The Synthesis of 3- and 5-Amino-1,2,4-Oxadiazoles. A Caveat

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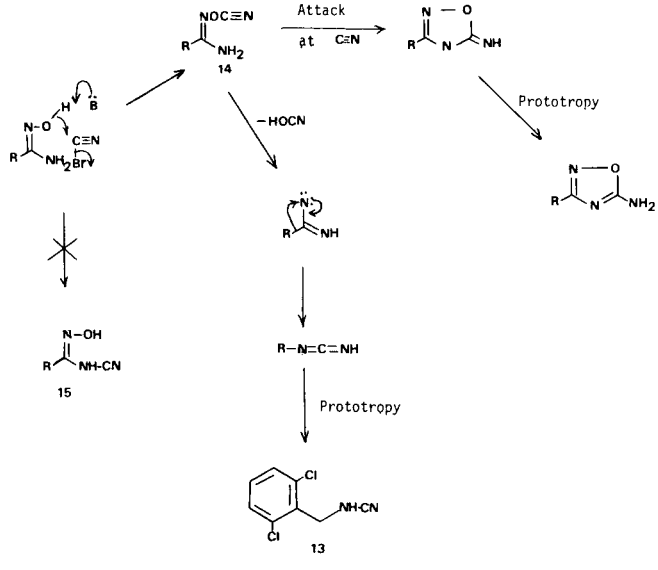
Evidence obtained from a single series of compounds demonstrates the need for care when assigning structures to amino-1,2,4-oxadiazoles using the methodology described in the literature. Certain synthetic methods can give rise to different position isomers in different series.

J. Heterocyclic Chem., **18**, 37 (1981).

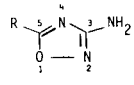
The chemistry of 3- and 5-amino-1,2,4-oxadiazoles (I and II), apart from the patent literature, is not extensively reported. However, conditions and methods for the unambiguous synthesis of both types of positional isomer have been defined independently by Huffmann and Schaeffer (1a,b), and Eloy and Deryckere (2). This article reports some results obtained in the course of a search for new pharmaceutic agents which are at variance with these authors' conclusions.

3-Amino-5(2,6-dichlorobenzyl)-1,2,4-oxadiazole **1a** (3,5) was synthesised initially from 2,6-dichlorophenylacetyl chloride (4) *via* the acylcyanamide **2**, followed by reaction with hydroxylamine hydrochloride in the presence of pyridine, in 77% overall yield. This reaction proceeds *via* the *N*-hydroxy-*N'*-acylguanidine **3a**, intermediates which in some cases, notably in our hands the α-methoxy-2,6-dichlorophenacyl compound **3b**, were isolable in a pure state. Alternatively, the oxadiazole **1a** could be obtained from hydroxylamine, and the acylisothiourea **4** (4) presumably once more by way of intermediate **3**. This mechanism is further supported by the fact that methoxylamine under these conditions condenses with the acylisothiourea **4** to give the *N*-methoxy-*N'*-acylguanidine **5** in 86% yield.



Scheme I (R = 2,6 - dichlorobenzyl)

Eloy, *et al.* (2), report that condensation of hydroxylamine with alkyl-*N*-cyanoamidines gives rise to 5-amino-1,2,4-oxadiazoles whereas the aryl analogues afford the corresponding 3-isomers. *N*-Cyano-2,6-dichlorophenyl-



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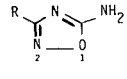

II

Comparative Physical Data on Compounds **1a** and **9**

Compound No.	M.p.	^{13}C Nmr Oxadiazole Ring Carbons (ppm)	^{13}C Nmr CH_2	Ir Cm^{-1} NH_2	Ir Cm^{-1} C=N
1a	186-187.5°	168.60 (C-3), 174.11 (C-5)	28.64	3370 3310 3220 3180	1630
9	233.5-234.5°	167.14 (C-5), 171.96 (C-3)	28.23	3320 3120	1665

