214. *Unsaturated Lactones. Part II. Phenolic Butenolides related to "Hexœstrol" and "Stilbœstrol."*

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Phenolic butenolides analogous to the synthetic œstrogens, 3 : 4-di-(*p*-hydroxyphenyl)-*n*-hexane (hexœstrol) and 3 : 4-di-(*p*-hydroxyphenyl)-*n*-hex-3-ene (stilbœstrol), have been prepared.

Since the discovery of the potent synthetic œstrogens now known as hexœstrol (Campbell, Dodds, and Lawson, *Nature*, 1938, **142**, 1121), stilbœstrol (Dodds, Golberg, Lawson, and Robinson, *Proc. Roy. Soc.*, 1939, *B*, **127**, 140), and dienœstrol (Dodds *et al.*, *loc. cit.*), the not unreasonable assumption has been made from time to time that the structural similarity between this type of œstrogen and œstradiol, noted by Dodds *et al.* (*loc. cit.*), might be paralleled in compounds having a similar diphenylhexane nucleus, but bearing groups characteristic of pharmacologically active steroids of other types.

Jaeger and Robinson (*J.*, 1941, 1744) prepared 3-(*p*-acetylphenyl)-4-(*p*-hydroxyphenyl)hex-3-ene, but this lacked progestational activity, probably because the phenolic hydroxyl group conferred œstrogenic activity on the compound. Linnell and Roushdi (*Quart. J. Pharm. Pharmacol.*, 1941, **14**, 270) reported that 3-(*p*-hydroxyphenyl)-4-(*m*-hydroxyacetylphenyl)hex-3-ene had rather less than one two-hundredth of the activity of deoxycorticosterone in prolonging the life of the young adrenalectomised rat. Corticosterone-like activity has been claimed for 3-(*p*-hydroxyacetylphenyl)- and 3-(*p*-acetoxyacetylphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane (Wellcome Foundation Ltd., Brownlee, and Duffin, B.P. 550,262).

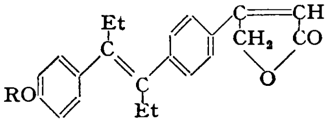
More recently, Biggerstaff and Wilds (*J. Amer. Chem. Soc.*, 1949, **71**, 2132) have prepared 3-(*p*-acetylphenyl)-4-(*p*-hydroxyphenyl)- and 3-(*p*-acetoxyacetylphenyl)-4-(*p*-acetoxyphenyl)-*n*-hex-3-ene, and also the corresponding hexanes. Their work is particularly interesting since they established the configuration of their products.

When the present work was started (1945), no extension of this principle had been made to include possible cardioactive substances bearing the butenolide or α-pyrone rings characteristic of the two main classes of cardiac aglycones. Elderfield and his collaborators (*J. Org. Chem.*, 1941, **6**, 260, 566, 577; 1942, **7**, 362, 444; 1943, **8**, 37, 129, 167; *J. Pharmacol.*, 1942, **74**, 381; 1943, **76**, 31; **77**, 401) had carried out some preliminary work on simple, substituted butenolides and α-pyrones and had found indications of cardioactivity in certain esters of coumalic acid and in a β-naphthyl butenolide. Part I of the present series (Campbell and Hunt, *J.*, 1947, 1176) was concerned with esters of coumalic and aconic acids.

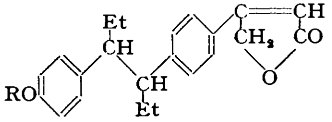
It was evidently desirable to prepare analogues of hexœstrol and stilbœstrol, in which one of the phenolic hydroxyl groups was replaced by the butenolide ring, thereby obtaining compounds which would bear some superficial resemblance to digitoxigenin. Linnell and Said (*J. Pharm. Pharmacol.*, 1949, **1**, 151) have claimed the preparation of 3-(*p*-2 : 5-dihydro-5-keto-3-furylphenyl)-4-(*p*-methoxyphenyl)-*n*-hex-3-ene (I), described as a pale yellow substance, m. p. 94—95°, which they were unable to demethylate.

