215. *Unsaturated Lactones. Part III. Symmetrical Aromatic Dibutenolides.*

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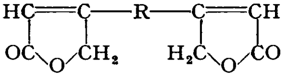
Symmetrical *pp'*-dibutenolides have been prepared from diphenyl, diphenyl ether, diphenylmethane, 1 : 2-diphenylethane, stilbene, and 3 : 4-diphenylhexane. The last butenolide is analogous in structure to the synthetic œstrogen, hexœstrol.

The *pp'*-dihydroxy-derivatives of diphenyl, diphenyl ether, diphenylmethane, 1 : 2-diphenylethane, and stilbene were found by Dodds and Lawson (*Proc. Roy. Soc.*, 1938, *B*, **125**, 222) to possess œstrogenic activity. 3 : 4-Di-(*p*-hydroxyphenyl)-*n*-hexane (hexœstrol) (Campbell, Dodds, and Lawson, *Nature*, 1938, **142**, 1121) was found to possess similar activity, but of a very much higher order. More recently, Ross (*J.*, 1945, 536, 538) has published the preparation of a series of methyl ketones and acetoxymethyl ketones, corresponding to the above diphenols and described by him as analogues of progesterone and corticosterone, respectively. Further examples of compounds of the latter type, but related to stilbene and αβ-diethylstilbene, have been described by Hager and Shonle (*J. Amer. Chem. Soc.*, 1946, **68**, 2167) and by Hager and Burgison (*J. Amer. Pharm. Assoc.*, 1950, **39**, 7).

When starting our work on butenolides analogous to the more potent of the synthetic œstrogens, we considered it interesting to prepare the *pp'*-dibutenolide from 3 : 4-diphenylhexane, for comparison with the corresponding *p*-hydroxy-*p'*-butenolide, both of which may be regarded as analogous to hexœstrol. The new butenolides (I)—(VI) have been prepared by lactonising the products from Reformatsky reactions between the corresponding bisacetoxymethyl ketones and ethyl bromoacetate.



(I; R = pp'-$C_6H_4{\cdot}C_6H_4{\cdot}$)
(II; R = pp'-$C_6H_4{\cdot}O{\cdot}C_6H_4{\cdot}$)
(III; R = pp'-$C_6H_4{\cdot}CH_2{\cdot}C_6H_4{\cdot}$)
(IV; R = pp'-$C_6H_4{\cdot}CH{:}CH{\cdot}C_6H_4{\cdot}$)
(V; R = pp'-$C_6H_4{\cdot}CH_2{\cdot}CH_2{\cdot}C_6H_4{\cdot}$)
(VI; R = pp'-$C_6H_4{\cdot}CHEt{\cdot}CHEt{\cdot}C_6H_4{\cdot}$)

pp'-Bisacetoxyacetyl-diphenyl, -diphenyl ether, -1 : 2-diphenylethane, and -3 : 4-diphenylhexane were described by Ross (*loc. cit.*), who prepared them by acetolysis of the corresponding bischloromethyl ketones, obtained by Friedel–Crafts reactions between the appropriate aromatic nucleus and chloroacetyl chloride. We have prepared di-(*p*-chloroacetylphenyl)methane in a similar manner and converted it into the bisacetoxymethyl ketone by treatment with fused potassium acetate in acetic acid. The bischloromethyl ketone was oxidised by chromic acid, yielding benzophenone-*pp'*-dicarboxylic acid, identified by its methyl ester; this confirms the expected di-*para*-substitution in the Friedel–Crafts reaction.

The above procedure is not available for the preparation of *pp'*-bisacetoxyacetylstilbene, since under the conditions of the Friedel–Crafts reaction with chloroacetyl chloride no crystalline product could be isolated (Ross, *loc. cit.*). Accordingly, a pure specimen of the acid chloride of stilbene-*pp'*-dicarboxylic acid (Bell and Waring, *J.*, 1948, 1024) was treated with a solution of diazomethane in benzene, and the crude diazoketone treated with boiling acetic acid, giving the required *pp'*-bisacetoxyacetyl-*trans*-stilbene as a white solid, melting at 206° and clearing at 226°. Hager and Shonle (*loc. cit.*), using an impure acid chloride in a dioxan solution of diazomethane, obtained the bisacetoxymethyl ketone as a yellow solid, m. p. 192—196°.

