135. *Synthesis of Some Derivatives of 3 : 4-Diphenyl-*n*-hexane.*

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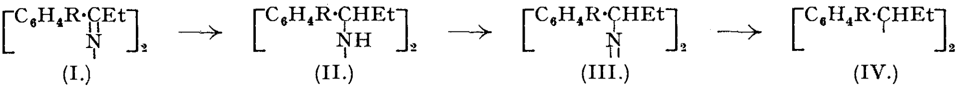
The two isomeric *pp'*-diamino-3 : 4-diphenyl-*n*-hexanes (IV; R = NH_2) were synthesised from p-*amino-* (I; R = NH_2) and p-*acetamido-propiophenoneazine* (I; R = NHAc) respectively by a route, (I) → (II) → (III) → (IV), employed first for the synthesis of hexœstrol (IV; R = OH) *via* its dimethyl ether by Földi and Fodor (*Ber.*, 1941, **74**, 589; cf. French Pat. 872,504; Hung. Priority 3 Jan., 1939; cf. Gilman, " Organic Chemistry ", 1945, II, p. 1485, and Bretschneider *et al.*, *Ber.*, 1941, **74**, 571). The steric configuration of these diamines was established by their conversion into *meso-* and *iso*-hexœstrol respectively (IV; R = OH). The *pp'*-diamino-3 : 4-diphenyl-*n*-hexanes and hexœstrol had been prepared in a similar way by Baker (*J. Amer. Chem. Soc.*, 1943, **65**, 1572) from *p*-propionamidopropiophenone azine, but no record of this paper had been available in Hungary. A new preparation of the two isomeric 3 : 4-diphenyl-*n*-hexanes (IV; R = H) by the azine route is also described. The crystalline isomer was converted *via* the pp'-*dinitro-* (IV; R = NO_2) and the pp'-*dibromo*-derivative (IV; R = Br) into the *meso-pp'*-diaminodiphenyl-*n*-hexane; the liquid 3 : 4-diphenyl-*n*-hexane yields by an analogous treatment the racemic diamine (IV; R = NH_2). The meso-NN'-*dicarbethoxy*-derivative (IV, R = $NH{\cdot}CO_2Et$) was also prepared.

In continuation of the work on 3 : 4-diphenyl-*n*-hexanes (Földi and Fodor, *loc. cit.*), we set out to synthesise some amino-analogues of synthetic sex hormones, especially as Lettré (*Z. physiol. Chem.*, 1943, **276**, 206) had found an amino-derivative of a natural hormone (equilin) to possess a high antimitotic activity. At first, *pp'*-diamino-3 : 4-diphenyl-*n*-hexane, an amino-analogue of hexœstrol, was prepared. This compound had been mentioned by Carlisle and Crowfoot (*J.*, 1941, 6; *Chem. Zentr.*, 1941, II, 1499), and Baker (*loc. cit.*) had recorded the preparation of these diamines by the ketazine route from *p*-propionamidopropiophenone, but we now record our results briefly, especially the preparation of new compounds, as our yields are better than Baker's (*loc. cit.*).

p-Acetamidopropiophenone azine (I; R = NH·Ac; for ketone, see Kunckell, *Ber.*, 1900, **33**, 2643) was converted *via* (II) into (III), an arylaliphatic azo-compound of relatively great stability (cf. ω-azotoluene, Thiele, *Annalen*, 1910, **376**, 265; Földi and Fodor, *loc. cit.*); at 240° it decomposed with evolution of nitrogen, yielding a mixture of the two stereoisomeric *pp'*-diacetamido-3 : 4-diphenyl-*n*-hexanes, separated by crystallisation. The sparingly soluble, higher-melting isomer was deacetylated by means of alcoholic potassium hydroxide, and the more soluble, lower-melting form by 3N-hydrochloric acid, to the corresponding diamines (IV; R = NH_2), m. p. 136—137° and 80° (uncorr.) respectively; Carlisle and Crowfoot (*loc. cit.*) record m. p. 140° for the *meso*-compound, but 98° for the racemate; Baker (*loc. cit.*) reported lower m. p.s, 132—134° and 63—65°, probably owing to incomplete separation of the two stereoisomers. We are unable to account for this discrepancy in the m. p. of the racemate as the method of the preparation of Carlisle and Crowfoot's compound, m. p. 98°, is unknown to us.

