Chemistry of Heterocyclic Compounds, Vol. 41, No. 6, 2005

DIOXIMES OF 1,3-DIKETONES IN THE TROFIMOV REACTION: NEW 3-SUBSTITUTED PYRROLES

A. B. Zaitsev, E. Yu. Schmidt, A. M. Mikhaleva, A. V. Afonin, and I. A.Ushakov

Dioximes of 1,3-diketones enter into the Trofimov reaction forming pyrroles containing an acyl or an O-vinyloxime substituent in position 3 of the pyrrole. In the case of sterically hindered dioximes the main reaction products are isoxazoles.

Keywords: acetylene, 3-acylpyrroles, O-vinyloximes, 1-vinylpyrroles, dioximes of 1,3-diketones, isoxazoles.

Heterocyclic compounds containing a 3-acylpyrrole fragment are of interest for making new pharmacological preparations. For example, the cannabinoid activity of 1-alkyl-3-(naphthoyl)pyrroles [1] and 1-alkyl-3-(naphthoyl)indoles [2] is known, as is the antibiotic activity of verrucarin E, 3-acetyl-4-hydroxymethylpyrrole, isolated from *Myrothecium verrucaria* [3]. 3-Acylpyrroles and other 3-substituted pyrroles obtained from them are precursors of liquid crystal materials [4] and polypyrroles [5], possessing high electrical conductivity in comparison with their 1-substituted analogs [6]. Such conjugated polymers may be used for example to construct gas sensors [7], and also sensors capable of distinguishing DNA molecules [8].

The acylation reaction used in the majority of cases for the synthesis of 3-acylpyrroles has low efficiency since electrophilic attack occurs predominantly at position 2 of the pyrrole ring. To direct substitution to position 3 it is necessary to introduce readily removable blocking groups into position 2 (a thiocarboxylate group [9]) or position 1 (triisopropylsilyl [10, 11], 1-phenylsulfonyl or 1-tosylsulfonyl [7, 12, 13]).

In the present work we have studied the possibility of synthesizing new 3-functionalized pyrroles with the aid of the Trofimov reaction [14-19] by the interaction of dioximes of acetylacetone (**1a**), benzoylacetone (**1b**), 5-ethylnonane-4,6-dione (**1c**), and 5,5-dimethylcyclohexane-1,3-dione (dimedone) (**1d**) with acetylene in the presence of KOH in DMSO.

The selectivity of the interaction of dioxime **1a** with acetylene depends strongly on the reaction temperature. At 100°C (1 h) the O-vinyloxime pyrrole derivative **2a** is formed exclusively (11% yield), and at 120°C (1 h) the main product is the 2,3'-bipyrrole **3** (7% yield).

Attention is attracted by the unusually high stability of the O-vinyloxime group of compound **2a** under the reaction conditions. The formation of a second pyrrole ring with its participation occurs only on increasing the temperature to 120°C. It is known that for O-vinyloximes of 3-acylindoles pyrrolization in the system KOH–DMSO is also hindered and at 100-105°C occurs completely only after 8-10 h [20]. The reduced reactivity of the O-vinyloxime function at position 3 of the pyrrole ring in O-vinyloximes of 3-acylindoles

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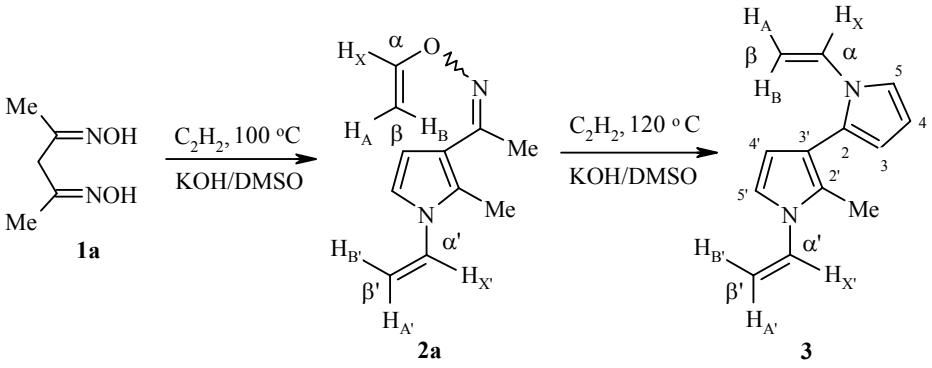
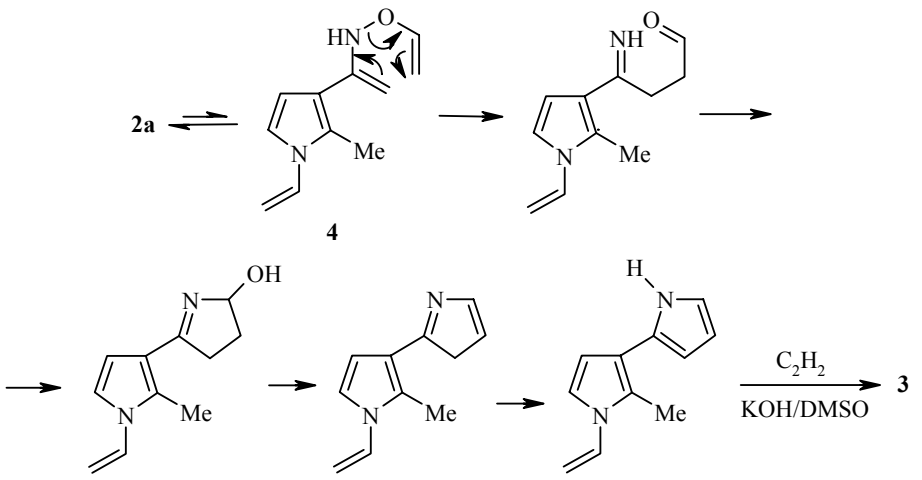
A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, Irkutsk 664033; e-mail: mikh@irioch.irk.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 839-847. June, 2005. Original article submitted May 12, 2003; revision submitted August 3, 2004.



