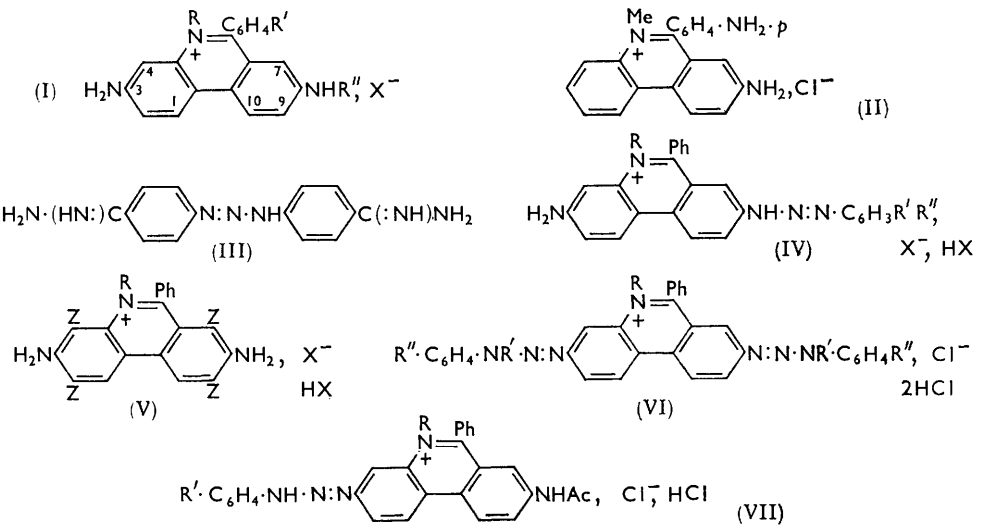
884. *The Search for New Trypanocides. Part IX.*[1] *Amidinophenyldiazoamino- and Amidinophenylazo-phenanthridinium Salts.*

By S. S. Berg, L. Bretherick, K. Washbourn, and W. R. Wragg.

m- and *p*-Amidinobenzenediazonium salts couple with 5-alkyl-3,8-diamino-6-arylphenanthridinium salts to give red diazoamino- and purple aminazo-derivatives, and with 8-amino-5-methyl-6-*p*-aminophenylphenanthridinium salts to give a mixture of red isomers. Diazotised 8-acetamido-3-amino-5-methyl-6-phenylphenanthridinium chloride and tetrazotised 5-alkyl-3,8-diamino-6-phenylphenanthridinium salts couple with *m*- and *p*-aminobenzamidines to give diazoamino-derivatives. The products possess considerable trypanocidal activity. Substitution in the amidinophenyl residue or the diazoamino-linkage was dystherapeutic.

The trypanocidal activity of phenanthridinium salts [2] and aromatic diamidines [3] is well known and, in the hope of enhancing the activity of dimidium chloride (I; R = Me, R′ = R″ = H, X = Cl), homidium chloride (I; R = Et, R′ = R″ = H, X = Cl), and phenidium chloride (II) against *Trypanosoma congolense* in cattle, it was decided to prepare a series of amidinophenyldiazoamino-derivatives which would also have structural relation to the curative trypanocide " Berenil " (III).[4,5]

p-Amidinobenzenediazonium chloride was coupled with homidium chloride in acetic acid–sodium acetate solution and an almost black crystalline mixture was obtained, from which purple and red isomeric compounds were separated. They were self-indicating on paper electrophoresis, the purple isomer being distinctly more mobile than the red, thus



providing a useful means of following the progress of separation procedures. Purity was finally assessed by spectrophotometric and polarographic determinations. The isomers were at first considered to be diazoamino-derivatives of homidium chloride [6] by substitution on to

