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EXPERIMENTAL CHEMOTHERAPY OF TRYPANOSOMIASIS. II. THE PREPARATION OF COMPOUNDS RELATED TO *p*-PHENYLENEDIGUANIDINE

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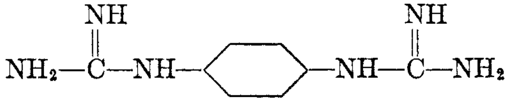
Investigations in our laboratories have shown that *p*-phenylenediguanidine (I) (1) possesses curative properties against *Trypanosoma equiperdum* in mice (2). A program was therefore undertaken to synthesize compounds structurally related to I.

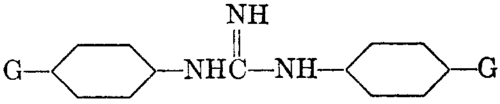


I

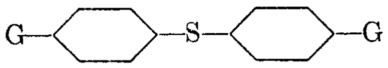
The meta analog of I was prepared and found to be inactive. The substitution of a chlorine atom or methyl group into the nucleus of I caused a sharp fall in activity. Similarly, alkyl or aryl substitution on the terminal nitrogen atoms resulted in a loss of activity.

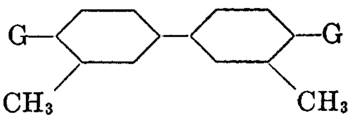
By linking the two guanidine groups with bridges other than the *p*-phenylene group it was found that active compounds resulted. The following guanidine derivatives are about as active as I:

XIV



XII





VIII XV

Compounds which contained only one guanidine group per molecule invariably possessed little or no trypanocidal activity. This result parallels the observation of King, Laurie, and York (3) that while the polymethylene diguanidines $\mathrm{NH_2}\overset{\mathrm{NH}}{\overset{\|}{\mathrm{C}}}\mathrm{—NH(CH_2)_{10-14}NH}\overset{\mathrm{NH}}{\overset{\|}{\mathrm{C}}}\mathrm{—NH_2}$ are active trypanocides, the corresponding alkyl guanidines are without effect.

Several biguanide analogs of I and of other guanidines were prepared but these were inactive or weakly active.

A number of guanidine derivatives of basic fuchsin were prepared in the hope of augmenting the well-known trypanocidal activity of the fuchsin dyes. The products were about as active as the parent dyestuffs, but because of high toxicity they were not exploited further.

The complete results of the parasitological tests are reported elsewhere (2).

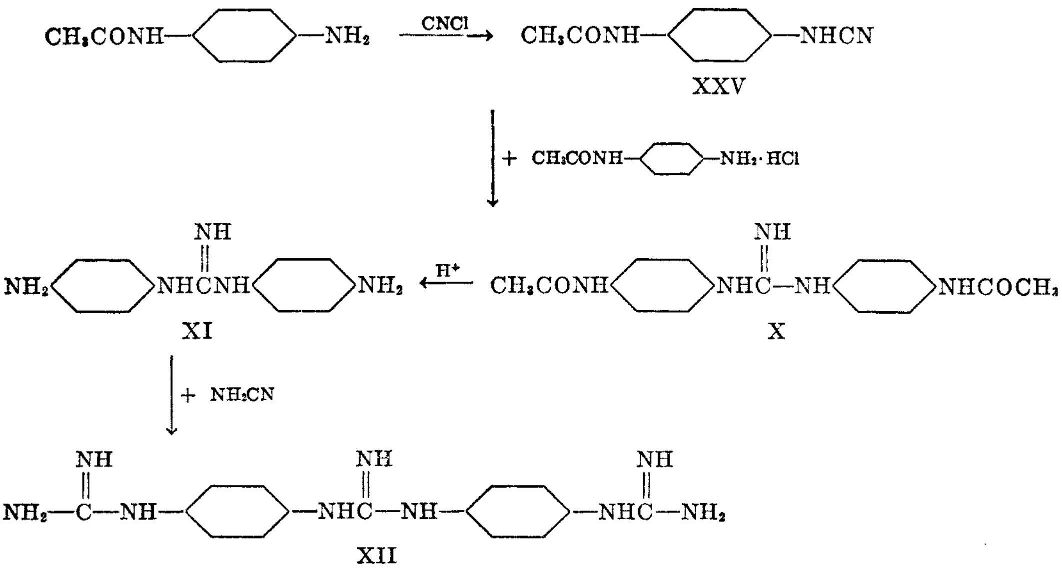
The guanidines were prepared by several procedures. The *p,p'*-monosubstituted diguanidines were made from the corresponding aromatic diamines, in the form of the hydrochloride salts, and cyanamide in alcohol (4, 5). The products were isolated as the free bases or carbonate salts or as the neutral hydrochlorides or picrates.

