SYNTHESIS AND STUDY OF THE TRANSFER OF SUBSTITUENT ELECTRONIC EFFECTS IN SUBSTITUTED 2,5-DIPHENYLOXAZOLES

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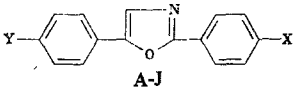
A series of para-substituted 2,5-diphenyloxazoles was synthesized using Robinson–Gabriel procedure and the transfer of substituent electronic effects in these compounds was examined.

2,5-Diaryloxazoles are used in scintillators, in electrochemiluminescent compositions, and in optical lasers [1, 2]. Their properties depend significantly on the nature of the substituents. The transfer of electronic effects in such heteroaromatic systems is significantly more complex than in benzene systems (see reviews by Jaffe [3], Johnson [4], and Mamaev [5]) and has not yet been treated quantitatively [6].

In the present work, we synthesized previously undescribed para-disubstituted 2,5-diphenyloxazoles B, C, F, G, I, and J. (Monosubstituted 2,5-diphenyloxazoles such as A and E have been reported in greater detail [6].) The nature of the transfer of the electronic effects of substituents at C-2 and C-5 in the oxazole ring was established for series A-H as well of transmission effects in series I and J relative to the change in the basicity constant in these series. The oxazole ring in these systems acts as a conducting unit between two substituted benzene rings which are located para relative to each other in the oxazole ring assuming that the aromatic system of oxazole is π-isoelectronic to the benzene system.



A-J

A-C Y=OCH_3, CH_3, H; **D,I** Y=OCH_3, H, Cl, Br; **E–G** X=OCH_3, CH_3, H; **H,J** X=OCH_3, H, Cl, Br; **A** X=H; Y=Cl, Br, CHO, NO_2; **B** X=CH_3; Y=Cl, Br; **C** X=OCH_3; **D** X=NH_3^+; **E** X=Cl, Br, CHO, NO_2; Y=H; **F** X=Cl, Br; Y=CH_3; **G** Y=OCH_3; **H** Y=$\overset{+}{N}H_3$; **I** X=NH_2; **J** Y=NH_2

The synthesis was carried out according to the Robinson–Gabriel procedure [6] by cyclization of α-amidoketones $YC_6H_4COCH_2NHCOC_6H_4X$ obtained, in turn, by acylation of the corresponding α-aminoketones. Virtually no limitations were encountered for this method related to the electronic nature of the para substituents. In order to obtain the amino and aldo derivatives (VI, XXII, and XXV-XXXVII), the formation of the corresponding functions should be formed in the oxazoles since these functional groups may be involved in the undesirable reactions in the Robinson–Gabriel synthesis and the oxazole ring in 2,5-diaryloxazoles is rather stable.

In contrast to methyl groups, which enhance the basicity of oxazoles [6], the introduction of a phenyl group at C-4 significantly lowers the basicity ($pK_{BH^+} = -1.21$, for the unsubstituted analog, $pK_{BH^+} = 0.8$) but has a significantly reduced effect at C-5 ($pK_{BH^+} = 0.26$) [6]. On the other hand, the introduction of phenyl groups at C-2 and C-5 leads to compensation of the basicity effects, apparently due to the effect of the phenyl group at C-2, relative to which the oxazole ring displays strong electron-withdrawing action. This double nature of the oxazole ring is in accord with the relative values of the total π-residual charges on the heteroring and phenyl groups attached at different positions of the heterocycle [7], in which the oxazole ring is π-electron-withdrawing relative to the phenyl ring at C-2 but a very weak

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π-electron donor relative to the phenyl group at C-5. These characteristics vary in the same direction as the basicities, although it is unwise to search for direct correlations since the residual charges in the π-approximation are unlikely to provide a complete characterization of the basic properties, which are determined primarily by the free electron pair of the nitrogen atom. We note that data has been reported on the electron-withdrawing properties of the 2-oxazolyl group relative to the bromomethyl substituent on the basis of a polarographic study [8]. Thus, the oxazole ring may be considered an amphoteric system capable of displaying electron-withdrawing or electron-donor properties depending on the site of substitution.

The introduction of substituents at the para position of 2,5-diphenyloxazoles leads to a change in the basicity of the oxazole ring (Table 1) described by linear correlation curves for pK_{BH^+} vs σ (Table 2, series A-H).

