

## 89. The Synthesis of 3,5-Diamino-1,2,4-oxadiazoles

1st Communication

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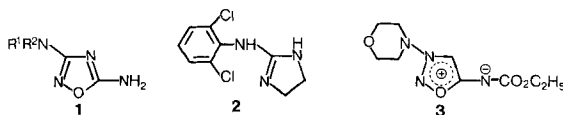
Dedicated to Professor *Edgardo Giovannini* on his 70th birthday

(13.III.80)

### Summary

Reaction of the 1-substituted-3-cyano-isothioureas **6** with hydroxylamine gave mixtures of the 5-amino-3-substituted-amino-1,2,4-oxadiazoles **1** and the isomeric 3-amino-5-substituted-amino-1,2,4-oxadiazoles **8** in which **1** usually predominated. The structural assignment of these products is discussed. In a second method, the 2-hydroxy-1-methyl-1-phenyl-guanidine **15** was converted to the corresponding 3-disubstituted-amino-5-trichloromethyl-1,2,4-oxadiazole **16**, a precursor to the 5-amino derivatives **17** by nucleophilic displacement of the trichloromethyl group.

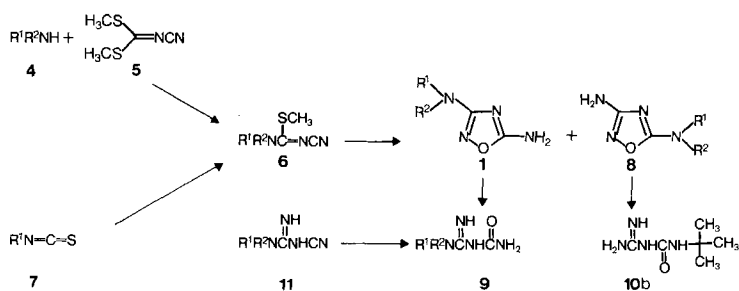
The structural resemblance of the 3-substituted-amino-5-amino-1,2,4-oxadiazoles **1** to the class of  $\alpha$ -adrenergic agonists represented by clonidine **2** and the vasodilating sydnone imide molsidomine **3** led us to prepare selected representatives of this system for cardiovascular evaluation. The early finding that 5-amino-3-phenylamino-1,2,4-oxadiazole (**1e**) elicits in the dog an increase of the cardiac contractility prompted the synthetic studies described below.



Although 1,2,4-oxadiazoles were first synthesized by *Tiemann* [1] in 1885 and interest has remained high in recent years [2] [3], only one example of a substituted 3,5-diamino-derivative has appeared in the literature. *Fromm & Fantl* [4] obtained an amino-phenylamino-1,2,4-oxadiazole by reaction of phenyldithiobiuret with hydroxylamine but could not ascertain by chemical means which isomer had been formed.

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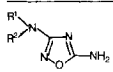
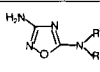
Scheme 1



Our initial approach to compounds of structure **1** involved the reaction of the cyanoisothioureas **6** with an excess of hydroxylamine. This process led invariably to a mixture of the 5-amino-3-substituted-amino-1,2,4-oxadiazole **1** and the corresponding 3-amino-5-substituted-amino isomer **8**. In some cases, the major product could be obtained pure by direct crystallization, but more generally a time consuming silica gel chromatography was required. The products were too weakly basic to form stable acid salts and each was characterized as its free base; the yield data are collected in *Table 1*.

The mixture of isomers presumably arises from a competition between the isothiourea and cyano moieties of **6** for attack by the hydroxylamine N-atom followed by cyclization-elimination. Both the reaction rate and the ratio of isomers are qualitatively dependent on the electronic nature of the substituents on **6**. The simple alkyl substituted analogs **6a-c** required several days at 50° to react fully

 Table I. Condensation of Isothioureas (**6**) with hydroxylamine (Procedure A)

