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Synthesis and Crystal Structure of *N*-Acryloylcytisine and *N*-(β-Morpholinopropionyl)cytisine

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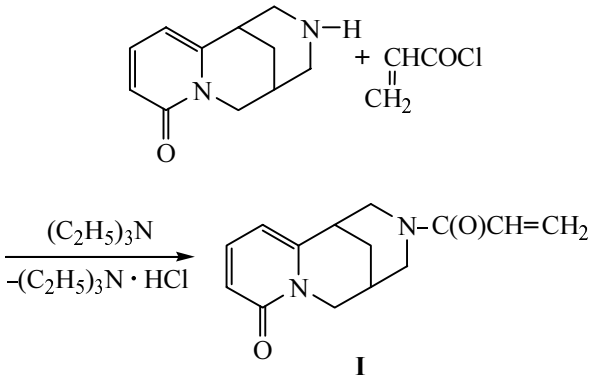
Abstract—*N*-acryloylcitisine and *N*-(β-morpholinopropionyl)cytisine were synthesized and spatial structures of compounds obtained were established by X-ray difraction analysis.

Investigations of antimicrobial activity of synthetic derivatives of cytisine revealed that it depended essentially on the chemical structure of the side chains of alkaloid attached to nitrogen [1–3].

Aiming at refining understanding of effect on the physiological activity of cytisine derivatives produced by various substituents with an activated double bond we synthesized N-acryloylcytisine (**I**) in 95% yield. The alkaloid was acylated with acryloyl chloride in anhydrous benzene by a standard procedure.



I

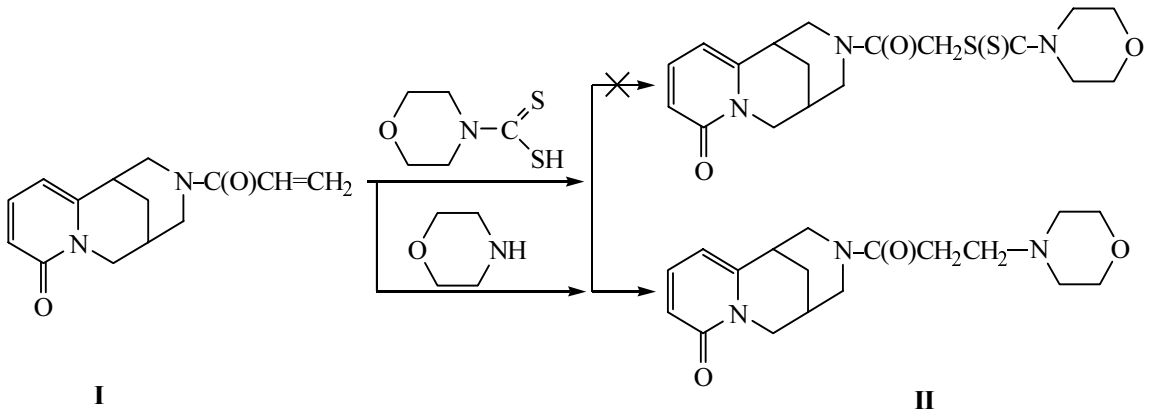
The acryl fragment of compound **I** was modified by adding morpholinodithiocarbamic acid made *in situ* from carbon disulfide and morpholine. The main product isolated from the reaction mixture was *N*-(β morpholinopropionyl)cytisine (**II**) obtained in 86% yield. Apparently the morpholinodithiocarbamic acid decomposed, and morpholine added to the *N*-acryloylcytisine across the double bond (see the scheme).

Compound **II** is a colorless crystalline substance soluble in most organic solvents. The structure of compounds **I** and **II** was established by means of IR, ^{1}H NMR spectroscopy, and X-ray diffraction analysis. General view of molecules **I** and **II** is presented on Figs. 1 and 2.

As demonstrated by the X-ray diffraction study the bond lengths and bond angles in the cytisine skeleton of structures **I** and **II** are close to those in N-methylcytisine (**III**) [4], *N*-cyanomethyl-cytisine (**IV**) [5], and *O,O*-dimethyl-*N*-cytisinylamidophosphate (**V**) [6] except for the the bond angles at the atom N^{12}. In molecules **III** and **IV** the atom N^{12} is present in a pyramidal coordination (sum of bond angles is 335.7° and 334.0° respectively), whereas in molecules **I** and **II**, like in molecule **V**, the coordination is trigonal-planar (bond angles sum is 360, 359.8, and 354.8° respectively).

