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1,4-Bis(4-guanylphenylethyl)benzenes as Potential Antitrypanosomal Agents

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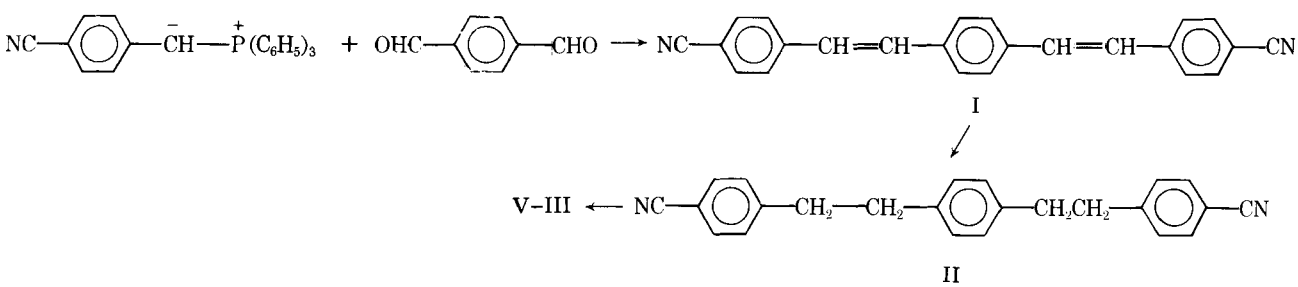
Abstract □ A series of 1,4-bis(4-guanylphenylethyl)benzenes, including masked amidines in which the guanyl function is incorporated into a heterocyclic ring, were prepared for screening as potential antitrypanosomal agents. Some of these compounds were active against *Trypanosoma rhodesiense* in mice. The diamidines were prepared by standard methods from 1,4-bis(4-cyanophenylethyl)benzene which was obtained from 1,4-bis(4-cyanostyryl)benzene by diimide reduction. The latter compound was prepared by the Wittig reaction between 4-cyanobenzylphosphonium ylide and terephthaldicarboxaldehyde.

Keyphrases □ Antitrypanosomal agents—potential, 1,4-bis(4-guanylphenylethyl)benzenes □ *Trypanosoma rhodesiense*—1,4-bis(4-guanylphenylethyl)benzenes, activity as antitrypanosomal agents □ Structure–activity relationships—1,4-bis(4-guanylphenylethyl)benzenes as potential antitrypanosomal agents

Aryl diamidines have been known to be useful antitrypanosomal agents for many years (1, 2). The aryl diamidines reported to exhibit antitrypanosomal activity fall into two general, apparently arbitrary, sets: those that have their guanyl functions separated by approximately 12Å and those that are separated by approximately 20Å (3). It is not known if this observation has any significance regarding the interaction of these compounds with their bioreceptor(s). A number of quite active aryl diamidines have been reported which fall into the category of the 12Å set (3–5) and this report describes efforts to synthesize compounds that fall into the 20Å class. Pentamidine (1), congocidin (1), and the terephthanilide amidines (6) are notable examples of the antitrypanosomal compounds that fall into the latter structural class. While pentamidine and the terephthanilide amidines have similar separation of the guanyl functions, they differ in that terephthanilide amidines probably exist in a planar conformation, whereas this is unlikely for pentamidine. The present study attempted to determine the effect on antitrypanosomal activity and binding to the bioreceptor for the terephthanilide amidine types which are conformationally more flexible. To test this point, 1,4-bis(4-guanylphenylethyl)benzene was synthesized along with related compounds in which the conformationally rigid carboxamido groups of the terephthanilide amidines were replaced by the conformationally flexible $-CH_2CH_2-$ units.

RESULTS AND DISCUSSION

The synthesis of the target diamidines was achieved by employing a conventional synthetic approach (Scheme I). The first step involves a Wittig reaction between the 4-cyanobenzylphosphonium ylide and terephthaldicarboxaldehyde to yield a bis-1,4-(4-cyanostyryl)benzene (I), the stereochemistry of which was not determined. The bis styryl



Scheme I

0022-3549/82/0400-0465$01.00/0

Table I—Antitrypanosomal Screening Results [a]

No.	Cures[b] or ΔMST[c] at given Dosage[d], mg/kg															
	640	424	320	212	160	106	80	53	40	26.5	20	13.3	10	5	2.5	1.25
III		5		5		5		3		1		1.30				
IV		2.3*D*		1.6*D*		0.6*D*		0.4*D*		0.5*D*		0.2*D*				
V		T[e]		5		5		4		2		2.4*D*				
VI[f]	5		5		5		5		5		5		5	5	4	1
VII[g]	5		5		5		5		5		5		5	5	4	4

[a] See Ref. 8. Antitrypanosomal testing was done at the Leo Rane Laboratory of the University of Miami under the direction of Dr. A. L. Ager, Jr. [b] A cure is defined as a 30-day increase in survival time of the treated animals over the controls. Five mice were used at each dosage level; hence, five is the maximum number of cures. [c] ΔMST is the increase in mean survival time of test animals *versus* controls in days. ΔMST is differentiated from cures by the use of *D*; *i.e.*, 1.3*D* = 1.6 days. [d] Dosage is in milligrams of compound per kilogram of body weight of the test animal (mice). [e] T = toxic death. [f] Pentamidine. [g] 2,5-Bis(guanylphenyl)furan.

compound I was subjected to a diimide-type reduction by the method of Dewey and Van Tamelen (7) and produced 1,4-bis(4-cyanophenylethyl)benzene (II). The bis-nitrile was converted into the corresponding imidate ester which was used directly to prepare the guanyl derivatives.

