SYNTHESIS OF HYDROXY DERIVATIVES OF 2,5-DIARYL-1,3,4-OXADIAZOLES

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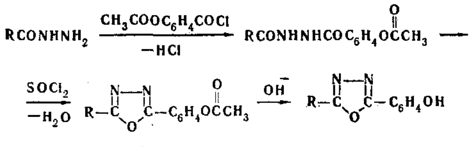
A method for the synthesis of hydroxy derivatives of 2,5-diaryl-1,3,4-oxadiazoles has been developed which consists in the preparation of acetoxy derivatives of oxadiazole with their subsequent saponification by means of an alcoholic solution of sodium hydroxide.

Hydroxy derivatives of 1,3,4-oxadiazole are being used in the preparation and stabilization of polymeric materials [1, 2], as physiologically active preparations [3, 4], in scintillation techniques [3], etc. The methods for the synthesis of hydroxy derivatives of 1,3,4-oxadiazole known in the literature have a partial nature in the majority of cases and cannot be regarded as general methods for their preparation [4–6]. In view of this, an investigation of hydroxy derivatives of 2,5-diaryl-1,3,4-oxadiazoles with the objects of finding convenient methods for their synthesis and of studying their properties appeared of interest.

The present work was devoted to the development of a method for the synthesis of 2-(p-acetoxyphenyl)- and 2-(p-hydroxyphenyl)-5-aryl-1,3,4-oxadiazoles, which were obtained in accordance with the equation



The diaroylhydrazines were obtained by the reaction of p-acetoxybenzoyl chloride with carboxylic acid hydrazides at room temperature in dry pyridine.

When a 1-(p-acetoxybenzoyl)-2-aroylhydrazine was boiled in an excess of thionyl chloride, hydrogen chloride and sulfur dioxide were liberated and a 2-acetoxybenzoyl-5-aryl-1,3,4-oxadiazole was formed. The cyclodehydration of the 1-acetoxybenzoyl-2-aroylhydrazines can also be effected in phosphorus oxychloride. However, in this case, side reactions evidently take place which affect the purity of the resulting product.

When an equimolecular amount of sodium hydroxide was added to an ethanolic solution of a 2-acetoxyphenyl-5-aryl-1,3,4-oxadiazole, saponification of the acetoxy group took place. The resulting 2-hydroxyphenyl-5-aryl-1,3,4-oxadiazole was isolated by acidifying the reaction mixture with hydrochloric acid. This did not lead to the cleavage of the oxadiazole ring, as takes place in the alkaline saponification of 2-(p-ethoxycarbonylphenyl)-5-phenyl-1,3,4-oxadiazole where, in addition to the hydrolysis of the ester grouping, the opening of the oxadiazole ring takes place with the formation of the corresponding 1-benzoyl-2-(p-carboxybenzoyl)hydrazine [7]. In the case of 2-(p-acetoxyphenyl)-5-(p-ethoxycarbonylphenyl)-1,3,4-oxadiazole, hydrolysis is likewise accompanied by the cleavage of the oxadiazole ring.

EXPERIMENTAL

1-(p-Acetoxybenzoyl)-2-aroylhydrazines. A 50-ml three-necked flask fitted with a mechanical stirrer, dropping funnel, calcium chloride tube, and thermometer was charged with 0.1 mole of a carboxylic acid hydrazide and 10–15 ml of dry pyridine. To the resulting solution, with stirring and cooling, 0.1 mole of p-acetoxybenzoyl chloride in 5–8 ml of dry benzene was slowly added. The temperature of the reaction mixture was kept between 20° and 25° C. Then the mixture was stirred for 30 min, the benzene was distilled off in the vacuum of a water pump, and the contents of the flask were treated with water. The crystalline product that separated out was filtered off and was washed with water, 3% hydrochloric acid, and water again to neutrality.

The diaroylhydrazines obtained form colorless substances sparingly soluble in water and in aliphatic and aromatic hydrocarbons (see Table 1).