The steric configuration of the diamines is elucidated by the fact that the higher-melting isomer was converted by the diazo-method (cf. Baker, *loc. cit.*) into *meso*hexœstrol (Wessely and Welleba, *Ber.*, 1941, **74**, 777; cf. Carlisle and Crowfoot, *loc. cit.*); it is consequently *meso-pp'*-diamino-3 : 4-diphenyl-*n*-hexane; the lower-melting isomer similarly afforded the racemic *iso*hexœstrol (resolution by Wessely and Welleba, *loc. cit.*), and is therefore the racemic compound.



$$\left[C_6H_4R{\cdot}\underset{\underset{|}{N}}{\underset{\|}{C}}Et\right]_2 \longrightarrow \left[C_6H_4R{\cdot}\underset{\underset{|}{NH}}{\underset{|}{C}}HEt\right]_2 \longrightarrow \left[C_6H_4R{\cdot}\underset{\underset{\|}{N}}{\underset{|}{C}}HEt\right]_2 \longrightarrow \left[C_6H_4R{\cdot}\underset{|}{C}HEt\right]_2$$

(I.) (II.) (III.) (IV.)

By the same azine method, 4-aminopropiophenone (Kunckell, *loc. cit.*) was converted into the same *meso*-diamine, without isolation of any intermediates except the ketazine.

Finally, the steroisomeric 3 : 4-diphenyl-*n*-hexanes (IV; R = H), prepared from 1-bromopropylbenzene with ethylmagnesium bromide (Späth, *Monatsh.*, 1913, **34**, 2010) or with sodium (Lepin and Reich, *J. Russ. Phys. Chem. Soc.*, 1915, **47**, 154, 158), or from benzaldazine with ethylmagnesium bromide (Busch and Fleischmann, *Ber.*, 1910, **43**, 748), was prepared by the azine method from propiophenone azine (I; R = H) *via* 1 : 1-*diphenylazopropane* (III; R = H). Nitration of the " solid " 3 : 4-diphenyl-*n*-hexane led *via pp'*-dinitro-3 : 4-diphenyl-*n*-hexane (IV; R = NO_2) to the *meso*-diamine (IV; R = NH_2). The " liquid " 3 : 4-diphenylhexane similarly gave the racemic diamine (IV; R = NH_2). The " solid form " of diphenylhexane proved to be the *meso-*, and the " liquid form " the racemic compound (cf. Carlisle and Crowfoot, *loc. cit.*).

Another preparation of the *meso*-diamine was effected by bromination of the *meso*-compound (IV; R = H) to (IV; R = Br) (see Barber and Slack, *J.*, **1944**, 613), followed by treatment with aqueous ammonia under pressure at 200°.

meso-*pp'*-Diamino-3 : 4-diphenyl-*n*-hexane was assayed by Dr. L. Rigó by the Allen–Doisy test, and the results will be published elsewhere. However, Dodds *et al.* (*Proc. Roy. Soc.*, 1944, *B*, **132**, 83) show that this compound has a low œstrogenic activity (100 rat units per g.).

pp'-Diamino-3 : 4-diphenylhex-3-ene, an amino-analogue of stilbœstrol, has also a low œstrogenic activity (Vargha and Kovács, *Ber.*, 1942, **75**, 794). The hexane analogue will be examined by different tests for antimitotic and anticarcinogenic activity.

The NN'-*dicarbethoxy*-derivative (IV; R = $NH{\cdot}CO_2Et$) was also prepared in view of the influence of some amino-*s*-diarylethylenes, -arylurethanes, and other aromatic amines upon experimental animal tumours (*Ann. Rep. British Empire Cancer Campaign*, 1946, 25; cf. Boyland, *Biochem. J.*, 1946, **40**, 55).

