1,8-Naphthyridines. Part III (1). Synthesis of Some 6-Substituted-1,8-naphthyridin-2(1*H*)ones

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The syntheses of some 1,8-naphthyridines substituted in the 6-position with heterocyclic groups are described. A synthetic route to 6-amino-5,7-dimethyl-1,8-naphthyridin-2(1*H*)one is also presented.

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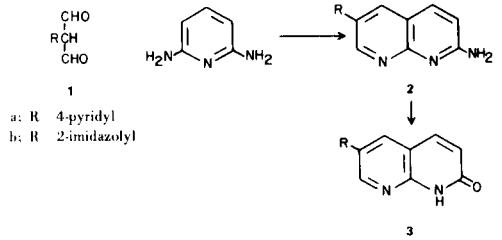
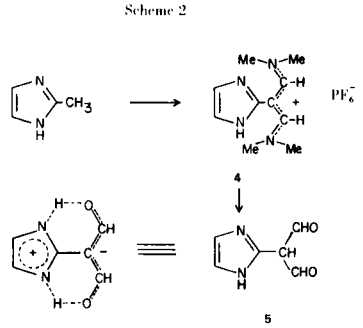
Few 1,8-naphthyridin-2(1*H*)ones with functionality in the 6-position have been reported. As part of a medicinal chemical program, it was desired to make some compounds of this type with 6-heterocyclyl substituents. These were found to be readily available by condensation of 2,6-diaminopyridine with heterocyclylmalondialdehydes followed by treatment of the product with nitrous acid, *e.g.*, 1 → 2 → 3.

Scheme 1



The known 2-(4-pyridyl)propane-1,3-dione (3) was used to prepare **2a**, and for **2b** the previously unknown 2-(2-imidazolyl)propane-1,3-dione was prepared as follows. Condensation of 2-methylimidazole with the phosgene/dimethylformamide Vilsmeier reagent followed by neutralization of the reaction mixture in the presence of hexafluorophosphate ions afforded the trimethinium salt **4**, which was hydrolysed to the malondialdehyde with sodium hydroxide. The nonequivalence of the two pairs of methyl groups in **4**, as a consequence of the partial sp^2 character of the C-C and C-N bonds, is a noteworthy feature of the nmr spectrum. Of the three possible configurations for this side chain, the one shown in Scheme 2 seems to be the most likely.

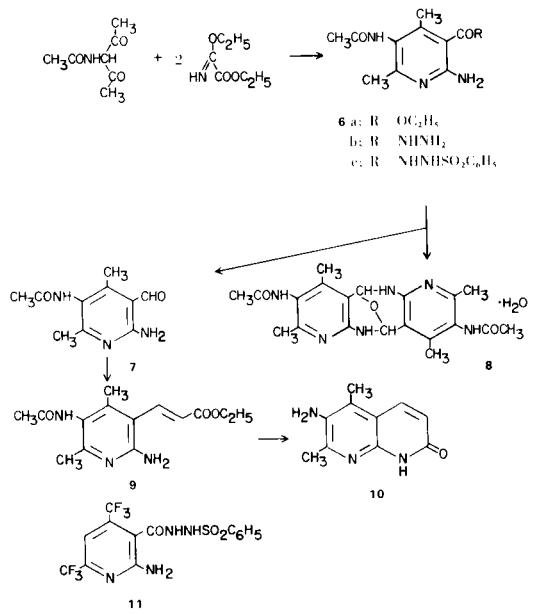
Scheme 2



Another 6-substituted-1,8-naphthyridinone, *viz*, 6-amino-5,7-dimethyl-1,8-naphthyridin-2(1*H*)one, was prepared from 5-acetamido-2-amino-4,6-dimethylnicotinaldehyde which was available from other (unpublished) syntheses in this area. The preparation of **7** followed a route similar to one employed by Albert and Reich (4) to prepare 2-aminonicotinaldehyde. In this case the desired aldehyde was the major product of the McFadyen Stevens reaction upon **6c** and only a small amount of the "dimer" **8** was isolated, provided the reaction time was kept short. This contrasts with our experience with **11** from which only the dimeric product was isolated (1). Structure **8** is supported by elemental analysis, mass spectrum and estimation of water of crystallization by Karl Fischer titration.

A Wittig condensation of **7** with triethyl phosphonoacetate gave **9** which upon prolonged boiling with ethanolic hydrochloric acid yielded **10.** Formation of the second ring has been carried out in the 1,5-naphthyridine series (5) in a similar way before, but using hydroxylamine and sodium methoxide to invert the geometry of the olefinic group and thus bring about cyclization. This example is the first application to the 1,8-naphthyridine series.

