THE CHEMISTRY OF 1,3,4-OXADIAZOLE DERIVATIVES

E. P. Nesynov and A. P. Grekov

CONTENTS

I. Introduction 508

II. Preparation of mono-substituted 1,3,4-oxadiazoles 508

III. Preparation of symmetrical 2,5-substituted 1,3,4-oxadiazoles 508

1. 2,5-Dialkyl-1,3,4-oxadiazoles 508

2. 2,5-Diaryl-1,3,4-oxadiazoles 508

IV. Preparation of asymmetrical 2,5-substituted 1,3,4-oxadiazoles 509

1. 2-Alkyl-5-aryl-1,3,4-oxadiazoles 509

2. 2,5-Diaryl-1,3,4-oxadiazoles 509

3. Derivatives of 2-amino-1,3,4-oxadiazole 510

4. Heterocyclic 2,5-substituted 1,3,4-oxadiazoles 510

V. Preparation of poly-1,3,4-oxadiazoles 511

1. Bis-1,3,4-oxadiazolyl derivatives 511

2. Poly-1,3,4-oxadiazole derivatives 511

VI. Properties and uses of 1,3,4-oxadiazole derivatives 512

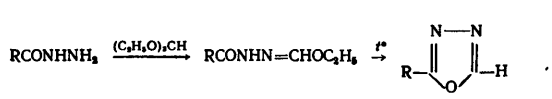
I. INTRODUCTION

There is now much experimental material on the chemistry of 1,3,4-oxadiazole derivatives, which are widely used in pharmacy, dyestuff production, scintillation technology, for the production of thermostable polymers, and in other fields of science and technology.

2,5-Substituted 1,3,4-oxadiazoles had been prepared before the end of the last century, but there have been no reviews on this subject; this article attempts to fill this gap, embracing the literature up to 1961, and including nearly all the most important material on the preparation and chemical properties of 2,5-substituted 1,3,4-oxadiazoles.

II. PREPARATION OF MONO-SUBSTITUTED 1,3,4-OXADIAZOLES

2-Aryl-1,3,4-oxadiazoles are prepared by the reaction of carboxylic acid hydrazides with excess of triethoxymethane [1-4]:

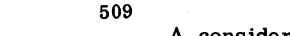


(I) (II)

The reaction is carried out at the boiling point of the triethoxymethane; the time of heating can be restricted to that necessary for complete dissolution of the hydrazide in the latter, which is usually several hours [2]. The amount of triethoxymethane can be as little as three moles per mole of hydrazide. At a lower temperature, compound (I) is formed in quantitative yield [1,3]; further heating converts this into compound (II). The method is a general one only when any functional substituents in the initial hydrazides are inert to the "ortho-ester".

In some cases 2-aryl-1,3,4-oxadiazoles can be obtained by conversion of functional groups in a previously prepared oxadiazole; for example, 2-(4-aminophenyl)-1,3,4-oxadiazole has been prepared by reduction of the (nitrophenyl)-oxadiazole with phenylhydrazine [2]. Reduction by agents which act in acid or alkaline media is inapplicable, because of the ready hydrolysis of the resulting oxadiazole under such conditions [2].

2-Amino-1,3,4-oxadiazole (III) is obtained by the removal of hydrogen sulphide from formyl thiosemicarbazide by means of lead oxide in ethanol [5,6]:

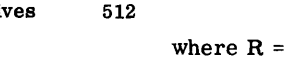


A considerable quantity of 3-mercapto-1,2,4-triazole is also produced.

III. PREPARATION OF SYMMETRICAL 2,5-SUBSTITUTED 1,3,4-OXADIAZOLES

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

Symmetrical 2,5-dialkyl-1,3,4-oxadiazoles (IV) are prepared [7-14] by the reactions

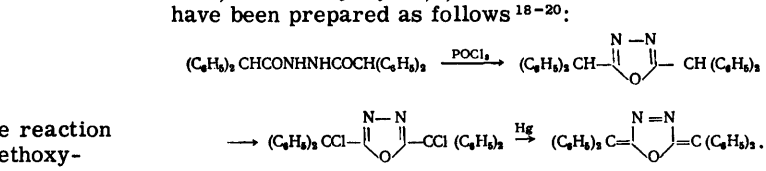


where R = alkyl.

Aliphatic acids react readily with hydrazine hydrate at room temperature, giving a quantitative yield [15] of the symmetrical 1,2-diacylhydrazines, which are cyclised to the corresponding oxadiazoles either by heating in a vacuum [9-11] or by the action of phosphorus pentoxide [7,9], zinc chloride [7,12,15], phosphorus pentachloride or phosphoryl chloride [16] in benzene, thionyl chloride [14], or the anhydride of the corresponding aliphatic acid [8,9,12,13]. 2,5-Dialkyl-1,3,4-oxadiazoles are also formed by prolonged heating of esters of the aliphatic acids with hydrazine hydrate at 150–230° [9,12] or by heating the corresponding tetraacylhydrazines at 300–350°:



2,5-Dibenzhydryl-1,3,4-oxadiazole and its derivatives have been prepared as follows [18-20]:



2. 2,5-Diaryl-1,3,4-oxadiazoles

These compounds (V) are usually prepared as follows [21,22]:



The preparation of the 1,2-diaroylhydrazine from the aromatic acid chloride and hydrazine hydrate is conveniently conducted in dry pyridine, which combines with the hydrogen chloride liberated in the reaction, so avoiding the

need for excess of hydrazine hydrate [23] or for carrying out the reaction in aqueous alkaline solution [24]. In the production of the oxadiazole there is no need for prolonged boiling of the diaroylhydrazine with the phosphoryl chloride, as is sometimes recommended [21]; it is quite sufficient to heat till the starting material is completely dissolved.

