

RESEARCH PAPERS

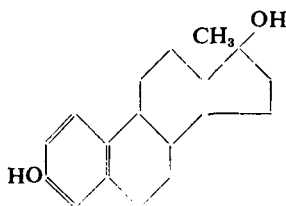
SYNTHETIC ŒSTROGENS

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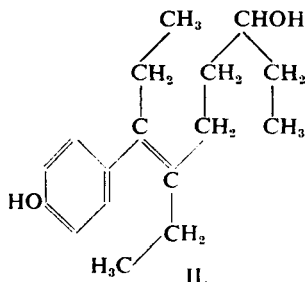
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It is remarkable that all the most active synthetic Œstrogens, with the exception of the Œstrogenic carboxylic acids of the doisyolic acid type, possess two phenolic hydroxyl groupings, and in this respect differ from the potent natural Œstrogen, Œstradiol (I), which has one phenolic and one alcoholic hydroxyl. It was considered of interest, therefore, to synthesise the compound II in an attempt to obtain a synthetic Œstrogen resembling, more closely, the Œstradiol structure with regard to the chemical nature of the functional groupings.

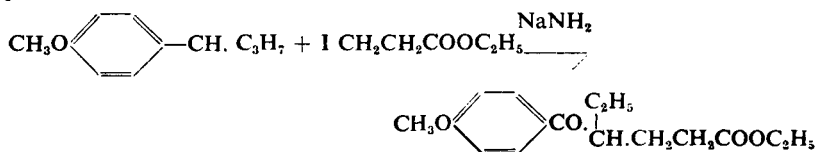


I.



II.

Attempts to synthesise 4-ethyl-5-(*p*-anisyl)- $\Delta^{4,5}$ -heptenoic acid as an intermediate in the production of II were unsuccessful. Ethyl 4-(*p*-methoxybenzoyl)-caproate (III) was obtained from ethyl β -iodopropionate¹ and the sodium enolate of *p*-methoxybutyrophenone².



III.

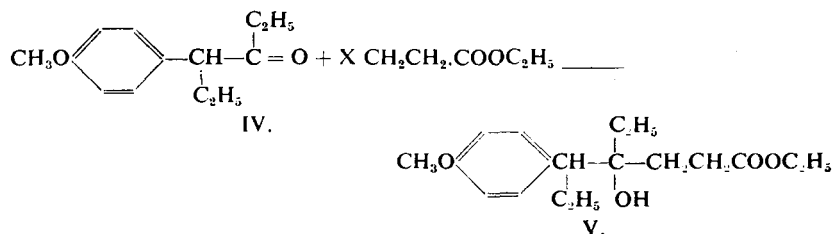
Treatment of III with one molar equivalent of ethyl magnesium iodide, or ethyl lithium, did not yield the anticipated hydroxyester. Similarly treatment of 4-(*p*-methoxybenzoyl)-caproic acid with three equivalents of ethyl magnesium iodide gave a theoretical recovery of the keto-acid.

An attempt to condense ethyl α -(*p*-anisyl)-butyrate with diethyl succinate using sodium as the condensing agent yielded succinyl succinate as the sole product. Similar results were obtained in the attempted condensation of ethyl α -phenylbutyrate with succinic ester using alcohol-free sodium ethoxide and α -phenylbutyryl chloride with succinic ester using triphenylmethyl sodium.

The successful reaction between 6-methoxytetralone and ethyl β -bromo-

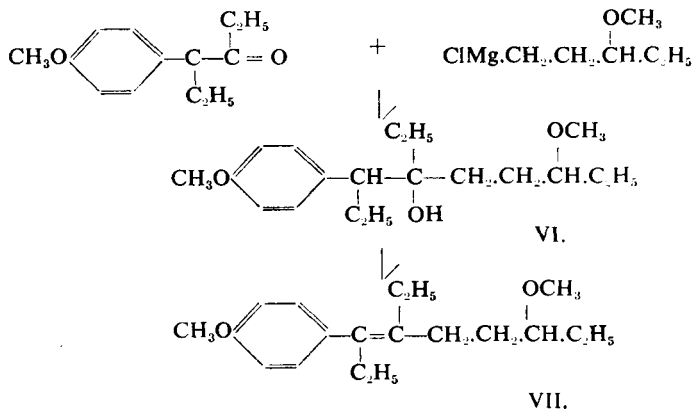
propionate using magnesium in toluene to produce β -(6-methoxy-3:4-dihydronaphthyl-(1))-propionic acid³, suggested that a similar reaction using 4-(*p*-anisyl)-3-hexanone (IV) in place of 6-methoxytetralone would yield the required intermediate.

