SYNTHESIS AND INVESTIGATION OF AZIRIDINO DIOXIMES

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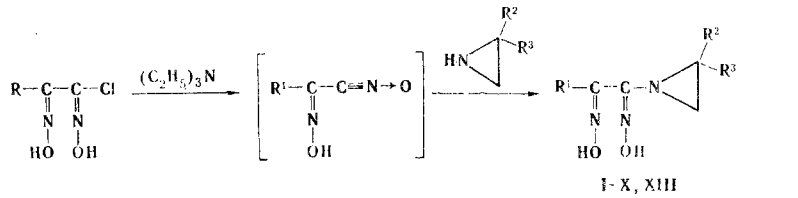
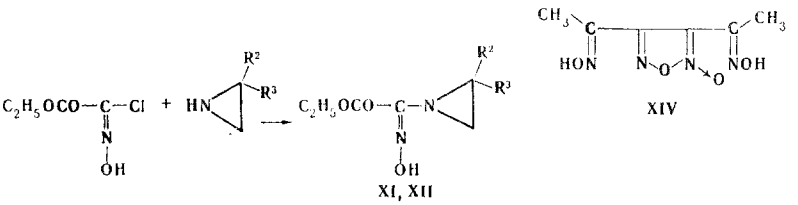
The reactions of chloroglyoximes with substituted aziridines were investigated. In the case of donor substituents in the aziridine the reaction takes place with the formation of anti-aziridino dioximes, while the formation of furoxanoglyoximes is also observed when electron-acceptor substituents are present. Aziridinofuroxans were obtained by oxidation of the aziridino dioximes. The barrier to inversion of the nitrogen atom in the aziridinofuroxans is 12.0 kcal/mole. The expansion of the aziridine ring of the aziridino dioximes, which leads to the formation of 1,2,4-oxadiazines, was investigated.

In conformity with the literature data the reaction of haloglyoximes with amines leads to substitution products, viz., aminoglyoximes, as well as nitrile oxides, which are converted to heterocyclic systems [1, 2]. In the case of ammonia the resulting aminoglyoximes have an anti-configuration, while amines react with haloglyoximes to give amphi-aminoglyoximes.

In order to study the configurations of the aziridinoglyoximes and their subsequent transformations we studied the reaction of chloroglyoximes and ethoxycarbonylformhydroxamic acid chloride with aziridines. We found that the reaction proceeds in different directions depending on the character of the substituents in the aziridine ring.



I-X, XIII



XIV

XI, XII

R=Cl, H, CH_3, C_6H_5, $COOC_2H_5$; R^1=H, CH_3, C_6H_5, $COOC_2H_5$; I $R^1=R^2=R^3=H$; II $R^1=CH_3$, $R^2=R^3=H$; III $R^1=C_6H_5$, $R^2=R^3=H$; IV R^1= aziridine, $R^2=R^3=H$; V $R^1=R^2=H$, $R^3=CONH_2$; VI $R^1=CH_3$, $R^2=H$, $R^3=CONH_2$; VII $R^1=C_6H_5$, $R^2=H$, $R^3=CONH_2$; VIII $R^1=R^3=CH_3$, $R^2=H$; IX R^1=2-methylaziridine, $R^2=H$, $R^3=CH_3$; X $R^1=C_6H_5$, $R^2=R^3=CH_3$; XI $R^1=COOC_2H_5$, $R^2=CONH_2$, $R^3=H$; XII $R^1=COOC_2H_5$, $R^2=R^3=H$; XIII $R^1=CH_3$, $R^2=H$, $R^3=CONH_2$

Aziridino dioximes I-X and XIII are formed with 2-alkyl-substituted and unsubstituted aziridines (Tables 1 and 2), whereas competitive dimerization of the intermediate nitrile oxide to give 3,4-diacetylfuroxan dioxime (XIV) was observed with aziridines that contain electron-acceptor groups in which the nitrogen atom has decreased nucleophilicity. In particular, aziridino dioximes are formed along with dioxime XIV in a ratio of 2:1 in the reaction of methylchloroglyoxime with aziridine-2-carboxylic acid isopropyl ester and amide. Aziridino dioximes were not formed at all in the reaction of dichloroglyoxime with the same aziridines, and the starting aziridines and products of polymerization of the nitrile oxides were isola-

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TABLE 1. Spectral Characteristics of I-XIII

