2, 5-DIALKYL-1, 3, 4-OXADIAZOLES

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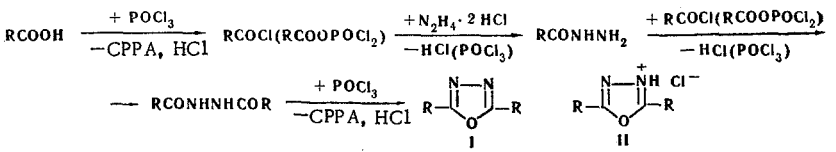
A single stage method has been developed for the preparation of 2, 5-dialky-1, 3, 4-oxadiazoles from aliphatic carboxylic acids, by boiling with hydrazine hydrochloride in phosphoryl chloride. A mechanism for the synthesis is suggested. The oxadiazoles are characterized, and the group refractivity of the 1, 3, 4-oxadiazole ring has been determined.

1, 3, 4-Oxadiazoles are usually prepared from carboxylic acids and hydrazides. All the reactions in these multistage syntheses are condensations, leading to activation of the acid molecules, and further reaction of the active species with hydrazine at both nitrogen atoms, followed by intramolecular self-condensation to give the oxadiazole. It is of course desirable, therefore, that conditions are selected which are suitable for each stage, and to carry out the synthesis in such a way that it is not necessary to isolate the various intermediate products. A number of papers have appeared which are devoted to the synthesis of 2, 5-diaryl-1, 3, 4-oxadiazoles by indirect methods from carboxylic acids [1-3].

We have reported previously [4] on the possibility, in principle, of a single-stage preparation of the hitherto difficultly-accessible 2, 5-dialkyl-1, 3, 4-oxadiazoles. It seemed that it would be possible to use phosphoryl chloride as the overall condensing agent. The use of polyphosphoric acid [1, 3] or sulfur trioxide [2] was contraindicated by the need to treat the reaction mixture with water if these reagents were used, whereas the use of phosphoryl chloride makes it possible to isolate the oxadiazoles by distillation, which is particularly valuable in the case of the readily-hydrolyzed lower homologs [5]. The reaction was successful when normal and iso-acids, from propionic upwards, were used, and also using mixed acids. In the latter case, a mixture of the two symmetrical and the unsymmetrical oxadiazoles was obtained. Halosubstituted and dibasic acids did not give oxadiazoles under these conditions.

In order to obtain satisfactory yields, it was found necessary to treat the reaction mixture, after completion of the main reaction, with phosphorus pentachloride in order to convert the non-volatile hydrolysis products of phosphoryl chloride which were formed in the reaction (chloropolyphosphoric acid, CPPA) into phosphoryl chloride. This treatment proved particularly valuable in the preparation of oxadiazoles, bearing substitutents from butyl upwards.

Bearing in mind the possibility of activating carboxylic acids by the formation of both their acid chlorides and the acylphosphoryl dichlorides, the single stage synthesis of I may be represented by the following scheme:



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In the case of capronyl chloride, we showed that the formation of the oxadiazole proceeded in the same way if, instead of the acid, the acylchloride was used; the acid chloride could therefore be an intermediate in the one-stage synthesis. However, this does not exclude a parallel course for the reaction via the acylchlorophosphate. The double reaction of hydrazine dihydrochloride with capronyl chloride also indicates the possibility of such a process, although similar reactions, as pointed out by Grekov [6], do not occur, in particular the reaction of acylhydrazine hydrochlorides with benzoyl chloride in benzene solution. We have observed no reaction of hydrazine dihydrochloride with phosphoryl chloride, even on boiling.

It has been found that, in order to avoid the formation of oily impurities, it is necessary to add the acid and the hydrazine hydrochloride at the same time, which results in the immediate reaction of the acid chloride or acyldichlorophosphate as it is formed, thus preventing the development of this process.

On distillation of the reaction mixtures, there was isolated in every case as by-product the hydrochloride of the oxadiazole (II), in addition to I. In order to confirm the structure of II, the hydrochloride of 2, 5-diethyl-1, 3, 4-oxadiazole was prepared by saturating the latter with hydrogen chloride. The salt-like structure of these compounds was indicated by the presence in the IR spectrum of a broad, intense band at 1850 cm^{-1}, attributed to deformational vibration of the $=\overset{+}{\underset{|}{N}}-H^{7}$ group [7].

