Synthesis and Antitrypanosomal Activity of Some Bis(4-guanylphenyl) Five- and Six-Membered Ring Heterocycles

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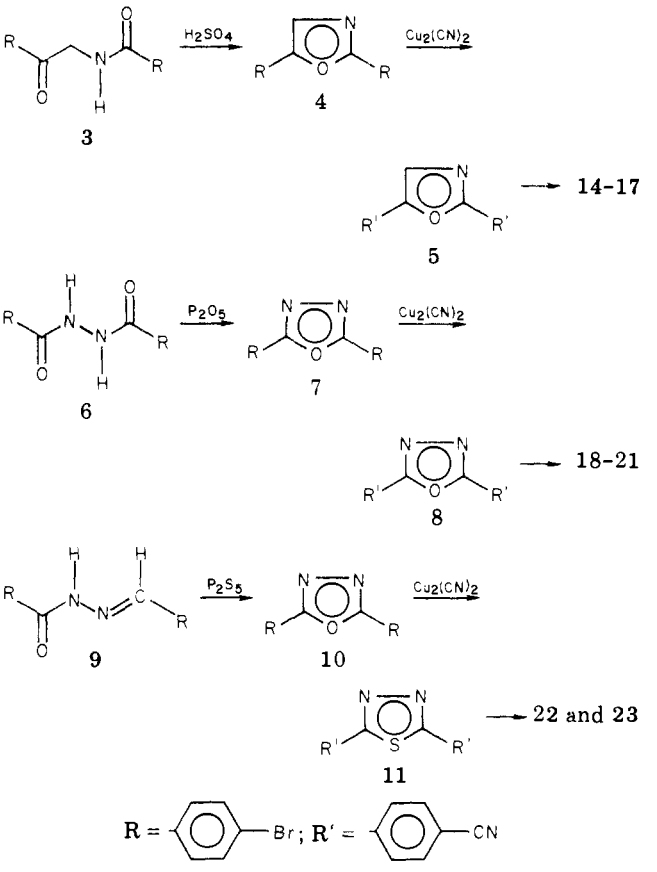
2,5-Bis(4-guanylphenyl)-1,3-oxazole, 2,5-bis(4-guanylphenyl)-1,3,4-oxadiazole and -1,3,4-thiadiazole, and 3,6-bis(4-guanylphenyl)pyridazine and several of their "cyclic guanyl" analogues have been synthesized. 2,5-Bis(4-guanylphenyl)-1,3-oxazole and -1,3,4-thiadiazole showed good activity, without acute toxicity, against *Trypanosoma rhodesiense* in mice, producing cures at a 3 mg/kg dosage level. This activity is comparable to stilbamidine, hydroxystilbamidine, and pentamidine in this test. In contrast, 2,5-bis(4-guanylphenyl)-1,3,4-oxadiazole shows a sharp reduction in activity in our test system. Generally, the cyclic guanyl analogues exhibit low orders of activity, and toxicity begins to appear at moderate dosage levels. All guanyl and cyclic guanyl compounds were synthesized from bisnitrile precursors by way of imidate ester hydrochlorides in a classical Pinner-type approach.

We have recently reported the synthesis of a series of substituted 2,5-bis(4-guanylphenyl)furans and related "cyclic amidines" which exhibit potent antitrypanosomal activity.[1] Several of these furan diamidines exhibited activity in mice superior to the standard antitrypanosomal drugs stilbamidine, hydroxystilbamidine, and pentamidine. One compound, 3,4-dimethyl-2,5-bis(4-guanylphenyl)furan (**1**), showed an excellent prolonged curative effect by providing complete protection to mice for 30 days after a single 5 mg/kg dose against a challenge of *T. rhodesiense*.[2] The prototype compound 2,5-bis(4-guanylphenyl)furan (**2**) and **1** have undergone extensive tests in higher animals.[2] More recently, we have reported a study of the antitrypanosomal activity of other five-membered heterocyclic analogues, including thiophene and *N*-methylpyrrole derivatives, which showed good activity, but none was superior to the original furan system.[3]

