1,2,4-Oxadiazoles. X (1). Aryl-1,2,4-oxadiazolecarbaldehydes

G. Palazzo

Institute of Pharmaceutical Chemistry, University of Turin, 10141 Turin, Italy

L. Baiocchi and G. Picconi*

Department of Chemistry, F. Angelini Research Institute, Viale Amelia 70, 00181 Rome Italy

Received April 5, 1979

This paper is dedicated to Professor L. Panizzi on the occasion of his 70th birthday.

The synthesis of 5-aryl-1,2,4-oxadiazole-3-carbaldehydes and 3-aryl-1,2,4-oxadiazole-5-carbaldehydes was attempted through several routes and achieved starting from both the corresponding chloromethyl and the dichloromethyl derivatives. These aldehydes are stabilized in the hydrated form and this peculiar behavior is discussed on the basis of the relevant spectroscopic data.

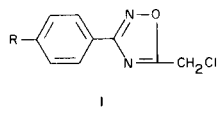
J. Heterocyclic Chem., **16**, 1469 (1979).

As part of a general program concerning potential antiviral and anti-tumoural agents, the preparation, as intermediates, of some aryl-1,2,4-oxadiazole aldehydes **9** and **10**, which are not described in the literature is reported in this paper.

In order to obtain these aldehydes, the same method described for the synthesis of the only known 1,3,4-oxadiazolecarbaldehyde *i.e.* selenium dioxide oxidation of a methyl group bound to the heterocyclic nucleus (2), was attempted at first. However, 3-methyl-5-phenyl-1,2,4-oxadiazole and 5-methyl-3-phenyl-1,2,4-oxadiazole (both already known) (3-4), when treated with this reagent under the same conditions described for 2-methyl-5-phenyl-1,3,4-oxadiazole, were recovered unaltered. Under more drastic conditions it was possible to obtain very small amounts of the aldehydes, but this method did not prove suitable from a preparative point of view due to the very poor yields which were obtained.

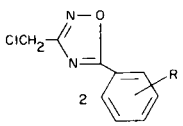
The possiblitiy of starting from the arylchloromethyl-1,2,4-oxadiazoles **1** and **2**, some of which have been reported in the literature and are easily obtainable, was

Table I



1

a) R=H (5)
b) R=Cl
c) R=OCH_3 (6)
d) R=NO_2

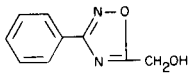


2

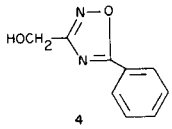
a) R=H (7)
b) R=p-Cl
c) R=p-OCH_3
d) R=p-NO_2
e) R=p-CH_3
f) R=o-CH_3
g) R=m-NO_2
h) R=o,p-Cl_2

therefore considered.

Consequently, the Sommelet reaction (8) was attempted on 5-chloromethyl-3-phenyl-1,2,4-oxadiazole **1a**. This reaction, when carried out in aqueous acetic acid, did not lead to the expected aldehyde, but gave the corresponding alcohol **3**. The same reaction on 3-chloromethyl-5-phenyl-1,2,4-oxadiazole **2** gave a mixture of products from which a minimal amount of the alcohol **4** was isolated.



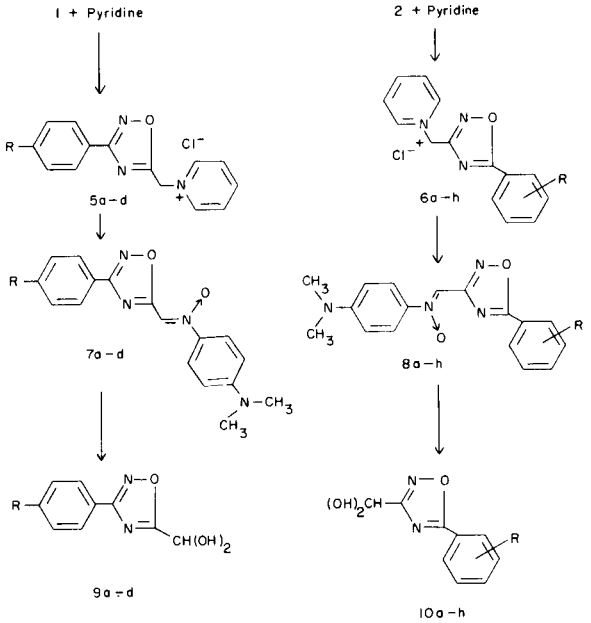
3



4

The general method of Kröhnke (9), outlined in Figure 1, was therefore utilized for the preparation of our aldehydes. Both the pyridinium salts **5** and **6**, and the nitrones **7** and **8** were obtained in excellent yields (Tables IIa, IIb, IIIa and IIIb). The behavior of some of these nitrones, when their cyrstallization from ehtanol was attempted, is described in the following paper. The crude compounds,

