## 112. *Attempts to find New Chemotherapeutic Amidines. Part III.* Nuclear Substituted Derivatives of 4 : 4′- and 3 : 3′-Diamidinostilbene.*

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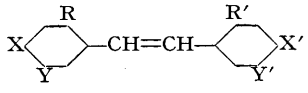
Syntheses of 2-*amino*-4 : 4′-*diamidinostilbene*, and the *dihydrochlorides of* 2-acetamido-, -chloro-, -bromo-, -iodo-, -hydroxy-, and -methoxy-4 : 4′-diamidinostilbene, and of 6 : 6′-dihydroxy-3 : 3′-diamidinostilbene, are described. The halogenated and monohydroxy compounds show greater trypanocidal activity than 4 : 4′-diamidinostilbene ("Stilbamidine"). The methoxy derivative is approximately as active, whilst the remainder are less active than Stilbamidine.

The preparation and trypanocidal activity of a number of aromatic diamidines were described by Ashley *et al.* (*J.*, 1942, 103) and it was suggested there that the effect of nuclear substitution might be examined. The present communication describes a number of stilbene derivatives of the type




where R = Y = Y′ = H, X = X′ = $NH_2 \cdot C(:NH)$, and R′ = $NH_2$, NHAc, Cl, Br, I, OH, and OMe, and also where X = X′ = H, R = R′ = OH, and Y = Y′ = $C(:NH) \cdot NH_2$.

The results of the biological testing of these compounds will be reported in detail elsewhere, but it can be stated here that presence of a halogen atom or hydroxy group in 4 : 4′-diamidinostilbene increases, while presence of a methoxy, amino, or acetamido group decreases, the trypanocidal activity. 6 : 6′-Dihydroxy-3 : 3′-diamidinostilbene is less active than Stilbamidine, and is not curative.

Nuclear substitution appears to have no effect on antimalarial activity, but introduction of halogen slightly increases the antibacterial activity.

* The papers by Ashley, Barber, Ewins, Newbery, and Self (*J.*, 1942, 103) and Barber and Stickings (*J.*, 1945, 167) are to be regarded as Parts I and II respectively of this series.

The starting material for all the monosubstituted diamidines was 2-*nitro*-4 : 4′-*dicyanostilbene*. On one occasion only this was obtained from the Sandmeyer reaction on 2-*nitro*-4 : 4′-*diaminostilbene* which was readily prepared by the series of reactions. Condensation of 2 : 4-dinitrotoluene with 4-acetamidobenzaldehyde (Ashley *et al.*, *J.*, 1942, 113) gave 2 : 4-dinitro-4′-acetamidostilbene, previously prepared by Ruggli and Dinger (*Helv. Chim. Acta*, 1941, **24**, 173) by acetylation of the dinitroamine obtained by reduction of 2 : 4 : 4′-trinitrostilbene with alcoholic ammonium sulphide. The m. p. of our product was considerably higher than that recorded by these workers. Reduction of 2 : 4-dinitro-4′-acetamidostilbene with alcoholic ammonium sulphide yielded 2-*nitro*-4-*amino*-4′-*acetamidostilbene*, which on hydrolysis gave 2-nitro-4 : 4′-diaminostilbene. All other attempts to prepare 2-nitro-4 : 4′-dicyanostilbene by this method failed, as the complex obtained from the Sandmeyer reaction decomposed with almost explosive violence when it was heated in a vacuum according to the method previously described (Ashley *et al.*, *J.*, 1942, 111). Subsequently 2-nitro-4 : 4′-dicyanostilbene was prepared by condensation of 2-nitro-4-cyanotoluene (Banse, *Ber.*, 1894, **27**, 2161; Soderman and Johnson, *J. Amer. Chem. Soc.*, 1925, **47**, 1392) with 4-cyanobenzaldehyde (Ashley *et al.*, *J.*, 1942, 115) in presence of piperidine. Attempts to effect condensation in alcoholic solution or with acetic anhydride as condensing agent were unsuccessful.

Reduction to 2-*amino*-4 : 4′-*dicyanostilbene* was accomplished by heating with stannous chloride in a mixture of glacial acetic and hydrochloric acids. Conversion to the iminoether hydrochloride and 2-*amino*-4 : 4′-*diamidinostilbene* was accomplished by the usual methods. 2-Acetamido-4 : 4′-diamidinostilbene, isolated as the *dihydrochloride*, was similarly prepared from 2-*acetamido*-4 : 4′-*dicyanostilbene*.

2-*Chloro*-4 : 4′-*dicyanostilbene* was obtained from the corresponding amine by the Gatterman diazo reaction. The diazonium chloride was decomposed in boiling 15% hydrochloric acid in presence of copper bronze; with more dilute acid a by-product giving fluorescent solutions was formed which was removed only with difficulty. Decomposition of the diazonium sulphate with cuprous bromide gave only a 9% yield of 2-*bromo*-4 : 4′-*dicyanostilbene*, but this was increased considerably by diazotisation in 51% hydrobromic acid and subsequent decomposition in presence of copper bronze and boiling 12% hydrobromic acid. Decomposition in presence of more dilute acid favoured formation of the above, or a similar, fluorescent by-product whilst 51% acid caused hydrolysis of the cyano groups.

2-*Iodo*-4 : 4′-*dicyanostilbene* was prepared from the diazonium sulphate by treatment with aqueous potassium iodide.

The above three dicyano compounds were converted into 2-chloro-, 2-bromo-, and 2-iodo-4 : 4′-diamidinostilbene (all isolated as *dihydrochlorides*) by the usual method.

