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PREPARATION OF DERIVATIVES OF AMIDINEUREA AND THEIR REACTIONS

B. SKOWROŃSKA-SERAFIN and T. URBAŃSKI

Department of Organic Technology, Institute of Technology, (Politechnika) Warszawa, 10

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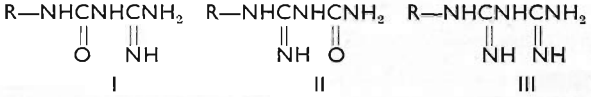
Abstract—A new method for preparing 1-amidine-3-arylureas or-3-alkylureas (I) from aryl or alkyl amine and cyanoguanidine or by hydrolysis of corresponding aryl or alkyl biguanides is described. The reaction of salts of amidineureas with primary or secondary amines to yield substituted ureas is described.

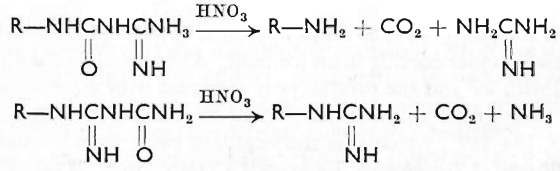
Aromatic amidineureas

MONOSUBSTITUTED aromatic derivatives of amidineureas can exist in two isomeric forms, viz. as 1-aryl-3-amidineureas (I) and 1-arylamidineureas (II).



I II III

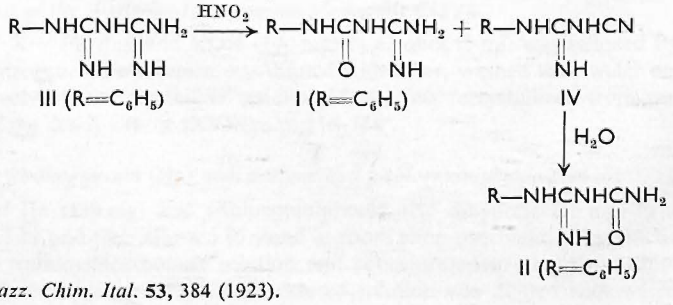
The isomers differ in behaviour when warmed with dilute nitric acid,[1] according to the equations:



Another reaction characterizing derivatives II is the formation of complex compounds with metals such as Cu, Ni. 1-Aryl-3-amidineureas (I) do not form such complexes.

The difference between the infra-red spectra of 1-phenyl-3-amidineurea and 1-phenylamidineurea, the simplest representatives of I and II respectively, indicate a new method (described later) to distinguish these isomers.

Unlike the compounds II, the 1-aryl-3-amidineureas (I) are little known. 1-Phenyl-3-amidineurea (I, R = C_6H_5) and some of its derivatives, were first prepared by Pellizzari.[1] In the course of the reaction phenylcyanguanidine (IV) was also formed. The latter is readily hydrolysed to 1-phenylamidineurea. (II, R = C_6H_5).

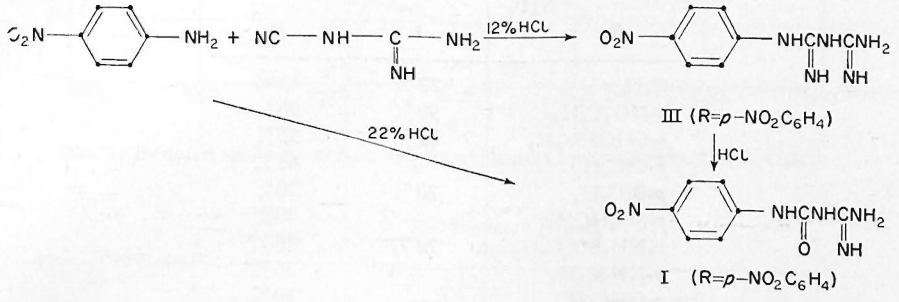


[1] G. Pellizzari, *Gazz. Chim. Ital.* **53**, 384 (1923).

Amidineureas and some aromatic derivatives (I) have also been prepared by Passerini[2], Junod[3] and Kundu and Ray[4].

A good yield of 1-amidine-3-*p*-nitrophenyl-urea (I, R = *p*-$NO_2C_6H_4$) is obtained when *p*-nitraniline reacts with cyanguanidine in a 22 per cent concentration of hydrochloric acid.[5,6]

p-Nitrophenylbiguanide (III, R = *p*-$NO_2C_6H_4$) is formed[7] when the concentration of hydrochloric acid is lower (12 per cent), but it is transformed into 1-amidine-3-*p*-nitrophenyl-urea (I, R = *p*-$NO_2C_6H_4$) by hydrolysis with 22 per cent hydrochloric acid.



This hydrolysis of biguanide derivatives (III, R = *p*-$CH_3CONHC_6H_4$) with hydrochloric acid was formerly observed by Mingoia and Ferreira,[8] but they ascribed the arylamidineurea structure (II, R = *p*-$NH_2C_6H_4$) to the product.

Starting from *p*-sulphamidephenylbiguanide in acid medium Kundu[9] obtained a compound which does not yield a complex with Cu and Ni and on this basis ascribed the structure I,(R = *p*-$NH_2SO_2C_6H_4$) to it. The structure was confirmed later by synthesis.

The correct structure for the product prepared by Mingoia and Ferreira[8] is I,(R = *p*-$NH_2C_6H_4$) as it is identical with that prepared by reduction of 1-amidine-3-*p*-nitrophenyl-urea.[10] (I, R = *p*-$NO_2C_6H_4$).

