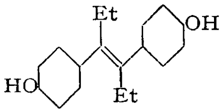
22. *New Synthetic Oestrogens. Part I. The Synthesis of* 4 : 4′-*Dihydroxy*-α : β : 2 : 2′-*tetramethylstilbene and* 4 : 4′-*Dihydroxy*-α : β : 2 : 2′-*tetramethyldibenzyl.*

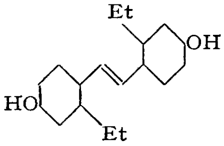
By B. J. F. Hudson and E. Walton.

The synthesis of a new stilboestrol analogue, 4 : 4′-*dihydroxy*-α : β : 2 : 2′-*tetramethylstilbene* (III), and a new synthesis of the corresponding hexoestrol analogue, 4 : 4′-dihydroxy-α : β : 2 : 2′-tetramethyldibenzyl (Bretschneider, de Jonge-Bretschneider, and Ajtai, *Ber.*, 1941, **74**, 571), are described. Both these substances have oestrogenic activity.

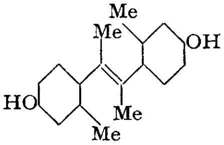
There is evidence that the physiological properties of stilboestrol (I) and hexoestrol can be attributed, at least in part, to their close structural relationship to the natural oestrogens (Dodds, Golberg, Lawson, and Robinson, *Proc. Roy. Soc.*, B, 1939, **127**, 140). On these grounds one might reasonably expect oestrogenic activity to be shown by the appropriately substituted nuclear-alkyl (stilbene) analogues of stilboestrol (II—VI) :



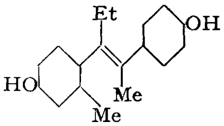
(I.)



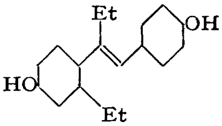
(II.)



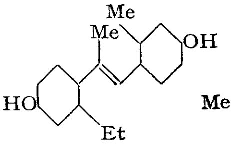
(III.)



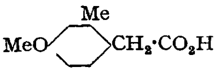
(IV.)



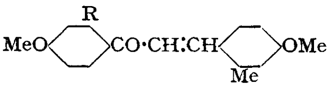
(V.)



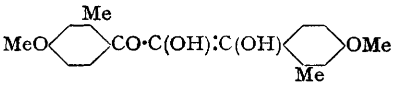
(VI.)



(VII.)



(VIII.)



(IX.)

Of these compounds Linnell and Shaikmahamud (*Quart. J. Pharm.*, 1942, **15**, 384) have prepared (II) by the treatment of *o*-ethylthioanisaldehyde with copper-bronze, followed by demethylation, but their product had only one thousandth of the activity of stilboestrol. B. R. Baker (*J. Amer. Chem. Soc.*, 1943, **65**, 1572) prepared the reduced form of (II) (4 : 4′-dihydroxy-2 : 2′-diethyldibenzyl) by heating the dihydroaldazine of 4-methoxy-2-ethylbenzaldehyde, followed by demethylation. This substance was reported to be entirely inactive.

Compounds (III—VI) have not hitherto been described, but Bretschneider *et al.* (*Ber.*, 1941, **74**, 571) have prepared the reduced form of (III), a hexoestrol analogue (probably the *meso*-stereoisomer), by the dihydroazine synthesis, starting with 4-hydroxy-2-methylacetophenone. Their compound was believed to be accompanied by its *dl*-stereoisomer, though the latter was not isolated. It was found to be slightly less active than hexoestrol when the two substances were compared in the Allen and Doisy test.

We have now prepared (III) by a well-known series of reactions (alkylation, Grignard reaction, dehydration and demethylation) from 2 : 2′-*dimethyldeoxyanisoin*. This intermediate ketone was obtained by a Friedel–Crafts condensation of *m*-methylanisole with the acid chloride of 4-*methoxy*-2-*methylphenylacetic acid* (VII), which was itself prepared from 4-methoxy-2-methylbenzaldehyde by the "azlactone" synthesis. By hydrogenation of the oily modification of the *dimethyl ether* of (III) a crystalline compound, apparently identical with the dimethyl ether prepared by Bretschneider *et al.* (*loc. cit.*), was obtained. It moreover afforded a diphenol, and the latter a diacetate, both agreeing in properties with the corresponding compounds described by these authors.

