continued for 36 hr. The mixture was added to hot H_2O and cooled, and the turbid aqueous solution was extracted with ether and acidified. A solid separated and on crystallization from aqueous methanol afforded 6 g (70%) of **17**, mp 142–144°. The analytical sample melted at 144–145°.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.75; H, 9.59.

Use of triethylene glycol or DMF in place of ethanol reduced the reaction time to a total of 10 hr but gave an inferior product.

γ-(1-Adamantyl)butyric Acid (18).—Sodium (2.5 g) was dissolved in absolute ethanol (50 ml, distilled over Mg) with stirring and protection from moisture and 15 ml of redistilled malonic ester was added dropwise, followed by 15 g of 1-(β-bromoethyl-adamantane). After stirring and refluxing for 5 hr, most of the ethanol was distilled, a solution of 20 g of KOH in 30 ml of H_2O was added, and the mixture was refluxed for 5 hr. More ethanol was removed by distillation and the mixture was cooled, acidified (H_2SO_4), and extracted with ether. The residue from evaporation of the ether was heated in an oil bath at 170–180° for 1 hr for decarboxylation and a solution of the crude acid in dilute KOH was decolorized with Norit, precipitated, and crystallized from aqueous methanol to give 11 g of **18**, mp 100–102°.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.56; H, 9.89.

δ-(1-Adamantyl)valeric Acid (20).—Three grams of β-(1-adamantyl)propionic acid (**17**) was reduced with $LiAlH_4$ and the resulting alcohol (oil) was refluxed with 48% HBr (8 g) and H_2SO_4 (2 g) for 4 hr. The mixture was extracted with hexane, and the extract was washed with Na_2CO_3, dried, and evaporated. Distillation of the residue gave 2.9 g of the bromide, bp 105° (0.15 mm). The malonic ester synthesis, performed as for **18**, gave 2.1 g of **20**, mp 111–112° (aqueous methanol).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.27; H, 10.15.

ε-(1-Adamantyl)hexanoic Acid.—Application to γ-(1-adamantyl)butyric acid of the above sequence: acid → alcohol → bromide [bp 118° (0.18 mm)] → malonic acid derivative gave the hexanoic acid in about 75% yield. After decolorization of a petroleum ether (bp 38–52°) solution with Norit and slow evaporation of solvent, the acid was obtained as soft solid melting at 61–64°.

Anal. Calcd for $C_{16}H_{26}O$: C, 76.75; H, 10.47. Found: C, 77.46; H, 10.39.

Synthesis of 2-Hydroxy-3-(ω-adamantylalkyl)-1,4-naphthoquinones.—Each acid chloride was obtained by reaction of the acid with 20–30% excess $SOCl_2$ in ether and removal of the ether and excess reagent at 50° (water pump). Addition of benzene and redistillation removed traces of reagent. Thionyl chloride was also used without solvent.

The diacyl peroxides were made by reaction of the acyl chloride with 90% H_2O_2 in the presence of pyridine.[13] The yields were generally above 90% but in a few instances some acid accompanied the peroxide. In such a case the acid was recovered in usable form by extraction of an ethereal solution with dilute alkali. The peroxides are solids melting in the range 90–110° with evolution of CO_2.

The first step in the synthesis involves decomposition of a diacyl peroxide in the presence of an equivalent amount of 2-hydroxy-1,4-naphthoquinone (obtainable from commercially available 1,4-naphthoquinone by the method of Fieser).[18] Thus a mixture of the diacyl peroxide and hydroxynaphthoquinone in acetic acid was heated at 100–110° for 4 hr, the acetic acid was distilled *in vacuo*, and the residue was digested with ether. Filtration of the ether left a residue consisting chiefly of hydroxynaphthoquinone. The ether layer was extracted several times with 1% Na_2CO_3 to recover acid derived from hydrolysis of the diacyl peroxide. Further extraction with 2% NaOH and acidification afforded the alkylated quinone, which was purified by crystallization from methanol or ethanol or by chromatography on silica gel. Yields were generally 40–50%. However, the major byproduct of an alkylation is the acid precursor, which can be recovered and recycled with substantial increase in yield. The fourth member of the series (n = 4, mp 120–121°) was obtained by Hooker oxidation and an analysis reported after termination of the work indicated too high an oxygen content, probably due to the presence of some of the intermediate ketol.

Potential Antimalarial Compounds.[1] IX.[2] Pyrimidine Derivatives of Urea and Guanidine

TADEUSZ URBAŃSKI, BARBARA SERAFIN,

Department of Organic Technology, Institute of Technology (Politechnika), Warsaw 10, Poland

AND JERZY ŻYLOWSKI

Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland

Received July 24, 1966
Revised Manuscript Received January 5, 1967

Several substituted derivatives of arylbiguanide and arylamidineurea were prepared and cyclized to the corresponding pyrimidines as additional proof of the structure of arylamidineurea derivatives. Cyclization of the amidineurea moiety to pyrimidine reduces both the toxicity and the antimalarial activity in mice when compared with the starting compounds.

