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1. *Bromination of Diphenylalkanes and the Preparation of Some Stilbene Derivatives. Part I. αβ-Diphenylethane.*

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The bromination of *αβ*-diphenylethane to yield 4 : 4′ : *α* : *β*-tetrabromo-*αβ*-diphenylethane is described. This tetrabromo-compound is directly converted by heating with cuprous cyanide in pyridine into 4 : 4′-dicyanostilbene, an intermediate for therapeutically important " Stilbamidine ".

4 : 4′-Diamidinostilbene (" Stilbamidine ") possesses therapeutic properties (Warrington Yorke *et al.*, *Ann. Trop. Med. Parasit.*, 1940 *et seq.*), and its preparation is therefore important. The manufacturing process devised presents novel features which may be of more general interest.

4 : 4′-Dicyanostilbene has been prepared by Lamb and White (J., 1939, 1256) and by Ashley (J., 1942, 108) from 4 : 4′-diaminostilbene by the Sandmeyer method. This method, however, presented great difficulties on a large scale, giving very poor yields even on a somewhat large laboratory scale.

It would seem preferable, therefore, to synthesise the stilbene molecule from components already containing the nitrile group. A review of published methods (cf. Linnell and Shann, *Quart. J. Pharm.*, 1939, 263), however, makes it evident that most of these cannot be applied satisfactorily with a substituent such as the cyano-group present. For example, although Kuhn and Winterstein (*Helv. Chim. Acta*, 1928, **11**, 103) regard the azine method as the best for preparing stilbene itself, it was not promising, for 4-cyanobenzaldazine had a very high m. p. and did not decompose smoothly at the high temperature required. [Since this work was completed, the preparation of 4 : 4′-dicyanostilbene by repeated sublimation of the azine has been described by Sah (*J. Amer. Chem. Soc.*, 1942, **64**, 1482), but the yield was not good.] 4-Cyanobenzyl chloride, as might be expected, did not yield a Grignard compound, so an attempt by this means to prepare 4 : 4′-dicyanophenylbenzylcarbinol (cf. Ruggli and Lang, *Helv. Chim. Acta*, 1938, **21**, 38) proved abortive. It has already been shown by one of us (J., 1942, 109) that 4-cyanobenzaldehyde under the conditions of the benzoin condensation gives 4 : 4′-dicyanodeoxybenzoin, but the yields are unsatisfactory. Linnell and Shann's attempts (*loc. cit.*) to devise new methods of synthesis did not invite further examination along those lines.

Ruggli's route (*Helv. Chim. Acta*, 1931, **14**, 541) to 2 : 2′-dicyanostilbene through 2-cyanobenzylsulphonyl chloride was not promising, as the yields in converting the sulphonyl chloride with a tertiary base into the stilbene were not good. Condensation of 4-cyanobenzaldehyde with 4-cyanophenylacetic acid would probably yield the desired stilbene, but the number of stages involved in the preparation of each intermediate led us to reject this possibility.

Some experiments on the bromination of αβ-diphenylethane, carried out with another object in view, suggested a new approach to the problem. According to Fittig (*Annalen*, 1866, **137**, 266), bromination of the hydrocarbon under mild conditions yields a mixture of 4-bromo- and 4 : 4′-dibromo-αβ-diphenylethanes, but we have not been able to reproduce these results. Bromination in non-hydroxylic solvents yielded somewhat impure αβ-dibromo-αβ-diphenylethane, m. p. 235°, which according to Wislicenus (*Ber.*, 1895, **28**, 2693) should be regarded as the *meso*-form. If a mixture of bromine and diphenylethane in acetic acid is boiled, however, an easily separable mixture of 4 : 4′ : α : β- and 2 : 4′ : α : β-tetrabromo-αβ-diphenylethanes, $C_6H_4Br\cdot CHBr\cdot CHBr\cdot C_6H_4Br$, is obtained. The former is identical with the product obtained by Wislicenus (*loc. cit.*) by addition of bromine to *trans*-4 : 4′-dibromostilbene. The bromination must involve a simultaneous attack on the aliphatic and the aromatic carbon atoms where substitution takes place, for αβ-dibromo-αβ-diphenylethane is not further brominated under the above conditions, and gradual addition of bromine to a solution of diphenylethane in boiling acetic acid yielded products containing less bromine than is required for the tetrabromo-compound. Bromination of 4 : 4′-dibromodiphenylethane in boiling acetic acid yielded the 4 : 4′ : α : β-tetrabromo-compound.

