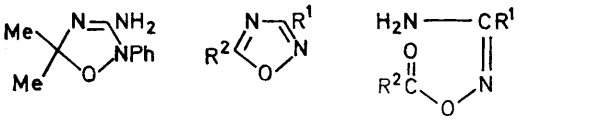
Some *N*-Hydroxy-*N*-methylamidines and 1,2,4-Oxadiazol-5(2*H*)-ones

By **Peter W. Seale** and **William K. Warburton,*** Organic Chemistry Department, Glaxo Research Ltd., Greenford, Middlesex

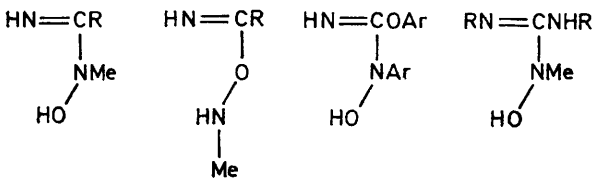
Aromatic and heterocyclic nitriles react with *N*-methylhydroxylamine to give *N*-hydroxy-*N*-methylamidines (4). The latter, when treated with ethyl chloroformate, give 1,2,4-oxadiazol-5(2*H*)-ones (9). Sodium borohydride reduces compound (9; R = *p*-C_6H_4Cl) to the corresponding oxadiazolidinone (10). The tautomeric structure of *p*-chlorobenzamide oxime is discussed.

ALTHOUGH 2,3-dihydro-1,2,4-oxadiazoles [1] and -oxadiazolones [2,3] and some corresponding 4,5-dihydro-compounds [4,5] are known, the only reported 2,5-dihydro-1,2,4-oxadiazoles [6] are the amine (1) and a few compounds derived from it. The method by which (1) was prepared (treating cyanamide with acetone and phenylhydroxylamine) does not appear to be widely applicable.

1,2,4-Oxadiazoles (2) are usually made by cyclodehydration of *O*-acyl amide oximes (3). In order to retain the 2,3-single bond, we required *N*-alkyl-*N*-hydroxyamidines (4). Such compounds have not been described, although Grigat *et al.*[7] have prepared some *N*-aryl compounds (5), and Zinner and Gross [8] have more recently prepared trisubstituted hydroxyguanidine derivatives (6).



(1) (2) (3)



(4) (4a) (5) (6)

When benzonitrile was treated with *N*-methylhydroxylamine in methanol, *N*-hydroxy-*N*-methylbenzamidine (4; R = Ph) was isolated in high yield. *p*-Chlorobenzonitrile, when similarly treated, gave the pure hydroxy-amidine (4; R = *p*-C_6H_4Cl) in *ca.* 90% yield; the hydroxy-amidines (4; R = *p*-bromophenyl, 5-nitro-2-furyl, and 5-nitrothiazol-2-yl) were prepared similarly. However benzonitrile and *p*-chlorobenzonitrile were unaffected by *N*-phenylhydroxylamine in refluxing alcohols.

Cyclic products were not obtained by treating the *N*-hydroxy-amidine (4; R = *p*-C_6H_4Cl or *p*-C_6H_4Br) with benzaldehyde, benzylidene chloride, formaldehyde, acetaldehyde, dimethoxymethane, carbon disulphide, acetyl chloride, or acetic anhydride. Usually no reaction occurred, but from the reaction between (4; R = *p*-C_6H_4Br) and aqueous acetaldehyde at 80° we obtained *p*-bromobenzamide. From the reaction between (4; R = *p*-C_6H_4Cl) and acetic anhydride in boiling chloroform we obtained *p*-chlorobenzoic acid, possibly formed during the aqueous work-up.

When (4; R = *p*-C_6H_4Cl) was treated with 1·24 equiv. of methyl chloroformate in chloroform containing pyridine, a mixture was obtained which appeared to consist of the *O*-acyl compound (7; R^1 = *p*-C_6H_4Cl, R^2 = Me) and the *NO*-diacyl compound (8; R^1 = *p*-C_6H_4Cl, R^2 = Me) in the ratio *ca.* 2 : 1. [The latter compound has been obtained in quantitative yield by treating (4) with 2·5 mol. equiv. of methyl chloroformate.] The i.r. spectrum of the mixture ($CHBr_3$) revealed two carbonyl bands ($\nu_{max.}$ 1790 and 1720 cm^{-1}), which we attribute to (8; R^1 = *p*-C_6H_4Cl, R^2 = Me), and a third carbonyl band (1752 cm^{-1}), which we attribute to the hydrogen-bonded compound (7; R^1 =

