786. *A Search for New Trypanocides. Part VI.* Amidinophenyldiazoamino-quinolinium and -quinazolinium Salts.*

By S. S. Berg.

m- and *p*-Amidinobenzenediazonium chlorides couple with 4,6-diaminoquinolinium and 4,6-diaminoquinazolinium salts to give stable diazoamino-compounds which have significant trypanocidal and babesicidal activity.

The high trypanocidal activity of isometamidium [I; R = *m*-C(:NH)·NH_2] and its positional isomer [I; R = *p*-C(:NH)·NH_2] has been described by Wragg *et al.*[1] and by Berg.[2] These compounds were prepared by coupling of the appropriate amidinobenzenediazonium chloride with 3,8-diamino-5-ethyl-6-phenylphenanthridinium chloride. Jensch[3] had earlier reported the condensation of *m*- or *p*-amidinobenzenediazonium chloride with *m*- or *p*-aminobenzamidine to give the corresponding diazoamino-compounds, which were active against trypanosoma and babesia infections. One of these compounds was the drug "Berenil." In view of the activity of the heterocyclic compounds described by Wragg *et al.*[1] and Berg,[2] and since 4,6-diamino-quinolines (II) and -quinazolines (III) are formally related to *m*-aminobenzamidine, it was decided to prepare analogous diazoamino-compounds by coupling their quaternary salts with *m*- and *p*-amidobenzenediazonium chlorides.

The quaternary salts (IV) used in these investigations were mentioned in various Patent Specifications[4] which claimed a series of pyrimidinium salts related to Antrycide. Although the preparations of the intermediate quinolinium salts were described, no details were given of the synthesis of the corresponding quinazolinium salts.

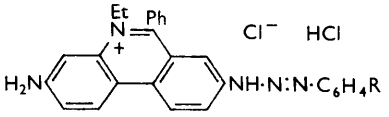
The basic intermediates required for the preparation of the 4,6-diaminoquinazolinium salts were 4-amino-6-nitroquinazoline[5] (Va) and 4-amino-2-methyl-6-nitroquinazoline (Vb). The preparation of the chloro-nitro-derivative (Vd) from 2-methyl-6-nitro-4-quinazolone (VIb)[6] and phosphorus pentachloride was only accomplished in poor yield. The thiol (Ve), however, was obtained in good yield by the reaction of the quinazolone (VIb) with phosphorus pentasulphide in xylene. Methylation of the thiol (Ve) in aqueous sodium hydroxide gave the methyl derivative (Vf), which was fused with ammonium acetate to give the amine (Vb). Passage of a slow stream of methylamine through a solution of the *S*-methyl compound (Vf) in dimethylformamide at 140° gave the 4-methylamino-derivative (Vg). The 4-ethylamino- and 4-dimethylamino-homologues were prepared similarly.

Morley and Simpson[5] failed to quaternise 4-amino-6-nitroquinazoline (Va) by prolonged

* Part V, Davis, *J.*, 1958, 828.

[1] Wragg, Washbourn, Brown, and Hill, *Nature*, 1958, **182**, 1005.
[2] Berg, *Nature*, 1960, **188**, 1107.
[3] Jensch, *Arzneimittel-Forschung*, 1955, **5**, 634.
[4] B.P. 634,818; 794,043; 696,692.
[5] Morley and Simpson, *J.*, 1948. 360.
[6] Bogert and Cook, *J. Amer. Chem. Soc.*, 1906, **28**, 888.

boiling with methyl iodide in methanol, and obtained instead an unstable addition product. Attempts to quaternise the nitroamines with methyl sulphate in boiling methanol gave unstable addition products, which in aqueous solution were reconverted into the parent nitro-amine. But fusion of the nitro-amines with methyl toluene-*p*-sulphonate at 140°, or heating the components in nitrobenzene at 170°, gave the required quaternary salts



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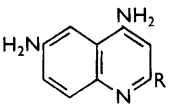

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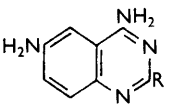

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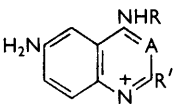