In view of the increased therapeutic ratios shown by the halogenated diamidines (I > Br > Cl) an attempt was next made to synthesise 2 : 2′-dibromo (or iodo)-4 : 4′-diamidinostilbene. The required 2 : 2′-*dinitro*-4 : 4′-*dicyanostilbene* was obtained in 11% yield by oxidation of 2-nitro-4-cyanotoluene with alcoholic sodium hypochlorite (cf. Green *et al.*, *J.*, 1907, 2076), whilst attempts to oxidise with air and alcoholic potassium hydroxide (Green *et al.*, *loc. cit.*) or with iodine and alcoholic potassium hydroxide (cf. Green and Baddiley, *J.*, 1908, 1725) gave none of the stilbene. 2 : 2′-Dinitro-4 : 4′-dicyanostilbene was eventually obtained in 33% yield by the action of alcoholic potassium hydroxide on 2-nitro-4-cyanobenzyl chloride (Banse, *Ber.*, 1894, **27**, 2162; cf. Walden and Kembaum, *ibid.*, 1890, **23**, 1958). Various methods were employed for reduction of 2 : 2′-dinitro-4 : 4′-dicyanostilbene to 2 : 2′-*diamino*-4 : 4′-*dicyanostilbene*; the best yield (50%) was obtained using stannous chloride in glacial acetic and hydrochloric acids. As 2-amino-4 : 4′-diamidinostilbene did not exhibit enhanced trypanocidal activity no attempt was made to prepare the corresponding 2 : 2′-diamino-diamidine, but the diamine was tetrazotised in hydrobromic acid solution and converted into 2 : 2′-*dibromo*-4 : 4′-*dicyanostilbene* by decomposition in presence of copper bronze. This, owing to its extreme insolubility, could not readily be converted into the iminoether and, after treatment with alcoholic hydrogen chloride for four weeks, over 90% was recovered unchanged.

2-*Hydroxy*-4 : 4′-*dicyanostilbene* was obtained from the corresponding amino compound by the diazo reaction, and readily yielded the iminoether and 2-hydroxy-4 : 4′-diamidinostilbene, isolated as the *dihydrochloride*.

In view of the increase of toxicity which occurs when aqueous solutions of Stilbamidine are exposed to sunlight or irradiated with ultra-violet light (Barber, Slack, and Wien, *Nature*, 1943, **151**, 107; Henry, *ibid.*, 1943, **152**, 690; Fulton and Yorke, *Ann. Trop. Med. Parasit.*, 1942, **36**, 134; Fulton, *ibid.*, 1943, **37**, 48; Kirk and Henry, *ibid.*, 1944, **38**, 99), the behaviour of 2-hydroxy-4 : 4′-diamidinostilbene dihydrochloride was studied under these conditions. After irradiation for 24 hours there was some increase in toxicity (private communication from Dr. R. Wien) but it was not so great as that observed with Stilbamidine.

Methylation of 2-hydroxy-4 : 4′-dicyanostilbene with methyl sulphate in presence of potassium carbonate and acetone readily yielded 4 : 4′-*dicyano*-2-*methoxystilbene*, which was converted by the usual method into 2-methoxy-4 : 4′-diamidinostilbene (isolated as the *dihydrochloride*). This proved to be approximately as active as Stilbamidine when administered intravenously.

Several attempts were made to prepare 2 : 2′-dihydroxy-4 : 4′-dicyanostilbene for conversion to the corresponding diamidine, by tetrazotisation of 2 : 2′-diamino-4 : 4′-dicyanostilbene and decomposition of the tetrazonium salt, but only amorphous products were isolated which resisted all attempts at purification.

The facile replacement of $^{-}NH_2$ by $^{-}OH$ in 2-amino-4 : 4′-dicyanostilbene and the inability to prepare a 2 : 2′-dihydroxy- from the corresponding 2 : 2′-diamino-derivative led to an attempt to synthesise 2-amino-2′-hydroxy (or methoxy)-4 : 4′-dicyanostilbene in order to determine whether an *o*-amino group might be replaced

in the presence of an *o'*-hydroxyl (or methoxyl) group. It was hoped to prepare 2-hydroxy-4-cyanobenzaldehyde from 2-nitro-4-cyanobenzaldehyde and subsequently to condense the aldehyde with 2-nitro-4-cyanotoluene. Several unsuccessful attempts were made to oxidise 2-nitro-4-cyanotoluene directly to the aldehyde with chromic acid and with selenium dioxide. Banse (*Ber.*, 1894, **27**, 2168) obtained 2-nitro-4-cyanobenzyl alcohol by the action of fuming nitric acid on 4-cyanobenzyl alcohol, but attempts to repeat this nitration with fuming nitric acid or with potassium nitrate and sulphuric acid were unsuccessful. 2-Nitro-4-cyanobenzyl alcohol was finally obtained from 2-nitro-4-cyanobenzyl chloride (*ibid.*, p. 2162) by conversion into the acetate with potassium acetate and subsequent hydrolysis with alcoholic hydrochloric acid. Although 4-cyanobenzyl alcohol is readily oxidised to the aldehyde by nitrogen tetroxide (Ashley *et al.*, *J.*, 1942, 115), and Cohen and Harrison (*J.*, 1897, 1057) described similar oxidations of 2- and 4-nitrobenzyl alcohols, yet under the same conditions 2-nitro-4-cyanobenzyl alcohol gave only traces of the aldehyde. The aldehyde was eventually obtained in poor yield by hydrolysis of the anil formed by condensation of 2-nitro-4-cyanotoluene with 4-nitrosodimethylaniline. Attempts to reduce this nitroaldehyde to the corresponding amine by ferrous hydroxide or sodium sulphide were unsuccessful.

