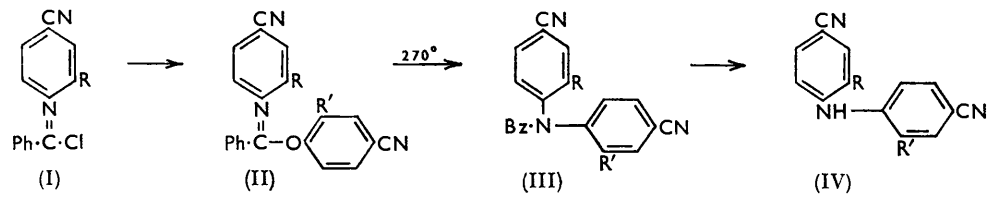
209. *The Search for Chemotherapeutic Amidines. Part XVIII.* Substituted 4,4′-Diamidinodiphenylamines.*

By A. P. T. Easson.

A series of 4,4′-diamidinodiphenylamines with substituents in the benzene rings and/or on the central amino-group is described. Most of the compounds are active against *Trypanosoma rhodesiense*, but the activity is less against *T. congolense*. The most active compound is 4,4′-diamidino-2-methoxydiphenylamine dihydrochloride with a therapeutic ratio (LD_{50}/CD_{50}) of 7·5 against the latter organism.

4,4′-Diamidinodiphenylamine,[1] one of the first aromatic diamidines to be synthesised, had only slight activity against *Trypanosoma congolense*. However, it was rather more active against *T. rhodesiense*.† Later [6] it was reported that nuclear substitution may have a marked effect on trypanocidal activity, so some substituted 4,4′-diamidinodiphenylamines have been synthesised; as a result, a few diamidines were obtained with therapeutic ratios of 4—7 against *T. congolense* but none was sufficiently active to justify further investigation.

Most of the substituted dinitriles needed for preparation of the diamidines were obtained from benzimidates by the Chapman rearrangement [7] as reported for the synthesis of the first member in this series;[1] but several modifications were introduced. Carbon tetrachloride as solvent replaced chlorobenzene in the preparation of the imidoyl chlorides (I). In the second stage the original mixture of solvents was at first used for all phenols except 4-hydroxy-3-nitrobenzonitrile whose sodium salt was insufficiently soluble in ethanol; in this instance pyridine gave satisfactory results. When pyridine was used with the other phenols or their sodium salts, the reaction time was shorter, but the yields of imidate (II) were smaller. The best results were obtained with triethylamine and the free phenols, in ether when a solvent was necessary: the reaction time was short and yields generally were much improved.



The imidates (II), with the exception of the nitro-compounds, rearranged to the benzoyldiphenylamines (III) in boiling biphenyl–diphenyl ether (cf. Chapman [7] and Wiberg and Rowland [8]). Removal of the benzoyl group to give the dicyanodiphenylamines (IV) was usually accomplished by hydrolysis with sodium hydroxide in ethylene glycol.

* Part XVII, Berg, *J.*, 1960, 5172.

† 4,4′-Diamidinodiphenylamine dihydrochloride (M & B 938) is of use in the preparation of selective media for *Haemophilus pertussis*;[2] it has also given encouraging results in the treatment of myelomatosis,[3] blastomycosis,[4] and histoplasmosis.[5]

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

[2] Lacey, *J. Gen. Microbiol.*, 1951, **5**, 6; *J. Hygiene*, 1954, **52**, 273. Nicholson and Turner, *J. Gen. Microbiol.*, 1954, **10**, 1.

[3] Ward, *Lancet*, 1958, *i*, 536; *J. Fac. Radiol.*, 1958, **9**, 221.

[4] Borelli and Rodriguez, *Trans. Roy. Soc. Trop. Med. Hyg.*, 1958, **52**, 289.

[5] Mackinnon and Stapff, *Trans. Roy. Soc. Trop. Med. Hyg.*, 1958, **52**, 290.

[6] Ashley and Harris, *J.*, 1946, 567; Berg and Newbery, *J.*, 1949, 642.

[7] Chapman, *J.*, 1925, **127**, 1992.

[8] Wiberg and Rowland, *J. Amer. Chem. Soc.*, 1955, **77**, 2205.

2,2′-Dichloro-4,4′-dicyanodiphenylamine was prepared by chlorination of 4,4′-dicyanodiphenylamine, nitration of which gave 4,4′-dicyano-2-nitro- and thence 2-amino-4,4′-dicyano-diphenylamine. Demethylation of 4,4′-dicyano-2-methoxydiphenylamine afforded the 2-hydroxy-compound, whence alkylation yielded the other alkoxy-derivatives.

Several 4,4′-dicyanodiphenylamines containing a substituent on the central nitrogen atom were prepared. For aliphatic substituent groups, alkylation was effected with an alkyl toluene-*p*-sulphonate. *NNN′N′*-Tetra-*p*-cyanophenyl-1,3-diaminopropane was prepared by this method from 4,4′-dicyanodiphenylamine and trimethylene ditoluene-*p*-sulphonate. For aryl substituents an Ullmann reaction was carried out.

Three 4,4′-dicyanodiphenylamines with substituents in the 2- or 2,2′-positions and also on the central nitrogen atom were prepared.

4,4′-Dicyanodiphenylamine reacted only very slowly with ethyl chloroformate in presence of potassium carbonate in boiling acetone, and a pure product was not obtained. Neither 4,4′-dicyano-2-methyl- nor 4,4′-dicyano-2-methoxy-diphenylamine formed an ethoxycarbonyl derivative. Although 4,4′-dicyano-2-nitrodiphenylamine did not react with methyl toluene-*p*-sulphonate, it readily gave the *N*-ethoxycarbonyl compound when treated with ethyl chloroformate. 4,4′-Dicyano-2-hydroxydiphenylamine gave a quantitative yield of 4,4′-dicyano-*N*-ethoxycarbonyl-2-ethoxycarbonyloxydiphenylamine, but, with an excess of the dinitrile, 6-cyano-3-*p*-cyanophenylbenzoxazolone was formed, which was best prepared by semihydrolysis of the above bisethoxycarbonyl compound. This gave an intermediate monoethoxycarbonyl derivative, which suffered ring closure, even at temperatures below its m. p., with formation of the benzoxazolone.

