New method for the annelation of the pyridine fragment to azines ✽

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The reaction of quinoxaline-2-carbaldehyde with ethyl (*E*)-3-aminocrotonate afforded ethyl 4-oxo-1,4-dihydropyrido[2,3-*b*]quinoxaline-3-carboxylate, which is a structural analog of nalidixic and 4-quinolone-3-carboxylic acids representing the basis of the known antibacterial drugs of the fluoroquinolone series.

Key words: S_NH methodology, intramolecular cyclizations, quinoxaline-2-carbaldehyde, dinucleophiles, enamino esters, 4-oxo-1*H*-pyrido[2,3-*b*]-quinoxaline.

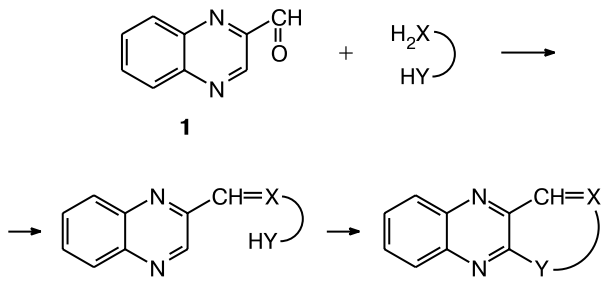
Nucleophilic substitution of hydrogen (S_NH) is finding increasing utility for the construction of new chemical C—C and C—X bonds (where X is O, N, S, or other heteroatoms) with the C_{sp^2} atom of an aromatic ring.[1] The nucleophilic attack on the sp^2-hybridized carbon atom devoid of substituents and S_NH reactions are widely used, in particular, for modification of π-deficient azines, including the construction of fused systems by forming two new bonds in tandem A_N—A_N and S_NH—S_NH reactions of azines with bifunctional nucleophiles.[2—9]

Earlier,[10,11] we have used a tandem of two successive reactions of quinoxaline-2-carbaldehyde (**1**) with 1,2- and 1,4-bifunctional nucleophilic reagents for the construction of fused systems by annelation of five- and seven-membered heterocycles to the pyrazine ring. This type of cyclization involves condensation of the exocyclic carbonyl group with one of the centers of the dinucleophile followed by intramolecular nucleophilic substitution of hydrogen (S_NH) in the pyrazine ring (Scheme 1).

In the present study, we report the use of the S_NH reaction as a key step in the reaction tandem for the annelation of the six-membered pyridine ring to quinoxalines. Data on the use of nucleophilic substitution of hydrogen for the annelation of the pyridine ring to the 1,4-diazine system are lacking in the literature.

The reaction of quinoxaline-2-carbaldehyde (**1**) with ethyl (*E*)-3-aminocrotonate as a 1,3-*C*,*N*-binucleophilic reagent afforded ethyl (*E*)-3-amino-2-hydroxy(quinoxalin-2-yl)methylcrotonate (**2**), which is a *C*-addition

Scheme 1



product of the enamine to the aldehyde group (Scheme 2). In the presence of acids, addition products of nucleophiles to the carbonyl group, including *C*-adduct **2**, undergo dissociation into the starting compounds. Taking this fact into account, alcohol **2** was oxidized to the keto derivative, *viz.*, ethyl (*E*)-3-amino-2-(quinoxalin-2-ylcarbonyl)crotonate (**3**).

The structures of compounds **2** and **3** were confirmed by ^1H and ^{13}C NMR spectroscopy, including ^{13}C—^1H HSQC and ^1H—^{13}C HMBC 2D NMR experiments. For example, the ^1H NMR spectrum of compound **2** has two doublets (δ 5.40 and 5.83) of the secondary alcohol fragment with the spin coupling constant $^3J_{H,H}$ = 7.0 Hz, which are absent in the spectrum of compound **3**.

