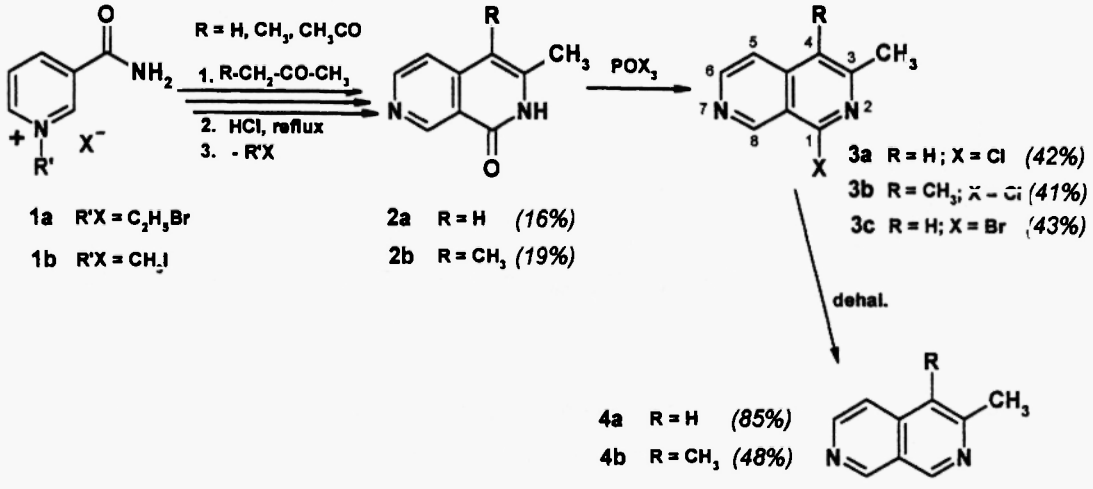
A METHOD FOR THE SYNTHESIS OF 3-METHYL-2,7-NAPHTHYRIDINE DERIVATIVES

Eugen Barbu* and Flavian Cuiban
Organic Chemistry Department, University of Ploiesti, Bd.Bucuresti 39, RO-2000, Ploiesti, Romania

Abstract: A synthetic route to 3-methyl-2,7-naphthyridine derivatives, used for pharmacological studies, is reported.

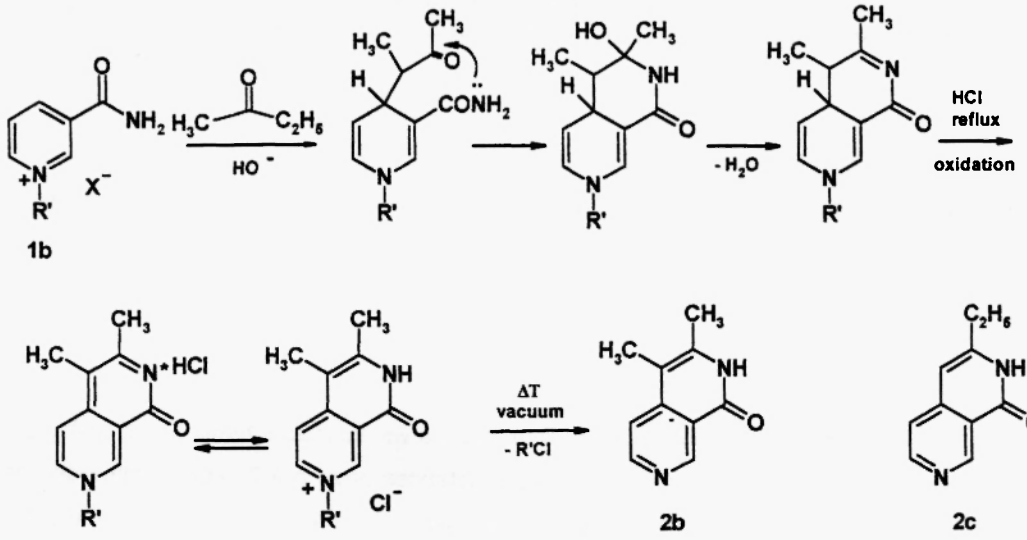
Introduction

Less studied than other isomers, 2,7-naphthyridines have found a widespread interest in the last years due to their pharmacological potential, because many active substances have a 2,7-naphthyridine skeleton as part of their molecule.(1) The cytotoxic marine alkaloids ascididerin and amphimedine(2) or the antifungal alkaloids from *Annonaceae*(3) are few of the recently reported examples. In order to investigate the relationship between structure and their pharmacological activity, we considered that simple 2,7-naphthyridine derivatives could play the role of appropriate models. In this paper we describe a facile synthetic method for the preparation of 3-methyl-2,7-naphthyridine derivatives, based on the condensation of the quaternized nicotinamide salts with ketones and subsequent derivatisation.(4,5)