Scheme 3



EXPERIMENTAL

Pmr spectra were recorded by Mr. S.-C. Ho and his colleagues in Varian A60A or EM 360 Spectrometers. The chemical shifts are in ppm using TMS as internal standard. Ir spectra were recorded on a Perkin Elmer 257 spectrometer. Melting points (uncorrected) were determined in a Thomas Hoover capillary apparatus. Microanalyses were performed by Dr. C. Daessle of Montreal and the authors thank Mr. Erwin Frank of Merck Frosst Laboratories for the Karl Fischer determination.

1,3-bis-Dimethylamino-2-(2-imidazolyl)trimethinium Hexafluorophosphate (**4**).

The Vilsmeier Haack reagent was prepared from a 2.7 *N* solution of phosgene in chloroform (296 ml., 0.8 mole) and dimethylformamide (78 ml., 1.0 mole). To this solution, cooled to 5-10°, was added with stirring 2-methylimidazole (16.4 g., 0.2 mole) in small portions during 1 hour. The mixture was stirred for 1½ hours at 5-10° and then overnight at room temperature. The reaction mixture was poured onto ice (260 g.); the chloroform layer was separated and washed with ice-water (40 ml.). To the combined aqueous solution, sodium hexafluorophosphate (33.6 g., 0.2 mole) was added, and the solution was treated with a little charcoal and filtered. The filtrate was cooled in an ice-bath and neutralized to *p*H 6-6.5 by the addition of sodium carbonate (74.2 g., 0.7 mole) in small portions with stirring. The salt **4** crystallized; it was collected, washed with a little ice-water and dried at 55° and ~ 20 Torr, 24.1 g., (35%), m.p. 168-172°. This material is pure enough to use in the next stage, but it can be recrystallized from 5 volumes of water from which it separates in glistening crystals, m.p. 191-192°; ir ν max (potassium bromide): 3620, 1612, 850; nmr δ (deuterioethanenitrile): 7.50 (s, 2H, 2 x methine), 7.11 (s, 2H, imidazole-H), 3.25 (s, 6H, 2 x Me), 2.43 (s, 6H, 2 x Me) (6).

Anal. Calcd. for $C_{10}H_{17}F_6N_4P \cdot \frac{1}{2}H_2O$: C, 34.59; H, 5.22; N, 16.14. Found: C, 34.51; H, 4.97; N, 16.16.

2-(2-Imidazolyl)propane-1,3-dione (**5**).

A solution of crude **4** (23.6 g., 68 mmoles) in 2 *N* sodium hydroxide solution (70 ml.) was maintained at 65-70° for 1 hour. Then, while still hot, the solution was treated dropwise with 6 *N* hydrochloric acid to *p*H 7-7.5. The product was collected after chilling at 5°, 7.88 g. (81.5%), m.p. 279-282° dec. A further 0.82 g, (8.5%) of product can be obtained by work up of the mother liquors.

Compound **5** crystallizes from hot water in pale cream needles, m.p. 280° dec.; ir ν max (potassium bromide): 3270, 1600, 1360, 1226; nmr δ (DMSO-d_6): 12.5 (br s, 2H, NH and enolic H), 9.10 (s, 2H, 2CHO), 7.08 (s, 2H, imidazole-H's).

Anal. Calcd. for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.96; H, 4.62; N, 20.10.

This compound gives a royal blue colour reaction with ferric chloride in methanol.

2-Amino-6-(4-pyridyl)-1,8-naphthyridine Dihydrochloride (**2a**).

A mixture of 2,6-diaminopyridine (3.27 g., 30 mmoles), 2-(4-pyridyl)propane-1,3-dione (4.50 g., 30 mmoles) and 85% phosphoric acid (30 ml.) was heated at 95-100° for 4 hours. Then it was cooled and poured into ice-water (200 ml.). The solid was collected after adjusting the *p*H to 7.5-8. The crude base, 5.9 g. (89%), was dissolved in hot methanol and to the hot filtered solution, excess ethanolic hydrogen chloride solution was added. The solution was cooled and the product collected, 5.0 g. (57%); ir ν max (potassium bromide): 3050 (v br), 1665, 1635, 1610; nmr δ (deuterium oxide + deuteriotrifluoroacetic acid): 9.35 (d, 1H, J = 2 Hz, H-7), 9.07 (d, 2H, J = 6½ Hz, α-pyr.-H), 8.93 (d, 1H, J = 2 Hz, H-5), 8.57 (d, 2H, J = 6½ Hz, β-pyr.-H), 8.52 (d, 1H, J = 10 Hz, H-4), 7.38 (d, 1H, J = 10 Hz, H-3).