In addition, in the ^1H NMR spectra of both compounds, the chemical shifts of the signals for the protons

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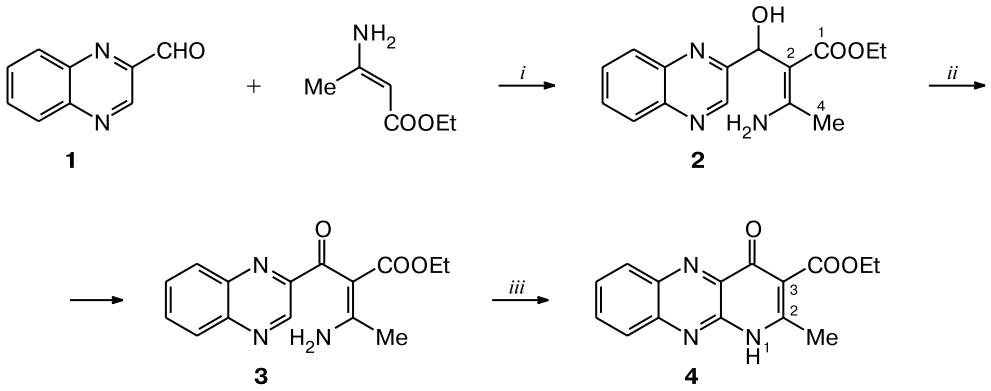
Scheme 2



Reagents and conditions: *i*. 5—7 °C; *ii*. $KMnO_4$, Me_2CO; *iii*. DMF, air.

of the ethoxycarbonyl fragment have untypical values (δ 3.60—3.70 for the methylene group and δ 0.30—0.60 for the methyl group). The protons of the amino group are nonequivalent and give resonance signals at δ 7.20 and 8.53 (in compound **2**) and at δ 9.05 and 10.63 (in compound **3**). To unambiguously establish the structures of the reaction products, we studied compound **3** by X-ray diffraction analysis.

The molecular structure of compound **3** in the crystal is shown in Fig. 1. The selected bond lengths, bond angles, and torsion angles are listed in Tables 1—3, respectively. In molecule **3**, the N(3)=C(3) bond is substantially shorter than the C(2)—C(3) bond (see Table 1). The structure of molecule **3** corresponds to the enamine structure with delocalization of the chelate type, as shown in Scheme 3.

Scheme 3 presents one of the most favorable conformations of molecule **3**, whereas Scheme 2 demonstrates its possible conformation at the instant when compound **3** is converted into compound **4**.

Passage of air through a boiling solution of compound **3** in DMF results in the intramolecular S_N^H reaction giving rise to ethyl 2-methyl-4-oxo-1*H*-pyrido[2,3-*b*]quinoxaline-3-carboxylate (**4**). This conclusion was drawn based on analysis of the NMR and mass spectra. Thus the ^{1}H NMR spectrum of compound **4** has no signals for the H(3′) atom of the pyrazine ring and protons of the amino

