62. *Attempts to find New Chemotherapeutic Amidines. Part IX. Derivatives of* 1 : 1-*Diphenylethylene and Naphthalene.*

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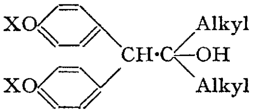
4 : 4′-Diamidino-derivatives of 1 : 1-diphenylethylene, 1 : 1-diphenyl-2-methyl-, and 1 : 1-diphenyl-2 : 2-dimethylethylene, and 6 : 6′-diamidino-derivatives of 1 : 3-di-β-naphthoxypropane, 1 : 5-di-β-naphthoxypentane, and 2 : 2′-dimethoxy-1 : 1′-dinaphthylmethane have been prepared. These products exhibited little or no trypanocidal activity.

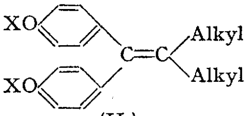
PREVIOUS papers from these laboratories have described the synthesis of diamidino-derivatives of stilbene and of substituted stilbenes (Ashley, Barber, Ewins, Newbery, and Self, *J.*, 1942, **103**; Barber, Slack and Woolman, *J.*, 1943, 99; Barber and Slack, *J.*, 1944, 612; Ashley and Harris, *J.*, 1946, 567). In view of the trypanocidal activities of 4 : 4′-diamidinostilbene ("Stilbamidine") (Kirk and Sati, *Ann. Trop. Med. Parasitol.*, 1940, **34**, 83; Napier, Sen Gupta, and Sen, *Indian Med. Gaz.*, 1942, **77**, 321) and of 4 : 4′-diamidino-αβ-dimethylstilbene (Fulton and Yorke, *Ann. Trop. Med. Parasitol.*, 1942, **36**, 131), it was decided to examine the properties of the isomeric compounds derived from 1 : 1-diphenylethylene, and to determine what effect, if any, was caused by the isomerism. Also, since 4′ : 4″-diamidino-1 : 3-diphenoxypropane ("Propamidine") and 4′ : 4″-diamidino-1 : 5-diphenoxypentane ("Pentamidine") are active trypanocidal agents, it was considered desirable to prepare the corresponding derivatives of naphthalene and ascertain what effect the extra benzene ring had on the activity.

Stoermer and Simon (*Ber.*, 1904, **37**, 4168) described the preparation of 4′-bromo-1 : 1-diphenylethylene by reaction of 4-bromobenzophenone with methylmagnesium iodide and decomposition of the resulting carbinol by distillation under reduced pressure. 4′ : 4″-*Dibromo*-1 : 1-*diphenylethylene*, 4′ : 4″-*dibromo*-1 : 1-*diphenyl*-2-*methylethylene*, and 4′ : 4″-*dibromo*-1 : 1-*diphenyl*-2 : 2-*dimethylethylene* were prepared by analogous reactions from 4 : 4′-dibromobenzophenone and methyl, ethyl, and *iso*propyl halides respectively. These dibromo-compounds were converted into the corresponding *dicyanides* by heating with cuprous cyanide in pyridine, and thence by the usual method into the diamidines (*hydrochlorides*), the salts of which were considerably more soluble in water than those of the isomeric, symmetrical compounds derived from stilbene. Each of the three diamidines was very slightly active trypanocidally, and hence isomerisation of the symmetrical stilbene into the unsymmetrical 1 : 1-diphenylethylene is accompanied by loss of trypanocidal activity in the diamidino-derivatives.

In view of the results of Foldi and Demjen (*Ber.*, 1941, **74**, 930) and those described in B.P. 537,976, where dehydration of a carbinol of type (I) gives either (II) or (III) according to whether the dehydration is effected with dilute acid or by boiling in toluene with phosphorus oxychloride, it was considered of interest to determine whether any radical migration occurred, with formation of 4 : 4′-dibromo-αβ-dimethylstilbene, when 4′ : 4″-dibromo-1 : 1-diphenyl*iso*propylcarbinol was dehydrated by heating in toluene solution with phosphorus oxychloride. No migration occurred and only 4′ : 4″-dibromo-1 : 1-diphenyl-2 : 2-dimethylethylene was isolated.



(I.)



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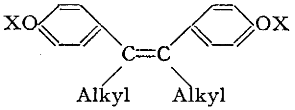

(III.)

