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

2nd Communication

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

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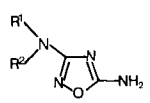
Summary

The 5-amino-3-arylamino-1,2,4-oxadiazoles **2** are conveniently prepared by oxidative cyclization of the arylamidinoureas **10**. The process is also capable of producing a variety of the 5-substituted-amino analogs **32** when the appropriately substituted guanidine **31** is employed as the substrate. Two different types of rearrangement leading to triazol-3-ones accompany cyclization depending on the choice of starting material. The structures of the rearranged products were established by X-ray crystallographic analysis and the reaction mechanisms leading to these unexpected products are discussed.

Introduction. – In the accompanying paper [1], we have described two methods for the preparation of the 5-amino-3-substituted-amino-1,2,4-oxadiazoles **1**. Although these procedures proved useful for the preparation of numerous analogs, continuing pharmacological interest in this class of compounds prompted the search for an improved approach capable of providing the 5-amino-3-anilino-1,2,4-oxadiazoles **2** on a large scale without the need for chromatographic purification.



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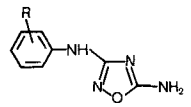

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The base-induced ring closure of haloamidinocarbonyl compounds of general structure **3** leading to 1,2,4-oxadiazoles has recently been reported [2–4]. The reaction proceeds *via* elimination of the elements of hydrogen chloride and the nitrenoid **4** is a postulated intermediate which undergoes electrocyclic ring closure to the observed **5**. The application of a similar approach to the production of **2**

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would require the amidinourea **10**. This compound possesses additional potentially reactive sites and offers increased complexity with respect to both the regioselectivity of chlorination and the direction of cyclization of the dehydrohalogenated intermediate.

Since halogenation is expected to occur on an unsubstituted, basic N-atom [5], chlorination of **10** should give predominantly **11**. Base treatment could result in removal of a proton from the N-atom *a* to the aromatic ring. The resulting nitrenoid species **8** (R^1 = ureido) should undergo ring closure followed by a proton shift to provide the benzimidazole **9** (R^1 = ureido). A similar transformation starting with the amidine **6** (R^1 = aryl), and proceeding through the corresponding **7** has been reported to furnish the benzimidazole **9** (R^1 = aryl), in fair to excellent yield [6] [7].

We would anticipate, however, that the proton on the N-atom *γ* to the aromatic ring of **11** would be most acidic. Its removal by base, in analogy with the above work, would lead to the nitrenoid **12**, ideally set up for an electrocyclic cyclization to the 1,2,4-oxadiazole **2** involving an electron pair on the carbonyl O-atom and an empty orbital on the electron deficient N-atom. An alternate electrocyclic process giving the triazolone **13** demands an unfavorable dipolar transition state and should not compete effectively. Although we have implicated a discrete nitrenoid intermediate, a similar conclusion is reached if departure of chloride from the anion derived from **11** is promoted by an intramolecular nucleophilic attack of the carbonyl O-Atom. We now describe the successful application of the oxidative cyclization strategy to the synthesis of **2** and its 5-substituted-amino analogs **32** as well as two unanticipated rearrangements.

Results and discussion. - The known phenylamidinourea hydrochloride **10a** (R = H) [8] was treated with sodium hypochloride solution. A less polar product

Scheme 1

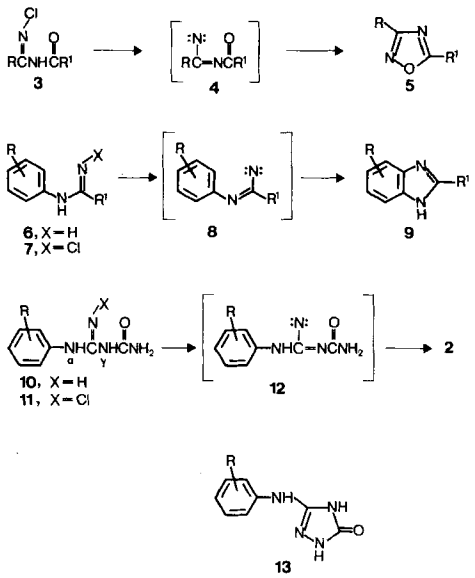


Table 1. *Yield of 1,2,4-oxadiazole* **2** *from amidinourea* **10**

Amidinourea **10**		1,2,4-Oxadiazole **2** Yield %
Number	R	
10a	H[a])	71
10b	2-Cl	71
10c	2-CH_3[a])	45
10d	2-OCH_3	34
10e	4-F	45
10f	2,3-diCl	70
10g	2,6-diCl	67

[a]) See [8].

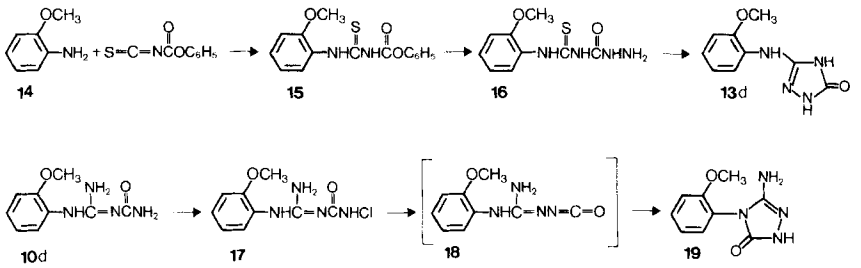
supposed to be **11a** formed rapidly and was isolated. Reaction of a methanolic solution of **11a** (R = H) with excess aqueous base led to a smooth conversion to the desired **2a** (R = H) in 70% yield. The identity of the product was verified by direct comparison with an authentic sample [1] (m.p., TLC., IR., MS.). In order to provide evidence for the generality of the process, **2f** *(Table 1)* produced as described below was also shown to be identical to a reference sample [1].

Several modifications to the above procedure proved expedient. When an aqueous solution of the hydrochloride salt of amidinourea **10** was treated with an equimolar amount of sodium hypochlorite solution, the corresponding *N*-chloro derivative **11** precipitated as it formed. The first drop of reagent in excess of the required amount strongly darkened the mixture. This served as a useful measure of the progress of the addition. The solid could be characterized, but more generally was employed directly in the next step. The crude solids were treated in methanol with a slight excess of aqueous potassium carbonate solution to effect ring closure to the oxadiazole **2**. The results of several representative experiments are collected in *Table 1*.

Thin layer chromatography (TLC.) of the mother liquors revealed in addition to traces of **2**, a second more polar substance. This was assumed to be the triazolone **13** resulting from a postulated alternate cyclization of the nitrenoid species **12**. No special effort was expended to isolate this side product, but in one experiment starting with the 2-methoxyphenylamidinourea **10d**, it separated with the major product and was isolated by fractional crystallization in 13% yield. Although the spectral data were consistent with the assigned triazolone structure **13d**, an independent chemical synthesis of this material was considered desirable.

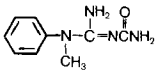
To this end, 2-methoxyaniline was condensed with phenoxycarbonylisothiocyanate (**14**) [9] to give the thiourea **15**. Reaction of **15** with excess hydrazine afforded the intermediate semicarbazide **16** which cyclized in refluxing ethanol to give the desired **13d** in 54% yield. Although the physical properties of **13d** was similar to that of the unknown side product, the compounds were clearly different. In order to determine the actual identity of the side product, an X-ray structural analysis revealed it to be the isomeric triazolone **19**. The drawings of the two conformers present in the solid state are presented in *Figure 1*. The details of the X-ray analysis are presented in a separate section.

Scheme 2



Presumably **19** arises from a competing attack of hypochlorite on the amidinourea **10d** leading to **17**. *Hoffmann*-type rearrangements of halogenated ureas are known [10] and in this case would proceed through the isocyanate **18** to the observed **19**.

One result may serve to limit the generality of the above method. The N^1-phenyl-N^1-methyl-N^2-carbamoylguanidine (**20**) [11] gave a chloro derivative as



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determined by TLC. using *o*-toluidine spray reagent to identify the spots of *N*-halogenated compounds. However, this intermediate did not react cleanly with base, but after several days at RT. was transformed to a multitude of products. The reason for this divergence is not clear; possibly the presence of the alkyl substituent directed halogenation to an other N-atom as in **17**.