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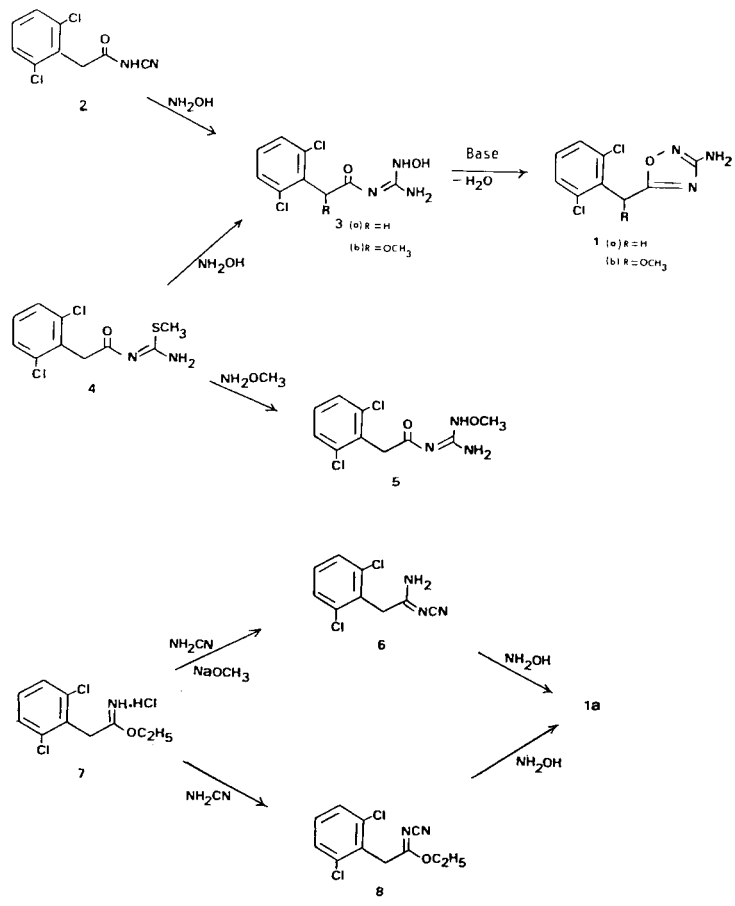


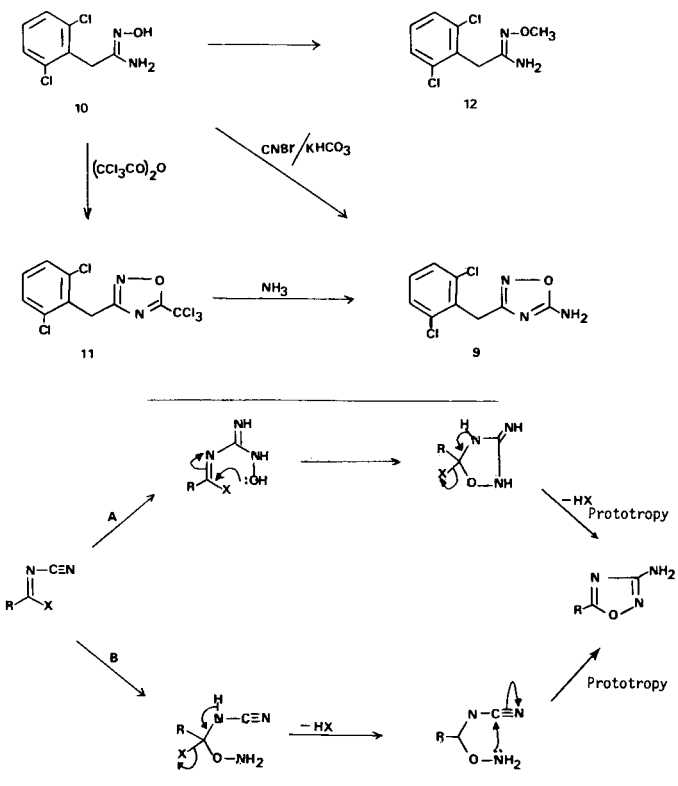
acetamidine **6** (5), however, obtained in 83% yield from the imidate base **7** with excess cyanamide, reacted cleanly with hydroxylamine to give the 3-amino compound **1a** in 96% yield, identical in all respects (ir, m.p., mixed m.p. tlc) with the product obtained by the above methods. This result is in direct contradiction to the conclusions of Eloy, *et al.* Under the same conditions, methoxylamine failed to react with *N*-cyanoacetamidine **6**.

