Synthesis of Naphthyridinone Derivatives as Potential Antimalarials

F. Ivy Carroll, Bertold D. Berrang and C. Preston Linn*

Chemistry and Life Sciences Group, Research Triangle Institute, Research Triangle Park, North Carolina 27709, USA

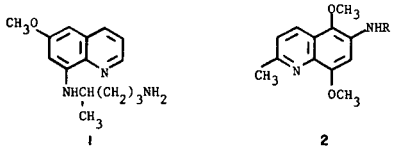
Received February 17, 1981

In this paper we present the synthesis of 8-(4'-amino-1'methyl-butylamino)-5-(β,β,β-trifluoroethoxy)-1,6--naphthyridine (**4**), 8-(4'-amino-1'methylbutylamino)-6-methyl-1,6-naphthyridine-5-one (**5**), two 1-alkyl-3-(4'--amino-1'-methylbutylamino)-7-methyl-1,8-naphthyridin-4-ones (**20a**) and **20b**), 3-(1'-amino-4'-methylbutyl-amino)-1-ethyl-7-methyl-1,8-naphthyridin-4-one (**20c**), and 4-(4'-diethylamino-1'-methylbutylamino)-7-methyl--1,7-naphthyridin-8-one (**28**). The compounds were evaluated for antimalarial activity in the *Plasmodium berghei* screen and found to be inactive.

J. Heterocyclic Chem., **18**, 941 (1981).

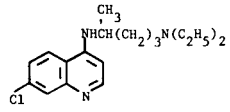
The 8-aminoquinolines, such as primaquine (**1**), are the most satisfactory drugs for the radically curative treatment (complete eradication of the parasites) of vivax malaria (1). Primaquine (**1**) is highly active against the primary exoerythrocytic form of *Plasmodium vivax* and *Plasmodium falciparum* and against the gametocytes of all four species of plasmodia that infect man (1). In addition, certain 6-(dialkylaminoalkylamino)-5,8-dimethoxyquinaldines have been reported to show activity in prophylactic screens (2).

In this paper we present the synthesis and biological evaluation of some 1,6-naphthyridinone and 1,8-naphthyridinone analogs of **1** and **2** respectively or their metabolites. In addition, we describe the synthetic and biological test results on a 1,7-naphthyridinone analog of chloroquine (**3**).



1

2



3

Chemistry

Chart 1 outlines the procedure used to prepare 8-(4'--amino-1'-methylbutylamino)-5-(β,β,β-trifluoroethoxy)--1,6-naphthyridine (**4**) and 8-(4'-amino-1'methylbutyl-amino)-6-methyl-1,6-naphthyridine-5-one (**5**). Starting with the known 2,4-dichloropyridine (**6**) (3), 2,4-di-(β,β,β--trifluoroethoxy)pyridine (**7**) was perpared which could be selectively nitrated in the 5-position to give **8a**. Only a small amount of the 3-nitro isomer **8b** was obtained. The directive effect of the trifluoroethoxy groups on the nitration of the pyridine ring is interesting since nitration of 2,4-diethoxypyridine gave mainly the 3-nitro derivative (4, 5). Treatment of **8a** with 3-aminopropanal diethylacetal at room temperature gave selectively the 4-substituted product **9**. When **9** was heated in phosphoric acid, a good yield of the 1,2-dihydroproduct **10** was obtained. Oxidation of **10** with chloranil gave the desired intermediate **11**. Mild hydrolysis of **11** followed by methylation gave **12**. Stannous chloride reduction of **11** and **12** gave the amines **13** and **14**, respectively. The alkylation of **13** and **14** with 4-iodo-1-phthalimidopentane in the presence of triethylamine, followed by removal of the phthaloylprotecting group with hydrazine in refluxing ethanol gave the desired compounds **4** and **5** (6).

Chart 2 outlines the reaction scheme developed for the preparation of the desired 1,8-napthridinones. Alkylation of ethyl 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (**15**) (7) with the appropriate alkyl iodide yielded **16**. Treatment of **16** with hydrazine afforded the hydrazide **17**. Curtius degradation of **17a** and acid hydrolysis of the resulting urethane (**18**) gave the desired amino derivatives **19a**. Similar treatment of **17b** gave the amine **19b** without isolation of the pure urethane. The amines **19a-b** were converted to the target compounds **20a-c** by standard procedures (6).

The 1,7-naphthyridinone target compound was prepared as outlined in Chart 3. Heating 3-acetylaminopyridine *N*-oxide (**21**) (8) with acetic anhydride gave, after hydrolysis, 3-amino-2-pyridone (**22**). Condensation of **22** with diethyl ethoxymethylene malonate yielded **23** which could be selectively methylated at the heterocyclic nitrogen. The resulting derivative **24** upon heating cyclized to the 1,7-naphthyridine **25**. Hydrolysis and decarboxylation of **25** afforded **26**. Treatment of **26** with a phosphorus oxychloride and phosphorus pentachloride mixture gave **27**. The intermediate **27** was treated with 4-amino-1-diethylaminopentane to give target compound **28**.

