138. *The Search for Chemotherapeutic Amidines. Part X. Substituted* 4 : 4′-*Diamidino-αω-diphenoxyalkanes and -diphenyl Ethers.*

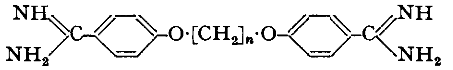
By S. S. Berg and (the late) G. Newbery.

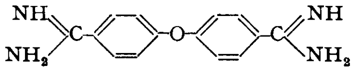
4 : 4′-Diamidino-αω-diphenoxyalkanes have been substituted, in the *o*-position to the ether linkage, with halogen, nitro-, amino-, methoxy-, and alkyl groups, and 4 : 4′-diamidinodiphenyl ether has been similarly substituted with halogen, nitro-, amino-, and hydroxy-groups. The products exhibited trypanocidal activity which was generally of a lower order than that of the parent diamidine.

In contrast, the antibacterial activity of diamidinodiphenyl ether was slightly increased by introduction of halogen, whilst there was a pronounced increase in activity with the halogenated diamidinodiphenoxyalkanes.

The discovery of the trypanocidal action of symmetrical diamidines of the types (I) and (II) (Ashley *et al.*, *J.*, 1942, 103) prompted an investigation into the effect of substituents in the *o*-position to the ether linkage. Ashley and Harris (*J.*, 1946, 567) described the preparation of a series of derivatives of 4 : 4′-diamidinostilbene (" Stilbamidine ") containing substituents in the 2-position. Of these products, the 2-hydroxy- and 2-halogeno-derivatives exhibited increased trypanocidal activity, while the antibacterial activity was only slightly, if at all, enhanced. In the present series, however, introduction of halogen caused a pronounced increase in antibacterial activity; the trypanocidal action was either decreased or not significantly affected. Both mono- and di-substituted derivatives have been prepared and tested; the biological results will be published elsewhere. A few results are reported by Wien (*Brit. J. Pharmacol.*, 1946, **1**, 65) and Wien, Harrison, and Freeman (*Lancet*, 1948, 711).

(I.)



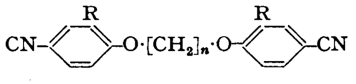


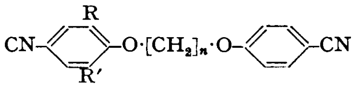
(II.)

The method of preparation of the diamidines was essentially that used by Ashley *et al.* (*loc. cit.*), which involved the conversion of the dicyanides into the di-iminoethers, and thence into the diamidines. The latter presented no special difficulty in isolation and purification, the water-soluble hydrochlorides or isethionates usually being prepared.

The substituted 4 : 4′-dicyano-αω-diphenoxyalkanes were prepared (*a*) in the case of dicyanides of the type (III; R = F, Cl, Br, I, NO_2, OMe) by condensation of the appropriate αω-dibromoalkane with the sodium salt of the substituted 4-cyanophenol in boiling ethanol; 2′ : 2″-*dinitro*-4′ : 4″-*dicyano*-1 : 5-*diphenoxypentane* was also prepared by nitration of 4′ : 4″-dicyano-1 : 5-diphenoxypentane; (*b*) in the case of dicyanides of the type (IV; R = Cl, Br, I, NO_2; R′ = R or H) by condensation of the appropriate 4-cyanophenoxyalkyl bromide with the sodium salt of the substituted 4-cyanophenol. The former were prepared by treating sodium 4-cyanophenoxide with excess of αω-dibromoalkane in water.

(III.)





(IV.)

4′ : 4″-*Dicyano*-2′ : 2″-*dimethyl*-1 : 5-*diphenoxypentane* and 4′ : 4″-*dibromo*-2′ : 2″-*dimethyl*-1 : 6-*diphenoxyhexane* were prepared by the action of cuprous cyanide in presence of pyridine or quinoline on 4′ : 4″-*dibromo*-2′ : 2″-*dimethyl*-1 : 5-*diphenoxypentane* and 4′ : 4″-*dibromo*-2′ : 2″-*dimethyl*-1 : 6-*diphenoxyhexane*, respectively, the bisdibromo-compounds being prepared by the condensation of the appropriate αω-dibromoalkane with sodium 4-bromo-2-methylphenoxide.

In attempts to demethylate 4′ : 4″-*dicyano*-2′ : 2″-*dimethoxy*-1 : 5-*diphenoxypentane* with the usual reagents, in order to prepare the corresponding dihydroxy-compound, there was no difference between the ease of fission of the methoxy- and the methylene ether linkages, and 4-cyanocatechol was obtained together with unchanged material in all experiments.

2-*Nitro*-4 : 4′-*dicyanodiphenyl ether*, prepared by condensation of 3-nitro-4-bromophenyl cyanide and sodium 4-cyanophenoxide, was the starting material for the preparation of the mono-nitro-, amino-, and -halogeno-substituted 4 : 4′-dicyanodiphenyl ethers. It was reduced to 2-*amino*-4 : 4′-*dicyanodiphenyl ether* by iron powder or stannous chloride–hydrochloric acid in boiling acetic acid. In the latter case, some monoamide was isolated. Conversion of the amino-group into halogen by standard methods proceeded smoothly.