N-Nitroso-dinitriles could not be prepared but the diamidines were readily nitrosated. 4,4′-Diamidinodiphenylamine dihydrochloride and its 2-methyl and 2-methoxy-derivatives afforded the corresponding diamidinodiphenyl-nitrosamines. These were separated from the reaction mixtures by precipitation of the bases or the sparingly soluble disulphates, and were isolated as dihydrochlorides or diacetates, all of which were stable except the dihydrochloride of 4,4′-diamidino-*N*-nitrosodiphenylamine.

Three other heterocyclic compounds derived from diphenylamine were prepared. Interaction of 2-amino-4,4′-dicyanodiphenylamine with formic acid gave 5-cyano-*p*-cyanophenylbenzimidazole. The corresponding 2-methylimidazole was made by boiling 2-acetamido-4,4′-dicyanodiphenylamine in biphenyl–diphenyl ether, whilst diazotisation of 2-amino-4,4′-dicyanodiphenylamine afforded 5-cyano-1-*p*-cyanophenylbenzo-1,2,3-triazole.

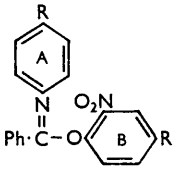
Rearrangement of the isomeric nitrobenzimidates (V and VI; R = H) was studied by Chapman.[9] The isomer (V; R = H) was smoothly converted into *N*-benzoyl-2-nitrodiphenylamine at a temperature much lower than that generally required for the reaction, but the isomer (VI; R = H) could not be rearranged. In the present work similar results were obtained when the rings A and B each contained a *p*-cyano-group; the compound (V; R = CN) was easily converted into the diphenylamine (VII) whereas the imidates (VI; R = CN) and the A,B-dinitro-analogue did not undergo rearrangement. Any explanation of the Chapman rearrangement, particularly with reference to these results with nitro-compounds, is difficult from the point of view of a mechanism involving free radicals. A mechanism which required ring closure and opening in the case of the nitro-compound (V; R = CN) would give a product isomeric with that obtained by nitration of 4,4′-dicyanodiphenylamine, whereas the same product is obtained from both reactions.

Although *N*-benzoyl-4,4′-dicyano-2-nitrodiphenylamine (VII) was readily obtained it was difficult to isolate a pure product after acid or alkaline hydrolysis. The compound was readily reduced with iron and acetic acid to 2-benzamido-4,4′-dicyanodiphenylamine (the benzoyl group must have migrated from the central nitrogen atom to the newly formed amino-group), and a pure product was not obtained after attempts to remove the benzoyl group. But 4,4′-dicyanodiphenylamine was readily nitrated and the product reduced to

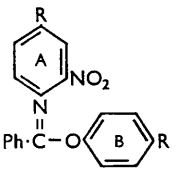
[9] Chapman, *J.*, 1927, 1745.

the required 2-amino-4,4′-dicyanodiphenylamine. Benzoyl chloride in pyridine converted this into 2-benzamido-4,4′-dicyanodiphenylamine (there are no known instances of benzoylation of the diphenylamine NH group under these conditions) which was identical with the product obtained by reduction of *N*-benzoyl-4,4′-dicyano-2-nitrodiphenylamine with iron in acetic acid.

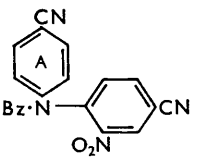
The dinitriles were usually sufficiently soluble in ethanol–chloroform and/or dioxan to afford the diethyl di-imidate dihydrochlorides smoothly, rapidly, and in theoretical



(V)



(VI)



(VII)

yield when the solutions or suspensions were treated with hydrogen chloride. *NNN′N′*-Tetra-*p*-cyanophenyl-1,3-diaminopropane readily gave the tetraimidate, but tri-*p*-cyanophenylamine, owing to its sparing solubility, did not react. Two of the fusion methods [10,11] for the direct conversion of nitriles into amidines gave only very poor yields of the required triamidine, but an almost theoretical yield of tri-imidate trihydrochloride was obtained by using very finely powdered trinitrile and 2-ethoxyethanol in chloroform–dioxan. The imidate hydrochlorides were readily converted by ethanolic ammonia into the amidine hydrochlorides, which usually crystallised as hydrates. In a few cases the amidines were more readily crystallised as acetates; these were generally anhydrous.

Unsuccessful attempts were made to reduce the diamidino-nitrosamines to asymmetrical hydrazines with hydrazine [12] and with zinc and acetic acid.[13] Diphenylnitrosamine itself with zinc and acetic acid gave about 30% of diphenylhydrazine and 60% of diphenylamine.

Most of the starting materials and intermediates were prepared by standard methods, but some modifications and alternative routes are described in the Experimental section.

Experimental

4-Hydroxy-3-methylbenzonitrile [14] was first prepared from 4-hydroxy-3-methylbenzaldehyde, but was more readily made from *o*-cresol.[15]

2-Chloro-4-cyanophenol was made as described by Berg and Newbery; [6] very vigorous stirring is needed to obtain a good yield.

4-Hydroxy-3-nitrobenzonitrile [16] was obtained by nitration of *p*-hydroxybenzonitrile with a 10% solution of nitric acid in acetic acid.

N-Benzoyl-4-cyano-2-methylaniline.—This *anilide*, prepared (75%) by treatment of 4-amino-3-methylbenzonitrile [14] (obtained from 4-bromo-2-methylacetanilide by means of cuprous cyanide in pyridine) in pyridine with benzoyl chloride, had m. p. 153° (from ethanol) (Found: N, 11·6. $C_{22}H_{15}N_3O$ requires N, 11·85%) and appeared to be dimorphous; it remelted, after fusion and solidification, at 138°.