[1] Part VIII, Berg, *J.*, 1963, 3635.
[2] Theobald and Schofield, *Chem. Rev.*, 1950, **46**, 171.
[3] Barber, *Proc. Internat. Congress Pure Appl. Chem.*, 1947, **13**, 355.
[4] Jensch, *Arzneimittel-Forsch.*, 1955, **5**, 634.
[5] Milne, Robson, and Livebandiza, *Vet. Record*, 1955, **67**, 280.
[6] Wragg, Washbourn, Brown, and Hill, *Nature*, 1958, **182**, 1005.

the 3- and 8-amino-groups, but by analogy with Berg's results in the *m*-amidino-series [1] the red isomer is now assigned the diazoamino-structure (IV; R = Et, R′ = H, R″ = *p*-amidino, X = Cl) and the purple isomer the amino-azo-structure (V; R = Et, R′ = H, R″ = *p*-amidino, X = Cl). Confirmation of these structures was obtained by the reductive fission of the red isomer to homidium, and of the purple isomer to the triamine described by Berg.[1] Both isomers were highly active against *Trypanosoma congolense* in mice [6] and in order to study structure–activity relations similar pairs of isomers were prepared by coupling *m*- and *p*-amidinobenzenediazonium chlorides with a number of phenanthridinium salts (I). The use of phenidium chloride (II) gave a complex mixture of isomers which were not separated. The most active pair of isomers was obtained from *m*-amidinobenzenediazonium chloride and homidium chloride; the mixture was first designated M & B 4404 and was later assigned the " open " name metamidium chloride hydrochloride. Of the two isomers, isometamidium, the red isomer (IV; R = Et, R′ = H, R″ = *m*-amidino, X = Cl) was the more active both therapeutically and prophylactically, but there was little difference in toxicity.[7] Substitution of the amidinophenyl residue with chlorine, bromine, or methoxyl in the *ortho*-position to the diazoamino- or azo-linkage was dystherapeutic. A fuller account of the biological studies has been published elsewhere.[7]

The coupling reactions were generally carried out in acetic acid–sodium acetate solution, and the product was obtained as a mixture from which the pure isomers were separated by fractional crystallisation as well-defined salts. The structure of the red diazoamino-compounds was confirmed by reductive fission to the parent diaminophenanthridinium salt, and evolution of the theoretical quantity of nitrogen when heated with cuprous chloride–3N-hydrochloric acid. The purple amino-azo-compounds did not evolve nitrogen when heated with cuprous chloride–3N-hydrochloric acid, and gave a highly coloured triamine on reduction with stannous chloride. In order to carry out the coupling in solution it was sometimes necessary to diazotise the amine in isethionic acid, and to use the isethionate of the appropriate phenanthridinium salt.

8-Acetyl derivatives of dimidium and homidium (I; R = Me or Et, R′ = H, R″ = Ac) were diazotised and coupled with *m*-aminobenzamidine to give red diazoamino-compounds (VII; R = Me or Et, R′ = *m*-amidino). Hydrolysis of the acetyl group, which was successful only in strong acid, ruptured the diazoamino-linkage, giving a mixture which was not separated.

Attempts to prepare the 3,8-di-*m*-amidinophenyldiazoamino-derivative of homidium chloride by coupling with an excess of *m*-amidinobenzenediazonium chloride was unsuccessful, only the metamidium isomers being obtained. Homidium chloride was readily tetrazotised, and coupling of the tetrazonium solution with *m*-aminobenzamidine gave the desired bis-compound (VI; R = Et, R′ = H, R″ = *m*-amidino), which was designated M & B 4596. It has been shown to possess high prophylactic activity against *Trypanosoma congolense*.[7,8] The use of *p*-amidino-*N*-methylaniline or *m*- and *p*-amidinophenylhydroxylamine in the coupling reaction gave bisdiazoamino-derivatives in which the linkage was substituted by methyl or hydroxyl groups. They were more toxic and less active than M & B 4596.

