

996. *The Search for Chemotherapeutic Amidines. Part XVII.**
 *$\alpha\omega$ -Di-*p*-amidinoanilinoalkanes.*

By S. S. BERG.

The diamidines (III) where n is 1, 2, 3, and 6, and the piperazine derivative (II) are described. They have no significant trypanocidal activity.

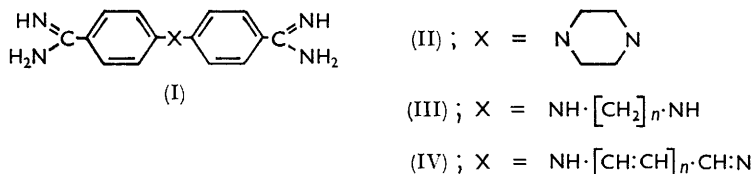
No aromatic diamidines of type (I) where X is $\text{NH}\cdot[\text{CH}_2]_n\cdot\text{NH}$ have been reported in this series of papers although the corresponding oxygen analogues ($\text{X} = \text{O}\cdot[\text{CH}_2]_n\cdot\text{O}$) were among the first to be prepared.¹ The compounds (III) where n is 1, 2, 3, and 6, together with the piperazine derivative (II), are now described.

The first member of the series (III; $n = 1$) was readily prepared by the reaction of formaldehyde with *p*-aminobenzamidine monohydrochloride, but attempts to obtain the next higher homologue (III; $n = 2$) by the condensation of the amino-amidine with

* Part XVI; Ashley, Berg, and MacDonald, *J.*, 1960, 4525.

¹ Ashley, Barber, Ewins, Newbery, and Self, *J.*, 1942, 116.

ethylene dibromide were unsuccessful. The corresponding dinitrile, 1,2-di-*p*-cyanoanilinoethane, was prepared, together with 1,4-di-*p*-cyanophenylpiperazine, by the condensation of *p*-aminobenzonitrile with ethylene dibromide in boiling 2-ethoxyethanol, and was also obtained from the reaction of 1,2-di-*p*-bromoanilinoethane with cuprous cyanide-pyridine.



1,4-Di-*p*-cyanophenylpiperazine was also prepared (but in variable yield) by the reaction of *p*-aminobenzonitrile with ethylene dibromide in the presence of sodium carbonate.

The condensation of *p*-aminobenzamidine monohydrochloride with 1,1,3,3-tetraethoxypropane † gave 1-*p*-amidinoanilino-3-*p*-amidinophenyliminoprop-1-ene dihydrochloride (IV; $n = 1$) but attempts to reduce this catalytically in aqueous solution to the corresponding propane caused fission with formation of *p*-aminobenzamidine. The condensation of *p*-aminobenzonitrile with 1,3-dibromopentane gave a poor yield (21.6%) of 1,3-di-*p*-cyanoanilinoethane. Subsequently an alternative method was used, and *p*-aminobenzonitrile was condensed with 1,1,3,3-tetraethoxypropane, and the resulting 1-*p*-cyanoanilino-3-*p*-cyanophenyliminoprop-1-ene was smoothly reduced catalytically in dimethylformamide to the propane. There was, however, no improvement in the overall yield (22%) from these two reactions. A different result was obtained in attempts to synthesise the analogous pentane derivative. *p*-Aminobenzamidine monohydrochloride condensed smoothly with the monosodio-derivative of glutaconic dialdehyde to give 1-*p*-amidinoanilino-5-*p*-amidinophenyliminopenta-1,3-diene (IV; $n = 2$) † which suffered fission during attempts to reduce it catalytically to the pentane, and a similar fission occurred during the reduction of the corresponding 1-*p*-cyanoanilino-5-*p*-cyanophenyliminopenta-1,3-diene (prepared from the sodio-derivative of the dialdehyde and *p*-aminobenzonitrile in dilute sulphuric acid; the use of hydrochloric acid in this condensation gave chlorine-containing products). The alternative synthesis from *p*-aminobenzonitrile and 1,5-dibromopentane was not attempted because it was considered very probable that this reaction would give 1-*p*-cyanophenylpiperidine (cf. Bader,² who obtained 4-amino-6-piperidinoquinaldine from 4,6-diaminoquinaldine and 1,5-dibromopentane).

1,6-Di-*p*-cyanoanilinoethane was prepared without difficulty from the amino-nitrile and 1,6-dibromohexane.

The dinitriles were converted into the diamidines by the usual Pinner method, and these were tested biologically as the dihydrochlorides, dimethanesulphonates, or disethionates.

Di-*p*-amidinoanilinoethane was inactive against *Trypanosoma congolense* infections in mice; the other diamidines were slightly active but not curative. 1,3-Di-*p*-amidinoanilinoethane had a therapeutic ratio (LD₅₀ : CD₅₀) of 22 when tested against *T. rhodesiense* infections in mice.