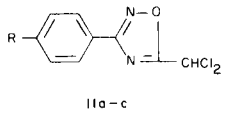
Figure 1



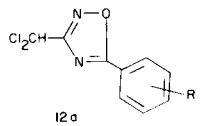
0022-152X/79/071469-07$02.25

when treated with aqueous hydrochloric acid, gave the corresponding hydrated aldehydes **9** and **10** in around 80% yields (see Tables IVa and IVb).

The possibility of obtaining the same aldehydes through a different approach was also considered, since the aryl-dichloromethyl-1,2,4-oxadiazoles **11** and **12**, of which only few examples have been described in literature, are easily obtainable from arylamidoximes and dichloroacetyl chloride or from dichloroacetylamidoxime and aroyl chlorides.



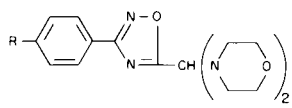
11a-c



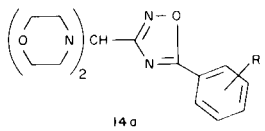
12a

The previously known **11a** (10) and the new **11c** and **12a** were thus prepared. In order to perform the step beginning with the dichloromethyl derivatives to give the corresponding aldehydes, the usual reagents described in the literature for this type of reaction were tried. Under these conditions, the starting product was always recovered unchanged.

On the contrary, in all of the three cases taken into consideration, the reaction to give the aldehydes easily took place when the general method suggested by Kerfanto (11) was used. The dichloromethyl derivatives were therefore transformed into the corresponding dimorpholinomethyl derivatives **13a,c** and **14a**, two of which (**13c** and **14a**) were isolated as solids; the third one was used as a crude intermediate. All three compounds were hydrolyzed with dilute hydrochloric acid at low temperature to give the corresponding hydrated aldehydes in good yields.



13a-c



14a

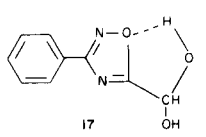
The hydrated aldehydes described in this paper underwent reactions which are typical of aldehydes, reducing ammonium silver nitrate, giving the corresponding phenyl hydrazones and semicarbazones, reacting with dimedone and giving dichloromethyl derivatives with phosphorus pentachloride. By sublimation under vacuum, (sometimes vacuum sublimation was repeated) they lose a water molecule giving the corresponding anhydrous aldehydes **15** and **16** reported in Tables Va and Vb. The latter compounds show a noticeable tendency to rehydrate when they come in contact with water or also after standing for several days in a moist atmosphere.

Uv, ir and nmr spectra of the products **9** and **10** are in accordance with the structures of the hydrated aldehydes. Uv spectra are, in fact, superimposable on those of the corresponding alkylaryl-1,2,4-oxadiazoles. Concerning the ir spectra, they lack the characteristic stretching frequency for the carbonyl group. The ir spectra also reveal a C=N band between 1550 and 1570 cm^{-1} and a C=C band around 1600 cm^{-1}. Nmr spectra are characterized by a signal between δ 6.1 and 6.3, assignable to the $CH(OH)_2$ proton for both **9** and **10**. Compounds **9** showed two signals, one between δ 3.3-3.4 and the other around δ 7.0. The same signals are found near δ 3.3 and between δ 6.6 and 6.8 in compounds **10**. The latter peaks disappear both in **9** and in **10** upon the addition of deuterium oxide.

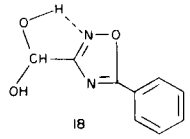
The spectra of the anhydrous aldehydes **15** and **16** are remarkably different from the preceding ones. The most intense band in the ir spectra is assignable to the carbonyl group between 1715-1725 cm^{-1}, whereas in the nmr spectrum, besides the signals of the benzene ring protons and of its substituents, only the aldehyde proton signal at δ 10.2 is noticeable.

