SYNTHESIS, STRUCTURE, AND SPECTRAL PROPERTIES OF SOME BIOXAZOLES

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Syntheses of systems containing two oxazole rings [2'-phenyl-, 2'-(2-furyl)-, and 2'-(2-thienyl)-2,5'-bioxazoles, and 2,2'-(2,5-furylene)bisoxazole] from aldehydes obtained by formylating 2-phenyl-, 2-(2-furyl)-, and 2-(2-thienyl)oxazole have been developed. Terephthalate and thiophen-2,5-dicarboxylate esters have been used to obtain 2,2'-(1,4-phenylene)- and 2,2'-(2,5-thienylene)bisoxazoles. The PMR, UV, and luminescence spectra of these systems have been examined, and quantum chemical calculations carried out in the PPP approximation.

We have previously [1, 2] developed syntheses of 2-phenyloxazole (Ia), 2-(2-furyl)oxazole (Ib), and 2-(2-thienyl)oxazole (Ic) by aromatization of the oxazolines by treatment with nickel peroxide. Some electrophilic substitution reactions of 2-phenyloxazole have been studied [1, 3], and it has been shown that under conditions which do not permit protonation of the nitrogen atom with consequent deactivation of the heterocycle the substituent enters in the 5-position of the oxazole nucleus. The possibility of formylating the oxazole ring is particularly attractive [1], since this would give a new C–C bond and introduce a functional group capable of a wide range of subsequent reactions.

The aim of this investigation was to examine the formylation of the 2-hetaryloxazoles (Ib) and (Ic), the conversion of the aldehydes so obtained and of the previously-synthesized [1] 2-phenyloxazole-5-aldehyde (IIa) into systems containing two oxazole rings, and a study of the spectral properties of the latter.

The hetaryloxazoles (Ib, c) contain fragments of activated heteroaromatic compounds with one heteroatom. For this reason it might be expected that the formyl group would enter, either exclusively or predominantly, the furan (or thiophen) ring rather than the oxazole ring. However, formylation of the thienyloxazole (Ic) gave 85% of a single compound, 2-(2-thienyl)oxazole-5-aldehyde (IIc), the structure of which was confirmed by its PMR spectrum, which contained signals for three thiophen ring protons with typical coupling constants (J_{34} 3.7 and J_{45} 5 Hz) in the aromatic region together with a singlet for the proton of the oxazole ring and a singlet at lower field for the aldehyde proton (Table 1). This finding is understandable, bearing in mind that the systems under consideration (Ia-c), unlike their biphenyl analogs, have two rings that are not equivalent, so that transfer of electron density to the oxazole moiety takes place. This follows from quantum chemical calculations for 2-phenyloxazole carried out in the valence approximation by the CNDO/2 method [4].

TABLE 1. PMR Spectra of Hetaryloxazolealdehydes (IIb), (IIc), and (III) (in deuteroacetone)

Compound	Chemical shifts, δ, ppm						Coupling constant J, Hz			
	oxazole ring		thiophen (furan) ring			CHO	45	3'4'	3'5'	4'5'
	4-H	5-H	3'-H	4'-H	5'-H					
IIc	8,07 s	- -	7,85 m	7,25 d.d	7,85 m	9,80 s	—	3,7	—*	5,0
IIb	8,19 s	—	7,40 d.d	6,79 d.d	7,94 d.d	9,86 s	—	3,76	0,9	1,80
III	7,44 d	8,17 d	7,31 d	7,62 d	—	9,78 s	0,5	3,76	—	—

*As a result of the superimposition of the 3'-H and 5'-H signals, it was not possible to measure the value of $J_{3'5'}$.

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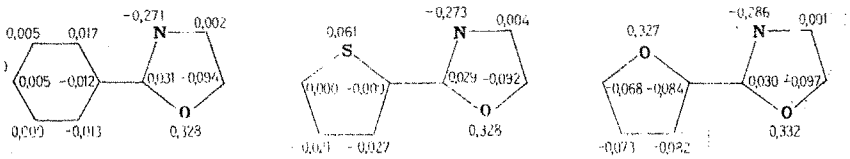


Fig. 1. Distribution of π-electron density in 2-aryl- and 2-hetaryloxazoles (Ia-c).

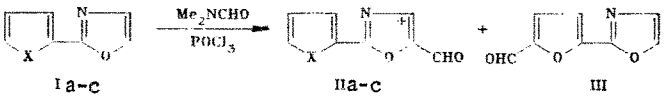
TABLE 2. PMR Spectra of 2-Aryl- and 2-Hetaryloxazolines

Compound	Solvent	Chemical shifts, δ, ppm						
		oxazoline ring*		oxazole ring†		benzene, thiophen or furan ring		
		4-H	5-H	4'-H	5'-H	o-H (3-H)	m-H (4-H)	p-H (5-H)
4,5-Dihydro-2-phenyloxazole	CCl_4	3,97	4,08	—	—	7,76 m (2H)	7,22m (3H)	
4,5-Dihydro-2-(2-thienyl)oxazole‡	CCl_4	4,07	4,22	—	—	7,49 d.d	6,97 d.d	7,35 d.d
4,5-Dihydro-2-(2-furyl)oxazole**	$CDCl_3$	4,10	4,20	—	—	6,87 d	6,38 d.d	7,45 d
VIIIa	$CDCl_3$	4,12	4,28	7,52	—	8,20 m (2H)	7,55 m (3H)	
VIIIb**	$CDCl_3$	4,14	4,29	7,65	—	7,21 d	6,69 d.d	7,93 d
VIIIc‡	$(CD_3)_2CO$	4,07	4,36	7,80	—	7,78 d.d	7,20 d.d	7,67 d.d
IX	$CDCl_3$	4,19	4,31	7,23	7,70	7,06 s (2H)		
Xa	$CDCl_3$	4,20	4,31	—	—	7,97s (4H)		
Xc	$CDCl_3$	4,20	4,33	—	—	7,27 s (2H)		

