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# PREPARATION OF DERIVATIVES OF AMIDINEUREA AND THEIR REACTIONS

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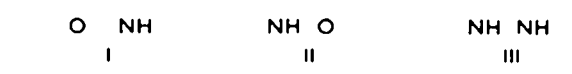
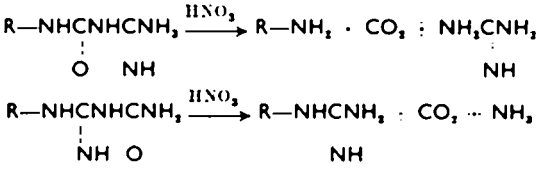
**Abstract**—A new method for preparing 1-amidine-3-arylureas or-3-alkylureas (I) from aryl or alkyl amine and cyanoguanidine or by hydrolysis of corresponding aryl or alkyl biguanides is described. The reaction of salts of amidineureas with primary or secondary amines to yield substituted ureas is described.

*Aromatic amidineureas*

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



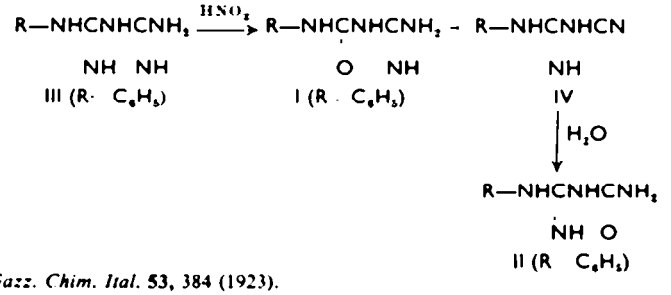
The isomers differ in behaviour when warmed with dilute nitric acid,[1] according to the equations:



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 = $C_6H_5$).

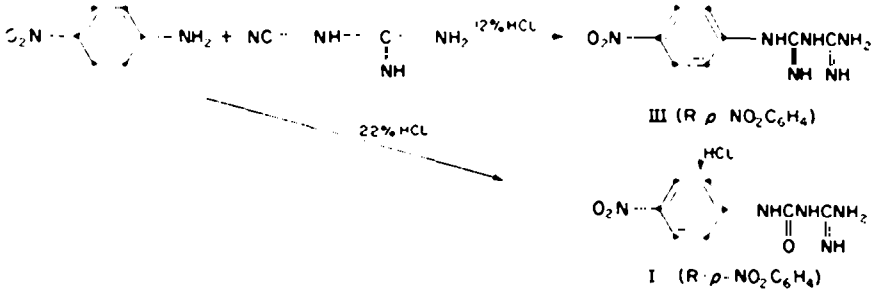


[1] G. Pellizzari, *Gazz. Chim. Ital.* **53**, 384 (1923).

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).

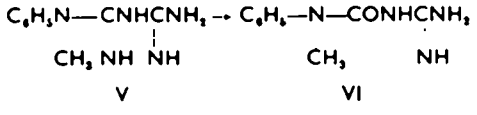
The preparation of amidineureas (I) from *m*- and *p*-aminophenols and *p*-chloroaniline was unsuccessful. Also the yield of I when using arylbiguanides prepared from some amines (III, R = *m*- and *p*-$OHC_6H_4$, $\beta$-naphthyl) is relatively low. This is probably due to instability of these amidineureas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

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

TABLE 1

| R-NHCONHCNH$_2$ (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%[a] |
| *p*-$OHC_6H_4$ | - | 10% |
| *m*-$OHC_6H_4$ | — | 14% |
| $\beta$-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.

