975. *Totally Synthetic Steroid Hormones. Part I. Œstrone and Related Œstrapolyenes.*

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Various total syntheses are described, of (±)-œstrone methyl ether and five of its stereoisomers, (±)-D-homo-œstrone methyl ether, (±)-D-homo-œstradiol methyl ether, (±)-equilenin methyl ether, (±)-D-homoequilenin methyl ether, (±)-isoequilenin, and related compounds. Preliminary accounts [1] have already been given of some of this work.

ŒSTRONE has been synthesised by a number of routes,[1-7] three of which have been reported in preliminary form by us.[1] All are highly stereoselective throughout, the most efficient [1b] giving (±)-œstrone methyl ether in 18% overall yield from 3-*m*-methoxy-phenylpropyl bromide, and, with minor modifications, providing syntheses of (±)-equilenin methyl ether, (±)-isoequilenin, and five of the seven stereoisomers of (±)-œstrone methyl ether. A full account of this and related work will now be given.

General Plan.—The syntheses are all derived from the initial concept of preparing a seco-œstratetraene of type (3) † and converting it into the corresponding seco-œstratriene (4) and thence, through a cyclodehydration reaction involving the 9-oxo-group, into œstrone methyl ether (6). Discoveries made during the reduction practice opened other avenues to œstrone and a variety of œstrogenic steroids. The completed work constitutes a group of related syntheses the chief of which are shown in the annexed Scheme. The dione (3) has been elaborated by two routes. One involves the alkylation in the 4-position of the indanedione (2) with the 2-*m*-methoxyphenylethyl radical, the other a Mannich–Robinson type of ring extension [8] of 2-methylcyclopentane-1,3-dione (11) [9] with the vinyl

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† The structural formulæ containing one or more asymmetric carbon atoms depict one diastereo-isomer but refer to racemic compounds throughout. Each racemate is arbitrarily represented by the diastereoisomer having the 13-methyl group in the β-configuration. Subsequently in the text the (±)-prefix will be omitted and the steroids and intermediates thereto are to be assumed to be racemic unless stated otherwise. The usual steroid sequence of lettering rings is followed. In the discussion, steroid nomenclature and numbering will be used to describe tri- and tetra-cyclic compounds.

[1] (a) Hughes and Smith, *Proc. Chem. Soc.*, 1960, 74; (b) *Chem. and Ind.*, 1960, 1022; (c) Belgian Patent, 1961, 595,384; (d) 595,385; (e) 595,386; (f) 595,387; (g) 595,388; (h) 600,244; (i) Smith, Hughes, and McLoughlin, *Experientia*, 1963, **19**, 177.

[2] (a) Anner and Miescher, *Helv. Chim. Acta*, 1948, **31**, 2173; (b) 1949, **32**, 1957; (c) 1950, **33**, 1379.

[3] (a) Johnson, Banerjee, Schneider, and Gutsche, *J. Amer. Chem. Soc.*, 1950, **72**, 1426; (b) Johnson, Banerjee, Schneider, Gutsche, Shelberg, and Chinn, *ibid.*, 1952, **74**, 2832.

[4] (a) Johnson and Christiansen, *J. Amer. Chem. Soc.*, 1951, **73**, 5511; (b) Johnson, Christiansen, and Ireland, *ibid.*, 1957, **79**, 1995.

[5] Cole, Johnson, Robins, and Walker, (a) *Proc. Chem. Soc.*, 1958, 114; (b) *J.*, 1962, 244.

[6] (a) Velluz, Nominé, Mathieu, Toramanoff, Bertin, Vignau, and Tessier, *Compt. rend.*, 1960, **250**, 1510; (b) Velluz, Nominé, and Mathieu, *Angew. Chem.*, 1960, **72**, 725.

[7] (a) Ananchenko, Leonov, Platonova, and Torgov, *Doklady Akad. Nauk S.S.S.R.*, 1960, **135**, 73; (b) Ananchenko, Limanov, Leonov, Rzheznikov, and Torgov, *Tetrahedron*, 1962, **18**, 1355.

[8] de Feu, McQuillin, and Robinson, *J.*, 1937, 53.

[9] Panouse and Sannié, *Bull. Soc. chim. France*, 1955, 1036.

ketone (10) proceeding through the isolable trione (12). The dione (3) gives œstrone methyl ether (6) through the dione (4) and the dehydro-œstrone (5) in a minimum of three stages. In a new reaction the trione (12) is converted by direct acid cyclodehydration into the œstrapentadiene (9) and thence in three further stages *via* the ketone (8) into œstrone methyl ether (6). The modification is the one of choice. Exactly parallel sequences have
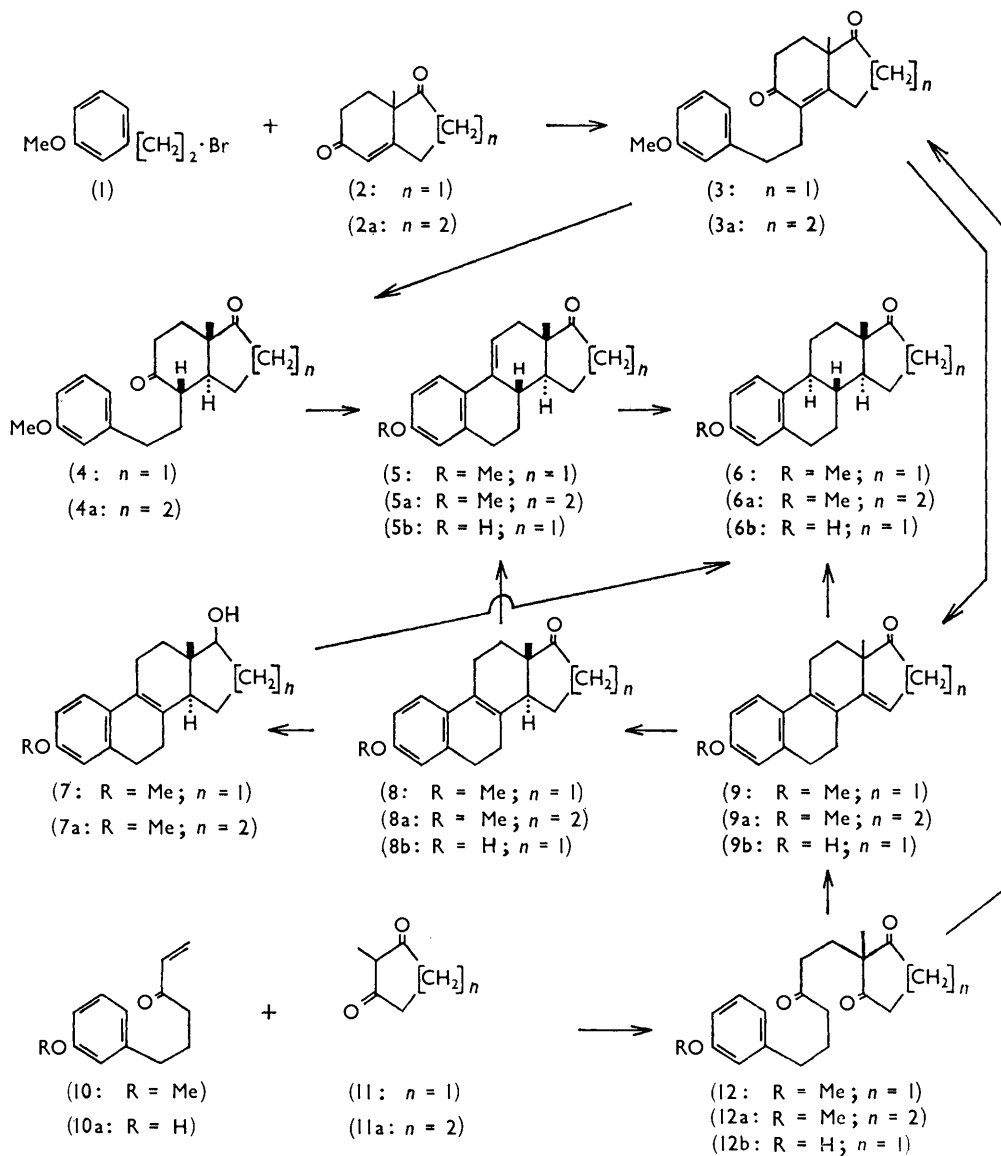
been developed for D-homo-œstrone methyl ether (6a), starting from either the octalin-dione (2) or 2-methylcyclohexane-1,3-dione (11a) through the trione (12a). The route through the dione (3) and that through the œstrapentaene (9) have been inter-related by the direct conversion of the former into the latter and by the rearrangement of the œstratetraene (8) to the isomer (5). A similar isomerisation of the ketone (8b) to (5b) forms the basis for converting the ketone (10a) into œstrone without the final

demethylation required in other syntheses.[1ab, 2-5,7] Various intermediates have been used as starting materials for syntheses not illustrated in the Scheme. Thus, D-homo-œstradiol has been prepared from the dione (3a) through intermediates having a partially reduced ring A; equilenin methyl ether, D-homoequilenin methyl ether, and isoequilenin have been formed in single operations from the ketones (8), (4a), and (12), respectively; and a total of five of the seven stereoisomers of œstrone methyl ether have been made from the group of ketones (3), (5), and (9). Also, a 3-deoxy-D-homo-œstrone of unknown stereochemistry has been obtained from the deoxy-analogue of the ketone (10a). Related synthetic phases will now be considered in turn. The order in which the individual rings were completed will be denoted as previously.[10]

9,10-*Seco-steroids* (A + CD ⟶ ACD, *and* A + D ⟶ AD ⟶ ACD).—The preparation of the diones (3) and (3a) from the diones (2) and (2a) depends on alkylation of the α-positions of the αβ-unsaturated ketone portions. Theoretically, the diones (2) and (2a) can each be monoalkylated at four possible positions. However, related αβ-unsaturated monoketones of the octalin,[11] hydrophenanthrene,[12,13] and steroid series [14] are alkylated preferentially at the α-positions. The choice in each case was therefore expected to lie between the α-position of the αβ-unsaturated ketone group and the position α- to the other ketone group. The dione (2a) reacted with one equivalent of potassium t-butoxide in benzene to form an enolate salt. Conditions thought likely to be equilibrating were chosen so as to form adequately the heteroannular dienolate anion (13), the necessary precursor of the required alkylation product. This anion was expected to be the most stable of the possible mono-enolate anions and in equilibrium with the others through the undissociated dione (2a). Treatment of the enolate solution with 2-*m*-methoxyphenyl-ethyl bromide gave a complex mixture. In this early work [15] no attempt was made to resolve it; the crude product was reduced with a limited amount of sodium borohydride [11] so as to transform any of the ketone (3a) into the ketol (14a) and then, in turn, reduced with lithium in liquid ammonia, to saturate the 8,14-double bond, and oxidised with chromium trioxide in pyridine [16] to convert any resulting ketol (15a) into the dione (4a). Careful chromatography of the resulting mixture gave a 1·7% overall yield of this dione, identical with a sample made later by an unambiguous route. A similar alkylation of the dione (2), followed by distillation, gave a 25% yield of the dione (3). The structure followed from the ultraviolet absorption spectrum, which indicates the substitution of an alkyl group for hydrogen in the 4-position of the indanedione (2), and the subsequent conversion into œstrone methyl ether. The low yields of alkylation products may be due to the decomposition of the diones (2) and (2a) induced by the base (cf. refs. 11 and 17). After the completion of our work,[1fh,18] Crispin and Whitehurst [19] reported preparation of this compound, in an undisclosed yield, by alkylation of the tetrahydropyranyl ether of 5,6,7,8-tetrahydro-1β-hydroxy-8β-methylindan-5-one [obtained through reduction of the dione (2)] and successive hydrolysis and oxidation of the product.

