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SYNTHESIS AND SPECTRAL PROPERTIES OF 2-METHYL-5-ARYL-1,3,4-OXADIAZOLES

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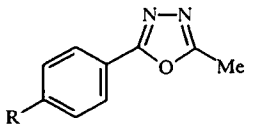
By heterocyclization of 1-acyl-2-aroylhydrazines under the influence of strong dehydrating substances, a series of 2-methyl-5-aryl-1,3,4-oxadiazoles has been synthesized and their UV, IR, and PMR spectra have been investigated. Through analysis of data on the influence of substituents on the position of the maximum in the electronic absorption spectrum, together with calculated data, it has been shown that the long-wave band of 2-methyl-5-phenyl-1,3,4-oxadiazole is due to an S_0–S_1 transition of the π–π^* type and that it is a charge transfer band for transfer from the phenyl radical to the oxadiazole ring; the 1,3,4-oxadiazole ring as a substituent has an electron-acceptor character.

Various 2,5 derivatives of 1,3,4-oxadiazoles have been proposed for use in various applications: optical brightening, fabric dyes, laser dyes, scintillation equipment, light stabilizers for polymeric materials, pesticides, etc. However, this broad spectrum of applied research has not been combined with the same sort of attention to working out theoretical questions, in particular those concerned with the aromaticity of the heterocycle and its electronic nature and transmission capability. In our opinion, it is desirable to obtain detailed information on these questions by examining simple model objects. For this purpose, we selected functionally para-substituted 2-methyl-5-aryl-1,3,4-oxadiazoles:



I–IX

I) R = H; II) R = *a*-naphthyl; III) R = Ph; IV) R = OMe; V) R = NMe_2; VI) R = Br; VII) R = COOMe; VIII) R = SO_2CHF_2; IX) R = NO_2

Along with the possibility of resolving theoretical questions in obtaining these compounds, we took into account their practical properties: possible short-time fluorescence and the presence of the reactive methyl group. This methyl group has CH-acid properties, providing a means for conversion to compounds with a more complex structure.

There are hardly any special studies reported in the literature on the synthesis and investigation of chemical properties of 2-alkyl-5-aryl-1,3,4-oxadiazoles, with the exception of two studies [1, 2]. Of the methods of synthesis that have been proposed for obtaining 2-alkyl-5-aryl derivatives, we will take note of three methods that are the most universal: interaction of aroylhydrazines with an iminomethyl [3] or orthoethyl [4] ester of the corresponding aliphatic acid, and interaction of an aroylhydrazine with an aliphatic acid chloride or anhydride, followed by cyclization of the resulting 1-acyl-2-aroylhydrazine in the presence of dehydrating substances [5].

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TABLE 1. Substituted 2-Methyl-5-phenyl-1,3,4-oxadiazoles

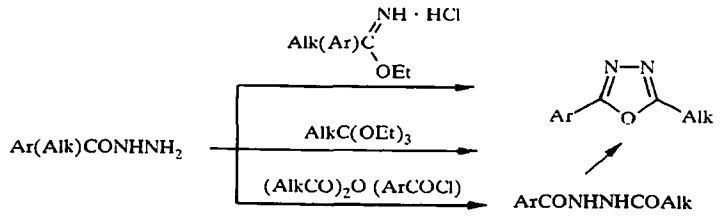
Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Electronic absorption spectrum. λ_{max}, nm (and $\varepsilon \cdot 10^{-4}$)		PMR spectrum, δ, ppm				IR spectrum, ν, cm^{-1}		Yield, %
		C	H	N		ethanol	heptane	CH_3	Ph			C–H (CH_3) (CCl_4)	1,3,4-oxadiazole ring (KBr)	
									H_o	H_M	H_R			
I*	$C_9H_8N_2O$				64...65	250 (1,72)	250 (1,66)	2,625	8,03	7,51		2838, 2908, 2935, 2960	1610, 1581, 1467, 1080, 1040, 980, 947, 653, 627	41
II	$C_{13}H_{10}N_2O$	74,5 / 74,3	4,5 / 4,8	13,1 / 13,3	153...155	285 (0,88)								84
III	$C_{15}H_{12}N_2O$				161...162	285 (3,95)		2,628	8,10	7,71	7,53...7,39	2862, 2940, 2980		87
IV*	$C_{10}H_{10}N_2O_2$	63,4 / 63,1	5,0 / 5,2	15,1 / 14,9	85...86	270 (2,96)		2,606	7,93	6,96	3,89	2834, 2908, 2927, 2940, 2955	1616, 1560, 1466, 1080, 1040, 980, 953, 660, 627	38
V*	$C_{11}H_{13}N_3O$	65,3 / 65,0	6,2 / 6,4	20,4 / 20,7	170...171	315 (3,40)	302 (2,36)	2,572	7,84	6,70	3,08	2811, 2886, 2897, 2935, 2977	1616, 1553, 1447, 1067, 1040, 974, 953, 660, 627	32
VI†	$C_9H_7N_2OBr$	45,4 / 45,2	2,8 / 2,9	11,8 / 11,7	110...112	260 (2,86)		2,637	7,88	7,61	—	2864, 2875, 2936, 2960, 2978		78
VII	$C_{11}H_{10}N_2O_3$	60,7 / 60,5	4,3 / 4,6	12,7 / 12,8	155...157	265 (1,86)								75
VIII‡	$C_{10}H_8N_2O_3SF_2$	36,8 / 36,5	3,1 / 2,9	10,3 / 10,2	165...166	260 (2,56)								74
IX	$C_9H_7N_3O_3$				170...172	280 (1,97)	287 (1,95)	2,673	8,21	8,36	—	2859, 2933, 2957	1609, 1480, 1080, 1026, 980, 953, 673, 627	83