Some substituted amidineureas are active against *Plasmodium gallinaceum in vivo.*[2a,b] One of these compounds, 1-(*p*-nitrophenyl)-3-amidineurea hydrochloride[3] (I), was assessed for its toxicity and subse-

$$p\text{-}NO_2C_6H_4NHCONHC(=NH)NH_2 \cdot HCl$$
I

quently used in a field trial in Tanganyika by Dr. D. F. Clyde on more than 500 subjects infected with *P. falciparum*, *P. malariae*, *P. vivax*, and *P. ovale*; it gave fairly satisfactory results though it showed no advantage in comparison with proguanil.[4] A detailed investigation of this compound, the method of produc-

(1) The financial support of this work from the World Health Organization is gratefully acknowledged.

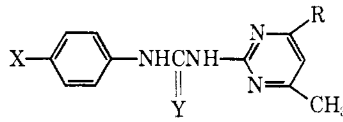
(2) Parts I–VIII are as follows, respectively: (a) Y. Ch. Chin, Y. Y. Wu, B. Skowrońska-Serafin, T. Urbański, and J. Venulet, *Nature*, **186**, 170 (1960); (b) Y. Ch. Chin, Y. Y. Wu, B. Skowrońska-Serafin, T. Urbański, J. Venulet, and K. Jakimowska, *Bull. Acad. Polon. Sci.*, **8**, 109 (1960); (c) B. Skowrońska-Serafin and T. Urbański, *Tetrahedron*, **10**, 12 (1960); (d) T. Urbański, B. Serafin, and D. Ksieżna, Polish Patent, 48,020 (1962); (e) T. Urbański, B. Serafin, D. F. Clyde, K. Jakimowska, M. Wutkiewicz, P. Nantka-Namirski, J. Venulet, G. O. Schlütz, J. Splawiński, and T. Potaczek, *Tetrahedron*, **20**, *Suppl. 1*, 463 (1964); (f) B. Serafin, T. Urbański, and J. Żylowski, *ibid.*, 469 (1964); (g) K. Jakimowska, M. Wutkiewicz, and J. Venulet, *Acta Physiol. Polon.*, **15**, 701 (1964); (h) M. Wutkiewicz and J. Venulet, *ibid.*, **16**, 885 (1965).

(3) Nitroguanil, T 72.

(4) *World Health Organ. Tech. Rept. Ser.*, **320**, 9 (1961).

TABLE I

MELTING POINTS, YIELDS, AND TOXICITY OF PYRIMIDINE DERIVATIVES PREPARED PREVIOUSLY BY OTHER ROUTES

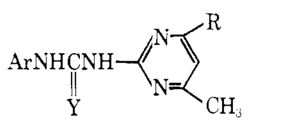


No.[a]	Y	X	R	Mp, °C	Formula	Yield, % Method A[b]	B	Ref	LD_{50} (mice), mg/kg ip
1+	NH	H	CH_3	207–209	$C_{13}H_{15}N_5$	64	67	*d*	247
2+	NH	NO_2	CH_3	237–239	$C_{13}H_{15}N_5O_2$	0	63	2f	1650
3+	NH	Cl	CH_3	209–211	$C_{13}H_{14}N_5Cl$	50	68	12	1505
4+	NH	H	OH	256–258	$C_{12}H_{13}N_5O$	74	65	*e*	2000
5+	NH	NO_2	OH	279–281	$C_{12}H_{12}N_6O_3$	0	62	*f*	1000
6	NH	F	OH	263–266	$C_{12}H_{12}N_5OF$	79	70	*f*	
7	NH	Cl	OH	287–288	$C_{12}H_{12}N_6OCl$	79	66	*f*	2500
8	NH	Br	OH	285	$C_{12}H_{12}N_5OBr$	80	75	*e*	2600
9	NH	I	OH	280–281	$C_{12}H_{12}N_5OI$	43	67	*e*	3000
10	NH	*c*	OH	263–265	$C_{16}H_{15}N_5O$	78	62	*e*	
11+	O	NO_2	CH_3	270–271	$C_{13}H_{13}N_5O_3$	0	33	2f, 13	600
12	O	F	CH_3	206–210	$C_{13}H_{13}N_4OF$	59	46	14	
13+	O	Cl	CH_3	210–211	$C_{13}H_{13}N_4OCl$	38	33	12	2000
14+	O	Br	CH_3	214–216	$C_{13}H_{13}N_4OBr$	50	51	14	
15	O	H	OH	275–276	$C_{12}H_{12}N_4O_2$	66	46	15	
16+	O	NO_2	OH	306–310 dec	$C_{12}H_{11}N_5O_4$	0	48	2f	1000
17	O	Cl	OH	292–294	$C_{12}H_{11}N_4O_2Cl$	69	46	11	