The preparation of the diones (3) and (3a) by Mannich–Robinson ring extension of the respective diones (11) and (11a) required as the second reactant the vinyl ketone (10), or a related β-substituted ketone from which it can be derived by an elimination reaction. We chose to make the vinyl ketone and cognate compounds by the following route. Condensation of 3-*m*-methoxyphenylpropyl bromide (17) with sodium acetylide in liquid ammonia gave the arylpentyne (18) in 90% yield. Appreciably lower yields were

[10] Pinder and Robinson, *Nature*, 1951, **167**, 484; *J.*, 1952, 1224.
[11] Cocker and Halsall, *J.*, 1957, 3441.
[12] Stork, Loewenthal, and Mukharji, *J. Amer. Chem. Soc.*, 1956, **78**, 501.
[13] Barltrop and Rogers, *Chem. and Ind.*, 1957, 397; *J.*, 1958, 2566.
[14] Atwater, *J. Amer. Chem. Soc.*, 1957, **79**, 5315.
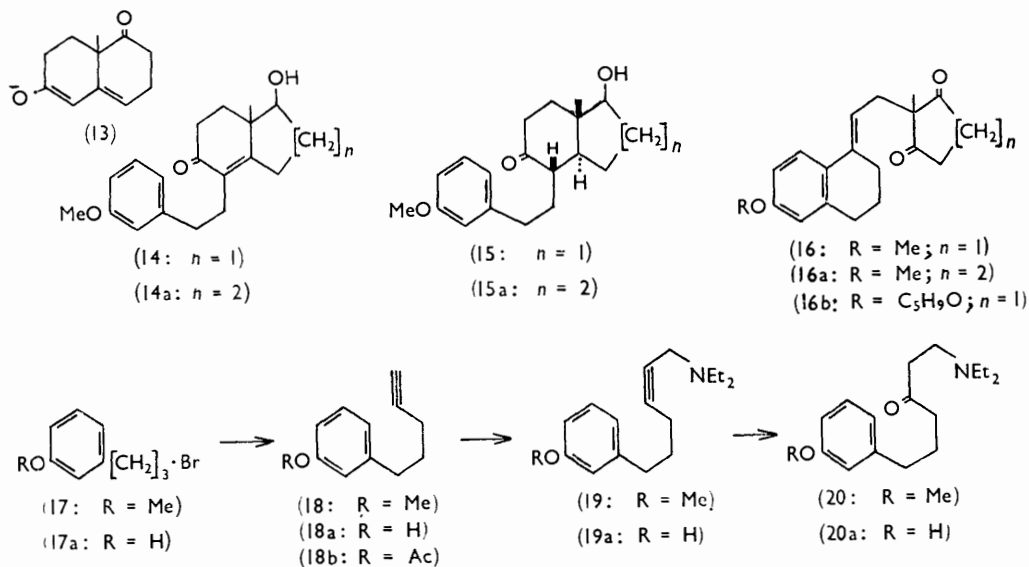[15] Hughes, M.Sc. Thesis, Manchester, 1957.
[16] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.
[17] Wendler, Slates, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 3816.
[18] McLoughlin, Ph.D. Thesis, Manchester, 1960.
[19] Crispin and Whitehurst, *Proc. Chem. Soc.*, 1962, 356.

obtained when the reaction was carried out in dimethylformamide.[20]   Under the usual Mannich condensation conditions [21] with formaldehyde and diethylamine the arylpentyne (18) gave the hexynylamine (19).   This was hydrated in sulphuric acid containing mercuric sulphate to the diethylamino-ketone (20), the structure of which follows from its ready conversion into the vinyl ketone (10).   Similar hydration reactions have been

(13)

(14: *n* = 1)
(14a: *n* = 2)

(15: *n* = 1)
(15a: *n* = 2)

(16: R = Me; *n* = 1)
(16a: R = Me; *n* = 2)
(16b: R = C$_5$H$_9$O; *n* = 1)

(17: R = Me)
(17a: R = H)

(18: R = Me)
(18a: R = H)
(18b: R = Ac)

(19: R = Me)
(19a: R = H)

(20: R = Me)
(20a: R = H)

observed with related diethylaminopropyne and diethylaminohexyne derivatives.[21,22]   In these cases the unidirectional mode of hydration has been associated with a polarisation of the type R·C$^{\delta+}$:C$^{\delta-}$·CH$_2$·NHEt$_2^+$.[21]   On distillation, the diethylamino-ketone (20) underwent partial elimination to give the vinyl ketone (10).   The extent of this elimination depended on the degree of fractionation and was increased by increasing the reflux ratio. A mixture of the ketones (10) and (20), rich in the latter, was condensed with 2-methylcyclohexane-1,3-dione (11a) under conditions [23,24] whereby diethylaminobutan-3-one and the dione gave the octalindione (2a).   The product was the trione (12a), which was cyclodehydrated to the dione (3a) by boiling in xylene containing triethylamine and benzoic acid [25] with continual removal of the water formed.   To prepare the trione (12) a mixture of the ketones (10) and (20) containing predominantly the vinyl component was treated with the dione (11) in refluxing methanol containing a little potassium hydroxide.[26] Conditions of low basicity were chosen so as to minimise the expected tendency of the trione (12) to undergo the retrograde Michael reaction (cf. ref. 26).   The trione (12) was converted into the dione (3) with triethylamine and benzoic acid in xylene as before, but the reaction was much more sluggish, requiring refluxing for several days to give high yields (80—90%).   The difference may be attributed to the increased strain introduced into the bicyclic system by the 5-membered ring component.   Samples of the triones (12) and (12a), obtained after extraction from the reaction mixture of the unchanged diones (8) and (8a) with base, invariably showed characteristic hydroxylic infrared absorption,

[20]   Jenny and Meier, *Angew. Chem.*, 1959, **71**, 245.
[21]   Islam and Raphael, *J.*, 1953, 2247.
[22]   Halsall and Thomas, *J.*, 1956, 2431.
[23]   Unpublished work by Friedman and (Sir R.) Robinson (Oxford).
[24]   Swaminathan and Newman, *Tetrahedron*, 1958, **2**, 88.
[25]   Wieland, Ueberwasser, Anner, and Miescher, *Helv. Chim. Acta*, 1953, **36**, 376.
[26]   Boyce and Whitehurst, *J.*, 1959, 2022.

presumably due to ketols, including those of the bridge-ring type (cf. ref. 27), formed by intramolecular aldolisation.

Œstrone from 9,10-*Seco-œstratetraenes* (ACD ⟶ ABCD).—Our first synthesis of œstrone [1a] proceeded from the dione (3a) through D-homo-œstrone methyl ether (5a) by reactions involving the saturation of the 8(14)-bond. A prime requirement for success was the stereoselective introduction of a 14α-hydrogen. The stereochemistry simultaneously produced at the 8-position was of less concern because of the possibility of forming the dione (4a) by epimerisation of the less stable 8α-isomer through the corresponding enol. The choice of the dione (3a) as the starting material for the first synthesis depended on the known methods for deriving *trans*-9-methyldecalin systems from related αβ-unsaturated ketones lacking α-substituents.[28]

Reduction of the dione (3a) with a limited amount of sodium borohydride in ethanol [11] gave the crystalline ketol (14a). The *cis*-relationship of the hydroxyl and methyl groups was assigned by analogy with the stereochemical course of the reduction of the dione (2a) with sodium borohydride.[28] Further reduction with lithium in liquid ammonia gave the ketol (15a) which was oxidised with chromium trioxide in pyridine to the dione (4a). This was identical with the substance made from the dione (2a) through alkylation. The *trans*-fusion of the decalin system was shown by the subsequent conversion into œstrone. The 8β-configuration was assigned on the likely assumption that the ketol (15a) or the dione made from it had undergone equilibration at some stage. Methanolic hydrochloric acid [29] converted the dione into a ketone shown to be the dehydro-œstrone methyl ether (5a) by the similarity of its ultraviolet absorption in ethanol [$\lambda_{max.}$ 262 mμ (ϵ 19,200)] to that of (+)-9(11)-dehydro-œstrone [30,31] [$\lambda_{max.}$ 263 mμ (ϵ 18,050) [31]] and related structures.[32,33] The ketone (5a) was also obtained in about 50% yield by catalytic hydrogenation of the dione (3a) over palladised charcoal in ethanol, followed by direct cyclisation of the crude product. The latter, from the efficiency of the overall process, must have contained a preponderance of stereoisomers having the *trans*-decalin system. Apparently therefore the dione (3a) is hydrogenated mainly by absorption of its α-face on the catalyst surface to give an 8α-stereoisomer of the dione (4a) which undergoes equilibration before conversion into the ketone (5a). Reduction with potassium in liquid ammonia and oxidation with chromic acid in acetone [34] converted the ketone (5a) into D-homo-œstrone methyl ether (6a) identical in infrared absorption spectrum with the (+)-enantiomer made by the ring enlargement of (+)-œstrone methyl ether.[35,36] By either route used for conversion of the dione (3a) into the ketone (5a), D-homo-œstrone methyl ether (6a) is made from 3-*m*-methoxyphenylpropyl bromide in an overall yield of 7·5%. On condensation with benzaldehyde it gave a benzylidene derivative apparently identical with that described earlier by Johnson and his colleagues.[3b] At this stage a formal total synthesis of the natural hormone was complete since the benzylidene derivative has been converted into œstrone *via* homomarrianolic acid.[2-4]

The conversion of the indane (3) into œstrone followed similar paths. Catalytic hydrogenation of the dione (3) and cyclisation of the resulting mixture of stereoisomers of the ketone (4) with methanolic hydrochloric acid gave a steroid formulated as 9(11)-dehydro-œstrone (5) on the basis of its ultraviolet absorption [$\lambda_{max.}$ 265 mμ (ϵ 18,000)] and conversion into œstrone methyl ether by reduction with potassium in liquid ammonia, and oxidation with chromic acid in acetone. The overall yield of the ketone (5) from the

[27] Johnson, Kurst, Clement, and Dutta, *J. Amer. Chem. Soc.*, 1960, **82**, 614.
[28] *E.g.*, Birch, Pride, and Smith, *J.*, 1958, 4688.
[29] Dodson and Muir, *J. Amer. Chem. Soc.*, (a) 1958, **80**, 5004; (b) 1961, **83**, 4627.
[30] Banes and Carol, *J. Biol. Chem.*, 1953, **204**, 509.
[31] Magerlein and Hogg, *J. Amer. Chem. Soc.*, 1958, **80**, 2220.
[32] Heer and Miescher, *Helv. Chim. Acta*, 1948, **31**, 219.
[33] Dorfmann, *Chem. Rev.*, 1953, **53**, 47.
[34] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2555.
[35] Goldberg and Studer, *Helv. Chim. Acta*, 1941, **24**, 478.
[36] Heusser, Herzig, Furst, and Plattner, *Helv. Chim. Acta*, 1950, **33**, 1093.

dione (3) was about 40%. It was improved to about 60% as follows. Reduction of the dione (3) with sodium borohydride as before gave a crystalline ketol (14). Hydrogenation, oxidation with chromium trioxide in pyridine, and the usual cyclodehydration transformed it into the ketone (5). Structure (14), with the hydroxyl *cis* to the 13-methyl group, was assigned to the ketol by analogy with the known mode of reduction of 17-oxo-steroids with metal hydride reagents.[37] This stereochemistry should assist the production of the *trans*-C/D ring fusion by catalytic hydrogenation by hindering the adsorption of the ketol (14) by its β-face on to the catalyst surface. This was confirmed by forming a crystalline benzoate from the mixture obtained by hydrogenating the ketol (14) and converting it by acid cyclisation, saponification, and potassium–ammonia reduction into œstra-1,3,5(10)-trien-3,17β-diol 3-methyl ether, identical with material made by sodium borohydride reduction of the totally synthetic œstrone methyl ether and having the same infrared absorption as the (+)-enantiomer. The formation of *trans*-hexahydroindanes by catalytic hydrogenation of the dione (3) and the ketol (14) is remarkable in view of the reported production of only the *cis*-stereoisomers by catalytic hydrogenation of the tetra-hydro-1β-hydroxy-8β-methylindan-5-one analogue of the ketol (14) lacking the *m*-methoxyphenylethyl side-chain, and of the corresponding benzoyl ester and trityl ether.[38]

Œstrone methyl ether was obtained from the ketone (5) in one stage by catalytic hydrogenation in ethanol over palladium, and also by conversion into the ketal (24) followed by lithium–ammonia reduction and acid hydrolysis. Neither method was more efficient than that already described. By using the best variant of the route (12) ⟶ (3) ⟶ (14) ⟶ (15) ⟶ (4) ⟶ (5) ⟶ (6), œstrone methyl ether is obtained from 3-*m*-methoxyphenylpropyl bromide in a yield of 14%.