A more obvious approach to (III) would be through the product of a benzoin condensation using 4-methoxy-2-methylbenzaldehyde. Repeated attempts to obtain 2 : 2′-dimethyldeoxyanisoin by this method have, however, not yielded the expected product. Apart from unchanged aldehyde, only a very small quantity of a substance, possibly 2 : 2′-*dimethylanisil*, has been isolated. It would appear that Linnell and Shaikmahamud (*loc. cit.*) in their attempted preparation of 2 : 2′-diethylanisoin have encountered a similar difficulty.

In view of the length of the method finally adopted for 2 : 2′-dimethyldeoxyanisoin (see above), attempts were made to shorten the process by utilising the chalkone, *αγ-di*-(4-*methoxy*-2-*methylphenyl*)*propen-α-one* (VIII, R = CH_3), as an intermediate. This compound was readily prepared from 4-methoxy-2-methylacetophenone and 4-methoxy-2-methylbenzaldehyde. However, treatment of (VIII, R = CH_3) with hydrogen peroxide led, not to the expected 2 : 3-epoxy-derivative, but to an unstable compound, possibly *αγ-di*-(4-*methoxy*-2-*methylphenyl*)*propendiolone* (IX), which oxidised spontaneously to 4-methoxy-2-methylbenzoic acid. Had the epoxy-compound been obtained, it should have been possible to proceed to 2 : 2′-dimethyldeoxyanisoin by the general method of W. Baker and Robinson (*J.*, 1932, 1798).

It is hoped to describe experiments leading to the synthesis of one or more of the remaining stilboestrol analogues (II, IV, V, and VI) in a later communication.

Biological assay of compound (III) and its dibenzyl analogue, carried out by Dr. G. Brownlee and Mr. A. F. Green at the Wellcome Physiological Research Laboratories, Beckenham, has shown that both these compounds possess considerable oestrogenic activity. Detailed results will be published elsewhere.

EXPERIMENTAL.

Melting points are uncorrected.

Pure 4-methoxy-2-methylbenzaldehyde was prepared in good yield by methylation of 4-hydroxy-2-methylbenzaldehyde (Gattermann and Berchelmann, *Ber.*, 1898, **31**, 1767), as described by Simonsen (*J.*, 1918, 777) for 2-methoxy-3-methylbenzaldehyde. Treatment of 4-methoxy-2-methylbenzaldehyde (14·0 g.) in ethanol (20 ml.) with potassium cyanide (5·1 g.) in water (17 ml.) yielded mainly unchanged aldehyde, b. p. 135—137°/15 mm., and a residual gum, from which a small quantity of pale yellow needles, m. p. 134—135°, was isolated by crystallisation from methanol. This substance appeared to be 2 : 2′-*dimethylanisil* (Found : C, 72·7; H, 6·0. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·1%).

α-(4-*Methoxyphenyl*)-*γ*-(4′-*methoxy*-2′-*methylphenyl*)*propen-α-one* (VIII, R = H).—A solution of *p*-methoxyacetophenone (10·4 g.) in 4-methoxy-2-methylbenzaldehyde (10·4 g.) was treated with a solution of sodium (1·6 g.) in methanol (80 ml.). After 12 hours, the crystalline precipitate was collected and washed with methanol and water. The *ketone* crystallised from methanol in pale yellow needles, m. p. 126—127° (16·4 g.) (Found : C, 76·8; H, 6·5. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%).

αγ-Di-(4-*methoxy*-2-*methylphenyl*)*propen-α-one* (VIII, R = Me) was prepared in a similar manner by treating a solution of 4-methoxy-2-methylbenzaldehyde (12·8 g.) and 4-methoxy-2-methylacetophenone (Eijkman, *Chem. Weekblad*, 1904, **1**, 453) (13·8 g.) in methanol (35 ml.) with a solution of sodium (2·0 g.) in methanol (65 ml.). It crystallised in yellow plates (19·5 g.), m. p. 74—76° (Found : C, 77·2; H, 6·9. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·8%).

Oxidation of the Chalkone (VIII; R = Me) *with Hydrogen Peroxide*.—Hydrogen peroxide (15%,. 13 ml.) was added to a solution of the chalkone (12·7 g.) in warm methanol (150 ml.), followed gradually by 2N-sodium hydroxide (11 ml.). The resulting oil, on extraction with ether in the usual way, was isolated as a pale yellow gum, which could not be crystallised. The gum was refluxed for 2 hours with ethanol (200 ml.) and 30% aqueous sodium hydroxide (25 ml.) and the solution poured into water and acidified. The ethereal extract, on evaporation, yielded an oil which crystallised from methanol or aqueous acetic acid to give stout yellow prisms (7·0 g.), m. p. 114—116°; this compound may have been *αγ-di*-(4-*methoxy*-2-*methylphenyl*)*propendiolone* (IX) (Found : C, 69·5; H, 6·1. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%). On standing in air, it oxidised to a white powder, which crystallised from acetic acid in needles, m. p. 175—176°, identical with 4-methoxy-2-methylbenzoic acid.