*Signals seen as partially overlapping multiplets, $J_{45} \simeq 7$-8 Hz.
†Signals seen as singlets, splitting with $J_{45} \simeq 0.7$ Hz not seen in the spectra (60 MHz).
‡In the thiophen ring $J_{34} \simeq 4$, $J_{35} \simeq 1.5$, $J_{45} \simeq 5.5$ Hz.
**In the furan ring, $J_{34} \simeq 3.5$, $J_{45} \simeq 2.5$ Hz.

Quantitative evaluation of the electron-acceptor capacity of the 2-oxazolyl residue in systems (Ia-c) may be made from ^{13}C NMR spectroscopic data for (Ia) [4], from which it follows that this residue functions as a substituent in the benzene ring with a σ_p^+ value of 0.33, i.e., it is intermediate in its deactivating effect between the bromine atom (σ_p^+ 0.23) and COOH (σ_p^+ 0.45).

We have here used the Pariser–Parr–Pople (PPP) method [5, 6] to calculate the distribution of π-electron density in the molecules (Ia-c). The results are shown in the molecular diagrams (Fig. 1). It will be seen that in 2-phenyl- and 2-(2-thienyl)oxazole sites with the highest π-electron density are the 5-positions of the oxazole ring, which is in accordance with the directivity of formylation. Only in the case of 2-(2-furyl)oxazole (Ib) are the free positions of the furan ring comparable in their π-electron density to that at the 5-position of the oxazole ring. This is in agreement with the results of the formylation of (Ib), in which around 90% of a mixture of 2-(2-furyl)oxazole-5-aldehyde and the isomeric 2-(5-formyl-2-furyl)oxazole (III) is obtained in a ratio of 1:2 (according to GLC and PMR). The isomers (IIb) and (III) were separated by column chromatography on silica gel, and the structures confirmed by PMR spectroscopy (Table 1).



Ia-c IIa-c III

I, II a X=CH=CH; b X=O; c X=S

Oxidation of the aldehydes (IIa, c) and (III) with Jones' reagent, and of (IIb) with silver oxide, proceeded smoothly to give the acids (IVa-c) and (VII). Reaction of the latter with ethanolamine gave the N-(2-hydroxyethyl)amides, which were then normally without isolation in the pure state reacted with thionyl chloride followed by potassium hydroxide to give readily 4,5-dihydro-2'-phenyl- (VIIIa), 4,5-dihydro-2'-(2-furyl)- (VIIIb), 4,5-dihydro-2'-thienyl)- (VIIIc), and 4,5-dihydro-2,2'-(2,5-furylene)bisoxazole (IX).

TABLE 3. PMR Spectra of Bioxazoles (XIa-c) and (XIIa-c)

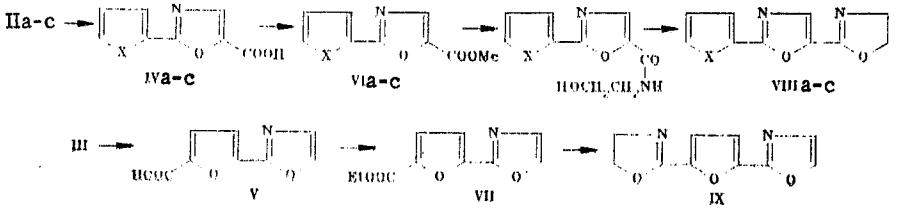
Compound*	Chemical shifts, δ, ppm					
	oxazole ring			benzene, furan, or thiophen ring		
	4-H	5-H	4'-H	o-H (3-H)	m-H (4-H)	p-H (5-H)
XIa	7,17 s	7,51 s	7,51 s	8,12 m (2H)	7,40 m (3H)	
XIb†	7,39 d	8,37 d	7,85 s	7,27 d,d	6,74 d,d	7,88 d,d
XIc‡	7,41 s	8,12 s	7,81 s	7,85 d,d	7,27 d,d	7,79 d,d
XIIa	7,76 s	8,17 s	—	7,30 s (4H)		—
XIIb**	7,36 s	8,08 s	—	7,25 s (2H)		—
XII c	7,60 s	7,92 s	—	7,23 s (2H)		—

*Solvent for (XIa), CCl_4; for (XIb, c) and (XIIb, c), $(CD_3)_2CO$; and for (XIIa), $CDCl_3$.

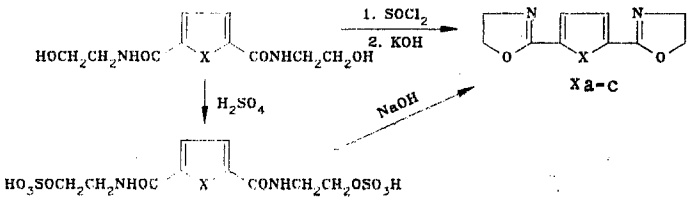
†In the spectrum (250 MHz), splitting of the oxazole ring protons was seen (J_{45} = 0.7 Hz), and also of the furan ring protons J_{34} = 3.5, J_{35} = 0.7, J_{45} = 1.8 Hz.

