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Five-Membered 2,3-Dioxo Heterocycles: LXI.* Reaction of 3-Aroyl-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones with α-Enamino Esters. Crystalline and Molecular Structure of Methyl 11-Benzoyl-2-*o*-hydroxyphenyl-3,4,10-trioxo-6,9-diphenyl-7-oxa-2,9-diazatricyclo[6.2.1.0^{1,5}]undec-5-ene-8-carboxylate

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Abstract—3-Aroyl-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones react with methyl 4-aryl-2-arylamino-4-oxobut-2-enoate to give substituted methyl 7-aryl-4,9-bis(aroyl)-3-hydroxy-1-(2-hydroxyphenyl)-2,6-dioxo-1,7-diazaspiro[4.4]nona-3,8-diene-8-carboxylates which undergo thermal cyclization to methyl 9-aroyl-4,7-diaryl-1-(2-hydroxyphenyl)-2,3,8-trioxo-2,3,7,8-tetrahydro-1*H*,6*H*-6,8a-methanopyrrolo[2,3-*e*][1,3]oxazepine-6-carboxylates. The crystalline and molecular structures of methyl 9-benzoyl-1-(2-hydroxyphenyl)-2,3,8-trioxo-4,7-diphenyl-2,3,7,8-tetrahydro-1*H*,6*H*-6,8a-methanopyrrolo[2,3-*e*][1,3]oxazepine-6-carboxylate was studied by X-ray analysis.

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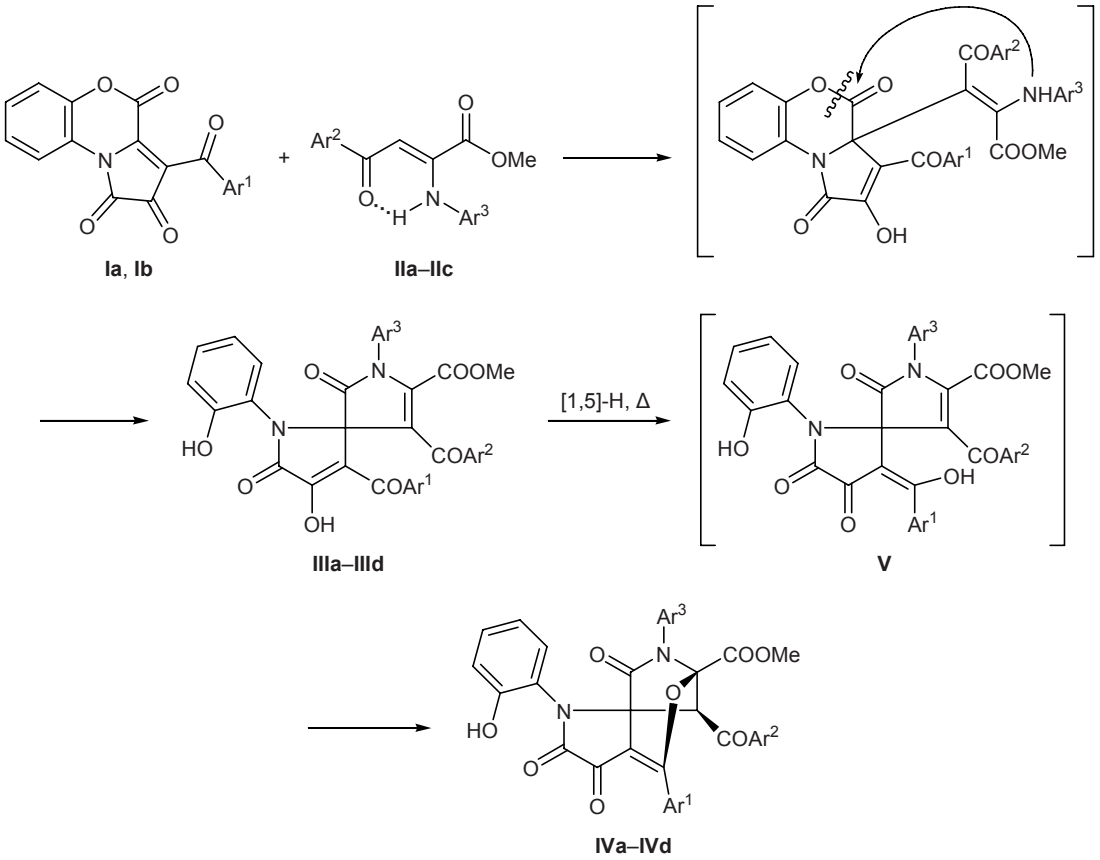
Substituted 4-acyl-2,3-dihydro-1*H*-pyrrole-2,3-diones, including those fused at the [*a*] side to nitrogen-containing heterocycles (hetareno[*a*]pyrrole-2,3-diones), are capable of reacting with difunctional nucleophiles to produce a broad spectrum of fused and spiro-fused heterocyclic systems [2, 3]. We previously showed that 4-acyl-2,3-dihydro-1*H*-pyrrole-2,3-diones fused to a 1,4-benzoxazine fragment, namely 3-aroyl-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones react with acyclic enamino ketones and β-enamino esters as 1,3-C,N-binucleophiles according to a scheme including successive attacks by the β-CH and NH groups of the enamine on the C^{3a} and C^4 atoms of pyrrolobenzoxazinetrione, respectively. These reactions are accompanied by opening of the 1,4-oxazine ring at the C^4–O^5 bond and lead to the formation of substituted 4-aroyl-3-hydroxy-1-(*o*-hydroxyphenyl)-1,7-diazaspiro[4.4]-nona-3,8-diene-2,6-diones and alkyl 4-aroyl-3-hydroxy-1-(2-hydroxyphenyl)-2,6-dioxo-1,7-diazaspiro-[4.4]nona-3,8-diene-9-carboxylates [4, 5].

