Synthesis, Spectroscopic Studies and the Mechanism of Formation of 4,5-Dihydro-1,2,4-oxadiazoles

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Nine 4,5-dihydro-1,2,4-oxadiazoles, **2a-i**, were synthesized by the reaction of benzamidoximes, **1a-i**, with aliphatic and aromatic aldehydes. None of these compounds were encountered in the literature. The ultraviolet, infrared and proton magnetic resonance spectral studies supported the cyclic structure. Structure determination of a chloral-benzamidoxime adduct, **15**, by X-ray crystallography helped us to suggest the mechanism of formation of 4,5-dihydro-1,2,4-oxadiazole from benzamidoxime and an aldehyde. Substances **2a,b,d,e,g,h**, showed some activity against fungus *Neurospora crassa*. Compound **2e** also presented growth inhibition in *Mycobacterium smegmatis*.

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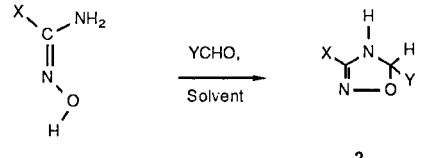
Introduction.

Several 1,2,4-oxadiazoles, especially those with amino or substituted amino groups as side chains, are known to possess biological activity [1]. However, 4,5-dihydro-1,2,4-oxadiazoles have not been much investigated for their pharmacological actions. In 1967, Ainsworth and collaborators [2] examined the action of some of them against *Nematospiroides dubius* but the results were negative. 3,4,5-Trisubstituted 5-hydro-1,2,4-oxadiazoles demonstrated bronchodilatory, anticholinergic, hypertensive, analgesic, anti-inflammatory, diuretic, antiulcer, vasodilatory, respiratory analeptic, and sedative properties [3]. There has been continuing interest in our laboratory in these compounds and therefore we prepared nine new substances **2a-i**, six with aryl groups at position 3 and alkyl at C-5 and three having 3,5-diaryl groups as substituents. We undertook this work in order to obtain more understanding about these heterocyclic compounds. This article, therefore, describes the synthesis, the mechanism of formation of 4,5-dihydro-1,2,4-oxadiazoles, the structure of a chloral-benzamidoxime adduct, and the preliminary biological activity tests of **2a,b,d,e,g,h**.

Results and Discussion.

The synthesis was achieved by dissolving the appropriate amidoxime (Scheme 1) in a small quantity of alcohol and adding sufficient water to make the solution slightly cloudy. If the solid separates, a little more alcohol is poured in to keep the solution clear. At this point the aliphatic aldehyde is added in excess. The contents are then stirred at room tempature for an extended period of time

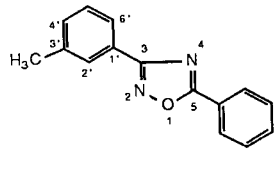
Scheme 1



1 2

	X	Y		X	Y
a,	o-Tolyl	CH_3	**f,**	m-Tolyl	Ph
b,	o-Tolyl	CH_3CH_2	**g,**	p-BrPh	CH_3
c,	o-Tolyl	Ph	**h,**	p-BrPh	CH_3CH_2
d,	m-Tolyl	CH_3	**i,**	p-BrPh	Ph
e,	m-Tolyl	CH_3CH_2			

before work-up. The reaction of amidoxime and benzaldehyde was carried out in acetic acid at room temperature. After the reaction was over, the solvents evaporated under vacuum and the residue chromatographed to obtain the pure product. In one case, **2f**, after the completion of the reaction, air was bubbled in the flask for a long time to transform excess benzaldehyde to benzoic acid, and later



3

the contents were treated with sodium bicarbonate to remove the acids before chromatography. In this experi-

ment, only 5-phenyl-3-(*m*-tolyl)-1,2,4-oxadiazole, **3**, was obtained. Thus, it is clear that 4,5-dihydro-1,2,4-oxadiazole formed initially was transformed to **3** because of oxygen in the air. Therefore, care must be taken in preparing 5-aryl-4,5-dihydrooxadiazoles.