Anal. Calcd. for $C_{13}H_{10}N_4 \cdot 2HCl$: C, 52.89; H, 4.09; Cl, 24.02; N, 18.98. Found: C, 53.01; H, 4.34; Cl, 24.06; N, 18.85.

2-Amino-6-(2-imidazolyl)-1,8-naphthyridine (**2b**).

Condensation of 2,6-diaminopyridine with **5** as described above gave a theoretical yield of crude base **2b**. Purification of the product by dissolution of the compound in 6 *N* hydrochloric acid followed by slow basification of the filtered solution with 5 *N* sodium hydroxide gave fine yellow needles in 70% yield, m.p. 337-345° dec.; ir ν max (potassium bromide): 1635, 1428, 817; nmr δ (DMSO-d_6): 9.32 (d, 1H, J = 2½ Hz, H-7), 8.56 (d, 1H, J = 2½ Hz, H-5), 8.04 (d, 1H, J = 9 Hz, H-4), 7.24 (s, 2H, imidazole-H), 7.13 (s, ~2½ H, NH_2 & H_2O), 6.95 (d, 1H, J = 9 Hz, H-3).

Anal. Calcd. for $C_{11}H_9N_5 \cdot \frac{1}{4}H_2O$: C, 61.24; H, 4.43; N, 32.46. Found: C, 61.30; H, 4.32; N, 32.70.

6-(4-Pyridyl)-1,8-naphthyridin-2(1*H*)one (**3a**).

A solution of **2a** (5.00 g., 16.9 mmoles) in trifluoroacetic acid (50 ml.) was stirred in an ice-bath while finely powdered sodium nitrite (3.00 g., 43.4 mmoles) was added in small portions. The mixture was stirred in the cooling bath for 1 hour and allowed to warm to 25° before pouring it onto crushed ice (300 g.). A solid precipitated and was collected; it was dissolved in water and the solution was neutralized with ammonium hydroxide yielding 3.6 g. (95%) of **3a**, m.p. 295-305°. The monohydrochloride of **3a** was prepared by recrystallizing the base from 6 *N* hydrochloric acid, 3.2 g. (73%), m.p. > 350°; ir ν max (potassium bromide): 1665, 1633, 1615, 1569, 1217; nmr δ (deuterium oxide/perdeuterioacetic acid with TMS as external standard): 9.95 (d, 1H, J = 2 Hz, H-7), 9.29 (d, 2H, J = 7 Hz, α-pyr.-H), 9.10 (d, 1H, J = 2 Hz, H-5), 8.80 (d, 2H, J = 7 Hz, β-pyr.-H), 8.47 (d, 1H, J = 9½ Hz, H-4), 7.14 (d, 1H, J = 9½ Hz, H-3).

Anal. Calcd. for $C_{13}H_9N_3O \cdot HCl$: C, 60.12; H, 3.88; Cl, 13.65; N, 16.18. Found: C, 60.29; H, 4.28; Cl, 13.87; N, 16.34.

6-(2-Imidazolyl)-1,8-naphthyridin-2(1*H*)one (**3b**).

A solution of sodium nitrite (1.03 g., 14.9 mmoles) in water (3 ml.) was added slowly at 2-5° to a stirred mixture of **2b** (1.94 g., 9.19 mmoles) in 40% sulfuric acid. The reaction was allowed to warm to room temperature and then it was heated at 60° for 2 hours, before pouring it into ice-water and basifying with ammonium hydroxide. The solid (2.23 g.) was collected and purified by dissolution in a hot mixture of water (70 ml.) and acetic acid (90 ml.) and reprecipitation from the filtered solution with ammonium hydroxide; 1.58 g. (81%) of **3b**, m.p. > 350°, was obtained; ir ν max (potassium bromide): 3350 (v br), 1665 (br), 1422, 1299, 990, 807; nmr δ (DMSO-d_6): 8.90 (d, 1H, J = 2 Hz, H-7), 8.43 (d, 1H, J = 2 Hz, H-5), 7.86 (d, 1H, J = 9 Hz, H-4), 7.07 (s, 2H, imidazole-H), 6.62 (d, 1H, J = 9 Hz, H-3).

Anal. Calcd. for $C_{11}H_8N_4O$: C, 62.25; H, 3.80; N, 26.40. Found: C, 62.40; H, 3.84; N, 26.41.

Ethyl 5-Acetamido-2-amino-4,6-dimethylnicotinate (**6a**).