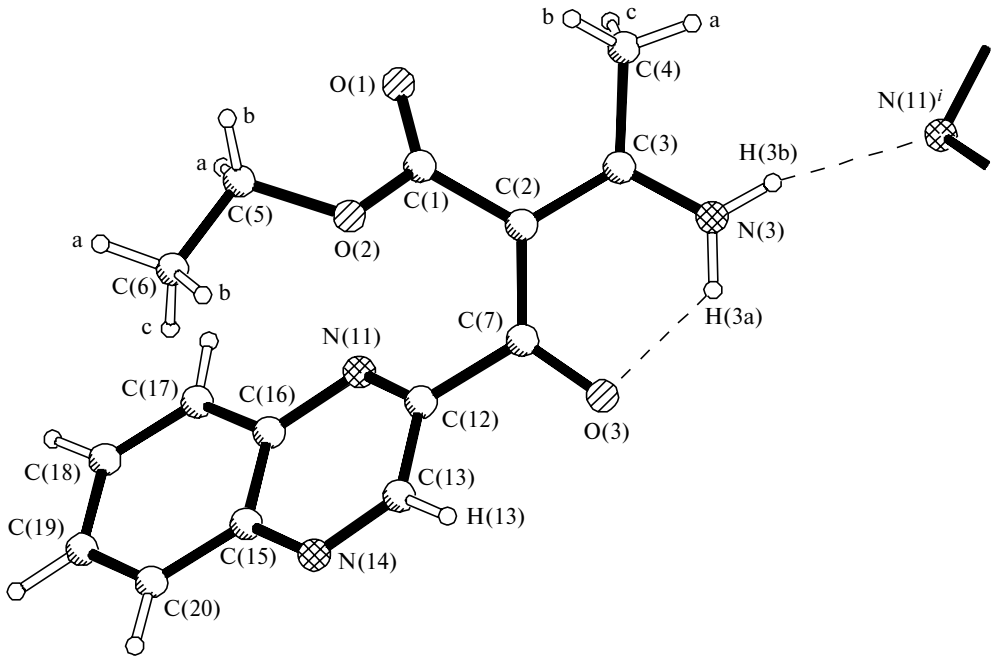


Fig. 1. Molecular structure of compound **3** in the crystal based on the results of X-ray diffraction study. Hydrogen bonds are indicated by dashed lines.

Scheme 3

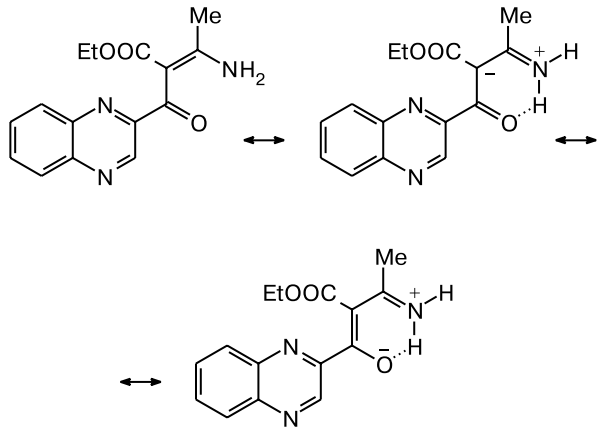


Table 1. Selected bond lengths (*d*) in molecule **3**

Bond	*d*/Å	Bond	*d*/Å
O(1)=C(1)	1.212(2)	C(3)—C(4)	1.492(3)
O(2)—C(1)	1.342(2)	C(5)—C(6)	1.492(4)
O(2)—C(5)	1.441(3)	C(7)—C(12)	1.511(3)
O(3)=C(7)	1.238(3)	N(11)=C(12)	1.312(3)
N(3)=C(3)	1.308(3)	N(11)—C(16)	1.372(2)
N(3)—H(3a)	0.91(3)	C(12)—C(13)	1.414(3)
N(3)—H(3b)	0.87(3)	N(14)=C(13)	1.304(3)
C(1)—C(2)	1.463(3)	N(14)—C(15)	1.366(3)
C(2)—C(3)	1.412(2)	C(15)—C(16)	1.411(3)
C(2)—C(7)	1.436(3)		

Table 2. Selected bond angles (ω) in molecule **3**

Angle	ω/deg	Angle	ω/deg
C(1)—O(2)—C(5)	118.2(2)	O(2)—C(5)—C(6)	107.5(2)
C(3)—N(3)—H(3a)	119(2)	O(3)—C(7)—C(2)	124.6(2)
C(3)—N(3)—H(3b)	122(2)	O(3)—C(7)—C(12)	115.2(2)
H(3a)—N(3)—H(3b)	119(3)	C(2)—C(7)—C(12)	120.1(2)
O(1)—C(1)—O(2)	122.4(2)	C(12)—N(11)—C(16)	116.5(2)
O(1)—C(1)—C(2)	126.5(2)	N(11)—C(12)—C(7)	119.7(2)
O(2)—C(1)—C(2)	111.0(2)	N(11)—C(12)—C(13)	122.0(2)
C(1)—C(2)—C(3)	119.5(2)	C(7)—C(12)—C(13)	118.1(2)
C(1)—C(2)—C(7)	120.1(2)	C(12)—C(13)—N(14)	122.8(2)
C(3)—C(2)—C(7)	120.1(2)	C(13)—N(14)—C(15)	116.7(2)
N(3)—C(3)—C(2)	121.4(2)	N(14)—C(15)—C(16)	120.8(2)
N(3)—C(3)—C(4)	116.0(2)	N(14)—C(15)—C(20)	119.8(2)
C(2)—C(3)—C(4)	122.6(2)		

group of enamine but shows a signal for the cyclic NH fragment (δ 12.68). In addition, the chemical shifts of the protons of the ester fragment become typical of this system.

