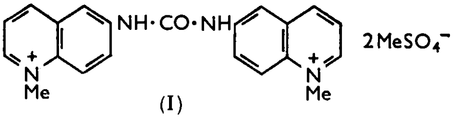
1010. *The Search for Chemotherapeutic Amidines. Part XIX.** *3,3'-Diamidinocarbanilide and its Congeners.*

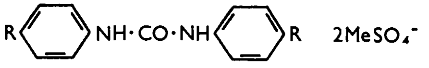
By S. S. Berg.

The preparation of 3,3'-diamidinocarbanilide di-isethionate, a new babesicidal drug, is described. Modifications to its structure have produced compounds of lower activity.

The activity of ureas against babesial infections in cattle, sheep, horses, and goats has been reported by Schönhofer and Henecka[1] and by Mack.[2] The bisquinolinium urea (" Quinuronium sulphate ") (I) is widely used in the treatment of natural infections of bovine redwater, and the carbanilides (II) and (III) have recently been developed in the U.S.S.R.



(I)



(II) R = NMe_3^+
(III) R = $NMePr_2^+$

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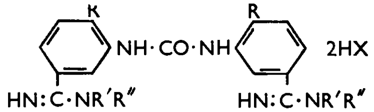
* Part XVII, Berg. *J.*, 1960, 5172; Part XVIII, Easson, *J.*, 1961, 1029.

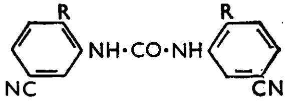
[1] Schönhöfer and Henecka, Fiat Review of German Science, " Chemotherapy," 1939—1946, Vol. XLIII, p. 57.

[2] Mack, *Vet. Rev. Annot.*, **3**, 57.

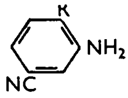
In view of the antiprotozoal activity of many aromatic diamidines, and the use of 4,4′-diamidinodiphenyl ether (phenamidine) in the treatment of canine babesiasis, it seemed desirable to examine a series of diamidinocarbanilides for babesicidal activity. 4,4′-Diamidinocarbanilide diacetate was shown to be inactive against *Babesia rodhaini* in mice at half the lethal dose. The *meta*-isomer (IV; R = R′ = R″ = H, X = Cl), however, showed considerable activity in the screening test, and subsequent investigations were therefore confined to *meta*-amidines.



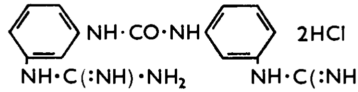
(IV)



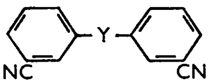
(V) a: R = H
b: R = Cl
c: R = OMe



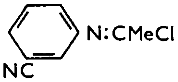
(VI) a: R = H
b: R = Cl
c: R = OMe



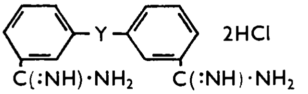
(VII)



(VIII) a: Y = NH·C(:NH)·NH
b: Y = N:CMe·NH
c: Y = NH·CS·NH



(X)



(IX) a: Y = NH·C(:NH)·NH
b: Y = N:CMe·NH
c: Y = NH·CS·NH

The dicyano-compounds (Va–c) were prepared by condensating the appropriate aminobenzonitrile (VIa–c) with carbonyl chloride in pyridine. They were converted into the di-imidates and thence into the diamidines. The latter were tested biologically as their water-soluble dihydrochlorides, dihydrobromides, or di-isethionates.

An alternative preparation by the reaction of *m*-aminobenzamidine monohydrochloride with carbonyl chloride or 3,5-dimethylpyrazole-1-carboxyamide gave a poor yield only of the diamidine (IV; R = R′ = R″ = H, X = Cl), and none was obtained by fusion of this amine with urea.

In an attempt to improve the chemotherapeutic properties of the compound (IV; R = R′ = R″ = H, X = Cl or $HO{\cdot}CH_2{\cdot}CH_2{\cdot}SO_3$) the following modifications were made to the structure of the diamidine: (1) The amidino-groups were replaced by other basic groups, (2) the urea linkage was replaced by related groups, and (3) substituents were introduced into the benzene rings. All of these modifications gave compounds of lower babesicidal activity.

Fusion of *m*-aminodimethylaniline with urea gave 3,3′-bisdimethylaminocarbanilide which gave a diquaternary salt with methyl sulphate.

3,3′-Diaminocarbanilide dihydrochloride was condensed with cyanamide to give the diguanidine (VII).

m-Aminobenzonitrile with cyanogenbromide gave the dinitrile (VIIIa) which was converted into the diamidine (IXa).