The 4-(*p*-anisyl)-3-hexanone required was obtained by the action of diethyl cadmium on α -(*p*-anisyl)-butyryl chloride, the product being found to be identical with that formed by the action of ethyl iodide on *p*-methoxybenzyl-ethyl-ketone in the presence of alcohol-free sodium ethoxide⁴. On refluxing ethyl β -bromopropionate⁵, magnesium and 4-(*p*-anisyl)-3-hexanone in toluene only a very poor yield of the product V was obtained. Substituting ethyl β -iodopropionate for the bromo analogue and conducting the experiment in ether gave a similar poor yield of V.



An attempt to remove the elements of water from this by heating on a water-bath with 2 per cent. of iodine for 1 hour was unsuccessful.

The preparation of the Grignard complex from γ -methoxyamyl chloride⁶ proved difficult, 6 hours' refluxing with activated magnesium in ether being required for completion of the reaction. Addition of 4-(*p*-anisyl)-3-hexenone to 2 equivalents of this Grignard complex gave, on working up in the normal way, a 67 per cent. yield of 3-(*p*-anisyl)-4-ethyl-7-methoxy-4-nonanol (VI). Dehydration by heating on a water-bath for 1 hour with 1 per cent. of iodine yielded an ethylenic compound. Ozonolysis of this compound gave an 88 per cent. yield of *p*-methoxypropiophenone, identified as its 2:4-dinitrophenylhydrazone and indicated VII as the structure of the olefine.



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Demethylation of VII was achieved by heating with hydrogen bromide and acetic acid in an atmosphere of carbon dioxide for 2 hours. Purification of the product by adsorption chromatography on alumina yielded a viscous brown oil which contained no methoxyl and two active hydrogens. Carbon and hydrogen analysis agreed with that calculated for 3(*p*-hydroxyphenyl)-4-ethyl-7-hydroxy- $\Delta^{3,4}$ -nonene (II). The failure to isolate the two possible geometrical isomers on chromatographic adsorption of II suggests that the product consisted of only one isomer. The use of iodine for the formation of the double bond and hydrogen bromide for demethylation of VII supplied conditions suitable for the interconversion of geometrical isomers and would be expected to produce the more stable form which in most cases of *cis-trans* pairs has the *trans*-configuration. It appears likely, therefore, that the compound II possesses the *trans* structure.

We are indebted to Professor Buttle and Dr. F. J. Dyer, of the Pharmacological Department of this School for the biological examination of compounds VII and II. The dimethyl ether VII was found to be inactive on administration in arachis oil solution of 20 mg. per 20 g. mouse. The phenolic alcohol II, in propylene glycol solution, was found to possess less than 1/40,000 of the activity of stilbœstrol.

EXPERIMENTAL

Ethyl 4-(p-methoxybenzoyl)caproate.



The sodium enolate of *p*-methoxybutyrophenone was prepared by adding 50 g. of the ketone, dissolved in 50 ml. of dry benzene, in 10 aliquot parts at 10 minute intervals, to 12 g. of finely powdered sodamide in 250 ml. of dry benzene, the mixture being refluxed vigorously until no further ammonia was evolved. To the cooled benzene solution was added gradually, with rapid stirring, a solution of 55.6 g. of ethyl β -iodopropionate in 30 ml. of dry benzene, the reaction flask being kept cold in an ice bath. After completion of the addition, stirring was continued for 1 hour at room temperature and then with refluxing for 30 minutes. The cooled product was poured into 300 ml. of water, the benzene layer was separated and the aqueous layer extracted twice with benzene. The combined benzene solution and extracts were washed with sodium thiosulphate solution and finally dried over anhydrous sodium sulphate. Evaporation of the benzene and distillation of the residue *in vacuo* yielded a golden yellow oil, b.pt. 180° to 182°C./1.2 mm. Yield, 35 to 40 per cent. of theoretical. Found: Eq. Wt. 273; $\text{C}_{16}\text{H}_{25}\text{O}_4$ requires 278.

