34. *Bromination of Diphenylalkanes and the Preparation of Some Stilbene Derivatives. Part II.* βγ-*Diphenyl*-n-*butane.*

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The method of bromination of αβ-diphenylethane (Barber *et al.*, this vol., p. 1) has now been extended to βγ-diphenyl-*n*-butane, and the preparation of 4 : 4′-diamidino-αβ-dimethylstilbene accomplished.

The therapeutic activity of 4 : 4′-diamidinostilbene (stilbamidine) has led to the investigation of homologous stilbene derivatives. The preparation of 4 : 4′-dicyanostilbene from αβ-diphenylethane through its tetrabromo-derivative (Barber *et al.*, *loc. cit.*) suggested that a similar method might be used with the next higher homologue.

Both the *meso*- (solid) and the racemic (liquid) form of βγ-diphenyl-*n*-butane (I) were readily obtained from α-phenylethyl chloride and magnesium.

Attempted brominations of the hydrocarbon in chloroform or nitrobenzene were unsuccessful, the hydrocarbon being either recovered unchanged or converted into a tar, but bromination in 95% acetic acid gave a mixture of 4 : 4′-*dibromo*-βγ-*diphenyl*-n-*butane* (II) and 4 : 4′ : β : γ-*tetrabromo*-βγ-*diphenyl*-n-*butane* (III).

The tetrabromo-compound separated readily from the hot reaction mixture in a pure condition. When *meso*-βγ-diphenyl-*n*-butane was used, the more soluble *meso*-dibromo-compound crystallised from the mother-liquors on cooling; from the racemic hydrocarbon, a liquid dibromo-compound was isolated as a dark tarry liquid on dilution of the bromination liquors with water. This was contaminated with a small amount of (III) and could not be distilled until zinc dust reduction, followed by catalytic hydrogenation, had removed this impurity. When distillation was attempted without these precautions, decomposition of the contaminating material rapidly set in.

The orientation of (II) was confirmed by the production of a small amount of the *meso*-compound from α-(*p*-bromophenyl)ethyl chloride by the action of sodium. Further bromination of both *meso*- and *dl*-dibromodiphenylbutanes was not achieved. This was in marked contrast to the behaviour of dibromodiphenylethane, which can be further brominated in the αβ-positions in glacial acetic acid solution (*loc. cit.*). In further contrast to the bromination of diphenylethane no 2 : 4′-dibromo-product has been obtained from numerous brominations in this series and, apart from the three compounds already reported, only a small amount of a hexabromo-derivative has on one occasion been isolated.

Reduction of 4 : 4′ : β : γ-tetrabromo-βγ-diphenyl-*n*-butane with cuprous salts in pyridine did not proceed satisfactorily, but reduction with zinc dust in glacial acetic acid was rapid, a mixture of cis- and trans-4 : 4′-*dibromo*-αβ-*dimethylstilbenes* (IV) being produced.

The proportion of *cis*- to *trans*-isomer may depend on the configuration of the tetrabromo-compound; the latter is presumably a mixture of the *meso*- and the racemic form and a preponderance of the *meso*-form would give a larger proportion of *cis*-stilbene (cf. reduction of the low-melting form of αβ-dibromo-αβ-diphenylethane to give *iso*-stilbene; Otto and Stoffel, *Ber.*, 1897, **30**, 1799).

The conversion of *cis*-dibromodimethylstilbene into the higher-melting *trans*-form was accomplished by heating in nitrobenzene solution containing a trace of iodine (Ruggli, *Helv. Chim. Acta*, 1937, **20**, 39), or by the addition of hydrogen bromide to give 4 : 4′ : β-*tribromo*-βγ-*diphenyl*-n-*butane* (V), followed by thermal decomposition. This method of eliminating a molecule of hydrogen bromide was preferable to treatment with alcoholic potash, which gave an oil.

Attempts to prepare the stilbene directly from (II) by catalytic dehydrogenation failed.

Both *cis*- and *trans*-dibromodimethylstilbene were oxidised by chromic acid to *p*-bromobenzoic acid and on

catalytic reduction the *cis*-form readily absorbed two atoms of hydrogen to give *meso*-4 : 4'-dibromo-βγ-diphenyl-*n*-butane. *trans*-Dibromodimethylstilbene could not be reduced catalytically. Similarly, the *cis*-compound took up two atoms of bromine instantaneously to give (III), but the *trans*-form did not absorb bromine in the cold.

The conversion of (II) (both forms) and (IV) (*trans*-form) into the corresponding *nitriles* was effected by heating with cuprous cyanide in pyridine (cf. B.P. 543,204), but the product from *cis*-4 : 4'-dibromo-αβ-dimethylstilbene was a thick gum which resisted purification. Only moderate yields (47%) were obtained in the case of the stilbene, but the substitution of quinoline for pyridine effected a marked improvement, the best results being obtained when a mixture of cuprous cyanide and (IV) was fed slowly into the boiling solvent. We attribute the poor yields obtained by the usual method to the formation of a stable metallic complex between the nitrile initially formed and unconverted cuprous cyanide.