Number	Pseudothiourea	ref.	Oxadiazole yield %	
				
	R <sup>1</sup> R <sup>2</sup> N-		<b>1</b>	<b>8</b>
<b>6a</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> NH-	[8]	4	11
<b>6b</b>	(CH <sub>3</sub> ) <sub>3</sub> CNH-	-	4	52
<b>6c</b>	piperidino	-	24	2
<b>6d</b>	4-methylpiperazino	-	27	-
<b>6e</b>	anilino	[7]	43	11
<b>6f</b>	4-methoxyanilino	[7]	23	16
<b>6g</b>	4-methylanilino	[7]	26	8
<b>6h</b>	4-chloroanilino	[9]	44	-
<b>6i</b>	4-nitroanilino	-	58	-
<b>6j</b>	3,4-dichloroanilino	-	68	-
<b>6k</b>	3,4-dimethoxyanilino	-	20	3
<b>6l</b>	3-hydroxyanilino	-	19	4
<b>6m</b>	3-methoxyanilino	[10]	49	5
<b>6n</b>	2,3-dimethylanilino	-	24	-
<b>6p</b>	2,3-dichloroanilino	-	49	-
<b>6q</b>	benzylamino	[8]	19	25

while the reactions of the aryl, benzyl, and piperazinyl derivatives were complete after several hours. Although the yield data in *Table 1* ignore the often considerable losses suffered during purification, a trend towards relatively higher yields of the 3-substituted amino isomer **1** with increasing electronegativity of the substituents on **6** is clearly discernable. Thus, the *p*-methoxyphenyl derivative **6f** gave a 1.4 to 1 ratio of **1f** and **8f** respectively while the relatively electron poor substrates such as **6h**, **i**, **j** and **p** gave essentially only the desired isomer **1**. Even in these most favorable instances, the isomer **8** formed and was clearly detectable by thin layer chromatography (TLC.). Possibly increase in the electronegativity of the substituents on **6** causes an increase in the electrophilicity at both sites of attack with a more profound effect on the proximal isourea center.

The assignment of the aryl and benzyl substituted isomers was readily accomplished by means of their mass spectra (MS.). In general, the 3-substituted-amino isomers **1** gave a fragment at  $m/z$   $M-43$  representing the loss of isocyanic acid whereas the corresponding **8** gave a fragment at  $m/z$   $M-57$  representing the loss of  $\text{CH}_3\text{N}_3$  and the formation of an aryl (benzyl) isocyanate. The empirical formulas of the key fragments derived from **1e**, **8e**, and **8q** were confirmed by high resolution MS. analysis. The behaviour of the isomers on silica gel TLC. was also indicative as, with the exception of **1a** and **1b**, **8** always ran slightly faster than the corresponding **1** on elution with 1:9 methanol/chloroform.

While the MS. fragmentations of the alkyl substituted analogs **1a-d** were inconclusive, more definitive results could be obtained from the derived ring-opened amidinoureas **9** and **10**. Compounds **1a-d** as well as **8b** were hydrogenated over Pd/C to give good yields of **9a-d** and **10b** respectively (*Table 2*). The structures of **9a** and **9b** were established by comparison with authentic samples prepared by acid catalyzed hydrolysis of the known cyanoguanidines **11a** [5] and **11b** [6]. Further,

Table 2. Reductive ring opening (Procedure B)

Starting 1,2,4- oxa- diazole	Pro- duct	Yield %	M.p. °C (Solvent of cryst.)	IR. (KBr) $\text{cm}^{-1}$	MS. $m/z$ (%)	Formula (M)	Analysis %			
							Found			
							C	H	Cl	N
<b>1a</b>	<b>9a</b>	60	126-128	1720	159 (100) <sup>a)</sup>	$\text{C}_6\text{H}_{14}\text{N}_4\text{O} \cdot \text{HCl}$ (194.67)	37.02	7.77		28.78
			Alc-Eth	1675	142 (16)		36.76	7.85		28.90
			1620	116 (16)						
<b>1b</b>	<b>9b</b>	77	177-178	1737	158 (56)	$\text{C}_6\text{H}_{14}\text{N}_4\text{O} \cdot \text{HCl}$ (194.67)	37.02	7.77	18.21	28.78
			A	1702	143 (11)		36.72	7.74	18.45	28.58
			1686	58 (100)						
<b>8b</b>	<b>10b</b>	70	160-161	1663	158 (4)	$\text{C}_6\text{H}_{14}\text{N}_4\text{O}$ (158.21)	45.55	8.92		35.41
			Eth	1605	143 (31)		45.55	9.01		35.57
				58 (100)						
<b>1c</b>	<b>9c</b>	75	131-132	1649	170 (33)	$\text{C}_7\text{H}_{14}\text{N}_4\text{O}$ (170.22)	49.39	8.29		32.92
			Ip-Eth	1612	127 (11)		49.32	8.29		33.16
				84 (100)						
<b>1d</b>	<b>9b</b>	35	198-199	1735	186 (100) <sup>a)</sup>	$\text{C}_7\text{H}_{15}\text{N}_5\text{O} \cdot 2\text{HCl}$ (258.16)	32.57	6.64	27.47	27.13
			Ip-Eth	1667	169 (61)		32.37	6.72	27.07	26.92
				143 (57)						