Since **1** and **2** are diamidines of a structural type different from the standard antitrypanosomal diamidines, they constitute a lead which merits further investigation. Because we had been successful in enhancing the activity of the furan system by altering substituents directly attached to the furan ring,[1] it seemed worthwhile to attempt to more dramatically affect the electronic properties of the spacer unit (furan ring) by manipulation of the ring system itself. Since it is assumed that the mode of action of these diamidines involved interaction with the protozoan kinetoplast DNA,[4] the structural modifications to be affected should not have the potential to adversely alter these interactions. Consequently, we decided to change the spacer unit by direct introduction of heteroatoms into the five-membered ring. These types of modifications should not appreciably alter the DNA-binding capacity of the system and should result in molecules with different absorption and distribution patterns. This report deals with the preparation and antitrypanosomal activity of representative diamidines of the 2,5-bis(4-guanylphenyl)-1,3-oxazole, 2,5-bis(4-guanylphenyl)-1,3,4-oxadiazole and -1,3,4-thiadiazole, and 3,6-bis(4-guanylphenyl)pyridazine types.

Chemistry. The synthesis of the 2,5-bis(4-guanylphenyl)-1,3-oxazole types, as well as the 2,5-bis(4-guanylphenyl)-1,3,4-oxadiazole and -1,3,4-thiadiazole compounds, was achieved employing conventional approaches as outlined in Scheme I. The conversion of the bisnitrile into the various amidine types was carried out as previously described.[1]

Scheme I



The 3,6-bis(4-guanylphenyl)pyridazines (**24–26**) were synthesized by way of 3,6-bis(4-bromophenyl)pyridazine (**12**) according to our standard procedure for conversion of aryl bromides into aryl nitriles, although the yield was very low (18%). Conversion of 3,6-bis(4-cyanophenyl)-pyridazine (**13**) into the corresponding guanyl derivatives was achieved by our conventional approach,[1] but these reactions also gave poor yields. While this work was in progress, the synthesis of two of the compounds (**14** and **18**), listed in Table I, was reported.[5]

Biological Activity. The heterocyclic diamidines shown in Table II were tested for antimalarial activity by screening against *Plasmodium berghei* in mice,[6] and no significant activity was observed. The test results obtained when these compounds were screened against *Trypano-*

(1) B. P. Das and D. W. Boykin, *J. Med. Chem.*, **20**, 531 (1977).
(2) E. A. Steck, Walter Reed Army Institute of Research, personal communication.
(3) B. P. Das and D. W. Boykin, *J. Med. Chem.*, **20**, 1219 (1977).
(4) B. A. Newton, "Trypanosomiasis and Leishmaniasis with Special Reference to Chagas Disease", Elsevier, Amsterdam, 1974, p 285–307.
(5) O. Dann, H. Fick, B. Pietzner, E. Walkenhorst, R. Fernbach, and D. Zeh, *Justus Liebigs Ann. Chem.*, 160 (1975).
(6) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

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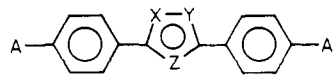
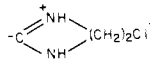
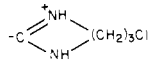
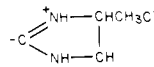
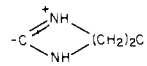
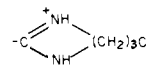
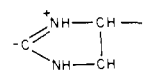
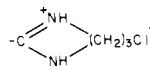
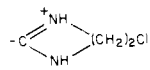
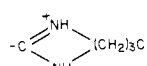
Table I. Diaryl Five- and Six-Membered Heterocycles Amidines