N-Benzoyl-4-cyano-2-nitroaniline, obtained similarly, had m. p. 144—146° (from ethanol).

Benzimidates.—The *N*-benzoyl-*p*-cyanoaniline (1 mol.), phosphorus pentachloride (0·98 mol.), and carbon tetrachloride (*ca.* 4 mol.) were heated under reflux. At the end of the reaction, the solvent and phosphoryl chloride were removed *in vacuo*. The residual imidoyl

[10] Oxley, Partridge, and Short, *J.*, 1948, 303; Partridge and Short, *J.*, 1947, 390.
[11] Peyron and Peyron, *Bull. Soc. chim. France*, 1953, **20**, 846.
[12] von Rothenburg, *Ber.*, 1893, **26**, 2060.
[13] Fischer, *Annalen*, 1878, **190**, 175.
[14] Paschen, *Ber.*, 1891, **24**, 3673.
[15] Ashley and MacDonald, *J.*, 1957, 1668.
[16] Auwers and Röhrig, *Ber.*, 1897, **30**, 997.

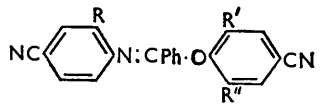
chlorides were solids (usually with low m. p.); they were readily hydrolysed by atmospheric moisture, and were not purified or characterised further. They were condensed with various *p*-hydroxybenzonitriles by one of the following processes:

(*A*) *p*-Hydroxybenzonitrile (1·1 mol.) was added to sodium ethoxide (1 mol.) in ethanol which was stirred and cooled in ice. The benzimidoyl chloride (1 mol.) in ether–chloroform was added in one portion, with stirring and cooling, followed by anhydrous sodium carbonate (0·25 mol.). The mixture was stirred at 0° for 1—2 hr. and then at room temperature for 3—4 hr. Next day the solid was filtered off and washed with water. Most of the benzimidate was usually present in this solid, but sometimes more remained in the ether–chloroform–alcohol filtrate. The products were generally recrystallised from alcohol.

(*B*) The dry sodium salt of the *p*-hydroxybenzonitrile (1 mol.) in dry pyridine was mixed with the molten benzimidoyl chloride (but the 3-nitro-chloride was first dissolved in pyridine). The mixture was heated on the steam-bath for a few min. Water was then added, and the oily precipitate which soon crystallised was filtered off and recrystallised.

(*C*) The *p*-hydroxybenzonitrile (1 mol.) and the benzimidoyl chloride were melted together. (If crystallisation occurred when the melt was cooled to about 80°, the solid was dissolved when cool, by adding a solvent, usually ether, but dioxan was used for the less soluble substances.) Anhydrous triethylamine (1·5 mol.) was then added, ether, if present, was evaporated, and the mixture refluxed for 2 hr. Water and a slight excess of acetic acid were then added and the benzimidates generally separated as oils which soon crystallised. They were usually recrystallised from alcohol and are recorded in Table 1.

TABLE 1. *Benzimidates.*



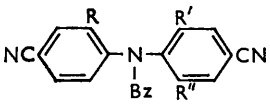
R	R′	R″	Process	Yield (%)	M. p.	Formula	Found N (%)	Reqd. N (%)
H	Me	H	A	63	142·5°	$C_{22}H_{15}N_3O$	12·25	12·5
H	Me	H	B	39	136—138	—	—	—
H	Me	H	C[a]	76	140—141	—	—	—
Me	H	H	A	45	104·5	$C_{22}H_{15}N_3O$	12·4	12·5
Me	H	H	B	—	102—104	—	—	—
Me	Me	H	A	79[b]	125—129	—	—	—
Me	Me	H	B	58[b]	123—126	—	—	—
Me	Me	H	C	83[b]	125—127	—	—	—
H	Cl	H	A[d]	25[b]	135—136	$C_{21}H_{12}ClN_3O$	11·5	11·7
Me	Cl	H	A[d]	36[b]	124	$C_{22}H_{14}ClN_3O$	11·3	11·3
H	Cl	Cl	A[d]	24[b]	167—168	$C_{21}H_{11}Cl_2N_3O$	10·8	10·7
H	NO_2	H	A[d]	47[b]	136	$C_{21}H_{12}N_4O_3$	15·1	15·2
H	NO_2	H	B	69[b]	135—136	—	—	—
H	NO_2	H	C[e]	64	134—136	—	—	—
NO_2	H	H	A	78[b]	192	$C_{21}H_{12}N_4O_3$	15·2	15·2
NO_2	NO_2	H	B	96[b]	198	$C_{21}H_{11}N_5O_5$	17·0	16·9
H	OMe	H	C	60	147—148	$C_{22}H_{15}N_3O_2$	11·95	11·9

[a] Et_2O as solvent. [b] Crude yield. [c] Product difficult to purify; the crude material was used in the Chapman rearrangement. [d] Methods B and C were not tried. [e] Dioxan as solvent. [f] The intermediate N-(*4-cyano-2-nitrophenyl*)*benzimidoyl chloride* suffered practically no decomposition when crystallised from ethanol (m. p. 142°) (Found: N, 14·9. $C_{14}H_8ClN_3O_2$ requires N, 14·7%). Ley (*Ber.*, 1898, **31**, 242) reported that *N*-(*o*-nitrophenyl)benzimidoyl chloride was less rapidly decomposed by alcohol than other imidoyl chlorides.