<sup>a)</sup> Chemical ionization mass spectrum

**10b** proved distinct from **9b**, both, with regard to physical data (IR., NMR., MS.) and TLC. mobility<sup>2)</sup>. The structures of **9c** and **9d** could easily be verified through their MS. Each yielded a prominent fragment at  $m/z$  *M*-43 representing loss of isocyanic acid.

The starting isothioureas **6** were generally prepared according to *Davidson & Peak* [7] by reaction between the appropriate amine **4** and an equimolar amount of dimethyl *N*-cyanocarbonimidodithioate (**5**) [11]. In cases where the reaction was slow, side reactions intervened and the desired product could not be conveniently isolated. The conditions were then modified so that the product **6** crystallized as it formed. This was accomplished in the case of *t*-butylamine by employing a large excess of the amine in a saturated ether/hexane solution of **5** at RT. and for 3,4-dichloroaniline by employing a large excess of the amine, but in a minimum volume of refluxing ethanol. The 4-nitrophenyl and 2,3-dichlorophenyl derivatives **6i** and **6p** were prepared through reaction of the isothiocyanates **7i** and **7p** with sodium cyanamide followed by iodomethane [12]. The data for the new isothioureas **6** are collected in *Table 3*.

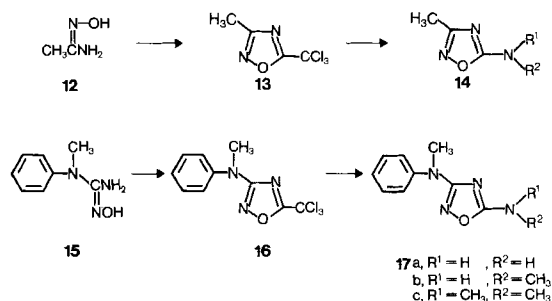
Table 3. 1-Substituted-3-cyano-2-methyl-isothioureas **6**

Compound	Procedure	Yield %	M.p. °C (Solvent of cryst.)	IR. (KBr) cm <sup>-1</sup>	MS. <i>m/z</i> (%)	Formula (M)	Analysis %				
							Calc. Found				
							C	H	Cl	N	S
<b>6b</b>	D	83	126-129 Alc-Eth	2178 1556	171 (3) 156 (28) 124 (35)	C <sub>7</sub> H <sub>13</sub> N <sub>3</sub> S (171.26)	49.09	7.65		24.54	18.72
							49.27	7.76		24.70	19.04
<b>6c</b>	E	93	59-61 Eth-H	2190 1561	183 (26) 136 (100) 109 (49)	C <sub>8</sub> H <sub>13</sub> N <sub>3</sub> S (183.27)	52.43	7.15		22.93	17.49
							52.61	7.30		22.85	17.66
<b>6d</b>	E	93	66-67 E-H	2174 1562	198 (9) 183 (13) 151 (74)	C <sub>8</sub> H <sub>14</sub> N <sub>4</sub> S (198.28)	48.46	7.12		28.26	16.17
							48.45	7.16		28.68	16.50
<b>6i</b>	F	94	188-193 Alc-DMF	2200 2170 1624	236 (22) 188 (100) 158 (36)	C <sub>9</sub> H <sub>8</sub> N <sub>4</sub> O <sub>2</sub> S (236.24)	45.76	3.41		23.72	13.57
							45.97	3.47		23.79	13.65
<b>6j</b>	G	67	190-191 Alc	2178 1584	259 (2) 211 (100)	C <sub>9</sub> H <sub>7</sub> Cl <sub>2</sub> N <sub>3</sub> S (260.14)	41.55	2.71	27.26	16.15	12.32
							41.52	2.76	27.31	16.13	12.59
<b>6k</b>	E	89	190-192 A	2165 1595	251 (15) 203 (100) 188 (44)	C <sub>11</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub> S (251.30)	52.57	5.21		16.72	12.76
							52.40	5.18		16.52	12.83
<b>6l</b>	E	85	160-162 A	2198 1624	207 (76) 160 (52) 159 (100)	C <sub>9</sub> H <sub>9</sub> N <sub>3</sub> OS (207.25)	52.16	4.38		20.28	15.47
							52.11	4.54		20.23	15.31
<b>6n</b>	E	51	188-190 A	2195 2170 1535	219 (59) 172 (79) 131 (100)	C <sub>11</sub> H <sub>13</sub> N <sub>3</sub> S (219.31)	60.25	5.98		19.16	14.62
							60.67	6.03		18.95	14.47
<b>6p</b>	F	82	187-188 Alc	2186 1586	259 (4) 224 (100) 211 (63)	C <sub>9</sub> H <sub>7</sub> Cl <sub>2</sub> N <sub>3</sub> S (260.14)	41.55	2.71	27.26	16.15	12.32
							41.52	2.79	27.31	16.07	12.50