EXPERIMENTAL.

(All m. p.s are uncorrected.)

p-*Acetamidopropiophenone Azine* (I; R = NHAc).—*p*-Acetamidopropiophenone (90·5 g.) was dissolved in hot alcohol (300 c.c.), and hydrazine hydrate (25 c.c.) and glacial acetic acid (20 c.c.) added. The mixture was refluxed for 15 mins. on a steam-bath, and the *azine* crystallised. After cooling, filtration, and washing with alcohol, it had m. p. 268—270° (84 g.; 93%). The product is pure, but may be recrystallized from nitrobenzene (Found: C, 69·65; H, 6·98. $C_{22}H_{26}O_2N_4$ requires C, 69·8; H, 6·9%).

p-*Aminopropiophenone Azine* (I; R = NH_2).—The ketone (5 g.) was dissolved in hot methanol (25 c.c.), and hydrazine hydrate (1 c.c.) and glacial acetic acid (1·5 c.c.) added; the mixture was boiled for 30 mins. on the steam-bath, then diluted with water (25 c.c.) and cooled. The *ketazine* (4·6 g.) separated as golden-yellow crystals, m. p. 140—141° (Found: C, 73·8, 73·8; H, 7·3, 7·8. $C_{18}H_{22}N_4$ requires C, 73·9; H, 7·5%).

pp'-*Diacetamido*-s-*bis*-(1-*phenylpropyl*)*hydrazine* (II; R = NHAc).—A suspension of the foregoing ketazine (38 g.) in ethanol (1400 c.c.) was stirred in the presence of palladium–charcoal catalyst (4 g., containing 20% $PdCl_2$, and saturated previously with hydrogen) in a three-necked flask connected with a source of hydrogen under atmospheric pressure, at 60°. After 6 hrs., 5400 c.c. of hydrogen had been absorbed (theor., 4400 c.c.), and a colourless solution obtained; the catalyst was filtered off, and a portion of the filtrate evaporated to dryness in a vacuum (with a stream of hydrogen passing through a capillary); white crystals (2 g.) resulted, m. p. 178—185°, and could be recrystallised from methanol–water (1 l.) in an atmosphere of hydrogen as it is very sensitive to oxygen. The greater part of the solution was transformed into the corresponding azo-compound (below).

s-*Di*-1 : 1'-(p-*acetamidophenyl*)*azopropane* (III; R = NHAc).—(*a*) Anhydrous potassium acetate (20 g.) was added to a solution of the foregoing hydrazo-compound (35 g.) in alcohol (1500 c.c.) cooled to 5°, and iodine (22 g.) added slowly. The iodine was decolorised and a crystalline solid separated; this was filtered off (23 g.), and the mother-liquor poured into water, affording a second crop (7 g.), and the filtrate, when evaporated until alcohol-free, gave a further 4 g. of the *azo*-compound. After recrystallisation from *n*-butanol, colourless crystals resulted which underwent partial decomposition at 200—260° (Found: C, 70·0; H, 7·3. $C_{22}H_{28}O_2N_4$ requires C, 69·4; H, 7·4%).

(*b*) The hydrazo-compound (23·4 g.) in alcohol (1500 c.c.) was mechanically stirred in an atmosphere of oxygen in the presence of 2N-sodium hydroxide (1·7 c.c.) and 10% copper sulphate solution (1·7 c.c.); 970 c.c. of oxygen were absorbed (theor., 990 c.c.); the azo-compound crystallised, and was filtered off and dried (10 g.), m. p. 200—300° (evolution of nitrogen). The mother-liquor on evaporation afforded a further 13 g. of the same compound.

