

138. *Synthetic Analogues of Progesterone.*

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A number of methyl ketones derived from stilbene, dibenzyl, and triphenylethylene have been synthesised for examination for progestational activity.

ROBINSON and JAEGER (J., 1941, 744) prepared 4-hydroxy-4'-acetyl- $\alpha\beta$ -diethyl- and - α -methyl- β -ethyl-stilbene. Owing to the presence of the phenolic group these compounds had appreciable oestrogenic activity and this would have been sufficient to mask any progestational activity which they possessed. It was only possible to state that these substances had less than one-sixtieth of the activity of progesterone. The preparation of

4: 4'-dihydroxy-diacetyl- and 4-methoxy-4'-hydroxy-3'-acetyl- $\alpha\beta$ -diethylstilbene has been described (Wellcome Foundation Ltd., Brownlee and Duffin, B.P. 550,262); these compounds are stated to have oestrogenic properties. In the same patent, progesterone-like activity is claimed for 4-methoxy-4'-acetyl- and 4-methoxy-4'-chloroacetyl- $\alpha\beta$ -diethylidibenzyl, and 4'-chloroacetyl- $\alpha\beta$ -diethylidibenzyl 4-chloroacetate. Walker (J., 1942, 347) prepared and tested ω -acetoxy-4-(4'-acetoxyphenoxy)-, 4-(4'-hydroxyphenoxy)-, and 3-hydroxy-4-(4'-hydroxyphenoxy)-acetophenone, but none exhibited progestational activity.

Consideration of the foregoing suggested that the type of compound most likely to show luteal hormone-like activity would be a non-phenolic methyl ketone related to stilbene or dibenzyl. The preparation of a number of such compounds is now described.

Condensation of dibenzyl with one equivalent of acetyl chloride in the presence of aluminium chloride gave a mixture which could not be resolved, but on treatment with an excess of the acid chloride an almost theoretical yield of 4: 4'-*diacetyldibenzyl* was obtained. The Grignard reagent obtained from α -chloropropylbenzene was refluxed with its equivalent of the same chloro-compound. A small yield of $\alpha\beta$ -diethylidibenzyl, m. p. 85—88°, was thereby obtained; most of the product was a liquid mixture of isomerides. Moritz and Wolfenstein (*Ber.*, 1899, 32, 2533) described the hydrocarbon as having m. p. 88°, Spath (*Monatsh.*, 1913, 34, 2009) records m. p. 92—93°, and Carlisle and Crowfoot (J., 1941, 6) gave 89—90°. Brownlee, Copp, Duffin, and Tonkin (*Biochem. J.*, 1943, 37, 575) prepared diethylidibenzyl by hydrogenation of $\alpha\beta$ -diethylstilbene and found m. p. 83—84°. 4: 4'-*Diacetyl- $\alpha\beta$ -diethylidibenzyl* was obtained in excellent yield by the action of an excess of acetyl chloride on the hydrocarbon.

Stilbene gave a resinous product when treated with one equivalent of acetyl chloride, but with an excess of the reagent 4: 4'-*diacetylstilbene* was obtained. The yield of diketone was very variable, the maximum (13%) being obtained on only one occasion, and the average was 5%.

Ethyl deoxybenzoin was treated with ethylmagnesium bromide, and the α -hydroxy- $\alpha\beta$ -diethylidibenzyl thus obtained was dehydrated by heating under reflux with phosphoric oxide in benzene solution. The oily product, when heated with iodine, yielded a small quantity of $\alpha\beta$ -diethylstilbene, m. p. 74—75°. Dehydration of the carbinol could give rise to several isomerides differing in the position of the double linkage and also in steric configuration. The stability of our solid product to heating with iodine suggests that it is the true stilbene derivative (compare Wessely and Kleedorfer, *Naturwiss.*, 1939, 27, 567). The compound obtained by Duffin *et al.* (*loc. cit.*) was probably a mixture of isomers, as was also the liquid obtained by Ramart-Lucas and Anagostopoulos (*Compt. rend.*, 1928, 186, 1626) and Kharasch and Kleiman (*J. Amer. Chem. Soc.*, 1943, 65, 9). Carlisle and Crowfoot (*loc. cit.*) describe the pure hydrocarbon as having m. p. 70—71°. On treatment with an excess of acetyl chloride, $\alpha\beta$ -diethylstilbene gave a poor yield of 4: 4'-*diacetyl- $\alpha\beta$ -diethylstilbene*.

It is well known that certain triphenylethylene derivatives exhibit a hormone-like activity, and it was thought desirable to prepare an acetyl compound to be tested for progestational activity. Triphenylethylene was prepared by the method of Adkins and Zartman (*Org. Synth.*, Coll. Vol. II, p. 606). As in the previous cases, no definite product could be obtained by the action of acetyl chloride unless a large excess of the reagent was used: under these conditions 4: 4': 4'-*triacetyltriphenylethylene* was obtained.

EXPERIMENTAL.

