# SYNTHESIS OF 4-SUBSTITUTED-3-ETHOXYCARBONYL(CARBOXY)-1,5-NAPHTHYRIDINES, AND THEIR PROPERTIES AND BIOLOGICAL ACTIVITY

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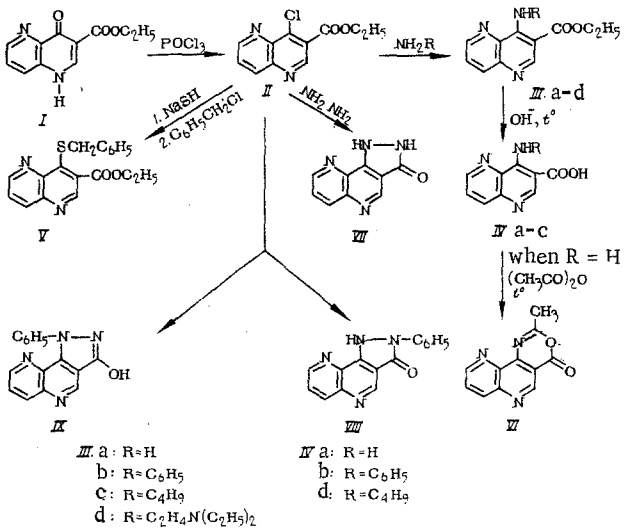
In continuation of a search for compounds with antibacterial activity in the 1,5-naphthyridine series, some 4-amino derivatives of 3-ethoxycarbonyl-1,5-naphthyridine (IIIa-d), and the carboxylic acids (IVa-c) from the esters (IIIa-c), have been obtained starting from 4-oxo-1,4-dihydro-3-ethoxycarbonyl-1,5-naphthyridine (I) via the corresponding 4-chloro-3-ethoxycarbonyl derivative (II). Reaction of (II) with NaSH and benzyl chloride afforded the benzylthio-derivative (V). Heating the o-aminoacid (IVa) with acetic anhydride gave 2-methyl-4-oxo-4H-3,1-oxazino[5,4-c]-1,5-naphthyridine (VI).




Reaction of (II) with hydrazine hydrate afforded an oxo-derivative of a new heterocyclic system, pyrazolo[4,3-c]-1,5-naphthyridine (VII). A similar reaction with phenylhydrazine resulted in the formation of two isomers with the same molecular mass and elemental composition. The IR spectra of these compounds showed that one of them was in the tautomeric lactam form (presence of νC=O amide absorption at 1625 $cm^{-1}$, and νNH at 2700 $cm^{-1}$), and the other in the lactim form (νOH assoc. absorption at 2500 $cm^{-1}$, and absence of an amide νC=O band). For the compound occurring in the oxo-form, the most likely structure is (VIII), since its existence in the tautomeric hydroxy-form would involve disruption of the aromatic naphthyridine ring, and for the compound with the hydroxy-structure, the corresponding structure, (IX). The structures of the isomers were confirmed by mass spectrometry. The mass spectrum of (IX) contained fragments with m/e 245, 244, and 129, corresponding to the elimination from the molecular ion of the groups OH, $H_2O$, and CONH, whereas these fragments were absent from the mass spectrum of (VIII).

The antimicrobial activity of the compounds was examined *in vitro* by standard methods against four species of Gram-positive bacteria, five species of Gram-negative bacteria, and

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five species of pathogenic fungi. The most active compound was (IIIc). Its minimum bacteriostatic concentration towards Gram-positive and Gram-negative bacteria was 3.9-7.8 μg/ml. This compound displayed moderate activity towards dermatitis fungi. Antifungal activity was also detected in (IIIb) (minimum fungistatic concentration 31.2 μg/ml). The remaining compounds were almost inactive, failing to suppress the growth of the microorganisms in concentrations of 500-1000 μg/ml.

## EXPERIMENTAL

Mass spectra were obtained on a Varian MAT-112 mass spectrometer, ionizing electron energy 70 eV, ionization chamber temperature 180°C, with direct introduction of the sample into the ion source. IR spectra were recorded on a Perkin-Elmer 457 spectrophotometer. TLC was carried out on Silufol-254 plates in the systems methanol—ethyl acetate (9:1) and methanol—$NH_4OH$ (10:1) for (V) and (VI). Visualization by UV.