The compounds obtained could, in addition to II, be assigned several structures, both cyclic and acyclic, with covalent chlorine bonds, which could not be ruled out on the basis of their IR spectra. However, the absence of signals in the NQR Cl^{35} spectrum of these compounds is in agreement with structure II alone, in which the chloride is present as the anion.

The II were obtained as extremely hygroscopic, low-melting, easily-distilled compounds which decomposed completely in contact with water. On heating in vacuo, they lost hydrogen chloride with the formation of I.

The single-stage synthesis of 2, 5-dimethyl-1, 3, 4-oxadiazole directly from acetic acid was not very successful, owing partly to the high volatility of acetyl chloride, entraining hydrogen chloride, and to the volatility of the oxadiazole hydrochloride in comparison with that of the base. Better yields were obtained by using NN'-diacetylhydrazine, but most satisfactory was the use of acetic anhydride and hydrazine dihydrochloride.

The 2, 5-dialkyl-1, 3, 4-oxadiazoles were liquids with weak, noncharacteristic odors, readily miscible with organic solvents. The lower members were readily soluble in water, but the solubility decreased with increasing size of the alkyl radicals. 2-Ethyl-5-hexyl- and 2-isopropyl-5-hexyl-1, 3-, 4-oxadiazole were insoluble in water. The lower I were readily hydrolyzed in neutral aqueous solution. Hydrolysis of diethyloxadiazole with an equimolar amount of water led to the rapid formation of NN'-dipropionyl-hydrazine, whilst 2, 5-dipentyl-1, 3, 4-oxadiazole exhibited considerable hydrolytic stability.

The NMR spectrum of 2, 5-dimethyl-1, 3,4-oxadiazole exhibits a single peak at $\delta = 2.40$ ppm, which falls in the range between the value for the group $\delta_{CH_3-\underset{|}{C}=}$ in dimethyl derivatives of carbo- and heterocycles [8], and differs from dimethyl ketazine: 2.00 and 1.82 [9]. This emphasizes the aromatic structure of the 1, 3, 4-oxadiazoles.

The IR spectrum of 2, 5-diethyl-1, 3, 4-oxadiazole in the multiple bond vibrational region shows two strong bands with frequencies 1562 and 1593 cm^{-1}, which are probably due to vibration of the oxadiazole ring. These bands are shifted substantially towards lower frequencies in comparison with azines [10], which is also a consequence of the aromaticity of the oxadiazole ring. It is interesting that, in the Raman spectrum, both vibrations are active, although at short wavelength and much reduced in intensity. The oxadiazoles are also distinguished from the related azines [10], in the IR spectra of which only γ_{as} is active, whilst in the Raman spectra, ν_s is active. It is suggested that this difference is connected with the considerable differences in the nature of the oscillating groups, in our case being concerned with aromatic ring vibrations.

The group refractivity for the 1, 3, 4-oxadiazole ring was determined by calculation from the observed molar refraction values for the group refractions of the two alkyl groups. The mean value for the group refraction for the 1, 3, 4-oxadiazole ring, obtained by the least-squares method, was 12.57 ± 0.04,

which is the same, within the limits of experimental error, with the value calculated by the additive method, using a refractivity for the nitrogen atom determined from iminoesters [11].

EXPERIMENTAL

2, 5-Dialkyl-1, 3, 4-oxadiazoles. All the 1, 3, 4-oxadiazoles, with the exception of 2, 5-dimethyl-1, 3, 4-oxadiazole, were obtained by the following method. A mixture of 0.4 mole of the carboxylic acid (or 0.2 mole of each acid in the synthesis of unsymmetrical oxadiazoles), 0.2 mole of hydrazine hydrochloride, and 1.8 mole of phosphoryl chloride was heated at 60-80° for 1-2 h, then boiled until the hydrazine salt had dissolved, and evolution of hydrogen chloride had ceased (6-8 hr). To the cooled reaction mixture was added 0.6 mole of phosphorous pentachloride, and the mixture was boiled for a further 7-9 h. The phosphoryl chloride was then distilled in vacuo, and the residue was treated with 100 ml of dry chloroform or benzene. The insoluble impurities were filtered off, the solvent removed, and the product redistilled in vacuo. The 2, 5-dialkyl-1, 3, 4-oxadiazoles thus obtained were contaminated with salt. This mixture was kept for 1-2 h in vacuo at a temperature somewhat lower than the bp of the oxadiazole, then slowly distilled, which in most cases gave the pure oxadiazole: the procedure was repeated if necessary. For final purification, the oxadiazoles were distilled again in vacuo (Table 1).