It is appropriate to comment on the fact that 1,2,4-oxadiazolecarbaldehydes exist preferably in the hydrated state and not in the more common carbonyl form. In the field of heterocyclic chemistry, this phenomenon is almost peculiar for these aldehydes, even though some other rare examples are described in literature as, for example, the *N*-oxide of pyridinecarbaldehyde (12) and 2-phenyl-1,3,4-thiadiazole-5-carbaldehyde (13).

The nmr spectra give a plausible interpretation of the structure of our aldehydes, since they show the non-equivalence of the two OH protons (δ ~3.3 *versus* ~6.8) in accordance with structures **17** and **18** in which stabiliza-



17



18

Table Ia

3-Aryl-5-chloromethyl-1,2,4-Oxadiazoles **1**

Compound No.	Yield %	M.p. °C	Formula	Analysis			
				C	H	N	Cl
1b	57	58-60°	$C_9H_6Cl_2N_2O$	Calcd. 47.19	2.64	12.23	
				Found 47.37	2.81	12.04	
1d	64	86-88°	$C_9H_6ClN_3O_3$	Calcd. 45.11	2.52	17.54	14.80
				Found 44.98	2.50	17.96	14.51

Table Ib

5-Aryl-3-chloromethyl-1,2,4-oxadiazoles **2**

Compound No.	Yield %	M.p. °C B.p./Torr	Formula	Analysis			
				C	H	N	Cl
2b	70	81-83°	$C_9H_6Cl_2N_2O$	Calcd. 47.18	2.64	12.23	30.96
				Found 47.27	2.94	12.31	30.43
2c	39	68-69°	$C_{10}H_9ClN_2O_2$	Calcd. 53.46	4.04	12.47	
				Found 53.28	4.03	12.61	
2d	73	116-117°	$C_9H_6ClN_3O_3$	Calcd. 45.11	2.52	17.54	14.80
				Found 44.98	2.41	17.15	14.77
2e	41	63-65°	$C_{10}H_9ClN_2O$	Calcd. 57.56	4.35	13.43	
				Found 57.25	4.63	12.10	
2f	51	120°/0.4	$C_{10}H_9ClN_2O$	Calcd. 57.56	4.35	13.43	
				Found 57.42	4.63	13.51	
2g	71	93-95°	$C_9H_6ClN_3O_3$	Calcd. 45.11	2.52	17.54	14.80
				Found 45.24	2.60	17.71	14.85
2h	60	85-89°	$C_9H_5Cl_3NO$	Calcd. 43.32	2.09	16.84	42.63
				Found 43.04	2.18	16.91	42.31

Table IIa

5-Pyridinium Methyl-1,2,4-oxadiazole **5** Hydrochlorides

Compound No.	Yield %	M.p. °C	Formula	Analysis			
				C	H	N	Cl⁻
5a	81	187-189°	$C_{14}H_{12}ClN_3O$	Calcd. 61.43	4.42	15.35	12.95
				Found 61.32	4.31	15.48	12.74
5b	80	125-127°	$C_{14}H_{11}Cl_2N_3O$	Calcd. 54.56	3.60	13.64	11.50
				Found 54.36	3.42	13.81	11.18
5c	69	164-165°	$C_{15}H_{14}ClN_3O_2$	Calcd. 59.31	4.65	13.83	
				Found 59.42	4.44	14.01	
5d	85	221-222°	$C_{14}H_{11}ClN_4O_3$	Calcd. 52.67	3.48	17.58	
				Found 52.43	3.44	17.69	

Table IIb

3-Pyridinium Methyl-1,2,4-oxadiazole **6** Hydrochlorides

Compound No.	Yield %	M.p. °C	Formula	Analysis			
				C	H	N	Cl⁻
6a	60	220° dec	$C_{14}H_{12}ClN_3O$	Calcd. 61.43	4.42	15.33	12.95
				Found 61.52	4.71	15.60	12.87
6b	80	245° dec	$C_{14}H_{11}Cl_2N_3O$	Calcd. 54.56	3.60	13.64	11.50
				Found 54.81	3.58	13.64	11.70
6c	73	242° dec	$C_{15}H_{14}ClN_3O_2$	Calcd. 59.31	4.65	13.83	
				Found 59.60	4.72	13.70	
6d	52	227° dec	$C_{14}H_{11}ClN_4O_3$	Calcd. 52.76	3.48	17.58	
				Found 52.75	3.47	17.59	
6e	55	208-210°	$C_{15}H_{14}ClN_3O$	Calcd. 62.61	4.90	14.60	12.32
				Found 62.66	5.01	14.55	12.08
6f	74	219° dec	$C_{15}H_{14}ClN_3O$	Calcd. 62.61	4.90	14.60	12.32
				Found 62.58	4.89	14.58	12.11
6g	85	227-229°	$C_{14}H_{11}ClN_4O_3$	Calcd. 52.76	3.48	17.58	11.12
				Found 52.96	3.51	17.47	10.86
6h	74	224° dec	$C_{14}H_{10}Cl_3N_3O$	Calcd. 49.08	2.94	12.27	10.35
				Found 49.22	3.02	12.27	10.01