Symmetrical 2,5-diaryl-1,3,4-oxadiazoles are also obtained directly from the corresponding diaroylhydrazines by heating at 180–350° [7,9,15,17,25-29] or by the action of phosphorus pentoxide [19,26-32], thionyl chloride [19,28] or oxalyl chloride [33]. The reaction product of the hydrazide with chlorinating agents can be cyclised to the oxadiazole by means of silver nitrate [28,34-37]. 2,5-Diaryl-1,3,4-oxadiazoles are also produced by heating mono- or tri-acylhydrazines [17,25,38]:

$$2\,ArCONHNH_2 \xrightarrow{\Delta} (V) + N_2H_4 + H_2O,$$

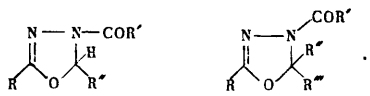
$$ArCONHN(COAr)_2 \xrightarrow{\Delta} (V) + ArCOOH;$$

by heating the silver salts of 1,2-diaroylhydrazines [39], by the action of iodine on the silver or mercury salts of the acylhydrazones (VI) [40]:

$$\underset{(VI)}{ArCONHN{=}CHAr} \xrightarrow{Ag} ArC(OAg){=}N{-}N{=}CHAr \xrightarrow{I_2} ArC(OI){=}N{-}N{=}CHAr \rightarrow (V),$$

and also, from the hydrazones (VI), by heating [40], by chlorination in carbon tetrachloride [41], or by boiling with a dilute alkaline solution of potassium cyanoferrate(III) or with isopentyl nitrite [40].

The action of acid chlorides on silver salts of the hydrazones (VI) produces dihydrooxadiazoles of type:

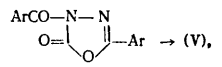


Of interest also is the preparation of aryl 1,3,4-oxadiazoles by the reaction of carboxylic acid monoacylhydrazides with iminium-ether chlorides at 80–160° [42] or by treatment of their reaction product with nitrous acid [43-46]:

$$ArC(=NH)NHNHCOAr \rightleftarrows ArC(NH_2){=}N{-}N{=}C(OH)Ar \xrightarrow{HNO_2}$$

$$\xrightarrow{HNO_2} ArC(OH){=}N{-}N{=}C(OH)Ar \rightarrow (V).$$

2,5-Diaryl-1,3,4-oxadiazoles have also been obtained by the decomposition of substituted 1,3,4-oxadiazol-5-ones at 280° [47,48]:



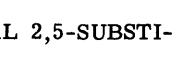
and by the hydrolysis of 3,6-diaryl-1,2-dihydro-1,2,4,5-tetrazines in the presence of mineral acids or alkalis [44,47-49].

IV. PREPARATION OF ASYMMETRICAL 2,5-SUBSTITUTED 1,3,4-OXADIAZOLES

1. 2-Alkyl-5-aryl-1,3,4-oxadiazoles

These compounds (VII) are obtained as follows [50]:

$$RCOOC_2H_5 \xrightarrow{N_2H_4} RCONHNH_2 \xrightarrow{ArCOCl} RCONHNHCOAr \rightarrow$$



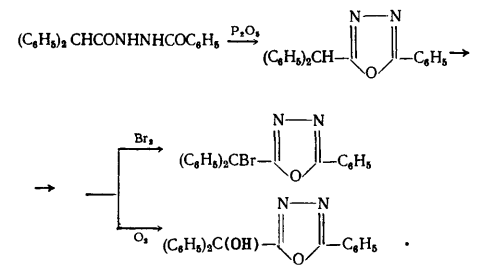
(VII).

The aliphatic acid hydrazides are produced from the esters and hydrazine hydrate in a satisfactory yield at room temperature; under other conditions the hydrazides are readily converted into symmetrical 1,2-diacylhydrazines [51]. The kinetics of benzoylation of aliphatic hydrazides shows that the 1,2-diacylhydrazines are obtained in quantitative yield in dilute solutions at room temperature [51]. Cyclisation of the diacylhydrazines into oxadiazoles is carried out as described in Section III.

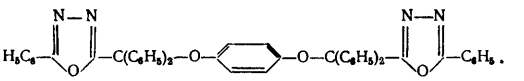
2-Alkyl-5-aryl-1,3,4-oxadiazoles can be prepared from hydrazides and "acid ortho-esters" [1] under conditions analogous to those used for 2-aryl-1,3,4-oxadiazoles (see Section II):

$$ArCONHNH_2 \xrightarrow{(C_2H_5O)_3CR} ArCONHN{=}CROC_2H_5 \xrightarrow{\Delta} (VII).$$

An interesting method is the preparation of oxadiazole derivatives from diphenylmethyl derivatives of 2-phenyl-1,3,4-oxadiazole, which are obtained by heating *N*-benzoyl-*N'*-diphenylacetylhydrazine with phosphorus pentoxide [52]:



The bromine atom of the 5-(bromodiphenylmethyl)-2-phenyl-1,3,4-oxadiazole is replaced by the hydroxy-group by heating with aqueous alkali or by the ethoxy-group by reaction with sodium ethoxide [19,53]. Shaking with mercury in benzene in an atmosphere of carbon dioxide produces 9,9'-bis-(5-phenyl-1,3,4-oxadiazol-2-yl)-9,9'-bifluorenyl; in the presence of oxygen the product is bis[diphenyl-(5-phenyl-1,3,4-oxadiazol-2-yl)methyl] peroxide [53], which on dissolving in sulphuric acid decomposes to give 5-benzoyl-2-phenyl-1,3,4-oxadiazole [54]. Heating 5-(bromodiphenylmethyl)-2-phenyl-1,3,4-oxadiazole with mercury in the presence of *p*-quinone gives the ether [52]:



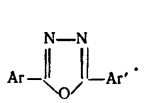
2-Alkoxy-5-aryl-1,3,4-oxadiazoles are also obtained by direct alkylation of oxadiazolones [55,56].

2. 2,5-Diaryl-1,3,4-oxadiazoles

These compounds are generally prepared as follows [51,57]:

$$ArCOCl \xrightarrow{Ar'CONHNH_2} ArCONHNHCOAr' \rightarrow$$

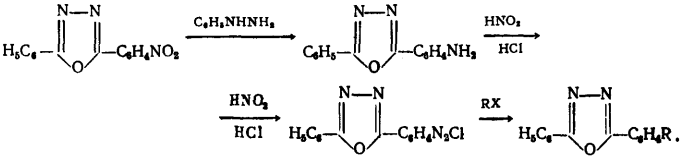
$$\rightarrow [ArC(OH){=}NN{=}C(OH)Ar'] \xrightarrow{POCl_3} ArCCl{=}NN{=}CClAr' \xrightarrow{H_2O}$$



Most of the mixed aryl 1,3,4-oxadiazoles have been prepared by this method [21,50,58,59], and also uni- and bi-functionally substituted 2,5-diphenyl-1,3,4-oxadiazoles [21,57,60], the reaction conditions and yields being substantially independent of the position and type of substituent. Contrary to literature data, the diaroylhydrazines are formed in the

cold; elevated temperatures produce significant amounts of by-products, the symmetrical diaroylhydrazines of the type $(C_6H_5CONH)_2$ and $(XC_6H_4CONH)_2$, particularly when the benzene ring contains electron-accepting substituents. At the cyclisation stage, the period of heating the diaroylhydrazine with phosphoryl chloride can be restricted to the time necessary for its complete dissolution, instead of the boiling for several hours recommended in the literature [21].