The uv spectra of **2a-c** in solutions (methanol) showed maxima at 225 nm (not well defined) and 271 nm (Table 1) due to $\pi \rightarrow \pi^*$ transitions. The reported [4] maxima for the compound, 5,5-pentamethylene-3-*p*-tolyl-Δ^2-1,2,4-oxadiazoline, are 230 and 285 nm (ethanol). It is obvious therefore that the *ortho* methyl group causes steric problem

Table 1

Ultraviolet Spectral Properties of 4,5-Dihydro-1,2,4-oxadiazoles [a]

Compound	λ max (nm)	ε	Compound	λ max (nm)	ε
2a	225.0	—	**2f**	230.0	15,658
	271.0	3,345		284.0	3,416
2b	225.0	—	**2g**	240.5	19,664
	271.0	2,692		295.0	5,035
2c	225.0	—	**2h**	240.5	24,872
	268.0	2,261		295.0	6,154
2d	230.0	16,111	**2i**	241.0	22,800
	285.0	4,722		295.0	4,890
2e	230.0	16,371			
	285.0	4,722			

[a] Methanol was used as the solvent for **2a-c,g,h** and ethanol for **2d-f, i**.

with the heterocyclic ring an upsets planarity. Compounds **2g-i** on the other hand absorbed at 240.5 and 295 nm. The spectra are similar to that for 5,5-pentamethylene-3-*p*-bromophenyl-Δ^2-1,2,4-oxadiazoline [4].

The infrared spectra (chloroform) of **2a-c** showed absorption around 3420 cm^{-1} due to >NH and another vibration between 1610-1640 cm^{-1}. The latter exhibited splitting and these are presumably due to C=N and C=C vibrations. For **2g-i**, there were unresolved doublets in the same region. Compound **2i** was not soluble in chloroform, so a (potassium bromide) pellet was used to record the spectrum. Mathis and collaborators [5] found C=N absorption at 1596 cm^{-1} for certain Δ^2-1,2,4-oxadiazolines.

The nmr spectra of 3-aryl-5-alkyl-4,5-dihydrooxadiazoles had characteristic H-5 signals in the range expected [6]. The methine protons of **2c,f,i** appeared around δ 6.4 (about 1.0 ppm downfield compared to the C-5 alkyl substituents). This is also consistent with the C-5 phenyl substituent. In fact, the nmr spectra support the cyclic structure. Table 2 records the chemical shifts of all the protons of **2**.

Although the first oxadiazoline was prepared [7] in 1884 and since then many more of them have been synthesized and their properties studied [1,8], the mechanism of its formation by the reaction of an amidoxime with an aldehyde has not yet been settled. Only in 1973, Malavaud and col-

Scheme 2

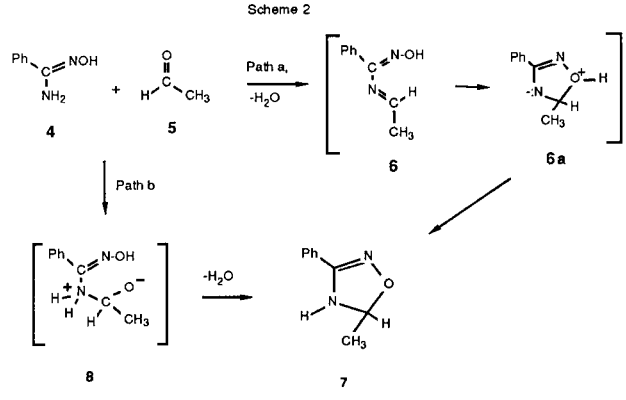


Table 2

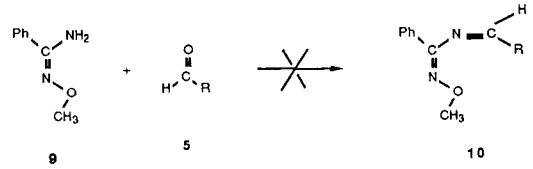
60 MHz Proton Resonance Spectra of 4,5-Dihydro-1,2,4-oxadiazoles, **2a-i**, in ppm [a]

