

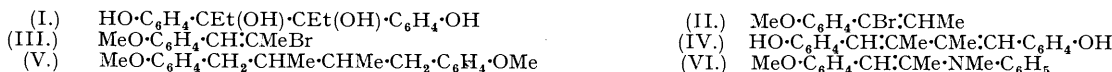
163. Dienoestrol.

By G. I. HOBDAY and W. F. SHORT.

A second form (m. p. 94—95°) of $\gamma\delta$ -bis-4-hydroxyphenylhexane- $\gamma\delta$ -diol (I) has been isolated and on dehydration affords $\gamma\gamma$ -bis-4-hydroxyphenylhexan- δ -one (VII), the methyl ether of which is reduced to stilboestrol dimethyl ether (IX). Either β -chloro- α -*p*-anisyl- Δ^{α} -propene or α -chloro- α -*p*-anisyl- Δ^{α} -propene can be obtained from anethole dichloride, and the corresponding bromo-compounds have been prepared. The α -bromo-compound and magnesium afford dienestrol dimethyl ether, and the β -bromo-compound, to which the α -structure was assigned by Balaban *et al.* (*loc. cit.*), similarly yields $\alpha\delta$ -di-*p*-anisyl- $\beta\gamma$ -dimethyl- $\Delta^{\alpha\gamma}$ -butadiene.

THE important oestrogen dienestrol, $\gamma\delta$ -bis-4-hydroxyphenyl- $\Delta^{\beta\delta}$ -hexadiene, (m. p. 227—228°) was prepared by Dodds, Golberg, Lawson, and Robinson (*Nature*, 1938, **142**, 34; *Proc. Roy. Soc.*, 1939, *B*, **137**, 162) from *p*-hydroxypropiophenone by reduction to $\gamma\delta$ -bis-4-hydroxyphenylhexane- $\gamma\delta$ -diol (I), m. p. 204—206°, followed by dehydration with acetyl chloride and acetic anhydride to $\gamma\delta$ -bis-4-acetoxyphenyl- $\Delta^{\beta\delta}$ -hexadiene and hydrolysis. Balaban, Jones, and British Colloids (B.P. 547,027) state that dienestrol, m. p. 192°, may be obtained from the dimethyl ether, m. p. 161°, resulting from the action of magnesium upon a compound, formulated as α -bromo- α -*p*-anisyl- Δ^{α} -propene (II) and obtained by the action of dilute aqueous sodium hydroxide on $\alpha\beta$ -dibromo- β -*p*-anisylisobutyric acid. The lower m. p. attributed to dienestrol by Balaban *et al.* might be due to the fact that they had isolated a different stereoisomer, but the present authors had good theoretical reasons for thinking that the elimination of hydrogen bromide and carbon dioxide from $\alpha\beta$ -dibromo- β -*p*-anisylisobutyric acid would produce β -bromo- α -*p*-anisyl- Δ^{α} -propene (III), so that the final product of the synthesis would

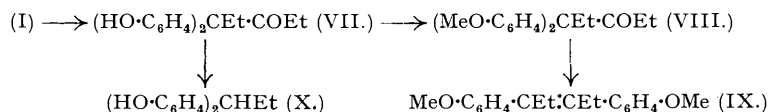
be $\alpha\delta$ -bis-4-hydroxyphenyl- $\beta\gamma$ -dimethyl- $\Delta^{\alpha\gamma}$ -butadiene (IV). In agreement with this conclusion, ozonolysis of the dimethyl ether, m. p. 163° , gave a 73% yield of anisaldehyde together with diacetyl, and catalytic reduction afforded a compound, m. p. $68-69^\circ$, which must be $\alpha\delta$ -di-*p*-anisyl- $\beta\gamma$ -dimethylbutane (V), since it is also obtained by the action of magnesium on β -chloro- α -*p*-anisylpropane. The bromide (III) is also obtained by the action of alcoholic sodium ethoxide (1.1 mols.) on anethole dibromide and affords β -*p*-anisyl- α -methylacrylic acid, m. p. 158° , by the successive action of magnesium and carbon dioxide. The isomeric bromo-compound (II) has now been prepared by the addition of hydrogen bromide to 1-*p*-anisylprop-1-yne, obtained by digesting anethole dichloride successively with pyridine and methyl-alcoholic potash. A small yield of dienestrol is obtained from this bromide by the successive action of magnesium and anhydrous cupric chloride, followed by demethylation of the product with methylmagnesium iodide.