enabled the isolation for the first time of a mixture of the corresponding O-vinyloximes containing an α-methylene group [20], which was not possible up to the present time on vinylation of alkyl-, aryl-, and 2-hetaryl ketoximes [19, 21].

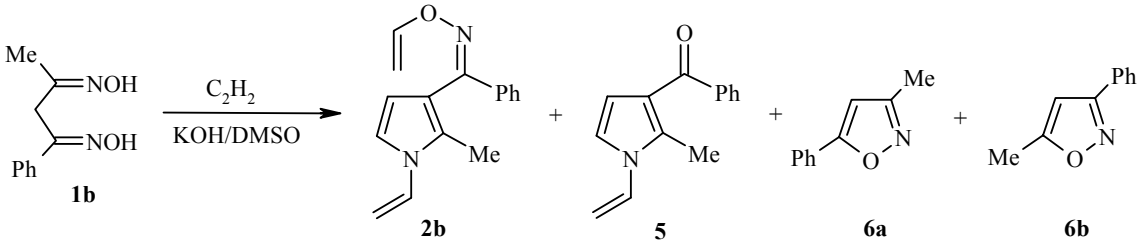


Probably the hindering of the pyrrolization process of compound **2a** is the result of the increased electron density at position 3 of the pyrrole ring compared with position 2. The electron-donating effect of the heterocycle on the O-vinyloxime group must lead to a reduction of the CH-acidity of the neighboring methyl group, which is unfavorable for tautomeric conversion of compound **2a** into the enehydroxylamine **4**, [3,3] sigmatropic rearrangement of which leads to bipyrrole **3**.

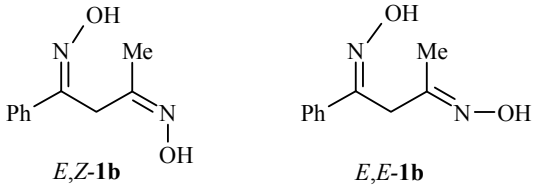
It is also possible that hindrance of the pyrrolization process is a consequence of steric obstacles linked with the presence of the heterocycle and the methyl group, which leads to disturbance of the coplanarity of the double bonds in the O-vinyloxime substituent, necessary for a facile [3,3] sigmatropic rearrangement.

Lower reaction selectivity is observed for dioxime **1b**. At 100°C a mixture of pyrroles **2b** (4% yield), **5** (13% yield), and isoxazoles **6a,b** (18% yield) is formed already after 5 min. According to data of ^{1}H NMR spectra the ratio **2b**:**5**:**6a**:**6b** ≈ 1:3:2:2.

This mixture indicates that on interacting compound **1b** with acetylene two competing reactions take place. These are pyrrolization leading to oxime **2b** and its deoximation product **5**, and also intramolecular nucleophilic addition of one oxime group to the other at the C=N bond with the formation of compounds **6a,b**.



An interesting fact in the present case is the regiospecific pyrrolization of dioxime **1b** with the participation of the oxime function of the acetyl fragment. This is probably caused by the higher nucleophilicity and lower steric hindrance of the acetyl oxime group enabling its addition to acetylene. In view of the relative ease of *E,Z*-isomerization of oxime functions under the reaction conditions [19], it may be suggested that the marked regiospecificity is not linked with the configuration of the oxime functions of dioxime **1b**, which is a mixture of *E,Z*- and *E,E*-isomers (configurations of the PhC=N and MeC=N bonds respectively) at a ratio of 1:1 (^{1}H NMR).