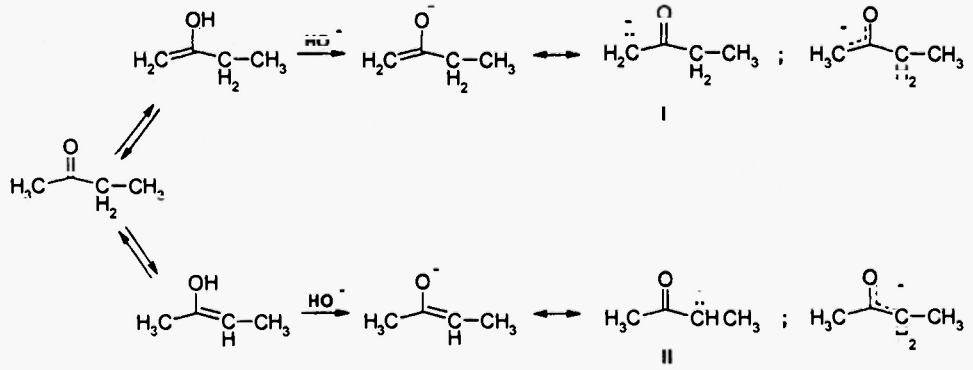


Results and discussions

2,7-Naphthyridine ring formation takes place through a 1,4-dihydropyridine type intermediate and is explained in detail (for the particular case of the synthesis of 2b) in the following scheme. Thus, by condensation of the nicotinamide salt 1b with ethyl methyl ketone, new derivatives 2b, and then 3b, 3c and 4b, were obtained. Annulation to the pyridinium salt of nicotinamide is a consequence of a Michael addition of the ketone-enolate, followed by the second ring closure through a nucleophilic attack of the amide nitrogen to the carbonyl group. Loss of water from the bicyclic 1,4-dihydropyridine thus formed, followed by air oxidation in acidic medium and pyrolitic elimination of the alkyl halides led to naphthyridinones 2.



Unexpected formation of 2b instead of 2c was obviously due to the fact that the nucleophile attack to the pyridinium salt 1b was achieved preferentially by the internal anion of the ethyl methyl ketone (II, see scheme below) and not by the marginal one (I), as would be expected from the inductive electronic effects.



We ascribed this behaviour to the involved keto-enolic equilibria, which are favoured by the dipole-dipole interactions between the carboxamide group and the enol, the reaction being thermodynamically controlled.

Condensation with acetyl acetone did not yield the expected naphthyridinone. We explained these results by the greater stability of the acetyl acetone carbanion comparatively to the ethyl methyl ketone one and by its concurential self-condensation. Poor results for the condensation of N-benzyl nicotinamide with acetyl acetone were also previously reported.(6) Naphthyridinones 2a,b were halogenated with phosphorus oxyhalides (POX_3, X = Cl, Br) and then the halogen was removed by treatment with hydrazine and subsequent oxidation with copper sulphate. We obtained higher dehalogenation yields by reduction with organotin compounds (TBTH) and we found this method more convenient than the classical ones, *i.e.* hydrazine – copper (II) sulphate or catalytic hydrogenation.(4,7)

Experimental

General Remarks: Melting points were determined on Büchi Melting Point B-540 and Böetius hotstage microscope PHMK 05 apparatus. NMR spectra were recorded on Jeol GSX FT (operating at 270.05 MHz for ^{1}H) and Bruker spectrometers (300.13 MHz for ^{1}H). Mass spectra were determined with Jeol JMS-DX 303 and Jeol VG ZAB spectrometers. Isobutane was used for the chemical ionisation mass spectra. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and a Heλios α Unicam spectrometer was used to record the UV-VIS spectra. APT and DEPT experiments were performed in order to clarify the ^{13}C-NMR signal assignments.

3-Carboxamide-1-alkyl-pyridinium halides 1a,b*:* To a solution of nicotinamide (13.3 g; 109 mmol) in absolute methanol (40 ml), an excess of alkyl halide (300 mmol) was added and the reaction mixture was gently refluxed under stirring (an efficient condenser was required) for 4 h (96 h for alkyl bromide). After cooling, crystals formed were filtered, washed with cold anhydrous methanol and dried to afford salt 1a (5.25 g; 19.9 mmol; 91 %), yellow crystals, m.p. 206-207 °C, and 1b respectively (12 g; 52 mmol; 48 %), white crystals, m.p. 212-215 °C (lit.(8)).