Anethole dibromide and boiling dimethylaniline afford β -(*N*-methylanilino)anethole (VI) with elimination of methyl bromide, and the unsaturated amine yields anisaldehyde and acetomethylanilide on oxidation. The elimination of hydrogen chloride from anethole dichloride is controlled by the reagent employed. Thus, pyridine produces β -chloro- α -*p*-anisyl- Δ^{α} -propene, b. p. $135-136^\circ/10$ mm., which is also obtained by the action of phosphorus pentachloride on anisylacetone. Ozonolysis affords a 60% yield of anisaldehyde and the successive action of magnesium and carbon dioxide yields β -*p*-anisyl- α -methylacrylic acid, and a small amount of $\alpha\delta$ -di-*p*-anisyl- $\beta\gamma$ -dimethyl- $\Delta^{\alpha\gamma}$ -butadiene. The same formula has been ascribed without proof to the products obtained from anethole and phosphorus pentachloride by Ladenburg (*Annalen*, *Suppl.*, 1877, **8**, 90) and by the distillation of anethole dichloride (Darzens, *Compt. rend.*, 1897, **124**, 564).

α -Chloro- α -*p*-anisyl- Δ^{α} -propene, m. p. 43° , is obtained by the action of alcoholic potash on anethole dichloride or from *p*-methoxypropiofenone and phosphorus pentachloride; this isomer resembles α -bromostyrene (Dufraisse, *Compt. rend.*, 1921, **172**, 162) in being readily oxidised in air and we were unable to convert it into dienestrol dimethyl ether by the action of magnesium.

The pinacol (I) has been obtained from *p*-hydroxypropiofenone and aluminium amalgam in moist ether (Dodds *et al.*, *loc. cit.*) or by electrolytic reduction (Glaxo Laboratories, Robinson, and Resuggan, B.P. 523,515). Its dimethyl ether, m. p. 194° , can be obtained from *p*-methoxypropiofenone by reduction electrolytically or with magnesium amalgam and from *p*-anisylmagnesium bromide and dipropionyl, conveniently prepared from propionin and selenium dioxide. Electrolytic reduction of *p*-benzoyloxypropiofenone results in the simultaneous elimination of the benzoyl group and the main product is an isopinacol, m. p. $94-95^\circ$. The isopinacol, which is probably the racemic form of (I), also accompanies the pinacol when the electrolytic reduction of *p*-hydroxypropiofenone is carried out under different conditions and may be separated by taking advantage of its greater solubility in cold acetic acid. The isopinacol is rapidly converted into $\gamma\gamma$ -bis-4-hydroxyphenylhexan- δ -one (VII), m. p. 136° , by hot glacial acetic acid or by mineral acids and, although there are indications that the isopinacol affords a dibenzoate, the pure compound could not be isolated owing to the ease with which it is transformed into $\gamma\gamma$ -bis-4-benzoyloxyphenylhexan- δ -one, m. p. 178° . The keto-phenol (VII) does not react with any of the usual ketonic reagents, but affords a diacetate, m. p. $91-92^\circ$, and a liquid dimethyl ether (VIII), which yields 4 : 4'-dimethoxybenzophenone on oxidation with chromic anhydride and stilboestrol dimethyl ether (IX), m. p. 124° , on reduction with sodium and amyl alcohol. When the keto-phenol (VII) is fused with potash, it affords $\alpha\alpha$ -bis-4-hydroxyphenylpropane (X), m. p. 134° , which has been synthesised by Wessely, Kerschbaum, Kleedorfer, Prillinger, and Zajic (*Monatsh.*, 1940, **73**, 127). Methylation of the phenol (X) yields $\alpha\alpha$ -di-*p*-anisylpropane, m. p. 44° , which is identical with the product obtained by reducing $\alpha\alpha$ -di-*p*-anisyl- Δ^{α} -propene with sodium and amyl alcohol. The propene was obtained by Gattermann (*Ber.*, 1889, **22**, 1129) as a by-product of a Friedel-Crafts reaction with anisole and propionyl chloride, but the structure assigned to it by him has been disputed by Skraup and Freundlich (*Annalen*, 1923, **431**, 268) on the ground that it depresses the m. p. of an isomeric compound obtained from 4 : 4'-dimethoxybenzophenone and ethylmagnesium bromide, has a yellow colour, and does not exhibit halochromy with concentrated sulphuric acid. We find, however, that Gattermann's compound crystallises from alcohol in colourless plates, m. p. 101° , which give a red coloration with concentrated sulphuric acid.