αβ-Dibromodiphenylethanes can be reduced readily by means of zinc dust to the corresponding stilbene derivatives, but the somewhat large volumes involved made an alternative process desirable. An excellent reducing agent was cuprous chloride or bromide in hot pyridine solution. When these experiments were carried out we were not conversant with the use of pyridine alone for this purpose. According to Pfeiffer (*Ber.*, 1912, **45**, 1810), pyridine eliminates hydrogen bromide from the dibromides having racemic configuration, and bromine from the *meso*-forms. The behaviour of the tetrabromo-compound is in accordance with this, but for smooth decomposition and good yields a considerable excess of pyridine must be used.

The conversion of the dibromo-stilbenes into the dinitriles was readily achieved by heating with cuprous cyanide in pyridine. B.P. 488,642 claims that it is essential to use the theoretical quantity of pyridine, but we have not found the proportion of pyridine to be of importance within fairly wide limits. These two stages, *viz.*, reduction of the tetrabromo-compound to the dibromostilbene and conversion of this into the dicyanostilbene, have been effected in one operation by using cuprous cyanide instead of the chloride or bromide as the reducing agent, the reaction then becoming $(C_6H_4Br{\cdot}CHBr{\cdot})_2 \xrightarrow{4\,CuCN} (CN{\cdot}C_6H_4{\cdot}CH{:})_2$. The form in which the halogen is eliminated has not been settled.

If only 2 mols. of cuprous cyanide are used, the product is the dibromostilbene. Moreover, if the tetrabromo-compound is first boiled with pyridine, and 2 mols. of cuprous cyanide are then added, the product is still only the dibromostilbene. The form in which the bromine is combined with the pyridine in this elimination does not appear to have been studied, but it must be fairly reactive. It is hoped to examine these reactions further, and particularly to determine whether the effect of a cuprous salt on the racemic form of the dibromide is to eliminate hydrogen bromide or bromine.

It seems that the reaction can take place in more than two stages, the reduction of the αβ-bromine atoms being the first, and the successive replacement of the nuclear bromine atoms being the second and third. 4-*Bromo*-4′-*cyanostilbene* has now been isolated in traces from mother-liquors from the crystallisation of considerable quantities of 4 : 4′-dicyanostilbene. We have not isolated the *cis*-compound by this method but its formation is not excluded.

The 2 : 4′-isomer underwent a similar series of reactions and 2 : 4′-*dicyanostilbene* was obtained. As this yields only a *mono-amidine* and this class of compound is not likely to prove of practical interest, this series of stilbene derivatives was not explored further. The orientation was settled by oxidation to a mixture of *o*- and *p*-bromobenzoic acids.

The greater availability of 4 : 4′-dicyanostilbene has made possible the preparation of some further derivatives of this series. This compound readily took up 2 atoms of bromine to give the *dibromo*-compound $(CN{\cdot}C_6H_4{\cdot}CHBr{\cdot})_2$, and this was readily converted by alcoholic potash into the *monobromostilbene* $CN{\cdot}C_6H_4{\cdot}CBr{:}CH{\cdot}C_6H_4{\cdot}CN$, which on more drastic treatment yielded 4 : 4′-*dicyanotolane*. 4 : 4′ : α : β-Tetrabromodiphenylethane underwent a similar series of reactions, but more drastic conditions were required for removal of the second bromine atom.