In the case of *p*-aminobenzylamine hydrochloride, reaction with cyanamide in alcohol or water gave only a monoguanidine derivative. The guanidino group is assumed to be attached to the benzene ring inasmuch as benzylamine hydrochloride fails to react with cyanamide under these conditions, while aniline hydrochloride yields phenylguanidine readily (5).

On the other hand, *p*-aminobenzylamine reacts with methylisothiourea sulfate to yield an isomeric monoguanidino derivative in which the guanidino group is probably attached to the side-chain methyl group. It was found possible to introduce a second guanidino group by treating *p*-guanidinobenzylamine dihydrochloride with slightly more than one equivalent of dilute alkali and then reacting with aqueous cyanamide.

The 1,6-diisopropyl-, dilauryl- and diphenyl-*p*-phenylenediguanidines were prepared by fusion of the requisite cyanamides with *p*-phenylenediamine dihydrochloride.

1,3-Bis-(*p*-guanidinophenyl)guanidine (XII) was prepared according to the following sequence of reactions:



The biguanide derivatives were prepared from the amine hydrochlorides and dicyandiamide either by fusion (6) or in aqueous solution (7). In the case of *p*-aminobenzyl amine, only one biguanido group formed, presumably from the aromatic amino group.

In Table I are listed the various guanidine and biguanide derivatives, together with melting point data and yields.

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EXPERIMENTAL

Isopropyl-, dodecyl-, (8) *and phenyl-cyanamide* (9). These cyanamides were prepared by distillation of one equivalent of cyanogen chloride into an ice-cold solution of two equivalents of the required base in ether or benzene. After filtration of the hydrochloride of the base, the product was recovered by evaporation of the filtrate *in vacuo* at 25°. All three were obtained in high yields as light yellow oils and were used without further purification.

p-Acetamidophenylcyanamide (*XXV*). Into a stirred slurry of 25 g. of *p*-aminoacetanilide and 8.4 g. of calcium carbonate in 600 cc. of water there was distilled, during one hour, 10.3 g. of cyanogen chloride. After being stored for fifteen hours, the crystalline product was filtered and washed with water; yield 27 g. (91%), m.p. 178–182°. After two recyrstallizations from 50% ethanol, the m.p. was 181–184°.

Anal. Calc'd for $C_9H_9N_3O$: N, 24.0. Found: N, 24.1.

3,3'-Diisopropyl-1,1'-(p-phenylene)diguanidine (*V*). A mixture of 2.5 g. of isopropylcyanamide and 2.4 g. of *p*-phenylenediamine dihydrochloride was heated to 105–110° whereupon an exothermic reaction took place. The melt was kept at a bath temperature of 105–110° for three-quarters of an hour, whereupon the contents had almost completely solidified. The product was dissolved in water, treated with Norit and filtered. The filtrate was treated with a large excess of 5 *N* alkali; the free base separated in the form of glistening plates, m.p. 216–218° (dec.); yield 2.1 g. One recrystallization from ethanol raised the m.p. to 223–225° (dec.).

A portion of the base was dissolved in alcoholic hydrochloric acid and excess ether was added. The resulting dihydrochloride, m.p. 289–291°, was then recrystallized three times from alcohol-ether; m.p. 291–293°.

Anal. Calc'd for $C_{14}H_{26}Cl_2N_6$: C, 48.2; H, 7.5; N, 24.0.
Found: C, 47.8; H, 8.1; N, 23.5.

3,3'-Dilauryl-1,1'-(p-phenylene)diguanidine (*VI*). A mixture of 4.2 g. of dodecylcyanamide and 1.8 g. of *p*-phenylenediamine dihydrochloride was heated slowly to 140° whereupon slow fusion took place and the inner temperature rose to 150°. After three-quarters of an hour the mixture was cooled, the sticky material was leached with hot ethanol and filtered from a small amount of phenylenediamine hydrochloride. The alcoholic solution was treated with Norit, filtered and concentrated to 50 cc. About 150 cc. of ether was added and the dihydrochloride settled out as a fine powder, m.p. 240–265°; yield 1.5 g. After two recrystallizations from ethanol, the m.p. was 260–265°.

