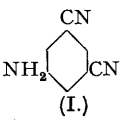
18. *The Search for Chemotherapeutic Amidines. Part IV. Two Polyamidines.*

By H. J. Barber and R. Slack.

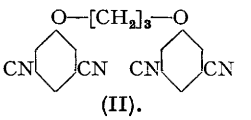
Tetrakis-p-*amidinophenylethylene* has been prepared from the corresponding cyanide. Attempts to prepare tetra-amidinodiphenoxypropane from the corresponding tetracyanide yielded only 5-*cyano*-3 : 3′ : 5′-*triamidino*-α*γ*-*diphenoxypropane*.

All the amidines hitherto examined by us have been mono- or di-amidines, and the object of the present work was to prepare polyamidines as closely allied as possible to the therapeutically interesting stilbene or diphenoxyalkane diamidines. Since aromatic cyano-groups with an *o*-substituent are difficult to convert into amidines, the choice of compound is limited to 3 : 5 : 3′ : 5′-tetracyanodiphenoxyalkanes or the corresponding stilbenes. The synthesis of the latter class presented extreme difficulties and was rejected in view of the unfavourable indications with the more accessible products. For the former series, 3 : 5-dicyanophenol was the most useful intermediate, since it could yield many of the polycyanides corresponding to the dicyanides successfully employed in these laboratories for preparing the therapeutically active diamidines.

3 : 5-*Dicyanoaniline* (I) was readily obtained from methyl 3 : 5-dinitrobenzoate *via* the 5-nitro-3-aminobenzoate, the 5-*nitro*-3-*cyanobenzoate*, and 3-*nitro*-5-*cyanobenzamide*, and 1-nitro-3 : 5-dicyanobenzene, but attempts to convert it into 3 : 5-dicyanophenol were frustrated by simultaneous hydrolysis of the cyano-groups. The non-volatility of the phenol in steam precluded the use of the procedure advocated by Hodgson (*J. Amer. Chem. Soc.*, 1940, **62**, 230).



(I.)

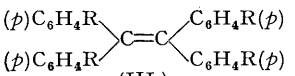


(II).

An alternative route to the *tetracyanide* (II) was successfully accomplished. 3 : 5-Dibromoaniline, prepared from *p*-nitroaniline by dibromination, elimination of the amino-group, and reduction of the nitro-group, was converted into the corresponding phenol which gave 3 : 5 : 3′ : 5′-*tetrabromo*-α*γ*-*diphenoxypropane* with trimethylene dibromide in alcoholic potash. The tetracyanide (II) was obtained in the usual manner by using cuprous cyanide.

This tetracyanide failed to yield a tetraiminoether, reaction ceasing at the *tri-iminoether* stage. This surprising result suggests a substituent ortho- to one of the cyano-groups. This could arise from a Claisen-type rearrangement during the conversion of the tetrabromo-compound into the tetracyanide (II), but no phenolic properties could be detected in the latter. Migration of the cyano-group has been reported in replacement of $-SO_3H$ by $-CN$ in the naphthalene series (King and Wright, *J.*, 1939, 253), but similar behaviour in the present series is most unlikely, the most probable reason for incomplete reaction being the insolubility of the tri-iminoether hydrochloride.

Tetra-*p*-amidinotetraphenylethylene [III, $R = R_1 = R_2 = R_3 = C(:NH)\cdot NH_2$] can be considered as a substituted diamidinostilbene and might be expected to possess some trypanocidal activity, although in the alkylstilbene diamidine series the activity decreases in ascending the homologous series (Barber and Slack, *J.*, 1944, 612); of interest, too, was the effect on toxicity arising from four amidine groups in the same molecule.



(III.)

Direct cyanation of tetrakis-*p*-bromophenylethylene (III; $R = R_1 = R_2 = R_3 = Br$) (Norris *et al.*, *Ber.*, 1910, **43**, 2940; *J. Amer. Chem. Soc.*, 1916, **38**, 702; 1909, **42**, 2805) was achieved easily with cuprous cyanide in boiling quinoline, but in pyridine replacement of the halogen groups was incomplete.

Tetrakis-p-*cyanophenylethylene* was incompletely converted into the corresponding iminoether with chloroform as diluent, but with a large excess of absolute alcohol alone, complete reaction occurred and the pure *iminoether base* was isolated. Treatment with ammonium isethionate for a considerably longer time than is usually necessary for diamidines gave *tetrakis*-p-*amidinophenylethylene tetraisethionate*.

Both the tri- and the tetra-amidine described above were devoid of trypanocidal activity

when tested against *T. equiperdum* infection in mice, and, compared with the aromatic diamidines, *e.g.*, diamidinostilbene or diamidinodiphenoxypropane, showed a considerably enhanced toxicity due, presumably, to the increased number of amidine groups.