<sup>2)</sup> TLC. mobility on silica gel (2:23:75 NH<sub>4</sub>OH/CH<sub>3</sub>OH/CHCl<sub>3</sub>) **9b**, 0.38; **10b**, 0.18.

The methodology described above was unsuited to the preparation of the 3-(*N*-methyl-*N*-phenyl) derivatives **17** since *N*-methylaniline did not react cleanly with **5** to give the required starting isothiourea **6**. Similar difficulties have been reported previously [7]. An alternate approach was suggested by the work of *Eloy & Lenaers* [13] who have treated acetamide oxime **12** with trichloroacetic anhydride to give the 5-trichloromethyl-1,2,4-oxadiazole **13**. The trichloromethyl moiety of **13** was readily displaced by a variety of amines providing access to the 5-amino substituted products **14**.

In the present work, this device could be extended to the unstable hydroxyguanidine **15** [14] [15]. A THF solution of **15** was stirred at RT. with excess trichloroacetic anhydride to give a 65% yield of the crude oxadiazole **16** directly. Conversion to the amino derivatives **17a-c** was accomplished by treatment of **16** with an ethanolic solution of the appropriate amine in 43-79% yield. The hydroxyguanidine **15** failed to afford **17a** in several attempts to effect reaction with cyanogen bromide even though similar reactions with amide oximes have been reported [16].



### Experimental Part

Melting points (m.p.) were determined on a *Toutli* apparatus and are uncorrected. IR. spectra were taken on a *Beckman* IR 9 instrument. MS. were recorded on a *AEI* MS 9 spectrometer. For TLC. precoated silica gel plates (F 254, *Merck*, Darmstadt) were used. Abbreviations in the *Tables* are: A acetonitrile; Alc ethyl alcohol; DMF dimethyl formamide; E ethyl acetate; Eth ether; H hexane; Ip 2-propanol; PE petroleum ether, b.p. 30-60°.

The authors wish to thank Drs. *W. Arnold*, *L. Chopard*, *W. Meister* and *A. Discherl* for the spectroscopic determinations and microanalyses.

**Procedure A.** - *Condensation of hydroxylamine with the 1-substituted-3-cyano-2-methyl-isothioureas 6*. A solution of 0.05 mol of the appropriate **6** together with 30 g (0.43 mol) of hydroxylamine hydrochloride and 60 ml (0.43 mol) of triethylamine in 500 ml of DMF was stirred at 50°. In the case of aromatic derivatives, **6**, R<sup>1</sup> = Aryl, R<sup>2</sup> = H, the reaction was complete after several h. In the case of alkyl derivatives **6**, R<sup>1</sup> and/or R<sup>2</sup> = alkyl, generally required several days and additional quantities of hydroxylamine hydrochloride and triethylamine were added every 48 h.