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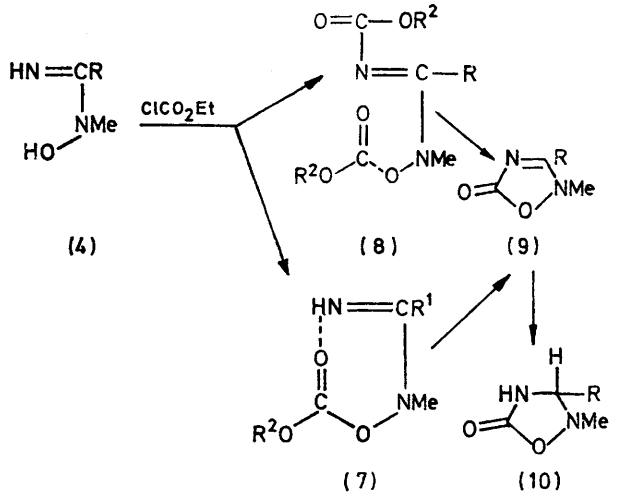
[2] A. R. Katritzky, B. Wallis, R. T. C. Brownlee, and R. D. Topsom, *Tetrahedron*, 1965, **21**, 1681.
[3] B. W. Nash, R. A. Newberry, R. Pickles, and W. K. Warburton, *J. Chem. Soc.* (*C*), 1969, 2794.
[4] F. Tiemann, *Ber.*, 1889, **22**, 2412.
[5] G. D'Alo, M. Perghem, and P. Grunanger, *Ann. Chim.* (*Italy*), 1963, **53**, 1405.
[6] R. Hull and R. Farrand, *J. Chem. Soc.*, 1963, 6028.
[7] E. Grigat, R. Pütter, and C. König, *Chem. Ber.*, 1965, **98**, 144.
[8] G. Zinner and H. Gross, *Chem. Ber.*, 1972, **105**, 1709.

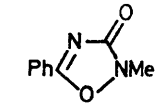
p-C_6H_4Cl, R^2 = Me). The n.m.r. spectrum of the mixture ($CDCl_3$) showed five methyl groups, three of which (τ 6·19, 6·42, and 6·66) we assign to the two *O*-methyl groups and the *N*-methyl group of (8; R^1 = p-C_6H_4Cl, R^2 = Me), and two of which (τ 6·33 and 6·52) we assign to the *O*- and the *N*-methyl group, respectively, of (7; R^1 = p-C_6H_4Cl, R^2 = Me). The aromatic protons appear as an AB quartet (τ 2·52 and 2·74, J 8·5 Hz) and a collapsed AB quartet (τ 2·62), assigned to (7; R^1 = p-C_6H_4Cl, R^2 = Me) and (8; R^1 = p-C_6H_4Cl, R^2 = Me), respectively. Spectroscopic evidence points to a similar composition for mixtures obtained by treating (4; R = p-C_6H_4Cl, p-C_6H_4Br, 5-nitrothiazol-2-yl, or 5-nitro-2-furylvinyl) with ethyl chloroformate in pyridine.

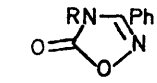


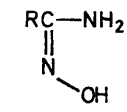
Thermal cyclization of the product obtained by treating (4) with ethyl chloroformate gave the 2-methyl-1,2,4-oxadiazol-5(2*H*)-ones (9; R = phenyl, p-chlorophenyl, *trans*-p-chlorostyryl, 5-nitro-2-furyl, 5-nitro-2-furylvinyl, or 5-nitrothiazol-2-yl) in yields of 47—61%. The cyclization of the *O*-acyl compounds (7) to form oxadiazolones (9) is not surprising. However, a sample of the *NO*-diacyl compound (8; R^1 = p-ClC_6H_4, R^2 = Me) kept for 27 days at room temperature had changed into the oxadiazolone (9; R = p-ClC_6H_4).

