

The Synthesis of 1 : 2 : 4-Oxadiazoles.

By KENNETH CLARKE.

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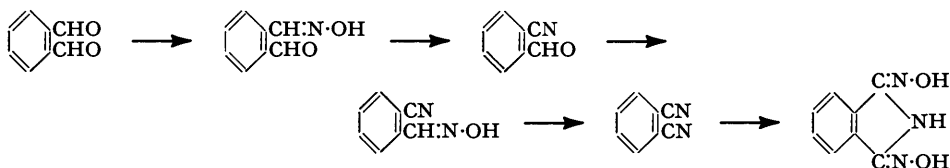
The reaction, first described by Tiemann and Kruger, of nitriles with hydroxylamine to give amidoximes has been extended to a series of substituted nitriles and 3-cyanopyridine. Subsequent acylation and cyclisation gave the corresponding 1 : 2 : 4-oxadiazoles. Condensation of phthalonitrile with hydroxylamine 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: $2\text{Ar}\cdot\text{CH}\cdot\text{N}\cdot\text{OH} \longrightarrow \begin{matrix} \text{N}\cdot\text{Car} \\ | \\ \text{Car}\cdot\text{N} \end{matrix} \text{O}$. Musante obtained a few 1 : 2 : 4-oxadiazoles by condensation of phenylhydrazine hydrochloride with chloroaloximes (*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-dihydroxyiminoisoindoline) (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 dialdioxime, 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 $\frac{1}{2}$ 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 (%)			Formula	Required (%)		
			C	H	N		C	H	N
<i>Amidoximes, R·C(NH₂)·N·OH.</i>									
Ph	80°	C ₆ H ₆	—	—	—	—	—	—	—
<i>p</i> -C ₆ H ₄ Me	147	Aq. EtOH	—	—	18.9	C ₈ H ₁₀ ON ₂	—	—	18.7
<i>o</i> -MeO·C ₆ H ₄	123	C ₆ H ₆	—	—	16.9	C ₈ H ₁₀ O ₂ N ₂	—	—	16.9
<i>p</i> -C ₆ H ₄ Br	146	Aq. EtOH	39.3	3.3	13.0	C ₇ H ₇ ON ₂ Br	39.1	3.25	13.0
<i>p</i> -NO ₂ ·C ₆ H ₄ ·CH ₃	170	H ₂ O	49.0	4.6	21.6	C ₈ H ₇ O ₂ N ₃	49.2	4.6	21.5
3-Pyridyl	134	C ₆ H ₆	52.4	4.9	30.8	C ₈ H ₇ ON ₃	52.6	5.1	30.7
<i>O-Acetylamidoximes, R·C(NH₂)·N·OAc.</i>									
Ph	96	EtOH	—	—	—	—	—	—	—
<i>p</i> -C ₆ H ₄ Me	132	C ₆ H ₆	62.5	6.35	14.5	C ₁₀ H ₁₂ O ₂ N ₂	62.5	6.25	14.6
<i>o</i> -MeO·C ₆ H ₄	130	C ₆ H ₆ -Pet	—	—	13.5	C ₁₀ H ₁₂ O ₃ N ₂	—	—	13.5
<i>p</i> -C ₆ H ₄ Br	145	EtOH	41.8	3.6	10.9	C ₉ H ₉ O ₂ N ₂ Br	42.0	3.5	10.9
<i>p</i> -NO ₂ ·C ₆ H ₄ ·CH ₃	145	EtOH	50.8	4.5	18.0	C ₁₀ H ₁₁ O ₄ N ₃	50.6	4.6	17.7
3-Pyridyl	147	EtOH-C ₆ H ₆	53.6	5.0	23.2	C ₈ H ₉ O ₂ N ₃	53.6	5.0	23.5
<i>O-Benzoylamidoximes, R·C(NH₂)·N·OBz.</i>									
Ph	148 ^b	EtOH	—	—	—	—	—	—	—
<i>p</i> -C ₆ H ₄ Me	173	EtOH	—	—	11.2	C ₁₅ H ₁₄ O ₂ N ₂	—	—	11.0
<i>o</i> -MeO·C ₆ H ₄ ^c	—	EtOH	—	—	—	—	—	—	—
<i>p</i> -C ₆ H ₄ Br	161	EtOH	52.5	3.4	8.8	C ₁₄ H ₁₁ O ₂ N ₂ Br	52.7	3.45	8.7
<i>p</i> -NO ₂ ·C ₆ H ₄ ·CH ₃	148	Aq. EtOH	59.9	4.3	14.0	C ₁₅ H ₁₃ O ₄ N ₃	60.2	4.35	14.0
3-Pyridyl	194	C ₆ H ₆	64.7	4.6	17.1	C ₁₃ H ₁₁ O ₂ N ₃	64.7	4.6	17.4

