

Synthesis of 2-(3,3-Dicyano-2-propenylidene)-4,4,5,5-tetramethyldioxolane and Its Reactions with Hydrazine and Primary Amines

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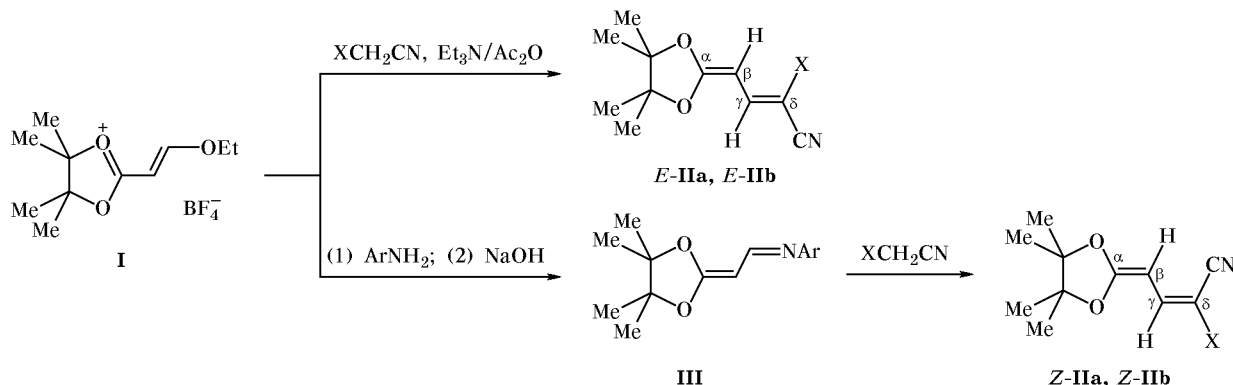
Abstract—Reactions of 2-(β -ethoxyvinyl)-4,4,5,5-tetramethyl-4,5-dihydro-1,3-dioxol-1-ium salts with cyanomethylene compounds gave the corresponding 2-(2-propenylidene)-1,3-dioxolane derivatives which reacted with hydrazine and primary amines to afford, respectively, 3-(2-hydroxy-1,1,2-trimethylpropoxy)pyrazole and 1-substituted 6-amino-5-cyanopyridin-2(1*H*)-ones.

We previously studied reactions of 2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-4,5-dihydro-1,3-dioxol-1-ium perchlorate with amines [1]. The present communication describes the reaction of analogous tetrafluoroborate **I** with carbanions generated from compounds having an activated methylene group, malononitrile and ethyl cyanoacetate, in acetic anhydride in the presence of triethylamine. As a result, the corresponding cyanomethylene derivatives **IIa** and **IIb** were obtained in 58 and 65% yield, respectively (Scheme 1). Compound **IIa** was also formed in a quantitative yield in the reaction of Schiff base **III** with malononitrile. Ethyl cyanoacetate failed to react with **III**.

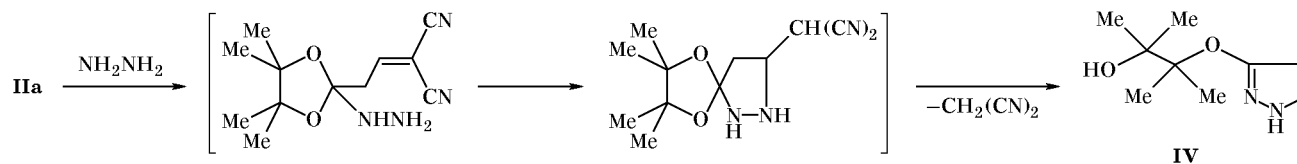
According to the spectral data, compounds **IIa** and **IIb** exist as mixtures of *cis* and *trans* isomers with respect to the $C^\alpha=C^\beta$ and $C^\gamma=C^\delta$ double bonds. In fact, the cyano groups in **IIa** give rise to two bands in the IR spectrum in the region 2220–2235 cm^{-1} , and methyl groups appear in the ^1H NMR spectrum as two six-proton peaks, indicating that both cyano and methyl groups are nonequivalent.