tion through a hydrogen bond is significant. On the other hand it must be pointed out that the oxadiazole nucleus has the same behavior as that of an aromatic ring particularly deficient in electrons. In fact, in the nmr spectra, the methyl protons of 3-methyl-5-phenyl-1,2,4-oxadiazole and of 5-methyl-3-phenyl-1,2,4-oxadiazole fall near δ

Table IIIa

5-1,2,4-Oxadiazolyl Nitrones **7**(2)

Compound No.	Yield %	M.p. °C	Formula		Analysis C	H	N
7a	86	158° dec	$C_{17}H_{16}N_4O_2$	Calcd.	66.22	5.23	18.17
				Found	66.01	5.31	18.33
7b	87	188° dec	$C_{17}H_{15}ClN_4O_2$	Calcd.	59.57	4.41	16.35
				Found	59.57	4.42	16.41
7c	85	178° dec	$C_{18}H_{18}N_4O_3$	Calcd.	63.82	5.36	16.56
				Found	63.58	5.40	16.68
7d	90	190° dec	$C_{17}H_{15}N_5O_4$	Calcd.	57.78	4.28	19.82
				Found	57.12	4.52	19.22

(a) These compounds were obtained in crude form and could not be recrystallized.

Table IIIb

3-1,2,4-Oxadiazolyl Nitrones **8** (2)

Compound No.	Yield %	M.p. °C	Formula		Analysis C	H	N
8a	82	100° dec	$C_{17}H_{16}N_4O_2$	Calcd.	66.22	5.23	18.17
				Found	66.07	5.38	18.59
8b	63	95° dec	$C_{17}H_{15}ClN_4O_2$	Calcd.	59.57	4.41	16.37
				Found	59.33	4.70	16.33
8c	76	120° dec	$C_{18}H_{18}N_4O_3$	Calcd.	63.89	5.36	16.56
				Found	63.80	5.68	16.70
8d	71	208° dec	$C_{17}H_{15}N_5O_4$	Calcd.	57.78	4.28	19.82
				Found	57.81	4.29	19.77
8e	81	149° dec	$C_{18}H_{18}N_4O_2$	Calcd.	67.06	5.63	17.38
				Found	66.80	5.76	17.34
8f	88	88-89° dec	$C_{18}H_{18}N_4O_2$	Calcd.	67.06	5.63	17.38
				Found	67.35	5.39	17.24
8g	87	174° dec	$C_{17}H_{15}N_5O_4$	Calcd.	57.78	4.28	19.82
				Found	57.01	4.04	19.52
8h	67	145° dec	$C_{17}H_{14}Cl_2N_4O_2$	Calcd.	54.12	3.74	14.85
				Found	54.12	3.77	14.67

(a) These compounds were obtained in crude form and could not be recrystallized.

Table IVa

1,2,4-Oxadiazole-5-carbaldehyde Hydrates **9**

Compound No.	Yield %	M.p. °C	Formula		Analysis C	H	N
9a	75	105-108°	$C_9H_8N_2O_3$	Calcd.	56.25	4.20	14.58
				Found	56.12	4.24	15.33
9b	67	114-116°	$C_9H_7ClN_2O_3$	Calcd.	47.70	3.11	12.36
				Found	47.78	3.21	12.09
9c	32	85-86°	$C_{10}H_{10}N_2O_4$	Calcd.	54.04	4.54	12.61
				Found	54.12	4.61	12.44
9d	51	124-126°	$C_9H_7N_3O_5$	Calcd.	45.57	2.98	17.72
				Found	45.26	3.23	18.03

