INVESTIGATION OF SUBSTITUTED 1,3-OXAZOLIDINES USING ^1H AND ^{13}C NMR SPECTROSCOPY

F. A. Alimirzoev, V. P. Lezina, and A. U. Stepanyants

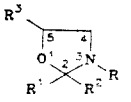
UDC 547.787:543.422.25:541.65

The characteristics of the ^1H and ^{13}C NMR spectra of 1,3-oxazolidines with substituents in the 2-, 3-, and 5-positions have been studied. The relation of the spectral characteristics to the structure and configuration of the compounds has been examined, and information on the transmission of the substituent effect through the atoms of nitrogen and oxygen has been obtained.

1,3-Oxazolidines, nitrogen-containing analogs of five-membered cyclic acetals, which are widely used in organic synthesis, form part of the structure of biologically active and medicinal compounds, and serve as convenient models for studying complex natural products containing the 1,3-oxazolidine fragment. Information about the structure and physicochemical properties of these compounds can also be used to determine the effect of their structural features on biological activity.

At the present time, there is fairly detailed coverage of the structure and analysis of the spectral characteristics of 1,3-dioxanes [1, 2], 1,3-dioxacyclanes and their sulfur-containing analogs [3-5], while data concerning 1,3-oxazolidines is extremely sparse [6]. It was therefore of interest to examine the NMR spectra of 1,3-oxazolidines with a wide range of substituents in order to obtain information about their structure and the transmission of the substituent effect through the nitrogen and oxygen atoms, and also to determine and classify their spectral characteristics.

In the present work the ^1H and ^{13}C NMR spectra of 23 1,3-oxazolidines with substituents at the 2-, 3-, and 5-positions of the ring have been analyzed:



I-XXIII

1. I—VI R=C_6H_5, R^1=R^3=H, I R^2=H, II R^2=$CH(CH_3)_2$, III R^2=C_6H_5, IV R^2=p-$(CH_3)_2NC_6H_4$, V R^2=p-$CH_3OC_6H_4$, VI R^2=m-$NO_2C_6H_4$; 2. VII—XII R=C_3H_7, R^3=H, VII R^1=R^2=H, VIII R^1=H, R^2=C_2H_5, IX R^1=H, R^2=$CH(CH_3)_2$, X R^1=H, R^2=C_6H_5, XI R^1=R^2=*cyclo*-$(CH_2)_4$, XII R^1=R^2=*cyclo*-$(CH_2)_5$; 3. XIII—XVII R=*i*-C_4H_9, R^1=R^3=H, XIII R^2=H, XIV R^2=CH_3, XV R^2=C_2H_5, XVI R^2=$CH(CH_3)_2$, XVII R^2=C_6H_5; 4. XVIII, XIX R=*cyclo*-C_6H_{11}, R^1=R^3=H, XVIII R^2=H, XIX R^2=$CH(CH_3)_2$; 5. XX R=C_2H_5, R^1=R^2=R^3=H; 6. XXI—XXIII R=C_6H_5, R^1=H, R^3=CH_3, XXI R^2=H, XXII**a**, **b** R^2=C_2H_5, XXIII**a**, **b** R^2=$CH(CH_3)_2$

Identification of the signals and the characteristics of the ^1H and ^{13}C NMR spectra, obtained experimentally and with the help of computer analysis, are given in Tables 1-5 and on Figs. 1 and 2. The type of multiplicity of the methylene protons at the 4- and 5-positions (A_2B_2 system) in compounds I, VII, XIII, and XX (Tables 1 and 2) indicates that these compounds undergo a rapid pseudorotation. Verification of assignment of the signals from the 5-CH_2 and 4-CH_2 groups can be provided by the spectrum of compound XXI, in which the protons at $C_{(4)}$ and $C_{(5)}$ give a sharp spectrum of type AMX, which lays the foundation for an unequivocal determination of the distinctive region of their chemical shifts.

Introduction of an alkyl or aryl substituent into the 2-position leads to a nonequivalence of the methylene protons of the ring, the spectrum of which comprises an ABCD spin system in the region 2.8-4.0 ppm. Analysis of this system was carried out by studying the spectra recorded at high frequencies with the inclusion of computer analysis and double

Institute of Chemical Physics, Academy of Sciences of the USSR, Moscow 117977. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1255-1260, September, 1986. Original article submitted April 23, 1985.