In the ^1H NMR spectrum of **IIa**, protons at C^β and C^γ give two one-proton doublets at δ 5.25 (β -H) and 7.65 ppm (γ -H), for the substituents on C^α and C^δ are equivalent. The ^1H NMR spectrum of compound **IIb** ($X = \text{CO}_2\text{Et}$) contains two pairs of doublets with similar coupling constants, their ratio being equal to

Scheme 1.



Scheme 2.



~14:1. These data indicate that one isomer of **IIb** prevails. According to the results of PM3 semiempirical calculations, the enthalpy of formation of the *Z* isomer of **IIb** (−121.8352 kcal/mol) is slightly greater (by 2 kcal/mol) than the enthalpy of formation of *E*-**IIb** (−119.7919 kcal/mol). We believe that the first of these is the major isomer as more thermodynamically stable; nevertheless, we realize that this assumption is not doubtless.

Dicyanomethylene derivative **IIa** was brought into reaction with hydrazine hydrate. The reaction begins with nucleophilic attack on the C² atom which, according to the MNDO calculations, has the maximal overall ($\sigma + \pi$) positive charge (0.294). The subsequent closure of five-membered nitrogen-containing heteroring, elimination of malononitrile, and intramolecular prototropic opening of the spiro dioxolane ring leads to 3-(2-hydroxy-1,1,2-trimethylpropoxy)pyrazole (**IV**) (Scheme 2). The structure of product **IV** was confirmed by spectral data. Its ¹H NMR spectrum contains two one-proton doublets from 4-H and 5-H at δ 5.60 and 7.35 ppm with a vicinal coupling constant of 2.38 Hz, two six-proton singlets from four methyl groups (which are equivalent in pairs), and two H–D-exchangeable signals at δ 11.90 (NH) and 4.70 ppm (OH). The hydroxy group is strongly shielded, so that its proton signal is observed in a strong field. The OH group gives rise to an intense broadened band at 3127 cm^{−1} in the IR spectrum, which overlaps the NH stretching vibration band.

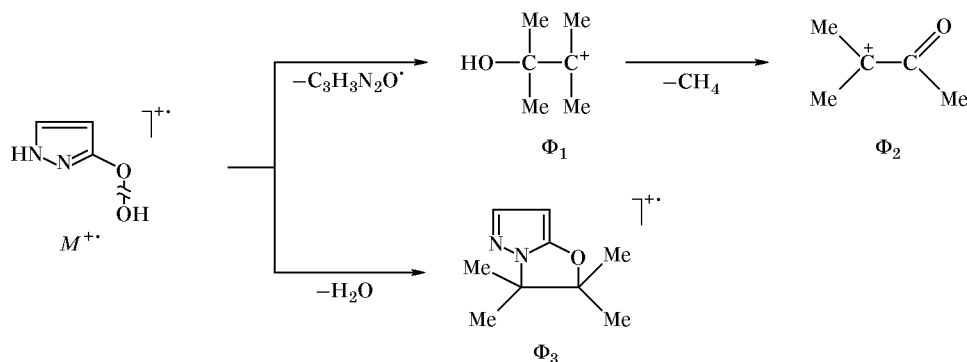
The mass spectrum of compound **IV** does not contradict the assumed structure. The molecular ion of **IV**

(*m/z* 184, *I*_{rel} < 1%) is very unstable. Its main fragmentation pathway includes elimination of pyrazolyl-oxy radical (C₃H₃N₂O[•]) with formation of stable cation Φ_1 (*m/z* 101, *I*_{rel} 98%) which then loses methane molecule to give Φ_2 (*m/z* 85, *I*_{rel} 100%). Another fragmentation pathway includes elimination of water molecule, affording low-stable radical cation Φ_3 (*m/z* 100, *I*_{rel} 2%) (Scheme 3).