4-(p-methoxybenzoyl)caproic acid. $\text{CH}_3\text{OC}_6\text{H}_4\text{CO.CH}\overset{\text{C}_2\text{H}_5}{\underset{|}{\text{C}}}\text{H}_2\text{.CH}_2\text{COOH.}$

10 g. of the ethyl ester were refluxed with 100 ml. of N alcoholic potash for 3 hours. The cooled solution was diluted to 500 ml. with water and acidified with hydrochloric acid. The acid was filtered off and recrystallised from 40 per cent. aqueous alcohol, yielding 8.5 g. (94.5

per cent. of theory) of creamy white crystals, m.pt. 83.5° to 84° C. Found: C, 66.5; H, 6.86; CH_3O , 10.9 per cent., Eq. Wt. 250.8; $\text{C}_{14}\text{H}_{18}\text{O}_2$ requires C, 67.2; H, 7.2; CH_3O , 12.4 per cent., Eq. Wt. 250.

Diethyl p-methoxyphenylethylmalonate.

23.3 g. of sodium was added to 330 g. of absolute alcohol. After the solution had cooled to about 60° C. a mixture of 150 g. of ethyl oxalate and 194 g. of ethyl *p*-methoxyphenyl acetate⁷ was added quickly with rapid stirring. The temperature, which dropped to about 40° C., was brought back to 60° C. and held at that temperature until the sodium salt of *p*-methoxyphenyl oxalacetic ester separated thickly. This occurred in about 2 or 3 minutes. The mixture was held at 60° C. for a further 30 minutes, after which the sodium salt was acidified with 70 g. of concentrated sulphuric acid diluted with 200 ml. of water. The mixture formed two layers. After verifying that the aqueous layer was acid to congo-red, the ester was taken into benzene, care being taken to avoid the crystallisation of sodium sulphate decahydrate by keeping the temperature above its melting-point. The benzene was distilled under reduced pressure. The distillation flask was then fitted with a still head carrying a thermometer dipping beneath the surface of the liquid, and an air condenser. The ester was heated on an oil bath, raising the temperature to 190° C. in 30 minutes and held at that temperature for a further hour. The crude *p*-methoxyphenylmalonic ester was then fractionated under reduced pressure yielding 235 g. (86.5 per cent. of theoretical) of a yellow oil. B.pt. 159° to 161° C./2 mm. Hg.

Diethyl p-methoxyphenylethylmalonate. $\text{CH}_3\text{OC}_6\text{H}_4\cdot\text{C}(\text{C}_2\text{H}_5)(\text{COOC}_2\text{H}_5)_2$.

14.6 g. of sodium was dissolved in 175 ml. of absolute alcohol and to the solution of sodium ethoxide so formed was added, at 50° to 60° C., 180 g. of diethyl *p*-methoxyphenylmalonate. When the temperature had fallen to about 35° C., 103.75 g. of ethyl iodide were added as rapidly as possible and the temperature held at 35° C. for 6 hours with stirring. The alcohol was then removed by distillation, the residue diluted with 250 ml. of water and made acid to methyl red with acetic acid. A little sodium sulphite was added to remove any free iodine and the ester taken into benzene. After removal of the solvent the ester was distilled under reduced pressure, yielding 164 g. of a yellow oil with a boiling point identical with the starting material. Yield, 82.5 per cent. of theoretical. Eq. Wt. found 147.7; $\text{C}_{15}\text{H}_{22}\text{O}$ requires 147.

