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SYNTHESIS AND CRYSTAL STRUCTURE OF 5-AMINO-7-BENZYLSELENO-8-CYANO-3-ETHOXYCARBONYL-4-(2-FURYL)-1,2-DIMETHYL-1,4-DIHYDRO-1,6-NAPHTHYRIDINE

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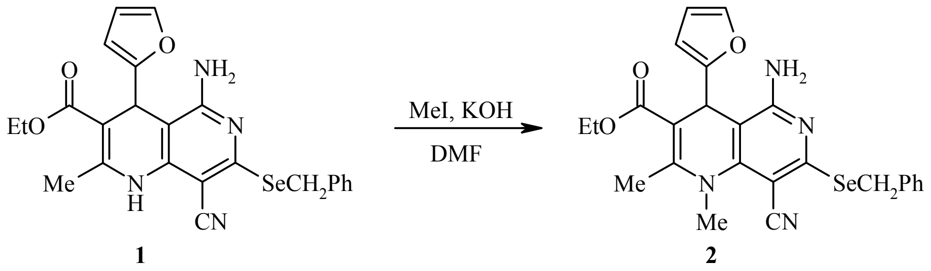
5-Amino-7-benzylseleno-8-cyano-3-ethoxycarbonyl-4-(2-furyl)-1,2-dimethyl-1,4-dihydro-1,6-naphthyridine was obtained by N-alkylation. X-ray crystallography showed the presence of two symmetrically conformers in the crystal.

Keywords: 1,4-dihydro-1,6-naphthyridine, N-alkylation, X-ray crystallography.

N-Alkylation of substituted 4-oxo-1,4-dihydronaphthyridine-3-carboxylic acids and their esters has been described in the literature with the objective of preparing antibacterial analogs of nalidixic acids (nevigramon) and enoxacine, in particular in [1-7]. An assumption in these methods of alkylation of naphthyridinecarboxylic acid and their derivatives is the necessity to use a considerable excess of the alkylating agent and base (NaH or K_2CO_3), carrying out the reaction on heating in DMF, frequently for a long time.

In reviewing investigations in the field of valuable compounds with antibacterial activity among substituted alkylseleno-1,6-naphthyridines [8, 9], we have alkylated ethyl ester of substituted 1,4-dihydro-1,6-naphthyridine-3-carboxylic acid (**1**) with methyl iodide under mild conditions (in DMF in the presence of aqueous KOH at room temperature) to obtain the N-methyl derivative **2**.



To confirm the structure unambiguously, and thus to establish the regioselectivity of the reaction, an X-ray crystallographic study of compound **2** has been carried out. This study has shown that there are two symmetrically independent molecules (**A** and **B**) in the crystal of compound **2** which are markedly different in their conformations (Fig. 1 and 2, Tables 1 and 2).

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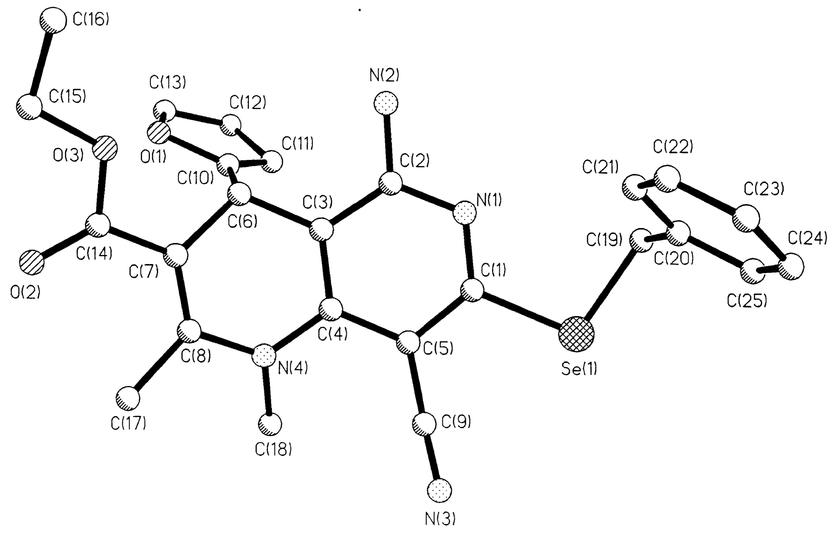

Fig. 1. General View of Molecule **2A** (H atoms not shown).