In view of these difficulties, it was decided to attempt the synthesis of 4 : 4'-dinitro-2 : 2'-dihydroxystilbene and then to replace the nitro by cyano groups. The oxidation of various substituted 4-nitrotoluenes to stilbenes is described by Green and Baddiley (*J.*, 1908, 1721) but we found that neither 4-nitro-2-hydroxy- nor 4-nitro-2-acetoxy-toluene was oxidised to the corresponding stilbene by alkaline sodium hypochlorite. As 4 : 4'-dinitro-2 : 2'-dimethoxystilbene had been prepared by Green and Baddiley (*ibid.*, p. 1724) by the two stage oxidation of 4-nitro-2-methoxytoluene with atmospheric oxygen and alcoholic potassium hydroxide it was thought that this intermediate might be utilised and demethylation attempted later. Oxidation of 4-nitro-2-methoxytoluene under the above conditions proceeds through the initial formation of 4 : 4'-dinitro-2 : 2'-dimethoxydibenzyl, which is oxidised to the corresponding stilbene at a higher temperature. Although the first stage was readily carried out, all attempts to accomplish the second were unsuccessful, but the required product was obtained by bromination of the dibenzyl derivative in glacial acetic acid to yield *αβ-dibromo-4 : 4'-dinitro-2 : 2'-dimethoxydibenzyl* which was converted to *4 : 4'-dinitro-2 : 2'-dimethoxydibenzyl* by heating with cuprous chloride and pyridine (cf. Bance, Barber, and Woolman, *J.*, 1943, 3). The dinitro compound was readily reduced to *4 : 4'-diamino-2 : 2'-dimethoxystilbene*, but all attempts to replace the amino by cyano groups or by bromine gave infusible solids which could not be crystallised or sublimed.

Attention was next turned to the readily accessible 5-bromo-2-methoxybenzaldehyde (Perkin *Annalen*, 1868, **145**, 304) which was condensed with 2-nitro-4-cyanotoluene to give *5-bromo-2'-nitro-4'-cyano-2-methoxystilbene*. It was hoped with this compound to settle the point whether after reduction the amino could be replaced by the hydroxyl group in presence of the *o*-methoxyl group. It was realised that the synthesis, if successful, would lead to a substituted 3 : 4'-diamidinostilbene, but it was known (*J.*, 1942, 106) that the 3 : 4'-diamidines did exhibit trypanocidal activity although of a somewhat lower degree than the symmetrical 4 : 4'-derivatives.

Reduction of 5-bromo-2'-nitro-4'-cyano-2-methoxystilbene with stannous chloride yielded, in addition to *5-bromo-2'-amino-4'-cyano-2-methoxystilbene*, another product which was soluble in alkali and had the composition of the amino compound plus an extra atom of oxygen. The constitution of this product, which readily yielded a crystalline methyl ether, was not conclusively established; but it was considered to be *5-bromo-2'-amino-5'* (or 6')*-hydroxy-4'-cyano-2-methoxystilbene* formed by alkaline hydrolysis of the corresponding nuclear chloro-compound formed as a by-product in the reduction. Attempts to replace the amino group in 5-bromo-2'-amino-4'-cyano-2-methoxystilbene by hydroxyl gave amorphous material which was insoluble in alkali and could not be crystallised or sublimed.

The availability of 5-bromo-2-methoxybenzaldehyde suggested that an attempt might be made to synthesise 6 : 6'-dihydroxy-3 : 3'-diamidinostilbene, and the method, if successful, might be modified so as to prepare the corresponding 2 : 2'-dihydroxy-4 : 4'-diamidinostilbene. Although 3 : 3'-diamidines are definitely less active than the 4 : 4'-isomerides (*J.*, 1942, 106) it was hoped that the presence of the two hydroxyl groups would enhance the activity, similarly to the effect of the single hydroxyl group on the activity of 4 : 4'-diamidinostilbene. Actually, 6 : 6'-dihydroxy-3 : 3'-diamidinostilbene unexpectedly proved to have only slight trypanocidal activity without any curative effect.

The first attempt to prepare a stilbene from 5-bromo-2-methoxybenzaldehyde was by use of the corresponding thioaldehyde (cf. Wood, *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 1234). None of the attempts to convert this into a stilbene by sublimation, heating with copper bronze, or boiling with cuprous chloride in pyridine was successful. Thermal decomposition of *3 : 3'-dibromo-6 : 6'-dimethoxybenzylideneazine* (cf. Curtius and Jay, *J. pr. Chem.*, 1889, **39**, 45; Linnell and Sharma, *Quart. J. Pharm.*, 1939, **12**, 263) yielded only traces of 3 : 3'-dibromo-6 : 6'-dimethoxystilbene which was finally obtained and converted into 6 : 6'-dihydroxy-3 : 3'-diamidinostilbene by the following method.