According to Campbell and O'Connor (*J. Amer. Chem. Soc.*, **1939**, **61**, 2897), catalytic reduction of acetylene compounds in presence of Raney nickel yields almost exclusively the *cis*-olefins, whereas with a precious-metal catalyst mixtures are encountered, as is well known. The dicyanotolane on reduction in presence of Raney nickel catalyst yielded the required cis-4 : 4′-*dicyanostilbene*, which underwent the normal rearrangement to the *trans*-form in boiling nitrobenzene containing a trace of iodine (cf. Ruggli, *Helv. Chim. Acta*, **1937**, **20**, 39).

New amidines of this series were prepared, notably 4 : 4′-*diamidinotolane* (as *dihydrochloride*) and cis-4 : 4′-*diamidinostilbene* corresponding to "Stilbamidine," which is in the *trans*-form. None of these amidines exhibited any very exceptional trypanocidal properties.

Further experimental work in this group is in progress and has been extended to the preparation of higher homologues.

EXPERIMENTAL.

αβ-Dibromo-αβ-diphenylethane.—(*a*) Bromine, in several vols. of carbon tetrachloride, was added slowly to a nearly boiling solution of αβ-diphenylethane (10 g.) in carbon tetrachloride (55 c.c.) until the colour of bromine persisted. 18 G. (4 atoms) of bromine were required. 7 G. of solid separated while still hot, and were recrystallised from glacial acetic acid; m. p. 182—225° (decomp.).

(*b*) αβ-Diphenylethane (85 g.) and bromine (117 c.c. = 368 g., 10 atoms) were boiled together in carbon tetrachloride (230 c.c.) for 4½ hours. Hydrogen bromide was evolved, and a crystalline solid began to separate after 5 mins. The solid was filtered off hot and washed with light petroleum; yield 130 g. (83%); m. p. 233—237° (decomp.). 5 G., recrystallised from 350 c.c. of glacial acetic acid [0·7 g., insoluble in the boiling solvent, was removed, m. p. 242° (decomp.)], gave 3·3 g. of m. p. 230—235° (Found: Br, 46·8. Calc. for $C_{14}H_{12}Br_2$: Br, 47·0%).

Attempts to brominate αβ-Dibromo-αβ-diphenylethane.—(*a*) A solution of bromine (5 atoms) in nitrobenzene was added slowly to a boiling solution of αβ-dibromo-αβ-diphenylethane (16·9 g.) in nitrobenzene (30 c.c.). 5·1 G. of solid separated which, after recrystallisation from glacial acetic acid, gave 4·5 g., m. p. 205—208° (Found: Br, 47·6%); this depressed the m. p. of 4 : 4′-dibromostilbene and was probably impure αβ-dibromo-compound.

(*b*) αβ-Dibromo-αβ-diphenylethane, boiled in glacial acetic acid with an excess of bromine for 6 hours, did not evolve hydrogen bromide and was recovered unchanged.

4 : 4′ : α : *β-Tetrabromo-αβ-diphenylethane.*—A solution of αβ-diphenylethane (30 g.) in glacial acetic acid (330 c.c.) and water (16 c.c.) containing bromine (41 c.c. = 131 g., 10 atoms) was refluxed until no more tetrabromo-compound separated (about ½ hour). The latter was removed hot, and washed with glacial acetic acid and then ether; yield 32 g. (39%); m. p. 235—245° (decomp.).

2 : 4′ : α : *β-Tetrabromo-αβ-diphenylethane.*—The hot glacial acetic acid mother-liquors from the above bromination deposited 2 : 4′ : α : *β-tetrabromo-αβ-diphenylethane* on cooling; yield 30 g. (36%); m. p. 170—175° (Found: Br, 64·1. $C_{14}H_{10}Br_4$ requires Br, 64·2%). No pure product was obtained from the tarry liquid produced by dilution of the filtrate with water.

Addition of Bromine to a Boiling Solution of αβ-Diphenylethane in Glacial Acetic Acid.—Bromine (80 c.c. = 225 g., 9·7 atoms) was added gradually (8 mins.) to a boiling solution of αβ-diphenylethane (60 g.) in glacial acetic acid (440 c.c.) and water (22 c.c.); solid crystallised after 2 mins. Boiling was continued for 2 hours, and the product was then filtered off from the hot solution. The filtrate after cooling deposited 30 g. of solid, m. p. 160—195°.