The different configuration of nitrogen in molecules **III** and **IV**, on the one hand, and in molecules **I, II**, and **V**, on the other hand, is due to mesomeric effect involving a lone electron pair of atom N^{12} and conjugation system of the acryloyl moiety or the double bond P^1=O^2 in compound **V.** Therewith the bond N^{12}–C^{14} gets shorter, and the bond C^{14}=O^{14} somewhat longer as compared to standard values (Table1). The dihydropyridine ring in structures **I** and **II** is planar within ±(0.015, 0.017) Årespectively, the carbonyl oxygen O^2 is located practically in this plane (its deviation from the plane is 0.06 Å for **I** and 0.05 Å for **II**). The tetrahydropyridine ring $N^1C^6C^7C^8C^9C^{10}$ takes a conformation of *distorted sofa* [ΔC_s^8 6.3 (**I**), ΔC_s^8 7.29 (**II**), with deviation of the bridging atom C^8 from the mean plane of the other atoms of the ring by 0.74 (**I**), 0.72 (**II**) Å]. Piperidine ring has a *distorted chair* conformation [ΔC_s^7 0.58 Å(min.), ΔC_s^8 3.55 Å(max) (**I**), ΔC_s^7 0.92 Å(min), ΔC_s^8 3.68 Å(max)

Scheme.



I **II**

(**II**)]. The morpholine ring $N^{17}C^{21}C^{22}O^{20}C^{18}C^{19}$ in **II** molecule is present in the *chair* conformation [ΔC_S^{19} 1.47 Å(min), ΔC_S^{17} 1.84 Å (max)].

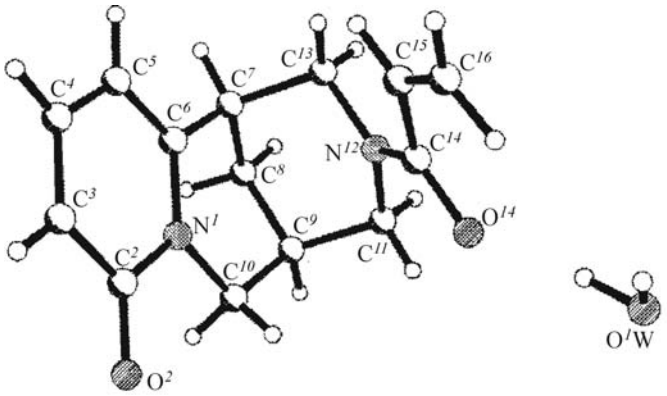


Fig. 1. Structure of N^{12}-acryloylcytisine (**I**) molecule.

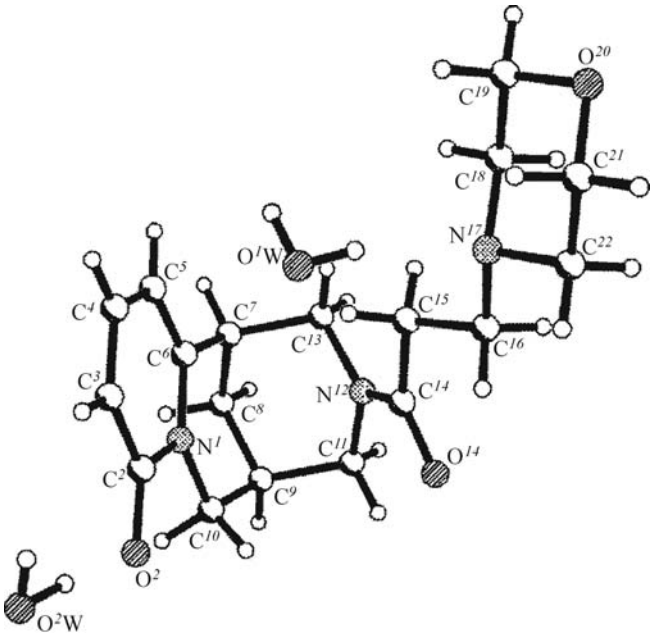


Fig. 2. Structure of N^{12}-(b-morpholinopropionyl)cytisine (**II**).

The comparison of torsion angles in the cytisine fragment of molecules **I** and **II** with the respective angles in molecules **III** and **IV** shows that the difference does not exceed 8.6° (Table2).