‡In the 60 MHz spectrum, the protons of the oxazole ring are seen as broadened singlets, coupling constants in the thiophen ring: J_{34} = 3.5, J_{35} = 1.0, J_{45} = 5.0 Hz.

**In the oxazole ring J_{45} = 0.7 Hz.



Similarly, dimethyl thiophen-2,5-dicarboxylate (obtained from adipic acid by a modification of the standard methods [7, 8]) was converted via its N-(2-hydroxyethylamide) into the bisoxazoline (Xc). However, the benzene analog (Xa) was obtained in low yields on successive treatment of terephthalic acid NN'-bis-(2-hydroxyethyl)amide with thionyl chloride and potassium hydroxide. This N-(2-hydroxyethyl)amide was therefore converted into the sulfate by treatment with sulfuric acid, and this on treatment with sodium hydroxide gave (Xa).



The structures of the oxazolines (VIIIa-c), (IX), and (Xa, c) followed from the methods of synthesis and were in accordance with their PMR spectra (Table 2). In the same Table are given for comparison the PMR spectra of 2-phenyl-, 2-(2-furyl)-, and 2-(2-thienyl)-oxazolines, the preparation of which has been described previously [1, 2].

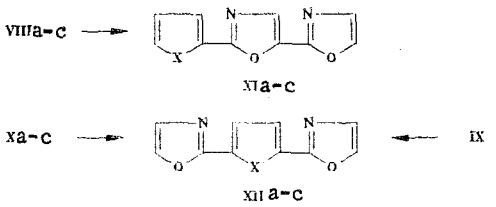
On treatment with nickel peroxide, the oxazolines (VIIIa-c) were converted into the corresponding 2'-phenyl and 2'-hetaryl-2,5'-bioxazoles (XIa-c), and (Xa), (IX), and (Xc) into p-phenylene-2,2'-bisoxazole, 2,5-furylene-2,2'-bisoxazole, and 2,5-thienylene-2,2'-bisoxazole (XIIa-c) respectively. As in the preparation of 2-aryl- and 2-hetaryloxazoles [2], the corresponding carboxamides were obtained as by-products, but the yields of the required compounds, particularly in the cases of the bisoaxazolines (Xa, c) and the furyl-substituted oxazoline (VIIIb), were much lower than in the syntheses of the monooxazoles (Ia-c). The PMR spectra of (XIa-c) and (XIIa-c) demonstrate their aromatic character and confirm their structures (Table 3). The yields, melting points, and elemental analyses for (II-XII) are given in Table 4.

TABLE 4. Properties of the Compounds Obtained

Compound	mp, °C*	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N(S)		C	H	N(S)	
IIa	72—74								85
IIb	158—159	59,3	3,1	8,8	$C_8H_5NO_3$	58,9	3,1	8,6	27
IIc	110—112	53,4	3,0	8,1 (17,5)	$C_8H_5NO_2S$	53,6	2,8	7,8 (17,9)	85
III	133—136	—	—	8,6	$C_8H_5NO_3$	58,9	3,1	8,6	40
IVa	217—218	63,4	3,9	7,6	$C_{10}H_7NO_3$	63,5	3,7	7,4	77
IVb	242—243 (decomp.)	53,7	2,7	7,9	$C_8H_5NO_4$	53,6	2,8	7,8	91
IVc	245—250 (decomp.)	49,7	3,3	7,1 (16,1)	$C_8H_5NO_3S$	49,2	2,6	7,2 (16,4)	78
V	229—231 (decomp.)	53,3	2,6	7,6	$C_8H_5NO_4$	53,6	2,8	7,8	46
VIa	90—91	65,2	4,4	6,8	$C_{11}H_9NO_3$	65,0	4,5	6,9	97
VIb	116—118	56,2	4,0	7,1	$C_9H_7NO_4$	56,0	3,7	7,3	91
VIc	108—109	51,7	3,5	6,8 (15,2)	$C_9H_7NO_3S$	51,7	3,4	6,7 (15,3)	90
VII	87—89	58,2	4,6	6,5	$C_{10}H_9NO_4$	58,0	4,4	6,8	66
VIIIa	118—119	66,6	4,6	12,8	$C_{12}H_{10}N_2O_2$	67,3	4,7	13,1	91
VIIIb	138—139	59,6	3,7	13,1	$C_{10}H_8N_2O_3$	58,8	3,9	13,7	83
VIIIc	119—121	54,2	3,8	12,8 (14,4)	$C_{10}H_8N_2O_2S$	54,5	3,7	12,7 (14,6)	62
IX	182—184	58,7	3,8	14,1	$C_{10}H_8N_2O_3$	58,8	3,9	13,7	91
Xc	136—138	53,9	4,4	12,5 (14,2)	$C_{10}H_{10}N_2O_2S$	54,0	4,5	12,6 (14,4)	90
XIa	113—115	67,9	3,6	13,7	$C_{12}H_8N_2O_2$	67,9	3,8	13,2	39
XIb	115—117	59,4	3,4	13,6	$C_{10}H_6N_2O_3$	59,4	3,0	13,9	14
XIc	94—95	55,5	2,7	13,0 (14,7)	$C_{10}H_6N_2O_2S$	55,0	2,8	12,8 (14,7)	34
XIIa	221—222	67,7	3,7	13,1	$C_{12}H_8N_2O_2$	67,9	3,8	13,2	8
XIIb	177—179	59,4	3,3	13,6	$C_{10}H_6N_2O_2$	59,4	3,0	13,9	26
XIIc	124—128	55,3	3,1	13,1 (14,6)	$C_{10}H_6N_2O_2S$	55,0	2,8	12,8 (14,7)	16

*Compounds (IIa), (VIIIa, b), (IX), (Xc), and (XIb, c) were crystallized from hexane; (IIb, c), (III), (VIa-c), (VII), (XIa), and (XIIb, c) from heptane; (VIIIc) from propan-2-ol, and (XIIa) from ethanol.