Anal. Calc'd for $C_{32}H_{62}Cl_2N_6$: N, 14.0. Found: N, 14.1.

3,3'-Diphenyl-1,1'-(p-phenylene)diguanidine (*VII*). This compound was prepared in a similar manner to V. The reaction became exothermic at 120° whereupon the heating bath was removed. The liberated base was recrystallized from ethanol; m.p. 209–211° (dec.). The hydrochloride melted at 253–257° after two recrystallizations from ethanol-ether.

TABLE I
Compounds Related to *p*-Phenylenediguanidine

COMPOUND	M.P. °C. BASE	M.P. °C. HYDROCHLORIDE	M.P. °C. OTHER SALT	% YIELD
II *m*-Phenylenediguanidine			Carbonate gas evoln. at 155; dec. 215	30
III *o*-Chloro-*p*-phenylenediguanidine	237–240 (dec.)	302–305 (dec.)		28
IV *o*-Methyl-*p*-phenylenediguanidine	226–229 (dec.)	290–292 (dec.)		36
V 3,3′-Diisopropyl-1,1′-(*p*-phenylene)diguanidine	223–225 (dec.)	291–293 (dec.)		58
VI 3,3′-Dilauryl-1,1′-(*p*-phenylene)diguanidine		260–265		25
VII 3,3′-Diphenyl-1,1′-(*p*-phenylene)diguanidine	209–211 (dec.)	253–257		69
VIII Bis-(4-guanidinophenyl) sulfide (13)			Carbonate 140–146 (dec.)	58
IX Bis-(4-guanidinophenyl)sulfone		263–265 (dec.)	Picrate 271–273 (dec.)	30
X 1,3-Bis-(*p*-acetamidophenyl)guanidine	143–146	303–311 (dec.)		97
XI 1,3-Bis-(*p*-aminophenyl)guanidine	204–208 (dec.)	265–275 (dec.)		87
XII 1,3-Bis-(*p*-guanidinophenyl)guanidine		292–295		32
XIII 1,3-Bis-(*p*-ureidophenyl)guanidine		198–200 (dec.)		67
XIV 1,3-Bis-(*p*-guanidinophenyl)urea			Carbonate sinters 135; dec. 148	61
XV 3,3′-Dimethyl-4,4′-diguanidinobiphenyl	219–223 (dec.)		Picrate>270 (dec.)	91
XVI *p*-Guanidinobenzylguanidine			Picrate 250–253 (dec.)	38
XVII *p*-Guanidinobenzylamine	172–176	257–260 (dec.)	Picrate 242–243 (dec.)	63
XVIII *p*-Aminobenzylguanidine			Sulfate 195–202 (dec.) Picrate>197 (dec.)	93
XIX 4,4′,4″-Triguanidinodiphenyl-3-tolylmethane (15)			Carbonate>330 (dec.)	65
XX 3,3′-Dimethyl-4,4′-diguanidino-4″-aminotriphenylmethane (15)			Carbonate (amorphous)	76
XXI 4-Aminophenyl-4′,4″-diguanidinophenyltolylmethane (15)			Carbonate (amorphous)	64
XXII *p*-Biguanidobenzylamine		>250 (dec.)		44
XXIII *p*-Phenylenedibiguanide	218–219 (dec.)	270–278 (dec.)		61
XXIV *o*-Chloro-*p*-phenylenedibiguanide	208–210 (dec.)	240–243 (dec.)		54

Anal. Calc'd for $C_{20}H_{22}Cl_2N_6$: N, 20.1. Found: N, 20.2.