On completion of the reaction (TLC., 9:1 CHCl<sub>3</sub>/MeOH), the mixture was poured onto 2 l of water and extracted with 3 × 500 ml of ethyl acetate. The combined organic layers were washed with 2 × 500 ml of water and 1 × 500 ml of brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue could either be crystallized directly from EtOH/hexane (**1h**, **i**, **j**, **p**) or was chromatographed on silica gel (100:1 w/w) with 1-5% MeOH/CHCl<sub>3</sub>. Except in the cases of the butyl and *t*-butyl derivatives, the first component eluted was the isomer **8** followed by **1**. The results are summarized in *Tables 1* and *4*.

**Procedure B.** - *Hydrogenation of the 1,2,4-oxadiazoles 1a-d and 8b*. A solution of the oxadiazole in EtOH containing an equimolar amount of aqueous 1N HCl was hydrogenated over an equal

Table 4. 3,5-Disubstituted-1,2,4-oxadiazoles

Com- pound	M.p. °C (Solvent of cryst.)	IR. (KBr) cm <sup>-1</sup>	MS. m/z (%)	Formula (M)	Analysis %			
					Calc. Found	C	H	Cl
<b>1a</b>	90-93 Eth-Hex	1685	156 (16)	C <sub>6</sub> H <sub>12</sub> N <sub>4</sub> O (156.19)	46.14	7.74		35.87
			140 (48) 113 (100)		46.32	7.78		36.04
<b>1b</b>	182-184 E-H	1696	156 (21)	C <sub>6</sub> H <sub>12</sub> N <sub>4</sub> O (156.19)	46.14	7.74		35.87
			141 (39) 100 (100)		46.11	7.81		35.74
<b>1c</b>	178-180 Alc	1691	168 (94)	C <sub>7</sub> H <sub>12</sub> N <sub>4</sub> O (168.20)	49.99	7.19		33.31
			127 (28) 55 (100)		50.12	7.14		33.37
<b>1d</b>	238 dec. Alc	1681	183 (22)	C <sub>7</sub> H <sub>13</sub> N <sub>5</sub> O · HCl (219.68)	38.27	6.42	16.14	31.88
			166 (54) 43 (100)		38.06	6.42	16.27	31.87
<b>1e</b>	183-184 E-H	1692	176 (100)	C <sub>8</sub> H <sub>8</sub> N <sub>4</sub> O (176.18)	54.54	4.58		31.80
			133 (57) 77 (73)		54.59	4.73		31.99
<b>1f</b>	173-175 Ip	1680	206 (100)	C <sub>9</sub> H <sub>10</sub> N <sub>4</sub> O <sub>2</sub> (206.20)	52.42	4.89		27.17
			191 (28) 163 (6)		52.58	5.08		27.33
<b>1g</b>	184-186 E-H	1686	190 (100)	C <sub>9</sub> H <sub>10</sub> N <sub>4</sub> O (190.21)	56.83	5.30		29.46
			146 (47) 132 (36)		57.19	5.47		29.38
<b>1h</b>	176-177 Alc-PE	1680	210 (100)	C <sub>8</sub> H <sub>7</sub> ClN <sub>4</sub> O (210.62)	45.62	3.35	16.83	26.60
		1665	193 (10) 167 (11)		45.63	3.50	17.04	26.64
<b>1i</b>	268-270 Alc-DMF	1710	221 (100)	C <sub>8</sub> H <sub>7</sub> N <sub>5</sub> O <sub>3</sub> (221.18)	43.44	3.19		31.66
		1676	132 (20) 105 (44)		43.50	3.15		31.67
<b>1j</b>	199-201 E-H	1695	244 (92)	C <sub>8</sub> H <sub>6</sub> Cl <sub>2</sub> N <sub>4</sub> O (245.06)	39.21	2.47	28.93	22.86
			201 (32) 166 (100)		39.29	2.59	29.01	22.61
<b>1k</b>	186-187 Alc-PE	1674	236 (100)	C <sub>10</sub> H <sub>12</sub> N <sub>4</sub> O <sub>3</sub> (236.23)	50.84	5.12		23.72
			221 (51) 193 (14)		50.93	5.18		23.82
<b>1l</b>	213-215 Alc-PE	1690	192 (100)	C <sub>8</sub> H <sub>8</sub> N <sub>4</sub> O <sub>2</sub> <sup>a</sup> (192.18)	50.05	4.41		28.47
			175 (35) 149 (35)		50.15	4.48		28.40
<b>1m</b>	156-157 E-H	1683	206 (100)	C <sub>9</sub> H <sub>10</sub> N <sub>4</sub> O <sub>2</sub> (206.20)	52.42	4.89		27.17
			190 (26) 173 (26)		52.50	4.94		27.05
<b>1n</b>	151-153 E-H	1674	204 (100)	C <sub>10</sub> H <sub>12</sub> N <sub>4</sub> O (204.23)	58.81	5.92		27.43
			161 (30) 146 (54)		58.85	5.83		27.09
<b>1p</b>	217-219 Alc	1685	244 (38)	C <sub>8</sub> H <sub>6</sub> Cl <sub>2</sub> N <sub>4</sub> O (245.06)	39.21	2.47	28.93	22.86
			209 (6) 201 (4) 166 (100)		39.33	2.37	28.77	22.83