In continuation of our studies on reactions of hetarene-fused pyrrole-2,3-diones with binucleophiles in the present work we examined reactions of 3-aroyl-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones **Ia** and **Ib** with methyl 4-aryl-2-arylamino-4-oxobut-2-enoates **IIa**–**IIc** as potential 1,3-C,N-binucleophiles (α-enamino esters). Compounds **Ia** and **Ib** reacted with esters **IIa**–**IIc** at a ratio of 1:1 in boiling anhydrous benzene to give in 20–25 min (the dark violet color typical of initial pyrrolobenzoxazinetriones **I** disappeared) substituted methyl 7-aryl-4,9-bisaroyl-3-hydroxy-1-(2-hydroxyphenyl)-2,6-dioxo-1,7-diazaspiro-[4.4]nona-3,8-diene-8-carboxylates **IIIa**–**IIId** in high yield (Scheme 1). Attempted recrystallization of compounds **IIIa**–**IIId** from ethyl acetate resulted in their cyclization to methyl 9-aroyl-4,7-diaryl-1-(2-hydroxyphenyl)-2,3,8-trioxo-2,3,7,8-tetrahydro-1*H*,6*H*-6,8a-methanopyrrolo[2,3-*e*][1,3]oxazepine-6-carboxylates **IVa**–**IVd** whose structure was proved by X-ray analysis of a single crystal of **IVb**.**

* For communication LX, see [1].

** For preliminary communication, see [6].

Scheme 1.

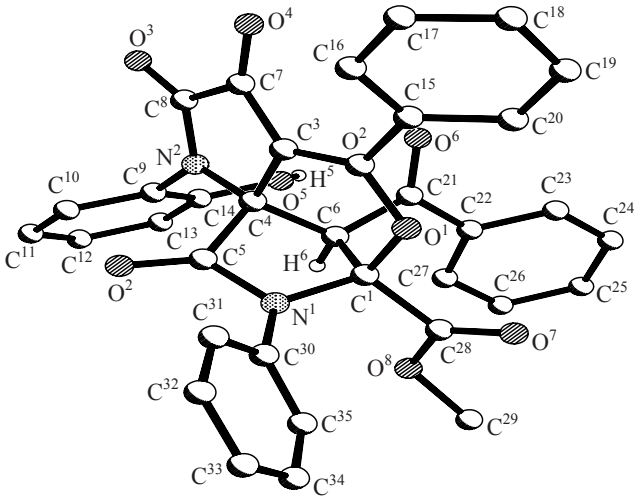


I, Ar^1 = Ph (**a**), 4-BrC_6H_4 (**b**); **II**, Ar^2 = Ph, Ar^3 = 4-MeC_6H_4 (**a**); Ar^2 = Ar^3 = Ph (**b**); Ar^2 = 4-$EtOC_6H_4$, Ar^3 = 4-MeC_6H_4 (**c**); **III**, **IV**, Ar^1 = Ar^2 = Ph, Ar^3 = 4-MeC_6H_4 (**a**); Ar^1 = Ar^2 = Ar^3 = Ph (**b**); Ar^1 = Ph, Ar^2 = 4-$EtOC_6H_4$, Ar^3 = 4-MeC_6H_4 (**c**); Ar^1 = 4-BrC_6H_4, Ar^2 = 4-$EtOC_6H_4$, Ar^3 = 4-MeC_6H_4 (**d**).