In both molecules the central bicyclic system $N_{(1)}N_{(4)}C_{(1-8)}$ is only approximately planar (within limits of 0.286 Å in molecule **2A** and 0.314 Å in molecule **2B**). The grouping $N_{(1)}N_{(4)}C_{(1-6)}$ is effectively planar (displacement of atoms from least squares plane does not exceed 0.033 Å in molecule **2A** and 0.045 in molecule **2B**), while atoms $C_{(7)}$ and $C_{(8)}$ are displaced by -0.623 and -0.500 Å respectively in molecule **2A** and by 0.712 and 0.631 Å respectively in molecule **2B**. Calculations of the modified Kremer-Pople parameters [10] (for molecule **2A** $S = 0.47$, $\theta = 77.99°$, Ψ 7.98°; for molecule **2B** $S = 0.50$, $\theta = 76.56°$, $\Psi = 3.17$) show that the heterocycle $N_{(4)}C_{(3,4,6,7,8)}$ has a twist-tub conformation.

One of the basic structural differences between molecules **2A** and **2B** is in the orientation of the groups $C_{(14)}O_{(2)}O_{(3)}C_{(15)}C_{(16)}$ relative to the central bicyclic system. While in molecule **2A** the torsion angle $C_{(8)}C_{(7)}C_{(14)}O_{(2)}$ is -16.6°, the corresponding angle in molecule **2B** is 173.0°. Moreover, the furan ring in molecule **2A** $O_{(1)}C_{(10-13)}$ is rotated relative to the central bicyclic system by 76.4°, while in molecule **2B** this ring

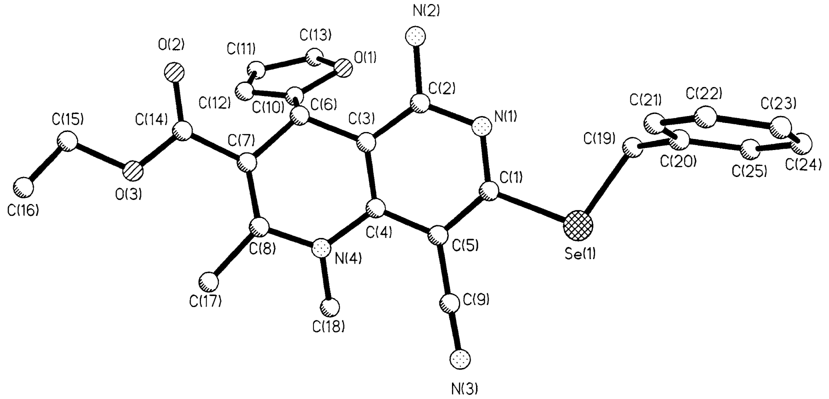

Fig. 2. General view of molecule **2B** (H atoms not shown).

TABLE 1. Basic Bond Lengths (*d*) in the Two Symmetrically Independent Molecules (**A** and **B**) of Compound **2**

Bond	*d*, Å		Bond	*d*, Å	
	Molecule **2A**	Molecule **2B**		Molecule **2A**	Molecule **2B**
$Se_{(1)}-C_{(1)}$	1.915(6)	1.924(7)	$C_{(1)}-C_{(5)}$	1.405(9)	1.399(11)
$Se_{(1)}-C_{(19)}$	1.950(8)	1.929(10)*	$C_{(2)}-C_{(3)}$	1.411(8)	1.397(10)
		1.951(10)*	$C_{(3)}-C_{(4)}$	1.370(8)	1.373(9)
$N_{(1)}-C_{(1)}$	1.314(8)	1.314(9)	$C_{(3)}-C_{(6)}$	1.498(8)	1.500(9)
$N_{(1)}-C_{(2)}$	1.336(7)	1.338(8)	$C_{(4)}-C_{(5)}$	1.421(8)	1.418(9)
$N_{(2)}-C_{(2)}$	1.341(8)	1.346(8)	$C_{(5)}-C_{(9)}$	1.402(10)	1.404(11)
$N_{(4)}-C_{(8)}$	1.385(8)	1.377(9)	$C_{(6)}-C_{(10)}$	1.493(9)	1.487(10)
$N_{(4)}-C_{(4)}$	1.396(8)	1.403(9)	$C_{(7)}-C_{(8)}$	1.312(9)	1.353(9)
$N_{(4)}-C_{(18)}$	1.491(9)	1.464(9)	$C_{(7)}-C_{(14)}$	1.482(9)	1.460(10)
$C_{(10)}-C_{(6)}$	1.493(9)	1.487(10)	$C_{(8)}-C_{(17)}$	1.504(10)	1.507(10)