Bromination of 4 : 4′-*Dibromodiphenylethane.*—(a) *In chloroform.* 4 : 4′-Dibromo-αβ-diphenylethane (1·7 g.), dissolved in chloroform (10 c.c.), was treated with bromine (1·8 g., 2·2 atoms) and refluxed for 24 hours. Reaction was very slow and much bromine was unused. 0·5 G. of tetrabromo-compound, m. p. 245—247°, separated on cooling.

(b) *In acetic acid.* 4 : 4′-Dibromo-αβ-diphenylethane (1·7 g.) in glacial acetic acid (15 c.c.) was refluxed with bromine (4·5 g.) for 2 hours. The product separated rapidly, and was filtered hot and washed with acetic acid; yield 2·06 g. (83%), m. p. 245—247° (decomp.).

4 : 4′-*Dibromostilbene*.—Cuprous chloride (6·3 g.) was mixed with 4 : 4′ : α : β-tetrabromo-αβ-diphenylethane (12·3 g.) and added to pyridine (25 c.c.). The solid mass produced was melted, boiled under reflux for 1 hour, and poured into about 100 c.c. of concentrated hydrochloric acid. The solid, after being separated and washed with concentrated hydrochloric acid and water, consisted of 8·3 g. of grey solid, m. p. 195—205°, which on recrystallisation from glacial acetic acid gave 6·1 g., m. p. 206—210° (yield 72%).

4 : 4′-*Dicyanostilbene*.—Crude 4 : 4′-dibromostilbene (8·2 g. from a similar preparation to the above) was mixed with cuprous cyanide (6·0 g.) and pyridine (6·5 c.c.) and refluxed, the temperature of the metal-bath being raised to 220° and maintained thereat for 1 hour. The molten mixture was poured into warm concentrated hydrochloric acid (about 100 c.c.), from which the solid was filtered off, washed with concentrated hydrochloric acid, and recrystallised from pyridine; yield 3·6 g., m. p. 282—284°.

Treatment of 4 : 4′ : α : β-*Tetrabromo-αβ-diphenylethane with Cuprous Cyanide and Pyridine*.—(a) *With* 4 *mols. of cuprous cyanide*. The tetrabromo-compound (200 g.) was mixed with cuprous cyanide (224 g.) and pyridine (225 c.c.) and refluxed in a bath at 200—210° for 1½ hours. More pyridine (480 c.c.) was then added, and the whole boiled for 5 mins. to effect more complete solution, and poured hot into 1200 c.c. of concentrated hydrochloric acid. The solid was filtered off hot, washed with about 400 c.c. of hot concentrated hydrochloric acid and then with water, and dried at 100°. 95 G. of product were obtained which, after recrystallisation from nitrobenzene, gave 64 g. of almost pure, pale brown 4 : 4′-dicyanostilbene (70% yield), m. p. 275—280°. If the crude material was sublimed before crystallisation, the yield was higher.

(b) *With* 2 *mols. of cuprous cyanide*. A 60% yield of dibromostilbene was obtained, together with 20% of other, unidentified material. No dicyanostilbene was isolated.

(c) *With* 2 *mols. of cuprous cyanide after boiling in pyridine*. The tetrabromo-compound was boiled for 1 hour in pyridine, 2 mols. of cuprous cyanide were then added, and the mixture heated at 200—210° for a further 1½ hours. There was a considerable evolution of gas which may have contained cyanogen, hydrogen cyanide, and cyanogen bromide. From the reaction mixture a 30% yield of dibromostilbene was obtained but no other product was identified.