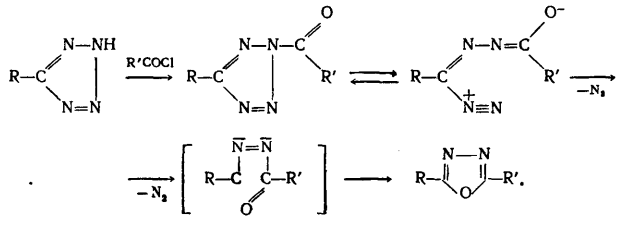
This method may be hindered by reaction of functional groups with the reagents used; the following procedure was devised to circumvent this [61]:



The 5-(aminophenyl)-2-phenyl-1,3,4-oxadiazoles are obtained in good yield using phenylhydrazine as reducing agent [57,61]. This method has been used for the partial reduction of dinitrophenyl-1,3,4-oxadiazoles in 1-methylnaphthalene as solvent, one of the nitro-groups in 2,5-di-(*p*-nitrophenyl)- and 2,5-di-(*m*-nitrophenyl)-1,3,4-oxadiazole being reduced fairly readily. In 2,5-di-(*o*-nitrophenyl)-1,3,4-oxadiazole, however, both nitro-groups are reduced simultaneously.

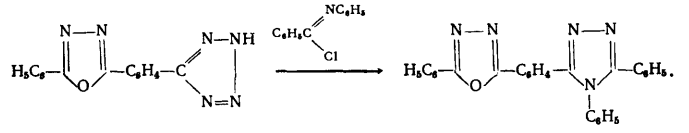
The nitro-group is also readily reduced to the amino-group if the 2,5-diphenyl-1,3,4-oxadiazole contains other substituents in addition, or if a phenyl ring is replaced by pyridyl, *e.g.* in the formation of 2-(*p*-aminophenyl)-5-(β-pyridyl)-1,3,4-oxadiazole. However, the presence of a heterocyclic residue makes amino-substituted 1,3,4-oxadiazoles considerably more difficult to obtain, because of their substantially lower chemical stability and the difficulty of isolating them from the reaction mixture. The amino-group in 1,3,4-oxadiazoles participates in all reactions appropriate to a primary aromatic amino-group [57], so that a whole series of substituted 1,3,4-oxadiazoles were able to be obtained, the chemical structures of which were fully confirmed by other methods of preparation.

Asymmetrical 2,5-diaryl-1,3,4-oxadiazoles can be obtained in good yield by heating 5-substituted tetrazoles with carboxylic acid chlorides in pyridine; the following has been suggested [62] as the reaction mechanism:



Acid anhydrides are also used as acylating agents.

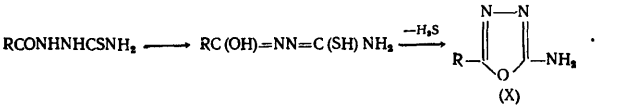
The action of imidoyl chlorides on compound (VIII) produces compound (IX), in which an oxadiazole ring and a triazole ring are joined by a benzene ring [63]:



(VIII) (IX)

3. Derivatives of 2-Amino-1,3,4-oxadiazole

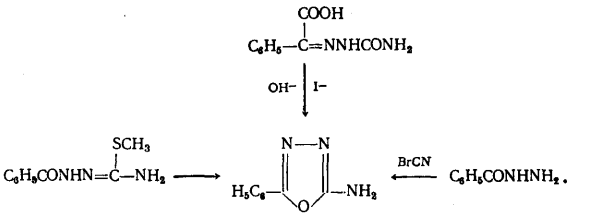
2-Amino-1,3,4-oxadiazole (X) and its derivatives are obtained by the elimination of hydrogen sulphide from thiosemicarbazides by means of lead monoxide [5,6,64]:



(X)

Good yields are obtained by heating a solution of the thiosemicarbazide in 95% ethanol with a tenfold excess of lead monoxide for several hours [5,6,64].

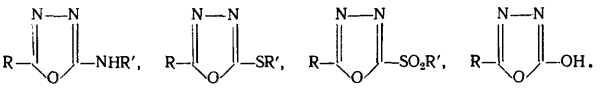
2-Amino-5-phenyl-1,3,4-oxadiazole has been prepared by the following routes [65]:



Heating the thiosemicarbazide derivatives

$$RCONHNHCSNHR' \text{ and } RCONHN{=}C(SCH_3)NHR',$$

or the action of dehydrating agents on them, has given the corresponding oxadiazoles [66-68]:

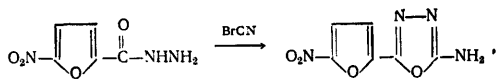


The action of a 5% sodium hypobromite solution on benzaldehyde semicarbazone produces 2-amino-5-phenyl-1,3,4-oxadiazole [69]. A number of other derivatives of 2-amino-5-phenyl-1,3,4-oxadiazole have also been prepared [70-77].

4. Heterocyclic 2,5-Substituted 1,3,4-Oxadiazoles

1,3,4-Oxadiazoles containing various heterocyclic substituents have been prepared analogously to the 2,5-diaryl-1,3,4-oxadiazoles [78-81]. The preparation of the heterocyclic acid acylhydrazides from the acid chlorides and the hydrazides must be carried out in the cold, since the use of elevated temperature gives, in addition to the main reaction product, the diacylated hydrazides $RCONHN(COR)_2$, which on hydrolysis gives the original monoacylhydrazide. In the preparation of aroylhydrazides in boiling solutions, symmetrical 1,2-diaroylhydrazines are also obtained, in addition to the other products specified [82]. The usual solvent for the production of acylhydrazides is pyridine, which binds the hydrogen chloride liberated in the reaction, and thus favours more complete utilisation of the initial reactants and, in the case of pyridinecarboxylic acid acylhydrazides, the production of the product as the free base. However, the extraction of the acylhydrazides from the reaction mixture is more difficult, because of their good solubility in pyridine [82].