Compound	PMR spectrum, δ, ppm		IR spectrum, ν, cm^{-1}				
	aziridine	—OH	C=N	CH (aziridine)	C=O	aziridine	NH_2
I	2,12	10,85; 11,47	1630	3020	—	1230	—
II	2,09	10,89; 11,62	1620	3070	—	1230	—
III	2,18	10,65; 11,36	1625	3060	—	1230	—
IV	2,09	10,46; —	1630	3070	—	1230	—
V	2,08	10,73; 11,35	1630	3070	1680	1230	3210
VI	2,32 (CH_2) 2,77 (CH)	10,55; 11,17	1630	3060	1680	1230	3180
VII	2,19 (CH_2) 2,63 (CH)	9,50; 10,04	1640	3030	1680	1230	3280
VIII	2,18 (CH) 1,94 (CH_2)	10,49; 11,22	1630	3050	—	1230	—
IX	1,85 (CH_2) 2,16 (CH)	10,22; —	1629	3080	—	1230	—
X	2,24	9,22; 9,30	1610	3080	—	1230	—
XI	2,27 (CH_2) 2,87 (CH)	11,16; —	1630	3060	1730 1679	1230	3210
XII	2,11	11,18; —	1630	3060	1730	1230	—
XIII	2,12	11,33; 10,71	1600	3050	1730	1230	—

TABLE 2. Characteristics of I-XXIII

Compound	mp. °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
I	45	37,1	5,4	30,3	$C_4H_7N_3O_2$	37,2	5,4	30,5	40
II	152—154	43,8	6,7	30,1	$C_5H_9N_3O_2$	43,7	6,7	30,0	59
III	151—153	57,3	5,4	19,4	$C_{10}H_{11}N_3O_2$	57,5	5,3	19,5	45
IV	166	41,2	6,0	31,7	$C_6H_{10}N_4O_2$	41,3	5,9	31,9	47
V	139—140	34,6	4,7	30,4	$C_5H_8N_4O_3$	34,8	4,6	30,5	53
VI	172	29,2	4,2	25,6	$C_6H_{10}N_4O_3$	29,0	4,2	25,4	59
VII	147	52,3	4,7	21,9	$C_{11}H_{12}N_4O_3$	52,2	4,8	22,0	53
VIII	137—138	46,5	7,0	26,6	$C_6H_{11}N_3O_2$	46,8	7,1	26,7	74
IX	154—156	48,1	7,0	28,2	$C_8H_{14}N_4O_2$	48,2	7,0	28,2	68
X	—	61,6	6,2	18,3	$C_{12}H_{15}N_3O_2$	61,8	6,4	18,0	69
XI	170—173	41,5	5,3	20,6	$C_7H_{11}N_3O_4$	41,7	5,3	20,5	55
XII	94—96	45,8	6,1	17,6	$C_6H_{10}N_2O_3$	45,5	6,3	17,7	54
XIII	158—159	48,3	6,5	18,2	$C_9H_{15}N_3O_4$	48,1	6,5	18,3	52
XIV	144—145	36,0	4,0	28,0	$C_6H_8N_4O_4$	36,1	4,0	27,9	30
XVA XVB	72—73 76—77	59,0	4,4	20,4	$C_{10}H_9N_3O_2$	59,0	4,4	20,4	44
XVI	91—93	42,3	4,8	33,3	$C_6H_8N_4O_2$	42,4	4,7	33,2	46
XVII	—	46,1	5,8	25,8	$C_6H_9N_3O_2$	46,3	5,8	26,9	58
XVIII	56—58	48,5	6,1	28,6	$C_8H_{12}N_4O_2$	48,9	6,1	28,7	50
XIX	98—99	62,4	5,6	18,3	$C_{12}H_{13}N_3O_2$	62,3	5,6	18,1	51
XX	—	42,3	4,9	29,6	$C_5H_7N_3O_2$	42,6	5,0	29,7	42
XXI	109—110	58,1	5,3	20,2	$C_{10}H_{11}N_3O_2$	58,5	5,4	20,5	78
XXII	97—99	45,8	6,1	17,5	$C_6H_{10}N_2O_3$	45,6	6,3	17,7	80
XXIIIA, B	205—206 209—210	48,6	6,9	28,4	$C_8H_{14}N_4O_2$	48,4	7,7	28,2	80