Compounds 4, 5, 15, 16a-b, 17a-b, 20a-c and 28 were tested for blood schizonticidal activity against *P. berghei* in mice (9). Testing was carried out at the Rane

0022-152X/81/050941-06$02.25

Chart 1

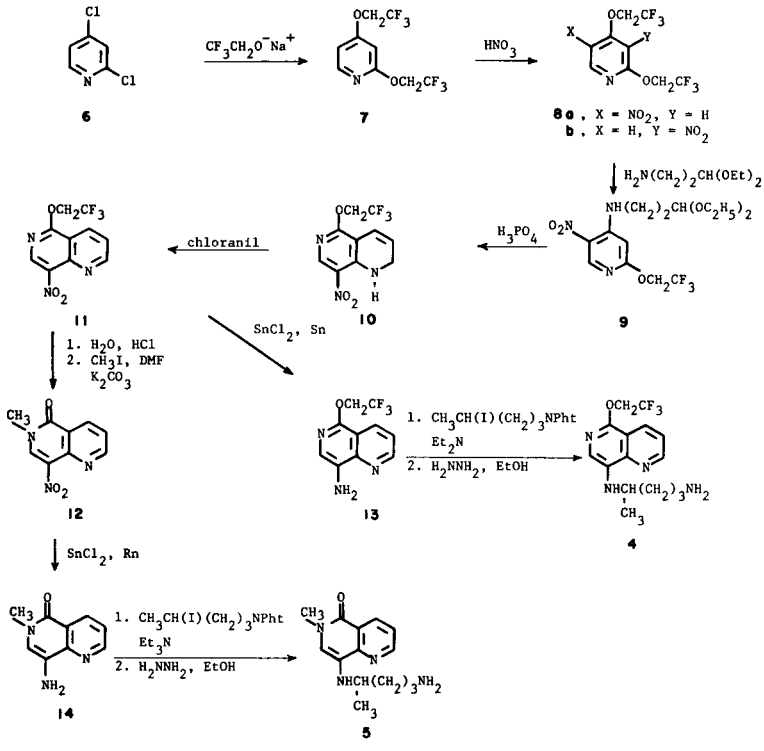


Chart 2

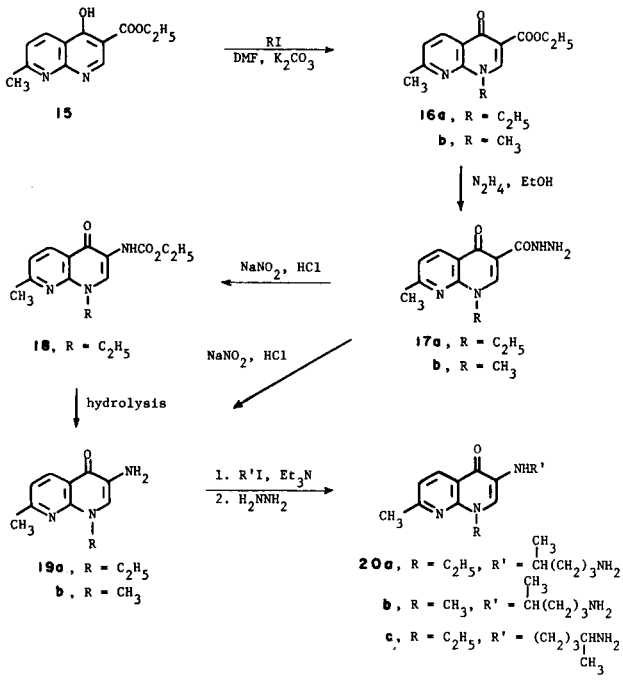
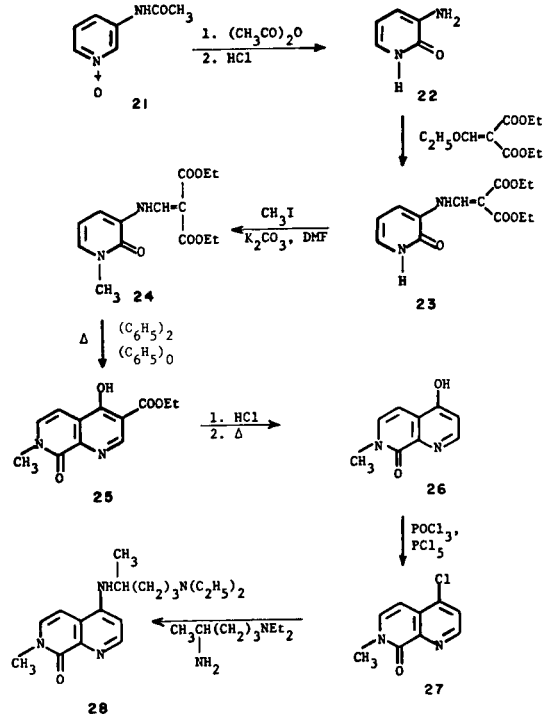


Chart 3



Laboratory, Unversity of Miami, Miami, FL. the compounds were all inactive at the highest dosage level tested.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage microscope using a calibrated thermometer. Ir spectra were measured with a Perkin Elmer Model 267 or 467 Grating Infrared Spectrophotometer. Nmr spectra were recorded on a Varian Model HA-100 spectrameter using tetramethylsilane as an internal standard. Ms were determined on an AEI-MS 902 spectrometer. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Illinois or Integral Microanalytical Laboratories, Inc., Raleigh, North Carolina.

2,4,-Di-(β,β,β-trifluoroethyoxy)pyridine (**7**).

Into 40 ml of trifluoroethanol 3 g of sodium were introduced carefully with ice cooling over a period of 6 hours. The mixture was stirred at room temperature until all of the metal had reacted. This mixture was autoclaved with 6 g of 2,4-dichloropyridine (**6**) (3) at 150° for 14 hours. The product was evaporated under diminished pressure and dissolved in 20 ml of water. The resulting suspension was extracted twice with chloroform. Ater evaporation of the chloroform, 9 g (80%) of **7** remained as a light brown oil. Distillation of a small sample gave the analytical sample, bp 59-60° at 1 mmHG; nmr (deuteriochloroform): δ 4.29, 4.65 (2 q, CH_2-CF_3); 6.2 (d, H_3); 6.47 (2 d, H_5); 7.83 (d, H_6) ppm.

Anal. Calcd. for $C_9H_7F_6NO_2$: C, 39.29; H, 2.57; N, 5.09. Found: C, 39.19; H, 2.64; N, 5.25.