α -(*p*-Anisyl)-butyric acid. $\text{CH}_3\text{OC}_6\text{H}_4\text{CH}(\text{C}_2\text{H}_5)\text{COOH}$.

100 g. of *p*-methoxyphenylethylmalonic ester were saponified by refluxing on a water-bath with 750 ml. of 10 per cent. alcoholic potash for 3 hours. The cooled solution was diluted with 3 l. of water and acidified with hydrochloric acid and the precipitated acid filtered off at the pump. Evaporation of the filtrate to about half its volume gave, on cooling, a fourth crop of crystals. Recrystallisation from light petroleum (40° to 60° C.) yielded 63 g. of needle-shaped crystals, m.pt. 64° to 65° C. Yield, 92 per cent. of theoretical. Found: C, 68.5; H, 7.3; CH_3O , 14.9 per cent., Eq. Wt. 193. $\text{C}_{11}\text{H}_{14}\text{O}_3$ requires C, 68.8; H, 7.2; CH_3O , 16.0 per cent., Eq. Wt. 194.

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α-(p-Anisyl)-butyryl chloride. $\text{CH}_3\text{OC}_6\text{H}_4\text{CH}(\text{C}_2\text{H}_5)\text{COCl}$.

39 g. of *α-(p-anisyl)-butyric acid* was refluxed with 70 g. of thionyl chloride for 3 hours. The excess of thionyl chloride was distilled off and the residue distilled under reduced pressure, yielding a pale yellow pungent liquid. B.pt. $120^\circ\text{C}/4$ mm. Hg. pressure. Yield 40 g., 94 per cent. of theoretical.

4-(p-Anisyl)-3-hexanone. $\text{CH}_3\text{O.C}_6\text{H}_4\text{CH}(\text{C}_2\text{H}_5).\text{CO.C}_2\text{H}_5$.

Ethyl magnesium bromide was prepared from 13.6 g. of ethyl bromide and 3 g. of magnesium in 100 ml. of absolute ether. The solution was cooled in an ice bath and 12 g. of dry, finely powdered cadmium chloride added. After refluxing for 45 minutes the mixture gave no colour with Michler's ketone indicating the absence of any Grignard complex. The reflux was replaced by a condenser set for distillation and nearly all the ether removed by heating on a water-bath. 50 ml. of dry benzene was then added and 20 ml. distilled. A further 50 ml. of dry benzene was then added to the mixture. The reflux condenser was replaced and to the cooled benzene solution of diethyl cadmium, was added, with stirring, a solution of 21.3 gm. of *-(p-anisyl)-butyryl chloride* in 20 ml. of benzene, during about 3 minutes. The mixture was stirred at room temperature for 15 minutes and then at 40°C . for 2 hours. The cooled reaction mixture was decomposed by pouring on to 150 g. of ice and 70 ml. of 2N sulphuric acid. The benzene layer was separated and the lower aqueous layer shaken with three further quantities of benzene. The combined benzene solution and extracts were washed with dilute sodium carbonate solution and finally dried over anhydrous sodium sulphate. The benzene was removed under reduced pressure and the crude ketone fractionated, yielding a colourless oil boiling at 132° to $134^\circ\text{C}/2.5$ mm. Hg. pressure. Yield, 71 per cent. of theoretical.

Semicarbazone: m.pt. 131.5° to 132°C . Found: C, 64; H, 8.05; N, 15.4 per cent.; $\text{C}_{14}\text{H}_{21}\text{N}_3\text{O}$ requires C, 63.8; H, 7.96; N, 15.9 per cent.

2:4-Dinitrophenylhydrazone: m.pt. 91.5 to 92°C . Found: C, 58.8; H, 5.7; N, 14.8 per cent.; $\text{C}_{19}\text{H}_{21}\text{N}_4\text{O}_5$ requires C, 59.25; H, 5.45; N, 14.5 per cent.

3-(p-Anisyl)-4-methyl- $\Delta^{3,4}$ -hexene, $\text{CH}_3\text{O.C}_6\text{H}_4.\text{C}(\text{C}_2\text{H}_5):\text{C}(\text{CH}_3).\text{C}_2\text{H}_5$.