5-Bromo-2-methoxyphenylacetic acid was first described by Knorr and Horlein (*Ber.*, 1909, **42**, 3500) who prepared it from 5-bromo-2-methoxybenzyl alcohol by way of the chloride and cyanide. We obtained it readily from 5-bromo-2-methoxybenzaldehyde which by condensation with hippuric acid yielded *2-phenyl-4-(5'-bromo-2'-methoxybenzylidene)-5-oxazolone*. This on hydrolysis with 10% sodium hydroxide gave *5-bromo-2-methoxyphenylpyruvic acid* which was oxidised to 5-bromo-2-methoxyphenylacetic acid by alkaline hydrogen peroxide. Condensation of 5-bromo-2-methoxybenzaldehyde with sodium 5-bromo-2-methoxy-

phenylacetate in presence of zinc chloride and acetic anhydride (cf. Ruggli and Dinger, *Helv. Chim. Acta, loc. cit.*) yielded cis-3 : 3′-*dibromo*-6 : 6′-*dimethoxystilbene-α-carboxylic acid* together with a small amount of trans-3 : 3′-*dibromo*-6 : 6′-*dimethoxystilbene* formed by spontaneous decarboxylation of the *trans*-acid. The *cis*-acid, when heated in quinoline solution with copper chromite, was smoothly decarboxylated to cis-3 : 3′-*dibromo*-6 : 6′-*dimethoxystilbene*. This was readily converted into the *trans*-isomeride when heated in nitrobenzene solution with a trace of iodine (cf. Ruggli, *Helv. Chim. Acta*, 1937, **20**, 39). *cis*-3 : 3′-Dibromo-6 : 6′-dimethoxystilbene when heated with cuprous cyanide and pyridine was converted into cis-3 : 3′-*dicyano*-6 : 6′-*dimethoxystilbene* which was readily isomerised to the *trans*-compound. Demethylation of both *cis*- and *trans*-3 : 3′-dicyano-6 : 6′-dimethoxystilbene to trans-6 : 6′-*dihydroxy*-3 : 3′-*dicyanostilbene* was effected by heating to 200° with pyridine hydrochloride (Prey, *Ber.*, 1941, **74**, 1219); attempts to demethylate by heating with ethylmagnesium iodide (Späth, *Monatsh.*, 1914, **35**, 319) were unsuccessful. The dicyano compound was only slowly converted into the iminoether by treatment with alcoholic hydrogen chloride, and after four weeks nearly 30% was recovered unchanged. The diamidine *dihydrochloride* was prepared and isolated in the usual way.

## Experimental.

2 : 4-*Dinitro*-4′-*acetamidostilbene*.—A mixture of 2 : 4-dinitrotoluene (9·1 g.), 4-acetamidobenzaldehyde (8·1 g.), and piperidine (6 drops) was heated at 140° for 1 hour. The melt, which soon solidified, was cooled and ground with a small amount of alcohol. The practically pure residue (7·4 g.) crystallised from glacial acetic acid in orange-red rods or needles, m. p. 262° (Ruggli and Dinger (*loc. cit.*) give m. p. 237°) (Found: N, 12·8. Calc. for $C_{16}H_{13}O_5N_3$: N, 12·8%).

2-*Nitro*-4-*amino*-4′-*acetamidostilbene*.—Hydrogen sulphide was bubbled for 2 hours through a gently refluxing mixture of 2 : 4-dinitro-4′-acetamidostilbene (10 g.) in aqueous ammonia (40 c.c.; *d* 0·880) and alcohol (120 c.c.). After cooling, the glistening red crystalline precipitate of the *amine* was filtered off and washed with alcohol and carbon disulphide. Yield, 8 g. It crystallised from glacial acetic acid in red needles, m. p. 238—239° (Found: N, 13·8. $C_{16}H_{15}O_3N_3$ requires N, 14·1%).

2-*Nitro*-4 : 4′-*diaminostilbene*.—The above acetamido compound (2 g.) was boiled under reflux for 2 hours with alcohol (20 c.c.) and hydrochloric acid (20 c.c.; *d* 1·16). Basification of the diluted mixture with aqueous ammonia (*d* 0·880) converted the orange hydrochloride into the purplish-brown diamine. This was purified by dissolving in very dilute hydrochloric acid and filtering from insoluble material. The *base* crystallised from alcohol in maroon-coloured plates or thin prisms, m. p. 156° (Found: N, 16·3. $C_{14}H_{13}O_2N_3$ requires N, 16·5%).

2-*Nitro*-4 : 4′-*dicyanostilbene*.—(*a*) A suspension of 2-nitro-4 : 4′-diaminostilbene hydrochloride, prepared from the base (5 g.) and hydrochloric acid (10 c.c.; *d* 1·16) mixed with ice, was tetrazotised by addition of sodium nitrite (3 g.) in water (10 c.c.). The mixture was poured into a solution of cuprous cyanide (5 g.) in water (15 c.c.) containing potassium cyanide (6·5 g.). Decomposition was completed by heating on the steam-bath for ½ hour and the dark chocolate-brown solid was collected, washed, and dried. Sublimation in a vacuum at 220—240° gave a small amount of golden-yellow *product* which crystallised first from glacial acetic acid and then from nitrobenzene in clusters of yellow prismatic needles, m. p. 288° (Found: N, 15·2. $C_{16}H_9O_2N_3$ requires N, 15·3%).

(*b*) A mixture of 2-nitro-4-cyanotoluene (44 g.), 4-cyanobenzaldehyde (40 g.), and piperidine (5 c.c.) was heated under reflux on the steam-bath for 36 hours. The cold melt was triturated with a little glacial acetic acid; the yellow residue crystallised from glacial acetic acid or nitrobenzene in yellow needles, m. p. 290°. Yield, 45 g. (54%) (Found: N, 15·2%).