Nitration of 4 : 4′-dicyanodiphenyl ether with fuming nitric acid yielded 2 : 2′-*dinitro*-4 : 4′-*dicyanodiphenyl ether*, the constitution of which was proved by fission with boiling piperidine (cf. Le Fèvre, Saunders, and Turner, *J.*, 1927, 1172), whereupon 2-nitro-4-cyanophenol (prepared by nitration of 4-cyanophenol) and *N*-(2-nitro-4-cyanophenyl)piperidine were obtained. It was reduced to 2 : 2′-*diamino*-4 : 4′-*dicyanodiphenyl ether* with iron powder in boiling acetic acid, and converted into 2 : 2′-*di-iodo*-4 : 4′-*dicyanodiphenyl ether* by the standard procedure.

4 : 4′-*Dicyano*-2-*methoxydiphenyl ether* was prepared by fusion of the potassium salt of 4-cyanoguaiacol with 4-bromophenyl cyanide. Treatment with aluminium chloride in nitrobenzene at 55° gave 2-*hydroxy*-4 : 4′-*dicyanodiphenyl ether*.

The substituted 4-cyanophenols were prepared as follows : 2-methoxy-4-cyanophenol by the method of Marcus (*Ber.*, 1891, **24**, 3654) ; 2-chloro- and 2-bromo-4-cyanophenol by chlorination, and bromination, respectively, of 4-cyanophenol in chloroform. A method similar to that used by Paal (*Ber.*, 1895, **28**, 2413) for iodination of 4-hydroxybenzaldehyde was developed for the preparation of 2-*iodo*-4-*cyanophenol* and 2 : 6-di-iodo-4-cyanophenol. 2-*Fluoro*-4-*cyanophenol* was obtained from 2-fluoro-4-nitroanisole by successive demethylation, reduction, diazotisation, and Sandmeyer reaction. Nitration of 4-cyanophenol gave the 2-nitro-derivative.

2′ : 2″-*Dinitro*-4′ : 4″-*diamidino*-1 : 5-*diphenoxypentane dihydrochloride* was reduced catalytically in the presence of Raney nickel to 2′ : 2″-*diamino*-4′ : 4″-*diamidino*-1 : 5-*diphenoxypentane dihydrochloride*.

EXPERIMENTAL.

2-*Chloro*-4-*cyanophenol*.—4-Cyanophenol (5·9 g.) in chloroform (100 c.c.) was stirred at room temperature and treated during 0·25 hour with a solution of chlorine (3·5 g.) in chloroform (10 c.c.). After 5 minutes' warming on the steam-bath, hydrogen chloride was evolved and the solution became colourless. The solvent was removed under reduced pressure, and the residue crystallised from water (130 c.c.) in long white needles (4·2 g.), m. p. 155° (Biltz, *Ber.*, 1904, **37**, 4034, m. p. 155°).

2-*Bromo*-4-*cyanophenol*.—A mixture of 4-cyanophenol (11·9 g.) in chloroform (200 c.c.) and bromine (16 g.) was warmed until a vigorous reaction occurred, and after this had subsided, the solution was boiled under reflux until colourless (2—3 hours). Hydrogen bromide was copiously evolved at first, after which some crystallisation occurred. The solvent was then removed under reduced pressure, and the residue crystallised from water (200 c.c.) to give long white needles (13 g.), m. p. 156—157° (Auwers and Reis, *Ber.*, 1896, **29**, 2359, m. p. 155°).

A portion of the residue which was insoluble in water crystallised from 20% aqueous ethanol in white needles (1 g.), m. p. 188°, and was shown to be 2 : 6-dibromo-4-cyanophenol.

2-*Iodo*-4-*cyanophenol and* 2 : 6-*Di-iodo*-4-*cyanophenol*.—A solution of 4-cyanophenol (10 g.) and iodine (20 g.) in ethanol (250 c.c.) and water (600 c.c.) was boiled under reflux for 24 hours. The red solution was decolorised by addition of sodium hydrogen sulphite, and cooled to 20°. The colourless product crystallised in needles (2·2 g.) from 50% ethanol, m. p. 205—206°, and was identical with a sample of 2 : 6-di-iodo-4-cyanophenol prepared by the method of Auwers and Reis (*loc. cit.*). The mother liquors from the reaction were concentrated, under reduced pressure, to 300 c.c., 2-*iodo*-4-*cyanophenol* separating on cooling. It was recrystallised thrice from water and formed long white needles (3·5 g.), m. p. 144° (Found : N, 5·6; I, 51·8. C_7H_4ONI requires N, 5·7; I, 51·8%).

2-*Fluoro*-4-*nitrophenol*.—2-Fluoro-4-nitroanisole (1 g.) (Schiemann and Miau, *Ber.*, 1933, **66**, 1179) and aluminium chloride (1·25 g.) were well mixed, and heated for 3 hours on the steam-bath. Water (20 c.c.) was added, and the crystals which separated on cooling were filtered off, dissolved in 2N-sodium carbonate (15 c.c.) at 60—70° (charcoal), and the hot yellow solution acidified with hydrochloric acid (*d* 1·16). The product crystallised from water (20 c.c.) in white fluffy needles or pale yellow plates (0·5 g.), m. p. 117—118° (Found : N, 8·7. $C_6H_4O_3NF$ requires N, 8·9%).

