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Synthesis and Structure of 3-(Hydroxycarbamoyl)-2,2,5,5-tetramethyl-2,5-dihydropyrrol-1-oxyl

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Abstract—Hydroxyamination of 3-chlorocarbonyl-2,2,5,5-tetramethyl-2,5-dihydropyrrol-1-oxyl gave previously unknown 3-(hydroxycarbamoyl)-2,2,5,5-tetramethyl-2,5-dihydropyrrol-1-oxyl whose structure was determined by X-ray analysis. The hydroxamic acid fragment has *cis* configuration, and the carbonyl group occupies distorted *trans* position with respect to the double bond in the planar dihydropyrrole ring.

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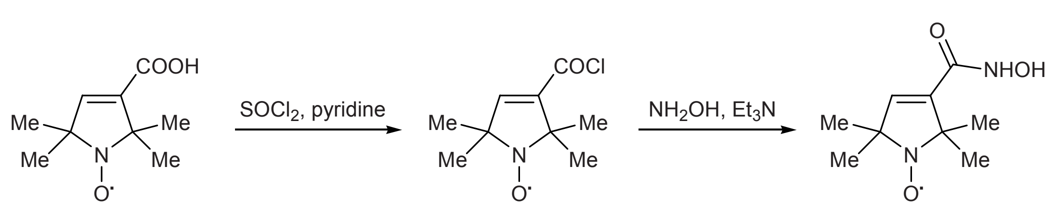
Hydroxamic acids give strong complexes with various transition metals and thus inhibit a number of metalloenzymes such as histone deacetylase [1], cyclooxygenase [2], etc. In addition, they are capable of acting as nitrogen oxide donors [2, 3]. As a result, hydroxamic acids exhibit a broad spectrum of biological activity, including hypotensive, antitumor, antiphlogistic, and antiviral action [1–3]. Nitroxyl radicals possess antioxidant properties and affect various pathologies that are accompanied by oxidative stress [4]. Two nitroxyl radicals having substituted hydroxamic acid functionalities have been reported in the literature. The first of these contains a hydroxamic acid moiety as a part of imidazolidine ring [5], and the second is 3-(*N*-methyl-*N*-methoxycarbamoyl)-2,2,5,5-tetramethyl-2,5-dihydropyrrol-1-oxyl; the latter was obtained as intermediate product in the synthesis of 3-formyl-2,2,5,5-tetramethyl-2,5-dihydropyrrol-1-oxyl [6]. Nitroxyl radicals having unsubstituted CONHOH group were not reported, but such compounds attract interest due to their potential biological activity and as model structures for studying biological activity by the spin label technique.

In the present article we describe the synthesis and structure determination of a new hydroxamic acid, 3-(hydroxycarbamoyl)-2,2,5,5-tetramethyl-2,5-dihydropyrrol-1-oxyl (**III**). Initial 3-carboxy-2,2,5,5-tetramethyl-2,5-dihydropyrrol-1-oxyl (**I**) is one of the most accessible carboxy-containing nitroxyl radicals; simultaneously, compound **I** is one of a few analogs that can be smoothly converted into the corresponding acid chloride (**II**) [7].

The reaction of chloride **II** with hydroxylamine in anhydrous acetonitrile readily occurred at ~0°C. According to the TLC data (eluent ethyl acetate), the reaction was almost complete immediately after mixing the reactants. The spot of compound **III** (R_f 0.35) turns dark red on spraying with a solution of $FeCl_3$, which is typical of hydroxamic acids [8–10]. Apart from compound **III**, the reaction mixture also contained other products (TLC) with larger R_f values; these compounds are not discussed in the present communication. We succeeded in isolating pure hydroxamic acid **III** in 54% yield without resorting to chromatographic methods (see Experimental).

Scheme 1.