Several unsuccessful attempts were made to prepare 4′ : 4″-dibromo-1 : 1-diphenyl-2 : 2-diethylethylene by interaction of 4 : 4′-dibromobenzophenone with *iso*amyl bromide and subsequent dehydration, but reduction of the ketone occurred and only 4 : 4′-dibromobenzhydrol was isolated. This accords with the results of Davies, Dixon, and Jones (*J.*, 1930, 1916) on the reaction of benzophenone with *iso*amyl bromide. Similarly substitution of cetyl bromide for *iso*amyl bromide (with the object of synthesising a diamidine which might be soluble in oil) led to reduction of the ketone, and formation of a wax-like hydrocarbon.

The only diamidino-derivatives of naphthalene which were known at the time when this work was in progress were 2 : 6- and 2 : 7-diamidinonaphthalene (King and Wright, *J.*, 1939, 253); these exhibited trypanocidal activity. In view of the activity of 4′ : 4″-diamidino-1 : 3-diphenoxypropane and 4′ : 4″-diamidino-1 : 5-diphenoxypentane it was decided to attempt the synthesis of the corresponding naphthalene homologues. 1 : 5-*Di*-α-*naphthoxypentane*, prepared by condensation of α-naphthol with pentamethylene dibromide, was readily brominated in chloroform at room temperature to 2′ : 2″ : 4′ : 4″-*tetrabromo*-, or in more dilute solution at a lower temperature to 4′ : 4″-*dibromo*-1 : 5-*di*-α-*naphthoxypentane* [cf. bromination of anisole (Michaelis and Weitz, *Ber.*, 1887, **20**, 49; Bodroux, *Compt. rend.*, 1903, **136**, 378); bromination of 1-naphthyl ethyl ether (Marchetti, *Gazzetta*, 1879, **9**, 544); bromination of diphenyl ether (Maihle and Murat, *Compt. rend.*, 1912, **154**, 603; Le Fèvre, Saunders, and Turner, *J.*, 1927, 1169)]. Reaction of the latter with cuprous cyanide in pyridine yielded 4′ : 4″-*dicyano*-1 : 5-*di*-α-*naphthoxypentane*. No attempt was made to prepare the di-iminoether since these are not readily formed from 1-cyanonaphthalenes, and application of the sodamide method (Ewins *et al.*, B.P. 538,463) failed to yield any appreciable quantity of basic material.

6-Bromo-2-naphthol, prepared by reduction of 1 : 6-dibromo-2-naphthol (Fries and Schimmelschmidt, *Ber.*, 1925, **58**, 2840), was condensed with trimethylene and pentamethylene dibromides giving 6′ : 6″-*dibromo*-1 : 3-*di*-β-*naphthoxypropane* and 6′ : 6″-*dibromo*-1 : 5-*di*-β-*napthoxypentane* respectively. These were converted into the *dicyanides* by reaction with cuprous cyanide in pyridine and thence by the usual method into the corresponding diamidines.

6-Bromo-2-methoxynaphthalene condensed readily with formaldehyde in acid solution to give 6′ : 6″-*dibromo*-2′ : 2″-*dimethoxydi*-α-*naphthylmethane*, which was converted by the usual method into 6′ : 6″-*dicyano*- and 6′ : 6″-*diamidino*-2′ : 2″-*dimethoxydi*-α-*naphthylmethane*.

The above diamidino-derivatives of naphthalene formed hydrochlorides which were only very slightly soluble in water, and the solutions exhibited a marked tendency to form gels. None exhibited any significant trypanocidal activity.

An unsuccessful attempt was also made to prepare a diamidino-derivative of a dinaphthylethylene. 6-Bromo-2-methoxynaphthalene readily underwent chloromethylation yielding 6-*bromo*-2-*methoxy*-1-*chloromethylnaphthalene*. The chlorine atom in this compound was extremely reactive, and a few minutes' heating with methyl alcohol was sufficient to yield the corresponding methyl ether. Cook, Downer, and Hornung (*J.*, 1941, 502) described the preparation of 2 : 2′-dimethoxydi-α-naphthylethylene by reaction of 2-methoxy-1-chloromethylnaphthalene with silver nitrate, but the reaction of 6-bromo-2-methoxy-1-chloromethylnaphthalene with silver nitrate followed a very different course,* and no 6 : 6′-dibromo-2 : 2′-dimethoxydi-α-naphthylethylene was formed.

EXPERIMENTAL.

4 : 4′-*Dibromobenzophenone*.—This was prepared by bromination of diphenylmethane followed by oxidation with chromic acid, as described by Goldthwaite (*Amer. Chem. J.*, 1903, **30**, 448). The product (overall yield 20—25%) had m. p. 173°.