Purified dioxan was found to be the best solvent in Reformatsky reactions with these ketones, causing better dispersion of the zinc complexes which are formed as the reactions proceed. The crude products from the Reformatsky reactions were generally lactonised without further purification by heating them with hydrogen bromide in acetic acid, or in certain cases with hydrochloric–acetic acids. Lactonisation was frequently accompanied by formation of extremely insoluble amorphous materials, from which the required products were separated by extraction with a powerful solvent, such as *cyclo*hexanone, acetic acid, or nitrobenzene. In the preparation of the dibutenolides of diphenyl and diphenyl ether, the insoluble fraction formed the major part of the crude reaction product. It was not possible to effect purification of these insoluble materials by normal means, but ultimate analyses, carried out on specimens freed as far as possible from extraneous matter, gave results which indicated empirical formulæ identical with those of the corresponding butenolides. They probably arise from polymolecular condensations of butenolide precursors.

The required dibutenolides were obtained as crystalline solids. Those from diphenyl and stilbene were brightly coloured, the former lemon-yellow, the latter orange. In this, and in their degree of conjugation, they exhibit a resemblance to pulvinic acid dilactone, which has been reported to cause systolic arrest of the isolated frog heart in concentrations of the same order as those required to produce a similar effect with ouabain and digitoxin (Giarman, *J. Pharmacol.*, 1949, **96**, 119). All the new dibutenolides described are very sparingly soluble in physiologically compatible solvents; this has precluded their adequate testing for cardioactivity.

EXPERIMENTAL.

The zinc powder was prepared as described in the preceding paper.

pp′-*Di*-(2 : 5-*dihydro*-5-*keto*-3-*furyl*)*diphenyl* (I.)—4 : 4′-Bisacetoxyacetyldiphenyl (Ross, *loc. cit.*) (9 g.) was mixed with zinc powder (9 g.) and purified dioxan (Hess and Frahm, *Ber.*, 1938, **71**, 2629) (90 ml.) and the whole heated to boiling. Ethyl bromoacetate (8 ml.) was then added slowly as the reaction proceeded, the mixture being heated under reflux for 1 hour. The crude reaction product, obtained as a sticky solid by treating the cooled mixture with dilute sulphuric acid in the usual manner, was dissolved in acetic acid (40 ml.), fuming hydrochloric acid (40 ml.) was added, and the whole heated under reflux for 1 hour, with stirring. A brown solid which separated during the lactonisation was filtered off, dried, and continuously extracted for several hours with boiling *cyclo*hexanone. On cooling, the extract deposited light brown material (1·5 g.). Several recrystallisations from *cyclo*hexanone gave the *dibutenolide* (I) as lemon-yellow needles, decomposing above 320° (Found : C, 75·5; H, 4·5. $C_{20}H_{14}O_4$ requires C, 75·5; H, 4·4%). The *cyclo*hexanone-insoluble *substance* (3 g.) was completely insoluble in a very wide range of solvents. A portion was dried under high vacuum at 150° (Found : C, 74·6; H. 4·7. $C_{20}H_{14}O_4$ requires C, 75·5; H, 4·4%).

pp′-*Di*-(2 : 5-*dihydro*-5-*keto*-3-*furyl*)*diphenyl Ether* (II).—*pp*′-Bisacetoxyacetyldiphenyl ether (Ross, *loc. cit.*) (9 g.) was submitted to a Reformatsky reaction exactly as above but with 16·2 g. of ethyl bromoacetate, and lactonisation was effected by acetic anhydride (50 ml.) and concentrated hydrochloric acid (50 ml.) (vigorous initial reaction). The dark brown solid which separated was filtered off and continuously extracted for several hours with boiling glacial acetic acid. The crude solid obtained by adding water to this extract was filtered off and dried (3 g.). Repeated recrystallisation from *cyclo*hexanone gave the *dibutenolide*, m. p. 243—244° (Found : C, 72·0; H, 4·55. $C_{20}H_{14}O_5$ requires C, 71·9; H, 4·2%). When the product from a similar Reformatsky reaction to the above was heated under reflux with a solution of hydrogen bromide in acetic acid for 90 minutes, a considerable quantity of insoluble material was obtained. This *substance* was also insoluble in a wide range of solvents (Found : C, 72·3; H, 4·6%).