Thus, we demonstrated for the first time that the pyridine ring can be annelated to quinoxalines by *C*-addition of aminoenoates to the carbonyl group followed by the intramolecular S_NH reaction. It should be noted that the 4-oxopyridine-3-carboxylic acid fragment is involved in many highly active synthetic antibacterial drugs, *viz.*, fluorinated analogs of oxolinic and nalidixic acids.[12] Generally, structural modifications of fluoroquinolones leave the pyridine fragment containing the carboxy and carbonyl groups intact because this fragment is necessary for binding with DNA gyrase. The known procedures for the construction of the quinolone system are, as a rule, based on reactions of electrophilic reagents with derivatives of fluoroanilines or fluorobenzoic acids.[13] The final step of the process, *viz.*, intramolecular cyclization, occurs as either *ipso*-substitution or nucleophilic substitution of hydrogen. Thus, we developed a new in principle procedure for the annelation of the 4-oxopyridine-3-carboxylic acid fragment to pyrazines.

Table 3. Selected torsion angles (τ) in molecule **3**

Angle	τ/deg
O(1)—C(1)—O(2)—C(5)	11.7(3)
C(2)—C(1)—O(2)—C(5)	−168.4(2)
O(1)—C(1)—C(2)—C(3)	41.4(3)
O(2)—C(1)—C(2)—C(3)	−138.4(2)
O(1)—C(1)—C(2)—C(7)	−143.7(2)
O(2)—C(1)—C(2)—C(7)	36.5(2)
C(1)—C(2)—C(3)—N(3)	174.7(2)
C(1)—C(2)—C(3)—C(4)	−3.9(3)
C(7)—C(2)—C(3)—N(3)	−0.2(3)
C(7)—C(2)—C(3)—C(4)	−178.7(2)
C(1)—C(2)—C(7)—O(3)	−164.2(2)
C(1)—C(2)—C(7)—C(12)	17.7(3)
C(3)—C(2)—C(7)—O(3)	10.7(3)
C(3)—C(2)—C(7)—C(12)	−167.4(2)
C(2)—C(7)—C(12)—N(11)	41.8(3)
C(2)—C(7)—C(12)—C(13)	−141.7(2)
O(3)—C(7)—C(12)—C(13)	40.0(3)
C(1)—O(2)—C(5)—C(6)	160.0(2)
N(3)—C(3)—C(4)—H(4a)	−15(2)
C(2)—C(3)—C(4)—H(4b)	43(2)

Crystal and molecular structure of compound 3. In molecule **3**, the lengths of the C(1)—C(2), C(2)—C(3), and C(2)—C(7) bonds at the formally trivalent C(2) atom (charge −1) (see Fig. 1) differ noticeably due to the different effect of π conjugation. The average length of these three formally single $C^-(sp^2)$—$C(sp^2)$ bonds is 1.437(17) Å, which is close to the average length of analogous bonds in similar structures (methanides, ethanides, *etc.*).[14] The lengths of other covalent bonds in molecule **3** are in the ranges usual for these types of bonds. The distribution of the bond lengths in the quinoxalinyl substituent of **3** is characteristic of the quinoxaline bicycle.[14]

The conformation of molecule **3** is characterized by the torsion angles τ (see Table 3) and the following

interplanar angles. The mean-square planes of three nearly planar fragments consisting of four atoms each, *viz.*, O(1)O(2)C(1)C(2), C(2)C(3)C(4N(3), and C(2)C(7)O(3)C(12), form angles of 39.0(1), 2.8(2), and 14.4(2)°, respectively, with the mean-square plane of the central four-atom C(1)C(2)C(3)C(7) fragment. The central C(2) atom of the latter fragment slightly deviates from the C(1)C(3)C(7) plane through three other atoms by 0.037(2) Å toward the O(1) atom.

In molecule **3**, nine of ten nonhydrogen atoms of the quinoxalinyl substituent are virtually in a single plane to within ±0.020(2) Å, whereas the tenth atom, *viz.*, C(12), slightly deviates from this plane (by 0.063(3) Å) toward the C(2) atom. The quinoxalinyl substituent is twisted about the C(7)—C(12) bond; the angles between its mean-square plane and the mean-square planes of the attached C(2)C(7)O(3)C(12) fragment and the central C(1)C(2)C(3)C(7) fragment are 40.7(1)° and 49.8(1)°, respectively.