Rearrangement of the Benzimidates to Benzoyldiphenylamines.—Except in three cases (R = R″ = H, R′ = NO_2; R = NO_2, R′ = R″ = H; and R = R′ = NO_2, R″ = H) (Table 1), the benzimidates were dissolved in an approximately equal weight of Dowtherm (a mixture of biphenyl and diphenyl ether) and the solution was boiled for 1—2 hr. The benzoyl compounds (isolated by addition of ether) were crystallised from ethanol and are recorded in Table 2. The benzoyl derivative (R′ = R″ = H, R = Me) was not characterised but was hydrolysed directly to the corresponding diphenylamine (Table 3). One benzimidate (R = R″ = H, R′ = NO_2) rearranged smoothly in boiling anisole and even in boiling pyridine, tars being formed at higher temperatures. Two benzimidates (R = NO_2, R′ = R″ = H; R = R′ = NO_2, R″ = H) were unaffected at the lower temperatures and decomposed at 200°.

2(or 2,2′)-*Substituted* 4,4′-*Dicyanodiphenylamines* (Table 3).—Compounds 1—5 were prepared by hydrolysis of the corresponding *N*-benzoyl derivatives. A 10% solution of sodium hydroxide (1 mol.) in 75% ethylene glycol was added, in one portion, to the benzoyl compound dissolved in boiling ethylene glycol (3—4 parts). The mixture was boiled for a few min. and the product was precipitated by water and recrystallised from acetic acid.

TABLE 2. *Benzoyldiphenylamines.*



R	R′	R″	Yield (%)	M. p.	Formula	Found N (%)	Reqd. N (%)
H	Me	H	94	165—167° [a]	$C_{22}H_{15}N_3O$	12·8	12·5
Me	Me	H	98	159—160 [b]	$C_{23}H_{17}N_3O$	12·15	11·95
H	Cl	H	84	170—172	$C_{21}H_{22}ClN_3O$	11·9	11·8
Me	Cl	H	80	167—168	$C_{22}H_{14}ClN_3O$	11·6	11·3
H	Cl	Cl	54	204—205	$C_{21}H_{11}Cl_2N_3O$	10·55	10·7
H	NO_2	H	99	234—237	$C_{21}H_{12}N_4O_3$	15·4	15·2
H	OMe	H	88	152—154	$C_{22}H_{15}N_3O_2$	12·2	11·9

[a] This product was dimorphous; another form, m. p. 172·5°, was usually, but not always, obtained by crystallisation from the reaction mixture. This compound was prepared from both the isomeric benzimidates, R = R″ = H, R′ = Me, and R′ = R″ = H, R = Me, of Table 1. The rearrangement also occurred in absence of a solvent at 270°. [b] This product was dimorphous; a form with m. p. 132—133° was obtained by crystallisation from acetic acid or by solidification of the melt from the higher-melting form.

TABLE 3. *Ring-substituted* 4,4′-*dicyanodiphenylamines* (IV).

No.	R	R′	Yield (%)	M. p.	Formula	Found N (%)	Reqd. N (%)
1	Me	H	85	222°	$C_{15}H_{11}N_3$	17·9	18·0
2	Cl	H	60	211 [a]	$C_{14}H_8ClN_3$	16·25	16·6
3	Me	Me	38	199—200	$C_{16}H_{13}N_3$	16·6	17·0
4	Me	Cl	73 [b]	198	$C_{15}H_{10}ClN_3$	15·85	15·7
5	OMe	H	86	145—146	$C_{15}H_{11}N_3O$	16·85 [c]	16·9
6A [d]	NO_2	H	—	186—191	—	—	—
6B [e]	NO_2	H	95	191	$C_{14}H_8N_4O_2$	21·2	21·2
7	NH_2	H	83	238—239	$C_{14}H_{10}N_4$	23·7	23·9
8	NHAc	H	75 [g]	238—240 [f]	—	—	—
9	NHBz	H	—	233—235 [f]	$C_{21}H_{14}N_4O$ [h]	16·3	16·5
10	Cl	Cl	— [i]	243—244	$C_{14}H_7Cl_2N_3$	15·2	14·6
11	OH	H	55	257—258	$C_{14}H_9N_3O$	18·1 [c]	17·9
12	OEt	H	76	169—170	$C_{16}H_{13}N_3O$	16·3 [c]	16·0
13	OPr^n	H	73	135—136 [j]	$C_{17}H_{15}N_3O$	15·1 [c]	15·2
14	$O{\cdot}CH_2{\cdot}CH{:}CH_2$	H	70	135—136	$C_{17}H_{13}N_3O$	15·3 [c]	15·3
15	OBu^n	H	80	114—115	$C_{18}H_{17}N_3O$	14·6 [c]	14·4

[a] Dimorphous; resolidified melt remelted at 182°. [b] This, the best yield, was obtained by slow addition of the sodium hydroxide solution (1·15 mol.) to the benzoyl compound in boiling ethylene glycol. [c] In many instances the Dumas method gave consistently low results with diphenylamine derivatives containing an oxygen atom in the 2-position, but the Kjeldahl method was satisfactory. [d] Product formed by the Chapman rearrangement. [e] Product formed by nitration of 4,4′-dicyanodiphenylamine. Decomp. [g] By acetylation of the amino-compound (no. 7) with acetic anhydride in pyridine. [h] By reduction of *N*-benzoyl-4,4′-dicyano-2-nitrodiphenylamine (Table 2) with iron and acetic acid, or by benzoylation of the amino-compound (no. 7) in pyridine. The product was crystallised from aqueous dioxan (Found: C, 74·3; H, 4·4. Required: C, 74·5; H, 4·2%). [i] 4,4′-Dicyanodiphenylamine, partly dissolved in warm acetic acid, was treated with chlorine until a permanent excess remained. The product was crystallised successively from acetic acid, dioxan, and ethanol, but a pure sample was not obtained. [j] Mixed m. p. with no. 14 was 124—128°.