I II III

Hydroxamic acid **III** is a yellow high-melting crystalline substance; its structure was confirmed by the data of elemental analysis, IR, ESR, UV, and mass spectra, and X-ray analysis. The IR spectrum of a crystalline sample of **III** contained absorption bands at 1620 (C=C), 1663 (C=O), 3200 (N–H), and 2600–2800 cm^{-1} (br, O–H). The three latter bands are typical of hydroxamic acids [8–10]. In the UV spectrum of **III** we observed a strong band in the region λ 200–350 nm (λ_{max} 208 nm, ε ≈ 10^4 l mol^{-1} cm^{-1}) and a shoulder at λ 232 nm. The band at λ_{max} 208 nm is characteristic of C=C–C=O group in α,β-unsaturated carboxylic acid derivatives with *s-trans* orientation of the C=C and C=O groups [11]. This band obscures a weaker π–π* band belonging to the nitroxyl group; therefore, the latter appears as a shoulder at λ 232 nm. The yellow color of compound **III** originates from weak *n*–π* absorption of the nitroxyl group (λ_{max} 400 nm, ε ≈ 5 l × mol^{-1} cm^{-1} [12]. The ESR spectrum of a dilute solution of **III** consists of three lines due to coupling with ^{14}N. At ~20°C in water, the hyperfine coupling constant a_N is equal to 1.63 mT, which is typical of nitroxyl radicals belonging to the dihydropyrrole series [13]. In the high-resolution mass spectrum of **III** (negative ion registration) we observed $[M - H]^-$ ion peak whose *m*/*z* value coincided with the calculated one. Also, fragment ion peaks with *m*/*z* 168 and 183 were present; the corresponding ions appeared as a result of elimination of CH_3 and N=O from $[C_9H_{14}N_2O_3]^-$.

The independent part of the crystalline structure of hydroxamic acid **III** includes one molecule (Fig. 1). The principal interatomic distances and bond angles in molecule **III** are listed in Tables 1 and 2. The dihydropyrrole ring is planar: deviations of atoms from the mean-square plane do not exceed 0.02 Å. The N^1–O^1 bond length (1.278 Å) is typical of nitroxyl radicals [14]. The N^1–O^1 bond lies almost in the pyrrole ring plane: the angle between the $C^3N^1C^4$ plane and N^1–O^1 bond is as small as 0.5°. The lengths of the double C^1=C^2 and C^9=O^2 bonds are 1.310(4) and 1.234(4) Å, respectively (Table 1), and they coincide within experimental error with those reported for structurally related 3-carbamoyl-2,2,5,5-tetramethyl-2,5-dihydropyrrol-1-oxyl [14]. As in other hydroxamic acids [15], the $O^2C^9N^2O^3$ fragment has *cis* configuration. Unlike pyridine-3-carbohydroxamic acid molecule in which the C(O)NO group is almost planar [15], the torsion angle $O^2C^9N^2O^3$ in molecule **III** is 9.8°. The C^9–N^2 bond is shortened to 1.332 Å as a result of conjugation between unshared electron pair on the nitrogen atom and

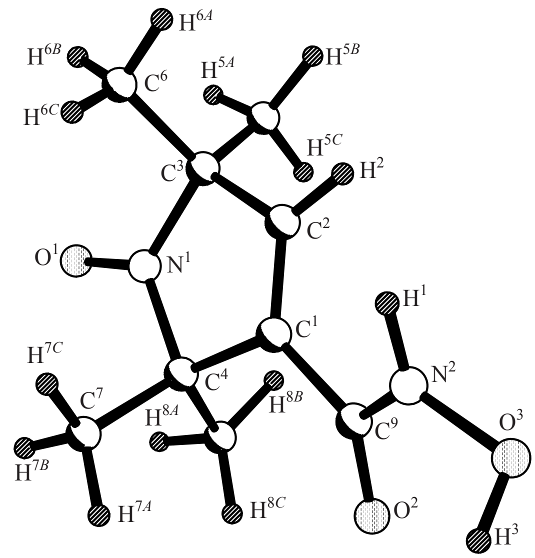


Fig. 1. Structure of the molecule of 3-(hydroxycarbamoyl)-2,2,5,5-tetramethyl-2,5-dihydropyrrol-1-oxyl (**III**) according to the X-ray diffraction data.