†For elemental composition and empirical formula, see [2].



Examination of the UV absorption and fluorescence spectra for the bioxazoles (XIa-c) and (XIIa-c) shows that these compounds absorb strongly and fluoresce efficiently in organic solvents (Table 5). Their spectral properties have much in common, despite the fact that they differ considerably in the positions of the absorption and fluorescence maxima. For instance, in spectra of all the compounds the π,π^* bands predominate, which is typical of heteroaromatic systems. The PMR data (Table 3) for these compounds (XIa-c) and (XIIa-c) show them to possess a general aromatic π-system (for criteria of heteroaromaticity, see [9]). The absorption spectra show that, in all instances, the most intense is the long-wavelength band. This band is the widest, and is generally structureless; only in a few cases does vibrational structure appear. The fluorescence spectrum is virtually a mirror image of the absorption spectrum.

When polar solvents are used instead of neutral solvents, the maxima of the long-wavelength bands in the absorption spectra and the fluorescence band are shifted to longer wavelengths. The effect of solvent on the position of the long-wavelength maximum is quite small, no greater than 12 nm (Table 5). The fluorescence bands are shifted to longer wavelengths by between 2

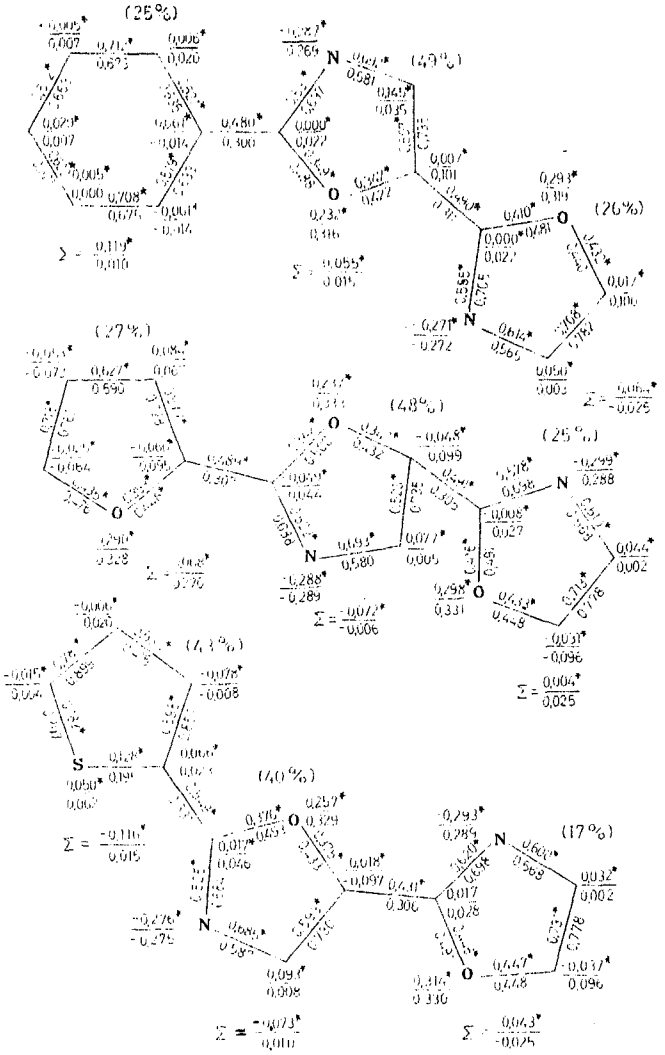
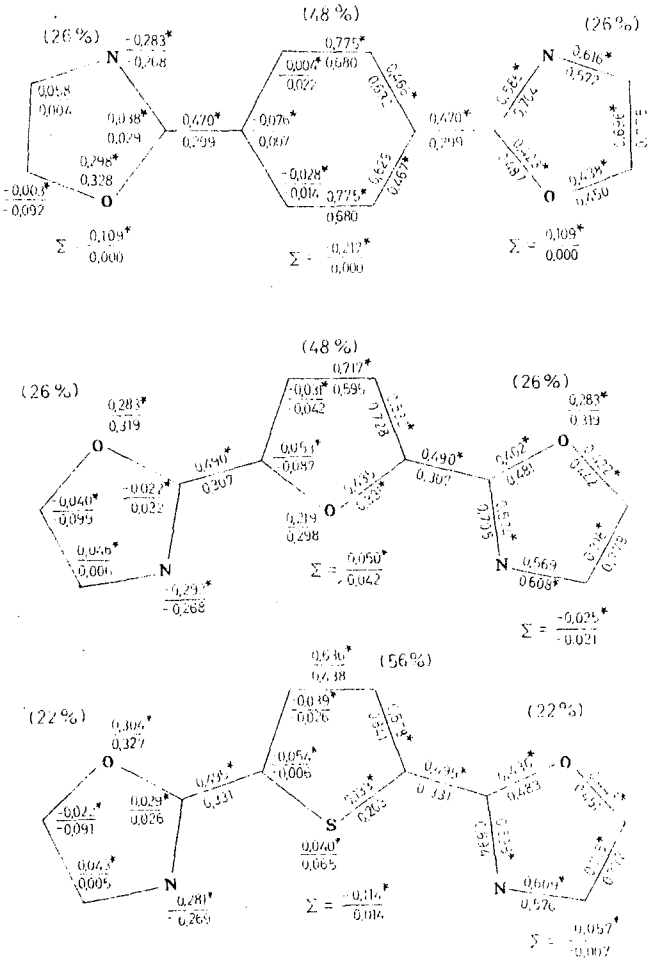