Compound no. 6A was prepared by hydrolysis of the corresponding *N*-benzoyl derivative with potassium carbonate in ethylene glycol–anisole containing a little water. The product resisted purification but an almost theoretical yield of pure nitro-compound (no. 6B) was obtained as follows: 4,4′-Dicyanodiphenylamine (40 g.) was ground with acetic acid (200 ml.), and concentrated nitric acid (400 ml.) was added. The mixture was stirred and the temperature kept below 26°. The product began to separate in *ca.* 15 min. and after a total time of 25 min. water was added, and the 4,4′-*dicyano*-2-*nitrodiphenylamine* was isolated and crystallised from anisole.

2-Amino-4,4′-dicyanodiphenylamine (Table 3, no. 7).—Reduced iron (45 g.) was gradually added to 4,4′-dicyano-2-nitrodiphenylamine (24 g.) in boiling dimethylformamide (60 ml.) and acetic acid (40 ml.). A few drops of water were added during the reduction and the mixture was heated to maintain the reaction. After 30 min. at the b. p. hot water (400 ml.) was added gradually, and the hot mixture was filtered. The solid and filtrate were worked up separately to give the amine (83%) which crystallised from anisole.

Compounds prepared from 4,4′-Dicyano-2-methoxydiphenylamine (Table 3, nos. 12—15).—Demethylation of 4,4′-dicyano-2-methoxydiphenylamine by Prey's method [17] gave the 2-hydroxy-derivative. At the required temperature (197—203°), part of the reaction mixture (1 mol. of methoxy-compound and 1·5 mol. of anhydrous pyridine hydrochloride) tended to sublime. A little Dowtherm or quinoline was added, which dissolved the sublimate, and returned it to the reaction mixture. After 4 hr. the cooled mixture was stirred with aqueous alcohol, and the solid was dissolved in a mixture of dimethylformamide and dioxan. Any methoxy-compound was precipitated by an excess of cold 5N-sodium hydroxide and acidification of the filtrate gave the 2-hydroxy-derivative (55%) which was recrystallised from acetic acid. The other 2-alkoxy-compounds were obtained by alkylation of this with the appropriate halides (ethyl and butyl iodides; propyl and allyl bromides) and potassium carbonate in boiling acetone; they were crystallised from ethanol.

*Alkyl Toluene-*p*-sulphonates.*—1,3-Trimethylene ditoluene-*p*-sulphonate (86%), m. p. 95—96°, *1,5-pentamethylene ditoluene-*p*-sulphonate* (85%), m. p. 80% (from ethanol) (Found: S, 15·9. $C_{19}H_{24}O_6S_2$ requires S, 15·5%), and 2-hydroxyethyl toluene-*p*-sulphonate, a syrup [*phenylurethane* (from ethanol), m. p. 135—136° (Found: N, 4·25. $C_{16}H_{17}NO_5S$ requires N, 4·2%)], were prepared by the silver salt method.[18]

Preparation of 4,4′-Dicyanodiphenylamines Substituted on the Central Nitrogen Atom (Table 4).—N-*Alkyl derivatives.* 4,4′-Dicyanodiphenylamine (1 mol.), with the requisite alkyl toluene-*p*-sulphonate (1·2—1·5 mol.), potassium carbonate (1 mol.), anisole, and a trace of copper bronze were boiled under reflux. The water formed in the reaction was distilled off and replaced by anisole. After the resulting solution had been refluxed for 3—4 hr. ether or chloroform was added and the mixture was filtered. The solvent was evaporated and the anisole removed *in vacuo*. The residue was washed with light petroleum (b. p. 40—60°) and recrystallised from ethanol.

TABLE 4. N-*Substituted 4,4′-dicyanodiphenylamines.*

N-Subst.	Crystd. from	Yield (%)	M. p.	Formula	Found N (%)	Reqd. N (%)
Me	EtOH	89	153°	$C_{15}H_{11}N_3$ [a]	17·9	18·0
Et	EtOH	55	122—123	$C_{16}H_{13}N_3$ [b]	16·5	17·0
Pr^n	EtOH	63	96	$C_{17}H_{15}N_3$	16·0	16·1
Allyl	EtOH	71	111—112	$C_{17}H_{13}N_3$	15·9	16·2
Bu^n	Et_2O	41 [c]	80—81	$C_{18}H_{17}N_3$	15·15	15·3
n-C_6H_{13}	EtOH	60	77	$C_{20}H_{21}N_3$	13·8	13·85
$[CH_2]_3$ [d]	Dioxan	50	211—212	$C_{31}H_{22}N_6$	17·7	17·6
Ph	EtOH	78	190—191	$C_{20}H_{13}N_3$	13·9	14·25
p-NO_2·C_6H_4	Ph·NO_2	80	346	$C_{20}H_{12}N_4O_2$	16·5	16·45
p-NH_2·C_6H_4	—	73	275	— [e]	—	—
p-NC·C_6H_4	H·CO·NMe_2	57	342	$C_{21}H_{12}N_4$ [f]	17·6	17·5

[a] The alkyl group was labile and was determined by the Zeisel method (Found: "OMe," 13·3. Required: "OMe," 13·3%). [b] The alkyl group was labile (Found: "OEt," 18·0. Required: "OEt," 18·2%). [c] 1·2 mol. of K_2CO_3 used. [d] The compound is *NNN′N′*-tetra-*p*-cyanophenyl-1,3-diaminopropane. [e] The *acetyl derivative*, m. p. 206—207°, crystallised from aq.EtOH (Found: N, 15·8. $C_{22}H_{16}N_4O$ requires N, 15·9%). [f] Found: C, 78·6; H, 3·9. Required: C, 78·8; H, 3·8%.

N-*Aryl derivatives.* 4,4′-Dicyanodiphenylamine (1 mol.), in presence of potassium carbonate (1 mol.) and a trace of copper bronze, was treated in boiling nitrobenzene for 4—6 hr. with an excess of (*a*) iodobenzene, (*b*) *p*-bromonitrobenzene, or (*c*) *p*-bromobenzonitrile. The products from (*a*) and (*b*) were isolated by addition of chloroform and evaporation of the solvents after treatment with charcoal. The solid from (*c*) was filtered off when cold, and washed with ether, and then with water. The dried solid was extracted with hot dimethylformamide to give the product.