2 : 4′-*Dibromostilbene*.—2 : 4′ : α : β-Tetrabromo-αβ-diphenylethane (270 g.) was refluxed for 1½ hours with cuprous chloride (130 g.) dissolved in pyridine (600 c.c.). The mixture was poured into hydrochloric acid (1200 c.c., *d* 1·16), and the product extracted with ether. The crude *dibromostilbene* obtained after removal of ether was distilled in a vacuum, b. p. 185—185°/2 mm., and the distillate recrystallised from alcohol; m. p. 84—85°; yield 116 g., 63% (Found : C, 49·8; H, 3·2. $C_{14}H_{10}Br_2$ requires C, 49·7; H, 3·0%).

Oxidation. The above dibromo-compound (2 g.), dissolved in acetone (10 c.c.), was treated with potassium permanganate (10% solution in 80% acetone) until a permanent excess persisted. After 1½ hours the manganese dioxide was removed, and the solution evaporated to dryness. The residue was dissolved in sodium hydroxide solution and shaken with ether to remove non-acidic material. The mixed acids obtained on acidification had m. p. 220—245°. The *o*-bromobenzoic acid present was converted by boiling with sodium acetate containing a trace of cupric acetate into salicylic acid (cf. Hurtley, J., 1929, 1870), the presence of which was shown by the ferric chloride colour reaction, by conversion into methyl salicylate, and by isolation of a slightly impure salicylic acid (m. p. 149—152°; lit. 159°). *p*-Bromobenzoic acid was also separated in a slightly impure form, m. p. 246—247° (lit. 251°).

2 : 4′-*Dicyanostilbene* was obtained from the corresponding tetrabromo-compound in the same manner as the 4 : 4′-isomer. It was isolated by treating the crude product with hydrochloric acid, extracting it with benzene, filtering off insoluble residue, and evaporating the extract. The residual crude dinitrile was purified by vacuum sublimation or distillation. It formed flat prisms from glacial acetic acid, m. p. 136—137° (Found : C, 83·5; H, 4·3; N, 12·2. $C_{16}H_{10}N_2$ requires C, 83·5; H, 4·4; N, 12·2%).

αβ-Dibromo-4 : 4′-*dicyano-αβ-diphenylethane*.—4 : 4′-Dicyanostilbene (9·2 g.) was dissolved in nitrobenzene (50 c.c.) at 200°, and a solution of bromine (2 c.c.) in nitrobenzene (20 c.c.) run in below the surface during 5 mins. in a bright light. Absorption of bromine was rapid, and only traces of hydrogen bromide were liberated. The *product*, which crystallised on cooling, was washed with a little nitrobenzene and ether; yield 12·4 g. (80%), m. p. 269° (decomp.) (Found : N, 7·35; Br, 41·0. $C_{16}H_{10}N_2Br_2$ requires N, 7·2; Br, 41·0%).

4 : 4′ : α-*Tribromostilbene*.—4 : 4′ : α : β-Tetrabromo-αβ-diphenylethane (5 g.), finely powdered, was suspended in boiling ethyl alcohol (100 c.c.), and a solution of potassium hydroxide (1·2 g.) in methyl alcohol (10 c.c.) run in during 10 mins. with vigorous stirring. After a further 10 mins. the solution was filtered from potassium bromide and a little unchanged tetrabromo-compound, diluted with water (10 c.c.), treated with charcoal (0·2 g.), filtered, and diluted to give 70% alcohol. The *product* crystallised in slender prisms (2·8 g.; 70%), m. p. 82—83°. After recrystallisation from methyl alcohol, the m. p. was unaltered but was not sharp, probably owing to the presence of the stereoisomer (Found : Br, 57·6. $C_{14}H_9Br_3$ requires Br, 57·55%).

α-Bromo-4 : 4′-*dicyanostilbene*.—αβ-Dibromo-4 : 4′-dicyanodiphenylethane (19·6 g.) was suspended in boiling methyl alcohol (100 c.c.), and 10% methyl-alcoholic potash (30 c.c.) run in during 4 mins. The solution was filtered from unchanged material (4·8 g.) and poured into water. The gum which separated hardened slowly and a solid was separated by trituration with methyl alcohol. The *product* was obtained pure, m. p. 144—145° (Found : C, 62·4; H, 2·3. $C_{16}H_9N_2Br$ requires C, 62·1; H, 2·9%), in small yield after repeated crystallisation from methyl alcohol. The m. p. changed on heating, and the substance was probably contaminated with the *trans*-form. If melted, super-cooled, and then remelted, it had m. p. 130—132°.