Compound	C_5-C*H*$_3$	C_5-CH_2C*H*$_3$	Ar-C*H*$_3$	$-CH_2-$	>CH–	>NH	Ar
2a	1.50 d	—	2.50 s	—	5.64 m	4.58 b	7.00-7.25 m (3H) 7.25-7.46 m (1H)
2b	—	0.87 t	2.33 s	1.23-1.87 m	5.40 m	5.50 b	6.80-7.40 m (4H)
2c	—	—	2.52 s	—	6.39 d	5.10 b	6.93-7.67 m (9H)
2d	1.49 d	—	2.33 s	—	5.63-5.93 m	5.10 b	7.13-7.37 m (2H) [b] 7.37-6.67 m (2H) [c]
2e	—	1.00 t	2.33 s	1.62-2.00 m	5.62 q	4.80 b	7.17-7.33 m (2H) [b] 7.33-7.67 m (2H) [c]
2f	—	—	2.32 s	—	6.37 s	5.00 b	7.00-7.57 m (9H)
2g	1.48 d	—	—	—	5.70 m	4.59 b	7.40 s (4H)
2h	—	0.97 t	—	1.65 m	5.45 m	4.98 b	7.38 s (4H)
2i	—	—	—	—	6.45 s [d]	2.53 b [e]	7.20-8.00 (9H)

[a] Compounds **2a-h** were run in deuteriochloroform and **2i** in a mixture of deuteriochloroform and acetone-d_6. [b] *meta* and *para* protons. [c] *ortho* protons. [d] A very dilute solution in deuteriochloroform showed a doublet. [e] Exchanged when deuterium oxide was added in the nmr tube.

laborators [9] attempted to explain the mechanism and considered two possibilities: 1) formation of an aldimine **6** (Scheme 2) as an intermediate followed by cyclization to give compound **2** through path *a*, 2) formation of an intermediate **8** where presumably the hydroxyl oxygen of the oxime part attacks the acetal carbon in the S_N2 manner to displace a molecule of water (path *b*). In both cases, formation of an N-C linkage between -NH_2 and carbonyl carbon was thought a reasonable step. In order to see the validity of the mechanism, the French researchers tried to react *O*-methylbenzamidoxime, **9**, with acetaldehyde **5a** without any success. Hence, it is obvious that aldimine is not the intermediate in the reaction of benzamidoxime and an aliphatic aldehyde (Scheme 3).

Scheme 3



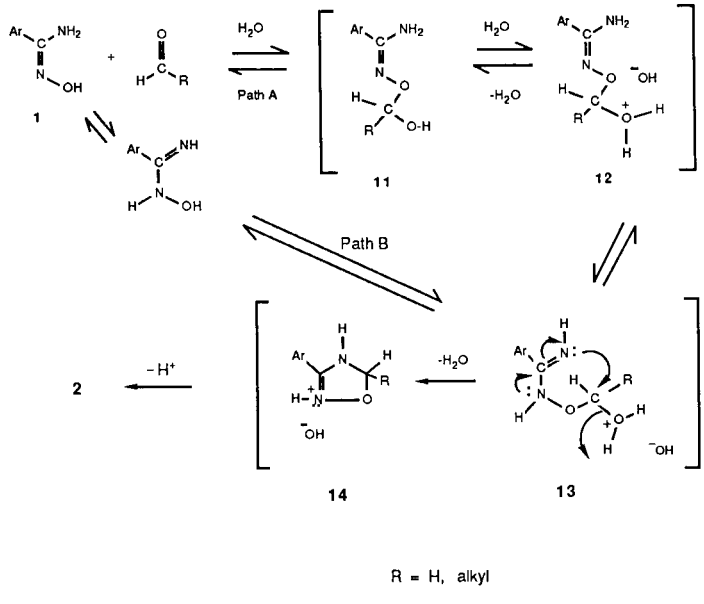
a, R = CH_3

b, R = CH_3CH_2

We also tried to condense propionaldehyde **5b** with **9** in order to prepare **10b** but only the starting material was recovered [10]. This led us to believe that a protonated hemiacetal **13** could be the intermediate [4]. The discussion below will show that it is the hemiacetal resulting from reaction of the -OH function of the amidoxime with the aldehyde which is the intermediate and should eventually form oxadiazoline.

Scheme 4

Mechanism of Formation of 4,5-Dihydro-1,2,4-oxadiazoles

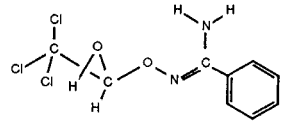


R = H, alkyl

Compound **1**, in its amino-oxime form, initially reacts with an aliphatic aldehyde to provide an unstable hemiacetal, **11** (Path A), protonation of which with water yields **12** (Scheme 4). Alternatively, **1**, in its tautomeric state, may combine with the aldehyde followed by protonation (Path B). In any event, the conformation of the intermediate requries an arrangement as shown in **13** for effective cyclization. Once **14** is formed, it can readily lose a proton to afford **2**.