According to both sets of authors, *N*-cyanoimidates react with hydroxylamine to give exclusively 5-amino-1,2,4-oxadiazoles regardless of the substituent on the imidate. However, once more in our series, only the 3-isomer **1a** was obtained. Ethyl *N*-cyano-2,6-dichlorophenylacetamidate **8**, synthesised from the imidate hydrochloride **7** and the cyanamide, reacted with hydroxylamine to afford compound **1a** in 96% yield. As in the case of the *N*-cyanoacetamidine, methoxylamine did not react with the *N*-cyanoimidate under these conditions.

The elusive 5-amino isomer **9** was eventually obtained by two seemingly unambiguous routes. The amidoxime **10**, prepared from 2,6-dichlorophenylacetonitrile and hydroxylamine hydrochloride in aqueous alcoholic carbonate in 75% yield, gave the required oxadiazole **9** in low (26%) yield on treatment with cyanogen bromide in methanol in the presence of potassium bicarbonate (6). Alternatively, condensation of trichloracetic anhydride with amidoxime **10** gave 5-trichloromethyl-1,2,4-oxadiazole **11** in 80% yield, which with ethanolic ammonia at 100°, smoothly afforded the oxadiazole **9** in essentially quantitative yield (7). The products obtained by these two procedures were identical and demonstrably different by all the usual criteria from the isomer obtained previously (see Table).

Amidoxime **10** was readily converted to its *O*-methyl ether **12**. This compound failed to react with cyanogen bromide under the conditions used from the amidoxime, suggesting that initial nucleophilic attack is by the hydroxyl group (or its conjugate anion) and not the amino function (Scheme I). Indeed, in one reaction of the amidoxime with cyanogen bromide, a product was isolated which corresponded (ir, microanalysis) to the cyanamide **13**, which might be construed as arising from loss of cyanic acid from intermediate **14** perhaps *via* a sort of aza-Curtius Reaction (see Scheme I), but not from an intermediate such as **15**.

No ready rationalisation of these results is evident; it seems unlikely that steric effects of the 2,6-dichloro group are an important factor, especially as the reactions proceed readily under mild conditions and in high yield. Inspection of CPK models of *N*-cyanoamidine **6** and



Scheme II (R = 2,6 - dichlorobenzyl)
(X = OEt or NH_2)

N-cyanoimidate **8** shows that the carbon of the nitrile group is readily accessible and the sp^2 carbon of the imidate group is not unduly sterically hindered so that nucleophilic attack at either of these sites is feasible. Condensation with free hydroxylamine, the only possible species present under our reaction conditions, can be explained in two ways: (i) initial attack by the hydroxylamine nitrogen at the nitrile carbon followed by cyclisation through attack by the oxygen at the imidate carbon (Route A, Scheme II); or (ii) initial attack by the hydroxylamine oxygen at the imidate carbon followed by addition of the nitrogen to the nitrile group (Route B, Scheme II). Contrary to what might be expected, the admittedly indirect and negative evidence offered by the attempted condensations with methoxylamine tends to support the second mechanism. It is of interest to note that the amino oxadiazole resulting from condensation of hydroxylamine with benzoylcyanamide (3-amino-5-phenyl-1,2,4-oxadiazole by analogy with the above results) corresponded [m.p. 164°, lit. (1a) m.p. 164-165.5°] to that obtained and assigned as such by Huffman and Schaeffer from hydroxylamine and *N*-cyanobenzamide.

These results, obtained in a single series, demonstrate that caution in assignment of structures to amino-1,2,4-oxadiazoles should be exercised and suggest the need for verification of structures already assigned to compounds in the literature.

EXPERIMENTAL

Melting points were determined on a Büchi SMP 20 (Tottoli) apparatus and are uncorrected. ^{1}H-nmr spectra were recorded on either a Perkin Elmer R12 or an R24 instrument. Ir spectra were recorded on a Perkin Elmer 297 spectrophotometer. Microanalyses were performed by the Service Analytique of L.E.R.S. Synthelabo.

3-Amino-5-(2,6-dichlorobenzyl)-1,2,4 oxadiazole (**1a**).

i. From Acylcyanamide (**2**).