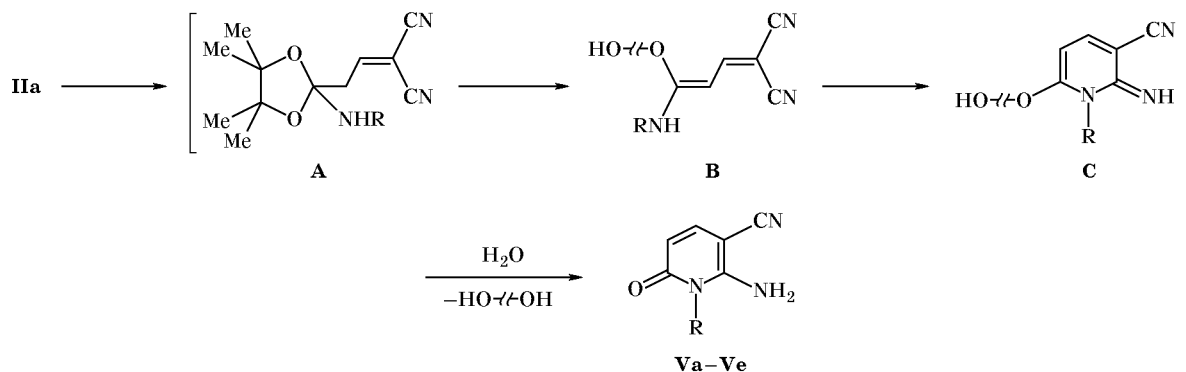
Thus in the reaction of dinitrile **IIa** with hydrazine the cyclization does not involve the cyano group. However, just heterocyclizations with participation of a cyano group attract interest, for in this case heterocyclic systems having amino and cyano groups in the *ortho* position with respect to each other could be obtained. We succeeded in effecting such a heterocyclization with the use of primary amines instead of a difunctional N-nucleophile (hydrazine).

We examined reactions of dicyano derivative **IIa** with primary aromatic and aliphatic amines and with benzylamine. Aromatic amines failed to react with **IIa** even under fairly severe conditions (heating in a high-boiling solvent or fusion). By contrast, primary aliphatic amines, benzylamine, and 2-furylamine readily reacted with compound **IIa** on mixing the reactants in an alcoholic solution at room temperature. The reaction was complete in a few hours, and the products were 1-substituted 6-amino-5-cyanopyridin-2(1*H*)-ones **Va–Ve** which were isolated in 68–93% yield (Scheme 4). Presumably, as in the reaction with hydrazine, nucleophile attacks the C² atom of the dioxolane ring to give intermediate A. Proton migration from the methylene unit on the ring oxygen atom

Scheme 3.



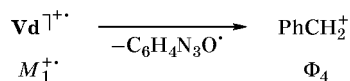
Scheme 4.



is accompanied by opening of the dioxolane ring (A → B), and the subsequent intramolecular cyclization with participation of one cyano group leads to pyridin-2-imine C with a pinacol moiety on C⁶. The ether fragment undergoes base-catalyzed hydrolysis by the action of water present in the reaction mixture. This is indirectly supported by the results of MNDO calculations, according to which the imino nitrogen atom possesses the greatest negative charge (−0.256) and the highest positive charge (+0.310) is localized on C⁶ of the pyridine ring.

The IR spectra of pyridin-2-ones Va–Ve contain absorption bands typical of N–H stretching vibrations in the region 3200–3400 cm^{−1}, triple C≡N bond absorption at about 2200 cm^{−1}, and amide carbonyl band at 1630–1640 cm^{−1}. Compounds Va–Ve show in the ¹H NMR spectra signals from protons in the pyridine ring (3-H and 4-H) at δ 5.6–6.0 and 7.2–7.4 ppm and amino group protons at δ 7.4–7.6 ppm. In the spectra of Vb (R = *i*-Bu) and Vd (R = PhCH₂), signals from protons of the amino group are located in a stronger field (δ 5.4 and 5.1 ppm, respectively), presumably due to shielding by the 1-substituent. In addition, the ¹H NMR spectra of Va–Ve contain signals from protons of the 1-substituents, which are specific for each particular product. 1-Benzyl derivative Vd was also characterized by mass spectrum. The main fragmentation path of the molecular ion M₁⁺ (*m/z* 225, *I*_{rel} ~25%) is decomposition into benzyl cation Φ₄ (*m/z* 91, *I*_{rel} 100%) and a radical fragment having the structure of 6-amino-5-cyanopyridin-2-one (Scheme 5).

Scheme 5.



EXPERIMENTAL

The IR spectra were recorded on a Specord 71IR spectrometer from samples dispersed in mineral oil. The ¹H NMR spectra were obtained on Avance DPX-250 and Unity-300 instruments using HMDS as internal reference. The mass spectra were measured on a Finnigan Mat Inco-50 mass spectrometer (electron impact, 70 eV; direct sample admission into the ion source heated to 180°C). The purity of the products was checked by TLC on aluminum oxide using chloroform as eluent.

