3-Amino- and 3-Cyano-1,2,4-oxadiazole

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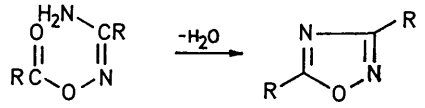
3-Amino-1.2.4-oxadiazole (3a) has been prepared from t-butoxycarbonylamino-1,2,4-oxadiazole (3h), and also from hydroxyguanidine and formyl fluoride. The amine is unexpectedly stable; on acid hydrolysis it gives hydroxyguanidine. 3-Cyano-1,2,4-oxadiazole (3m), prepared by dehydration of 1.2.4-oxadiazole-3-carboxamide (3l). is highly reactive but thermally stable. Some reactions of the amine (3a) and the nitrile (3m) are described.

3,5-DIARYL-1,2,4-OXADIAZOLES were prepared by cyclodehydration of *O*-acylamide oximes [1] as early as 1884, but the first 3,5-dialkyl-1,2,4-oxadiazole was not isolated [2] until 1959. 3-Phenyl- and 3-methyl-1,2,4-oxadiazole [3] were prepared in 1961 by treating the appropriate amide oximes with formic acetic anhydride and dehydrating the resultant *O*-formyl-amide oximes *in*

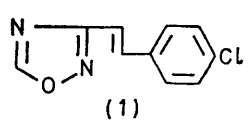
[1] F. Tiemann and P. Krüger, *Ber.*, 1884, **17**, 1685.
[2] J. Barrans, *Compt. rend.*, 1959, **249**, 1096.
[3] F. Eloy and C. Moussebois, *Chem. and Ind.*, 1961, 292.

situ. 3-Aryl-1,2,4-oxadiazoles were prepared more conveniently in 1963 by treating amide oximes with triethyl orthoformate [4] in the presence of boron trifluoride. 3-*p*-Chlorophenyl-1,2,4-oxadiazole slowly decomposes,[5] even at 0°, and 3-methyl-1,2,4-oxadiazole [6] and 1,2,4-oxadiazole [7] are even less stable. We now report the preparation, the isolation, and some of the reactions of 3-amino- and 3-cyano-1,2,4-oxadiazole, compounds that have proved unexpectedly stable.



3-*p*-Chlorostyryl-1,2,4-oxadiazole (1) has anthelmintic activity in sheep.[8] We set out to prepare some similar compounds in which the carbon–carbon double bond was replaced by a carbon–nitrogen double bond, *e.g.* the Schiff base (2; R = Cl). For this purpose we needed the amine (3a).

Treating hydroxyguanidine with triethyl or trimethyl orthoformate in the presence of boron trifluoride, with formic acetic anhydride, or with formic acid did not give 3-amino-1,2,4-oxadiazole, but when pure hydroxyguanidine was treated with an excess of formyl fluoride [9] in ether containing triethylamine, the amide (3b) was obtained in 18% yield; hydrolysis with methanolic



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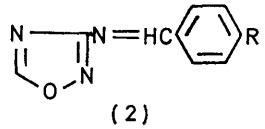

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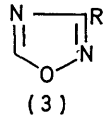
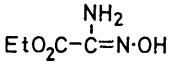


(3)

a; R = NH_2
b; R = NH·CHO
c; R = CO_2Et
d; R = CO·NH·NH_2
e; R = CON_3
f; R = NCO
g; R = NH·CO_2·CH_2Ph
h; R = NH·CO_2·CMe_3
i; R = N:CH·NMe_2
j; R = COCl
k; R = CS·NH_2
l; R = CO·NH_2
m; R = CN
n; R = C(OEt):NH
o; R = $C(NH_2)$:N·OH



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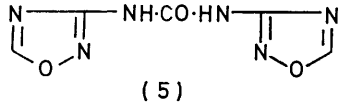


(5)

hydrochloric acid at room temperature gave the amine (3a) in 20% yield. However the reactions were not easily repeated, and we sought a better preparation of (3a).

Ethoxycarbonylformamide oxime [10] (4) reacted smoothly with triethyl orthoformate in the presence of boron trifluoride to give the ester (3c). This ester was converted by conventional methods through the hydrazide (3d), the azide (3e), and the isocyanate (3f) (not isolated pure) into the urethanes (3g and h). The benzylurethane (3g) gave hydroxyguanidine on catalytic hydrogenation or acid hydrolysis, but the t-butylurethane (3h) was readily converted into the amine (3a) by trifluoroacetic acid. The overall yield of (3a) from the ester (4) was 24%. The amine sublimes without decomposition at *ca.* 60° and 1 mmHg; a sample remained pure (i.r. spectrum and m.p.) when stored for 567 days at room temperature.