Dienoestrol is somewhat resistant to methylation, but affords a *mono*- and a *di*-methyl ether, m. p. 142° and $130-131^\circ$ respectively. These are demethylated to dienestrol by methylmagnesium iodide, but afford an isomeric compound, m. p. 189° , with alcoholic potash at 220° .

(Note added September 28th, 1943.) Reduction of the compound, m. p. 189° , obtained by the demethylation of dienestrol dimethyl ether with alcoholic potash, in presence of palladised charcoal affords a mixture of hexoestrol and isohexoestrol in the ratio 2 : 1. The compound cannot therefore be $\gamma\delta$ -bis-4-hydroxyphenyl- $\Delta^{\alpha\epsilon}$ -hexadiene. Oxidation of the corresponding dimethyl ether with potassium permanganate in aqueous acetone

gives a small yield of anisil, and ozonolysis affords a trace of anisil and some acetaldehyde (2:4-dinitrophenylhydrazone, m. p. 167—168°). The compound is therefore probably a stereoisomeride of dienestrol and may be called *isodienoestrol*. The liquid dimethyl ether of *isodienoestrol* affords hexoestrol dimethyl ether, m. p. and mixed m. p. 145°, as main product by reduction in presence of palladised charcoal.

EXPERIMENTAL.

1-*p*-Anisylprop-1-yne.—Crude β -chloro-*a-p*-anisyl- Δ^a -propene, b. p. 135—136°/10 mm. (150 g.), potassium hydroxide (135 g.; 2.9 mols.), and methanol (225 c.c.), refluxed for 8 hours, afforded 1-*p*-anisylprop-1-yne (90 g. or 75%) as a colourless liquid, b. p. 115—117°/9 mm. (Found: C, 82.3; H, 7.3. $C_{10}H_{10}O$ requires C, 82.2; H, 6.8%).

a-Chloro-*a-p*-anisyl- Δ^a -propene.—(1) Anethole dichloride (257 g.), when refluxed for 4 hours with a solution of sodium (55 g.; 2.8 atoms) in absolute alcohol (1 l.) gave the crude chloride, b. p. 108—110°/6 mm. (115 g. or 53.6%). *a*-Chloro-*a-p*-anisyl- Δ^a -propene, m. p. 43°, was isolated by freezing (Found: Cl, 19.0. $C_{10}H_{11}OCl$ requires Cl, 19.5%).

(2) Phosphorus pentachloride (55 g.; 1.06 mols.) was added in portions with shaking to *p*-methoxypropiphenone (41 g.) at -5°; after 12 hours, the product was isolated with ether and hydrolysed for 12 hours at room temperature with a solution of potassium hydroxide (14 g.; 1 mol.) in water (14 c.c.) and alcohol (126 c.c.). *p*-Methoxypropiphenone was removed by adding a concentrated aqueous solution of hydroxylamine hydrochloride (7 g.) and potassium hydroxide (11 g.), removing the solvent under diminished pressure, and washing an ethereal solution of the residue with water. The yield of *a*-chloro-*a-p*-anisyl- Δ^a -propene, m. p. 43°, was 20 g. or 44%.

β -Chloro-*a-p*-anisyl- Δ^a -propene.—(1) This compound, b. p. 135—136°/10 mm., was obtained in 57% yield by heating anethole dichloride and pyridine (2.3 mols.) on the steam-bath for 2 hours, the operation being repeated with the same amount of pyridine (Found: Cl, 19.4, 19.3. $C_{10}H_{11}OCl$ requires Cl, 19.5%).

(2) A 24% yield of this chloro-compound was also obtained from anisylacetone and phosphorus pentachloride, the same technique being used as that employed in preparing the *a*-isomer. The structure of the material obtained from anethole dichloride and pyridine was verified (*a*) by the production of anisaldehyde (isolated as 2:4-dinitrophenylhydrazone, m. p. 254°) in 60% yield on ozonolysis in chloroform solution with 3% ozonised oxygen and (*b*) by the isolation of β -*p*-anisyl- α -methylacrylic acid, m. p. 158°, and of *ad*-di-*p*-anisyl- β - γ -dimethyl- $\Delta^{\alpha\gamma}$ -butadiene, m. p. 162° (see below), from the products obtained by the successive action of magnesium (5 g.) and of carbon dioxide on a solution of the chloro-compound (25 g.) in anhydrous ether (125 c.c.).

