SYNTHESIS AND PROPERTIES OF AZOLES AND THEIR DERIVATIVES.

33.* SYNTHESIS OF 1,3,4-OXADIAZOLES THAT CONTAIN AN INDOLYL GROUP

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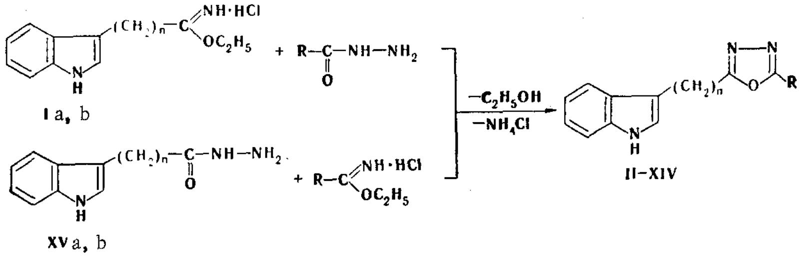
2,5-Disubstituted oxadiazoles with indole residues were synthesized by condensation of the hydrochlorides of the corresponding imido esters with hydrazines, as well as by cyclization of hydrazides by the action of $POCl_3$. 2-Substituted oxadiazoles of the same series were obtained by condensation of the corresponding hydrazides with ethyl orthoformate.

In a continuation of our research on the synthesis and study of the transformations of imido ester hydrochlorides of indolyl carboxylic acids [1] we examined their reaction with some hydrazides in order to obtain the corresponding 1,3,4-oxadiazoles, regarding which limited data are available.

As a result of the condensation of indole-3-carboxylic (Ia) and 3-indolylacetic (Ib) acid ethyl imido ester hydrochlorides with hydrazides we obtained the corresponding 2,5-disubstituted 1,3,4-oxadiazoles (II-XIV), which contain indole residues (method A). Since hydrochloride Ia is less active than Ib [1], the reactions with it were carried out under more severe conditions. Better yields of oxadiazoles II-VIII are obtained in the case of equimolar ratios of the components, whereas better yields of IX-XIV are obtained with a ratio of hydrochloride Ib to the hydrazide of 1.25 : 1.

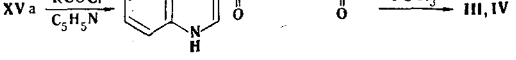


II—VIII n=0: II R=CH_3; III R=C_6H_5; IV R=4-$O_2NC_6H_4$; V R=4-ClC_6H_4; VI R=5-nitro-2-furyl VII R=3-indolyl; VIII R=3-indolylmethyl; IX—XIV n=1, IX R=CH_3, X R=C_6H_5, XI R=4-$O_2NC_6H_4$, XII R=4-ClC_6H_4; XIII R=5-nitro-2-furyl; XIV R=3-indolylmethyl; Ia, XVa n=0; b n=1

To obtain 1,3,4-oxadiazoles II-XIII we also used the reaction of indole-3-carboxylic (XVa) and 3-indolylacetic (XVb) and hydrazides with carboxylic acid ethyl imido ester hydrochlorides (method B); the yields of oxadiazoles (Table 1) were lower in this case than the yields obtained by method A.

For the synthesis of 1,3,4-oxadiazoles III and IV we also used the cyclodehydration of the corresponding N^1,N^2-diacylhydrazines (XVIa, b) in the presence of phosphorus oxychloride, which is accompanied by pronounced resinification of the reaction mixture, as a result of which we were able to isolate oxadiazoles III and IV in no higher than 25-30% yields.

It is known [2] that symmetrical 2,5-disubstituted 1,3,4-oxadiazoles can be obtained from carboxylic acids and a hydrazine salt in the presence of polyphosphoric acid (PPA), which is simultaneously the dehydrating agent and the solvent. We demonstrated that this method can also be used for the synthesis of symmetrical indolyloxadiazoles VII and XIV from the corresponding acids of the indole series.



XVIa, b a R=C_6H_5; b R=4-$O_2NC_6H_4$

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*See [1] for Communication 32.

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TABLE 1. 2,5-Disubstituted 1,3,4-Oxadiazoles II-XIV