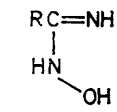
N-Methylhydroxylamine could conceivably react with aromatic nitriles [9] to give not (4) but the isomeric compounds (4a). However acylation of (4a; R = Ph) with ethyl chloroformate and subsequent cyclization would give the known [2,3] 2-methyl-5-phenyl-1,2,4-oxadiazol-3(2*H*)-one (9a) (m.p. 115°), and not (9; R = Ph) (m.p. 134—135°).

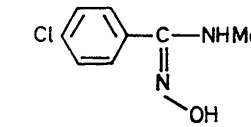
The oxadiazolinone (9; R = p-C_6H_4Cl) was reduced by sodium borohydride to the corresponding oxadiazolidinone compound (10), which was not obtained pure and slowly decomposed at room temperature. The structure (10) is supported by elemental analysis and by i.r. and n.m.r. data (see Experimental section).





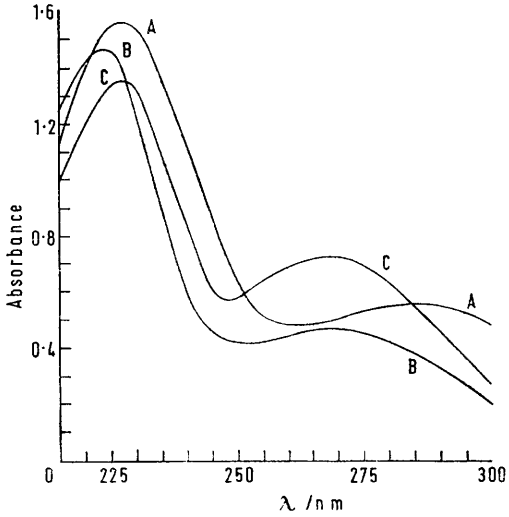






3-Phenyl-1,2,4-oxadiazol-5(4*H*)-one (11; R = H) has been methylated [2,10,11] to give an *N*-methyl compound which, as Katritzky *et al.* have observed,[2] could be either 4-methyl-3-phenyl-1,2,4-oxadiazol-5(4*H*)-one (11; R = Me) or, less probably, the 2*H*-compound (9; R = Ph). The 4*H*-compound (11; R = Me) was later prepared by D'Alo *et al.*[5] from *N*-methylbenzamide oxime; it is identical with the oxadiazolone (m.p. 117—119°) obtained by treating (11; R = H) with diazomethane, but differs from (9; R = Ph) (m.p. 134—135°).

Tiemann and Krüger [12] observed in 1884 that amide oximes could be written in the tautomeric forms (12a) and (12b), and expressed the opinion that (12a) predominated. Ponzio [13] produced some evidence to the contrary, but Bell *et al.*[14] studied the i.r. and the n.m.r. spectra of several amide oximes, including benzamide oxime, and concluded that in solution they existed solely in the amino-oxime form (12a). Brandt [15] reviewed the chemical and spectroscopic (i.r. and n.m.r.) properties of amide oximes and reached the same conclusion.



The u.v. spectra of *N*-hydroxy-*N*-methyl-p-chlorobenzamidine (A), *N*-methyl-p-chlorobenzamide oxime (13) (B), and p-chlorobenzamide oxime (C)

[9] L. Stephenson, W. K. Warburton, and M. J. Wilson, *J. Chem. Soc.* (*C*), 1969, 861.
[10] G. Ponzio, *Gazzetta*, 1923, **53**, 507.
[11] R. Gomppa, *Chem. Ber.*, 1960, **93**, 208.
[12] F. Tiemann and P. Krüger, *Ber.*, 1884, **17**, 1685.
[13] G. Ponzio, *Gazzetta*, 1931, **61**, 704.
[14] C. L. Bell, C. N. V. Nanbury, and L. Bauer, *J. Org. Chem.*, 1964, **29**, 2873.
[15] L. Brandt, *Mededel. vlaam. chem. Ver.*, 1967, **29**, 56.

We prepared *N*-methyl-*p*-chlorobenzamide oxime (**13**) by treating *p*-chlorobenzohydroxamoyl chloride [16] with methylamine, and compared its u.v. spectrum (solution in ethanol) with the spectra of *p*-chlorobenzamide oxime [9] and *N*-methyl-*N*-hydroxy-*p*-chlorobenzamidine (**4**; R = *p*-C_6H_4Cl) (see Figure). The similarity between the spectra of *p*-chlorobenzamide oxime and (**13**) leads to the conclusion that *p*-chlorobenzamide oxime exists (at least in dilute ethanolic solution) mainly or entirely in the form (12a).