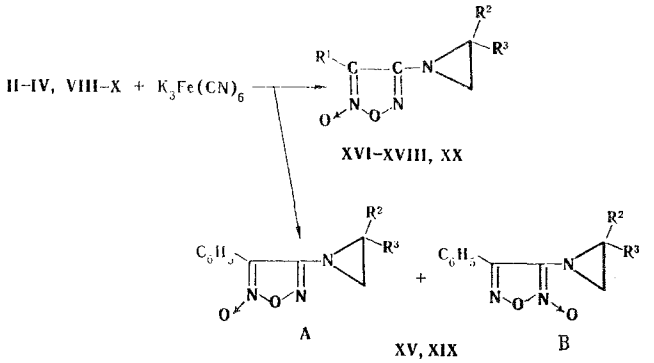
ted. The formation of only aziridinoglyoximes XI and XII was observed in the reaction of monochloroglyoxime with 2-substituted and unsubstituted aziridines (Tables 1 and 2).

We established that aziridino dioximes retain the **anti-configuration** of the starting glyoximes. (The formation of red complexes was observed when aziridino dioximes I-X and XIII were treated with nickel nitrate.)

In a study of the subsequent transformations due to the presence of oxime groups and an aziridine ring we investigated the transformations of the aziridino dioximes under the influence of the oxidizing agent potassium ferricyanide in an aqueous solution of ammonia or alkali at room temperature. We isolated the corresponding aziridinofuroxans XV-XIX as the final products (Tables 1 and 3). The IR spectra of XV-XIX contain characteristic bands at 1630 and 900 cm^{-1} (furoxan) and at 1230 and 3020-3100 cm^{-1} (aziridine). A signal of protons of an aziridine ring at δ 2.18-2.67 ppm is observed in the PMR spectra of the aziridinofuroxans. Signals of protons of OH groups are absent at weak field (Tables 2 and 4).

TABLE 3. Spectral Characteristics of Aziridinofuroxans XV-XX

Compound	IR spectrum, ν, cm^{-1}			PMR spectrum, δ, ppm			
	aziridine	furoxan	aziridine (δ)	aziridine	CH_3 in aziridine	CH_3	Ph
XVA,B	3060	1600	1230	2,41	—	—	7,47—8,18
XVI	3100	1620	1230	2,63	—	—	—
XVIIB	3080	1620	1230	2,21 (CH_2) 2,52 (CH)	1,38	2,16	—
XVIII	3100	1600	1230	2,18 (CH_2) 2,56 (CH)	1,39	—	—
XIX	3080	1600	1230	2,44	1,14	—	7,46—8,13
XX	3020	1630	1230	2,43	—	2,14	



XV $R^2=R^3=H$; XVI $R^1=$ aziridino $R^2=R^3=H$; XVII $R^1=R^2=CH_3$, $R^3=H$; XVIII $R^1=$2-methylaziridino $R^2=CH_3$, $R^3=H$; XIX $R^2=R^3=CH_3$; XX $R^1=CH_3$, $R^2=R^3=H$

The oxidation of anti-1-phenyl-2-aziridino dioximes leads to the formation of a mixture of two furoxan isomers A and B in a ratio of 3:1. Isomer B, being thermodynamically unstable, undergoes quantitative isomerization to isomer A when it is refluxed in toluene. In order to establish the structures of the isomers obtained and the effect of the configuration of the starting aziridino dioxime on the stereo specificity of the oxidation we studied the oxidation of an amphi-1-phenyl-2-aziridino dioxime [3] with potassium ferricyanide. In accordance with [3], the formation of isomer XVB was expected in the oxidation of this isomer; however, it follows from the results of our studies that a mixture of isomers XVA and XVB is formed, as in the oxidation of anti-aziridino dioxime III. Consequently, the formation of furoxan isomers in this case does not depend on the configuration of the aziridino dioxime undergoing oxidation. The presence of a mixture of isomers can probably be explained by the rather close rates of formation of aziridino furoxans XVA and XVB.

The mixture of isomers XVA and XVB was separated into the individual isomers by means of preparative thin-layer chromatography (TLC). An absorption maximum at 282 nm is observed in the electronic spectrum of the more stable isomer (Fig. 1). A comparison with the UV spectra of the isomers of aminophenylfuroxans [3] made it possible to assume that the XVA structure corresponds to this isomer. Isomer XVB has a longer wave absorption band at 295 nm.