4′ : 4″-*Dibromo*-1 : 1-*diphenylethylene*.—Finely powdered 4 : 4′-dibromobenzophenone (62 g.) was added gradually to the Grignard reagent prepared from magnesium (7·9 g.), methyl iodide (44·5 g.), and ether (150 c.c.). After the initial reaction, more ether was added, and the mixture was gently refluxed for 0·5 hour. After treatment with ice and ammonium chloride, the ethereal solution yielded an oil which soon crystallised (70 g.). This was distilled at 224—230°/15 mm.; the distillate (44 g.) after crystallisation from alcohol had m. p. 84° (Found : Br, 49·0. $C_{14}H_{10}Br_2$ requires Br, 47·5%). Oxidation with chromic acid yielded 4 : 4′-dibromobenzophenone, showing that no migration of a phenyl group had occurred.

4′ : 4″-*Dicyano*-1 : 1-*diphenylethylene*.—A mixture of the above dibromo-compound (45 g.) cuprous cyanide (33 g.), and pyridine (33 c.c.) was heated at 200—220° (internal temp.) for 1·75 hours. The cold melt was extracted several times with hot hydrochloric acid (*d* 1·16), and the residue finally crystallised thrice from alcohol. The *dicyanide* crystallised in pale yellow prisms, m. p. 158—160° (Found : N, 11·9. $C_{16}H_{10}N_2$ requires N, 12·2%).

4′ : 4″-*Diamidino*-1 : 1-*diphenylethylene*.—The *dihydrochloride* was prepared *via* the di-iminoether dihydrochloride by the usual method. It crystallised from dilute hydrochloric acid in colourless plates or needles (Found : N, 15·2; Cl, 19·0. $C_{16}H_{16}N_4,2HCl,2H_2O$ requires N, 15·1; Cl, 19·0%).

4′ : 4″-*Dibromo*-1 : 1-*diphenyl*-2-*methylethylene*.—This was prepared similarly to the diphenyl derivative by using 4 : 4′-dibromobenzophenone (58 g.), magnesium (8 g.), ethyl iodide (52 g.), and ether (250 c.c.). The *compound* was a colourless oil (40 g.), b. p. 144—148°/0·08 mm. After removal of a small amount of unchanged ketone by treatment with Girard-T reagent, it crystallised from alcohol in colourless needles or long prisms, m. p. 64—66° (Found : Br, 45·0, 45·3. $C_{15}H_{12}Br_2$ requires Br, 45·45%).

4′ : 4″-*Dicyano*-1 : 1-*diphenyl*-2-*methylethylene*.—This was prepared by the usual method from the above dibromo-compound (7 g.), cuprous cyanide (7 g.), and pyridine (4 c.c.). The *dicyanide* (3·3 g.), purified by distillation under reduced pressure, crystallised from alcohol in colourless prisms, m. p. 120—122° (Found : N, 11·45. $C_{17}H_{12}N_2$ requires N, 11·5%).

4′ : 4″-*Diamidino*-1 : 1-*diphenyl*-2-*methylethylene*.—This was prepared by the usual method from the cyanide (3 g.) in a mixture of chloroform (12 c.c.) and alcohol (5 c.c.). The *dibenzoate* crystallised from 50% aqueous alcohol in clusters of prisms or needles, m. p. 276° (decomp.) (Found : N, 10·3. $C_{17}H_{18}N_4,2C_7H_6O_2$ requires N, 10·7%).

4′ : 4″-*Dibromo*-1 : 1-*diphenyl*-2 : 2-*dimethylethylene*.—This was prepared similarly to the monomethyl

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* This reaction, and the behaviour of related compounds, will be described by one of us (J. N. A.) in a subsequent communication.

derivative but from 4 : 4′-dibromobenzophenone (50 g.), magnesium (5·4 g.), *iso*propyl bromide (27 g.), and ether (125 c.c.). The *product* (37 g.) had b. p. 120°/21 mm. and crystallised from alcohol in colourless plates, m. p. 96° (Found : Br, 43·8. $C_{16}H_{14}Br_2$ requires Br, 43·7%).

In another experiment the reaction mixture was not heated, and after decomposition of the Grignard complex, the ether was removed at a low temperature. Part of the semi-solid material (5 g.) was boiled for 4 hours with toluene (15 c.c.) and phosphorus oxychloride (50 g.). After cooling, the mixture was poured on ice, and the toluene layer separated and dried (sodium sulphate). After removal of toluene under reduced pressure, the product was crystallised from alcohol; it melted at 94—95° and was shown by direct comparison to be 4′ : 4″-dibromo-1 : 1-diphenyl-2 : 2-dimethylethylene. Hence dehydration of the carbinol with phosphorus oxychloride had not caused any rearrangement.