0009-3122/86/2209-1017$12.50 © 1987 Plenum Publishing Corporation

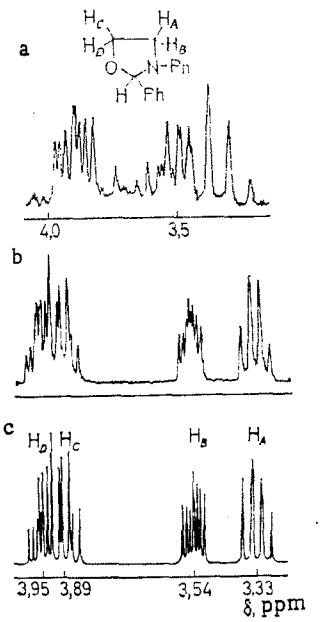


Fig. 1. Experimental and theoretical ^1H NMR spectra of 2,3-diphenyl-1,3-oxazolidine: a) at 100 MHz; b) at 294 MHz; c) calculated for a four-spin system ABCD on BÉSM-22.

resonance experiments (Fig. 1b, 2a, Tables 1-3). A complete interpretation of the spectra of oxazolidines I-XXIII makes it possible to assess the transmission of the substituent effect through the nitrogen and oxygen atoms.

Analysis of the data in Tables 1 and 2 shows that introduction of a substituent into the 2-position leads to a considerably greater displacement downfield of the signals from the protons at $C_{(4)}$ than for those at $C_{(5)}$; in other words, the transmission of the substituent effect through the nitrogen atom is stronger than through the oxygen atom and is virtually independent of the nature of the substituent in the series of compounds investigated. The nature of the substituent on the $C_{(2)}$ carbon atom has virtually no effect on the position of the signals from the protons of the N-phenyl ring.

As was to be expected [7], the methyl protons of compound II are magnetically nonequivalent ($\Delta\delta$ = 1.17 ppm), which is due to the asymmetry of the $C_{(2)}$ atom, in other words, to the presence of a chiral center at the β-position.

TABLE 1. Characteristics of ^1H NMR Spectra of N-Phenyl-1,3-oxazolidines Found Experimentally (recorded at 294 MHz) and Theoretically by Computer Calculation of a Four-Spin System of Type ABCD (in brackets)

Compound	Chemical shifts of ring protons, δ, ppm					Chemical shifts of substituent protons, δ, ppm		Absolute values of spin-spin coupling consants of ring protons, Hz					
	2-H	4-H		5-H									
		A—H	B—H	C—H	D—H	R	R'	$^2J_{AB}$	$^3J_{AC}$	$^3J_{AD}$	$^3J_{BC}$	$^3J_{BD}$	$^2J_{CD}$
I	4,58	3,08	3,08	3,85	3,85	6,25, 7,02, 6,56							
II	4,81	3,23 (3,30)	3,35 (3,45)	3,75 (3,86)	3,93 (4,01)	6,38, 7,15, 6,68	2,05, 0,58, 0,76	8,18 (8,16)	7,15 (7,14)	5,92 (5,92)	3,27 (3,26)	7,77 (7,75)	8,36 (8,36)
III	5,69	3,23 (3,37)	3,45 (3,54)	3,78 (3,89)	3,83 (3,95)	6,32, 6,89, 6,55	7,22	8,18 (7,99)	6,53 (6,53)	6,51 (6,53)	5,51 (5,55)	7,16 (7,14)	8,38 (8,36)
IV	5,64	3,22 (3,34)	3,48 (3,52)	3,73 (3,86)	3,78 (3,91)	6,35, 7,0 6,57	6,5, 7,11 2,8	7,96 (7,97)	6,51 (6,53)	6,51 (6,53)	5,53 (5,55)	7,14 (7,14)	8,36 (8,36)
V	5,67	3,26 (3,32)	3,46 (3,51)	3,81 (3,87)	3,85 (3,94)	6,31, 6,99, 6,55	6,71, 7,21 3,55	8,16 (8,16)	7,16 (7,14)	5,90 (5,92)	3,27 (3,26)	7,73 (7,75)	8,36 (8,26)
VI	5,42	3,27 (3,33)	3,43 (3,53)	3,78 (3,89)	3,82 (3,93)	6,30, 6,97, 6,58	7,38—7,74	8,17 (3,16)	7,15 (7,14)	5,95 (5,92)	3,26 (3,26)	7,75 (7,74)	8,36 (8,36)