Further experiments have shown that (A) amines and cyanoguanidine in the presence of excess acid and (B) the hydrolysis of arylbiguanides (III) can be used to prepare compounds I.

Starting from a number of aromatic amines both reactions (A) and (B) have been carried out.[5,6,10–12] Generally speaking, a better yield of amidineureas (I) can be obtained by hydrolysing biguanides (III) according to (B). In some instances, however, the method (A) being simpler is advised. This applies to such amines as aniline, *p*-nitroaniline and *p*-aminobenzoic acid, which give yields of 80–90 per cent.

[2] R. Passerini, *Boll. Sci. Fac. Chim. Ind. Bologna* **9**, 27 (1951).
[3] E. Junod, *Helv. Chim. Acta* **35**, 1670 (1952).
[4] N. Kundu and P. Ray, *Indian Chem. Soc.* **29**, 811 (1952); *Chem. Abstr.* **48**, 2600 (1954).
[5] T. Urbański, B. Skowrońska-Serafinowa and H. Dabrowska, *Roczn. Chem.* **27**, 65 (1953).
[6] T. Urbański, B. Skowrońska-Serafin, H. Dabrowska and J. Jankowska, *Bull. Acad. Pol. Sci.* Cl. III, **1**, 74 (1953).
[7] F. H. S. Curd and F. L. Rose, *J. Chem. Soc.* **365** (1946).
[8] Q. Mingoia and P. C. Ferreira, *An. Fac. Farm. Odontol. Univ. Sao Paulo* **7**, 43 (1949); *Chem. Abstr.* **45**, 1971 (1951).
[9] N. Kundu, *Sci. & Cult.* **15**, 449 (1950); *Chem. Abstr.* **44**, 9367 (1950).
[10] T. Urbański, B. Skowrońska-Serafin and H. Dabrowska, *Roczn. Chem.* **28**, 423 (1954).
[11] T. Urbański, B. Skowrońska-Serafin and H. Dabrowska, *Bull. Acad. Pol. Sci.* Cl. III, **2**, 453 (1954).
[12] T. Urbański, B. Skowrońska-Serafin and H. Dabrowska, *Roczn. Chem.* **29**, 450 (1955).

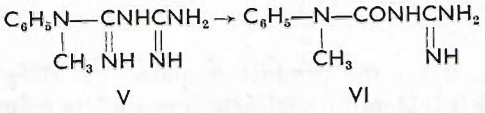
The preparation of amidineureas (I) from *m*- and *p*-aminophenols and *p*-chloroaniline was unsuccessful. Also the yield of I when using arylbiguanides prepared from some amines (III, R = *m*- and *p*-OHC_6H_4, β-naphthyl) is relatively low. This is probably due to instability of these amidineureas on warming with acids.

Table 1 gives the yields of arylamidineureas (I) prepared by reactions (A) and (B).

TABLE 1

R-NHCONHCNH₂ (NH) R	Yield of the reactions A	B
C_6H_5	83%	65%
p-$NO_2C_6H_4$	90%	90%
p-$COOHC_6H_4$	82%	95%
p-ClC_6H_4	—	65%
p-BrC_6H_4	20%	70%
p-$SO_3HC_6H_4$	—	50%
p-$NH_2SO_2C_6H_4$	20%	60%
p-$NH_2C_6H_4$	—	80%[8]
p-OHC_6H_4	—	10%
m-OHC_6H_4	—	14%
β-naphthyl	—	20%

Similarily, when 1-phenyl-1-methylbiguanide (V) was hydrolysed with hydrochloric acid, 1-phenyl-1-methyl-3-amidineurea (VI) resulted.[13]



V VI

Infra-red absorption spectra

Infra-red absorption spectra of four derivatives of 1-aryl-3-amidineurea (I, R = C_6H_5, hydrochloride; R = *p*-HO—C_6H_4, sulphate; R = *m*-HO—C_6H_4, sulphate; R = *p*-$NH_2SO_2C_6H_4$, hydrochloride) and the isomeric 1-phenylamidineurea (II, R = C_6H_5, hydrochloride) were examined in a Nujol mull, the ratio of substance/Nujol being 1 : 1. Infra-red spectrophotometer Hilger H–800 with sodium chloride prism was used.

The results are shown on Figs. 1–5 and the main frequencies are given in Table 2.

An exact assignment of some frequencies of derivatives of urea is complicated by the enolization and possible existence of a few polar forms of urea. In the region 1200–1000 cm^{-1} mono- and 1,4-disubstituted derivatives of benzene give frequencies which coincide with those of the $-NH_2$ group attached to an aliphatic chain.

All examined compounds give frequencies in the region 3500–3300 cm^{-1}. They are formed by NH_2 and phenolic groups (the latter in the compounds I, R = *p*- and *m*-$HO{\cdot}C_6H_4$) bonded by intermolecular hydrogen bonds. The structure I (Figs. 1–4) gives a strong absorption in the region 1695–1680 cm^{-1}, typical for a group C=O in

[13] T. Urbański, B. Skowrońska-Serafin, A. Matusiak, A. Tyczyński and M. Zarukiewicz, *Roczn. Chem.* In press.

