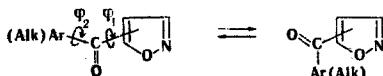


CONFORMATIONS OF CARBONYL DERIVATIVES
OF ISOXAZOLE IN SOLUTION

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We have continued our work on the s-cis, trans isomerism of carbonyl derivatives of azoles by using dipole moment measurements to examine the solution conformations of some isoxazolyl ketones (I)-(IV) (Table 1).



The conjugation of two aromatic radicals with the carbonyl group is known to be a mixture when they are coplanar. Nevertheless the coplanarity of hetaryl phenyl ketones is often prevented by steric interactions.

The nonplanarity of these molecules can be characterized by the dihedral angles φ_1 and φ_2 . Both rings compete with each other for maximum conjugation with the carbonyl group. Work using various techniques has established that the hetaryl radicals are more susceptible than phenyl rings to conjugation with carbonyl and consequently that $\varphi_1 \ll \varphi_2$ [1-4].

Among monoheterocyclic compounds, the closest analogs of 5- and 4-acylisoxazoles are the equivalent furan derivatives [5, 6]. Dipole moment and Kerr effect measurements and NMR spectroscopy have revealed that in 2-furyl phenyl ketones the angle $\varphi_1 = 0^\circ$ while φ_2 can vary within the limits $\pm 50-70^\circ$; the content of the O,O-cis form in the solution varies from 100 to 50%, depending on the nature of the substituent on the furan ring [7, 8].

We have found that both conformers of 3-methyl-5-benzoylisoxazole (I) are also present in solution (Table 1) but that as a result of the presence of the second heteroatom—the nitrogen atom—the content of the N,O-cis form is much lower. Here, as in furyl phenyl ketones, steric interactions cause the phenyl fragment to emerge from the trigonal plane of the carbonyl through $\varphi_2 = 50-70^\circ$. We were unable to find the angle φ_2 from Kerr effect measurements, having no accurate value for the polarizability tensor of isoxazole. However, the extremely low experimental Kerr constants of compounds (I)-(IV) [$K_E = 46 \times 10^{-12}$ for (I); 20×10^{-12} for (II); 469×10^{-12} for (III); and 290×10^{-12} for (IV)] indirectly imply that the two rings are not coplanar.

The isomeric 5-methyl-3-benzoylisoxazole (II) exists solely as the N,O-trans form in solution. The major factor responsible for the stabilization of this structure is the Coulomb repulsion of the similarly charged pyridine-type nitrogen atom and the carbonyl oxygen, as in α -carbonylpyridines [9, 10].

Dipole moment measurements indicate that 3-acetyl-5-phenylisoxazole (III) also exists almost solely as the N,O-trans form; moreover the value of the dipole moment does not exclude the possibility that in this case the acetyl group may lie slightly out of the plane of the heterocycle. The experimental dipole moment is almost identical to the calculated value for dihedral angle $\varphi_1 = 20^\circ$ ($\mu_{\text{calc}} = 2.30 \text{ D}$ at 20°C). This is in good agreement with work on 2-acetylpyridines [11], -thiophenes [12], etc., which are not planar but have $\varphi_1 \sim 25-30^\circ$.

Conversely, in 3-phenyl-4-acetylisoxazole (IV), where the effect of the ring heteroatoms is significantly reduced by their considerable separation from the conformationally mobile group, both conformations become almost equally probable with a slight predominance of the N,O-cis form. In this case the maximum conjugation of the π -system of the heterocycle and the carbonyl double bond seems to be the decisive factor. The hypothesis that the acetyl group and isoxazole ring are coplanar is not contradicted by the value of the dipole

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TABLE 1. Experimental and Calculated Dipole Moments and Conformer Ratios of Carbonyl Derivatives of Isoxazole (CCl₄ Solution)

No.	Compound	Concen- tration range, wt. % · 10 ²	∞P_2 , cm ³	R_E , cm ³	μ, D	$\mu_{\text{calc}, D}$		Content of N, O-trans form, %
						N,O-cis	N,O-trans	
I	3-methyl-5-benzoyl-isoxazole	0.41—0.71	160,901	54,075	2.26	5.66	1.02	87
II	3-benzoyl-5-methyl-isoxazole	0.35—1.47	132,298	54,679	1.92	6.03	1.97	100
III	3-acetyl-5-phenylisoxazole	0.22—0.91	157,564	55,582	2.21	5.38	1.81	94
IV	3-phenyl-4-acetyl-isoxazole	0.26—1.12	189,249	54,958	2.54	2.71	2.14	32

moment. The conformer ratio is identical to the published figure for 4-formylpyrazole derived from NMR spectroscopy [13], which shows it to be a mixture of equal amounts of both conformers. In the case of β -carbonyl derivatives of pyridine the content of the N,O-trans form to 70–73% is also reduced [7, 14]. Extended Hückel and Dewar σ, π quantum-chemical calculations support the equiprobability of both forms for 4-carbonyl-containing isoxazoles ($-\Delta E = 0.8$ kJ/mole) [15].