In the crystal structure of **3**, there are a strong intramolecular N(3)—H(3a)...O(3) hydrogen bond and an intermolecular N(3)—H(3b)...N(11)^i hydrogen bond (see Fig. 1). The interatomic distances and angles corresponding to these hydrogen bonds are as follows: N(3)...O(3), 2.620(2) Å; H(3a)...O(3), 1.92(3) Å; N(3)...N(11)^i, 3.070(2) Å; H(3b)...N(11)^i, 2.24(2) Å; ∠(N(3)—H(3a)...O(3)), 133(2)°; and ∠(N(3)—H(3b)...N(11)^i), 161(2)°; the symmetry transformation i is $3/2 - x$, $y - 1/2$, $1/2 - z$. In the crystal, molecules **3** are linked in infinite chains along the y axis by the intermolecular N(3)—H(3b)...N(11)^i hydrogen bonds (the molecules are related by screw axes 2_1).

Except for the above-mentioned intermolecular hydrogen bonds, all other short intermolecular contacts in the crystal structure of **3** are close to or slightly smaller than the sums of the van der Waals radii of the corresponding atoms.

The crystal structure of **3** can also be described as consisting of centrosymmetrical "dimers," which are formed apparently by very weak stacking interactions between two antiparallel bicyclic (quinoxaline) moieties of two adjacent molecules **3** and **3**′ ($1 - x$, $1 - y$, $-z$). The interplanar distance between these molecules is 3.638(5) Å.

Experimental

The ^{1}H NMR spectra were recorded on Bruker WM-250 and Bruker DRX-400 spectrometers operating at 250 and 400 MHz, respectively; the ^{13}C NMR spectra were measured and 2D experiments were carried out on a Bruker DRX-400 spectrometer operating at 100 MHz; Me_4Si was used as the internal standard. The mass spectra were obtained on a Varian MAT 311A spectrometer (accelerating voltage was 3 kV, cathode emission current was 300 μA, energy of ionizing electrons was 70 eV, direct inlet of the sample into the ion source).

Ethyl (*E*)-3-amino-2-hydroxy(quinoxalin-2-yl)methylcrotonate (2). Ethyl (*E*)-3-aminocrotonate (2.3 g, 18.0 mmol) was added to a solution of aldehyde **1** (2 g, 12.6 mmol) in acetonitrile (30 mL) at 5—7 °C. The reaction mixture was kept at this temperature for 20 min and the precipitate that formed was filtered off. Compound **2** was obtained in a yield of 3.1 g (87%), m.p. 110—111 °C (from acetonitrile). Found (%): C, 62.6; H, 5.8; N, 14.7. $C_{15}H_{17}N_3O_3$. Calculated (%): C, 62.7; H, 6.0; N, 14.6. ^{1}H NMR (DMSO-d_6), δ: 0.63 (t, 3 H, $CH_2C\underline{H}_3$, $^3J_{H,CH_2}$ = 7.1 Hz); 2.17 (s, 3 H, CH_3); 3.67 and 3.74 (both dq, 2 H, $C\underline{H}_2CH_3$, $^2J_{AB}$ = 10.8 Hz, $^3J_{H,CH_3}$ = 7.1 Hz); 5.40 (d, 1 H, OH, $^3J_{H,CH}$ = 4.8 Hz); 5.83 (d, 1 H, C<u>H</u>OH, $^3J_{H,OH}$ = 4.8 Hz); 7.20 and 8.53 (both br.s, 1 H each, NH_2); 7.76, 7.79, 7.99, and 8.07 (all m, 1 H each, H(5′), H(6′), H(7′) H(8′)); 9.17 (s, 1 H, H(3′)). ^{13}C NMR (DMSO-d_6), δ (assignment of the signals was made based on ^{13}C—^{1}H HSQC and ^{1}H—^{13}C HMBC correlation experiments): 13.75 ($CH_2\underline{C}H_3$); 20.06 (C(4)); 57.63 ($\underline{C}H_2CH_3$); 69.84 (CHOH); 95.70 (C(2)); 128.38, 128.70, 128.72, 129.66 (C(5′), C(6′), C(7′), C(8′)); 140.31 and 140.39 (C(4a′), C(8a′)); 144.89 (C(3′)); 161.31 (C(2′)); 161.93 (C(3)); 168.35 (C(1)). MS (EI, 70 eV), m/z (I_{rel} (%)): 287 $[M]^+$ (25), 269 (15), 241 (14), 212 (8), 184 (10), 159 (10), 158 (65), 156 (15), 132 (10), 131 (11), 130 (21), 129 (35), 112 (100).