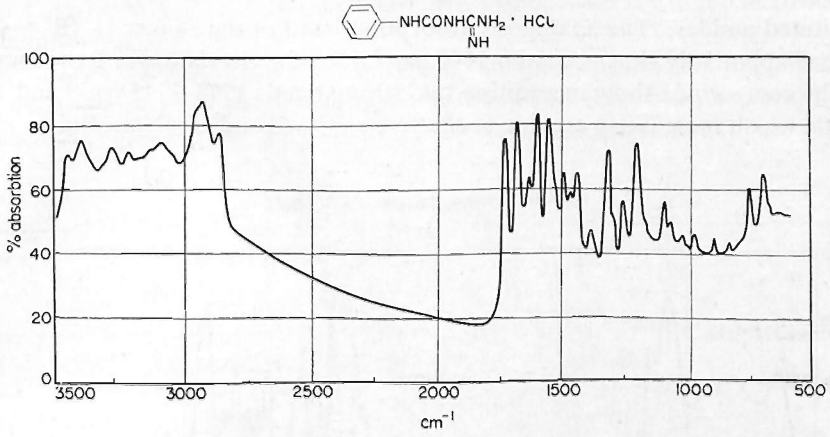


FIG. 1. Infra-red spectrum of 1-phenyl-3-amidineurea hydrochloride (I, R = C_6H_5).

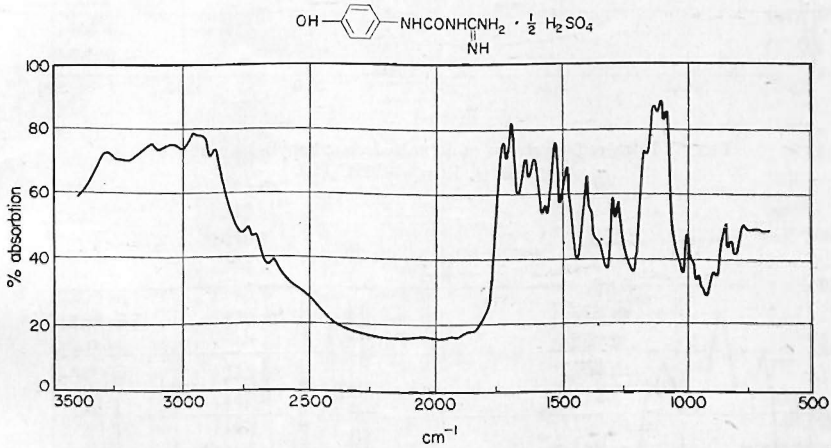


FIG. 2. Infra-red spectrum of 1-(*p*-hydroxyphenyl)-3-amidineurea-sulphate (I, R = *p*-OHC_6H_4).

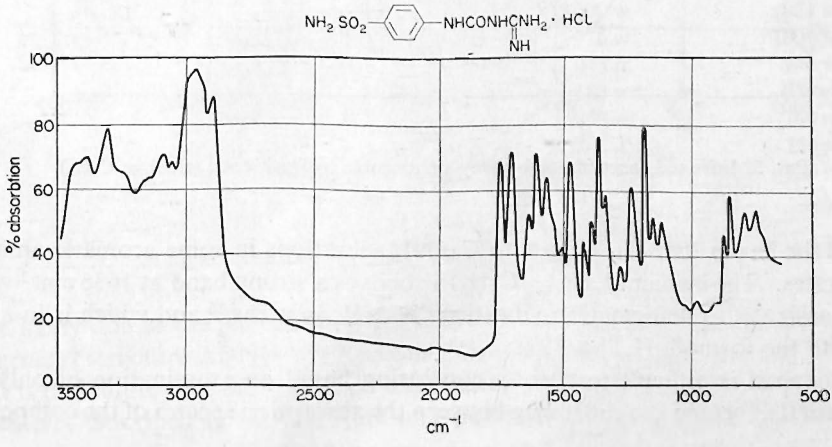


FIG. 3. Infra-red spectrum of 1-(*p*-sulphamidophenyl)-3-amidineurea sulphate (I, R = *p*-$SO_2NH_2C_6H_4$).

N-substituted amides. The analogous absorption band of the isomer II, (R = C_6H_5, Fig. 5) has apparently the maximum 1660 cm^{-1}, i.e. of a clearly lower frequency.

All the compounds show in addition two strong bands 1728–1715 cm^{-1} and 1620–1600 cm^{-1} which most likely are due to the groups C=O and C=NH. Boivin *et al.*[14]

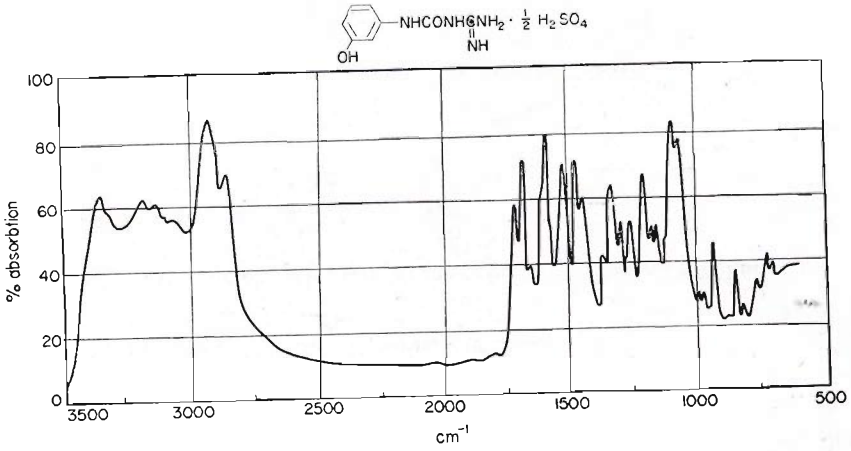


FIG. 4. Infra-red spectrum of 1-(*m*-hydroxyphenyl)-3-amidineurea sulphate (I, R = *m*-OHC_6H_4).