no.	X	Y	Z	A	mp, °C[f]	% yield[g]	mol formula
5[a]	N	CH	O	CN	289-290	64	$C_{17}H_9N_3O$
8[b]	N	N	O	CN	300-301	50	$C_{16}H_8N_4O$
11[c]	N	N	S	CN	279-280	65	$C_{16}H_8N_4S$
13[d]	CH	CH	-N=N-	CN	349-350	18	$C_{18}H_{10}N_4$
14[e]	N	CH	O	$-C(=\overset{+}{N}H_2)NH_2Cl^-$	355-356	80	$C_{17}H_{17}Cl_2N_5O\cdot0.5H_2O$
15[e]	N	CH	O		376-378	69	$C_{21}H_{21}Cl_2N_5O$
16[e]	N	CH	O		384-386	95	$C_{23}H_{25}Cl_2N_5O$
17[e]	N	CH	O		351-353	64	$C_{23}H_{25}Cl_2N_5O\cdot0.5H_2O$
18[e]	N	N	O	$-C(=\overset{+}{N}H_2)NH_2Cl^-$	358-360	80	$C_{16}H_{16}Cl_2N_6O$
19[e]	N	N	O		384-385	58	$C_{22}H_{20}Cl_2N_6O\cdot0.5H_2O$
20[e]	N	N	O		401-402	60	$C_{22}H_{24}Cl_2N_6O$
21[e]	N	N	O		359-360	70	$C_{22}H_{24}Cl_2N_6O$
22[e]	N	N	S	$-C(=\overset{+}{N}H_2)NH_2Cl^-$	350-351	38	$C_{16}H_{16}Cl_2N_6S$
23[e]	N	N	S		460-462	68	$C_{22}H_{24}Cl_2N_6S$
24[e]	CH	CH	-N=N-	$-C(=\overset{+}{N}H_2)NH_2Cl^-$	364-365	11	$C_{18}H_{18}Cl_2N_6$
25[e]	CH	CH	-N=N-		>470	38	$C_{22}H_{22}Cl_2N_6\cdot H_2O$
26[e]	CH	CH	-N=N-		400-402	64	$C_{24}H_{26}Cl_2N_6\cdot2H_2O$

[a] Recrystallized from DMF; analyzed for C and H and the results were within ±0.3% of the calculated values. [b] Recrystallized from $CHCl_3$; analyzed for C and H and the results were within ±0.3% of the calculated values. [c] Recrystallized from dioxane; analyzed for C and H and the results were within ±0.3% of the calculated values. [d] Recrystallized from $(CH_3)_2CO$; analyzed from C and H and the results were within ±0.3% of the calculated values. [e] Recrystallized from absolute ethanol; analyzed for C, H, and N and the results were within ±0.3% of the calculated values. [f] All melting points are uncorrected; compounds 14-26 melted with decomposition. [g] The yields of 7-19 are based upon the imidate ester hydrochloride.

soma rhodesiense in mice[7] are shown in Table II. Results for stilbamidine (**27**), hydroxystilbamidine (**28**), pentamidine (**29**), and the furan lead compound **2** are included in the table for comparison.

The previously noted pattern of higher toxicity and lower activity for the "cyclic amidines" observed for the analogous furan,[1] thiophene,[3] and *N*-methylpyrrole[3] series continues to appear in the various systems reported here. The oxazole **14** and the thiadiazole **22** show comparable activity to the standard drugs **27**–**29** and to **2**. Thus, the introduction of one or two heterocyclic nitrogens into the spacer unit has no significant effect on antitrypanosomal activity of the potential drug in these cases. On the other hand, the oxadiazole compound **18** shows a pronounced drop in activity and exhibits acute toxicity at the highest dosage tested. Thus, it appears that alteration of the spacer unit can dramatically and adversely affect the antitrypanosomal activity of this system in the screen used here. Interestingly, in another test system using *T. rhodesiense* in mice, **14** and **18** are reported to have comparable activity.[5] Although an insufficient amount of the sample was available for testing of the true guanyl derivative (**22**) of the pyridazine, the test results available from the cyclic amidines of these types continue to exhibit low orders of activity and some toxicity.

We have previously observed a marked enhancement of activity by substituents on the furan system, whereas here we observe a significant reduction of antitrypanosomal activity. These and earlier[1] results show that the antitrypanosomal activity of these types can be appreciably affected by modifications of the five-membered ring heterocyclic spacer. Further modification along these lines does not seem warranted until more information is available about their mode of action.

Experimental Section

Melting points reported under 300 °C were taken on a Thomas-Hoover melting point apparatus, melting points of compounds melting above 300 °C were obtained on a Mel-Temp apparatus, and all melting points are uncorrected. IR spectra were recorded on all new compounds with a Perkin-Elmer Model 337 spectrometer, ^1H NMR were recorded on selected compounds with

(7) L. Rane, D. S. Rane, and K. E. Kinnamon, *Am. J. Trop. Med. Hyg.*, **25**, 395 (1976).