2-*Fluoro*-4-*aminophenol*.—A boiling solution of 2-*fluoro*-4-*nitrophenol* (1 g.) in 2N-acetic acid (15 c.c.) was treated carefully with reduced iron powder (1 g.). When the vigorous reaction subsided, the insoluble material was collected, and the filtrate evaporated to dryness under reduced pressure. The residue was treated with saturated aqueous sodium hydrogen carbonate (20 c.c.), and thoroughly extracted with ether. The extract yielded 2-*fluoro*-4-*aminophenol*, which crystallised from benzene in pale brown prisms (0·4 g.), m. p. 162° (Found : N, 11·2. C_6H_6ONF requires N, 11·0%).

2-*Fluoro*-4-*cyanophenol*.—A suspension of 2-fluoro-4-aminophenol (0·3 g.) in hydrochloric acid (*d* 1·16; 0·6 c.c.) was added, all at once, to a mixture of sodium nitrite (0·2 g.) and ice (5 g.). After being stirred for ½ hour, the solution was neutralised (litmus) with sodium carbonate, and added to a stirred solution of potassium cuprocyanide (0·6 g.) in water (5 c.c.) at 90°. The dark, frothy, mixture was stirred at 90° for 0·5 hour, cooled, acidified (litmus) with hydrochloric acid (*d* 1·16) and saturated with sodium chloride. The mixture was thoroughly extracted with ether, and the extract yielded a solid which was sublimed at 90—110°/0·3 mm. The *phenol* crystallised from light petroleum (b. p. 80—100°) in colourless needles (0·2 g.), m. p. 134° (Found : C, 61·5; H, 3·0; N, 10·3. C_7H_4ONF requires C, 61·3; H, 2·9; N, 10·2%).

2-*Nitro*-4-*cyanophenol*.—4-Cyanophenol (3 g.) in acetic acid (5 c.c.) was treated with nitric acid (*d* 1·42; 1 c.c.). After the vigorous reaction had subsided, the solution was cooled, and the product filtered off, washed with water, and crystallised from dilute acetic acid to give yellow plates (3·1 g.), m. p. 144° (Auwers and Röhrig, *Ber.*, 1897, **30**, 997, m. p. 143—145°).

3-4′-*Cyanophenoxypropyl Bromide*.—A mixture of 1 : 3-dibromopropane (32·3 g.), 4-cyanophenol (11·9 g.), sodium hydroxide (4 g.), and water (60 c.c.) was boiled under reflux for 6 hours. After cooling, 4′ : 4″-dicyano-1 : 3-diphenoxypropane (2·0 g.) was filtered off, and the oil was extracted with ether. The ethereal solution after being washed with water, N-sodium hydroxide, and then water yielded a fraction (10 g.), b. p. 70—110°/0·5 mm. (consisting mainly of 1 : 3-dibromopropane), and the required *bromide*, a colourless oil (20 g.), b. p. 158—161°/0·5 mm. It solidified on standing, and crystallised from ligroin in white needles, m. p. 40° (Found : N, 5·8; Br, 33·2. $C_{10}H_{10}ONBr$ requires N, 5·8; Br, 33·3%). In the preparations described below, the distilled product was used without further purification.

5-4′-Cyanophenoxyamyl Bromide.—1 : 5-Dibromopentane (37 g.), 4-cyanophenol (11·9 g.), sodium hydroxide (4 g.), and water (60 c.c.) were boiled under reflux for 6 hours, and the mixture worked up as described for the propyl homologue. The *bromide* (25 g.) distilled as a colourless oil, b. p. 156—158°/0·02 mm., which solidified immediately; m. p. 60—62°. It crystallised in white prismatic needles from ethanol, m. p. 64° (Found : N, 5·1; Br, 30·1. $C_{12}H_{14}ONBr$ requires N, 5·2; Br, 30·0%).

6-4′-Cyanophenoxyhexyl Bromide.—1 : 6-Dibromohexane (39 g.) (*Org. Synth.*, **20**, 24), 4-cyanophenol (11·9 g.), sodium hydroxide (4 g.) and water (60 c.c.) were boiled under reflux for 12 hours. The *bromide* distilled as a colourless oil (16 g.), b. p. 160—162°/0·01 mm., which solidified on standing. It crystallised in thick colourless needles from methanol, m. p. 47—49° (Found : N, 4·9; Br, 28·4. $C_{13}H_{16}ONBr$ requires N, 5·0; Br, 28·3%).

The *substituted* 4 : 4′-*dicyano-αω-diphenoxyalkanes* (yields 55—65%) listed in Table I were prepared by the method described by Ashley *et al.* (*J.*, 1942, 103).

TABLE I.