The amine (3a) was converted into Schiff bases (2; R = H or Cl) by heating with the diethyl acetal of benzaldehyde or of *p*-chlorobenzaldehyde respectively (it did not react with the aldehydes); into the formamidine (3i) by dimethylformamide dimethyl acetal; and into the urea (5) by the isocyanate (3f). The amine (3a) was not acylated by the azide (3e), although both this azide and the acid chloride (3j) acylated *p*-chloroaniline and 1-aminoadamantane. [The acid chloride (3j) was obtained by treating the hydrochloride of the hydrazide (3d) with chlorine, a method suggested [11] by Carpino's work.]

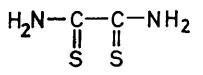
When the amine (3a) was heated for 10 min in refluxing 5N-hydrochloric acid, hydroxyguanidine was formed; it was isolated as the picrate in 37·5% yield. It has been reported [12] that acid hydrolysis of 5-methyl-1,2,4-oxadiazole gives acetic acid and the ' decomposition products ' of formamide oxime. There is, however, no previous report of the degradation of a 1,2,4-oxadiazole, with isolation of the amide oxime from which the oxadiazole originated.

3-Amino-1,2,4-oxadiazole was recovered unchanged after treatment with bromine in aqueous solution. It was degraded to unidentified fragments by fuming nitric acid in acetic anhydride, and by nitrosyl chloride in chloroform (nitrosyl chloride converts 3-amino-5-phenyl-1,2,4-oxadiazole into 3-chloro-5-phenyl-1,2,4-oxadiazole [13]).

Dithio-oxamide (6) could not be converted into the unknown cyanoformamide oxime by removal of the elements of hydrogen sulphide through the action of silver nitrate, silver oxide, or mercuric oxide, and subsequent reaction [14] with hydroxylamine. Treatment of dithio-oxamide with 1 equiv. of hydroxylamine gave thiocarbamoylformamide oxime (7), but this compound was not converted into the oxadiazole (3k) by triethyl orthoformate, or into the corresponding 4,5-dihydro-1,2,4-oxadiazole by formaldehyde.

[4] M. Arbasino and P. Gruenanger, *Chimica e Industria.*, 1963, **45**, 1238.
[5] C. Ainsworth, *J. Heterocyclic Chem.*, 1966, **3**, 470.
[6] R. Lenaers, C. Moussebois, and F. Eloy, *Helv. Chim. Acta*, 1962, **45**, 441.
[7] C. Moussebois, R. Lenaers, and F. Eloy, *Helv. Chim. Acta*, 1962, **45**, 446.
[8] J. A. Claisse, G. I. Gregory, and W. K. Warburton, S. Af. P. 6801,861 (*Chem. Abs.*, 1970, **72**, 21696).
[9] G. A. Olah and S. J. Kuhn, *J. Amer. Chem. Soc.*, 1960, **82**, 2380.
[10] W. K. Warburton, *J. Chem. Soc.* (*C*), 1966, 1522.
[11] L. A. Carpino, *Chem. and Ind.*, 1956, 123.
[12] F. Eloy, *Fortschr. Chem. Forsch.*, 1965, **4**, 807, 834.
[13] F. Eloy, A. Deryckere, and A. van Overstraeten, *Bull. Soc. chim. belges*, 1969, **78**, 47.
[14] L. Stephenson, W. K. Warburton, and M. J. Wilson, *J. Chem. Soc.* (*C*), 1969, 861.

The ester (3c) was converted by ethanolic ammonia into the amide (3l) in 83% yield (liquid ammonia opened the oxadiazole ring), and the amide was dehydrated by phosphorus pentoxide to give the nitrile (3 m) in 75% yield. The nitrile distils in air (b.p. 145°) without decomposition; it is highly toxic to mammals.