Compound	mp, °C*	PMR spectrum, ppm	Found, %			Empirical formula	Calculated, %			Yield, %	
			C	H	N		C	H	N	A	B
II	138—139	2,50 (3H, s., CH_3), 7,05—7,84 (5H, m , indole), 8,22 (1H, s NH)	66,2	4,52	21,2	$C_{11}H_9N_3O$	66,3	4,5	21,1	86	70
III	260—261	6,90—7,80 (10H, m, aromatic protons), 8,14 (1H, s., NH)	73,6	4,2	16,2	$C_{16}H_{11}N_3O$	73,6	4,2	16,1	91	73
IV	302—304	7,22—7,98 (9H, m, aromatic protons), 8,25 (1H, s, NH)	62,7	3,3	18,1	$C_{16}H_{10}N_4O_3$	62,7	3,3	18,3	85	76
V	262—264	7,10—7,80 (9H, m, aromatic protons), 8,20 (1H, s, NH)	65,0	3,4	14,1	$C_{16}H_{10}N_3OCl$	64,9	3,4	14,2	88	80
VI	222—224	7,08—7,84 (5H, m, indole), 7,17 (1H, d., 3-H furan), 7,72 (1H, d, 4-H furan), 8,16 (1H, s., NH)	55,2	2,6	18,5	$C_{14}H_8N_4O_4$	55,3	2,6	18,4	79	64
VII	172—173	7,12—7,86 (10H, m, indole), 8,12 (2H, s., 2NH)	72,2	3,8	18,3	$C_{18}H_{12}N_4O$	72,0	4,0	18,6	89	—
VIII	210—212	3,96 (2H, s., CH), 7,05—7,80 (10H, m., indole), 8,12 (1H, s., NH), 8,20 (1H, s , NH)	72,5	4,4	17,6	$C_{19}H_{14}N_4O$	72,6	4,4	17,8	88	72
IX	200—201,5 †	2,50 (3H, c, CH), 4,00 (2H, s , CH), 7,12—7,90 (5H, m , indole), 8,08 (1H, s., NH)	—	—	19,8	$C_{12}H_{11}N_3O \cdot C_6H_3N_3O_7$	—	—	19,7	80	63
X	110—111	4,14 (2H, s., CH_2), 6,90—7,73 (10H, m, aromatic protons), 8,04 (1H, s , NH)	74,4	4,8	15,5	$C_{17}H_{13}N_3O$	74,2	4,7	15,3	75	62
XI	227—228	4,20 (2H, s., CH_2), 7,24—7,92 (9H, m, aromatic protons), 8,16 (1H, s ., NH)	63,8	3,7	17,3	$C_{17}H_{12}N_4O_3$	63,7	3,7	17,5	76	68
XII	207—209	4,10 (2H, s, CH_2). 7.10—7,80 (9H, m, aromatic protons), 8,08 (1H, s., NH)	—	—	13,8	$C_{17}H_{12}N_3ClO$	—	—	13,6	79	65
XIII	185—186	3,94 (2H, s., CH_2), 7,10—7,84 (5H, m., indole), 7,19 (1H, d, 3-H furan), 7,70 (1H, d., 4-H furan), 8,14 (1H, s, NH)	58,1	3,2	18,0	$C_{15}H_{10}N_4O_4$	58,0	3,2	18,1	75	60
XIV	180—182	4,04 (4H, s ., $2CH_2$), 7,08—7,74 (10H, m, indole), 8,10 (2H, s , 2NH)	73,0	4,9	16,9	$C_{20}H_{16}N_4O$	73,2	4,9	17,1	74	—

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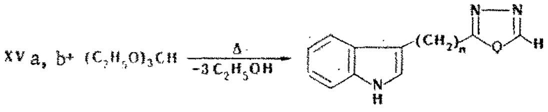
*The compounds were crystallized: II and X from aqueous alcohol, III from nitromethane, IV, V, VII, VIII, XI, and XIV from aqueous dimethylformamide, VI and XII from 75% alcohol, and XIII from 50% CH_3COOH.

†The melting point of the picrate, which was crystallized from aqueous acetone.

In this research we also obtained monosubstituted 1,3,4-oxadiazoles of the indole series (XVII and XVIII). For their synthesis we selected a widely used method — the reaction of acid hydrazides with ethyl orthoformate.



XVII n -0, XVIII n = 1

Despite previous indications [3] that 3 moles of the ortho ester per mole of the hydrazide are sufficient for the realization of such transformations, we found that in this case it is more expedient to carry out the condensation of hydrazides XVa, b with ethyl orthoformate at a hydrazide-to-orthoformate ratio of 1:15.

An intense absorption band at 3240-3285 cm^{-1}, which is characteristic for indole NH groups with strong hydrogen bonds, is observed in the IR spectra of 1,3,4-oxadiazoles II-XIV. Absorption bands with variable intensities at 1630-1670 cm^{-1} and extremely intense maxima at 1595-1615 and 1470-1490 cm^{-1} are present in the region of stretching vibrations of C = N and C = C bonds of heteroaromatic rings. The latter group of bands is characteristic for the 1,3,4-oxadiazole ring [4]. The presence of this ring is also confirmed by absorption bands at 1220-1250 and 1020-1045 cm^{-1}, which are related to the C—O—C stretching vibrations in 1,3,4-oxadiazoles [5].