[a] + = pyrimidine derivatives tested for antimalarial activity. [b] After 7 days. [c] p-XC_6H_4 = β-naphthyl. [d] M. Ridi, S. Checchi, and P. Pappini, *Ann. Chim.* (Rome), **44,** 769 (1954); *Chem. Abstr.*, **52,** 17285 (1958). [e] F. H. S. Curd and F. L. Rose, British Patent 581,345 (1946); *Chem. Abstr.*, **41,** 3126 (1947). [f] F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 365 (1946).

tion, analysis, drug form, and pharmacology, was also carried out.[2d,e,g,h] It appeared interesting to study whether the replacement of the amidine group in II and III by a pyrimidine ring to yield IV and V, respectively, would alter the biological activity of II and III.

ArNHCONHC(=NH)NH$_2$ ArNHC(=NH)NHC(=NH)NH$_2$
II III



IV, Y = O; R = OH or CH_3
V, Y = NH; R = OH or CH_3

Chemistry.—The biguanides III were obtained in the usual way from the salts of primary amines and cyanoguanidine in aqueous solution.[5]

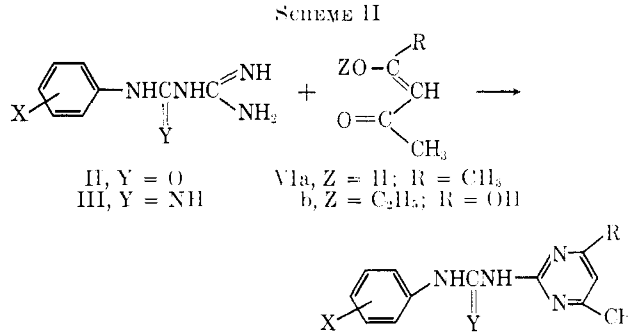
The 1-aryl-3-amidineureas II are only little known.[6–9] In a number of papers,[2c,10] a new simple method of synthesis of these compounds was described, in which amidineurea derivatives are formed by refluxing primary aromatic amines with cyanoguanidine in excess HCl. In some instances it is advantageous to use biguanides as starting materials; when refluxed in excess HCl they furnish the corresponding amidineureas (Scheme I).

SCHEME I

$$\mathrm{ArNH_2\cdot HCl + NCNHC({=}NH)NH_2 \longrightarrow III\cdot HCl}$$
$$\mathrm{III\cdot HCl \xrightarrow{HCl\cdot H_2O} II\cdot HCl}$$
$$\mathrm{ArNH_2\cdot HCl + NCNHC({=}NH)NH_2 \xrightarrow{HCl\cdot H_2O} II\cdot HCl}$$

The cyclization of amidineureas and biguanides with acetoacetic ester or acetylacetone resulted in formation of pyrimidine derivative (Scheme II). Compounds IV and V are listed in Tables I and II.

SCHEME II



II, Y = O
III, Y = NH

VIa, Z = H; R = CH_3
b, Z = C_2H_5; R = OH

IV, Y = O
V, Y = NH

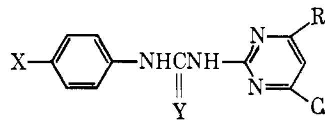
The reactions of II with VIa or VIb form a new way of synthesis of 2-pyrimidylurea derivatives IV; they also give new evidence for formula II for amidineurea derivatives claimed in our former paper;[2c] their isomers IIa do not react with VIa or b to give pyrimidines because of the absence of the C(=NH)NH$_2$ group in their molecules.