Table II. Antitrypanosomal Screening Results[a]

	cures[b] or ΔMST[c] at dosage,[d] mg/kg																	
no.	640	424	320	212	160	106	80	53	40	26.5	20	13.3	10	6.6	5	3.3	2.5	1.25
14	5		5		5		5		5		5		5		5		3	1.8D
15		1.6D				0.4D				0.2D								
16	T[e]		T		T		2		5		5		5		3		3	2.7D
17		T		6.8D		5.2D		2.4D		2.2D		1.0D						
18	T				0.8D				0.8D									
19	T				1.0D				0.8D									
20		T				T				5		1		1.3D				
21		T				T				T								
22		2		5		5		5		5		5		4		3		2D
23		T				T			1.1D	T								
25			5		3		1		1.1D		1.1D		0.3D					
26						T	1		4		4		1					
2[f]	5		5		5		5		5		5		5		5		4	4
27[g]	5		5		5		5		5		5		5		5		5	2
28[h]	5		5		5		5		5		5		5		5		5	2
29[i]	5		5		5		5		5		5		5		5		4	1

[a] See ref 7. Antimalarial and 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 over the controls. Five mice were used per dosage level; hence, five is the maximum number of cures. [c] ΔMST is the increase in mean survival time of test animals vs. controls in days. ΔMST is differentiated from cures by the use of D, i.e., 1.6D = 1.6 days. [d] Dosage is in milligrams of compound per kilogram of body weight of the test animal. [e] T = toxic death. [f] 2,5-Bis(guanylphenyl)furan. [g] Stilbamidine. [h] Hydroxystilbamidine. [i] Pentamidine.

a Varian A-60A instrument, and ^{13}C NMR spectra on selected compounds were obtained with a JEOL FX-60 instrument. All spectra were in accord with the structures assigned. Elemental analyses were performed by Atlantic Microlab, Atlanta, Ga.

Compounds **3**, **7**, **10**, and **12** were prepared according to literature procedures and used to synthesize the corresponding bisnitriles as outlined below. The method outlined for the preparation of **14** is representative for the preparation of **18**, **22**, and **24**. The cyclic amidines **16**, **17**, **19**–**21**, **23**, **25**, and **26** were prepared by the method detailed for **15**.

α-(4-Bromobenzamido)-4-bromoacetophenone (3). A solution of *p*-bromobenzoyl chloride, 22 g (0.1 mol), in 200 mL of ether was added, with stirring, to a suspension of 26 g (0.1 mol) of α-amino-4-bromoacetophenone hydrochloride[8] in 500 mL of ether and 80 mL of triethylamine. The mixture was stirred for 15 min, and the solid material was filtered and washed with water, dilute NaOH solution, dilute HCl, and water. The solid was dried to yield 22.9 g (57%), mp 197–198 °C. Recrystallization was from $CHCl_3$, which raised the melting point to 203–204 °C. Anal. ($C_{15}H_{11}Br_2NO_2$) C, H.

2,5-Bis(4-bromophenyl)-1,3-oxazole (4). The amide **3** (6 g, 0.018 mol) was treated with 30 mL of concentrated H_2SO_4 for 10 min at room temperature. The red solution was poured into cold water and the solid material which separated was filtered. Recrystallization from ethanol yielded 4.5 g (79%), which melted at 173–174 °C. Anal. ($C_{15}H_9Br_2NO$) C, H.

2,5-Bis(4-cyanophenyl)-1,3-oxazole (5). The dibromo compound **4** (3.5 g, 0.011 mol), was mixed with 1.2 g (0.07 mol) of $Cu_2(CN)_2$ in 20 mL of quinoline, refluxed for 2 h, poured into dilute HCl, filtered, washed, dissolved in acetone, and passed through a column of alumina. This solution was concentrated to give 1.6 g of the oxazole product (64%), mp 273–276 °C. Recrystallization was from DMF, mp 289–290 °C.

2,5-Bis(4-cyanophenyl)-1,3,4-oxadiazole (8). To a suspension of 7.8 g (0.02 mol) of 2,5-bis(4-bromophenyl)-1,3-oxadiazole[9] (**7**) in 100 mL of quinoline was added 4.2 g (0.025 mol) of $Cu_2(CN)_2$, and the mixture was refluxed for 2.5 h. The reaction mixture was poured into 2 M HCl solution, and the solid was filtered. Recrystallization from $CHCl_3$ gave 3.5 g of solid, which melted at 307–309 °C.

