VALERIAN ALKALOIDS: FIRST TOTAL SYNTHESIS OF A NAPHTHYRIDYL METHYL KETONE

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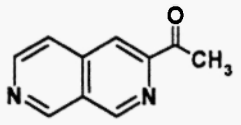
Abstract: The first synthetic route to the naphthyridyl methyl ketone 1, which has been isolated from valerian (and is thought to be responsible for its physiological effects) is now reported.

Introduction

Compounds containing the 2,7-naphthyridine ring structure have found widespread interest in the last few years. Recent examples of derivatives having pharmacological potential - among them natural polycyclic alkaloids with high antimicrobial and anticancer activities - have called our attention to the 2,7-naphthyridine pharmacophoric group.(1)

One of the few naturally occuring bicyclic 2,7-naphthyridines is naphthyridyl methyl ketone 1, isolated from valerian (*Valeriana officinalis*), a plant from which various preparations have been used therapeutically due to the sedative and tranquillizing activity.(2) Also, many pharmaceutical products (Extraveral, Valenal, Valerina *etc.*) based on cultivated plants are commercially available. Despite this wide use, the active constituent of valerian has not been unequivocally identified. Formerly, valepotriates have been held responsible for it but this view has been strongly disputed by others.(3,4) The naphthyridyl methyl ketone 1 was isolated from valerian in too small amounts to allow proper pharmacological testing, but studies on concentrates of alkaloid have indicated 1 to be responsible for the mentioned physiological effects.(5) These facts, together with the generally increased interest in 2,7-naphthyridine derivatives, many of which are natural products, prompted us to investigate a synthetic route to compound 1.



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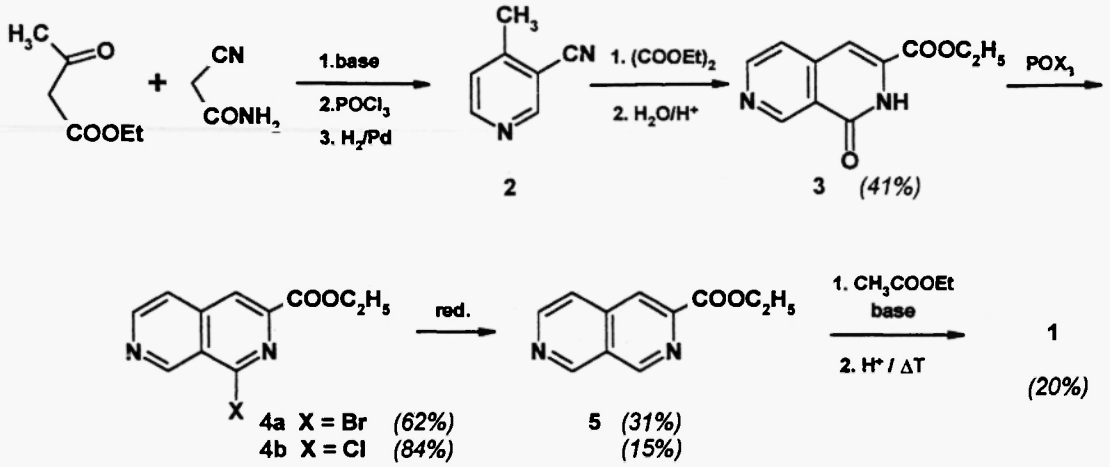
Results and discussions

Here we report the first total synthesis of alkaloid 1, so that a complete pharmacological screening is now possible. The cyanopicoline 2 was prepared from ethyl acetoacetate and cyanoacetamide.(6) Compound 2 was condensed with diethyl oxalate and the product was cyclized to ethyl-1(*2H*)-oxo-2,7-naphthyridine-3-

carboxylate 3 (40 % yields were obtained, instead of only 10 % previously reported for this reaction).(7) Halogenation of the cyclic product and subsequent reduction afforded the previously unknown naphthyridine derivatives 4a,b and 5. While compounds 4a,b can be dehalogenated catalytically (H_2/Pd), higher yields were obtained by reduction with tributyltin hydride in benzene. The β-ketoester obtained by condensation of 5 with ethyl acetate was hydrolyzed and decarboxylated without isolation of intermediates to afford ketone 1.



Experimental

General Remarks: Melting points were determined on a Büchi Melting Point B-540 apparatus. NMR spectra were recorded on Jeol GSX FT (270.05 MHz - ^{1}H) and Bruker spectrometers (300.13 MHz - ^{1}H). Mass spectra were determined with Jeol JMS-DX 303 and Jeol VG ZAB spectrometers.