The method used for the preparation of butenolides from acetoxymethyl ketones in all experiments to be described was that employed by Linville and Elderfield (*J. Org. Chem.*, 1941, **6**, 270). Using this method, we have carried out a Reformatsky reaction, with ethyl bromoacetate, on the *trans*-3-(*p*-acetoxyacetylphenyl)-4-(*p*-acetoxyphenyl)-*n*-hex-3-ene of Biggerstaff and Wilds (*loc. cit.*) and, by treating the crude reaction product with a mixture of hydrochloric and acetic acids, have obtained therefrom the phenolic butenolide (II). This butenolide was methylated; the product, a white solid, melted at 164° and was evidently quite distinct from Linnell and Said's product. In order to investigate this discrepancy, an acetoxymethyl ketone was prepared from *trans*-3-(*p*-carboxyphenyl)-4-(*p*-methoxyphenyl)-*n*-hex-3-ene (Neher and Miescher, *Helv. Chim. Acta*, 1946, **29**, 449; see also Biggerstaff and Wilds, *loc. cit.*), through the diazo-ketone. This acetoxymethyl ketone was a solid, m. p. 94°, whereas the ketone obtained by Linnell and Said was an oil, having a far from satisfactory analysis (*loc. cit.*). The solid ketone was converted into the corresponding butenolide by the Elderfield–Reformatsky process, the product melting at 164° and showing no depression of m. p. on admixture with the methoxy-butenolide obtained as above by methylation of the phenolic butenolide. On the evidence available, we are unable to account for this most notable difference between our acetoxymethyl ketone and butenolide and Linnell and Said's corresponding products.

3-(*p*-Methoxyphenyl)-4-phenyl-*n*-hexane has been described by Brownlee, Copp, Duffin, and Tonkin (*Biochem. J.*, 1943, **37**, 575); this substance was subjected, by Brownlee and Duffin (*loc. cit.*), to a Friedel–Crafts reaction with chloroacetyl chloride, yielding a substance, m. p. 139—141°, assumed to be 3-(*p*-chloroacetylphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane. An example in the same patent specification refers to the corresponding 3-(*p*-acetoxyacetylphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane, but no physical characteristics are given. We have carried out an acetolysis of the chloro-ketone and have obtained an acetoxymethyl ketone melting at 99°. That this ketone had arisen by chloroacetylation in the *p*-position of the unsubstituted phenyl nucleus was demonstrated by comparison with a specimen prepared from 3-(*p*-carboxyphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane, by reaction of its acid chloride with diazomethane and acetolysis of the diazomethyl ketone formed. The two specimens were identical, having m. p. and mixed m. p. 99°; the ultimate analysis was also satisfactory.



(I; R = Me.) (II; R = H.)



(III; R = Me.) (IV; R = H.)

The 3-(*p*-carboxyphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane above was first prepared in this investigation from the *p*-acetylphenylhex-3-ene prepared by Jaeger and Robinson (*loc. cit.*) from the corresponding 4-cyano-compound. The ketone, which was oily and presumably a mixture of the *cis*- and *trans*-isomers, was hydrogenated, by aid of palladium-black. The crude product partly crystallised and was recrystallised to give the saturated ketone, m. p. 134°. This ketone was then oxidised with sodium hypobromite to the methoxy-acid. Demethylation of a small quantity of this acid with a solution of hydrogen bromide in acetic acid gave 3-(*p*-carboxyphenyl)-4-(*p*-hydroxyphenyl)-*n*-hexane, m. p. 166°. Biggerstaff and Wilds (*loc. cit.*) have since described both acids, which they have prepared from Jaeger and Robinson's 3-(*p*-cyanophenyl)-4-(*p*-methoxyphenyl)hex-3-ene by a different route. They have, moreover, shown by degradation that the acids have the same configuration about the central carbon atoms as that existing in hexœstrol (*meso*). The structure of the acetoxymethyl ketone is thus completely defined.