The reaction of arylamidoxime with an aromatic aldehyde has been carried out in glacial acetic acid which functioned as a catalyst as well as a solvent.

An attempt to isolate the intermediate hemiacetal failed. However, the reaction of benzamidoxime with chloral provided a crystalline compound in almost quantitative yield. Recrystallization gave mp 135°. Reaction of chloral with benzamidoxime was thought [11] to provide a 1:1 complex, but its structure was never determined. An X-ray analysis [12] of this compound conclusively indicated a hemiacetal structure **15**. The formation of **15** is strong and clear evidence for the proposed mechanism. The details of the X-ray results will be published elsewhere.



15

Our attempts to cyclize **15** to a 4,5-dihydro-1,2,4-oxadiazole failed. Substance **15** remained unaffected when stirred for 3 days at room temperature in glacial acetic acid. At higher temperatures (70, 85 and 100°), **15** changed to resinous material from which no product could be isolated. Refluxing **15** in dichloromethane containing boron trifluoride etherate produced presumably the starting benzamidoxime and other products but not the expected cyclic one. A molecular model of **15** having the necessary arrangement (similar to **13**) shows the serious steric problems due to three chlorine atoms disfavoring cyclization.

Biological Activity Tests.

Compounds, **2a-i**, were tested against bacteria, *Escherichia coli, Bacillus subtilis, Staphylococcus aureus, Streptococcus fecalis* and *Mycobacterium smegmatis* but no activity was observed. *Candida albicans* also did not respond to these oxadiazolines. Compounds **2a,b,d,e,g,h**, however, showed weakly positive results when tested against fungus *Neurospora crassa*; 100 μg/ml of a solution (methanol-water, 1:4) produced partial inhibition of growth, whereas 300 μg/ml inhibited the growth completely. Compound **2e** presented similar growth inhibitory effect in *Mycobacterium smegmatis.*

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Elemental analyses of compound **2a-e,g-i** were performed by Dr. Riva M. da Cruz (Instituto de Química, Universidade de São Paulo, São Paulo), of substance **2f** by Centro de Pesquisas de Rhodia, Paulinia, S.P., and of **3** by Petrobrás, Rio de Janeiro. Ultraviolet spectra were recorded either on Carl-Zeiss, model DMR 21, or on Cary 18 Varian Associates. Infrared spectra were obtained on Perkin-Elmer, Infracord model 337. Proton magnetic resonance spectra were measured on Varian A-60, T-60 or XR-100 MHz using tetramethylsilane as internal reference and deuteriochloroform as solvent unless otherwise stated.

5-Methyl-3-(*o*-tolyl)-4,5-dihydro-1,2,4-oxadiazole (**2a**).

To *o*-tolylamidoxime (0.50 g, 3.33 mmoles) in ethanol (3.0 ml) was added distilled water (20 ml) and then acetaldehyde (4.0 ml). The mixture was stirred for 4 days in a stoppered flask at room temperature. Extraction of the product from chloroform, drying (sodium sulfate) and solvent removal left a semi-solid mass. Chromatography of this material over silica gel using benzene-hexane (1:1) gave **2a** which upon crystallization from benzene-*n*-hexane provided 0.10 g (17%) of pure crystals, mp 66-66.5°.

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.18; H, 6.86; N, 15.90. Found: C, 67.94; H, 6.41; N, 15.80.

5-Ethyl-3-(*o*-tolyl)-4,5-dihydro-1,2,4-oxadiazole (**2b**).

The same method as described above was followed except that only 10 ml of water and 3.5 ml of propionaldehyde were employed for 0.5 g of *o*-tolylamidoxime. Chromatography over silica gel followed by work-up and crystallization from ethyl acetate-hexane yielded 0.22 g (35%) of **2b**, mp 51°.

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.43; H, 7.42; N, 14.73. Found: C, 69.62; H, 7.56; N, 14.80.

5-Phenyl-3-(*o*-tolyl)-4,5-dihydro-1,2,4-oxadiazole (**2c**).

o-Tolylamidoxime (0.50 g, 3.33 mmoles) was dissolved in glacial acetic acid (2.50 ml) and freshly distilled benzaldehyde (2.0 ml) was added. The contents were stirred at room temperature for a period of four days under nitrogen. The liquids were then evaporated under vacuum. The remaining material was chromatographed over silica gel. The fractions containing **2c** were combined, solvent evaporated and the solid crystallized from benzene-*n*-hexane to afford 0.35 g (44%) of the compound with mp 100-101°.