ArNHC(=NH)NHCONH$_2$
IIa

(5) J. Colon, *J. Prakt. Chem.*, [2] **84**, 403 (1911).
(6) E. Junod, *Helv. Chim. Acta*, **35**, 1970 (1952).
(7) N. Kundu and P. Ray, *J. Indian Chem. Soc.*, **29**, 811 (1953); *Chem. Abstr.*, **48**, 2600 (1954).
(8) R. Passerini, *Bull. Sci. Fac. Ind. Bologna*, **9**, 27 (1951).
(9) G. Pellizzari, *Gazz. Chim. Ital.*, **53**, 384 (1923).
(10) (a) T. Urbański, B. Skowrońska-Serafin, and H. Dąbrowska, *Roczniki Chem.*, **27**, 65 (1953); (b) T. Urbański, B. Skowrońska-Serafin, H. Dabrowska, and J. Jankowska, *Bull. Acad. Polon., Sci. Classe III*, **1**, 74 (1953); (c) T. Urbański, B. Skowrońska-Serafin, and H. Dąbrowska, *Roczniki Chem.*, **28**, 423 (1954); (d) *ibid.*, **29**, 450 (1955); (e) T. Urbański and B. Skowrońska-Serafin, *Bull. Acad. Polon. Sci., Classe III*, **4**, 361, 363 (1956); (f) *Roczniki Chem.*, **30**, 1189 (1956); (g) T. Urbański, B. Skowrońska-Serafin, and G. Chądzyński, *ibid.*, **33**, 1333 (1959); (h) T. Urbański, B. Skowrońska-Serafin, A. Matusiak, A. Tyrzyński, and M. Zarukiewicz, *ibid.*, **33**, 1383 (1959); (i) T. Urbański, B. Skowrońska-Serafin, and J. Żylowski, *ibid.*, **33**, 1377 (1959); (j) T. Urbański and B. Serafinowa, *ibid.*, **36**, 679 (1962).

TABLE II

MELTING POINTS, ANALYSIS, YIELD, AND TOXICITY OF THE NEW PYRIMIDINE DERIVATIVES



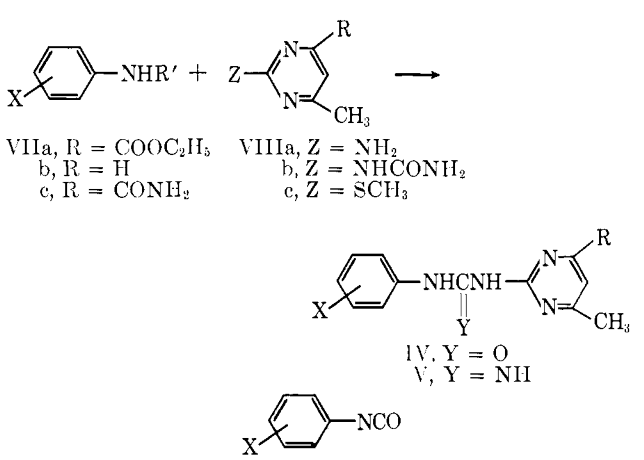
No.[a]	Y	X	R	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Yield, % Method A[b]	Yield, % Method B	LD$_{50}$ (mice), mg/kg ip
1+	NH	F	CH_3	223–226	$C_{13}H_{14}FN_5$	60.22	5.45	27.01	60.12	5.39	27.14	66	71	510
2+	NH	Br	CH_3	188–191	$C_{13}H_{14}BrN_5$	48.76	4.41	21.88	49.12	4.69	21.77	76	51	900
3+	NH	I	CH_3	178–180	$C_{13}H_{14}IN_5$	42.52	3.85	19.07	42.60	4.01	19.16	41	54	730
4	NH	*c*	CH_3	240–243	$C_{17}H_{17}N_5$	70.08	5.88	24.04	69.92	6.01	24.06	54	58	...
5+	O	H	CH_3	198–200	$C_{13}H_{14}N_4O$	64.46	5.83	23.13	64.93	6.19	23.57	48	35	2000
6	O	I	CH_3	208–210	$C_{13}H_{13}IN_4O$	42.41	3.56	15.23	42.42	3.53	14.97	20[d]	29	3250
7	O	*c*	CH_3	204–207	$C_{17}H_{16}N_4O$	69.84	5.52	19.17	70.05	5.44	19.38	40	19	
8	O	F	OH	297–302	$C_{12}H_{11}FN_4O_2$	54.92	4.23	21.37	54.75	4.41	21.56	48	52	
9	O	Br	OH	285–286	$C_{12}H_{11}BrN_4O_2$	44.59	3.43	17.34	44.97	3.56	17.13	77	55	
10	O	I	OH	273–275	$C_{12}H_{11}IN_4O_2$	38.93	2.99	15.14	39.01	3.02	14.98	27	42	
11	O	*c*	OH	283–285	$C_{16}H_{14}N_4O_2$	65.29	4.80	19.03	65.38	5.0	19.30	58	25	

[a] + = pyrimidine derivatives tested for antimalarial activity. [b] After 7 days. [c] p-XC_6H_4 = β-naphthyl. [d] After 60 days.

The question arose whether IV and V, which are analogs of the amidineureas II and biguanides III but with a pyrimidine ring instead of the amidine moiety, would be more active against parasites than the noncyclic compounds II and III. Two methods were used in the preparation of these compounds, both involving condensation of arylamidineureas (II) or arylbiguanides (III) with acetylacetone (VIa) or ethyl acetoacetate (VIb) (see Experimental Section).