In some experiments, the potassium–ammonia reduction of the ketone (5) was incomplete. Coles *et al.*[5b] failed to reduce various 8-dehydro-D-homo-œstrone derivatives with metals in liquid ammonia in the absence of water. Our difficulty was solved by a more reliable procedure in which lithium in liquid ammonia is used with aniline as a co-solvent. Strel'tsova and Shilov[39] have observed the conversion of diphenylacetylene into 1,2-diphenylethane by sodium in liquid ammonia containing aniline or *p*-toluidine, reactions probably involving stilbene as an intermediate. Metal–ammonia reagents are currently believed to reduce styrenoid systems by the successive addition of electrons from the metal, and protons from the ammonia (pK_a 33).[40–42] Analine (pK_a 26), apart from any solvent effect, may assist the process by increasing the availability of protons in the reaction medium.

Œstrone from Œstra-1,3,5(10),8,14-*pentaenes* (AD ⟶ ABCD, *and* ACD ⟶ ABCD).— During investigations on the conversion of the trione (12) into the dione (3) by strong acids, we obtained a ketone $C_{19}H_{20}O_2$, $\nu_{max.}$ 1730 cm.$^{-1}$, $\lambda_{max.}$ 313 mμ (ε 35,000) in ethanol. Suitable reagents for the conversion were toluene-*p*-sulphonic acid in benzene, polyphosphoric acid at 50—60°, and alcoholic hydrochloric acid, the two former being the more efficient. Knowing that 8-dehydro-14β-œstrone shows $\nu_{max.}$ 275 (ε 20,900),[32] and applying Woodward's rules,[43] we assigned structure (9) to the ketone and it was confirmed as follows. Selective catalytic hydrogenation at atmospheric pressure gave a ketone, $\lambda_{max.}$ 278 mμ (ε 15,000), formulated as 8-dehydro-œstrone methyl ether (8). Effective catalyst–solvent combinations were Raney nickel and dioxan or benzene, and 2% palladised calcium carbonate and benzene. Reduction of the ketone (8) with potassium

[37] (a) Bachmann and Dreiding, *J. Amer. Chem. Soc.*, 1950, **72**, 1323; (b) St. Andre, MacPhillamy, Nelson, Shabica, and Scholz, *J. Amer. Chem. Soc.*, 1952, **74**, 5506; (c) Fieser and Fieser, " Steroids," Reinhold, New York, 1959, p. 467.

[38] Boyce and Whitehurst, *J.*, 1960, 4547.

[39] Strel'tsova and Shilov, *Ukrain. khim. Zhur.*, 1956, **22**, 489 (*Chem. Abs.*, 1957, **51**, 4330).

[40] Birch, *Quart. Rev.*, 1950, **4**, 69.

[41] Smith, " Organic Reactions in Liquid Ammonia," Vieweg und Sohn, Braunschweig, 1963, pp. 226—230.

[42] Nagata, Terasawa, Hirai, and Takeda, *Chem. and Pharm. Bull. (Japan)*, 1961, **9**, 709.

[43] Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 72, 76.

in liquid ammonia and oxidation with chromic acid in acetone then gave œstrone methyl ether, identical in infrared absorption with the (+)-enantiomer.   With the most efficient conditions at each stage, this route gives œstrone methyl ether in 11·5% yield from 3-*m*-methoxyphenylpropyl bromide.   The figure can be increased to 18% by converting the ketone (8) into the alcohol (7), carrying out the reduction with the lithium–aniline–ammonia reagent, and oxidising the resulting œstradiol methyl ether to œstrone methyl ether as before.   A further route to œstrone from the indanedione (2) was established by direct cyclodehydration of the dione (3) to the ketone (9) with polyphosphoric acid at 60°.[18,1fh,19]

D-Homo-œstrone methyl ether can be synthesised directly from the trione (12) through the ketones (9a) and (8a).   The latter may be converted into the ketone (6a) with or without preliminary reduction with sodium borohydride.   In each case the overall yield from 3-*m*-methoxyphenylpropyl bromide is 20—22%.[1f]   Ananchenko and Torgov[44] have developed an independent synthesis of the ketone (9a) from 6-methoxy-1-vinyl-1-tetralol[45] and 2-methylcyclohexane-1,3-dione, proceeding through the seco-œstrone (16a), and have converted it into D-homo-œstrone methyl ether (6a) by methods[7] similar to those outlined here.   More recently the same authors,[46] as well as Crispin and Whitehurst[47] and we, have independently shown that use of 2-methylcyclopentane-1,3-dione leads to the œstrapentaene (9) through the seco-œstrone (16).   Apparently, this dione has previously been obtained as a gum;[47] we have prepared it as crystals, m. p. 77—78°.   Methanolic hydrochloric acid at *ca.* 40° is the reagent of choice for the cyclisation, although, in contradiction of other reports,[47] we have found anhydrous toluene-*p*-sulphonic acid in benzene at room temperature to be not much less effective.
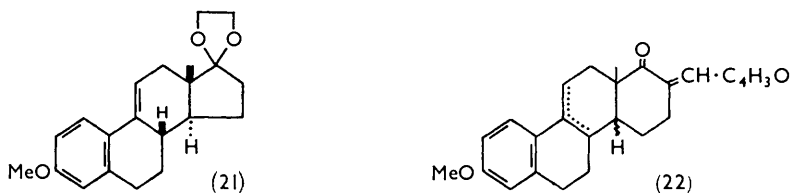
We turn now to transformations which link the ACD ⟶ ABCD, and AD ⟶ ABCD, routes and have some theoretical implications.   They are the conversion of the 8-dehydro-œstrone (8) into the corresponding 9(11)-dehydro-isomer (5) by boiling methanolic hydrochloric acid, and the formation of the ketal (21) by Salmi[48] ketalisation of the ketone (5) in yields of 85% and *ca.* 90%, respectively.   If, as seems likely, the first reaction occurs under equilibrating conditions, the ketone (5) must be more stable than its isomer (8). Under the same conditions the ketone (8a) gave a mixture shown by its ultraviolet absorption [$\lambda_{max.}$ 267 mμ (ε 16,000)] to contain equimolar amounts of the ketones (5a) and (8a), indicating comparable stabilities for this isomeric pair.   These energy relations are, at first sight, somewhat surprising, since an 8-olefinic bond is hyperconjugated with five hydrogen atoms whereas a 9(11)-olefinic bond is hyperconjugated with only three (cf. ref. 49).   However, the Δ^8-isomers contain a homoannular diene-like system in ring B whereas the Δ^9-isomers contain a heteroannular diene-like system extending over rings B and C, and it is to be presumed (*e.g.*, from the acid-catalysed conversion of steroidal 2,4-dienes into 3,5-dienes[50]) that the first system is destabilising with respect to the second.

[44] Ananchenko and Torgov, *Doklady Akad. Nauk S.S.S.R.*, 1959, **127**, 553.
[45] Nazarov, Torgov, and Verkholetova, *Doklady Akad. Nauk S.S.S.R.*, 1957, **112**, 1067.
[46] Torgov, *Pure Appl. Chem.*, 1963, **6**, 525.
[47] Crispin and Whitehurst, *Proc. Chem. Soc.*, 1963, 22.
[48] Salmi, *Ber.*, 1938, **71**, 1803.
[49] Turner, Meador, and Winkler, *J. Amer. Chem. Soc.*, 1957, **79**, 4122.
[50] Rao and Gollberg, *Tetrahedron*, 1962, **18**, 1251.

The balance of controlling factors must be delicate since in related cases, *e.g.*, with ketones of type (22), the Δ^8-14β-isomer is formed by acid treatment of the $\Delta^{9(11)}$-8α,14β-isomer.[4b]

Œstrone from 3-Hydroxyœstra-1,3,5(10),8,14-pentaen-17-one (AD ⟶ ABCD).—All the syntheses of œstrone which we have so far described involve a final demethylation of œstrone methyl ether by molten pyridine hydrochloride. The method is efficient, but unsuitable for large-scale working. Accordingly it seemed worthwhile to devise a synthesis which would avoid this step. The route chosen followed closely the lines of our most efficient synthesis of œstrone methyl ether and was as follows. 3-*m*-Hydroxy-phenylpropyl alcohol on refluxing with 48% hydrobromic acid gave the bromide (17a). This, on condensation with sodium acetylide in dimethylformamide, gave 80—85% yields of the arylpentyne (18a), which was acetylated to the ester (18b). The use of xylene as a co-solvent[51] at the condensation stage gave inferior results. Mannich condensation with diethylamine and formaldehyde under the usual conditions then afforded the amine (19a). The ester (18b) rather than the phenol (18a) was used at this stage to avoid amino-methylation of the aromatic nucleus (cf. ref. 52). Mercuric-ion-catalysed hydration then gave the keto-amine (20a). Polymerisation accompanied attempted distillation of this substance; it was therefore used directly for the next stage of condensation with 2-methyl-cyclopentane-1,3-dione (11). The transformation of the amine (20a) into the trione (12b) involves the concomitant production of diethylamine which, being strongly basic, may be expected to induce retrograde Michael condensation. To counteract this possibility the condensation was carried out with an excess of the acidic dione (8) (pK_a expected to be *ca.* 4—5 from the value 4·5 for cyclopentane-1,3-dione[53]) and gave the highest yields of the crude trione (12b) with 2·25 mol. Cyclisation with toluene-*p*-sulphonic acid in benzene gave the expected ketone (9b). The substance was also obtained by the methanolic hydrochloric acid cyclisation of the tetrahydropyranyloxyseco-œstrone (16b) prepared by condensation of 2-methylcyclopentane-1,3-dione and 6-pyranyloxy-1-vinyl-1-tetralol. The last compound has independently been converted through the seco-œstrone (16a) into the œstrapentaene (9a).[7b] Selective catalytic hydrogenation of the ketone (9b) in benzene over palladised charcoal furnished 8-dehydro-œstrone (5b). The olefinic bond in this substance proved unexpectedly resistant to reduction with metals and ammonia, even in the presence of aniline or ethanol, despite the previous report that the analogous styrene, 5,6-dihydro-1-naphthol, is readily reduced in ammonia to 5-hydroxy-tetralin by potassium and ethanol in liquid ammonia.[54] Electron addition, which would be the first reductive step,[40-42] will be hindered by delocalisation of the phenoxide charge over the styrenoid system [(23) ⟷ (24)] and additional inhibitory factors may be the trisubstitution of the olefinic bond and the insolubility of the phenoxide substrates in the reaction medium. The synthesis was completed by catalytic hydrogenation of 9(11)-dehydro-œstrone (5b) formed by acid-induced isomerisation of the ketone (8b).

