Derivatives of 2-Alkoxy-8-amino-1 : 5-naphthyridines.

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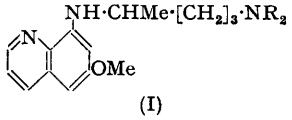
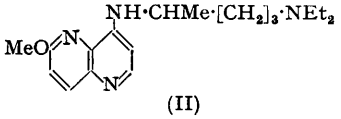
Derivatives of 2-alkoxy-8-amino-1 : 5-naphthyridines have been synthesised for examination for antimalarial activity. The ring system was built up (*a*) by condensation of 5-amino-2-butoxypyridine with ethyl ethoxymethylenemalonate and cyclisation of the product, and (*b*) by condensation of 5-amino-2-butoxypyridine and ethyl acetoacetate by the Conrad–Limpach method.

THE synthesis of 4-dialkylaminoalkylamino-1 : 5-naphthyridines was undertaken because of their structural relationship to 4-dialkylaminoalkylaminoquinolines which have high antiplasmodial activity provided the 6- or the 7-position bears a chloro- or lower alkoxy-substituent (Magidson and Rubtsov, *J. Gen. Chem. Moscow*, 1937, **7**, 1896; Andersag, Breitner, and Jung, G.P. 683,692/1939; Galperin, *Amer. Rev. Soviet Med.*, 1944, **1**, 220). A further point of interest is that pamaquine (I; R = Et) and primaquine (I; R = H) are the most effective of the known antimalarials against the secondary exo-erythrocytic stages of *Plasmodium vivax* (Report by Council on Pharmacy and Chemistry, *J. Amer. Med. Assoc.*, 1952, **149**, 1558); 8-(4-diethylamino-1-methylbutylamino)-2-methoxy-1 : 5-naphthyridine (II) has a structural contour similar to that of pamaquine inasmuch as the substituted amino-side-chain is *peri* to a ring-nitrogen atom. In the first instance, because of limited availability of starting materials, work was confined to derivatives of 2-alkoxy-8-amino-1 : 5-naphthyridines; synthesis of derivatives of 4-amino-7-chloro-1 : 5-naphthyridines will be reported later.



(I)



(II)

Condensation of 5-amino-2-butoxypyridine with ethyl ethoxymethylenemalonate and cyclisation of the resulting ethyl β-(2-butoxy-5-pyridylamino)-α-ethoxycarbonylacrylate by the method of Price and Roberts (*J. Amer. Chem. Soc.*, 1946, **68**, 1204) gave ethyl 6-butoxy-4-hydroxy-1 : 5-naphthyridine-3-carboxylate. Hydrolysis and decarboxylation of the acid in diphenyl ether afforded 2-butoxy-8-hydroxy-1 : 5-naphthyridine which with phosphoryl chloride yielded the 8-chloro-compound; reaction of the latter at high

temperature with 4-amino-1-diethylaminopentane gave 2-butoxy-8-(4-diethylamino-1-methylbutylamino)-1 : 5-naphthyridine. For the preparation of 8-amino-2-butoxy-1 : 5-naphthyridine it was preferable to convert the chloro- into the phenoxy-compound and treat this in boiling ammonium acetate with ammonia.

Cyclisation of a β-3-pyridylaminoacrylic ester would give a 1 : 5- or a 1 : 7-naphthyridine according as cyclisation occurred at the 2- or the 4-position of the pyridine nucleus. Cyclisation is essentially an attack by a cationoid reagent on the pyridine nucleus and the point of attack will be governed by the relative electron density at the two positions. That the electron density at $C_{(2)}$ is higher than that at $C_{(4)}$ in 3-aminopyridine is shown by chlorination to 2-chloro-3-aminopyridine in 90% yield (Schick, Binz, and Schultz, *Ber.*, 1936, **69**, 2593) and by cyclisation of 2-(6-alkoxy-3-pyridylamino)benzoic acids to 1 : 10-diazaanthracenes (Besly and Goldberg, *J.*, in the press; cf. the Skraup cyclisation with 3-aminopyridine, Klisiecki and Sucharda, *Roczn. Chem.*, 1927, **7**, 204; Bobranski and Sucharda, *Ber.*, 1927, **60**, 1081). There is therefore little doubt that the compounds described in this communication are 1 : 5-naphthyridines.