2,5-Bis(4-cyanophenyl)-1,3,4-thiadiazole (11). 2,5-Bis(4-bromophenyl)-1,3,4-thiadiazole[10] (**10**; 2.1 g, 0.0053 mol) and $Cu_2(CN)_2$ (1.5 g, 0.0167 mol) were refluxed in quinoline (15 mL) for 3 h. After the mixture cooled, the solid was extracted several times with $CHCl_3$, and this solution was washed with 2 M HCl and with H_2O. The $CHCl_3$ layer was dried over $CaSO_4$ and evaporated to yield 1 g (65%) of yellow crystals. They were dissolved in dioxane and passed through a short alumina column, using dioxane as eluent; after recrystallization from dioxane, a melting point of 279–280 °C was obtained.

3,6-Bis(4-cyanophenyl)pyridazine (13). Quinoline (30–40 mL) was added to 3,6-bis(4-bromophenyl)pyridazine[11] (**12**; 7 g, 0.018 mol), and $Cu_2(CN)_2$ (4.9 g, 0.054 mol) and the mixture was refluxed for 2 h. After the mixture cooled, the solid was extracted with $CHCl_3$. This solid was refluxed in acetone (2500 mL) for 24 h and filtered. The acetone solution was passed through an alumina column and the eluent was evaporated to near dryness. Yellow crystals (0.7 g) were collected, which melted at 349–350 °C. The $CHCl_3$ extract was washed twice with 10% HCl, dried, and evaporated. The solid was treated as above with acetone and passed through an Al_2O_3 column to give an additional 0.2 g (combined yield 18%).

2,5-Bis(4-guanylphenyl)-1,3,4-oxadiazole Dihydrochloride (14). The bisnitrile **5** (2.5 g, 0.009 mol) was dissolved in 125 mL of dioxane and 25 mL of ethanol, cooled in an ice bath, and HCl 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 white solid (imidate ester hydrochloride) which formed was filtered and dried under vacuum: yield 4.5 g; mp 360–362 °C dec. The dried imidate ester was checked for contamination with starting material by examining the nitrile region of its IR spectra. A suspension of 2.2 g of the imidate ester in 75 mL of absolute ethanol was prepared and dry NH_3 was passed through the cold suspension until saturated. The mixture was shaken at room temperature for 3 days in a pressure bottle. The solid which formed was filtered and dried, yield 1.8 g. The dry solid was dissolved in 1200 mL of absolute ethanol saturated with HCl gas. The volume was reduced to about 200 mL under vacuum. The solid which appeared was filtered, dried, and recrystallized from ethanol: yield 1.2 g; mp 358–360 °C dec.

2,5-Bis[4-(2-imidazolinyl)phenyl]-1,3,4-oxadiazole Dihydrochloride (15). The corresponding imidate ester hydrochloride (0.87 g, 0.002 mol) was suspended in 100 mL of ethanol, ethylene diamine (0.24 g, 0.004 mol) was added, and the mixture was refluxed for 12 h. The solid product was filtered, washed with ethanol, and dried. The solid was dissolved in 1000 mL of absolute ethanol and saturated with dry HCl gas. The solution was filtered

(8) L. L. Bambas, H. D. Troutman, and L. M. Long, *J. Am. Chem. Soc.*, **72**, 4445 (1950).
(9) R. Stolle and A. Weindel, *J. Prakt. Chem.*, **74** (2), 2 (1906).
(10) R. Stolle and A. Johannissien, *J. Prakt. Chem.*, **69** (2), 480 (1904).
(11) N. Campbell and N. M. Khanna, *J. Chem. Soc.*, suppl issue no. 1, S33 (1949).

and concentrated to 250 mL. Solid material appeared and was filtered, washed with ethanol, dried, and recrystallized from absolute ethanol: yield 0.4 g; mp 384–385 °C dec.

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Synthesis of 2,4-Disubstituted 6-Methoxy-8-aminoquinoline Analogues as Potential Antiparasitics

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A series of 2,4-disubstituted 8-aminoquinoline analogues were synthesized and evaluated against *Plasmodium berghei* in mice and *Leishmania donovani* in hamsters. 8-[[6-(Diethylamino)hexyl]amino]-2-ethyl-6-methoxy-4-methylquinoline (**8a**) possessed significant activity against *L. donovani*. 2-Ethyl-4-methylprimaquine (**7a**) was evaluated against *Plasmodium cynomolgi* in rhesus monkey and found to have activity equal to that of primaquine.