(23)   (24)

D-Homo-œstradiol from Reduced A-Ring Intermediates (ACD ⟶ ABCD).—Reduction of the ketol (14a) successively with lithium and ammonium chloride in liquid ammonia and with lithium and ethanol in liquid ammonia converted it into the crystalline enol ether (25) which was hydrolysed with acetic acid. The crude product [mainly the ketone (26)] upon treatment with methanolic hydrochloric acid gave, not the expected $\alpha\beta$-unsaturated

[51] Rutledge, *J. Org. Chem.*, 1959, **24**, 840.
[52] Blicke, *Org. Reactions*, 1942, **1**, 303.
[53] Waller, Wolf, Hutchings, Williams, Broschard, and Goldman, *J. Amer. Chem. Soc.*, 1952, **74**, 4978.
[54] Eastham and Larkin, *J. Amer. Chem. Soc.*, 1959, **81**, 3652.

ketone (27), but a mixture of ketones $C_{19}H_{30}O_3$, $\nu_{max.}$ 3430 and 1704 cm.$^{-1}$, which did not react with tetranitromethane and had ultraviolet absorption characteristic of a saturated ketone. Fractional crystallisation resolved it into two apparently isomeric components showing broadly similar but distinct infrared absorption. The major component formed a monoacetate and analysis showed one active hydrogen atom. Lack of material prevented a similar examination of the minor component. We formulate the components as the isomers (28; $R^1 = H_2$ or O; $R^2 = O$ or H_2, respectively), which could be formed through the intramolecular acid-catalysed addition of the 9-hydroxyl group to the 5-position in structure (29) which is an enol common to the isomeric ketones (26) and (27). Similar intermolecular additions of alcohols to αβ-unsaturated ketones are well known.[55]

The diol (26) on oxidation with chromic acid in acetone gave the crystalline trione (31). This was converted into the tetracyclic dione (32) by adsorption on Florex and elution with benzene–ether. The dione (32) was identified by Hibbert dehydration[56] to the dienone (33), $\nu_{max.}$ 302 mμ (ε 16,700) (characteristic of an œstra-4,9-dien-3-one).[57] Since the adsorbent was slightly basic we believe that the tetracyclic dione (32) was formed through an intramolecular aldolisation involving the anion (30) formed by appropriate deprotonation of the dione (31) or its Δ^4-isomer. On attempted isomerisation with palladised charcoal in refluxing ethanol[6] the dienone (33) gave an intractable product. Under

(25)

(26 : $\Delta^{5(10)}$)

(27 : Δ^4)

(28)

(29)

(30)

(31)

(32)

(33; W = CO)

(34; W = CH·OH)

(35)
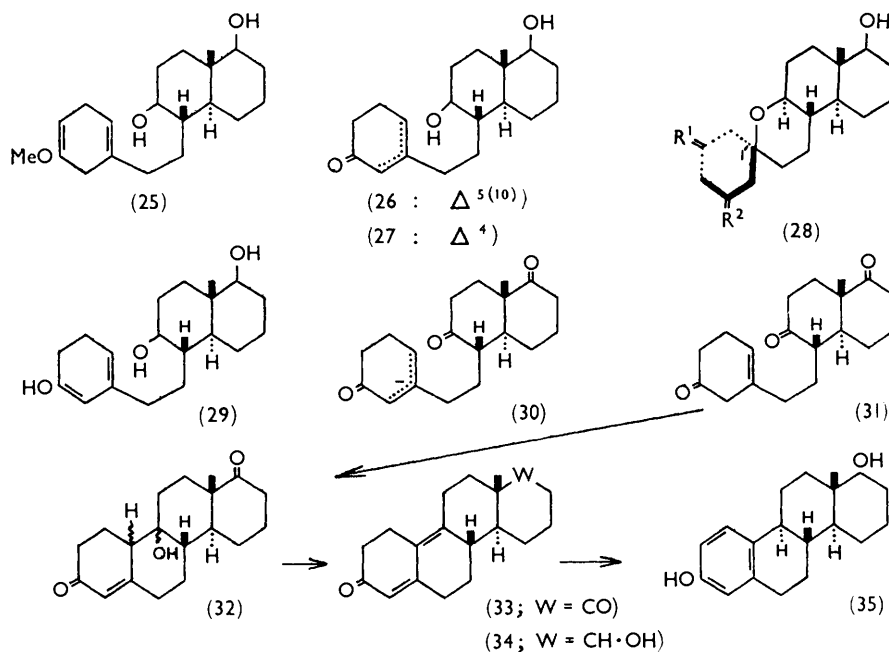
similar conditions the ketol (34), formed from it by selective sodium borohydride reduction, was transformed in 18% yield into the D-homo-œstradiol (35) identical with the substance made by demethylation and sodium borohydride reduction of totally synthetic D-homo-œstrone methyl ether (6a). By this route the D-homo-œstradiol is made from the ketol (14a) in an overall yield of 1·8%.

8ξ,9ξ-3-*Deoxy*-D-*homo-œstrone.*—The success of the shorter syntheses of œstrone and D-homo-œstrone methyl ethers prompted an investigation of analogous routes to 3-deoxy-œstrones from the readily available 3-phenylpropyl bromide. Accordingly, the bromide

[55] Hoffmann, *J. Amer. Chem. Soc.*, 1927, **49**, 552.
[56] Hibbert, *J. Amer. Chem. Soc.*, 1915, **37**, 1749.
[57] Farkas, Fornefeld, Kraay, Perelman, and Rapala, *J. Amer. Chem. Soc.*, 1960, **82**, 2402.

was converted by our general method into a mixture of the ketone (36) and the corre-
sponding β-diethylamino-ketone which was converted into the trione (37) by the usual
condensation with 2-methylcyclohexane-1,3-dione. Treatment with acid under a variety
of conditions gave only the dione (38) and none of the required 3-deoxy-analogue of the
ketone (9a). The same dione was obtained by triethylamine–benzoic acid cyclisation
of the trione. It was converted into the saturated dione (40) by sodium borohydride
reduction, lithium–ammonia reduction, and chromic acid–acetone oxidation, but this dione
resisted cyclisation with alcoholic mineral acids even under reflux. Indeed, the dione (40)
could be obtained in high yield by boiling the mixture of stereoisomers formed by catalytic
hydrogenation of the dione (38) with mineral acid. Cyclisation of the dione occurred with
polyphosphoric acid at 90° but was accompanied by dehydrogenation to what is probably
3-deoxy-D-homoequilenin (43). An olefin of type (42) would cyclise directly to an
œstratriene thereby minimising the possibility of dehydrogenation. It was synthesised
as follows. The ketal (39) was selectively formed from the dione (38) and one mol. of
ethylene glycol, and was reduced by lithium in liquid ammonia and sodium borohydride to
the alcohol (41). This was dehydrated by conversion into the methanesulphonate and
adsorption on alkaline alumina,[58] and the gummy product, which is formulated as the
ketal (42), was treated with polyphosphoric acid at 90° to give, after acid hydrolysis, a

(36)   (37)   (38: W = CO)
(39: W = $C_3H_4O_2$)

(40)   (41)   (42)

(43)   (44)
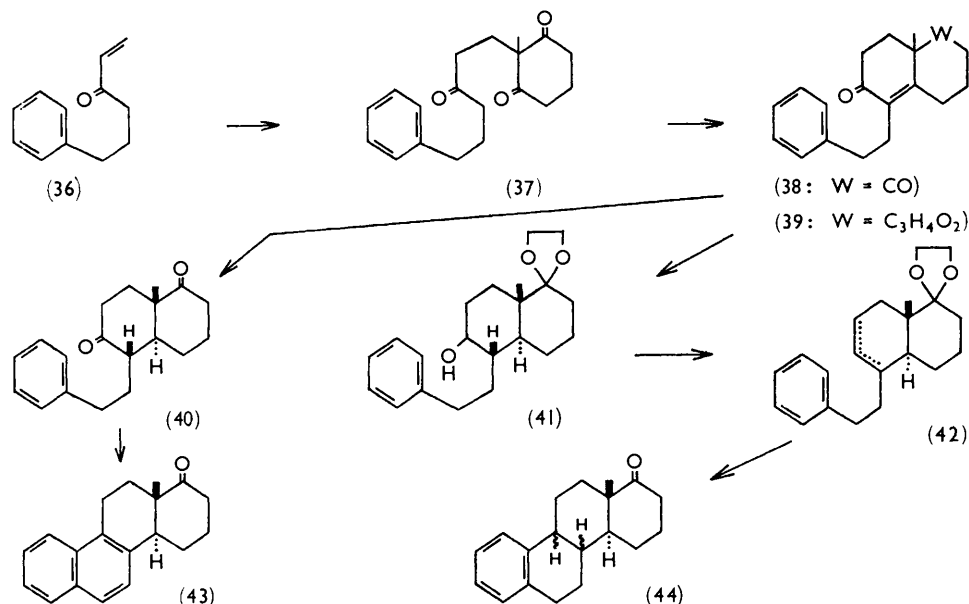
ketone formulated as the deoxyœstrone (44). The low overall yield combined with the
lack of stereochemical control at the cyclisation stage and the potential availability of
3-deoxyœstrones by Kenner deoxygenation[59] of the œstrones have caused the abandon-
ment of this route.

Mechanisms for the Cyclodehydrations to Œstratetra- and -penta-enes.—The cyclodehydr-
ations of the tricyclic diones (4) and (4a) to the respective œstratetraenes (5) and (5a)
presumably involve initial protonation of the 9-oxo-groups followed by electrophilic
cyclisation of the resulting cation, leading to the alcohols (45). Deprotonation and
dehydration then complete the formation of the steroid (5) or (5a). The cyclisation of the
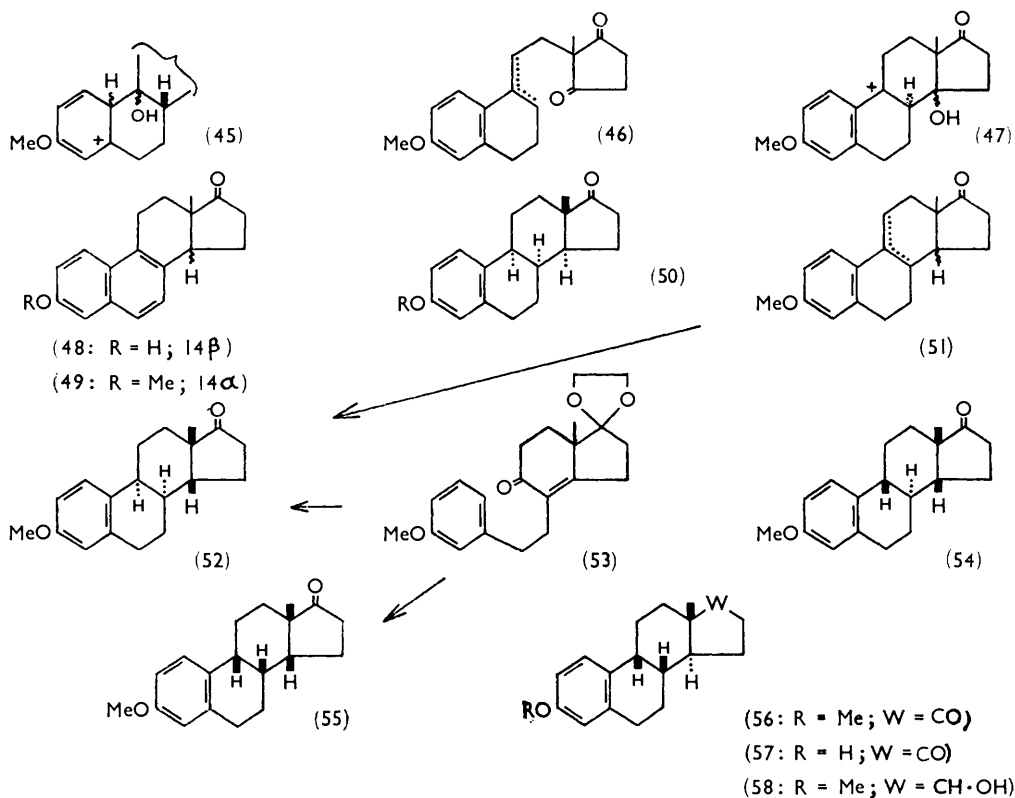dione (3) to the ketone (9) may proceed similarly, the dehydration of the intermediate

[58] Douglas, Ellington, Meakins, and Swindells, *J.*, 1959, 1720.
[59] (a) Kenner and Williams, *J.*, 1955, 522; (b) Fishman, *Chem. and Ind.*, 1958, 1556; (c) Pelletier
and Locke, *J. Org. Chem.*, 1958, **23**, 131.

Δ^8-analogue of the alcohol (45) giving the heteroannular 8,14- rather than the less stable homoannular 8(14),9(11)-diene. The more stringent conditions required presumably reflect the lower electrophilicity of the 9-position in the initially formed allylic cation.

The double cyclodehydration represented by the conversion of the bicyclic trione (12) into the œstrapentaene (9) may, theoretically, involve tricyclic intermediates of the ACD and ABD types. The dione (3) is probably not an intermediate since it is recovered unchanged under the usual reaction * conditions. We suggest that cyclisation proceeds through initial protonation of the 9-oxo-group to a tricyclic intermediate (46) with unsaturation at the 8- or 9(11)-position. The $\Delta^{9(11)}$-isomer would correspond to the seco-œstatetraene (16). The œstrapentaene (9) would be formed from this substance by protonation of the 14-oxo-group, addition of the resulting cationic centre to the double bond (which must now be in the 8-position), and deprotonation and dehydration of the intermediate alcohol (47).