2-Chloro-1,4-phenylenediguanidine (III). A mixture of 12.9 g. of 2-chloro-1,4-phenylenediamine dihydrochloride, 7.8 g. of cyanamide and 60 cc. of dry ethanol was refluxed two and one-half hours. The mixture was cooled to 5° for several hours and the white crystalline product was filtered; crude yield 5 g., m.p. 294–300° (dec.). A 2-g. portion of the hydrochloride was dissolved in water, the solution was cooled to 5° and an excess of 50% potassium hydroxide was added. The liberated base was filtered and recrystallized from water, separating as hexagonal plates, m.p. 237–240° (dec.); weight 1.1 g. The base was pulverized and triturated with alcoholic hydrochloric acid. The hydrochloride was filtered, washed with ethanol, and recrystallized twice as follows; the solid was suspended in ethanol, the mixture was warmed to 50° and enough water was added to effect solution; after filtration ether was added to the point of persistent turbidity. The dihydrochloride separated in clusters of needles, m.p. 302–305° (dec.).

Anal. Calc'd for $C_8H_{13}Cl_3N_6$: C, 32.0; H, 4.3; N, 28.0.
Found: C, 32.7; H, 4.9; N, 27.9.

2-Methyl-1,4-phenylenediguanidine (IV). This compound was prepared in the same manner as III. The base melted at 226–229° (dec.) and the dihydrochloride at 290–292° (dec.).

Anal. Calc'd for $C_9H_{16}Cl_2N_6$: C, 38.7; H, 5.7; N, 30.1.
Found: C, 39.1; H, 6.3; N, 30.4.

m-Phenylenediguanidine (II). This compound was made in a similar manner to III. However, a crystalline hydrochloride was not isolated. Instead, the product was converted to the crystalline carbonate which was purified by dissolving in acid and reprecipitating with potassium carbonate; m.p. 215° (dec.), with gas evolution at 155°.

Anal. Calc'd for $C_8H_{12}N_6 \cdot H_2CO_3$: C, 42.5; H, 5.5; N, 33.0.
Found: C, 42.5; H, 4.7; N, 33.3.

4,4'-4"-Triguanidinodiphenyl-3-tolylmethane (XIX) (15). This compound was prepared in a similar manner to II. The product was isolated as the carbonate salt; m.p. 330° (dec.).

Anal. Calc'd for $C_{23}H_{27}N_9 \cdot 1\frac{1}{2}H_2CO_3$: C, 56.3; H, 5.5; N, 24.1.
Found: C, 56.6; H, 5.7; N, 24.2.

3,3'-Dimethyl-4,4'-diguanidino-4"-aminotriphenylmethane (XX).[1] This compound was made from the corresponding triamine trihydrochloride similarly to the preparation of II. The carbonate salt was obtained as an amorphous solid with an indefinite melting point.

Anal. Calc'd for $C_{23}H_{27}N_7 \cdot H_2CO_3$: C, 62.1; H, 6.3.
Found: C, 62.3; H, 7.1.

4-Aminophenyl-4',4"-diguanidinophenyltolylmethane (XXI) (15).[1] This compound was prepared from the triamine trihydrochloride and two equivalents of cyanamide similarly to II. The carbonate salt was obtained as an amorphous solid with an indefinite melting point.

Anal. Calc'd for $C_{22}H_{25}N_7 \cdot H_2CO_3$: C, 61.5; H, 6.1; N, 21.8.
Found: C, 61.5; H, 6.0; N, 20.0.

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[1] The exact position of the methyl groups in relation to the guanidino groups is not known.

1,3-Bis-(p-guanidinophenyl)urea (XIV). This compound was made from N,N′-bis-(4-aminophenyl)urea dihydrochloride (16) by reaction with cyanamide in a similar manner to II. The product was isolated as the carbonate salt, decomposing at 148° with sintering at 135°.

Anal. Calc'd for $C_{15}H_{18}N_8O \cdot H_2CO_3$: C, 49.0; H, 5.2; N, 28.9.
Found: C, 50.3; H, 5.8; N, 27.5.

Bis-4-(aminophenyl)sulfide. This compound has been prepared by Nietzki and Bothof (10) and by Hodgson (11). It may be prepared more conveniently by the reduction of bis-(4-nitrophenyl)sulfide (12) in the following manner: A hot solution of 72.5 g. of stannous chloride dihydrate in 80 cc. of 12 *N* hydrochloric acid was added during one minute to a hot solution of 14 g. of bis-(4-nitrophenyl)sulfide in 150 cc. of acetic acid. After a few minutes the solution was evaporated to dryness *in vacuo*, the crystalline residue was dissolved in water and excess 50% alkali was added. The liberated base was filtered, washed with alkali, then with water and dried; yield 9.8 g. (90%), m.p. 103–106°. The dihydrochloride (13) is formed by dissolving the base in ethanol, adding ethanolic hydrochloric acid and precipitating with ether.