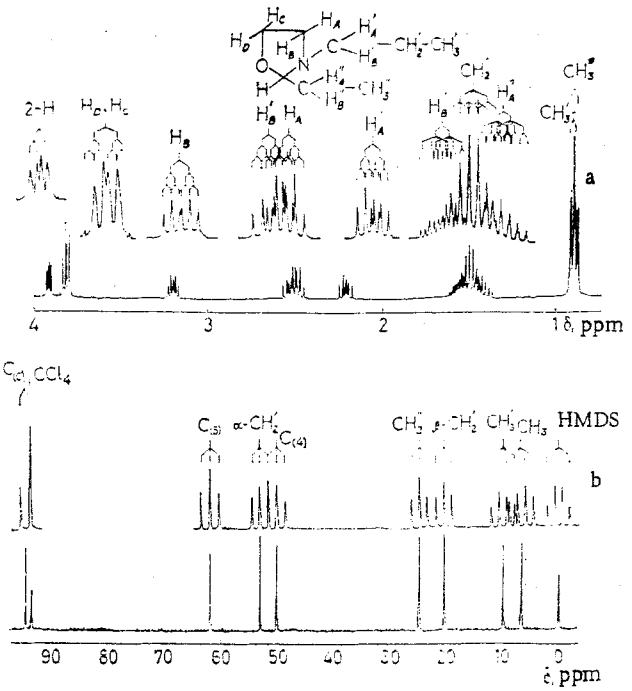


Fig. 2. Assignment of signals in the NMR spectra of 2-ethyl-3-n-butyl-1,3-oxazolidine: a) ^{1}H NMR spectrum at 360 MHz; b) ^{13}C NMR spectra with complete and partial decoupling from protons at 90.55 MHz.

TABLE 2. ^{1}H NMR Chemical Shifts of Substituted 1,3-Oxazolidines

Compound	Ring protons, δ, ppm					Substituents, δ, ppm	
	2-H	4-H		5-H		R	R¹
		A—H	B—H	C—H	D—H		
VII	4,16	2,84	2,84	3,67	3,67	0,88, 1,45, 2,41	
VIII	3,92	2,48	3,2	3,82	3,82	0,89, 1,49, 2,21, 2,53	0,89, 1,42, 1,54
IX	3,72	2,46	3,09	3,68	3,72	0,87, 1,44, 2,22, 2,46	0,82, 0,86, 1,59
X	4,72	2,54	3,23	3,9	3,93	0,83, 1,43, 1,48, 2,19, 2,41	7,23, 7,29, 7,38
XI		2,8	2,8	3,71	3,71	0,84, 1,30, 2,31	1,3—1,8
XII		2,8	2,8	3,7	3,7	0,83, 1,32, 2,3	1,2—1,75
XIII	4,05	2,75	2,75	3,58	3,58	0,87, 1,57, 2,18	
XIV	3,92	2,56	3,14	3,83	3,88	0,85, 0,88, 1,63, 2,03, 2,18	1,14
XV	3,85	2,4	3,11	3,74	3,74	0,85, 0,88, 1,63, 2,06, 2,18	0,86, 1,39, 1,51
XVI	4,87	2,36	3,04	3,63	3,68	0,83, 0,88, 1,59, 2,05, 2,18	0,80, 0,85, 1,18
XVII	4,68	2,44	3,13	3,81	3,88	0,84, 0,87, 1,58, 2,04, 2,1	7,08, 7,14, 7,29
XVIII	4,16	2,78	2,78	3,74	3,74	1,0—2,0	
XIX	4,06	2,84	2,94	3,57	3,62	1,0—2,0	0,77, 0,84, 2,32
XX	4,04	2,73	2,73	3,54	3,54	0,98, 2,43	

Analysis of the characteristics of the spectra in the series of 1,3-oxazolidines with different substituents on the nitrogen atom shows that in comparison with compound XX the signals from the methylene protons of compounds I, VII, XIII, and XVIII are shifted to lower field, while the magnitude of change in chemical shift is virtually identical for the 4-H and 5-H protons and increases in the series of compounds indicated. We should mention that the signal from the 2-H proton, whose downfield shift increases in the series i-C_4H_9, C_3H_7, cyclo-C_6H_{11}, C_6H_5 (XIII, VII, XVIII, I), is very sensitive to the nature of the substituent on the nitrogen atom.