D-*Homoequilenin Methyl Ether*, 3-*Deoxy*-D-*homoequilenin, Equilenin Methyl Ether, and Isoequilenin.*—The dione (4) with polyphosphoric acid at 70° gives D-homoequilenin methyl ether [15] closely similar in ultraviolet absorption spectrum to equilenin [60] and agreeing well

(45)   (46)   (47)

(48: R = H; 14β)
(49: R = Me; 14α)

(50)   (51)

(52)   (53)   (54)

(55)   (56: R = Me; W = CO)
(57: R = H; W = CO)
(58: R = Me; W = CH·OH)

in its melting point and that of its semicarbazone with the literature values.[61]   Related dehydrogenations have been observed as side reactions in hydrofluoric acid cyclisations leading to dihydronaphthalene derivatives.[62]   The ketone (8) is smoothly dehydrogenated

* As will be described in Part II, the 13-ethyl analogue of the trione (12) is cyclised to the corresponding 13-ethylgonapentaene with toluene-*p*-sulphonic acid at or below room temperature.

[60] Bachmann, Cole, and Wilds, *J. Amer. Chem. Soc.*, 1940, **62**, 824.
[61] Burnop, Elliot, and Linstead, *J.*, 1940, 727.
[62] Johnson, Erickson, and Ackerman, *J. Amer. Chem. Soc.*, 1952, **74**, 2251.

by selenium dioxide, in boiling t-butyl alcohol containing pyridine,[63] to equilenin methyl ether (49), which has been converted into (+)-equilenin.[60] The trione (12) with pyridine hydrochloride at 220° gives directly isoequilenin[60] (48) in a reaction presumably involving demethylation and isomerisation of the initially formed ketone (9).

Stereoisomers of Œstrone and its Methyl Ether.—8α-Œstrone (50; R = H) and its methyl ether (50; R = Me)[64] have been obtained by hydrogenation over palladium catalysts of the œstrapentanenes (9b) and (9), respectively. 8α-Œstrone was also obtained by pyridine hydrochloride demethylation at 210° of 8α-œstrone methyl ether. The inefficiency of the demethylation (yield *ca.* 40%, cf. ref. 64) is to be compared with the considerably more efficient demethylations of œstrone methyl ether and other of its stereoisomers.[3b,4b,64] The difference may be due to instability arising from a 1,3-diaxial interaction between the 7-position and the 18-methyl group in the ketones (50; R = H and Me).

8α,14β- and 13α-Œstrone methyl ether, (52) and (54),*[64] respectively, have been made from the gummy mixture of ketols obtained by lithium–ammonia reduction of the ketol (14). Oxidation with chromium trioxide–pyridine, and the usual cyclisation with methanolic hydrochloric acid, converted the ketols into a mixture of the 8- and 9(11)-dehydro-œstrones, m. p. 80—120°, $\lambda_{max.}$ (in EtOH) 274 mμ (ε 16,000), represented as (51). Further reduction with lithium in ammonia and oxidation with chromium trioxide in pyridine gave a product, separated by chromatography upon alumina into the isomers (52) and (54), obtained in overall yields of 45% and 35%, respectively, from the mixture of ketones (51). The result indicates that metal–ammonia reduction of the ketol (14) leads predominantly to saturated ketols having *cis*-hexahydroindane groupings. 8α,13α-Œstrone methyl ether (55) *[64] and the previously obtained isomer (52) were prepared from the ketal (53) made selectively from the ketone (3). Hydrogenation of the ketal in ethanol over palladised charcoal and treatment of the crude product with methanolic hydrochloric acid gave a second mixture of 8- and 9(11)-dehydro-œstrones (51), m. p. 85—89°, $\lambda_{max.}$ (in MeOH) 272 mμ (ε 16,000), which on further catalytic hydrogenation and chromatography afforded the isomers (52) and (55) in 48% and 8% yields, respectively, from the dehydro-œstrone mixture. The 9β-isomer (56)[64] was prepared in admixture with an approximately equal proportion of œstrone methyl ether by hydrogenating the ketal (21) over palladised charcoal in acetic anhydride–acetic acid and hydrolysing the product with mineral acid. The separation of the isomers was facilitated by the differences in their physical properties. Œstrone methyl ether, which is high melting and readily crystallised, was removed by direct crystallisation. The 9β-isomer (56), which has converse properties, remained as a gum closely similar in infrared absorption[64] to the authentic material. It was demethylated by pyridine hydrochloride to 9β-œstrone (57), apparently identical with the authentic material, and also reduced by sodium borohydride to a 9β-œstradiol 3-methyl ether (58), m. p. 140—141°. Oxidation of the alcohol with chromium trioxide in pyridine then gave the crystalline 9β-œstrone methyl ether, m. p. 67—68° (lit.,[64] 68°), identical with an authentic sample.

EXPERIMENTAL

Evaporations were carried out under reduced pressure. Ultraviolet specta refer to ethanol solutions. Infrared spectra designated (a), (b), (c), (d), and (e) refer to liquid films, carbon disulphide solutions, chloroform solutions, potassium bromide discs, and Nujol mulls, respectively. Light petroleum had b. p. 60—80° unless indicated otherwise. Florex is the 30/60 grade of Florida fuller's earth supplied by the Florin Co., Warren, Pa. Magnesol is a hydrated magnesium acid silicate supplied by Westvaco Chlorine Products Corp., South Charleston, W.V., and prepared for chromatography by Pearl and Dickey's method.[65]

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* The structural formulæ represent racemates, so there is no inconsistency in the numbering.

[63] Bowers, Denot, Sanchez, and Ringold, *Tetrahedron*, 1959, **7**, 153.
[64] Johnson, David, Dehm, Highet, Warnhoff, Wood, and Jones, *J. Amer. Chem. Soc.*, 1958, **80**, 661.
[65] Pearl and Dickey, *J. Amer. Chem. Soc.*, 1951, **73**, 863.

Celite is a diatomaceous earth supplied by the Johns-Manville Celite Division, New York. Polyphosphoric acid refers to the grade provided by the Victor Chemical Works, Division of Stauffer Co., 385 Madison Ave., New York 17.

3-m-*Methoxyphenylpropyl Bromide* (17).—3-Methoxycinnamic acid [66] (144 g.) in ethanol (250 c.c.) containing Adams catalyst (1 g.) was shaken with hydrogen until 1 mol. had been taken up (8 hr.). Filtration and evaporation gave 3-*m*-methoxyphenylpropionic acid, m. p. 41—45° (from ether) (lit.,[67] 45°). The acid (130 g.) in ether (600 c.c.) was added portionwise to a stirred suspension of lithium aluminium hydride (30 g.) in ether (800 c.c.) so as to maintain gentle boiling. The supension was then stirred for 1 hr. at room temperture and for 1 hr. under reflux. Excess of reagent was decomposed with ethanol, water was added, and the precipitate was dissolved by adding 2N-sulphuric acid. The product was isolated with ether and yielded 3-*m*-methoxyphenylpropyl alcohol (120 g.), b. p. 153—155°/16 mm. (lit.,[68] 147°/10·5 mm.). Phosphorus tribromide (86 g.) in benzene (150 c.c.) was added portionwise with stirring to the alcohol (125 g.) in benzene (200 c.c.) (ice-bath). The mixture was kept (ice-bath) for 1 hr., heated at 60° (bath) for 3 hr., cooled, and poured on to crushed ice (1 kg.). The product, isolated in the usual way with benzene, gave 3-m-*methoxyphenylpropyl bromide* (131 g.), b. p. 146—148°/17 mm., n_D^{18} 1·5497 (Found: C, 52·5; H, 5·7; Br, 35·0. $C_{10}H_{13}BrO$ requires C, 52·4; H, 5·7; Br, 34·9%).

3-m-*Hydroxyphenylpropyl Alcohol*.—*m*-Hydroxycinnamic acid [69] (85 g.) in ethanol (360 c.c.) containing Adams catalyst (1 g.) was shaken with hydrogen until 1 mol. had been taken up (8 hr.). Filtration and evaporation gave 3-*m*-hydroxyphenylpropionic acid (85 g.), m. p. 110—111° (lit.,[69] 111°). This acid (85 g.) in tetrahydrofuran (80 c.c.) was added portionwise to a vigorously stirred suspension of lithium aluminium hydride (30 g.) in tetrahydrofuran (1500 c.c.). Stirring was continued under reflux for 8 hr. and the *product*, isolated with ether, had b. p. 142—144°/0·1 mm., m. p. 49—53° (Found: C, 71·4; H, 7·8. $C_9H_{12}O_2$ requires C, 71·0; H, 7·95%).

3-m-*Hydroxyphenylpropyl Bromide* (17a).—3-*m*-Hydroxyphenylpropyl alcohol (33·5 g.) was refluxed with stirring in 48% hydrobromic acid (25 c.c.) for 6 hr. The *product*, isolated with ether, had b. p. 103—105°/0·1 mm. (38·3 g.) (Found: C, 50·3; H, 5·1; Br, 36·9. $C_9H_{11}BrO$ requires C, 50·2; H, 5·1; Br, 37·1%).

5-m-*Methoxyphenylpent*-1-*yne* (18).—(*a*) 3-*m*-Methoxyphenylpropyl bromide (14 g.) in tetrahydrofuran (15 c.c.) was added with stirring to sodium acetylide (from sodium, 1·84 g.) in liquid ammonia (125 c.c.). After 22 hours' stirring, ammonium chloride (3 g.) was added, followed by water (50 c.c.). The *product*, isolated with ether, had b. p. 76°/0·06 mm. (9·7 g.), $\nu_{max.}$(a) 3270, 2120, 1600, 785, and 690 cm.$^{-1}$ (Found: C, 82·2; H, 7·8. $C_{12}H_{14}O$ requires C, 82·7; H, 8·1%).

(*b*) Dimethylformamide (120 c.c.) was added to sodium acetylide (from sodium 4·6 g.) in liquid ammonia (250 c.c.). After evaporation of the ammonia, 3-*m*-methoxyphenylpropyl bromide (25 g.) was added with stirring and the mixture was stirred at 60—70° for 2·5 hr. The cooled mixture was added to crushed ice and the *product*, isolated with ether, had b. p. 78—80°/0·1 mm. (11 g.), identical with that prepared as in (*a*).

5-m-*Hydroxyphenylpent*-1-*yne* (18a) *and* 5-m-*Acetoxyphenylpent*-1-*yne* (18b).—3-*m*-Hydroxyphenylpropyl bromide (30 g.) in dimethylformamide (50 c.c.) was added dropwise with stirring to sodium acetylide (from sodium, 10·2 g.) in dimethylformamide (400 c.c.). The mixture was stirred at 60° for 4 hr., then cooled, and ice–water was cautiously added. After adjustment of the pH to 5 with 2N-hydrochloric acid, the mixture was saturated with sodium chloride and the product isolated with ether. A portion was distilled to give 5-m-*hydroxyphenylpent*-1-*yne*, b. p. 86°/0·1 mm. (Found: C, 82·0; H, 7·6. $C_{11}H_{12}O$ requires C, 82·5; H, 7·55%). The crude pentyne was kept overnight with acetic anhydride (20 c.c.) in pyridine (50 c.c.); the 5-m-*acetoxyphenylpent*-1-*yne* (24·2 g.) had b. p. 105—110°/0·1 mm. (Found: C, 77·3; H, 6·7. $C_{13}H_{14}O_2$ requires C, 77·2; H, 7·0%).

5-*Phenylpent*-1-*yne*.—3-Phenylpropyl bromide [70] (248 g.) was added portionwise with stirring to sodium acetylide (from sodium, 43·75 g.) in dimethylformamide (880 c.c.)–xylene (1120 c.c.), and the mixture was stirred for 5 hr. at 25°; the 5-*phenylpent*-1-*yne* (121 g.) had b. p. 94°/50 mm. (Found: C, 91·7; H, 8·1. $C_{11}H_{12}$ requires C, 91·6; H, 8·4%).

[66] Brand and Horn, *J. prakt. Chem.*, 1927, **115**, 374.
[67] Ingold and Piggott, *J.*, 1923, 1502.
[68] Robinson and Schlittler, *J.*, 1935, 1288.
[69] Tiemann and Ludwig, *Ber.*, 1882, **15**, 2043.
[70] Perlman, Davidson, and Bogert, *J. Org. Chem.*, 1936, **1**, 300.

1-*Diethylamino*-6-m-*methoxyphenylhex*-2-*yne* (19).—5-*m*-Methoxyphenylpent-1-yne (8 g.) was kept in dioxan (25 c.c.) containing water (2·5 c.c.), trioxan (0·5 g.), 30% formalin (5·5 g.), diethylamine (4 g.), acetic acid (2·75 g.), and cuprous chloride (0·13 g.) at 70° for 16 hr. The cooled solution was basified with 2N-sodium hydroxide and extracted with ether, and the ether solution washed with water and extracted with 3N-hydrochloric acid. The acid solution was washed with ether and basified with 2N-sodium hydroxide; the *product*, isolated with ether, had b. p. 130—131°/0·1 mm. (10·6 g.) (Found: C, 78·9; H, 9·55. $C_{17}H_{25}NO$ requires C, 78·7; H, 9·7%).