Signals of five aromatic protons of the indole ring (7.00-7.94 ppm) are observed in the PMR spectra of 5-(3-indolyl)-1,3,4-oxadiazoles II-VIII and XVIII. The 2-H signal of the pyrrole ring shows up in the form of a doublet at 7.70-7.84 ppm (J = 2.5-4.0 Hz) and is shifted to weak field as compared with unsubstituted indole and 3-phenylindole (6.68 and 7.03 ppm, respectively [6]). In the spectra of compounds in which the rings are separated by a methylene group (IX-XIV and XVIII) the signal of this proton is observed at 7.35-7.40 ppm; we assigned the singlet with an intensity of 2H at 3.94-4.20 ppm to the resonance of the protons of the methylene link.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in d_6-DMSO and d_6-acetone were obtained with a Tesla BS-487C spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard. Monitoring of the course of the reaction and the purity of the compounds obtained was accomplished by means of thin-layer chromatography (TLC) on activity II Al_2O_3 in benzene—methanol (5 : 1) (development with iodine vapors).

Imido ester hydrochlorides Ia, b were obtained previously in [1].

Indole-3-carboxylic Acid Hydrazide (XVa). A mixture of 16.4 g (0.093 mole) of methyl indole-3-carboxylate and 45 ml (0.93 mole) of freshly distilled hydrazine hydrate in 120 ml of ethylene glycol was stirred at 110°C for 20 h, after which it was cooled and poured into 1 liter of water. The resulting precipitate was removed by filtration, washed with water, dried in vacuo over P_2O_5, and crystallized from alcohol to give 13.0 g (79%) of hydrazide XVa with mp 228-229.5°C (mp 229-231°C [7]).

3-Indolylacetic Acid Hydrazide (XVb). A mixture of 25.1 g (0.133 mole) of methyl 3-indolylacetate and 10 ml (0.2 mole) of freshly distilled hydrazine hydrate in 150 ml of absolute alcohol was refluxed with stirring for 6 h, after which the solvent and excess hydrazine hydrate were removed at reduced pressure, and the residue was crystallized from absolute alcohol—hexane (1 : 1) to give 16.6 g (66%) of hydrazide XVb with mp 142-143°C (mp 140-141°C [7]).

2-Substituted 5-(3-Indolylmethyl)-1,3,4-oxadiazoles (IX-XIV). A) A mixture of 0.025 mole of imido ester hydrochloride Ib and 0.02 mole of the corresponding hydrazide in 40 ml of absolute alcohol was refluxed with stirring for 4 h, after which it was cooled to 0°C, and the precipitated ammonium chloride was removed by filtration. The filtrate was evaporated to dryness, and the residue was crystallized from a suitable solvent. In the preparation of 1,3,4-oxadiazoles IX and X the colored oil that remained after removal of the solvent was chromatographed with a column filled with Al_2O_3 and benzene—methanol (10 : 1). After removal of the solvent, IX was obtained in the form of a light-yellow uncrystallizable oil with R_f 0.61, which was identified in the form of the picrate. Compound X was obtained in the form of an oil, which crystallized after it was allowed to stand in the cold.

B) A mixture of 0.02 mole of hydrazide XVb and 0.028 mole of the ethyl imido ester hydrochloride of the corresponding acid in 40 ml of absolute alcohol was refluxed with stirring for 5 h, after which it was worked up as indicated above.

Compounds III-VI were insoluble in alcohol, acetone, dioxane, tetrahydrofuran (THF), chloroform, and ether and were soluble only in dimethylformamide (DMF) or dimethyl sulfoxide (DMSO). All of the remaining 1,3,4-oxadiazoles (II and VII-XIV) were quite soluble in alcohols, acetone, DMF, and DMSO but insoluble in hydrocarbons, chloroform, and ether.

N^1-Benzoyl-N^2-(3-indolyl)hydrazine (XVIa). A 4.92-g (0.035 mole) sample of benzoyl chloride was added gradually to a stirred solution of 6.12 g (0.035 mole) of hydrazide IVa in 50 ml of absolute pyridine, after which the reaction mixture was refluxed with stirring for 2.5 h, cooled, and poured into 400 ml of cold water. The resulting precipitate was removed by filtration, washed with water, and dried to give 6.93 g (71%) of hydrazine IVIa with mp 182-183.5°C (from alcohol) and R_f 0.14 [benzene—methanol (5 : 1)]. IR spectrum: 3200-3310, 3150 (NH); 1645, 1630 (C=O); 1590-1600 (indole ring); 1545-1560 (NH); 1140 (N—N); 750, 725 cm^{-1} (CH). Found: 14.8%. $C_{16}H_{13}N_3O_2$. Calculated: 15.0%.