The starting amidinoureas **10** were generally available by reaction of the appropriate anilines **21** with dicyanoimide (**22**) giving the cyanoguanidines **23** [12]

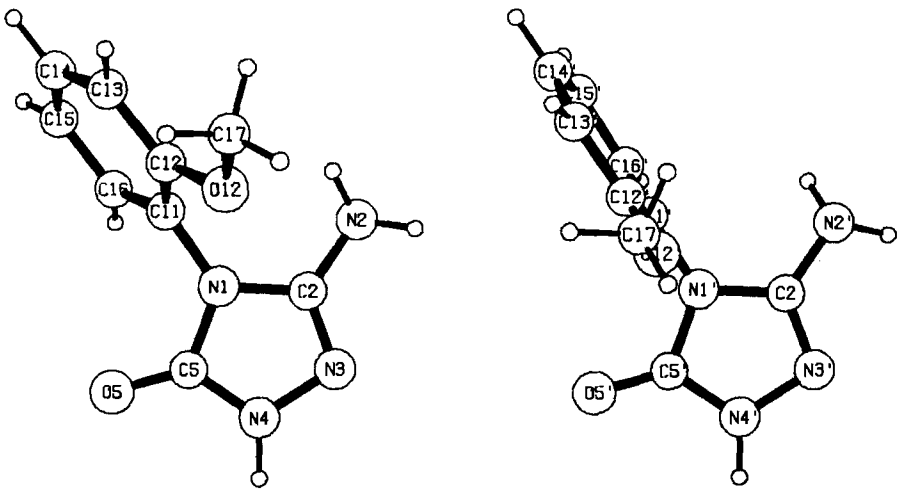
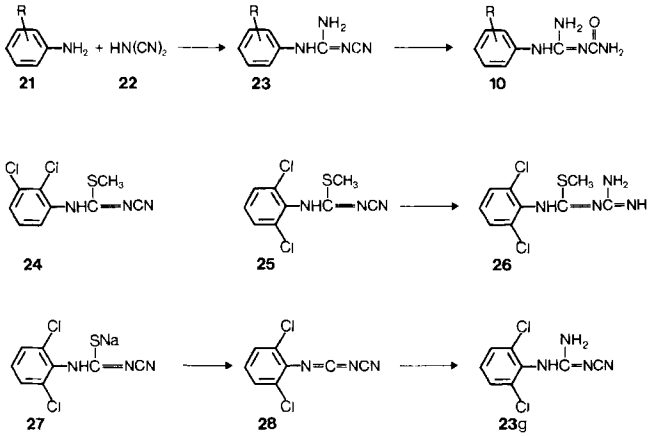


Fig. 1. *Drawing of 5-(2-methoxyphenylamino)-1,2-dihydro-3*H*-1,2,4-triazol-3-one* (**19**) *showing both conformations present in the solid state*

Scheme 3



which were readily hydrolyzed to **10**. The properties of the new compounds thus prepared are summarized in *Table 11*. The dichloroanilines **21f** (R = 2,3-dichloro) and **21g** (R = 2,6-dichloro) failed to react with dicyanoimide and an alternate synthetic route to the corresponding nitriles **23f** and **23g** was required. Derivative **23f** was readily prepared through the action of ammonia on the methylisothiourea **24** [1].

The isomeric methylisothiourea **25** was obtained from the reaction of sodium cyanamide with 2,6-dichlorophenylisothiocyanate followed by treatment with methyl iodide. Attempted production of **10g** by reaction of **25** with ammonia gave the guanidine **26** resulting from attack of ammonia on the nitrile moiety of **25**. This direction of nucleophilic attack away from the isothiourea center is clearly a result of steric hindrance provided by the *o*-chlorine atoms on the benzene ring of **25**.

In order to circumvent this difficulty, the crude sodium salt **27** suspended in THF/ammonia and treated by mercuric chloride produced **23g** in 65% yield. The reaction presumably proceeds through the intermediacy of the carbodiimide **28** which is trapped by ammonia. The generation of cyanocarbodiimides from the corresponding isothioureas has been described [13], but the method requires handling dilute solutions of the unstable carbodiimides and is not well suited to the reaction scales encountered in the present work.

With the above results in hand, an attempt was made to extend the utility of the oxidative cyclization to the synthesis of 3,5-diamino-1,2,4-oxadiazoles **32** bearing substituents on both amino N-atoms. The starting materials were easily available from the reaction of the phenylguanidines **29** with the isocyanates **30**. When equimolar amounts of the reagents were allowed to react for short periods, the required N^2-carbamoylguanidines **31** formed together with the products of two fold acylation from which **31** could be separated by fractional crystallization in 30–68% yield *(Table 12)*.

When subjected to the cyclization conditions described above, the N^2-carbamoylguanidine **31** were easily transformed into the 1,2,4-oxadiazoles **32** *(Table 2)*. In each example, the desired product was accompanied by a polar

Table 2. *Yield of the 1,2,4-oxadiazole* **32** *and the 1,2,4-triazolone* **33** *from the carbamoylguanidine* **31**

N^2-carbamoylguanidine **31**			1,2,4-Oxadiazole **32**	1,2,4-Triazolone **33**
Number	R	R^1	Yield %	Yield %
31a	H	CH_3	40	8
31b	H	C_2H_5	46	16
31c	H	$(CH_3)_3C$	76	4
31d	H	C_6H_5	25	18
31e	4-Cl	CH_3	59	21
31f	4-CH_3	CH_3	31	26
31g	2-Cl	CH_3	51	14
31h	3,4-diCl	CH_3	65	1.5
31i	2,6-diCl	CH_3	54	1.3

substance later identified as **33** *(vide infra)*. As in the case of **2**, the oxadiazoles **32**, with exception of **32d**, separated from the reaction mixtures when these were diluted with water and concentrated. The triazolones **33** were obtained by extraction of the mother liquors followed by silica gel chromatography.

Since the spectral data of the oxadiazoles **32** *(Table 13)* were not sufficiently informative to define the structures, two of them (**32d** and **32e**) were hydrogenated over Pd/C giving the N^2-carbamoylguanidines **31**. In the case of **32e**, loss of the aryl halogen accompanied ring opening giving **31a**. These results confirm the absence of rearrangement during the cyclizations and support the assigned 1,2,4-oxadiazole structure for **32**. The triazolone **33d** was resistant to hydrogenation even under forcing conditions[2]).

The microanalytical and physical chemical data suggested that the products obtained from the aqueous mother liquors were triazolones *(Table 13)*. The structure **37** was first considered on the assumption that a substituent might modify the electronic or steric properties of the terminal N-atom allowing it to compete with the urea O-atom during cyclization. Halogenation on a terminal N-atom and rearrangement similar to that observed with the amidinourea **10d** is precluded on mechanistic grounds [5].

In order to furnish chemical evidence regarding the structure of these polar materials, an authentic sample of **37e** was prepared in a manner analogous to that employed for the synthesis of the triazolone **13d**. The readily available phenylcarbamate **34** was allowed to react with methylhydrazine giving the semicarbazide **35**. The structure of **35** was verified by conversion to the *Schiff* base **36**. Refluxing a solution of **35** in ethanol promoted cyclization to **37e** with the loss of hydrogen sulfide.

The corresponding unknown product was different from **37e** and we again determined the actual course of the cyclization by X-ray crystallographic analysis. The results indicated the structure to be **33e** *(vide infra)*. A drawing is presented in *Figure 2*.

Formation of the rearranged triazolones **33** accompanying the cyclization of the chloroamidinoureas **38** to the 1,2,4-oxadiazoles **32** can be rationalized by the

[2]) Hydrogen pressure of 68 atm. at 100° over Pd/C.

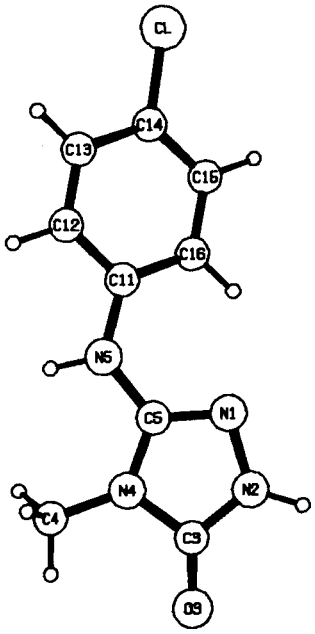


Fig. 2. *Drawing of 5-(4-chlorophenylamino)-2,4-dihydro-4-methyl-3H-1,2,4-triazol-3-one* (**33e**)

mechanism depicted in *Scheme 5*. An intramolecular displacement of chloride by the N-atom γ to the aromatic ring of **38** would lead to the diazirine **39**. Further reaction with base would cause opening to the carbodiimide **40** which could finally close intramolecularly to the observed **33**.