EXPERIMENTAL

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

N-*Hydroxy*-N-*methyl*-p-*chlorobenzamidine* (**4**; R = *p*-ClC_6H_4).—*p*-Chlorobenzonitrile (16·0 g) was dissolved in a solution of *N*-methylhydroxylamine in methanol (200 ml) [from *N*-methylhydroxylamine hydrochloride (16·0 g) and methanolic sodium methoxide]. The solution was heated under reflux for 1·5 h, the solvent was removed, and the residue was extracted with chloroform, giving *N*-hydroxy-*N*-methyl-*p*-chlorobenzamidine (18·5 g, 86%), m.p. 146—150°. A *sample* recrystallized from chloroform–light petroleum (b.p. 80—100°) had m.p. 160—162°, $\lambda_{max.}$ 225 and 284 nm (ε 14,700 and 4400), $\nu_{max.}$ ($CHBr_3$) 3500 (OH), 3340 (NH), 1638 (C=N), and 831 cm^{-1} (*p*-C_6H_4), τ ($CDCl_3$) 6·67 (CH_3), 2·68 (collapsed ABq, *p*-C_6H_4), and 3·88 (OH and NH) (Found: C, 51·5; H, 5·0; Cl, 19·9; N, 14·8. $C_8H_9ClN_2O$ requires C, 52·0; H, 4·9; Cl, 19·2; N, 15·2%). The *picrate* had m.p. 142—145° [from chloroform–light petroleum (b.p. 80—100°)] (Found: C, 40·65; H, 3·2; Cl, 8·5; N, 17·3. $C_{14}H_{12}ClN_5O_8$ requires C, 40·5; H, 2·9; Cl, 8·55; N, 16·9%). Similarly were prepared: *N*-hydroxy-*N*-methylbenzamidine (**4**; R = Ph) (41%), m.p. 94—96° [from methylene chloride–light petroleum (b.p. 40—60°)], $\lambda_{max.}$ 272·5 nm (ε 4200) [*picrate*, m.p. 166—168° (from aqueous ethanol) (Found: C, 44·1; H, 3·6; N, 18·0. $C_{14}H_{13}N_5O_8$ requires C, 44·3; H, 3·4; N, 18·5%)]; *N*-hydroxy-*N*-methyl-*p*-bromobenzamidine (**4**; R = *p*-BrC_6H_4) (89%), m.p. 160—162° [from chloroform–light petroleum (b.p. 80—100°)], $\lambda_{max.}$ 229 and 286·5 nm (ε 15,500 and 4800) [*picrate*, m.p. 165—167° (from methanol) (Found: C, 36·8; H, 2·7; N, 15·3. $C_{14}H_{12}BrN_5O_8$ requires C, 36·8; H, 2·6; N, 15·3%)]; *N*-hydroxy-*N*-methyl-5-nitrofuran-2-carboxamidine (**4**; R = 5-nitro-2-furyl) (80%), m.p. 122° (decomp.) [from chloroform–light petroleum (b.p. 40—60°)], $\lambda_{max.}$ 279 and 380 nm (ε 11,000 and 7000), $\nu_{max.}$ ($CHBr_3$) 3500 (OH), 3360 (NH), and 1508 and 1350 cm^{-1} (NO_2); N-*hydroxy*-N-*methyl*-5-*nitrothiazole*-2-*carboxamidine* (**4**; R = 5-nitrothiazol-2-yl) (78%), m.p. 190° (decomp.) (from methanol), $\lambda_{max.}$ 296·5 and 420·5 nm (ε 12,200 and 4400) (Found: C, 29·8; H, 3·0; N, 28·0; S, 15·9. $C_5H_6N_4O_3S$ requires C, 29·7; H, 3·0; N, 27·7; S, 15·9%).

Reaction of N-*Hydroxy*-N-*methyl*-p-*chlorobenzamidine with Methyl Chloroformate*.—The amidine (922 mg) was dissolved in ethanol-free chloroform (15 ml) containing dry pyridine (491 mg) and the solution was cooled to −40°. Methyl chloroformate (585 mg) in chloroform (5 ml) was added dropwise, with stirring, during 20 min, at −40°. The mixture was kept at this temperature for 2 h, washed with ice–water (25 ml), dried (Na_2SO_4), and cooled to −40°. Some of the solution (5 ml) was evaporated to dryness at 25° to give a pale gum (359 mg). The i.r. and the n.m.r. spectrum of this mixture are recorded in the Discussion section.