On subjecting this ketone to a Reformatsky reaction with ethyl bromoacetate, a crude product was obtained, which, after being heated with a mixture of hydrochloric and acetic acids, yielded the methoxy-butenolide (III), 3-(*p*-2 : 5-dihydro-5-keto-3-furylphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane, m. p. 200°. Treatment of the crude Reformatsky product under more vigorous conditions, with hydrogen bromide in acetic acid, caused demethylation, in addition to lactonisation, yielding the hydroxy-butenolide, 4-(*p*-2 : 5-dihydro-5-keto-3-furylphenyl)-3-(*p*-hydroxyphenyl)-*n*-hexane (IV), m. p. 136°. This phenolic butenolide was also obtained by demethylation of the above methoxy-butenolide (III) with a solution of hydrogen bromide in acetic acid.

The phenolic butenolide (IV) was also prepared by the same procedure, 3-(*p*-acetoxyacetylphenyl)-4-(*p*-acetoxyphenyl)-*n*-hexane (Biggerstaff and Wilds, *loc. cit.*) being used in the Reformatsky reaction.

The four new butenolides all gave strong positive reactions in the Légal test; they have been submitted for pharmacological investigation.

Experimental.

The zinc powder used in Reformatsky reactions was prepared from a commercial grade by washing with 5% hydrobromic acid, followed by water several times, then alcohol, acetone, and finally ether. The product was dried in high vacuum over a Bunsen flame. In each case, the Reformatsky reaction was initiated by addition of a crystal of iodine. The benzene used was dried over sodium.

4-(p-2 : 5-*Dihydro*-5-*keto*-3-*furylphenyl*)-3-(p-*hydroxyphenyl*)-n-*hex*-3-*ene* (II).—A mixture of zinc powder (3·2 g.) and 4-(*p*-acetoxyacetylphenyl)-3-(*p*-acetoxyphenyl)-*n*-hex-3-ene (3·4 g.) (Biggerstaff and Wilds, *loc. cit.*) was covered with dry benzene (60 ml.), of which 30 ml. were then distilled off. Ethyl bromoacetate (3·5 g.) in dry benzene (5 ml.) was then added to the refluxing mixture in four portions, with constant stirring, during 15 minutes. The reaction commenced almost immediately and continued gently for 20 minutes, in an oil-bath at 100°. The bath-temperature was then raised to 120°, and the heating of the stirred mixture continued for 30 minutes. After cooling, alcohol (2 ml.) was added, followed by 10% hydrochloric acid (30 ml.) and a little ether to assist in dispersing the zinc complex. After removal of the zinc by filtration, the benzene solution was separated, washed twice with water, and dried ($MgSO_4$). Removal of the solvent left a gummy, yellow product (5·6 g.), a portion of which (4·2 g.) was heated with stirring under reflux with concentrated hydrochloric acid (50 ml.). in an atmosphere of nitrogen for 90 minutes. The cooled mixture was then poured into ice-water and extracted with ether. The ether extract was washed thoroughly with sodium hydrogen carbonate solution and passed through a short column of alumina (Spence, standard). After elution with more ether, the solvent was evaporated, and the solid residue recrystallised from a little benzene. The *butenolide* (II) was a pale yellow, microcrystalline powder (0·82 g.), m. p. 165°, raised to 171—172° by further recrystallisation (charcoal) from methyl acetate–*cyclo*hexane (Found: C, 79·0; H, 6·6. $C_{22}H_{22}O_3$ requires C, 79·0; H, 6·65%).

4-(p-2 : *5-Dihydro-5-keto-3-furylphenyl*)-3-(p-*methoxyphenyl*)-n-*hex-3-ene* (I).—(*a*) The foregoing phenolic butenolide (50 mg.), dissolved in dioxan (1 ml.), was shaken for 1 hour with methyl sulphate (20 mg.), with gradual addition of 0·5N-sodium hydroxide solution (0·33 ml.), causing separation of solid material. Water was added, and the product extracted with a little benzene. Addition of light petroleum (b. p. 40—60°) induced the separation of a small amount of sticky material which was rejected. On evaporation of the solution, the residue (20 mg.) crystallised, and was recrystallised from methyl acetate–light petroleum (b. p. 40—60°), giving the *butenolide* (I) in colourless plates, m. p. 164° (mixed m. p. with the phenolic butenolide, 139—144°) (Found: C, 78·8; H, 6·7. $C_{23}H_{24}O_3$ requires C, 79·3, H, 6·9%).