Compound.	Solvent.	Crystalline form.	M. p.	Formula.	Found, %.	Required, %.
2′ : 2″-Difluoro-4′ : 4″-dicyano-1 : 3-diphenoxypropane	HOAc	Pale cream needles	209°	$C_{17}H_{12}O_2N_2F_2$	N, 8·9	9·0
2′-Bromo-4′ : 4″-dicyano-1 : 3-diphenoxypropane	,,	White needles	162—163	$C_{17}H_{13}O_2N_2Br$	N, 7·8 Br, 22·2	7·9 22·4
2′ : 2″-Dibromo-4′ : 4″-dicyano-1 : 3-diphenoxypropane	,,	Long white needles	194	$C_{17}H_{12}O_2N_2Br_2$	Br, 36·6	36·7
2′-Iodo-4′ : 4″-dicyano-1 : 3-diphenoxypropane	,,	Long white prismatic needles	164	$C_{17}H_{13}O_2N_2I$	I, 31·2	31·4
2′ : 2″-Di-iodo-4′ : 4″-dicyano-1 : 3-diphenoxypropane	,,	White needles	194	$C_{17}H_{13}O_2N_2I_2$	I, 47·6	47·9
2′ : 6′-Di-iodo-4′ : 4″-dicyano-1 : 3-diphenoxypropane	,,	White needles	153	$C_{17}H_{12}O_2N_2I_2$	N, 5·3 I, 47·8	5·3 47·9
2′-Nitro-4′ : 4″-dicyano-1 : 3-diphenoxypropane	50% HOAc	Pale yellow needles	152	$C_{17}H_{13}O_4N_3$	C, 63·0 H, 4·1 N, 13·0	63·2 4·0 13·0
2′ : 2″-Dichloro-4′ : 4″-dicyano-1 : 5-diphenoxypentane	HOAc	White prismatic needles	151	$C_{19}H_{16}O_2N_2Cl_2$	N, 7·5 Cl, 18·9	7·5 18·9
2′-Bromo-4′ : 4″-dicyano-1 : 5-diphenoxypentane	,,	White needles	112	$C_{19}H_{17}O_2N_2Br$	Br, 20·7	20·8
2′ : 2″-Dibromo-4′ : 4″-dicyano-1 : 5-diphenoxypentane	80% HOAc	Long white needles	137	$C_{19}H_{16}O_2N_2Br_2$	Br, 34·4	34·5
2′-Iodo-4′ : 4″-dicyano-1 : 5-diphenoxypentane	EtOH	White needles	100	$C_{19}H_{17}O_2N_2I$	N, 6·7 I, 29·3	6·5 29·4
2′ : 2″-Di-iodo-4′ : 4″-dicyano-1 : 5-diphenoxypentane	Dil. HOAc	White needles	137	$C_{19}H_{16}O_2N_2I_2$	N, 5·2 I, 44·8	5·0 45·5
4′ : 4″-Dicyano-2′ : 2″-dimethoxy-1 : 5-diphenoxypentane	EtOH	White leaflets	134	$C_{21}H_{22}O_4N_2$	C, 68·6 H, 5·6 N, 7·8	68·8 6·0 7·7
2′ : 2″-Dichloro-4′ : 4″-dicyano-1: 6-diphenoxyhexane	$CHCl_3$	White prisms	157—158	$C_{20}H_{18}O_2N_2Cl_2$	N, 7·1	7·2
2′-Iodo-4′ : 4″-dicyano-1 : 6-diphenoxyhexane	EtOH	Large white needles	124	$C_{20}H_{19}O_2N_2I$	N, 6·4 I, 28·2	6·3 28·2
2′ : 2″-Di-iodo-4′ : 4″-dicyano-1 : 6-diphenoxyhexane	HOAc	Large colourless plates	163	$C_{20}H_{18}O_2N_2I_2$	N, 5·0 I, 43·8	4·9 44·4
4′: 4″-Dibromo-2′ : 2″-dimethyl-1 : 6-diphenoxyhexane	$COMe_2$	Colourless plates	116—118	$C_{20}H_{24}O_2Br_2$	C, 52·5 H, 5·1 Br, 34·8	52·6 5·3 35·1

2′ : 2″-*Dinitro*-4′ : 4″-*dicyano*-1 : 5-*diphenoxypentane.*—4′ : 4″-Dicyano-1 : 5-diphenoxypentane (20 g.) was added to fuming nitric acid (65 c.c.), with ice-cooling, during 5 minutes. After standing at 0° for 10 minutes the solution was poured into ice-water (200 c.c.) and the precipitate was filtered off, washed with water, and crystallised (charcoal) from acetic acid. The *dinitro*-compound separated in creamy prisms (23·5 g.), m. p. 159°, identical with a sample prepared by the standard procedure (Found : C, 57·5; H, 4·1; N, 14·2. $C_{19}H_{16}O_6N_4$ requires C, 57·6; H, 4·0; N, 14·2%).

4′ : 4″-*Dibromo*-2′ : 2″-*dimethyl*-1 : 5-*diphenoxypentane*.—4-Bromo-*o*-cresol (Claus and Jackson, *J. pr. Chem.*, 1888, **38**, 324) was condensed with 1 : 5-dibromopentane by the standard procedure. The *product* crystallised in white needles from ethanol–benzene, m. p. 74° (Found : C, 51·8; H, 5·3; Br, 36·7. $C_{19}H_{22}O_2Br_2$ requires C, 51·6; H, 5·2; Br, 36·2%).