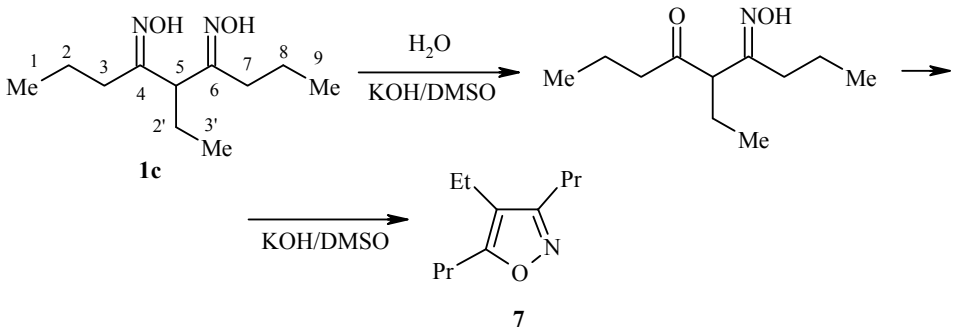


The ease of deoximation of compound **2b** leading to pyrrole **5** is probably linked to the acceptor influence of the phenyl substituent increasing the tendency of the neighboring O-vinyloxime group to nucleophilic attack by hydroxide ion at the carbon atom.

Regiospecific pyrrolization with the participation of the more acidic methylene group in dioximes **1a,b** is one further indirect confirmation of the mechanism of the Trofimov reaction, including a [3,3] sigmatropic rearrangement of the enehydroxylamines formed as a result of a prototropic tautomerization of O-vinyloximes [19]. The latter must proceed readily on increasing the acidity of the methylene (methyl) group bound directly to the O-vinyloxime function.

On the basis of the results obtained it is also possible to explain the more ready pyrrolization of O-vinyloximes containing an α-methylene group. The enehydroxylamines formed in this case with a disubstituted ethylene fragment are thermodynamically more stable and consequently their formation must proceed more readily.

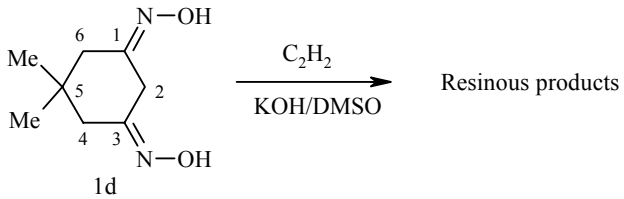
On introducing dioxime **1c** into the Trofimov reaction only 4-ethyl-3,5-di(*n*-propyl)isoxazole **7** (21% yield) was isolated from the reaction mixture by column chromatography. This is formed by intramolecular cyclization of the initial dioxime.



It is possible that the steric effect of the propyl sidegroups hinders addition of the oxime functions to acetylene.

It was shown that the formation of isoxazole **7** occurs under the action of water present in the KOH–DMSO system. However at a concentration of water commensurate with the concentration of dioxime **1c**, only traces of product **7** are formed and practically all the initial dioxime remains unreacted. Probably a preliminary deoximation (hydrolysis) of one of the oxime groups is necessary for cyclization, and the second adds relatively readily to the electron-deficient carbonyl group formed.

The interaction of dimedone dioxime **1d** with acetylene under Trofimov reaction conditions also did not lead to the formation of pyrroles or O-vinyloximes. The reaction mixture was strongly resinified.



1d

Probably the conformation of compound **1d** hinders its conversion into a pyrrole under the action of acetylene and the formation of resinous compounds is the result of the condensation of products of deoximation and breakdown of the cyclohexane ring under the action of the KOH–DMSO system. It is also possible that this behavior of dioxime **1d** is linked with its *Z,Z*-configuration, leading to a steric interaction of the oxime functions, thus reducing their reactivity.

COSY and NOESY methods of homonuclear 2D spectroscopy and HSQC and HMBC methods of heteronuclear 2D spectroscopy were used for the assignment of signals in the NMR spectra of the compounds obtained. The paramagnetic broadening agent $Gd(fod)_3$ was used for assigning the signals of isomers **6a,b**.

Evidence of the existence of 5,5-dimethylcyclohexane-1,3-dione dioxime **1d** as the *Z,Z*-isomer is the displacement in the ^{13}C NMR spectrum of the signal for atom $C_{(2)}$ by 34.2 ppm towards high field compared with the initial ketone (57.35 ppm). The *syn* effect observed here is two times greater compared with the known value for cyclohexanone oxime (-15.8 ppm [22]).

The chemical shift of the $C_{(Ph)}$-*i* atom in oxime **2b** (136.45 ppm) indicates the *Z*-configuration of its O-vinyloxime group [23]. The low-field displacement of the $C_{(3)}$ atom signal in compound **2a** (117.96 ppm) relative to the $C_{(3)}$ signal of compound **2b** (113.99 ppm) indicates the *E*-configuration of the considered group in oxime **2a** [24]. On the basis of the chemical shift of the methyl group carbon atoms in dioxime **1a** (13.08 ppm) it may be concluded that it exists as the *E,E*-isomer [24].