2-*Phenyl*-4-(4′-*methoxy*-2′-*methylbenzylidene*)-5-*oxazolone*.—4-Methoxy-2-methylbenzaldehyde (100·7 g.), hippuric acid (120 g.), powdered fused sodium acetate (56 g.) and acetic anhydride (171 g.) were heated together at 100° for 4 hours with occasional shaking. The crystalline condensation product was collected and washed first with methanol (*ca.* 600 ml.) and then with boiling water (2 l.). A sample of the resulting *oxazolone* (136 g.) crystallised from ethyl acetate–ethanol in bright yellow needles, m. p. 144° (Found : C, 73·6; H, 5·0. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·1%).

Methyl 4-*Methoxy*-2-*methylphenylacetate*.—The oxazolone (136 g.) was refluxed with 10% sodium hydroxide solution

(1000 ml.) for 6 hours. The filtered solution was well stirred and treated at 0° with hydrogen peroxide (28%, 100 ml.), which was slowly added over ½ hour. After two hours, the liquid was acidified with concentrated hydrochloric acid and extracted with ether. The dried ethereal extract, on evaporation, afforded a mixture of benzoic and 4-methoxy-2-methylphenylacetic acids. This mixture was treated with methanol (800 ml.) and concentrated sulphuric acid (20 ml.) and refluxed for 3 hours. Half the methanol was removed, the residue poured into water (1 l.) and the ethereal extract washed with dilute sodium carbonate solution and dried. Fractionation of this extract gave methyl benzoate (44 g.), b. p. 77—90°/10 mm., and methyl 4-methoxy-2-methylphenylacetate (55·3 g.), b. p. 147—149°/10 mm., as an odourless, strongly refracting oil.

4-*Methoxy*-2-*methylphenylacetic Acid* (VII).—The methyl ester (55·3 g.), potassium hydroxide (40 g.), water (80 ml.) and methanol (300 ml.) were refluxed for 3 hours and the residue, after removal of most of the methanol, diluted with water and acidified. The resulting precipitate, crystallised from water (1 l.) containing enough acetic acid to yield a homogeneous solution at the boiling point, gave 4-*methoxy*-2-*methylphenylacetic acid* in glistening leaflets (44·9 g.), m. p. 104—106° (Found: C, 66·6; H, 6·7. $C_{10}H_{12}O_3$ requires C, 66·6; H, 6·7%). The acid (VII) (44·9 g.) with thionyl chloride (60 g.) was refluxed for 1 hour; on distillation the acid chloride (42·5 g.) was obtained as a colourless liquid with a pleasant aromatic odour, b. p. 147—149°/12 mm. On treatment with ammonia, the acid chloride gave 4-*methoxy*-2-*methylphenylacetamide*, which crystallised from water in stout needles, m. p. 162—163° (Found: N, 8·0. $C_{10}H_{13}O_2N$ requires N, 7·8%).

2 : 2′-*Dimethyldeoxyanisoin*.—Powdered aluminium chloride (30·5 g.) was added to a mixture of *m*-methylanisole (37 g.) and dry carbon disulphide (300 ml.) at 0°. The temperature was then reduced to −10° and 4-methoxy-2-methylphenylacetyl chloride (30 g.) was slowly added with stirring over 15 minutes; stirring was continued for 1—2 hours and then the mixture was refluxed for 1 hour, decomposed with ice and hydrochloric acid and the volatile products removed by steam-distillation. The residual oil and water mixture was shaken with ether (250 ml.), and the solid that had separated during 12 hours was collected and crystallised twice from methanol to give colourless prisms of 2 : 2′-*dimethyldeoxyanisoin* (12·8 g.), m. p. 93—94° (Found: C, 76·1; H, 7·2. $C_{18}H_{20}O_3$ requires C, 76·0; H, 7·1%). A further 3·5 g., m. p. 91—92°, was obtained from the mother-liquors and from the original ether extract.

