The Synthesis of 1 : 2 : 4-Oxadiazoles.

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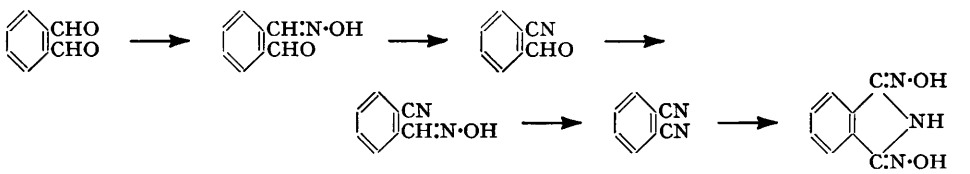
The reaction, first described by Tiemann and Kruger, of nitriles with hydroxylamine to give amidoximes has been extended to a series of substituted nitriles and 3-cyanopyridine. Subsequent acylation and cyclisation gave the corresponding 1 : 2 : 4-oxadiazoles. Condensation of phthalonitrile with hydroxylamine gave the " dioxime " of phthalimide.

LITTLE work (Marson *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 2902) has been carried out on the 1 : 2 : 4-oxadiazoles, possibly owing to the low bacteriocidal activity of 1 : 2 : 5-oxadiazoles (furazans). Beckmann prepared 1 : 2 : 4-oxadiazoles by oxidation of oximes (*Ber.*, 1889, **22**, 1589), but the value of this method is limited because it gives symmetrically substituted oxadiazoles: $2Ar{\cdot}CH{:}N{\cdot}OH \longrightarrow \begin{matrix} N{\cdot}CAr \\ | \quad > O \\ CAr{:}N \end{matrix}$. Musante obtained a few 1 : 2 : 4-oxadiazoles by condensation of phenylhydrazine hydrochloride with chloroaldoximes (*Gazzetta*, 1938, **68**, 331). Tiemann and Kruger (*Ber.*, 1884, **17**, 126), however, found that nitriles condense with hydroxylamine hydrochloride to form amidoximes, and, *e.g.*, benzamidoxime with acetic anhydride or benzoyl chloride yielded 5-methyl-3-phenyl- and 3 : 5-diphenyl-1 : 2 : 4-oxadiazole respectively.

In view of the known activity of the intermediate amidoximes against trypanosomes (Lamb and White, *J.*, 1939, 1253) and rickettsia (Andrews, King, and Walker, *Proc. Roy. Soc.*, 1946, *B*, **133**, 20), the reaction has been applied to the synthesis of amidoximes and the corresponding 1 : 2 : 4-oxadiazoles from some substituted benzonitriles, 3-cyanopyridine, and phthalodinitrile. The yields, with one exception, were 75—90%. *o*-Nitrobenzonitrile undergoes hydrolysis to the *o*-nitrobenzamide.

The condensation of phthalonitrile is of particular interest in that the product is the " dioxime " of phthalimide (1 : 3-dihydroxyimino*iso*indoline) (85% yield) and not the diamidoxime. Wibaut and Kampschmidt (*Rec. Trav. chim.*, 1952, **71**, 601) recently obtained a very small yield of this product by reaction of phthalaldehyde with hydroxylamine—the main product is the " monoxime," and they suggested that the " dioxime " results by further reaction of the " monoxime." It seems more probable, however, that the former is derived from phthalonitrile. Phthalaldehyde and hydroxylamine might be expected to form a little dialdoxime, which under the mildly alkaline conditions of the reaction, could give rise to phthalonitrile and thence, by reaction with more hydroxylamine, be transformed to " phthalimide dioxime " (cf. Reissert, *Ber.*, 1908, **41**, 3815):



The " dioxime " forms a diacetate and a dibenzoate. It is converted into phthalimide by nitric–sulphuric acid as described by Wibaut and Kampschmidt for the hydrolysis of the " monoxime."

The amidoximes and the oxadiazoles synthesised are being tested for bacteriocidal activity.

EXPERIMENTAL

p-*Bromobenzamidoxime.*—*p*-Bromobenzonitrile (10 g.) was heated with anhydrous sodium carbonate (10 g.) and hydroxylamine hydrochloride (14 g.) in water (150 ml.) on a steam-bath for 1½ hr., sufficient ethanol being added to maintain a clear solution. The *amidoxime*, which separated on cooling, crystallised from ethanol as flat prisms (10·5 g.), m. p. 146—147°.