TABLE 3. Spin-Spin Coupling Constants of Ring Protons of Substituted 1,3-Oxazolidines, J, Hz

Compound	$^2J_{AB}$	$^3J_{AC}$	$^3J_{AD}$	$^2J_{BC}$	$^3J_{BD}$	$^2J_{CD}$
VIII	9,5	6,0	6,0	6,0	6,0	7,4
IX	9,9	7,0	7,2	5,1	7,2	7,5
X	9,0	7,2	7,3	3,6	7,2	7,8
XIV	9,2	7,0	7,0	4,0	7,0	7,8
XV	9,5	7,0	7,0	5,0	6,5	8,0
XVI	9,0	6,5	7,2	4,5	5,4	8,0
XVII	9,0	7,1	7,4	3,6	7,2	7,8

TABLE 4. ^{13}C NMR Chemical Shifts of Substituted 1,3-Oxazolidines

Compound	Ring carbon atoms, δ, ppm			Substituents, δ, ppm		
	$C_{(2)}$	$C_{(4)}$	$C_{(5)}$	R	R^3	R^1, R^2
I	78,44	43,8	64,92	143,67, 110,43, 127,12, 115,24		
II	91,97	46,47	63,46	144,36, 111,27, 127,04, 115,27		29,43, 13,43, 16,3
III	90,0	46,36	62,98	144,39, 111,44, 127,36, 116,1		138,46, 126,55, 125,62, 126,55
IV	89,7	45,98	62,28	143,83, 110,05, 126,74, 115,25		148,72, 125,96, 111,05, 125,96
V	89,24	45,9	64,44	143,9, 111,06, 126,9, 115,41		147,4, 126,28, 111,76, 130,16, 52,66
VI	85,74	45,9	62,83	143,67, 111,27, 127,21, 116,42		143,67, 130,01, 127,21, 126,67, 122,63
VII	84,66	50,5	61,57	54,27, 20,68, 9,8		
VIII	95,41	50,44	62,26	53,44, 20,59, 9,86		24,94, 6,57
IX	99,28	50,73	62,73	54,5, 20,86, 9,9		29,99, 14,27, 16,95
X	95,16	49,88	62,63	52,38, 20,24, 9,75		138,53, 126,18, 125,78, 125,78
XI	92,03	48,96	62,0	47,32, 20,78, 9,9		
XII	92,46	48,74	61,5	47,95, 20,95, 9,8		30,95, 21,53, 24,11
XIII	82,28	51,72	63,28	61,74, 26,96, 19,1		
XIV	90,67	50,49	62,19	59,62, 26,1, 18,36, 19,1		18,01
XV	95,52	50,82	62,03	60,09, 26,27, 18,64, 19,1		24,96, 6,51
XVI	100,26	51,49	63,45	61,5, 26,45, 18,79, 19,34		29,97, 17,16, 14,05
XVII	95,81	50,64	62,89	58,62, 26,1, 18,64, 19,18		139,46, 127,03, 126,65, 126,65
XVIII	82,86	47,92	63,71	58,94, 30,54, 23,07, 24,54		
XIX	96,58	45,89	63,44	59,1, 31,06, 24,05, 24,62		28,62, 17,17, 15,14
XX	84,19	46,13	61,66	50,25, 12,58		
XXI	78,77	50,82	72,28	143,71, 127,11, 110,22, 115,24	16,7	
XXIIa	89,7	52,89	70,84	145,15, 128,22, 116,02, 111,44	16,85	24,4, 10,21
XXIIb	91,02	53,7	71,58	146,05, 128,22, 116,18, 112,06	16,33	24,65, 6,62
XXIIIa	92,3	53,97	70,75	145,15, 128,22, 116,41, 112,13	16,31	28,19, 16,0, 12,5
XXIIIb	93,19	53,97	71,45	146,05, 128,22, 115,95, 113,13	16,78	30,6, 17,52, 13,9

The isopropyl group in compounds II, XVI, and XIX, and the aryl groups in oxazolidines III, VI, and XVII give rise to a shift of the signal from the 2-H proton downfield, this effect being most clearly marked in the case of the ortho-nitrophenyl substituent (VI), for which, by analogy with 1,3-dioxanes [6], the formation of an intramolecular hydrogen bond is to be expected.

Comparison of the carbon spectra of compounds I-VI (Table 4) shows that the type of substituent on the $C_{(2)}$ carbon atom has a considerable influence on the magnitudes of the chemical shifts of ^{13}C nuclei in the oxazolidine ring and has no effect on the position of ^{13}C signals from the substituents on the nitrogen atom. For oxazolidines II, IX, and XVI, a magnetic nonequivalence of the carbon nuclei in the isopropyl group is displayed ($\Delta\delta$ = 2.03-3.11 ppm), resulting from the chirality of $C_{(2)}$.