A mixture of 3-acetamidopentane-2,4-dione (7) (67.70 g., 0.431 mole) and ethyl ethoxycarbonylacetimidate (8) (137.1 g., 0.862 mole) was heated at 100° overnight. On cooling the mixture partially solidified. It was filtered and the solid was slurried with 2-propanol (40 ml.), refiltered and washed on the filter with 2-propanol, 45.3 g. (42%), m.p. 168.5-170°. Work up of the mother liquors gave another 8.67 g. (8%), m.p. 166-168°. On recrystallization from chloroform, **6a** is obtained as colourless platelets, m.p. 169-170°; ir ν max (potassium bromide): 3515, 3180 (br), 1655, 1617, 1275, 1250; nmr δ (DMSO-d_6): 9.29 (s, 1H, NH), 6.50 (s, 2H, NH_2), 4.44 (q, 2H, J = 7½ Hz, OCH_2), 2.21 & 2.19 (2 s, 2 x 3H, 2 CH_3), 2.06 (s, 3H, CH_3CO), 1.32 (t, 3H, J = 7½ Hz, CH_3).

Anal. Calcd. for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.02; H, 6.90; N, 16.81.

5-Acetamido-2-amino-4,6-dimethylnicotinic Acid Hydrazide (**6b**).

A mixture of **6a** (45.3 g., 0.18 mole) and hydrazine hydrate (100 ml.) was stirred in an oil-bath at 120° for 2 hours. The mixture was cooled and the product collected. A second crop was obtained by evaporating the filtrate to about half its volume, giving a total of 38.1 g. (89%), m.p. 293° dec. An analytically pure sample of **6b** was obtained by diluting a filtered aqueous solution of the crude product with methanol, dec. at ~309°; ir ν max (potassium bromide): 3485, 3460, 3350, 3230 (br), 1650, 1530, 1298; nmr δ (DMSO-d_6): 9.63 (br s, 1H, NH), 9.22 (s, 1H, NH), 5.64 (s, 2H, NH_2), 4.49 (br s, 2H, NH_2), 2.13, 2.01 & 1.97 (3 s, 3 x 3H, 3 CH_3).

Anal. Calcd. for $C_{10}H_{15}N_5O_2$: C, 50.62; H, 6.37; N, 29.51. Found: C, 50.84; H, 6.60; N, 29.60.

N'-(5-Acetamido-2-amino-4,6-dimethylnicotinoyl)-N^2-benzenesulphonylhydrazine (**6c**).

To a solution of crude **6b** (34.4 g., 0.145 mole) in *N* sodium hydroxide solution (348 ml.) was added with vigorous stirring at room temperature benzenesulphonyl chloride (31.1 g., 0.16 mole) in one portion. Complete solution occurred after about 3/4 hour, with a maximum temperature of 36°. On pouring this solution into a stirred mixture of acetic acid (8.3 ml.) and water (250 ml.), **6c** was precipitated. The solid was collected washed by slurrying with water (150 ml.), refiltered and dried affording 49.52 g. (90%) of **6c**, m.p. 216-218°. In order to prepare an analytical specimen the solid (1.5 g.) was dissolved in hot (100°) dimethylformamide (7.5 ml.) and the filtered solution was diluted with methanol (5 ml.) and water (15 ml.) giving 1.11 g. of pure **6c**, m.p. 233-234° dec.; ir ν max (potassium bromide): 3465, 3350, 3290, 1655, 1147; nmr δ (DMSO-d_6): 10.91 & 10.21 (2 br s, 2 x 1H, SO_2NH & CONH), 9.25 (s, 1H, CONH), 7.7-8.3 (m, 5H, aryl H), 5.55 (s, 2H, NH_2), 2.17, 2.04 & 1.92 (3 s, 3 x 3H, 3 CH_3).

Anal. Calcd. for $C_{16}H_{19}N_5O_4S$: C, 50.92; H, 5.07; N, 18.56; S, 8.48. Found: C, 51.24; H, 4.97; N, 18.76; S, 8.75.

5-Acetamido-2-amino-4,6-dimethylnicotinaldehyde (**7**).

Ethylene glycol (80 ml.) was heated to 160° (oil-bath at 170°) and **6c** (8.00 g., 21.2 mmoles) was added. When the temperature had returned to 160°, anhydrous sodium carbonate (5.60 g.) was added with vigorous stirring. After 15 seconds, the flask was removed from the oil bath, but stirring was continued as the reaction mixture cooled. Then it was poured into water (320 ml.) and the mixture was continuously extracted with methylene chloride for 24 hours yielding 2.93 g. (67%) of solid from the extract. Compound **7** can be recrystallized from alcohol from which it separates in silky yellow needles, m.p. 270-275° dec., on fairly rapid heating; ir ν max (potassium bromide): 3375, 3160 (br), 1660 (br), 1371, 1296, 788, 776; nmr δ (DMSO-d_6): 10.51 (s, 1H, CHO), 9.38 (s, 1H, CONH), 7.88 (s, 2H, NH_2), 2.41, 2.27 & 2.10 (3 s, 3 x 3H, 3 CH_3).