The amidoxime (2 g.) reacted rapidly with acetic anhydride (4 ml.). After ½ hr. the excess of anhydride in the crystalline mass was decomposed by water and aqueous ammonia, and the O-*acetyl* derivative crystallised from ethanol as prisms (2·2 g.), m. p. 145°.

p-Bromobenzamidoxime (2 g.) was treated for 4 hr. at room temperature with benzoyl chloride (4 ml.). Water and aqueous ammonia were added, and the O-*benzoyl* derivative crystallised from ethanol as plates (2·6 g.), m. p. 161°.

These and other *compounds* similarly prepared are recorded in the Tables.

R	M. p.	Solvent [a]	Found (%) C	H	N	Formula	Required (%) C	H	N
Amidoximes, R·C(NH$_2$):N·OH.									
Ph	80°	C_6H_6	—	—	—	—	—	—	—
p-C_6H_4Me	147	Aq. EtOH	—	—	18·9	$C_8H_{10}ON_2$	—	—	18·7
o-MeO·C_6H_4	123	C_6H_6	—	—	16·9	$C_8H_{10}O_2N_2$	—	—	16·9
p-C_6H_4Br	146	Aq. EtOH	39·3	3·3	13·0	$C_7H_7ON_2Br$	39·1	3·25	13·0
p-NO_2·C_6H_4·CH_2	170	H_2O	49·0	4·6	21·6	$C_8H_9O_3N_3$	49·2	4·6	21·5
3-Pyridyl	134	C_6H_6	52·4	4·9	30·8	$C_6H_7ON_3$	52·6	5·1	30·7
O-*Acetylamidoximes*, R·C(NH$_2$):N·OAc.									
Ph	96	EtOH	—	—	—	—	—	—	—
p-C_6H_4Me	132	C_6H_6	62·5	6·35	14·5	$C_{10}H_{12}O_2N_2$	62·5	6·25	14·6
o-MeO·C_6H_4	130	C_6H_6–Pet	—	—	13·5	$C_{10}H_{12}O_3N_2$	—	—	13·5
p-C_6H_4Br	145	EtOH	41·8	3·6	10·9	$C_9H_9O_2N_2Br$	42·0	3·5	10·9
p-NO_2·C_6H_4·CH_2	145	EtOH	50·8	4·5	18·0	$C_{10}H_{11}O_4N_3$	50·6	4·6	17·7
3-Pyridyl	147	EtOH–C_6H_6	53·6	5·0	23·2	$C_8H_9O_2N_3$	53·6	5·0	23·5
O-*Benzoylamidoximes*, R·C(NH$_2$):N·OBz.									
Ph	148 [b]	EtOH	—	—	—	—	—	—	—
p-C_6H_4Me	173	EtOH	—	—	11·2	$C_{15}H_{14}O_2N_2$	—	—	11·0
o-MeO·C_6H_4 [c]	—	EtOH	—	—	—	—	—	—	—
p-C_6H_4Br	161	EtOH	52·5	3·4	8·8	$C_{14}H_{11}O_2N_2Br$	52·7	3·45	8·7
p-NO_2·C_6H_4·CH_2	148	Aq. EtOH	59·9	4·3	14·0	$C_{15}H_{13}O_4N_3$	60·2	4·35	14·0
3-Pyridyl	194	C_6H_6	64·7	4·6	17·1	$C_{13}H_{11}O_2N_3$	64·7	4·6	17·4

[a] Pet = light petroleum (b. p. 60—80°). [b] Tiemann gives 140°. [c] Even benzoylation with less than 1 mol. proportion of acid chloride at −5° gave the *dibenzoyl* derivative, m. p. 139° (Found: C, 70·7; H, 4·7; N, 7·6, 7·4. $C_{22}H_{18}O_4N_2$ requires C, 70·6; H, 4·8; N, 7·5%).

1 : 2 : 4-*Oxadiazoles*.

3-Subst.	M. p.	Solvent [a]	Found (%) C	H	N	Formula	Required (%) C	H	N
3-*Substituted* 5-*methyl*-1 : 2 : 4-*oxadiazoles*.									
Ph	41°	Pet	—	—	—	—	—	—	—
p-C_6H_4Me	80	Aq. EtOH	—	—	15·8	$C_{10}H_{10}ON_2$	—	—	16·1
o-MeO·C_6H_4	121	C_6H_6–Pet	—	—	14·6	$C_{10}H_{10}O_2N_2$	—	—	14·7
p-C_6H_4Br	103	EtOH	44·9	2·9	11·9	$C_9H_7ON_2Br$	45·2	2·9	11·7
p-NO_2·C_6H_4·NO_2 [b]	68	Aq. EtOH	54·9	4·2	18·9	$C_{10}H_9O_3N_3$	54·8	4·1	19·2
3-Pyridyl	113	Pet	59·9	4·3	25·8	$C_8H_7ON_3$	59·6	4·3	26·1
3-*Substituted* 5-*phenyl*-1 : 2 : 4-*oxadiazoles*.									
Ph	108	EtOH	—	—	—	—	—	—	—
p-C_6H_4Me	107	,,	—	—	11·6	$C_{15}H_{12}ON_2$	—	—	11·9
o-MeO·C_6H_4	117	,,	—	—	11·0	$C_{15}H_{12}O_2N_2$	—	—	11·1
p-C_6H_4Br	112	,,	55·8	3·05	9·0	$C_{14}H_9ON_2Br$	55·8	3·0	9·3
p-NO_2·C_6H_4·CH_2 [c]	132	,,	64·3	3·9	15·0	$C_{15}H_{11}O_3N_3$	64·1	3·9	14·9
3-Pyridyl	142	,,	69·7	4·15	19·1	$C_{13}H_9ON_3$	69·9	4·0	18·8