(*b*) 4-(*p*-Carboxyphenyl)-3-(*p*-methoxyphenyl)-*n*-hex-3-ene (m. p. 176°) (Neher and Miescher, *loc. cit.*) (2·8 g.) was converted into the acid chloride by heating under reflux for 2 hours with benzene (15 ml.), thionyl chloride (2 ml.), and 2 drops of pyridine. The crude acid chloride, freed from excess of thionyl chloride and benzene, crystallised in pale yellow rosettes. Ether (20 ml.) was added, and the solution decanted from pyridine hydrochloride and added slowly, with stirring, to an ethereal solution of diazomethane prepared from nitrosomethylurea (10 g.) (Arndt and Amende, *Z. angew. Chem.*, 1931, **43**, 444), kept below 5°. The mixture was set aside overnight, and the ether evaporated under reduced pressure, leaving 4-(p-*diazoacetylphenyl*)-3-(p-*methoxyphenyl*)-n-*hex-3-ene* as a yellow solid. A portion, recrystallised from benzene–light petroleum, had m. p. 136—137° (Found: N, 8·3. $C_{21}H_{22}O_2N_2$ requires N, 8·4%). The diazoketone was added in portions to boiling acetic acid (30 ml.) during 10 minutes and the yellow solution was then heated under reflux for a further 30 minutes. The mixture was cooled and poured into water, and the gummy product extracted with ether. The ethereal solution was washed with water and with sodium hydrogen carbonate solution and dried ($MgSO_4$), and the ether removed. The residue crystallised, and was twice recrystallised from acetone–light petroleum, yielding 4-(p-*acetoxyacetylphenyl*)-3-(p-*methoxyphenyl*)-n-*hex-3-ene* (1·7 g.), m. p. 96° (Found: C, 74·9; H, 7·2. $C_{23}H_{26}O_4$ requires C, 75·4; H, 7·1%). This ketone (1·5 g.) was dissolved in dry benzene (20 ml.), zinc powder (1·45 g.) was added, and the mixture heated to boiling. A solution of ethyl bromoacetate (2·25 ml.) in benzene (10 ml.) was then added dropwise. The reaction proceeded smoothly and the mixture was heated under reflux for 1 hour. After cooling, the mixture was treated with dilute sulphuric acid in the usual manner; evaporation of the separated and washed benzene solution left a gum, which was heated under reflux, in an atmosphere of nitrogen, with a mixture of concentrated hydrochloric acid (20 ml.) and acetic acid (5 ml.), with stirring for 1 hour. An equal quantity of the hydrochloric–acetic acid mixture was then added, and the mixture heated under reflux for a further hour. After cooling, the product was extracted with benzene, and the extract washed with sodium hydrogen carbonate solution. The dried benzene solution was passed through a column of alumina, which was then eluted with more benzene. Evaporation of the benzene eluates yielded a crystalline residue (0·4 g.) which was twice recrystallised from benzene–*cyclo*hexane, giving the product in colourless plates, m. p. 163—164°, not depressed on admixture with the material obtained as in (*a*) (Found: C, 79·0; H, 7·0%).

3-(p-*Acetylphenyl*)-4-(p-*methoxyphenyl*)-n-*hexane*.—3-(*p*-Acetylphenyl)-4-(*p*-methoxyphenyl)-*n*-hex-3-ene (Jaeger and Robinson, *loc. cit.*) (5·76 g.), dissolved in acetone (20 ml.), was shaken in hydrogen with palladium black (0·2 g.). The theoretical volume of hydrogen was absorbed in 3½ hours. After removal of catalyst, the acetone was distilled off, leaving an oily product which partly crystallised when kept. The crystalline material, collected and washed with methanol, had m. p. 110—120°, raised to 134° on recrystallisation from methanol (Biggerstaff and Wilds, *loc. cit.*, give m. p. 135—137° for this substance) (Found: C, 81·0; H, 8·4. Calc. for $C_{21}H_{26}O_2$: C, 81·2; H, 8·4%). Its 2 : 4-dinitrophenylhydrazone had m. p. 177°, and its semicarbazone, m. p. 221°.