The ^{13}C NMR spectra of furoxans XVA and XVB confirm the veracity of the configurations of these isomers. It is known [4-6] that the signal of the carbon atom bonded to the N-oxide group in the furoxans is shifted 40 ppm to strong field with respect to the signal of the second carbon atom of the furoxan ring. In a comparison of the chemical shifts of the carbon atoms bonded to identical substituents in XVA and XVB this shift turns out to be approximately the same value (40 ppm).

Only one methylaziridinofuroxan isomer, which did not undergo isomerization when it was heated in toluene, was formed in the oxidation of the anti-1-methyl-2-aziridino dioxime. These conclusions follow from an analysis of the ^{13}C NMR and UV spectra and the data from TLC. An analysis of the ^{13}C NMR spectra of the reaction product and a comparison of the chemical shifts with the spectral data for 3-phenyl-4-aziridinofuroxan (XVA) show that this compound has the XX structure; a comparison of their electronic spectra (λ_{max} 252 nm for XX) also confirms this.

TABLE 4. ^{13}C NMR Spectra of Aziridinofuroxan Isomers

Compound	δ_c			
	furoxan			aziridine
	C—Ph	C—N	C—CH_3	CH_2
XVA	111,3	162,9	—	28,9
XVB	152,7	122,9	—	29,7
XX	—	162,6	108,4	29,6

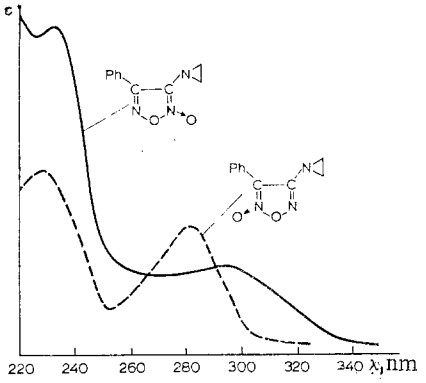


Fig. 1. UV spectra of 3-phenyl-4-aziridinofuroxan (XVA) and 4-phenyl-3-aziridinofuroxan (XVB).

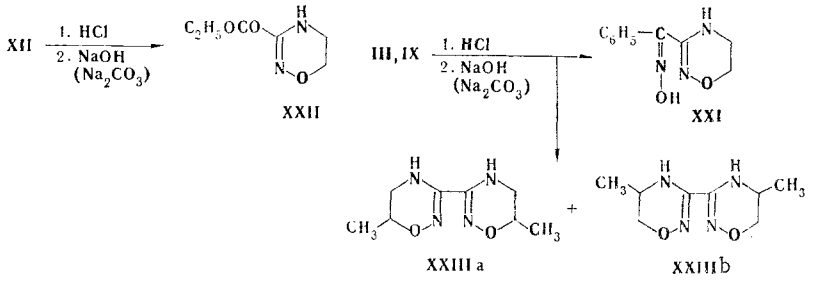
In order to ascertain the effect of the furoxan ring on the height of the barrier to inversion of the nitrogen atom of aziridines we determined the barriers to inversion of the nitrogen atoms of the thermodynamically stable isomers of 3-phenyl-4-aziridinofuroxan (XVA) and 3-phenyl-4-(2,2-dimethylaziridino)furoxan (XIX).

The coalescence temperature of the signals of the protons of the aziridine ring for XVA is −32°C, $\Delta\nu$ = 13.8 Hz, and activation energy ΔG^*_c = 12.4 kcal/mole. In the case of 2,2-disubstituted aziridine XIX T°_c = −38°C, $\Delta\nu$ = 13.4 Hz, and ΔG^*_c = 12.0 kcal/mole. Consequently, in aziridinofuroxans the pyramid of the nitrogen atom is not stable at room temperature. The effect of the furoxan ring on the pyramidal stability of the nitrogen atom in aziridinofuroxans is comparable to the effect of the phenyl ring (ΔG^*_c = 11.9 kcal/mole), which increases the rate of inversion of the nitrogen atom owing to delocalization of its free electron pair by the aromatic ring.

The presence of an aziridine fragment in the aziridino dioxime systems suggests the possibility of transformations involving expansion of the three-membered ring. In order to study the properties of the aziridino dioximes we investigated the possibility of conversion of some aziridino dioximes to 1,2,4-oxadiazine derivatives. The corresponding 1,2,4-oxadiazines are formed in all cases by the action of mineral acid on the aziridino dioximes with the subsequent addition of an alkaline agent. The reaction proceeds through opening of the aziridine ring with subsequent formation of an oxadiazine ring [7]. A band at 3300 cm^{-1} (νNH) is observed in the IR spectra of the 1,2,4-oxadiazines, and the δ (1230 cm^{-1}) and ν (3060-3080 cm^{-1}) bands characteristic for aziridines are absent.