Fig. 2. Distribution of π-electron density and The values of the π-charges in the ground state the excited state $S_{\pi\pi^*}$ (in the numerator). The given in the ground and excited (indicated by (%) are given above the rings.

and 22 nm. Consequently, the Stokes shift ($\Delta\nu = \nu_{fluor} - \nu_{abs}$) is dependent on the solvent and on the compound; for spectra obtained in cyclohexane and alcohol, it varies from 34 to 80 nm. This dependence of the magnitude of the Stokes shift on solvent is apparently due to changes in molecular configuration on excitation [10]. The compounds examined here may exist as several conformers, of which that which is the most stable in a given solvent predominates. The tricyclic structure of (XIa-c) and (XIIa-c) is formed from a combination of one benzene, furan, or thiophen ring with two oxazole rings, the three rings being either coplanar, or rotated relative to each other.

In order to interpret the absorption and luminescence spectra, quantum chemical calculations of the electronic structures of (XIa-c) and (XIIa-c) were carried out using the PPP method [5, 6]. The calculations were carried out for coplanar molecules with different orientations of the rings relative to each other. The calculations showed that the conformation shown in Fig. 2 is the most likely. Molecular diagrams of the distribution of π-electron density both in the ground (S^0) and excited states ($S_{\pi\pi^*}{}^1$) show that the nitrogen atom of the oxazole ring carries a substantial negative charge, and may function as an electron-donor, whereas the oxygen and sulfur atoms may function as strong and weak electron-acceptors respectively, the magnitude of the π-charges on these atoms varying little on excitation. It is necessary to bear in mind that the carbon atoms in the free positions of the oxazole rings



π-bond orders in bioxazoles (XIa-c) and (XIIa-c). S^0 are given at the atoms (denominator), and for π-bond orders for the intercyclic bonds are an asterisk) states. Excitation localizations

(the 5-position) carry an appreciable negative charge (∿0.1 e), these charges being substantially reduced on excitation when the π-electron density is transferred to the disubstituted oxazole ring and the benzene, furan, or thiophen moieties in the cases of structures (XIa-c), or to the "central" benzene, furan, or thiophen ring in (XIIa-c). A measure of the considerable redistribution of electron density taking place at the atoms and fragments of the molecules on excitation is provided by the magnitudes of the intramolecular charge transfer between fragments of the molecules [11, 12], the direction and magnitude of which depend on which ring (benzene, furan, or thiophen) is present in the molecule. Intramolecular charge transfer is greatest in the benzene ring and least in the thiophene ring.

In addition to changes in intramolecular charge transfer, both types of systems (XIa-c and XIIa-c) show successive bathochromic and bathyfluoric shifts in the absorption and fluorescence maxima, and decreased quantum yields in the series of molecules containing the benzene, furan, and thiophen rings. It will be seen that excitation results in substantial changes in all the bond orders, the order of the intercyclic C–C bonds being particularly strongly increased, and this enables the molecule in its excited state $S^1_{\pi\pi^*}$ (i.e., at the instant of emission of a quantum of light) to be regarded as being more planar than in the ground state S^0. The excitation localization numbers indicate that approximately half of the excitation energy is localized at the central fragment in (XIa-c) and (XIIa-c), through which charge transfer is also effected. From the literature reports reviewed, in particular in [13], it may be assumed that

TABLE 5. UV Absorption and Fluorescence Spectra of Bioxazoles

Compound	Solvent	Maximum, nm		Stokes shift, ν, nm	Relative quantum yield, η
		absorption	fluoresence		
XIa	Cyclohexane	302	356	54	0,37
	Ethanol	302	378	76	0,48
XIb	Cyclohexane	310	360	50	0,35
	Ethanol	314	367	53	0,36
XIc	Cyclohexane	318	398	80	0,18
	Ethanol	320	400	80	0,17
XIIa	Cyclohexane	308	344	36	0,60
	Ethanol	309	350	41	0,71
XIIb	Cyclohexane	318	358	40	0,42
	Ethanol	321	363	42	0,63
XIIc	Cyclohexane	337	384	47	0,13
	Ethanol	338	390	52	0,14

the introduction of chromophoric groups into the position of maximum localization of excitation (the 5-position in these compounds) will provide compounds with useful optical properties. In order to predict reliably the spectral and luminescent properties of the molecules discussed here, it will be necessary to examine the dependence of the orbital character and the relative distributions of excited states on their electronic structure (spatial structure and type of heteroatom) [14]. Such a study will form the subject of succeeding communications.