π electrons of the carbonyl group. The C^2=C^1–C^9=O^2 fragment adopts distorted *trans* configuration, the torsion angle $C^2C^1C^9O^2$ being 31.7°; this indicates weak conjugation between the carbonyl group and the C^1=C^2 bond. The same also follows from the C^1–C^9 bond length (1.485 Å) which exceeds standard value (1.44±0.01 Å) for the middle C–C bond in conjugated C=C–C=O fragment [16]. The crystalline structure of compound **III** may be represented as layers parallel to the *ab* unit cell plane. Here, a unit cell includes two layers (Fig. 2). Molecules **III** in a layer are linked through hydrogen bonds N^2–$H^1\cdots O^1$ ($N^2\cdots O^1$ 2.85, $H^1\cdots O^1$ 1.89 Å, $\angle N^2H^1O^1$ 161.2°) and C^2–$H^2\cdots O^3$ ($C^2\cdots O^3$ 3.38, $H^2\cdots O^3$ 2.53 Å, $\angle C^2H^2O^3$ 147.1°). The layers are linked to each other through intermolecular hydrogen bonds $O^2\cdots H^3$–O^3 ($O^2\cdots O^3$ 2.62, $O^2\cdots H^3$ 1.66 Å, $\angle O^3H^3O^2$ 169.3°) (Fig. 3).

Table 1. Bond lengths *d* in the molecule of 3-(hydroxycarbamoyl)-2,2,5,5-tetramethyl-2,5-dihydropyrrol-1-oxyl (**III**)

Bond	*d*, Å	Bond	*d*, Å
O^3–N^2	1.393(4)	O^2–C^9	1.234(4)
N^1–O^1	1.278(4)	N^1–C^3	1.473(5)
N^1–C^4	1.484(5)	N^2–C^9	1.332(5)
C^1–C^2	1.310(5)	C^1–C^9	1.485(5)
C^1–C^4	1.517(5)	C^4–C^7	1.514(6)
C^4–C^8	1.517(6)	C^3–C^2	1.497(5)
C^3–C^6	1.514(7)	C^3–C^5	1.522(7)

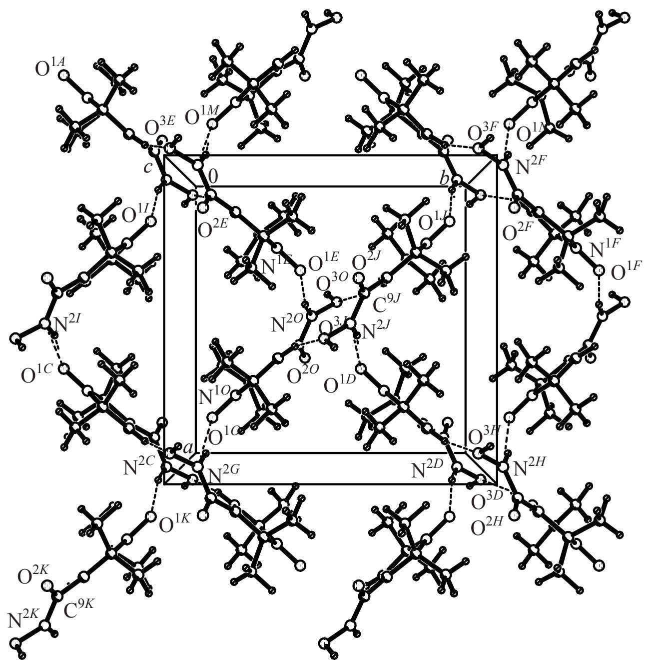


Fig. 2. Crystalline structure of 3-(hydroxycarbamoyl)-2,2,5,5-tetramethyl-2,5-dihydropyrrol-1-oxyl (**III**) (projection of a layer onto the *ab* plane of a unit cell). Hydrogen bonds are shown with dashed lines.