N-*Methyl*-N′-*methoxycarbonyl*-N-*methoxycarbonyloxy*-p-*chlorobenzamidine* (**8**; R^1 = *p*-ClC_6H_4, R^2 = Me).—*N*-Hydroxy-*N*-methyl-*p*-chlorobenzamidine (922 mg) was treated as in the preceding experiment with methyl chloroformate (1·07 g), to give the diacyl compound as a viscous oil (1·51 g, 100%), $\nu_{max.}$ ($CHBr_3$) 1791 (O·CO_2R), 1717 (C=N·CO_2R), 1634 (C=N), and 838 cm^{-1} (*p*-C_6H_4), τ ($CDCl_3$) 6·66 (N·CH_3), 6·42 and 6·19 (OCH_3), and 2·62 (collapsed ABq, *p*-C_6H_4). The oil later changed into a yellow solid, m.p. *ca.* 160°, shown (i.r. spectrum) to be the crude oxadiazolone (**9**; R = *p*-ClC_6H_4). Recrystallization from ethanol gave the oxadiazolone in 75% yield, m.p. 172—174° (Found: C, 51·4; H, 3·4; N, 13·5. Calc. for $C_9H_7ClN_2O_2$: C, 51·3; H, 3·3; N, 13·3%), identical (i.r. and n.m.r. spectra) with the compound described earlier.

2-*Methyl*-3-*phenyl*-1,2,4-*oxadiazol*-5(2H)-*one* (**9**; R = Ph).—*N*-Hydroxy-*N*-methylbenzamidine (900 mg) in dry pyridine (20 ml) was stirred, and ethyl chloroformate (0·60 ml, 0·683 g) was added dropwise below 0°. The mixture was allowed to warm to room temperature during 1 h, then heated under reflux for 1 h, cooled, and poured into water (100 ml). The solution was made acid with 2N-hydrochloric acid. Isolation with ethyl acetate gave a solid residue (1·07 g), which was recrystallized from 50% aqueous methanol (8 ml) to give the *oxadiazolone* (522 mg, 49·5%), m.p. 134—135°, $\lambda_{max.}$ 241 nm (ε 14,900), $\nu_{max.}$ ($CHBr_3$) 1770 (C=O), and 762 cm^{-1} (Ph), τ ($CDCl_3$) 6·20 (N·CH_3) and 2·05—2·60 (centred at 2·33, Ph) (Found: C, 61·3; H, 4·65; N, 15·9. $C_9H_8N_2O_2$ requires C, 61·4; H, 4·6; N, 15·9%). The i.r. and the n.m.r. spectrum of this compound differ from those of 2-methyl-5-phenyl-1,2,4-oxadiazol-3(2*H*)-one.[3]

Similarly were prepared: 3-p-*chlorophenyl*-2-*methyl*-1,2,4-*oxadiazol*-5(2H)-*one* (**9**; R = *p*-ClC_6H_4) (54%), m.p. 168·5—170° (from propan-2-ol), $\lambda_{max.}$ 248·5 nm (ε 19,500) (Found: C, 51·2; H, 3·5; Cl, 17·0; N, 13·3. $C_9H_7ClN_2O_2$ requires C, 51·3; H, 3·3; Cl, 16·9; N, 13·3%); 2-*methyl*-3-(5-*nitro*-2-*furyl*)-1,2,4-*oxadiazol*-5(2H)-*one* (**9**; R = 5-nitro-2-furyl) (44%), m.p. 179—180°, $\lambda_{max.}$ 224 and 300 nm (ε 13,900 and 16,800) (Found: C, 40·0; H, 2·5; N, 19·6. $C_7H_5N_3O_5$ requires C, 39·8; H, 2·4; N, 19·9%); 2-*methyl*-3-(5-*nitrothiazol*-2-*yl*)-1,2,4-*oxadiazol*-5(2H)-*one* (**9**; R = 5-nitrothiazol-2-yl) (47%), m.p. 200—201°, $\lambda_{max.}$ 228·5 and 304 nm (ε 10,000 and 13,900) (Found: C, 31·7; H, 1·8; N, 24·7; S, 13·9. $C_6H_4N_4O_4S$ requires C, 31·6; H, 1·8; N, 24·6; S, 14·1%).