2-(p-Acetoxyphenyl)-5-aryl-1,3,4-oxadiazoles. A round-bottomed flask fitted with a reflux condenser and a bubble counter was charged with 1-(p-acetoxybenzoyl)-2-aroylhydrazine and a tenfold amount (by weight) of thionyl chloride. The initial hydrazine dissolved completely with the evolution of hydrogen chloride and sulfur dioxide. After the end of the reaction, the excess of thionyl chlorides was distilled off. The contents of the flask were treated with water and the precipitate that separated was filtered off, dried, and crystallized. This process gave pure acetoxyoxadiazoles which formed colorless crystalline substances insoluble in water and readily soluble in aromatic hydrocarbons (see Table 2).

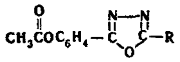
5-Aryl-2-(p-hydroxyphenyl)-1,3,4-oxadiazoles. A solution of 1 mM of a 2-(p-acetoxyphenyl)-5-aryl-1,3,4-oxadiazole in 20–30

Table 1

1-(p-Acetoxybenzoyl)-2-aroylhydrazines $CH_3COOC_6H_4CONHNHCOR$

R	Mp, °C	Solvent for crystallization	Empirical formula	N, %		Yield, %
				found	calculated	
C_6H_5	192	Methanol	$C_{16}H_{14}N_2O_4$	9.29	9.39	92
м-$CH_3C_6H_4$	191—192	Methanol	$C_{17}H_{16}N_2O_4$	8.96	8.97	90
p-$CH_3C_6H_4$	198—199	Methyl ethyl ketone	$C_{17}H_{16}N_2O_4$	9.07	8.97	98
o-$NO_2C_6H_4$	225—226	Methanol	$C_{16}H_{13}N_3O_6$	12.36	12.24	91
м-$NO_2C_6H_4$	228—229	Methylcellosolve	$C_{16}H_{13}N_3O_6$	12.20	12.24	95
p-$C_2H_5OOCC_6H_4$	202—204	Methanol	$C_{19}H_{18}N_2O_6$	7.92	7.95	91

Table 2

2-(p-Acetoxyphenyl)-5-aryl-1, 3, 4-oxadiazoles 
$CH_3\overset{O}{\overset{\|}{C}}OC_6H_4-\underset{O}{\overset{N-N}{C\quad C}}-R$

R	Mp, °C	Empirical formula	N, %		Yield, %
			found	calculated	
C_6H_5	250—251*	$C_{14}H_{10}N_2O_2$	11.59	11.76	96
м-$CH_3C_6H_4$	279—280	$C_{15}H_{12}N_2O_2$	11.08	11.16	98
p-$CH_3C_6H_4$	264—265	$C_{15}H_{12}N_2O_2$	11.16	11.16	98
м-$NO_2C_6H_4$	253—255	$C_{14}H_9N_3O_4$	14.82	14.84	95

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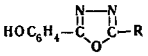
*According to the literature [5]: mp 254—255° C.

Table 3

5-Aryl-2-(p-hydroxyphenyl)-1, 3, 4-oxadiazoles 
$HOC_6H_4-\underset{O}{\overset{N-N}{C\quad C}}-R$

R	Mp, °C	Solvent for crystallization	Empirical formula	N, %		Yield, %
				found	calculated	
C_6H_5	153—154*	Methanol	$C_{16}H_{12}N_2O_3$	10.01	9.99	90
м-$CH_3C_6H_4$	142—143	Methanol	$C_{17}H_{14}N_2O_3$	9.60	9.52	98
p-$CH_3C_6H_4$	144—145	Methanol	$C_{17}H_{14}N_2O_3$	9.42	9.52	97
o-$NO_2C_6H_4$	145—146	Methylcellosolve	$C_{16}H_{11}N_3O_5$	13.25	12.92	94
м-$NO_2C_6H_4$	168—170	Methylcellosolve	$C_{16}H_{11}N_3O_5$	12.98	12.92	95
p-$C_2H_5OOCC_6H_4$	163—164	Methylcellosolve	$C_{19}H_{16}N_2O_5$	8.21	8.38	88

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*According to the literature [5]: mp 149° C.

ml of methanol was treated in drops with 5 ml of 0.2 N caustic soda solution, and then 1 ml of 20% hydrochloric acid was added. A crystalline product deposited that was separated off, dried, and crystallized from methylcellosolve.

The p-hydroxy derivatives of 2, 5-diaryl-1, 3, 4-oxadiazoles consist of colorless crystalline substances sparingly soluble in water and aromatic hydrocarbons and readily soluble in dimethylformamide and hexamethylphosphoramide (see Table 3).

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