1-*Diethylamino*-6-*phenylhex*-2-*yne*.—The method of the previous experiment was used to convert 5-phenylpent-1-yne (20 g.) into 1-diethylamino-6-phenylhex-2-yne (27·1 g.), b. p. 104—106°/2 mm. (Found: C, 83·9; H, 10·1. $C_{16}H_{23}N$ requires C, 83·8; H, 10·1%).

6-m-*Methoxyphenylhex*-1-*en*-3-*one* (10).—1-Diethylamino-6-*m*-methoxyphenylhex-2-yne (8 g.) was kept with mercuric sulphate (0·45 g.) in water (25 c.c.)–sulphuric acid (2·5 c.c.) at 75° for 1 hr. under nitrogen. The cooled solution was basified with 3N-sodium hydroxide, mercuric oxide was filtered off, and the product was collected with ether. It showed $\nu_{max.}(a)$ 1710 cm.$^{-1}$ and was evidently the crude ketone (20). Distillation with minimal reflux ratio gave a mixture of the ketones (20) and (10), denoted *A*, b. p. 140—145°/0·01 mm., $\nu_{max.}(a)$ 1710 and 1680 cm.$^{-1}$, with the former predominating. Distillation through a short Vigreux column gave a mixture, *B*, of the same two ketones, b. p. 96°/0·003 mm., $\nu_{max.}(a)$ 1710 and 1680 cm.$^{-1}$, with the ketone (10) predominating (Found: N, 1·6. Calc. for $C_{17}H_{27}NO_2$: N, 5·05%). A portion of the mixture *B* in ether was washed with dilute hydrochloric acid, water, and aqueous sodium hydrogen carbonate, and dried; the *product* had b. p. 117°/0·5 mm., $\nu_{max.}(a)$ 1675 cm.$^{-1}$ (Found: C, 76·3; H, 8·0. $C_{13}H_{16}O_2$ requires C, 76·4; H, 7·9%).

2-(6-m-*Methoxyphenyl*-3-*oxohexyl*)-2-*methylcyclopentane*-1,3-*dione* (12).—The ketone mixture *B* (6 g.) was refluxed for 10 hr. with 2-methylcyclopentane-1,3-dione [9,26] (3·5 g.) in methanol (10 c.c.) containing a trace of potassium hydroxide. Most of the methanol was evaporated, ether (25 c.c.) and benzene (25 c.c.) were added, and the solution was washed with water, aqueous sodium hydrogen carbonate, and 3N-hydrochloric acid, and dried. The *product* was suitable for use in subsequent stages. A portion was distilled and had b. p. 220° (bath)/0·02 mm. (Found: C, 72·3; H, 7·45. $C_{19}H_{24}O_4$ requires C, 72·1; H, 7·65%).

5,6,7,8-*Tetrahydro*-4-3′-*methoxyphenethyl*-8-*methylindane*-1,3-*dione* (3).—(*a*) A mixture of the foregoing crude trione (12) (26·5 g.) in xylene (194·5 c.c.) containing benzoic acid (11·0 g.) and triethylamine (10·6 c.c.) was refluxed for 7 days with continuous removal of the water formed (Dean–Stark apparatus). The cooled solution was diluted with ether (100 c.c.) and washed with aqueous sodium hydrogen carbonate, water, 2N-sulphuric acid, and water, and dried. The product was taken up in light petroleum–benzene and adsorbed on neutral alumina. Benzene–ether (4 : 1) eluted the *product* (22 g.), b. p. 160—190° (bath)/0·05 mm., $\lambda_{max.}$ 249 mμ (ε 9000), $\nu_{max.}(a)$ 1740, 1660, 1600, 780, and 690 cm.$^{-1}$ (Found: C, 76·7; H, 7·6. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4%).

(*b*) 5,6,7,8-Tetrahydro-8-methylindane-1,5-dione [26] (5·55 g.) in benzene (30 c.c.) was added under nitrogen to potassium t-butoxide (from potassium, 1·45 g.) in benzene (150 c.c.). The stirred solution was slowly distilled (column packed with Fenske rings), to remove the benzene–t-butyl alcohol azeotrope, and 3-methoxyphenethyl bromide [71] (8 g.) in benzene (50 c.c.) was added dropwise with stirring during 15 min. to the cooled solution. The mixture was stirred at room temperature for 1 hr. and under reflux for 1 hr. The cooled solution was washed with 0·5N-hydrochloric acid and water and dried. Distillation of the product gave a fraction (2·1 g.), b. p. 160—190° (bath)/0·05 mm., $\lambda_{max.}$ 245 mμ (ε 8300) which on redistillation gave the product, identical with that prepared as in (*a*).

5.6,7,8 - *Tetrahydro* - 1β - *hydroxy* - 4 - 3′ - *methoxyphenethyl* - 8β - *methylindan*-5-*one* (14).—Sodium borohydride (32 g.) in ethanol (30 c.c.) was added to the foregoing dione (3) (1·23 g.) in ethanol (30 c.c.) at 8°; after 12 min. acetic acid was added to decompose the excess of reagent, the solution was evaporated to dryness, water was added, and the *product*, isolated with ether, had m. p. 88—90° [from light petroleum (b. p. 40—60°)–di-isopropyl ether] (0·96 g.) (Found: C, 75·7; H, 8·0. $C_{19}H_{24}O_3$ requires C, 76·0; H, 8·05%).

5β-*Hydroxy*-1-3′-*methoxyphenethyl*-10β-*methyl*-Δ^{1(9)}-*octal*-2-*one* (14a).—The mixture of ketones (10) and (20), *A* (9 g.) was kept at reflux for 15 hr. with 2-methylcyclohexane-1,3-dione [72] (4 g.) in benzene (46 c.c.) containing pyridine (3·5 c.c.). The cooled solution was

[71] Collins and Smith, *J.*, 1956, 4308.

[72] (*a*) Stetter and Dierichs, *Chem. Ber.*, 1952, **85**, 66; (*b*) Stetter and Coenen, *ibid.*, 1954, **87**, 990.

washed with 3N-hydrochloric acid, water, and brine, and dried. The product, evidently the trione (12a), showed $\nu_{max.}$(a) 1700, 1710, and 1720 cm.$^{-1}$ An aliquot part (8·2 g.) was refluxed for 24 hr. (Dean–Stark apparatus) in xylene (30 c.c.) containing triethylamine (2·9 c.c.) and benzoic acid (3·5 g.). The cooled solution was diluted with ether and washed with aqueous sodium hydrogen carbonate, water, 2N-sulphuric aid, and water, and dried. The product was distilled to give a viscous oil, evidently the dione (3a) (6·5 g.), b. p. 185—193°/0·05 mm., $\lambda_{max.}$ 250 mμ (ε 10,000), $\nu_{max.}$(a) 1710 and 1670 cm.$^{-1}$. Sodium borohydride (0·55 g.) in ethanol (80 c.c.) was added to the oil (3 g.) in ethanol (80 c.c.) at 8°, and left for 12 min.; the *product* had m. p. 96—97° (from ether) (1·98 g.), $\lambda_{max.}$ 250 mμ (ε 12,000), $\nu_{max.}$(e) 3380 and 1670 cm.$^{-1}$ (Found: C, 76·2; H, 8·2. $C_{20}H_{26}O_3$ requires C, 76·4; H, 8·35%).

5-3′-*Methoxyphenethyl*-9β-*methyl-trans-decalin*-1,6-*dione* (4a).—(a) The ketol (14a) (2·8 g.) in tetrahydrofuran (30 c.c.) was added with stirring to lithium (0·35 g.) in liquid ammonia (300 c.c.). After 5 min. the blue colour was discharged with sodium nitrite and the product, isolated with ether–benzene, was kept overnight with chromium trioxide (4 g.) in pyridine (70 c.c.). Water was added and the *product*, isolated with ether–benzene and recrystallised from ether and then light petroleum–ethyl acetate, had m. p. 92—93° (1·72 g.), $\nu_{max.}$(e) 1710 cm.$^{-1}$ (Found: C, 76·25; H, 8·25. $C_{20}H_{26}O_3$ requires C, 76·4; H, 8·35%).

(b) 9-Methyl-$\Delta^{5(10)}$-octalin-1,6-dione (3·2 g.) in benzene (25 c.c.) was added with stirring under nitrogen to potassium t-butoxide (from potassium, 0·67 g.) in benzene (100 c.c.) and the solution was slowly distilled (column packed with Fenske rings) to remove the benzene–t-butyl alcohol azeotrope. 3-Methoxyphenethyl bromide (3·41 g.) in benzene (15 c.c.) was added and the mixture was refluxed with stirring for 19 hr. The product was isolated in the usual way and adsorbed on Florex (40 g.). The column was washed with light petroleum and eluted with ether to give a gum (3·22 g.) which was kept for 12 min. with sodium borohydride (0·55 g.) in ethanol (160 c.c.) at 8°. The product (2·91 g.) in tetrahydrofuran (20 c.c.) was added with stirring to lithium (0·6 g.) in liquid ammonia (200 c.c.) and after 10 min. the blue colour was discharged with ethanol. The product (2·78 g.) was kept overnight with chromium trioxide (4 g.) in pyridine (70 c.c.). Water (200 c.c.) was added and the product was isolated with benzene. The gum (2·42 g.) was taken up in light petroleum–benzene and adsorbed on alumina (150 g.). Benzene–ether (1 : 1) eluted crystals which were recrystallised from light petroleum–benzene to give the product (0·097 g.), m. p. and mixed m. p. 86—88°, and same infrared spectrum as material prepared as in (a) (Found: C, 76·1; H, 8·25%).

1β-*Benzoyloxy*-4,5,6,7-*trans*-8,9-*hexahydro*-4-3′-*methoxyphenethyl*-8β-*methylindan*-5-*one*.—The ketol (14) (6 g.) was catalytically hydrogenated as previously described and the product was kept for 16 hr. at room temperature in pyridine (36 c.c.)–benzoyl chloride (18 c.c.). Chromatography on alumina gave the *product* (3·5 g.), m. p. 96—98° (from methanol–ether) (Found: C, 76·6; H, 7·3. $C_{26}H_{30}O_4$ requires C, 76·8; H, 7·4%).

3-*Methoxy*-D-*homo-œstra*-1,3,5(10),9(11)-*tetraen*-17a-*one* (5a).—(a) The dione (3a) (2 g.), obtained by cyclising the trione (12a) as previously described, in ethanol (50 c.c.) containing 10% palladised charcoal was shaken with hydrogen until uptake ceased (178 c.c., 1·17 mol., 5 hr.). Filtration and evaporation gave a gum which was kept in methanol (32 c.c.)–10N-hydrochloric acid (8 c.c.) at room temperature for 3 hr. and at 0° for 1 hr. The precipitate gave the *product* (0·96 g.), m. p. 172—175° (from ethanol–ethyl acetate), $\lambda_{max.}$ 262 mμ (ε 18,700). A sample obtained after three similar recrystallisations had m. p. 183—184°, $\lambda_{max.}$ 262 mμ (ε 19,200) (Found: C, 80·75; H, 8·05. $C_{20}H_{24}O_2$ requires C, 81·0; H, 8·2%).

(b) The dione (4a) (0·5 g.) was cyclised as before in ethanol (8 c.c.)–10N-hydrochloric acid to give, from ethanol–ethyl acetate, the same product as that prepared in (a) (0·322 g.), m. p. 172—175°.

3-*Methoxyœstra*-1,3,5(10),9(11)-*tetraen*-17-*one* (5).—(a) The foregoing ketol (14) (0·91 g.) in ethanol (50 c.c.) containing 10% palladised charcoal (0·3 g.) was shaken with hydrogen until 1 mol. had been taken up. Filtration and evaporation gave a gum, $\lambda_{max.}$ 273 and 280 mμ (ε 2000 and 1900), which was kept with chromium trioxide (0·85 g.) in pyridine (25 c.c.) for 20 hr. Ethyl acetate (50 c.c.) was added and the mixture passed through alumina (8 g.) covered by a layer of Celite (4 g.). The gummy product, $\nu_{max.}$(a) 1740, 1710, 1600, 780, and 690 cm.$^{-1}$, was kept in methanol (20 c.c.)–10N-hydrochloric acid (4 c.c.) at room temperature for 4 hr. The solution was added to brine and the product (0·45 g.) collected with ether–benzene, had m. p. 136—140° (from ethanol–ethyl acetate), $\lambda_{max.}$ 264 mμ (ε 18,800). The analytical sample had m. p. 146—147° (Found: C, 81·0; H, 8·0. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·85%).