Thus the conformation of rings in the cytosine molecule crystal is relatively rigid. Therewith the tetrahydropyridine ring is more susceptible to the effect of substituent attached to atom N^{12}, and the influence of the latter affects the symmetry. The piperidine ring with a good precision conserves its symmetry disregarding the dimensions of the substituent at N^{12} that is equatorially directed, and atom N^{12} can change its configuration due to the mesomeric effect.

The above reasoning suggests a conclusion that introducing substituents to atom N^{12} virtually does not affect the conformation of the cytisine skeleton (Tables 1–3).

In the IR spectra of compounds **I** and **II** appears a characteristic absorption band of carbonyl group (C=O)

Table 1. Bond lengths (*d*, Å) in molecules **I** and **II**

Bond	*d*, Å (**I**)	*d*, Å (**II**)	Bond	*d*, Å (**I**)	*d*, Å (**II**)
N^1–C^6	1.370(3)	1.368(3)	C^{11}–N^{12}	1.467(3)	1.461(3)
N^1–C^2	1.403(3)	1.403(3)	N^{12}–C^{14}	1.349(3)	1.354(3)
N^1–C^{10}	1.489(3)	1.484(3)	N^{12}–C^{13}	1.458(3)	1.456(3)
C^2–O^2	1.240(3)	1.237(3)	C^{14}–O^{14}	1.235(3)	1.218(3)
C^2–C^3	1.427(3)	1.424(4)	C^{14}–C^{15}	1.474(3)	1.520(3)
C^3–C^4	1.346(4)	1.337(4)	C^{15}–C^{16}	1.290(4)	1.512(3)
C^4–C^5	1.403(4)	1.404(3)	C^{16}–N^{17}	–	1.464(3)
C^5–C^6	1.361(3)	1.360(3)	N^{17}–C^{18}	–	1.450(4)
C^6–C^7	1.503(3)	1.507(3)	N^{17}–C^{22}	–	1.472(3)
C^7–C^8	1.523(3)	1.522(3)	C^{18}–C^{19}	–	1.505(4)
C^7–C^{13}	1.535(3)	1.537(3)	C^{19}–O^{20}	–	1.430(3)
C^8–C^9	1.514(3)	1.524(4)	O^{20}–C^{21}	–	1.406(4)
C^9–C^{10}	1.527(3)	1.515(3)	C^{21}–C^{22}	–	1.502(4)
C^9–C^{11}	1.532(3)	1.528(3)			