Comparison of the correlation dependences for series A-D with those for series E-H, ρ_{A-D}/ρ_{E-H} (Table 2) indicates that the effect of the substituent at C-2 (σ_2) on the basicity of the heterocycle is approximately twice that of the substituent at C-5 (σ_5). This relationship also apparently holds for monosubstituted oxazoles since the ρ_5 values calculated for the 5-phenyloxazole series (series K in Table 2, the experimental data for pK_{BH^+} were taken from the work of Brown and Ghosh [9]) are similar in value to the ρ_5 values for series A-D. A linear correlation is found for ρ_2 vs σ_5, indicating that the sensitivity of the oxazole ring to the effect of substituents at C-2 (ρ_2) is structurally dependent on the nature of the substituent at C-5 (σ_5):

$$\rho_2 = (1.76 \pm 0.01) + (1.60 \pm 0.03)\sigma_5 \quad (S_{tot} = 0.01,\ r = 0.999).$$

On the other hand, ρ_5 is virtually independent of σ_2 [$\rho_5(\sigma_2) \approx 0.12$]. In other words, the capacity to transmit a stronger electronic effect from C-2 (ρ_2) to the heterocyclic nitrogen atom is very sensitive to substitution at C-5 (a weaker interaction with the heterocycle obtaines in this case) and this effect is more pronounced as σ_5 increases, while the interaction of substituents at C-5 (ρ_5) with the basic site of the heterocycle is only slightly affected by substitution at C-2 (stronger interaction with the heterocycle is noted in this case).

These features of the interaction of the substituent and heterocycle in oxazoles also account for the transmission capacity of the oxazole ring. Comparison of the ρ values of series I and J indicates that the oxazole ring has different transmission capacity from C-2 and from C-5. The transmission from C-5 to C-2 (ρ_I/ρ_J) is approximately twice that in the opposite direction. This finding is in accord with the observation that substitution at C-5 enhances the interaction of the substituent at C-2 (in this case, the 2-aniline substituent which is the reaction site) with the oxazole ring and as a result, an increase in its transmitting capacity is apparently observed relative to the effect of substitution at C-2 on the 5-aniline reaction site which, in this case, weakly interacts with the heterocycle and the effect of substitution at C-2 on the heterocycle is not very pronounced.

EXPERIMENTAL

All the oxazoles obtained were purified on a semicontinuous chromatographic column [15] packed with alumina with heptane, benzene, or toluene as eluent. In the purification of amino derivatives of 2,5-diphenyloxazole, these samples were initially treated with 5% aqueous ammonia or 5% ammonia in water–ethanol.

The pK_{BH^+} basicity constants were determined spectrophotometrically on Specord UV-VIS and SF-16 spectrometers in aqueous solution at 25°C. The spectra of the saturated forms of the compounds studied (protonated or neutral) were taken in solutions with pH in the range of the $pK_{BH^+} \pm 2$ pH units. The equilibrium forms of the compounds were obtained in acetic acid–sodium acetate buffer solutions (for $pK_{BH^+} \approx 3$) or hydrochloric acid solutions of different concentrations (for $pK_{BH^+} < 2$).

1-(4-Nitrophenyl)-4-(4-bromophenyl)-2-aza-1,4-butanedione. A suspension of 6 g of the hydrochloride salt of α-aminomethyl 4-bromophenyl ketone was prepared in a solution of 50 ml anhydrous pyridine and 50 ml dioxane at room temperature. A sample of 4.8 g of p-nitrobenzoyl chloride was added over 10 min with vigorous stirring. The temperature of the reaction mass rose to 40°C as a result of the exothermal reaction. A dark-brown solution was formed which, after 10 min, yielded a brown, flaky precipitate. The reaction mass was cooled to room

TABLE 1. Basicity Constants (pK_{BH^+}) of 2,5-Diphenyloxazole Derivatives

Compound	X	Y	Mp, deg C	pK_{BH^+}	Compound	X	Y	Mp, deg C	pK_{BH^+}
I	H	H	72 [10]	0,84	XX	Cl	H	120; 117 [10]	0,41
II	H	OCH_3	80; 80 [10]	1,05	XXI	Br	H	118; 116 [13]	0,40
III	H	CH_3	84	0,91	XXII	CHO	H	156	0,02
IV	H	Cl	108; 106 [10]	0,70	XXIII	NO_2	H	206; 204 [12]	−0,61
V	H	Br	105; 104 [10]	0,65	XXIV	Cl	CH_3	152	0,58
VI	H	CHO	123	0,57	XXV	Br	CH_3	168	0,56
VII	H	NO_2	192; 191 [11]	0,35	XXVI	OCH_3	NH_3^+	—	0,85
VIII	CH_3	OCH_3	127	1,26	XXVII	H	NH_3^+	—	0,50
IX	CH_3	CH_3	112	1,12	XXVIII	Cl	NH_3^+	—	0,27
X	CH_3	Cl	152	0,88	XXIX	Br	NH_3^+	—	0,26
XI	CH_3	Br	168	0,87	XXX	NH_2	OCH_3	189	3,22
XII	OCH_3	OCH_3	139	1,41	XXXI	NH_2	H	181; 175 [14]	3,01
XIII	OCH_3	CH_3	—	1,34	XXXII	NH_2	Cl	211	2,87
XIV	NH_3^+	OCH_3	—	0,27	XXXIII	NH_2	Br	210	2,80
XV	NH_3^+	H	—	0,06	XXXIV	OCH_3	NH_2	199	3,71
XVI	NH_3^+	Cl	—	−0,10	XXXV	H	NH_2	176	3,68
XVII	NH_3^+	Br	—	−0,05	XXXVI	Cl	NH_2	188	3,52
XVIII	OCH_3	H	103; 101 [12]	1,25	XXXVII	Br	NH_2	185	3,51
XIX	CH_3	H	75; 75 [10]	1,04					

*Crystallization solvents: I-III, VIII, IX, XVIII, XIX, and XXIV from hexane; IV, V, X-XII, XX, XXI, and XXV from heptane; VI, XXII, XXX, XXXI, and XXXV from ethanol; VII, XXIII, XXXII-XXXIV, XXXVI, and XXXVII from benzene.