* The two values for the geometric parameters cited correspond to two disordered positions.

is disordered in two almost perpendicular positions: the dihedral angles between this ring and the central bicyclic system are 69.0 and 75.2°, while the dihedral angle between the two positions of the ring $O_{(1)}C_{(10-13)}$ is 77.2°. The orientation of the $SeCH_2Ph$ substituent relative to the bicyclic systems is different in molecules **2A** and **2B**: in molecule **2A** the torsion angle $C_{(1)}Se_{(1)}C_{(19)}C_{(20)}$ is 97.7°. whereas in molecule **2B** the torsion angles $C_{(1)}Se_{(1)}C_{(19)}C_{(20)}$ for the two disordered positions of this group are -124.5 and -164.9°. Therefore molecules **2A** and **2B** are different conformers of molecule **2**.

The shortened intermolecular contacts $N_{(2)}$(**B**)···$O_{(2)}$(**B**) 2.861(8), $N_{(2)}$(**B**)···$O_{(2)}$(**A**) 3.164(8), $N_{(2)}$(**A**)···$N_{(3)}$(**B**) 3.146(8), and $N_{(2)}$(**A**)···$N_{(3)}$(**A**) 3.111(8) Å indicate the possibility of the formation of a complex three-dimensional system of hydrogen bonds in the crystal of naphthyridine **2** (see Fig. 3).

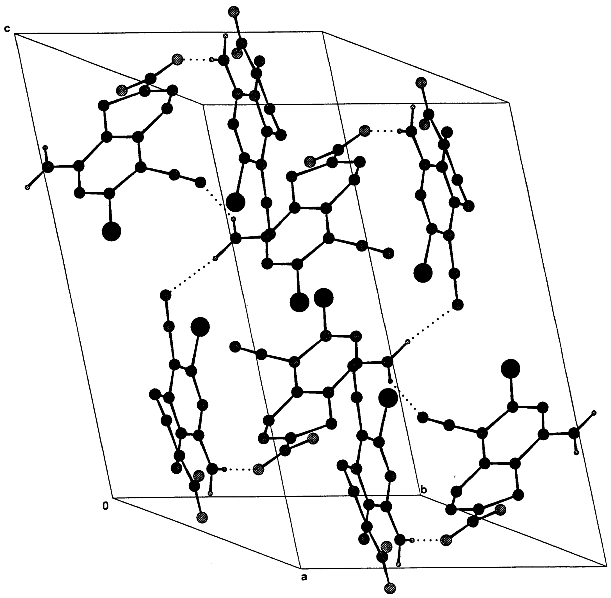

Fig. 3. Fragment of the crystal packing of compound **2**. For simplification the groupings $C_{(19-25)}$, $O_{(1)}C_{(10-13)}$ and atoms $C_{(15)}$, $C_{(16)}$, $C_{(17)}$, and $C_{(18)}$ are not shown.