To verify the structure of the new pyrimidinyl ureas (IV) we also prepared these compounds by condensing aromatic urethans (VIIa) with 2-aminopyrimidines (VIIIa),[11] aromatic primary amines (VIIb) with 2-pyrimidylureas (VIIIb),[11,12] or aryl isocyanates (IX) with 2-aminopyrimidines (VIIIa)[13,14] (Scheme III). The compound obtained from phenylurea (VIIc,

SCHEME III

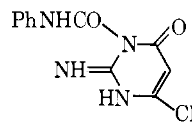


VIIa, R = $COOC_2H_5$ VIIIa, Z = NH_2
b, R = H b, Z = $NHCONH_2$
c, R = $CONH_2$ c, Z = SCH_3

IV, Y = O
V, Y = NH

IX

X = H) and 2-methylmercapto-4-hydroxy-6-methylpyrimidine (VIIIc, R = OH)[15] was found to have the structure IV (R = OH; X = H) and not that of 1-phenylcarbamyl-2-imino-4-methyl-6-ketodihydropyrimidine.[15]



Some hydroxy derivatives of pyrimidines (IV, R = OH) were obtained in form of their sodium salts. The bases (IV, R = OH) also form unstable hydrochlorides. They decompose evolving HCl when heated and readily hydrolyze in aqueous solution.

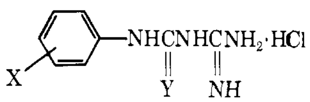
Toxicity.—The toxicity of the biguanide, amidineurea, and pyrimidine derivatives was determined using Kärber's method;[16] the compounds were administered parenterally to white mice weighing 16–20 g in the form of a suspension in 2.5% of gum arabic. The results are given in Tables I, II, and III. In general, the pyrimidine derivatives were found to be of low toxicity.

Antimalarial Activity.—The antimalarial activity of the pyrimidine derivatives IV and V was tested against *P. berghei* in mice by Dr. F. Hawking, National Institute for Medical Research, London. The animals were inoculated intraperitoneally with *P. berghei* (approximately 5 × 10^6 parasites/mouse); the test compounds were given once daily intraperitoneally during 4 days, the first dose being given 4 hr after inoculation. Three mice were used for each dose. On day 5, *i.e.*, 24 hr after the last dose, blood films were taken from all of the mice and the percentage of red blood cells containing parasites was estimated and compared with that of the controls. Antimalarial action was indicated by a reduction in the degree of parasitemia to 10–20% of that of the controls. Thirteen pyrimidine derivatives (indicated by a plus sign in Table I) containing different substituents were tested for their antimalarial activity.

At doses of 0.5, 1.0, 2.0, 2.5, 5.0, and 10.0 mg/20-g mouse, no activity was found. Nitroguanil given intraperitoneally also showed no antimalarial activity and was found to be highly toxic. In previous experiments in avian malaria and in clinical trials, this compound was administered orally and proved to be of low toxicity and of a marked activity. The question

(11) R. B. Ashworth, A. I. Crowther, F. H. S. Curd, and F. L. Rose, *J. Chem. Soc.*, 581 (1948).
(12) S. Birtwell, *ibid.*, 1725 (1953).
(13) R. C. O'Neill and A. J. Basso, U. S. Patent 2,762,742 (1956).
(14) Ng. Ph. Buu-Hoi, Ng. D. Xuong, and V. T. Suu, *J. Chem. Soc.*, 2815 (1958).
(15) M. Ridi and S. Checchi, *Ann. Chim.* (Rome), **44**, 28 (1954); *Chem. Abstr.*, **49**, 4658 (1955).
(16) G. Kärber, *Arch. Exptl. Pathol. Pharmakol.*, **162**, 480 (1931).

TABLE III
TOXICITY OF SOME MONOARYL DERIVATIVES OF BIGUANIDE AND AMIDINEUREA



No.	Ref	Y	X	LD_{50} (mice), mg/kg ip
1	5	NH	H	290
2	5	NH	m-NO_2	261
3	e	NH	p-NO_2	165
4	e	NH	o-Cl	267
5	e	NH	m-Cl	186
6	e	NH	p-Cl	247
7	e	NH	p-Br	265
8		NH	p-F[b]	262
9	10a	NH	p-COOH[a]	4000
10	f	NH	p-SO_3H[a]	4000
11	7	NH	p-SO_2NH_2	774
12		NH	m-$B(OH)_2$[b]	4000
13	10i	. . .	c	165
14	10b, 10c	O	H	1125
15	10a, 10b	O	p-NO_2	225[g,h]
16		O	m-NO_2[b]	130
17	8	O	o-Cl[b]	195
18	8	O	m-Cl[b]	65
19	10c	O	p-Cl	82
20	10d	O	p-Br	71
21		O	p-F[b]	200
22	10a	O	p-COOH[a]	1025
23	10c	O	p-SO_3H[a]	2640
24	10d	O	p-SO_2NH_2	4000
25		O	m-$B(OH)_2$[b]	570
26	10i	O	d	77
27	10c	O	p-NH_2	1000 (*po*)