As a result of the investigations carried out the possibility has been shown of synthesizing by the Trofimov reaction 2,3'-bipyrroles, 3-acylpyrroles, and their O-vinyloxime derivatives, unavailable in practice. It has been established that the determining influence on the direction of the reaction proves to be the character of the substituent in the 1,3-dioxime. The presence of bulky substituents or a six-membered ring makes side reactions completely dominant.

In spite of the relatively low yields the compounds obtained or their analogs may after optimizing the synthetic conditions become a basis for building new pharmacological preparations and contemporary high-technology materials.

EXPERIMENTAL

The ^1H NMR (400 MHz) and ^{13}C (101 MHz) spectra were recorded on a Bruker 400DPX spectrometer, internal standard was HMDS (δ 0.055 ppm for ^1H and 2.00 ppm for ^{13}C). The IR spectra were obtained on a Bruker ISF 25 instrument. A Finnigan MAT 8200 spectrometer was used to record the mass spectra.

Acetylacetone Dioxime (1a). Acetylacetone (16.00 g, 159.8 mmol) was added to a mixture of hydroxylamine hydrochloride (27.76 g, 399.6 mmol) and sodium acetate (32.78 g, 399.6 mmol) in methanol (100 ml). The mixture obtained was stirred for 5 h then left for 16 h at room temperature. The precipitated solid NaCl was filtered off, and washed with methanol. The total methanol solution was evaporated almost to dryness in vacuum on a water bath (<50°C). Cold water (100 ml) was added to the residue, the mixture was thoroughly stirred, the precipitated crystals were filtered off, washed with cold water (4 × 20 ml), and dried in the air. Dioxime **1a** (11.37 g, 54.7%) was obtained as white needle-like crystals; mp 128-134°C (mp 149-150°C [25-27], 105°C [28]). IR spectrum (KBr), ν, cm^{-1}:3176 (OH), 3100 (CH), 2882 (CH), 1666 (C=N), 989 (N–O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 10.49 (2H, s, 2NOH); 2.93 (2H, s, CH_2); 1.69 (6H, s, $2CH_3$). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 152.29 (C=NOH); 41.65 (CH_2); 13.08 (CH_3). Found, %: C 46.60; H 7.95; N 21.53. $C_5H_{10}N_2O_2$. Calculated, %: C 46.14; H 7.74; N 21.52.

Benzoylacetone Dioxime (1b). Sodium acetate (8.10 g, 98.7 mmol) and hydroxylamine hydrochloride (6.86 g, 98.7 mmol) in methanol (30 ml) were stirred for 10 min. Benzoylacetone (4.00 g, 24.7 mmol) was added to the obtained mixture, the reaction mixture was stirred for 4 days at room temperature, and then poured into cold water (100 ml). After 3 h the precipitated solid was filtered off, washed with cold water, dried in vacuum, and a mixture (1:1) of the *E,E*- and *E,Z*-isomers of dioxime **1b** (3.08 g, 65%) was obtained as a white powder; mp 84-86°C. IR spectrum (KBr), ν, cm^{-1}: 3247 (OH), 3206 (CH), 3079 (CH), 2894 (CH), 1597 (C=N), 1569 (Ph), 1498 (Ph), 930 (N–O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, mixture of isomers of **1b**: *E,E*-**1b** 11.42 and 10.44 (2H, two br s, NOH); 7.76 (2H, m, H_{Ph}-*o*); 7.30 (3H, m, H_{Ph}-*m*, H_{Ph}-*p*); 3.41 (2H, s, CH_2); 1.69 (3H, s, CH_3); *E,Z*-**1b** 11.49 and 10.65 (2H, two br s, NOH); 7.76 (2H, m, H_{Ph}-*o*); 7.30 (3H, m, H_{Ph}-*m*, H_{Ph}-*p*); 3.61 (2H, s, CH_2); 1.58 (3H, s, CH_3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm, mixture of isomers: *E,E*-**1b** 153.66 and 153.30 (Me<u>C</u>=N, Ph<u>C</u>=N); 137.39 (C_{Ph}-*i*); 129.63 (C_{Ph}-*m*); 127.25 (C_{Ph}-*o*); 126.87 (C_{Ph}-*p*); 32.60 (CH_2); 14.80 (CH_3); *E,Z*-**1b** 153.89 and 152.19 (Me<u>C</u>=N, Ph<u>C</u>=N); 137.25 (C_{Ph}-*i*); 130.26 (C_{Ph}-*p*); 129.99 (C_{Ph}-*o*); 129.85 (C_{Ph}-*m*); 26.36 (CH_2); 19.95 (CH_3). Found, %: C 61.97; H 6.31; N 14.56. $C_{10}H_{12}N_2O_2$. Calculated, %: C 62.49; H 6.29; N 14.57.

