STUDIES IN THE FIELD OF OXADIAZOLE DERIVATIVES

III. Preparation and Properties of Some Substituted 1, 3, 4-Oxadiazoles*

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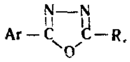
The preparation of some aryl- and methyl-substituted 1, 3, 4-oxadiazoles and the oxidation of methyl groups attached to the oxadiazole rings to aldehyde groups are described.

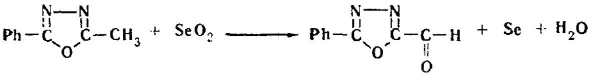
In this work we are continuing studies on the synthesis of 1, 3, 4-oxadiazole derivatives which themselves possess fluorescent properties or contain active groups (such as methyl, aldehyde, and amino groups) in the oxadiazole ring, permitting them subsequently to be converted into new fluorescent compounds of this class.



$Ar = C_6H_4OCH_3$-p,
$C_6H_4Cl = p$, $C_6H_4NO_2 = p$,
$R = C_6H_4N(CH_3)_2 = p$,
CH_3

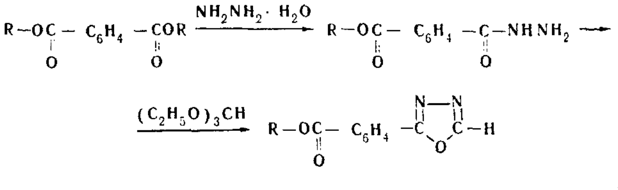
The syntheses of the aryloxadiazoles described in this paper are based on previous work [2, 3]. However, the preparation of arylmethyloxadiazoles containing such substituents as phenyl and chlorophenyl is characterized by features connected with the hydrolytic instability of the oxadiazole ring [2, 3]. Thus, in contrast to the preparation of the diaryloxadiazoles, it proved to be extremely important to maintain definite temperature conditions (80° C) for the cyclodehydration of the acetylaroylhydrazines with phosphorus oxychloride and also to use measures preventing the hydrolysis of the product to the corresponding acetylaroylhydrazines or even hydrazides during isolation and purification (such measures being intensive cooling and extraction of the product with ether, simultaneously with the pouring of the reaction mixture into water, and careful neutralization of the extracts). However, the presence of a nitro group in the phenyl radical of a substituted oxadiazole stabilizes the 1, 3, 4-oxadiazole ring, and such compounds may even be obtained by the usual method.

Oxidation of a methyl group attached to an oxadiazole ring by selenium dioxide in a neutral medium leads to the formation of an oxadiazolealdehyde:



Aldehydes of the oxadiazole series were previously unknown.

Esters of 1,3,4-oxadiazolylbenzoic acid were synthesized by analogy with previous work [4, 5]:



Aminooxadiazoles were obtained by oxidizing acetylthiosemicarbazides with metal oxides in an aqueous medium in better yields than those obtained in anhydrous organic solvents, as described previously [6–8].

Oxadiazole derivatives synthesized (see Experimental), apart from VI, fluoresce in the ultraviolet region of the spectrum. Among them, 2-(p-methoxyphenyl)-5-(p-dimethylaminophenyl)-1, 3, 4-oxadiazole (II) is a very effective scintillation activator in α-methylnaphthalene [9]. The spectral characteristics of II in α-methylnaphthalene are as follows: λ_{max}^{abs} 347 nm ($\varepsilon = 37 \times 10^3$); λ_{max}^{fl} 410 nm. In ethanol, three absorption bands were found: λ'_{max} 226 nm ($\varepsilon = 12 \times 10^3$); λ''_{max} 276 nm ($\varepsilon = 15.5 \times 10^3$); and λ'''_{max} 343 nm ($\varepsilon = 45.6 \times 10^3$). Three similar absorption bands are found in the ultraviolet absorption spectra of other substituted 2, 5-diphenyl-1, 3, 4-oxadiazoles in ethanol, and their nature has been discussed previously [10].

EXPERIMENTAL

1-(p-Methoxybenzoyl)-2-(p-dimethylaminobenzoyl)hydrazine (I). With stirring, an equimolecular amount of p-dimethylaminobenzoyl chloride was added to a solution of 0.1 mole of p-methoxybenzoyl hydrazide in anhydrous pyridine heated to 60° C, and, after cooling, the mixture was poured into ice water. The resulting precipitate was recrystallized from dimethylformamide, dioxane, and glacial acetic acid. Colorless crystals, soluble in dioxane and dimethylformamide, less soluble in ethanol, insoluble in benzene and water. Yield 89%, mp 237° C. Found, %: C 65.37; H 6.01; N 13.67. Calculated for $C_{17}H_{19}N_3O_3$, %: C 65.14; H 6.07; N 13.41.