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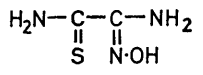

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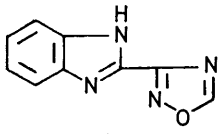

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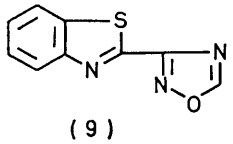

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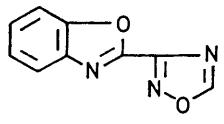

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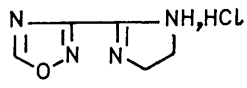

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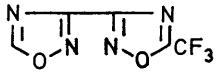

(12)

Treatment of the nitrile (3m) with hydrogen chloride in ethanol gave the hydrochloride of the imidate (3n). The imidate reacted with *o*-phenylenediamine to give the benzimidazole (8), with *o*-aminobenzenethiol to give the benzothiazole (9), and with *o*-aminophenol to give the benzoxazole (10). With hydrogen sulphide, the nitrile (3m) gave the thioamide (3k), which reacted with hydroxylamine to give the amide oxime (3o) [the same amide oxime was obtained directly from the nitrile (3m) and hydroxylamine]; the nitrile (3m) also reacted with ethylenediamine to give the imidazoline (11) (isolated as the hydrochloride). The amide oxime (3o) was converted by trifluoroacetic anhydride into the oxadiazole (12). The nitrile (3m) and the amide (3l) failed to give a ketone when treated with *p*-chlorobenzylmagnesium bromide.

EXPERIMENTAL

U.v. spectra were measured for solutions in ethanol. T.l.c. was carried out on Merck Kieselgel 254 plates in benzene containing varying proportions of ethyl acetate. ^{1}H N.m.r. spectra were recorded at 60 MHz.

3-*Formamido*-1,2,4-*oxadiazole* (3b).—Hydroxyguanidine[15] (2·02 g) was suspended in dry ether (40 ml), and triethylamine (9 ml) was added. The mixture was cooled to −78° and redistilled formyl fluoride[9] (*ca.* 5 ml) was added, with stirring. The mixture was stirred at −78° for 30 min, then allowed to warm to room temperature overnight. The ether was decanted and the residue was dissolved in water. The solution was extracted with chloroform and the combined organic solutions were dried (Na_2SO_4), filtered, and evaporated to dryness, leaving crude 3-*formamido*-1,2,4-*oxadiazole* (560 mg, 18%), m.p. *ca.* 110°, $\nu_{max.}$ (Nujol) 1702 and 1682 cm^{-1} (amide), τ([$^2H_6$]Me_2SO) 0·46 (CH) and 1·08 (CH) (Found: C, 30·7; H, 2·9; N, 34·6. $C_3H_3N_3O_2$ requires C, 31·9; H, 2·7; N, 37·2%).

3-*Amino*-1,2,4-*oxadiazole* (3a).—The preceding compound (374 mg) was dissolved in methanol (25 ml) and 10N-hydrochloric acid (3 ml) was added. The solution was left for 24 h, then evaporated to dryness. The residue was shaken with ethyl acetate and saturated sodium hydrogen carbonate solution, and the aqueous layer was separated and extracted with more ethyl acetate. The combined extracts were dried (Na_2SO_4) and evaporated, leaving the amine (56 mg, 20%), m.p. 114° (after sublimation), identical (i.r. and n.m.r. spectra) with the compound described later.

Ethyl 1,2,4-*Oxadiazole*-3-*carboxylate* (3c).—Ethoxycarbonylformamide oxime (39·6 g) was mixed with triethyl orthoformate (180 ml) and boron trifluoride–ether complex (0·9 ml) was added. The mixture was heated under reflux for 1 h and filtered. The filtrate was evaporated under reduced pressure and the residue was dissolved in chloroform. The solution was washed with 2N-hydrochloric acid, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), and evaporated, leaving the *oxadiazole* (3c) (33·9 g, 80%), m.p. 41—43°, b.p. 80—90° (bath) at 0·6 mmHg; no $\lambda_{max.}$ between 220 and 350 nm (Found: C, 42·0; H, 4·4; N, 20·1. $C_5H_6N_2O_3$ requires C, 42·25; H, 4·3; N, 19·7%).

1,2,4-*Oxadiazole*-3-*carbohydrazide* (3d).—The preceding compound (5·96 g) was stirred in dry ethanol (29 ml) and 98% hydrazine hydrate (3·15 ml) was added during 20 min at *ca.* 15°. The mixture was stirred for 30 min more at 0°, then the solid was filtered off and washed with ethanol, leaving the *hydrazide* (5·26 g, 97%), m.p. 112° (decomp.), $\lambda_{max.}$ 242—243 nm (ε 3950) (Found: C, 27·9; H, 3·5; N, 43·7. $C_3H_4N_4O_2$ requires C, 28·1; H, 3·15; N, 43·7%).