2.4-Di-(β,β,β-trifluoroethoxy)-5-nitropyridine (**8a**).

Under ice cooling, 9 g of **7** were added dropwise with stirring to 80 ml of fuming nitric acid. After completed addition, 80 ml of concentrated sulfuric acid were added slowly to the solution, and the resulting mixture was heated at 90-95° for 5 hours. After cooling to room temperature, the product was poured into 500 g crushed ice with vigorous stirring. Filtration of the white precipitate gave 4.2 g (40%) of **8a** which had mp 88-90°. A sample of **8a** recrystallized from 2-propanol-water for analysis had mp 105-107°; nmr (deuteriochloroform): δ 4.47 (q, CH_2CF_3): 4.78 (q, CH_2CF_3); 6.33 (s, H_3); 8.67 (s, H_6) ppm.

Anal. Calcd. for $C_9H_6F_6N_2O_4$: C, 33.77; H, 1.89; N, 8.75. Found: C, 34.15; H, 1.63; N, 8.56.

From the filtrates above a small sample of 2,4-di-β,β,β-trifluoroethoxy-3-nitropyridine (**8b**) was obtained, mp 63°; nmr (deuteriochloroform): δ 4.45 (q, CH_2CF_3); 4.77 (q, CH_2CF_3); 6.57 (d, H_5); and 8.08 (d, H_6) ppm.

Anal. Calcd. for $C_9H_6F_6N_2O_4$: C, 33.77; H, 1.89, N, 8.75. Found: C, 33.57; H, 1.76; N, 8.80.

4-(3',3'-Diethoxypropylamino)-5-nitro-2-(β,β,β-trifluoroethoxy)-pyridine (**9**).

The 3-aminopropionaldehyde diethyl acetal required for the synthesis of **9** was obtained by autoclaving 5 g (0.03 mole) of 3-chloro-1,1-diethoxypropane in 10 ml of dimethylformamide solution with 6.5 g (0.035 mole) of potassium phthalimide at 145° for 5 hours. The resulting brown suspension was diluted with water, extracted with methylene chloride and evaporated to a brown syrup. This syrup was purified by silica gel chromatography using methylene chloride as eluent. The product (7.0 g, 83%) was refluxed with 2 equivalents of hydrazine in methanol for 2 hours. After filtration of the cooled mixture, the solvent was evaporated and the residue dissolved in methylene chloride. The solution was filtered and concentrated to give 3.2 g (87%) of the propionaldehyde derivative as a yellow oil; nmr (deuteriochloroform): δ 1.15 (t, CH_3CH_2O); 1.8 (m, CHCH_2); 2.2 (broad 5, NH_2); 2.8 (m, CHCH_2CH_2); 3.5 (m, OCH_2CH_3); and 4.55 (t, CH-CH_2) ppm.

A chloroform solution of the product (3.2 g, 0.022 mole, in 20 ml was combined with a solution of 7 g (0.025 mole) of **8a** in 100 ml of chloroform. The mixture turned yellow immediately and warmed due to an exothermic reaction. After 1 hour, the solvent was evaporated by a combination of heating on the steam bath followed by freeze-drying. The resulting yellow syrup crystallized spontaneously to yield 7.8 g (97%) of **9**. The crude yellow product was used without purification for subsequent cyclization. The analytical sample prepared by recrystallization from a mixture of ether and heptane had mp 119-120°; nmr (DMSO-d_6): δ 1.1 (t, CH_3CH_2O); 1.8 (m, CH-CH_2); 3.4 (m, CH-CH_2-CH_2, OCH_2-CH_3); 4.5 (t, CH-CH_2); 4.9 (q, CH_2-CF_3); 6.9 (s, H_3); and 8.7 (s, H_6) ppm.

Anal. Calcd. for $C_{14}H_{20}F_3N_3O_5$: C, 45.78; H, 5.49; N, 11.44. Found: C, 45.85; H, 5.49; N, 11.48.

8-Nitro-5-(β,β,β-trifluoroethyoxy)-1,2-dihydro-1,6-naphthyridine (**10**).

A sample of pyridine intermediate **9** (12 g, 0.033 mole) was heated in 100 ml of 85% phosphoric acid at 100° for 2 hours. The cooled mixture was poured onto 700 g of ice and filtered. This gave 6.5 g (76%) of the intermediate **10** as an orange-yellow powder which had m.p. 165° after recrystallization from a chloroform and ethanol mixture; nmr (DMSO-d_6): δ 4.4 (m, NHCH_2-CH=); 4.9 (q, CH_2CF_3); 5.7, 6.3 (2d, H_3,H_4); 8.3 (broad s, NH); 8.6 (s, H_7) ppm.

Anal. Calcd. $C_{10}H_8F_3N_3O_3$): C, 43.65; H, 2.93; N, 15.27; Found: C, 43.43; H, 2.96; N, 14.84.

8-Nitro-6-methyl-1,6-naphthyridin-5-one (**12**).

The intermediate **10** (6.5 g, 0.025 mole) was dissolved in 510 ml of chloroform and refluxed with 7.5 g (0.03 mole) of chloranil for 2.5 hours. The mixture was cooled to 0°, filtered and the filtrate concentrated to dryness. The yellow-brown residue was heated with 200 ml of 15% hydrochloric acid on a hot water bath for 1 hour. After cooling and removal of the insoluble material by filtration, the yellow-brown solution was concentrated and the residue dried under vacuum overnight. This gave 5 g (0.021 mole) of the naphthyridinone as the hydrochloride salt. The compound was dissolved in 50 ml of dimethylformamide, potassium carbonate (35 g) was added as a solid and the suspension vigorously stirred while 1.5 g (0.01 mole) of methyl iodide were added. The temperature rose to 30° and was maintained at this temperture for 1.5 hours. An additional 1.5 g of methyl iodide were introduced with stirring, and after 2 hours, an additional 0.7 g of the same material was added. The mixture was stirred at room temperature overnight. The inorganic matter was separated by filtration, and the solvents were removed *in vacuo*. Partitioning the residue with chloroform and water provided 3.7 g of **12** as a light brown material.