Of interest is the preparation of heterocyclic derivatives of 2-amino-1,3,4-oxadiazole from cyanogen bromide and the heterocyclic acid hydrazide [56]:



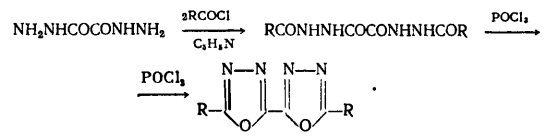
or by reaction of the heterocyclic acid chloride with thiosemicarbazide with subsequent cyclisation to the oxadiazole [56].

A number of heterocyclic derivatives of 1,3,4-oxadiazole have been prepared by these methods [1,40,83-88].

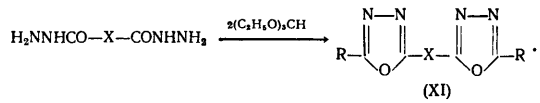
V. PREPARATION OF POLY-1,3,4-OXADIAZOLES

1. Bis-1,3,4-oxadiazolyl Derivatives

Bi-(1,3,4-oxadiazolyl)s are obtained by the general method for 2,5-substituted 1,3,4-oxadiazoles [21,89]:



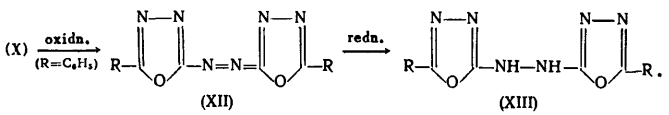
The same method is applied to bis-(1,3,4-oxadiazolyl) derivatives in which the oxadiazole rings are separated by hydrocarbon chains, by using the hydrazide of the appropriate dicarboxylic acid. In many cases the production of the secondary dihydrazide from the primary dihydrazide and the appropriate acid chloride in pyridine also gives significant amounts of a substance corresponding in properties and analysis to the diaroylhydrazine, and which with phosphoryl chloride produces the 2,5-disubstituted 1,3,4-oxadiazole. Bis-(1,3,4-oxadiazolyl) compounds of type (XI) in which R = H have been prepared by the action of triethoxymethane on the primary dihydrazide followed by cyclisation [1,89]:



(XI)

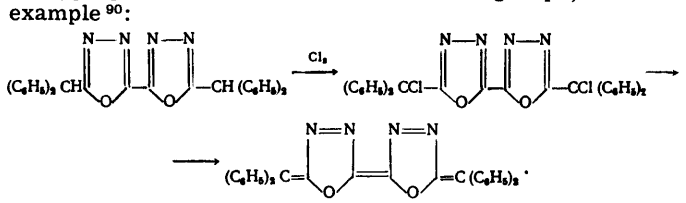
The action of triethoxymethane on malonodihydrazide gives a derivative of bis-(1,3,4-oxadiazolyl)methane in which the hydrogen atoms of the methylene group have been replaced by the group $=CH-OC_2H_5$.

Oxidation of 2-amino-1,3,4-oxadiazole derivatives gives azooxadiazoles (XII), which can be reduced to the corresponding hydrazo-compounds (XIII) [5]:

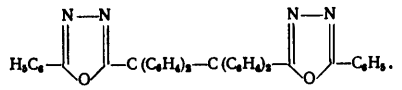


(XII) (XIII)

Other bis-(1,3,4-oxadiazolyl) compounds can be obtained by appropriate conversions of functional groups, for example [90]:



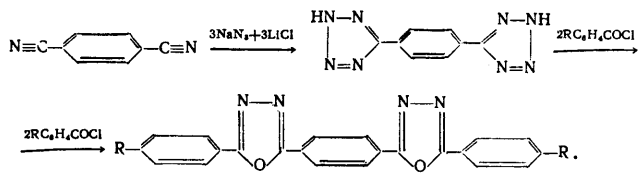
Bis-(1,3,4-oxadiazole) compounds such as the following have also been prepared [20,52]:



Other methods can also be used to obtain bisoxadiazole compounds [30,40,91].

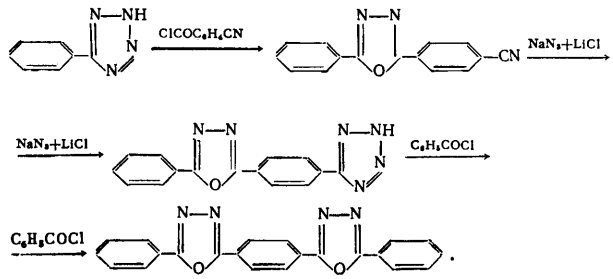
2. Poly-1,3,4-oxadiazole Derivatives

The thermal decomposition of 5-substituted 2-acyltetrazoles at 60–120° produces 1,3,4-oxadiazoles [62]. This is the basis of a procedure for the preparation of polyaryls containing up to nine rings in the molecule by reacting 5-phenyltetrazole or 1,2-di(tetrazol-5-yl)benzene with acid chlorides RC_6H_4COCl, where R = H, *p*-NO_2, or *p*-CN, [92] *e.g.*

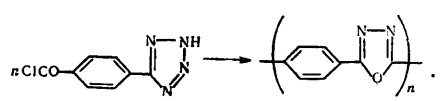


The terminal nitrile groups of the reaction product of *p*-cyanobenzoyl chloride with 1,4-di(tetrazol-5-yl)benzene can again be reacted with lithium azide in boiling dimethylformamide to produce tetrazole rings, which in their turn can be reacted with the acid chlorides, etc., so increasing the number of oxadiazole rings in the chain.