1,2,4-*Oxadiazole*-3-*carbonyl Azide* (3e).—Sodium nitrite (0·540 g) in water (1·5 ml) was added at 0°, with stirring, during 40 min, to a suspension of the hydrazide (3d) (0·896 g) in 2N-hydrochloric acid (10 ml) and glacial acetic acid (4 ml). The mixture was kept in the dark for 2·5 h at 0—5°, then water was added and the product was isolated with chloroform. Removal of the solvent left the *azide* (0·38 g, 39%), m.p. 89—90°, $\lambda_{max.}$ 241 nm (ε 4580) (Found: C, 26·0; H, 0·9; N, 50·3. $C_3HN_5O_2$ requires C, 25·9; H, 0·7; N, 50·4%).

3-*Benzyloxycarbonylamino*-1,2,4-*oxadiazole* (3g).—The preceding compound (46 mg) was added to dry xylene (11 ml) containing benzyl alcohol (36 mg) and the mixture was heated to 140° during 30 min. Evaporation to dryness left the *urethane* (71 mg, 99%), m.p. 138—140°, no $\lambda_{max.}$ between 220 and 350 nm (Found, after sublimation: C, 54·75; H, 4·1; N, 18·8. $C_{10}H_9N_3O_3$ requires C, 54·8; H, 4·1; N, 19·2%).

3-t-*Butoxycarbonylamino*-1,2,4-*oxadiazole* (3h).—Decomposition of the azide (3e) in xylene in the presence of t-butyl alcohol, as in the previous experiment, gave the *urethane* in quantitative yield, m.p. 87—90°, no $\lambda_{max.}$ between 220 and 350 nm (Found, after sublimation: C, 45·4;

[15] S. Nakatsu, *Mem. Fac. Sci. Kyushu Univ. Ser. C*, 1958, **3**, 43 (*Chem. Abs.*, 1959, **53**, 10034).

H, 6·0; N, 23·2. $C_7H_{11}N_3O_3$ requires C, 45·4; H, 6·0; N, 22·7%).

3-*Amino*-1,2,4-*oxadiazole* (3a).—The preceding urethane (2·57 g) was stirred at room temperature for 1 h in trifluoroacetic acid (10 ml). The solvent was removed under reduced pressure, and the residue was sublimed at *ca.* 60° and 1 mmHg to give the amine (0·53 g, 45%), m.p. 112°, no $\lambda_{max.}$ between 220 and 350 nm (Found: C, 28·2; H, 3·6; N, 48·8. $C_2H_3N_3O$ requires C, 28·2; H, 3·6; N, 49·4%).

3-*Benzylideneamino*-1,2,4-*oxadiazole* (2; R = H).—The preceding compound (425 mg) was heated under reflux in benzaldehyde diethyl acetal (2 ml) for 5 min. The solution was cooled to 50°, then light petroleum (b.p. 40—60°; 3 ml) was added, and the solution was allowed to cool to room temperature. The solid that separated was filtered off and washed with light petroleum to give the *Schiff base* (463 mg, 53·5%), m.p. 88—89°, $\lambda_{max.}$ 272·5 nm (ε 7500) (Found: C, 62·4; H, 4·2; N, 24·3. $C_9H_7N_3O$ requires C, 62·4; H, 4·1; N, 24·3%).

3-p-*Chlorobenzylideneamino*-1,2,4-*oxadiazole* (2; R = Cl).—This compound, prepared similarly (42%), had m.p. 169—170°, $\lambda_{max.}$ 282 nm (ε 21,800) (Found: C, 52·4; H, 2·8; Cl, 17·1; N, 20·0. $C_9H_6ClN_3O$ requires C, 52·1; H, 2·9; Cl, 17·1; N, 20·3%).

N^1N^1-*Dimethyl*-N^2-(1,2,4-*oxadiazol*-3-*yl*)*formamidine* (3i).—A suspension of 3-amino-1,2,4-oxadiazole (170 mg) in benzene (10 ml) was stirred with dimethylformamide dimethyl acetal (260 mg) at room temperature for 2 h. The solution was evaporated under reduced pressure and the residue was extracted with boiling light petroleum (b.p. 80—100°). The solution on cooling deposited the *formamidine* (151 mg, 54%), m.p. 104—105°, $\lambda_{max.}$ 253 nm (ε 19,900) (Found: C, 42·8; H, 5·6; N, 40·0. $C_5H_8N_4O$ requires C, 42·9; H, 5·75; N, 40·0%).