4′ : 4″-*Dicyano*-2′ : 2″-*dimethyl*-1 : 5-*diphenoxypentane*.—A mixture of 4′ : 4″-dibromo-2′ : 2″-dimethyl-1 : 5-diphenoxypentane (14·6 g.), cuprous cyanide (7·5 g.), and pyridine (12 c.c.) was heated at 195—205° for 5 hours. The cooled melt was crystallised from acetic acid and then from ethanol. The *product* separated in buff prisms from ethanol (8·2 g.), m. p. 142° (Found : C, 75·6; H, 6·7; N, 8·0. $C_{21}H_{22}O_2N_2$ requires C, 75·5; H, 6·6; N, 8·1%).

4′ : 4″-*Dicyano*-2′ : 2″-*dimethyl*-1 : 6-*diphenoxyhexane*.—4′ : 4″-Dibromo-2′ : 2″-dimethyl-1 : 6-diphenoxyhexane (4·5 g.), cuprous cyanide (2·2 g.), and dry quinoline (3 c.c.) were heated at 270° for ½ hour. The cooled melt was crystallised from acetic acid, and then from acetone–methanol. The *product* formed colourless nodules (1·7 g.), m. p. 143—144° (Found : C, 76·1; H, 7·0; N, 7·9. $C_{22}H_{24}O_2N_2$ requires C, 76·0; H, 6·9; N, 8·0%).

2-*Nitro*-4 : 4′-*dicyanodiphenyl Ether*.—Sodium 4-cyanophenoxide (2·2 g.), 4-bromo-3-nitrophenyl cyanide (3·4 g.) (Borsche, Stackmann, and Makaroff-Semljanski, *Ber.*, 1916, **49**, 2224), and ethanol (20 c.c.) were heated under reflux for 2·5 hours. The *ether* crystallised on cooling, and the large green crystals were filtered off, and washed with ethanol, water, and ethanol. It formed large pale yellow prisms from ethanol, m. p. 151° (Found : N, 15·8. $C_{14}H_7O_3N_3$ requires N, 15·8%).

2-*Amino*-4 : 4′-*dicyanodiphenyl Ether*.—(*a*) 2-Nitro-4 : 4′-dicyanodiphenyl ether (9·5 g.) in boiling acetic acid (100 c.c.) was carefully treated with a hot solution of stannous chloride (50 g.) in 2N-hydrochloric acid (50 c.c.). A vigorous reaction ensued and after addition was complete (0·25 hour) the solution was boiled for 5 minutes, cooled to 5—10°, and poured into excess of 50% aqueous sodium hydroxide at 10—15°. The *base* was filtered off, washed free from alkali, and dissolved in warm dilute hydrochloric acid (1 : 1). After treatment with charcoal, the solution was neutralised (Congo-red) with saturated sodium acetate, cooled in ice, and the white solid filtered off. It formed white needles from ethanol (4·1 g.), m. p. 160° (Found : N, 17·9 $C_{14}H_9ON_3$ requires N, 17·8%). In some experiments, a sparingly soluble *monoamide* was obtained, and was separated from the required compound by fractional crystallisation from ethanol. It crystallised in white rhombs from ethanol, m. p. 168—170° (Found : C, 61·4; H, 4·1; N, 15·6. $C_{14}H_{11}O_2N_3$ requires C, 61·5; H, 4·0; N, 15·4%).

(*b*) The boiling acetic acid solution, prepared as in (*a*), was carefully treated with reduced iron powder (9·5 g.), whereupon a vigorous reaction ensued. Water (10 c.c.) was added during the reaction, and after addition of iron was complete (20 minutes), the solution was boiled for 5 minutes, filtered, and poured into water (1 l.). The pink solid was filtered off, and treated as in (*a*). It formed white needles (6·2 g.) from ethanol, m. p. 160°.

2-*Chloro*-4 : 4′-*dicyanodiphenyl Ether*.—2-Amino-4 : 4′-dicyanodiphenyl ether (2·8 g.) was added to hydrochloric acid (*d* 1·16; 11 c.c.). The pasty hydrochloride was added, all at once, to a mixture of ice (15 g.) and sodium nitrite (1·1 g.) in water (3 c.c.). After a few minutes, the resulting solution was added dropwise to a mechanically stirred solution of cuprous chloride (2·3 g.) in hydrochloric acid (*d* 1·16; 8 c.c.) at 20—25°, and the mixture was then stirred at 90—95° for one hour. After cooling, the solid was filtered off, washed successively with water, 2N-sodium hydroxide, water, 2N-hydrochloric acid, and water, and dried. The dark brown solid (2·5 g.) was sublimed at 140—150°/0·05 mm. and yielded the *ether* in white needles, m. p. 116—117°. It formed colourless prismatic needles (1·8 g.) from methanol, m. p. 118° (Found : N, 11·2; Cl, 13·9. $C_{14}H_7ON_2Cl$ requires N, 11·0; Cl, 13·9%).