*Obtained by method of [7].

†Br content: Found 33.9%, calculated 33.5%.

‡S content: Found 11.9%, calculated 11.7%.

By the reaction of acetic anhydride with aroylhydrazines in an inert solvent at room temperature, 1-acetyl-2-aroylhydrazines have been obtained (Stage 1), and these have been heterocyclized by the action of strong dehydrating agents (phosphoryl chloride), forming 2-methyl-5-aryl-1,3,4-oxadiazoles (Stage 2). In the presence of a weak dehydrating agent, acetic anhydride, there is no heterocycle formation (even after refluxing the aroylhydrazines in excess acetic anhydride for several hours).



One of the decisive factors in selecting a method of synthesis is the availability of the original reagents, and hence it is natural to be interested in the third of the above-listed methods, with the use of aliphatic acid chlorides or anhydrides. This method is widely used as a modern preparative and commercial method for the synthesis of 2,5-diaryl-1,3,4-oxadiazoles; consequently, the details of the method have been thoroughly worked out. However, information available on the use of this method to obtain 2-alkyl-5-aryl-1,3,4-oxadiazoles is limited to [1, 2], according to which 2-alkyl-5-aryloxadiazoles are capable of recyclization in acidic media (in the stage of segregating the final product). Let us note, however, that in this case, a stabilizing effect of electron-acceptor substituents was observed, whether these substituents were in the alkyl or the aryl part of the molecule, in the process of hydrolysis. On the basis of this information, compounds VI-IX, which contain electron-acceptor substituents in the phenyl radical, were prepared and isolated under conditions that are normal for this particular method [6].

The unsubstituted compound I and compounds IV and V with donor substituents were obtained by interaction of acetiminoethyl ester with hydrazides of the corresponding aromatic acids, following procedures given in [7]. In these experiments, variations of the solvent (alcohol, dioxane, pyridine, acetic acid) did not give any substantial increases of product yield (30-40% relative to hydrazide).

The influence of the aryl radical (number of aromatic rings) on the susceptibility of the products to acid hydrolysis was not investigated. However, our first attempts at synthesis of compounds with a biphenyl III or naphthyl II substituent by means of the two stage scheme, using excess phosphoryl chloride as the cyclodehydrating agent, proved to be successful. Thus, we have demonstrated the feasibility of obtaining 2-alkyl-5-aryl-1,3,4-oxadiazoles under conditions that are typical for synthesis of 2,5-diaryl derivatives.

The compositions and structures of all of the synthesized compounds were confirmed by elemental analysis and by IR and PMR spectroscopy.

In the PMR spectra, signals are manifested from aromatic protons, the methyl group, and protons of the functional substituents. Signals of the protons of the benzene ring were assigned on the basis of chemical shifts characteristic for derivatives of benzene, along with spin-spin coupling constants corresponding to the ortho position of the hydrogen atoms [8]. The signal of the methyl-group protons of 2-methyl-5-phenyloxadiazole are shifted downfield by 0.125 ppm relative to the analogous signal of 2,5-dimethyloxadiazole [9], probably as a consequence of a stronger donor influence of the methyl group in comparison with phenyl; the signal of the functional substituents is located in the 2.572-2.673 ppm interval and is determined by the position of the substituent in the phenyl radical (see Table 1).