5.15 g. of *4-(p-anisyl)-3-hexanone*, dissolved in 20 ml. of absolute ether, was added during 15 minutes, with cooling and stirring, to 1.5 equivalents of methyl magnesium iodide in 30 ml. of ether. The mixture was then refluxed for 3 hours, cooled, and then decomposed by pouring on to 50 g. of ice and 35 ml. of dilute sulphuric acid. The ethereal layer was separated and the aqueous portion extracted thoroughly with ether. The combined ethereal solution and extracts were washed with sodium thiosulphate solution and dried over anhydrous sodium sulphate. Distillation yielded a colourless oil boiling at 99° to $105^\circ\text{C}/0.8$ mm. Hg. pressure. Yield 3.38 g.

Distillation, under reduced pressure, of this oil with 2 per cent. of iodine and purification of the distillate in the normal manner yielded a colourless oil distilling at a bath temperature of 95° to 100°C . and 0.05

mm. Hg. pressure. Found C, 81.56; H, 9.3; CH₃O, 15.3 per cent.; C₁₄H₂₀O requires C, 82.3; H, 9.8; CH₃O, 15.2 per cent.

The compound contained no active hydrogen.

Demethylation of 3-(p-Anisyl)-4-methyl-Δ^{3,4}-hexene.

1.5 g. of the above methoxy compound was heated with three equivalents of methyl magnesium iodide under a reflux condenser, the temperature being raised slowly to 165°C. and then maintained at this temperature for 3 hours. The cooled reaction mixture was then decomposed with ice and dilute sulphuric acid, the ethereal layer separated and the aqueous layer extracted with ether. The combined ethereal solution and extracts were washed with sulphate solution and then extracted with dilute aqueous sodium hydroxide. Acidification of the alkaline extract with dilute sulphuric acid, extraction with ether and distillation yielded a yellow glass distilling at 108° to 118°C./0.8 mm. Hg. pressure. *Ethyl 4-ethyl-5-(p-anisyl)-4-hydroxyheptanoate.*



- A. 5.15 g. of 4-(p-anisyl)-3-hexanone was refluxed with 0.61 g. of magnesium and 4.43 g. of ethyl β-bromopropionate in 50 ml. of dry toluene. Addition of 0.3 g. of iodine started the reaction. After 3 hours refluxing, the mixture was cooled and decomposed with ice and dilute sulphuric acid, the toluene layer separated and the aqueous layer extracted with ether. The combined toluene solution and ethereal extracts were washed with dilute sodium thio-sulphate solution and finally dried over anhydrous sodium sulphate. Distillation yielded 0.38 g. of a light yellow, semi-solid substance boiling at 145° to 155°C./0.3 mm. Hg. pressure.
- B. As method A, except for the use of ethyl β-iodopropionate in place of the β-bromo analogue and ether instead of toluene. 6 hours refluxing was required for solution of the magnesium. On work-up, as before, there was obtained a yellow semi-solid fraction distilling at 115° to 120°C./0.05 mm. Hg., which proved to be the same as that obtained in A. Yield, 0.55 g. Found: C, 69.7; H, 8.7; CH₃O, 10.7 per cent.; C₁₈H₂₅O₄ requires C, 70.1; H, 9.08; CH₃O, 10.05 per cent.

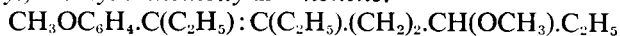
3-(p-Anisyl)-4-ethyl-7-methoxy-4-nonanol.



1.2 g. of magnesium turnings, 30 ml. of dry ether and 6.8 g. of freshly distilled γ-methoxyamyl chloride were refluxed together, with stirring. Two or 3 drops of methyl iodide helped to initiate the reaction which was very slow, requiring 6 hours for completion. To the cooled ethereal solution of γ-methoxyamyl magnesium chloride was added, during 30 minutes, 5.15 g. of 4-(p-anisyl)-3-hexanone dissolved in 10 ml. of dry ether. Stirring was continued and the mixture refluxed for 4 hours. Decomposition of the complex with ice and dilute sulphuric acid, yielded,

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on working up, 5.15 g. of a viscous yellow oil boiling at 140° to 145°C./0.04 mm. Hg. pressure. Found: C, 74.3; H, 10.38; CH₃O, 20.06 per cent.; C₁₉H₃₂O₃ requires C, 74.02; H, 10.39; CH₃O, 20.13 per cent.
3-(p-Anisyl)-4-ethyl-7-methoxy-Δ^{3,4}-nonene.