EXPERIMENTAL

Theoretical calculations of electronic structure and the properties of the molecules in π-electronic approximation were carried out by the PPP method [5, 6] using the Hinze–Jaffe system of parameters [15]. Calculations were carried out using a program based on a modification of the PPP method which has been described previously [16]. The two-center coulombic integrals $\gamma_{\mu\nu}$ were calculated from the Mataga–Nishimoto equation [17].

PMR spectra were obtained on Tesla BS-467 (60 MHz) and Bruker WM-250 radiospectrometers with TMS as internal standard. The solvents used are given in the footnotes to Tables 1-3.

The electronic absorption spectra of the compounds in solution were measured on a Specord M-4030 spectrophotometer. The spectra were recorded at room temperature. The concentrations of the solutions were varied between 10^{-3} and 10^{-5} mole/liter. The accuracy of measurement of the positions of the absorption maxima was not less than ± 10 cm^{-1}, of the optical density $\pm 1\%$, and the molar extinction coefficient ε not less than $\pm(3\text{-}4)\%$, depending primarily on errors in the determination of the concentrations of the solutions. Absorption spectra were constructed in the form of plots of the decimal molar extinction coefficient ε against the frequency ν, cm^{-1}.

Fluorescence and excitation spectra were obtained on an SLM-4800S spectrofluorimeter (USA) with two monochromators with holographic diffraction gratings with a linear dispersion of 2 nm/mm. Excitation was carried out with an Osram XBO-450 lamp (450 W). The spectra were recorded using a photomultiplier in two-channel mode. The spectra were recorded in the memory of a microprocessor, and constructed using a graph-plotter in the form of plots of quantum intensity against wavelength λ, nm, or frequency, ν, cm^{-1}. Fluorescence spectra were corrected on a computer for the spectral characteristics of the photomultiplier used. The concentrations of the solutions of the compounds under study were 10^{-5}-10^{-7} mole/liter. Measurement of quantum yields for the compounds was carried out in dilute solution by a comparative method, by comparison with the quantum yield of a standard. The standard employed was anthracene, the quantum yield of which was taken to be $\eta = 0.22$, in a concentration not exceeding 10^{-5} mole/liter [18, 19]. The errors in the measurement of quantum yields were not greater than 10%. For optical measurements, a standard quartz cell with an optical path length of 10 mm was used.

Chromatographic analyses were carried out on an LKhM-80 chromatograph with a flame ionization detector, stainless steel column 2 mm × 1.5 mm, 5% SE-30 on Chromaton N-AW-DMCS (A) or 2 mm × 1.5 m, 15% Carbowax 20 M on Chromaton N-AW-DMCS (B), T 185°C, carrier gas nitrogen, 20 ml/min.

The properties of compounds (II)-(XII) are given in Table 4.

2-Phenyloxazole-5-aldehyde (IIa). To 6 g (41 mmole) of 2-phenyloxazole (Ia) in 20 ml of DMF was added dropwise with stirring at 0-5°C 8.5 ml of $POCl_3$, and the mixture stirred at the same temperature for a further 10 min, then for 7 h at 95°C. The mixture was cooled, poured on

to ice, extracted with chloroform, the extract washed with water, and filtered through a layer of silica gel L 40/100 approximately 5 cm thick. The residue after removal of the chloroform contained (GLC, column A) 93% of the aldehyde (IIa) and 7% of the oxazole (Ia). Recrystallization from hexane gave 6.1 g (85%) of (IIa), mp 72-74°C (cf. [1]). On a previous occasion [1], more severe conditions during the workup of the reaction mixture gave a yield of ∿60% of (IIa).

Formylation of 2-(2-Furyl)oxazole (Ib). The reaction was carried out as in the formylation of (Ia), but the mixture was heated for 1.5 h at 90°C until the starting material (Ib) had disappeared (GLC, column B), and the cooled reaction mixture was neutralized with K_2CO_3 solution. From 4.6 g (34 mmole) of the oxazole (Ib) there was obtained 4.95 g (89%) of a mixture of aldehydes (IIb) and (III) in a ratio of 1:2 (GLC, column B, and PMR). Chromatography on a column of silica gel L 40/100, eluent chloroform, gave 1.5 g of (IIb) and 2.2 g of (III).

2-(2-Thienyl)oxazole-5-aldehyde (IIc). The conditions used for the formylation of (Ic) were similar to those described above for the oxazole (Ia), except that the mixture was kept for 5 h at 90°C. From 4.8 g (30 mmole) of (Ic) there was obtained 4.85 g of (IIc).

2-Phenyloxazole-5-carboxylic Acid (IVa). To a solution of 0.8 g (4.6 mmole) of the aldehyde (IIa) in 7 ml of acetone was added at 5-10°C a solution of 0.46 g of CrO_3 in 1.5 ml of water, followed by the dropwise addition of 0.35 ml of conc. sulfuric acid. The resulting solution was stirred for 1 h at ∿20°C, then poured into water and extracted with ether. Following washing with water and drying over $MgSO_4$, the ether was removed to give 0.67 g of the acid (IVa). Acids (IVc) and (V) were obtained similarly.

2-(2-Furyl)oxazole-5-carboxylic Acid (IVb). To a solution of 1.65 g of silver nitrate in 7 ml of water was added 0.75 g (4.6 mmole) of the aldehyde (IIb) and 30 ml of dioxane, followed by the dropwise addition with stirring of a solution of 0.8 g of NaOH in 20 ml of water. The mixture was stirred for 2 h at ∿20°C, filtered, the solid washed with warm water, and the combined aqueous dioxane solution acidified with hydrochloric acid and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$, and the ether removed to give 0.75 g of the acid (IVb).