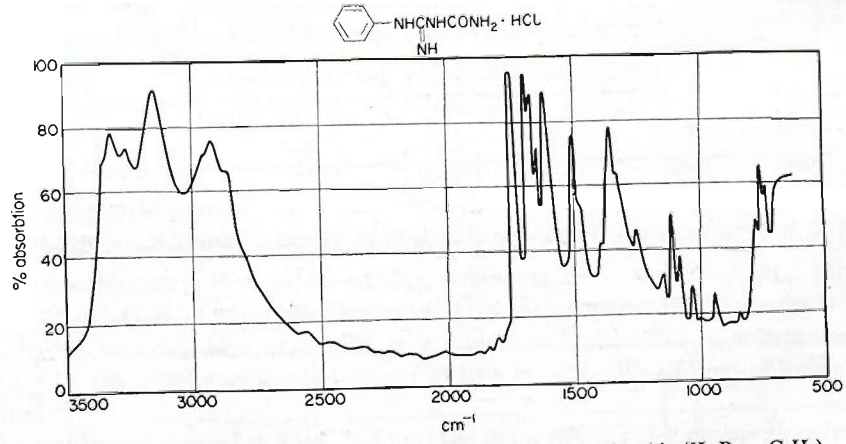


FIG. 5. Infra-red spectrum of 1-phenylamidineurea hydrochloride (II, R = C_6H_5).

assigned the bands 1710–1670 cm^{-1} to C=NH vibrations in some aromatic amidine-urea nitrates. The isomer II, (R = C_6H_5) also gives a strong band at 1636 cm^{-1} which may be assigned to deformation vibrations of NH_2 in ureas,[15] and which is in agreement with the formula II.

Although it is difficult to draw a conclusion based on examination of only one substance (II), the marked difference between the absorption spectra of the compounds

[14] P. Boivin, W. Brigeo and J. Boivin, *J. Canad. Chem.* **32**, 242 (1954).
[15] H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, *Infra-red Determination of Organic Structures*. Van Nostrand, New York (1949).

I ($R = C_6H_5$) and II ($R = C_6H_5$) may give new evidence for the different structures of these compounds.

Boivin *et al.*[14] found bands 1380–1310 cm^{-1} in the examined nitrates of amidineureas, assigning them to the N=O bands in the nitrate ions, but we found the same frequencies (1374–1320 cm^{-1}) in the hydrochlorides and sulphates. These bands are

TABLE 2. INFRA-RED FREQUENCIES

	I Ar-NHCONHC—NH_2·HX (NH)				II
Ar	C_6H_5	*p*-OHC_6H_4	*p*-$SO_2NH_2C_6H_4$	*m*-HOC_6H_4	$C_6H_5NHCNHCONH_2$· (NH) HCl
HX	HCl	$\frac{1}{2}H_2SO_4$	HCl	$\frac{1}{2}H_2SO_4$	
Fig.	1	2	3	4	5
	3465 s	3300 s	3425 s	3425 s	3310 s
	3410 s	3113 s	3370 s	3194 s	3250 s
	3290 s	1715 s	3290 s	1724 s	3135 s
	3219 s	1684 s	3068 s	1695 s	1720 s
	3095 s	1625 s	1725 s	1660 w	1660 s
	1728 s	1590 s	1688 s	1618 m	1636 s
	1680 s	1535 m	1614 s	1540 s	1620 s
	1620 m	1512 s	1580 s	1495 s	1590 s
	1595 s	1450 s	1550 s	1453 s	1563 m
	1555 s	1374 s	1495 w	1370 w	1545 w
	1500 m	1335 w	1454 s	1338 s	1480 s
	1460 m	1270 w	1400 m	1314 m	1453 m
	1445 m	1250 m	1373 m	1287 w	1375 w
	1377 w	1235 m	1339 s	1266 m	1332 s
	1320 s	1140 s	1320 s	1212 s	1313 s
	1260 m	1105 s	1263 w	1180 m	1233 m
	1210 s	1185 s	1205 s	1158 m	1140 w
	1118 m	1060 s	1161 s	1085 s	1100 m
	980 w	978 w	1125 m	1065 s	1074 m
	905 w	932 w	1092 m	1000 w	1028 w
	838 w	872 w	1008 w	976 w	1006 w
	763 m	825 m	970 w	945 m	945 w
	714 s	807 w	890 w	885 w	838 w
		755 w	843 m	852 m	760 m
			880 s	820 w	750 s
			770 m	775 w	730 m
				730 m	
				710 m	

more likely due to the stretching vibrations of a C—N band in secondary amines of the general structure Ar-NH—R[16] present in both I and II.

It is difficult to find more detailed assignment of the bands as the number of urea derivatives described in the literature and examined is very small. Examination of

[16] R. B. Barnes, R. C. Gore, U. Lidell and V. Z. Williams, *Infra-red Spectroscopy*. New York (1944).

infra-red absorption spectra of a larger number of urea and guanidine derivatives is being continued.