^a Pet = light petroleum (b. p. 60–80°). ^b Tiemann gives 140°. ^c Even benzylation with less than 1 mol. proportion of acid chloride at –5° gave the *di*benzoyl derivative, m. p. 139° (Found: C, 70.7; H, 4.7; N, 7.6, 7.4. C₂₂H₁₈O₄N₂ requires C, 70.6; H, 4.8; N, 7.5%).

1:2:4-Oxadiazoles.

3-Subst.	M. p.	Solvent ^a	Found (%)			Formula	Required (%)		
			C	H	N		C	H	N
<i>3-Substituted 5-methyl-1:2:4-oxadiazoles.</i>									
Ph	41°	Pet	—	—	—	—	—	—	—
<i>p</i> -C ₆ H ₄ Me	80	Aq. EtOH	—	—	15.8	C ₁₀ H ₁₀ ON ₂	—	—	16.1
<i>o</i> -MeO·C ₆ H ₄	121	C ₆ H ₆ -Pet	—	—	14.6	C ₁₀ H ₁₀ O ₂ N ₂	—	—	14.7
<i>p</i> -C ₆ H ₄ Br	103	EtOH	44.9	2.9	11.9	C ₉ H ₉ ON ₂ Br	45.2	2.9	11.7
<i>p</i> -NO ₂ ·C ₆ H ₄ ·NO ₂ ^b	68	Aq. EtOH	54.9	4.2	18.9	C ₁₀ H ₉ O ₃ N ₃	54.8	4.1	19.2
3-Pyridyl	113	Pet	59.9	4.3	25.8	C ₈ H ₉ ON ₃	59.6	4.3	26.1
<i>3-Substituted 5-phenyl-1:2:4-oxadiazoles.</i>									
Ph	108	EtOH	—	—	—	—	—	—	—
<i>p</i> -C ₆ H ₄ Me	107	"	—	—	11.6	C ₁₅ H ₁₂ ON ₂	—	—	11.9
<i>o</i> -MeO·C ₆ H ₄	117	"	—	—	11.0	C ₁₅ H ₁₂ O ₂ N ₂	—	—	11.1
<i>p</i> -C ₆ H ₄ Br	112	"	55.8	3.05	9.0	C ₁₄ H ₉ ON ₂ Br	55.8	3.0	9.3
<i>p</i> -NO ₂ ·C ₆ H ₄ ·CH ₃ ^c	132	"	64.3	3.9	15.0	C ₁₅ H ₁₁ O ₃ N ₃	64.1	3.9	14.9
3-Pyridyl	142	"	69.7	4.15	19.1	C ₁₃ H ₉ ON 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 $\frac{1}{2}$ hr. ^c Cyclisation in boiling acetic acid for $\frac{1}{2}$ 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-*Dihydroxyiminoisoindoline*).—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 C₈H₇O₂N₃ : 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. C₁₂H₁₁O₄N₃ 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 *di-benzoyl* 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. C₂₂H₁₅O₄N₃ requires C, 68.5; H, 3.89; N, 10.9%).

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THE UNIVERSITY, HULL.

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