Methyl 2-Phenyloxazole-5-carboxylate (VIa). To 2.5 g (13.2 mmole) of the acid (IVa) in 50 ml of methanol was added 0.5 ml of conc. sulfuric acid, and the mixture boiled for 6 h. Excess methanol was distilled off slowly (over 2 h), and the residue poured into water, extracted with ether, the extract washed with aqueous potassium carbonate, and dried over $MgSO_4$. Removal of the ether gave 2.38 g of the ester (VIa). Similarly obtained were the methyl esters (VIb, c) and the ethyl ester (VII).

4,5-Dihydro-2'-phenyl-2,5'-bioxazole (VIIIa). To 2 g (10 mmole) of the ester (VIa) was added 5 ml of ethanolamine, and the mixture heated for 3 h at 150°C (in a bath). The methanol was then distilled off, followed by excess ethanolamine (at 170°C, 20 mm) (in a bath). To the resulting N-(2-hydroxyethyl)amide of the acid (IVa) was added, after cooling and without further purification, 8 ml of $SOCl_2$, and the resulting solution was heated for 1 h at 60°C. Excess $SOCl_2$ was distilled off at 60°C (20 mm), and to the solid residue was added 6 g of KOH in 10 ml of water and 10 ml of benzene. The mixture was boiled with stirring for 2.5 h, then cooled and extracted with benzene. The benzene extract was washed with water, the benzene removed, and the residue recrystallized from heptane to give 1.92 g of (VIIIa) (91% yield). In one experiment, the intermediate N-(2-hydroxyethyl)amide of 2-phenyloxazole-5-carboxylic acid was isolated in quantitative yield, mp 149-150°C (from benzene). Found, %: C 61.9; H 5.2; N 12.0. $C_{12}H_{12}N_2O_3$. Calculated, %: C 62.1; H 5.2; N 12.1.

Oxazolines (VIIIb, c) and (IX) were obtained similarly from the esters (VIb, c) and (VII) respectively, without isolation of the N-(2-hydroxyethyl)amides.

4,5,4',5'-Tetrahydro-2,2'-(1,4-phenylene)bisoxazole (Xa). To 20 g of ethanolamine was added portionwise at 140-160°C 8 g (41 mmole) of dimethyl terephthalate, and the mixture kept for 30 min at 150°C. After cooling, the solid was filtered off, and washed with water and chloroform to give 9.9 g (95%) of terephthalic acid bis-N-(2-hydroxyethyl)amide, which could not be obtained in an analytically pure state. The bisamide (8.6 g) was added in small portions with stirring to 8 g of conc. sulfuric acid, then conc. sulfuric acid (8 g) was added to the mixture with ice-cooling, and the resulting solution heated for 40 min at 140°C. After cooling, 60 ml of absolute ethanol was added with cooling, and the mixture stirred for 10 min at ∿20°C. The solid which separated was filtered off, and washed with two portion of

15 ml of absolute alcohol to give 10.5 g (71%) of the acid sulfate of terephthalic acid bis-N-(2-hydroxyethyl)amide, mp 192-193°C, which was dissolved without further purification in 100 ml of water. To this solution was added with stirring a cold solution of 50 g of NaOH in 100 ml of water. After keeping for 15 h at 20°C, the resulting suspension was boiled with stirring for 5 h, the solid filtered off, and washed with water to give 2.7 g (50%) of the bisoxazole (Xa), mp 241-243°C (for lit. value, see [20]).

4,5,4',5'-Tetrahydro-2,2'-(2,5-thienylene)bisoxazole (Xc). To 15 g (103 mmole) of adipic acid was added 80 ml of $SOCl_2$ and 1.8 ml of pyridine, and the resulting solution was boiled for 24 h. Excess $SOCl_2$ was distilled off, the bath temperature being raised gradually from 130 to 155°C. The residue was twice distilled in vacuo to give 13.1 g of thiophen-2,5-dicarbonyl chloride, bp 150-152°C (11 mm), mp 42-43°C, yield 61% (lit. values see [7, 21]). To 4 g (19 mmole) of the diacid chloride was added 25 ml of methanol, the mixture becoming warm and a solid separating. After keeping at room temperature for 20 min, the mixture was poured into 300 ml of chilled water, extracted with ether, the extract washed with sodium carbonate solution and water, dried over $MgSO_4$, and evaporated to give 3.65 g of dimethyl thiophen-2,4-dicarboxylate, mp 142-146°C, yield 95% (for lit. values, see [21]). To 4.6 g (23 mmole) of this diester was added 8 ml of ethanolamine, methanol distilled off over 2.5 h, bath temperature 135-140°C, and the residue washed with water (2 × 20 ml), the solid being separated by decantation. Filtration gave 4.16 g (73%) of thiophen-2,5-dicarboxylic acid bis-N-(2-hydroxyethyl)amide, mp 214-216°C. Recrystallization from alcohol gave a solid mp 220-221°C. Found, %: C 46.1; H 5.7; N 10.5; S 12.1. $C_{10}H_{14}N_2O_4S$. Calculated, %: C 46.5; H 5.5; N 10.8; S 12.4. Successive treatment of 4 g (13.5 mmole) of the bisamide with 35 ml of $SOCl_2$ and 20 g of KOH in 40 ml of water as described above for (VIIIa) gave 3.11 g of the bisoxazoline (Xc).