Reaction of *m*-acetamidobenzonitrile with phosphorus pentachloride gave the imidoyl chloride (X) which condensed with *m*-aminobenzonitrile to give the dinitrile (VIIIb) and thence the diamidine (IXb). The thiocarbanilide (VIIIc) was similarly prepared from *m*-aminobenzonitrile and thiocarbonyl chloride. Attempts to convert it into the diamidine (IXc) by the Pinner method,[3] or by direct fusion with ammonium benzenesulphonate, caused profound decomposition. No reaction occurred between *m*-aminobenzamidine monohydrochloride and 3,5-dimethylpyrazole-1-thiocarboxyamide.

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[3] Ashley, Barber, Ewins, Newbery, and Self, *J.*, 1942, 103.

3,3′-Diamidino- and 3,3′-di-(*N*-methylamidino)-carbanilide dihydrochlorides were the most active compounds in mice in the screening test. As the former compound was the least toxic to calves, it was chosen for field trial. The activity of its di-isethionate against *Babesia divergens* in calves has been reported by Ashley *et al.*[4] and its efficacy in the field treatment of cattle in veterinary practice by Beveridge *et al.*[5]

TABLE 1.

Activity of some *mm*′-diamidines (2-R,5-R′-C_6H_3·NH)$_2$CO against *Babesia rodhaini* in mice.

2-Subst.	5-Subst.	LD$_{50}$ (mg./g.) subcutaneous	ED$_{50}$ (mg./g.) subcutaneous
H	·C(:NH)·NH_2	0·08	0·0038
H	·C(:NH)·NHMe	0·1	0·0011
OMe	·C(:NH)·NH_2	0·3	0·082
H	·NH·C(:NH)·NH_2	0·1	0·046

The activity of the more active compounds against *Babesia rodhaini* in mice is summarised in Table 1; the biological data were kindly supplied by Mr. J. M. S. Lucas of the Veterinary Research Division.

EXPERIMENTAL

3,3′-*Dicyanocarbanilides* (V).—Carbonyl chloride (1 mole) in anhydrous toluene (450 ml.) was added during 0·5 hr. to a stirred solution of the appropriate aminobenzonitrile (1·9 moles) in anhydrous pyridine (925 ml.). The exothermic reaction was controlled and the temperature kept below 30° by cooling in ice. Then the mixture was stirred for 0·5 hr. at 95—100°. After being cooled to 40°, it was added to ice-water (5·3 l.), and the precipitate was filtered off, washed with water, and crystallised. The results are recorded in Table 2.

3,3′-*Dicyanothiocarbanilide*.—This was prepared similarly from *m*-aminobenzonitrile (3·5 g.) and thiocarbonyl chloride (0·95 ml.) as pink prisms (1·8 g., 41%), m. p. 163° (from ethanol or ethyl acetate). It contained traces of solvent which could not be removed below the decomposition point (Found: C, 63·9; H, 4·0; N, 18·6; S, 10·9; Ac, 3·4. $C_{15}H_{10}N_4S,0{\cdot}25C_4H_8O_2$ requires C, 64·0; H, 4·0; N, 18·7; S, 10·7; Ac, 3·6%).

NN′-*Di*-m-*cyanophenylguanidine*.—*m*-Aminobenzonitrile (23·6 g.) and cyanogen bromide (10·6 g.) in anhydrous ethanol (100 ml.) were refluxed overnight. Ether (4 vol.) was added to the cold reaction mixture, and the solid was filtered off and ground with 2N-sodium hydroxide. The *dinitrile* crystallised from aqueous ethanol as cream needles (15·2 g., 58%), m. p. 162—163° (Found: C, 69·1; H, 4·25; N, 26·8. $C_{15}H_{11}N_5$ requires C, 68·95; H, 4·25; N, 26·8%).

NN′-*Di*-m-*cyanophenylacetamidine*.—*m*-Acetamidobenzonitrile (23 g.) (Bogert and Kohnstamm[6]) was added to a solution of phosphorus pentachloride (30·1 g.) in anhydrous benzene (288 ml.) which was cooled with water. The mixture was refluxed for 0·25 hr., a clear solution being obtained. The solvent was distilled off under reduced pressure from a bath at 50°, and anhydrous benzene (432 ml.) was added. *m*-Aminobenzonitrile (17·3 g.) in anhydrous

TABLE 2.

Dicyano-compounds (V).

R	Yield (%)	Cryst. from	Crystalline form	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N
H	77	EtOH	Pink prisms	205—206°	68·4	3·9	21·8	$C_{15}H_{10}N_4O$	68·7	3·8	21·4
Cl[a]	43·5	NMe_2·CHO	White needles	330 (decomp.)	—	—	16·9	$C_{15}H_8Cl_2N_4O$[c]	—	—	16·9
OMe[b]	84·8	,,	Yellow needles	315—316	64·0	4·6	17·4	$C_{17}H_{14}N_4O_3$	63·35	4·35	17·4

[a,b] Prepared by Blanksma and Petri's method (*Rec. Trav. chim.*, 1947, **66**, 365); (*a*) m. p. 93—94°; (*b*) m. p. 84°. [c] Found: Cl, 21·4. Reqd.: Cl, 21·45%.