Compounds **IIIa**–**IIId** are light yellow crystalline substances which melt at high temperature with decomposition; they are readily soluble in dimethylformamide and dimethyl sulfoxide, poorly soluble in common organic solvents, and insoluble in saturated hydrocarbons and water. Compounds **IIIa**–**IIId** showed a positive test (cherry color) for enolic and phenolic hydroxy groups on treatment with an alcoholic solution of iron(III) chloride.

The IR spectra of **IIIa**–**IIId** contained absorption bands due to stretching vibrations of hydroxy groups (a broad band at 3150–3170 cm^{-1}), ester (1760–1772 cm^{-1}) and lactam carbonyl groups (two peaks in the region 1723–1737 cm^{-1}), and acetyl and aroyl carbonyl groups (two peaks in the region 1620–1675 cm^{-1}). In the ^1H NMR spectra of solutions of **IIIa**–**IIId** in DMSO-d_6 we observed signals from protons in the aromatic rings and substituents attached thereto, a singlet from the ester methoxy group (δ 3.20–3.34 ppm), a singlet from the phenolic hydroxy proton (δ 9.80–9.84 ppm), and a broadened singlet from the enolic proton (δ 12.50–12.60 ppm). The spectral parameters of compounds **IIIa**–**IIId** resemble those reported for analogous 4-aroyl-3-hydroxy-1-(*o*-hydroxyphenyl)-1,7-diazaspiro[4.4]nona-3,8-diene-2,6-diones [4, 5] and substituted spiro[indole-3,2′-pyrroles] [1] whose structure was proved by X-ray analysis.

Compounds **IVa**–**IVd** are colorless crystalline substances with high decomposition points; they are readily soluble in dimethylformamide and dimethyl sulfoxide, poorly soluble in common organic solvents, and insoluble in saturated hydrocarbons and water. Compounds **IVa**–**IVd** showed a positive test (cherry color) for phenolic hydroxy group on treatment with an alcoholic solution of iron(III) chloride. In the IR spectra of **IVa**–**IVd**, stretching vibrations of the O–H group appeared as a broad band at 3220–3241 cm^{-1}, the ester carbonyl group gave rise to absorption at 1767–1776 cm^{-1}, one or two peaks in the region 1721–



Structure of the molecule of methyl 9-benzoyl-1-(2-hydroxyphenyl)-2,3,8-trioxo-4,7-diphenyl-2,3,7,8-tetrahydro-1*H*,6*H*-6,8a-methanopyrrolo[2,3-*e*][1,3]oxazepine-6-carboxylate (**IVb**) according to the X-ray diffraction data.

1756 cm^{-1} corresponded to the lactam and ketone (C^3=O) carbonyl groups, and the band at 1700–1709 cm^{-1} was assigned to the aroyl carbonyl group. Compounds **IVa**–**IVd** displayed in the ^{1}H NMR spectra (DMSO-d_6) signals from aromatic protons and protons in the substituents at the aromatic rings; protons of the ester methoxy group resonated as a singlet at δ 3.22–3.34 ppm, the 9-H signal appeared as a singlet at δ 5.15–5.29 ppm, and the OH proton gave a singlet at δ 9.91–10.01 ppm. The ^{13}C NMR spectrum of **IVd** in DMSO-d_6 contained the following signals, δ_C, ppm: 189.11 (**C**OC_6H_4), 176.95 (C^4=O), 167.87 and 163.07 (C^8=O, C^2=O), 159.80 (**C**OOMe), 154.07 (C^{4a}), 137.68–106.49 (C_{arom}), 92.44 (C^6), 65.29 (C^{8a}), 63.72 (C^9), 53.76 (OCH_2), 44.52 (OCH_3), 20.49 (CH_3), 14.40 (CH_2**C**H_3).