5-Amino-2-methoxypyridine and ethyl ethoxymethylenemalonate gave similar compounds in good yield, but decarboxylation was difficult. Standard methods yielded unchanged material or effected extensive charring; by heating the silver salt at low pressure, however, 8-hydroxy-2-methoxy-1 : 5-naphthyridine was obtained but the yield was so small that further work was precluded. Condensation of 5-amino-2-methoxypyridine with ethyl ethoxalylacetate in presence of acetic acid and cyclisation of the resulting ethyl β-ethoxycarbonyl-β-(2-methoxy-5-pyridylamino)acrylate yielded ethyl 4-hydroxy-6-methoxy-1 : 5-naphthyridine-2-carboxylate. Decarboxylation of the corresponding carboxylic acid by standard procedures again presented difficulty but was finally accomplished in refluxing diphenyl ether and dibutyl phthalate. This route was abandoned because of shortage of material.

Condensation of 5-amino-2-methoxypyridine and ethyl acetoacetate by the Conrad–Limpach method gave 4-hydroxy-6-methoxy-2-methyl-1 : 5-naphthyridine. Conversion of this into 4-chloro-6-methoxy-2-methyl-1 : 5-naphthyridine and reaction of the latter with 4-amino-1-diethylaminopentane yielded 4-(4-diethylamino-1-methylbutylamino)-6-methoxy-2-methyl-1 : 5-naphthyridine. The 6-butoxy-analogue was obtained in a similar manner.

2-*n*-Butoxy-8-(4-diethylamino-1-methylbutylamino)-1 : 5-naphthyridine at a daily oral dosage of 40 mg./kg. had the same suppressive activity as 50 mg./kg. of mepacrine against *P. gallinaceum* in chicks; against *P. berghei* in mice, it had the same activity as mepacrine. 6-Methoxy- and 6-*n*-butoxy-4-(4-diethylamino-1-methylbutylamino)-2-methyl-1 : 5-naphthyridine showed no activity against *P. gallinaceum* in chicks at daily oral dosages of 50 mg./kg.

Experimental

Ethyl 6-Butoxy-4-hydroxy-1 : 5-naphthyridine-3-carboxylate.—A mixture of 5-amino-2-*n*-butoxypyridine (Besly and Goldberg, *loc. cit.*; 27 g.) and ethyl ethoxymethylenemalonate (35 g.) was heated for 1 hr. on the steam-bath, the ethanol formed being allowed to escape. The *ethyl β-(2-butoxy-5-pyridylamino)-α-ethoxycarbonylacrylate* (56 g.) solidified on cooling and was pure enough for the cyclisation; a sample crystallised from dilute alcohol in colourless needles, m. p. 54° (Found: N, 8·5. $C_{17}H_{24}O_5N_2$ requires N, 8·3%).

This compound (56 g.) was added during 10 min. to vigorously boiling diphenyl ether (200 g.), the ethanol escaping *via* a short air-condenser. Boiling was continued for a further 15 min., the solution cooled, and *ethyl 6-butoxy-4-hydroxy-1 : 5-naphthyridine-3-carboxylate* [38 g.; m. p. 268° (decomp.)] was precipitated by addition of ligroin (300 c.c.; b. p. 60—80°). Digestion with acetone did not raise the m. p. (Found: C, 62·4; H, 6·4; N, 10·0. $C_{15}H_{18}O_4N_2$ requires C, 62·1; H, 6·2; N, 9·7%).

2-Butoxy-8-hydroxy-1 : 5-naphthyridine.—The foregoing ester (31 g.) was heated on the water-bath with N-sodium hydroxide (600 c.c.) for 4 hr., and the cooled and filtered (charcoal) solution acidified to Congo-red with hydrochloric acid; the precipitated *acid* (23 g.; m. p. 244°) crystallised from alcohol in colourless needles, m. p. 246° (decomp.) (Found: N, 10·7. $C_{13}H_{14}O_4N_2$ requires N, 10·7%). Adding the acid (23 g.) to refluxing diphenyl ether (50 g.) and,

after 15 min., cooling and adding ligroin (b. p. 60—80°) precipitated 2-*butoxy*-8-*hydroxy*-1 : 5-*naphthyridine* (17·5 g.), m. p. 170°. This crystallised from dilute ethanol in colourless leaflets, m. p. 172° (Found : C, 65·2; H, 6·3; N, 13·0. $C_{12}H_{14}O_2N_2$ requires C, 66·0; H, 6·4; N, 12·8%).