An attempt to brominate *meso*-4 : 4'-dicyano-βγ-diphenyl-*n*-butane in glacial acetic acid was unsuccessful.

We have not isolated any 4-bromo-4'-cyano-αβ-dimethylstilbene from this cyanation reaction, but by analogy with the unsubstituted stilbene it is presumably formed as an intermediate. *trans*-4 : 4'-Dicyano-αβ-dimethylstilbene did not absorb bromine in the cold to give βγ-dibromo-4 : 4'-dicyano-βγ-diphenyl-*n*-butane.

The two 4 : 4'-diamidino-βγ-diphenyl-*n*-butanes and *trans*-4 : 4'-diamidino-αβ-dimethylstilbene have been prepared and the activity of the last against *T. congolense* is extremely promising (Fulton and Warrington-Yorke, *Ann. Trop. Med. Parasit.*, 1942, **36**, 131). The investigations are continuing.

Experimental.

Phenylmethylcarbinol.—This was prepared in 68% yield from benzaldehyde by a method essentially that described by Grignard (*Zentr.*, 1901, II, 623), and also, in 95% yield, as follows: Acetophenone (40 g.) in methanol (100 c.c.) was reduced catalytically at 30 atms. in the presence of Raney nickel (1·5 g.). Reduction was complete (95% uptake) in 35 minutes, the maximum temperature attained being 60°. After removal of the catalyst and solvent the residue was vacuum-distilled, b. p. 92—93°/16 mm.; yield, 39·6 g.

*βγ-Diphenyl-*n*-butane* (cf. Engler and Bethge, *Ber.*, 1874, **7**, 112).—α-Phenylethyl chloride (118 g.) in dry ether (300 c.c.) was added to magnesium (10 g.) in ether (100 c.c.) at such a rate that the mixture boiled vigorously. Refluxing was continued overnight and after the reaction mixture had been worked up in the known manner the solvent was removed and the residue distilled. The distillate (63 g.), b. p. 132—134°/1 mm., was boiled with methanol (100 c.c.), from which the solid (*meso*-)hydrocarbon separated in white plates (23 g.) (24·5%), m. p. 124° (lit., 125—126°). Removal of the methanol from the mother-liquor left the crude racemic hydrocarbon, which was purified by fractional distillation, b. p. 153—156°/14 mm.; yield, 38 g. (38·6%) (Found: C, 91·0; H, 8·0. Calc. for $C_{16}H_{18}$: C, 91·4; H, 8·6%).

4 : 4' : β : γ-*Tetrabromo-βγ-diphenyl-*n*-butane.—*meso*-βγ-Diphenyl-*n*-butane (20 g.) was suspended in glacial acetic acid (208 c.c.) and water (7·8 c.c.), bromine (93 g.) added, and the whole refluxed for 4 hours. The mother-liquor was decanted, and the heavy sandy crystals of the *tetrabromo*-compound washed three times with boiling glacial acetic acid and finally with water; yield 13 g. (25%); m. p. 178—185° (decomp.) (Found: C, 36·5; H, 2·5; Br, 61·5. $C_{16}H_{14}Br_4$ requires C, 36·5; H, 2·7; Br, 60·8%).

An identical tetrabromo-compound (58·5 g.), m. p. 170—180° (decomp.), was obtained in a similar manner from 100 g. of the racemic hydrocarbon.

meso-**4 : 4'-*Dibromo-βγ-diphenyl-*n*-butane.**—The acid liquors resulting from the bromination of *meso*-βγ-diphenyl-*n*-butane were cooled, and the crystalline deposit recrystallised from glacial acetic acid, giving the pure *dibromo*-compound, m. p. 160—161°; yield 11 g. (31%) (Found: Br, 43·3. $C_{16}H_{16}Br_2$ requires Br, 43·6%).

dl-**4 : 4'-*Dibromo-βγ-diphenyl-*n*-butane.**—The acid liquors from the bromination of the racemic hydrocarbon were diluted with water to about 2 l., zinc dust (10 g.) added, and the mixture heated on the steam-bath (mechanical stirring) for 30 mins. The oil was extracted with ether, washed, dried, and hydrogenated for 1 hour at 50 lb. per sq. in., Adams's platinum catalyst being used. The solvent was then removed, and the residue vacuum-distilled to give the dl-*dibromo*-compound as a pale yellow oil, b. p. 166—171°/0·3—0·4 mm.; yield 60 g. (34·5%) (Found: Br, 44·0%).