Table IVb

1,2,4-Oxadiazole-3-carbaldehyde Hydrates **10**

Compound No.	Yield	M.p. °C	Formula		Analysis C	H	N
10a	80	90-91°	$C_9H_8N_2O_3$	Calcd.	56.25	4.20	14.58
				Found	56.01	4.28	14.59
10b	78	109°	$C_9H_7ClN_2O_3$	Calcd.	47.70	3.11	12.36
				Found	47.93	3.34	12.00
10c	25	102-103°	$C_{10}H_{10}N_2O_4$	Calcd.	54.05	4.54	12.61
				Found	54.30	4.72	12.95
10d	56	192-195°	$C_9H_7N_3O_5$	Calcd.	45.57	2.98	17.72
				Found	45.71	2.79	17.83
10e	65	100-102°	$C_{10}H_{10}N_2O_3$	Calcd.	58.25	4.89	13.58
				Found	58.64	4.89	13.36
10f	51	72-73°	$C_{10}H_{10}N_2O_3$	Calcd.	58.25	4.89	13.58
				Found	58.15	4.97	13.71
10g	51	90-92°	$C_9H_7N_3O_5$	Calcd.	45.57	2.98	17.72
				Found	45.83	2.90	17.66
10h	43	100°	$C_9H_6Cl_2N_2O_3$	Calcd.	41.40	2.32	10.73
				Found	41.48	2.52	10.50

Table Va

1,2,4-Oxadiazole-5-carbaldehydes **15**

Compound No.	M.p. °C	Formula		Analysis C	H	N
15a	112-114°	$C_9H_6N_2O_2$	Calcd.	62.07	3.47	16.09
			Found	62.19	3.46	16.16
15b	85-87°	$C_9H_5ClN_2O_2$	Calcd.	51.82	2.42	13.43
			Found	51.88	2.40	13.40
15c	107-108°	$C_{10}H_8N_2O_3$	Calcd.	58.82	3.95	13.72
			Found	59.10	3.95	13.84
15d	140-142°	$C_9H_5N_3O_4$	Calcd.	49.32	2.30	19.18
			Found	49.29	2.23	19.18

Table Vb

1,2,4-Oxadiazole-3-carbaldehydes **16**

Compound No.	M.p. °C	Formula		Analysis C	H	N
16a	67-69°	$C_9H_6N_2O_2$	Calcd.	62.07	3.47	16.09
			Found	61.88	3.58	16.20
16b	125-128°	$C_9H_5ClN_2O_2$	Calcd.	51.82	2.42	13.43
			Found	51.90	2.58	13.72
16c	113-114°	$C_{10}H_8N_2O_3$	Calcd.	58.82	3.95	13.72
			Found	58.74	4.14	13.87
16d	198-199°	$C_9H_5N_3O_4$	Calcd.	49.32	2.30	19.18
			Found	49.60	2.33	19.25
16e	107-108°	$C_{10}H_8N_2O_2$	Calcd.	63.82	4.29	14.89
			Found	64.02	4.31	14.86
16f	42-45°	$C_{10}H_8N_2O_2$	Calcd.	63.82	4.29	14.89
			Found	64.09	4.40	14.59

2.5. This position is the same as the one corresponding to the methyl protons of *p*-nitrotoluene (δ 2.5) (14) and is at lower field than the methyl protons in toluene (δ 2.2). It is known that electron withdrawing groups favour the formation of hydrated aldehydes (eg., chloral hydrate) and therefore the most reliable explanation of this phenomenon seems to be that both factors (electronic considerations and formation of the hydrogen bond) contribute to the stability of the hydrated form.

EXPERIMENTAL

The uv spectra were recorded in 95% ethanol solutions on a Perkin Elmer 550 Spectrophotometer. The ir spectra were obtained on a Perkin Elmer 257 Spectrophotometer. The nmr spectra (δ, TMS as the internal standard) were obtained on a Perkin-Elmer 24 Spectrometer. The melting points were taken on a Büchi apparatus and are uncorrected. Elemental analyses were performed on a Carlo Erba C,H,N apparatus. The Authors express their thanks to Dr. Pietro Ridolfi for the spectra and microanalyses.

The following compounds were obtained according to described procedures (3,4).

3-Methyl-5-phenyl-1,2,4-oxadiazole.

This compound had nmr (deuteriochloroform): 2.45 (s, 3H, $-CH_3$)7.45 (m, 3H, H arom.), 8.10 (m, 2H, H arom.).

5-Methyl-3-phenyl-1,2,4-oxadiazole.

This compound had nmr (deuteriochloroform): 2.55 (s, 3H, $-CH_3$), 7.45 (m, 3H, H arom.), 8.14 (m, 2H, H arom.).