Reaction of Capronyl Chloride with Hydrazine Hydrochloride in Phosphoryl Chloride. A portion of capronyl chloride [46.27 g (0.344 mole)] and 18.05 g (0.172 mole) of hydrazine hydrochloride were boiled in phosphoryl chloride for 10 h. The mixture was fractionated to give 67.8% of 2, 5-dipentyl-1, 3, 4-oxadiazole.

2, 5-Dimethyl-1, 3, 4-oxadiazole. a) From NN'-Diacetylhydrazine in Phosphoryl Chloride, followed by Treatment with Phosphorus Pentachloride. A mixture of 5.00 g (0.043 mole) of NN'-diacetylhydrazine and 20 ml (0.219 mole) of phosphoryl chloride was heated. At 70-77°, rapid solution of the solid took place, accompanied by rapid evolution of hydrogen chloride. The solution was boiled for 1 h, cooled, and treated with 9.9 g (0.048 mole) of phosphorus pentachloride. After boiling for a further 2 h, the mixture was distilled in vacuo to give a yield of 85.8%.

b) From NN'-diacetylhydrazine and Thionyl Chloride in Dioxane. A mixture of 5.00 g (0.043 mole) of NN'-diacetylhydrazine, 4 ml of thionyl chloride, and 50 ml of dioxane was heated. The reaction proceeded similarly to that described above. After boiling for 3 h, the mixture was fractionated in vacuo to give 1.1 g (21%) of 2, 5-dimethyl-1, 3, 4-oxadiazole, identical with that obtained by method a).

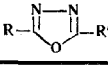
c) From Acetic Acid and Anhydrous Hydrazine. To 5 ml (5 g, 0.157 mole) of hydrazine was added dropwise with stirring and water cooling a solution of 18 ml (0.315 mole) of acetic acid in 50 ml of dioxane followed by 35 ml (0.436 mole) of thionyl chloride. The mixture was kept at 50° for 1 h, then boiled until evolution of hydrogen chloride ceased (4 h). A small quantity of solid was filtered off, and the filtrate was distilled in vacuo to give 1.8 g (11.7%) of the oxadiazole, having the same constants as the product of reaction a).

d) From Acetic Anhydride and Hydrazine Hydrochloride. A mixture of 21 g (0.2 mole) of hydrazine hydrochloride and 61.26 g (0.6 mole) of acetic anhydride was boiled until the solid had dissolved completely, and the evolution of hydrogen chloride had ceased (9 h). The mixture was boiled for a further h, cooled, and subjected to slow fractional distillation at atmospheric pressure. The fraction boiling at 150-250° was redistilled several times to give 6.1 g (31%) of product identical with that obtained by method a).

2, 5-Dimethyl-1, 3, 4-Oxadiazole Hydrochloride. A portion of acetic acid [36 ml (0.57 mole)], 26.1 g (0.25 mole) of hydrazine hydrochloride, and 136 ml (0.53 mole) of phosphoryl chloride were heated with stirring at 68-75° for 2 h, then boiled for 3 h 30 min. The reaction mixture was cooled, and 120 g (0.57 mole) of phosphorus pentachloride was added. The mixture was boiled for a further 4 h, then distilled in vacuo to give 4.66 g of the oxadiazole salt, which was purified for analysis by sublimation in vacuo at 10 mm (Table 2).

2, 5-Diethyl-1, 3, 4-Oxadiazole Hydrochloride. a) Dry hydrogen chloride was passed through 3.26 g (0.027 mole) of 2, 5-diethyl-1, 3, 4-oxadiazole, the temperature rising rapidly to 144°. The viscous mass was crystallized in vacuo at 10 mm, without heating above 35°. The crystalline product was treated with n-pentane, filtered off, and dried to give 3.1 g (70%) of product.

b) Obtained together with the oxadiazole by reaction of propionic acid with hydrazine hydrochloride followed by distillation of the reaction mixture. After washing with n-hexane under dry carbon dioxide, the product was identical with the salt obtained by method a).