NN′-*Bis*-(1,2,4-*oxadiazol*-3-*yl*)*urea* (5).—The azide (3e) (139 mg) was heated for 30 min under reflux in dry xylene (10 ml) containing 3-amino-1,2,4-oxadiazole (85 mg). The hot solution was decanted from a little dark solid and allowed to cool; it deposited the *urea* (52 mg, 26·5%), m.p. 189°, no $\lambda_{max.}$ between 220 and 350 nm (Found: C, 30·7; H, 2·2; N, 42·9. $C_5H_4N_6O_3$ requires C, 30·6; H, 2·1; N, 42·8%).

1,2,4-*Oxadiazole*-3-*carbonyl Chloride* (3j).—Dry hydrogen chloride was passed for 2 h at 10—15° through a solution of the hydrazide (3d) (11·96 g) in dry methanol (630 ml). The methanol was removed, then dry nitromethane (30 ml) was added and removed under reduced pressure. More nitromethane (200 ml) was added, the mixture was cooled to 10°, hydrogen chloride was passed in for 45 min, then chlorine was passed in for 1 h. When the evolution of nitrogen ceased, the chlorine was removed in a stream of nitrogen, the suspension was filtered, and the filtrate was evaporated to give the crude acid chloride, (10·2 g, 82%). A sample was obtained purer by distillation (b.p. 47—47·5° at 2·5 mmHg), $\nu_{max.}$ (CS_2) 1785 cm^{-1} (COCl), τ ($CDCl_3$) 1·00 (CH). In a similar experiment the acid chloride was obtained in 92% yield.

N(3)-p-*Chlorophenyl* 1,2,4-*Oxadiazole*-3-*carboxamide*.—*p*-Chloroaniline (584 mg) in dry benzene (6 ml) was added during 30 min at 12—14° to a stirred solution of the acid chloride (3j) (268 mg) in benzene (5 ml). After 1·5 h at 20°, the suspension was kept at 0° for 16 h, then filtered. The solid was stirred with ethyl acetate (25 ml) and the solution was filtered and evaporated to dryness, leaving the *anilide* (348 mg, 77%), m.p. 156—157°, $\lambda_{max.}$ 271—272 nm (ε 11,300) (Found: C, 48·4; H, 3·05; Cl, 15·8; N, 18·8. $C_9H_6ClN_3O_2$ requires C, 48·3; H, 2·7; Cl, 15·9; N, 18·8%). The same compound (i.r. spectrum), m.p. 156—158°, was obtained in 97% yield by treating *p*-chloroaniline with the azide (3e) in chloroform.

N(3)-1-*Adamantyl* 1,2,4-*Oxadiazole*-3-*carboxamide*.—The azide (3e) (350 mg) was added to a solution of 1-aminoadamantane (370 mg) in chloroform (15 ml). The solution was left for 24 h, then evaporated to dryness under reduced pressure. The residue was recrystallized from aqueous methanol to give the *amide* (167 mg, 27%), m.p. 141—142°, $\lambda_{max.}$ 230 nm (ε 3900) (Found: C, 63·4; H, 6·9; N, 16·8. $C_{13}H_{17}N_3O_2$ requires C, 63·1; H, 6·9; N, 17·0%).

Acid Hydrolysis of 3-*Amino*-1,2,4-*oxadiazole*.—3-Amino-1,2,4-oxadiazole (30 mg) dissolved in 5N-hydrochloric acid (5 ml) was heated under reflux for 10 min, then evaporated to dryness under reduced pressure. The residue was dissolved in water (0·1 ml), and saturated aqueous picric acid (3 ml) was added. Hydroxyguanidine picrate (26 mg, 37·5%) separated as yellow needles, m.p. 165° (decomp.), $\nu_{max.}$ (Nujol) 1530 and 1348 (NO_2), and 3430 and 3400 cm^{-1} (NH_2) (Found: C, 27·6; H, 2·6; N, 27·1. $C_7H_8N_6O_8$ requires C, 27·6; H, 2·6; N, 27·6%), identical (i.r. spectrum) with the picrate prepared from hydroxyguanidine sulphate, and with the picrates isolated after hydrogenolysis or acid hydrolysis of the benzylurethane (3 g).