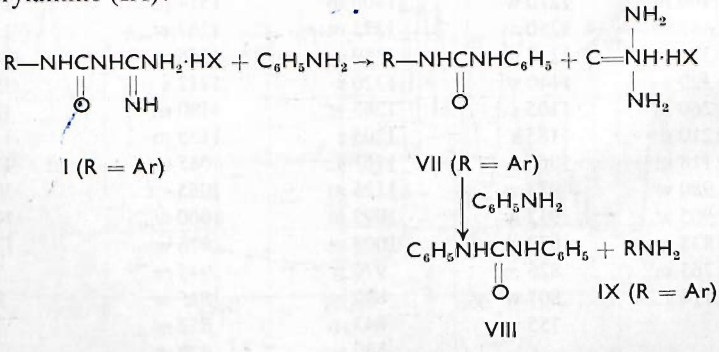
Aliphatic amidineureas

Preliminary experiments on the preparation of aliphatic amidineureas (I) by analogous reactions (A) and (B) have been carried out using benzylamine and n-butylamine.[13] In both cases we failed to obtain I directly from amines and cyanoguanidine according to the method (A). Aliphatic amines do not readily react with cyanoguanidine and thus, alkylbiguanides (III) are not prepared in aqueous solution, but require fusion of amine salts with cyanoguanidine. Also, hydrolysis of biguanides (III) to yield I (reaction B) occurred with a small yield in both cases. Benzylbiguanide (III, R = $C_6H_5CH_2$), yielded 11 per cent 1-amidine-3-benzylurea (I, R = $C_6H_5CH_2$) when hydrolysed with hydrochloric acid. In addition a number of decomposition products (benzylamine, guanidine, CO_2 and NH_3) were formed and a small quantity of unchanged benzylbiguanide remained.

In the case of n-butylbiguanide the yield of 1-amidine-3-(n-butyl)-urea (I, R = n-C_4H_9) was still lower; when the time of heating was shorter and the concentration of hydrochloric acid lower, a considerable amount of unchanged biguanide was left. When the time was longer and the concentration of the acid larger, a complete decomposition into n-butylamine, guanidine, CO_2 and NH_3 was produced, most likely due to instability of butylamidineurea on heating with conc. hydrochloric acid.

Reaction of amidineureas (I) *with primary and secondary amines*

Salts of arylamidineureas readily react with excess aniline to yield in the first instance 1-aryl-3-phenylurea (VII) and guanidine. Prolonged boiling yields carbanilide (VIII) and arylamine (IX):

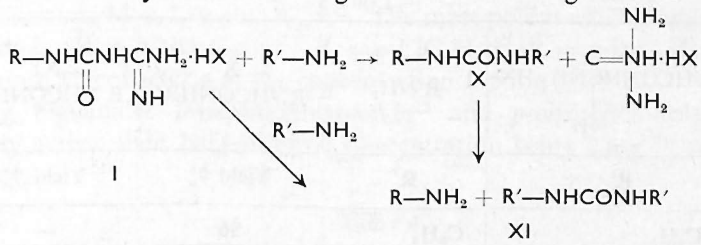


Very often the transformation of arylphenylureas into carbanilide was so fast that isolation of the intermediate (VII) was impossible.

The reaction of arylamidineureas with *o*-, *m*- and *p*-toluidine,[17] 2-aminopyridine,[18,19] cyclohexylamine, piperidine and n-butylamine[20] have been examined. In all these instances compounds of the type VII (R = $C_6H_4CH_3$ *o*-, *m*-, *p*-, 2-pirydyl, C_5H_{11}, piperidyl, n-C_4H_9) were formed, but symmetrical derivatives of urea of the

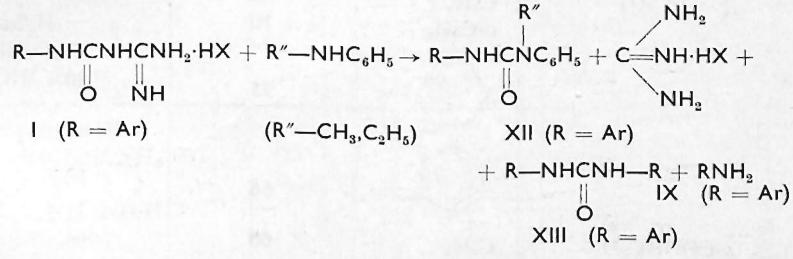
[17] T. Urbański, B. Skowrońska-Serafin and G. Chadzyński, *Roczn. Chem.* In press.
[18] T. Urbański and B. Skowrońska-Serafin, *Bull. Acad. Pol. Sci.* Cl. III, **4**, 361 (1956).
[19] B. Skowrońska-Serafin and T. Urbański, *Roczn. Chem.* **30**, 1189 (1956).
[20] T. Urbański, B. Skowrońska-Serafin and J. Zyolwski, *Roczn. Chem.* In press.

type (XI) were not always obtained. In general the following reaction can be given:

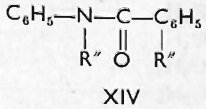


The reaction of salts of the arylamidineureas with amines is a convenient method of preparing disubstituted derivatives of urea of the general formula X. Table 3 gives the disubstituted ureas (X) and (XI) prepared by this method.

The reaction of salts of 1-aryl-3-amidineureas with secondary aromatic–aliphatic amines has a different trend.[17,19,21] When a salt of aryl amidineura (I, R = Ar) is warmed to boiling with N-methyl or N-ethyl-aniline, 1-aryl-1-alkyl-3-arylurea (XII) and a guanidine salt is obtained together with a small quantity of sym-diarylurea (XIII). Prolonged boiling reduces the yield of XII, increases the yield of XIII and arylamine, and produces tarry decomposition products.