Such a rearrangement finds ample precedent. *Büchi et al.* [14] allowed the 1,2,4-oxadiazole **41** to react with sodium hydride in DMF and obtained in addition to the anticipated imidazole **42**, a pyrazole **43** in 1:3 ratio. They postulate a mechanism proceeding through the diazirine **44** and the carbodiimide **45**. In a more closely related example, the ethoxycarbonylguanidine **46** is reported to undergo exclusive rearrangement to the 1,3,4-oxadiazole **48** *via* the chloro derivative **47** [15]. This

Scheme 4

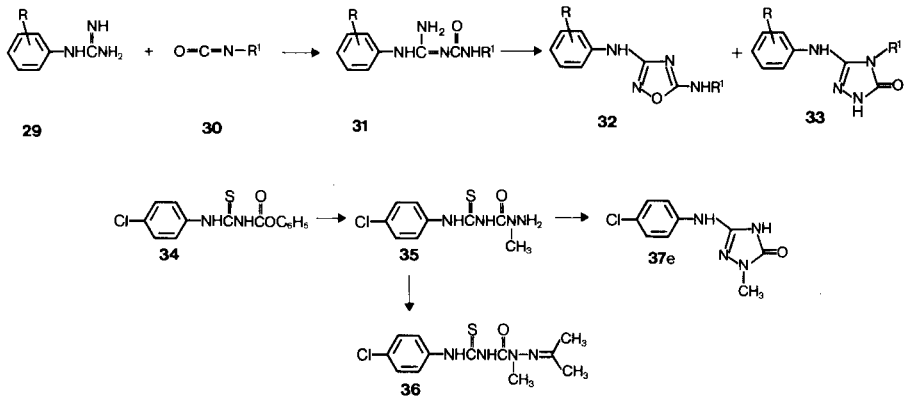


Table 3. *Final atomic parameters for* **19** *with standard deviations in parentheses*

Atom	X	Y	Z	B
O(5)	0.4971(2)	0.5966(2)	0.7120(2)	[a]
O(12)	0.6954(3)	0.6850(2)	1.0806(2)	[a]
O(5)′	−0.1828(3)	0.7141(2)	0.5223(2)	[a]
O(12)′	0.0923(3)	0.8653(2)	0.3764(2)	[a]
N(1)	0.5941(3)	0.7616(2)	0.8948(2)	[a]
N(2)	0.7659(3)	0.9536(2)	1.0464(2)	[a]
N(3)	0.8453(3)	0.8697(2)	0.8594(2)	[a]
N(4)	0.7568(3)	0.7622(2)	0.7607(2)	[a]
N(1)′	0.1129(3)	0.6980(2)	0.4870(2)	[a]
N(2)′	0.3558(3)	0.6187(2)	0.4042(2)	[a]
N(3)′	0.0387(3)	0.5068(2)	0.3514(2)	[a]
N(4)′	−0.1173(3)	0.5419(2)	0.3891(2)	[a]
C(2)	0.7431(3)	0.8653(2)	0.9374(2)	[a]
C(2)	0.1744(4)	0.6042(2)	0.4124(2)	[a]
C(5)	0.6065(3)	0.6954(2)	0.7800(2)	[a]
C(11)	0.4578(4)	0.7215(2)	0.9581(2)	[a]
C(12)	0.5120(4)	0.6776(2)	1.0503(2)	[a]
C(13)	0.3775(4)	0.6306(3)	1.1067(3)	[a]
C(14)	0.1969(5)	0.6308(3)	1.0698(3)	[a]
C(15)	0.1425(5)	0.6752(4)	0.9805(4)	[a]
C(16)	0.2742(4)	0.7213(3)	0.9217(3)	[a]
C(17)	0.7532(5)	0.6424(3)	1.1783(3)	[a]
C(5)′	−0.0788(4)	0.6562(2)	0.4705(2)	[a]
C(11)′	0.2163(3)	0.8249(2)	0.5463(2)	[a]
C(12)′	0.2026(3)	0.9117(2)	0.4881(2)	[a]
C(13)′	0.3015(4)	1.0356(3)	0.5454(3)	[a]
C(14)′	0.4149(4)	1.0685(3)	0.6565(3)	[a]
C(15)′	0.4317(4)	0.9835(3)	0.7138(3)	[a]
C(16)′	0.3288(4)	0.8595(3)	0.6586(2)	[a]
C(17)′	0.0817(4)	0.9484(3)	0.3083(3)	[a]
HN(2)A	0.895	0.996	1.079	4.5
HN(2)B	0.720	0.918	1.103	4.5
HN(4)	0.800	0.741	0.687	4.0
H(13)	0.417	0.597	1.174	5.0
H(14)	0.101	0.595	1.111	6.0
H(15)	0.008	0.676	0.958	7.0
H(16)	0.238	0.753	0.854	6.0
H(17)A	0.892	0.653	1.192	6.0
H(17)B	0.691	0.553	1.159	6.0
H(17)C	0.722	0.694	1.254	6.0
HN(2)A′	0.383	0.539	0.372	4.5
HN(2)B′	0.437	0.662	0.481	4.5
HN(4)′	−0.241	0.488	0.360	4.0
H(13)′	0.291	1.101	0.504	4.5
H(14)′	0.486	1.158	0.697	5.0
H(15)′	0.518	1.011	0.795	5.0
H(16)′	0.335	0.796	0.700	4.5
H(17)A′	−0.003	0.902	0.228	6.0
H(17)B′	0.209	0.982	0.296	6.0
H(17)C′	0.033	1.020	0.352	6.0

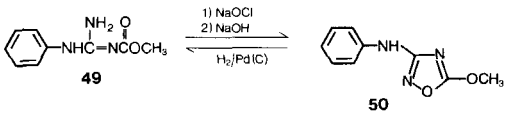
[a] Anisotropic thermal parameters are given in *Table 4*.

Table 4. *Final anisotropic thermal parameters for* **19** *with standard deviations in parentheses.* The anisotropic temperature factor has the form $\exp(-(h^2B11+k^2B22+l^2B33+2hkB12+2hlB13+2klB23))$

Atom	$B11\times10^4$	$B22\times10^4$	$B33\times10^4$	$B12\times10^4$	$B13\times10^4$	$B23\times10^4$
O(5)	164(4)	72(2)	79(2)	−21(2)	27(2)	− 7(2)
O(12)	195(5)	106(2)	89(2)	4(3)	10(2)	49(2)
O(5)′	179(4)	82(2)	76(2)	25(2)	45(2)	24(2)
O(12)′	238(5)	78(2)	76(2)	− 1(2)	− 5(2)	38(2)
N(1)	150(5)	58(2)	55(2)	−16(2)	34(2)	11(2)
N(2)	234(6)	81(2)	63(2)	−40(3)	41(3)	0(2)
N(3)	183(5)	70(2)	60(2)	−29(3)	32(3)	7(2)
N(4)	171(5)	77(2)	57(2)	−19(3)	36(3)	3(2)
N(1)′	156(5)	52(2)	62(2)	8(2)	30(2)	17(2)
N(2)′	181(5)	80(2)	84(2)	30(3)	37(3)	11(2)
N(3)′	197(5)	65(2)	69(2)	18(3)	31(3)	15(2)
N(4)′	168(5)	64(2)	67(2)	3(3)	22(3)	17(2)
C(2)	148(5)	61(3)	55(2)	−14(3)	22(3)	15(2)
C(2)	177(6)	59(3)	57(2)	22(3)	35(3)	21(2)
C(5)	141(5)	63(3)	61(2)	3(3)	27(3)	15(2)
C(11)	186(6)	57(2)	61(2)	− 6(3)	35(3)	12(2)
C(12)	166(6)	62(3)	63(2)	−19(3)	14(3)	10(2)
C(13)	236(8)	95(3)	69(3)	−31(4)	37(4)	21(2)
C(14)	227(8)	123(4)	109(3)	−21(5)	61(4)	39(3)
C(15)	179(7)	156(5)	157(5)	27(5)	75(5)	62(4)
C(16)	133(6)	103(3)	113(3)	15(3)	40(3)	40(3)
C(17)	299(9)	100(3)	85(3)	31(4)	1(4)	35(3)
C(5)′	171(6)	60(3)	54(2)	17(3)	25(3)	25(2)
C(11)′	135(5)	58(3)	61(2)	10(3)	29(3)	11(2)
C(12)′	145(6)	58(3)	72(3)	12(3)	34(3)	17(2)
C(13)′	176(6)	59(3)	104(3)	6(3)	45(4)	14(2)
C(14)′	195(7)	75(3)	108(3)	− 6(4)	56(4)	−16(3)
C(15)′	175(7)	123(4)	70(3)	3(4)	17(3)	−14(3)
C(16)′	179(6)	104(3)	58(2)	25(4)	20(3)	17(2)
C(17)′	229(7)	117(3)	108(3)	41(4)	43(4)	71(3)

transformation is also suspected to occur *via* a diazirine. The structure of **48** was confirmed by X-ray analysis.

The latter result prompted us to reinvestigate a report by *Goetz* [3] that the related carbomethoxyguanidine **49** was converted to the 1,2,4-oxadiazole **50** by an oxidative cyclization process. When **49** was treated under our standard conditions, an 86% yield of a single product was obtained with the melting point reported by *Goetz*. Catalytic reduction of a sample afforded the starting guanidine **49**, confirming the original assignment of **50** as a 1,2,4-oxadiazole.