5-Ethylnonane-4,6-dione Dioxime (1c). Sodium acetate (8.86 g, 108.0 mmol) and hydroxylamine hydrochloride (7.51 g, 108.1 mmol) in methanol (15 ml) were stirred for 10 min. 5-Ethylnonane-4,6-dione (5.00 g, 27.1 mmol) was added to the obtained mixture, the reaction mixture was stirred for 8 days at room temperature, and then poured into cold water (50 ml). The precipitated solid was filtered off, washed with cold water, dried in vacuum, and dioxime **1c** (3.34 g, 58% yield) was obtained as a white powder (3:2 mixture of *E,E*- and *E,Z*-isomers); mp 80-84°C. IR spectrum (KBr), ν, cm^{-1}: 3260 (OH), 3152 (CH), 2967 (CH), 2936 (CH), 2875 (CH), 1652 (C=N), 966 (N-O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz), mixture of isomers of dioxime **1c**: *E,E*-**1c** 10.49 (2H, s, 2NOH); 2.91 (1H, t, $^3J_{5,1'}$ = 7.5, H-5); 2.31-1.32 (10H, m, CH_2); 0.85 (6H, t, $^3J_{1,2} = {}^3J_{8,9}$ =7.4, $C_{(1)}H_3$ and $C_{(9)}H_3$); 0.81 (3H, t, $^3J_{1',2'}$ = 7.3, $C_{(2')}H_3$); *E,Z*-**1c** 10.60 (1H, s, *Z*-NOH); 10.49 (1H, s, *E*-NOH); 4.12 (1H, dd, $^3J_{5,1'a}$ = 6.8, $^3J_{5,1'b}$ = 8.3, H-5); 2.31-1.32 (10H, m, CH_2); 0.85 (6H, t, $^3J_{1,2} = {}^3J_{8,9}$ =7.4, $C_{(1)}H_3$ and $C_{(9)}H_3$); 0.81 (3H, t, $^3J_{1',2'}$ = 7.3, $C_{(2')}H_3$). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm, mixture of isomers: *E,E*-**1c** 157.70 ($C_{(4)}$, $C_{(6)}$); 51.46 ($C_{(5)}$; 28.37 ($C_{(3)}$, $C_{(7)}$); 21.67 ($C_{(1')}$); 18.79 ($C_{(2)}$, $C_{(8)}$); 14.51 ($C_{(1)}$, $C_{(9)}$; 12.21 ($C_{(2')}$); *E,Z*-**1c** 157.00 ($C_{(4)}$-*E*); 156.58 ($C_{(6)}$-*Z*); 42.83 ($C_{(5)}$); 31.42 ($C_{(3)}$); 29.68 ($C_{(7)}$); 21.10 ($C_{(1')}$); 19.18 ($C_{(2)}$); 18.60 ($C_{(8)}$); 14.25 ($C_{(1)}$); 14.02 ($C_{(9)}$); 12.10 ($C_{(2')}$). Found, %: C 61.40; H 10. 44; N 13.01. $C_{11}H_{22}N_2O_2$. Calculated, %: C 61.65; H 10.35; N 13.07.

5,5-Dimethylcyclohexane-1,3-dione Dioxime (1d). Finely powdered NaOH (3.57 g, 89.2 mmol) was added in portions to a mixture of 5,5-dimethylcyclohexane-1,3-dione (5.00 g, 35.7 mmol) and hydroxylamine hydrochloride (6.20 g, 89.2 mmol), ethanol (20 ml), and water (2 ml). The mixture was stirred at room temperature for 1 h, and then poured into cold water (100 ml). The precipitated solid was filtered off, washed with cold water, and dried in vacuum. Dioxime **1d** (2.35 g, 39%) was obtained as a white powder; mp 155-158°C. IR spectrum (KBr), ν, cm^{-1}: 3191 (OH), 3093 (CH), 2959 (CH), 2889 (CH), 1648 (C=N), 976 (N–O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 10.43 (2H, s, NOH); 3.34 (2H, s, $C_{(2)}H_2$); 2.14 (4H, s,

$C_{(4)}H_2$, $C_{(6)}H_2$); 0.85 (6H, s, CH_3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 152.59 ($C_{(1)}$, $C_{(3)}$); 43.86 ($C_{(4)}$, $C_{(6)}$); 31.69 ($C_{(5)}$); 27.37 (CH_3); 23.15 ($C_{(2)}$). Found, %: C 56.42; H 8.82; N 15.83. $C_8H_{14}N_2O_2$. Calculated, %: C 56.45; H 8.29; N 16.46.