The aminobenzamidines used were prepared by the Pinner method from the appropriate nitriles, and *p*-amidino-*N*-methylaniline by the method of Ashley and Berg.[9] *m*- and *p*-Amidinophenylhydroxylamine were prepared by partial reduction of the corresponding nitrobenzamidines.

Experimental

Water of crystallisation was determined by the Karl Fischer method.

Coupling Reaction.—General procedure. The aminobenzamidine hydrochloride (0·25 mole) in water (225 ml.) and concentrated hydrochloric acid (56·5 ml.) was diazotised at 0—5° by

[7] Brown, Hill, and Holland, *Brit. J. Pharmacol.*, 1961, **17**, 396.
[8] Berg, Brown, Hill, and Wragg, *Nature*, 1961, **192**, 367.
[9] Ashley and Berg, *J.*, 1957, 3089.

addition of sodium nitrite (17·6 g.) in water (100 ml.). The excess of nitrous acid was removed by addition of sulphamic acid, and the diazonium solution was added in one portion to a stirred solution of the phenanthridinium salt (0·25 mole) in water (600 ml.) at 0—5°. Saturated aqueous sodium acetate (600 ml.) was immediately added, and the mixture was stirred at 0—10° for 1 hr. Sodium chloride (45 g.) and sodium acetate (61·5 g.) in water (450 ml.) were then added, and after a further 1 hr. the resultant precipitate was filtered off, washed with saturated aqueous sodium chloride solution, and dried over sulphuric acid. The product, which was obtained as its chloride hydrochloride, was examined by paper electrophoresis to confirm the presence of the isomers, and the absence of significant amounts of starting material. Inorganic impurity was separated by crystallisation from methanol–ether, or conversion of the product into its sparingly soluble *bromide hydrobromide*, which was washed free from sodium bromide with 96% w/v aqueous acetone. Separation of the pure isomers was effected by fractional crystallisations of the *chlorides* or *bromides* from methanol or water, purity being determined by paper electrophoresis in 3N-acetic acid, and finally by polarographic determinations. Metathesis of the products to more water-soluble salts was readily carried out in methanolic solution by using IR-400 Amberlite ion-exchange resin charged with the appropriate anion. In this way the products listed in Tables 1—4 were obtained.

TABLE 1.

Mixed isomers (IV and V) from 3,8-diaminophenanthridinium salts (I).

No.	R	R′	R″	X	Yield (%)	Decomp. pt.	Formula
1	Me	H	*p*-Amidino	Cl	66	285—288°	$C_{27}H_{24}ClN_7,HCl,1·5H_2O$
2	Et	H	*p*-Amidino	Cl	66	283—285	$C_{28}H_{26}ClN_7,HCl,1·5H_2O$
3	Me	H	*m*-Amidino	Cl *	66	240—242	$C_{27}H_{24}ClN_7,HCl,0·5C_2H_5·OH,3H_2O$
4	Et	H	*m*-Amidino	Br	88	242—247	$C_{28}H_{26}BrN_7,HBr,2H_2O$
5	Et	H	*m*-Amidino	Cl *	80	220—230	$C_{28}H_{26}ClN_7,HCl,3H_2O$
6	Et	*o*-Br	*p*-Amidino	Cl	76·5	258—260	$C_{28}H_{25}BrClN_7,HCl,3H_2O$
7	Et	*o*-Cl †	*m*-Amidino	Cl	40·8	265—270	$C_{28}H_{25}Cl_2N_7,HCl,3H_2O$

* Obtained by metathesis of the bromide hydrobromide. † Substituent is *para* to the amidino-group.