Table 4 (continued)

Com- pound	M.p. °C (Solvent of cryst.)	IR. (KBr) cm <sup>-1</sup>	MS. m/z (%)	Formula (M)	Analysis %			
					Calc. Found			
					C	H	Cl	N
<b>1q</b>	179-181 E-H	1664	190 (11)	C <sub>9</sub> H <sub>10</sub> N <sub>4</sub> O (190.21)	56.83	5.30		29.46
			173 (39)		56.90	5.28	29.51	
			91 (100)					
<b>8a</b>	74-75 Eth-H	1669	156 (59)	C <sub>6</sub> H <sub>12</sub> N <sub>4</sub> O (156.19)	46.14	7.74		35.87
			100 (88)		46.41	7.83	35.88	
			84 (100)					
<b>8b</b>	183-184 E-H	1644	156 (14)	C <sub>6</sub> H <sub>12</sub> N <sub>4</sub> O (156.19)	46.14	7.74		35.87
			141 (2)		46.15	7.75	35.46	
			100 (100)					
<b>8c</b>	174-178 Alc	1635	168 (100)	C <sub>7</sub> H <sub>12</sub> N <sub>4</sub> O (168.20)	49.99	7.19		33.31
			112 (48)		50.00	7.30	33.15	
			84 (58)					
<b>8e</b>	150-153 E-H	1655	176 (100)	C <sub>8</sub> H <sub>8</sub> N <sub>4</sub> O (176.18)	54.54	4.58		31.80
			119 (49)		54.36	4.57	31.57	
			57 (82)					
<b>8f</b>	178-181 Ip-H	1684	206 (48)	C <sub>9</sub> H <sub>10</sub> N <sub>4</sub> O <sub>2</sub> <sup>b</sup> (206.20)	52.53	5.01		26.78
			149 (100)		52.66	5.04	26.76	
<b>8g</b>	178-180 E-H	1680	190 (100)	C <sub>9</sub> H <sub>10</sub> N <sub>4</sub> O <sup>c</sup> (190.21)	56.78	5.39		28.79
			133 (71)		56.90	5.40	28.88	
			57 (85)					
<b>8k</b>	176-177 E-H	1637	236 (100)	C <sub>10</sub> H <sub>12</sub> N <sub>4</sub> O <sub>3</sub> <sup>c</sup> (236.23)	50.91	5.19		23.28
			179 (100)		51.08	5.19	23.27	
<b>8l</b>	196-197 E-H	1654	192 (88)	C <sub>8</sub> H <sub>8</sub> N <sub>4</sub> O <sub>2</sub> (192.18)	50.00	4.20		29.15
			135 (100)		49.99	4.28	28.99	
			109 (32)					
<b>8m</b>	146-147 E-H	1637	206 (100)	C <sub>9</sub> H <sub>10</sub> N <sub>4</sub> O <sub>2</sub> <sup>c</sup> (206.20)	52.47	4.98		26.60
			149 (87)		52.33	4.85	26.65	
			148 (51)					
<b>8q</b>	145-146	1676	190 (23)	C <sub>9</sub> H <sub>10</sub> N <sub>4</sub> O (190.21)	56.83	5.30		29.46
			1635		57.04	5.43	29.61	
			132 (4)					
			91 (100)					

<sup>a</sup>) Contains 0.05 mol Alc. <sup>b</sup>) Contains 0.10 mol Ip. <sup>c</sup>) Contains 0.05 mol E.

weight of 5% Pd/C at atmospheric pressure. On completion of the reaction (0.5-1 h), the solvent was evaporated and the product was either crystallized directly from EtOH/ether or converted to the free base for characterization. The results are summarized in Table 2.