The structure of molecule **IVb** is shown in figure. All double bonds in structure **IVb** are localized. The bond lengths and bond angles do not differ from the corresponding standard values. Molecules **IVb** in crystal are linked to centrosymmetric dimers through intermolecular hydrogen bonds O^5–$H^5\cdots O^3$ ($-x+1$, $-y$, $-z+1$) with the following parameters O^5–H^5 0.880, $H^5\cdots O^3$ 1.846, $O^5\cdots O^3$ 2.704 Å, $\angle O^5H^5O^3$ 164.68°.

Presumably, the reaction follows a scheme analogous to that proposed by us previously [1, 4, 5]. In the first step, the activated β-CH group of the enamino fragment in ester **II** adds at the C^{3a} carbon atom of pyrrolobenzoxazinetrione **I**. The subsequent *Z*–*E* isomerization, pyrrole ring closure via intramolecular attack by the free amino group on the lactone carbonyl carbon atom in the benzoxazine ring, and cleavage of the latter at the C^4–O^5 bonds yields 2,3′-spiro-fused bipyrroles **III**. Intramolecular cyclization of compounds **III** to bridged structures **IV** on attempted recrystallization from ethyl acetate involves addition of the enolic hydroxy group in hydroxymethylidene tautomer **V** at the C^5 atom of the neighboring pyrrole ring. We believe that the presence of an electron-withdrawing methoxycarbonyl group in position *8* of 1,7-diazaspiro[4.4]nona-3,8-diene-8-carboxylates **III** enhances electrophilicity of C^8 as compared to structurally related compounds reported by us previously [1, 4, 5], thus favoring intramolecular nucleophilic attack by the enolic hydroxy group.

The described reaction is the first example of intramolecular cyclization of 1,7-diazaspiro[4.4]nona-3,8-diene-8-carboxylates with selective formation of difficultly accessible bridged 6,8a-methanopyrrolo[2,3-*e*]-[1,3]oxazepine system.

EXPERIMENTAL

The IR spectra were recorded on an FSM-1201 spectrometer from samples dispersed in mineral oil. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-400 instrument (at 400 MHz for ^{1}H) from solutions in DMSO-d_6 using tetramethylsilane as internal reference. The purity of the products was checked by TLC on Silufol plates using ethyl acetate or ethyl acetate–benzene (1:5) as eluent; spots were visualized by treatment with iodine vapor.

Methyl 4,9-dibenzoyl-3-hydroxy-1-(2-hydroxyphenyl)-7-(4-methylphenyl)-2,6-dioxo-1,7-diazaspiro[4.4]nona-3,8-diene-8-carboxylate (IIIa). A solution of 1.0 mmol of compound **Ia** and 1.0 mmol of ester **IIa** in 10 ml of anhydrous benzene was heated for 25 min under reflux (the mixture turned colorless). The mixture was cooled, and the precipitate was filtered off, and washed with ethyl acetate (2×1 ml) and hexane (5 ml). Yield 85%, mp 184–185°C. IR spectrum, ν, cm^{-1}: 3170 br (OH), 1760 (COOMe), 1732 (C^6=O), 1727 (C^2=O), 1675 and 1625 (4-C=O, 9-C=O). ^{1}H NMR spectrum, δ, ppm: 3.23 s (3H, OMe), 2.25 s (3H, Me), 6.92–7.97 m (18H, H_{arom}), 9.84 s (1H, OH, phenol), 12.50 br.s (1H, OH, enol). Found, %: C 70.32; H 4.16; N 4.58. $C_{36}H_{26}N_2O_8$. Calculated, %: C 70.35; H 4.26; N 4.56.

Compound **IIIb**–**IIId** were synthesized in a similar way.

Methyl 4,9-dibenzoyl-3-hydroxy-1-(2-hydroxyphenyl)-2,6-dioxo-7-phenyl-1,7-diazaspiro[4.4]-nona-3,8-diene-8-carboxylate (IIIb). Yield 87%,

mp 200–202°C. IR spectrum, ν, cm^{-1}: 3152 br (OH), 1770 (COOMe), 1737 (C^6=O), 1724 (C^2=O), 1672 and 1620 (4-C=O, 9-C=O). ^{1}H NMR spectrum, δ, ppm: 3.20 s (3H, OMe), 7.10–7.98 m (19H, H_{arom}), 9.80 s (1H, OH, phenol), 12.60 br.s (1H, OH, enol). Found, %: C 70.10; H 4.00; N 4.55. $C_{35}H_{24}N_2O_8$. Calculated, %: C 70.00; H 4.03; N 4.66.