2-*Amino*-4 : 4′-*dicyanostilbene*.—A hot solution of crystalline stannous chloride (200 g.) in hydrochloric acid (200 c.c.; *d* 1·16) was added to a suspension of 2-nitro-4 : 4′-dicyanostilbene (39·6 g.) in boiling glacial acetic acid (800 c.c.). Reduction occurred rapidly and, after further boiling for 4 minutes, the mixture was cooled and the crystalline stannichloride collected and decomposed with 25% sodium hydroxide solution. The *amine* crystallised from glacial acetic acid in yellow needles, m. p. 232°. Yield, 23 g. (65%) (Found: N, 17·1. $C_{16}H_{11}N_3$ requires N, 17·1%). Solutions of the amine in organic solvents exhibit an intense green fluorescence.

2-*Acetamido*-4 : 4′-*dicyanostilbene* was obtained in 52% yield from the amine (1·8 g.) by heating with acetic anhydride (50 c.c.) and fused sodium acetate (2 g.) at 100° for ½ hour. It crystallised from dioxan in colourless needles, m. p. 285° (Found: N, 14·4. $C_{18}H_{13}ON_3$ requires N, 14·6%).

2-*Amino*-4 : 4′-*diamidinostilbene* prepared by the usual method crystallised from methyl alcohol in yellow needles, m. p. 250°. Yield, 30% (Found: N, 24·2; equivalent by titration, 136. $C_{16}H_{17}N_5$ requires N, 25·1%; equivalent, 139·5).

2-Acetamido-4 : 4′-diamidinostilbene was obtained similarly from 2-acetamido-4 : 4′-dicyanostilbene. The *dihydrochloride* crystallised from dilute hydrochloric acid in pale yellow needles, m. p. 321° (decomp.) (Found: Cl, 16·2. $C_{18}H_{19}ON_5,2HCl$ requires Cl, 16·5%).

2-*Chloro*-4 : 4′-*dicyanostilbene*.—A suspension of 2-amino-4 : 4′-dicyanostilbene (2 g.) in hydrochloric acid (20 c.c.; *d* 1·16) was diazotised during ½ hour with sodium nitrite (1·6 g.) in water (5 c.c.). The suspension of the diazonium salt was poured into a boiling mixture of copper bronze (2 g.), hydrochloric acid (75 c.c.; *d* 1·16), and water (100 c.c.). The residue after filtering was crystallised from pyridine. Recrystallisation from nitrobenzene afforded the *compound* (0·6 g.) as puce-coloured needles, m. p. 242° (Found: N, 10·6; Cl, 13·4. $C_{16}H_9N_2Cl$ requires N, 10·7; Cl, 13·0%).

2-Chloro-4 : 4′-diamidinostilbene was prepared by the usual method; the *dihydrochloride* crystallised from methyl alcohol or hydrochloric acid in colourless needles, m. p. >320° (Found: N, 14·4; Cl, 27·1. $C_{16}H_{15}N_4Cl,2HCl,H_2O$ requires N, 14·4; Cl, 27·1%).

2-*Bromo*-4 : 4′-*dicyanostilbene*.—2-Amino-4 : 4′-dicyanostilbene (4 g.) was diazotised in 50% hydrobromic acid (40 c.c.) at 5—10° with sodium nitrite (3·2 g.) in water (5 c.c.); urea (2 g.) was then added to decompose the excess of nitrous acid. The solution, diluted with water (50 c.c.), was poured into a boiling suspension of copper bronze (2 g.) in hydrobromic acid (12%; 150 c.c.). After being collected, the *product* crystallised from pyridine in puce-coloured needles, m. p. 241°. Yield, 2·1 g. (Found: N, 8·9; Br, 25·8. $C_{16}H_9N_2Br$ requires N, 9·1; Br, 25·9%).

2-Bromo-4 : 4′-diamidinostilbene was prepared by the usual method; the crude *dihydrochloride* obtained by precipitation with hydrochloric acid (*d* 1·16) was washed with acetone, and crystallised from methyl alcohol in colourless needles (Found: N, 12·8; total halogen as Cl, 23·3. $C_{16}H_{15}N_4Br,2HCl,2H_2O$ requires N, 12·4; total halogen as Cl, 23·6%).

2-*Iodo*-4 : 4′-*dicyanostilbene*.—Ice (75 g.) was added to a solution of 2-amino-4 : 4′-dicyanostilbene (5 g.) in sulphuric acid (25 c.c.; *d* 1·84). The suspension of the amine sulphate was diazotised at 5—10° during 1 hour with sodium nitrite (4 g.) in water (15 c.c.). Urea (4 g.) was then added, and after 10 minutes the mixture was treated with potassium iodide (10 g.) in water (10 c.c.) and stirred for 3·5 hours, diluted to 250 c.c., and boiled under reflux for 30 minutes, then cooled, and the residue was collected and washed with aqueous sodium thiosulphate. The *compound* crystallised

(charcoal) from glacial acetic acid in clusters of pale yellow needles, m. p. 237°. Yield, 4·4 g. (59%) (Found: N, 7·9; I, 35·8. $C_{16}H_9N_2I$ requires N, 7·9; I, 35·6%).

2-Iodo-4 : 4′-diamidinostilbene was prepared in the usual manner; the *dihydrochloride* crystallised from an aqueous solution by addition of acetone in colourless needles (yield, 60%), m. p. >320° (Found: N, 11·5; I, 26·6. $C_{16}H_{15}N_4I,2HCl,H_2O$ requires N, 11·6; I, 26·4%).