**Procedure C.** - Hydrolysis of the 1-substituted-3-cyanoguanidines **11a** and **11b**. A solution of **11a** [5] or **11b** [6] in 20 volumes of 6N HCl was stirred overnight. The solvent was evaporated and the residue recrystallized from EtOH/ether or acetonitrile to give **9a** and **9b** respectively which were identical (m.p., TLC., IR., MS.) to the products obtained from the reduction of **1a** and **1b**.

**Procedure D.** - 1-*t*-Butyl-3-cyano-2-methyl-isothiourea (**6b**). A solution of 50 g (0.342 mol) of **5** and 100 ml of *t*-butylamine in 1 l of ether and 500 ml of hexane was left at RT. for 10 days and the precipitate was collected (Table 3).

**Procedure E.** - Preparation of 1-substituted-3-cyano-2-methyl-isothioureas **6**. Equimolar amounts of amine and dimethyl *N*-cyanocarbonimidodithioate (**5**) [11] were heated in EtOH according to the method described in [7]. Data for the new compounds are summarized in Table 3.

**Procedure F.** - Preparation of 1-substituted-3-cyano-2-methyl-isothioureas **6i** and **6p**. The method [12] is illustrated by the synthesis of 1-cyano-3-(2,3-dichlorophenyl)-2-methyl-isothiourea (**6p**). To a solution made of 4.1 g (0.18 g-atom) of Na in 500 ml of EtOH was added 7.6 g (0.18 mol) of cyanamide. On dissolution, 36.1 g (0.177 mol) of 2,3-dichlorophenyl isothiocyanate was added and a slightly exothermic reaction ensued. After 1 h at 25°, 48 ml (0.77 mol) of CH<sub>2</sub>I<sub>2</sub> was added dropwise, the mixture was stirred overnight and the resulting white precipitate was collected (Table 3).

**Procedure G.** - 1-Cyano-3-(3,4-dichlorophenyl)-2-methyl-isothiourea (**6j**). A solution of 100 g (0.617 mol) of 3,4-dichloroaniline and 50 g (0.342 mol) of **5** in 100 ml of EtOH was refluxed for 48 h. After cooling, the reaction mixture was diluted with 100 ml of ether to precipitate **6j** (Table 3).

**2-Hydroxy-1-methyl-1-phenylguanidine (15)**. A suspension of 42 g (0.318 mol) of *N*-methyl-*N*-phenylcyanamide, 80 g (1.15 mol) of hydroxylamine hydrochloride, and 93.5 g (1.14 mol) of sodium acetate in 800 ml of DMF was stirred at RT. overnight. The mixture was diluted with 2 l of water and washed with 2 × 500 ml of ethyl acetate. The aqueous phase was made strongly basic with NaOH and extracted with 3 × 500 ml of ethyl acetate. The combined organic layers were washed with 1 × 500 ml of water, 1 × 300 ml of brine, dried (K<sub>2</sub>CO<sub>3</sub>) and concentrated. The residue was acidified with ethanolic HCl-solution and was crystallized from EtOH/ether to give 41.25 g (64%) of the hydrochloride of **15**, m.p. 193–195° after recrystallization from EtOH/ether ([14]: 189°).

C <sub>8</sub> H <sub>12</sub> ClN <sub>3</sub> O	Calc.	C 47.65	H 6.00	Cl 17.58	N 20.84%
(201.66)	Found	„ 47.72	„ 6.13	„ 17.68	„ 20.62%

The hydrochloride (41.2 g, 0.204 mol) was dissolved in 400 ml of water and 29 g (0.21 mol) of K<sub>2</sub>CO<sub>3</sub> was added. The resulting white suspension was stirred 15 min and was extracted with 3 × 200 ml of CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with 1 × 200 ml of brine, dried (K<sub>2</sub>CO<sub>3</sub>) and evaporated to give 32 g (95%) of the free base of **15**, m.p. 101–103° ([15]: 102°).