Experimental.

Methyl 5-nitro-3-aminobenzoate was obtained by semi-reduction of methyl 3 : 5-dinitrobenzoate (Cohen and McCandlish, *J.*, 1905, **87**, 1266).

Methyl 5-Nitro-3-cyanobenzoate.—Methyl 5-nitro-3-aminobenzoate (53 g.) was finely powdered, suspended in a mixture of hydrochloric acid (80 c.c., *d* 1·16) and ice (*ca.* 200 g.), and diazotised at 0—10° with sodium nitrite (19 g.) in water (100 c.c.). After being stirred for ½ hour, the diazo-solution was filtered from a little flocculent material and run during 1 hour into a well-stirred mixture of potassium cuprocyanide solution (CuCN, 25 g.; KCN, 37 g.; water, 150 c.c.) and benzene (200 c.c.) at 5—10°. The whole was kept for 1 hour at 60—70°, filtered, and the benzene separated. The solid and the aqueous layer were each washed with more benzene, and the combined benzene extracts washed successively with dilute sodium hydroxide solution and water before removal of the benzene. The residual crude solid was distilled (b. p. 148—155°/2 mm.) or vacuum-sublimed before being crystallised from ethyl alcohol (*ca.* 15 c.c./g.). Yield 45—50%; m. p. 137—138° (Found : N, 13·8. $C_9H_6O_4N_2$ requires N, 13·6%).

5-Nitro-3-cyanobenzamide.—The powdered *ester* was kept with occasional shaking for several days in a stoppered flask with saturated ethyl-alcoholic ammonia (7 c.c./1 g.). It gradually dissolved and the *amide* slowly crystallised. Yield 75—80%. Recrystallisation from acetic acid gave prisms, m. p. 188—189° (Found : N, 21·6. $C_8H_5O_3N_3$ requires N, 22·0%).

1-Nitro-3 : 5-dicyanobenzene.—The amide (8 g.) was boiled under reflux in dry xylene (100 c.c.) with phosphoric oxide (10 g.) for 5 hours. The clear xylene solution was decanted from the sticky pentoxide mass, and the dicyanide crystallised in pure condition. A further crop was obtained on concentrating the xylene. Yield 70—75%; m. p. 205° (Bennett and Wain, *J.*, 1936, 1108, give 205°) (Found : N, 24·1. Calc. for $C_8H_3O_2N_3$: N, 24·3%).

3 : 5-Dicyanoaniline (I).—The nitro-compound (5·7 g.) was first converted into a finely divided form by dissolution in glacial acetic acid and precipitation with water, and reduced in alcohol (90 c.c.) with tin (10 g.) and hydrochloric acid (45 c.c., *d* 1·16) overnight at 35—40°. The filtered solution was concentrated, and the crude amine obtained by precipitation with sodium hydroxide. The product was dissolved in hot alcohol, treated with charcoal, filtered, and precipitated with water. After dissolution in 4N-hydrochloric acid, the *amine* was precipitated with ammonia. Yield 50%; m. p. 189—190° (Found : N, 28·6. $C_8H_5N_3$ requires N, 29·4%). Reduction with iron or with Adams's platinum oxide catalyst failed.

3 : 5-Dibromophenol was obtained from 3 : 5-dibromoaniline by using the general conditions given by Hodgson (*loc. cit.*), but as this phenol was only slightly volatile in steam, it was extracted with benzene and distilled in a vacuum; b. p. 120—122°/2—3 mm., m. p. 79—80°; yield 50%.

3 : 5 : 3′ : 5′-Tetrabromo-αγ-diphenoxypropane.—**3** : 5-Dibromophenol (30 g.) in ethyl alcohol (50 c.c.) was treated with a solution of potassium hydroxide (6—7 g.) in methanol (50 c.c.) and 1 : 3-dibromopropane (12 g.) and the solution boiled overnight. The *product* which separated, together with potassium bromide, was filtered off and washed with water and was then sufficiently pure for the next stage. Yield 75—80%, m. p. 123—124° (Found : Br, 59·7. $C_{15}H_{12}O_2Br_4$ requires Br, 59·0%).

3 : 5 : 3′ : 5′-Tetracyano-αγ-diphenoxypropane (II).—The tetrabromo-compound (12·0 g.) was mixed with dry cuprous cyanide (9·4 c.c.) and dry pyridine (10 c.c.) and heated in a metal-bath. A little pyridine was distilled out to enable an internal temperature of 200° to be maintained. After 2½ hours the melt was cooled somewhat, diluted with pyridine (12 c.c.), and poured into hydrochloric acid (70 c.c., *d* 1·16) at 50°. The solid was collected, washed with 2N-hydrochloric acid, then with water, and dried. Attempts to purify this failed, probably since some conversion of cyanide to amide had occurred. The crude product was therefore boiled in xylene (100 c.c.) with phosphoric oxide (10 g.) for 2 hours. Recrystallisation from glacial acetic acid gave the pure *compound*, m. p. 188°, in 50% yield (Found : N, 17·4. $C_{19}H_{12}O_2N_4$ requires N, 17·1%).