4 : 4′-*Dicyanotolane* was obtained from the preceding monobromostilbene but was best prepared directly from 4 : 4′-dicyano-αβ-dibromo-αβ-diphenylethane. This (50 g.) was suspended in a mixture of ethyl alcohol (640 c.c.) and 10% methyl-alcoholic potash and refluxed for 2 hours; the solid was then collected hot, washed with a little hot alcohol and with water, and dried in the oven. The product (18·85 g.) was recrystallised from glacial acetic acid (550 c.c.); yield 16·7 (64·5%), m. p. 252—255°. The alcoholic liquors deposited a further 5·85 g. of the crude product on cooling (Found : N, 12·0; C, 84·4; H, 3·5. $C_{16}H_8N_2$ requires N, 12·3; C, 84·2; H, 3·5%).

4-*Bromo*-4′-*cyanostilbene*.—Residues from mother-liquors of crystallisations of 4 : 4′-dicyanostilbene (kindly supplied by Mr. J. F. Grove, of these laboratories) were sublimed at 250°/1 mm. The product had m. p. 180—220°. Extraction with benzene gave a more soluble fraction which, on fractional crystallisation from glacial acetic acid, gave colourless prisms, m. p. 187—188° (Found : Br, 27·9; N, 5·3. $C_{15}H_{10}NBr$ requires Br, 28·1; N, 4·9%).

2-*Cyano*-4-*amidinostilbene* was obtained in the usual way. On basifying a solution of the hydrochloride, it formed fine prisms, m. p. 200—205° (decomp.) (Found : N, 16·5. $C_{16}H_{13}N_3$ requires N, 17·1%). Attempts to obtain the diamidine by the sodamide method (B.P. 538,463) failed.

4 : 4′-*Diamidinotolane dihydrochloride* was obtained in the usual way from the dinitrile through the iminoether. It formed a hemihydrate (Found : N, 16·1; loss at 100°/2 mm., 3·0. $C_{16}H_{14}N_4,2HCl,\frac{1}{2}H_2O$ requires N, 16·3; H_2O, 2·6%).

cis-4 : 4′-*Dicyanostilbene*.—4 : 4′-Dicyanotolane (34 g.) was suspended in dioxan (350 c.c.), 3·5 g. of Raney nickel catalyst added, and the suspension shaken in hydrogen (30 atm.) for 23 mins. at 60°. The uptake was 1·2 g.-mols. After separation of the catalyst and standing, a small amount of unchanged material separated. This was removed, and the solution concentrated under reduced pressure. On cooling, the cis-*stilbene* crystallised in heavy prisms, m. p.

152—154°; yield 30 g. (87·5%) (Found : N, 12·0. $C_{16}H_{10}N_2$ requires N, 12·2%). On boiling in nitrobenzene solution with a trace of iodine for a few minutes, it was converted into the *trans*-compound, m. p. 278—280·5°.

cis-4 : *4′-Diamidinostilbene.*—This was prepared in the usual manner from the dinitrile through the iminoether. The solution of the amidine hydrochloride was treated with dilute sulphuric acid to remove some *trans*-4 : 4′-diamidinostilbene as its sparingly soluble sulphate. The *trans*-compound may have been formed in the preparation of the iminoether or its conversion into amidine, or it may have been derived from a small quantity of the *trans*-isomer present in the original *cis*-stilbene dinitrile. The base was obtained as an almost white crystalline solid on adding 50% sodium hydroxide solution to an aqueous solution of the hydrochloride; it was a *monohydrate*, m. p. 204—206° (decomp.) (Found : N, 19·75; loss, 4·35. $C_{16}H_{16}N_4,H_2O$ requires N, 19·8; H_2O, 6·4%).

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