2,6-Dichlorophenylacetyl chloride (4) (13.38 g., 0.06 mole) in acetone (50 ml.) was added slowly to a solution of cyanamide (2.64 g. excess) in water (50 ml.) at 10-15° (ice bath) containing 40% sodium hydroxide solution to bring the *p*H to 12; the *p*H was maintained at *ca.* 12 by occasional addition of 40% sodium hydroxide. When addition was complete the mixture was stirred until no acid chloride remained (0.5-1 hour); it was filtered from a small insoluble residue and acidified to *ca.* *p*H 2 with dilute hydrochloric acid, when the intermediate acylcyanamide **2** crystallised out. This was filtered, washed well with water, dried at the pump, and then dissolved in ethanol (125 ml.) containing hydroxylamine hydrochloride (6.72 g., 0.096 mole) and pyridine (25 ml.).

After stirring at room temperature overnight, the crystalline product which formed was filtered, washed with ethanol, then with ether and was dried, yield 9.65 g., m.p. 182-185° (66%), of compound **1a**. The reaction liquors were evaporated to dryness, diluted with water and basified with 40% sodium hydroxide. Further product (1.65 g.) precipitated on standing, total yield 11.30 g. (77%). The pure product was obtained on recrystallization from ethanol as colourless crystals, m.p. 186-187.5°.

Anal. Calcd. for $C_9H_7Cl_2N_3O$: C, 44.29; H, 2.89; Cl, 29.05; N, 17.21. Found: C, 44.33; H, 2.93; Cl, 29.00; N, 17.13. For spectral data see Table.

ii. From Acylisothiourea (**4**).

S-Methyl-*N*-(2,6-dichlorophenylacetyl)isothiourea (4) (1.3 g., 0.005 mole) and hydroxylamine hydrochloride (1.04 g., 0.015 mole) were dissolved in methanol (10 ml.) and 5.08*M* sodium methoxide solution (2.95 ml., 0.015 mole) was added. The mixture was stirred and refluxed for 0.75 hour (evolution of methanethiol) and then was diluted with water (*ca.* 70 ml.). The cooled solution was filtered to give 0.6 g. of compound **1a** (49%), which when recrystallised once from ethanol had m.p. 184-185°, mixed melting point with product obtained by Method i 184-185.5°.

N-methoxy-*N'*-(2,6-dichlorophenylacetyl)guanidine (**5**).

S-Methyl-*N*-(2,6-dichlorophenylacetyl)isothiourea (8.31 g., 0.03 mole), methoxylamine hydrochloride (7.5 g., 0.09 mole) and 5.5*M* sodium methoxide solution (16.4 ml., 0.09 mole) in methanol (175 ml.) were refluxed together for 0.75 hour (evolution of methanethiol). The solution was filtered and the filtrate was evaporated to dryness. The crystalline residue was taken up with water and filtered. The solid was washed well with water and dried at the pump. The crude product was recrystallised directly from ethyl acetate/hexane to give compound **5**, yield 1st crop 6.17 g., m.p. 187-188°, 2nd crop 0.97 g., m.p. 182°, total yield 7.14 g. (86%). A sample recrystallised for analysis had m.p. 187.5-188°; nmr (deuteriochloroform): 3.75 (3H, s, OCH_3), 4.16 (2H, s, CH_2), 6.22 (2H, bs, NH_2), 7.16-7.53 (3H, m, Ar*H*), 7.97 (1H, bs, NH). The signals at 6.22 and 7.97 ppm disappeared on exchange with deuterium oxide.

Anal. Calcd. for $C_{10}H_{11}Cl_2N_3O_2$: C, 43.50; H, 4.02; Cl, 25.68; N, 15.22. Found: C, 43.49; H, 3.93; Cl, 25.85; N, 15.33.

Ethyl 2,6-Dichlorophenylacetimidate Hydrochloride (**7**).

Dry hydrogen chloride gas was bubbled through a suspension of

2,6-dichlorophenylacetonitrile (2.23 g., 0.012 mole) in dry ether (50 ml.) and ethanol (0.61 g., 0.0132 mole) cooled in an ice bath. The nitrile slowly dissolved to give a clear solution which was then stirred 65 hours at 0°. The crystalline product **7** (2.25 g., m.p. 216.5-218°) was filtered, washed well with dry ether and dried *in vacuo*. A second crop (0.2 g.), m.p. 214.5-216.5°, was obtained on dilution of the mother liquors with ether (total yield 2.47 g.) (77%); ir (nujol mull): 1660 cm^{-1}.