Thus, in these isoxazolyl ketones the hetaryl-CO- fragment is in general almost planar. The structures correspond to the maximum distance between the similarly charged atoms and an energy gain in conjugation. The nonplanarity of isoxazolyl phenyl ketones, like furyl ketones, is effected by rotation of the phenyl fragment out of the plane of the rest of the molecule. The conformational equilibrium state depends significantly on the position of the rotating group in the hetero ring and can vary within wide limits.

EXPERIMENTAL

Spectra were recorded on: PMR: a Jeol C-60 with hexamethyldisiloxane (HMDS) as internal standard; UV: a Hitachi ESP-3 in ethanol; and IR: a Perkin-Elmer 457 in Vaseline oil. Dielectric constants were measured with an accurate BM-400G-Tesla capacitance bridge; densities were measured hydrostatically. Dipole moments were calculated from the Fuit equation [19] to ± 0.2 D (at 25°C). Kerr constants were measured and calculated by the procedure described earlier [20].

Values and directions of group moments were taken from figures for aromatic methyl ketones in the case of the acetyl group [19] and from figures for benzophenone for the C-benzoyl group [21]. The value and orientation of the dipole moment and the geometry of isoxazole came from microwave work [22]. The error in the determination of the conformer ratios did not exceed 3–5%.

The solvent was CCl₄, purified by the procedure of [23].

3-Benzoyl-5-methylisoxazole (II). To a suspension of aluminum chloride (12.4 g, 0.093 mole) in absolute benzene (25 ml) cooled by ice-water was added a solution of 3-methylisoxazole-4-carbonyl chloride (4.4 g, 0.03 mole) in benzene (25 ml). The reaction mixture was stirred at 20°C for 2 days and then poured onto ice and the organic layer was separated. The aqueous layer was extracted with benzene. After removal of the solvent, the residue was distilled under vacuum and the fraction with bp 157–159°C (7 mm) was collected. The yield was 3.2 g (57%), mp 44–45°C after recrystallization (from hexane and ethanol). PMR spectrum (in CCl₄): 2.38 (3H, s, CH₃), 6.36 (1H, s, isoxazole 4-H), 7.15–7.62 (3H, m, m aromatic protons), 8.05–8.45 (2H, m, o aromatic protons). UV spectrum: λ_{max} 261 nm (log ε 4.09). IR spectrum: 1660 cm⁻¹ (C=O). Found: C 70.5; H 4.8; N 7.5%. C₁₁H₉NO₂. Calculated: C 70.6; H 4.9; N 7.5%.

3-Methyl-5-benzoylisoxazole (I) was prepared in the same way from the appropriate isoxazolcarbonyl chloride. The yield was 70%, bp 160–162°C (7 mm), mp 70.5–71.5°C (from petroleum ether) [16]. 3-Acetyl-5-phenylisoxazole (III) and 3-phenyl-4-acetylisoxazole (IV) were prepared by literature methods [17, 18].

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STUDIES IN THE ISOXAZOLE SERIES.

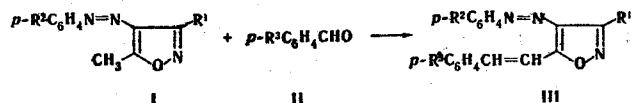
36.* CONDENSATION OF 4-ARYLAZO-5-METHYL-ISOXAZOLES WITH AROMATIC ALDEHYDES

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The introduction of electron-accepting substituents into position 4 of isoxazole activates the methyl group on the C₍₅₎ atom in aldol condensation-crotonization reactions. As a result, 5-methylisoxazoles containing nitro [2-4], benzoyl, and cyano [5] groups can be condensed with benzaldehyde; moreover in 3,5-dimethylisoxazole derivatives condensation takes place selectively at 5-methyl group [2, 5]. The phenylazo group has not been demonstrated to have this effect in isoxazole, although instances have been described in the aromatic series [6, 7].

Despite the roughly identical chemical shifts of the 5-methyl protons in the PMR spectra of 4-phenylazo- and 4-nitro-3,5-dimethylisoxazoles, deuterium exchange at the 5-CH₃ group of the 4-nitro derivative proceeds much more rapidly than in the 4-phenylazo compound [8]. We have found that 4-phenylazo-5-methylisoxazoles also condense with aromatic aldehyde in the presence of a stronger base (KOH instead of piperidine) and that the reaction takes place selectively at the 5-CH₃ group.



I, III a-f R³=H; a R¹=CH₃, R²=H; b R¹=R²=CH₃; c R¹=CH₃, R²=OCH₃; d R¹=CH₃, R²=Br; e R¹=C₆H₅, R²=H; f R¹=CH₃, R²=NO₂; II, III g-k R¹=CH₃; g R²=H, R³=NO₂; h R²=NO₂, R³=NO₂; i R²=H, R³=N(CH₃)₂; k R²=NO₂, R³=N(CH₃)₂

The UV spectra of the synthetic 5-styryl-3-methyl-4-phenylazoisoxazole (IIIa)-(IIId), (IIIe)-(IIIf)-(IIIk) resemble that of 5-styryl-3-phenyl-4-phenylazoxazole (IIIe) (Table 1). In the PMR spectra of compounds (III) the

*For communication 35 see [1].