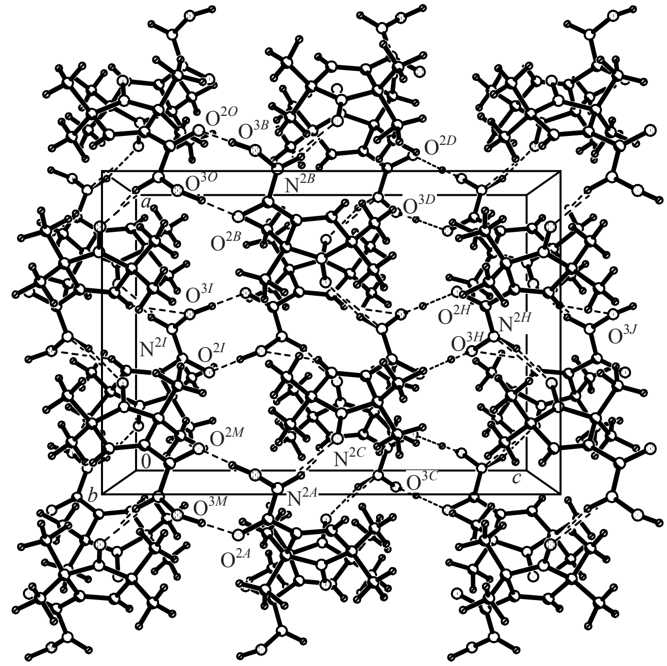


Fig. 3. Crystalline structure of 3-(hydroxycarbamoyl)-2,2,5,5-tetramethyl-2,5-dihydropyrrol-1-oxyl (**III**) (projection of a layer onto the *ac* plane of a unit cell). Hydrogen bonds are shown with dashed lines.

EXPERIMENTAL

The IR spectrum was recorded in the frequency range from 400 to 4000 cm^{-1} on a Specord 75IR spectrometer. The UV spectrum was obtained on a Specord UV-Vis spectrophotometer. The ESR spectrum was measured at room temperature on an EPA-2M instrument. The high-resolution mass spectrum was recorded on an LTQFT instrument (electrospray ionization, negative ion detection, emitter voltage 3 kV); compound **III** was introduced as a solution in 50% aqueous acetonitrile, flow rate 1 μl/min. The melting point was determined using an RNMK melting point apparatus. Thin-layer chromatography was performed on Silufol UV-254 plates. Initial acid **I** was prepared according to the procedure described in [17]. Hydroxylamine hydrochloride was recrystallized from methanol prior to use.

Table 2. Bond angles ω in the molecule of 3-(hydroxycarbamoyl)-2,2,5,5-tetramethyl-2,5-dihydropyrrol-1-oxyl (**III**)

Angle	ω, deg	Angle	ω, deg
$O^1N^1C^3$	123.0(3)	$O^1N^1C^4$	121.7(3)
$C^3N^1C^4$	115.2(3)	$C^9N^2O^3$	119.8(3)
$C^2C^1C^9$	126.5(3)	$C^2C^1C^4$	112.8(3)
$C^9C^1C^4$	120.6(3)	$O^2C^9N^2$	123.7(3)
$O^2C^9C^1$	121.7(3)	$N^2C^9C^1$	114.6(3)
$N^1C^4C^7$	109.6(4)	$N^1C^4C^1$	98.9(3)
$C^7C^4C^1$	112.0(3)	$N^1C^4C^8$	108.7(3)
$C^7C^4C^8$	111.4(4)	$C^1C^4C^8$	115.5(4)
$N^1C^3C^2$	99.5(3)	$N^1C^3C^6$	109.5(4)
$C^2C^3C^6$	113.9(4)	$N^1C^3C^5$	111.3(4)
$C^2C^3C^5$	111.6(4)	$C^6C^3C^5$	110.6(4)
$C^1C^2C^3$	113.6(3)		