[17] Prey, *Ber.*, 1941, **74**, 1219.
[18] Emmons and Ferris, *J. Amer. Chem. Soc.*, 1953, **75**, 2257.

N-p-*Aminophenyl*-4,4′-*dicyanodiphenylamine*.—4,4′-Dicyano-*N*-*p*-nitrophenyldiphenylamine (1·7 g.), dissolved in boiling dimethylformamide (15 ml.) and acetic acid (2·5 ml.), was treated with reduced iron (2·5 g.) in about five portions, two drops of water being added with each. When reduction was complete the mixture was cooled and treated with water and 5N-sodium hydroxide, and the solid filtered off. Extraction with boiling dioxan, and careful addition of water to the extract, gave the amine (1·25 g.) (see Table 4).

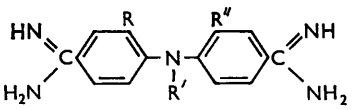
4,4′-*Dicyano*-2-*methoxy*-N-*methyldiphenylamine*.—A mixture of 4,4′-dicyano-2-methoxydiphenylamine (1 g.), methyl toluene-*p*-sulphonate (1 g.), potassium carbonate (0·8 g.), copper bronze (trace), and anisole (10 ml.) was refluxed for 3 hr. After addition of water, the anisole layer was separated, dried, and evaporated. The N-*methyl derivative* (0·95 g.), m. p. 149—150°, crystallised from ethanol (Found: N, 16·0. $C_{16}H_{13}N_3O$ requires N, 16·0%). A mixed m. p. with the starting material (m. p. 145—146°) was depressed below 135°.

4,4′-*Dicyano*-2,N-*dimethyldiphenylamine*.—This *compound*, prepared (94%) from 4,4′-dicyano-2-methyldiphenylamine and methyl toluene-*p*-sulphonate, had m. p. 112° (from ethanol) (Found: N, 16·7; NMe, 11·35. $C_{16}H_{13}N_3$ requires N, 17·0; NMe, 11·7%).

5-*Cyano*-1-p-*cyanophenylbenzimidazole*.—This *imidazole* was obtained in theoretical yield by boiling 2-amino-4,4′-dicyanodiphenylamine (5 g.) in 98—100% formic acid (25 ml.) for 1·5 hr. After crystallisation from acetic acid it had m. p. 289° (Found: N, 22·6. $C_{15}H_8N_4$ requires N, 22·95%).

5-*Cyano*-1-p-*cyanophenyl*-2-*methylbenzimidazole*.—A mixture of 2-amino-4,4′-dicyanodiphenylamine (12·5 g.), pyridine (50 ml.), and acetic anhydride (30 ml.) was boiled for 0·5 min. Addition of water gave the 2-acetamido-derivative (12·0 g.), m. p. 238—240° (decomp.), converted in boiling Dowtherm (40 ml.) in 1·5—2 hr. into the *imidazole* (8·4 g., 76%), m. p. 233° (from dioxan) (Found: N, 21·6. $C_{16}H_{10}N_4$ requires N, 21·7%).

TABLE 5. *Diamidines.*



No.	R	R′	R″	Prep. of imidate: Solvent	Time (days)	Amidine salt	Crystn. solvent	Yield (%)	M. p.
1	Me	H	H	$CHCl_3$	4	2HCl	H_2O	94	—
2	H	Me	H	,,	2	,,	Aq.EtOH & Et_2O	63	330° [a]
3	H	Et	H	EtOH	1	,,	,,	57	— >300
4	Cl	H	H	$CHCl_3$	3	,,	H_2O	38	>300
5	H	Ph	H	$CHCl_3$–dioxan	6	,,	Aq.$COMe_2$	70	>300
6	H	Bz	H	$CHCl_3$	12	,,	,,	31	280 [a]
7	Me	Me	H	,,	7	,,	Aq.$COMe_2$–EtOH	47	285 [a]
8	H	Bu^n	H	,,	4	Diacetate	Aq.$COMe_2$	63	275—280
9	H	Allyl	H	,,	5	,,	H_2O or Aq.$COMe_2$	67	271—273 [a]
10	H	Pr^n	H	$CHCl_3$–Et_2O	1	2HCl	Aq.$COMe_2$	78	232—238
11	H	*p*-C_6H_4·C(:NH)·NH_2	H	$CHCl_3$–dioxan [g]	10	3HCl	,,	50	370—375
12	NH_2	H	H	EtOH	6	2HCl	H_2O	54	310 [a]
13	H	$[CH_2]_3$ [i]	H	,,	2	4HCl	Aq.$COMe_2$	67	300—310 [a]
14	H	*p*-C_6H_4·NH_2	H	,,	6	Diacetate	,,	37	169 [a]
15	Me	Bz	Cl	,,	1	,,	AcOH	—	225—230 [a]
16	Me	H	Cl	Dioxan	2	2HCl	H_2O	70	>350
17	H	n-C_6H_{13}	H	$CHCl_3$–Et_2O	6	Diacetate	Aq.$COMe_2$	63	265 [a]
18	Cl	H	Cl	,,	4	2HCl	40% EtOH	90	>350
19	Me	H	Me	Dioxan	5	,,	Aq.$COMe_2$	75	>350
20	OMe	H	H	$CHCl_3$	3	,,	,,	64	110—115 [j]
21	OH	H	H	Dioxan–Et_2O	4	,,	,,	54	338—340 [a]
22	OEt	H	H	$CHCl_3$	6	,,	,,	85	115—117 [j]
23	OBu^n	H	H	,,	1	,,	,,	85	133—134 [j]
24	OAllyl	H	H	,,	3	,,	,,	79	108—110 [j]
25	OPr^n	H	H	,,	2	,,	,,	78	125—128 [j]
26	H	NO	H	—	—	,,	,,	88	>300
27	OMe	Me	H	$CHCl_3$	2	Dipropionate	,,	44	193—201
28	OMe	NO	H	,,	—	Diacetate	,,	69	192—193
29	Me	NO	H	,,	—	,,	,,	93	227—228 [a]