Anal. Calcd. for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.83; H, 6.46; N, 20.44.

3,9-Diacetamido-2,4,8,10-tetramethyl-5,11-epoxy-5,6,11,12-tetrahydrodipyrido[2,3-*b*:2',3'-*f*]diazocine (**8**).

If heating was prolonged in the McFadyen-Stevens reaction (2 minutes), a yellow solid **8** (276 mg.) collected at the methylene chloride/water interface during the extraction. Compound **8** can be purified by diluting a filtered solution in hot (100°) dimethyl sulfoxide with methanol, dec. > 330°; ir ν max (potassium bromide): 3255, 1655, 1585, 1525 & 1490 (br d); nmr δ (deuteriotrifluoroacetic acid): 6.84 (s, 2H, 2 methines), 2.68, 2.61 & 2.53 (3 s, 18H, 6 x CH_3); mass spectrum m/e = 396; water content, Calcd. for $1H_2O$: 4.35%. Found by Karl Fischer titration: 4.23%.

Anal. Calcd. for $C_{20}H_{24}N_6O_3 \cdot H_2O$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.61; H, 6.17; N, 20.19.

Ethyl 3-(5-Acetamido-2-amino-4,6-dimethylpyrid-3-yl)acrylate (**9**).

Triethylphosphonoacetate (5.60 g., 25 mmoles) in dry glyme (10 ml.) was added to a stirred suspension of sodium hydride (600 mg., 25 mmoles) in glyme (40 ml.) at 0-5°. When hydrogen evolution had ceased, **8** (4.14 g., 20 mmoles) was added in small portions during 30 minutes and the mixture was stirred at room temperature for 3 days. The solid was collected, washed with 1:1 ethanol/acetonitrile and dried, 4.93 g. (90%), m.p. 204-205° (incompletely). The solid was recrystallized from acetonitrile (150 ml.) giving a total of 4.166 g. (75%) of **8**, m.p. 204.5-205.5; ir ν max (potassium bromide): 3315, 3200, 1682, 1272, 1183; nmr δ (DMSO-d_6): 9.07 (s, 1H, CONH), 7.62 (d, 1H, J = 16 Hz, -CH=), 6.24 (d, 1H, J = 16 Hz, =CH-), 5.82 (s, 2H, NH_2), 4.20 (q, 2H, J = 7 Hz, OCH_2), 2.23, 2.04, 2.01 (3 s, 3 x 3H, 3 CH_3), 1.25 (t, 3H, J = 7 Hz, CH_3).

Anal. Calcd. for $C_{14}H_{19}N_3O_3$: C, 60.63; H, 6.91; N, 15.15. Found: C, 60.85; H, 6.90; N, 15.12.

6-Amino-5,7-dimethyl-1,8-naphthyridin-2(1*H*)one Hydrochloride (**10**).

A mixture of **9** (2.48 g., 8.94 mmoles) and 6 *N* hydrochloric acid (24.8 ml.) was heated under reflux for 6 days. The yellow-amber solution was filtered through a glass-fibre filter disc and

diluted slowly (over ~ 15 minutes) with ethanol (75 ml.) to precipitate the product; 1.043 g. (52%), m.p. 325° dec. A second crop of 561 mg. (28%), m.p. 295° dec., was obtained by evaporation of the mother liquors and treating the residue with a mixture of 12 *N* hydrochloric acid (1 ml.) and ethanol (5 ml.). Compound **10** was purified by reprecipitation from aqueous ethanolic hydrochloric acid solution by addition of 2-propanol. Dark yellow crystalline powder, m.p. 325° dec.; ir ν max (potassium bromide): 3315, 3200, 1660, 1372, 838; nmr δ (deuteriotrifluoroacetic acid): 8.51 (d, 1H, J = 10 Hz, H-4), 7.22 (d, 1H, J = 10 Hz, H-3), 3.03 & 2.91 (2 s, 2 x 3H, 2 CH_3).

Anal. Calcd. for $C_{10}H_{11}N_3O \cdot HCl$: C, 53.22; H, 5.36; Cl, 15.71; N, 18.61. Found: C, 53.28; H, 5.80; Cl, 15.79; N, 18.62.

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