	Found (%)					Required (%)				
No.	C	H	Cl	N	H_2O	C	H	Cl	N	H_2O
1	59·4	5·2	13·3	17·7	4·7	59·4	5·15	13·0	18·0	4·95
2	60·15	4·6	12·6	17·65	4·6	60·1	5·35	12·7	17·55	4·8
3 ‡	56·4	5·5	11·4	16·6	9·05	56·4	5·7	11·9	16·5	9·05
4 §	50·9	4·7		14·6	5·4	51·25	4·75		15·0	5·65
5	57·0	5·4	12·2	16·8	8·9	57·2	5·6	12·1	16·7	9·2
6 ¶			10·8	14·9	8·4			10·7	14·75	8·1
7			17·2	15·6	8·4			17·2	15·8	8·7

‡ EtO, 3·7. Req. 3·8%. § Br, 24·7. Req. 24·35%. ¶ Br, 12·0. Req. 12·0%.

TABLE 2.

Mixed isomers * derived from phenidium chloride (II).

No.	Substituted benzenediazonium chloride	Yield (%)	Decomp. pt.	Formula
1	*p*-Amidino	8	202—203°	$C_{27}H_{24}ClN_7,CH_3·CO_2H,0·5H_2O$
2	*m*-Amidino	12	234—240	$C_{27}H_{24}ClN_7,HCl,6H_2O$

* Crystallised from water (red crystals).

	Found (%)					Required (%)				
No.	C	H	Cl	N	H_2O	C	H	Cl	N	H_2O
1 †	63·5	4·8	6·9	17·9	2·0	63·2	5·3	6·45	17·7	1·6
2	52·7	6·05	11·25	16·1	17·3	52·0	5·75	11·4	15·7	17·3

† Ac, 7·4. Req. 7·8%.

Coupling of p-*Amidinobenzenediazonium Isethionate and* 3,8-*Diamino-5-methyl-6-*p-*nitrophenylphenanthridinium Isethionate* (I; R = Me, R′ = *p*-NO_2, R″ = H, X = $C_2H_5O_4S$).—*p*-Aminobenzamidine monohydrochloride [10] (2·5 g.) in water (15 ml.) and 10N-isethionic acid

[10] Easson and Pyman, *J.*, 1931, 2994.

(3·9 ml.) was diazotised at 0—5° by addition of sodium nitrite (1·3 g.) in water (15 ml.). The excess of nitrous acid was removed by sulphamic acid, and the diazonium solution was added, all at once, to a stirred aqueous solution of 3,8-diamino-5-methyl-6-*p*-nitrophenylphenanthridinium isethionate [prepared by addition of 10N-isethionic acid (1·5 ml.) to a suspension of the

TABLE 3.

Red diazoamino-compounds (IV).

No.	R	R′	R″	X	Yield (%)	Cryst. from	Decomp. pt.	Formula
1	Me	H	*p*-Amidino	Cl	12	MeOH	248—250°	$C_{27}H_{24}ClN_7,HCl,2H_2O$
2	Bt	H	*p*-Amidino	Cl	12	MeOH	236—240	$C_{28}H_{26}ClN_7,HCl,3H_2O$
3	Me	H	*m*-Amidino	Br	15	MeOH	245—246	$C_{27}H_{24}BrN_7,HBr,1{\cdot}5H_2O$
4	Et	H	*m*-Amidino	Br	29	MeOH	245—247	$C_{28}H_{26}BrN_7,HBr,H_2O$
5	Et	H	*m*-Amidino	Cl *	28	MeOH	244—245	$C_{28}H_{26}ClN_7,HCl,2H_2O$
6	Et	H	*m*-Amidino	$CH_3{\cdot}SO_3$ †	26	EtOH–$COMe_2$	228	$C_{29}H_{29}N_7O_3S,CH_3{\cdot}SO_3H,2H_2O$
7	Et	H	*m*-Amidino	$C_2H_5O_4S$ †	24	MeOH–$COMe_2$	235	$C_{30}H_{31}N_7O_4S,C_2H_6O_4S,2H_2O$
8	Me	*o*-MeO ‡	*m*-Amidino	Cl	22·6	H_2O–EtOH	247—248	$C_{28}H_{26}ClN_7O,HCl,\frac{2}{3}H_2O$
9	Et	*o*-MeO ‡	*m*-Amidino	Cl	27·2	H_2O–EtOH	264	$C_{29}H_{28}ClN_7O,HCl,2{\cdot}25H_2O$
10	Et	*o*-Br	*p*-Amidino	Cl	17	MeOH–$COMe_2$	260—264	$C_{28}H_{25}BrClN_7,HCl,2H_2O$

* Obtained by metathesis of the bromide hydrobromide. † Obtained by metathesis of the chloride hydrochloride. ‡ Substituent is *para* to the amidino-group.