3-Carboxyethyl-1(2H)-oxo-2,7-naphthyridine 3: To a solution of 3-cyano-4-picoline 2 (3.54 g; 30 mmol) and diethyl oxalate (15 ml; 0.11 mol) in dry benzene, potassium *t*-butoxide (7.27 g; 64,8 mmol) was gradually added under a nitrogen atmosphere with vigorous stirring. After 36 h the precipitate formed was filtered off, washed with anhydrous ether and dried. The salt obtained was dissolved in water (800 ml) and the solution was acidified with HCl to pH = 3. The resulting suspension was stirred for 24 h, diluted with water (to 3000 ml, pH ~ 5), stirred for another 2 h and then extracted with chloroform. Usual work up, chromatography on silica gel (CH_2Cl_2 / EtOH 20:1) and recrystallization from EtOH afforded 3 (2.65 g, 12.15 mmol, 41 %), m.p. 226-229 °C, ^{1}H-NMR (Bruker, $CDCl_3$, 300.13 MHz, TMS, δ): 9.67 (s, 1H, H-8); 9.61 (broad s, 1H, NH); 8.86 (d, 1H, H-6, $J_{6,5}$ = 5.5 Hz); 7.51 (dd, 1H, H-5, $J_{5,6}$ = 5.5 Hz, $J_{5,4}$ = 0.7 Hz); 7.29 (d, 1H, H-4, $J_{4,5}$ = 0,7 Hz); 4.49 (q, 2H, CH_2, $J_{CH_2CH_3}$ = 7.1 Hz); 1.46 (t, 3H, CH_3, $J_{CH_2CH_3}$ = 7.1 Hz); ^{13}C-NMR (Bruker, $CDCl_3$, 75.46 MHz, TMS, δ): 161.1 (COO); 160.9 (C-1); 152.1 (C-8); 151.3 (C-6); 141.5 (C-4a); 132.4 (C-3); 122.5 (C-8a); 120.6 (C-5); 108.4 (C-4); 63.2 (CH_2); 14.2 (CH_3); MS (EI, m/z): 218 (M^+, 100). 3-Carboxyethyl-1-oxopyrano[3,4-c]pyridine (lit.(7)) (0.790 g, 3.60 mmol, 12 %) m.p. 144-145.5 °C was also isolated.

1-Bromo-3-carboxyethyl-2,7-naphthyridine 4a: Finely ground compound 3 (0.4 g, 1.83 mmol) and excess $POBr_3$ (1.3 g, 4.53 mmol) were intimately mixed and slowly heated to 100 °C in a stoppered flask. After 3.5h

the cooled solid residue was treated with ice water, neutralized with $NaHCO_3$ and extracted with CH_2Cl_2. Usual work up, chromatography on silica gel (CH_2Cl_2 / EtOH 20:1) and recrystallization from heptane afforded bromo derivative 4a (0.32 g, 1.14 mmol, 62 %), m.p. 113-114.5 °C. ^{1}H-NMR (Bruker, $CDCl_3$, 300.13 MHz, TMS, δ): 9.73 (s, 1H, H-8); 8.89 (s, 1H, H-6, $J_{6,5}$ = 5.4 Hz); 8.44 (s, 1H, H-4); 7.73 (d, 1H, H-5, $J_{5,6}$ = 5.4 Hz); 4.50 (q, 2H, CH_2, $J_{CH_2CH_3}$ = 7.1 Hz); 1.44 (t, 3H, CH_3, $J_{CH_2CH_3}$ = 7.1 Hz); ^{13}C-NMR (Bruker, $CDCl_3$, 75.46 MHz, TMS, δ): 163.6 (COO); 153.7 (C-8); 148.8 (C-6); 145.3 (C-1); 144.9 (C-3); 140.3 (C-4a); 124.5 (C-8a); 122.4 (C-4); 119.9 (C-5); 62.5 (CH_2); 14.3 (CH_3); MS (EI, m/z): 282/280 (1:1, M^+, 8); 210/208 (1:1, M^+-CO_2-C_2H_4, 100). A small amount of dibromoderivative (0.025 g, 0.07 mmol, 3.8 %) was isolated.

3-Carboxyethyl-1-chloro-2,7-naphthyridine 4b: Compound 3 (1.345 g, 6.16 mmol) and $POCl_3$ (7 ml, 77 mmol) were heated at 150° C for 6 h in a stainless steel autoclave. Cooling, treatment with ice water, neutralization with $NaHCO_3$, extraction with chloroform and the usual work up afforded a solid residue which was chromatographed over a short column of neutral alumina II (Brockmann scale), solvent CH_2Cl_2 to give chloro derivative 4b (1.220 g, 5.14 mmol, 84 %), m.p. 113-114 °C (a sample recrystallized from EtOH showed the same m.p.). ^{1}H-NMR (Jeol, $CDCl_3$, 270.05 MHz, TMS, δ): 9.83 (s, 1H, H-8); 8.93 (d, 1H, H-6, $J_{6,5}$ = 5.7 Hz); 8.48 (d, 1H, H-4, $J_{4,5}$ = 0.7 Hz); 7.82 (dd, 1H, H-5, $J_{5,6}$ = 5.7 Hz, $J_{5,4}$ = 0.7 Hz); 4.54 (q, 2H, CH_2, $J_{CH_2CH_3}$ = 7.1 Hz); 1.48 (t, 3H, CH_3, $J_{CH_2CH_3}$ = 7.1 Hz); ^{13}C-NMR (Jeol, $CDCl_3$, 67,80 MHz, TMS, δ): 163.8 (COO); 152.5 (C-1); 151.6 (C-8); 148.9 (C-6); 144.5 (C-3); 140.6 (C-4a); 122.8 (C-8a); 122.2 (C-4); 120.0 (C-5); 62.6 (CH_2); 14.3 (CH_3); MS (EI, m/z): 238/236 (1:3, M^+, 15); 166/164 (1:3, M^+-CO_2-C_2H_4, 100).