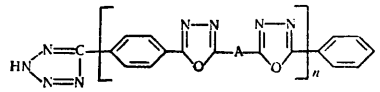
Polyoxadiazoles can also be obtained from 5-phenyltetrazole and *p*-cyanobenzoyl chloride [92]:



Polymers with an even number of aromatic rings can be prepared from 4-(tetrazol-5-yl)benzoyl chloride, which contains both the functions necessary for forming the oxadiazole ring [92]:



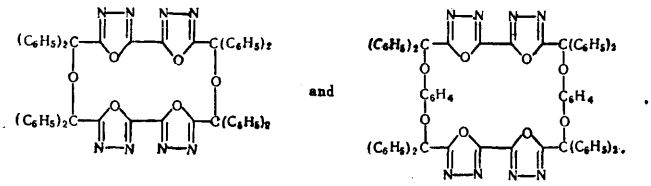
The action of dibasic acid chlorides on 1,4-di(tetrazol-5-yl)benzene gives the polymers [93]:



where n = 17–50.

The polyoxadiazoles are obtained in yields of up to 96%, and have a high melting point and a low solubility in organic solvents. It is thought that higher-molecular-weight polyoxadiazoles with alternating benzene and oxadiazole rings could be obtained by introducing a methyl or alkoxy-group. If pyridine nuclei are introduced between the oxadiazole rings the resulting polymers are black and are soluble in formic acid and phenol.

Cyclic polyoxadiazoles have also been prepared[20]:



VI. PROPERTIES AND USES OF 1,3,4-OXADIAZOLE DERIVATIVES

2,5-Substituted 1,3,4-oxadiazoles are colourless substances; the lower alkyl derivatives are liquids which distil without decomposition. Replacement of an alkyl residue by an aryl radical considerably raises the melting and boiling points. Usually the asymmetrical 1,3,4-oxadiazole derivatives melt and boil at lower temperatures than the symmetrical compounds. The presence of substituents of various electronic types on the aryl residues of the oxadiazoles leads to the appearance of colour in the compounds. Certain 2,5-substituted 1,3,4-oxadiazoles which have no strong electron-accepting groups luminesce in the crystalline state, in non-polar solvents or solvents of low polarity, and in polystyrene[81,94-97].

2-Hydroxy-5-aryl-1,3,4-oxadiazoles may exist in the keto-form[47,48,98-101].

Methylation of 2-amino-5-phenyl-1,3,4-oxadiazole with methyl iodide produces 2,3-dihydro-2-imino-3-methyl-5-phenyl-1,3,4-oxadiazole, while acetylation and nitrosation proceed normally; this shows that 2-amino-5-phenyl-1,3,4-oxadiazole can react either in the imino- or the amino-form[102].

The solubility of oxadiazoles in water varies with the substituents present[50]; thus while 2,5-dimethyl-1,3,4-oxadiazole is miscible with water in all proportions[7], the solubility of 2,5-diphenyl-1,3,4-oxadiazole in water is only 0.03%.

Aqueous solutions of mineral acids and alkalis cause rupture of the heterocyclic ring, with formation of the corresponding hydrazide. 2-Aryl-1,3,4-oxadiazoles hydrolyse almost instantaneously as soon as they are dissolved, giving the primary hydrazides and formic acid[2,5,7,10,103,104]. The tendency of oxadiazoles to hydrolyse decreases with their solubility[50].

Concentrated sulphuric acid (sp. gr. 1.84) does not sulphonate 2,5-diphenyl-1,3,4-oxadiazole even at 100° for 4 h or longer, but only produces the double sulphate, which hydrolyses readily in dilute aqueous solution to regenerate the initial 2,5-diphenyl-1,3,4-oxadiazole[105].

Concentrated nitric acid (sp. gr. 1.51) readily nitrates 2,5-diphenyl-1,3,4-oxadiazole to a mixture of the *o'o"*-, *m'm"*-, and *p'p"*-dinitro-compounds (in yield of 40, 20, and 27% respectively)[105].

A mixture of concentrated nitric and sulphuric acids nitrates 2,5-diphenyl-1,3,4-oxadiazole to 5-(*m*-nitrophenyl)-2-phenyl- and 2,5-di-(*m*-nitrophenyl)-1,3,4-oxadiazole in yields of 31 and 38%[105].

As has already been stated, a nitrophenyl group in a 1,3,4-oxadiazole is readily reduced to aminophenyl by phenylhydrazine. Reducing agents which require acidic or alkaline media (zinc dust, sodium disulphide) are unsuitable, since under such conditions the oxadiazole ring is attacked, producing first the corresponding hydrazide, and then hydrazine and aromatic acids[2,61].

The amino-group in an aminophenyl-1,3,4-oxadiazole can be diazotised and replaced by other substituents, for example halogens and the hydroxy- or cyano-groups, which in their turn can be used to provide further functionally substituted 1,3,4-oxadiazoles[57,61]. The diazotised amino-groups couple readily, producing azo-dyestuffs[106,107].

In dilute hydrochloric acid 2-amino-5-phenyl-1,3,4-oxadiazole reacts with nitrous acid to give 2-nitrosamino-5-phenyl-1,3,4-oxadiazole, which can be reduced to 2-hydrazino-5-phenyl-1,3,4-oxadiazole; this with nitrous acid produces 2-azido-5-phenyl-1,3,4-oxadiazole[5].

2-Hydrazino-5-phenyl-1,3,4-oxadiazole with benzaldehyde gives the corresponding substituted hydrazone, which is decomposed by hydrochloric acid and steam into benzaldehyde, benzoic acid, and $H_2NNHCONHNH_2$.[5]

Phenylhydrazinium chloride opens the oxadiazole ring of 2-amino-5-aryl-1,3,4-oxadiazoles, producing diaminoguanidine[108].

Heating 5-alkyl-2-amino-1,3,4-oxadiazoles with hydrazine hydrate gives 3-alkyl-4,5-diamino-1,2,4-triazoles in low yields[109].

Alkaline reactants convert 2-amino-5-phenyl-1,3,4-oxadiazole into 2-phenyl-1,3,4-triazol-5-one[65].

Raney nickel destroys the heterocyclic ring of 1,3,4-oxadiazoles, giving the corresponding amides[110].

Molecular bromine does not brominate 2,5-diphenyl-1,3,4-oxadiazole, but forms only complexes between the oxadiazole and the bromine[111]; a mixture of chlorine and iodine produces a complex of the 2,5-diphenyl-1,3,4-oxadiazole with iodine chloride[41]. In alcoholic solution 1,3,4-oxadiazoles also readily give complexes with $AgNO_3$ and $HgCl_2$.[7,9,15,28,29,112]

2-Substituted 1,3,4-oxadiazoles can be determined by potentiometric titration with sodium nitrite[103,104]; 2,5-diaryl-1,3,4-oxadiazoles can be analysed argentometrically[112].