	Found (%)					Required (%)				
No.	C	H	Cl	N	H_2O	C	H	Cl	N	H_2O
1	59·0	5·25	12·8	17·9	6·4	59·4	5·25	12·8	17·7	6·5
2	57·1	5·8	12·5	17·05	9·4	57·4	5·65	12·1	16·7	9·25
3 *	51·5	4·5		15·6	4·5	51·2	4·3		15·5	4·3
4 †	52·4	5·0		15·0	3·0	52·65	4·6		15·3	2·8
5	58·95	5·4	12·9	17·4	6·3	59·1	5·45	12·5	17·2	6·35
6 ‡	52·5	5·25		14·5	5·2	52·5	5·4		14·2	5·25
7 §	51·4	5·2		12·9	4·6	51·4	5·5		13·1	4·8
8			12·6	17·3	2·15			12·6	17·4	1·95
9	58·6	5·7	12·05	16·55	6·8	58·0	5·55	11·8	16·2	6·7
10 ¶	52·1	5·0	10·8	15·2	5·9	52·0	4·65	11·0	15·15	5·6

* Br, 25·75. Req. 25·2%. † Br, 24·6. Req. 25·0%. ‡ S, 9·15. Req. 9·3%. § S, 8·5. Req. 8·6%. ¶ Br, 12·3. Req. 12·35%.

TABLE 4.

Purple amino-azo-compounds (V).

No.	R	R′	R″	X	Yield (%)	Cryst. from	Decomp. pt.	Formula
1	Me	H	*p*-Amidino	Cl	50	Water	290°	$C_{27}H_{24}ClN_7,HCl,1{\cdot}5H_2O$
2	Et	H	*p*-Amidino	Cl	40	Water	287—289	$C_{28}H_{26}ClN_7,HCl,1{\cdot}5H_2O$
3	Me	H	*m*-Amidino	Cl	26	Water	278—279	$C_{27}H_{24}ClN_7,HCl,2{\cdot}5H_2O$
4	Et	H	*m*-Amidino	Br *	26	Water	236—238	$C_{28}H_{26}BrN_7,HBr,2H_2O$
5	Et	H	*m*-Amidino	Cl	30	Water	258—260	$C_{28}H_{26}ClN_7,HCl,1{\cdot}5H_2O$
6	Et	*o*-Br	*p*-Amidino	Cl	20	MeOH–$COMe_2$	282	$C_{28}H_{25}BrClN_7,HCl,3H_2O$

* Obtained by metathesis of the bromide hydrobromide.

	Found (%)					Required (%)				
No.	C	H	Cl	N	H_2O	C	H	Cl	N	H_2O
1	59·4	5·2	12·8	18·0	4·7	59·4	5·15	13·0	18·0	4·95
2	60·8	5·35	12·55	17·5	4·9	60·1	5·35	12·7	17·55	4·8
3	57·7	5·0	12·3	17·7	8·3	57·6	5·2	12·6	17·4	8·0
4 *	51·5	4·85		14·7	5·3	51·25	4·75		15·0	5·65
5	60·3	5·25	12·5	17·7	4·3	60·1	5·35	12·7	17·55	4·8
6 †	52·4	5·0	10·9	14·9	5·6	52·0	4·65	11·0	15·15	5·6

* Br, 24·4. Req. 24·35%. † Br, 12·2. Req. 12·35%.

pseudo-base obtained from 3,8-diamino-5-methyl-6-*p*-nitrophenylphenanthridinium chloride [11] (5·65 g.) in water (415 ml.)] at 0—5°. Saturated aqueous sodium acetate (40 ml.) was immediately added, and the solution was stirred at 0—10° for 3 hr. Sodium chloride (100 g.)