Thiocarbamoylformamide Oxime (7).—Dithio-oxamide (19·2 g) was added to a methanolic hydroxylamine solution (200 ml) [prepared from hydroxylamine hydrochloride (11·12 g) by neutralization with sodium methoxide in methanol]. The solution was heated under reflux for 6 h, then kept overnight at 20°, and evaporated to dryness. The residue was dissolved in ethyl acetate, then extracted into 2N-hydrochloric acid. The acid layer was neutralized to pH 7 (sodium hydrogen carbonate) and the *amide oxime* (9·63 g, 50·5%), was isolated with ethyl acetate; m.p. 140—141°, $\lambda_{max.}$ 288—289 nm (ε 9600) (Found, after sublimation: C, 20·5; H, 4·5; N, 35·3. $C_2H_5N_3OS$ requires C, 20·15; H, 4·2; N, 35·25%).

1,2,4-*Oxadiazole*-3-*carboxamide* (3l).—Dry ammonia was passed for 1·5 h at 5—10° through a solution of the ester (3c) (54·7 g) in ethanol (310 ml). The solid was filtered off and washed with a little ethanol, leaving the amide (36·6 g, 84%). A *sample* recrystallized from tetrahydrofuran–benzene had m.p. 174°, no $\lambda_{max.}$ between 220 and 350 nm (Found: C, 32·2; H, 2·8; N, 37·2. $C_3H_3N_3O_2$ requires C, 31·9; H, 2·7; N, 37·2%).

1,2,4-*Oxadiazole*-3-*carbonitrile* (3m).—The preceding amide (9·7 g) and phosphoric anhydride (25 g) were mixed well, then heated for 1·5 h at 120—150° and 0·2 mmHg. The product was collected at < −20°. Some unchanged amide was mixed with fresh phosphoric anhydride and heated as before. The total yield of *nitrile* was 6·1 g (75%); it had b.p. 145°, n_D^{23} 1·4363, no $\lambda_{max.}$ between 220 and 350 nm, $\nu_{max.}$ (CS_2) 2270 cm^{-1} (CN), τ ($CDCl_3$) 0·98 (CH) (Found: C, 38·1; H, 1·4; N, 44·0. C_3HN_3O requires C, 37·9; H, 1·1; N, 44·2%).

Ethyl 1,2,4-*Oxadiazole*-3-*carboximidate Hydrochloride*.—The nitrile (3m) (3·30 g) in dry benzene (12 ml) and dry ethanol (2·1 ml) was treated with dry hydrogen chloride for 1·5 h at 0—5°, then kept in a sealed flask for 72 h at 0°. The solid was filtered off and washed with ether to give the imidate hydrochloride (5·39 g, 87·5%), m.p. 162—163° (decomp.), no $\lambda_{max.}$ between 220 and 350 nm, $\nu_{max.}$ (Nujol) 1200 and 1745 cm^{-1} (CO_2Et), τ (D_2O) 0·58 (CH), 5·46, and 8·60 (C_2H_5).

3-(*Benzimidazol-2-yl*)-1,2,4-*oxadiazole* (8).—*o*-Phenylenediamine (3·24 g) was added, with stirring, at 0°, to the foregoing imidate hydrochloride (5·31 g) in dry methanol (120 ml). The mixture was left at 0° for 45 min, then allowed to warm to 20° during 3 h. The volume was reduced to 25 ml and the solid was filtered off and washed with methanol, leaving the benzimidazole (3·30 g, 59%), m.p. >330°, which formed *needles*, m.p. >330° (from aqueous ethanol), $\lambda_{max.}$ 294 nm (ε 17,300) (Found: C, 57·7; H, 3·4; N, 30·0. $C_9H_6N_4O$ requires C, 58·1; H, 3·25; N, 30·1%).