4′ : 4″-*Dicyano*-1 : 1-*diphenyl*-2 : 2-*dimethylethylene*.—This was made by the usual method from the above dibromo-compound (36 g.), cuprous cyanide (22·5 g.), and pyridine (23 c.c.). The *dicyanide* (13 g.) had b. p. 284°/27 mm., and crystallised from methyl alcohol in colourless plates, m. p. 90° (Found : N, 10·8. $C_{18}H_{14}N_2$ requires N, 10·85%).

4′ : 4″-*Diamidino*-1 : 1-*diphenyl*-2 : 2-*dimethylethylene*.—The *dihydrochloride* crystallised from methyl alcohol–acetone in small prisms (Found : N, 14·0; Cl, 17·8. $C_{18}H_{20}N_4,2HCl,2H_2O$ requires N, 13·95; Cl, 17·7%).

1 : 5-*Di*-α-*naphthoxypentane*.—α-Naphthol (14·4 g.) was boiled in alcohol (50 c.c.) containing sodium ethoxide (from 2·3 g. of sodium) with pentamethylene dibromide (11·5 g.) for 3 hours. After removal of the alcohol, the *compound* was extracted with boiling light petroleum (b. p. 60—80°) and then recrystallised twice from alcohol. It separated in glistening colourless plates (4 g.), m. p. 80—81° (Found : C, 83·8; H, 6·5. $C_{25}H_{24}O_2$ requires C, 84·3; H, 6·7%).

4′ : 4″-*Dibromo*-1 : 5-*di*-α-*naphthoxypentane*.—Bromine (5·6 g.) in chloroform (40 c.c.) was added slowly to a stirred ice-cold solution of 1 : 5-di-α-naphthoxypentane (6 g.) in chloroform (40 c.c.). The temperature was then allowed to rise slowly to 15°. Evaporation of the chloroform gave the *compound*, which crystallised from acetone in colourless prisms, m. p. 100° (Found : Br, 31·0. $C_{25}H_{22}O_2Br_2$ requires Br, 31·1%).

2′ : 2″ : 4′ : 4″-*Tetrabromo*-1 : 5-*di*-α-*naphthoxypentane*.—Bromine (2·8 g.) in chloroform (5 c.c.) was added to 1 : 5-di-α-naphthoxypentane (3 g.) in chloroform (5 c.c.). Rapid reaction occurred and the *tetrabromo*-compound soon crystallised. It formed colourless needles from chloroform–alcohol, m. p. 136° (Found : Br, 47·35. $C_{25}H_{20}O_2Br_4$ requires Br, 47·5%).

4′ : 4″-*Dicyano*-1 : 5-*di*-α-*naphthoxypentane*.—A mixture of the above dibromo-compound (2·6 g.), cuprous cyanide (1 g.), and pyridine (1 c.c.) was heated at 180—200° for 1·5 hours. The reaction mixture was extracted with cold hydrochloric acid (*d* 1·16) and the crude *dicyanide* (1·9 g.) crystallised from acetic acid; m. p. 177° (Found : N, 7·05. $C_{27}H_{22}O_2N_2$ requires N, 6·9%).

6′ : 6″-*Dibromo*-1 : 3-*di*-β-*naphthoxypropane*.—A mixture of 6-bromo-2-naphthol (20 g.) in alcohol (60 c.c.), potassium hydroxide (5 g.) in water (10 c.c.), and trimethylene dibromide (10 g.) was boiled under reflux for 20 hours. After removal of most of the alcohol, and addition of water, the pasty solid was washed with ether. The *product* (12 g.) crystallised from glacial acetic acid in long flat prisms, m. p. 177° (Found : Br, 32·8. $C_{23}H_{18}O_2Br_2$ requires Br, 32·9%).

6′ : 6″-*Dicyano*-1 : 3-*di*-β-*naphthoxypropane*.—A mixture of the dibromo-compound (7 g.), cuprous cyanide (3·5 g.), and pyridine (3 c.c.) was heated for 2 hours while the temperature of the melt was maintained at 200—210°. The *dicyanide* was worked up in the usual way and crystallised from glacial acetic acid in colourless needles (3·5 g.), m. p. 220—222° (Found : N, 7·3. $C_{25}H_{18}O_2N_2$ requires N, 7·4%).

6′ : 6″-*Diamidino*-1 : 3-*di*-β-*naphthoxypropane*.—This was prepared by the usual method from the dicyanide. The *di-isethionate* crystallised from alcohol–acetone; m. p. 259° (Found : N, 8·2. $C_{25}H_{24}O_2N_4,2C_2H_6O_4S$ requires N, 8·4%).