pp'-*Diacetamido*-3 : 4-*diphenyl*-n-*hexane* (IV; R = NHAc).—The foregoing azo-compound (5·5 g.), suspended in diphenyl ether (5·5 c.c.), was heated in an air-bath to 240°; between 200° and 240° nitrogen was evolved (300 c.c., theor., 320 c.c.). After cooling, the mixture was treated with cold methanol (10 c.c.), filtered, washed with methanol (10 c.c.), and dried; white crystals (2·0 g.) of meso-pp'-*diacetamido*-3 : 4-*diphenyl*-n-*hexane* were obtained. After recrystallisation from ethyl acetoacetate or nitrobenzene, they had m. p. 318—321° (Found: C, 75·1; H, 8·4; N, 7·95. $C_{22}H_{28}O_2N_2$ requires C, 75·0; H, 8·0; N, 8·0%).

The methanolic mother-liquor was evaporated in a vacuum to dryness; the partly crystalline residue was dissolved in ether (10 c.c.) and cooled, and the resulting crystals were filtered off, washed with ether (20 c.c.) and dried (2·2 g.). After recrystallisation from alcohol–water, the racemic diacetamido-compound, had m. p. 190° (Found: C, 75·0; H, 8·0%).

pp'-*Diamino*-3 : 4-*diphenyl*-n-*hexane* (IV; R = NH_2).—(a) *From the corresponding acetamido-compound.* The acetamido-compound (2·5 g.; m. p. 320°) was boiled with alcohol (72·5 c.c.) and potassium hydroxide (14·5 g.) in a water-bath for 6 hrs., evaporated in a vacuum to dryness, and water (25 c.c.) added to the crystalline residue; the crystals (1·9 g.) were filtered off, and recrystallised from diluted alcohol (50%), or benzene–light petroleum (1 : 1); colourless prisms, m. p. 136—137°, of the *meso*-form were obtained.

Hydrochloride. The base (0·27 g.) was dissolved in 0·1N-hydrochloric acid (20 c.c.), and the solution cooled with ice and saturated with hydrogen chloride. The *dihydrochloride* (0·30 g.) crystallised in glistening needles, m. p. 338° (Found: C, 63·5; H, 7·9. $C_{18}H_{24}N_2,2HCl$ requires C, 63·3; H, 7·7%).

The racemic diamino-compound (0·7 g.) was obtained by heating the diacetamido-diphenylhexane (m. p. 190°) (1 g.) for 4 hrs. with 3N-hydrochloric acid (40 c.c.) and neutralising with ammonia; needles (from aqueous methanol), m. p. 80° (Found: C, 80·6; H, 9·0. Calc. for $C_{18}H_{24}N_2$: C, 80·5; H, 9·0%).

(b) *From* p-*aminopropiophenone azine* (I; R = NH_2). The solution of the amino-ketazine (5·98 g.)

in methanol (110 c.c.) and palladium-charcoal catalyst (0·5 g.) were shaken with hydrogen at room temperature and pressure. After 10 hrs. 870 c.c. of hydrogen had been absorbed (theor., 870 c.c.) and a colourless solution resulted. Anhydrous potassium acetate (4 g.) was added, the mixture cooled to 0°, and iodine (5 g.) added in small portions; the solution was diluted with water (300 c.c.), neutralised with potassium carbonate, and extracted with ether. The residue left on evaporation of the ether, a pale yellow oil, was heated in high vacuum in an oil-bath to 170°, nitrogen being evolved. The product yielded after recrystallisation from alcohol a small quantity of the *meso*-diamino-compound, m. p. 136—137° alone and mixed with the specimen obtained as in (a).

(c) *From* pp′-*dinitro*-3 : 4-*diphenyl*-n-*hexane* (IV; R = NO_2). (1) The dinitro-compound (2 g.; m. p. 170°) in alcohol (145 c.c.) was added to a suspension of palladium–charcoal catalyst (1 g.) in alcohol (20 c.c.), saturated previously with hydrogen, and shaken at room temperature and pressure. After 7 hrs., 830 c.c. of hydrogen had been absorbed (theor., 820 c.c.), and 4N-hydrogen chloride in anhydrous alcohol (6 c.c.) was then added, and the solution evaporated to dryness. The crystalline hydrochloride was recrystallised from alcohol and yielded 1·03 g. of pure hydrochloride, m. p. 332° alone and mixed with a specimen obtained as in (a). The mother-liquor yielded, after evaporation, recrystallisation, and neutralisation, a further 0·47 g. of the *meso*-diamino-compound, m. p. and mixed 136—137°.