3-Methyl-1(2H)-oxo-2,7-naphthyridine 2a*.* To a solution of 3-carboxamide-1-ethyl-pyridinium bromide 1a (10 g; 43.27 mmol) in a mixture of water (90 ml) and freshly distilled acetone (70 ml), a concentrated solution of sodium hydroxide (5.6 g NaOH in water, 20 ml) was added gradually, under stirring. The reaction mixture was stirred at r.t. for 48 h. Concentrated HCl (25 ml) was added and the mixture was refluxed for 1 h. After removal of solvents, the dry residue was refluxed in absolute ethanol and the suspension was cooled down, filtered and washed thoroughly on filter with absolute ethanol. The ethanolic filtrates were collected, evaporated and the yellow residue was sublimed at 5×10^{-2} mbar and 290-300°C. The sublimate was then recrystallized from boiling water to afford white crystals of 3-methyl-1(2*H*)-oxo-2,7-naphthyridine 2a (1.11 g; 6.9 mmol; 16%), m.p. 262-264°C (lit.(4) 264°C), which has a strong white-blue fluorescence in the UV light (254 nm). ^{1}H-NMR (DMSO-[D_6], 300.13 MHz, TMS, δ): 11.61 (broad s, 1H, NH); 9.20 (s, 1H, H-8); 8.59 (d, 1H, H-6, $J_{6,5}$ = 5.4 Hz); 7.41 (d, 1H, H-5, $J_{5,6}$ = 5.4 Hz); 6.30 (s, 1H, H-4); 2.22 (s, 3H, CH_3). ^{13}C-NMR (DMSO-[D_6], 75.46 MHz, TMS, δ): 162.1 (C-1); 150.7 (C-8); 149.8 (C-6); 145.0 (C-3); 143.6 (C-4a); 119.4 (C-8a); 118.9 (C-5); 101.4 (C-4); 19.2 (CH_3). UV-VIS (MeOH, nm): 205 (0.930); 222 (1.289); 244 (0.909); 303 (1.148).

3,4-Dimethyl-1(2H)-oxo-2,7-naphthyridine 2b was prepared starting from 3-carboxamide-1-methyl-pyridinium iodide 1b (5.25 g; 19.88 mmol) and freshly distilled 2-butanone (80 ml; 887 mmol). Working procedure was similar to the preparation of 3-methyl-1(2*H*)-oxo-2,7-naphthyridine 2a. Recrystallization from boiling water yielded colourless prismatic crystals of 3,4-dimethyl-1(2*H*)-oxo-2,7-naphthyridine 2b (0.650 g; 3.73 mmol; 19 %), m.p. 275-275.5°C, showing a strong blue fluorescence in the UV light (254 nm). ^{1}H-NMR ($CDCl_3$, 300.13 MHz, TMS, δ): 11.46 (broad, 1H, NH); 9.57 (d, 1H, H-8, $J_{8,5}$ = 0.6 Hz); 8.73 (d, 1H, H-6, $J_{6,5}$ = 5.7 Hz); 7.42 (dd, 1H, H-5, $J_{5,6}$ = 5.7 Hz, $J_{5,8}$ = 0.6 Hz); 2.44 (s, 3H, 3-CH_3); 2.21 (s, 3H, 4-CH_3). ^{13}C-NMR ($CDCl_3$, 300.13 MHz, TMS, δ): 163.5 (C-1); 150.9 (C-8); 150.8 (C-6); 144.0 (C-3); 139.8 (C-4a); 119.4 (C-8a); 116.0 (C-5); 107.4 (C-4); 17.7 (3-CH_3); 11.7 (4-CH_3). MS (m/z): <EI> 174 (M^+, 100); 173 (M^+ - 1, 42); 159 (M^+ - CH_3, 8); <CI, isobutane> 349 (M + MH^+, 50); 175 (MH^+, 100). IR (KBr 1%, cm^{-1}): 3157 (ν_{NH}); 1661 ($\nu_{C=O}$). UV-VIS (MeOH, nm/abs): 206 (1.112); 219 (1.092); 224 (1.074); 247 (0.686); 314 (0.980); 336 (0.620).