Anal. Calcd. for $C_{10}H_{11}Cl_2NO \cdot HCl$: C, 44.72; H, 4.50; Cl (total) 39.60; N, 5.22; Cl^-, 13.20. Found: C, 44.78; H, 4.61; Cl (total), 39.59; N, 5.21; Cl^- 13.16.

N-Cyano-2,6-dichlorophenylacetamidine (**6**).

Ethyl 2,6-dichlorophenylacetimidate hydrochloride (10.74 g., 0.04 mole) and cyanamide (8.4 g., 0.2 mole) were dissolved in methanol (75 ml.) and 5.08*M* sodium methoxide solution (7.9 ml., 0.04 mole) was added. The mixture was stirred for 5 hours at 40°, then diluted with water, allowed to stand and the product was filtered. The solid was washed well with water and then dried *in vacuo* yielding the desired product **6** (7.6 g.) (83%), m.p. 208.5-211°. A sample recrystallised from ethanol had m.p. 212.5-213.5°; ir (nujol mull): 3270, 3110, 2230 (w), 2195 (s), 1675 cm^{-1}; nmr (DMSO-d_6): 4.10 (2H, s, CH_2), 7.25-7.7 (3H, m, ArH), 8.60 (2H, bs, NH_2). The latter signal disappeared on exchange with deuterium oxide.

Anal. Calcd. for $C_{19}H_7Cl_2N_3$: C, 47.40; H, 3.09; Cl, 31.09; N, 18.42. Found: C, 47.37; H, 3.25; Cl, 30.96; N, 18.51.

Ethyl-*N*-cyano-2,6-dichlorophenylacetimidate (**8**).

Ethyl-2,6-dichlorophenylacetimidate hydrochloride (13.43 g., 0.05 mole) and cyanamide (10.5 g., 0.25 mole) were heated at 40° in ethanol (100 ml.) for 20 hours. The ethanol was removed, the residue taken up with dichloromethane and the mixture washed once with water. The dried (magnesium sulfate) organic solution was evaporated to give an oily solid which was triturated with pentane and filtered, to give a white crystalline solid (6.64 g.). This was recrystallised from hexane, after filtration to remove an insoluble impurity, to give pure **8** as colourless crystals, m.p. 74-75.5° (5.95 g.) (46%). A sample recrystallised from hexane had m.p. 76.5-78°; ir (nujol mull): 2195 (s), 1605 (s) cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}Cl_2N_2O$: C, 51.39; H, 3.92; Cl, 27.58; N, 10.89. Found: C, 51.37; H, 3.99; Cl, 27.60; N, 10.78.

Action of Hydroxylamine on *N*-Cyanoamidine (**6**).

N-Cyanoamidine **6** (0.46 g., 0.002 mole), hydroxylamine hydrochloride (0.21 g., 0.003 mole) and triethylamine (0.31 g., 0.003 mole) were refluxed together for 3.5 hours in methanol. The solution was diluted with water and the precipitated solid was filtered, washed well with water and dried (0.45 g.) (92%), m.p. 186-187°, mixed melting point with 3-amino oxadiazole **1a**, 186-187°. Ir and tlc behaviour of the products was identical. The product was obtained in similar yield if the reaction mixture was allowed to stand for 17 hours at room temperature.

Action of Hydroxylamine on *N*-Cyanoimidate (**8**).

The *N*-cyanoimidate **8** (0.52 g., 0.002 mole), hydroxylamine hydrochloride (0.15 g., 0.0022 mole) and triethylamine (0.22 g., 0.0022 mole) were stirred together for 17.5 hours at room temperature in methanol (10 ml.). A precipitate started to form after just 0.5 hour. Water was added to the solution, the product was filtered, washed well with water and dried (0.45 g.), m.p. 184.5-186°. A second crop (0.02 g.) was obtained on concentration of the mother liquors (total yield 0.47 g.) (96%). Mixed melting point with 3-amino-1,2,4-oxadiazole **1a** was 185.5-187°. Ir and tlc behaviour of the products was identical.

2,6-Dichlorophenylacetamidoxime (**10**).