2-*Butoxy*-8-*chloro*-1 : 5-*naphthyridine*.—The foregoing compound (17·5 g.) and phosphoryl chloride (50 c.c.) were heated on the steam-bath for 1 hr. and the mixture poured on an excess of crushed ice with vigorous stirring. Sodium acetate was added until the aqueous solution was neutral to Congo-red, and the liquor extracted with ether (500 c.c.). The ether solution was washed with saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated; 2-*butoxy*-8-*chloro*-1 : 5-*naphthyridine* (15·1 g.) was obtained as a crystalline mass, m. p. 39°, which crystallised from ligroin (b. p. 40—60°) in colourless prisms, m. p. 40° (Found : N, 11·8; Cl, 14·7. $C_{12}H_{13}ON_2Cl$ requires N, 11·8; Cl, 15·0%).

2-*Butoxy*-8-*phenoxy*-1 : 5-*naphthyridine*.—The foregoing chloro-compound (9 g.) was heated at 160° with a solution of potassium hydroxide (2·2 g.) in phenol (15 g.) for 3 hr.; the solution was cooled and poured into an excess of 2N-sodium hydroxide, and the whole extracted with ether. The ethereal solution was washed several times with dilute aqueous sodium hydroxide. then water, and dried; removal of the ether left 2-*butoxy*-8-*phenoxy*-1 : 5-*naphthyridine* as a light oil (9·5 g.) (Found : N, 9·4. $C_{18}H_{18}O_2N_2$ requires N, 9·5%).

8-*Amino*-2-*butoxy*-1 : 5-*naphthyridine*.—Dry ammonia was passed into a mixture of the foregoing compound (9·5 g.) and ammonium acetate (50 g.) at 150° for 4 hr. The flux was cooled, diluted with water (150 c.c.), and, after addition of acetic acid (10 c.c.), filtered (charcoal) and basified with aqueous ammonia; 8-*amino*-2-*butoxy*-1 : 5-*naphthyridine* (6·7 g.) separated as an oil which rapidly solidified. Crystallisation from ligroin (b. p. 40—60°) gave colourless leaves, m. p. 96—98° (Found : C, 65·9; H, 7·0; N, 19·3. $C_{12}H_{15}ON_3$ requires C, 66·4; H, 6·9; N, 19·4%).

2-*Butoxy*-8-(4-*diethylamino*-1-*methylbutylamino*)-1 : 5-*naphthyridine*.—2-Butoxy-8-chloro-1 : 5-naphthyridine (13 g.), 4-amino-1-diethylaminopentane (44 g.), and copper bronze (2 g.) were heated together at 180—190° for 18 hr. The cooled solution was diluted with 5N-sodium hydroxide and extracted with ether. Distillation of the dried ethereal solution gave a considerable quantity of 4-amino-1-diethylaminopentane and then 2-*butoxy*-8-(4-*diethylamino*-1-*methylbutylamino*)-1 : 5-*naphthyridine* as a colourless oil, b. p. 230—234°/2 mm. (7 g., 30%) (Found : N, 15·8. $C_{21}H_{34}ON_4$ requires N, 15·6%); there was extensive decomposition during the distillation. The *dipicrate* separated from alcohol in yellow leaves, m. p. 170—172° (Found : C, 48·6; H, 4·8; N, 17·2. $C_{21}H_{34}ON_4,2C_6H_3O_7N_3$ requires C, 48·5; H, 4·9; N, 17·2%).

2-*Butoxy*-1 : 5-*naphthyridine*.—2-Butoxy-8-chloro-1 : 5-naphthyridine (5 g.), hydrazine hydrate (25 g., 95%), and ethanol (50 c.c.) were refluxed together for 6 hr., then diluted with water (200 c.c.). The crude hydrazino-compound was collected, washed with water, and suspended in boiling water (50 c.c.), and a concentrated aqueous solution of copper sulphate (10 g.) was added during 5 min. Boiling was continued for 1 hr., and the liquor made alkaline with ammonia and distilled in steam. Ether-extraction of the distillate gave 2-*butoxy*-1 : 5-*naphthyridine* as an oil, b. p. 296—298° (Found : N, 13·9. $C_{12}H_{14}ON_2$ requires N, 13·9%). The *picrate* separated from alcohol in yellow needles, m. p. 135° (Found : N, 16·6. $C_{18}H_{17}O_8N_5$ requires N, 16·2%).

The following were prepared from 5-amino-2-methoxypyridine by the methods described above.

Ethyl β-(2-*methoxy*-5-*pyridylamino*)-α-*ethoxycarbonylacrylate* (85%), colourless leaflets, m. p. 90° (Found : N, 9·7. $C_{14}H_{18}O_5N_2$ requires N, 9·5%).