2-*Bromo*-4 : 4′-*dicyanodiphenyl Ether*.—This was prepared similarly to the chloro-derivative (sublimation temperature 200—210°/0·04 mm.). It crystallised in white rhombs from methanol, m. p. 124° (Found : N, 9·5; Br, 26·3. $C_{14}H_7ON_2Br$ requires N, 9·3; Br, 26·7%).

2-*Iodo*-4 : 4′-*dicyanodiphenyl Ether*.—2-Amino-4 : 4′-dicyanodiphenyl ether (6 g.) was added to 50% sulphuric acid (30 c.c.). The thick paste of sulphate was diluted with water (90 c.c.) and diazotised at 5—8° with sodium nitrite (9 g.) in water (30 c.c.). The mixture was treated at 5—10° with urea (9 g.) to remove excess of nitrous acid, and then with potassium iodide (6 g.) in water (60 c.c.). Next day the mixture was heated at 90° for 10 minutes, and the dark red solid collected. It was washed successively with water, 2N-sodium hydroxide, water, aqueous sodium thiosulphate, and water, and dried at 60°. The *ether* (6 g.) sublimed at 200—220°/0·1 mm., and crystallised in near-white rhombs from methanol (4·7 g.), m. p. 154° (Found : N, 8·1; I, 36·5. $C_{14}H_7ON_2I$ requires N, 8·1; I, 36·8%).

2 : 2′-*Dinitro*-4 : 4′-*dicyanodiphenyl Ether*.—4 : 4′-Dicyanodiphenyl ether (10 g.) was added to fuming nitric acid (100 c.c.) with stirring and, after 2 hours, the solution was poured on ice, and the precipitate collected by filtration and washed with water. The *ether* formed large yellow prisms (10 g.) from acetic acid, m. p. 192° (Found : C, 54·1; H, 1·9; N, 17·9. $C_{14}H_6O_5N_4$ requires C, 54·2; H, 1·9; N, 18·0%). Fission with piperidine gave 2-nitro-4-cyanophenol, m. p. 145°, and *N*-(2-nitro-4-cyanophenyl)piperidine, m. p. 111° (Borsche, Stackmann, and Makaroff-Semljanski, *loc. cit.*, give m. p. 110—111°).

2 : 2′-*Diamino*-4 : 4′-*dicyanodiphenyl Ether*.—2 : 2′-Dinitro-4 : 4′-dicyanodiphenyl ether was reduced with iron in acetic acid. The *diamino-ether* formed golden needles from ethanol, m. p. 223—225° (Found : N, 22·3. $C_{14}H_{10}ON_4$ requires N, 22·4%).

2 : 2′-*Di-iodo*-4 : 4′-*dicyanodiphenyl Ether*.—This was prepared similarly to the monoiodo-compound (sublimation temperature 245—255°/0·05 mm.). It crystallised in near-white rhombs from methanol, m. p. 178° (Found : N, 6·0; I, 54·0. $C_{14}H_6ON_2I_2$ requires N, 5·9; I, 53·8%).

4 : 4′ *Dicyano*-2-*methoxydiphenyl Ether*.—A mixture of potassium 4-cyanoguaicoxide (16 g.) (Marcus, *Ber.*, 1891, **24**, 3654), 4-bromophenyl cyanide (32 g.) (Borsche, Stackmann, and Makaroff-Semljanski, *loc. cit.*), and copper bronze (0·8 g.) was heated to 160°; an exothermic reaction occurred, the temperature rose to 200°, and the melt was heated for a further 3 hours at 160°. After cooling, the solid was ground with ether and water, and dried in a vacuum. The *ether* sublimed at 260—280°/0·05 mm. and crystallised from 50% aqueous acetic acid in colourless rectangular plates (6 g.), m. p. 125—126° (Found : C, 71·8; H, 3·8; N, 11·0. $C_{15}H_{10}O_2N_2$ requires C, 72·0; H, 4·0; N, 11·2%).

2-*Hydroxy*-4 : 4′-*dicyanodiphenyl Ether*.—4 : 4′-Dicyano-2-methoxydiphenyl ether (2 g.) was added

TABLE II.