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.54; H, 5.50; N, 11.72.

5-Methyl-3-(*m*-tolyl)-4,5-dihydro-1,2,4-oxadiazole (**2d**).

The method described for **2a** was adopted. Starting from **1d** (0.50 g, 3.33 mmoles), and work-up provided a product which after chromatography over silica gel yielded 0.15 g (26%) of **2d**. Crystallization from chloroform-hexane gave pure product having mp 95-95.5°.

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.18; H, 6.86; N, 15.90. Found: C, 68.29; H, 6.49; N, 15.75.

5-Ethyl-3-(*m*-tolyl)-4,5-dihydro-1,2,4-oxadiazole (**2e**).

Starting from *m*-tolylamidoxime (0.50 g, 3.33 mmoles) and following the procedure described in **2b**, we obtained the product which after chromatography gave 0.35 g (55%) of **2e**. Crystallization from chloroform-hexane provided pure material, mp 62°.

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.43; H, 7.42; N, 14.73. Found: C, 69.11; H, 7.16; N, 15.06.

5-Phenyl-3-(*m*-tolyl)-4,5-dihydro-1,2,4-oxadiazole (**2f**).

m-Tolylamidoxime (0.50 g, 3.33 mmoles), benzaldehyde (1.0 ml), and glacial acetic acid (4.0 ml) were stirred for 5 days at room temperature. Removal of the liquids left a residue. Liquid chromatography on silica gel eluting first with *n*-hexane and then with hexane-chloroform afforded the desired compound still contaminated with a trace quantity of benzaldehyde. Therefore, this material was dissolved in methylene chloride, some sodium bisulfite added and stirred for an hour. Filtration and solvent evaporation yielded 0.20 g (25%) of **2f**. This was recrystallized from ether-petrol ether (40-60°) and had mp 99-100°.

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.40; H, 5.90; N, 11.70.

3-(*p*-Bromophenyl)-5-methyl-4,5-dihydro-1,2,4-oxadiazole (**2g**).

Essentially, the procedure was the same as described for the preparation of **2a** except that the quantity of the solvents was changed. Thus, *p*-bromobenzamidoxime (1.0 g, 4.6 mmoles) in a mixture of alcohol (3 ml) and water (18 ml) was treated with acetaldehyde (4 ml) and stirred for 3 days. Chromatography followed by work-up furnished 0.41 g (37%) of **2g** after crystallization from ethanol and water, mp 144-145°.

Anal. Calcd. for $C_9H_9BrN_2O$: C, 44.81; H, 3.73; N, 11.62. Found: C, 45.00; H, 3.73; N, 11.66.

3-(*p*-Bromophenyl)-5-ethyl-4,5-dihydro-1,2,4-oxadiazole (**2h**).

Following the method described above and using propionaldehyde instead of acetaldehyde, we obtained, after normal work-up, **2h** in 76% yield. When crystallized from alcohol-water, the compound melted at 110-111°.

Anal. Calcd. for $C_{10}H_{11}BrN_2O$: C, 47.24; H, 4.33. Found: C, 47.18; H, 4.28.

3-(*p*-Bromophenyl)-5-phenyl-4,5-dihydro-1,2,4-oxadiazole, (**2i**).

We adopted the same procedure as shown for **2c**. Starting from **1i** (1.0 g), glacial acetic acid (2.5 ml) and benzaldehyde (4.0 ml) followed by work-up provided a compound weighing 0.44 g (31%). Crystallization from alcohol gave the mp 175-176°.

Anal. Calcd. for $C_{14}H_{11}BrN_2O$: C, 55.45; H, 3.66; N, 9.23; Br, 26.38. Found: C, 55.35; N, 3.89; N, 9.20; Br, 26.69.