Ethyl 4-*hydroxy*-6-*methoxy*-1 : 5-*naphthyridine*-3-*carboxylate* (81%), colourless needles (from alcohol), m. p. 268° (decomp.) (Found: C, 57·8; H, 5·0; N, 11·4. $C_{12}H_{12}O_4N_2$ requires C, 58·0; H, 4·8; N, 11·3%). This gave an *acid* (90%), m. p. >310° (decomp.) (Found : N, 12·8. $C_{10}H_8O_4N_2$ requires N, 12·7%). Heating the acid with boiling diphenyl ether or quinoline and copper failed to effect decarboxylation. The silver salt (3·0 g.; prepared by addition of aqueous silver nitrate to an ammoniacal solution of the acid, filtering, and drying at 100°) was heated in a graphite bath to 360—380° (bath-temp.) at 1 mm. for ½ hr. The sublimate and charred residue were extracted with alcohol; evaporation of the solvent and crystallisation of the residue gave 8-*hydroxy*-2-*methoxy*-1 : 5-*naphthyridine* (0·25 g.) in yellow needles, m. p. 270° (Found : N, 15·6. $C_9H_8O_2N_2$ requires N, 15·9%).

Ethyl β-*Ethoxycarbonyl*-β-(2-*methoxy*-5-*pyridylamino*)*acrylate*.—A mixture of 5-amino-2-methoxypyridine (31 g.) and ethyl ethoxalylacetate (31·3 g.) in glacial acetic acid (120 c.c.) was

stirred at 40—50° for 4 hr. and then kept at room temperature overnight. The solution was diluted with water, adjusted to pH 7 with 5N-sodium hydroxide, and extracted with ether. The ethereal solution was washed with 0·5N-hydrochloric acid (4 × 100 c.c.), 0·5N-sodium hydroxide (4 × 100 c.c.), and then water and dried (K_2CO_3); evaporation yielded a residual oil (31 g.). Distillation of a portion gave the pure *ester* as a yellow viscous oil, b. p. 176—180°/1 mm. (Found : N, 9·7. $C_{14}H_{18}O_5N_2$ requires N, 9·5%).

4-Hydroxy-6-methoxy-1 : 5-naphthyridine-2-carboxylic Acid.—The foregoing crude ester (28 g.) was added during 10 min. to refluxing diphenyl ether (120 g.) down a short air-condenser, thus permitting escape of ethanol. The mixture was refluxed a further 10 min., then cooled, and the precipitate was collected and washed with ligroin (b. p. 60—80°); *ethyl 4-hydroxy-6-methoxy-1 : 5-naphthyridine-2-carboxylate* remained as a light tan powder (22 g.), m. p. 224—226° (Found : N, 11·2. $C_{12}H_{12}O_4N_2$ requires N, 11·3%). This was heated at 100° for 6 hr. with N-sodium hydroxide (250 c.c.), and the solution made strongly acid with hydrochloric acid; the precipitate of *4-hydroxy-6-methoxy-1 : 5-naphthyridine-2-carboxylic acid hydrochloride* [21 g.; m. p. 270° (decomp.)] was collected and washed with cold alcohol (Found : N, 10·6; Cl, 13·2. $C_{10}H_9O_4N_2Cl$ requires N, 10·9; Cl, 13·8%).

8-Hydroxy-2-methoxy-1 : 5-naphthyridine.—The foregoing hydrochloride (30 g.) was mixed to a paste with dibutyl phthalate and refluxed with diphenyl ether (100 g.) for 20 min. The cooled mixture was filtered, and the solid washed with ligroin and extracted with boiling alcohol. Evaporation of the solvent, and recrystallisation and sublimation of the residue, gave *8-hydroxy-2-methoxy-1 : 5-naphthyridine* (3 g.) (Found : N, 15·0%), m. p. 270° alone and in admixture with a sample made as described above.

4-Hydroxy-6-methoxy-2-methyl-1 : 5-naphthyridine.—Ethyl acetoacetate (36 g.), 5-amino-2-methoxypyridine (34 g.), acetic acid (2 c.c.), and ethyl alcohol (100 c.c.) were refluxed together for 4 hr. Removal of solvent at reduced pressure left almost pure *ethyl β-(2-methoxy-5-pyridylamino)-β-methylacrylate* (67 g.) which crystallised from alcohol in colourless leaves, m. p. 72° (Found : N, 11·9. $C_{12}H_{16}O_3N_2$ requires N, 11·9%).

Cyclisation of this (67 g.) in refluxing diphenyl ether (335 g.) as described above gave *4-hydroxy-6-methoxy-2-methyl-1 : 5-naphthyridine* (42 g.; m. p. 290°) which crystallised from alcohol in colourless needles, m. p. 294—296° (decomp.) (Found : C, 62·9; H, 3·2; N, 14·9. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·3; N, 14·7%).