5-Cyano-3 : 3′ : 5′-triamidino-αγ-diphenoxypropane.—3 : 5 : 3′ : 5′-Tetracyano-αγ-diphenoxypropane (II) (3·3 g.) in dry dioxan (20 c.c.) and ethyl alcohol (5·7 c.c.) was saturated at 0° with hydrogen chloride and kept at room temperature for 7 days. On converting the resulting iminoether into amidine, there was obtained, not the expected 3 : 5 : 3′ : 5′-tetra-amidine, but 5-cyano-3 : 3′ : 5′-triamidino-αγ-diphenoxypropane hydrochloride which crystallised as a *dihydrate* on addition of its concentrated aqueous solution to acetone [Found : N, 18·8; Cl, 20·5; (N : Cl = 2·33 : 1); loss at 100°/1 mm., 5·2. $C_{19}H_{21}O_2N_7,3HCl,2H_2O$ requires N, 18·7; Cl, 20·35; (N : Cl = 2·33 : 1); H_2O, 6·8%].

Repeated attempts to convert 3 : 5 : 3′ : 5′-tetracyano-αγ-diphenoxypropane into the corresponding tetraiminoether were unsuccessful. An ethyl-alcoholic suspension of the tetracyanide, saturated at 0° with hydrogen chloride and kept for 14 days at room temperature, likewise gave, on conversion into amidino-compound, the monocyano-triamidine (Found : N, 18·3%). When the dioxan–ethyl alcohol suspension of the tetracyanide saturated at 0° with hydrogen chloride was kept at room temperature for 19 days and the resulting iminoether isolated as the hydrochloride, it proved to be the *tri-iminoether hydrochloride* (Found : OEt, 23·2, 23·8. $C_{25}H_{30}O_5N_4,3HCl$ requires OEt, 23·4. $C_{27}H_{36}O_6N_4,4HCl$ requires OEt, 27·4%). The sodamide method of B.P. 538,463 was equally unsuccessful.

Tetrakis-p-cyanophenylethylene.—Tetrakis-*p*-bromophenylethylene (45·0 g.) was intimately mixed with dry cuprous cyanide (38·5 g.), and the mixture fed slowly into quietly boiling quinoline (150 c.c.). After 1 hour's heating under reflux, the mixture was poured into hot concentrated hydrochloric acid (500 c.c.), and the residue collected by filtration while hot, and washed well with water. The crude solid was then dissolved in boiling glacial acetic acid, filtered (charcoal), and precipitated with water. Recrystallisation from glacial acetic acid gave the *tetracyanide* as pale yellow, blunt needles (15·0 g.),

m. p. 346—348°. Further recrystallisation from the same solvent gave the pure compound, m. p. 352—353° (87% return) [Found: N, 12·8; *M* (Rast), 425. $C_{30}H_{16}N_4$ requires N, 13·0%; *M*, 432].

Tetraphenylethylenetetra-p-*iminoethyl Ether*.—The finely ground cyanide (5·0 g.) in dry ethanol (50 c.c.) was saturated with dry hydrogen chloride at 0°. After standing for 3 weeks in a closed tube at room temperature, the crude iminoether hydrochloride was separated by filtration, washed with ether, and converted into the corresponding base by treatment with excess of sodium carbonate solution and chloroform. The chloroform layer was separated, washed till neutral, dried, and the solvent evaporated. Crystallisation of the residue from benzene gave the *iminoether* as colourless needles (3·2 g.), m. p. (decomp.) 225° (Found: C, 73·8; H, 6·5; N, 9·3; OEt, 29·2. $C_{38}H_{40}O_4N_4$ requires C, 74·0; H, 6·48; N, 9·1; OEt, 29·2%).

Tetrakis-p-*amidinophenylethylene*.—The iminoether base (1·0 g.) was heated for 18 hours at 50—60° with aqueous alcohol (3 c.c.; 9 c.c.) containing ammonium isethionate (1·4 g.). The clear solution was evaporated to dryness at 10 mm. (temp. 40°), and the residue treated with acetone and filtered. The solid (1·6 g.) was dissolved in the minimum quantity of water, and the solution filtered (charcoal) and poured slowly with stirring into acetone (100 c.c.) at 0°. The micro-crystalline *amidine isethionate* was filtered off, washed with acetone, and dried in a vacuum (Found: C, 44·8; H, 5·4; N, 11·2. $C_{38}H_{52}O_{16}N_8S_4$ requires C, 45·5; H, 5·2; N, 11·2%).

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