885. *The Search for New Trypanocides. Part X.*[1] *Phenyldiazoamino- and Phenylazo-phenanthridinium Salts.*

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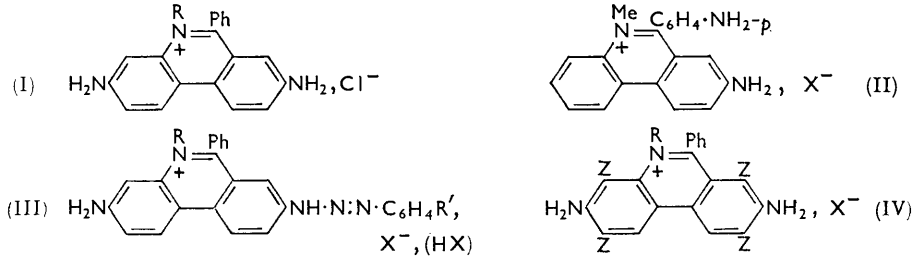
o-, *m*-, and *p*-Substituted benzenediazonium salts couple with 5-alkyl-3,8-diamino-6-phenylphenanthridinium chlorides and 8-amino-6-*p*-aminophenyl-5-methylphenanthridinium isethionate to give a mixture of diazoamino- and amino-azo-derivatives which possess trypanocidal activity. *m*- and *p*-Guanidinoiminomethylbenzenediazonium chloride couple with 3,8-diamino-5-ethyl-6-phenylphenanthridinium chloride to give almost exclusively the diazoamino-derivatives, whereas diazotised *p*-aminophenyltrimethylammonium chloride gives mainly the amino-azo-derivative.

In view of the high activity against *Trypanosoma congolense* of the products of coupling *m*- and *p*-amidinobenzenediazonium chloride with dimidium chloride (I; R = Me), homidium chloride (I; R = Et), and phenidium chloride (II; X = Cl), it was decided to prepare analogous compounds in which the amidino-group was replaced by other electronegative substituents in order to extend the knowledge of the structure–activity relation in this series. The coupling reactions were carried out in acetic acid–sodium acetate solution, and the products were assigned diazoamino- or amino-azo-structures in accordance with the results described in Parts VIII and IX of this series.[1,2]



p-Guanidinobenzenediazonium chloride did not couple with homidium chloride, although the *meta*-isomer behaved normally. *m*- and *p*-Guanidinoiminomethylbenzenediazonium chloride gave almost exclusively the red diazoamino-derivatives of homidium chloride, whereas diazotised *p*-aminophenyltrimethylammonium chloride gave mainly the purple amino-azo-derivative.

Most of the amines used in these investigations were commercially available. *m*-Aminobenzylideneaminoguanidine was obtained by the reduction of the product formed by condensing *m*-nitrobenzaldehyde and aminoguanidine carbonate, a method[3] which has been described for the *para*-isomer. *m*- and *p*-Aminoguanidine were obtained by Miller's method.[4]

The biological results have been reported elsewhere.[5]

Experimental

Water of crystallisation was determined by the Karl Fischer method.

Coupling was carried out by the method of Berg, Bretherick, Washbourn, and Wragg.[1] In this way the products listed in Tables 1 and 2 were obtained.

[1] Part IX, Berg, Bretherick, Washbourn, and Wragg, preceding paper.
[2] Berg, *J.*, 1963, 3635.
[3] Bernstein, Yale, Losee, Hasling, Martins, and Lott, *J. Amer. Chem. Soc.*, 1951, **73**, 906.
[4] Miller, *J.*, 1949, 2722.
[5] Brown, Hill, and Holland, *Brit. J. Pharmacol.*, 1961, **17**, 396.

m-*Nitrobenzylideneaminoguanidine*.—A suspension of *m*-nitrobenzaldehyde (30 g.) in ethanol (50 ml.) and water (300 ml.) was heated on the steam-bath and treated, in one portion, with aminoguanidine hydrogen carbonate (27 g.) in water (250 ml.) containing potassium hydroxide (22·4 g.). Ethanol (100 ml.) was added, and heating was continued for 10 min.,

TABLE 1.

Red diazoamino-compounds (III).