(*b*) The dione (3) [0·95 g., obtained as previously described by cyclodehydration of the trione (12)] in ethanol (50 c.c.) containing 10% palladised charcoal (0·2 g.) was shaken with hydrogen until 1 mol. had been taken up. The gummy product, $\lambda_{max.}$ 272 and 280 mμ (ε 2100 and 2000), was cyclised in methanol (20 c.c.)–10N-hydrochloric acid (4 c.c.) and worked up as in (*a*) to give the same product (0·335 g.), m. p. 135—140°, $\lambda_{max.}$ 264 mμ (ε 18,700), with identical infrared absorption.

3-*Methoxyœstra*-1,3,5(10),8,14-*pentaen*-17-*one* (9).—(*a*) The trione (12) (6·7 g.) was refluxed for 30 min. in benzene (100 c.c.) containing anhydrous toluene-*p*-sulphonic acid (from the monohydrate, 2·4 g.) (Dean–Stark water-separator). The cooled solution was washed with aqueous sodium hydrogen carbonate and water, and dried. The gummy product, distilled at 210° (bath)/0·5 mm., gave the *product* (3·9 g.), m. p. 115—116° (from methanol), $\lambda_{max.}$ 313 mμ (ε 35,100) (Found: C, 81·1; H, 7·0. $C_{19}H_{20}O_2$ requires C, 81·4; H, 7·2%).

(*b*) The trione (12) (3 g.) was heated for 4 min. at 90° in benzene (100 c.c.) containing phosphoric acid (15 g.; *d* 1·8) and phosphoric anhydride (6 g.). The cooled mixture was added to water and the product, isolated with ether–ethyl acetate, was recrystallised from methanol. It (2 g.) had m. p. 115—116° and was identical with that prepared as in (*a*).

(*c*) * 6-Methoxy-1-vinyl-1-tetralol [45] (7 g.) was refluxed for 18 hr. under nitrogen in methanol (25 c.c.) containing 2-methylcyclopentane-1,3-dione (6 g.) and potassium hydroxide (0·03 g.). The cooled solution was diluted with water and extracted with ether, and the ethereal solution washed with aqueous sodium hydrogen carbonate and brine, and dried. Three recrystallisations from methanol gave 2-(6-*methoxy-1-naphthylidene*)*ethyl-2-methylcyclopentane*-1,3-*dione* (16) (3·1 g.), m. p. 77—78°, $\lambda_{max.}$ 267 mμ (ε 18,000), $\nu_{max.}$(d) 3000, 1755, 1725, 1600, 1570, and 1495 cm.$^{-1}$ (Found: C, 76·6; H, 7·4. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4%). 10N-Hydrochloric acid was added to this dione (0·5 g.) in methanol (15 c.c.) at 40° until the solution just became turbid. The mixture was allowed to cool to room temperature and after 1 hr. the precipitate was filtered off and recrystallised from methanol to give the product (0·4 g.), m. p. 112—115°, undepressed by material made as in (*a*), $\lambda_{max.}$ 313 mμ (ε 34,500).

The dione (16) (2·1 g.) in benzene (10 c.c.) was added to toluene-*p*-sulphonic acid (from the monohydrate, 2 g.) in benzene (65 c.c.) at room temperature. After 3 hr. ether was added and the solution was washed with water and dried. The product was distilled at 220° (bath temperature)/0·1 mm. and the distillate was recrystallised from methanol to give the product (1·24 g.), m. p. 112—115°, undepressed by material prepared as in (*a*), $\lambda_{max.}$ 313 mμ (ε 35,000).

3-*Methoxy*-D-*homo-œstra*-1,3,5(10),8,14-*pentaen*-17a-*one* (9a).—(*a*) The trione (12a) [2 g., prepared as previously described from the mixture of ketones (10) and (20) and 2-methylcyclohexane-1,3-dione], was refluxed for 2 hr. in benzene (35 c.c.) containing anhydrous toluene-*p*-sulphonic acid (from the monohydrate, 1 g.) (Dean–Stark water-separator). Recrystallised from light petroleum, methanol, and ethanol, the *product* (0·5 g.) had m. p. 139—141°, $\lambda_{max.}$ 310 mμ (ε 30,000) (Found: C, 81·45; H, 7·7. $C_{20}H_{22}O_2$ requires C, 81·6; H, 7·5%).

(*b*) The mixture, B, of ketones (10) and (20) (40 g.) reacted as previously described with 2-methylcyclohexane-1,3-dione (26·5 g.) in benzene (189 c.c.)–pyridine (20 c.c.). The product (50 g.) in benzene (500 c.c.) was added under nitrogen with stirring to polyphosphoric acid (250 g.) at 70° (bath). After stirring for 2 hr. crushed ice was added, and extraction with ether gave the product (9a) (34·8 g.), m. p. 138—140° (from ethanol).

3-*Hydroxyœstra*-1,3,5(10),8,14-*pentaen*-17-*one* (9b).—(*a*) 5-*m*-Acetoxyphenylpent-1-yne (24·2 g.) was kept under nitrogen at 70° for 16 hr. in dioxan (35 c.c.) containing water (5 c.c.), diethylamine (16 c.c.), 40% formalin (14 c.c.), acetic acid (7·3 c.c.), trioxan (1·4 g.), and cuprous chloride (0·36 g.). The cooled mixture was basified to pH 8·8 with ice-cold saturated aqueous sodium hydrogen carbonate; the product, after isolation with ether, was a viscous oil (32·8 g.). An portion (8·3 g.) was kept under nitrogen at 75° for 95 min. in 2N-sulphuric acid (25 c.c.) containing mercuric sulphate (0·45 g.). The cooled solution was basified to pH 8·8 with 3N-sodium hydroxide, and acidified to pH 6; the product (7·34 g.), after isolation with ether, was a viscous oil. It was refluxed in methanol for 10 hr. with 2-methylcyclopentane-1,3-dione (7 g.), the solvent was evaporated, the residue dissolved in ether, and the solution washed with N-sulphuric acid, aqueous potassium hydrogen carbonate, and brine. The product (4·7 g.) was refluxed for 35 min. in benzene (85 c.c.) containing anhydrous toluene-*p*-sulphonic acid (from the monohydrate, 0·5 g.) (Dean–Stark water-separator). The cooled solution was washed with water, dried, and evaporated. The crystalline residue (4·4 g.) was taken up in benzene (40 c.c.)

* Experiment carried out at Wyeth Laboratories Inc., Radnor, Pa.

and adsorbed on Florex (150 g.). Elution by benzene gave the *product* (3·1 g.), m. p. 225—230° (decomp.) (from di-isopropyl ether), $\lambda_{max.}$ 313 mμ (ε 30,000) (Found: C, 81·15; H, 7·0. $C_{18}H_{18}O_2$ requires C, 81·2; H, 6·8%).

The foregoing ketone (1 g.) was kept with acetic anhydride (3 c.c.) in pyridine (3 c.c.) for 4 hr. at 0° and the product, in benzene, was passed through Florex (10 g.) and recrystallised from methanol to give 3-*acetoxyœstra*-1,3,5(10),8,14-*pentaen*-17-*one* (0·6 g.), m. p. 182—184°, $\lambda_{max.}$ 307 mμ (ε 28,100) (Found: C, 78·1; H, 6·5. $C_{20}H_{20}O_3$ requires C, 77·9; H, 6·5%).

(*b*) * 6-Hydroxy-1-tetralone (4 g.) was kept for 3 days at room temperature in dihydropyran (15 c.c.)–tetrahydrofuran (10 c.c.) containing 2 drops of 10N-hydrochloric acid. The product, recrystallised from methanol, gave 6-tetrahydropyranyloxy-1-tetralone (5·5 g.), m. p. 91—93° (Found: C, 73·4; H, 7·26. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%). This ketone (5·5 g.) was kept with vinylmagnesium chloride (from magnesium, 1·42 g.) in tetrahydrofuran (20 c.c.) for 16 hr., the mixture was added to ice-cold aqueous ammonium chloride and extracted with ether, and the ethereal solution washed with aqueous sodium hydrogen carbonate and brine. The product (6·1 g.), $\nu_{max.}$(a) 3390, 1639, and 1653 cm.$^{-1}$ (evidently crude 6-tetrahydropyranyloxy-1-vinyl-1-tetralol) was refluxed with 2-methylcyclopentane-1,3-dione (3 g.) for 8 hr. in methanol (50 c.c.) containing potassium hydroxide (0·06 g.). Most of the methanol was evaporated, ether (50 c.c.) and benzene (50 c.c.) were added, and the solution was washed with 10% aqueous sodium hydroxide, water, and brine. The product, $\lambda_{max.}$ 270 mμ (ε 10,200), $\nu_{max.}$ 3333, 1724, and 1600 cm.$^{-1}$ [evidently the crude seco-œstrone (16b)] was stirred with methanol (20 c.c.) containing 10N-hydrochloric acid (2 c.c.) for 5 min., water (3 c.c.) was added, and the mixture was cooled to 0°. The product was filtered off and washed with aqueous methanol. The crude product (3·4 g.) had m. p. 216—220°, undepressed by material prepared as in (*a*) and raised to 222—225°, after recrystallisation.

3-*Methoxyœstra*-1,3,5(10),8-*tetraen*-17-*one* (8).—(*a*) 3-Methoxyœstra-1,3,5(10),8,14-pentaen-17-one (2 g.) in benzene (60 c.c.) containing 2% palladised calcium carbonate (1 g.) was shaken with hydrogen until 1 mol. had been taken up. Filtration and evaporation gave the *product* (1·4 g.), m. p. 118—119° (from methanol), $\lambda_{max.}$ 278 mμ (ε 15,000) (Found: C, 80·5; H, 7·9. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·85%).

(*b*) 3-Methoxyœstra-1,3,5(10),8,14-pentaen-17-one (1 g.) in dioxan (33 c.c.) containing Raney nickel [73] (*ca.* 0·5 g.) was shaken with hydrogen until 1 mol. had been taken up. The product, after recrystallisation from ethanol and methanol, was identical with that prepared as in (*a*).

3-*Methoxy*-D-*homo-œstra*-1,3,5(10),8-*tetraen*-17a-*one* (8a).—The ketone (9a) (11 g.) in tetrahydrofuran (100 c.c.) containing 2% palladised calcium carbonate (6 g.) was shaken with hydrogen until 1 mol had been taken up (3 min.). Filtration and evaporation gave the *product* (9·5 g.), m. p. 119—124° (from ethanol–ethyl acetate). A sample of m. p. 125—128° had $\lambda_{max.}$ 276 mμ (ε 16,200) (Found: C, 80·9; H, 7·85. $C_{20}H_{24}O_2$ requires C, 81·0; H, 8·2%).

This ketone (0·05 g.) was refluxed in ethanol (2·5 c.c.)–10N-hydrochloric acid (0·5 c.c.) for 15 min. The solution was rapidly cooled (ice-bath), water was added, and the precipitate was filtered off, washed with aqueous methanol, and dried to give a mixture of ketones (0·046 g.), m. p. 140—163°, $\lambda_{max.}$ 267 mμ (ε 16,100). An equimolar mixture of the ketones (5a) and (8a) had $\lambda_{max.}$ 266 mμ (ε 16,100).

3-*Hydroxyœstra*-1,3,5(10),8-*tetraen*-17-*one* (8b).—3-Hydroxyœstra-1,3,5(10),8,14-pentaen-17-one (1·4 g.) in di-2-methoxyethyl ether (15 c.c.)–benzene (10 c.c.) containing 2% palladised calcium carbonate (0·8 g.) was shaken with hydrogen until 1 mol. had been taken up. The mixture was filtered, the benzene evaporated, and the *product* (0·65 g.), obtained by precipitation with water and recrystallisation from methanol containing a little tetrahydrofuran, had m. p. 240—242° (decomp.), $\lambda_{max.}$ 280 mμ,(ε 15,000), $\nu_{max.}$(d) 3200 and 1715 cm.$^{-1}$ (Found: C, 80·3; H, 7·5. $C_{18}H_{20}O_2$ requires C, 80·6; H, 7·5%).