EXPERIMENTAL

Di-p-amidinoanilinoethane Dihydrochloride.—*p*-Aminobenzamidine monohydrochloride (8.5 g.) in ethanol (50 ml.) and aqueous formaldehyde (40%; 2 ml.) were refluxed for 0.5 hr. The white product (5.7 g.) was filtered off and washed with ethanol and acetone. The salt crystallised from methanol-acetone (1 : 2; 112 ml.) in needles (4.3 g., 49%), m. p. 236–238° (Found: Cl, 20.2; N, 23.7. C₁₅H₁₈N₈·2HCl requires Cl, 20.0; N, 23.65%). The pH of a 3% w/v aqueous solution was 7.0.

† This was first carried out by our colleague, Dr. E. Crundwell, B.Sc.

² Bader, J., 1956, 3293.

1,2-Di-*p*-cyanoanilinoethane.—A stirred mixture of cuprous cyanide (6.8 g.) and anhydrous pyridine (10 ml.) was heated to 120—130° to give a clear brown solution. 1,2-Di-*p*-bromoanilinoethane, m. p. 105—108° (9.25 g.) (Schouten³), was added, and the bath temperature was raised to 215—220°. Pyridine was distilled off while the internal temperature was 195—200°, and the thick melt was stirred at this temperature for 3 hr. The hot melt was quickly added to potassium cyanide (20 g.) in ice-water (50 ml.); the oil which separated quickly hardened. The liquor was poured off and the residual mass was ground with 2*N*-hydrochloric acid. The brown granular solid (14.5 g.) was filtered off, washed with water, dried, and sublimed at 300—310°/0.1 mm. The yellow sublimate (0.45 g.) of the *dicyano-compound* after being ground and washed with ether, crystallised from acetic acid as pale yellow needles (0.33 g.; 5%), m. p. 205—206° (Found: C, 72.7; H, 5.4; N, 21.3. C₁₆H₁₄N₄ requires C, 73.3; H, 5.35; N, 21.4%).

Condensation of *p*-Aminobenzonitrile with Ethylene Dibromide.—*p*-Aminobenzonitrile (100 g.), sodium hydrogen carbonate (142 g.), ethylene dibromide (160 g.; 73 ml.), and 2-ethoxyethanol (400 ml.) were refluxed for 18 hr. (bath at 140—150°). The mixture was cooled to 10°, and the insoluble material (A) was filtered off. The filtrate was diluted with water (600 ml.), and the brown granular solid (B) was filtered off and washed with water. *p*-Aminobenzonitrile (51 g.) was recovered from the mother liquors. The solid (B) was crystallised from methanol (1700 ml.), and the product (18 g.), m. p. 185—203°, was sublimed at 280—290°/0.07 mm. A low-melting fraction, and a main fraction (11 g.), m. p. 200—205°, were obtained. Crystallisation of the latter from acetic acid (200 ml.) gave 1,2-di-*p*-cyanoanilinoethane (9 g.; 8.3%), m. p. 208—209°, identical with the product described above.

The product (A) was washed with 2-ethoxyethanol and ground with water; the mixture was filtered, and the solid boiled with methanol (300 ml.) and then sublimed at 310—315°/0.07 mm. The main fraction (7.6 g.), m. p. 259—267°, was crystallised from anisole (200 ml.); 1,4-di-*p*-cyanophenylpiperazine (6.6 g.; 5.5%) separated as pale yellow needles, m. p. 275—277° (Found: C, 74.7; H, 5.55; N, 19.5. C₁₈H₁₆N₄ requires C, 75.0; H, 5.55; N, 19.45%). It was also prepared as follows: *p*-Aminobenzonitrile (5 g.), anhydrous sodium carbonate (4.25 g.), and ethylene dibromide (7.1 g., 3.25 ml.) were stirred and refluxed at 150—155° (bath) for 3 hr. The mixture was cooled in ice and filtered, and the solid was washed with hot water and then ethanol, boiled with 2-ethoxyethanol (2 × 100 ml.), and crystallised from anisole (55 ml.). The product (1.4 g., 23%) separated as yellow needles, m. p. 270—272°, identical with the authentic sample (this method of preparation gave variable results, the yield quoted being the highest obtained).