Table 2. Torsion angles (ω, deg) in molecules **I** and **II**

Angle	ω (**I**)	ω (**II**)	Angle	ω (**I**)	ω (**II**)
$C^6N^1C^2O^2$	176.64(19)	176.5(2)	$C^8C^9C^{11}N^{12}$	58.1(2)	57.8(3)
$C^{10}N^1C^2O^2$	–1.2(3)	–1.1(3)	$C^{10}C^9C^{11}N^{12}$	–65.2(3)	–64.5(3)
$C^6N^1C^2C^3$	–3.2(3)	–3.5(3)	$C^9C^{11}N^{12}C^{14}$	122.0(2)	117.6(2)
$C^{10}N^1C^2C^3$	178.99(18)	178.9(2)	$C^9C^{11}N^{12}C^{13}$	–56.5(3)	–56.2(3)
$O^2C^2C^3C^4$	–177.4(2)	–177.0(3)	$C^{14}N^{12}C^{13}C^7$	–121.1(2)	–116.8(2)
$N^1C^2C^3C^4$	2.5(3)	3.0(3)	$C^{11}N^{12}C^{13}C^7$	57.3(2)	56.5(2)
$C^2C^3C^4C^5$	–0.5(3)	–0.5(4)	$C^6C^7C^{13}N^{12}$	62.8(2)	63.0(2)
$C^3C^4C^5C^6$	–0.9(3)	–1.8(4)	$C^8C^7C^{13}N^{12}$	–59.8(2)	–59.5(2)
$C^4C^5C^6N^1$	0.2(3)	1.4(3)	$C^{13}N^{12}C^{14}O^{14}$	–176.0(2)	177.8(2)
$C^4C^5C^6C^7$	–176.82(19)	–172.6(2)	$C^{11}N^{12}C^{14}O^{14}$	5.7(3)	5.0(4)
$C^2N^1C^6C^5$	2.0(3)	1.4(3)	$C^{13}N^{12}C^{14}C^{15}$	4.8(3)	–2.4(3)
$C^{10}N^1C^6C^5$	179.57(18)	178.8(2)	$C^{11}N^{12}C^{14}C^{15}$	–173.5(2)	–175.3(2)
$C^2N^1C^6C^7$	179.05(16)	175.56(19)	$O^{14}C^{14}C^{15}C^{16}$	4.6(4)	21.7(4)
$C^{10}N^1C^6C^7$	–3.3(3)	–7.0(3)	$N^{12}C^{14}C^{15}C^{16}$	–176.2(3)	–158.1(2)
$C^5C^6C^7C^8$	–152.57(19)	–154.5(2)	$C^{14}C^{15}C^{16}N^{17}$	–	–172.3(2)
$N^1C^6C^7C^8$	30.4(2)	31.4(2)	$C^{15}C^{16}N^{17}C^{18}$	–	–63.0(3)
$C^5C^6C^7C^{13}$	85.6(2)	83.9(2)	$C^{15}C^{16}N^{17}C^{22}$	–	175.8(2)
$N^1C^6C^7C^{13}$	–91.4(2)	–90.2(2)	$C^{16}N^{17}C^{18}C^{19}$	–	–177.9(2)
$C^6C^7C^8C^9$	–60.5(2)	–59.5(2)	$C^{22}N^{17}C^{18}C^{19}$	–	–56.4(3)
$C^{13}C^7C^8C^9$	60.9(2)	60.6(2)	$N^{17}C^{18}C^{19}O^{20}$	–	58.5(4)
$C^7C^8C^9C^{10}$	64.8(2)	64.5(2)	$C^{18}C^{19}O^{20}C^{21}$	–	–58.0(4)
$C^7C^8C^9C^{11}$	–60.0(2)	–59.4(2)	$C^{19}O^{20}C^{21}C^{22}$	–	57.9(3)
$C^6N^1C^{10}C^9$	7.6(3)	12.5(3)	$C^{18}N^{17}C^{22}C^{21}$	–	55.9(3)
$C^2N^1C^{10}C^9$	–174.56(16)	–169.88(18)	$C^{16}N^{17}C^{22}C^{21}$	–	180.0(2)
$C^8C^9C^{10}N^1$	–38.9(2)	–41.6(3)	$O^{20}C^{21}C^{22}N^{17}$	–	–57.9(3)
$C^{11}C^9C^{10}N^1$	84.7(2)	81.1(2)			

Table 3. Bond angles (ω, deg) in structures **I** and **II**

Angle	ω (I)	ω (II)	Angle	ω (I)	ω (II)
$C^6N^1C^2$	122.68(2)	122.60(19)	$N^1C^{10}C^9$	114.40(2)	115.0(2)
$C^6N^1C^{10}$	123.17(2)	122.91(19)	$N^{12}C^{11}C^9$	110.23(2)	111.02(17)
$C^2N^1C^{10}$	114.12(2)	114.44(19)	$C^{14}N^{12}C^{13}$	126.89(2)	126.79(18)
$O^2C^2N^1$	119.50(2)	119.2(2)	$C^{14}N^{12}C^{11}$	120.26(2)	120.0(2)
$O^2C^2C^3$	125.3(2)	125.7(2)	$C^{13}N^{12}C^{11}$	112.84(2)	112.84(17)
$N^1C^2C^3$	115.2(2)	115.1(2)	$N^{12}C^{13}C^7$	109.52(2)	109.73(19)
$C^4C^3C^2$	122.0(2)	122.1(2)	$O^{14}C^{14}N^{12}$	120.87(2)	121.2(2)
$C^3C^4C^5$	120.3(2)	120.5(2)	$O^{14}C^{14}C^{15}$	120.49(2)	121.6(2)
$C^6C^5C^4$	119.6(2)	119.4(2)	$N^{12}C^{14}C^{15}$	118.63(2)	117.3(2)
$C^5C^6N^1$	120.1(2)	120.1(2)	$C^{16}C^{15}C^{14}$	122.6(3)	110.91(19)
$C^5C^6C^7$	120.8(2)	120.9(2)	$N^{17}C^{16}C^{15}$	–	112.68(18)
$N^1C^6C^7$	119.04(2)	118.68(19)	$C^{18}N^{17}C^{16}$	–	113.35(19)
$C^6C^7C^8$	111.35(2)	112.0(2)	$C^{18}N^{17}C^{22}$	–	108.6(2)
$C^6C^7C^{13}$	109.35(2)	107.72(16)	$C^{16}N^{17}C^{22}$	–	109.14(17)
$C^8C^7C^{13}$	110.03(2)	110.43(18)	$N^{17}C^{18}C^{19}$	–	110.7(2)
$C^7C^8C^9$	106.57(2)	106.37(17)	$O^{20}C^{19}C^{18}$	–	111.3(2)
$C^{10}C^9C^8$	109.94(2)	109.51(19)	$C^{21}O^{20}C^{19}$	–	109.8(2)
$C^{10}C^9C^{11}$	112.55(2)	112.21(19)	$O^{20}C^{21}C^{22}$	–	111.9(2)
$C^8C^9C^{11}$	110.4(2)	110.2(2)	$N^{17}C^{22}C^{21}$	–	110.6(2)