The reaction differs from that with primary amines in that the sym-diarylurea (XIII) contains the same R-groups as the original arylamidineurea and dialkylcarbanilide (XIV) which would be analogous to carbanilide (VIII) is not formed.



When XII is boiled with an excess of N-alkylarylamine, it is recovered unchanged after several hours.

Biological activity

All derivatives of guanidine described in this paper possess a pronounced biological activity and have been examined against TB, tumor cells and malaria.

Toxicity. Amidineureas (I) proved to be of relatively low toxicity,* the LD_{50} being, when taken per os 1–3 g/kg, and when applied intravenously 0·1 g/kg. Biguanides are of much higher toxicity, β-naphthylbiguanide[23] being LD_{50} per 0·1 g/kg.

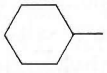
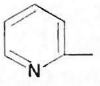
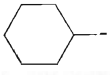
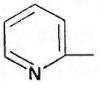
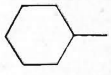
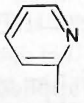
* These were examined by Dr. J. Venulet, Miss K. Jakimowska and Miss A. Urbańska.

[21] T. Urbański and B. Skowrońska-Serafin, *Bull. Acad. Pol. Sci.* Cl. III, **4**, 363 (1956).

[22] T. Urbański, B. Serafinowa, S. Malinowski, S. Ślopek, I. Kamieńska, J. Venulet and K. Jakimowska, *Gruźlica* **20**, 153, 293 (1952).

[23] T. Urbański, S. Malinowski, B. Skowrońska-Serafin, B. Chechelska, H. Dabrowska, J. Falecki, D. Gürne, S. Ślopek, I. Kamieńska, J. Venulet, K. Jakimowska and A. Urbańska, *Gruźlica* **22**, 681 (1954).

TABLE 3

I $R—NHCONHCNH_2 \cdot HX$ (NH)	$R'NH_2$	X $RNHCONHR'$	XI $R'NHCONHR'$
R	R′	Yield %	Yield %
C_6H_5	C_6H_5	96	—
	o-$CH_3C_6H_4$	58	65
	m-$CH_3C_6H_4$	42	67
	p-$CH_3C_6H_4$	68	79
	n-C_4H_9	94	—
		75	75
		50	—
p-$NO_2C_6H_4$	C_6H_5	80	60
	n-C_4H_9	10	—
		95	80
		66	10
p-$COOHC_6H_4$	C_6H_5	60	98
p-$SO_3HC_6H_4$	C_6H_5	—	70
p-$NH_2SO_2C_6H_4$	C_6H_5	90	60
p-ClC_6H_4	C_6H_5	40	62
p-BrC_6H_4	C_6H_5	30	70
p-OHC_6H_4	C_6H_5	—	80
m-OHC_6H_4	C_6H_5	—	80
p-$NH_2C_6H_4$	C_6H_5	—	65
β-naphthyl	C_6H_5	51	80
	piperidine	94	—
		92	88
	n-C_4H_9	98	—
		20	—
$C_6H_5CH_2$	$C_6H_5CH_2$	90	—
	C_6H_5	75	30
n-C_4H_9	n-C_4H_9	90	—
	C_6H_5	50	30

Antituberculous activity. This was examined* *in vitro* by means of *Mycobacterium smegmatis* strains, Myc. 279 and $H_{37}Rv$. The most potent among amidineureas were compounds I. ($R = p\text{-}NO_2C_6H_4$;[22] $R = p\text{-}ClC_6H_4$;[23] $R = p\text{-}BrC_6H_4$.[24]) They were active against Mycobacteria at the concentration 1–5 mg %.

Among biguanides β-naphthylbiguanide[23] and *p*-nitrophenylbiguanide[24] were particularly active, their bacteriostatic concentration being 2 mg % and 8–15 mg % respectively.

TABLE 4

Compounds I $R—NHCONHCNH_2$ ‖ $NH\cdot HCl$ R	Kind of cells								
	Ehrlich ascites carcinoma			Amytal ascites sarcoma			Leucocytes of guinea pigs		
	concentration of compounds in μg/ml								
	1000	100	10	1000	100	10	1000	100	10
p-$NO_2C_6H_4$	+++	+++	+++	+++	+++	+++	+++	+++	+++
C_6H_5	+++	+++	++	+++	+++	++	+++	+++	+
p-BrC_6H_4	+++	+++	++	+++	+++	++	+++	+++	+++
p-$NH_2C_6H_4$	—	—	—	—	—	—	+++	++	+
m-OHC_6H_4	—	—	—	—	—	—	+++	+++	++
Compounds III $R—NHCNHCNH_2$ ‖ ‖ NH $NH\cdot HCl$ R									
p-$CH_3C_6H_4$	—	—	—	—	—	—	+++	+++	+++
β-naphthyl	+++	+++	++	+++	+++	++	+++	+++	+++
p-BrC_6H_4	±	±	—	±	±	±	+++	++	++
p-$NO_2C_6H_4$	+++	++	+	+++	++	+	+++	+++	+++
Mercuric chloride	+++	+++	+++	+++	+++	+++	+++	+++	+++

All substances were ineffective *in vivo* against experimental TB in mice, rats and guinea pigs.*

Antineoplastic activity. Experiments *in vitro* were carried out by Ślopek and Mordarski using the modified Miyamura test with three types of tumor cells, namely, Ehrlich ascites carcinoma, amytal ascites sarcoma and leucocytes of guinea pig.[25]

Table 4 tabulates the result of these tests.

The experiments *in vivo* will be carried out.

* By Professor S. Ślopek and Dr. M. Janowiec.