1-(2-Methyl-1-vinyl-3-pyrrolyl)ethanone O-Vinyloxime (2a). A mixture of dioxime (**1a**) (1.95 g, 15.0 mmol) and finely powdered KOH.0.5 H_2O (0.84 g, 12.9 mmol) in DMSO (100 ml) was saturated in an autoclave (0.5 liter) with acetylene (initial pressure 14 atm) at room temperature. The reaction mixture was heated to 100°C, maintained at this temperature for 1 h, then cooled. Water (100 ml) was added, and the mixture extracted with ether (4 × 40 ml). The total ether extract was washed with water (3 × 30 ml), and dried over K_2CO_3. After removing the ether, the red liquid was chromatographed on a column (basic Al_2O_3, hexane) and product **2a** (0.32 g, 11%) was isolated as a clear light yellow liquid as a mixture of *E*- and *Z*-isomers (1:2), n_D^{20} 1.5668. IR spectrum (film), ν, cm^{-1}: 3115 (CH), 3069 (CH), 3048 (CH), 2923 (CH), 1640 (C=C), 1602 (pyrrole ring), 1555 (pyrrole ring), 1307 (C–N), 1191 (C–O), 993 (N–O). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): (1H, dd, $^3J_{BX}$ = 14.3, $^3J_{AX}$ = 6.7, H_X); 6.90 (1H, dd, $^3J_{B'X'}$ = 15.6, $^3J_{A'X'}$ = 8.9, $H_{X'}$); 6.88 (1H, d, $^3J_{4',5'}$ = 3.2, H-5'); 6.25 (1H, d, $^3J_{4',5'}$ = 3.2, H-4'); 5.13 (1H, dd, $^2J_{A'B'}$ = -0.8, $H_{B'}$); 4.75 (1H, dd, $^3J_{AX'}$ = 8.9, $H_{A'}$); 4.56 (1H, dd, $^2J_{AB}$ = -1.4, H_B); 4.05 (1H, dd, $^3J_{AX}$ = 6.7, H_A); 2.47 (3H, s, $C_{(2)}H_3$); 2.21 (3H, s, N=C–CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 155.22 (C=N); 152.81 ($C_{(\alpha)}$); 130.47 ($C_{(\alpha')}$); 127.89 ($C_{(2)}$); 117.96 ($C_{(3)}$); 115.99 ($C_{(5)}$); 109.98 ($C_{(4)}$); 100.08 ($C_{(\beta')}$); 87.30 ($C_{(\beta)}$); 15.21 (N=C–$\underline{CH_3}$); 11.96 (2-CH_3). Found, %: C 69.20; H 7.62; N 14.61. $C_{11}H_{14}N_2O$. Calculated, %: C 69.45; H 7.42; N 14.72.

1,1'-Divinyl-2'-methyl[2,3']bipyrrole (3). The reaction mixture obtained as described above was heated to 120°C and maintained at this temperature for 1 h. After processing analogously to that described above and removing the ether from the residue (dark-red resinous mass) product **3** (0.21 g, 7%) was isolated by column chromatography (basic Al_2O_3, hexane), n_D^{20} 1.5968. IR spectrum (film), ν, cm^{-1}: 3136 (CH), 3107 (CH), 3036 (CH), 2960 (CH), 2918 (CH), 2866 (CH), 1645 (C=C), 1603 (pyrrole ring), 1559 (pyrrole ring), 1323 (C–N). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.08 (1H, dd, $J_{3,5}$ = $J_{4,5}$ = 3.2, H-5); 6.97 (1H, d, $J_{4',5'}$ = 3.1, H-5'); 6.88 (1H, dd, $^3J_{B'X'}$ = 15.8, $^3J_{A'X'}$ = 8.9, $H_{X'}$); 6.85 (1H, dd, $^3J_{BX}$ = 15.9, $^3J_{AX}$ = 9.0, H_X); 6.27 (1H, t, $J_{3,4}$ = 3.2, H-4); 6.17 (1H, d, $J_{4',5'}$ = 3.1, H-4'); 6.05 (1H, dd, $J_{3,4}$ = 3.2, H-3); 5.13 (1H, dd, $^2J_{A'B'}$ = -1.1, $H_{B'}$); 5.06 (1H, dd, $^2J_{AB}$ = -0.9, H_B); 4.71 (1H, dd, $^3J_{A'X'}$ = 8.9, $H_{A'}$); 4.56 (1H, dd, $^3J_{AX}$ = 9.0, H_A); 2.20 (3H, s, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 131.86 ($C_{(\alpha)}$); 130.60 ($C_{(\alpha')}$); 128.84 ($C_{(2)}$); 127.75 ($C_{(2')}$); 116.17 ($C_{(5)}$); 115.50 ($C_{(5')}$); 113.32 ($C_{(3')}$); 112.03 ($C_{(4')}$); 109.86 ($C_{(4)}$); 109.77 ($C_{(3)}$); 98.52 ($C_{(\beta')}$); 96,74 ($C_{(\beta)}$); 10.60 (CH_3). Found, %: C 78.46; H 6.90; N 14.05. $C_{13}H_{14}N_2$. Calculated, %: C 78.75; H 7.12; N 14.13.