Ultraviolet[81,95,97,113-118], infrared[92,119], luminescence[81,95-97,120], and Raman spectra[121] of 1,3,4-oxadiazole derivatives have been investigated. Dipole moments have been measured[122], the normal vibrational frequencies of the oxadiazole ring have been calculated[123], and polarographic studies have been made[124,125]. The scintillation efficiency of 1,3,4-oxadiazole derivatives has been determined in toluene[59,126-128] and polystyrene[94-96,129-131].

1,3,4-Oxadiazoles are widely used in pharmacy as anti-tubercular preparations[75,76,83-85], in the production of vat dyes[60,132-148] and azodyes[106,107,148], in colour photography[149-151], in scintillator technology[59,95,96,126,127,129-131], and for the production of thermostable polymers[92,93].

1. C.Ainsworth, J.Amer.Chem.Soc., 77, 1148 (1955).
2. A.P.Grekov, O.P.Shvaika, and L.M.Egupova, Zhur.

Obshch.Khim., 29, 2027 (1959).
3. C.Runti, L.Sindellari, and C.Nisi, Ann.Chim.(Italy), 49, 1649 (1959).
4. M.Vincent, J.Maillard, and M.Benard, Bull.Soc.chim. France, 1580 (1962).
5. R.Stolle and K.Fehrenbach, J.prakt.Chem., [2], 122, 298 (1929).
6. S.De, J.Indian Chem.Soc., 7, 651 (1930).
7. R.Stolle, Ber., 32, 797 (1899).
8. R.Stolle and H.Hille, J.prakt.Chem., [2], 69, 481 (1904).
9. R.Stolle and H.Hille, J.prakt.Chem., 69, 150 (1904).
10. R.Stolle and F.Delschaft, J.prakt.Chem., 69, 506 (1904).
11. R.Stolle and C.Schätzlein, J.prakt.Chem., 69, 503 (1904).
12. R.Stolle and G.Zinsser, J.prakt.Chem., 69, 491 (1904).
13. R.Stolle and L.Gutmann, J.prakt.Chem., 69, 500 (1904).
14. R.Stolle and F.Helwerth, J.prakt.Chem., 88, 315 (1913).
15. W.Harris and K.Stone, J.Org.Chem., 23, 2032 (1958).
16. R.Stolle, Ber., 45, 282 (1912).
17. R.Stolle, J.prakt.Chem., [2], 68, 466 (1903).
18. R.Stolle and J.Laux, Ber., 44, 1127 (1911).
19. R.Stolle, H.Münzel, and F.Wofl, Ber., 46, 2346 (1913).
20. H.Aspelund, Acta Acad.Aboensis, 6, No.12, 15 (1932).
21. N.Hayes, B.Rogers, and D.Ott, J.Amer.Chem.Soc., 77, 1850 (1955).
22. A.P.Grekov, in Sbornik "Khimicheskie Reaktivy i Preparaty" (Collected Papers on Chemical Reagents and Preparations), Moscow, 1961, p.131.
23. H.Wieland, A.Hintermaier, and J.Dennstedt, Annalen, 452, 6 (1927).
24. R.Stolle, J.prakt.Chem., [2], 74, 13 (1906).
25. O.Silberrad, J.Chem.Soc., 77, 1189 (1900).
26. G.Pellizzari, Atti Accad.Reale Lincei, Rend.Class Sci.fis. mat.nat., 8, 328 (1899).
27. M.Bogert and J.Tuttle, J.Amer.Chem.Soc., 38, 1359 (1916).
28. R.Stolle and A.Bambach, J.prakt.Chem., [2], 74, 15 (1906).
29. R.Stolle and H.Foerster, J.prakt.Chem., 69, 382 (1904).
30. R.Stolle and V.Kind, J.prakt.Chem., 68, 130 (1903).
31. R.Stolle and A.Johaniss, J.prakt.Chem., 69, 474 (1904).
32. R.Stolle, J.prakt.Chem., 137, 327 (1933).
33. T.Folpmers, Rec.Trav.chim., 34, 52 (1915); Chem.Zentr., I, 1159 (1915).
34. R.Stolle and A.Weindel, J.prakt.Chem., [2], 74, 11 (1906).
35. E.Günter, Ber., 21, 516 (1888).
36. R.Stolle and K.Thoma, Annalen, 252, 61 (1889).
37. R.Stolle, J.prakt.Chem., [2], 73, 289 (1905).
38. R.Stolle, J.prakt.Chem., 69, 154 (1904).
39. R.Stolle and A.Benrat, J.prakt.Chem., 70, 163 (1904).
40. R.Stolle and E.Münch, J.prakt.Chem., 70, 393 (1904).
41. R.Stolle, J.prakt.Chem., 85, 388 (1912).
42. H.Weidinger and J.Kranz, German P. 1 067 439 (1960); Ref. Zhur.Khim., 19L208 (1961).
43. A.Pinner, Annalen, 297, 263 (1897).