2 : 2′-*Dinitro*-4 : 4′-*dicyanostilbene*.—(*a*) A hot solution of 2-nitro-4-cyanotoluene (5 g.) in pyridine (15 c.c.) and alcohol (150 c.c.) was treated with sodium hypochlorite solution (25 c.c. containing 16% of available chlorine) followed immediately by sodium hydroxide (50 c.c.; 33%). The mixture was heated on the steam-bath for 5 minutes, filtered, and the residue washed with water and alcohol. It crystallised from cresylic acid in pale yellow needles, m. p. 338°. Yield, 0·5 g. (11%).

(*b*) 2-Nitro-4-cyanobenzyl chloride (30 g.) in alcohol (100 c.c.) was heated on the steam-bath while alcoholic potassium hydroxide (60 c.c.; 20%) was added gradually with agitation. The residue, after filtration, was washed with water and alcohol; the *compound* crystallised from cresylic acid in yellow needles, m. p. 342°. Yield, 9·2 g. (38%) (Found: N, 17·2. $C_{16}H_8O_4N_4$ requires N, 17·5%).

2 : 2′-*Diamino*-4 : 4′-*dicyanostilbene*.—2 : 2′-Dinitro-4 : 4′-dicyanostilbene (6·8 g.), suspended in boiling glacial acetic acid (150 c.c.), was treated with a hot solution of crystalline stannous chloride (60 g.) in hydrochloric acid (60 c.c.; *d* 1·16). The mixture was boiled for 5 minutes, cooled, and filtered. The residual stannichloride was decomposed by aqueous sodium hydroxide (25%) and the *base* crystallised from dioxan (charcoal). It formed yellow needles, m. p. 291—292°. Yield, 2·8 g. (50%) (Found: N, 21·3. $C_{16}H_{12}N_4$ requires N, 21·5%).

2 : 2′-*Dibromo*-4 : 4′-*dicyanostilbene*.—2 : 2′-Diamino-4 : 4′-dicyanostilbene (1 g.) in hydrobromic acid (10 c.c.; 48%) and water (6 c.c.) was tetrazotised at 0—5° with sodium nitrite (1 g.) in water (5 c.c.). Copper bronze (0·5 g.) was added, and the mixture heated on the steam-bath until decomposition was complete. The precipitate was crystallised from pyridine; recrystallisation from nitrobenzene gave the *compound* as clusters of feathery needles, m. p. 314°. Yield, 0·8 g. (Found: N, 7·7; Br, 38·8. $C_{16}H_8N_2Br_2$ requires N, 7·3; Br, 41·0%).

2-*Hydroxy*-4 : 4′-*dicyanostilbene*.—2-Amino-4 : 4′-dicyanostilbene (6·5 g.) in boiling glacial acetic acid (250 c.c.) was treated with sulphuric acid (2N; 130 c.c.). The solution was quickly cooled and diazotised at 5—10° with sodium nitrite (2·1 g.) in water (10 c.c.) added during 1½ hours. The resulting solution was boiled for 15 minutes with sulphuric acid (55%; 450 c.c.). The mixture was diluted and cooled; the solid *product* crystallised from alcohol in lemon-yellow prismatic needles, m. p. 296°. Yield, 3·6 g. (55%) (Found: N, 11·0. $C_{16}H_{10}ON_2$ requires N, 11·3%).

2-Hydroxy-4 : 4′-diamidinostilbene was prepared by the usual method. The *dihydrochloride* crystallised from dilute hydrochloric acid in pale yellow needles, m. p. 357° (decomp.). Yield, 70% (Found: N, 15·7. $C_{16}H_{16}ON_4,2HCl$ requires N, 15·5%).

4 : 4′-*Dicyano*-2-*methoxystilbene*.—A suspension of 2-hydroxy-4 : 4′-dicyanostilbene (1·2 g.) and anhydrous potassium carbonate (1·2 g.) in methyl sulphate (2 c.c.) and acetone (20 c.c.) was boiled for 4 hours. The solid *product*, obtained by dilution with water, crystallised from dioxan in colourless feathery needles, m. p. 239°. Yield, 1 g. (78%) (Found: N, 10·7. $C_{17}H_{12}ON_2$ requires N, 10·4%).

2-Methoxy-4 : 4′-diamidinostilbene was prepared by the usual method. The *dihydrochloride* crystallised from dilute hydrochloric acid in feathery needles, m. p. 320° (decomp.). Yield, 50% (Found: N, 12·9; Cl, 16·7. $C_{17}H_{16}ON_4,2HCl,3H_2O$ requires N, 13·3; Cl, 16·9%).

2-*Nitro*-4-*cyanobenzaldehyde*.—2-Nitro-4-cyanotoluene (50 g.), 4-nitrosodimethylaniline (53 g.), and sodium carbonate (15 g.) in alcohol (250 c.c.) were refluxed for 4 days, two further additions of 4-nitrosodimethylaniline (25 g.) being made at intervals of 24 hours. The hot mixture was filtered and the black residue washed with hot water and alcohol; it yielded 17·3 g. of black crystalline anil, m. p. 206—208°. Hydrolysis with boiling hydrochloric acid (1 : 1; 170 c.c.) for 15 minutes, followed by extraction with ether and crystallisation from water, gave 6·2 g. of colourless needles, m. p. 114—115° (Found: N, 16·0. Calc. for $C_8H_4O_3N_2$: N, 15·9%).