[a] Free base. [b] See Experimental Section. [c] β-Naphthylbiguanide. [d] 1-(β-Naphthyl)-3-amidineurea. [e] Footnote *f*, Table I. [f] P. Ray and J. Siddhanta, *J. Indian Chem. Soc.*, **20**, 250 (1943); *Chem. Abstr.*, **38**, 3920 (1944).

arose whether nitroguanil was ineffective against *P. berghei*, or whether the difference depended on the route of administration. Therefore, nitroguanil was tried orally against *P. berghei* in mice; at a dose 2.0 mg/mouse on 4 successive days it showed antimalarial activity as high as that of 0.1 mg ip of chloroquine diphosphate on 4 successive days. Nitroguanil was much better tolerated orally than intraperitoneally.

In the light of these results it seemed necessary to reexamine the oral activity of other compounds, especially the cyclic nitroguanil derivatives (**2**, **5**, **11**, **16**, Table I). However, no oral activity was found for these compounds. Thus, it appears that the cyclization of the amidine group to a pyrimidine ring reduces both toxicity and antimalarial activity.

Experimental Section

Arylamidineureas (II) and Arylbiguanides (III) (Table III). ***m*-Boronophenylbiguanide.**—*m*-Aminophenylboronic acid hydrochloride[17] (13.6 g, 0.1 mole), dicyandiamide (9.25 g, 0.11 mole), and H_2O (70 ml) were refluxed for 1.5 hr; *m*-boronophenylbiguanide hydrochloride separated on cooling; mp 302–303°, yield 14.5 g (70%).

Anal. Calcd for $C_8H_{12}BN_5O_2 \cdot HCl$: N, 27.19. Found: N, 26.94.

[17] F. R. Bean and J. R. Johnson, *J. Am. Chem. Soc.*, **54**, 4415 (1932).

The product was dissolved in H_2O (400 ml) and $NaHCO_3$ (4.32 g) was added; on cooling, *m*-boronophenylbiguanide precipitated; mp 320°, insoluble in water and ethanol, yield 10.0 g (80%).

Anal. Calcd for $C_8H_{12}BN_5O_2$: C, 43.63; H, 5.45; N, 31.81. Found: C, 43.28; H, 5.43; N, 31.51.

1-(*m*-Boronophenyl)-3-amidineurea.—*m*-Boronophenylbiguanide hydrochloride (5 g, 0.02 mole) refluxed for 1.5 hr with 15 ml of 10% HCl yielded 1-(*m*-boronophenyl)-3-amidineurea hydrochloride (2.0 g, 40%), crystallized from 15% HCl, mp 214–216° dec.

Anal. Calcd for $C_8H_{11}BN_4O_3 \cdot HCl$: N, 21.67. Found: N, 21.83.

The hydrochloride (1 g) in 15 ml of hot H_2O made alkaline with $NaHCO_3$ (0.3 g) gave the base, mp >320°, insoluble in water and ethanol.

Anal. Calcd for $C_8H_{11}BN_4O_3$: C, 43.83; H, 5.02; N, 24.65. Found: C, 44.02; H, 5.14; N, 24.92.

1-(*m*-Nitrophenyl)-3-amidineurea.—To a solution of *m*-nitroaniline (13.8 g, 0.1 mole) in concentrated HCl (17 ml) and H_2O (11 ml), dicyandiamine (8.4 g, 0.1 mole) was added at 50°; the mixture was heated until an exothermic reaction began and then refluxed for 30 min. The crude hydrochloride was recrystallized from H_2O; mp 225–227°; when made basic with 10% NaOH it gave the product (7.1 g, 36%), mp 197–198°, from ethanol.

Anal. Calcd for $C_8H_9N_5O_3$: C, 43.02; H, 4.06; N, 31.39. Found: C, 43.30; H, 4.24; N, 31.42.

Picrate, from H_2O, 250° dec.

Anal. Calcd for $C_8H_9N_5O_3 \cdot C_6H_3N_3O_7$: N, 24.79. Found: N, 24.93.

Nitrate, mp 202–203° dec.

Anal. Calcd for $C_8H_9N_5O_3 \cdot HNO_3$: N, 29.37. Found: N, 29.16.

1-(*o*- and -*m*-Chlorophenyl)-3-amidineureas from the Corresponding Biguanides.—Chlorophenylbiguanide hydrochloride (19 g, 0.08 mole) was refluxed for 20 min with 8% HCl (25 ml). The product was separated and made basic with 10% NaOH; *ortho* isomer, mp 124–125°,[8] yield 12.3 g (58%); *meta* isomer, mp 93–94°,[8] yield 13.3 g (62%).