The X-ray diffraction data for a single crystal of compound **III** (flat prism, 0.15 × 0.1 × 0.05 mm) were acquired on a Bruker P-4 automatic four-circle diffractometer (graphite monochromator, λMoK_α 0.71073 Å, temperature 293 K, θ/2θ scanning). The unit cell parameters were determined and refined from 35 reflections in the θ range from 10 to 15º. The experimental set of reflections was measured in the θ range from 2.46 to 24.99º, the total number of independent reflections was 1686, among which 846 reflections had intensities $I > 2\sigma(I)$. Unit cell parameters: $a = 11.615(2)$, $b = 11.768(1)$, $c = 16.445(3)$ Å; $\alpha = \beta = \gamma = 90º$; $V = 2247.8(6)$ $Å^3$; $d_{calc.} = 1.177$ g/cm^3, space group *Pbcn*; $Z = 8$. The structure was solved by the direct method. The positions and thermal parameters of non-hydrogen atoms were refined first in isotropic and then in anisotropic approximation by the full-matrix least-squares procedure. The coordinates of atoms and their equivalent temperature factors are aavailable from the authors. Hydrogen atoms were visualized by Fourier difference syntheses, and their positions were refined in isotropic approximation. All calculations were performed using SHELXTL software package [18]. The final divergence factors were $R_1 = 0.0451$ [846 reflections with $I > 2\sigma(I)$] and $R_2 = 0.1071$ (all 1688 reflections); goodness of fit 0.911.

3-(Hydroxycarbamoyl)-2,2,5,5-tetramethyl-2,5-dihydropyrrol-1-oxyl (III). A solution of 1.22 g (6 mmol) of acid chloride **II** in 6 ml of acetonitrile was added over a period of 20 min to a mixture of 0.63 g (9 mmol) of hydroxylamine hydrochloride and 1.67 ml (12 mmol) of triethylamine in 12 ml of anhydrous acetonitrile under stirring in an argon atmosphere and cooling with ice. The cooling bath was removed, and the mixture was stirred for 1 h at ~20°C. The solution was separated from the precipitate of triethylamine hydrochloride, and the precipitate was washed with ethyl acetate (3×6 ml). The solution was combined with the washings and evaporated, and the orange solid residue was washed with diethyl ether (2×10 ml) with grinding to remove products soluble in diethyl ether. The residue still contained a considerable impurity of triethylamine hydrochloride. To remove the latter, the product was extracted with hot ethyl acetate (5×8 ml), the extract being separated by centrifugation. The extracts were evaporated to obtain 0.86 g of orange crystals which were recrystallized from acetonitrile. Yield 0.65 g (54%), yellow flat prisms, mp 180–181.5°C (decomp.). UV spectrum (EtOH), λ_{max}, nm (ε, l mol^{-1} cm^{-1}): 208 (1.03×10^4), 232 sh (5.2×10^3). IR spectrum (mineral oil), ν, cm^{-1}: 1620 (C=C), 1663 (C=O), 3200 (N–H), 2600–2800 (O–H). ESR spectrum (H_2O): 3 lines, $a_N = 1.63$ mT. Mass spectrum, m/z (I_{rel}, %): 198.091 (100) $[M - H]^-$ (calculated: $[M - H]^-$ 198.1004), 183.09 (62) $[M - CH_4]^-$, 168.09 (4) $[M - HNO]^-$, 151.09 (0.5), 124.09 (1). Found, %: C 54.51; H 7.63; N 14.10. $C_9H_{15}N_2O_3$. Calculated, %: C 54.26; H 7.59; N 14.06. *M* 199.230.

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