Bis-(4-guanidinophenyl)sulfide (VIII).[2] A mixture of 6.7 g. of bis-(4-aminophenyl)-sulfide dihydrochloride, 3.0 g. of cyanamide, and 45 cc. of ethanol was refluxed five hours, cooled to 25° and treated with four volumes of ether. The resulting gum was triturated several times with ether, dissolved in water, and treated with excess potassium carbonate. The carbonate salt crystallized on rubbing. After one recrystallization from water the yield amounted to 5.0 g.; m.p. 140–146° (dec.).

Anal. Calc'd for $C_{14}H_{16}N_6 \cdot H_2CO_3 \cdot \frac{1}{2}H_2O$: C, 48.6; H, 5.1; N, 22.6.
Found: C, 48.6; H, 5.8; N, 21.6.

Bis-(4-aminophenyl)sulfone dihydrochloride. One hundred grams of bis-(4-aminophenyl)sulfone was dissolved in 200 cc. of water and 80 cc. of 12 *N* hydrochloric acid and excess alcoholic hydrochloric acid was added. The salt was filtered and washed with ethanol; yield 116 g., m.p. 243–248°, (dec.). The hydrochloride dissolves readily in a limited amount of water but on further dilution the free base crystallizes out.

Bis-(4-guanidinophenyl)sulfone (IX). A solution of 12 g. of cyanamide in 40 cc. of ethanol was added during twenty minutes, to a refluxing mixture of 32 g. of bis-(4-aminophenyl)sulfone dihydrochloride and 100 cc. of ethanol. The mixture was then refluxed six hours and filtered from traces of suspended matter. The resulting clear, light brown, neutral solution was treated with excess alcoholic picric acid. After two hours the yellow precipitate was filtered and leached twice with boiling ethanol; m.p. 258–263° (dec.). The yield from a 40-cc. aliquot of the reaction filtrate was 6.3 g. This was suspended in 12 *N* hydrochloric acid. The liberated picric acid was extracted with benzene until a benzene wash failed to give a yellow color when shaken with alkali. The hydrochloric acid solution was evaporated to dryness *in vacuo* and the crystalline dihydrochloride was recrystallized from 90% ethanol and ether. After three recrystallizations the m.p. was 263–265° (dec.).

Anal. Calc'd for $C_{14}H_{18}Cl_2N_6O_2$: C, 41.5; H, 4.4; N, 20.7.
Found: C, 41.3; H, 5.5; N, 21.0.

When an aqueous solution of the purified dihydrochloride was treated with aqueous picric acid, the dipicrate precipitated; m.p. 270–272° (dec.). After one recrystallization from water the m.p. was 271–273° (dec.).

Anal. Calc'd for $C_{26}H_{22}N_{12}O_{16}S$: C, 39.5; H, 2.8; N, 21.3.
Found: C, 39.6; H, 3.2; N, 21.7.

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[2] Braun and Ludwig (13) have prepared this compound and characterized it as the free base, the sulfate, and the picrate.

1,3-Bis-(p-acetamidophenyl)guanidine (*X*). A mixture of 3.5 g. of *p*-acetamidophenylcyanamide, 3.7 g. of *p*-aminoacetanilide hydrochloride, and 125 cc. of chlorobenzene was refluxed two and one-half hours, cooled, and the product was filtered. The yield of crude hydrochloride was 7 g., m.p. 303–311° (dec.).

The hydrochloride is insoluble in alcohol and cold water; it is slightly soluble in hot water and soluble in cold 12 *N* hydrochloric acid.

An aqueous suspension of the hydrochloride was treated with excess alkali. The liberated base was filtered and recrystallized three times from 20% ethanol; m.p. 143–146° (dec.).

Anal. Calc'd for $C_{17}H_{19}N_5O_2$: N, 21.6. Found: N, 20.7.

1,3-Bis-(p-aminophenyl)guanidine (*XI*). A mixture of 14.7 g. of 1,3-bis-(*p*-acetamidophenyl)guanidine and 250 cc. of 12 *N* hydrochloric acid was refluxed forty minutes and then evaporated to dryness *in vacuo*. The crystalline hydrochloride was slurried in ethanol and filtered; yield 12.5 g., m.p. 265–275° (dec.).