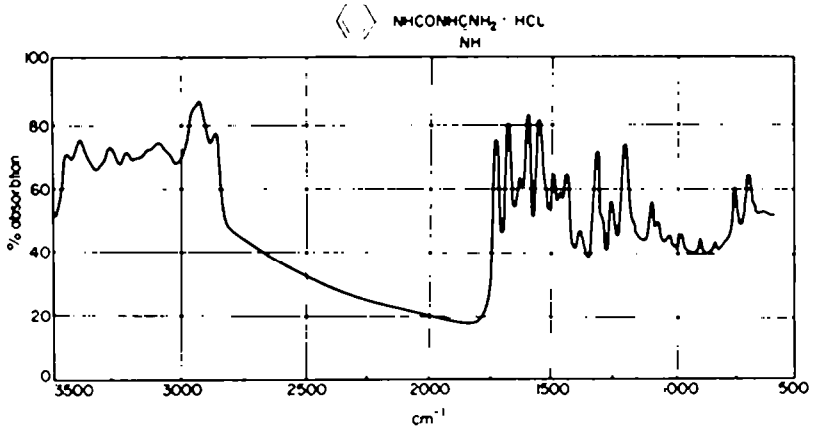



FIG. 1. Infra-red spectrum of 1-phenyl-3-amidineurea hydrochloride (I, R = $C_6H_4$).

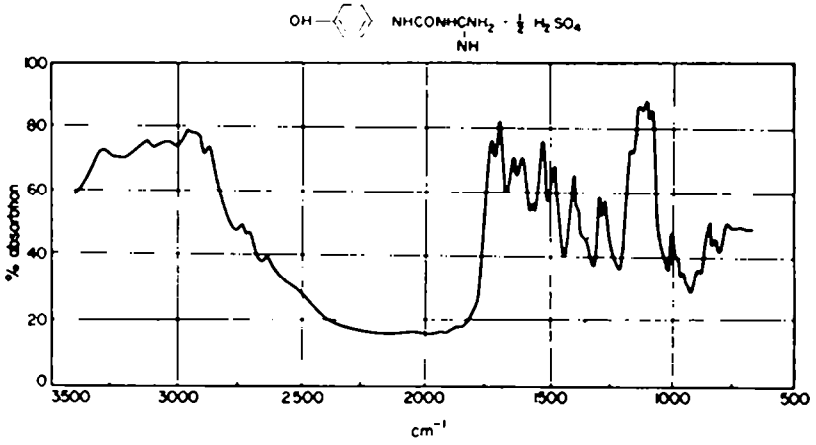



FIG. 2. Infra-red spectrum of 1-(*p*-hydroxyphenyl)-3-amidineurea-sulphate (I, R = *p*-$OHC_6H_4$).

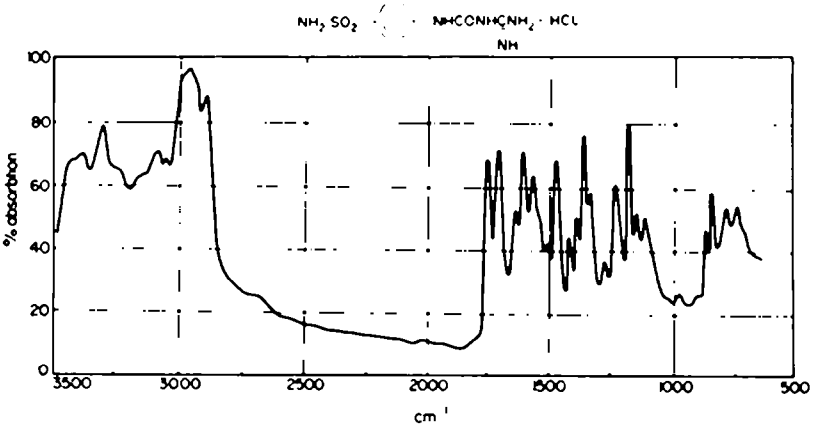



FIG. 3. Infra-red spectrum of 1-(*p*-sulphamidophenyl)-3-amidineurea sulphate (I, R = *p*-$SO_2NH_2C_6H_4$).