2,4,4,5,5-Pentamethyl-4,5-dihydro-1,3-dioxol-1-ium perchlorate was described previously [2]. 2,4,4,5,5-Pentamethyl-4,5-dihydro-1,3-dioxol-1-ium tetrafluoroborate used by us as precursor of 2-β-ethoxyvinyl derivative I was synthesized for the first time.

2,4,4,5,5-Pentamethyl-4,5-dihydro-1,3-dioxol-1-ium tetrafluoroborate. Boron trifluoride–ether complex, 7 ml (25 mmol), was added dropwise under stirring to a solution of 5.7 g (25 mmol) of pinacolone hydrate in 17 ml of acetic anhydride. The resulting transparent solution was left to stand for 15 min at room temperature, cooled with ice, and diluted with 1.5 volume of diethyl ether. The colorless crystals were filtered off, thoroughly washed with ether, and dried. Yield 5.6 g (96%), mp 185–186°C. Found, %: C 42.00; H 6.34. C₈H₁₅BF₄O₂. Calculated, %: C 41.74; H 6.52.

2-(2-Ethoxyvinyl)-4,4,5,5-tetramethyl-4,5-dihydro-1,3-dioxol-1-ium tetrafluoroborate (I). Freshly distilled triethyl orthoformate, 5 ml (25 mmol), was added under stirring to a suspension of 5.8 g (25 mmol) of 2,4,4,5,5-pentamethyl-4,5-dihydro-1,3-dioxol-1-ium tetrafluoroborate in 10 ml of acetic anhydride. The mixture was slightly warmed under continuous stirring so that to avoid vigorous boiling.

When the solution turned pale yellow, it was quickly cooled, 5 ml of diethyl ether was added, and crystallization of the product was initiated by grinding of the separated oily layer with a glass rod. When the crystallization started, an additional 15 ml of ether was added on cooling. After complete crystallization, the precipitate was filtered off, washed with ether, and dried in air. Yield 7.6 g (94%), light yellow powder, mp 101–101.5°C. Found, %: C 48.31; H 6.45. $C_{12}H_{20}BF_4O_3$. Calculated, %: C 48.16; H 6.69. The IR and 1H NMR spectra of product **I** were in agreement with those of the corresponding perchlorate [1].

2-[2-(4-Methoxyphenylimino)ethenylidene]-4,4,5,5-tetramethyl-1,3-dioxolane (III). *p*-Anisidine, 2.38 g (20 mmol), was added to a solution of 5.55 g (20 mmol) of compound **I** in acetic acid, and the mixture was slightly warmed until it became homogeneous. It was then cooled, and the precipitate of 2-[2-(4-methoxyphenylamino)viny]-4,4,5,5-tetramethyl-4,5-dihydro-1,3-dioxol-1-ium tetrafluoroborate was filtered off, washed with diethyl ether, and dried in air. Yield 6.7 g (92%), mp 173°C (from acetic acid). A 4.8-g amount of the product was added in portions to a solution of 1 g of sodium hydroxide in a 1:20 water–alcohol mixture. The mixture was slightly warmed under stirring to obtain a homogeneous solution. The solution was cooled and diluted with an equal volume of water. The precipitate was filtered off, washed with water, and dried in air. Yield 3 g (98%), mp 99–100°C (from isooctane) [2].

2-(3,3-Dicyano-2-propenylidene)-4,4,5,5-tetramethyl-1,3-dioxolane (IIa). *a*. To a suspension of 4.3 g (15 mmol) of tetrafluoroborate **I** in 1.5 ml of acetic anhydride we added 1 g (15 mmol) of malononitrile, and 1.5 ml (15 mmol) of triethylamine was then added dropwise. The mixture turned dark and was heated for 5 min at 60–70°C on an air bath. The solution was cooled, diluted with 5 ml of water, and left to stand until complete hydrolysis of acetic anhydride. The yellow precipitate was filtered off and dried in air. Recrystallization from isooctane (with hot filtration) gave 1.85 g (57%) of colorless crystals with mp 97–98°C. IR spectrum, ν , cm^{-1} : 1620 (C=C), 2236 (C≡N). 1H NMR spectrum ($CDCl_3$), δ , ppm: 1.40 s (6H, 2CH₃), 1.42 s (6H, 2CH₃), 5.25 d (1H, β -CH, $J = 12.84$ Hz), 7.65 d (1H, γ -CH, $J = 12.84$ Hz). Found, %: C 66.26; H 6.51; N 12.65. $C_{12}H_{14}N_2O_2$. Calculated, %: C 66.06; H 6.42; N 12.84.