Compound.	Solvent.	Crystalline form.	M. p.*	Formula.	Found, %.	Re-quired, %.
2′:2″-Difluoro-4′:4″-diamidino-1 : 3-diphenoxypropane disulphate	2N-H_2SO_4	White needles	256°	$C_{17}H_{18}O_2N_4F_2,2H_2SO_4$	C, 37·4 H, 3·2 N, 10·3	37·5 3·3 10·3
2′-Bromo-4′ : 4″-diamidino-1 : 3-diphenoxypropane dihydrochloride dihydrate	2N-HCl	White needles	237	$C_{17}H_{19}O_2N_4Br,2HCl,2H_2O$	N, 9·1 H_2O, 7·0	9·2 7·2
2′:2″-Dibromo-4′:4″-diamidino-1 : 3-diphenoxypropane dihydrochloride	0·5N-HCl	White needles	308—309	$C_{17}H_{18}O_2N_4Br_2,2HCl$	N, 10·4 Cl, 13·2	10·3 13·1
2′:2″-Dibromo-4′:4″-diamidino-1 : 3-diphenoxypropane di-isethionate	EtOH	Colourless prismatic needles	226 †	$C_{17}H_{18}O_2N_4Br,2C_2H_6O_4S$	N, 7·9 Br, 22·1	7·8 22·2
2′-Iodo-4′ : 4″-diamidino-1 : 3-diphenoxypropane dihydrochloride	2N-HCl	White prisms	274	$C_{17}H_{19}O_2N_4I,2HCl$	N, 10·8	10·9
2′-Iodo-4′ : 4″-diamidino-1 : 3-diphenoxypropane di-isethionate	EtOH	White prisms	150—152	$C_{17}H_{19}O_2N_4I,2C_2H_6O_4S$	N, 8·3 I, 18·0	8·1 18·3
2′ : 2″-Di-iodo-4′ : 4″-di-amidino-1 : 3-diphenoxypropane dihydrochloride	N-HCl	White prismatic needles	302	$C_{17}H_{18}O_2N_4I_2,2HCl$	N, 8·7	8·8
2′ : 6′-Di-iodo-4′ : 4″-diamidino-1 : 3-diphenoxypropane dihydrochloride dihydrate	0·5N-HCl–MeOH	White plates	195—196	$C_{17}H_{18}O_2N_4I_2,2HCl,2H_2O$	N, 8·2 H_2O, 5·5	8·3 5·4
2′-Nitro-4′ : 4″-diamidino-1 : 3-diphenoxypropane dihydrochloride monohydrate	2N-HCl	Pale yellow needles	240	$C_{17}H_{19}O_4N_5,2HCl,H_2O$	N, 15·7 H_2O, 3·8	15·7 4·0
2′:2″-Dichloro-4′:4″-diamidino-1 : 5-diphenoxypentane dihydrochloride	MeOH–$COMe_2$	White prisms	260°	$C_{19}H_{22}O_2N_4Cl_2,2HCl$	N, 11·5	11·6
2′-Bromo-4′ : 4″-diamidino-1 : 5-diphenoxypentane dihydrochloride	2N-HCl	White prisms	241	$C_{19}H_{23}O_2N_4Br,2HCl$	N, 11·4	11·4
2′:2″-Dibromo-4′:4″-diamidino-1 : 5-diphenoxypentane dihydrochloride	MeOH–HCl (*d* 1·16)	White prisms	264	$C_{19}H_{22}O_2N_4Br_2,2HCl$	N, 9·9	9·9
2′-Iodo-4′ : 4″-diamidino-1 : 5-diphenoxypentane dihydrochloride	H_2O	White prisms	253—254	$C_{19}H_{23}O_2N_4I,2HCl$	N, 10·6 Cl, 13·5	10·6 13·4
2′ : 2″-Di-iodo-4′ : 4″-di-amidino-1 : 5-diphenoxypentane dihydrochloride	N-HCl	White needles	276—277	$C_{19}H_{22}O_2N_4I_2,2HCl$	N, 8·2	8·3
2′ : 2″-Dinitro-4′ : 4″-diamidino-1 : 5-diphenoxypentane dihydrochloride monohydrate	MeOH–$COMe_2$	Yellow prisms	270	$C_{19}H_{22}O_6N_6,2HCl,H_2O$	N, 16·1 H_2O, 3·6	16·1 3·5
4′ : 4″-Diamidino-2′ : 2″-dimethoxy-1 : 5-diphenoxypentane dihydrochloride	2N-HCl	White prisms	251	$C_{21}H_{28}O_4N_4,2HCl$	N, 11·8 Cl, 15·2	11·9 15·0

* All with decomposition except those marked †.