TABLE 2. Basic Bond Angles (ω) in the Two Symmetrically Independent Molecules (**A** and **B**) of Compound **2**

Angle	ω, deg		Angle	ω, deg	
	Molecule **2A**	Molecule **2B**		Molecule **2A**	Molecule **2B**
$C_{(1)}$–$Se_{(1)}$–$C_{(19)}$	100.1(3)	104.0(8)*,	$C_{(2)}$–$C_{(3)}$–$C_{(6)}$	122.4(6)	123.4(6)
		92.5(6)*	$C_{(3)}$–$C_{(4)}$–$N_{(4)}$	118.8(6)	118.7(6)
$C_{(1)}$–$N_{(1)}$–$C_{(2)}$	117.7(6)	116.8(7)	$C_{(3)}$–$C_{(4)}$–$C_{(5)}$	119.2(6)	119.7(7)
$C_{(8)}$–$N_{(4)}$–$C_{(4)}$	119.5(6)	119.7(6)	$N_{(4)}$–$C_{(4)}$–$C_{(5)}$	121.9(6)	121.3(6)
$N_{(1)}$–$C_{(1)}$–$C_{(5)}$	124.0(6)	124.9(7)	$C_{(1)}$–$C_{(5)}$–$C_{(4)}$	117.2(6)	116.6(7)
$N_{(1)}$–$C_{(2)}$–$C_{(3)}$	123.8(6)	124.6(7)	$C_{(3)}$–$C_{(6)}$–$C_{(7)}$	109.5(5)	110.0(5)
$C_{(4)}$–$C_{(3)}$–$C_{(2)}$	117.8(6)	117.4(6)	$C_{(8)}$–$C_{(7)}$–$C_{(6)}$	119.8(6)	119.4(6)
$C_{(4)}$–$C_{(3)}$–$C_{(6)}$	119.8(6)	119.2(6)	$C_{(7)}$–$C_{(8)}$–$N_{(4)}$	120.7(6)	119.8(6)

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* Geometrical parameters cited are for the two disordered positions.