The following compounds were obtained by the sequence of reactions described above; the yields and the solvents used for crystallisation are in parentheses.

4-Chloro-6-methoxy-2-methyl-1 : 5-naphthyridine (90%), pale yellow prisms (from ligroin, b. p. 40—60°), m. p. 108° (Found : N, 13·4; Cl, 17·3. $C_{10}H_9ON_2Cl$ requires N, 13·4; Cl, 17·0%).

4-Phenoxy-6-methoxy-2-methyl-1 : 5-naphthyridine (85%), colourless needles (from dilute ethanol), m. p. 114° (Found : N, 10·1. $C_{16}H_{14}O_2N_2$ requires N, 10·5%).

4-Amino-6-methoxy-2-methyl-1 : 5-naphthyridine (58%), colourless needles (from ether–ligroin), m. p. 172° (Found : C, 63·8; H, 5·9; N, 22·4. $C_{10}H_{11}ON_3$ requires C, 63·5; H, 5·8; N, 22·2%).

4-(4-Diethylamino-1-methylbutylamino)-6-methoxy-2-methyl-1 : 5-naphthyridine (40%), a yellow oil, b. p. 220—224°/1 mm. (Found : N, 17·1. $C_{19}H_{30}ON_4$ requires N, 17·0%) [*dipicrate*, yellow aggregates (from acetone), m. p. 148° (decomp.) (Found : C, 47·3; H, 4·4; N, 17·9. $C_{31}H_{36}O_{15}N_{10}$ requires C, 47·2; H, 4·6; N, 17·7%)].

Ethyl β-(2-butoxy-5-pyridylamino)-β-methylacrylate (95%), colourless leaflets (from dilute alcohol), m. p. 55° (Found : N, 10·2. $C_{15}H_{22}O_3N_2$ requires N, 10·1%).

6-Butoxy-4-hydroxy-2-methyl-1 : 5-naphthyridine (78%), colourless needles (from alcohol), m. p. 246° (Found : C, 67·3; H, 7·0; N, 12·3. $C_{13}H_{16}O_2N_2$ requires C, 67·2; H, 6·9; N, 12·1%).

6-Butoxy-4-chloro-2-methyl-1 : 5-naphthyridine (92%), colourless prisms (from ligroin, b. p. 60—80°), m. p. 62° (Found : N, 11·3; Cl, 14·3. $C_{13}H_{15}ON_2Cl$ requires N, 11·2; Cl, 14·2%).

6-Butoxy-2-methyl-4-phenoxy-1 : 5-naphthyridine (85%), colourless needles (from dilute ethanol), m. p. 66—68° (Found : N, 9·2. $C_{19}H_{20}O_2N_2$ requires N, 9·1%).

4-Amino-6-butoxy-2-methyl-1 : 5-naphthyridine (70%), colourless needles (from dilute ethanol), m. p. 142° (Found : C, 67·1; H, 7·4; N, 18·2. $C_{13}H_{17}ON_3$ requires C, 67·5; H, 7·4; N, 18·2%).

6-Butoxy-4-(4-diethylamino-1-methylbutylamino)-2-methyl-1 : 5-naphthyridine (40%), an orange oil, b. p. 230—234°/1 mm. (Found : N, 14·9. $C_{22}H_{36}ON_4$ requires N, 15·0%) [*dioxalate*, nearly colourless needles (from alcohol), m. p. 166° (Found : C, 56·0; H, 7·2; N, 10·3. $C_{26}H_{40}O_9N_4$ requires C, 56·6; H, 7·3; N, 10·2%)].

2-*Butoxy*-6-*methyl*-1 : 5-*naphthyridine monohydrate*, colourless needles, m. p. 56°, very soluble in alcohol and easily sublimed (Found: C, 66·2; H, 8·0; N, 11·9. $C_{13}H_{18}O_2N_2$ requires C, 66·6; H, 7·7; N, 12·0%) [*picrate* (from alcohol), pale yellow needles, m. p. 131° (Found: N, 15·9. $C_{19}H_{19}O_8N_5$ requires N, 15·8%)].

2-*Methoxy*-6-*methyl*-1 : 5-*naphthyridine*, colourless needles (after sublimation at 1 mm.), m. p. 52° (Found: C, 68·6; H, 5·6; N, 16·2. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·7; N, 16·1%) [*picrate*, yellow needles (from alcohol), m. p. 190° (Found: C, 47·0; H, 3·4; N, 17·6. $C_{16}H_{13}O_8N_5$ requires C, 47·6; H, 3·2; N, 17·4%)].

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