49 **50**

The above reasoning, taken together with the data in *Table 2*, indicate that the partitioning of the intermediates between direct cyclization leading to 1,2,4-oxadiazoles and rearrangement is rather subtly determined by the substitution on the starting materials. Electron-withdrawing groups on the aromatic ring of the

Table 5. *Bond Lengths (Å) in* **19**
Estimated standard deviation for a typical C–C bond length is 0.006 Å

	Unprimed	Primed
O(5)–C(5)	1.239	1.237
O(12)–C(12)	1.353	1.357
O(12)–C(17)	1.438	1.436
N(1)–C(2)	1.380	1.384
N(1)–C(5)	1.382	1.391
N(1)–C(11)	1.438	1.429
N(2)–C(2)	1.358	1.360
N(3)–N(4)	1.402	1.400
N(3)–C(2)	1.290	1.303
N(4)–C(5)	1.327	1.336
C(11)–C(12)	1.384	1.391
C(11)–C(16)	1.385	1.379
C(12)–C(13)	1.400	1.390
C(13)–C(14)	1.366	1.374
C(14)–C(15)	1.360	1.368
C(15)–C(16)	1.401	1.397

Table 6. *Bond Angles (°) in* **19**.
Estimated standard deviation for a typical C–C–C bond angle is 0.4°

	Unprimed	Primed
C(12)–O(12)–C(17)	116.9	118.1
C(2)–N(1)–C(5)	106.9	107.6
C(2)–N(1)–C(11)	128.0	126.0
C(5)–N(1)–C(11)	124.9	124.7
N(4)–N(3)–C(2)	103.7	103.2
N(3)–N(4)–C(5)	112.7	113.9
N(1)–C(2)–N(2)	121.6	121.9
N(1)–C(2)–N(3)	112.1	111.9
N(2)–C(2)–N(3)	126.1	126.2
O(5)–C(5)–N(1)	126.3	126.4
O(5)–C(5)–N(4)	129.1	130.2
N(1)–C(5)–N(4)	104.6	103.4
N(1)–C(11)–C(12)	118.9	118.7
N(1)–C(11)–C(16)	119.5	120.3
C(12)–C(11)–C(16)	121.6	121.0
O(12)–C(12)–C(11)	116.7	115.4
O(12)–C(12)–C(13)	124.2	125.4
C(11)–C(12)–C(13)	119.1	119.2
C(12)–C(13)–C(14)	118.8	119.3
C(13)–C(14)–C(15)	122.6	122.0
C(14)–C(15)–C(16)	119.6	119.2
C(11)–C(16)–C(15)	118.3	119.3

Scheme 5

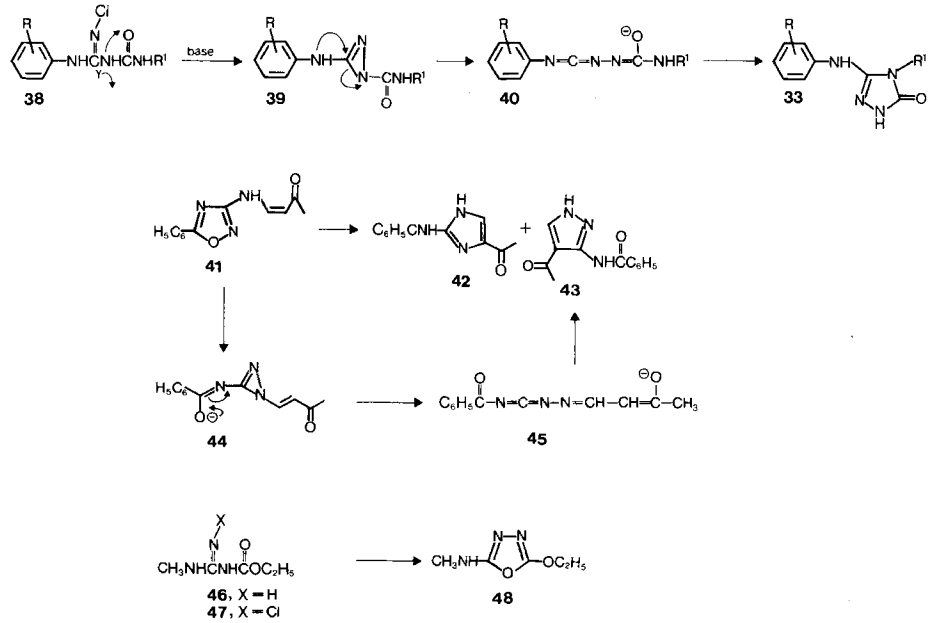


Table 7. *Final atomic parameters for* **33e** *with standard deviations in parentheses*

Atom	X	Y	Z	B
Cl	0.	−0.0513(4)	0.	a)
O(3)	1.2019(10)	0.5639(9)	0.2263(8)	a)
O(20)	0.9887(13)	0.3735(10)	0.5635(8)	a)
N(1)	0.8036(12)	0.3263(11)	0.2280(9)	a)
N(2)	0.9543(13)	0.4054(11)	0.2891(9)	a)
N(4)	0.9738(11)	0.4527(9)	0.0782(7)	a)
N(5)	0.7117(11)	0.3030(10)	−0.0032(8)	a)
C(3)	1.0611(13)	0.4823(12)	0.2033(9)	a)
C(4)	1.0490(17)	0.5039(16)	−0.0458(10)	a)
C(5)	0.8245(13)	0.3585(10)	0.1012(9)	a)
C(11)	0.5470(13)	0.2173(11)	0.0055(10)	a)
C(12)	0.4774(16)	0.1380(12)	−0.1083(10)	a)
C(13)	0.3166(17)	0.0555(13)	−0.1101(11)	a)
C(14)	0.2106(14)	0.0507(11)	0.0060(11)	a)
C(15)	0.2757(17)	0.1271(12)	0.1197(11)	a)
C(16)	0.4439(15)	0.2089(13)	0.1208(10)	a)
C(21)	1.0861(23)	0.2473(18)	0.6231(16)	a)
HN(2)	0.979	0.404	0.383	4.0
HN(5)	0.753	0.323	−0.091	4.0
HO(20)	0.891	0.400	0.615	5.0
H(3)A	1.107	0.411	−0.091	6.0
H(3)B	1.149	0.585	−0.027	6.0
H(3)C	0.949	0.550	−0.106	6.0
H(12)	0.548	0.145	−0.193	4.0
H(13)	0.273	−0.003	−0.192	4.0
H(15)	0.198	0.124	0.202	4.0
H(16)	0.491	0.264	0.205	4.0
H(21)A	1.193	0.217	0.570	7.0
H(21)B	0.996	0.154	0.628	7.0
H(21)C	1.129	0.275	0.716	7.0

a) Anisotropic thermal parameters are given in *Table 8.*

carbamoylguanidine **31** seem to favour 1,2,4-oxadiazole formation. A further indication that electronic effects are important is provided by a comparison of the results obtained with the guanidines **46** and **49** in which the alkyl substituted derivative underwent rearrangement exclusively whereas the corresponding aryl derivative cyclized with essentially no rearrangement. In order to more closely define the parameters influencing the reaction course, a quantitative study would be required in which isomer ratios in the crude reaction mixtures were determined.

In conclusion, oxidative cyclization of the arylguanidines **10** and **31** has proved useful for the synthesis of a variety of 3-arylamino-1,2,4-oxadiazoles. The occurrence of rearrangements competing with the expected cyclizations suggest that the products obtained from reactions related to those reported herein be assigned with care.

Crystallography. Crystals of **19** are triclinic, space group $P\bar{1}$, with $a = 7.505(3)$, $b = 11.559(2)$, $c = 11.922(2)$ Å, $\alpha = 107.26(2)$, $\beta = 97.98(3)$, $\gamma = 101.22(2)°$ and $d_{calc} = 1.445$ g cm^{-3} for $Z = 4$ ($C_9H_{10}N_4O_2$, $M = 206.21$).

Crystals of **33e** are monoclinic, space group *Pn*, with $a = 7.148(2)$, $b = 8.460(2)$, $c = 10.032(2)$ Å, $\beta = 92.15(2)°$ and $d_{calc} = 1.493$ g cm^{-3} for $Z = 2$ ($C_9H_9ClN_4O \cdot CH_3OH$, $M = 272.69$).