2-Methyl-1-vinyl-3-pyrrolyl Phenyl Ketone O-Vinyloxime (2b), 2-Methyl-1-vinyl-3-pyrrolyl Phenyl Ketone (5), 3-Methyl-5-phenylisoxazole (6a), and 5-Methyl-3-phenylisoxazole (6b). A mixture of dioxime **2a** (4.00 g, 20.8 mmol) and finely powdered KOH·0.5 H_2O (2.71 g, 41.7 mmol) in DMSO (50 ml) was saturated with acetylene. The mixture was then rapidly heated and maintained at 100°C for 5 min. After working up, the residue after removal of the ether was chromatographed on a column (basic Al_2O_3, hexane–ether, 3:1). Pyrrole **2b** (0.20 g, 4%) (clear amber liquid), pyrrole **5** (0.55 g, 13%) (clear viscous amber liquid), and a mixture of isoxazoles **6a** and **6b** (0.59 g, 18%) (clear viscous amber liquid) were isolated.

Oxime 2b. n_D^{24} 1.6010. IR spectrum (film), ν, cm^{-1}: 3114 (CH), 3061 (CH), 2918 (CH), 2860 (CH), 1642 (C=C), 1603 (pyrrole ring), 1591 (Ph), 1572 (pyrrole ring), 1495 (Ph), 1308 (C–N), 1172 (C–O), 989 (N–O). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.58 (2H, m, H_{Ph}-*o*); 7.39 (1H, m, H_{Ph}-*p*); 7.34 (2H, m, H_{Ph}-*m*); 7.05 (1H, dd, $^3J_{BX}$ = 14.1, $^3J_{AX}$ = 6.7, H_X); 7.00 (1H, d, $^3J_{4',5'}$ = 3.1, H-5'); 6.88 (1H, dd, $^3J_{B'X'}$ = 15.5, $^3J_{A'X'}$ = 8.9, $H_{X'}$); 6.24 (1H, d, $^3J_{4',5'}$ = 3.1, H-4'); 5.17 (1H, dd, $^2J_{A'B'}$ = -0.8, $H_{B'}$); 4.77 (1H, dd, $^3J_{A'X'}$ = 8.9, $H_{A'}$); 4.67 (1H, dd, $^2J_{AB}$ = -1.4, H_B); 4.15 (1H, dd, $^3J_{AX}$ = 6.7, H_A); 2.02 (3H, s, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 155.65 (C=N); 152.95 ($C_{(\alpha)}$); 136.45 (C_{Ph}-*i*); 130.22 ($C_{(\alpha')}$); 129.91 ($C_{(2)}$); 129.74 (C_{Ph}-*p*); 128.50 (C_{Ph}-*o*); 128.32 (C_{Ph}-*m*); 115.98 ($C_{(5)}$); 113.99 ($C_{(3)}$); 111.70 ($C_{(4)}$); 99.66 ($C_{(\beta')}$); 88.07 ($C_{(\beta)}$); 12.19 (CH_3). Found, %: C 76.37; H 6.10; N 10.95. $C_{16}H_{16}N_2O$. Calculated, %: C 76.16; H 6.39; N 11.10.

Ketone 5. n_D^{22} 1.6170. IR spectrum (film), ν, cm^{-1}: 3116 (CH), 3057 (CH), 3027 (CH), 2921 (CH), 1639 (C=C and C=O), 1598 (pyrrole ring), 1577 (pyrrole ring), 1500 (Ph), 1311 (C-N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.81 (2H, m, H_{Ph}-*o*); 7.47 (3H, m, H_{Ph}-*m*, H_{Ph}-*p*); 6.98 (1H, dd, $^3J_{B'X'}$ = 15.5, $^3J_{A'X'}$ = 8.8, $H_{X'}$); 6.91 (1H, d, $^3J_{4',5'}$ = 3.0, H-5'); 6.43 (1H, d, $^3J_{4',5'}$ = 3.0, H-4'); 5.28 (1H, dd, $^2J_{A'B'}$ = -0.8, $H_{B'}$); 4.94 (1H, dd, $^3J_{A'X'}$ = 8.8, $H_{A'}$); 2.60 (3H, s, CH_3). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm: 192.40 (C=O); 140.40 (C_{Ph}-*i*); 135.95 ($C_{(2)}$); 131.28 (C_{Ph}-*p*); 129.70 ($C_{(\alpha)}$); 129.17 (C_{Ph}-*o*); 128.08 (C_{Ph}-*m*); 121.47 ($C_{(3)}$); 115.77 ($C_{(5)}$); 113.40 ($C_{(4)}$); 102.22 ($C_{(\beta)}$); 11.42 (CH_3). Found, %: C 79.88; H 6.86; N 6.75. $C_{14}H_{13}NO$. Calculated, %: C 79.59; H 6.20; N 6.63.