[a] Pet = light petroleum (b. p. 60—80°). [b] Cyclisation by steam-distillation or in boiling glacial acetic acid for ½ hr. [c] Cyclisation in boiling acetic acid for ½ hr.

3-p-*Bromophenyl*-5-*methyl*-1 : 2 : 4-*oxadiazole*.—(*a*) *p*-Bromobenzamidoxime (2 g.) was heated for 3—4 min. with acetic anhydride (6 ml.), the solution solidifying on cooling. After decomposition of the unused anhydride and recrystallisation from ethanol, 3-p-*bromophenyl*-5-*methyl*-1 : 2 : 4-*oxadiazole* was obtained as colourless prisms (2·1 g.), m. p. 103°.

(*b*) *O*-Acetyl-*p*-bromobenzamidoxime (0·5 g.) was heated just above its m. p. (*i.e.*, 150°), and the product cooled and crystallised from ethanol (yield, 0·38 g.).

3-p-*Bromophenyl*-5-*phenyl*-1 : 2 : 4-*oxadiazole*.—(*a*) *p*-Bromophenylbenzamidoxime (2 g.) was heated with benzoyl chloride (5 ml.) until a clear solution was obtained (3—4 min.). The

product solidified on cooling, and, after it had been freed from excess of benzoyl chloride with aqueous ammonia, the *oxadiazole* crystallised from ethanol as colourless prisms (2·7 g.), m. p. 112°.

(*b*) *O*-Benzoyl-*p*-bromobenzamidoxime (0·5 g.) was kept above its m. p. for 3 min. The resulting oxadiazole (0·35 g.) was crystallised from ethanol.

These and other *oxadiazoles* are recorded in the Tables.

Phthalimide "Dioxime" (1 : 3-*Dihydroxyimino*isoindoline).—Phthalonitrile (5 g.) was heated with sodium carbonate (10 g.) and hydroxylamine hydrochloride (14 g.) in water (150 ml.) and ethanol (50 ml.) on a steam-bath for 1½ hr., the product gradually crystallising. It recrystallised from acetic acid or dilute pyridine as pale straw-coloured prisms (6 g.), m. p. 271° (Wibaut *et al.*, *loc. cit.*, give m. p. 264°) (Found: C, 54·6; H, 4·0; N, 24·1. Calc. for $C_8H_7O_2N_3$: C, 54·2; H, 3·95; N, 23·8%).

The product (1 g.) was added gradually to a stirred mixture of 65% nitric acid (25 ml.) and concentrated sulphuric acid (25 ml.) at room temperature. After ¾ hr., the solution was poured into water, and the precipitate was collected and crystallised from ethanol, to give phthalimide (0·65 g.), prisms, m. p. and mixed m. p. 133°.

The "dioxime" (1·0 g.) was heated with excess of acetic anhydride (5 ml.) until a clear solution was obtained, then cooled, diluted with water, and set aside until the solid *diacetyl* derivative separated. Crystallisation from aqueous ethanol gave the *diacetate* (1·1 g.) as colourless prisms, m. p. 192° (Found: C, 55·2; H, 4·3; N, 16·2. $C_{12}H_{11}O_4N_3$ requires C, 55·2; H, 4·2; N, 16·1%).

The "dioxime" (1·0 g.) was heated with excess of benzoyl chloride (6 ml.) until a clear solution was obtained. On cooling, excess of benzoyl chloride was decomposed by aqueous ammonia. The resulting *dibenzoyl* derivative was rather insoluble in ethanol and was crystallised by dissolving it in chloroform and adding a large volume of ethanol, being obtained as pale yellow prisms (1·9 g.), m. p. 248° (Found: C, 68·2; H, 4·1; N, 10·8. $C_{22}H_{15}O_4N_3$ requires C, 68·5; H, 3·89; N, 10·9%).

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