TABLE 2. Correlation Parameters for Derivatives of 2,5-Diphenyloxazoles in a Plot for $pK_a = pK^\circ + \rho\sigma_n$

Series	$pK^\circ_{BH^+}$	$-\rho$	S	r
A	0,84±0,04	0,64±0,01	0,03	0,992
B	1,04±0,07	0,71±0,01	0,03	0,986
C	1,25±0,05	0,59±0,01	0,01	0,991
D	0,08±0,02	0,69±0,07	0,03	0,988
E	0,79±0,01	1,76±0,02	0,04	0,999
F	0,91±0,08	1,50±0,02	0,03	0,996
G	1,05±0,08	1,33±0,01	0,02	0,996
H	0,53±0,01	1,17±0,05	0,02	0,998
I	3,66±0,01	0,48±0,06	0,02	0,999
J	3,06±0,01	0,84±0,16	0,06	0,968
K	0,38±0,07	0,79±0,16	0,12	0,962

temperature and poured into cold water with stirring. The precipitate was washed with water until the pyridine odor was no longer detected in the wash water, dried at 50°C, and crystallized from benzene. A yield of 4.5 g (52%) brown, scaly crystals was obtained, mp 192°C (from benzene). Found: C 54.6: H 4.8; Br 21.9; N 6.8%. Calculated for $C_{15}H_{11}BrN_2O_4$: C 54.2; H 4.6; Br 21.7; N 6.6%.

2-(4-Nitrophenyl)-5-(4-bromophenyl)oxazole. A mixture of 4.3 g 1-(4-nitrophenyl)-4-(4-bromophenyl)-2-aza-1,4-butanedione and 20 ml conc. H_2SO_4 was heated at 60°C for 15 min. The dark-brown solution formed was cooled to room temperature and was poured with stirring into ice water. The yellow precipitate was filtered, washed with water until the wash water was neutral, dried at 70°C, crystallized from 2-propanol, and purified on a semicontinuous-action alumina column with benzene as eluent to give 3.8 g (93%) product as yellow crystals, mp 183°C (from benzene). Found: C 52.2; H 2.6; Br 23.3; N 8.3%. Calculated for $C_{15}H_9BrN_2O_3$: C 52.2; H 2.6; Br 23.5; N 8.1%.

Oxazoles IX-XI, XXIV, and XXV were prepared analogously.

2-(4-Aminophenyl)-5-(4-bromophenyl)oxazole (XXXIII). A sample of 30 g hydrazine hydrate and 1.7 g freshly prepared Raney nickel were added in small portions concurrently to a suspension of 7.4 g 2-(4-nitrophenyl)-5-(4-bromophenyl)oxazole* heated at reflux. The reaction mass

*The solvent and its volume were omitted in the Russian original — Publisher.

was heated at reflux for 1 h until the solution was decolorized and then the solution was heated at reflux for an additional 30 min, cooled, and poured into ice water. The precipitate was filtered off and treated with 5% aqueous ammonia. The light cream-colored product was filtered, washed with water until the wash water was neutral, dried, and crystallized from 5:1 ethanol—conc. aqueous ammonia to yield 6.2 g XXXIII (92%) as light cream-colored needles, mp 210°C (from benzene). Found: C 56.9; H 3.3; Br 25.1; N 8.6%. Calculated for $C_{15}H_{11}BrN_2O$: C 57.1; H 3.5; Br 25.3; N 8.9%.

Oxazoles XXX-XXXVII were obtained by analogous procedures.

2-(4-Tolyl)-5-(4-methoxyphenyl)oxazole (VIII). A suspension of 5.7 g 1-(4-tolyl)-4-(4-methoxyphenyl)-2-aza-1,4-butanedione in 16 ml $POCl_3$ was heated at reflux for 30 min. The dark-brown solution formed was cooled and poured into ice water. The gray precipitate was filtered, washed with water until the wash water was neutral, dried, crystallized from ethanol, and purified by chromatography on a semicontinuous-action column using hexane as eluent to give 5.0 g (95%) colorless needles, mp 127°C (from hexane). Found: C 76.8; H 5.6; N 5.4%. Calculated for $C_{17}H_{15}NO_2$: C 76.7; H 5.7; N 5.3%.

Oxazoles XII and XIII were prepared by analogous procedures.

The elemental analyses of the newly synthesized oxazoles III, VIII-XIII, XX-XXII, XXX, and XXXII-XXXVII and their intermediates corresponded to their chemical formulas within experimental error.

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