1-Chloro-3-methyl-2,7-naphthyridine 3a. 3-Methyl-1(2*H*)-oxo-2,7-naphthyridine 2a (250 mg; 1.56 mmol) and phosphorus oxychloride (3.5 ml; 37.9 mmol) were heated to 140°C for 6 h in a stainless steel autoclave. The cooled reaction mixture was poured on crushed ice, neutralized with sodium carbonate (sat. sol.) and extracted with methylene chloride. The organic layer was dried on sodium sulphate, evaporated and the residue was chromatographed on silica gel S, with methylene chloride/methanol 20:1. Recrystallization from diethyl ether afforded colourless needle-shaped crystals of 1-chloro-3-methyl-2,7-naphthyridine 3a (116 mg; 0.65 mmol; 42 %), m.p. 104-105°C (lit.(4) 106°C). ^{1}H-NMR ($CDCl_3$; 270.05 MHz, TMS, δ): 9.60 (s, 1H, H-8); 8.68 (d, 1H, H-6, $J_{6,5}$ = 5.7 Hz); 7.50 (d, 1H, H-5, $J_{5,6}$ = 5.7 Hz); 7.35 (s, 1H, H-4); 2.64 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$, 270.05 MHz, TMS, δ) 155.8 (C-3); 151.3 (C-8); 151.1 (C-1); 147.7 (C-6); 141.3 (C-4a); 120.3 (C-8a); 118.4 (C-4); 117.1 (C-5); 24.2 (CH_3). UV-VIS (MeOH, nm): 213 (1.131); 229 (0.626); 286 (0.148).

1-Chloro-3,4-dimethyl-2,7-naphthyridine 3b was prepared from 3,4-dimethyl-1(2*H*)-oxo-2,7-naphthyridine 2b (520 mg; 2.98 mmol) and phosphorus oxychloride (6 ml; 65 mmol) by the same procedure as that one used for 1-chloro-3-methyl-2,7-naphthyridine 3a. Final chromatography on silica gel S, with methylene chloride/ methanol 40:1 and recrystallization from absolute ethanol gave colourless crystals of 1-chloro-3,4-dimethyl-2,7-naphthyridine 3b (235 mg; 1.22 mmol; 41 %), m.p. 113-114.5°C. ^{1}H-NMR ($CDCl_3$, 300.13 MHz, TMS, δ): 9.44 (s, 1H, H-8); 8.60 (d, 1H, H-6, $J_{6,5}$ = 6.0 Hz); 7.53 (d, 1H, H-5, $J_{5,6}$ = 6.0 Hz); 2.54 (s, 3H, 3-CH_3); 2.37 (s, 3H, 4-CH_3). ^{13}C-NMR ($CDCl_3$, 300.13 MHz, TMS, δ): 152.8 (C-1); 151.3 (C-8); 148.0 (C-3); 147.2 (C-6); 140.4 (C-4a); 123.0 (C-4); 119.9 (C-8a); 115.4 (C-5); 22.5 (3-CH_3); 13.1 (4-CH_3). MS (m/z): <EI> 192 (M^+, 100), intensities in accordance with the calculated isotopic cluster; 177 (M^+ - CH_3, 13); 157 (M^+ - Cl, 7); 151 (M^+ - CH_3 - C_2H_2, 17); 116 (M^+ - CH_3-CH_2-Cl, 19); <CI, isobutane> 385 (M + MH^+, 4); 249 (M + *t*Bu^+, 3); 193 (MH^+, 100). UV-VIS (MeOH, nm): 221 (1.556); 279 (0.208); 307 (0.163); 321 (0.166).

1-Bromo-3-methyl-2,7-naphthyridine 3c. Finely grounded 3-methyl-1(2*H*)-oxo-2,7-naphthyridine 2a (600 mg; 3.74 mmol) and phosphorus oxybromide (3.3 g; 11.49 mmol) were intimately mixed and heated to 100°C for 3.5 h in a stoppered flask. The cooled reaction mixture was poured into ice water, neutralized with sodium bicarbonate (sat. sol.) and extracted with methylene chloride. Drying on magnesium sulphate and solvent removal afforded a solid residue which was chromatographed on silica gel S (methylene chloride/ethanol

20:1). Sublimation in vacuum (6×10^{-2} mbar) at 100°C yielded colourless needle-shaped crystals of 1-bromo-3-methyl-2,7-naphthyridine 3c (360 mg; 1.61 mmol; 43 %), decomp. over 120°C. ^{1}H-NMR ($CDCl_3$, 300.13 MHz, TMS, δ): 9.57 (t, 1H, H-8, $J_{8,5}$ = 0.7 Hz); 8.69 (d, 1H, H-6, $J_{6,5}$ = 5.8 Hz); 7.48 (dd, 1H, H-5, $J_{5,6}$ = 5.7 Hz); 7.38 (m, 1H, H-4, $J_{5,8}$ = 0.7 Hz); 2.67 (d, 3H, CH_3, $J_{CH_3,5}$ = 0.7 Hz). ^{13}C-NMR ($CDCl_3$, 300.13 MHz, TMS, δ): 156.2 (C-3); 153.2 (C-8); 147.5 (C-6); 143.9 (C-1); 140.9 (C-4a); 122.0 (C-8a); 118.1 (C-4); 117.2 (C-5); 24.0 (CH_3). MS (m/z): <EI> 222 (M^+, 72), intensities in accordance with the calculated isotopic cluster; 143 (M^+ - Br, 100); 116 (M^+ - Br - HCN, 52).