b. To a suspension of 1.56 g (5.7 mmol) of Schiff base **III** in 2.5 ml of acetonitrile we added 0.375 g (5.7 mmol) of malononitrile, and the mixture was heated for 45 min under reflux. It was then cooled and

treated with 5 ml of 5% hydrochloric acid. The precipitate was filtered off, washed on a filter with 5% hydrochloric acid and several portions of water, squeezed, and dried in air. Yield 1.13 g (91%).

2-(3-Cyano-3-ethoxycarbonyl-2-propenylidene)-4,4,5,5-tetramethyl-1,3-dioxolane (IIb) was synthesized as described above (method *a*) from 0.285 g (1 mmol) of tetrafluoroborate **I** and 0.1 ml (1 mmol) of ethyl cyanoacetate. Yield 0.17 g (64%), mp 93–94°C (from isooctane). IR spectrum, ν , cm^{-1} : 1690 (C=O, ester), 2220 (C≡N). 1H NMR spectrum (DMSO- d_6), δ , ppm: 1.20 t (3H, OCH₂CH₃), 1.40 s (6H, 2CH₃), 1.44 s (6H, 2CH₃), 4.18 q (2H, OCH₂), 5.02 d (2.8H, β -CH, *Z* isomer, $J = 13.0$ Hz), 6.04 d (0.2H, β -CH, *E* isomer, $J = 13.0$ Hz), 7.50 d (0.2H, γ -CH, *E* isomer, $J = 13.0$ Hz), 8.00 d (2.8H, *Z* isomer, $J = 13.0$ Hz). Found, %: C 63.23; H 7.32; N 5.05. $C_{14}H_{19}NO_4$. Calculated, %: C 63.40; H 7.17; N 5.28.

3-(2-Hydroxy-1,1,2-trimethylpropoxy)pyrazole (IV). Ethanol, 0.1 ml, and hydrazine hydrate, 0.1 ml (3 mmol), were added to 0.22 g (1 mmol) of compound **IIa**. The mixture was heated for 40 min at 60°C on a water bath and cooled, and an equal volume of water was added to the thickened material. The precipitate was filtered off, dried in air, and recrystallized from benzene. Yield 0.15 g (81%), colorless crystals, mp 75°C. IR spectrum, ν , cm^{-1} : 1530, 3130 (O–H, N–H). 1H NMR spectrum (DMSO- d_6), δ , ppm: 1.10 s (6H, 2CH₃), 1.30 s (6H, 2CH₃), 4.7 s (1H, OH), 5.6 d (1H, β -CH, pyrazole, $J = 2.34$ Hz), 7.30 d (1H, α -CH, pyrazole, $J = 2.34$ Hz). Found, %: C 58.51; H 8.89; N 15.10. $C_9H_{16}N_2O_2$. Calculated, %: C 58.70; H 8.70; N 15.22.

6-Amino-1-benzyl-5-cyanopyridin-2(1H)-one (Vd). A mixture of 1.1 g (5 mmol) of dicyano derivative **IIa** and 1 ml (10 mmol) of benzylamine was left to stand overnight on exposure to air. The mixture was carefully acidified to a weakly acidic reaction by adding 5% hydrochloric acid and diluted with water, and the precipitate was filtered off, washed with water, and dried. Yield 0.95 g (84%), mp 195°C (from 2-propanol). IR spectrum, ν , cm^{-1} : 1635 (C=O); 2190 (C≡N); 3420, 3440 (NH₂). 1H NMR spectrum ($CDCl_3$), δ , ppm: 5.10 s (2H, NH₂), 5.30 s (2H, CH₂), 6.05 d (1H, β -CH, pyridine, $J = 9.38$ Hz), 7.30 d (1H, γ -CH, pyridine, $J = 9.38$ Hz), 7.2–7.4 m (5H, H_{arom}). Found, %: C 69.21; H 4.81; N 18.66. $C_{13}H_{11}N_3O$. Calculated, %: C 69.33; H 4.89; N 18.67.