The PMR spectra of XIX-XXI do not contain signals of the protons of the aziridine ring at δ 1.85-2.18 ppm and signals that characterize the oxime group at δ 10.5-11.18 ppm. (Scheme, top, following page.)

Bis-1,2,4-oxadiazines XXIIIa and XXIIIb are formed in the case of 1,2-bis(2-methylaziridino)glyoxime IX. The ^1H NMR spectra of the reaction product correspond to two sets of A_3MXY spin systems. The ratio of the components in the spectra changes with repeated recrystallization. Consequently, we are dealing with two independent isomers. We were able to separate them by repeated recrystallization (from benzene). The parameters of the ^1H NMR spectra for the isomers are presented in Table 5.



On the basis of the fact that constants of spin–spin coupling between NH and H_XH_Y in isomer XXIIIa and between NH and H_M in isomer XXIIIb are observed in thoroughly purified samples it may be assumed that the isomers differ with respect to the location of the CH_3 group in the ring — in XXIIIa the latter is adjacent to the oxygen atom (the 6 position), whereas in XXIIIb it is adjacent to the nitrogen atom (the 5 position). This interpretation explains the small J_{XY} value in XXIIIb as compared with XXIIIa. The ^{13}C NMR spectra recorded with incomplete decoupling of the protons confirm this interpretation (see the experimental section).

Thus in the reaction of 1,2-bis(2-methylaziridino)glyoxime with mineral acid the aziridine ring undergoes virtually identical opening at both N–C bonds. The identical character of the NMR signals from both rings in XXIIIa,b constitutes evidence that a possible mixed isomer is not formed in the reaction.

The pronounced difference in the constants of spin–spin coupling between the H_M and H_X and H_Y protons in XXIIIa,b (Table 5) indicates the nonplanar structure of the ring with a primarily pseudoequatorial orientation of the CH_3 group.

EXPERIMENTAL

The electronic spectra of solutions of the compounds in hexane were recorded with a Specord UV-vis spectrophotometer. The IR spectra of Nujol suspensions of the compounds were recorded with a Specord 75-IR spectrometer. The PMR spectra of solutions of the compounds in d_6-DMSO and $CDCl_3$ were recorded with a Perkin–Elmer R12B spectrometer with tetramethylsilane as the internal standard. The ^{13}C NMR spectra of solutions of the compounds in d_6-DMSO and $CDCl_3$ were recorded with a Bruker WH-90 spectrometer at 22.63 MHz. The composition of the reaction mixtures and the purity of the products were monitored by thin-layer chromatography (TLC) on Silufol plates.

The characteristics of the compounds obtained are presented in Tables 2-4.

1,2-Bis(2-methylaziridino)glyoxime (IX). A solution of 7.9 g (0.05 mole) of dichloroglyoxime in 100 ml of ether was added dropwise with stirring at 0-5°C to a solution of 7.4 g (0.13 mole) of 2-methylaziridine and 13.1 g (0.13 mole) of triethylamine in 100 ml of ether, and the mixture was maintained at this temperature for 1 h. The precipitate was removed by filtration, the filtrate was evaporated, and the reaction product was recrystallized from ethyl acetate.

Aziridinoglyoxime IV was similarly obtained.

1-Phenyl-2-aziridinoglyoxime (III). A solution of 2.4 g (0.012 mole) of α-chloro-2-phenylglyoxime in ether was added dropwise to an ether solution of 0.78 ml (0.014 mole) of ethyleneimine, and the mixture was maintained at this temperature for 30 min and then at room temperature for 1-1.5 h. The precipitate was removed by filtration, the filtrate was evaporated, and the reaction product was washed with water.

Aziridinoglyoximes I, II, V, VIII, and X were similarly obtained. Ethoxycarbonylglyoximic acid chloride was used as the starting oxime in the case of XI and XII.