3-Methyl-2,7-naphthyridine 4a. A mixture of 1-bromo-3-methyl-2,7-naphthyridine (220 mg; 0.98 mmol), azobisisobutironitrile (150 mg; 0.91 mmol) and tributyltin hydride (1.5 g; 5.15 mmol) in dry benzene (15 ml) was refluxed under vigorous stirring for 96 h. After evaporation of solvent, the reaction mixture was washed on a silica gel column with petroleum ether until the complete removal of excess TBTH. Chromatography with methylene chloride/ethanol 20:1 afforded a crude product which was distilled in vacuum ($4\text{-}6\times10^{-2}$ mbar) at 40-50°C to yield colourless prismatic crystals of 3-methyl-2,7-naphthyridine (120 mg; 0.83 mmol; 85 %), m.p. 35-37°C (lit.(4) 39°C). ^{1}H-NMR ($CDCl_3$, 300.13 MHz, TMS, δ): 9.28 (s, 1H, H-8); 9.26 (s, 1H, H-1); 8.58 (d, 1H, H-6, $J_{6,5}$ = 5.8 Hz); 7.47 (d, 1H, H-5, $J_{5,6}$ = 5.8 Hz); 7.39 (s, 1H, H-4); 2.67 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$, 300.13 MHz, TMS, δ): 156.4 (C-3); 152.6 (C-8); 152.2 (C-1); 146.7 (C-6); 139.0 (C-4a); 122.1 (C-8a); 118.5 (C-4); 116.9 (C-5); 24.5 (CH_3). MS (m/z): <EI> 144 (M^+, 100); 143 (M^+ - 1, 18); 129 (M^+ - CH_3, 3); 117 (M^+ - HCN, 21).

3,4-Dimethyl-2,7-naphthyridine 4b. To a solution of 1-chloro-3,4-dimethyl-2,7-naphthyridine (130 mg; 0.67 mmol) in absolute ethanol (2 ml), an excess of hydrazine hydrate 90 % (0.6 ml) was added and the reaction mixture was refluxed for 15 min on a water bath. After cooling, the yellow precipitate was filtered, washed with cold anhydrous ethanol and then dissolved in a solution of glacial acetic acid (4 ml) and water (5 ml). The obtained clear solution was added in portions, under stirring, over a hot 10 % cupric sulphate solution (20 ml) and heated on a boiling water bath for 1 h. The cooled solution was made alkaline (pH ~ 8-9) with concentrated ammonia and extracted with diethyl ether. Drying on sodium sulphate and removal of ether afforded a solid residue which was chromatographed on silica gel S, solvent methylene chloride/methanol 15:1. Sublimation in vacuum (30 mbar) at 90-95°C yielded colourless needle-shaped crystals of 3,4-dimethyl-2,7-naphthyridine (51 mg; 0.32 mmol; 48 %), m.p. 103-104°C. ^{1}H-NMR ($CDCl_3$, 300.13 MHz, TMS, δ): 9.30 (s, 1H, H-8); 9.16 (s, 1H, H-1); 8.67 (d, 1H, H-6, $J_{6,5}$ = 6.0 Hz); 7.71 (d, 1H, H-5, $J_{5,6}$ = 6.0 Hz); 2.72 (s, 3H, 3-CH_3); 2.54 (s, 3H, 4-CH_3). ^{13}C-NMR ($CDCl_3$, 300.13 MHz, TMS, δ): 153.9 (C-1); 153.2 (C-8); 149.8 (C-3); 146.7 (C-6); 138.4 (C-4a); 123.1 (C-4); 122.3 (C-8a); 115.7 (C-5); 23.1 (3-CH_3); 13.4 (4-CH_3). MS (m/z): <EI> 158 (M^+, 100); 157 (M^+ - 1, 40); 143 (M^+ - CH_3, 8); 130 (M^+ - HCN - H, 12); 117 (M^+ - CH_3 - C_2H_2, 30); <CI, isobutane> 317 (M + MH^+, 70); 159 (MH^+, 100).

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