β -(*N*-Methylanilino)anethole.—An exothermic reaction occurred when anethole dibromide (308 g.) was mixed with dimethylaniline (250 c.c.; 2 mols.) and, after 24 hours, the mixture was washed with dilute acid and water, to remove dimethylaniline, dried, and distilled. Fraction (1), b. p. 112—113°/7 mm., probably consisted of 1-*p*-anisylprop-1-yne, and fraction (2), b. p. 200—205°/1 mm., solidified on cooling and crystallised from alcohol in colourless leaflets, m. p. 116° (Found: C, 80.8; H, 7.8; N, 5.4. $C_{17}H_{19}ON$ requires C, 80.6; H, 7.5; N, 5.5%). The yield was 100 g. or 39.5% and oxidation with potassium permanganate in acetone solution afforded anisaldehyde (2:4-dinitrophenylhydrazone, m. p. 254°) and acetomethylanilide, m. p. 103°.

β -Bromo-*a-p*-anisyl- Δ^a -propene (III).—(1) *a* β -Dibromo- β -*p*-anisylisobutyric acid and dilute aqueous sodium hydroxide under the conditions described by Balaban *et al.* (*loc. cit.*) afforded β -bromo-*a-p*-anisyl- Δ^a -propene, b. p. 130—132°/6 mm., in 73% yield (Found: Br, 35.1. $C_{10}H_{11}OBr$ requires Br, 35.25%).

(2) Anethole dibromide and 1.7*N*-alcoholic potash (1.1 mols.) gave a 40% yield of the same compound when boiled for 3 hours. When the product obtained by either method was converted into a Grignard reagent and carbonated at -10°, it afforded β -*p*-anisyl- α -methylacrylic acid, m. p. 158°, in 25% yield and the structure was further confirmed by conversion of the bromide into *ad*-di-*p*-anisyl- β - γ -dimethyl- $\Delta^{\alpha\gamma}$ -butadiene (see below).

ad-Di-*p*-anisyl- β - γ -dimethyl- $\Delta^{\alpha\gamma}$ -butadiene (as IV).—The preceding bromo-compound was brought into reaction with magnesium as described by Balaban *et al.* (*loc. cit.*); the product crystallised from light petroleum-benzene in colourless laminae, m. p. 163°. Ozonisation of the unsaturated compound (0.1 g.) in chloroform (25 c.c.) with 0.5% ozone for 3 hours at 0°, decomposition of the ozonide with water, and distillation of the liquid furnished a distillate with a strong odour of diacetyl and which afforded nickel dimethylglyoxime after reaction with hydroxylamine. Anisaldehyde (0.06 g. or 73%) was obtained by extracting the residue with ether and was identified by the preparation of its semicarbazone, m. p. 209°, and 2:4-dinitrophenylhydrazone, m. p. 254°. [Stilboestrol dimethyl ether, m. p. 124°, afforded *p*-methoxypropiphenone (2:4-dinitrophenylhydrazone, m. p. 190—191°) when ozonised under the same conditions.]

ad-Di-*p*-anisyl- β - γ -dimethylbutane (V).—(i) A solution of the aforesaid unsaturated compound (0.55 g.) in warm acetone (100 c.c.) was shaken with hydrogen in the presence of 6% palladium-charcoal (1 g.), 2.1 mols. of hydrogen being absorbed in 2 hours. The resulting mixture of tetrahydro-compounds (0.49 g.), m. p. 68—75°, on crystallation from alcohol afforded a portion (0.45 g.), m. p. 73—75°, and the mother-liquor deposited crystals, m. p. 67—73°, which on sublimation at 170°/1 mm. and recrystallisation from alcohol furnished *ad*-di-*p*-anisyl- β - γ -dimethylbutane, m. p. 68—69° (Found: C, 80.6; H, 8.6. $C_{22}H_{26}O_2$ requires C, 80.5; H, 8.7%). There was a depression in m. p. when this preparation was mixed with *aw*-di-*p*-anisylhexane, m. p. 70—71°, prepared by the method of Richardson and Reid (*J. Amer. Chem. Soc.*, 1940, **62**, 413). (ii) Reduction of anisylacetone (50 g.) with sodium (50 g.; 7.1 atoms) and absolute alcohol (600 c.c.) gave the secondary alcohol (11 g. or 22%), b. p. 108—109°/2 mm., which afforded β -chloro-*a-p*-anisylpropane, b. p. 89—90°/1 mm., with hydrogen chloride in benzene solution. The yield was 43%, and the chloro-compound gave the butane, m. p. and mixed m. p. 68°, when a dry ethereal solution was boiled with a large excess of magnesium for 4 hours.