Methyl 4-benzoyl-9-(4-ethoxybenzoyl)-3-hydroxy-1-(2-hydroxyphenyl)-7-(4-methylphenyl)-2,6-dioxo-1,7-diazaspiro[4.4]nona-3,8-diene-8-carboxylate (IIIc). Yield 86%, mp 189–190°C. IR spectrum, ν, cm^{-1}: 3152 br (OH), 1772 (COOMe), 1736 (C^6=O), 1723 (C^2=O), 1673 and 1622 (4-C=O, 9-C=O). ^{1}H NMR spectrum, δ, ppm: 1.23 t (3H, C**H**$_3$CH$_2$, J = 6.9 Hz), 2.24 s (3H, Me), 3.34 s (3H, OMe), 3.52 q (2H, OCH_2, J = 6.9 Hz), 7.08–7.90 m (17H, H_{arom}), 9.82 s (1H, OH, phenol), 12.60 br.s (1H, OH, enol). Found, %: C 69.19; H 4.50; N 4.26. $C_{38}H_{30}N_2O_9$. Calculated, %: C 69.29; H 4.59; N 4.25.

Methyl 4-(4-bromobenzoyl)-9-(4-ethoxybenzoyl)-3-hydroxy-1-(2-hydroxyphenyl)-7-(4-methylphenyl)-2,6-dioxo-1,7-diazaspiro[4.4]nona-3,8-diene-8-carboxylate (IIId). Yield 86%, mp 209–210°C. IR spectrum, ν, cm^{-1}: 3150 br (OH), 1770 (COOMe), 1736 (C^6=O), 1723 (C^2=O), 1671 and 1620 (4-C=O, 9-C=O). ^{1}H NMR spectrum, δ, ppm: 1.23 t (3H, C**H**$_3$CH$_2$, J = 6.9 Hz), 2.24 s (3H, Me), 3.30 s (3H, OMe), 3.50 q (2H, OCH_2, J = 6.9 Hz), 7.17–7.87 m (16H, H_{arom}), 9.83 s (1H, OH, phenol), 12.60 br.s (1H, OH, enol). Found, %: C 61.76; H 3.92; Br 10.84; N 3.76. $C_{38}H_{29}BrN_2O_9$. Calculated, %: C 61.88; H 3.96; Br 10.83; N 3.80.

Compounds **IVa**–**IVd** were obtained by recrystallization of 1.0 mmol the corresponding compound **IIIa**–**IIId** from ethyl acetate.

Methyl 9-benzoyl-1-(2-hydroxyphenyl)-7-(4-methylphenyl)-2,3,8-trioxo-4-phenyl-2,3,7,8-tetrahydro-1*H*,6*H*-6,8a-methanopyrrolo[2,3-*e*][1,3]-oxazepine-6-carboxylate (IVa). Yield 90%, mp 190–191°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 3230 br (OH), 1770 (COOMe), 1755 (C^2=O), 1724 (C^3=O, C^8=O), 1700 (COPh). ^{1}H NMR spectrum, δ, ppm: 2.24 s (3H, Me), 3.23 s (3H, OMe), 5.25 s (1H, 9-H), 6.92–7.97 m (18H, H_{arom}), 10.01 s (1H, OH). Found, %: C 70.28; H 4.21; N 4.49. $C_{36}H_{26}N_2O_8$. Calculated, %: C 70.35; H 4.26; N 4.56.

Methyl 9-benzoyl-1-(2-hydroxyphenyl)-2,3,8-trioxo-4,7-diphenyl-2,3,7,8-tetrahydro-1*H*,6*H*-6,8a-methanopyrrolo[2,3-*e*][1,3]oxazepine-6-carboxylate (IVb). Yield 92%, mp 201–203°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 3227 br (OH), 1776 (COOMe), 1751 (C^2=O), 1721 (C^3=O, C^8=O), 1707 (COPh). ^{1}H NMR spectrum, δ, ppm: 3.22 s (3H, OMe), 5.29 s (1H, 9-H), 6.94–7.98 m (19H, H_{arom}), 10.01 s (1H, OH). Found, %: C 69.89; H 4.07; N 4.70. $C_{35}H_{24}N_2O_8$. Calculated, %: C 69.92; H 4.03; N 4.66.