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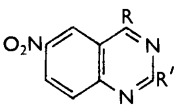
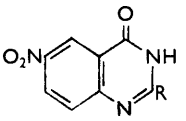
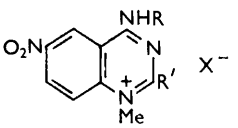


(Va); R = NH_2, R′ = H
(Vb); R = NH_2, R′ = Me
(Vc); R = Cl, R′ = H
(Vd); R = Cl, R′ = Me
(Ve); R = SH, R′ = Me
(Vf); R = SMe, R′ = Me
(Vg); R = NHMe, R′ = Me



(VIa); R = H
(VIb); R = Me



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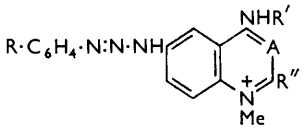

(VIIIa); R = *m*-amidino (VIIIb); R = *p*-amidino

(VII; R = R′ = H or Me, $X^- = p\text{-}C_6H_4Me\cdot SO_3^-$). Addition of ammonia to aqueous solutions of these salts precipitated stable bases which were converted into the quaternary chlorides when treated with hydrochloric acid. Catalytic reduction of the nitro-amine quaternary chlorides gave the corresponding diamines (IV; A = N).

p-Aminobenzamidine monohydrochloride prepared by Crundwell's method [7] and *m*-aminobenzamidine monohydrochloride obtained by the catalytic reduction of *m*-nitrobenzamidine hydrochloride [8] were diazotised in hydrochloric acid solution. The coupling reactions were carried out by rapidly mixing the diazonium solutions with aqueous solutions of the appropriate quaternary salts at 5—15°, followed immediately by the addition of aqueous sodium acetate to render the mixture neutral to Congo Red. Addition of sodium chloride precipitated the crude products as chloride hydrochlorides, from which the desired diazoamino-compounds were obtained by crystallisation from aqueous solvents. When the diazoamino-compounds were warmed with 12N-sulphuric acid or cuprous chloride–3N-hydrochloric acid, nitrogen (1 mol.) was rapidly liberated.

Only 6-*m*-amidinophenyldiazoamino-4-amino-1,2-dimethylquinolinium chloride hydrochloride (as VIIIa; A = CH) had appreciable activity against *Trypanosoma congolense* in mice, but it was considerably less active than isometamidium. Activity against *Trypanosoma rhodesiense* in mice was most marked in the *p*-amidino-series, 6-*p*-amidinophenyldiazoamino-4-amino-1,2-dimethylquinazolinium chloride hydrochloride (as VIIIb; A = N) being comparable in activity to Pentamidine. In contrast the *m*-amidino-series was more active against *Babesia rodhaini* in mice, most of the compounds being considerably more active than Berenil. The high activity of 6-*m*-amidinophenyldiazoamino-4-amino-1,2-dimethylquinazolinium chloride hydrochloride (as VIIIa; A = N) against *Babesia canis* in dogs has recently been reported by Berg and Lucas.[9]

[7] Crundwell, *J.*, 1956, 368.
[8] Easson and Pyman, *J.*, 1931, 2994.
[9] Berg and Lucas, *Nature*, 1961, **189**, 64.

The more important biological results, kindly supplied by Messrs. J. Ford-Robertson, J. Hill, J. M. S. Lucas, and T. G. Mitchell, are recorded in Table 1.

TABLE 1. *Toxic and curative subcutaneous doses of amidinophenyldiazoamino-quinolinium* (VIII; A = CH) *and -quinazolinium salts* (VIII; A = N) *in mice infected with trypanosomes or babesia.*

R	R′	R″	A	xH_2O	Organism	LD_{50} (mg./g.)	CD_{50} (mg./g.)	Ratio
p-C(:NH)·NH_2	Me	H	N	0	*Trypanosoma rhodesiense*	0·125	0·0002	625
m-C(:NH)·NH_2	Me	,,	CH	2	*Trypanosoma congolense*	0·25	0·00625	40
,,	,,	,,	,,	,,	*Babesia rodhaini*	,,	0·0014	178
,,	Ph	,,	,,	,,	,, ,,	,,	0·0023	109
,,	Me	,,	N	1·75	,, ,,	0·15	0·0011	135
,,	Me	Me	,,	2·5	,, ,,	0·09	0·0013	69