α-(p-*Bromophenyl*)*ethyl Alcohol.*—The method of preparation was essentially that of Ziegler and Tiemann (*Ber.*, 1922, **55**, 3406). Some of the carbinol lost water on distillation to give a mixture of *p*-bromostyrene, m. p. 114—115°, and the required carbinol, b. p. 127—130°/11—12 mm.; yield, 27 g. The urethane (recrystallised from alcohol) had m. p. 103—104° (Quelet, *Bull. Soc. chim.*, **45**, 75, gives m. p. 103—104°).

α-(p-*Bromophenyl*)*ethyl Chloride.*—The above alcohol (25 g.) was cooled to 0°, thionyl chloride (15·8 g.) added in portions of 0·5 c.c., the mixture heated on the steam-bath for 1¼ hours, poured on ice, and stirred for 30 minutes, and the product separated, washed till neutral with sodium carbonate solution, dried (calcium chloride), and distilled to give a pinkish pungent oil, b. p. 115—120°/11—12 mm.; yield, 22 g. (81%).

Condensation of α-(p-*Bromophenyl*)*ethyl Chloride in Presence of Sodium.*—The chloride (22·0 g.), which would not react with magnesium in ether, was refluxed with sodium wire (1·8 g.) in dry benzene for 60 hours. The solution was then filtered, the solvent removed, and the product fractionated. The fraction distilling at 100—200°/12 mm. (2 g.) was treated with 30 c.c. of boiling methanol, from which sparkling prisms were deposited (0·3 g.), m. p. 155°, identical with *meso*-4 : 4'-dibromo-βγ-diphenyl-*n*-butane.

Reduction of **4 : 4' : β : γ-*Tetrabromo-βγ-diphenyl-*n*-butane with Zinc.**—Unsuccessful attempts were made to dehydrogenate 4 : 4'-dibromo-βγ-diphenyl-*n*-butane with palladised charcoal at 300° or with copper chromite in boiling nitrobenzene and to reduce 4 : 4' : β : γ-tetrabromo-βγ-diphenyl-*n*-butane with cuprous chloride in pyridine at 200° or with cuprous cyanide in boiling quinoline.

The following experiments, carried out with different samples of 4 : 4' : β : γ-tetrabromo-βγ-diphenyl-*n*-butane, illustrate the wide variation in the results obtained.

(*a*) 4 : 4' : β : γ-Tetrabromo-βγ-diphenyl-*n*-butane (4·6 g.) was suspended in boiling glacial acetic acid (25 c.c.), and zinc dust (1·0 g.) cautiously added. After refluxing for 15 minutes, the liquor was decanted into water. The oil obtained rapidly solidified; it crystallised from alcohol (20 c.c.) in white prisms (2·27 g.), m. p. 90—92°, of cis-4 : 4'-*dibromo-αβ-dimethylstilbene* (Found: Br, 43·7. $C_{16}H_{14}Br_2$ requires Br, 43·7%).

(*b*) 4 : 4' : β : γ-Tetrabromo-βγ-diphenyl-*n*-butane (288 g.) was suspended in glacial acetic acid (1 l.) and reduced as before with zinc dust (50 g.). The solid obtained by decantation into water was dried, washed with ether, and recrystallised from glacial acetic acid, from which it was obtained in yellow plates (115 g.), m. p. 125—128° (Found: Br, 44·0%). The ethereal washings contained the *cis*-compound contaminated with some of the *trans*-form.

Oxidation of the stilbenes obtained from (*a*) and (*b*) with chromic acid in acetic acid gave *p*-bromobenzoic acid, m. p. 250°, in 67% yield from the *cis*- and 72% yield from the *trans*-compound.

Conversion of cis-4 : 4′-*Dibromo-αβ-dimethylstilbene into the* trans-*Form.*—The *cis*-compound (0·1 g.) was refluxed in nitrobenzene (1·0 c.c.) containing a trace of iodine. Slow crystallisation produced a yellow solid (0·07 g.), m. p. 125—126°, not depressed by authentic *trans*-dibromodimethylstilbene.

4 : 4′ : *β-Tribromo-βγ-diphenyl*-n-*butane.*—A solution of *cis*-4 : 4′-dibromo-αβ-dimethylstilbene (30·3 g.) in dry chloroform (180 c.c.) was saturated with dry hydrogen bromide at 0°, the solvent removed under reduced pressure at 35—40°, and the residual solid triturated with glacial acetic acid (30—40 c.c.), washed, and dried in a vacuum. The *tribromo*-compound separated from glacial acetic acid in white rhombs (29 g.) m. p. 112—115° (decomp.) (Found : Br, 53·9. $C_{16}H_{15}Br_3$ requires Br, 53·8%).