[11] Walls and Whittaker, *J.*, 1950, 41.

was added, and the resultant precipitate was washed with saturated aqueous sodium chloride and dried over sulphuric acid. Addition of acetone (600 ml.) to a methanolic solution (120 ml.) of the crude product gave the mixed isomers (4·9 g.; 56·2%) as black crystals, decomp. 278—280° (Found: C, 55·8; H, 4·1; Cl, 11·7; N, 19·0; H_2O 2·7. Calc. for $C_{27}H_{23}ClN_8O_2,HCl,H_2O$: C, 55·8; H, 4·5; Cl, 12·2; N, 19·2; H_2O, 3·1%). Coupling with *m*-amidinobenzenediazonium isethionate gave the mixed isomers as black crystals (50%), decomp. 267° (Found: C, 55·7; H, 4·9; Cl, 12·0; N, 19·0; H_2O, 3·4%).

Reductive Fission of the Red Isomer (IV; R = Et, R′ = H, R″ = *p*-amidino, X = Cl).—Berg's method [1] gave homidium chloride which was isolated as its 8-acetyl derivative (I; R = Et, R′ = H, R″ = Ac), red needles (73%), decomp. 288—290°, undepressed on admixture with an authentic sample.[12]

Reductive Fission of the Purple Isomer (V; R = Et, R′ = H, R″ = *p*-amidino, X = Cl).—5-Ethyl-5,6-dihydro-6-methoxy-6-phenyl-*x*,3,8-triaminophenanthridine was similarly obtained as mauve needles (57%), m. p. 155—157° (decomp.), identical with the triamine described by Berg.[1]

8-*Acetamido*-3-(m-*amidinophenyldiazoamino*)-5-*methyl*-6-*phenylphenanthridinium Chloride* (VII; R = Me, R′ = *m*-amidino).—A suspension of 8-acetamido-3-amino-5-methyl-6-phenyl phenanthridinium chloride [12] (14·8 g.) in N-hydrochloric acid (240 ml.) was diazotised at 5–10° by sodium nitrite (4 g.), the excess of nitrous acid was removed by sulphamic acid, and the solution was treated at 5—10° with a solution, in one portion, of *m*-aminobenzamidine monohydrochloride [13] (7·0 g.) in 2N-hydrochloric acid (16 ml.) and water (24 ml.). Saturated aqueous sodium acetate (150 ml.) was immediately added, and the mixture was stirred at 10—15° for 2 hr. Sodium chloride (20 g.) was added, the gum was separated and dissolved in water (400 ml.), and sodium chloride (40 g.) added. The precipitate was washed with saturated aqueous sodium chloride solution and crystallised from ethanol (280 ml.) and water (120 ml.). The *product* (12·8 g., 55·5%) separated as yellow crystals, decomp. 277—278° (Found: Cl, 12·15; N, 16·85; Ac, 7·0; H_2O 4·6. $C_{29}H_{26}ClN_7O,HCl,1·5H_2O$ requires Cl, 12·1; N, 16·7; Ac, 7·3; H_2O, 4·6%). Warming with cuprous chloride in 3N hydrochloric acid liberated nitrogen (1 mol.). 8-*Acetamido*-3-(m-*amidinophenyldiazoamino*)-5-*ethyl*-6-*phenylphenanthridinium chloride* (VII; R = Et, R′ = *m*-amidino) was similarly prepared as yellow crystals (from aqueous ethanol) (67%), decomp. 224—226° (Found: C, 52·6; H, 6·2; Cl, 10·4; N, 14·6; Ac, 6·8; H_2O, 16·0. $C_{30}H_{28}ClN_7O,HCl,6H_2O$ requires C, 52·8; H, 6·0; Cl, 10·4; N, 14·6; Ac, 6·3; H_2O, 15·8%).