5-Phenyl-3-(*m*-tolyl)-1,2,4-oxadiazole (**3**).

m-Tolylamidoxime (0.50 g, 3.33 mmoles) was dissolved in 8 ml of glacial acetic acid and 3 ml of freshly distilled benzaldehyde added. This mixture was stirred at room temperature for 4 days. Air was then bubbled in the solution to transform the remaining benzaldehyde to benzoic acid. The acids were neutralized with a saturated aqueous solution of sodium bicarbonate and extracted with chloroform. The solvent layer was taken in a round bottom flask, some solid bicarbonate added and stirred overnight in order to remove benzoic acid. Filtration followed by solvent removal and subsequent chromatography over silica gel using initially *n*-hexane and gradually increasing the polarity by adding chloroform provided the required oxadiazole. Crystallization and recrystallization from alcohol-water gave 0.2 g (25%) of crystals, mp 87-88°; ^{1}H-nmr (deuteriochloroform): 90 MHz δ 2.43 (s, 3H, CH_3); four sets of narrow multiplets: 1) 7.30-7.43 (2H, H-2′ and H-6′), 2) 7.90-8.07 (2H, H-4′ and H-5′), 3) 7.43-7.67 (3H, *meta* and *para* protons of Ph group), and 4) 8.10-8.36 (2H, *ortho* protons of Ph ring).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.24; H, 5.12; N, 11.86. Found: C, 76.30; H, 5.00; N, 11.70.

O-(2,2,2-Trichloro-1-hydroxyethyl)benzamidoxime (**15**).

Benzamidoxime (0.5 g, 3.7 mmoles) was dissolved in dry ether and chloral (0.545 g, 3.7 mmoles), freshly generated from chloral hydrate, added to the solution and refluxed for 3-4 hours under dry conditions. After cooling, ether was evaporated and a quantitative yield of hemiacetal, **15**, was obtained. This was dissolved in a large quantity of benzene at 60° and filtered. Cooling the solvent provided crystals, mp 135°, lit [11] mp 135°.

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REFERENCES AND NOTES

† Taken in part from the M.S. thesis of M.V.S.F.

[1] L. B. Clapp, "Comprehensive Heterocyclic Chemistry", Vol **6**, A. R. Katritzky, C. W. Rees and K. T. Potts, eds, Pergamon Press Ltd., Oxford, England, 1984, p 365, and references cited therein.

[2] C. Ainsworth, W. E. Buting, J. Davenport, M. E. Callender and M. C. McCowen, *J. Med. Chem.*, **10**, 208 (1967).

[3] C. Fauran, H. Bergeron, G. Raynaud, J. Thomas and J. Eberle, *French Demande,* 2,262,513 (Cl. A61K, CO7D), 26 Sept., 1975, Appl. 74 07, 002, 01 March, 1974; *Chem. Abstr.*, **84**, P121843v (1976).

[4] R. M. Srivastava and J. F. C. de Albuquerque, *Quím. Nova,* **7**, 58 (1984).

[5] R. Mathis, T. N'Gando M'Pondo and J. Barrans, *C. R. Acad. Sci.,* Ser. C, **275**, 567 (1972).

[6] R. M. Srivastava and I. M. Brinn, *J. Org. Chem.*, **42**, 1555 (1977).

[7] F. Tiemann, *Ber.*, **17**, 126 (1884).

[8] L. B. Clapp, "Advances in Heterocyclic Chemistry", Vol **20**, A. R. Katritzky, ed, Academic Press, 1976, p 65.

[9] C. Malavaud, M. T. Boisdon and J. Barrans, *Bull. Soc. Chim. France,* 2996 (1973).

[10] T. M. Beltrão, M. S. thesis, Universidade Federal de Pernambuco, Recife.

[11] E. Falck, *Ber.*, **19**, 1481 (1886).

[12] *O*-(2,2,2-Trichloro-1-hydroxyethyl)benzamidoxime $C_9H_9Cl_3N_2O_2$, crystallized in monoclinic space group $P2_1/a$ with cell constants a = 11.881(7), b = 9.338(4), c = 12.098(5) A and β 118.01 (4)°. Z = 4, V = 1185(1) A^3, d_c = 1.59 g/cm^3. Data were collected with a Nicolet R3m/E diffractometer, and the analysis used the SHELXTL program system (Nicolet XRD Corp., Madison, WI, USA). The structure was determined by direct methods and refined by least squares to R = 0.027, Rw = 0.044 for 1506 unique observed reflections and 148 independent parameters.

The atomic coordinates are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK. Any request should be accompanied by the full literature citation for this communication.

Supplementary material available: thermal motion parameters, bond lengths and angles.