3-(p-*Carboxyphenyl*)-4-(p-*methoxyphenyl*)-n-*hexane*.—The above ketone (1·5 g.) was shaken for 5 hours with a mixture of dioxan (5 ml.) and sodium hypobromite solution (from bromine, 1 ml.; sodium hydroxide, 1·76 g.; and ice-water, 10 ml.). Next morning, the slight excess of hypobromite was removed by sodium pyrosulphite solution. The insoluble sodium salt was collected, washed with water, and decomposed by warming it for 15 minutes with dilute sulphuric acid. The crude product was collected and dried (1·38 g., 91%); after recrystallisation from *cyclo*hexane the m. p. was 166—168° (corr. 169·5—171·5°), not depressed on admixture with a specimen of the acid prepared by the method of Biggerstaff and Wilds (*loc. cit.*) (Found: C, 77·2; H, 8·0. Calc. for $C_{20}H_{24}O_3$: C, 76·9; H, 7·7%).

Demethylation. The above methoxy-acid (200 mg.) was heated under reflux for 2 hours with a 50% solution of hydrogen bromide in acetic acid, then cooled and poured into water. The collected solid, recrystallised three times from benzene–*cyclo*hexane had m. p. 166°, not depressed on admixture with a specimen of 3-(*p*-carboxyphenyl)-4-(*p*-hydroxyphenyl)-*n*-hexane prepared by the method of Biggerstaff and Wilds (*loc. cit.*).

3-(p-*Acetoxyacetylphenyl*)-4-(p-*methoxyphenyl*)-n-*hexane*.—(*a*) 3-(*p*-Carboxyphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane (1 g.) was heated under reflux for 1 hour with thionyl chloride (1 ml.), benzene (3 ml.), and pyridine (1 drop). Excess of thionyl chloride was distilled off with the benzene, and the residue dried over soda-lime. The crude acid chloride was dissolved in ether (10 ml.), and the solution added slowly, with stirring, to an ethereal solution of diazomethane (from nitrosomethylurea, 5 g.) at a temperature between 0° and 5°. After 2 hours at room temperature the solvent was removed by evaporation under reduced pressure. The crude diazo-ketone, which separated as a yellow solid, was heated with acetic acid (10 ml.) on the water-bath for 2 hours. Most of the acid was then distilled off at reduced pressure, and the residue treated with water. Ether-extraction yielded a gum, which on dissolution in warm methanol and cooling, deposited crystals (0·27 g.). Repeated recrystallisation from methanol (charcoal) gave the pure *hexane*, m. p. 99° (Found : C, 74·8; H, 7·8. $C_{23}H_{28}O_4$ requires C, 75·0; H, 7·7%).

(*b*) 3-(*p*-Chloroacetylphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane (Brownlee and Duffin, *loc. cit.*) (3 g.) was refluxed for 2 hours with acetic acid (10 ml.) and fused potassium acetate (4 g.). The acid was then distilled off under reduced pressure, and the residue treated with water and extracted with ether. Evaporation of the washed and dried ethereal solution gave the crude product, which after two recrystallisations from methanol had m. p. 99°, not depressed on admixture with a specimen prepared as above; the yield was 2 g. (Found : C, 75·2; H, 7·7%).