3-Ethoxycarbonyl-4-chloro-1,5-naphthyridine (II). 3-Ethoxycarbonyl-4-hydroxy-1,5-naphthyridine (I) (1.0 g, 45.8 mmole) was boiled in 30 ml of $POCl_3$ for 4 h, then the $POCl_3$ was removed *in vacuo*, and the residue treated with ice and $NH_4OH$ to pH 7.0. Continuous extraction with heptane followed by removal of the heptane gave 0.65 g (27.5 mmole) of (II), mp 68.5-69.5°C (from heptane), yield 65% of theory, $R_f$ 0.7 (violet). Found, %: Cl 14.78; N 11.86. $C_{11}H_9ClN_2O_2$. Calculated, %: Cl 14.98; N 11.84.

3-Ethoxycarbonyl-4-amino-1,5-naphthyridine (IIIa). A solution of 1.0 g (42.3 mmole) of (II) in 35 ml of 19% ethanolic ammonia was heated in an autoclave for 2 h at 100°C, then evaporated to dryness *in vacuo*. The residue was treated with benzene, then the latter was evaporated to give 0.9 g (41.4 mmole) of (IIIa), mp 122-123°C (from heptane), $R_f$ 0.56 (blue), yield 98%. Found, %: C 60.8; H 5.5; N 19.3, $C_{11}H_{11}N_3O_2$. Calculated, %: C 60.8, H 5.1, N 19.4. IR spectrum, ν, $cm^{-1}$: 3390 ($NH_2$), 1685 (C=O).

Similarly, from (II) were obtained 3-ethoxycarbonyl-4-butylamino-1,5-naphthyridine (IIIc)[by heating with butylamine for 4 h at 160°C, mp 61.5-62°C (from heptane), $R_f$ 0.45, yield 95.5%. Found, %: C 65.89; H 6.95; N 15.4. $C_{15}H_{19}N_3O_2$. Calculated, %: C 65.91; H 7.0; N 15.37], and 3-ethoxycarbonyl-4-β-diethylaminoethylamino-1,5-naphthyridine (IIId) [by heating with β-diethylaminoethylamine for 8 h at 160-165°C, mp 49.5-50°C (from hexane), $R_f$ 0.06, yield 42.7%. Found, %: C 65.0; H 7.73; N 17.95. $C_{17}H_{24}N_4O_2$. Calculated, %: C 64.53; H 7.64; N 17.7].

3-Ethoxycarbonyl-4-phenylamino-1,5-naphthyridine (IIIb). A mixture of 0.5 g (21 mmole) of (II) and 1 ml of aniline was boiled in 5 ml of anhydrous alcohol for 2 h, then it was evaporated to dryness *in vacuo*, and treated with water to give 0.6 g (20.5 mmole) of (IIIb), mp 97.5-98°C (from heptane), $R_f$ 0.65, yield 97.4%. Found, %: C 68.84; H 5.29; N 14.12. $C_{17}H_{15}N_3O_2$. Calculated, %: C 69.6; H 5.15; N 14.3.

3-Carboxy-4-amino-1,5-naphthyridine (IVa). Compound (IIIa) (0.7 g, 32.2 mmole) was boiled in 5 ml of 1 N NaOH for 5 min. The resulting solution was acidified to pH 5.0 with acetic acid, to give 0.6 g (31.8 mmole) of (IVa), mp 300-301°C (from water), $R_f$ 0.26, yield 98.6%. Found, %: C 56.7; H 3.6; N 21.9. $C_9H_7N_3O_2$. Calculated, %: C 57.1; H 3.7; N 22.21. IR spectrum, ν, $cm^{-1}$: 3150, 3300 ($NH_2$), 1640 (C=O).

Similarly obtained were 3-carboxy-4-anilino-1,5-naphthyridine (IVb)[mp 232°C (from water), $R_f$ 0.4, yield 74.9%. Found, %: C 63.9; H 5.2; N 14.86. $C_{15}H_{13}N_3O_2$. Calculated, %: C 63.6; H 4.6; N 14.83], and 3-carboxy-4-butylamino-1,5-naphthyridine (IVc) [mp 255-256°C (decomp., from methanol), $R_f$ 0.42, yield 95.5%. Found, %: C 63.44; H 6.16; N 17.25. $C_{13}H_{15}N_3O_2$. Calculated, %: C 63.66; H 6.16; N 17.13].