Mixture of Isoxazoles 6a and 6b (1:1). Mp 32°C. IR spectrum (film), ν, cm^{-1}: 3130 (CH), 3057 (CH), 2926 (CH), 2855 (CH), 1642 (isoxazole ring), 1610 (isoxazole ring), 1593 (Ph), 1575 (Ph), 1502 (Ph). Found, %: C 76.26; H 6.10; N 9.03. $C_{10}H_9NO$. Calculated, %: C 75.45; H 5.70; 8.80. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, mixture: compound **6a** 7.76 (2H, m, H_{Ph}-*o*); 7.44 (3H, m, H_{Ph}-*m*, H_{Ph}-*p*); 6.37 (1H, s, H-4); 2.36 (3H, s, CH_3); compound **6b** 7.79 (2H, m, H_{Ph}-*o*); 7.46 (3H, m, H_{Ph}-*m*, H_{Ph}-*p*); 6.30 (1H, s, H-4); 2.48 (3H, s, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm, mixture: compound **6a** 169.59 ($C_{(5)}$); 160.36 ($C_{(3)}$); 129.97 (C_{Ph}-*p*); 128.91 (C_{Ph}-*m*); 127.56 (C_{Ph}-*i*); 125.72 (C_{Ph}-*o*); 100.17 ($C_{(4)}$); 11.53 (CH_3); compound **6b** 169.88 ($C_{(5)}$); 162.52 ($C_{(3)}$); 129.79 (C_{Ph}-*p*); 128.84 (C_{Ph}-*m*); 126.89 (C_{Ph}-*i*); 126.71 (C_{Ph}-*o*); 12.33 (CH_3).

4-Ethyl-3,5-dipropylisoxazole (7). A mixture of dioxime **1c** (1.00 g, 4.7 mmol), finely powdered KOH·0.5 H_2O (0.61 g, 9.3 mmol), and water (0.9 g, 50 mmol) in DMSO (15 ml) was stirred at 100°C for 2 h. After cooling, water (30 ml) was added, and the mixture was extracted with ether (4 × 10 ml). The total ether extract was washed with water (3 × 10 ml), and dried over K_2CO_3. After removing the ether, the residue was column chromatographed (basic Al_2O_3, ether) and isoxazole **7** (0.21 g, 25%) (clear colorless liquid) and initial dioxime **1c** (0.24 g, 24%) were isolated. Isoxazole **7**. n_D^{21} 1.4592. IR spectrum (film), ν, cm^{-1}: 2964 (CH), 2936 (CH), 2873 (CH), 1630 (isoxazole ring). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.61 (2H, t, $^3J_{\alpha,\beta}$ = 7.5, α-CH_2 in Pr); 2.55 (2H, t, $^3J_{\alpha,\beta}$ = 7.6, α-CH_2 in Pr); 2.31 (2H, q, $^3J_{\alpha,\beta}$ = 7.6, CH_2 in Et); 1.70 (4H, m, β-CH_2 in Pr); 1.08 (3H, t, CH_3 in Et); 0.99 (3H, t, $^3J_{\beta,\gamma}$ = 7.4, CH_3 in Pr); 0.94 (3H, t, $^3J_{\beta,\gamma}$ = 7.4, CH_3 in Pr). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 167.96 ($C_{(5)}$); 162.90 ($C_{(3)}$); 114.64 ($C_{(4)}$); 27.54 ($C_{Pr\text{-}\alpha}$); 27.28 ($C_{Pr\text{-}\alpha}$); 21.33 ($C_{Et\text{-}\alpha}$); 15.44 ($C_{Et\text{-}\beta}$, $C_{Pr\text{-}\beta}$); 15.13 ($C_{Pr\text{-}\beta}$); 14.11 ($C_{Pr\text{-}\gamma}$); 13.86 ($C_{Pr\text{-}\gamma}$). Mass spectrum, *m/z* (I_{rel}, %): 181 (2) $[M]^+$; 166 (37) $[M\text{-}Me]^+$; 152 (77) $[M\text{-}Et]^+$; 138 (100) $[M\text{-}Pr]^+$; 124 (18); 110 (49); 96 (33). Found, %: C 72.75; H 10.20; N 7.90. $C_{11}H_{19}NO$. Calculated, %: C 72.88; H 10.56; N 7.73.

The work was carried out with the financial support of the Russian Fund for Fundamental Investigations (Project Nos. 03-03-32472 and 2241.2003.3) and of the Presidium of the Russian Academy of Sciences (Project No. 10002-251/P-25/155-305/200404-072).

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