γ δ -Bis-4-hydroxyphenylhexane- γ δ -diol (Pinacol, m. p. 204—206°).—This compound, prepared from *p*-hydroxypropiphenone by reduction with aluminium amalgam (Dodds *et al.*, *loc. cit.*) or by electrolytic reduction (Glaxo Laboratories, Robinson, and Resuggan, B.P. 523,515), has been further characterised by the preparation of a *dibenzoate*, m. p. 235—236° (Found: C, 75.1; H, 5.9; Bz, 41.3. $C_{32}H_{30}O_6$ requires C, 75.4; H, 5.9; Bz, 41.2%), and a *ditoluene-p-sulphonate*, prisms from benzene, m. p. 205° (Found: C, 62.2; H, 5.5. $C_{32}H_{34}O_8S_2$ requires C, 62.8; H, 5.6%).

γ δ -Di-*p*-anisylhexane- γ δ -diol.—The dimethyl ether of the preceding pinacol crystallised from ethyl acetate in prisms, m. p. 194° (Found: C, 73.0; H, 7.9. $C_{20}H_{26}O_4$ requires C, 72.7; H, 7.9%), and afforded γ γ -di-*p*-anisylhexan- δ -one (see below) as main product when dehydrated by boiling with acetic anhydride-acetyl chloride. It was prepared by three methods: (1) A solution of *p*-methoxypropiphenone (32 g.) and mercuric chloride (11.5 g.) in dry ether (150 c.c.) was added to fine magnesium turnings (10 g.) and dry benzene (100 c.c.), and the mixture boiled for 48 hours. After addition of water (25 c.c.) and 1 hour's boiling, the product was acidified with hydrochloric acid, and the benzene layer washed, dried, and evaporated. Distillation afforded 28 g. of recovered ketone, and crystallisation of the solid residue from benzene-alcohol gave 1 g. of the pure methyl ether. (2) Electrolysis of a solution of *p*-methoxypropiphenone (22 g.) and sodium hydroxide (20 g.) in alcohol (200 c.c.) and water (50 c.c.), the method described in B.P. 523,515 for the reduction of *p*-hydroxypropiphenone being used, afforded 4.9 g. (22%) of γ δ -di-*p*-anisylhexane- γ δ -diol. (3) A mixture of selenium dioxide (12 g.) and propionoin (20 g.), prepared from ethyl propionate in 52—55% yield by the method of Snell and McElvain (*J. Amer. Chem. Soc.*, 1931, **53**, 750), was slowly distilled; the aqueous distillate, b. p.

90—130°, afforded dipropionyl, b. p. 129—130°, after drying and fractionation. The yield, 7 g. (35.5%), was decreased when the propionyl was diluted with alcohol. A solution of dipropionyl (15 g.) in dry ether (100 c.c.) was slowly added to a Grignard reagent prepared from *p*-bromoanisole (118 g.; 4.7 mols.), magnesium (15.3 g.), and dry ether (500 c.c.); after 3 days, the mixture was refluxed for 2 hours and decomposed with ice-cold hydrochloric acid. After removal of ether and anisole (37 g.) the solid was crystallised from benzene, and 5.75 g. (13%) of $\gamma\delta$ -di-*p*-anisylhexane- $\gamma\delta$ -diol, m. p. 192—194°, were obtained.