Difficulties in further processing of **12** suggested a need to purify this intermediate carefully before submitting it to reduction and alkylation. Hence, crude **12** was passed through a silica gel column using chloroform as eluent. The recovered product was recrystallized from chlorofrom-2-propanol for additional purification. This gave 3.2 g (63%) of analytically pure **12**, mp 191-192°; nmr (deuteriochloroform): δ 3.6 (s, NCH_3); 7.4 (q, H_3); 8.45 (s, H_7); 8.57 (2d, H_4); 8.95 (2d, H_2) ppm.

Anal. Calcd. for $C_9H_7N_3O_3$: C, 52.69; H, 3.44; N, 20.48. Found: C, 52.61;H, 3.31; N, 20.53.

8-Amino-6-methyl-1,6-naphthyridin-5-one (**14**).

Pure **12** (3.2 g, 0.016 mole) was reduced with stannous chloride under standard conditions (6). The amine **14** was recovered as bright yellow needles (2.5 g, 91%) which darkened rapidly upon exposure to air; nmr (deuteriochloroform): δ 3.54 (s, NCH_3); 6.79 (s, H_7); 7.37 (1, H_3); 8.64 (2d, H_4); 8.82 (2d, H_2). Because of its instability, **14** was immediately subjected to alkylation.

8-(4'-Amino-1'-methylbutylamino)-6-methyl-1,6-naphthyridin-5-one (**5**) Resorcylate.

A solution of 2.4 g (0.014 mole) of **14** in 2.5 ml of dimethylformamide was heated under argon to 80°, while a mixture of 5 g (0.015 mole) of 4-iodo-1-phthalimidopentane and 2 g (0.02 mole) of triethylamine was added dropwise with stirring in 4 hours. Heating at 85° was continued for 2 hours, then the product was isolated by partitioning between chloroform and water. Evaporation of the chloroform solution *in vacuo* gave crude alkylated material as a brown syrup. This was chromatographed on silica

gel using chloroform-acetone as eluent. Thus, 0.7 g of alkylated material that was pure by tlc analysis was isolated. Rechromatography of an additional impure fraction gave 2.5 g of pure product; nmr (deuteriochloroform): nmr δ 1.2 (d, CH_3CH); 3.5 (s, NCH_3); 6.3 (s, H_7); 7.33 (q, H_3); 7.67 (m, phtahaloyl); and 8.64 (m, H_2, H_4) ppm. Hydrazinolysis by standard procedure (6) of this material gave the unstable free amine **5** (1.2 g. 72%). It was immediately converted to the resorcylate in the following manner. An ethanolic solution (50 ml) of 1.2 g (0.005 mole) of**5** was mixed with 3 g (0.02 mole) of resorcylic acid dissolved in 10 ml of ethanol. The yellow-brown mixture was added dropwise to 400 ml of ether with vigorous stirring over a 45 minute period. The resorcylate crystallized as a bright yellow powder. It was collected by filtration, thoroughly washed with ether and immediatly dried under vacuum. The analytically pure salt of **5** was somewhat hygroscopic. Solutions upon exposure to oxygen darkened quickly at room temperature but could be stored for weeks if kept under nitrogen at -25°. The salt weighted 1.8 g (92%) and had mp 172-174° dec; nmr (DMSO-d_6): δ 1.17 (d, CH_3CH); 3.52 (s, NCH_3); 6.03 (m, resorcylate); 6.8 (s, H_7); 7.5 (m, H_3, resorcylate); 8.5 (2d, H_4); and 8.87 (2d, H_2) ppm.

Anal. Calcd. for $C_{21}H_{26}NO_5 \cdot \frac{1}{2}H_2O$): C, 59.26; H, 6.43; N, 13.23. Found: C, 59.29; H, 6.07; N, 13.23.

8-Nitro-5-(β,β,β-trifluoroethoxy)-1,6-naphthyridine (**11**).

For oxidation, 4 g (0.015 mole) of **10** and 4 g (0.016 mole) of chloranil were heated in 100 ml of tetrahydrofuran on the water bath. After 2 hours, the solvent was evaporated and the residue dissolved in methylene chloride. The insoluble matter was removed by filtration, and the soluble portion was chromatographed on silica gel using methylene chloride as eluent to give **11** (3 g, 75%) as white crystals, mp 130-132°; nmr (deuteriochloroform): δ 4.8 (q, CH_2CF_3); 7.4 (q, H_3); 7.57 (s, H_7); 8.44 (2d, H_4); and 8.9 (2d, H_2) ppm.

Anal. Calcd. for $C_{10}H_6F_3N_3O_3$: C, 43.65; H, 2.20; N, 15.27. Found: C, 44.09; H, 2.20; N, 15.40.

8-Amino-5-(β,β,β-trifluoroethoxy)-1,6-naphthyridine (**13**).

The nitro compound **11** (3 g, 0.011 mole) was dissolved in 100 ml of tetrahydrofuran. Ethanol (100 ml) was added to the solution and the mixture cooled to 0°. While maintaining a temperature of 0-5°, 100 ml of dilute hydrochloric acid (1:4) was added to the solution with efficient stirring followed by 600 mg of tin powder and 9 g (0.04 mole) of stannous chloride. The mixture turned intensively yellow immediately, then dark brown. After 45 minutes, the suspension was neutralized with sodium carbonate and precipitated salts were dissolved with sodium hydroxide. The clear solution was extracted with methylene chloride and the extract after drying with sodium sulfate chromatographed on silica gel, using methylene chloride-ethyl acetate as solvent. This provided 1.2 g (45%) of a yellow crystalline solid which darkened rapidly upon storage and was therefore immediately submitted to alkylation. The analytical sample prepared by recrystallization from a mixture of methylene chloride and hexane had mp 119-120°; nmr (Deuteriochloroform): δ 4.8 (q, CH_2CF_3); 7.41 (q, H_3); 8.58 (s, H_7); 8.47 (2d, H_4); 8.90 (2d, H_2) ppm.