Di-(p-*chloroacetylphenyl*)*methane*.—Diphenylmethane (25 g.) was dissolved in carbon disulphide (150 ml.) and powdered aluminium chloride (50 g.) was added to the stirred mixture. A solution of chloroacetyl chloride (50 ml.) in carbon disulphide (50 ml.) was then added slowly, the flask being cooled in cold water. The mixture was stirred for 1 hour at room temperature, and the decanted carbon disulphide layer discarded. The residue was treated with a mixture of ice and hydrochloric acid, and a yellow solid filtered off. This was crystallised from methanol and repeatedly recrystallised from alcohol (95%). The resulting *di*-(p-*chloroacetylphenyl*)*methane* (10·3 g.) was nearly colourless and of m. p. 123° (Found : C, 63·6; H, 4·6; Cl, 22·9. $C_{17}H_{14}O_2Cl_2$ requires C, 63·55; H, 4·4; Cl, 22·1%).

Oxidation. The above chloro-ketone (0·5 g.) was boiled under reflux for 3 hours with a mixture of sodium dichromate (3 g.) and sulphuric acid (30 ml. of 25% v/v). Water was then added; the precipitated solid, when washed and dried, did not melt below 340°. The dimethyl ester, prepared through the acid chloride had m. p. 225° (Found : C, 68·4; H, 4·8. Calc. for $C_{17}H_{14}O_5$: C, 68·3; H, 4·7%); Limpricht (*Annalen*, 1900, **312**, 92) states that benzophenone-4 : 4′-dicarboxylic acid sublimes without melting below 360° and that the dimethyl ester melts at 225°.

Di-(p-*acetoxyacetylphenyl*)*methane*.—Di-(*p*-chloroacetylphenyl)methane (7·8 g.) was boiled under reflux for 2½ hours with a mixture of acetic acid (32 ml.), acetic anhydride (8 ml.), and fused potassium acetate (10 g.). The mixture was cooled and poured into water (200 ml.), and the solid collected. Several recrystallisations from alcohol (95%) yielded the substituted *diketone* (5 g.), m. p. 114° (Found : C, 68·2; H, 5·8. $C_{21}H_{20}O_6$ requires C, 68·4; H, 5·5%).

Di-(p-2 : 5-*dihydro*-5-*keto*-3-*furylphenyl*)*methane* (III).—A mixture of di-(*p*-acetoxyacetylphenyl)-methane (4·6 g.), zinc powder (4·6 g.), and dioxan (46 ml.) was condensed with ethyl bromoacetate (8·3 g.), and the product worked up in the usual manner. The sticky, solid reaction product was dissolved in acetic acid (30 ml.), and the solution filtered and heated under reflux for 1 hour with concentrated hydrochloric acid (30 ml.). The mixture was cooled and poured into water, and the separated solid dried and recrystallised three times from dioxan (charcoal). The *dibutenolide* (III) (1 g.) had m. p. 256° (Found : C, 75·5; H, 5·0. $C_{21}H_{16}O_4$ requires C, 75·9; H, 4·8%).

