5]naphthyridine 5-Oxide Dihydrochloride (XX).

N^{α},N^{α}-Diethyl-6-methoxytoluene-α,3-diamine dihydrochloride (5,8) (5.0 g., 0.018 mole) and 10 g. of phenol was heated on a steam bath for 1 hour. To this hot solution was added 5.3 g. (0.018 mole) of 7,10-dichloro-2-methoxybenzo[*b*][1,5]naphthyridine 5-oxide (XVI) and 5 g. of phenol, and the mixture was stirred and heated on a steam bath for 2.5 hours. The mixture was then poured into acetone containing 2 equivalents of a 2-propanol-hydrogen chloride mixture, and the precipitate was collected and dissolved in water. The solution was made alkaline with ammonium hydroxide and the base was extracted with chloroform. The combined chloroform extracts were dried over anhydrous potassium carbonate, the chloroform was removed *in vacuo*, and the residue was triturated with acetone containing an excess of a 2-propanol-hydrogen chloride mixture. Crystallization of the crude product from 2-propanol-acetone afforded 5.2 g. (52%) of orange-red crystals, m.p. 219-220° dec.

Anal. Calcd. for $C_{25}H_{27}ClN_4O_3 \cdot 2HCl \cdot H_2O$: C, 53.82; H, 5.60; H_2O, 3.23. Found: C, 53.73; H, 5.29; H_2O, 2.60.

2-Butoxy-7-chloro-10-[[3-[(diethylamino)methyl]-*p*-anisidino]-benzo[*b*][1,5]naphthyridine (XXI).

2-Butoxy-7,10-dichlorobenzo[*b*][1,5]naphthyridine (XXIII) (12) (5.0 g., 0.016 mole) and N^{α},N^{α}-diethyl-6-methoxytoluene-α,3-diamine dihydrochloride (5,8) (4.3 g., 0.016 mole) were allowed to react in phenol according to the procedure described for the preparation of 7-chloro-10-[[3-[(diethylamino)methyl]-*p*-anisidino]-2-methoxybenzo[*b*][1,5]naphthyridine 5-oxide dihydrochloride (XX). The crude hydrochloride was converted to the base which was recrystallized from acetonitrile to give 4.0 g. (51%) of pure base as yellow crystals, m.p. 119-120°.

Anal. Calcd. for $C_{28}H_{33}ClN_4O_2$: C, 68.21; H, 6.75; N, 11.36. Found: C, 68.02; H, 6.68; N, 11.32.

2-Butoxy-7-chloro-10-[[4-(diethylamino)-1-methylbutyl]amino]-benzo[*b*][1,5]naphthyridine 5-Oxide (XXII).

2-Butoxy-7,10-dichlorobenzo[*b*][1,5]naphthyridine 5-oxide (XXIV) (3.0 g., 0.0009 mole) and N^1,N^1-diethyl-1,4-pentanediamine (2.5 g., 0.0012 mole) were stirred and heated in 10 g. of phenol on a steam bath for 3 hours. The cooled reaction mixture was poured into a mixture of 300 ml. of acetone and 4 ml. of a 25% 2-propanol-hydrogen chloride mixture, and the crude hydrochloric acid salt was collected by filtration and dissolved in water. The solution was made alkaline with aqueous sodium hydroxide and extracted with ether. The combined ether extracts were washed with water, dried over anhydrous potassium carbonate, and concentrated on a rotary evaporator. The residual dark purple oil was crystallized twice from acetonitrile to give 1.9 g. (46%) of pure product as maroon crystals, m.p. 71-73°.

Anal. Calcd. for $C_{25}H_{35}ClN_4O_2$: C, 65.41; H, 7.69; N, 12.21. Found: C, 65.33; H, 7.64; N, 12.24.

2-Butoxy-7,10-dichlorobenzo[*b*][1,5]naphthyridine 5-Oxide (XXIV).

2-Butoxy-7,10-dichlorobenzo[*b*][1,5]naphthyridine (XXIII) (12) (10.0 g., 0.031 mole) and *m*-chloroperbenzoic acid (80%) (7.0 g., 0.034 mole) were allowed to react in chloroform utilizing the procedure employed for the preparation of 7,10-dichloro-2-methoxybenzo[*b*][1,5]naphthyridine 5-oxide (XVI). The product (10.0 g., 96%) was obtained as yellow crystals from 2-propanol, m.p. 135-137°.

Anal. Calcd. for $C_{16}H_{14}Cl_2N_2O_2$: C, 56.99; H, 4.18; N, 8.31. Found: C, 57.26; H, 4.30; N, 8.33.