Anal. Calcd. for $C_{10}H_8F_3N_3O$: C, 49.39; H, 3.31; N, 17.28. Found: C, 49.31; H, 3.28; N, 17.00.

8-(4'-Amino-1'methylbutylamino)-5-(β,β,β-trifluoroethoxy)-1,6-naphthyridine (**4**) Trifumarate.

A solution of 2.4 g (0.01 mole) of **13** in 0.7 ml of dimethylformamide was heated with stirring under argon at 85-90° while a mixture of 7 g (0.02 mole) of 4-iodo-1-phthalimidopentane and 3 g (0.03 mole) of triethylamine was introduced dropwise over a period of 4 hours. The brown product was partitioned with methylene chloride and water. The organic phase was purified by passing through a silica gel column. The product was eluted with methylene chloride-acetone solvent. This gave 2.5 g (53%) of alkylated matter and 1.2 g (0.005 mole) of starting amine. The latter dissolved in 0.5 ml of dimethylformamide was resubmitted to alkylation at 105° adding 3.5 g (0.01 mole) of alkylating agent as above and 2 g (0.02 mole) of triethylamine in 2 hours with stirring. Heating at 105° was continued for an additional 2 hours. The dark brown mixture was cooled and partitioned between methylene chloride-water. The organic layer was chromatographed as described above which gave an additional 1.1 g (48%) of alkylated materials as pure yellow syrup; nmr (deuteriochloroform): δ 1.29 (d, CH_3CH); 4.78 (q, CH_2CF_3); 7.28 (s, H_7); 7.48 (q, H_3); 7.7 (m, Phth.); 8.44 (2d, H_4); 8.85 (2d, H_2) ppm.

The alkylated product (3.6 g) was treated with hydrazine in ethanol in the usual way for removal of the protecting group. This provided 1.8 g (70%) of **4**. The free amino compound **4** (1.8 g, 0.0055 mole) dissolved in ethanol was treated with an alcoholic solution of 2.2 g (0.019 mole) of fumaric acid. The yellow solution was concentrated *in vacuo* to 20 ml, an equal volumn of 2-propanol was added and the solution cooled to -15°. This furnished a trifumarate salt (by nmr analysis) as yellow crystalline material of mp > 130° dec, 2.5 g (69%); nmr (DMSO-d_6); δ 1.2 (d, CH_3CH); 4.96 (q, CH_2CF_3); 6.46 (s, CH = CH fumarate); 7.36 (s, H_7); 7.64 (q, H_3); 8.94 (m, H_2) ppm.

Anal. Calcd. for $C_{27}H_{31}F_3N_4O_{13} \cdot H_2O$: C, 46.69; H, 4.79; N, 8.07. Found: C, 46.87; H, 4.71; N, 8.12.

1-Ethyl-7-methyl-1,8-naphthyridin-4-one-3-carboxhydrazide (**17a**).

A solution of 11.7 g (0.045 mole) of ethyl 1-ethyl-7-methyl-1,8-naphthyridine-4-one-3-carboxylate (**16a**) (10) in tetrahydrofuran-methanol (2:1) containing two equivalents of hydrazine was refluxed for 2 hours. During this time, all material went into solution. After cooling at 0° for several hours, the hydrazide **17a** was separated by filtration. A second crop was recovered by concentrating and cooling the mother liquor. Combined yield 9.4 g (86%), mp 192-193°. nmr (deuteriochloroform): δ 1.45 (t, CH_3-CH_2N); 2.66 (s, CH_3); 4.51 (q, CH_3CH_2N); 7.18 (d, H_6); 8.57 (d, H_5); 8.80 (s, H_2) ppm.

Anal. Calcd. for $C_{12}H_{14}N_4O_2$: C, 58.52; H, 5.73; N, 22.75. Found: C, 58.03; H, 5.60; N, 22.71.

3-Amino-1-ethyl-7-methyl-1,8-naphthyridin-4-one (**19a**).

Compound **17a** (5 g, 0.02 mole) was dissolved in 150 ml of ice cold 2*N* hydrochloric acid and transferred to a 2 l Erlenmeyer flask. A mixture of 150 ml of ether and 150 ml of methylene chloride was added and the temperature of the contents adjusted to 8°. Within a one-half hour period a concentrated solution of 1.6 g of sodium nitrite was added dropwise with vigorous stirring. The aqueous layer was separated and reextracted with chloroform. The two organic phases were each washed with sodium bicaronate and dried over sodium sulfate and subsequently over magnesium sulfate. After evaporation, the ether phase gave 4.5 g of urethane **18**, the chloroform extract yielded 0.2 g of **18**, combined yield 4.7 g (85%). nmr (deuteriochloroform): δ 1.2; 1.32 (2t, OCH_2CH_3, NCH_2-CH_3); 2.6 (s, CH_3); 4.07; 4.42 (2 q, OCH_2-CH_3, NCH_2-CH_3); 7.15 (d, H_6); 8.32 (d, H_5); 8.6 (s, H_2) ppm.

Anal. Calcd. for $C_{14}H_{17}N_3O_3$: C, 61.07; H, 6.23; N, 15.26. Found: C, 60.97; H, 6.21; N, 15.50.