N^1-(4-Nitrobenzoyl)-N^2-(3-indolyl)hydrazine (XVIb). This compound, with mp 215-217°C (from aqueous DMF) and R_f 0.08 [benzene—methanol (5 : 1)], was similarly obtained in 68% yield. IR spectrum: 3210-3300, 3130 (NH); 1640, 1625 (C=O); 1600-1605 (indole ring); 1565 (NO_2); 1540-1550 (NH); 1135 (N−N); 750, 735 cm^{-1} (CH). Found: N 17.4%. $C_{16}H_{12}N_4O_4$. Calculated %: N 17.3%.

Cyclodehydration of N^1-Aroyl-N^2-(3-indolyl)hydrazines (XVIa, b). A mixture of 0.02 mole of hydrazide XVIa, b and 25 ml of phosphorus oxychloride was refluxed for 45 min, after which it was cooled and poured into 200 g of ice. The aqueous mixture was neutralized to pH 7.5 with ammonium hydroxide, and the resulting amorphous black precipitate was removed by filtration, washed with water, dried, and extracted by heating with acetone−DMF (5 : 1) (three 25 ml portions). The extract was evaporated to dryness at reduced pressure, and the residue was crystallized from an appropriate solvent. This procedure gave 1,3,4-oxadiazoles III (30% yield) and IV (25% yield), which were idential to the previously synthesized samples.

2,5-Di(3-indolyl)-1,3,4-oxadiazole (VII). A mixture of 3.54 g (0.022 mole) of indole-3-carboxylic acid and 1.36 g (0.013 mole) of hydrazine dihydrochloride in 30 ml of PPA was stirred at 175°C for 5 h, after which it was cooled and poured into 200 ml of water. The aqueous mixture was neutralized with a saturated solution of $NaHCO_3$, and the resulting precipitate was removed by filtration and crystallized from aqueous IMF with activated charcoal (DMF : H_2O = 1 : 1.5) to give 1.52 g (46%) of oxadiazole VII with mp 171-172.5°C.

2,5-Bis(3-indolylmethyl)-1,3,4-oxadiazole (XIV). This compound, with mp 180-181.5°C (from aqueous DMF), was similarly obtained in 61% yield from 3-indolylacetic acid by reaction at 165°C for 4 h.

2-(3-Indolyl)-1,3,4-oxadiazole (XVII). A solution of 5.0 g (0.0285 mole) of hydrazide XVa in 105.5 g [0.71 mole (112 ml)] of freshly distilled ethyl orthoformate was refluxed with stirring for 15 h, after which the excess ethyl orthoformate was removed at reduced pressure, and the residue was crystallized from aqueous alcohol (alcohol : H_2O = 1 : 2) to give 4.63 g (88%) of XVII with mp 193-195°C and R_f 0.40 [benzene−methanol (10 : 1)]. IR spectrum: 3040-3130 (NH); 1670 (C=N); 1590-1600 (indole ring); 1640 (1,3,4-oxadiazole ring); 1250, 1220, 1010 (=C−O−C=); 750 cm^{-1} (CH). PMR spectrum (d_6-acetone): 8.52 (1H, s, NH), 8.14 (1H, s, oxadiazole 5-H), 7.74 (1H, d, indole 2-H, J = 3.0 Hz), and 7.05-7.80 ppm (5H, m, indole). Found: C 65.0; H 3.8; N 22.5%. $C_{10}H_7N_3O$. Calculated %: C 64.9; H 3.8; N 22.7%.

2-(3-Indolylmethyl)-1,3,4-oxadiazole (XVIII). A solution of 3.40 g (0.018 mole) of hydrazide XVb in 66.6 [0.44 mole (71 ml)] of freshly distilled ethyl orthoformate was refluxed with stirring for 12 h, after which the excess ethyl orthoformate was removed at reduced pressure, and the residue was dissolved in 10 ml of methanol and chromatographed with a column filled with Al_2O_3 (3.0 × 25 ml) by elution with benzene−methanol (5 : 1). Removal of the solvents gave 3.0 g (85%) of XVIII in the form of viscous colored oil with R_f 0.52. IR spectrum (mineral oil): 3250 (NH); 2960 (CH_2); 1655 (C=N); 1595-1605 (indole ring); 1465 (1,3,4-oxadiazole ring); 1250, 1020 (=C−O−C=); 750 cm^{-1} (CH). PMR spectrum (d_6-acetone): 8.22 (1H, s, NH), 8.02 (1H, s, oxadiazole 5-H), 7.12-7.90 (5H, m, indole), 7.74 (1H, d, indole 2-H, j = 2.5 Hz), and 3.95 ppm (2H, s, CH_2). The picrate of XVIII had mp 128-129°C (dec., from aqueous alcohol). Found: N 19.4%. $C_{11}H_9N_3O \cdot C_6H_3N_3O_7$. Calculated: N 19.6%.

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