EXPERIMENTAL

4-Mercapto-2-methyl-6-nitroquinazoline.—A stirred suspension of finely powdered 2-methyl-6-nitroquinazol-4-one (103 g.) and phosphorus pentasulphide (113 g.) in anhydrous xylene (2 l.) was refluxed for 4 hr. and then cooled to 15°. Sodium hydroxide (70 g.) in water (350 ml.) was added, and the mixture vigorously stirred for ¼ hr. The aqueous layer was separated and acidified at 10—15° with 2N-acetic acid. The *thiol* was precipitated as red granules (100 g., 90%), m. p. 246—249° (decomp.). A sample crystallised from benzene as pale red prisms, m. p. 253—255° (decomp.) (Found: N, 18·65; S, 13·9. $C_9H_7N_3O_2S$ requires N, 19·0; S, 14·5%).

2-Methyl-4-methylthio-6-nitroquinazoline.—Methyl sulphate (50 ml.) was added to a stirred solution of 4-mercapto-2-methyl-6-nitroquinazoline (100 g.) in 0·5N-sodium hydroxide (2 l.). Precipitation of the product was complete after 3 hr. The solid was filtered off and washed successively with 0·1N-sodium hydroxide and water. Crystallisation from ethanol (4·5 l.) gave pink or yellow needles (66 g., 62%), m. p. 178—179°. A sample was recrystallised from light petroleum (b. p. 60—80°), forming pale yellow needles, m. p. 181—183° (Found: N, 17·8; S, 13·35. $C_{10}H_9N_3O_2S$ requires N, 17·9; S, 13·6%).

4-Amino-2-methyl-6-nitroquinazoline.—2-Methyl-4-methylthio-6-nitroquinazoline (56 g.) and ammonium acetate (336 g.) were fused at 190° for 0·5 hr., methanethiol then being evolved. After the mixture had been cooled to 20°, water (1 l.) was added and the solid filtered off and ground with 2N-sodium hydroxide; the mixture was refiltered, and the residue washed with water and crystallised from methanol. The *nitro-amine* (44 g., 90·5%) separated as yellow needles, m. p. 331—333° (Found: C, 53·15; H, 4·2; N, 27·9. $C_9H_8N_4O_2$ requires C, 52·95; H, 3·9; N, 27·45%).

2-Methyl-4-methylamino-6-nitroquinazoline.—Methylamine was passed through a solution of 2-methyl-4-methylthio-6-nitroquinazoline (25 g.) in dimethylformamide (150 ml.) at 140°. After 2 hr., the solution was cooled, and diluted with water (300 ml.), and the yellow precipitate filtered off. Crystallisation from ethanol gave yellow needles (23 g.; 99%), m. p. 226—227° (Found: N, 25·3. $C_{10}H_{10}N_4O_2$ requires N, 25·6%). *4-Ethylamino-*, yellow needles (from ethanol), m. p. 222—223° (Found: C, 57·15; H, 5·7; N, 23·8. $C_{11}H_{12}N_4O_2$ requires C, 56·9; H, 5·2; N, 24·1%), and *4-dimethylamino-2-methyl-6-nitroquinazoline*, yellow needles, m. p. 188—189° (Found: C, 56·8; H, 5·25; N, 24·1. $C_{11}H_{12}N_4O_2$ requires C, 56·9; H, 5·2; N, 24·1%), were prepared similarly.

Quaternisation of the Nitro-amines.—(*a*) An intimate mixture of the nitro-amine (0·1 mol.) and methyl toluene-*p*-sulphonate (0·11 mol.) was fused at 140° for 0·5 hr.; the melt solidified. The solid was ground and heated at 140° for a further 1 hr. After being cooled the solid was washed with ethanol or acetone, and the methotoluene-*p*-sulphonate crystallised from water.