Both 2- and 4-substituted 6-methoxy-8-aminoquinoline analogues have been reported to possess antimalarial activity comparable to that of primaquine.[1,2] In addition, some of the compounds have shown activity against *Leishmania donovani* in hamsters.[3] In this paper we describe the syntheses of some 2,4-disubstituted 6-methoxy-8-aminoquinoline analogues which possess CH_3, C_2H_5, and $CH_2{=}CH-$ substituents in the 2 and 4 positions and report antiparasitic test data for these compounds.

Chemistry. Scheme I outlines the procedures used to prepare target compounds **7a,b** and **8a,b**. Condensation of 4-methoxy-2-nitroaniline (**1**) with 3-penten-2-one under Skraup conditions gave 2,4-dimethyl-6-methoxy-8-nitroquinoline (**2**). Subjection of **2** to Mannich condensation followed by quaternization gave **3**. Treatment of **3** with base yielded the 4-methyl-2-vinylquinoline (**4**). Catalytic reduction of **4** gave 8-amino-2-ethyl-6-methoxy-4-methylquinoline (**5**), whereas reduction with stannous chloride gave 8-amino-6-methoxy-4-methyl-2-vinylquinoline (**6**). Attachment of the 4-amino-1-methylbutyl side chain to **5** and **6** followed standard procedure to give **7a** and **7b**, respectively.[2] Alkylation of **5** with 6-(diethylamino)hexyl bromide gave the expected product **8a**; however, alkylation of **6** with this reagent gave the hydrogen bromide addition product **8b**.

The synthesis of target compounds **7c** and **8c** is shown in Scheme II. Condensation of **1** with the 2-chloropropyl ethyl ketone (**9**)[4] under Skraup conditions gave 4-ethyl-6-methoxy-2-methyl-8-nitroquinoline (**10**). Stannous chloride reduction of **10** yielded the aminoquinoline (**11**). Attachments of the 4-amino-1-methylbutyl and 6-(diethylamino)hexyl side chains to **11** followed standard procedure to **7c** and **8c**.

Biological Testing. Compound **7a** was tested for radical curative activity against *P. cynomolgi* in rhesus monkeys. The test was carried out at the SEATO Medical Research Laboratory, Bangkok.[5,6] Primaquine diphosphate, which cures 90% of monkeys in this test system when administered at a dose of 1.3 mg/kg (1.0 mg/kg of free base) per day for 7 days, in combination with chloroquine serves as the standard for this test. Compound **7a** showed 3/4 cures at 1.0 mg/kg (free base).

Compounds **8a–c** and **7b–c** were tested for blood schizonticidal activity against *P. berghei* in mice[7] (Table I). Testing was carried out at the Rane Laboratory, University of Miami, Miami, Fla. Compound **7c** was active at 320 and 40 mg/kg; all other compounds were inactive at the highest dose level tested (640 mg/kg). Compound **8b** was toxic at 160 and 640 mg/kg; none of the other compounds were toxic as judged by the Rane screen.

The compounds **8a–c** and **7a** were also evaluated for antileishmanial activity against *Leishmania donovani* in hamsters by the well-established 8-day testing method (Table I).[8–10] Compound **8a** which showed a *G* index of 130, was the most active of the compounds tested.

Examination of the data in Table I shows that the 2,4-disubstituted 8-aminoquinoline analogues are, with the

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(10) Tests were carried out by Dr. W. L. Hanson, University of Georgia, Athens, Ga. The percent suppression [seven animals per drug level, 208, 52, and 13 (mg/kg)/day] when compared to infected, untreated controls (seven to ten animals) is calculated and a Glucantime index (*G*) computed [$G = (SD_{90}$ for Glucantime)/(SD_{90} for the new drug)], where SD_{90} = 90% suppression of parasites. The intramuscular route is routinely used in the initial test. Drug is administered twice a day for 4 consecutive days. (c) Glucantime is the proprietary name for meglumine antimoniate.

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