3-Carboxyethyl-2,7-naphthyridine 5: *a)* from 4a – Bromo derivative 4a (90 mg, 0.32 mmol), tributyltin hydride (320 mg, 1.1 mmol) and azobisisobutyronitrile (60 mg, 0.36 mmol) were heated to reflux under argon in dry benzene (20 ml) for 96 h. The reaction mixture was concentrated and washed onto a silica gel column with petroleum ether to remove excess TBTH. Chromatography with CH_2Cl_2 / EtOH 20:1 and recrystallization from toluene / heptane afforded ester 5 (20 mg, 0.1 mmol, 31 %), m.p. 106.5-107 °C. ^{1}H-NMR (Bruker, $CDCl_3$, 300.13 MHz, TMS, δ): 9.50 (s, 1H, H-8); 9.49 (s, 1H, H-1); 8.82 (d, 1H, H-6, $J_{6,5}$ = 5.8 Hz); 8.54 (s, 1H, H-4); 7.77 (d, 1H, H-5, $J_{5,6}$ = 5.8 Hz); 4.54 (q, 2H, CH_2, $J_{CH_2CH_3}$ = 7.2 Hz); 1.47 (t, 3H, CH_3 , $J_{CH_2CH_3}$ = 7.2 Hz); ^{13}C-NMR (Bruker, $CDCl_3$, 75.46 MHz, TMS, δ): 164.7 (CO); 152.7 (C-8); 152.6 (C-1); 147.7 (C-6); 145.2 (C-3); 138.3 (C-4a); 124.2 (C-8a); 121.9 (C-4); 119.8 (C-5); 62.1 (CH_2); 14.1 (CH_3); MS (EI, m/z): 202 (M^+, 1); 130 (M^+-CO_2-C_2H_4, 100).

b) from 4b – A mixture of chloro derivative 4b (315 mg, 1.33 mmol), $Pd/CaCO_3$ (80 mg) and anhydrous sodium acetate (175 mg, 1.95 mmol) in anhydrous methanol (50 ml) was hydrogenated under TLC control. After filtration and removal of solvent, the residue was taken up with water, neutralized with $NaHCO_3$ and extracted with CH_2Cl_2. The usual work up afforded a solid that was chromatographed on alumina II (Brockmann) eluting with CH_2Cl_2 to yield, after recrystallization from toluene / heptane, ester 5 (40 mg, 0.19 mmol, 15 %), same analytical data as above.

3-Acetyl-2,7-naphthyridine 1: To a mixture of ester 5 (60 mg, 0.29 mmol) and dry ethyl acetate (55 mg, 0.62 mmol) in dry benzene (10 ml) stirred under argon, potassium *t*-butoxide (52 mg; 0.46 mmol) was added and the reaction mixture was heated to reflux for 1.5 h. After cooling, conc. HCl (0.1 ml) was added and the

mixture refluxed for another 1.5 h, cooled, made alkaline with $NaHCO_3$ (half-satd.) and extracted with CH_2Cl_2. Usual work up and chromatography on silica gel (EtOAc) afforded ketone 1 as colorless crystals (10 mg, 0.058 mmol, 20 %), m.p. 126-128 °C (lit.[3] 130 °C). ^{1}H-NMR (Bruker, $CDCl_3$, 300.13 MHz, TMS, δ): 9.51 (s, 1H, H-8); 9.45 (s, 1H, H-1); 8.81 (d, 1H, H-6, $J_{6,5}$ = 5.8 Hz); 8.42 (s, 1H, H-4); 7.79 (d, 1H, H-5, $J_{5,6}$ = 5.8 Hz); 2.83 (s, 3H, CH_3); ^{13}C-NMR (Bruker, $CDCl_3$, 75.46 MHz, TMS, δ): 199.6 (CO); 152.7 (C-8); 152.3 (C-1); 150.6 (C-3); 147.6 (C-6); 138.5 (C-4a); 124.6 (C-8a); 120.6 (C-4); 118.3 (C-5); 26.5 (CH_3); MS (EI, m/z): 172 (M^+, 100); HR-MS calculated for $C_{10}H_8N_2O$: 172.06366; found 172.06356 (61).

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