(*b*) A suspension of the nitro-amine (0·1 mol.) and methyl toluene-*p*-sulphonate (0·11 mol.) in anhydrous nitrobenzene (140 ml.) was heated at 170° for 0·5 hr. Partial solution was obtained before the quaternary salt separated. After the mixture had cooled to 20°, the solid was filtered off, washed with acetone, and treated as described below.

Addition of the methotoluene-*p*-sulphonate, dissolved in boiling water (50 ml. per g.), to concentrated aqueous ammonia and ice, precipitated a yellow base, which was washed with water and ground with 2N-hydrochloric acid. The quaternary chloride was washed with acetone and crystallised. In this way the products listed in Table 2 were obtained.

The 4,6-diaminoquinazolinium salts listed in Table 3 were prepared by the reduction of the

TABLE 2. *Aminonitroquinazolinium salts* (VII).

R	R′	X	Yield (%)	Cryst. form	Cryst. from	M. p. (decomp.)	Formula	Found (%)	Required (%)
H	H	*p*-SO_3·C_6H_4Me	53	White needles	0·1N-HCl	335°	$C_{16}H_{16}N_4O_5S$	N, 14·9 S, 8·8	N, 14·9 S, 8·8
H	H	Cl	74·5[a]	White prisms	H_2O–EtOH	307—309°	$C_9H_9ClN_4O_2,\frac{1}{2}H_2O$	N, 22·4 Cl, 14·3 H_2O, 3·6	N, 22·45 Cl, 14·2 H_2O, 3·6
H	Me	*p*-SO_3·C_6H_4Me	61	Yellow plates	H_2O	301°	$C_{17}H_{18}N_4O_5S$	N, 14·2 S, 8·6	N, 14·3 S, 8·2
H	Me	Cl	83[a]	White needles	2N-HOAc–HCl	266—267°	$C_{10}H_{11}ClN_4O_2,H_2O$	C, 43·7 H, 5·15 N, 20·4 Cl, 13·3 H_2O, 6·5	C, 44·0 H, 4·8 N, 20·5 Cl, 13·0 H_2O, 6·6
Me	Me	*p*-SO_3·C_6H_4Me	75	Yellow needles	H_2O	266—268°	$C_{18}H_{20}N_4O_5S$	C, 53·6 H, 5·1 N, 13·5 S, 8·3	C, 53·5 H, 4·95 N, 13·85 S, 7·95
Me	Me	Cl	60[a]	White needles	EtOH	289—290°	$C_{11}H_{13}ClN_4O_2$	C, 49·3 H, 4·9 N, 20·7 Cl, 12·8	C, 48·8 H, 4·8 N, 20·7 Cl, 13·1
Et	Me	*p*-SO_3·C_6H_4Me	64	Brown prisms	H_2O	245—255°	—	—	—
Et	Me	I	90	Yellow needles	EtOH	259—260°	$C_{12}H_{15}IN_4O_2$	C, 38·8 H, 4·4 N, 14·8 I, 33·9	C, 38·5 H, 4·0 N, 14·95 I, 33·9

[a] These are the yields obtained when the methotoluene-*p*-sulphonates are converted into methochlorides.

TABLE 3. *Aminoquinazolinium salts* (IV; A = N).

R	R′	Yield (%)	Cryst. from	M. p. (decomp.)	Formula	Found (%)	Required (%)
H	H	67	H_2O–MeOH	344—346°	$C_9H_{11}ClN_4$	N, 26·65 Cl, 17·1	N, 26·6 Cl, 16·9
H	Me	98	H_2O	319—320°	$C_{10}H_{13}ClN_4,H_2O$	N, 23·1 Cl, 14·55 H_2O, 7·3	N, 23.1 Cl, 14·65 H_2O, 7·4
Me	Me	90	H_2O–EtOH	313—315°	$C_{11}H_{15}ClN_4,1·25H_2O$	N, 21·45 Cl, 13·9 H_2O, 8·7	N, 21·45 Cl, 13·6 H_2O, 8·6

TABLE 4. *Salts* (VIIIb; R′ = H, R″ = Me).