2,6-Dichlorophenylacetonitrile (18.6 g., 0.1 mole) and hydroxylamine hydrochloride (8.7 g., 0.125 mole) were stirred and refluxed for 6 hours in ethanol containing potassium carbonate (13.8 g., 0.1 mole) and water (25 ml.). On cooling the product crystallised, the solution was then diluted with water, and was filtered. After it had been washed well with water, the solid product was dried and recrystallised from ethyl acetate/hexane, m.p. 173-174.5° (13.02 g.). A second crop (3.37 g.), m.p. 156.5-161.5° was obtained from the crystallisation liquors (total yield 16.39 g.) (75%); nmr (DMSO-d_6): 3.80 (2H, s, CH_2), 5.58 (2H, bs, NH_2), 7.2-7.7 (3H, m, ArH), 9.1 (1H, s, OH); ir (nujol mull): 3470 (s), 3340, 1665 cm^{-1}.

Anal. Calcd. for $C_8H_8Cl_2N_2O$: C, 43.86; H, 3.68; Cl, 32.37; N, 12.79; O. 7.30. Found: C, 43.91; H, 3.68; Cl, 32.35; N, 12.56; O, 7.32.

O-Methyl-2,6-dichlorophenylacetamidoxime (**12**).

The above amidoxime **10** (2.19 g., 0.01 mole) in dry DMF (5 ml.) was slowly added to a suspension of sodium hydride (50% dispersion in oil, 0.53 g., 0.011 mole) in DMF (5 ml.). Further DMF (25 ml.) was added to control the frothing which resulted, due to the insoluble nature of the sodium salt. When reaction had ceased (*ca.* 0.5 hour) a solution of methyl iodide (1.55 g., 0.011 mole) in DMF (5 ml.) was added. The solution became warm and clear. After it had stirred for 0.75 hour at room temperature, the solvent was removed *in vacuo*, the residue was taken up with water and acidified with 2*N* hydrochloric acid. The acid solution was extracted twice with ether, then basified with solid potassium carbonate. The solid product which formed was extracted into ether and the aqueous layer extracted once more with ether. The combined dried (magnesium sulfate) extracts were evaporated to give the crude product (1.9 g.) (81%) as an oil which rapidly crystallised. Recrystallisation from hexane gave colourless plates, m.p. 81.5-82.5° (1.37 g.) (59%). A sample recrystallised for analysis had m.p. 82.5-83.5°; nmr (deuteriochloroform): 3.70 (3H, s, OCH_3), 3.80 (2H, s, CH_2), 4.47 (2H, bs, NH_2), 6.9-7.35 (3H, m, ArH). The signal at 4.47 ppm disappeared on shaking with deuterium oxide; ir (nujol mull): 3480 (s), 3310 (b), 3150, 1640 cm^{-1}.

5-Trichloromethyl-3(2,6-dichlorobenzyl)-1,2,4-oxadiazole (**11**).

2,6-Dichlorophenylacetamidoxime (2.2 g., 0.01 mole), trichloroacetic acid (6.5 g., *ca.* 4 molar equivalents) and trichloroacetic anhydride (6.5 g., *ca.* 2 molar equivalents) were heated to 115° and kept 20 minutes at this temperature. The mixture was diluted with water and cooled. The crystalline product was filtered, washed well with water, dried and recrystallised from hexane (2.07 g.), m.p. 87-88°. A second crop (0.61 g.), m.p. 87-88° was obtained on concentration of the mother liquors (total yield 2.67 g.) (77%). A sample was recrystallised from methanol for analysis, m.p. 86.5-87.5°; ir (nujol mull): 1570 (s) cm^{-1}.

Anal. Calcd. for $C_{10}H_5Cl_5N_2O$: C, 34.67; H, 1.45; Cl, 51.17; N, 8.09; O, 4.62. Found: C, 34.78; H, 1.63; Cl, 51.00; N, 8.24; O, 4.50.

5-Amino-3(2,6-Dichlorobenzyl)-1,2,4-oxadiazole (**9**).

i. From Amidoxime (**12**).

Cyanogen bromide (0.58 g., 5.5 mmoles) was added to a stirred solution of 2,6-dichlorophenylacetamidoxime (1.1 g., 5 mmoles) and potassium bicarbonate (0.55 g., 5.5 mmoles) in methanol (50 ml.) and the mixture was stirred for 1.25 hours at room temperature. The solution was diluted with water, the white solid which precipitated was filtered, washed well with water and dried *in vacuo* (0.85 g.). Recrystallisation from aqueous ethanol afforded 0.32 g. of crude oxadiazole **9** (26%) which was recrystallised from ethanol as colourless prisms, m.p. 232-234.5°. Evaporation of the ethanol from the initial crystallisation liquors afforded a white crystalline solid (0.21 g.) which was pure on tlc.