For hydrolysis the urethane product (4.4 g) was subjected to autoclaving with concentrated hydrochloric acid (15 ml) at 150° for 2 hours. The cooled solution was evaporated to a small volume, made basic with sodium hydroxide and extracted with chloroform. The extract, after washing with water and drying over sodium sulfate, gave 1.5 g (46%) of **19a** as yellow crystalline material. The analytical sample prepared by recrystallization from 2-propanol had mp 133-135°; nmr (deuteriochloroform): δ 1.35 (t, CH_3CH_2N); 2.6 (s, CH_3); 4.38 (q, CH_3-CH_2N); 6.91 (d, H_6); 7.3 (s, H_2); 8.48 (d, H_5) ppm; high resolution mass spectrum m/e required for $C_{11}H_{13}N_3O$, 203.1058, observed 203.1056.

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.68. Found: C, 65.40; H, 6.43; N, 20.60.

3-(4'-Amino-1'-methylbutylamino)-1-ethyl-7-methyl-1,8-naphthyridin-4-one (**20a**) Dihydrobromide.

A stirred solution of 3 g (0.015 mole) of **19a** in 1 ml of dimethylformamide was heated under argon in an oil bath kept at 85° while a solution of 10 g (0.03 mole) of 4-iodo-1-phthalimidopentane in 3 g (0.03 mole) of triethylamine was added dropwise over a period of 10 hours. The

yellow-brown product was extracted with benzene and filtered. The benzene mixture was washed with water and evaporated to a syrup. This was purified by silica gel chromatography using chloroform eluent to give 6 g of alkylated material as a yellow oil. An alcoholic solution of the product was refluxed with two equivalents of hydrazine for 2 hours. The cooled and filtered solution was concentrated and redissolved in methylene chloride. After filtration and removal of the solvent **20a** (2.7 g, 64%) was recovered as a yellow oil. It was treated with two equivalents of hydrogen bromide in ethanol and tetrahydrofuran solution. Upon concentration and addition of excess tetrahydrofuran, the hydrobromide salt of **20a** began to crystallize in light yellow prisms which after washing with tetrahydrofuran and 2-propanol weighed 3 g and had mp 265° dec, nmr (DMSO-d_6): δ 1.33 (m, CH_3-CH_2N, CH_3-CH); 2.62 (s, CH_3); 4.5 (q, CH_3-CH_2N); 7.32 (d, H_6); 8.4 (d, H_5); 8.6 (s, H_2) ppm.

Anal. Cacld. for $C_{16}H_{26}Br_2N_4O$: C, 42.69; H, 5.82; N, 12.44. Found: C, 42.35; H, 5.81; N, 12.21.

3-(1'-Amino-4'-methylbutylamino)-1-ethyl-7-methyl-1,8-naphthyridin-4-one (**20c**) Fumarate.

Compound **19a** (2.6 g, 0.013 mole) was dissolved in 2 ml of hot dimethylformamide. To this solution a mixture of 6 g (0.018 mole) of 1-iodo-4-phthalimidopentane and 2 g (0.02 mole) of triethylamine was added with stirring at 85° under argon. After completed addition (3 hours), the resulting brown solution was heated another one-half hour at 90°. The mixture was concentrated *in vacuo*, dissolved in methylene chloride and extracted with water. The organic layer was concentrated to a syrup and purified by silica gel column chromatography, using methylene chloride-ethyl acetate in ethanol solution containing 2 g (0.06 mole) of hydrazine for 3 hours. The cooled and filtered solution was evaporated to dryness and dissolved in methylene chloride. An insoluble portion was removed by filtration, and the filtrate was evaporated to a yellow-brown sticky material (1.9 g, 0.087 mole) which was treated with 1.0 g (0.087 mole) fumaric acid in ethanol solution. The light yellow fumarate which crystallized at -20° overnight was collected and washed with 2-propanol. The product weighed 2.0 g (69%) and had mp 165-166° dec after vacuum drying at 100° (3 hours).

Anal. Calcd. for $C_{24}H_{32}N_4O_9$ C, 55.37; H, 6.20 N, 10.76. Found: C, 55.32; H, 6.63 N, 10.56.

3-Amino-1,7-dimethyl-1,8-naphthyridin-4-one (**19b**).

The naphthyridinone **16a** (11) (8.1 g, 0.033 mole) was dissolved in 50 ml of ethanol and 40 ml of methanol containing 2.1 g (0.07 mole) of hydrazine were added, and the resulting mixture refluxed for 3 hours. After cooling, a light brown precipitate was separted by filtration and washed with ethanol to yield 7.0 g (92%) of hydrazide (**17b**); mp 230-240°; nmr (DMSO-d_6); δ 2.61 (s, CH_3-Ar); 3.96 (s, N-CH_3); 7.3 (d, H_6); 8.35 (d, H_5); and 8.78 (s, H_2) ppm.

A sample of the hydrazide recrystallized from dimethylformamide after treatment with Norit A had mp 243-244°.

Anal. Calcd. for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.12. Found: C, 56.99; H, 5.24; N, 23.94.

The main portion of the hydrazide (6.5 g, 0.026 mole) without further purification was dissolved in 180 ml of 2*N* hydrochloric acid and cooled to 5°. The resulting suspension was stirred rapidly with 300 ml of ether-methylene chloride (1:1) while a concentrated solution 2.0 g (0.029 mole) of sodium nitrite was added at such a rate that the temperature did not exceed 10°. Stirring was continued for one-half hour, the organic phase separated and washed with water. The aqueous reaction mixture was reextracted with chloroform and the extract combined with the methylene chloride-ether phase. After drying with magnesium sulfate, the solution was diluted with 100 ml of ethanol and concentrated to a small volume on the steam bath. The remainder was taken up in 50 ml of ethanol and refluxed for 1 hour. Removal of the solvents yielded 4.8 g (65%) of crude material, mp ~125°. This material was autoclaved with concentrated hydrochloric acid at 145° for 2.5 hours. The cooled solution was made basic with sodium hydroxide and exhaustively extracted with chloroform. Concentration gave 3.3 g (91%) of **19b** as a yellow crystalline solid, mp 155-160° dec. The analytical sample prepared by recrystallization from aqueous ethanol had mp 155-157° dec; nmr (DMSO-d_6): δ 2.53 (s, CH_3-Ar); 3.78 (s, N-CH_3); 7.04 (d, H_6); 7.5 (s, H_2); and 8.3 (d, H_5) ppm; high resolution mass spectrum m/e required for $C_{10}H_{11}N_3O$, 189.0901; observed 189.0904.