1-Methyl-2-(2-carbamoylaziridino)glyoxime (VI). An ether solution of 1.37 g (0.01 mole) of 1-methyl-2-chloroglyoxime was added dropwise at −2 to +2°C to a solution of 1.52 g (0.015 mole) of triethylamine and 0.86 g (0.01 mole) of aziridinecarboxylic acid amide in a mixture of 100 ml of methanol and 20 ml of diethyl ether, and the mixture was maintained at this temperature for 1 h. The precipitate was removed by filtration, the filtrate was evaporated, the residue was washed with acetone, and the acetone solution was evaporated. The product was separated by means of TLC on plates with silica gel [chloroform–diisopropyl ether (4:1)] to

TABLE 5. ^{1}H NMR Spectra of Bis-1,2,4-oxadiazine Isomers in $CDCl_3$

Isomers	δ, ppm					J, Hz			
	CH_3	NH	H_M	H_X	H_Y	CH_3–H_M	MX	MY	XY
XXIIIa*	1,29	5,7	3,69	3,12	3,35	6,1	8,2	2,8	−11,2
XXIIIb†	1,17	5,6	3,39	3,39	3,96	6,1	6,5	2,9	−9,7

*$^3J_{NH-H_X}$ = 1.1 Hz, and $^3J_{NH-H_Y}$ = 2.5 Hz.
†$^3J_{NH-H_M}$ = 1.9 Hz.

give VI (Table 2) and dioxime XIV in the form of an oil, which began to crystallize when toluene (2:1) was added. IR spectrum: 1629 (furoxan), 933 (N–O), and 1650 cm^{-1} (C=N). PMR spectrum: δ 1.87 (3H, s, CH_3), 12.09 (1H, s, OH), 12.31 (1H, s, OH), and 2.09 ppm (3H, s, CH_3).

Glyoximes VII and XIII were similarly obtained.

Oxidation of Anti-Phenylaziridinoglyoxime (III). A solution of 14 g of potassium ferricyanide in 50 ml of water was added dropwise at 15°C to a solution of 2.05 g (0.01 mole) of aziridinoglyoxime III in 16.4 ml of 10% ammonium hydroxide and 16 ml of water, and the mixture was allowed to stand for 3 h. The precipitate was removed by filtration, washed with water, and recrystallized from alcohol and water. The product, which was a mixture of isomers XVa and XVb, was separated by means of TLC on plates with silica gel [chloroform–diisopropyl ether–ethanol (3:1:0.2)] to give 0.66 g of XVa and 0.22g of XVb.

The oxidation of amphi-1-phenyl-2-aziridinoglyoxime gave a similar mixture.

Aziridinofuroxans XV-XVIII and XX were similarly obtained.

3-Ethoxycarbonyl-1,2,4-oxadiazine (XXII). A solution of 2 ml of hydrochloric acid in 5 ml of acetone was added dropwise with stirring at 0-5°C in the course of 0.5 h to a solution of 0.79 g (0.005 mole) of oxime XII in 100 ml of acetone, and the mixture was allowed to stand at room temperature for 24 h. The acetone was evaporated, water was added to the residue, and the solution was neutralized with sodium carbonate or alkali and extracted with ether. The ether extract was dried with anhydrous sodium sulfate and evaporated to give 0.8 g of XXII.

Oxadiazines XXI and XXIII were similarly obtained. Bis-1,2,4-oxadiazine XXIII was isolated from the mixture by means of TLC on plates with silica gel [hexane–ether (1:3)]. IR spectrum of oxadiazine XXI: 1620 (C=N), 1645 (C=N–OH), and 3350 cm^{-1} (NH). PMR spectrum of oxadiazine XXI, δ: 3.59 (t, 2H, CH_2O), 3.38 (t, 2H, CH_2), 7.42 (m, 5H, C_6H_5), and 11.73 ppm (s, 1H, N–OH). IR spectrum of oxadiazine XXII: 1610 (C=N) and 3350 cm^{-1} (NH). PMR spectrum of oxadiazine XXII, δ: 1.25 (t, 3H, CH_3), 4.11 (q, 2H, CH_2), 3.22 (t, 2H, CH_2), and 3.58 ppm (t, 2H, CH_2O). IR spectrum of oxadiazine XXIIIa, b −1620 cm^{-1} (C=N). ^{13}C NMR spectrum of XXIIIa, δ: 144.9* (s, C=N), 69.4 (d, O–C), 44.1 (t, CH), and 17.9 ppm (q, CH_3). ^{13}C NMR spectrum of XXIIIb, δ: 144.7 (s, C=N), 68.2 (t, O–C), 44.9 (d, CH), and 16.9 ppm (q, CH_3).

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*The multiplicity is indicated under off-resonance conditions.