TABLE 5. (*Continued.*)

No.	Formula	Found (%) N	Cl	Loss	Required (%) N	Cl	H_2O
1	$C_{15}H_{17}N_5,2HCl,3H_2O$	17·8	17·8	13·1	17·8	18·0	13·7
2	$C_{15}H_{17}N_5,2HCl,H_2O$	19·4	19·9	[b]	19·6	19·8	
3	$C_{16}H_{19}N_5,2HCl$	19·6	20·1	[c]	19·8	20·1	
4	$C_{14}H_{14}ClN_5,2HCl,3H_2O$	17·1	[d]	11·1	16·9		10·9
5	$C_{20}H_{19}N_5,2HCl,2H_2O$	15·9	16·2	8·35	16·0	16·2	8·25
6	$C_{21}H_{19}N_5O,2HCl,4H_2O$	13·65	14·25	15·0 [e]	13·9	14·2	14·5
7	$C_{16}H_{19}N_5,2HCl,3H_2O$	17·3			17·2		
8	$C_{18}H_{23}N_5,2C_2H_4O_2$	16·2			16·3		
9	$C_{17}H_{19}N_5,2C_2H_4O_2$	16·8			16·9		
10	$C_{17}H_{21}N_5,2HCl,2H_2O$	17·3	17·2	4·6 [f]	17·3	17·6	4·7
11	$C_{21}H_{21}N_7,3HCl,4H_2O$	17·8		12·7	17·8		13·0
12	$C_4H_{16}N_6,2HCl,3H_2O$	21·3		11·5 [h]	21·3		11·6
13	$C_{31}H_{34}N_{10},4HCl,3·25H_2O$	18·5		7·8	18·6		7·8
14	$C_{20}H_{20}N_6,2C_2H_4O_2,H_2O$	17·3		3·2	17·5		3·7
15	$C_{22}H_{20}ClN_5O,2C_2H_4O_2,1·5H_2O$	12·7		4·9	12·7		4·5
16	$C_{15}H_{16}ClN_5,2HCl,1·5H_2O$	17·5	17·9	4·2	17·4	17·7	4·5
17	$C_{20}H_{27}N_5,2C_2H_4O_2$	15·3			15·3		
18	$C_{14}H_{13}Cl_2N_5,2HCl,3H_2O$	15·35		11·5	15·6		12·0
19	$C_{16}H_{19}N_5,2HCl,H_2O$	18·6	19·2	4·8	18·8	19·1	4·85
20	$C_{15}H_{17}N_5O,2HCl,4H_2O$	16·35	16·7	16·9	16·3	16·6	16·9
21	$C_{14}H_{15}N_5O,2HCl,2·5H_2O$	17·9	18·35	4·95 [k]	18·1	18·35	4·65
22	$C_{16}H_{19}N_5O,2HCl,3H_2O$ [l]	16·9	[m]	12·2	16·6		12·7
23	$C_{18}H_{23}N_5O,2HCl,3H_2O$	15·4	15·5	12·1	15·5	15·7	11·9
24	$C_{17}H_{19}N_5O,2HCl,4H_2O$ [n]	15·2	15·8	11·5	15·4	15·65	11·9
25	$C_{17}H_{21}N_5O,2HCl,3H_2O$	15·95	16·3	11·3	16·0	16·15	11·3
26	$C_{14}H_{14}N_6O,2HCl,2H_2O$ [o]	21·5	18·3	9·1	21·5	18·2	9·2
27	$C_{16}H_{19}N_5O,2C_3H_6O_2,0·6H_2O$	15·2		2·45	15·3		2·45
28	$C_{15}H_{16}N_6O_2,2C_2H_4O_2,1·75H_2O$ [p]	18·1		6·6	18·1		6·8
29	$C_{15}H_{16}N_6O,2C_2H_4O_2,0·33H_2O$ [q]	19·8		1·4 [r]	19·9		1·4

[a] Decomp. [b] The NMe reacted in the Zeisel determination (Found: "OMe," 8·7. Required: "OMe," 9·0%). [c] The NEt reacted in the Zeisel determination (Found: "OEt," 13·5. Required: "OEt," 12·7%). [d] Found: Total Cl, 26·0. Required: total Cl, 25·8%. [e] This salt lost $2H_2O$ over H_2SO_4 *in vacuo*. [f] Only $1H_2O$ is lost. [g] 2-Ethoxyethanol was used as the alcohol in this prepn. [h] Only $2·5H_2O$ lost. [i] This compound is *NNN'N'*-tetra-*p*-amidinophenyl-1,3-diaminopropane. M. p. determined in short sealed tube. [k] Only $1H_2O$ was lost. [l] A *tetrahydrate* was also isolated, but it tended to lose water when exposed to air (Found: N, 15·4; Cl, 16·3; loss at 135°/13 mm., 16·3. $C_{16}H_{19}N_5O,2HCl,4H_2O$ requires N, 15·8; Cl, 16·3; H_2O, 16·3%). [m] Found: OEt, 10·9. Required: OEt, 10·6%. [n] Only $3H_2O$ was lost. [o] Prepared by nitrosation of 4,4'-diamidinodiphenylamine. [p] Prepared by nitrosation of 4,4'-diamidino-2-methoxydiphenylamine. [q] Prepared by nitrosation of 4,4'-diamidino-2-methyldiphenylamine. [r] At 135°/15 mm.