$\gamma\delta$ -Bis-4-hydroxyphenylhexane- $\gamma\delta$ -diol (isoPinacol, m. p. 94—95°).—The isopinacol was obtained as by-product when *p*-hydroxypropiofenone was reduced electrolytically as described in B.P. 523,515 and could be separated from the pinacol by taking advantage of its greater solubility in cold acetic acid. On one occasion when a faulty porous pot was used the isopinacol was the main product of the reduction. Benzoylation of *p*-hydroxypropiofenone by the Schotten-Baumann method afforded *p*-benzoyloxypropiofenone, which crystallised from alcohol in needles, m. p. 117° (Found: C, 75.6; H, 5.5. $C_{16}H_{14}O_3$ requires C, 75.6; H, 5.5%). Electrolysis of a solution of the benzoyl derivative (20 g.) and sodium hydroxide (10 g.) in dioxan (200 c.c.) and water (50 c.c.), the apparatus and technique described in the patent mentioned above being used, and rebenzoylation of the product by the Schotten-Baumann method resulted in the production of 10 g. of $\gamma\gamma$ -bis-4-benzoyloxyphenylhexan- δ -one, m. p. 178°, so that the isopinacol must be the main product of the reduction. The low-melting form of $\gamma\delta$ -bis-4-hydroxyphenylhexane- $\gamma\delta$ -diol separated from cold acetic acid as a white microcrystalline powder, m. p. 94—95° (Found: C, 71.5; H, 7.1; *M*, cryoscopic in camphor, 309. $C_{18}H_{22}O_4$ requires C, 71.5; H, 7.3%; *M*, 302). The compound was very labile and readily underwent pinacolin rearrangement when warmed with acids. Benzoylation by the Schotten-Baumann method produced a product, m. p. 175°, which probably contained the dibenzoate (Found: C, 77.2; H, 5.7. $C_{32}H_{30}O_6$ requires C, 75.4; H, 5.9%. $C_{32}H_{28}O_5$ requires C, 78.0; H, 5.7%), but only $\gamma\gamma$ -bis-4-benzoyloxyphenylhexan- δ -one (see below) could be obtained by fractional crystallisation and this ketone was readily obtained in pure condition when the crude benzoate was digested with acetic acid for a few minutes.

$\gamma\gamma$ -Bis-4-hydroxyphenylhexan- δ -one.—When the isopinacol was warmed with acid, it afforded $\gamma\gamma$ -bis-4-hydroxyphenylhexan- δ -one, which separated from benzene-light petroleum (b. p. 100°) in prisms, m. p. 136° (Found: C, 76.0; H, 7.1. $C_{18}H_{20}O_3$ requires C, 76.1; H, 7.0%). The dibenzoate crystallised from benzene-light petroleum in prismatic needles, m. p. 178° (Found: C, 77.7; H, 5.8. $C_{32}H_{28}O_5$ requires C, 78.0; H, 5.7%), and afforded the phenol when boiled with 10% alcoholic potash. The ketone afforded an acetate, m. p. 91—92°, but did not react with hydroxylamine, semicarbazide or 2:4-dinitrophenylhydrazine. Methylation with methyl sulphate and aqueous sodium hydroxide yielded a liquid dimethyl ether, which afforded 4:4'-dimethoxybenzophenone, m. p. 143—144° (2:4-dinitrophenylhydrazone, m. p. 200—201°), when oxidised with chromic anhydride in acetic acid solution. The dimethyl ether (2 g.) was reduced with sodium (6 g.) in boiling amyl alcohol (40 c.c.) to stilboestrol dimethyl ether (0.05 g.), m. p. and mixed m. p. 124°. When $\gamma\gamma$ -bis-4-hydroxyphenylhexan- δ -one or its diacetate (1 g.) and potassium hydroxide (2 g.) were maintained at 200° for $\frac{1}{2}$ hour, the neutral product obtained crystallised in prisms, m. p. 134° (Found: C, 78.9; H, 7.0. Calc. for $C_{18}H_{16}O_2$: C, 78.9; H, 7.0%), apparently identical with the *aa*-bis-4-hydroxyphenylpropane described by Wessely *et al.* (*loc. cit.*). Methylation with methyl sulphate and aqueous sodium hydroxide afforded *aa*-di-*p*-anisylpropane, m. p. 44°. *aa*-Di-*p*-anisyl- Δ^1 -propene, prepared as described by Gattermann (*loc. cit.*), had b. p. 180—185°/1 mm. and crystallised from alcohol in colourless plates, m. p. 101°. Reduction of the propene (2 g.) with sodium (2 g.) in boiling amyl alcohol (30 c.c.) afforded unchanged propene (1.1 g.) and a small amount of *aa*-di-*p*-anisylpropane, m. p. and mixed m. p. 44°.