Anal. Calcd. for $C_{10}H_{11}N_3O \cdot 1/4\ H_2O$: C, 62.00; H, 5.98; N, 21.69. Found: C, 62.40; H, 5.82; N, 21.64.

4-(4'-Amino-1'-methybutylamino)-1,7-dimethyl-1,8-naphthyridine-4-one (**20b**) Dihydrobromide.

The amino compound **19b** (2.8 g, 0.014 mole) was heated and stirred with 1.7 ml of dimethylformamide at 85° under argon. Within a period of 4 hours a solution of 10 g (0.03 mole) of 4-iodo-1-phthalimidopentane in 3.6 g (0.036 mole) of triethylamine was added. Heating was continued for 1 hour beyond the addition, and an excess of benzene was added. The resulting solid was separated by filtration. The brown residue after evaporation of the benzene was purified by silica gel column chromatography using chloroform-15% ethyl acetate as the eluent. Concentration of the product fractions gave 5.3 g (90%) of the protected amino compound; nmr (deuteriochloroform): δ 1.15 (d, CH-CH_3); 2.55 (s, CH_3-Ar); 3.85 (s, N-CH_3); 6.8 (s, H_2); 6.85 (d, H_6); 76 (m, C_6H_4); and 8.45 (d, H_5) ppm.

The removal of the phthaloyl protecting group was accomplished as usual by refluxing 5.3 g (0.013 mole) of the product with 1 g (0.031 mole) of hydrazine in 50 ml ethanol. After 2 hours, the solution was cooled, a white precipitate was separated by filtration, and the residue was concentrated to an oil. The oil was dissolved in 30 ml of methylene chloride, filtered and freeze-dried to yield 3.0 g (85%) of **20b**. An ethanolic solution of the product was treated with hydrobromic acid. The mixture was evaporated to a small volume and diluted with 20 ml of ethanol. From the cooled solution 3.6 g (75%) of a white dihydrobromide of **20b** crystallized, mp 246°, nmr (DMSO-d_6): δ 1.22 (d, CH-CH_3); 2.66 (s, CH_3-Ar); 3.94 (s, N-CH_3); 7.34 (d, H_6); 8.4 (d, H_5); and 8.4 (s, H_2) ppm.

Anal. Calcd. for $C_{15}H_{24}Br_2N_2O \cdot 1/2H_2O$: C, 40.56; H, 5.67; N, 12.61. Found: C, 40.26; H, 5.48; N, 12.42.

3-(2-Oxopyridyl)aminomethylene Malonic Ester (**23**).

3-Acetylamino-pyridine *N*-oxide (**21**; 63.5 g, 0.45 mole) (8) was refluxed in 300 ml of acetic anhydride for 4 hours. After concentration of the resulting mixture *in vacuo*, 300 ml of 3*N* hydrochloric acid were added and refluxing continued for another 4 hours. The solvents were evaporated and the remaining residue vacuum dried. Chromatography of the crude product on silica gel using chloroform-ethanol as eluent furnished 15.7 g (35%) of **22** (11); nmr (deuteriochloroform and deuteriomethanol): δ 6.1 (t, H_5); 6.55 (d, H_4); and 6.65 (d, H_6) ppm.

The pyridine derivative **22** was heated with 30 g (0.14 mole) of diethyl ethoxymethylenemalonate for 2 hours on a steam bath. The brown hot reaction mixture was diluted with 2-propanol. This immediately triggered crystallization of **23** (18 g, 45%) as light gray material which had mp 199-200°; nmr (deuteriochloroform): δ 1.31, 1.39 (2 t, CH_3CH_2); 4.21, 4.35 (2 q, CH_3CH_2); 6.3 (t, H_5); 7.2 (d, H_4); and 8.41 (d, H_6) ppm.

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 56.06; H, 5.80, N, 9.75.

3-(1-Methyl-2-oxopyridyl)aminomethylene Malonic Ester (**24**).

The pyridone **23** (3.5 g, 0.013 mole) was dissolved in 40 ml of dimethylformamide. To the stirred solution were added 1.8 g (0.013 mole) of methyl iodide and 10 g of potassium carbonate. After stirring for 16 hours, the inorganic matter was removed by filtration. The filtrate was concentrated to a small volume and partitioned with chloroform and water. The organic phase after removal of the solvent *in vacuo* crystallized upon treatment with 2-propanol. The *N*-methyl compound **24** (2.8 g, 76%) had mp 107-110°; nmr (deuteriochloroform): δ 1.3, 1.35 (2t, CH_3CH_2); 3.6 (s, NCH_3); 4.20, 4.35 (2q, CH_3CH_2); 6.1 (t, H_5); 7.06 (m, H_4); and 8.38 (d, H_2) ppm.

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.14; H, 6.16, N, 9.52. Found: C, 56.97; H, 5.99; N, 9.48.

Ethyl 4-Hydroxy-7-methyl-1,7-naphthyridin-8-one-3-carboxylate (**25**).