5-*Cyano*-1-p-*cyanophenyl*-2-*phenylbenzimidazole*, prepared similarly from 2-benzamido-4,4'-dicyanodiphenylamine and crystallised from ethanol, had m. p. 182° (Found: N, 17·6. $C_{21}H_{12}N_4$ requires N, 17·5%) and was dimorphous; after melting it solidified slowly and remelted at 199°.

5-*Cyano*-1-p-*cyanophenylbenz*-1,2,3 *triazole*.—A mixture of 2-amino-4,4'-dicyanodiphenylamine (10 g.), ethanol (100 ml.), 7·5N-isethionic acid (5 ml.), water (10 ml.), and concentrated hydrochloric acid (5 ml.) was treated, at 10°, with sodium nitrite (5 g.) in water (10 ml.) and ethanol (5 ml.). After being kept at room temperature for 3 hr. the mixture afforded the required *product* (95%), which crystallised from dioxan or acetic anhydride, m. p. 284° (Found: N, 28·0. $C_{14}H_7N_5$ requires N, 28·6%).

4,4'-*Dicyano*-N-*ethoxycarbonyl*-2-*nitrophenylamine*.—A mixture of 4,4'-dicyano-2-nitrodiphenylamine (1 g.), ethyl chloroformate (2 ml.), potassium carbonate (1 g.), and acetone (10 ml.) was refluxed for 2 hr. Addition of water precipitated an oil which crystallised when rubbed with light petroleum (b. p. 40—60°). The *product* (0·8 g.) separated from alcohol in pale yellow crystals, m. p. 123—124° (Found: N, 16·7. $C_{17}H_{12}N_4O_4$ requires N, 16·65%).

4,4'-*Dicyano*-N-*ethoxycarbonyl*-2-*ethoxycarbonyloxydiphenylamine*.—The was prepared similarly from 4,4'-dicyano-2-hydroxydiphenylamine (2 g.), ethyl chloroformate (5 ml.), potassium carbonate (2 g.), and acetone (50 ml.). The *product* crystallised from ethanol (charcoal) and had m. p. 131·5—132·5° (Found: N, 11·2. $C_{20}H_{17}N_3O_5$ requires N, 11·1%). If the reaction was carried out with an excess of dinitrile [dinitrile (2 g.), ethyl chloroformate (0·6 ml.) and acetone (30 ml.)] the product was 6-*cyano*-3-p-*cyanophenylbenzoxazolone*, m. p. 290° (Found: N, 16·0. $C_{15}H_7N_3O_2$ requires N, 16·1%), which was prepared best as follows: A cold solution

of sodium hydroxide (1·46 g., 1 mol.) in a little water and sufficient ethanol to make 24 ml. was added gradually to the diethoxycarbonyl compound (13·8 g., 1 mol.) dissolved in cold dioxan (50 ml.) and ethanol (50 ml.). After 2—3 hr. addition of concentrated hydrochloric acid (5 ml.) and then dilution with water (700 ml.) gave an oil which quickly crystallised. The solid was boiled in Dowtherm for 5—10 min. and afforded 6-cyano-3-*p*-cyanophenylbenzoxazolone (8·8 g., 93%).

Preparation of Diamidine Salts from the Dinitriles (Table 5).—The nitriles were converted into the amidines, through the imidates, by the usual Pinner procedure. The amidines were often isolated as hydrochlorides, which were usually hydrated. Some of the more soluble hydrochlorides were not readily crystallised, and in such cases the bases were isolated and converted into the acetates which were somewhat less soluble and generally anhydrous. When heated at 95°/15 or at 135°/15 mm., or kept in an evacuated desiccator, some of the hydrochlorides lost all, and others part, of their water of crystallisation. When the salts were dehydrated to the maximum extent and then exposed to the atmosphere, all regained part, and some regained all, of the water of hydration.

4,4′-*Diamidino*-2-*methoxy*-N-*nitrosodiphenylamine*.—Addition of sodium nitrate (5·5 g.) in water (15 ml.) to a cold solution of 4,4′-diamidino-2-methoxydiphenylamine dihydrochloride (10·7 g.) in water (80 ml.) precipitated the sparingly soluble nitrite as a gelatinous solid. 2N-Hydrochloric acid (40 ml.) was added during 5—10 min. with cooling and stirring, and the precipitate rapidly redissolved. The solution was kept for 1 hr. 5N-Sodium hydroxide (25 ml.) was then added, and the nitrosamine base was collected and suspended in water; it became gummy. The gum was washed with water and dissolved in 20% acetic acid. Acetone was slowly added with scratching to give the crystalline diacetate (8·0 g.), m. p. 192—193° (decomp.) (see Table 5).

5-*Amidino*-1-p-*amidinophenylbenzimidazole*.—The di-imidoate was prepared in chloroform–dioxan, and the *diamidine dihydrochloride* (76%) crystallised from aqueous acetone, then having m. p. 305° (Found: N, 19·8; Cl, 16·8. $C_{15}H_{14}N_6,2HCl,4H_2O$ requires N, 19·9; Cl, 16·8%).

5-*Amidino*-1-p-*amidinophenyl*-2-*methylbenzimidazole dihydrochloride* (67%) (from water), m. p. 265—270° (Found: N, 20·4; H_2O, 8·5. $C_{16}H_{16}N_6,2HCl,2H_2O$ requires N, 20·4; H_2O, 8·8%), and 5-*amidino*-1-p-*amidinophenylbenzo*-1,2,3-*triazole dihydrochloride* (78%) (from acetone–dilute hydrochloric acid), m. p. >350° (Found: N, 23·8; H_2O, 13·6. $C_{14}H_{13}N_7,2HCl,3H_2O$ requires N, 24·1; H_2O, 13·3%), were prepared similarly.

The author thanks Dr. H. J. Barber, F.R.I.C., and Dr. J. N. Ashley, F.R.I.C., for their interest and helpful discussions, and Mr. S. Bance, B.Sc., F.R.I.C., for the analyses.

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

[*Received, July 8th*, 1960.]