1,2-Di-*p*-amidinoanilinoethane Dimethanesulphonate.—This was prepared from 1,2-di-*p*-cyanoanilinoethane (27.5 g.) suspended in 2-ethoxyethanol (650 ml.) at 0—5° and saturated with hydrogen chloride. After 10 days, the resulting mixture of di-imidoester dihydrochloride and unchanged dinitrile (18 g.) was treated with saturated ethanolic ammonia (390 ml.) at 55—60°. The *diamidine dihydrochloride* (7.5 g.) crystallised from water in cream plates, m. p. 353° (decomp.) (Found: Cl, 17.8; N, 21.15; H₂O, 6.6. C₁₆H₂₀N₆·2HCl·1.5H₂O requires Cl, 17.9; N, 21.2; H₂O, 6.8%). A solution of the dihydrochloride (7.5 g.) in water (800 ml.) (prepared by heating to 70—80°) was cooled to 10—15°, and basified with 50% w/v aqueous sodium hydroxide. The base was filtered off, washed with water, and dried over silica gel *in vacuo*. The white solid (6.0 g.) was suspended in methanol (80 ml.), and methanesulphonic acid in methanol (9.6 w/v; 5.5 ml.) was added. The *dimethanesulphonate* quickly crystallised and was recrystallised from methanol (560 ml.). The product separated as pale yellow prisms (7.1 g.; 53.5% overall), m. p. 301—302° (Found: N, 17.2; S, 13.3. C₁₆H₂₀N₆·2CH₃O₃S requires N, 17.2; S, 13.1%). The pH of a 2% w/v aqueous solution was 6—7.

1,4-Di-*p*-amidinophenylpiperazine Di-isethionate.—This was prepared similarly from finely ground 1,4-di-*p*-cyanophenylpiperazine (8.4 g.) suspended in 2-ethoxyethanol (150 ml.), and saturated with hydrogen chloride at 0.5°. The *diamidine dihydrochloride* (6 g.) in water (750 ml.) was basified with 50% w/v aqueous sodium hydroxide, at 15—20°, and the base was filtered off, washed with water, and dissolved in warm 2*N*-isethionic acid (20 ml.). After being cooled in ice, the *di-isethionate* was filtered off. The crude product (6.5 g.) was recrystallised from methanol (350 ml.), forming yellow needles (5.5 g., 43.5%), m. p. 328° (decomp.) (Found: N, 14.15; S, 11.1; H₂O, 2.7. C₁₈H₂₂N₆·2C₂H₅O₄S·H₂O requires N, 14.2; S, 10.8; H₂O, 3.05%). The pH of a 2% w/v aqueous solution was 7.

³ Schouten, *Rec. Trav. chim.*, 1937, **56**, 541.

1-*p*-Cyanoanilino-3-*p*-cyanophenyliminoprop-1-ene.—*p*-Aminobenzonitrile (12 g.) dissolved in 2*N*-hydrochloric acid (100 ml.) and water (150 ml.), was heated on the steam-bath, and treated with 1,1,3,3-tetraethoxypropane (12 ml.). The mixture was stirred for 1 hr., then cooled in ice, and the yellow precipitate (15 g.) filtered off and washed with ethanol and ether. A solution in 95% aqueous pyridine (300 ml.) was diluted with water (300 ml.), and the fluffy yellow *product* (11 g.; 58%) filtered off. It had m. p. 227—229° (Found: C, 74.8; H, 4.8; N, 20.3. $C_{17}H_{12}N_4$ requires C, 75.0; H, 4.4; N, 20.6%).

1,3-*Di-p*-cyanoanilinopropane.—(a) *p*-Aminobenzonitrile (11.8 g.), 1,3-dibromopropane (5.2 ml.), sodium hydrogen carbonate (8.4 g.), and 2-ethoxyethanol (50 ml.) were refluxed overnight. The mixture was added to water (2 vol.), and the oil which separated soon hardened. The stiff gum was triturated with isopropyl alcohol (25 ml.), and the solid was filtered off and crystallised from aqueous ethanol, giving the *dinitrile* as pale yellow needles (3 g.; 21.6%), m. p. 159—161° (Found: C, 74.2; H, 5.7; N, 20.0. $C_{17}H_{16}N_4$ requires C, 73.9; H, 5.8; N, 20.3%).

(b) 1-*p*-Cyanoanilino-3-*p*-cyanophenyliminoprop-1-ene (11 g.) in dimethylformamide (700 ml.) was hydrogenated at room temperature with platinum oxide (1.6 g.) as catalyst; the absorption of hydrogen (2 l.; 85%) was completed in 1.5 hr. After the removal of catalyst the solution was diluted with water (1350 ml.), and the precipitate was filtered off, washed with water, and crystallised from ethanol (200 ml.) and water (20 ml.). The product (4.15 g., 38%) was identical with the above dinitrile.