Table 8. *Final anisotropic thermal parameters for* **33e** *with standard deviations in parentheses.* The anisotropic temperature factor has the form $\exp(-(h^2B11+k^2B22+l^2B33+2hkB12+2hlB13+2klB23))$

Atom	$B11\times10^4$	$B22\times10^4$	$B33\times10^4$	$B12\times10^4$	$B13\times10^4$	$B23\times10^4$
Cl	208(6)	195(5)	141(4)	−82(5)	−20(4)	−14(4)
O(3)	148(14)	198(14)	47(6)	−34(12)	−25(7)	−24(8)
O(20)	257(19)	223(14)	46(6)	86(15)	0(9)	25(9)
N(1)	146(16)	178(15)	46(7)	−40(14)	−15(8)	14(9)
N(2)	179(18)	192(16)	29(7)	−32(15)	−20(9)	6(9)
N(4)	128(15)	115(12)	24(7)	−25(11)	−31(7)	2(7)
N(5)	121(14)	131(12)	41(7)	−31(11)	−20(8)	1(8)
C(3)	137(18)	139(15)	19(7)	7(14)	−31(8)	−7(8)
C(4)	218(25)	181(18)	43(9)	−88(19)	−6(12)	6(11)
C(5)	119(16)	100(12)	38(8)	−16(12)	−19(9)	−10(9)
C(11)	137(19)	90(12)	47(8)	−1(12)	−31(10)	−7(9)
C(12)	229(24)	94(14)	48(9)	7(15)	−22(12)	−11(9)
C(13)	201(23)	129(16)	58(10)	−19(16)	−43(11)	−6(10)
C(14)	140(19)	80(13)	100(12)	−26(13)	−35(12)	4(10)
C(15)	197(23)	117(15)	78(11)	−16(16)	−3(13)	−6(11)
C(16)	186(21)	121(15)	48(9)	−23(15)	−7(10)	−15(9)
C(21)	278(32)	183(21)	133(17)	55(22)	−38(18)	−8(16)

The intensity data for both compounds were measured on a *Hilger-Watts* four-circle diffractometer (Ni filtered Cu*Ka* radiation, $\theta-2\theta$ scans, pulse height discrimination). The approximate sizes of the crystals used for data collection were $0.25\times0.25\times0.8$ mm (**19**) and $0.2\times0.2\times0.3$ mm (**33e**). The crystals of **33e** were coated with a thin layer of epoxy cement in order to retard deterioration of the

Table 9. *Bond Lengths (Å) in* **33e**. Estimated standard deviation for a typical C–C bond length is 0.022 Å

Cl–C(14)	1.734
O(3)–C(3)	1.235
N(1)–N(2)	1.391
N(1)–C(5)	1.315
N(2)–C(3)	1.340
N(4)–C(3)	1.403
N(4)–C(4)	1.440
N(4)–C(5)	1.359
N(5)–C(5)	1.379
N(5)–C(11)	1.388
C(11)–C(12)	1.399
C(11)–C(16)	1.397
C(12)–C(13)	1.345
C(13)–C(14)	1.413
C(14)–C(15)	1.377
C(15)–C(16)	1.386
O(20)–C(21)	1.397

Table 10. *Bond Angles (°) in* **33e**. Estimated standard deviation for a typical C–C–C bond angle is 1.6°

N(2)–N(1)–C(5)	102.3
N(1)–N(2)–C(3)	113.7
C(3)–N(4)–C(4)	123.4
C(3)–N(4)–C(5)	106.2
C(4)–N(4)–C(5)	130.1
C(5)–N(5)–C(11)	127.1
O(3)–C(3)–N(2)	129.1
O(3)–C(3)–N(4)	126.8
N(2)–C(3)–N(4)	104.0
N(1)–C(5)–N(4)	113.9
N(1)–C(5)–N(5)	125.4
N(4)–C(5)–N(5)	120.7
N(5)–C(11)–C(12)	118.4
N(5)–C(11)–C(16)	123.6
C(12)–C(11)–C(16)	118.0
C(11)–C(12)–C(13)	122.5
C(12)–C(13)–C(14)	119.2
Cl–C(14)–C(13)	118.5
Cl–C(14)–C(15)	121.9
C(13)–C(14)–C(15)	119.6
C(14)–C(15)–C(16)	120.4
C(11)–C(16)–C(15)	120.2

crystal due to loss of solvent of crystallization. The data for **33e** were corrected for absorption ($\mu = 29.0$ cm^{-1}). Both structures were solved by a multiple solution procedure [16] and were refined by full-matrix least-squares. In the final refinements, anisotropic thermal parameters were used for the non-hydrogen atoms and isotropic temperature factors were used for the H-atoms. The H-atoms were included in the structure factor calculations but their parameters were not refined.

For **19**, 2395 of the 2552 independent reflections for $\theta < 57°$ were considered to be observed [$I > 2.5\sigma(I)$]. The final unweighted and weighted discrepancy indices were R = 0.050 and wR = 0.067 for the 2395 observed reflections. The final difference map has no peaks greater than ± 0.1 e A^{-3}. There are two independent molecules of **19** in the unit cell. There is about a 22° difference in rotation about the C(11)–N(1) bonds in the two conformers. The final atomic parameters are listed in *Tables 3* and *4*. Bond lengths and bond angles in the two independent molecules of **19** are given in *Tables 5* and *6*.

For **33e**, 1027 of the 1063 accessible reflections for $\theta < 70°$ were considered to be observed. The structure refined to only R = 0.093 and wR = 0.119. The largest peaks on the final difference map were ± 0.9 e A^{-3}. The relatively high R values are probably due to deterioration of the crystal, which occurred to a limited extent despite the epoxy coating. The final atomic parameters are listed in *Tables 7* and *8*. Bond lengths and bond angles in **33e** are given in *Tables 9* and *10*.

Experimental Part

Melting points were determined on a *Büchi* 510 capillary apparatus and are uncorrected. IR. spectra were recorded on a *Beckman* IR 9 or a *Digilab* FT5 Model 14 apparatus. NMR. data were obtained on a *Varian* A-60, HA-100 or XL-100 instrument and the chemical shifts are given in ppm relative to tetramethylsilane as an internal standard. MS. were recorded on a *AEI* MS9, *CEC* 21-103 or a *Varian* CH-5 spectrometer. For TLC., precoated silica gel plates (F254, *Merck*, Darmstadt) were used. Abbreviations in *Tables 11–13* are: A acetonitrile; Alc ethyl alcohol; E ethyl acetate; Eth diethyl ether; H hexane; and M methyl alcohol.

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5-Amino-3-phenylamino-1,2,4-oxadiazole (**2a**) *and* (N^2*-chloro*-N^1*-phenylamidino)urea* (**11a**). A solution of 5.00 g (0.0233 mol) of (N^1-phenylamidino)urea hydrochloride (**10a**) [8] and 5 ml (0.005 mol) of 1N HCl in 150 ml of MeOH was cooled to −55° and treated dropwise with 17.5 ml (0.026 mol) of 1.5N sodium hypochlorite solution. After completion of the addition, the mixture was allowed to warm to −10° over 1 h, poured onto ice, and extracted with ethyl acetate. After washing with water and saturated brine and drying (Na_2SO_4), the solvent was evaporated to give 5.02 g (100%) of **11a**, m.p. 108–110° (dec.). A portion was recrystallized twice from MeOH/hexane to give an analytical sample, m.p. 118–119° (dec.). – IR. (KBr): 3436, 3224, 1708, 1616, 1593. – MS. (chemical ionization): 213 ($M+H$, 38), 179 (100), 162 (85).

$C_8H_9ClN_4O$	Calc.	C 45.19	H 4.27	Cl 16.67	N 26.35%
(212.64)	Found	„ 44.94	„ 4.27	„ 17.11	„ 26.39%

A solution of 1.00 g (0.0047 mol) of crude **11a** in 20 ml of MeOH was treated at 0° with 2.5 ml (0.005 mol) of 2N NaOH. After 10 min, the mixture was diluted with 20 ml of water and concentrated to half volume. The precipitated **2a** amounted to 0.58 g (70%), m.p. 174–178°. Recrystallization from EtOH/hexane gave m.p. 180–182° identical to an authentic sample [1] (mixed m.p., TLC., IR., MS.).

General procedure for the oxidative cyclization of guanidine derivatives **10** *and* **31** *in water.* A solution of the guanidine hydrochloride in 30 ml/g of water was cooled to 0° (ice/salt bath) and 1.0 eq. of sodium hypochlorite was added dropwise as the intermediate chloroguanidine began to precipitate. The addition was continued until the last drop caused a distinct darkening of the mixture (95–100% of the theoretical quantity). After an additional 15 min, the precipitate was collected and washed with water. The chloroguanidines so obtained are stable, tan to cream colored solids. The moist filter cake was dissolved in 30 ml/g of MeOH and treated with a 20% excess of K_2CO_3 in water at 0°. The cyclizations were generally complete after 1 h at 0°, but in some cases it was necessary to allow the mixture to warm to RT.