3,8-*Di*-(m-*amidinophenyldiazoamino*)-5-*ethyl*-6-*phenylphenanthridinium Chloride Dihydrochloride* (VI; R = Et, R′ = H, R″ = *m*-amidino).—A stirred suspension of homidium chloride (199 g., 0·5 mole) in 2N-hydrochloric acid (1·34 l.) was tetrazotised at 0° by sodium nitrite (72 g., 1·06 mole) in water (400 ml.). The excess of nitrous acid was removed by sulphamic acid, and the stirred tetrazonium solution was treated at 0—5°, in one portion, with *m*-aminobenzamidine monohydrochloride (171·6 g., 1 mole) in water (600 ml.) and 2N-hydrochloric acid (400 ml.). Saturated aqueous sodium acetate (1·75 l.) was immediately added, and the mixture was stirred at 0—5° for 1 hr. The resultant precipitate was washed with 17·5% w/v aqueous sodium chloride (3 × 3 l.), and then with 1·75% w/v aqueous sodium chloride solution (3 × 1 l.) and dried over sulphuric acid to give a brown granular solid, decomp. 245°, containing sodium chloride. Since attempts to crystallise the product caused decomposition with loss of nitrogen, it was used without further purification. Paper electrophoresis in 3N-acetic acid showed one slow-moving brown spot. The percentage of "active" cation present in the product was determined by analysis, and by the quantity of nitrogen (2 mole per cation) evolved on heating with cuprous chloride–3N-hydrochloric acid. The following is a typical analysis (Found: C, 44·0; H, 5·5; Cl, 14·0; N, 15·5; Na, 2·7; H_2O, 17·6. Calc. for $C_{35}H_{32}ClN_{11},2HCl,NaCl,9·5H_2O$: C, 44·5; H, 5·6; Cl, 15·0; N, 16·3; Na, 2·45; H_2O, 18·2%). Addition of an aqueous solution of sodium naphthalene-2-sulphonate (18·75 g.) (0·082 mole) to a solution of the product (25 g.) (0·025 mole) in water (2·5 l.) precipitated the *naphthalene-2-sulphonate* (30 g., 93%) as a black solid, decomp. from 221° (Found: C, 61·5; H, 4·6; N, 12·4; S, 7·5; H_2O, 3·6. $C_{45}H_{39}N_{11}O_3S,2C_{10}H_8O_3S,2·5H_2O$ requires C, 61·0; H, 4·7; N, 12·1; S, 7·5; H_2O, 3·55%).

The compounds listed in Table 5 were similarly prepared.

[12] Walls, B.P. 740,027.
[13] Berg, *J.*, 1961, 4041.

TABLE 5.

Bis-diazoamino-compounds (VI).

No.	R	R′	R″	Yield (%)	Decomp. pt.	Formula
1	Me	H	*m*-Amidino	82	243°	$C_{34}H_{30}ClN_{11},2HCl,1{\cdot}75NaCl,2H_2O$
2	Et	Me	*p*-Amidino	74·5	228	$C_{37}H_{36}ClN_{11},2HCl,6H_2O$
3	Et	OH	*p*-Amidino	65	from 303	$C_{35}H_{32}ClN_{11}O_2,2HCl,2{\cdot}5H_2O$
4	Et	OH	*m*-Amidino	66	from 285	$C_{35}H_{32}ClN_{11}O_2,2HCl,3{\cdot}5H_2O$

	Found (%)					Required (%)				
No.	C	H	Cl	N	H_2O	C	H	Cl	N	H_2O
1 *			20·7	18·0	4·1			20·2	18·4	4·3
2	50·7	5·5	12·1	17·7	14·1	51·2	5·5	12·3	17·8	15·0
3	52·3	4·7	13·7	19·0	5·4	53·0	4·9	13·4	19·4	5·7
4	51·2	5·0	13·6	18·5	7·6	52·0	5·05	13·15	19·0	7·8

* Na, 5·1. Req. 4·8%.