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]

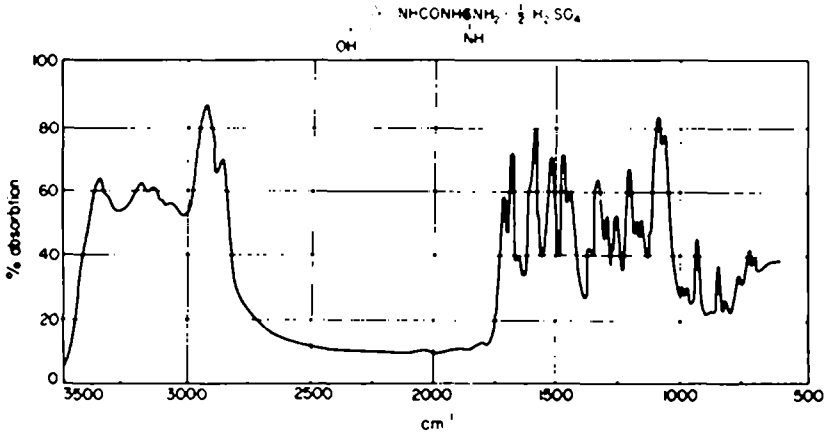



FIG. 4. Infra-red spectrum of 1-(*m*-hydroxyphenyl)-3-amidineurea sulphate (I, R = *m*-$OHC_6H_4$).

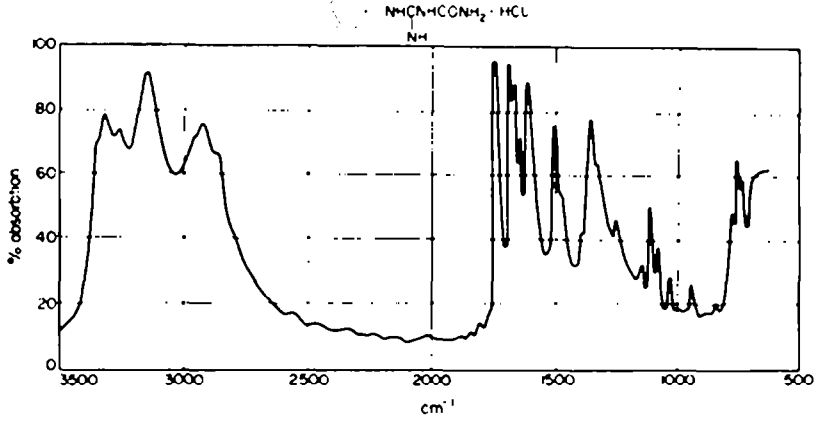



FIG. 5. Infra-red spectrum of 1-phenylamidineurea hydrochloride (II, R = $C_6H_5$).

assigned the bands 1710–1670 cm $^{-1}$ to C=NH vibrations in some aromatic amidineurea 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)-$NH_2$·HX | | | | II |
|---|---|---|---|---|---|
| Ar | $C_6H_5$ | *p*-$OHC_6H_4$ | *p*-$SO_2NH_2C_6H_4$ | *m*-$HOC_6H_4$ | $C_6H_5NHC(=NH)NHCONH_2$·HCl |
| HX | HCl | ½$H_2SO_4$ | HCl | ½$H_2SO_4$ | |
| 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.

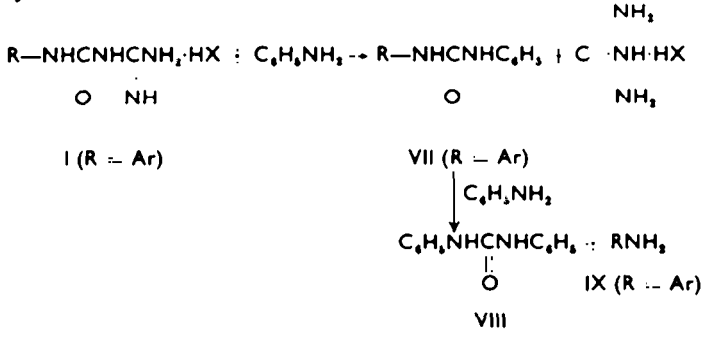
*Aliphatic amidineureas*

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):

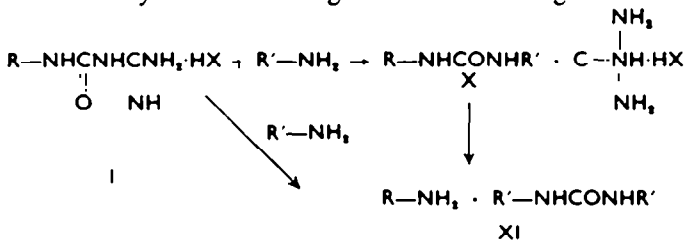



Very often the transformation of arylphenylureas into carbanilide was so fast that isolation of the intermediate (VII) was impossible.