It was converted to the base by the addition of alkali. The base was filtered and washed with a little water; m.p. 204–208° (dec.).

Anal. Calc'd for $C_{13}H_{15}N_5 \cdot \frac{1}{2}H_2O$: N, 28.0. Found: N, 28.0.

1,3-Bis-(p-guanidinophenyl)guanidine (*XII*). A mixture of 1.25 g. of the diaminodiphenylguanidine trihydrochloride, 0.46 g. of cyanamide, and 15 cc. of ethanol was refluxed four hours. The mixture was cooled and the hydrochloride of the product was filtered; yield 0.5 g.; m.p. 287–291°. After two recrystallizations from 90% alcohol and ether, the m.p. was 292–295°.

Anal. Calc'd for $C_{15}H_{22}Cl_3N_9$: C, 41.4; H, 5.1; N, 29.0.
Found: C, 41.4; H, 5.6; N, 28.7.

1,3-Bis-(p-ureidophenyl)guanidine (*XIII*). A solution of 3.5 g. of 1,3-bis-(*p*-aminophenyl)guanidine trihydrochloride in 20 cc. of water was added to a solution of 1.6 g. of potassium cyanate in 15 cc. of water. The temperature rose spontaneously to about 40° and an oil separated. On cooling to 5° and standing the oil crystallized. The product was filtered and washed with cold water; yield 2.4 g. m.p. 193–198° (dec.). The hydrochloride was dissolved in 60 cc. of hot water, the solution was treated with Norit and filtered. Upon cooling the filtrate to 5°, a thin film of oil separated. This was removed by filtration through Norit and Celite. Upon scratching and further cooling the filtrate deposited colorless crystals; m.p. 198–200° (dec.).

Anal. Calc'd for $C_{15}H_{18}ClN_7O_2$: N, 26.9. Found: N, 27.1.

3,3'-Dimethyl-4,4'-diguanidinobiphenyl (*XV*). A mixture of 14.2 g. of *o*-tolidine dihydrochloride, 6.3 g. of cyanamide, and 100 cc. of ethanol was refluxed one day, the solution was evaporated to dryness *in vacuo*, the residue was dissolved in water, treated with Norit, and filtered. The filtrate was then cooled and made alkaline. A gum separated which crystallized on rubbing. The base was filtered, washed with alkali, then with water, and dried in a desiccator over sulfuric acid; yield 13.5 g., m.p. 219–223° (dec.). The hydrochloride was obtained from the base as a gum.

The picrate formed in aqueous solution. After two recrystallizations from water it decomposed above 270° without melting.

Anal. Calc'd for $C_{28}H_{26}N_{12}O_{14}$: N, 22.3. Found: N, 22.4.

p-Guanidinobenzylamine (*XVII*). To a boiling solution of 10 g. of *p*-aminobenzylamine dihydrochloride (14) in 10 cc. of water was added, during the course of one hour, a solution of 5 g. of cyanamide in 12 cc. of water. The solution was then refluxed an additional fifteen minutes, cooled to 0–5° and treated with a large excess of 50% alkali. The resulting crystalline base was filtered, washed with a little 5 *N* alkali and recrystallized from ethanol-ether; m.p. 172–176°. The base was dissolved in water, neutralized with hydrochloric acid and evaporated to dryness. The resulting dihydrochloride was recrystallized from 90% alcohol and ether; yield 7.5 g., m.p. 250–260° (dec.). After two more recrystallizations the m.p. was 257–260° (dec.).

Anal. Calc'd for $C_8H_{14}Cl_2N_4$: C, 40.5; H, 5.9; N, 23.7.
Found: C, 40.8; H, 7.3; N, 23.4.

The *dipicrate* of *p*-guanidinobenzylamine was formed readily in aqueous solution and after two recrystallizations from water, the m.p. was 242–243° (dec.).

Anal. Calc'd for $C_{20}H_{18}N_{10}O_{14}$: C, 38.6; H, 2.9; N, 22.5.
Found: C, 38.7; H, 3.5; N, 22.3.

p-Aminobenzylguanidine (*XVIII*). A mixture of 2.4 g. of *p*-aminobenzylamine (free base), 5.0 g. of methylisothiourea sulfate, and 20 cc. of ethanol was refluxed six hours. The white crystalline sulfate was filtered and washed with ethanol; m.p. 195–202° (dec.); yield 5.7 g. The sulfate was dissolved in water and treated with picric acid. The yellow *dipicrate* was filtered and recrystallized three times from water; it decomposes above 197° without melting.