at 1670–1675 cm^{-1}. In the ^1H NMR spectrum of compound **II** the protons attached to the alkaloid skeleton give rise to signals in the characteristic regions of spectra [3], and methylene protons appear as resonances at 2.52–2.75 ppm

The structure of compound **II** was also proved by an independent preparation in reaction of N-acryloylcytisine (**I**) with morpholine in alcohol.

EXPERIMENTAL

IR spectra were recorded on spectrometer UR-20 from samples pelletized with KBr, ^1H NMR spectra were registered on VARIAN MERCURY-300 instrument, operating frequency 300 MHz internal reference HMDS..

N*12*-Acryloylcytisine (I) was prepared by a standard procedure from the alkaloid and acryloyl chloride in the presence of triethylamine in anhydrous benzene in 95% yield, mp 130°C.

N*12*-(β-Morpholinopropionyl)cytisine (II). (a) To a solution of 1.44 g of *N*-acryloylcytisine and 0.38 g of carbon disulfide in ethanol was slowly added 0.435 g of morpholine dissolved in ethanol. The mixture was heated at stirring till the precipitate of morpholine salt with carbon disulfide completely dissolved. On distilling off the solvent 1.57 g (77%) of compound **II** was isolated.

(b) To a solution of 1.44 g of *N*-acryloylcytisine in ethanol was slowly added 0.435 g of morpholine dissolved in ethanol. The mixture was stirred at room temperature for 30–60 min. The solvent was distilled off to obtain 1.96 g (96%) of compound **II**, mp 66–67°C (from benzene). Found, %: C 65.31; H 7.57; N 12.76. $C_{18}H_{25}N_3O_3$. Calculated, %: C 65.23; H 7.60; N 12.68.

X-ray diffraction study. The unit cell parameters and intensity of 1262 independent reflections of compound **I** were measured on a diffractometer Bruker P4 (MoK_α radiation, graphite monochromator, θ/2θ-scanning, $2\theta \le 48°$). Crystals monoclinic, *a* 8.3253(7), *b* 7.2838(5), *c* 11.3181(8) Å, β 105.512(5)°, *V* 661.33(9) Å^3, d_{calc} 1.317 g/cm^3, *Z* 2. $C_{16}H_{23}N_2O_3$, space group $P2_1$. In calculations 1217 reflections were used with $I > 2\sigma(I)$. Extinction correction was done using ψ-curves. The final divergence factors were R 0.030 and $_wR$ 0.077.

The unit cell parameters and intensity of 1931 independent reflections of compound **II** were measured on a diffractometer Siemens P2 (CuK_α radiation, graphite monochromator, θ/2θ-scanning, $2\theta \le 70.03°$). Crystals monoclinic, *a* 11.2792(18), *b* 7.0995(12), *c* 11.847(3) Å, β 97.370(16)°, *V* 940.8(3) Å^3, d_{calc} 1.297 g/cm^3, *Z* 2. $C_{18}H_{29}N_3O_5$, space group $P2_1$. In calculations 1217 reflections were used with $I > 2\sigma(I)$. Extinction correction was done using ψ-curves. The final divergence factors were R 0.0394 and $_wR$ 0.104.

The structures were solved by the direct method and refined by full-matrix least-squares procedure in anisotropic approximation for nonhydrogen atoms with the use of software SHELXS-97 θ SHELXL-97. Hydrogen atoms were placed geometrically in the *rider* model.

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