Dienoestrol.—The reaction between 1-*p*-anisylprop-1-yne and a 32% (w./v.) solution of hydrogen bromide in acetic acid was exothermic; the temperature rose rapidly if the mixture were not cooled and decomposition occurred. Dry hydrogen bromide (16.5 g.; 1 mol.) was passed into an ice-cold solution of the propyne (30 g.) in benzene (100 c.c.) and, after 2 hours at 0°, 20 c.c. of the solvent were removed in a vacuum at 20°; hardly any hydrogen bromide was liberated. Half the residual solution was added to magnesium turnings (2.5 g.; 0.5 atom) and ether (100 c.c.) and, when the brisk reaction had subsided, the mixture was boiled for an hour; after the addition of another 2.5 g. of magnesium and the rest of the benzene solution, the mixture was refluxed for a further 2 hours, and anhydrous cupric chloride (28 g.; 1 mol.) then added. When the vigorous reaction abated, the mixture was boiled for 12 hours, and the product worked up in the usual way. Distillation afforded (i) anethole (9 g.), b. p. 80—85°/1.5 mm., (ii) 3 g., b. p. 104—105°/1.5 mm., probably the propyne, and (iii) a resinous residue (14 g.). The last was dissolved in ether and evaporated with a solution of methylmagnesium iodide (from magnesium, 3.1 g., methyl iodide, 19 g., and ether, 150 c.c.). When the residue was heated to 170°, there was a vigorous reaction with some carbonisation. The product was decomposed with ice-cold dilute hydrochloric acid, and a solution of the alkali-soluble portion of the product precipitated with carbon dioxide. The precipitate, sublimed at 130°/1 mm., afforded dienioestrol (0.05 g.), m. p. and mixed m. p. 230—233°.

When dienioestrol (5 g.) and an ethereal solution of diazomethane (140 c.c.; 2.2 mols.) were kept at room temperature for 4 days, 3.5 g. of dienioestrol were recovered and 0.7 g. of *dienoestrol monomethyl ether* obtained. This was soluble in alcoholic alkali and separated from aqueous alcohol in needles, m. p. 142° (Found: C, 81.0; H, 7.2; OMe 11.1. $C_{19}H_{20}O_2$ requires C, 81.4; H, 7.1; OMe, 11.1%). Methylation of dienioestrol in *n*-sodium hydroxide (4.3 mols.) with methyl sulphate (4.0 mols.) afforded the monomethyl ether in 73% yield together with the *dimethyl ether*, m. p. 130—131° (Found: C, 81.4; H, 7.5; OMe, 21.4, 21.5. $C_{20}H_{22}O_2$ requires C, 81.6; H, 7.5; OMe, 21.1%). The mono- and the di-methyl ether were obtained in 29 and 30% yield respectively when dienioestrol, methyl iodide (3.6 mols.), and 0.2*N*-methyl-alcoholic potash (1.2 mols.) were boiled for an hour. Ozonolysis of dienioestrol dimethyl ether in glacial acetic acid solution afforded a 16% yield of anisil, m. p. 133°, characterised by conversion into 2:3-di-*p*-anisylquinoline, m. p. and mixed m. p. 149—150° (Found: C, 77.2; H, 5.4; N, 7.8. $C_{22}H_{18}O_2N_2$ requires C, 77.2; H, 5.3; N, 8.2%). *Dienoestrol dibenzyl ether* separated from benzene in prisms, m. p. 205° (Found: C, 85.4; H, 6.5. $C_{32}H_{30}O_2$ requires C, 85.9; H, 6.8%). *Dienoestrol ditoluene-*p*-sulphonate* had m. p. 168° (Found: C, 66.2; H, 5.1. $C_{32}H_{30}O_6S_2$ requires C, 66.8; H, 5.2%). *Dienoestrol dibenzoate* separated from benzene-light petroleum in needles, m. p. 224° (Found: C, 80.3; H, 5.3. $C_{32}H_{26}O_4$ requires C, 81.0; H, 5.3%).

Demethylation of dienioestrol dimethyl ether with methylmagnesium iodide (2.5 mols.) at 175° regenerated dienioestrol, but demethylation with alcoholic potash at 220° afforded an isomeric compound, m. p. 189° (Found: C, 81.1; H, 6.8. $C_{18}H_{18}O_2$ requires C, 81.2; H, 6.7%), which afforded a liquid methyl ether.