6-Amino-5-cyano-1-methylpyridin-2(1H)-one (Va) was synthesized in a similar way from 1.05 g (5 mmol) of compound **IIa** and 1 ml (10 mmol) of 70% aqueous methylamine. Yield 0.5 g (69%). Pale yellow crystals, mp ~267°C (decomp., from ethanol).

IR spectrum, ν , cm^{-1} : 1640 (C=O); 2200 (C \equiv N); 3390, 3340 (NH₂). ¹H NMR spectrum (DMSO-*d*₆), δ , ppm: 3.3 s (3H, NCH₃), 5.62 d (1H, β -CH, pyridine, $J = 9.31$ Hz), 7.35 d (1H, γ -CH, pyridine, $J = 9.31$ Hz), 7.6 s (2H, NH₂). Found, %: C 55.74; H 4.82; N 28.42. C₇H₇N₃O. Calculated, %: C 56.38; H 4.70; N 28.19.

6-Amino-5-cyano-1-isobutylpyridin-2(1H)-one (Vb) was synthesized in a similar way from 0.375 g (1.7 mmol) of dinitrile **IIa** and 0.25 ml (3.5 mmol) of isobutylamine. Yield 0.185 g (84%). Light yellow powder, mp ~200°C (decomp., from 2-propanol). IR spectrum, ν , cm^{-1} : 1640 (C=O); 2200 (C \equiv N); 3190, 3350 (NH₂). ¹H NMR spectrum (CDCl₃), δ , ppm: 0.95 d (6H, 2CH₃, $J = 6.67$ Hz), 2.15 m (1H, CH₂CHMe₂, $J = 6.67$, 7.65 Hz), 3.85 d (2H, CH₂-CHMe₂, $J = 7.65$ Hz), 5.4 s (2H, NH₂), 5.9 d (1H, β -CH, pyridine, $J = 9.31$ Hz), 7.25 d (1H, γ -CH, pyridine, $J = 9.31$ Hz). Found, %: C 63.00; H 6.65; N 22.23. C₁₀H₁₃N₃O. Calculated, %: C 62.83; H 6.81; N 21.99.

6-Amino-1-butyl-5-cyanopyridin-2(1H)-one (Vc) was synthesized in a similar way from 1.05 g (5 mmol) of dinitrile **IIa** and 2 ml (30 mmol) of butylamine. Yield 0.65 g (68%). Light yellow powder, mp 166–167°C (from 2-propanol). IR spectrum, ν ,

cm^{-1} : 1640 (C=O); 2200 (C \equiv N); 3220, 3350 (NH₂). ¹H NMR spectrum (DMSO-*d*₆), δ , ppm: 0.83 t (3H, CH₃, $J = 7.25$ Hz), 1.2–1.5 m (4H, CH₂CH₂Me), 3.9 t (2H, CH₂N, $J = 7.76$ Hz), 5.6 d (1H, β -CH, pyridine, $J = 9.3$ Hz), 7.35 d (1H, γ -CH, pyridine, $J = 9.3$ Hz), 7.5 s (2H, NH₂). Found, %: C 62.41; H 7.11; N 22.62. C₁₀H₁₃N₃O. Calculated, %: C 62.83; H 6.81; N 21.99.

6-Amino-5-cyano-1-furfurylpyridin-2(1H)-one (Ve) was synthesized in a similar way from 0.7 g (3 mmol) of dinitrile **IIa** and 0.6 ml (6 mmol) of furfurylamine. Yield 0.55 g (80%), mp 210–211°C (from ethanol). IR spectrum, ν , cm^{-1} : 1640 (C=O); 2200 (C \equiv N); 3230, 3420 (NH₂). ¹H NMR spectrum (DMSO-*d*₆), δ , ppm: 5.2 s (2H, CH₂), 5.68 d (1H, β -CH, pyridine, $J = 9.31$ Hz), 6.35 m (2H, 3-H, 5-H, furan), 7.40 d (1H, γ -CH, pyridine, $J = 9.31$ Hz), 7.55 m (1H, 4-H, furan), 7.6 s (2H, NH₂). Found, %: C 60.99; H 4.11; N 19.82. C₁₁H₉N₃O₂. Calculated, %: C 61.40; H 4.17; N 19.53.

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