3-(p-2 : 5-*Dihydro*-5-*keto*-3-*furylphenyl*)-4-(p-*methoxyphenyl*)-n-*hexane* (III).—3-(*p*-Acetoxyacetylphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane (2 g.) was mixed with zinc powder (1·9 g.) and dry benzene (20 ml.). The mixture was heated to boiling, and ethyl bromoacetate (3 ml.) in benzene (10 ml.) was added dropwise during 15 minutes, with stirring. More zinc (0·5 g.) was then added, and the mixture heated under reflux for 1 hour. The cooled mixture was treated with dilute sulphuric acid in the usual manner, ether being added to the benzene solution to assist in dispersal of the zinc complex. The benzene solution was washed with water and with sodium hydrogen carbonate solution and then evaporated. The crude reaction product (3·3 g.) was heated under reflux, with stirring, with concentrated hydrochloric acid (20 ml.) and acetic acid (5 ml.) for 1 hour. The mixture was then cooled, and the solid material collected and washed with water. After repeated recrystallisation from benzene (charcoal), the required *ketone* was obtained as colourless plates, m. p. 200° (0·57 g.) (Found : C, 79·0; H, 7·5. $C_{23}H_{26}O_3$ requires C, 78·8; H, 7·5%). By adsorption on alumina and elution with benzene a further 0·28 g. of almost pure product was obtained.

3-(p-2 : 5-*Dihydro*-5-*keto*-3-*furylphenyl*)-4 (p-*hydroxyphenyl*)-n-*hexane* (IV).—(*a*) The crude product from a Reformatsky reaction between ethyl bromoacetate (12·6 g.) and 3-(*p*-acetoxyacetylphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane (9 g.), carried out as described above, was heated under reflux for 4 hours, in an atmosphere of nitrogen, with a 50% solution of hydrogen bromide in acetic acid (100 ml.); after the first 2 hours a further 50 ml. of the hydrogen bromide solution was added. The cooled mixture was poured into ice-water and extracted with benzene. After being washed with sodium hydrogen carbonate solution, the extract was poured on an alumina column. Elution with chloroform yielded a small quantity of yellow oil, which was discarded. Elution with ethyl acetate then yielded a pale yellow oil which rapidly crystallised. Recrystallisation from benzene gave the *butenolide* (IV) (3 g.), m. p. 136° (Found : C, 78·25; H, 7·1. $C_{22}H_{24}O_3$ requires C, 78·5; H, 7·2%).

(*b*) A mixture of zinc powder (1·9 g.) and 3-(*p*-acetoxyacetylphenyl)-4-(*p*-acetoxyphenyl)-*n*-hexane (2 g.) (Biggerstaff and Wilds, *loc. cit.*) was covered with dry benzene (50 ml.), of which 30 ml. were then distilled off. Ethyl bromoacetate (3 ml.) in benzene (10 ml.) was then added, during 10 minutes, with constant stirring to the mixture boiling under reflux. Solid material commenced to separate almost immediately; after 15 minutes, two further portions of zinc powder (0·5 g. each) were added at 5-minute intervals. The mixture was then heated under reflux for 20 minutes and cooled. After treatment in the usual manner with dilute sulphuric acid, the separated benzene solution was evaporated, and the residue (3·4 g.) heated under reflux with stirring for 90 minutes, in an atmosphere of nitrogen, with concentrated hydrochloric acid (50 ml.) and glacial acetic acid (5 ml.). The mixture was poured into water and extracted with ether. The ethereal extract was well washed with sodium hydrogen carbonate solution and evaporated, yielding a gum which crystallised from ethyl acetate–*cyclo*hexane (1·3 g.). Repeated recrystallisation from benzene (charcoal) yielded the pure product (0·86 g.), m. p. 136°, not depressed on admixture with the substance obtained as under (*a*) (Found : C, 78·05; H, 7·1; active H, 0·37. Calc. for $C_{22}H_{24}O_3$: C, 78·5; H, 7·2; active H, 0·30%).

(*c*) 3-(*p*-2 : 5-Dihydro-5-keto-3-furylphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane (III) (0·2 g.) was heated under reflux for 4 hours with a 50% solution of hydrogen bromide in acetic acid (5 ml. plus a further 2·5 ml. after 2 hours). After cooling, water was added, and the solid filtered off. Two recrystallisations from benzene gave the product in colourless prisms (94 mg.), m. p. 136°, not depressed on admixture with the substance obtained as under (*a*) or (*b*).

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