Similarly were prepared: 3-(*benzothiazol-2-yl*)-1,2,4-*oxadiazole* (9) (50%), m.p. 145—147° (from methanol), $\lambda_{max.}$ 245 and 286 nm (ε 8400 and 14,100) (Found: C, 53·0; H, 2·55; N, 21·0; S, 15·7. $C_9H_5N_3OS$ requires C, 53·2; H, 2·5; N, 20·7; S, 15·8%); and 3-(*benzoxazol-2-yl*)-1,2,4-*oxadiazole* (10) (62%) (after being heated under reflux for 1·5 h), m.p. 158—159°, $\lambda_{max.}$ 280 nm (ε 14,300) (Found: C, 57·9; H, 2·8; N, 22·7. $C_9H_5N_3O_2$ requires C, 57·8; H, 2·7; N, 22·45%).

1,2,4-*Oxadiazole*-3-*thiocarboxamide* (3k).—A solution of the nitrile (3m) (16·98 g) in dry benzene (170 ml) was saturated with hydrogen sulphide. Diethylamine (0·85 ml) was added, and more hydrogen sulphide was passed in for 2 h. The solution was left for 4 h more, then the solid was filtered off and washed with benzene, leaving pale-yellow needles (22·52 g, 98%), m.p. 174—175° (decomp.). Recrystallization of a sample from acetone–light petroleum (b.p. 60—80°) gave the *thioamide*, m.p. 167—168° (decomp.), $\lambda_{max.}$ 306 nm (ε 6500) (Found: C, 27·7; H, 2·3; N, 32·7. $C_3H_3N_3OS$ requires C, 27·9; H, 2·3; N, 32·6%).

1,2,4-*Oxadiazole*-3-*carboxamide Oxime* (3o).—The nitrile (3m) (190 mg) was added to a methanolic solution (15 ml) of hydroxylamine prepared by neutralizing hydroxylamine hydrochloride (417 mg) with methanolic sodium methoxide. The solution was evaporated to dryness and the residue in ethyl acetate was extracted into 2N-hydrochloric acid. The acid extract was neutralized and the amide oxime (116 mg, 45%) was isolated with ethyl acetate; it had m.p. 114—115° (lit.,[6] 115°), $\lambda_{max.}$ 242—243 nm (ε 3950) (Found: C, 27·9; H, 3·5; N, 43·7. Calc. for $C_3H_4N_4O_2$: C, 28·1; H, 3·15; N, 43·7%). Treatment of the thioamide (3k) gave the hydrated amide oxime in 90% yield, m.p. 136—137° (Found: C, 26·8; H, 3·3; N, 40·75. $C_3H_4N_4O_2,0{\cdot}5H_2O$ requires C, 26·3; H, 3·7; N, 40·8%).

3-(4,5-*Dihydroimidazol-2-yl*)-1,2,4-*oxadiazole Hydrochloride* (11).—The thioamide (3k) (1·161 g) was added to dry methanol (100 ml) containing ethylenediamine (0·594 g). The mixture was left at *ca.* 20° for 66 h, then filtered. The filtrate was evaporated to dryness at <20° and the residue in dry methanol (24 ml) was treated with dry hydrogen chloride for 1·5 h. Dry ether (100 ml) was added and the mixture was kept at 0° for 4 days. Filtration gave the *hydrochloride* (0·369 g, 21%), m.p. 170—180° (decomp.), $\lambda_{max.}$ 268 nm (ε 2600) (Found: C, 33·7; H, 4·1; Cl, 20·3; N, 32·1. $C_5H_7ClN_4O$ requires C, 34·4; H, 4·0; Cl, 20·3; N, 32·1%).

5-*Trifluoromethylbi*-1,2,4-*oxadiazol*-3-*yl* (12).—Trifluoroacetic anhydride (50 g) was added during 1 h at 0° to the anhydrous amide oxime (3o) (4·43 g) in trifluoroacetic acid (70 ml). After 1 h more at 0°, the suspension was filtered to give the O-*acylamide oxime* (5·0 g, 65%), m.p. 146° (decomp.), $\lambda_{max.}$ 261 nm (ε 3800) (Found: C, 26·9; H, 1·4; N, 25·2. $C_5H_3F_3N_4O_3$ requires C, 26·8; H, 1·3; N, 25·0%). The solid was heated at 144—147° and 0·6 mmHg and the product was collected at −70° to give the crude oxadiazole (3·60 g, 45%). Sublimation gave the *oxadiazole*, m.p. 33°, no $\lambda_{max.}$ between 220 and 350 nm (Found: C, 28·7; H, 0·8; F, 26·3; N, 27·8. $C_5HF_3N_4O_2$ requires C, 29·1; H, 0·5; F, 27·6; N, 27·2%).

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