4-Amino-3-bromobenzamidine.—4-Amino-3-bromobenzonitrile [14] (25 g.) in 2-ethoxyethanol (250 ml.) was saturated at 0—5° with anhydrous hydrogen chloride and kept for a week. The solid was filtered off, washed with anhydrous ether, and heated in anhydrous-ethanolic ammonia (290 ml.) at 50—60° for 6 hr. After filtration from ammonium chloride, the solution was evaporated under reduced pressure, and the residual gum was triturated with acetone. The insoluble material was filtered off and crystallised from 2N-hydrochloric acid (75 ml.), yielding the *monohydrochloride* (6·8 g., 49·5% based on the nitrile used) as white rhombs, m. p. 262° (decomp.) (Found: Cl, 14·1; N, 16·7. $C_7H_8BrN_3,HCl$ requires Cl, 14·2; N, 16·8%).

The following were similarly prepared from the appropriate nitriles: [15] *3-Amino-4-chloro-*, needles (from 5N-hydrochloric acid), decomp. 264° (Found: Cl, 43·9; N, 17·5. $C_7H_8ClN_3,2HCl$ requires Cl, 44·0; N, 17·3%), and *3-amino-4-methoxy-benzamidine dihydrochloride*, needles (from methanol–concentrated hydrochloric acid), decomp. 277° (Found: Cl, 30·0; N, 17·65. $C_8H_{11}N_3O,2HCl$ requires Cl, 30·0; N, 17·65%).

m-*Amidinophenylhydroxylamine.**—Zinc powder (7·85 g.) was added during 0·25 hr. to a stirred suspension of *m*-nitrobenzamidine hydrochloride [16] (10·45 g.), ammonium chloride (3·2 g.), and ethanol (200 ml.), the temperature rising from 18·5° to 30·5°. After a further 0·25 hr., the mixture was cooled to 5° and filtered, and the residue washed with cold ethanol (20 ml.). 4·9N-Ethereal hydrogen chloride (10 ml.) was added to the solution, followed by ether (400 ml.); the pale yellow *dihydrochloride* (3·7 g., 33%) that separated had m. p. 162—164° (decomp.) (Found: C, 37·2; H, 4·95; Cl, 31·7; N, 18·6. $C_7H_9N_3O,2HCl$ requires C, 37·5; H, 4·95; Cl, 31·65; N, 18·75%). p-*Amidinophenylhydroxylamine dihydrochloride* (30%), a pale yellow powder, m. p. 237—239° (decomp.) (Found: Cl, 31·9; N, 18·9%), was similarly prepared from *p*-nitrobenzamidine hydrochloride.[17]

Thanks are offered to Dr. H. J. Barber, F.R.I.C., and Dr. J. N. Ashley, F.R.I.C., for their interest, Mr. S. Bance, B.Sc., F.R.I.C., for the analyses, and to our colleagues of the Experimental Chemotherapy Division for the biological results.

THE RESEARCH LABORATORIES,
MAY & BAKER LTD., DAGENHAM, ESSEX. [*Received, January 17th,* 1963.]

* These experimental details were kindly supplied by MM. Robert and Gaillard, Société des Usines-Chimiques Rhône-Poulenc, Vitry, France.

[14] Crundwell, *J.*, 1956, 368.
[15] Blanksma and Petri, *Rev. Trav. chim.*, 1947, **66**, 365.
[16] Forsyth, Nimkar, and Pyman, *J.*, 1926, 800.
[17] Pinner and Gradenwitz, *Annalen*, 1897, **298**, 49.