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[4] Ashley, Berg, and Lucas, *Nature*, 1960, **185**, 461.

[5] Beveridge, Thwaite, and Shepherd, *Vet. Rec.*, 1960, **72**, 383.

[6] Bogert and Kohnstamm, *J. Amer. Chem. Soc.*, 1903, **25**, 482.

TABLE 3.

Diamidines, $\{5\text{-}[NR'R''\cdot C(:NH)],2\text{-}R\text{-}C_6H_3\}_2Y,2HX,xH_2O$.

No.	Y	R	R′	R″	X	x	Alcohol and solvent for imidate prep.	Cryst. solvent	Form	Decomp. pt.	Yield (%)
1	NH·CO·NH	H	H	H	Cl	1	$EtOH–CHCl_3$	MeOH–$COMe_2$	Needles	286°	79
2	NH·CO·NH	H	H	H	$C_2H_5O_4S$ [a]	0	$EtOH–CHCl_3$	MeOH–$COMe_2$	Needles	256 (m. p. 209—210)	78
3	NH·CO·NH	H	Me	H	Cl	1·5	$EtOH–CHCl_3$	3N-HCl	Needles	273—274 (soften 210)	62
4	NH·CO·NH	H	Et	H	Br	1	$EtOH–CHCl_3$	MeOH–$COMe_2$	Prisms	302—305	32
5	NH·CO·NH	H	Me	Me	Br	1·75	$EtOH–CHCl_3$	Aq.NaBr	Needles	300—302	48·6
6	NH·CO·NH	Cl	H	H	Cl	1	$HO\cdot[CH_2]_2\cdot OEt$	2N-HCl	Prisms	280—282	21
7	NH·CO·NH	OMe	H	H	Cl	1	$HO\cdot[CH_2]_2\cdot OEt$	N-HCl	Needles	285—286	39·5
8	NH·C(:NH)·NH	H	H	H	Cl [b]	2	$HO\cdot[CH_2]_2\cdot OEt$	MeOH–EtOAc	—	254	55·6
9	N:CMe·NH	H	H	H	Cl [b]	0·5	$EtOH–CHCl_3$	MeOH–$COMe_2$	—	357	27·5

[a] Isethionate. [b] Contains 2·25HCl.

No.	Found (%) C	H	Hal	N	H_2O	Formula	Required (%) C	H	Hal	N	H_2O
1	46·3	5·25	18·4	22·0	4·85	$C_{15}H_{16}N_6O,2HCl,H_2O$	46·5	5·2	18·35	21·7	4·65
2	—	—	—	15·1	—	$C_{15}H_{16}N_6O,2C_2H_6O_4S$ [c]	—	—	—	15·3	—
3	—	—	16·6	20·1	6·0	$C_{17}H_{20}N_6O,2HCl,1{\cdot}5H_2O$	—	—	16·8	19·8	6·4
4	—	—	30·5	15·6	3·4	$C_{19}H_{24}N_6O,2HBr,H_2O$	—	—	30·0	15·7	3·4
5	—	—	29·9	15·6	5·6	$C_{19}H_{24}N_6O,2HBr,1{\cdot}75H_2O$	—	—	29·2	15·4	5·8
6	—	—	31·2	18·9	3·85	$C_{15}H_{14}Cl_2N_6O,2HCl,H_2O$	—	—	31·15	18·4	3·95
7	—	—	15·6	18·7	3·9	$C_{17}H_{20}N_6O_3,2HCl,H_2O$	—	—	15·8	18·8	4·0
8	43·8	6·0	19·4	23·2	9·0	$C_{15}H_{17}N_7,2{\cdot}25HCl,2H_2O$	43·8	5·6	19·4	23·7	8·7
9	50·2	5·65	20·4	21·9	2·3	$C_{16}H_{18}N_6,2{\cdot}25HCl,0{\cdot}5H_2O$	50·2	5·55	20·55	22·0	2·3

[c] Found: S, 11·6. Reqd. S, 11·7%.

benzene (144 ml.) was slowly added to the stirred boiling solution of the imidoyl chloride, and a solid separated. After being refluxed for a further 3 hr., the mixture was cooled to 20°, and the solid was filtered off and dissolved in pyridine (575 ml.). Water (1725 ml.) was added to the filtered solution. The precipitate crystallised from ethanol as cream prisms (24·4 g., 65·3%), m. p. 186—188° (Found: C, 73·5; H, 4·8; N, 21·5. $C_{16}H_{12}N_4$ requires C, 73·85; H, 4·6; N, 21·55%).

The *diamidines* in Table 3 were prepared from the respective dicyano-compounds by the Pinner method (cf. Ashley *et al.*[3]).