(2) The vacuum-distilled dinitro-compound (4 g.) from liquid 3 : 4-diphenyl-*n*-hexane was dissolved in alcohol (100 c.c.) and hydrogenated catalytically as above. The resulting hydrochloride crystallised with difficulty; it was basified, the amino-compound extracted with ethyl acetate, the solvent evaporated, and the residual oil acetylated with acetic anhydride (10 c.c.) by heating on a water-bath; after evaporation, the acetyl compound was crystallised from aqueous acetic acid (1 : 1). Crystals of racemic *pp*′-diacetamido-3 : 4-diphenyl-*n*-hexane were isolated, m. p. 190—191° alone and mixed with an authentic specimen.

(d) *From* pp′-*dibromo*-3 : 4-*diphenyl*-n-*hexane.* The dibromo-compound, m. p. 168° (400 mg.), cuprous iodide (40 mg.), and concentrated aqueous ammonia (12 c.c.) were heated in a sealed tube to 205°. After 10 hrs. the tube was opened, the crystals (295 mg.) filtered off, treated with 0·1N-hydrochloric acid (20 c.c.), filtered from unchanged bromo-compound (175 mg.), then neutralised with concentrated ammonia. The *meso*-diamino-compound (100 mg.) was obtained, m. p. and mixed m. p. with the compound prepared as in (a) 136—137°.

1 : 1′-*Diphenylazopropane* (III; R = H).—Propiophenone azine (17 g.) was suspended in alcohol, added to a palladium–charcoal catalyst (1 g.) saturated with hydrogen, and shaken with hydrogen at 60° under atmospheric pressure. After 6 hrs. the theoretical quantity of hydrogen had been absorbed. The colourless solution of the hydrazo-compound was treated in the usual manner with iodine, and poured into water; a colourless oil and white crystals separated. The latter had m. p. 55° after recrystallisation from light petroleum (Found: C, 81·0; H, 8·3; N, 10·6. $C_{18}H_{22}N_2$ requires C, 81·2; H, 8·2; N, 10·5%), and both these and the liquid, on thermal decomposition, afforded a mixture of the two isomeric 3 : 4-diphenyl-*n*-hexanes, as follows.

3 : 4-*Diphenyl*-n-*hexane* (IV; R = H).—The reaction mixture obtained in the preceding experiment (16 g.) was heated to 170°; the theoretical volume (1200 c.c.) of nitrogen was evolved, and the residue was distilled in vacuum. 5 G. of lower-boiling by-product were followed by 7·5 g. of the isomers (IV; R = H), which were separated in the usual manner; the solid, *meso*-form, recrystallised from alcohol, had m. p. 92° (cf. Kohler, *Amer. Chem. J.*, 1906, **35**, 395). The liquid form was distilled; b. p. 298° (cf. Lepin and Reich, *loc. cit.*).

pp′-*Dinitro*-3 : 4-*diphenyl*-n-*hexane* (IV; R = NO_2).—(1) meso-*Form.*—The *meso*-diphenylhexane (5 g.) was added in small portions to concentrated ice-cold nitric acid (50 c.c.). The brown solution was kept for 5 mins. at 0°, then poured into ice-water (400 g.); pale yellow crystals separated. Recrystallised twice from glacial acetic acid, the pure *dinitro*-derivative (2·79 g.) was obtained, m. p. 170° (Found: C, 65·6; H, 6·3. $C_{18}H_{20}O_4N_2$ requires C, 65·8; H, 6·15%). From the mother-liquor of the recrystallisation a *trinitro*-derivative (probably the 2 : 2′ : 4-trinitro-compound) (2·18 g.) was isolated, m. p. 126—127° (Found: C, 57·7; H, 5·4. $C_{18}H_{19}O_6N_3$ requires C, 57·9; H, 5·1%).