The target compounds (III–V) were screened against *Trypanosoma rhodensiense* in mice (8), and the results are shown in Table I. Included for comparison in Table I are test results from the same screening program for pentamidine and 2,5-bis(4-guanylphenyl)furan, a very effective 12Å-type compound reported previously (3). The bis-guanyl compound (III) showed good activity, providing cures down to a dosage level of 26 mg/kg. Its activity was significantly lower than that of pentamidine or the furan derivative included in Table I. Interestingly, the two masked amidines showed markedly different activities. The imidazolinyl compound (IV) was essentially devoid of activity; however, the related pyrimidinyl (V), while toxic at high dosages, was slightly more active than the parent compound III at low dosage levels. In a large number of 12Å types (3–5), the masked amidines have generally shown limited activity.

EXPERIMENTAL[1]

Melting points reported under 300° were taken using an oil-bath melting point apparatus; the melting points of compounds melting above 300° were obtained using a solid block apparatus and all melting points are uncorrected. Satisfactory IR spectra were reported for all new compounds; the expected PMR spectra were recorded on all new compounds in [^{2}H]chloroform or [^{2}H]dimethylsulfoxide (tetramethylsilane standard).

1,4-Bis(*p*-cyanostyryl)benzene (I)—4-Cyanobenzyl triphenylphosphonium bromide (10 g, 0.02 mole) was added, under a nitrogen atmosphere, to a solution containing 0.03 mole of freshly prepared sodium ethoxide in 180 ml of ethanol. The solution was stirred for ~5 min and terephthaldicarboxaldehyde (1.4 g, 0.01 mole) dissolved in 100 ml of ethanol was added dropwise. After addition was complete the reaction mixture was stirred for 3.5 hr under a nitrogen atmosphere during which time crystals appeared. The solid (1.1 g, 17%) was filtered and recrystallized from ethanol mp 280–282°.

Anal.—Calc. for $C_{24}H_{16}N_2$: C, 86.74; H, 4.81. Found: C, 86.66; H, 4.95.

1,4-Bis(*p*-cyanophenylethyl)benzene (II)—*p*-Toluenesulfonylhydrazide (9) (4.0 g, 0.02 mole) in 50 ml of ethylene glycol monomethylether was added in portions to a refluxing suspension of the bis-styryl compound (3.3 g, 0.01 mole) in 100 ml of ethylene glycol monomethylether, under a nitrogen atmosphere. After addition was complete, the mixture was refluxed for 16 hr. The volume of solvent was reduced to ~30 ml and 2.8 g (83%) was obtained on cooling. The product was dissolved in methylene chloride, passed through a short alumina column, and the solvent was evaporated. Recrystallization from chloroform and dimethylsulfoxide gave a solid which melted 208–211°.

Anal.—Calc. for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.33. Found: C, 85.56; H, 5.99; N, 8.27.

1,4-Bis(4′-guanylphenylethyl)benzene Dihydrochloride (III)—The bis-nitrile (1.4 g, 0.004 mole) was dissolved in 100 ml of dioxane and 25 ml of ethanol, cooled in an ice bath, and hydrogen chloride gas was passed through it until the solution was saturated. The mixture was placed in a pressure bottle and shaken for 3 days at room temperature. The solid (imidate ester hydrochloride) that formed was filtered, dried under vacuum, and checked for unreacted starting material by examining the nitrile region of its IR spectra. A suspension of 1.5 g of imidate ester in 100 ml of absolute ethanol was prepared and dry ammonia was passed through the cold suspension until it was saturated. The mixture was shaken at room temperature for 3 days in a pressure bottle. The yellow solid that formed was dissolved in absolute ethanol saturated with hydrogen chloride gas; concentration of the solution gave 1.1 g (63%) of yellow solid which was recrystallized from ethanol, mp 345–346° (dec).

Anal.—Calc. for: $C_{24}H_{28}Cl_2N_4$: C, 65.01; H, 6.32; N, 12.64. Found: C, 64.81; H, 6.37; N, 12.53.

1,4-Bis[4-(2-imidazolinyl)phenylethyl]benzene (IV)—The imidate ester hydrochloride (2.9 g, 0.0054 mole) was suspended in 75 ml ethanol, ethylene diamine (0.65 g, 0.11 mole) was added, and the mixture was refluxed for 16 hr. The solid product was filtered, washed with ethanol, and dried. The solid was dissolved in absolute ethanol and the solution was saturated with dry hydrogen chloride gas. The solution was filtered and then concentrated until crystals began to appear; 1.9 g (78%), mp 298–303° (dec).

Anal.—Calc. for $C_{28}H_{32}Cl_2N_4$: C, 67.87; H, 6.46; N, 11.31. Found: C, 67.41; H, 6.56; N, 11.02.

1,4-Bis[4-(1,4,5,6-tetrahydro-2-pyrimidinyl)phenylethyl]benzene (V)—The imidate ester hydrochloride (1.9 g, 0.0043 mole) was suspended in 75 ml of ethanol and 1,3-propanediamine (0.64 g, 0.009 mole) was added and the mixture was refluxed overnight during which time a solid formed. The solid was washed with ethanol and dried. It was then dissolved in absolute ethanol and the solution was saturated with dry hydrogen chloride gas. The solution was filtered and concentrated until crystals formed; 1.4 g (61%), mp 345–350° (dec.).

Anal.—Calc. for $C_{30}H_{36}Cl_2N_4(0.5)H_2O$: C, 67.66; H, 7.00; N, 10.52. Found: C, 67.55; H, 6.83; N, 10.32.

[1] Elemental analyses were performed by Atlantic Microlab, Atlanta, Georgia.

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