2-*Methyl*-3-trans-(5-*nitro*-2-*furylvinyl*)-1,2,4-*oxadiazol*-5(2H)-*one* (**9**; R = *trans*-5-nitro-2-furylvinyl).—3-(5-Nitro-2-furyl)acrylonitrile (10·0 g) suspended in dry methanol (50 ml) was stirred for 2 h at room temperature with methanolic methylhydroxylamine (100 ml) [from *N*-methylhydroxylamine hydrochloride (10·0 g)]. Concentration to 50 ml and cooling gave the crude hydroxyamidine (3·06 g, 24%), m.p. 198° (decomp.), $\nu_{max.}$ (Nujol) 3386 (NH), 3300—3000 (bonded OH), 1350 and 1492 (NO_2), and 942 cm^{-1} (*trans*-CH=CH). The hydroxyamidine was dissolved in pyridine (25 ml) and treated at −30° with ethyl chloroformate (1·14 g). The reaction was worked up as described above, and the product was heated

[16] T. Farley, F. H. Rathmann, and D. Tangen, *Proc. N. Dakota. Acad. Sci.*, 1959, **13**, 61 (*Chem. Abs.*, 1960, **54**, 5619).

under reflux in toluene (100 ml) for 15 min. Evaporation to dryness gave the *oxadiazolone* (1·90 g, 13%), m.p. 212° (decomp.) (from methanol), $\lambda_{max.}$ 242·5, 293·5, and 350 nm (ε 13,400, 19,500, and 22,300) (Found: C, 45·6; H, 3·1; N, 17·8. $C_9H_7N_3O_5$ requires C, 45·6; H, 3·0; N, 17·7%).

3-p-*Chlorostyryl*-2-*methyl*-1,2,4-*oxadiazol*-5(2H)-*one* (9; R = *p*-chlorostyryl) (17%), m.p. 271—272° (decomp.) (from dimethylformamide), $\lambda_{max.}$ 226, 232, and 303 nm (ε 13,000, 11,500, and 30,600) (Found: C, 55·8; H, 3·7; Cl, 15·0; N, 12·2. $C_{10}H_{11}ClN_2O$ requires C, 55·8; H, 3·8; Cl, 15·0; N, 12·2%), was prepared similarly.

3-p-*Chlorophenyl*-2-*methyl*-1,2,4-*oxadiazolidin*-5-*one* (10).—3-*p*-Chlorophenyl-2-methyl-1,2,4-oxadiazol-5(2*H*)-one (200 mg) was dissolved in ethanol (10 ml) and tetrahydrofuran (5 ml). Sodium borohydride (40 mg) was added and the solution was stirred at room temperature for 1 h, then poured into water (25 ml). The suspension was neutralized with acetic acid. Isolation with chloroform gave the *oxadiazolidinone* (151 mg, 75%), m.p. 94—96°, $\nu_{max.}$ (Nujol) 3250 (bonded NH), 1752, and 1723 cm^{-1} (carbonyl in non-planar ring), τ ($CDCl_3$) 7·12 (NMe), 4·79 (CH), and 2·61 (collapsed ABq, *p*-C_6H_4) (Found: C, 51·9; H, 4·7; Cl, 16·1; N, 13·2. $C_9H_9N_2ClO_2$ requires C, 50·8; H, 4·3; Cl, 16·7; N, 13·2%).

N-*Methyl*-p-*chlorobenzamide Oxime* (13).—A solution of *p*-chlorobenzohydroxamoyl chloride [16] (3·8 g) in ether (25 ml) was saturated at 0° with methylamine, then extracted with 2N-hydrochloric acid. The extract was neutralized (solid $NaHCO_3$) to give the *amide oxime* (1·5 g, 33%), m.p. 131—133°, raised to 136—137° by recrystallization from benzene, $\lambda_{max.}$ 269 nm (ε 3500) (Found: C, 51·9; H, 4·8; Cl, 19·1; N, 15·9. $C_8H_9ClN_2O$ requires C, 52·0; H, 4·9; Cl, 19·2; N, 15·2%).

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