2'-Phenyl-2,5-bioxazole (XIa). To a solution of 2.42 g (11.3 mmole) of the oxazoline (VIIIa) in 80 ml of benzene was added 10 g of nickel peroxide [22], and the mixture boiled with stirring for 1 h. A further 5 g of nickel peroxide was then added, and boiling continued for 1 h (until starting material (VIIIa) was no longer present according to TLC on Silufol, eluent chloroform). The mixture was filtered, the solid washed with benzene, and the combined benzene solutions evaporated to give 0.94 g of the bioxazole (XIa) (Tables 3 and 4). The solid nickel peroxide was washed with acetone, and removal of the acetone gave 0.15 g (7%) of 2-phenyloxazole-5-carboxamide, mp 164-166°C (from chloroform). Found, %: N 14.9. $C_{10}H_8N_2O_2$. Calculated, %: N 14.9. PMR spectrum [$(CD_3)_2CO$]: 2.98 (s, 2H, NH_2), 7.50 (m, 3H, m- and p-H of the benzene ring), 7.70 (s, 1H, 4-H), 8.15 ppm (m, 2H, o-H).

2'-(2-Furyl)-2,5'-bioxazole (XIb). From 0.3 g (1.5 mmole) of the oxazoline (VIIIb) on treatment with 3.5 g of nickel peroxide as described in the previous experiment there were obtained 0.04 g of the bioxazole (XIb) (Tables 3 and 4), and 0.18 g (67%) of 2-(2-furyl)-oxazole-5-carboxamide, mp 148-150°C (from benzene). Found, %: C 53.8; H 3.3; N 15.1. $C_8H_6N_2O_2$. Calculated, %: C 53.9; H 3.4; N 15.7. PMR spectrum [$(CD_3)_2CO$]: 2.95 (s, 2H, NH_2), 7.20 (d.d., 1H, 4'-H), 7.75 (d, 1H, 3'-H), 7.92 (s, 1H, oxazole 4-H), 7.97 ppm (d, 1H, 5'-H, $J_{3'4'}$ = 4 Hz, $J_{4'5'}$ = 2 Hz).

2'-(2-Thienyl)-2,5'-bioxazole (XIc). From 1.05 g (4.8 mmole) of the oxazoline (VIIIc) on treatment with 7.3 g of nickel peroxide as described for the oxazole (XIa), there were obtained 0.35 g of the bioxazole (XIc) (Tables 3 and 4) and 0.25 g (25%) of 2-(2-thienyl)-oxazole-5-carboxamide, mp 144-145°C (from benzene). Found, %: N 14.3. $C_8H_6N_2O_2S$. Calculated, %: N 14.4. PMR spectrum [$(CD_3)_2CO$]: 2.99 (s, 2H, NH_2), 7.25 (d.d., 1H, 4'-H), 7.77 (s, 1H, oxazole 4-H), 7.79 (d, 1H, 3'-H), 7.88 ppm (d, 1H, 5'-H, $J_{3'4}$ = 3.6, $J_{4'5'}$ = 5.0 Hz).

1,4-Phenylene-2,2'-bisoxazole (XIIa). From 1.0 g (4.6 mmole) of the bisoxazole (Xa) and 9 g of nickel peroxide, as for (XIa), there was obtained 0.08 g of the oxazole (XIIa).

2,5-Furylene-2,2'-bisoxazole (XIIb). From 0.5 g (2.5 mmole) of the oxazoline (IX) and 4 g of nickel peroxide as described for (XIa), there was obtained 0.13 g of the bisoxazole (XIIb).

2,5-Thienylene-2,2'-bisoxazole (XIIc). From 2.5 g (11.5 mmole) of the bisoxazoline (Xc) and 30 g of nickel peroxide, as described for (XIa), there was obtained 0.39 g of the bisoxazole (XIIc).

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COURSE OF BROMINATION OF THIAZOLE AND 2-METHYLTHIAZOLE

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Bromination of thiazole by bromine in the presence of aluminum chloride in neutral solvent or without solvent takes place at the 2-position. Such an orientation contradicts the traditional addition–cleavage mechanism, and agrees with the ylid mechanism of electrophilic substitution. 2-Methylthiazole brominates at the 5-position, and the reaction is impeded in the presence of aluminum chloride; this is due to heterocycle deactivation by complexation with the Lewis acid at the nitrogen atom.

We recently showed [1] that 2-phenylthiazole is smoothly brominated at the 5-position of the thiazole ring by bromine in a neutral solvent (benzene or chloroform). 2-Phenylthiazole can be considered as an analog of biphenyl. As established by ^{13}C NMR spectra and quantum chemical calculations [2], already in the ground state there is a transfer of electron density from the benzene ring to the thiazole; this is apparently the reason, to a substantial extent, for the high reactivity of the thiazole ring in electrophilic substitution.

In the present work we have studied the bromination of unactivated unsubstituted thiazole and of 2-methylthiazole. It is known that thiazole can not be brominated by bromine in a neutral solvent: only the perbromide is formed [3]. We used conditions that had previously permitted pyridine to be brominated [4], viz., the action of bromine in the presence of a catalytic amount of $AlCl_3$ in carbon tetrachloride or without solvent. Here we obtained a small yield of a mixture in which the main product, and also the only monobromothiazole, was 2-

*Deceased.

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