2-Butoxy-7-chloro-10-[[3-[(diethylamino)methyl]-*p*-anisidino]benzo[*b*][1,5]naphthyridine 5-Oxide (XXV).

2-Butoxy-7,10-dichlorobenzo[*b*][1,5]naphthyridine 5-oxide (XXIV) (2.5 g., 0.0074 mole) was condensed with N^{α},N^{α}-diethyl-6-methoxytoluene-α,3-diamine dihydrochloride (5,8) (1.9 g., 0.0067 mole) in phenol utilizing the procedure described for the preparation of 7-chloro-10-[[3-[(diethylamino)methyl]-*p*-anisidino]-2-methoxybenzo[*b*][1,5]naphthyridine 5-oxide dihydrochloride

(XX). The crude hydrochloride was converted to the base which was crystallized twice from methanol to give 2.0 g. (59%) of base as maroon crystals, m.p. 150.5-152°.

Anal. Calcd. for $C_{28}H_{33}ClN_4O_3$: C, 66.06; H, 6.53; N, 11.01. Found: C, 66.08; H, 6.59; N, 10.86.

2-Butoxy-8-[[5-(1-pyrrolidinyl)pentyl]amino]-1,5-naphthyridine Salt with 2 f. wt. β-Resorcylic Acid (XXVIb).

A mixture of 9.0 g. (0.038 mole) of 2-butoxy-8-chloro-1,5-naphthyridine (13), 30.0 g. (0.19 mole) of 1-(5-aminopentyl)-pyrrolidine, and 1.5 g. of copper powder was stirred and heated at 180-190° for 19 hours. The mixture was cooled, treated with 100 ml. of 5 *N* sodium hydroxide, and extracted with ether. The combined ether extracts were dried over anhydrous potassium carbonate and volatile materials were removed *in vacuo*. The residue was distilled using an oil diffusion pump to give 7.2 g. (53%) of the desired base as a yellow oil, b.p. 180-184°/0.005 mm.

The above base (6.2 g., 0.0174 mole) was dissolved in 500 ml. of ether and a solution of 8.0 g. (0.052 mole) of β-resorcylic acid in 300 ml. of ether was added with stirring. The salt that precipitated was collected by filtration, washed well with ether, and dried *in vacuo* at room temperature. The salt (9.8 g.) did not analyze correctly, and was therefore converted back to the base with aqueous sodium hydroxide. The base was extracted with ether, and the combined ether extracts were dried over anhydrous potassium carbonate. To the dry ether solution was then added 2 equivalents of β-resorcylic acid and the salt was collected, washed with ether, and dried in a vacuum desiccator over phosphorus pentoxide. The pale yellow salt thus obtained weighed 6.2 g. (24%), m.p. 80-110° dec.

Anal. Calcd. for $C_{21}H_{32}N_4O \cdot 2C_7H_6O_4 \cdot 0.7H_2O$: C, 62.06; H, 6.76; N, 8.27; H_2O, 1.86. Found: C, 62.04; H, 7.08; N, 8.30; H_2O, 1.86.

2-Butoxy-8-[3-[(diethylamino)methyl]-*p*-anisidino]-1,5-naphthyridine (XXVII).

A mixture of 5.0 g. (0.021 mole) of 2-butoxy-8-chloro-1,5-naphthyridine (13), 6.0 g. (0.021 mole) of N^{α},N^{α}-diethyl-6-methoxytoluene-α,3-diamine, and 50 g. of phenol was stirred and heated on a steam bath for 4 hours and the mixture was poured into 1 l. of acetone containing 5 ml. of concentrated hydrochloric acid. A precipitate formed upon the addition of petroleum ether. The precipitate was dissolved in 0.5 *N* hydrochloric acid, and the acid solution was washed with ether, treated with excess aqueous sodium hydroxide, extracted with ether, and the ether extracts were dried over anhydrous potassium carbonate. The ether was removed and the residue was crystallized from *n*-hexane at −20° to give 2.65 g. (33%) of yellow crystals, m.p. 78-80°.

Anal. Calcd. for $C_{24}H_{32}N_4O_2$: C, 70.56; H, 7.90; N, 13.72. Found: C, 70.38; H, 8.01; N, 13.80.

Acknowledgments.

The authors express their appreciation to Mr. Neil F. Haley, Miss Nancy Headen, Miss Joan D. Multhaup, and Mr. Frank H. Tendick for chemical assistance, and to Dr. Paul E. Thompson and co-workers for the antifilarial and antimalarial evaluation of these substances. We also thank Dr. J. M. Vandenbelt, Mr. R. B. Scott, and associates for the spectral data, and Mr. Charles E. Childs and co-workers for the microanalyses.

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Received November 13, 1969 Ann Arbor, Michigan 48106