In the IR spectra of the synthesized compounds in the solid phase (KBr tablets), a set of characteristic frequencies of the 1,3,4-oxadiazole ring is clearly manifested; these were identified on the basis of data reported in [10]. For aromatic [11] and heteroaromatic [12] compounds, including 2,5-dimethyl-1,3,4-oxadiazole [10], in the region of stretching vibrations of the methyl-group C–H (2800-3000 cm^{-1}) we observe a broad region of absorption with several maxima. Upon comparing our results on the spectra of solutions of the oxadiazoles in CCl_4 (c = 0.01-0.05 M, Table 1) with the results reported in [10-12], we note that they are in mutual agreement.

Subsequently, we made an attempt to develop a more effective method (in terms of product yield) for the synthesis of compounds with donor substituents. It appeared to us that the simplest way to arrive at a solution of this problem would be

the selection of an appropriate cyclodehydrating agent for the second stage in the third of the methods we have described. Cyclodehydration by means of mild dehydrating agents such as excess acetic anhydride or zinc chloride did not give any positive results. With the acetic anhydride, there was no formation of the heterocycle in the presence of the acetic anhydride; with the zinc chloride, we observed partial conversion. By the use of an equimolar quantity or a twofold excess of phosphoryl chloride, phosphorus pentoxide, or thionyl chloride in hydrocarbon solvents, the heteroring was closed, but the reaction products (as sometimes encountered also in the synthesis of 2,5-diaryl derivatives) precipitated in the form of oily crystals. Conversion of the products to a crystalline state requires treatment with water, which would lead to the appearance of an acidic medium and hence to hydrolysis.

With the aim of isolating and identifying the products from the hydrolysis of 2-methyl-5-phenyloxadiazole in performing the cyclodehydration with excess phosphoryl chloride, we carried out the synthesis of this compound by the typical method [6]. When the reaction mass was poured onto ice, a solution was formed; this was extracted successively with solvents differing in polarity: heptane, benzene, diethyl ether, methylene chloride, chloroform. Instead of the expected products of hydrolysis, i.e., hydrazine derivatives, we recovered only one particular substance from all of the extracts (total yield 85%), which was identified on the basis of melting point, electronic absorption spectrum, and PMR spectrum as 2-methyl-5-phenyloxadiazole. On the basis of this unexpected result, we performed analogous syntheses for compounds IV and V. Here, the same as in the case of compound I, we recovered oxadiazole derivatives, the structure of which was also confirmed by spectroscopic methods. Thus, we have established that 2-methyl-5-aryl-1,3,4-oxadiazoles are not hydrolyzed in acidic media (over the course of a day under the conditions of synthesis) and that they can be obtained by the conventional procedure. It can be assumed that this method will also be general for the series of 2-alkyl-5-aryloxadiazoles as a whole.

Compounds I-VII luminesce upon photoexcitation (both in the crystalline state and in solution) in the violet and blue regions; they may find applications as fluorescent materials, in particular as laser dyes. In view of these results, it is entirely logical to be interested in investigating the spectral and luminescence properties of this series of derivatives of 1,3,4-oxadiazole.