Nitration of *meso*-3 : 4-diphenyl-*n*-hexane in concentrated sulphuric acid yielded another *trinitro*-derivative (probably 2 : 4 : 4′-trinitro-); pale yellow plates from glacial acetic acid, m. p. 217—218° (Found: N, 11·3. $C_{18}H_{19}O_6N_3$ requires N, 11·3%).

(2) *Racemic form.* Liquid 3 : 4-diphenyl-*n*-hexane (5 g.) was added as above to concentrated nitric acid (40 c.c.) with cooling; the brown solution was kept for 5 mins. at 0°, and then poured into water. The resulting oil was extracted with chloroform, washed with sodium hydrogen carbonate solution until neutral, dried, and distilled at 250° (air-bath temp.)/8—10 mm. The resulting yellow oil was reduced to the amino-compound as described above.

meso-pp′-*Dibromo*-3 : 4-*diphenyl*-n-*hexane* (IV; R = Br).—*meso*-3 : 4-Diphenyl-*n*-hexane (230 mg.) was fused, and bromine (0·12 c.c.) added dropwise with stirring. Hydrogen bromide was evolved, and the resulting red-brown mixture (380 mg.) was recrystallised from alcohol (15 c.c.), forming glistening, colourless needles (160 mg.), m. p. 163°. Recrystallisation from alcohol (15 c.c.) gave 100 mg., m. p. 168°. Barber and Slack (*loc. cit.*) recorded m. p. 170—172° (Found: C, 55·2; H, 5·0. Calc. for $C_{18}H_{20}Br_2$: C, 54·6; H, 5·1%).

Hexœstrol (meso-pp′-*Dihydroxy*-3 : 4-*diphenyl*-n-*hexane*) (IV; R = OH).—The *meso*-diamino-compound (2·1 g.) was dissolved in a solution of sulphuric acid (11·8 g.) in water (850 c.c.), and on cooling, the sulphate crystallised in micro-crystals. The suspension was cooled to 0° and 2% aqueous sodium nitrite (60·7 c.c.) was added dropwise (30 mins.) with stirring. Diazotisation was complete in 1 hr., and the solution was then rapidly heated to boiling; nitrogen was evolved at 85°, and a crystalline solid separated. This was crude hexœstrol (2 g., dry), m. p. 182—183°. After recrystallisation from benzene, it had m. p. 186° (Found: C, 80·1; H, 8·05. Calc. for $C_{18}H_{22}O_2$: C, 80·0; H, 8·2%).

iso*Hexœstrol* (*Racemic* pp′-*Dihydroxy*-3 : 4-*diphenyl*-n-*hexane*) (IV; R = OH).—The racemic diamino-compound (0·1 g.) was dissolved in 5% sulphuric acid (10 c.c.), 2% sodium nitrite solution (2·6 c.c.) added dropwise with cooling to + 2°, and the mixture kept for 1 hr. at this temperature. Then sulphuric acid (1 g.) and a trace of sodium sulphite were added, followed by rapid heating to boiling. The phenolic product separated as a brown solid. After distillation at 150—170°/0·02 mm., it melted at 125—126° alone and on admixture with an authentic specimen.

meso-pp′-*Biscarbethoxyamino*-3 : 4-*diphenyl*-n-*hexane* (IV; R = $NH \cdot CO_2Et$).—The *meso*-diamino-compound (268 mg.) and ethyl chloroformate (2 g.) were heated on a water-bath, the unchanged ester evaporated, and the residue treated with water and filtered off. The crystalline product (348 mg.) had m. p. 198—200°, increased by recrystallisation from ethanol to 200°; it was soluble in hot alcohol, insoluble in water (Found: C, 69·9; H, 7·7. $C_{24}H_{32}O_4N_2$ requires C, 69·9; H, 7·8%).

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