Methyl 9-(4-ethoxybenzoyl)-1-(2-hydroxyphenyl)-7-(4-methylphenyl)-2,3,8-trioxo-4-phenyl-2,3,7,8-tetrahydro-1*H*,6*H*-6,8a-methanopyrrolo-[2,3-*e*][1,3]oxazepine-6-carboxylate (IVc). Yield 93%, mp 197–198°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 3241 br (OH), 1775 (COOMe), 1756 (C^2=O, C^3=O, C^8=O), 1709 (COC_6H_4). ^{1}H NMR spectrum, δ, ppm: 1.35 t (3H, C**H**$_3$CH$_2$, J = 7.0 Hz), 2.33 s (3H, Me), 3.33 s (3H, OMe), 4.13 q (2H, OCH_2, J = 7.0 Hz), 5.15 s (1H, 9-H), 6.89–7.92 m (17H, H_{arom}), 9.91 s (1H, OH). Found, %: C 69.24; H 4.60; N 4.19. $C_{38}H_{30}N_2O_9$. Calculated, %: C 69.29; H 4.59; N 4.25.

Methyl 4-(4-bromophenyl)-9-(4-ethoxybenzoyl)-1-(2-hydroxyphenyl)-7-(4-methylphenyl)-2,3,8-trioxo-2,3,7,8-tetrahydro-1*H*,6*H*-6,8a-methanopyrrolo-[2,3-*e*][1,3]oxazepine-6-carboxylate (IVd). Yield 93%, mp 210–211°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 3220 br (OH), 1767 (COOMe), 1753 (C^2=O), 1721 (C^3=O, C^8=O), 1707 (COC_6H_4). ^{1}H NMR spectrum, δ, ppm: 1.34 t (3H, C**H**$_3$CH$_2$, J = 7.0 Hz), 2.25 s (3H, Me), 3.34 s (3H, OMe), 4.13 q (2H, OCH_2, J = 7.0 Hz), 5.15 s (1H, 9-H), 6.81–7.91 m (16H, H_{arom}), 9.91 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 189.11 (9-CO), 176.95 (C^3), 167.87 and 163.07 (C^8, C^2O), 159.80 (**C**OOMe), 154.07 (C^{3a}), 137.68–106.49 (C_{arom}), 92.44 (C^6), 65.29 (C^{8a}), 63.72 (C^9), 53.76 (OCH_2), 44.52 (OCH_3), 20.49 (**C**H$_3$C$_6$H$_4$), 14.40 (CH$_2$**C**H$_3$). Found, %: C 61.85; H 3.94; Br 10.79; N 3.82. $C_{38}H_{29}BrN_2O_9$. Calculated, %: C 61.88; H 3.96; Br 10.83; N 3.80.

X-Ray diffraction data for compound IVb. Triclinic crystals, $C_{35}H_{24}N_2O_8$, with the following unit cell parameters: a = 11.162(2), b = 11.521(2), c = 12.389(3) Å; α = 103.37(3), β = 103.64(3), γ = 98.03(3)°; V = 1474.2(5) Å^3; M 600.56; d_{calc} = 1.353 g× cm^{-3}; Z = 2; space group P-1. The experimental reflection intensities were measured on a KM-4 Kuma Diffraction automatic four-circle diffractometer (χ-4 geometry, monochromatized MoK_α irradiation, ω/2Θ scanning, 2Θ ≤ 50.2°). Total of 5232 independent reflections were measured (R_{int} = 0.0289) with no correction for absorption (μ = 0.097 mm^{-1}). The structure was solved by the direct method using SIR92 program [7] with subsequent calculation of the electron density maps. Hydrogen atoms on O^5 and C^6 were localized by

difference synthesis of electron density, and positions of the other hydrogen atoms were set on the basis of geometry considerations. Full-matrix least-squares anisotropic refinement of positions of non-hydrogen atoms (SHELXL-97 [8]) was terminated at R_1 = 0.0498 [2631 reflections with $I \geq 2\sigma(I)$]; goodness of fit 0.986.

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