[24] T. Urbański, C. Bełżecki, B. Chechelska, B. Chylińska, H. Dabrowska, J. Falecki, D. Gürne, L. Halski, S. Malinowski, B. Serafinowa, J. Zylowski, S. Ślopek, I. Kamieńska, J. Venulet, M. Janowiec, K. Jakimowska, A. Urbańska and A. Kuzniecow *Gruźlica* **26**, 889 (1958).

[25] S. Ślopek, H. Mordarska, M. Mordarski, T. Urbański, Skowrońska-Serafin and H. Dabrowska, *Bull. Acad. Pol. Sci.* Cl. III, **6**, 355 (1958).

TABLE 5

Substrates						R—NHCONHC(NH)NH_2 I					
						Hydrochloride				Base	
R—NH_2		DCDA g	HCl (conc) ml	Water ml	Heating period	m.p.	Yield		Cryst. solvent	m.p.	Cryst. solvent
R	g						g	%			
p-$NO_2C_6H_4$	13·5	8·4	17·0	11·0	30 min	280–282 (dec.)	13·5	90	dil HCl	231–232°	alcohol
p-$COOHC_6H_4$	5·0	3·1	1·5[a]	71·5	15 min	247–248° [b]	8·0	82	dil H_2SO_4	198–200°	water
C_6H_5	6·5[c]	4·2	5·0	1·0	5 hr	163–164° [d]	9·3	83	dil HCl	—	—
p-$SO_2NH_2C_6H_4$	6·3[c]	2·4	—	15·0	1·5 hr	—	1·6	20	—	212–213°	water
p-BrC_6H_4	2·5	1·7	(1) 2·5 (2) 2·0	2·5 4·0	45 min[e] 30 min[f]	200°	1·0	20	dil HCl	171–172°	water

[a] Conc. H_2SO_4
[b] Sulphate
[c] Hydrochloride
[d] With 1 mole crystal water
[e] After heating the reaction mixture was made alkaline to pH 8
[f] After heating for 45 min 2·0 ml conc. HCl and 4 ml water were added and the mixture heated for further 30 min.

Antimalarial activity. Experiments with chicks infected with *Plasmodium gallinaceum** show the best results with the compound I(R = *p*-$NO_2C_6H_4$). A dose of 40 mg/kg kept the chicks free from parasites in the peripheral blood, and a dose of 20 mg/kg diminished greatly the peripheral parasites.[26]

TABLE 6

Substrates					R-NHCONHC(NH)NH_2 I					
RNHC(NH)NHC(NH)NH_2·HCl		HCl (conc) ml	Water ml	Heating period	Hydrochloride				Base	
R	g				m.p.	Yield g	Yield %	Cryst. solvent	m.p.	Cryst. solvent
p-$NO_2C_6H_4$	5·0	18·0	13·0	1 hr	—	4·5	90	—	231–232°[a]	alcohol
p-$COOHC_6H_4$	2·0[b]	40·0	40·0	2 hr	~ 350°	2·2	95	—	198–200°[c]	water
C_6H_5	3·0	3·3	4·7	1 hr	163–164°	2·0	65	dil HCl	—	—
p-$NH_2SO_2C_6H_4$	5·0	6·0	15·0	30 min	~ 220°	3·0	60	—	212–213°	water
p-ClC_6H_4	3·8	1·2	4·0	20 min	206–207°	2·4	65	water	143–144°	water
p-BrC_6H_4	3·0	1·7	4·2	45 min	—	1·5	70	water	171–172°[a]	water
p-$SO_3HC_6H_4$	7·5[b]	22·0	56·0	1 hr	—	3·2	50	—	267–269°	sat $NaHCO_3$
p-OHC_6H_4	5·0	1·2	3·8	1 hr	214–215°[e]	0·5	10	water	—	—
m-OHC_6H_4	5·0	1·2	3·8	1 hr	220–222°[e]	1·5	14	water	—	—
β-naphthyl	13·8	14·0	70·0	1·5 hr	279–281°	2·1	21	water	177–179°	dil alcohol
$C_6H_5CH_2$	3·6[f]	3·0	7·5	5 hr	167–168°[f]	0·4	11	water	142–144°	water
1-Phenyl-1-methyl-biguanid·HCl (V)	10·0	6·0	3·0	2 hr	237–238° (VI)	6·0	60	5%HCl		

[a] The precipitate was filtered, dissolved in water and made alkaline with dil NaOH
[b] Free base with 1 mole H_2O
[c] Hydrolysis of hydrochloride occurs on boiling with water
[d] The precipitate was filtered hot and recrystallized from sat $NaHCO_3$
[e] M.p. of sulphate ; after cooling the reaction mixture was filtered and the product recrystallized from dil H_2SO_4 with 1 H_2O
[f] *p*-Toluenosulphonate

EXPERIMENTAL

Preparation of arylamidineureas (I) *from amines and cyanoguanidine*

Example. *p*-Nitroaniline (13·8; 0·1 mole) were dissolved in 17 ml HCl and 11 ml water at 50°. Cyanoguanidine (8·4 g, 0·1 mole) was added and the mixture heated cautiously; a vigorous reaction gave a crystalline product. After refluxing for 30 min the mixture was chilled, filtered and the crystals were washed with 22% HCl and alcohol, to yield 13·5 g (90%) 1-(p-*nitrophenyl*)-3-*amidineurea hydrochloride*, m.p. 280–282° (decomp.)