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

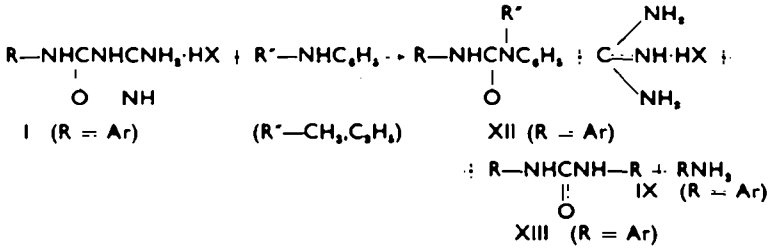
[17] T. Urbański, B. Skowrońska-Serafin and G. Chadzyński, *Roczn. Chem.* In press.
[18] T. Urbański and B. Skowrońska-Serafin, *Bull. Acad. Pol. Sci.* Cl. III, 4, 361 (1956).
[19] B. Skowrońska-Serafin and T. Urbański, *Roczn. Chem.* 30, 1189 (1956).
[20] T. Urbański, B. Skowrońska-Serafin and J. Zyołwski,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

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

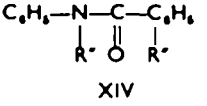


The reaction of salts of the arylamidineureas with amines is a convenient method of preparing disubstituted derivatives of urea of the general formula X. Table 3 gives the disubstituted ureas (X) and (XI) prepared by this method.

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, $\beta$-naphthylbiguanide[23] being $LD_{50}$ per 0·1 g/kg.

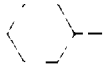
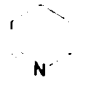
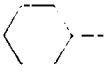
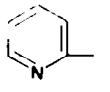
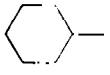
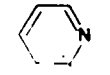
* These were examined by Dr. J. Venulet, Miss K. Jakimowska and Miss A. Urbańska.

[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—NHCONHCNH₂·HX (NH) | R'NH₂ | 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*-$NO_2C_6H_4$;[22] R = *p*-$ClC_6H_4$;[23] R = *p*-$BrC_6H_4$.[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 $R—NHCONHCNH_2$ \| $NH·HCl$ 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 $R-NHCNHCNH_2$ \| $NH\ NH·HCl$ 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. Dąbrowska, 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. Dąbrowska, *Bull. Acad. Pol. Sci.* Cl. III, **6**, 355 (1958).

TABLE 5

| Substrates | | | | | | R—NHCONHC(NH)NH₂ I | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Hydrochloride | | | | Base | |
| R—NH₂ R | g | DCDA g | HCl (conc) ml | Water ml | Heating period | m.p. | Yield g | Yield % | Cryst. solvent | m.p. | Cryst. solvent |
| *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 | 2·5 | 45 min[e] | 200° | 1·0 | 20 | dil HCl | 171 172° | water |
| | | | (2) 2·0 | 4·0 | 30 min[f] | | | | | | |

[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°[d] | 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)

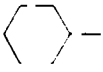
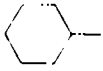
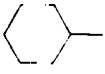
*Example.* Phenylbiguanide hydrochloride (3 g) were heated with 3·3 ml conc HCl for 1 hr. On cooling 1-*phenyl*-3-*amidineurea hydrochloride* precipitated; m.p. after recrystallization from dil HCl 163–164°, yield 2·0 g (65%). For other derivatives see Table 6.

*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)NH₂·HCl | | R′—NH₂ | | 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 | 189 190° | 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. | 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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