TABLE 3. Atomic Coordinates (× 10^4) in Structure **2**

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
1	2	3	4	5	6	7	8
$Se_{(1A)}$	168(1)	1698(1)	5761(1)	$N_{(4B)}$	4022(7)	-204(4)	2844(4)
$O_{(1A)}$	-4389(6)	4318(3)	9112(3)	$C_{(1B)}$	2661(9)	1907(5)	3122(5)
$O_{(2A)}$	-2617(7)	6553(4)	9007(4)	$C_{(2B)}$	3152(8)	1423(5)	1816(4)
$O_{(3A)}$	-4540(6)	5644(3)	8054(4)	$C_{(3B)}$	3546(8)	651(4)	1921(4)
$N_{(1A)}$	-2396(6)	2353(3)	6201(3)	$C_{(4B)}$	3490(8)	526(5)	2682(4)
$N_{(2A)}$	-4636(6)	2762(3)	6405(3)	$C_{(5B)}$	3065(8)	1177(5)	3327(4)
$N_{(3A)}$	762(9)	3456(5)	7204(5)	$C_{(6B)}$	4051(8)	-29(4)	1257(4)
$N_{(4A)}$	-58(6)	4447(4)	8357(4)	$C_{(7B)}$	5189(8)	-485(4)	1698(4)
$C_{(10A)}$	-3614(7)	3840(4)	8578(4)	$C_{(8B)}$	5063(8)	-600(4)	2441(4)
$C_{(1A)}$	-908(8)	2493(4)	6414(4)	$C_{(9B)}$	3229(9)	1171(5)	4176(5)
$C_{(2A)}$	-3117(7)	2919(4)	6667(4)	$C_{(10B)}$	2763(9)	-616(5)	573(5)
$C_{(3A)}$	-2373(7)	3623(4)	7405(4)	$C_{(14B)}$	6287(9)	-813(5)	1220(5)
$C_{(4A)}$	-820(7)	3751(4)	7633(4)	$C_{(15B)}$	8437(14)	-1507(9)	1156(8)
$C_{(5A)}$	-34(7)	3193(4)	7108(4)	$C_{(16B)}$	9559(17)	-1728(11)	1682(10)
$C_{(6A)}$	-3216(7)	4213(4)	7946(4)	$C_{(17B)}$	6021(10)	-1107(5)	2921(5)
$C_{(7A)}$	-2279(8)	5091(4)	8391(4)	$C_{(18B)}$	3354(11)	-591(6)	3365(5)
$C_{(8A)}$	-794(8)	5153(4)	8626(5)	$C_{(19B)}$	1200(29)	3543(14)	3360(15)
$C_{(9A)}$	1514(9)	3345(5)	7176(5)	$C_{(20B)}$	1972(23)	4438(17)	3775(17)
$C_{(11A)}$	-3450(8)	3104(5)	8735(5)	$C_{(21B)}$	3485(26)	4539(16)	3782(14)
$C_{(12A)}$	-4186(10)	3101(5)	9378(5)	$C_{(22B)}$	3991(45)	5363(17)	4357(20)
$C_{(13A)}$	-4690(9)	3857(6)	9599(5)	$C_{(23B)}$	3359(45)	6114(20)	4605(27)
$C_{(14A)}$	-3127(10)	5840(5)	8525(5)	$C_{(24B)}$	1918(46)	5802(17)	4587(29)
$C_{(15A)}$	-5484(11)	6315(6)	8101(7)	$C_{(25B)}$	1080(28)	5005(14)	4153(16)
$C_{(16A)}$	-6943(13)	5973(7)	7487(9)	$O_{(1B)}$	1468(21)	-304(14)	253(13)
$C_{(17A)}$	255(10)	5968(5)	9144(6)	$C_{(12B)}$	1404(72)	-1773(21)	-541(34)
$C_{(18A)}$	1477(9)	4407(6)	8894(5)	$C_{(11B)}$	2904(34)	-1333(14)	132(18)
$C_{(19A)}$	-1530(9)	953(5)	4846(5)	$C_{(13B)}$	664(43)	-1084(32)	-402(27)
$C_{(20A)}$	-1852(9)	1158(5)	4034(5)	$C_{(19B)}$*	1996(56)	3574(10)	3298(13)
$C_{(21A)}$	-2900(10)	1716(6)	3918(6)	$C_{(20B)}$*	1980(29)	4480(11)	3825(12)
$C_{(22A)}$	-3195(12)	1950(7)	3192(8)	$C_{(21B)}$*	3025(28)	5213(17)	4201(20)
$C_{(23A)}$	-2474(17)	1638(8)	2582(8)	$C_{(22B)}$*	2935(37)	5963(22)	4835(18)
$C_{(24A)}$	-1418(14)	1077(8)	2672(7)	$C_{(23B)}$*	1444(34)	6132(16)	4732(27)

TABLE 3 (continued)

1	2	3	4	5	6	7	8
$C_{(25A)}$	-1126(10)	839(6)	3413(6)	$C_{(24B)}$*	218(28)	5500(14)	4307(16)
$Se_{(1B)}$	2113(1)	2814(1)	3986(1)	$C_{(25B)}$*	549(24)	4702(15)	3857(18)
$O_{(2B)}$	6237(8)	-749(4)	530(4)	$O_{(1B)}$*	2048(16)	-1237(8)	797(8)
$N_{(1B)}$	2679(7)	2034(4)	2392(4)	$C_{(11B)}$*	2252(30)	-869(17)	-257(11)
$O_{(3B)}$	7332(7)	-1189(5)	1597(4)	$C_{(12B)}$*	917(47)	-1465(15)	-557(20)
$N_{(2B)}$	3201(7)	1614(4)	1102(4)	$C_{(13B)}$*	1037(30)	-1707(16)	100(15)
$N_{(3B)}$	3383(9)	1187(5)	4873(5)				

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* The atoms belonging to the furan and benzoyl groups of molecule **2B** are disordered over two positions with equal population density.

EXPERIMENTAL

Melting points were determined on a Kofler block. IR spectra of nujol mulls were recorded with an IKS-29 apparatus. ^{1}H NMR spectra of DMSO-d$_6$ solutions with TMS as internal standard were recorded on a Bruker AM-300 (300 MHz) spectrometer. The purity of compounds was monitored by TLC on Silufol UV-254 strips with 3:5 acetone–heptane as eluent and iodine vapor as developer.