6′ : 6″-*Dibromo*-1 : 5-*di*-β-*naphthoxypentane*.—A mixture of 6-bromo-2-naphthol (20 g.) in alcohol (50 c.c.), potassium hydroxide (5 g.) in water (10 c.c.), and pentamethylene dibromide (10·5 g.) was boiled under reflux for 20 hours. The *product* (16 g.) was isolated by removal of most of the alcohol and addition of water. It crystallised from acetic acid in colourless needles, m. p. 147—148° (Found : Br, 30·5. $C_{25}H_{22}O_2Br_2$ requires Br, 31·1%).

6′ : 6″-*Dicyano*-1 : 5-*di*-β-*naphthoxypentane*.—This was prepared by the usual method from the dibromo-compound (5 g.), cuprous cyanide (2·2 g.), and pyridine (3 c.c.). The *dicyano*-compound (2·8 g.) crystallised from acetic acid in colourless prisms, m. p. 182—183° (Found : N, 7·0. $C_{27}H_{22}O_2N_2$ requires N, 6·9%).

6′ : 6″-*Diamidino*-1 : 5-*di*-β-*naphthoxypentane*.—The *dihydrochloride* crystallised from dilute hydrochloric acid in fine fibres, m. p. 245° (Found : N, 9·9. $C_{27}H_{28}O_2N_4,2HCl,2H_2O$ requires N, 10·2%). The *di-isethionate* crystallised in colourless fibres from methyl alcohol–acetone, m. p. 194—195° (Found : N, 7·7. $C_{27}H_{28}O_2N_4,2C_2H_6O_4S,2H_2O$ requires N, 7·7%).

6 : 6′-*Dibromo*-2 : 2′-*dimethoxydi*-α-*naphthylmethane*.—A hot solution of 6-bromo-2-methoxynaphthalene (18 g.) in acetic acid (80 c.c.) was treated with a mixture of aqueous formaldehyde (40%; 12 c.c.) and acetic acid (12 c.c.). Sulphuric acid (1 c.c.) was added, and the mixture heated on the steam-bath. The *product* (17 g.) soon separated and after 15 minutes the mixture was cooled and filtered. The residue crystallised from anisole in colourless polyhedra, m. p. 246—248° (Found : Br, 32·3. $C_{23}H_{18}O_2Br_2$ requires Br, 32·9%).

6 : 6′-*Dicyano*-2 : 2′-*dimethoxydi*-α-*naphthylmethane*.—This was prepared by the usual method from the dibromo-compound (11 g.), cuprous cyanide (5·5 g.), and pyridine (5 c.c.). It (3·6 g.) crystallised from anisole in clusters of needles, m. p. 262—264° to a red liquid (Found : N, 7·3. $C_{25}H_{18}O_2N_2$ requires N, 7·4%).

6 : 6′-*Diamidino*-2 : 2′-*dimethoxydi*-α-*naphthylmethane*.—This was prepared by the usual method. The *di-isethionate* crystallised from methyl alcohol–acetone in clusters of colourless rods, m. p. 258—261° (Found : N, 8·4. $C_{25}H_{24}O_2N_4,2C_2H_6O_4S$ requires N, 8·4%).

6-*Bromo*-2-*methoxy*-1-*chloromethylnaphthalene*.—Hydrogen chloride was passed into a suspension of trioxymethylene (5 g.) in glacial acetic acid (60 c.c.) until a clear solution was obtained. A solution of

6-bromo-2-methoxynaphthalene (10 g.) in glacial acetic acid (50 c.c.) was then added, and passage of hydrogen chloride continued until crystals started to separate. After 24 hours the product (10·4 g.) was filtered off, washed with ether, and crystallised from light petroleum (b. p. 80—100°). 6-*Bromo*-2-*methoxy*-1-*chloromethylnaphthalene* separated in colourless needles, m. p. 137—139° (Found: C, 50·6; H, 3·8; total halogen as Br, 56·1. $C_{12}H_{10}OClBr$ requires C, 50·4; H, 3·5; total halogen as Br, 56·0%). When this product was boiled for a few minutes with a little methyl alcohol, it was converted into 6-*bromo*-2-*methoxy*-1-*methoxymethylnaphthalene*, which crystallised from methyl alcohol or light petroleum (b. p. 80—100°) in colourless plates or needles, m. p. 115—116° (Found: C, 55·2; H, 4·6; Br, 28·3; OMe, 20·5. $C_{13}H_{13}O_2Br$ requires C, 55·5; H, 4·6; Br, 28·5; OMe, 22·1%).

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