Compound **24** (2.7 g, 0.011 mole) was introduced all at once into 100 ml of refluxing Dowtherm A under nitrogen. The solution was kept under reflux for 25 minutes and then immediately cooled in a nitrogen jet as rapidly as possible. To the stirred solution was added an equal volume of hexane which caused 1.9 g (83%) of **25** to crystallize overnight as a light brown product. The analytical sample prepared by recrystallization from 95% ethanol had mp 283-285°; nmr (DMSO-d_6): δ 1.26 (t, CH_3CH_2); 3.56 (s, NCH_3); 4.20 (q, CH_3CH_2); 6.67 (d, H_5); 7.46 (d, H_6); and 8.19 (s, H_2) ppm.

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 57.91; H, 4.80; N, 11.25

4-Hydroxy-7-methyl-1,7-naphthyridin-8-one (**26**).

The preceding intermediate **25** (1.9 g, 0.008 mole) was refluxed with 100 ml of 2*N* hydrochloric acid overnight. An off-white precipitate resulted which was collected by filtration and vacuum dried. The yield was 1.4 g (79%), mp > 259° dec. The material was used without further treatment for decarboxylation in mineral oil at 290°. After stirring the solution for 20 minutes it was cooled rapidly to give 0.9 g (80%) of **26**, mp > 285° dec; nmr (deuteriochloroform and deuteriomethanol): δ 3.65 (s, CH_3N); 6.34 (d, H_3); 6.8 (d, H_5); 7.06 (d, H_6); 7.73 (d, H_2) ppm.

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.11; H, 4.82; N, 15.41.

4-chloro-7-methyl-1,7-naphthyridin-8-one (**27**).

Refluxing 6 g (0.034 mole) of **26** with 10 g (0.05 mole) of phosphorus pentachloride in 100 ml of phosphorus oxychloride gave a mixture of chlorinated products which could be resolved by silica gel chromatography using methylene chloride-acetone mixtures as solvent. The 4-chloro compound **27** was recovered as tan crystals, 1.4 g (21%), mp 172-173° after recrystallization from aqueous ethanol; nmr (deuteriochloroform): δ 3.68 (s, NCH_3); 6.65 (d, H_5); 7.25 (d, H_6); 7.53 (d, H_3); 8.66 (d, H_2) ppm. High resolution mass spectrum required for $C_9H_7ClN_2O$, 194.0247; observed 194.0244.

Anal. Calcd. for $C_9H_7ClN_2O$: C, 55.54; H, 3.63; N, 14.39. Found: C, 55.93; H, 3.63; N, 14.31.

4-(4'-Diethylamino-1'-methybutylamino)-7-methyl-1,7-naphthyridin-8-one (**28**) Resorcylate.

A mixture of 3.8 g (0.025 mole) 2-amino-4-diethylaminopentane and 1.8 g (0.009 mole) of **27** in 2 ml of dimethylformamide was heated with stirring under argon for 8 hours. At this time a homogeneous solution resulted. The product was concentrated *in vacuo* and dissolved in ethanol. An alcoholic solution of 4 g (0.026 mole) of resorcylic acid was added. The crude salt of **28** was precipitated by addition of 10 volumes of ether, which gave a sticky yellow material. Upon cooling the tan diresorcylate of **28** separated, 1.8 g (38%), mp 195-197° dec; nmr (DMSO-d_6): δ 1.2 (m, CH_3CH_2N, CH_3CH); 3.1 (q, CH_3CH_2N); 3.59 (s, CH_3N); 6.1 (m, resorcylate); 7.0 (d, H_6); 7.5 (m, resorcylate); 8.2 (d, H_2) ppm.

Anal. Calcd. for $C_{32}H_{40}N_4O \cdot H_2O$: C, 58.17; H, 6.71; N, 8.47. Found: c, 58.49; H, 6.85; N, 8.16.

Acknowledgement.

The authors wish to express their gratitude to Drs. E. A. Steck and R. E. Strube for many helpful suggestions and discussions during the course of this work. This work was supported by the U. S. Army Medical Research and Development Command under Research Contract DADA-17-74-C-4107. This paper has been designated as Contribution No. 1597 to the Army Research Program on Antiparasitic Drugs.

REFERENCES AND NOTES

(1) T. R. Sweeney and R. E. Strube, "Burger's Medicinal Chemistry," 4th Ed., M. E. Wolff, Ed., Interscience Publishers Inc., New York, N. Y., 1979, p.333.

(2) V. E. Finks, P. Nickel and O. Donn, *Arzneim.-Forsch.*, 1775 (1970).

(3) C. R. Kolder and H. U. den Hertog, *Rec. Trav. Chim.*, **72**, 285 (1953).

(4) *idem, ibid.*, **79**, 474 (1960).

(5) We also investigated the use of 2,4-diethoxy, 2,4-diisopropoxy and 2,4-di-t-butoxypyridinone as potential intermediates for the synthesis of 1,6-naphthyridinone target compound. We found that nitration of the 2,4-diethoxy derivative gave a mixture of both 3- and 5-nitro derivatives as reported (4) and that nitration of the other two derivatives led to decomposition.

(6) F. I. Carroll, B. Berrang, C. P. Linn and C. E. Twine, Jr., *J. Med. Chem.*, **22**, 694 (1979).

(7) G. R. Lappin, *J. Am. Chem. Soc.*, **70**, 3348 (1948).

(8) W. Hertz and D. R. K. Murty, *J. Org. Chem.*, **25**, 2242 (1960).

(9) T. S. Osdene, P. B. Russell and L. Rane, L., *J. Med. Chem.*, **10**, 431 (1967).

(10) G. Y. Lesher, E. Y. Froelich, M. D. Bruett, J. H. Bailey and R. P. Broundage, *J. Med. Pharm. Chem.*, **5**, 1063 (1962).

(11) After completion of this work, a report on a different preparation of **22** appeared: D. R. Hwang, G. R. Proctor and J. S. Driscoll, *J. Pharm. Sci.*, **69**, 1074 (1980).