44. V.Meyer and P.Jacobson, "Lehrbuch der organischen Chemie", Band 2, Teil 3, Berlin, 1923, p.644.
45. A.Pinner and N.Caro, Ber., 27, 3288 (1894).
46. A.Pinner, Annalen, 298, 16 (1897).
47. R.Stolle and K.Krauch, Ber., 45, 3307 (1912).
48. R.Stolle and K.Leverkus, Ber., 46, 4076 (1913).
49. E.Müller and L.Herrdegen, J.prakt.Chem., [2], 102, 142 (1920).
50. A.P.Grekov and R.S.Azen, Zhur.Obshch.Khim., 31, 407 (1961).
51. A.P.Grekov and M.S.Marakhova, Zhur.Obshch.Khim., 32, 542 (1962).
52. H.Aspelund, Acta Acad.Aboensis, Math.Phys., 5, 1 (1929); Chem.Zentr., I, 2415 (1929).
53. H.Aspelund, Ber., 63, 1197 (1930).
54. H.Aspelund, Ber., 63, 1353 (1930).
55. P.Schestakow, Ber., 45, 3273 (1912).
56. W.Sterman, J.Org.Chem., 26, 88 (1961).
57. A.P.Grekov and O.P.Shvaika, Zhur.Obshch.Khim., 30, 3802 (1960).
58. A.P.Grekov and R.S.Azen, Zhur.Obshch.Khim., 29, 1995 (1959).
59. A.P.Grekov and O.P.Shvaika, in Sbornik "Stsintillyatory i Stsintillyatsionnye Materialy" (Collected Papers on Scintillators and Scintillation Materials), Moscow, 1960, p.105.
60. W.Mueller and A.Siegrist, U.S.P. 2 835 520 (1958); Chem. Abs., 52, 17 290 (1958).
61. A.P.Grekov, L.N.Kulakova, and O.P.Shvaika, Zhur. Obshch.Khim., 29, 2054 (1959).
62. R.Huisgen, J.Sauer, and H.Sturm, Angew.Chem., 70, 272 (1959).
63. R.Huisgen, J.Sauer, and M.Seidel, Chem.Ber., 93, 2885 (1960).
64. R.Stolle and E.Gaertner, J.prakt.Chem., [2], 132, 209 (1931).
65. J.Howard and H.Burch, J.Org.Chem., 26, 1651 (1961).
66. E.Hoggarth, J.Chem.Soc., 1918 (1949).
67. E.Hoggarth, J.Chem.Soc., 1579 (1950).
68. E.Hoggarth, J.Chem.Soc., 4811 (1952).
69. G.Valenti and F.Maggio, Ann.Chim.(Italy), 42, 18 (1952).
70. G.Tappi and C.Migliardi, Arch.biol., 27, 170 (1941).
71. J.Bernstein and H.Yale, U.S.P. 2 832 787 (1958); Chem. Abs., 52, 14 703 (1958).
72. G.Tappi and C.Migliardi, Arch.biol., 28, 472 (1942).
73. G.Tappi and C.Migliardi, Ricerca sci., 12, 1056 (1941).
74. G.Tappi, Rec.Trav.chim., 62, 207 (1943).
75. J.Brooks, P.Charlton, P.Macey, D.Peak, and W.Short, J.Chem.Soc., 452 (1950).
76. D.Peak and T.Watkins, J.Chem.Soc., 3292 (1951).
77. G.Blankenstein and K.Möckel, Z.Chem., 2, 69 (1962).
78. A.P.Grekov and V.I.Grigor'eva, Zhur.Obshch.Khim., 31, 4012 (1961).
79. A.P.Grekov and E.P.Nesynov, Zhur.Obshch.Khim., 30, 3240 (1960).
80. A.P.Grekov and E.P.Nesynov, Zhur.Obshch.Khim., 31, 1122 (1961).
81. D.Ott, V.Kerr, N.Hayes, and E.Hansbury, J.Org.Chem., 25, 872 (1960).
82. A.P.Grekov and E.P.Nesynov, Zhur.Obshch.Khim., 30, 3237 (1960).
83. A.Novotny, Z.Bžezik, J.Přidel, and K.Kalfus, Cesk. Farm., 7, 517 (1958).
84. H.König, W.Seifken, and H.Offe, Chem.Ber., 87, 825 (1954).
85. F.Millan, F.Leonard, R.Meltzer, and J.King, J.Amer. Pharmaceut.Assoc.(Pract.Pharmaceut.Edn.), 42, 457 (1953).
86. A.L.Mndzhoyan, G.T.Tatevosyan, S.G.Agbalyan, and N.M.Divanyan, Dokl.Akad.Nauk Armen.SSR, 25, 207 (1957).
87. A.L.Mndzhoyan, G.T.Tatevosyan, A.G.Terzyan, and S.N.Ekmekdzhyan, Izv.Akad.Nauk Armen.SSR, Khim. Nauki, 11, 127 (1958).
88. S.Yoshida and M.Asai, J.Pharm.Soc.Japan, 74, 946 (1954); Chem.Abs., 49, 10 938 (1955).
89. A.P.Grekov and M.S.Solov'eva, Zhur.Obshch.Khim., 30, 1644 (1960).
90. R.Stolle and F.Schmidt, Ber., 45, 3122 (1912).
91. R.Stolle, J.prakt.Chem., [2], 70, 421 (1904).
92. J.Sauer, R.Huisgen, and H.Sturm, Tetrahedron, 11, 241 (1960).
93. C.Abshire and C.Marvel, Makromol.Chem., 44–46, 388 (1961).