Ethyl (*E*)-3-amino-2-(quinoxalin-2-ylcarbonyl)crotonate (3). Potassium permanganate (2.3 g, 15.0 mmol) was added to a solution of compound **2** (2 g, 6.9 mmol) in acetone (100 mL) at ~20 °C. The reaction mixture was kept for 20 h. The precipitate of MnO_2 was filtered off and washed with a large amount of acetone. The solutions were combined and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, chloroform) to give 1.2 g (62%) of compound **3**, m.p. 122—123 °C. Found (%): C, 63.2; H, 5.3; N, 14.8. $C_{15}H_{15}N_3O_3$. Calculated (%): C, 63.1; H, 5.3; N, 14.7. ^{1}H NMR (DMSO-d_6), δ: 0.32 (t, 3 H, $CH_2C\underline{H}_3$, $^3J_{H,CH_2}$ = 7.1 Hz); 2.36 (s, 3 H, CH_3); 3.60 (q, 2 H, $C\underline{H}_2CH_3$, $^3J_{H,CH_3}$ = 7.1 Hz); 7.91 (m, 2 H, H(6′), H(7′)); 8.04 and 8.15 (both m, 1 H each, H(5′), H(8′)); 9.05 and 10.63 (both br.s, 1H each, NH_2); 9.09 (s, 1 H, H(3′)). ^{13}C NMR (DMSO-d_6), δ: 13.08 (qt, $CH_2\underline{C}H_3$, $^1J_{C,H}$ = 126.6 Hz, $^2J_{C,CH_2}$ = 2.6 Hz); 21.57 (qdd, C(4), $^1J_{C,H}$ = 129.8 Hz, $^3J_{C,NH_2}$ = 8.2 Hz, $^3J_{C,NH_2}$ = 3.9 Hz); 58.76 (tq, $\underline{C}H_2CH_3$, $^1J_{C,H}$ = 146.9 Hz, $^2J_{C,CH_3}$ = 4.0 Hz); 99.67 (m, C(2)); 128.80, 129.08, 130.68, and 130.77 (all m, C(5′), C(6′), C(7′), C(8′)); 139.78 and 141.55 (both m, C(4a′), C(8a′)); 143.90 (d, C(3′), $^1J_{C,H}$ = 186.3 Hz); 153.55 (d, C(2′), $^2J_{C,H(3')}$ = 9.2 Hz); 168.15 (m, C(1)); 170.62 (m, C(3)), 189.76 (s, C=O). MS (EI, 70 eV), m/z (I_{rel} (%)): 285 $[M]^+$ (30), 184 (37), 157 (9), 156 (100), 129 (21), 128 (32). Pale-yellow transparent crystals of compound **3** suitable for X-ray diffraction study were prepared by recrystallization from benzene.

Ethyl 2-methyl-4-oxo-1*H*-pyrido[5,6-*b*]quinoxaline-3-carboxylate (4). Air was passed through a boiling solution of compound **3** (0.5 g, 1.7 mmol) in DMF (30 mL) for 5 h. The solvent was partially removed *in vacuo*, the solution was cooled, and the precipitate was filtered off. Compound **4** was obtained in a yield of 0.38 g (80%), m.p. 284—285 °C (from DMF). Found (%): C, 63.5; H, 4.6; N, 14.8. $C_{15}H_{13}N_3O_3$. Calculated (%): C, 63.6; H, 4.6; N, 14.8. ^{1}H NMR (DMSO-d_6), δ: 1.30 (t, 3 H, $CH_2C\underline{H}_3$, $^3J_{H,CH_2}$ = 7.0 Hz); 2.48 (s, 3 H, CH_3); 4.29 (q, 2 H, $C\underline{H}_2CH_3$, $^3J_{H,CH_3}$ = 7.1 Hz); 7.89, 8.01, 8.07, and 8.28 (all m, 1 H each, H(6), H(7), H(8), H(9)); 12.68 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 14.07 (qt, $CH_2\underline{C}H_3$, $^1J_{C,H}$ = 126.9 Hz, $^2J_{C,CH_2}$ = 2.8 Hz); 18.42 (q, CH_3, $^1J_{C,H}$ = 130.3 Hz); 60.59 (tq, $\underline{C}H_2CH_3$,