2-(p-Methoxyphenyl)-5-(p-dimethylaminophenyl)-1, 3, 4-oxadiazole (II). Five grams (17 mM) of I was boiled in 15 ml of phosphorus oxychloride until it dissolved and the solution was boiled for another 1 hr. A precipitate deposited which then redissolved. After the reaction mixture had been poured onto ice, the yellow precipitate that first separated out went into solution, and the reaction product was isolated by neutralizing the solution. The substance was heated in ethanol to the boil and, after cooling, was filtered off and crystallized from a mixture of ethanol and benzene; yield 3.3 g (65%). For further purification, a solution in a mixture of ethanol and benzene was passed through a column filled with layers of activated carbon and alumina, and the substance was then crystallized from dimethylformamide and again from a mixture of ethanol and benzene. Colorless crystals, soluble in benzene and dimethylformamide, less soluble in dioxane, sparingly soluble in ethanol, insoluble in petroleum ether

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*For part II, see [1].

and water; mp 187°C. Found, %: C 69.02; H 5.96; N 13.99. Calculated for $C_{17}H_{17}N_3O_2$, %: C 69.19; H 5.76; N 14.24.

1-Acetyl-2-(p-chlorophenyl)hydrazine (III). With stirring, 12 ml (0.117 mole) of acetic anhydride was added dropwise to a suspension of 20 g (0.117 mole) of p-chlorobenzhydrazide in methanol. An exothermic reaction took place. After an hour's standing, the precipitate was filtered off. Yield 21.8 g (87%). Colorless crystals, mp 211°C (from ethanol). Found, %: N 13.49. Calculated for $C_9H_9ClN_2O_2$, %: N 13.20.

5-(p-Chlorophenyl)-2-methyl-1,3,4-oxadiazole (IV). A mixture of 2 g (0.01 mole) of III and 1.8 ml of phosphorus oxychloride was heated in a water bath at 80°C for 6 hr and was left overnight. Then it was poured into a mixture of ice and ether with vigorous stirring. The aqueous layer was extracted several times with ether. The combined ethereal extracts were neutralized with ice-cold sodium carbonate solution and were washed with ice water to eliminate the sodium carbonate, and the ether was evaporated. Yield 1.37 g (75%). Colorless crystals, mp 107°C (from cyclohexane). Found, %: N 14.63. Calculated for $C_9H_7ClN_2O$, %: N 14.42.

1-Acetyl-2-(p-nitrobenzoyl)hydrazine (V). This was obtained from 22.4 g (0.123 mole) of p-nitrobenzhydrazide and 12.6 ml (0.123 mole) of acetic anhydride in a similar manner to III. Yield 26.1 g (95%) of a light yellow product; mp 235°C (from acetic acid). Found, %: N 19.09. Calculated for $C_9H_9N_3O_4$, %: N 18.83.

1-Methyl-2-(p-nitrophenyl)-1,3,4-oxadiazole (VI). A mixture of 2.2 g (0.01 mole) of V and 1.8 ml of phosphorus oxychloride was boiled until the solid had dissolved and then for another hour. The mixture was poured onto ice. The precipitate that deposited was filtered off and was washed with aqueous sodium carbonate solution and with water to neutrality. Yield 1.8 g (93%). Light yellow crystals, mp 166°C (from ethanol), soluble in benzene and insoluble in heptane and water. Found, %: N 20.57. Calculated for $C_9H_7N_3O_3$, %: N 20.48.

5-Phenyl-1,3,4-oxadiazole-2-aldehyde (VII). Nine grams (0.08 mole) of selenium dioxide was dissolved with heating in a mixture of 40 ml of dioxane and 3 ml of water, and then 15 g (0.08 mole) of 2-methyl-5-phenyl-1,3,4-oxadiazole was added to the solution and the mixture was boiled for 4 hr. As the reaction proceeded, a black precipitate of metallic selenium deposited and the solution became yellow. The selenium was filtered off and the solution was evaporated under vacuum. The product was distilled at 136–139°C (15 mm); the distillate rapidly set to a colorless crystalline mass. Distillation was repeated twice; yield 7 g (50%). Found, %: C 62.27; H 3.44; N 16.07. Calculated for $C_9H_6N_2O_2$, %: C 62.07; H 3.75; N 16.09. The aldehyde group was determined by heating the substance with a solution of hydroxylamine for 3 hr [11].

p-Methoxycarbonylbenzhydrazide (VIII). With stirring, 13.6 g (0.072 mole) of dimethyl terephthalate was boiled for 5 hr with 7 ml (0.22 mole) of hydrazine hydrate in 150 ml of methanol. The precipitate that deposited after cooling was filtered off. Yield 6.5 g (51%), mp 204°C (from a 1 : 1 mixture of methanol and dioxane). Found, %: N 14.35. Calculated for $C_9H_{10}N_2O_3$, %: N 14.40. Unchanged dimethyl terephthalate was recovered from the benzene mother liquor.