1,3-*Di-p*-amidoanilinopropane Dihydrochloride.—This was prepared from finely ground 1,3-di-*p*-cyanoanilinopropane (10 g.) suspended in anhydrous ethanol (200 ml.) saturated with hydrogen chloride at 0—5°. Nearly all the solid dissolved, and the di-imidoester dihydrochloride began to separate after 24 hr. After being kept for 1 week, the di-imidoester dihydrochloride (14.1 g.) was treated with saturated ethanolic ammonia (141 ml.) at 55—60°. The yellow diamidine dihydrochloride (10.5 g.) was dissolved in boiling water (100 ml.), and saturated brine (30 ml.) was added. The *product* (5.8 g.; 38%) separated as pale yellow plates, m. p. 316—318° (decomp.) (Found: Cl, 16.8; N, 19.9; H_2O , 8.35. $C_{17}H_{22}N_6 \cdot 2HCl \cdot 2H_2O$ requires Cl, 16.9; N, 20.0; H_2O , 8.6%). The pH of a 2% w/v aqueous solution was 7.0. The product was phototropic.

1-*p*-Cyanoaniline-5-*p*-cyanophenyliminopenta-1,3-diene.—Sodium glutaconic aldehyde dihydrate (1.55 g.) in water (50 ml.) was added to a stirred solution of *p*-aminobenzonitrile (2.36 g.) in 2*N*-sulphuric acid (20 ml.) and water (120 ml.) at 80—90°. The mixture was stirred for a further 10 min. at 80—90° and was then filtered. The *product* (2.5 g.; 84%), which was washed with hot water and acetone, decomposed at 140—144° (Found: C, 61.7; H, 6.55; N, 15.0; H_2O , 19.8. $C_{19}H_{14}N_4 \cdot 4H_2O$ requires C, 61.6; H, 5.95; N, 15.15; H_2O , 19.45%).

Reduction. The product (2.4 g.) in dimethylformamide (100 ml.) was reduced at atmospheric pressure at 30—35° in the presence of platinum oxide (0.24 g.). The absorption of hydrogen (96%; 520 ml.) was complete in $\frac{1}{2}$ hr. The catalyst was filtered off, and the brown solution was diluted with an equal volume of 2*N*-hydrochloric acid. The brown precipitate was filtered off, washed with water, and extracted with chloroform. The chloroform extracts were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The residual gum (2.0 g.) was triturated with ethanol, giving a brown solid (1.8 g.), m. p. 160—170°. Attempts to purify this were unsuccessful. The aqueous dimethylformamide filtrate was evaporated to dryness under reduced pressure. *p*-Aminobenzonitrile (0.2 g.), m. p. 83—86°, was obtained by grinding the residue with 2*N*-ammonia, and crystallisation of the insoluble material from water.

1,6-*Di-p*-cyanoanilino-hexane.—*p*-Aminobenzonitrile (94.4 g.), hexamethylene dibromide (97.6 g.; 72.1 ml.), sodium hydrogen carbonate (67.2 g.), 2-ethoxyethanol (400 ml.), and potassium iodide (a crystal) were stirred and refluxed for 24 hr. The inorganic material was filtered off and the solvent was distilled off under reduced pressure. The residual oil was cooled and stirred with 2*N*-hydrochloric acid (2 l.), and the mixture extracted with chloroform. The chloroform extract was washed with *n*-hydrochloric acid, and dried (Na_2SO_4). The solvent was distilled off under reduced pressure and the residual gum treated with an equal volume of ethanol. The mixture was cooled in ice, and the solid (15 g.) was filtered off and washed with ethanol; it had m. p. 156—166°. The filtrate was evaporated under reduced pressure and the residual gum was treated with an equal volume of ethanol to give a second crop (8 g.), m. p. 155—165°. The crude product (23 g.) was crystallised from acetic acid (120 ml.), giving brown prismatic needles of the *dinitrile* (16 g.; 12.6%), m. p. 165—167° (Found: C, 75.6; H,

6.75; N, 17.45. $C_{20}H_{22}N_4$ requires C, 75.5; H, 6.9; N, 17.6%). The residual gum was not examined.

1,6-Di-p-amidinoanilinohexane Di-isethionate.—This was prepared similarly to the other diamidines from a suspension of 1,6-di-*p*-cyanoanilinohexane (15 g.) in 2-ethoxyethanol (180 ml.) saturated with hydrogen chloride at 0–5°. The *di-isethionate* was crystallised successively from water and methanol. It formed yellow prisms (5.2 g.; 18.3%), m. p. 238–240° (Found: N, 13.8; S, 10.8. $C_{20}H_{28}N_6, 2C_2H_6O_4S$ requires N, 13.9; S, 10.5%). A 0.5% aqueous solution was neutral to litmus.

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THE RESEARCH LABORATORIES, MAY & BAKER LTD.,
DAGENHAM, ESSEX.

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