TABLE 1. 2,5-Dialkyl-1,3,4-oxadiazoles 

R	R′	Bp, °C (mm Hg)	n_D^{20}	d_4^{20}	MR found	MR ring	Molecular Formula	Found, %			Calculated, %			Yield, %
								C	H	N	C	H	N	
CH_3	CH_3	63 (10)	1,4441	1,0963	23,78	12,34	$C_4H_6N_2O$	48,82	6,26	29,20	48,96	6,16	28,56	*
C_2H_5	C_2H_5	82 (10)	1,4471	1,0173	33,14	12,47	$C_6H_{10}N_2O$	57,05	8,12	22,10	57,12	7,99	22,21	54,3
C_2H_5	n-C_6H_{13}	131,5 (8)	1,4508	0,9478	51,76	12,62	$C_{10}H_{18}N_2O$	66,50	10,14	15,38	65,90	9,96	15,37	26,6
n-C_3H_7	n-C_3H_7	102 (10)	1,4496	0,9747	42,49	12,58	$C_8H_{14}N_2O$	61,84	9,67	18,32	62,31	9,16	18,16	72,2
i-C_3H_7	i-C_3H_7	85 (12)	1,4412	0,9611	42,39	12,48	$C_8H_{14}N_2O$	62,37	9,45	18,16	62,31	9,16	18,16	37,7
i-C_3H_7	n-C_6H_{13}	139,5—140,5 (8)	1,4502	0,9347	56,46	12,70	$C_{11}H_{20}N_2O$	67,39	10,25	14,26	67,33	10,27	14,26	7,7
n-C_4H_9	n-C_4H_9	129—130 (12)	1,4508	0,9489	51,70	12,56	$C_{10}H_{18}N_2O$	65,80	9,84	15,35	65,90	9,96	15,37	62,8
i-C_4H_9	i-C_4H_9	117 (13)	1,4471	0,9380	51,90	12,76	$C_{10}H_{18}N_2O$	65,88	9,90	15,90	65,90	9,96	15,37	56,5
n-C_5H_{11}	n-C_5H_{11}	152 (10)	1,4524	0,9316	60,91	12,53	$C_{12}H_{22}N_2O$	68,76	10,57	13,48	68,53	10,54	13,32	70,3
n-C_6H_{13}	n-C_6H_{13}	119—120 (0,03)	1,4548	0,9196	70,30	12,68	$C_{14}H_{26}N_2O$	70,26	11,05	12,58	70,54	11,00	11,75	54,3

*See Experimental.

TABLE 2. 2, 5-Dialkyl-1, 3, 4-oxadiazole Hydrochlorides (II)

R	Mp, °C	Molecular formula	Found, %		Calculated, %	
			N	Cl	N	Cl
CH_3	90—93*	$C_4H_7ClN_2O$	20,31 20,49	25,94 26,13	20,82	26,35
C_2H_5	51—52	$C_6H_{11}ClN_2O$	17,00 17,32	21,40 21,60	17,23	21,80
n-C_5H_{11}	45—47	$C_{12}H_{23}ClN_2O$	11,34 11,38		11,35	

*Sublimed. Determined in a sealed capillary.

2, 5-Dipentyl-1, 3, 4-oxadiazole hydrochloride was obtained together with the free oxadiazole, and was isolated as described above.

Decomposition of 2,5-Diethyl-1,3,4-oxadiazole Hydrochloride. A portion of the salt [1.62 g (0.01 mole)] was heated at 60-70° for 4 h under a vacuum of 10 mm, hydrogen chloride being evolved from the melt. The temperature was then raised to 95°, and 0.51 g (40%) of 2, 5-diethyl-1, 3, 4-oxadiazole was distilled off.

Hydrolysis of 2, 5-dialkyl-1, 3, 4-oxadiazoles. A mixture of 1 g (0.008 mole) of 2, 5-diethyl-1, 3, 4-oxadiazole and 0.14 g (0.008 mole of water was converted into a colorless crystalline mass on standing for two days at room temperature. Recrystallization from light petroleum gave NN'-dipropionylhydrazine, mp 134-135° [12].

Under similar conditions, and on boiling an aqueous alcoholic solution of 2, 5-dipentyl-1, 3,4-oxadiazole, no hydrolysis occurred, but on standing in contact with atmospheric moisture for several months, crystals of NN'-dicapronylhydrazine, mp 157.5°, were formed (according to [13], mp 159°).

IR spectra were recorded on a UR-10 instrument. The compounds were trapped as drops between KBr discs, so that the layer thicknesses were not known. The recording rate was 150 cm^{-1}/min, using a retarder. The spectral slit width was varied in the spectral range under investigation according to pro gramme 4.

The Raman spectra were obtained in the liquid phase on an ISP-51 instrument, with a photoelectric recorder. The spectral slit width was ~4-5 cm^{-1}. Toluene was used as standard.

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