4: 4'-*Diacetyldibenzyl*.—Dibenzyl was prepared by refluxing benzylmagnesium chloride with an equivalent weight of benzyl chloride for 2 hours in ethereal solution. 5 G. of dibenzyl, 20 c.c. of dry carbon disulphide, and 10 g. of powdered aluminium chloride were introduced into a small flask carrying a reflux condenser, and then a mixture of 10 c.c. each of acetyl chloride and carbon disulphide was added dropwise. A vigorous reaction ensued, and when this had subsided the mixture was heated on a steam-bath until evolution of hydrogen chloride had ceased. A solid complex had then separated, and the supernatant liquor was decanted off, and the solid washed with fresh dry carbon disulphide. The complex was decomposed by grinding under iced water, and the precipitate filtered off and washed with water. The dried solid was dissolved in chloroform, and the solution allowed to percolate through a short column of alumina. The eluates, obtained by further washing with chloroform, gave a colourless solid, which crystallised from ethyl alcohol as large plates, m. p. 164—166° (Found: C, 81.2, 81.1; H, 7.4, 6.7. $C_{18}H_{18}O_2$ requires C, 81.2; H, 6.8%).

4: 4'-*Diacetyl- $\alpha\beta$ -diethylidibenzyl*.—The Grignard reagent prepared from 10 g. of α -chloropropylbenzene (Straus and Berkow, *Annalen*, 1913, 401, 152) and 1.6 g. of magnesium in 20 c.c. of ether was heated under reflux with a further 10 g. of the chloride for 2 hours. Dilute sulphuric acid was added, and the ethereal layer washed with water, dried, and evaporated. The resulting oil deposited solid on standing in an ice-chest; 1.5 g. of recrystallised $\alpha\beta$ -diethylidibenzyl, m. p. 85—88°, was obtained. To 3 g. of powdered aluminium chloride under 5 c.c. of carbon disulphide, were added 3 c.c. of acetyl chloride, and the mixture was warmed to form the complex. 1.25 G. of diethylidibenzyl were then added, and the mixture warmed on a steam-bath for $\frac{1}{2}$ hour. The solid product thus formed was washed with fresh carbon disulphide and decomposed with iced water. The solid was filtered off and washed with water followed by a little ether. Yield, 1.5 g. After two crystallisations from alcohol, the 4: 4'-*diacetyl- $\alpha\beta$ -diethylidibenzyl* had m. p. 171—173°; yield 0.8 g. (Found: C, 81.7; H, 8.2. $C_{22}H_{26}O_2$ requires C, 81.9; H, 8.1%).

4: 4'-*Diacetylstilbene*.—15 G. of stilbene, 30 c.c. of acetyl chloride, and 120 c.c. of dry carbon disulphide were mixed together, and 60 g. of powdered aluminium chloride were added during 20 minutes. The mixture was then kept for 3 hours at room temperature. The supernatant liquid was decanted from the complex, which was then decomposed with iced water. The aqueous suspension of the product was shaken with benzene, the mixture filtered, and the solid washed with benzene. The solid crystallised in the form of plates, m. p. 210—211°, from acetone or alcohol-chloroform (Found: C, 82.1, 81.4; H, 6.2, 6.1. $C_{18}H_{18}O_2$ requires C, 81.8; H, 6.1%).

4: 4'-*Diacetyl- $\alpha\beta$ -diethylstilbene*.—A solution of 45 g. of ethyldeoxybenzoin (Meyer and Oelkers, *Ber.*, 1888, 21, 1299) in 250 c.c. of ether was added to the Grignard reagent prepared from 9.65 g. of magnesium, 43.8 g. of ethyl bromide, and 200 c.c. of ether. After being warmed for 1 hour, the mixture was decomposed with ice-cold dilute sulphuric acid. The dried ethereal layer was evaporated, and the resulting oil was dissolved in 200 c.c. of benzene and heated for $\frac{1}{2}$ hour with 30 g. of phosphoric oxide. The cooled benzene solution was percolated through a short column of alumina to

remove any unchanged carbinol and then evaporated. The product was an oil, but after being heated at the b. p. with iodine, until the iodine sublimed out, and then being cooled, 2.5 g. of solid were deposited. After crystallisation from methanol, the diethylstilbene had m. p. 74—75° and formed flattened needles. 1.5 G. of the hydrocarbon were acetylated exactly as in the case of diethyldibenzyl. The product was recrystallised from alcohol, in which solvent it forms a highly fluorescent solution: yield 0.2 g. After two further crystallisations from methanol and being washed with ether, in which it is sparingly soluble, 4 : 4'-diacetyl- $\alpha\beta$ -diethylstilbene had m. p. 168—169° (Found : C, 82.3; H, 8.1. $C_{22}H_{24}O_2$ requires C, 82.4; H, 7.6%).

4 : 4' : 4''-Triacetyltriphenylethylene.—3 G. of triphenylethylene were added to the complex obtained by warming 12 g. of acetyl chloride with 11 g. of powdered aluminium chloride in 20 c.c. of carbon disulphide. The mixture was warmed for 10 minutes, and the supernatant liquid decanted from the resin. This resin was treated with iced water, and the product dried and dissolved in benzene. The solution was passed down a column of alumina, and the orange eluate gave a solid which could be crystallised from methanol-water. The 4 : 4' : 4''-triacetyltriphenylethylene thus obtained formed colourless, flattened needles, m. p. 150—152° (Found : C, 81.7, 81.3; H, 5.8, 5.9. $C_{26}H_{22}O_3$ requires C, 81.6; H, 5.8%).

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