αβ-Di-(4-*methoxy*-2-*methylphenyl*)*propan-α-one*.—2 : 2′-Dimethyldeoxyanisoin (12·1 g.) was added to a solution of sodium (3·3 g.) in ethanol (90 ml.) and the whole boiled for 15 minutes giving an orange solution. Methyl iodide (45 g.) was gradually added to the cooled solution and the mixture refluxed for 16 hours. The residue, after removal of methyl iodide and ethanol, was treated with water and extracted with ether; a quantity of starting material (*ca.* 5 g.) then separated. After 12 hours, the latter was removed and the ethereal layer dried and distilled. The oily distillate, after several days at 0° in 3 volumes of ether, deposited a further 0·9 g. of starting material, which was also removed. Fractionation of the filtrate gave the ketone as an oil (5·5 g.), b. p. 202—203°/1 mm.

4 : 4′-*Dimethoxy*-α : β : 2 : 2′-*tetramethylstilbene*.—A solution of the above ketone (4·5 g.) in dry ether was added to the Grignard reagent prepared from magnesium (0·55 g.) and methyl iodide (4·5 g.) in ether. After several hours, the product was decomposed with acid and worked up in the usual way by extraction with ether. The resulting oil recrystallised from hexane (A) in soft plates (2·8 g.), m. p. 91—98°, probably consisting of impure βγ-di-(4-methoxy-2-methylphenyl)-butan-γ-ol, which was converted to the stilbene derivative without further purification. The carbinol (2·8 g.) was dissolved in a saturated solution of hydrochloric acid in glacial acetic acid (12 ml.), allowed to stand for 24 hours, and then poured into water. The ethereal extract was well washed with sodium carbonate solution, dried, and fractionated to give an oil (2·0 g.), b. p. 172—173°/1—2 mm., which on crystallisation from methanol (B) yielded 4 : 4′-*dimethoxy*-α : β : 2 : 2′-*tetramethylstilbene* (0·75 g.), as prisms, m. p. 97—98° (Found: C, 80·9; H, 8·3. $C_{20}H_{24}O_2$ requires C, 81·0; H, 8·1%). A further crop (0·7 g.) was obtained from the hexane mother liquor (A) of the carbinol (see above). A crude oily isomer of the crystalline stilbene was isolated from both mother liquors (A) and (B) by evaporation.

4 : 4′-*Dimethoxy*-α : β : 2 : 2′-*tetramethyldibenzyl*.—The above oily isomer (1·5 g.) was dissolved in acetic acid (15 ml.) and hydrogenated at room temperature and 2 atm. in the presence of Adams' catalyst. The filtrate, diluted with water (8 ml.), gave crystals of the *dimethoxydibenzyl* derivative, which separated from methanol in long prisms (0·3 g.), m. p. 138—139° (Found: C, 80·5; H, 8·8. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·8%).

4 : 4′-*Dihydroxy*-α : β : 2 : 2′-*tetramethyldibenzyl*.—4 : 4′-Dimethoxy-α : β : 2 : 2′-tetramethyldibenzyl (0·23 g.) was boiled for 2 hours with glacial acetic acid (1·5 ml.) and hydriodic acid (*d*. 1·7) (1·0 ml.). The cooled liquid was added to water (20 ml.) and the colour removed by a trace of sodium thiosulphate. The precipitate, on recrystallisation from benzene, afforded the dihydroxydibenzyl derivative in long needles, drying to a white powder (0·14 g.), m. p. 189—190°. The diacetate crystallised from methanol in long prisms, m. p. 161—162° (cf. Bretschneider *et al.*, *loc. cit.*).

4 : 4′-*Dihydroxy*-α : β : 2 : 2′-*tetramethylstilbene* (III).—Crystalline 4 : 4′-dimethoxy-α : β : 2 : 2′-tetramethylstilbene (0·8 g.) was added to the Grignard reagent prepared from magnesium (0·5 g.) and methyl iodide (1·2 ml.) and the mixture heated at 170° until reaction had ceased (¾ hour). The buff powder was decomposed with ice and dilute hydrochloric acid, and the resulting gum extracted with hot benzene (20 ml.). The extract, dried, cleaned with charcoal, and cooled, yielded 4 : 4′-*dihydroxy*-α : β : 2 : 2′-*tetramethylstilbene* (III), which crystallised from benzene in characteristic needles (0·3 g.), m. p. 208—210°, containing solvent of crystallisation. On drying in air they changed into a white amorphous powder (0·3 g.), m. p. 208—210°, with characteristic "electric" properties (Found: C, 80·3; H, 7·8. $C_{18}H_{20}O_2$ requires C, 80·6; H, 7·5%).

Sincere thanks are due to Mr. A. Bennett for microanalyses and to the Wellcome Foundation Ltd. for permission to publish the results of this investigation.

DEVELOPMENT LABORATORIES, WELLCOME CHEMICAL WORKS, DARTFORD. [*Received*, *October* 10*th*, 1945.]