Thermal Decomposition of 4 : 4′ : *β-Tribromo-βγ-diphenyl*-n-*butane.*—The compound (25 g. in 5 g. portions) was heated at 150—200° for 10 minutes with constant stirring. The melts were washed out with boiling glacial acetic acid (200 c.c. in all); this was treated with charcoal and filtered hot. *trans*-4 : 4′-Dibromo-αβ-dimethylstilbene (15 g.) separated on cooling, m. p. 125—126°.

Catalytic Reduction of cis-4 : 4′-*Dibromo-αβ-dimethylstilbene.*—The compound (1·8 g.) was dissolved in acetone (50 c.c.) and treated with hydrogen in the presence of platinum catalyst (0·1 g.) for 2—3 minutes, the solution filtered, and the solvent distilled. Crystallisation of the residue from alcohol gave slightly impure *meso*-4 : 4′-dibromo-βγ-diphenyl-*n*-butane, m. p. 151—153°.

Addition of Bromine to cis-4 : 4′-*Dibromo-αβ-dimethylstilbene.*—The compound (0·8 g.) was dissolved in chloroform (5 c.c.), and bromine (0·4 g.) in chloroform (5 c.c.) added. There was an immediate uptake of bromine. The solvent was removed at 30°, and the residue recrystallised twice from chloroform–alcohol; m. p. 170—175° (decomp.).

dl-4 : 4′-*Dicyano-βγ-diphenyl*-n-*butane.*—*dl*-4 : 4′-Dibromo-βγ-diphenyl-*n*-butane (55 g.) was heated with cuprous cyanide (33 g.) and pyridine (40 c.c.) at 190—205° (internal temperature) for 2¼ hours. After dilution with pyridine (40 c.c.) the mixture was poured into concentrated hydrochloric acid (140 c.c.). The resulting gum was extracted with ether, and the extracts washed until neutral, dried, and distilled. The *dinitrile* was a pale yellow oil, b. p. 190—200°/1 mm. (Found : N, 10·4, 10·5. $C_{18}H_{16}N_2$ requires N, 10·75%).

meso-4 : 4′-*Dicyano-βγ-diphenyl*-n-*butane.*—*meso*-4 : 4′-Dibromo-βγ-diphenyl-*n*-butane (5·0 g.) was heated with cuprous cyanide (3·0 g.) and pyridine (5 c.c.) for 2 hours at 160—190° (internal temperature), the mixture poured into concentrated hydrochloric acid, and the *dinitrile* filtered off, washed with hydrochloric acid and water, dried, and recrystallised (charcoal) from glacial acetic acid; m. p. 196—198°; yield 2·47 g. (70%) (Found : N, 10·7. $C_{18}H_{16}N_2$ requires N, 10·75%).

4 : 4′-*Dicyano-αβ-dimethylstilbene.*—*trans*-4 : 4′-Dibromo-αβ-dimethylstilbene (10 g.) and cuprous cyanide (5·4 g.) were fed slowly into boiling quinoline (30 c.c.). Refluxing was continued for 20 minutes, and the mixture poured into hot concentrated hydrochloric acid (100 c.c.). The granular solid which separated was collected, washed with hydrochloric acid and water, dried at 100° in a vacuum, and sublimed at 240°/1 mm. The sublimate crystallised from glacial acetic acid in buff-coloured needles, m. p. 216°; yield 5·3 g. (74%) (Found : N, 10·9. $C_{18}H_{14}N_2$ requires N, 10·85%).

4 : 4′-*Diamidino-βγ-diphenylbutane.*—(1) The *meso*-form was obtained in the usual way through the imino-ether hydrochloride (10 days) in 71% yield. The *amidine dihydrochloride* crystallised from acidified water in heavy rhombs (Found : N, 13·6, 13·8. $C_{18}H_{22}N_4,2HCl,H_2O$ requires N, 13·8%).

(2) The racemic form was obtained in the usual way through the iminoether hydrochloride. The amidine hydrochloride could not be isolated directly, but the sulphate was precipitated from a hot solution of the hydrochloride by sulphuric acid, separating as a microcrystalline powder. By treatment of the sulphate with barium chloride, filtration, and precipitation with acetone the *dihydrochloride* was obtained in a crystalline form (Found : N, 14·4. $C_{18}H_{22}N_4,2HCl$ requires N, 14·8%).

trans-4 : 4′-Diamidino-αβ-dimethylstilbene was obtained in the usual way through the iminoether hydrochloride (7 days). The *amidine dihydrochloride* was precipitated in yellow needles from hot acidified water, by addition of concentrated hydrochloric acid (Found : N, 13·8; Cl, 17·5; loss in weight at 2·0 mm., 9·4. $C_{18}H_{20}N_4,2HCl,2H_2O$ requires N, 13·95; Cl, 17·7; H_2O, 9·0%).

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