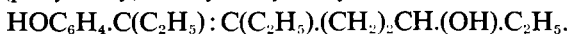
4.5 g. of 3-(*p*-anisyl)-4-ethyl-7-methoxy-4-nonenol and 50 mg. of iodine were heated together on a water-bath for 1 hour under a reflux air condenser. The resultant dark brown oil was dissolved in ether, washed with sodium thiosulphate solution and the ethereal solution then dried over anhydrous sodium sulphate. Distillation yielded a light yellow oil, boiling at 130° to 135°C./0.1 mm. Hg. pressure. Found: C, 78.08; H, 10.08; CH₃O, 21.48 per cent.; C₁₉H₃₀O₂ requires C, 76.63; H, 10.34; CH₃O, 21.38 per cent.

Ozonised oxygen was passed into a solution of 0.5 g. of the above ethylenic compound in 50 ml. of chloroform for the calculated time. The chloroform was then removed under reduced pressure and the ozonide decomposed with iced water. Extraction with ether and evaporation of the solvent yielded a semi-solid residue. This was dissolved in light petroleum (40° to 50°C.) and passed through a column of activated alumina. The chromatogram showed three zones, (1) a narrow dark band at the top, (2) a broad pale-yellow zone, (3) a narrow band exhibiting a blue fluorescence under ultra-violet light, near the bottom. Washing with light petroleum removed the lowest band, but continued washing did not appear to remove the yellow zone. Elutriation with benzene and ether removed the yellow zone leaving a small dark brown band at the surface. Evaporation of the solvents yielded:

- (a) 0.14 g. of a white wax-like substance which was insoluble in methyl and ethyl alcohols and water.
- (b) 20 mg. of an oil which gave a red oil on addition of a saturated alcoholic solution of 2:4-dinitrophenylhydrazine sulphate. Crystallisation of this oil could not be brought about.
- (c) 0.25 g. of an oil which yielded a 2:4-dinitrophenylhydrazine melting at 185° to 187°C.

Mixed melting-point with a sample of *p*-methoxypropiophenone 2:4-dinitrophenylhydrazine, 186° to 187° C.

3-(p-Hydroxy)-4-ethyl-7-hydroxy-Δ^{3,4}-nonene.



0.5 g. of 3-(*p*-anisyl)-4-ethyl-7-methoxy-Δ^{3,4} nonene was heated in an oil bath at 140° C. for 2 hours, with 1.5 ml. of 47 per cent. hydrobromic acid and 6 ml. of glacial acetic acid in an atmosphere of carbon dioxide. The reaction mixture was then cooled, diluted with water and made just alkaline with sodium hydroxide solution, keeping the mixture cold in an ice bath. The brown semi-solid product was taken into ether, the ethereal solution washed with water and finally dried. On distillation, 0.4 g. of a viscous brown oil was obtained.

A solution of this in 40 ml. of cyclohexane was passed through a column of activated alumina. Development of the chromatogram with

benzene revealed a narrow dark brown band at the top of the column, below this a broad yellow zone and at the bottom a narrow band exhibiting a blue fluorescence under ultra-violet light. Continued elutriation with benzene removed the blue-fluorescent band. A mixture of equal parts of benzene and acetone removed the yellow zone.

Distillation of this latter elutriate yielded 270 mg. of a very viscous oil which could not be crystallised. Found: C, 77.94; H, 9.91; CH_3O , 0 per cent.; $\text{C}_{17}\text{H}_{16}\text{O}_2$ requires C, 77.86; H, 9.92; CH_3O , 0 per cent.

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