TABLE 5. Characteristics of ^1H NMR Spectra of 5-Methyl-N-phenyl-1,3-oxazolidines

Compound	Chemical shifts of protons, δ, ppm				Chemical shifts of substituents, δ, ppm			Spin-spin coupling constants of ring protons, J, Hz			Spin-spin coupling constants of substituents, J, Hz	
	2-H	A—H	M—H	X—H	R^5	R	R^2	$^2J_{AM}$	$^3J_{AX}$	$^3J_{MX}$	$^5J_{4\text{-}CH_3}$	other groups
XXI	4,68 4,78	2,8	3,32	4,18	1,27	6,28, 7,05, 6,59		8,0	7,5	6,0	6,0	10,2, 6,0
XXIIa	4,96	2,77	3,42	3,92	1,29	7,13, 6,65, 6,43	1,79, 0,99	8,2	9,02	5,74	5,74	7,79, 7,5 2,0
XXIIb	5,02	3,01	3,48	4,33	1,26	7,1, 6,62, 6,4	1,66, 0,91	8,61	7,79	6,15	6,15	7,0, 5,33, 1,85
XXIIIa	4,98	2,83	3,43	3,94	1,27	6,49, 7,13, 6,64	2,24, 1,03, 0,88	8,2	9,02	5,74	5,74	6,0, 2,05
XXIIIb	4,93	2,96	3,57	4,35	1,2	2,12, 1,02, 6,59	2,12, 1,02, 0,77	8,61	7,79	6,15	6,15	6,5, 3,28

Compounds XXIIa, b and XXIIIa, b (Tables 4 and 5) are mixtures of diastereomers. The signals from the cis- and trans-forms have been identified from their spectra and their percentage composition in the mixtures was determined. Determination of configuration from the ^1H NMR spectra was carried out on the basis of examining the difference in chemical shifts of the ring protons of the two isomers and studying the values of the geminal and vicinal spin-spin coupling constants with application of the criteria given in [8]. In this work, it was shown that spin-spin coupling constants of geminal protons at $C_{(4)}$ for trans-isomers of substituted 1,3-oxathiolanes are slightly greater than those for cis-isomers (typical values are about 10.2 Hz and 9.8 Hz), whereas the vicinal constant of cis-isomers is considerably greater than that for trans-isomers (10.0 Hz and 6.0 Hz, respectively).

In our case, examination of the data in Table 5 shows that using these criteria the cis-configuration should be assigned to compounds XXIIa and XXIIIa, and the trans-configuration to compounds XXIIb and XXIIIb. The fact that in accordance with the data of [8] all signals from the ring protons of the cis-isomer are displaced to higher field in comparison with the signals from the trans-isomer serves as an additional criterion for such an assignment. On the basis of the identification carried out and examination of the integral intensities of the signals in the spectrum, it was shown that the ratio of cis- to trans-isomers for both pairs of compounds was 55:45, which was used as a basis for identifying the lines of the cis- and trans-isomers in the ^{13}C NMR spectra of compounds XXIIa, b and XXIIIa, b (Table 4).

Analysis of the characteristics displayed in the ^{13}C NMR spectra shows that the chemical shift of the signal from the methyl carbon at $C_{(5)}$ hardly varies for the cis- and trans-isomers, whereas the chemical shifts of $C_{(2)}$ and the substituent carbon atoms of the cis-isomer correspond to considerably lower field values. The chemical shifts of the carbons of the N-phenyl substituent for both isomers are alike, which suggests the same orientation of the lone pair. Thus, the values of the chemical shifts of $C_{(2)}$ and the carbon atoms of the substituent at the 2-position can be used to identify the cis- and trans-isomers from the ^{13}C NMR spectra.

EXPERIMENTAL

^1H NMR spectra were recorded at frequencies of 100, 294, and 360 MHz (Varian HA-100, OIKhF, and Bruker WH-360 spectrometers); ^{13}C NMR spectra were recorded at 25.15 and 90.55 MHz (Jeol PFT-100 and Bruker WH-360). For interpretation of complex multiplets in the ^1H NMR spectra, double proton-proton resonance was used. The series of ^{13}C NMR spectra was recorded under conditions of partial proton decoupling (Fig. 2b). The samples comprised 10-15% solutions in CCl_4. The internal standard was HMDS ($\Delta\delta_{HMDS-TMS}$ is 0.05 ppm for ^1H and 1.94 ppm for ^{13}C).

Calculation of the four-spin proton system of the oxazolidine ring was carried out at the Branch of the Institute of Chemical Physics, Academy of Sciences of the USSR on a BÉSM-22 computer using a program developed for analysis of complex high-resolution NMR spectra [9].