3-Aryl-5-chloromethyl-1,2,4-oxadiazoles and 5-aryl-3-chloromethyl-1,2,4-oxadiazoles (see Table I) were obtained starting from benzamidoximes and chloroacetyl chloride (Method A) or from chloroacetamidoxime and aroyl-chlorides (Method B) respectively, according to described procedures (5,7).

5-Hydroxymethyl-3-phenyl-1,2,4-oxadiazole (**3**).

A mixture of **1a** (4 g., 0.02 mole) and hexamethylenetetramine (5.6 g., 0.04 mole) in 50% acetic acid (25 ml.) was refluxed for 4 hours. After cooling, concentrated (10 ml.) was added and the solution was refluxed for 5 minutes. The cooled solution was diluted with water (40 ml.) and extracted four times with ethyl ether (50 ml. each time). The collected extracts were dried over sodium sulfate and evaporated. The residue was distilled to give 2.0 g. (56.8%) of an oil boiling at 125-126°/1 torr, m.p. 58-60°, recrystallized from hexane; nmr (deuteriochloroform): 4.90 (s, 1H, O*H*), 5.00 (s, 2H, C*H*$_2$—O), 7.55 (m, 3H, H arom.), 8.50 (m, 2H, H arom.).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.00; H, 4.51; N, 15.69.

Compound **4**.

This compound (yield 8%, m.p. 91-93°, recrystallized from hexane-ethyl acetate) was obtained in an analogous manner to **3**.

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.54; H, 4.58; N, 15.44.

Pyridinium Salts **5** and **6** (General Procedure).

A solution of **2a** (19.2 g., 0.07 mole) and pyridine (10.3 g., 0.14 mole) in absolute ethanol (40 ml.) was refluxed for 18 hours. After cooling the resulting solution was diluted with ethyl ether (150 ml.) and the precipitated solid was collected by suction and recrystallized from isopropyl alcohol. Analyses, yields and m.p. of the single products are reported in Tables IIa and IIb.

Nitrones **6** and **7**. (General Procedure).

To a solution obtained by mixing together a solution of **6a** (13 g., 0.05 mole) in water (80 ml.) and a solution of 4-nitroso-*N*,*N*-dimethylaniline (7.45 g., 0.05 mole) in ethanol (185 ml.), under good stirring and keeping the temperature above 10°, 1*N* sodium hydroxide (50 ml.) was added dropwise. Stirring was continued for ten more minutes and the solid, which precipitated, was recovered by filtration. It was washed several times with water, air-dried, and used in the following step. Concerning the recrystallization of these nitrones see the following paper. The m.p., yields and analyses obtained for the single products are reported in Tables IIIa and IIIb.

Hydrated Aldehydes **9** and **10** from Nitrones **7** and **8** (General Procedure).

Compound **8a** (30 g., 0.096 mole) was shaken for 15 minutes together with a mixture of 3*N* hydrochloric acid (300 ml.) and ethyl ether (300 ml.). The organic layer was separated and the aqueous phase was extracted twice with ethyl ether (150 ml.). The extracts were collected and the solvent was evaporated. The residue was recrystallized from water and air dried to give **9a** (semicarbazone, m.p. 247°, phenylhydrazone, m.p. 215-216° dimedone derivative, m.p. 175-177°). The m.p., yields and analyses obtained for the single products are reported in Tables IVa and IVb.

5-Dichloromethyl-3-*p*-methoxyphenyl-1,2,4-oxadiazole (**11c**).

This compound was obtained in 90% yield using the same procedure as described for **11a** (10) starting from *p*-methoxybenzamidoxime and dichloroacetyl chloride, m.p. 56-57° from hexane.

Anal. Calcd. for $C_{10}H_8Cl_2N_2O_2$: C, 46.36; H, 3.09; N, 10.87; Cl, 27.37. Found: C, 46.26; H, 3.01; N, 10.91; Cl, 27.65.

3-Dichloromethyl-5-phenyl-1,2,4-oxadiazole (**12a**).

This compound was obtained from dichloroacetamidoxime and benzoyl chloride in 45% yield, m.p. 56-58° from hexane-ethyl acetate.

Anal. Calcd. for $C_9H_6Cl_2N_2O$: C, 47.19; H, 2.64; N, 12.23; Cl, 30.96. Found: C, 46.98; H, 2.81; N, 12.11; Cl, 30.84.