The filtrate, concentrated and made alkaline with NaOH, yielded 5·8 g *p*-nitraniline. For other derivatives see Table 5.

Preparation of arylamidineureas (I) *from arylbiguanides* (III)

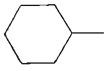
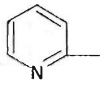
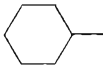
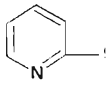
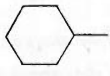
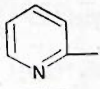
Example. Phenylbiguanide hydrochloride (3 g) were heated with 3·3 ml conc HCl for 1 hr. On cooling 1-*phenyl*-3-*amidineurea hydrochloride* precipitated; m.p. after recrystallization from dil HCl 163–164°, yield 2·0 g (65%). For other derivatives see Table 6.

Reaction of arylamidineureas (I) *with primary amines*

Example. 1-Phenyl-3-amidineurea hydrochloride (2·5 g) and 3 g *p*-toluidine were mixed and heated to a clear solution, and then refluxed gently for 1–2 min. After cooling dil HCl was added, the

* Carried out by Professor Yin-chiang Chin and Dr. Yun-yi Wu, Academy of Medical Sciences, Peking.
[26] Y. Ch. Chin, Y. Y. Wu, T. Urbański, B. Skowrońska-Serafin and J. Venulet, *Nature, Lond.* In press.

TABLE 7

Substrates					R—NHCONH—R′	
R—NHCONHC(NH)NH_2·HCl		R′—NH_2		Heating period	m.p.[a]	Yield %
R	g	R′	g			
C_6H_5	2·8	C_6H_5—	12·0	10 min	236–237°	96
	2·5	*o*-$CH_3C_6H_4$—	4·0	15 min	202–203°	58
	2·5	*m*-$CH_3C_6H_4$—	4·0	1–2 min	174–175°	42
	2·5	*p*-$CH_3C_6H_4$—	3·0	1–2 min	231–232°	68
	5·0	n-C_4H_9—	5·0	1 hr	130–131°	94
	5·0		5·0	2–3 min	182–183°	75
	5·0		5·0	2–3 min	189–199°	50
p-NO_2-C_6H_4	5·0	C_6H_5	15·0	1–3 min	218–219°	80
	10·0	n-C_4H_9	20·0	2 hr[b]	147–149°	traces
	5·0		10·0	2–3 min	205–207°	95
	1·0		2·0	1–2 min	242–247° subl.	66
p-COOH-C_6H_4	0·5	C_6H_5	10·0	10 min	300°	80
p-$NH_2SO_2C_6H_4$	1·0	C_6H_5	15·0	20 min	228–230°	90
p-Cl-C_6H_4	2·0	C_6H_5	10·0	1–2 min	237–238°	40
p-Br-C_6H_4	0·5	C_6H_5	3·0	1–2 min	243–245°	30
β-Naphthyl—	1·0	C_6H_5	5·0	1–2 min	237–238°	51
	5·0		10·0	20 min	204–205°	92
	5·0	n-C_4H_9	10·0	20 min	149–150°	98
	5·0		10·0	20 min	247–248°	20
	2·0		5·0	20 min	153–154°	94
$C_6H_5CH_2$	5·0[c]	$C_6H_5CH_2$	4·8	5 min	165–166	90
	5·0[c]	C_6H_5—	4·2	2 min	169–170°	75
n-C_4H_9—	5·0	n-C_4H_9—	5·0	1 hr	70–71°	95
	0·5	C_6H_5	1·0	1–2 min	129–130°	50

[a] After recrystallization
[b] Heating under presure 4·5 atm, 150–190°
[c] *p*-Toluenosulphonate

crude 1-*phenyl*-3-(p-*tolyl*)*urea* was filtered off and recrystallized from anhydrous ethanol; m.p. 231–232°, yield 1·6 g (68%). For other derivatives see Table 7.

Prolonged heating of the same reagents or of X with an excess amine, resulted in formation of disubstituted ureas (XI). For yields and m.p. see Table 2.

TABLE 8

Substrates						Product		
R—NCONHCNH₂·HCl (R′, NH)			R″—NH—		Heating period	RN—CON— (R′, R″)		
R	R′	g	R″	g		m.p.	Yield g	Yield %
C_6H_5—	H—	3·0[a]	CH_3—	8·0	1–2 min	104–105°	1·8	65
		5·0	C_2H_5—	15·0	5 min	85–86°	2·8	50
p-$NO_2C_6H_4$—	H—	3·0	CH_3—	5·0	5–10 min	124–125°	0·8	26
		5·0	C_2H_5—	15·0	5 min	77–79°	1·5	35
p-ClC_6H_4—	H—	5·0	C_2H_5—	28·0	20 min	123–124°	1·6	30
C_6H_5—	CH_3	5·0	CH_3—	7·0	50 min	121–122°	2·0	38

[a] nitrate

Reaction of arylamidineureas with N-*methyl and* N-*ethyl-aniline*

Example. In an open flask N-methylaniline (1·2 g) and 1-phenyl-3-amidineurea nitrate (3 g) were heated as rapidly as possible (with an open flame) to obtain a clear solution. After cooling dil HCl was added, the precipitate extracted with benzene, dried with anhydrous Na_2SO_4, and evaporated to dryness. The crude product was recrystallized from alcohol to yield 1-*methyl-carbanilide*, m.p. 104–105° (65%).

As an alternative procedure the precipitate formed after HCl acidification can be filtered, washed with H_2O, and recrystallized. For other derivatives see Table 8.

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