Anal. Calcd. for $C_8H_6Cl_2N_2$: C, 47.79; H, 3.01; Cl, 35.27; N, 13.93. Found: C, 47.79; H, 3.05; Cl, 35.04; N, 13.99.

This result, together with the ir spectrum [3180 (b), 2220 (s) cm^{-1}], suggested that this was 2,6-dichlorobenzyl cyanamide **13**.

ii. From Oxadiazole (**11**).

5-Trichloromethyl-3(2,6-dichlorophenyl)-1,2,4-oxadiazole (5.19 g., 0.015 mole) was heated for 2 hours in an autoclave at 100° in ethanol (100 ml.) saturated with ammonia. The solution was diluted with water (*ca.* 100 ml.) cooled in an ice bath and filtered to give oxadiazole **9** (3.25 g., 89%) as a pale yellow solid, m.p. 230-235°, identical with the product obtained by method i above. The pure compound was obtained by recrystallisation from methanol and had m.p. 233.5-235.5°. For spectral data see Table.

Anal. Calcd. for $C_9H_7Cl_2N_3O$: C, 44.29; H, 2.89 Cl, 29.05; N, 17.21. Found: C, 44.53; H, 2.97; Cl, 29.02; N, 16.98.

1[α-Methoxy-2,6-dichlorophenylacetyl]-2-hydroxyguanidine Hydrochloride (**3b**) (8).

When α-methoxy-2,6-dichlorophenylacetyl chloride (9) was submitted to the procedure used above for the synthesis of compound **1**, no precipitation of the oxadiazole occurred during the condensation with hydroxylamine. Removal *in vacuo* of the solvents followed by trituration of the residue with 1:1 isopropanol-water mixture afforded the crystalline title compound base which was filtered, dried and recrystallised from isopropanol/diisopropylether, m.p. 165°; ir (potassium bromide): 3480, 3360, 1705, 1680, 1660 cm^{-1}.

The hydrochloride, m.p. 210°, was obtained in an overall yield of 60% by addition of ethereal hydrogen chloride to a methanolic solution of the base followed by further dilution with ether; ir (potassium bromide): 3300 + broad absorption *ca* 3100, 1715, 1670, 1615, 1560, 1550 cm^{-1}; nmr (DMSO-d_6): 3.38 (3H, s, OCH_3), 5.73 (1H, s, C*H*), 7.45 (3H, s, ArH), 8.85 (2H, bs, NH_2), 10.20 (1H, bs, NH), 11.20 (1H, bs, OH).

Anal. Calcd. for $C_{10}H_{11}Cl_2N_3O_2 \cdot HCl$: C, 36.55; H, 3.68; Cl (total), 32.37; N, 12.79; Cl^-, 10.79. Found: C, 36.57; H, 3.61; Cl (total), 32.20; N, 12.85; Cl^-, 10.85.

The compound cyclised to the 3-amino-1,2,4-oxadiazole **1b**, on heating in 2*N* sodium hydroxide solution. Thus a solution of the above base (5 g., 0.017 mole) in 2*N* sodium hydroxide (100 ml.) was heated for 2 hours at 70°. The precipitated product was filtered, washed with water dried and recrystallised from DMF-water (3.2 g.) (69%), m.p. 219°; ir (potassium bromide): 3320, 3310, 3210, 1630, 1585, 1560 cm^{-1}; nmr (DMSO-d_6): 3.43 (3H, s, OCH_3), 6.19 (3H, s, + bs, C*H* + NH_2), 7.49 (3H, s, Ar*H*). The signal at 6.19 ppm collapsed to a 1H singlet on exchange with deuterium oxide.

Anal. Calcd. for $C_{10}H_9Cl_2N_3O_2$: C, 43.82; H, 3.31; Cl, 25.87; N, 15.33. Found: C, 44.12; H, 3.49; Cl, 25.77; N, 15.16.

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(8) I thank Mr. G. Cremer of these laboratories for the synthesis of these two compounds.

(9) This compound was synthesised from ethyl 2,6-dichloromamdelate (10), *via* the following sequence: (i) sodium hydride/DMF, methyl iodide 91%; (ii) potassium hydroxide, 95%; (iii) thionyl chloride.

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