Methyl p-(1,3,4-oxadiazol-2-yl)benzoate (IX). A mixture of 6 g (0.03 mole) of VIII and 120 ml of orthoformic ester was boiled for 9 hr. The reaction mixture became homogeneous. The excess of ether was distilled off, and the residue was crystallized from benzene (with alumogel) and ethanol. Colorless crystals, yield 3.5 g (56%), mp 151–152°C (from ethanol). Found, %: N 14.03. Calculated for $C_{10}H_8N_2O_3$, %: N 13.71.

p-Decyloxycarbonylbenzhydrazide (X). A mixture of 5 g (0.016 mole) of decyl terephthalate, 1 ml (0.031 mole) of hydrazine hydrate, and 15 ml of dioxane was heated at 130–140°C for 6 hr. The initially clear solution became turbid. After cooling, the precipitate was crystallized from ethanol (3 g : 25 ml), the insoluble dihydrazide of terephthalic acid (0.3 g) being separated by hot filtration. Colorless crystals, yield 1.7 g (49%), mp 111–112°C (from ethanol). Found, %: N 8.97. Calculated for $C_{18}H_{28}N_2O_3$, %: N 8.75.

Decyl p-(1,3,4-oxadiazol-2-yl)benzoate (XI). A mixture of 3 g (0.01 mole) of X in 45 ml of orthoformic ester was boiled for 15 hr, after which the excess of the orthoester was distilled off, the residue was poured into petroleum ether, and the precipitate was filtered off. Yield 1.9 g (65%); colorless crystals, mp 68°C (from a mixture of cyclohexane and petroleum ether). Found, %: N 8.65. Calculated for $C_{19}H_{26}N_2O_3$, %: N 8.49.

2-Amino-5-methyl-1,3,4-oxadiazole (XII). A solution of 10 g (0.08 mole) of acetylthiosemicarbazide in 100 ml of water was treated with 18 g (0.08 mole) of yellow mercuric oxide, and the mixture was boiled for 4 hr. The hot solution was filtered from the mercurous sulfide, and the filtrate was evaporated under vacuum almost to dryness. The residue was treated with 10 ml of 10% alkali to eliminate the unchanged acetylthiosemicarbazide. Yield 3.15 g (43%). Mp 183°C (from a mixture of benzene and ethanol) (183°C [6]).

The UV spectrum coincided with that given in the literature [6]. The absorption spectrum of II was plotted on a SF-4 spectrophotometer, and the fluorescence spectra were plotted as described previously [12].

REFERENCES

1. O. P. Shvaika and G. P. Klimisha, ZhOKh, **35**, 290, 1965.
2. R. Stolle and K. Thomä, J. pr. Chem., **73**, 288, 1906.
3. O. P. Shvaika and T. R. Mnatsakanova, ZhOKh, **34**, 2061, 1964.
4. C. Ainsworth, J. Am. Chem. Soc., **77**, 1148, 1955.
5. A. P. Grekov, O. P. Shvaika, and L. M. Egupova, ZhOKh, **29**, 2027, 1959.
6. R. Stolle and K. Fehrenbach, J. pr. Chem., **122**, 289, 1929.
7. J. D. Brooks, P. T. Charlton, P. E. Macey, D. A. Peak, and W. F. Short, J. Chem. Soc., 452, 1950.
8. R. M. Herbst and J. E. Klingbeil, J. Org. Chem., **23**, 1912, 1958.
9. O. P. Shvaika and T. R. Mnatsakanova, USSR patent no. 166 796; Byull. izobr., no. 23, 1964.
10. A. P. Grekov and O. P. Shvaika, Scintillators and Scintillation Materials, Vol. 2 [in Russian], izd. Kh. un-ta, Khar'kov, p. 5, 1963.
11. R. P. Lastovskii and Yu. I. Vainshtein, Technical Analysis in the Production of Intermediates and Dyes [in Russian], Goskhimizdat, Moscow, p. 135, 1958.
12. L. L. Nagornaya, T. R. Mnatsakanova, A. P. Grekov, and O. P. Shvaika, Opt. i spektr., **18**, 403, 1965.

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