TABLE II.—*continued.*

Compound.	Solvent.	Crystalline form.	M. p.*	Formula.	Found, %.	Required, %.
4′ : 4″-Diamidino-2′ : 2″-dimethyl-1 : 5-diphenoxypentane dihydrochloride	MeOH–COMe$_2$	White prisms	303—304	$C_{21}H_{28}O_2N_4,2HCl$	N, 12·8 Cl, 16·0	12·7 16·1
2′:2″-Dichloro-4′:4″-diamidino-1 : 6-diphenoxyhexane dihydrochloride hemihydrate	2N-HCl	White needles	274	$C_{20}H_{24}O_2N_4Cl_2,2HCl,\frac{1}{2}H_2O$	N, 11·1 Cl, 27·9	11·1 28·0
2′-Iodo-4′ : 4″-diamidino-1 : 6-diphenoxyhexane dihydrochloride	2N-HCl	Silver plates	242	$C_{20}H_{25}O_2N_4I,2HCl$	N, 9·9 I, 23·1	10·1 23·0
2′ : 2″-Di-iodo-4′ : 4″-diamidino-1 : 6-diphenoxyhexane dihydrochloride	0·1N-HCl	White needles	266	$C_{20}H_{24}O_2N_4I_2,2HCl$	N, 8·1 I, 37·2	8·3 37·4
4′ : 4″-Diamidino-2′ 2″-dimethyl-1 : 6-diphenoxyhexane dihydrochloride	2N-HCl	Buff plates	296—298	$C_{22}H_{30}O_2N_4,2HCl$	N, 12·2 Cl, 15·7	12·3 15·6
2-Chloro-4 : 4′-diamidinodiphenyl ether dihydrochloride monohydrate	6N-HCl	White needles	283—284	$C_{14}H_{13}ON_4Cl,2HCl,H_2O$	N, 15·3 Cl (ionised) 19·1 Cl, 28·4	15·1 19·0 28·0
2-Bromo-4 : 4′-diamidinodiphenyl ether dihydrochloride monohydrate	N-HCl	White prisms	210—211	$C_{14}H_{13}ON_4Br,2HCl,H_2O$	N, 13·3 Cl, 16·7	13·2 16·7
2-Iodo-4 : 4′-diamidinodiphenyl ether dihydrochloride	2N-HCl	White prismatic needles	254	$C_{14}H_{13}ON_4I,2HCl$	Cl, 15·6 N, 12·3	15·7 12·4
2 : 2′-Di-iodo-4 : 4′-diamidinodiphenyl ether dihydrochloride	N-HCl	White prisms	305—306 †	$C_{14}H_{12}ON_4I_2,2HCl$	N, 9·6 I, 43·8	9·7 43·9
2-Nitro-4 : 4′-diamidinodiphenyl ether dihydrochloride	H_2O	Yellow prisms	290	$C_{14}H_{13}O_3N_5,2HCl$	N, 18·8 Cl, 19·5	18·8 19·6
2-Amino-4 : 4′-diamidinodiphenyl ether dihydrochloride	2N-HCl	White prisms	264	$C_{14}H_{15}ON_5,2HCl$	N, 20·4 Cl, 21·1	20·5 21·3
2-Hydroxy-4 : 4′-diamidinodiphenyl ether dihydrochloride trihydrate	EtOH–HCl	White needles	259—260	$C_{14}H_{14}O_2N_4,2HCl,3H_2O$	N, 14·1 Cl, 17·6	14·1 17·8

to a solution of aluminium chloride (10 g.) in anhydrous nitrobenzene (50 c.c.). The mixture was stirred at 55° for 7 hours, and the cooled solution poured on ice. The nitrobenzene layer was separated, washed with water, and extracted twice with dilute sodium hydroxide. The alkaline solution was washed with chloroform and acidified with hydrochloric acid (*d* 1·16). The pink solid was filtered off and washed with water, the *ether* crystallising from 50% aqueous acetic acid in colourless plates (1 g.), m. p. 201° (Found : C, 71·2; H, 3·5; N, 12·1. $C_{14}H_8O_2N_2$ requires C, 71·2; H, 3·4; N, 11·9%).

The general procedure for the preparation of the *diamidines* was that used by Ashley *et al.* (*J.*, 1942, 103). In this way the products listed in Table II were obtained.

2′ : 2″-*Diamino*-4′ : 4″-*diamidino*-1 : 5-*diphenoxypentane*.—2′ : 2″-Dinitro-4′ : 4″-diamidino-1 : 5-diphenoxypentane dihydrochloride (6·5 g.) in warm water (70 c.c.) was rendered faintly alkaline to litmus with 15% aqueous ammonia (3·0 c.c.) and the solution was hydrogenated in presence of Raney nickel (1 g.) at 25—50° under 20 atm. Reduction was complete in 15 minutes and, after cooling and removal of the catalyst, the filtrate was concentrated under reduced pressure to 30 c.c., crystallisation then occurring. After addition of acetone the crystals were collected and crystallised from water. The *dihydrochloride dihydrate* separated in pale buff plates (2·8 g.), m. p. 247—248° (decomp.) (Found : N, 17·6; Cl, 14·8. $C_{19}H_{26}O_2N_6,2HCl,2H_2O$ requires N, 17·5; Cl, 14·9%).

Attempted Demethylation of 4′ : 4″-*Dicyano*-2′ : 2″-*dimethoxy*-1 : 5-*diphenoxypentane*.—(*a*) The dicyano-compound (2 g.) was added to a solution of aluminium chloride (20 g.) in anhydrous nitrobenzene (100 c.c.).

The mixture was stirred at 55° for 7 hours, solution then being nearly complete. The cooled mixture was filtered and poured on ice. The insoluble material (0·3 g.) was unchanged starting material. The nitrobenzene layer was separated, washed with brine, and extracted with dilute sodium hydroxide. The alkaline solution was washed with chloroform and acidified with hydrochloric acid (*d* 1·16). After saturation with sodium chloride, the solution was extracted with chloroform. The extract yielded 4-cyanocatechol (1 g.), white needles, m. p. 151—153°, identical with an authentic specimen.

(*b*) A mixture of the dicyano-compound (2 g.), and pyridine hydrochloride (12 g.) was heated at 180—190° for 5 hours, then poured into water (50 c.c.); some unchanged material (0·8 g.) separated. The filtrate when treated as in (*a*) gave 4-cyanocatechol (0·6 g.), m. p. 151—153°.

(*c*) Method (*b*) was repeated but with molecular proportions; unchanged material (1·6 g.) and 4-cyanocatechol (0·2 g.) were obtained.

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