*αβ-Dibromo*-4 : 4′-*dinitro*-2 : 2′-*dimethoxydibenzyl*.—4 : 4′-Dinitro-2 : 2′-dimethoxydibenzyl (20 g.) was boiled with glacial acetic acid (400 c.c.) and bromine (10 c.c.) for 2½ hours. The *product* (10 g.) separated from the boiling liquid in pale yellow hexagonal plates, m. p. 251° (decomp.) (Found on material recrystallised from glacial acetic acid: Br, 32·5. $C_{16}H_{14}O_6N_2Br_2$ requires Br, 32·6%). A further amount of slightly impure product, m. p. 247°, separated from the mother liquors on cooling.

4 : 4′-*Dinitro*-2 : 2′-*dimethoxystilbene*.—*αβ*-Dibromo-4 : 4′-dinitro-2 : 2′-dimethoxystilbene (26 g.), cuprous chloride (26 g.), and pyridine (35 c.c.) were heated at 200—220° for 2 hours. The reaction mixture was extracted repeatedly with hot hydrochloric acid (*d* 1·16) and the residue then washed with water. The *compound* crystallised from nitrobenzene in yellow prismatic needles, m. p. 275—276°. Yield, 14·2 g. (80%) (Found: N, 8·5. $C_{16}H_{14}O_6N_2$ requires N, 8·5%).

4 : 4′-*Diamino*-2 : 2′-*dimethoxystilbene*.—A hot solution of crystalline stannous chloride (16 g.) in hydrochloric acid (*d* 1·16; 16 c.c.) was added to a boiling mixture of 4 : 4′-dinitro-2 : 2′-dimethoxystilbene (2 g.) and glacial acetic acid (60 c.c.). The stannichloride quickly separated and was decomposed with 25% sodium hydroxide. The *diamine* crystallised from nitrobenzene in lemon-yellow needles (0·8 g.; 50%), m. p. 256° (Found: N, 10·3. $C_{16}H_{18}O_2N_2$ requires N, 10·4%).

5-*Bromo*-2′-*nitro*-4′-*cyano*-2-*methoxystilbene*.—A mixture of 5-bromo-2-methoxybenzaldehyde (5 g.; prepared in approximately 70% yield by bromination of 2-methoxybenzaldehyde in glacial acetic acid at 10°) and 2-nitro-4-cyanotoluene (4 g.) was heated with piperidine (0·75 c.c.) at 160° for 1½ hours. The cooled melt was extracted with cold glacial acetic acid, and the residue crystallised from glacial acetic acid. The *compound* formed yellow feathery needles (5 g.; 60%), m. p. 241° (Found: N, 8·0. $C_{16}H_{11}O_3N_2Br$ requires N, 8·0%).

5-*Bromo*-2′-*amino*-4′-*cyano*-2-*methoxystilbene*.—The above nitro compound (25 g.) in boiling glacial acetic acid (500 c.c.) was treated with a hot solution of stannous chloride (50 g.) in hydrochloric acid (*d* 1·16; 50 c.c.). The reaction mixture was diluted and filtered. The residual *product*, after extraction with dilute sodium hydroxide, crystallised from alcohol in needles, m. p. 148°. Yield, 6·8 g. (Found: N, 8·5. $C_{16}H_{13}ON_2Br$ requires N, 8·5%). An alcoholic solution of the amine exhibited an intense greenish-blue fluorescence.

Neutralisation of the alkaline filtrate gave a colourless precipitate of 5-*bromo*-2′-*amino*-5′(or 6′)-*hydroxy*-4′-*cyano*-2-*methoxystilbene* which crystallised from alcohol (charcoal) in clusters of prismatic needles (insoluble in aqueous sodium carbonate), m. p. 202° (Found: C, 55·1; H, 3·45; N, 7·8; Br, 23·1; OMe, 8·9. $C_{16}H_{13}O_2N_2Br$ requires C, 55·6; H, 3·8; N, 8·1; Br, 23·2; OMe, 8·9%). Treatment with methyl sulphate and sodium hydroxide yielded a colourless product which crystallised from dioxan in rhombs, m. p. 178°.

The above reduction was repeated using (*a*) the nitro compound (10 g.) and stannous chloride (30 g.); (*b*) the nitro compound (5 g.) and stannous chloride (6·5 g.). There were obtained 6·1 g. and 2·35 g. of crude amine and 2·05 g. and 2·15 g. of alkali-soluble material respectively.

3 : 3′-*Dibromo*-6 : 6′-*dimethoxybenzylideneazine*.—5-Bromo-2-methoxybenzaldehyde (10 g.) in boiling alcohol (130 c.c.) was treated with a solution of hydrazine prepared from hydrazine sulphate (5 g.) in 2N-sodium hydroxide (35 c.c.).

The yellow precipitate of the *azine* crystallised from pyridine (charcoal) in yellow prisms, m. p. 234°. Yield, 5 g. (47%) (Found : N, 6·8. $C_{16}H_{14}O_2N_2Br_2$ requires N, 6·8%). When the azine was heated under reduced pressure at 250—270° it sublimed unchanged. When heated at 250—270° in a vacuum with twice its weight of copper bronze a very small amount of impure 3 : 3′-dibromo-6 : 6′-dimethoxystilbene was obtained.

2-*Phenyl*-4-(5′-*bromo*-2′-*methoxybenzylidene*)-5-*oxazolone*.—5-Bromo-2-methoxybenzaldehyde (23 g.), hippuric acid (17·5 g.), fused sodium acetate (21 g.), and acetic anhydride (350 c.c.) were heated at 100° for 1½ hours. The mixture was treated with water; the *product* crystallised from glacial acetic acid in yellow needles, m. p. 179°. Yield, 26·8 g. (70%) (Found : N, 4·0. $C_{17}H_{12}O_3NBr$ requires N, 3·8%).