No.	R	R′	X	Yield (%)	Cryst. from	Decomp. pt.	Formula
1	Me	*m*-NH·C(:NH)·NH_2	Cl	18	H_2O–EtOH	236°	$C_{27}H_{25}ClN_8,HCl,H_2O$
2	Et	*m*-NH·C(:NH)·NH_2	Cl	10	MeOH	243	$C_{28}H_{27}ClN_8,HCl,1·5H_2O$
3	Et	*p*-CH:N·NH·C(:NH)·NH_2	Cl	65	MeOH	229	$C_{29}H_{28}ClN_9,HCl,4H_2O$
4	Et	*m*-CH:N·NH·C(:NH)·NH_2	Cl	67	MeOH	238	$C_{29}H_{28}ClN_9,HCl,3H_2O$
5	Me	*m*-CO·NH_2	Cl	35	H_2O–MeOH	218—220	$C_{27}H_{23}ClN_6O,2H_2O$
6	Et	*p*-CO·NH_2	Cl	10	MeOH	227—228	$C_{28}H_{25}ClN_6O,2H_2O$
7	Et	*m*-CO·NH_2	Cl	25	H_2O–MeOH	210—212	$C_{28}H_{25}ClN_6O,CH_3·OH,0·75H_2O$
8	Et	*o*-Cl	Cl	25	MeOH–Et_2O	251	$C_{17}H_{23}Cl_2N_5$
9	Et	*p*-Cl	Cl	18	H_2O–EtOH	265	$C_{17}H_{23}Cl_2N_5,0·5EtOH$
10	Et	*p*-CO_2 *		15	MeOH	232—234	$C_{28}H_{23}N_5O_2,4·25H_2O$
11	Et	*p*-$SO_2·NH_2$	Cl	5	H_2O–EtOH	225—227	$C_{27}H_{25}ClN_6O_2S,2H_2O$
12	Et	*m*-$SO_2·NH_2$	Cl	19	H_2O–EtOH	204—210	$C_{27}H_{25}ClN_6O_2S,3H_2O$
13	Et	*m*-NO_2	Br	5	MeOH	250	$C_{27}H_{23}BrN_6O_2$

* Forms an internal salt.

	Found (%)					Required (%)				
No.	C	H	Cl	N	H_2O	C	H	Cl	N	H_2O
1			12·8	20·4	3·4			12·85	20·4	3·25
2	58·8	5·45	12·5	19·5	4·9	58·5	5·4	12·4	19·5	4·7
3	54·2	6·1	10·8	19·7	12·0	53·9	5·7	11·0	19·5	11·1
4	54·7	5·5	11·1	20·6	8·9	55·4	5·5	11·3	20·1	8·6
5			7·05	16·0	7·4			6·8	16·2	6·9
6	62·4	5·4	6·65	15·5	7·0	62·0	5·4	6·55	15·5	6·7
7	64·5	5·8	6·4	15·6	2·6	64·3	5·5	6·6	15·5	2·6
8	66·3	4·8	14·4	14·1		66·4	4·7	14·5	14·3	
9 †	65·4	5·0	13·95	13·95		65·7	5·1	13·85	13·7	
10	62·4	6·05		13·15	14·1	62·5	5·9		13·0	14·3
11 ‡			6·3	14·6	6·2			6·3	14·8	6·4
12 §	55·1	5·7	5·85	14·2	9·1	55·2	5·3	6·05	14·3	9·25
13 ¶	59·3	4·4		15·1		59·6	4·2		15·4	

† EtO, 4·4. Req. 4·4%. ‡ S, 5·9. Req. 5·65%. § S, 5·6. Req. 5·5%. ¶ Br, 14·45. Req. 14·7%.

crystallisation occurring. The solution was cooled to 10°, and the crystals were filtered off, washed with water, and recrystallised from ethanol (900 ml.); the *product* (35 g., 86%) separated as fine yellow needles, m. p. 215—216° (Found: C, 47·3; H, 4·7; N, 30·1; OEt, 19·5. $C_3H_9N_5O_2,0·5EtOH$ requires C, 47·0; H, 5·2; N, 30·5; OEt, 19·6%).

m-*Aminobenzylideneaminoguanidine*.—*m*-Nitrobenzylideneaminoguanidine hemiethanolate (35 g.) in boiling 2N-aqueous acetic acid (350 ml.) was reduced by the gradual addition of reduced iron (35 g.). The mixture was heated on the steam-bath for 0·25 hr., and concentrated hydrochloric acid was added until a clear solution was obtained. On cooling, crystallisation occurred, and the *dihydrochloride* was filtered off, washed with acetone, and recrystallised from dilute aqueous hydrochloric acid (1 : 1) (400 ml.), separating as long white needles (27·5 g., 75%), m. p. 295° (softening at 270°) (Found: Cl, 28·7; N, 27·95. $C_8H_{11}N_5,2HCl$ requires Cl, 28·4; N, 28·0%).

Phenidium Isethionate (II; X = $C_2H_5O_4S$) (preparation by Mr. L. G. KING).—A solution of 8-amino-6-*p*-aminophenyl-5-methylphenanthridinium chloride (phenidium chloride) (170 g.) in boiling water (2 l.) was treated with sodium hydroxide (150 g.) in water (500 ml.). The mixture was extracted with butan-1-ol (2 × 1 l.), and the combined extracts were washed with water and added to ammonium isethionate (71·5 g.) in water (350 ml.). Butanol was removed by steam-distillation, and the aqueous solution was concentrated under reduced pressure to a thick syrup. Trituration with acetone (3 × 300 ml.) gave a solid *salt* which crystallised from

ethanol (450 ml.) as red prisms (173 g., 81·5%), m. p. 157—161° (Found: N, 9·7; S, 7·45. $C_{22}H_{23}N_3O_4S$ requires N, 9·9; S, 7·55%).