$^1J_{C,H}$ = 147.8 Hz, $^2J_{C,CH_3}$ = 4.4 Hz); 116.23 (q, C(3), $^3J_{C,CH_3}$ = 3.5 Hz); 127.30, 129.49, 130.32, and 133.13 (all m, C(6), C(7), C(8), C(9)); 136.38 (s, C(4a)); 140.63 and 142.42 (both m, C(5a), C(9a)); 145.01 (s, C(10a)); 152.90 (q, C(2), $^2J_{C,CH_3}$ = 5.6 Hz); 166.03 (t, C=O, $^3J_{C,CH_2}$ = 3.4 Hz); 173.85 (s, C(4)). MS (EI, 70 eV), m/z (I_{rel} (%)): 283 $[M]^+$ (49), 239 (32), 238 (69), 237 (100), 211 (63), 209 (11), 183 (57), 181 (10), 129 (11).

X-ray diffraction study of compound 3. The unit cell parameters of compound **3** and the intensities of reflections were measured on an automated Enraf-Nonius CAD-4 diffractometer (Cu-Kα radiation, graphite monochromator). Crystals of **3** are monoclinic, $C_{15}H_{15}N_3O_3$, molecular weight 285.30; at T = 20 °C a = 8.563(2), b = 8.720(1), c = 19.240(3) Å, β = 92.60(2)°, V = 1435.2(4) Å^3, Z = 4, d_{calc} = 1.320 g cm^{-3}, μ(Cu-Kα) = 7.77 cm^{-1}, space group $P2_1/n$.

The intensities of 3243 reflections were measured within a quadrant of reciprocal space (2θ ≤ 150°) from a single crystal of dimensions 0.36×0.41×0.57 mm using ω/2θ scanning. The intensities were measured using a special technique, where the final scanning was carried out for all, including very weak, reflections. After exclusion of 212 systematic absences and averaging of the intensities of 85 pairs of the equivalent $hk0$ and $\bar{h}k0$ reflections (R_{int} 0.060), the data set of measured $F^2(hkl)$ and $\sigma(F^2)$ included 2946 independent reflections.

The crystal structure of **3** was solved by direct methods using the SHELXS-97 program package[15] and refined by the full-matrix least-squares method against F^2 with anisotropic thermal parameters for all nonhydrogen atoms using the SHELXL-97 program package[15]. The least-squares refinement was carried out with the use of almost all independent reflections (including very weak reflections with $I < 2\sigma(I)$), except for several reflections for which measured F^2 are in poor agreement with the calculated values.

All H atoms of molecule **3** were located from the difference Fourier synthesis. Then the positional and isotropic thermal parameters of all H atoms were refined by the least-squares method. In the last cycle of the full-matrix least-squares refinement, the absolute shifts of all 244 variable parameters were smaller than 0.001σ. The final atomic coordinates and thermal parameters for the structure of **3** were deposited with the Cambridge Structural Database.[14]

The final R factors are R_1 = 0.072 and wR_2 = 0.196 for 2250 observed reflections with $I \geq 2\sigma(I)$; R_1 = 0.085 and wR_2 = 0.210 for all 2946 independent measured reflections; the goodness-of-fit S = 1.08 (wR_2 and S were determined as described in the manual[15]). In the final difference Fourier synthesis, $-0.21 < \Delta\rho \ll 0.19$ e Å^{-3}. The used f curves and anomalous dispersion corrections ($\Delta f'$ and $\Delta f''$) were taken from the International Tables for Crystallography.[16]

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