5-*Bromo*-2-*methoxyphenylpyruvic* acid.—The above azlactone (21 g.) was boiled under reflux with sodium hydroxide (10%; 105 c.c.) for 16 hours; the solution was diluted with water (100 c.c.) and treated at 0—10° with sulphur dioxide until acid (Congo red); benzoic acid was filtered off and the filtrate heated with hydrochloric acid (*d* 1·16; 20 c.c.). The crude acid (11·4 g.; 75%) was used directly in the subsequent oxidation. The *acid* crystallised from glacial acetic acid in colourless needles, m. p. 163° (Found : Br, 29·2. $C_{10}H_9O_4Br$ requires Br, 29·3%).

5-*Bromo*-2-*methoxyphenylacetic Acid*.—A solution of the crude acid obtained above (6·4 g.) in sodium hydroxide (10%; 150 c.c.) was stirred at 0—5° while hydrogen peroxide (20 vol.; 25 c.c.) was gradually added. After 16 hours, the solution was filtered and then acidified. The acid crystallised from methyl alcohol in colourless prismatic needles, m. p. 136°. Yield, 4·3 g. (78%) (Found : Br, 32·3. Calc. for $C_9H_9O_3Br$ : Br, 32·3%).

cis-3 : 3′-*Dibromo*-6 : 6′-*dimethoxystilbene*-α-*carboxylic Acid*.—A mixture of 5-bromo-2-methoxybenzaldehyde (44 g.), sodium 5-bromo-2-methoxyphenylacetate (52·8 g.), zinc chloride (4·5 g.), and acetic anhydride (385 c.c.) was heated at 140—150° for 24 hours and then poured into water. After some time, the sticky product was boiled with 2N-sodium carbonate. The yellow residue of trans-3 : 3′-*dibromo*-6 : 6′-*dimethoxystilbene* crystallised from glacial acetic acid in pale yellow needles, m. p. 214° (Found : Br, 40·0; OMe, 15·9. $C_{16}H_{14}O_2Br_2$ requires Br, 40·2; OMe, 15·6%). The cold filtrate from the extraction with sodium carbonate deposited the sodium salt of the *cis*-acid. Acidification yielded this *acid* as an oil which solidified after boiling with a little benzene, and crystallised from glacial acetic acid (charcoal) in prisms, m. p. 193°. Yield, 42 g. (45%) (Found : Br, 35·8; OMe, 13·8. $C_{17}H_{14}O_4Br_2$ requires Br, 36·2; OMe, 14·0%). The crude acid (without previous treatment with benzene) crystallised directly from acetic acid in a dimorphic form (long rectangular prisms), m. p. 224°.

cis-3 : 3′-*Dibromo*-6 : 6′-*dimethoxystilbene*.—The α-carboxylic acid (9·7 g.) was added gradually to a mixture of copper chromite (1 g.) and quinoline (40 c.c.) at 210—220°. The cold reaction mixture was treated with excess of 10% hydrochloric acid; extraction with ether yielded the *product* which crystallised from methyl alcohol (charcoal) in prisms, m. p. 104°. Yield, 5 g. (58%) (Found : Br, 40·5. $C_{16}H_{14}O_2Br_2$ requires Br, 40·2%). When heated with a trace of iodine in nitrobenzene it was converted into the *trans*-isomeride, m. p. 214°.

cis- *and* trans-3 : 3′-*Dicyano*-6 : 6′-*dimethoxystilbene*.—*cis*-3 : 3′-Dibromo-6 : 6′-dimethoxystilbene (4 g.) was heated with cuprous cyanide (4 g.) and pyridine (4 c.c.) at 210° for 1·5 hours. The mixture was extracted several times with hot hydrochloric acid (*d* 1·16); the residual cis-*acid* crystallised from alcohol in colourless prisms, m. p. 153°. Yield, 1·75 g. (60%) (Found : N, 9·8; OMe, 21·4. $C_{18}H_{14}O_2N_2$ requires N, 9·7; OMe, 21·4%). When heated with nitrobenzene containing a trace of iodine it was converted into the *trans*-isomeride, which formed colourless prisms, m. p. 241°.

trans-6 : 6′-*Dihydroxy*-3 : 3′-*dicyanostilbene*.—*cis*-3 : 3′-Dicyano-6 : 6′-dimethoxystilbene (14·4 g.) was heated with dry pyridine hydrochloride (36 g.) with exclusion of moisture at 200° for 5 hours. After extraction with water, the residue was dissolved in warm dilute sodium hydroxide (charcoal). The trans-*dicyano*-compound obtained after acidification crystallised from dioxan in clusters of colourless prismatic needles, m. p. 304°. Yield, 8 g. (Found : N, 10·7. $C_{16}H_{10}O_2N_2$ requires N, 10·7%). When *trans*-3 : 3′-dicyano-6 : 6′-dimethoxystilbene was demethylated under identical conditions, it yielded the same *trans*-6 : 6′-dihydroxy-3 : 3′-dicyanostilbene, m. p. 304°.

6 : 6′-*Dihydroxy*-3 : 3′-*diamidinostilbene*.—The dicyano-compound was converted into the di-iminoether and diamidine by the method already described. The *dihydrochloride* crystallised from dilute hydrochloric acid (1 : 1) in clusters of colourless needles, m. p. above 320° (Found : N, 3·4; Cl, 16·5. $C_{16}H_{16}O_2N_4,2HCl,2H_2O$ requires N, 3·4; Cl, 17·0%).

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