1-(*o*- and -*m*-Chlorophenyl)-3-amidineureas from *o*- and *m*-Chloroaniline. (a) A mixture of *o*-chloroaniline (12.7 g, 0.1 mole) and dicyandiamide (8.4 g, 0.1 mole) in concentrated HCl (9 ml) and H_2O (60 ml) was refluxed for 4 hr. The solution was concentrated *in vacuo* to *ca.* 20 ml, concentrated HCl (10 ml) was added, and the mixture refluxed for 30 min. When the resulting hydrochloride was made basic with 10% NaOH, 11.4 g (54%) of product, mp 124–125°,[8] was obtained.

(b) Similarly, *m*-chloroaniline (12.7 g, 0.1 mole) and dicyandiamide (8.4 g, 0.1 mole) were refluxed in concentrated HCl (10 ml) and H_2O (15 ml) for 5 hr, concentrated HCl (12 ml) was added, and the mixture was heated for 20 min to yield 1-(*m*-chlorophenyl)-3-amidineurea, mp 93–94°[8] (9.4 g, 44%).

***p*-Fluorophenylbiguanide.**—*p*-Fluoroaniline hydrochloride (14.7 g, 0.1 mole) and dicyandiamide (8.4 g, 0.1 mole) in 20 ml of H_2O were heated for 3 hr and left overnight and the precipitate was crystallized from H_2O; yield 16.2 g (70%), mp 219–222°.

Anal. Calcd for $C_8H_{10}FN_5 \cdot HCl$: C, 41.43; H, 7.48; N, 30.23. Found: C, 41.52; H, 7.35; N, 30.42.

The base had mp 140–142° (from benzene).

Anal. Calcd for $C_8H_{10}FN_5$: C, 49.22; H, 5.16; N, 35.88. Found: C, 49.38; H, 5.1; N, 35.83.

1-(*p*-Fluorophenyl)-3-amidineurea Hydrochloride.—To a solution of *p*-fluorophenylbiguanide hydrochloride (23.1 g, 0.1 mole) in 200 ml of 7% HCl was added portionwise with mechanical stirring 14 g (0.2 mole) of $NaNO_2$ at room temperature to yield the product (7.4 g, 32%), mp 163–166° (from H_2O).

Anal. Calcd for $C_8H_9FN_4O \cdot HCl$: C, 41.41; H, 4.35; N, 24.18. Found: C, 41.32; H, 4.5; N, 24.42.

1-Aryl-3-(4-hydroxy-6-methyl)-2-pyrimidylureas (IV, Y = O; R = OH) and 1-Aryl-3-(4-hydroxy-6-methyl)-2-pyrimidylguanidines (V, Y = NH; R = OH) (Tables I and II). Method A.—To a solution of 0.02 mole of arylamidineurea(II) or arylbiguanide (III) in 80% ethanol (15 ml) (II or III, X = I in 30 ml) and 10 *N* NaOH (1 ml, 0.01 mole), ethyl acetoacetate (0.04 mole) was added and the mixture was left for 7 days at room temperature to yield a solid product.

Method B.—Arylamidineurea (II) or arylbiguanide (III) (0.02 mole) and ethyl acetoacetate (0.04 mole) were heated at 120–130° for 1 hr, and the precipitate was collected and boiled with methanol to remove ethyl acetoacetate.

(a) The product (IV, R = OH) was suspended in H_2O and acidified with dilute acetic acid; the solid was washed with hot H_2O, boiled with CH_3OH, dissolved in 2% aqueous–alcoholic NaOH, and precipitated on cooling as the sodium salt; after crystallization from CH_3OH, the product was acidified with dilute acetic acid and boiled with H_2O.

(b) The crude product (V, R = OH) was suspended in H_2O, neutralized with dilute acetic acid, and recrystallized from pyridine or N-methylformamide.

Sodium salts of IV were obtained in 2% H_2O-alcohol solution of NaOH and recrystallized from alcohol; they crystallize with 1 mole of alcohol.

Hydrochlorides of IV were prepared in hot concentrated HCl, washed with absolute ether and dried *in vacuo;* they lose HCl on heating.

1-Aryl-3-(4,6-dimethyl-2-pyrimidyl)ureas (IV, Y = O; R = CH_3) and 1-Aryl-3-(4,6-dimethyl-2-pyrimidyl)guanidines (V, Y = NH; R = CH_3).—Both compounds of type IV and V were prepared according to methods A and B using acetylacetone instead of ethyl acetoacetate and recrystallized from acetone-ethanol solution, 1-butanol, or pyridine.