5-Dimorpholinomethyl-3-*p*-methoxyphenyl-1,2,4-oxadiazole (**13c**).

Compound **11c** (13 g., 0.05 mole) was dissolved in anhydrous morpholine (50 ml.) and the solution was heated on a steam bath for 30 minutes. The excess morpholine was removed in a rotary evaporator and the residue was treated with ethyl acetate. The morpholine hydrochloride which separated was removed by filtration and the filtrate was evaporated to give an oil which solidified when treated with water. After recrystallization from ethanol, 16.2 g. of **13c** were obtained, yield 90%, m.p. 124-125°.

Anal. Calcd. for $C_{18}N_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.55. Found: C, 60.11; H, 6.41; N, 15.62.

3-Dimorpholinomethyl-5-phenyl-1,2,4-oxadiazole (**14a**).

This compound was obtained from **12a** analogously to **13c** in 50% yield, m.p. 144-147° from ethanol.

Anal. Calcd. for $C_{17}H_{22}N_4O_3$: C, 61.80; H, 6.71; N, 16.96. Found: C, 61.81; H, 6.74; N, 16.59.

Hydrated Aldehydes from Dimorpholinomethyl Derivatives.

Compound **13c** (16.2 g., 0.04 mole) was dissolved at room temperature, under good stirring, in 2*N* hydrochloric acid (50 ml.). After 10 minutes the crystalline neeldes which separated were collected by suction and recrystallized from water. Thus, 4.3 g. (90%), m.p. 85° undepressed with a sample of **9c** obtained from the nitrone, were obtained.

Compounds **9a** and **10a** were obtained in the same manner from **13a** and **14a** in 83 and 75% yields, respectively.

5-Dichloromethyl-3-phenyl-1,2,4-oxadiazole (**13a**) From **9a**.

Compound **9a** (3.9 g., 0.02 mole) and phosphorus pentachloride (10.4 g., 0.05 mole) were mixed together in a round bottom flask. There was a release of heat and hydrogen chloride. When the reaction stopped (after about 10 minutes) the mixture was poured into triturated ice and the oil which separated was extracted with ether. The residue obtained after removal of the solvent was recrystallized giving 1.7 g. (37%) of **13a**, m.p. 46° undepressed with a sample obtained using the procedure described above.

Anydrous Aldehydes **15** and **16**.

The hydrated aldehydes **9** and **10** were sublimated at their melting temperature and under a vacuum of 0.3 torr. If the ir spectrum (nujol) showed the OH band, the sublimation was repeated a second time. The characteristics of the anhydrous aldehydes are reported in Tables Va and Vb.

REFERENCES AND NOTES

(1) G. Palazzo and G. Corsi, *Gazz. Chim. Ital.*, 93, 1196 (1963).

(2) T. R. Mnatasakanova and O. P. Shwika, *Khim. Geterotsikl. Soedin.*, 212 (1969); *Chem. Abstr.*, 71, 30414w (1969).

(3) E. Nordmann, *Ber.*, 17, 2754 (1884).

(4) F. Tiemann and P. Krüger, *ibid.*, 17, 1697 (1884).

(5) G. Palazzo, M. Tavella, G. Strani and B. Silverstrini, *J. Med. Chem.*, 4, 351 (1961).

(6) H. Breuer and U. D. Treuner, U.S. Patent 3,887,573 (1975).

(7) A. A. Sousa, H. C. Chitwood and J. A. Durden, French Patent 1,363,235 (1964).

(8) "Organic Reactions," VIII John Wiley and Sons, New York, N.Y., 1954, p. 197.

(9) F. Krönke, *Angew. Chem.*, 65, 605 (1953).

(10) B. S. Drach, V. A. Kovalev and A. V. Kirsanov, *Zh. Org. Khim.*, 12, 673 (1976).

(11) M. Kerfanto, *Compt. Rend.*, 252, 3457 (1961).

(12) D. Jerchel, T. Heider and H. Wagner, *Ann. Chem.*, 613, 153 (1958).

(13) J. Sandstrom, "Recent Advances in the Chemistry of 1,2,4-Thiadiazoles", in "Advances in Heterocyclic Chemistry", Vol. 9, Academic Press, New York, N.Y., 1968, p. 173.

(14) J. C. Grasselli, "Atlas of Spectral Data and Physical Constants for Organic Compounds", CRC Press, 1974.