5-Amino-7-benzylseleno-8-cyano-3-ethoxycarbonyl-4-(2-furyl)-1,2-dimethyl-1,4-dihydro-1,6-naphthyridine (2). 10% aqueous solution of KOH (1.15 ml, 2 mmol) was added with stirring to solution of 1,4-dihydronaphthyridine **1** (1.00 g, 2 mmol) in DMF (10 ml), followed by methyl iodide (0.13 ml, 2 mmol) over 5 min. The reaction mixture was stirred at room temperature for 4 h and then diluted with water (10 ml). The precipitate of compound **2** was filtered off, washed with water, and recrystallized from ethanol. Yield 0.76 g (74%); mp 185-187°C. IR spectrum (nujol), ν, cm^{-1}: 3216, 3323, 3420 (NH_2); 2192 (C≡N); 1674 (C=O); 1627 (δ NH_2). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 7.12-7.43 (6H, m, $C_{(5)}H$ furyl, H_{Ph}); 6.88 (2H, br. s, NH_2); 6.22 (1H, dd, *J* = 3.0 and 2.1, $C_{(4)}H$ furyl); 6.05 (1H, d, *J* = 3.0, $C_{(3)}H$ furyl); 5.13 (1H, s, $C_{(4)}H$); 4.41 and 4.47 (both 1H, both d, *J* = 12.5, $SeCH_2$); 4.16 (2H, q, *J* = 7.6, $CH_3C\underline{H_2}O$); 3.48 (3H, s, NCH_3); 2.46 (3H, s, 2-CH_3); 1.30 (3H, t, *J* = 7.6, $C\underline{H_3}CH_2O$). Found, %: C 59.02; H 4.84; N 10.89; Se 15.68. $C_{25}H_{24}N_4O_3Se$. Calculated, %: C 59.17; H 4.77; N 11.04; Se 15.56.

X-ray Crystallographic Study of Compound 2. X-ray crystallography of compound **2** monocrystal was carried out at room temperature on an automatic four-circle Enraf-Nonius CAD-4 diffractometer (λMo$K\alpha$ radiation, graphite monochromator, ratio of $\omega/2\theta$ scanning 1/2, θ_{max} 24°, segment of the sphere $0 \leq h \leq 10$, $-18 \leq k \leq 18$, $-19 \leq l \leq 18$). 22 reflexions with $12 < \theta < 13°$ were used to determine the unit cell parameters and orientation matrices of a crystal of compound **2** with linear parameters 0.16×0.25×0.31 mm. 7584 reflexions were measured, of which 7336 were independent (average *R* factor 0.030). Crystals of compound **2** are triclinic, $a = 9.173(2)$, $b = 16.595(3)$, $c = 16.844(3)$ Å; $\alpha = 108.10(3)$, $\beta = 104.23(3)$, $\gamma = 92.39(3)°$; $V = 2342.9(8)$ Å^3; $Z = 4$ (two symmetrically independent molecules); $d_{calc} = 1.44$ g/cm^3; $\mu = 1.637$ mm^{-1}; $F(000) = 1040$; space group $P1$ (No. 2). The structure was solved by the heavy atom method with refinement by least-squares in the full-matrix anisotropic approximation using the SHELXS [11] and SHELXL93 [12] suite of programmes. In the refinement 3792 reflexions with $I > 2\sigma(I)$ (694 refined parameters, 5.46 reflexions per parameter, weighting scheme used $\omega = 1/[\sigma^2(F\sigma^2] + (0.0855P)^2]$ where $P = (F\sigma^2 + 2Fc^2)/3$). The relative maximum (average) shift to error in the last cycle 0.56 (0.037). Corrections for anomalous dispersion were included but corrections for absorption were not. Most of the hydrogen atoms (~75%) were revealed objectively, the rest were placed by geometry. All hydrogen atoms were included in the calculations with fixed positions and thermal parameters.

The final values for the residual factors $R(1)(F) = 0.0703$ and $R_w(F^2) = 0.1500$, GOF 1.017. The residual electron densities from the difference Fourier synthesis were 0.37 and -0.43 e/Å^3. Atomic coordinates are cited in Table 3 (thermal parameters may be obtained from the authors).

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