3-Ethoxycarbonyl-4-benzylthio-1,5-naphthyridine (V). To a solution of 0.3 g (12.7 mmole) of (II) in 3 ml of methanol was added 0.9 ml of 10% NaSH solution, and the mixture was stirred for 30 min at 20°C. Benzyl chloride (0.6 ml, 52 mmole) was then added, the mixture kept for 3 h at 20-25°C, cooled to 5°C, and the (V) (0.3 g, 9.25 mmole) filtered off, mp 93-94°C (from aqueous DMF), $R_f$ 0.8, yield 72%. Found, %: C 66.92; H 4.56; N 8.61; S 9.8. $C_{18}H_{16}N_2O_2S$. Calculated, %: C 66.65; H 4.96; N 8.64; S 9.88.

2-Methyl-4-oxo-4H-1,3-oxazino[5,4-c]-1,5-naphthyridine (VI). Compound (IVa) (0.76 g, 40 mmole) was boiled in 20 ml of acetic anhydride under nitrogen for 15 min, cooled to 0°C, and 0.45 g (21 mmole) of (VI) filtered off, mp 204-205°C, $R_f$ 0.57, yield 52.8% Found, %: C 62.21; H 3.35; N 19.6. $C_{11}H_7N_3O_2$. Calculated, %: C 61.97; H 3.31; N 19.7. Mass spectrum, m/e: 213 $(M)^+$, 198 $(M-CH_3)^+$, 171 $(M-COCH_2)^+$, 170 $(M-COCH_3)^+$, 145 $(M-COCH_2CN)^+$, 143 $(M-COCH_2-CO)^+$.

1H-3-Oxo-2,3-dihydropyrazolo[4,3-c]-1,5-naphthyridine (VII). A mixture of 0.5 g (21.1 mmole) of (II), 1.5 ml (30.9 mmole) of hydrazine hydrate, and 5 ml of ethanol was stirred for 2 h at 25°C, and cooled to 5°C. The solid which separated was dissolved in 1 ml of 2.5 N NaOH, 4 ml of ethanol added, and the sodium salt of (VII) filtered off. This was dissolved in water, and the solution acidified to pH 5.0 to give 0.25 g (13.2 mmole) of (VII), mp > 350°C, $R_f$ 0.41, yield 62.7%. Found, %: C 57.35; H 3.2; N 30.04. $C_9H_6N_4O$. Calculated, %: C 58.0; H 3.25; N 30.09. IR spectrum, $\nu$, $cm^{-1}$: 3350, 3140, 3040 (NH), 1640-1620 (C=O).

1H-2-Phenyl-3-oxo-2,3-dihydropyrazolo[4,3-c]-1,5-naphthyridine (VIII) and 1-Phenyl-3-hydroxypyrazolo[4,3-c]-1,5-naphthyridine (IX). Compound (II) (0.6 g, 25.4 mmole) and 1.08 ml (100 mmole) of phenylhydrazine were stirred in 3 ml of anhydrous alcohol for 1 h at 20°C. The solid which separated was filtered off and washed with ether to give 0.44 g (16.8 mmole) of (IX), mp 324-325°C (from DMF), $R_f$ 0.75, yield 66.2%. Found, %: C 68.52; H 3.88; N 21.27. $C_{15}H_{10}N_4O$. Calculated, %: C 68.69; H 3.84; N 21.36. IR spectrum, $\nu$, $cm^{-1}$: 2500 (assoc. OH). Mass spectrum, m/e: 262 (M+), 245 (M−OH)+, 244 (M−$H_2O$)+, 219 (M−CONH)+, 233 (M−HCO, M−$N_2H$)+, 206 (M−$CON_2$, M−HCO, $HCN_2$)+, 205 (M−$HCON_2$)+, 129 (M−$PhN_2CO$)+, 77 (M−Ph)+.

The mother liquors were treated with ether to give 0.2 g (7.6 mmole) of (VIII), mp > 350°C, $R_f$ 0.86, yield 30%. Found, %: C 68.89; H 4.0; N 21.37. $C_{15}H_{10}N_4O$. Calculated, %: C 68.69; H 3.84; N 21.36. IR spectrum, $\nu$, $cm^{-1}$: 2700, 3100 (NH, br. w), 1625 (C=O). Mass spectrum, m/e: 262 $(M)^+$, 233 (M−HCO, M−$N_2H$)+, 206 (M−$CON_2$, M−HCO, $HCN_2$)+, 205 (M−$HCON_2$)+, 129 (M−$PhN_2CO$)+, 77 (M−Ph)+.