The authors are sincerely grateful to G. V. Lagodzinskaya, É. B. Fel'dman, and N. F. Sepetov for their assistance in the work, and to S. S. Zlotskii and V. V. Zorin for making available research items and for useful discussions.

LITERATURE CITED

1. D. Taverier and M. Anteunis, Tetrahedron, 27, 1677 (1971).
2. V. P. Lezina, A. U. Stepanyants, F. A. Alimirzoev, S. S. Zlotskii, and D. L. Rakhmankulov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 4, 792 (1976).
3. M. Goodman and F. Morehouse, Organic Molecules in Action, Gordon (1973).
4. E. Eliel, Angew. Chem., 24, 779 (1972).
5. M. Anteunis, Heterocycles, 4, 293 (1976).
6. F. A. Alimirzoev, A. A. Lapshova, V. V. Zorin, A. U. Stepanyants, V. P. Lezina, F. N. Latypova, S. S. Zlotskii, and D. L. Rakhmankulov, Zh. Prikl. Khim., No. 4, 911 (1980).
7. M. Van Gorcom and G. E. Hall, Quart. Rev., 22, 14 (1968).
8. R. Keskinen, A. Nikkila, and K. Pihlaja, Tetrahedron, 28, 3943 (1972).
9. G. V. Lagodzinskaya and A. A. Fomichev, Zh. Strukt. Khim., 8, 695 (1967).

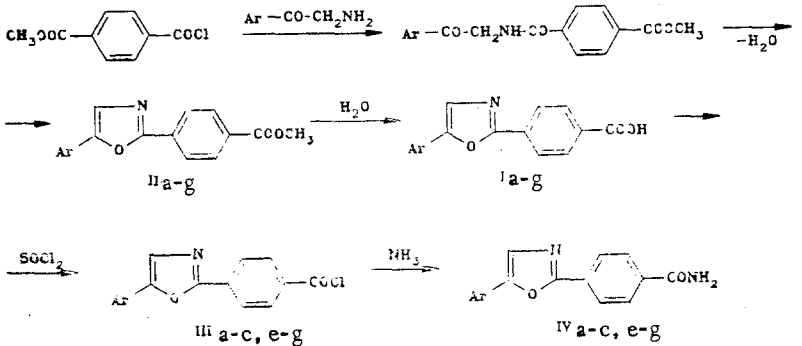
SYNTHESIS AND SPECTRAL AND LUMINESCENT PROPERTIES OF 4-(5-ARYLOXAZOYL-2)BENZOIC ACIDS AND THEIR DERIVATIVES

B. M. Krasovitskii, V. M. Shershukov, and V. L. Volkov

UDC 547.787.2.07'584'572:535.37:541.651

Condensation of acid chloride of monomethyl terephtalate with ω-aminomethylarylketones and subsequent cyclodehydration of the resulting amides in sulfuric acid or phosphorus oxychloride give rise to methyl 4-(5-aryloxazolyl-2)benzoates which led to the corresponding acids, acid chlorides, and amides. The effect of electron-withdrawing groups on the spectral and luminescent properties, as well as on the stability of substituted 2,5-diaryloxazoles toward UV irradiation has been investigated.

As a continuation of our studies [1-3], we have investigated the effect of structural transformations related to the replacement of the hydrogen atom in the aldehyde group by a hydroxyl, methoxyl, or amino group, or a chlorine atom on the spectral and luminescent properties of substituted 2,5-diaryloxazoles. From acid chloride of monomethyl terephthalate [4] and ω-aminomethylarylketones, we obtained in the Robinson–Gabriel reaction methyl 4-(5-aryloxazolyl-2)benzoates (II), and then by their hydrolysis, the corresponding carboxylic acids (I). From the latter, we obtained their acid chlorides (III) and amides (IV) (Table 1).



I—IV a Ar=C_6H_5; b Ar=4-CH_3—C_6H_4; c Ar=4-CH_3O—C_6H_4; d Ar=4-$(CH_3)_2N$—C_6H_4; e Ar=4-Cl—C_6H_4; f Ar=4-C_6H_5—C_6H_4; g Ar=I—$C_{10}H_7$

Scientific-Industrial Association "Monokristallreaktiv" ("Single Crystal Reagent"), Khar'kov 310141. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1261-1264, September, 1986. Original article submitted May 27, 1985.

 0009-3122/86/2209-1022$12.50 © 1987 Plenum Publishing Corporation