Reaction of m-*Aminobenzamidine Monohydrochloride with Carbonyl Chloride.*—A suspension of finely powdered *m*-aminobenzamidine monohydrochloride (3·65 g.) (Easson and Pyman [7]) in anhydrous pyridine (15 ml.) was treated at 5—10° with a solution of carbonyl chloride (0·75 ml.) in anhydrous toluene. There was mildly exothermic reaction and a brown gum separated. After being heated for 0·5 hr. on a steam bath, the mixture was cooled to 25°, and the liquor was decanted from the gum. Addition of ether to an ethanolic solution of the gum gave a sticky solid, which was crystallised twice from 2N-hydrochloric acid to give 3,3′-diamidinocarbanilide dihydrochloride hydrate (0·24 g., 7%), white needles, decomp. 286°.

Reaction of m-*Aminobenzamidine Monohydrochloride with* 3,5-*Dimethylpyrazole*-1-*carboxyamide.*—*m*-Aminobenzamidine monohydrochloride (3·45 g.) and 3,5-dimethylpyrazole-1-carboxyamide (1·4 g.) (Scott *et al.*[8,9]) were refluxed in 2-ethoxyethanol (7 ml.) for 5 hr. After being cooled, the precipitate was filtered off; it crystallised from 2N-hydrochloric acid to give 3,3′-diamidinocarbanilide dihydrochloride hydrate (0·35 g., 8·75%) as white needles, decomp. 286°.

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[7] Easson and Pyman, *J.*, 1931, 2991.

[8] Scott, *J. Amer. Chem. Soc.*, 1953, **75**, 1294, 4053.

[9] Scott, O'Donovan, Kennedy, and Reilly, *J. Org. Chem.*, 1957, **22**, 820.

Attempted Preparation of 3,3'-*Diamidinothiocarbanilide.*—(*a*) A suspension of 3,3'-dicyanothiocarbanilide (1·3 g.) in anhydrous chloroform (13 ml.) containing anhydrous ethanol (2 ml.) was saturated at 0° with anhydrous hydrogen chloride, a clear solution being obtained. After 7 days, a trace of insoluble material was filtered off, and the filtrate was diluted with anhydrous ether; this gave a foul-smelling gum. Attempts to isolate a pure imidate from the gum were unsuccessful. (*b*) A mixture of the dicyano-compound (1·5 g.) and ammonium benzenesulphonate (1·8 g.) was heated at 150°; profound decomposition occurred. At lower temperatures no reaction occurred. (*c*) *m*-Aminobenzamidine monohydrochloride (2·2 g.) and 3,5-dimethylpyrazole-1-thiocarboxyamide (1·0 g.) (Scott *et al.*[9]) in 2-ethoxyethanol (10 ml.) were refluxed for 5 hr. The solution was concentrated under reduced pressure, and the residual gum was dissolved in water. Addition of sodium bromide to the filtered solution precipitated *m*-aminobenzamidine monohydrobromide (2·0 g.), m. p. 72°.

3,3'-*Diguanidinocarbanilide Dihydrochloride Hemihydrate.*—3,3'-Diaminocarbanilide dihydrochloride (20 g.) (Brunner[10]), cyanamide (7 g.), and ethanol (53 ml.) were refluxed together overnight, a solution being obtained after 4 hr. The solid, which separated from the cold solution was filtered off and recrystallised from methanol–acetone. The *product* (12·8 g., 31·6%) separated as grey prisms, decomp. 270—272° (Found: Cl, 17·0; N, 27·2; H_2O, 2·4. $C_{15}H_{18}N_8O,2HCl,0{\cdot}5H_2O$ requires Cl, 17·4; N, 27·45; H_2O, 2·25%).

3,3'-*Bisdimethylaminocarbanilide.*—*m*-Aminodimethylaniline (31·3 g.) (Jaubert[11]) and urea (7 g.) were fused together at 148—152° for 2 hr. The solid was cooled and ground with ethanol. Crystallisation of this solid from 2-ethoxyethanol gave the *product* (14·8 g., 43·3%) as needles, m. p. 260—262° (Found: C, 67·65; H, 7·7; N, 18·5. $C_{17}H_{22}N_4O$ requires C, 67·5; H, 7·3; N, 18·5%). This with methyl sulphate in nitrobenzene gave the *dimethosulphate dihydrate*, plates (from methanol), decomp. 214—216° (Found: N, 9·45; S, 11·1; H_2O, 6·1. $C_{19}H_{28}N_4O^{2+},2CH_3SO_4^-,2H_2O$ requires N, 9·55; S, 10·9; H_2O, 6·15%).

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[10] Brunner, U.S.P. 2,503,797/1950.

[11] Jaubert, *Bull. Soc. chim. France*, 1899, **21**, 20.