Coupling of p-*Chlorobenzenediazonium Isethionate with Phenidium Isethionate.*—A solution of *p*-chloroaniline (3·1 g.) in water (20 ml.) and 10N-aqueous isethionic acid (5·2 ml.) was diazotised at 0—5° by sodium nitrite (1·7 g.) in water (20 ml.). The excess nitrous acid was removed by sulphamic acid, and the diazonium solution was added, in one portion, to phenidium isethionate (10 g.) in water (60 ml.) at 5—10°. Saturated aqueous sodium acetate (50 ml.) was

TABLE 2.

Purple amino-azo-compounds (IV).

No.	R	R′	X	Yield (%)	Cryst. from	Decomp. pt.	Formula
1	Et	*m*-NH·C(:NH)·NH_2	Cl	4 *	MeOH–$COMe_2$	247—250°	$C_{28}H_{27}ClN_8$,HCl,$2H_2O$
2	Me	*m*-CO·NH_2	Cl	20	MeOH	261—263	$C_{27}H_{23}ClN_6O$,H_2O
3	Et	*p*-CO·NH_2	Cl	35	MeOH	274—276	$C_{28}H_{25}ClN_6O$,H_2O
4	Et	*m*-CO·NH_2	Cl	12·5	MeOH	207—210	$C_{28}H_{25}ClN_6O$,$3·5H_2O$
5	Et	*o*-Cl	Cl	15	EtOH–Et_2O	251	$C_{27}H_{23}Cl_2N_5$,0·5EtOH
6	Et	*p*-Cl	Cl	18	H_2O–EtOH	283	$C_{27}H_{23}Cl_2N_5$,0·5EtOH
7	Et	*p*-CO_2 †		7	MeOH	225—228	$C_{28}H_{23}N_5O_2$,$3H_2O$
8	Et	*p*-SO_2·NH_2	Cl	25	MeOH	215—217	$C_{27}H_{25}ClN_6O_2S$,MeOH,H_2O
9	Et	*m*-SO_2·NH_2	Cl	11	MeOH	273—274	$C_{27}H_{25}ClN_6O_2S$,H_2O
10	Et	*m*-NO_2	Cl	48	MeOH	207—210	$C_{27}H_{23}ClN_6O_2$,$2H_2O$
11	Et	*p*-NMe_3^+ ‡	Br	41	H_2O	197—198	$C_{30}H_{32}Br_2N_6$,$2·5H_2O$
12	Et	*p*-CO·O·CH_2·CH_2·NEt_2 ‡	Cl	26	H_2O	185—190	$C_{34}H_{37}ClN_6O_2$,HCl,$3H_2O$

* Containing traces of the red diazoamino-isomer. † Internal salt. ‡ The diazoamino-isomer was not obtained pure.

	Found (%)					Required (%)				
No.	C	H	Cl	N	H_2O	C	H	Cl	N	H_2O
1	57·2	5·3	11·9	19·0	6·0	57·6	5·3	12·2	19·2	6·15
2			7·3	16·4	3·7			7·1	16·8	3·6
3	66·0	5·8	16·9	16·6	3·4	65·4	5·3	16·9	16·4	3·5
4	60·3	6·8	6·3	15·05	11·1	60·1	5·7	6·35	15·0	11·25
5 *	65·7	5·0	13·9	13·9		65·7	5·1	13·85	13·7	
6 †	65·5	5·2	13·45	14·0		65·7	5·1	13·85	13·7	
7	65·9	6·1		13·7	10·4	65·4	5·6		13·6	10·5
8 ‡	57·7	5·1	6·0	14·4	3·0	57·7	5·3	6·1	14·4	3·1
9 §	59·0	5·0	6·4	14·6	3·0	58·85	4·9	6·45	15·2	3·25
10	60·95	5·1	6·8	16·0	6·7	60·7	5·1	6·7	15·7	6·75
11 ¶	52·95	5·6		12·1	6·4	52·9	5·4		12·3	6·6
12	59·1	6·1	10·25	11·7	7·8	59·5	6·4	10·35	12·2	7·85

* EtO, 4·1. Req. 4·4%. † EtO, 4·3. Req. 4·4%. ‡ S, 6·1; MeO, 5·5. Req. S, 5·5; MeO, 5·3%. § S, 6·1. Req. 5·8%. ¶ Br, 22·9. Req. 23·4%.

added, and the mixture was stirred at 5—10° for 1 hr. The precipitate was filtered off, stirred with saturated aqueous sodium chloride, and crystallised from water. The chloride hydrochloride (7·1 g., 58%) of the mixed isomers was obtained as red crystals, m. p. 200° (decomp.) (Found: C, 61·4; H, 5·5; Cl, 13·1; N, 13·2; H_2O, 6·8. Calc. for $C_{26}H_{25}Cl_2N_5$,$2H_2O$: C, 61·3; H, 4·9; Cl, 13·9; N, 13·8; H_2O, 6·8%).

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