94. A.P.Grekov, N.P.Shimanskaya, and A.P.Kilimov, in Sbornik "Khimicheskie Reaktivy i Preparaty" (Collected Papers on Chemical Reagents and Preparations), Moscow, 1961, p.137.
95. N.P.Shimanskaya, A.P.Kilimov, and A.P.Grekov, Optika i Spektrosk., 6, 194 (1959).
96. N.P.Shimanskaya, A.P.Kilimov, A.P.Grekov, L.M.Egupova, and R.S.Azen, Optika i Spektrosk., 7, 366 (1959).
97. Yu.P.Panov, N.A.Adrova, and M.M.Koton, Optika i Spektrosk., 7, 29 (1959).
98. P.Shestakov and V.Kind, Zhur.Russ.Fiz.-Khim.Obshch., 40, 330 (1908).
99. O.Diels and A.Wagner, Ber., 45, 878 (1912).
100. O.Diels and H.Okada, Ber., 46, 1872 (1913).
101. M.Freund and F.Kuh, Ber., 23, 2821, 2843 (1890).
102. G.Werber and F.Maggio, Ann.Chim.(Italy), 52, 747(1962).
103. A.P.Grekov and O.P.Shvaika, Zhur.Anal.Khim., 15, 732 (1960).
104. A.P.Grekov and O.P.Shvaika, in Sbornik "Khimicheskie Reaktivy i Preparaty" (Collected Papers on Chemical Reagents and Preparations), Moscow, 1961, p.285.
105. A.P.Grekov and R.S.Azen, Zhur.Obshch.Khim., 31, 1919 (1961).
106. N.S.Dokunikhin, B.M.Krasovitskii, R.M.Matskevich, V.A.Blinov, and Z.Ya.Vitokhina, Zhur.Prikl.Khim., 32, 664 (1959).
107. B.M.Krasovitskii, R.M.Matskevich, N.S.Dokunikhin, and N.A.Trubitsyna, Zhur.Obshch.Khim., 30, 2608 (1960).
108. H.Gehlen and G.Röbisch, Naturwiss., 48, 403 (1961).
109. H.Gehlen and G.Röbisch, Annalen, 663, 119 (1963).
110. C.Ainsworth, J.Amer.Chem.Soc., 78, 1636 (1956).
111. A.P.Grekov and V.I.Grigor'eva, in Sbornik "Stsintillyatory i Stsintillyatsionnye Materialy" (Collected Papers on Scintillators and Scintillation Materials), Khar'kov, No.3, 1963, p.15.
112. O.P.Shvaika and A.P.Grekov, *ibid.*, No.3, 1963, p.21.
113. M.Milone, Gazzetta, 62, 154 (1932).
114. L.M.Kutsyna and E.T.Verkhovtseva, Optika i Spektrosk., 12, 785 (1962).
115. P.Grammaticakis, Bull.Soc.chim.France, 86 (1953).
116. A.P.Grekov and O.P.Shvaika, in Sbornik "Stsintillyatory i Stsintillyatsionnye Materialy" (Collected Papers on Scintillators and Scintillation Materials), Khar'kov, No.2, 1963, p.60.
117. A.P.Grekov and O.P.Shvaika, *ibid.*, No.3, 1963, p.5.
118. O.P.Shvaika and A.P.Grekov, *ibid.*, No.3, 1963, p.17.
119. M.Milone and E.Borello, Gazzetta, 81, 677 (1951).
120. L.M.Kutsyna, A.P.Grekov, E.A.Lupashko, and E.T.Verkhovtseva, in Sbornik "Stsintillyatory i Stsintillyatsionnye Materialy" (Collected Papers on Scintillators and Scintillation Materials), Khar'kov, No.2, 1963, p.203.
121. R.Manzoni-Ansidei, Atti Accad.naz.Lincei, Rend.Classe Sci.fis.mat.nat., 22, 444 (1935).
122. M.Milone, Gazzetta, 65, 182 (1935).
123. E.Borello and S.Nocilla, Gazzetta, 84, 435 (1954).
124. N.P.Shimanskaya and V.D.Bezuglyi, Zhur.Obshch.Khim., 33, 1726 (1963).
125. N.P.Shimanskaya and V.D.Bezuglyi, in Sbornik "Stsintillyatory i Stsintillyatsionnye Materialy" (Collected Papers on Scintillators and Scintillation Materials), Khar'kov, No.3, 1963, p.65.
126. N.Hayes, D.Ott, and V.Kerr, Nucleonics, 13, 38 (1955).
127. O.P.Shvaika and A.P.Grekov, Optika i Spektrosk., 7, 824 (1960).
128. O.P.Shvaika and A.P.Grekov, in Sbornik "Stsintillyatory i Stsintillyatsionnye Materialy" (Collected Papers on Scintillators and Scintillation Materials), Khar'kov, No.2, 1963, p.130.
129. N.A.Adrova, M.M.Koton, and F.S.Florinskii, Dokl.Akad.Nauk SSSR, 114, 311 (1957).
130. N.A.Adrova, V.N.Andreev, M.M.Koton, Yu.P.Panov, and N.S.Musaliev, Optika i Spektrosk., 7, 128 (1959).
131. L.L.Nagornaya, V.D.Bezuglyi, and A.P.Grekov, Optika i Spektrosk., 10, 555 (1961).
132. E.Klingsberg, J.Amer.Chem.Soc., 80, 5786 (1958).
133. F.Stilmar, U.S.P. 2464831 (1949); Chem.Abs., 43, 4484 (1949).
134. F.Stilmar, U.S.P. 2567132 (1949); Chem.Zentr., 124, 449 (1953).
135. F.Stilmar, U.S.P. 2511018 (1950); Chem.Abs., 46, 270 (1952).
136. F.Stilmar, U.S.P. 2601179 (1952); Chem.Abs., 47, 2500 (1953).
137. F.Stilmar, U.S.P. 2628230 (1953); Chem.Abs., 47, 10234 (1953).
138. F.Stilmar, U.S.P 2650962 (1953); Chem.Abs., 48, 1014 (1954).
139. P.Belschaw and F.Irving, German P. 831432 (1950); Chem.Zentr., 123, 7261 (1952).
140. P.Belschaw and F.Irving, B.P. 676699 (1952); Chem. Abs., 11695 (1952).
141. P.Belschaw and F.Irving, B.P. 705920 (1954); Chem. Abs., 48, 10352 (1954).
142. P.Belschaw and A.Robson, B.P. 705928 (1954); Chem. Abs., 48, 10352 (1954).
143. P.Belschaw and A.Robson, B.P. 705929 (1954); Chem. Abs., 48, 10353 (1954).
144. G.Schwechten and J.Singer, German P. 825111 (1951); Chem.Abs., 49, 630 (1955).
145. F.Ebel and R.Randebrock, German P. 955174 (1955); Chem.Abs., 53, 4753 (1959).
146. O.Trauth, German P. 1049025 (1959); Ref.Zhur.Khim., 3L140 (1961).
147. V.A.Titkov, Khim.Nauka i Prom., 3, 174 (1958).
148. B.M.Krasovskii, R.M.Matskevich, and N.I.Mal'tseva, Zhur.Obshch.Khim., 31, 2259 (1961).
149. K.Futaki, Y.Oyama, and T.Iwasaki, Phot.Sci.Eng., 4, 97 (1960).
150. P.Merckx, U.S.P. 2473166 (1949); Chem.Abs., 43, 8924 (1949).
151. P.Merckx, German P. 806936 (1951); Chem.Abs., 46, 7918 (1952).

Institute of Organic Chemistry
and Institute of Chemistry of
Polymers and Monomers,
Academy of Sciences of the
Ukrainian SSR

U.D.C. 547.91 : 547.92.547.96 + 541.144.7

THE FORMATION OF BIOCHEMICALLY IMPORTANT COMPOUNDS IN THE PRE-BIOLOGICAL STAGE OF THE EARTH'S DEVELOPMENT

A. G. Pasynskii and T. E. Pavlovskaya

CONTENTS

1. Introduction 515