Quantum-chemical calculations of 1,3,4-oxadiazole that is not substituted in positions 2 and 5, performed by the CNDO-CI method [13], showed that the lowest singlet excited state is a state of the $n-\pi^*$ type, and that the maximum of the band formed by this transition lies at 270 nm, while the allowed singlet state of the $\pi-\pi^*$ type is located higher (λ_{max}^{calc} 180 nm). However, in the experimental spectrum, there is no $n-\pi^*$ band, and only the end of the $\pi-\pi^*$ band is observed [14-15]. Addition of a phenyl radical to the oxadiazole ring results in a substantial change of the absorption spectra: In the 220-300 nm region, a single nonstructured band is observed, with a maximum at 245 nm (ε = 18,000) [16]. We have performed quantum-chemical calculations of the electronic structure of phenyloxadiazole and of the absorption spectrum, using the standard PPP procedure with an accounting for the interaction of 20 singly excited configurations. From an analysis of the electronic states it follows that the lowest excited singlet state is a state of the $\pi-\pi^*$ type; i.e., addition of a phenyl radical to the oxadiazole ring results in inversion of the $n-\pi^*$ and $\pi-\pi^*$ levels. The values calculated for the maxima of the absorption bands (λ_{max}^{calc} 251 and 198 nm) are in good agreement with the experimental values; and from a comparison of these numbers, it can be concluded that the long-wave band is due to an $S_0 \rightarrow S_1$ transition of the $\pi-\pi^*$ type and that the excitation forming this band is accompanied by charge transfer from the phenyl radical to the heterocycle. The experimental absorption spectrum of 2-methyl-5-phenyloxadiazole in ethanol is analogous to that of 5-phenyloxadiazole. When substituents differing in electronic nature are introduced into the phenyl radical, the energy of the long-wave transition is lowered, and the perturbing effect correlates with the strength of the electron-donor or acceptor properties (Table 1). Attention is drawn to the following relationship: The maxima of the long-wave bands of compounds with donor substituents undergo a considerably greater bathochromic shift (R = NMe_2, $\Delta\lambda_{max}^{hept}$ = 52 nm) in comparison with compounds with acceptor substituents (R = NO_2, $\Delta\lambda_{max}^{hept}$ = 37 nm) (Table 1). On this basis, we can express several considerations, while keeping our discussion within the framework of qualitative concepts of color theory. Derivatives of 2-methyl-5-phenyloxadiazole can be represented formally as disubstituted benzenes with one fixed substituent (the methyloxadiazoline fragment) and the other substituent variable (para-substituents differing in electronic nature). Then, from a comparison of the relationships observed in the electronic absorption spectra of the disubstituted benzenes in this series, we can conclude that the 1,3,4-oxadiazole ring, as a substituent, has an electron-acceptor character. This influence of the substituents that we have found can also be interpreted to mean that electron-donor substituents reinforce the electron shifts that are characteristic for the excited state of the unsubstituted molecule. On this basis, we can also assume that the oxadiazole ring, in relation to the phenyl radical in the excited state, is an acceptor. Thus, from the experimental data we have obtained on the influence of substituents on the position of the long-wave band, we can conclude that the excitation forming the long-wave band is related to transmission of

electron density from the phenyl radical to the oxadiazole ring. Such an evaluation of the 1,3,4-oxadiazole ring, obtained on the basis of experimental data, is in complete agreement with calculated data on the electronic structure of phenylhydrazole. Quantitative data on the acceptor character of the 1,3,4-oxadiazole ring as a substituent will be presented in subsequent communications.

EXPERIMENTAL

The PMR spectra were taken in a Tesla BS-487B spectrometer with a working frequency of 80 MHz. As a standard we used TMS, and as a solvent deuterochloroform. The IR spectra were recorded on a Specord IR-20 instrument in KBr tablets and in CCl_4 solutions. The electronic absorption spectra of ethanol and heptane solutions were obtained in an SF-4 spectrophotometer.

Compounds II, III, and VI-IX were obtained by the procedure of [6] from acetohydrazide and the corresponding aromatic acid chlorides, or acetic anhydride and hydrazides of the acids. Compounds I, IV, and V were obtained by the procedure of [7]. The individuality of the synthesized substances was monitored by TLC on Silufol UV-254 plates, eluent benzene, development in UV light.

The elemental analyses of compounds II and IV-VIII for C, H, N, Br, and S matched the calculated values.

2-Methyl-5-phenyl-1,3,4-oxazole. To a suspension of 6.8 g (0.05 mole) of benzoylhydrazine in 20 ml of isopropanol, at room temperature with mixing, 5.1 g (0.05 mole) of acetic anhydride was added over the course of 0.5 h. The reaction mixture was then stirred for 2 h additional, and the precipitate was filtered off and dried. The 1-benzoyl-2-acetylhydrazine that was obtained was refluxed in 40 ml of phosphoryl chloride until dissolved (10-15 min), and then the refluxing was continued for 1 h; the solution was cooled, poured onto ice, and extracted with benzene. The solvent was driven off, obtaining 6.5 g (72%) of a white crystalline substance, mp 70°C (from hexane). Electronic absorption spectrum (in ethanol), λ_{max}, nm (and $\varepsilon \cdot 10^{-4}$): 250 (1.72). PMR spectrum ($CDCl_3$) 2.625 (3H, s, CH_3); 7.51-8.03 (Ph).

Compounds IV-V were synthesized analogously. These products were identical to the substances obtained by the procedure of [7] as indicated by melting point, electronic absorption spectra, and PMR spectra.

The characteristics of the compounds that were synthesized here for the first time are listed in Table 1. The constants of the described compounds I, III, and IX correspond to the values given in the literature [2, 17, 18].

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