Acknowledgments.—We wish to express our gratitude to Dr. Bruce-Chwatt, Chief of Research and Technical Intelligence Division of Malaria Eradication, World Health Organization, for his kind interest in this research and aiding us with supplies of instruments and materials. We are greatly indebted to Dr. F. Hawking, National Institute for Medical Research, London, for the antimalarial tests, and to Dr. K. Jakimowska, Drug Institute, Warsaw, for the toxicity determinations.

An Apparent Correlation between the *in Vitro* Activity of Chloramphenicol Analogs and Electronic Polarizability[1]

ARTHUR CAMMARATA

Department of Chemistry and Pharmaceutical Chemistry, Medical College of Virginia, Richmond, Virginia 23219

Received February 20, 1967

An apparent correlation between the activity of chloramphenicol analogs, as determined by microbial kinetics, and the electronic polarizability of their aromatic substituents has been found which suggests the activity of chloramphenicol and its thiomethyl analog may arise, in part, by intramolecular charge transfer.

Recent attempts at correlating the biological activity of chloramphenicol analogs by means of the Hansch equation[2] suggest that the correlation, or lack of correlation, obtained by this equation depends markedly on the accuracy of the method used to evaluate biological activity. Hansch and associates[1a] reported a fairly good correlation (correlation coefficient, $r = 0.824$; *Escherichia coli*) for chloramphenicol analogs whose activities were determined by a serial dilution method.[3] In contrast, Garrett and co-workers[4] were unable to correlate many of the same chloramphenicol analogs studied by the Hansch group when their activities were determined by a more accurate kinetic method.

We wish to present an apparent correlation between the activity of chloramphenicol analogs, as determined by microbial kinetics,[4] and the electronic polarizability of their aromatic substituents. In light of this new correlation, it appears that a Hansch treatment can provide a fairly good, but not necessarily significant, correlation for chloramphenicols whose activities are determined by kinetic methods, provided the limits imposed by the parameters employed in this treatment are not exceeded.

Results and Discussion

The molar electronic polarizability of a substance is given by the Lorentz–Lorenz equation[5] as follows where

$$P_E = \frac{n^2 - 1}{n^2 + 2}\frac{M}{D} = \frac{4}{3}\pi N \alpha_E$$

n is the refractive index of the substance, M is its molecular weight, D is its density, N is Avogadro's number, and α_E is the electronic polarizability. A useful property of molar electronic polarizability, alternatively known as molar refraction, is its additivity, *i.e.*, the molar refraction of a substance may be represented as the sum of atomic or group refractions.[5b] Further, since electronic polarizability is expressed in units of volume, molar, atomic, or group refractions are a measure of molar, atomic, or group volumes, respectively.

When Fisher–Hirschfelder–Taylor models are made of the substituted benzenes corresponding to the aromatic nucleus of chloramphenicol analogs, it is noted that the activity of a chloramphenicol appears proportional to the volume which its aromatic substituent presents to a surface. Using atomic and group refractions[5b] as a measure of this volume, an excellent linear correlation is obtained with the inhibition constants[4] of all chloramphenicols except chloramphenicol itself and its thiomethyl analog (Table I). The correlation which is obtained, while empirical in origin, does have some theoretical justification.[6]

From a consideration of the partition function for a population of electrically uncharged molecules confronted with both an electrically conducting surface and an adjacent solution, Agin, *et al.*,[6] derived the equation

$$\ln C_s = K'\alpha_E + \ln C^*$$

(1) This investigation was supported in part by Grant AI 07811-01 from the National Institutes of Health.

(2) (a) C. Hansch, R. Muir, T. Fujita, P. P. Maloney, F. Geiger, and M. Streich, *J. Am. Chem. Soc.*, **85**, 2817 (1963); (b) C. Hansch and T. Fujita, *ibid.*, **86**, 1616 (1964).

(3) M. N. Shemyakin, M. N. Kolosov, M. M. Levitov, K. I. Germanova, M. G. Karapetyan, Yu. B. Shvetsov, and E. M. Bambdas, *J. Gen. Chem. USSR*, **26**, 885 (1956).

(4) E. R. Garrett, O. G. Wright, G. H. Miller, and K. L. Smith, *J. Med. Chem.*, **9**, 203 (1966).

(5) (a) P. Debye, "Polar Molecules," Dover Publications, Inc., New York, N. Y., 1929; (b) Y. K. Syrkin and M. E. Dyatkina, "Structure of Molecules and the Chemical Bond," Dover Publications, Inc., New York, N. Y., 1964.

(6) D. Agin, L. Hersh, and D. Holtzman, *Proc. Natl. Acad. Sci. U. S.*, **53**, 952 (1965).