The mixture was diluted with an equal volume of water and concentrated to precipitate the desired 1,2,4-oxadiazole. In the case of the products from the cyclizations of **10c** and **31c**, oils were obtained and the aqueous solution was extracted with ethyl acetate. The products from the extracts were

Table 11. *Data for the new amidinoureas* **10** *and cyanoguanidines* **23**

Number	R	Yield %	m.p. °C (Solvent of cryst.)	IR. (KBr) cm^{-1}	MS. *m/z* (%)	Formula (M)	Analysis Calc., Found C	H	Cl	N
10b	2-Cl	89	177–178	1733	212(5)	$C_8H_9ClN_4O \cdot HCl$	38.57	4.05	28.46	22.49
			Alc-Eth	1673	195(13)	(249.10)	38.04	4.17	28.43	22.25
				1636	177(17)					
					127(100)					
10d	2-OCH_3	87	162–164	1718	191(2)	$C_9H_{12}N_4O_2 \cdot HCl$	44.18	5.36	14.49	22.90
			Alc-Eth	1673	165(100)	(244.68)	44.45	5.40	14.90	22.41
					134(72)					
10e	4-F	80	201–202	1732	196(4)	$C_8H_9FN_4O \cdot HCl$	41.30	4.33	15.24	24.08
			Alc	1674	179(11)	(232.65)	41.24	4.34	15.28	24.12
					153(51)					
					111(100)					
10f	2,3,diCl	94	181–182	1735	246(7)	$C_8H_8Cl_2N_4O \cdot HCl$	33.89	3.20	37.51	19.76
			Alc	1664	229(16)	(283.55)	33.90	3.29	37.53	19.63
				1645	203(58)					
					161(100)					
10g	2,6-diCl	75	206–208	1743	246(2)	$C_8H_8Cl_2N_4O \cdot HCl$	33.89	3.20	37.51	19.76
			Alc-H	1686	229(7)	(283.55)	33.90	3.41	37.38	19.60
				1622	203(70)					
					161(100)					
23b	2-Cl	89	172–173	2180	194(6)	$C_8H_7ClN_4$	49.37	3.63	18.22	28.79
			Alc-W	1661	159(100)	(194.63)	49.46	3.59	18.34	28.80
				1632	152(11)					
23d	2-OCH_3	46	133–135	2172	190(46)	$C_9H_{10}N_4O$	56.83	5.30		29.46
			E	1645	159(100)	(190.21)	56.71	5.30		29.12
					108(46)					
23e	4-F	67	214–215	2188	178(100)	$C_8H_7FN_4$	53.93	3.96		31.45
			A	1656	161(5)	(178.17)	53.99	3.87		31.21
					137(85)					
					111(75)					
23f	2,3-diCl	83	245–246	2185	228(2)	$C_8H_6Cl_2N_4$	41.95	2.64	30.95	24.46
			Alc	1660	193(100)	(229.07)	42.16	2.61	30.97	24.18
				1625	161(22)					
23g	2,6-diCl	65	204–206	2188	228(1)	$C_8H_6Cl_2N_4$	41.95	2.64	30.95	24.46
			Alc-H	1680	193(100)	(229.07)	41.93	2.63	31.24	24.21
				1644	161(20)					

separated by silica gel column chromatography in 1:19 MeOH/$CHCl_3$ and 1:3 ethyl acetate/hexane respectively. The results are summarized in *Tables 1, 2,* and *13.*

The aqueous filtrate from the cyclization of the carbamoylguanidine **31** was saturated with NaCl and extracted with CH_2Cl_2. Chromatography of the extract on silica gel in ethyl acetate/hexane gave the triazolones **33** *(Tables 2* and *13).*

*5-Amino-4-(2-methoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one* (**19**). From 12.2 g (0.0499 mol) of N^1-(2-methoxyphenyl)amidinourea hydrochloride (**10d**) was obtained in the usual manner 3.52 g (34%) of 5-amino-3-(2-methoxyphenylamino)-1,2,4-oxadiazole **2d**, m.p. 201–203°. Concentration of the filtrate afforded after recrystallization from MeOH 1.34 g (13%) of **19**, m.p. 218–220°; recrystallization gave m.p. 221–222°. A sample was recrystallized from MeOH and submitted for X-ray analysis without drying. – IR. (KBr): 3440*m*, 3330*s*, 1711*s*, 1655*s*. – ^{1}H-NMR. ((D_6)-DMSO): 3.78 (*s*, 3 H, OCH_3); 5.20 (br., 2 H, NH_2); 6.8–7.67 (*m*, 4 H, arom.); 10.5 (br., 1 H, NH). – MS.: 206 (M^+, 100), 189 (17), 149 (15).

$C_9H_{10}N_4O_2$ (206.21) Calc. C 52.42 H 4.89 N 27.17% Found C 52.72 H 4.96 N 26.98%

1-(2-Methoxyphenyl)-3-phenoxycarbonylthiourea (**15**). To a solution of 14.82 g (0.153 mol) of potassium thiocyanate in 100 ml of acetone was added a solution of 23.1 g (0.148 mol) of phenyl chloroformate in 25 ml of acetone over 45 min. The resulting suspension was refluxed 10 min and cooled to RT. and a solution of 6.16 g (0.05 mol) of 2-methoxyaniline in 10 ml of acetone was added all at once. The resulting mixture was stirred overnight, filtered and washed with CH_2Cl_2. Concentration of the filtrate afforded 6.8 g (45%) of **15**, m.p. 171–172° and a further 4.7 g (31%) were obtained from the mother liquors, m.p. 168–169°. Recrystallization from CH_2Cl_2/hexane gave m.p. 174–175°. – IR. ($CHCl_3$): 3410, 1740, 1556. – MS.: 302 (M^+, 3), 271 (11), 227 (2), 94 (100).

$C_{15}H_{14}N_2O_3S$	Calc.	C 59.59	H 4.67	N 9.27	S 10.60%
(302.35)	Found	„ 59.42	„ 4.55	„ 9.25	„ 10.58%

Table 12. *Data for the carbamoylguanidins* **31**

Number	R	R^1	Yield %	m.p. °C (Solvent of cryst.)	IR. (KBr) cm^{-1}	MS. *m/z* (%)	Formula (M)	Analysis Calc., Found C	H	Cl	N
31a	H	CH_3	53	127–129 E-H	1650	192(28) 162(67) 161(32) 135(36)	$C_9H_{12}N_4O$ (192.22)	56.24 56.21	6.39 6.20		29.15 29.05
31b	H	C_2H_5	68	107–112 E-H	1703 1660 1630	206(26) 162(97) 93(100)	$C_{10}H_{14}N_4O$ (206.24)	58.24 58.52	6.84 7.07		27.17 27.32
31c	H	$(CH_3)_3C$	30	178–180 E-H	1711 1671	234(15) 162(100) 135(40) 93(82)	$C_{12}H_{18}N_4O$ (234.30)	61.52 61.54	7.74 7.57		23.91 23.71
31d	H	C_6H_5	61	148–150 E	1658	254(< 1) 162(8) 135(46) 119(100)	$C_{14}H_{14}N_4O$ (254.29)	66.13 66.26	5.55 5.75		22.03 21.82
31e	4-Cl	CH_3	45	160–161 Alc	1708 1675	226(34) 196(58) 169(22) 152(44)	$C_9H_{11}ClN_4O \cdot HCl$ (263.13)	41.08 40.87	4.60 4.71	26.95 27.11	21.29 21.14
31f	4-CH_3	CH_3	40	159–160 Alc-Eth	1730 1718 1665	206(44) 175(87) 132(57) 107(100)	$C_{10}H_{14}N_4O \cdot HCl$ (242.71)	49.49 49.18	6.23 6.20	14.61 14.55	23.08 22.80
31g	2-Cl	CH_3	62	136–137 E-H	1708[a] 1660	226(41) 196(100) 191(80) 127(100)	$C_9H_{11}ClN_4O$ (226.67)	47.69 47.83	4.89 4.96		24.72 24.51
31h	3,4-diCl	CH_3	38	137–138 E-H	1706[a] 1660	260(17) 230(28) 203(12) 186(15) 161(50)	$C_9H_{10}Cl_2N_4O$ (261.11)	41.40 41.48	3.86 3.77	27.16 26.93	21.46 21.40
31i	2,6-diCl	CH_3	62	190–191 E-H	1710 1655	dec.[b]	$C_9H_{10}Cl_2N_4O$ (261.11)	41.40 41.30	3.86 4.05		21.46 21.28

[a] ($CHCl_3$).

[b] ^{1}H-NMR. (DMSO): 2.69 (*d*, 3 H, $NHCH_3$); 6.14 (br., 2 H, NH); 6.89 (*m*, 1 H, arom.); 7.27 (*m*, 2 H, arom.); 7.52 (br., 1 H, N*H*CH_3); 8.54 (br., 1 H, NH).