**3-(*N*-Methyl-*N*-phenylamino)-5-trichloromethyl-1,2,4-oxadiazole (16)**. A solution of 30.4 g (0.184 mol) of **15** in 500 ml of ice cold THF was treated with 36.5 ml (0.20 mol) of trichloroacetic anhydride. The reaction mixture was maintained at RT. overnight and most of the solvent was removed *in vacuo*. The residue was diluted to 700 ml with ether and was washed 1 × 100 ml of water, 3 × 100 ml of sat. NaHCO<sub>3</sub>-solution, and dried (Na<sub>2</sub>SO<sub>4</sub>). Concentration gave 34.5 g (65%) of a red oil which was employed directly in the next step. A portion was chromatographed on silica gel eluting with 1:9 ether/hexane to give a colourless oil. - IR. (film): 1600, 1552. - MS.: 291 (*M*<sup>+</sup>, 35), 256 (9), 174 (100).

C <sub>10</sub> H <sub>8</sub> Cl <sub>3</sub> N <sub>3</sub> O	Calc.	C 41.06	H 2.76	Cl 36.36	N 14.36%
(292.56)	Found	„ 41.42	„ 2.76	„ 35.77	„ 14.14%

**5-Amino-3-(*N*-methyl-*N*-phenylamino)-1,2,4-oxadiazole (17a)**. A solution of 13 g (0.044 mol) of **16** in 100 ml of EtOH was cooled in an ice bath and saturated with NH<sub>3</sub>. The solution was heated in a closed vessel at 50° for 24 h and the residue from evaporation was crystallized from EtOH/hexane to give 4.75 g (56%) of **17a**, m.p. 158–162°. The mother liquors afforded a further 1.45 g (17%), m.p. 155–158°. - IR. (KBr): 3324, 3286, 1681. - MS.: 190 (*M*<sup>+</sup>, 100), 174 (98), 146 (53), 77 (98).

C <sub>9</sub> H <sub>10</sub> N <sub>4</sub> O (190.21)	Calc.	C 56.83	H 5.30	N 29.46%	Found C 56.85	H 5.34	N 29.27%
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**5-(*N*-methylamino)-3-(*N*-methyl-*N*-phenylamino)-1,2,4-oxadiazole (17b)**. A solution of 12 g (0.041 mol) of **16** in 100 ml of EtOH was saturated with methylamine at 0°, and warmed to 50° in a sealed bottle for 24 h. The residue on evaporation was recrystallized from EtOH/hexane to give 2.08 g (25%) of **17b**, m.p. 116–118°. The mother liquors were chromatographed on 300 g of silica gel eluting with 10% MeOH/toluene giving a further 4.56 g (54%), m.p. 116–118°. - IR. (KBr): 3330, 3210, 1675. - MS.: 204 (*M*<sup>+</sup>, 50), 174 (100).

C <sub>10</sub> H <sub>12</sub> N <sub>4</sub> O (204.23)	Calc.	C 58.81	H 5.92	N 27.43%	Found C 58.74	H 6.02	N 27.34%
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**5-(*N,N*-Dimethylamino)-3-(*N*-methyl-*N*-phenylamino)-1,2,4-oxadiazole (17c)**. Dimethylamine was passed through an ice cold solution of 15.15 g (0.052 mol) of **16** in 100 ml of EtOH for 20 min and



the vessel was sealed and warmed to a bath temperature of 50° for 72 h. The crude product was chromatographed on 1 kg of silica gel with 5% MeOH/toluene to give a yellow oil which was distilled to provide 5.17 g (46%) of **17c**, b.p. 125–135°/0.002 Torr. - IR. (KBr): 1660. - <sup>1</sup>H-NMR. (CDCl<sub>3</sub>): 7.25 (br. m, 5 H, arom.); 3.40 (s, 3 H, CH<sub>3</sub>); 3.07 (s, 6H, CH<sub>3</sub>). - MS.: 218 (M<sup>+</sup>, 58), 174 (100), 159 (18).

C<sub>11</sub>H<sub>14</sub>N<sub>4</sub>O (218.26) Calc. C 60.53 H 6.47 N 25.67% Found C 60.15 H 6.28 N 25.24%

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