pp′-*Bisacetoxyacetylstilbene*.—Stilbene-*pp*′-dicarboxyl chloride (8 g.) (Bell and Waring, *J.*, 1948, 1024) was added portionwise during 2 hours to a solution of diazomethane (from nitrosomethylurea, 30 g.) in benzene (300 ml.), kept at room temperature, and stirred continuously. Next morning, the benzene was distilled off under reduced pressure. The crude crystalline diazo-ketone was added gradually to a boiling mixture of acetic acid (100 ml.) and fused potassium acetate (5 g.). Boiling under reflux was continued for 30 minutes after completion of the addition. After cooling, the mixture was poured into water, and the separated solid washed with sodium carbonate solution, water, and methanol. Recrystallisation from acetic acid and from toluene gave the stilbene as fine white leaflets (6·5 g.), m. p. 206° to an opalescent liquid clearing sharply at 226° [Hager *et al.* (*loc. cit.*, 1946) report m. p. 192—196°] (Found : C, 69·3; H, 5·35. Calc. for $C_{22}H_{20}O_6$: C, 69·45; H, 5·3%).

pp'-*Di*-(2 : 5-*dihydro*-5-*keto*-3-*furyl*)*stilbene* (IV).—The above acetoxymethyl ketone (5 g.) was subjected to a Reformatsky reaction with ethyl bromoacetate (10 g.) and powdered zinc (5 g.) in dioxan (50 ml.). The reactants were added all at once and the mixture gently heated. After the initial vigorous reaction had subsided, the mixture was boiled under reflux, with stirring for 30 minutes. After cooling, the mixture was decomposed with dilute hydrochloric acid in the usual manner, and the product extracted with ether. The residue on evaporation of the ether was boiled and stirred, under reflux, for 45 minutes with a mixture of acetic acid (20 ml.) and concentrated hydrochloric acid (80 ml.), then poured into water; the yellow, solid product was collected and washed with potassium carbonate solution, water, and methanol. Extraction of this crude material with boiling acetic acid (charcoal) yielded the *dibutenolide* as an orange, microcrystalline powder (2 g.). When heated, this darkened above 300° and decomposed at about 360° (Found : C, 76·2; H, 4·7. $C_{22}H_{16}O_4$ requires C, 76·8; H, 4·7%).

1 : 2-*Di*-(p-2 : 5-*dihydro*-5-*keto*-3-*furylphenyl*)*ethane* (V).—1 : 2-Di(-*p*-acetoxyacetylphenyl)ethane (Ross, *loc. cit.*) (10 g.) was brought into reaction with ethyl bromoacetate (20 g.) and zinc powder (10 g.) in purified dioxan (100 ml.). The reaction was complete after 2 hours' heating, and the cooled mixture was then poured through a glass-wool plug into dilute sulphuric acid. The aqueous solution was decanted from the yellow semi-solid product, which was then heated under reflux, in an atmosphere of nitrogen, for 90 minutes with a 50% solution of hydrogen bromide in acetic acid (50 ml.). After cooling, the mixture was poured into water, and the *dibutenolide* filtered off, washed, dried, and recrystallised repeatedly from glacial acetic acid; m. p. 277° (Found : C, 76·2; H, 5·35. $C_{22}H_{18}O_4$ requires C, 76·25; H, 5·25%).

3 : 4-*Di*-(p-2 : 5-*dihydro*-5-*keto*-3-*furylphenyl*)-n-*hexane* (VI).—*pp'*-Bisacetoxyacetyl-3 : 4-diphenyl-*n*-hexane (Ross, *loc. cit.*) (4·3 g.) was brought into reaction with ethyl bromoacetate (10 g., 3 mols.) and zinc powder (6·5 g., 5 mols.) in dioxan (50 ml.). After being heated under reflux for 1 hour, the reaction mixture was treated in the usual manner, and the crude gummy product (5·5 g.) lactonised by being heated under reflux, in an atmosphere of nitrogen, for 2 hours with a 50% solution of hydrogen bromide in acetic acid (50 ml.). The crude product obtained by pouring the cooled mixture into water was recrystallised repeatedly from glacial acetic acid and then from alcohol by prolonged hot continuous extraction. Final purification was effected by recrystallisation twice from anisole and once from amyl alcohol; the *dibutenolide* formed white, silky needles, m. p. 303° (Found : C, 77·4; H, 6·8. $C_{26}H_{26}O_4$ requires C, 77·6; H, 6·5%).

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