Table 13. *Data for the 1,2,4-oxadiazoles* **2** *and* **32** *and the triazol-3-ones* **33**

Number	R	R^1	m.p. °C	IR. (KBr) cm^{-1}	MS. *m/z* (%)	Formula (M)	Analysis Calc., Found C	H	Cl	N
2b	2-Cl	–	203–204	1691	210(50)	$C_8H_7ClN_4O$	45.62	3.35	16.83	26.26
			Alc		175(5)	(210.62)	45.59	3.31	17.00	26.37
					132(100)					
2c	2-CH_3	–	155–157	1691	190(69)	$C_9H_{10}N_4O$	56.83	5.30		29.46
			E	1617	172(76)	(190.21)	56.65	5.18		29.13
					146(100)					
2d	2-OCH_3	–	201–203	1659	206(100)	$C_9H_{10}N_4O_2$	52.42	4.89		27.17
			Alc-M		191(5)	(206.21)	52.26	4.97		26.85
					134(23)					
2e	4-F	–	180–182	1693	194(100)	$C_8H_7FN_4O$	49.49	3.63		28.86
			Alc	1622	177(17)	(194.17)	49.53	3.71		28.83
					151(63)					
2g	2,6-diCl	–	239–240	1682	244(18)	$C_8H_6Cl_2N_4O$	39.21	2.47	28.93	22.86
			Alc-H		209(17)	(245.07)	39.28	2.34	29.19	22.61
					166(100)					
					124(22)					
32a	H	CH_3	160–162	1684	190(100)	$C_9H_{10}N_4O$	56.83	5.30		29.46
			E-H	1630	160(79)	(190.21)	56.72	5.01		29.52
					133(45)					
32b	H	C_2H_5	130–131	1670	204(100)	$C_{10}H_{12}N_4O$	58.81	5.92		27.43
			E-H	1620	160(83)	(204.23)	58.82	5.98		27.74
					133(54)					
					92(34)					
32c	H	$C(CH_3)_3$	100–101	1651	232(30)	$C_{12}H_{16}N_4O$	62.05	6.94		24.12
			E-H	1625	176(28)	(232.29)	61.82	6.97		24.08
					159(9)					
					133(18)					
32d	H	C_6H_5	181–182	1668	252(100)	$C_{14}H_{12}N_4O$	66.65	4.79		22.21
			E-H		160(45)	(252.28)	66.49	4.52		22.06
					133(60)					
32e	4-Cl	CH_3	193–194	1663	224(100)	$C_9H_9ClN_4O$	48.12	4.04	15.78	24.94
			Alc	1613	194(27)	(224.65)	47.96	3.90	15.69	24.82
					167(14)					
					132(44)					
32f	4-CH_3	CH_3	176–177	1675	204(100)	$C_{10}H_{12}N_4O$	58.81	5.92		27.43
			E-H	1625	174(40)	(204.23)	58.85	6.09		27.71
					146(34)					
32g	2-Cl	CH_3	130–131	1653[a])	224(35)	$C_9H_9ClN_4O$	48.12	4.04	15.78	24.94
			E-H		194(7)	(224.65)	48.03	3.87	15.54	24.94
					189(5)					
					159(5)					
					132(100)					
32h	3,4-diCl	CH_3	215–216	1665	258(100)	$C_9H_8Cl_2N_4O$	41.72	3.11	27.37	21.62
			Alc	1620	228(49)	(259.10)	41.86	3.08	27.62	21.55
					201(20)					
					145(16)					
32i	2,6-diCl	CH_3	161–162	1650[a])	258(11)	$C_9H_8Cl_2N_4O$	41.72	3.11	27.37	21.62
			E-H		223(18)	(259.10)	42.01	3.10	27.59	21.52
					186(6)					
					166(100)					

Table 13 (continued)

Number	R	R^1	m.p. °C	IR. (KBr) cm^{-1}	MS. *m/z* (%)	Formula (M)	Analysis Calc., Found C	H	Cl	N
33a	H	CH_3	178–181	1682	190(100)	$C_9H_{10}N_4O$	56.83	5.30		29.46
			E-H	1625	133(11)	(190.21)	56.81	5.33		29.34
					104(19)					
33b	H	C_2H_5	171–172	1732	204(100)	$C_{10}H_{12}N_4O$	58.81	5.92		27.43
			W	1708	176(45)	(204.23)	58.79	5.79		27.16
					145(35)					
33c	H	$C(CH_3)_3$	195–197	1705	232(15)	$C_{12}H_{16}N_4O$	62.05	6.94		24.12
			E-H	1620	176(100)	(232.29)	62.11	6.91		24.15
					119(11)					
33d	H	C_6H_5	211–212	1710	252(100)	$C_{14}H_{12}N_4O$	66.65	4.79		22.21
			E-M		235(4)	(252.28)	66.77	4.98		22.10
					208(6)					
					133(25)					
33e	4-Cl	CH_3	223–224	1711	224(100)	$C_9H_9ClN_4O$	48.12	4.04	15.78	24.94
			Alc-W	1701	195(2)	(224.65)	48.59	3.97	15.58	24.87
				1610	189(2)					
33f	4-CH_3	CH_3	231–232	1723	204(100)	$C_{10}H_{12}N_4O$	58.81	5.92		27.43
			Alc-W	1705	160(11)	(204.23)	58.58	6.01		27.52
					132(20)					
33g	2-Cl	CH_3	204–205	1718	224(52)	$C_9H_9ClN_4O$	48.12	4.04	15.78	24.94
			Alc-W		189(100)	(224.65)	48.03	3.91	15.63	24.62
					146(35)					
33h	3,4-diCl	CH_3	266–267	1708	258(100)	$C_9H_8Cl_2N_4O$	41.72	3.11	27.37	21.62
			Alc-W	1698	223(9)	(259.10)	41.86	3.15	27.08	21.69
				1620	229(5)					
					201(8)					
33i	2,6-diCl	CH_3	232–234	1726	258(39)	$C_9H_8Cl_2N_4O$	41.72	3.11	27.37	21.62
			Alc-W		223(100)	(259.10)	41.25	3.06	27.18	21.20
					180(22)					

[a]) ($CHCl_3$).

1-Carbazoyl-3-(2-methoxyphenyl)thiourea (**16**). A solution of 5.1 g (0.0168 mol) of **15** and 0.82 ml (0.0168 mol) of hydrazine hydrate in 50 ml of THF was stirred overnight at RT. The product separated and was collected in 2 crops to give 3.60 g (89%) of **16**, m.p. 167° (dec.). Recrystallization of a sample from $MeOH/CH_2Cl_2$/hexane raised the m.p. to 168° (dec.). – IR. (KBr): 3355, 3325, 3240, 1693. – ^{1}H-NMR. (DMSO): 3.83 (*s*, 3 H, OCH_3); 4,68 (br., 1 H, NH); 6.96 (*m*, 3 H, arom.); 8.45 (*d*×*d*, 1 H, arom.); 9.50 (br., 2 H, NH); 12.35 (br., 1 H, NH). – MS.: 206 ($M-H_2S$, 100), 187 (25), 175 (22).

$C_9H_{12}N_4O_2S$	Calc.	C 44.99	H 5.03	N 23.32	S 13.34%
(240.28)	Found	„ 44.94	„ 4.80	„ 23.38	„ 13.55%

5-(2-Methoxyphenylamino)-2,4-dihydro-3H-1,2,4-triazol-3-one (**13d**). A solution of 1.5 g (0.0063 mol) of **16** in 300 ml of EtOH was heated under reflux for 7 days. After cooling, 0.70 g (54%) of **13d**, m.p. 287–289°, separated. – IR. (KBr): 3375, 3210, 1712. – ^{1}H-NMR. (DMSO): 3.90 (*s*, 3 H, OCH_3); 6.90 (*m*, 3 H, arom.); 7.66 (*s*, 1 H, NH); 7.92 (*m*, 1 H, arom.); 9.92 (br., 1 H, NH); 10.49 (br., 1 H, NH). – MS.: 206 (M^+, 100), 187 (32), 175 (29).