A	Yield (%)	Cryst. form	Cryst. from	Decomp.	Formula	Found (%)	Required (%)
CH[a]	42	Red needles	H_2O–MeOH	294°	$C_{18}H_{20}ClN_7,HCl,H_2O$	C, 51·15 H, 6·0 N, 22·9 Cl, 16·7 H_2O, 4·0	C, 50·95 H, 5·5 N, 23·1 Cl, 16·75 H_2O 4·25
N	41	Orange needles	2N-HOAc–HCl	257—260°	$C_{17}H_{19}ClN_8,HCl,5H_2O$	N, 22·6 Cl, 14·35 H_2O, 17·6	N, 22·5 Cl, 14·3 H_2O, 18·1

[a] 4,6-Diaminoquinaldine methochloride was prepared by the method of B.P. 634,818.

aminonitroquinazolinium salts in aqueous solution, a platinum oxide catalyst being used; they all crystallised in yellow needles.

m-*Aminobenzamidine Monohydrochloride*.—*m*-Nitrobenzamidine hydrochloride (232 g.) in methanol (1392 ml.) was catalytically reduced at 70 lb./sq. in. at 41°, platinum oxide (4·65 g.) being used. Reduction was completed in 2·1 hr.; the catalyst was then filtered off and the solution evaporated under reduced pressure. The yellow product (185 g., 99%), m. p. 161—164° (Easson and Pyman [8] give m. p. 166°), was used without further purification (Found: N, 24·1; Cl, 21·3. Calc. for $C_7H_9N_3,HCl$: N, 24·5; Cl, 21·3%).

Coupling Reaction; *General Procedure.*—Aminobenzamidine monohydrochloride (0·1 mole) in water (85 ml.) and concentrated hydrochloric acid (24·5 ml.) was diazotised at 0—5° by sodium nitrite (7·0 g.) in water (30 ml.). Excess of nitrous acid was removed by addition of sulphamic acid, and the stirred diazonium solution was treated at 5—15°, all at once, with the

TABLE 5. *Salts* (VIIIa).

A	R′	R″	Yield (%)	Cryst. form [a]	Decomp.	Formula	Found (%)	Required (%)
CH	H	Me	56·5	Red needles	249°	$C_{18}H_{20}ClN_7,HCl,2H_2O$	N, 22·2 Cl, 16·0 H_2O, 8·1	N, 22·2 Cl, 16·05 H_2O, 8·15
CH	H	Ph [b]	51·5	Orange prisms	265°	$C_{23}H_{22}ClN_7,HCl,2H_2O$	N, 19·4 Cl, 13·7 H_2O, 7·4	N, 19·4 Cl, 14·0 H_2O, 7·15
N	H	H	52	Orange prisms	245°	$C_{16}H_{17}ClN_8,HCl,2{\cdot}75H_2O$	N, 25·05 Cl, 15·85 H_2O, 11·1	N, 25·3 Cl, 16·0 H_2O, 11·2
N	H	Me	58	Orange needles	241°	$C_{17}H_{19}ClN_8,HCl,3H_2O$	N, 24·6 Cl, 15·6 H_2O, 11·4	N, 24·4 Cl, 15·4 H_2O, 11·7
N	Me	Me	51	Yellow prisms	243—244°	$C_{18}H_{21}ClN_8,HCl,2{\cdot}5H_2O$	N, 23·8 Cl, 15·3 H_2O, 9·85	N, 24·0 Cl, 15·25 H_2O, 9·75

[a] All the compounds were crystallised from aqueous ethanol. [b] 4,6-Diamino-2-phenylquinolinium chloride was prepared by the method described in B.P. 794,043.

diaminoquaternary chloride in N-hydrochloric acid (100 ml.) and water (sufficient to ensure solution). Saturated aqueous sodium acetate (120 ml.) was immediately added, and the reaction mixture was stirred at 5—15° for 3 hr. Sodium chloride (85 g.) was added and the resultant precipitate was washed with saturated sodium chloride solution, and crystallised. In this way the products listed in Tables 4 and 5 were obtained.

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