Anal. Calc'd for $C_{20}H_{18}N_{10}O_{14}$: C, 38.6; H, 2.9; N, 22.5.
Found: C, 39.0; H, 3.3; N, 22.4.

p-Guanidinobenzylguanidine (*XVI*). Two and four-tenths grams of *p*-guanidinobenzylamine dihydrochloride was dissolved in 10.4 cc. of 1.06 *N* sodium hydroxide. The solution was brought to reflux and treated, during two hours, with 2.8 cc. of a 23% aqueous cyanamide solution.

Excess aqueous picric acid was added and the yellow dipicrate was filtered and recrystallized four times from water; yield 2.5 g., m.p. 250–253° (dec.). A mixture of the latter and the dipicrate of *p*-guanidinobenzylamine [m.p. 242–243° (dec.)] melted at 230–234° (dec.).

Anal. Calc'd for $C_{21}H_{20}N_{12}O_{14}$: C, 38.0; H, 3.0; N, 25.3.
Found: C, 38.7; H, 3.3; N, 25.4.

p-Biguanidobenzylamine dihydrochloride (*XXII*). A mixture of 9.8 g. of *p*-aminobenzylamine dihydrochloride, 8.4 g. of dicyandiamide, and 20 cc. of water was refluxed two hours and cooled to 5°. The white solid was filtered, washed with ethanol, and recrystallized three times from 85% ethanol-ether; yield 8 g. The crystals decomposed above 250° without melting.

Anal. Calc'd for $C_9H_{16}Cl_2N_6$: C, 33.8; H, 5.7; N, 30.1.
Found: C, 33.6; H, 6.1; N, 29.6.

p-Phenylenedibiguanide (*XXIII*). An intimate mixture of 2.7 g. of *p*-phenylenediamine dihydrochloride and 2.5 g. of dicyandiamide was heated in a tube at 150–160° (inner temperature) for one hour. The mixture fused partly. The mass was cooled, dissolved in water, decolorized with charcoal, cooled to 5°, and made alkaline with 5 *N* sodium hydroxide. The free base separated in the form of sparkling crystals which were filtered and washed with cold water; yield 2.7 g., m.p. 217–218° (dec.). After two recrystallizations from water, the m.p. was 218–219° (dec.).

Anal. Calc'd for $C_{10}H_{16}N_{10}\cdot H_2O$: C, 40.8; H, 6.1; N, 47.6.
Found: C, 41.0; H, 6.6; N, 46.6.

Acidification of the base with hydrochloric acid gives a tetra-hydrochloride, which crystallizes from the strongly acid solution. The salt was dissolved in water and hydrochloric acid was again added. The partially purified salt was then recrystallized from dilute alcohol and ether; m.p. 270–278° (dec.).

Anal. Calc'd for $C_{10}H_{20}Cl_4N_{10}$: C, 28.5; H, 4.7; N, 33.2; Cl, 33.7.
Found: C, 29.1; H, 5.2; N, 33.9; Cl, 32.0.

2-Chloro-1,4-phenylenedibiguanide (XXIV). A mixture of 4.3 g. of 2-chloro-1,4-phenylenediamine dihydrochloride, 3.4 g. of dicyandiamide, and 8 cc. of water was refluxed for two hours, the solution was evaporated to dryness, and the gummy residue was triturated with warm ethanol. The resulting crystals (4.2 g.) of the hydrochloride were filtered and recrystallized from 85% ethanol-water; m.p. 240–243° (dec.). The hydrochloride was converted to the base with 50% alkali and the resulting white crystalline base was recrystallized twice from water; m.p. 208–210° (dec.).

Anal. Calc'd for $C_{10}H_{15}ClN_{10}$: C, 38.7; H, 4.8; N, 45.2.
Found: C, 38.1; H, 4.9; N, 45.3.

SUMMARY

The preparation of a number of guanidine and biguanide derivatives related to *p*-phenylenediguanidine has been described; these were tested for trypanocidal activity.

PEARL RIVER, NEW YORK

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