$C_9H_{10}N_4O_2$ (206.21) Calc. C 52.42 H 4.89 N 27.17% Found C 52.32 H 5.04 N 26.72%

General preparation of the 1-aryl-2-cyanoguanidines (**23**). According to the procedure of *Curd et al.* [12], equimolar amounts of the appropriate aniline hydrochloride and sodium dicyanimide were stirred

at 60° in aqueous solution as the products precipitated. The new compounds thus prepared are described in *Table 11.*

2-Cyano-1-(2,3-dichlorophenyl)guanidine (**23f**). A solution of 11.0 g (0.042 mol) of 1-cyano-3-(2,3-dichlorophenyl)-2-methylisothiourea (**24**) [1] in 200 ml of EtOH was saturated with NH_3 at 0° and was heated to a bath temperature of 80° in a sealed flask overnight. On cooling, 7.2 g (74%) of **23f** was obtained, m.p. 243–245°. The filtrate yielded an additional 0.9 g, m.p. 239–241°. Both crops were used as such in the next step. Recrystallization of a sample from EtOH gave m.p. 245–246° *(Table 11).*

1-Cyano-3-(2,6-dichlorophenyl)-2-methylisothiourea (**25**). To a solution formed from 6.0 g (0.261 g-atom) of Na in 400 ml of EtOH was added 11.0 g (0.261 mol) of cyanamide, then 55.0 g (0.270 mol) of 2,6-dichlorophenylisothiocyanate [17]. After 2 h, 50 ml (0.80 mol) of CH_2I_2 were added to the yellow mixture which was allowed to stand at RT. overnight. The resulting mixture was cooled in an ice bath and the product was collected to yield 50.95 g (75%) of **25**, m.p. 195–198°. Recrystallization from EtOH/DMF gave m.p. 205–209°. – IR. (KBr): 3186, 2136. – MS.: 259 (M^+, 1), 224 (100), 211 (82).

$C_9H_7Cl_2N_3S$	Calc.	C 41.55	H 2.71	Cl 27.26	N 16.15	S 12.32%
(260.14)	Found	„ 41.58	„ 2.76	„ 27.30	„ 16.14	„ 12.33%

3-(Amidino)-1-(2,6-dichlorophenyl)-2-methylisothiourea hydrochloride (**26**). A solution of 5.00 g (0.0192 mol) of **25** in 100 ml of EtOH was saturated with NH_3 at 0°. The flask was sealed and heated to a bath temperature of 100° for 48 h. After cooling, the reaction mixture was concentrated and the residue was acidified with HCl and recrystallized from EtOH/ether to give 1.37 g (23%) of **26**, m.p. 215–218°. Recrystallization from MeOH/hexane gave m.p. 216–218°. TLC. of the mother liquors revealed a complex mixture containing starting material and only traces of the nitrile **23g**. – IR. (KBr): 3292, 3120, 1701, 1627. – MS.: 276 (M^+, 6), 229 (100), 212 (13), 186 (59).

$C_9H_{10}Cl_2N_4S \cdot HCl$	Calc.	C 34.47	H 3.54	Cl 33.91	N 17.86	S 10.22%
(313.63)	Found	„ 34.54	„ 3.56	„ 33.92	„ 17.72	„ 10.39%

3-Cyano-1-(2,6-dichlorophenyl)isothiourea sodium salt (**27**). To the solution formed from 15.0 g (0.652 g-atom) of Na in 1 l of EtOH was added a solution of 28.3 g (0.67 mol) of cyanamide dissolved in 200 ml of EtOH followed by 137.3 g (0.673 mol) of 2,6-dichlorophenylisothiocyanate [17]. The resulting clear yellow solution was stirred 1 h, concentrated and diluted with ether to give 157.6 g (90%) of crude **27**, m.p. > 340° which was used as such in the next step.

2-Cyano-1-(2,6-dichlorophenyl)guanidine (**23g**). To a solution of 13.4 g (0.050 mol) of **27** in 200 ml of THF and 50 ml of NH_3 was added 13.5 g (0.050 mol) of mercuric chloride. The reaction mixture was allowed to warm to RT. and stir overnight as NH_3 evaporated. The resulting black suspension was filtered through *Celite,* diluted with water and extracted with CH_2Cl_2. The product obtained after washing, drying (Na_2SO_4) and evaporation of the solvent was crystallized from EtOH/hexane to give 7.5 g (65%) of **23g**, m.p. 200–202°; recrystallization raised the m.p. to 204–206° *(Table 11).*

General preparation of the (N^1*-arylamidino)urea hydrochlorides* (**10**). A suspension of the nitrile **23** in 10 ml/g of 6N HCl was heated to a bath temperature of 100° for 1 h. The solvent was removed *in vacuo* and the residue recrystallized as indicated in *Table 11.*

General procedure for the preparation of the 1-aryl-2-(substituted-carbamoyl)guanidines **31**. A suspension of 29.6 g (0.15 mol) of phenylguanidine hydrogencarbonate in 50 ml of water and the mixture was acidified by careful addition of 6N HCl until solution was effected. The solution was made strongly basic with 25% NaOH and was extracted with 4× 125 ml of CH_2Cl_2. The combined organic layers were dried (K_2CO_3) and evaporated to give 20.4 g of phenylguanidine free base.

The phenylguanidines were dissolved in approximately 3 ml/mmol of acetonitrile, cooled to −20° and treated with 1.1 eq. of the appropriate isocyanate. After 1 h at −20°, the solvent was removed *in vacuo* and the residue was crystallized from the solvent mixtures indicated in *Table 12.* In the case of **31e**, purification of the crude product was effected by HPLC. using silica gel columns in a *Waters* Prep 500 instrument with 94:5:1 CH_2Cl_2/MeOH/NEt_3. Both, this compound and **31f**, were conveniently isolated as their hydrochloride salts. The results of these experiments are summarized in *Table 12.*

1-(4-Chlorophenyl)-3-phenoxycarbonylthiourea (**34**). This compound was prepared by the method employed in the synthesis of **15**. From 6.35 g (0.050 mol) of 4-chloroaniline was obtained 7.5 g (49%)

of **34**, m.p. 137–139°. Recrystallization from EtOH gave 3.2 g, m.p. 142–143°. – IR. ($CHCl_3$): 3405, 1737. – MS.: 306 (M^+, 15), 213 (5), 169 (38), 94 (100).

$C_{14}H_{11}ClN_2O_2S$	Calc.	C 54.81	H 3.61	Cl 11.56	N 9.13	S 10.45%
(306.77)	Found	„ 54.53	„ 3.70	„ 11.52	„ 8.96	„ 10.55%

1-(2-methylcarbazoyl)-3-(4-chlorophenyl)thiourea (**35**). A solution of 7.20 g (0.0234 mol) of **34** and 1.24 ml (0.0235 mol) of 1-methylhydrazine in 150 ml of THF was stirred overnight and concentrated as 3.95 g (65%) of **35**, m.p. 162–163° (dec.) separated. Recrystallization from $MeOH/CH_2Cl_2$ gave m.p. 167–168° (dec.). – IR. (KBr): 3335, 3319, 3240, 3190, 1682. – ^{1}H-NMR. (DMSO): 3.07 (*s*, 3 H, N–CH_3); 5.00 (br., 2 H, NH_2); 7.30 (*d*, 2 H, arom.); 7.62 (*d*, 2 H, arom.); 9.80 (br., 1 H, NH); 12.32 (br., 1 H, NH). – MS.: 258 (M^+, 49), 224 (18), 213 (40), 169 (100), 127 (76).

$C_9H_{11}ClN_4OS$	Calc.	C 41.78	H 4.29	Cl 13.70	N 21.66	S 12.39%
(258.73)	Found	„ 41.66	„ 4.23	„ 13.97	„ 21.52	„ 12.63%

1-(3-Isopropylidene-2-methylcarbazoyl)-3-(4-chlorophenyl)thiourea (**36**). A solution of 0.10 g (0.39 mmol) of **35** in 5 ml of acetone was stirred over 4A molecular sieves for 2 weaks. The reaction mixture was filtered and evaporated to give 85 mg of **36** as an oil. – IR. ($CHCl_3$): 3370, 1673. – ^{1}H-NMR. ($CDCl_3$): 1.94 (*s*, 3 H, N–CH_3); 2.07, 3.05 (*s*, 3 H each, *gem*-CH_3); 7.29 (*m*, 2 H, arom.); 7.62 (*m*, 2 H, arom.); 8.81 (br., 1 H, NH); 12.36 (br., 1 H, NH). – ^{13}C-NMR. ($CDCl_3$) (ppm downfield from TMS): 20.5, 25.5 (*gem*-CH_3), 35.8 (CH_3N). – MS.: 298 (M^+, 17), 169 (22), 86 (100).

*5-(4-Chlorophenylamino)-2-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one* (**37e**). A solution of 0.5 g (0.0019 mol) of **35** in 50 ml of EtOH was heated under reflux for 8 days. Upon cooling, 0.18 g (42%) of **37e**, m.p. 268–271° separated. Recrystallization from EtOH gave 0.090 g, m.p. 274–275°. – IR. (KBr): 3280, 3200, 1710, 1650. – MS.: 224 (M^+, 100), 179 (35), 152 (23).

$C_9H_9ClN_4O$	Calc.	C 48.12	H 4.04	Cl 15.78	N 24.94%
(224.65)	Found	„ 47.90	„ 4.06	„ 15.65	„ 25.17%

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