Isomerisation of 3-*Methoxyœstra*-1,3,5(10),8-*tetraen*-17-*one.*—The ketone (8) (1·27 g.) was refluxed for 10 min. in methanol (100 c.c.)–10N-hydrochloric acid (20 c.c.). The cooled solution was diluted with ether–benzene and washed with water, aqueous sodium hydrogen carbonate, and dried. The product, on recrystallisation from methanol, gave slightly impure 3-methoxy-œstra-1,3,5(10),9(11)-tetraen-17-one (1·24 g.), m. p. 138—145° undepressed by the material

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* Experiment carried out at Wyeth Laboratories Inc., Radnor, Pa.

[73] Pavlic and Adkins, *J. Amer. Chem. Soc.*, 1946, **68**, 1471.

m. p. 146—148° prepared as previously described, $\lambda_{max.}$ 265 mμ (ε 18,200), and converted in high yield into œstrone methyl ether as described below.

3-Hydroxyœstra-1,3,5(10),9(11)-tetraen-17-one (5b).—The ketone (8b) (0·15 g.) was kept under reflux in methanol (5 c.c.)–10N-hydrochloric acid (1 c.c.)–tetrahydrofuran (0·5 c.c.) for 15 min. The precipitate, formed by cooling to 0°, gave the *product* (0·085 g.), m. p. 250—252° (decomp.) (from methanol–ethanol), $\lambda_{max.}$ 265 mμ (ε 16,600), $\nu_{max.}$(d) 3200 and 1715 cm.$^{-1}$ (Found: C, 80·75; H, 7·5. $C_{18}H_{20}O_2$ requires C, 80·6; H, 7·5%).

3-Methoxyœstra-1,3,5(10),8-tetraen-17β-ol (7).—The ketone (8) (40 g.) was refluxed in ethanol (500 c.c.) with sodium borohydride for 1·5 hr. The *product* (37·5 g.), m. p. 130—133°, $\lambda_{max.}$ 280 mμ (ε 16,100), $\nu_{max.}$(d) 3226, 2793, 1600, 1563, and 1493 cm.$^{-1}$, when purified had m. p. 133—135° (from methanol) (Found: C, 80·4; H, 8·4. $C_{19}H_{24}O_2$ requires C, 80·2; H, 8·5%).

l7,17-Ethylenedioxy-3-methoxyœstra-1,3,5(10),9(11)-tetraene (21).— (*a*) 3-Methoxyœstra-1,3,5(10),9(11)-tetraen-17-one (4·1 g.) was kept at reflux for 17 hr. in benzene (400 c.c.) containing ethylene glycol (10·5 c.c.) and toluene-*p*-sulphonic acid (0·265 g.). The *product* (3·97 g.) had m. p. 132—134° (from methanol), $\lambda_{max.}$ 265 mμ (ε 24,000), $\nu_{max.}$(e) 1310, 1240, 1168, 1161, 1052, 812, and 802 cm.$^{-1}$ (Found: C, 77·1; H, 8·0. $C_{21}H_{26}O_3$ requires C, 77·3; H, 8·0%).

(*b*) 3-Methoxyœstra-1,3,5(10),8-tetraen-17-one (1·25 g.) was refluxed for 30 min. in benzene (120 c.c.) containing toluene-*p*-sulphonic acid (0·085 g.). Ethylene glycol (3 c.c.) was added and the solution refluxed for 16 hr. Working up gave slightly impure ketal (24) (1·33 g.), m. p. 124—127° (from methanol), undepressed by material prepared as in (*a*) and having an almost identical infrared absorption spectrum, $\lambda_{max.}$ 264 mμ (ε 18,800). It was also converted in high yield, by hydrogenation and hydrolysis, into a mixture of œstrone and 9β-œstrone methyl ethers.

3-Methoxy-D-homo-œstra-1,3,5(10)-trien-17aβ-ol.—(*a*) The ketone (5a) (0·5 g.) in tetrahydrofuran (35 c.c.) was added with stirring to potassium (0·35 g.) in liquid ammonia (125 c.c.). After 5 min. further metal (0·35 g.) was added and the stirring was continued for a further 30 min. After addition of ammonium chloride (2 g.) and water (75 c.c.), the product was collected with ether. It was recrystallised from methanol to give a methanolate (0·31 g.), m. p. 98—99°, which was sublimed at 85°/0·01 mm. to give the *product*, m. p. 138—140°, $\lambda_{max.}$ 278 and 287 mμ (ε 1700 and 1500), $\nu_{max.}$(e) 3252 cm.$^{-1}$ (Found: C, 80·2; H, 9·2. $C_{20}H_{28}O_2$ requires C, 79·95; H, 9·4%).

(*b*) The ketone (8a) (9·5 g.) was refluxed with sodium borohydride (3·5 g.) in methanol (150 c.c.) for 30 min., to yield an alcohol [presumably (7a)] (8 g.), m. p. 83—86° (from ethanol). Lithium (2 g.) was added portionwise with stirring to this alcohol in liquid ammonia (500 c.c.)–tetrahydrofuran (175 c.c.)–aniline (100 c.c.), the mixture was stirred for 1·5 hr., and ammonium chloride and water were added; the methanolate (5·25 g.) had m. p. 86—89° undepressed by that obtained as in (*a*).

3-Methoxyœstra-1,3,5(10)-trien-17β-ol.—(*a*) Sodium (2·2 g.) was added portionwise with stirring to the alcohol (7) (2·2 g.) in liquid ammonia (150 c.c.)–tetrahydrofuran (40 c.c.)–aniline (15 c.c.), stirring was continued for 20 min., ammonium chloride was added to discharge the blue colour, water was added, and the mixture extracted with ether. The *product* (1·8 g.) had m. p. 129—131° (from hexane), raised to m. p. 132—133° (from ethyl acetate) (Found: C, 79·5; H, 9·0. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·15%).

(*b*) 10N-Hydrochloric acid was added dropwise to 1β-benzoyloxy-4,5,6,7-*trans*-8,9-hexahydro-4-3′-methoxyphenethyl-8β-methylindan-5-one (0·193 g.) in methanol (10 c.c.) until the solution became turbid. The mixture was kept for 2 hr. and extracted with ether; the product (0·133 g.), m. p. 137—138° (from methanol), $\lambda_{max.}$ 263 mμ (ε 20,600), was hydrolysed in the usual manner with 5% aqueous potassium hydroxide. The product in tetrahydrofuran (5 c.c.)–aniline (5 c.c.) was added to lithium (0·07 g.) in liquid ammonia. After 10 min. ammonium chloride was added and the mixture extracted with ether. Recrystallisation from light petroleum–ether gave the product, m. p. 130—131°, identical with the material prepared as in (*a*) and having the same infrared absorption as the (+)-enantiomer.

D-Homo-œstrone Methyl Ether (6a).—D-Homo-3-methoxyœstra-1,3,5(10)-trien-17aβ-ol (0·1 g.) in acetone (30 c.c.) was treated with 8N-chromic acid [74] (0·3 c.c.). When the reaction was complete (30 sec.) water (50 c.c.) was added. Extraction with ether–benzene gave the *product* (0·07 g.), m. p. 155—157° (from ethanol), $\lambda_{max.}$ 278 and 286 mμ (ε 2000 and 1900), identical in

[74] Djerassi, Engle, and Bowers, *J. Org. Chem.*, 1956, **21**, 1547.

infrared absorption with the (+)-enantiomer [35,36] (Found: C, 80·3; H, 8·7. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·8%). The benzylidene derivative, prepared by refluxing the ketone with benzaldehyde in methanol containing sodium methoxide, had m. p. 145—146° (lit.,[3b] 146—147°).

Œstrone Methyl Ether (6).—(*a*) The ketone (5) (0·23 g.) in tetrahydrofuran (40 c.c.) was added with stirring to potassium (0·25 g.) in liquid ammonia (200 c.c.). After 5 min. more potassium (0·25 g.) was added and the stirring was continued for 1 hr. after which the blue colour was discharged with ammonium chloride (1 g.). Working up gave a gum which was treated in acetone (50 c.c.) with 8N-chromic acid (0·5 c.c.). Chromatography on alumina gave œstrone methyl ether (0·16 g.), m. p. 139—142° (from methanol); a sample of m. p. 143—144° (lit.,[3b] 143—144°) had infrared absorption identical with that of the (+)-enantiomer made from (+)-œstrone (Found: C, 79·9; H, 8·35. Calc. for $C_{19}H_{24}O_2$: C, 80·2; H, 8·5%).

(*b*) The ketone (5) (0·1 g.) in methanol (50 c.c.) containing palladium black [30] (0·3 g.) was shaken with hydrogen until 1 mol. had been taken up (2 hr.). The gum obtained after filtration and evaporation was chromatographed on alumina to give œstrone methyl ether, m. p. 141—143°.

(*c*) Sodium (0·22 g.) was added portionwise with stirring to the ketone (5) [0·211 g., from isomerisation of the ketone (8)] in aniline (12·5 c.c.)–liquid ammonia (60 c.c.). Stirring was continued for 30 min. and ammonium chloride (1 g.) and water (50 c.c.) were added. The mixture was extracted with ether and the ether solution was washed free from aniline with 3N-hydrochloric acid, and then washed with water, aqueous sodium hydrogen carbonate, and water, and dried. The product, in acetone (25 c.c.), was treated with 8N-chromic acid as before to give œstrone methyl ether (0·114 g.), m. p. 142—143° (from methanol).

(*d*) The ketal (21) (0·09 g.) in tetrahydrofuran (10 c.c.) was added with stirring to lithium (0·2 g.) in liquid ammonia (100 c.c.). After 30 min., ammonium chloride was added; the product had $\lambda_{max.}$ 279 mμ (ε 1900). It was refluxed for 30 min. in methanol (20 c.c.)–N-sulphuric acid (2 c.c.). The cooled solution was diluted with water and extracted with benzene, to give œstrone methyl ether (0·06 g.), m. p. 139—141° (from methanol).

(*e*) The ketone (8) (0·25 g.) in tetrahydrofuran (15 c.c.) was added with stirring to potassium (0·1 g.) in liquid ammonia (70 c.c.). Further metal (0·3 g.) was added portionwise during 5 min. and the mixture was stirred for 1 hr. The blue colour was discharged with ammonium chloride (2 g.), water was added, and the product collected with ether. It was treated in acetone (30 c.c.) with 8N-chromic acid (0·3 c.c.), to give œstrone methyl ether (0·114 g.), m. p. 137—142° (from ethanol), raised to 143—144° by further recrystallisation.

(*f*) 8N-Chromic acid (3·6 c.c.) was added to 3-methoxyœstra-1,3,5(10)-trien-17β-ol (3 g.) in acetone (150 c.c.) containing anhydrous magnesium sulphate (6 g.). After 2 min. isopropyl alcohol (9 c.c.) was added, followed by sodium hydrogen carbonate (6 g.). The solvent was evaporated, water (100 c.c.) was added, and the mixture was extracted with ether, to give œstrone methyl ether (2·4 g.), m. p. 140—142° (from methanol).

Œstrone (6b).—The ketone (5b) (0·1 g.) in ethanol (5 c.c.)–tetrahydrofuran (3 c.c.) containing 10% palladised charcoal (0·04 g.) was shaken with hydrogen until uptake was complete. Œstrone (0·062 g.) had m. p. 230—236° (from methanol), raised to 252—254° (lit.,[60] 253—255°) by three further recrystallisations.

1,2,3,4,4aβ,4bα,5,6,7,8,8a,9,10,10aα - *Tetradecahydro* - 8β - *hydroxy* - 8aβ-*methyl* - 1 - *oxaphenanthrene*-2-*spiro*-1-*cyclohexan*-3-*one Isomers* (28; $R^1 = H_2$, $R^2 = O$ and $R^1 = O$, $R^2 = H_2$).—The ketol (14) (4·55 g.) was reduced with lithium (0·6 g.) in tetrahydrofuran (50 c.c.)–liquid ammonia (350 c.c.) as before. The crude product in tetrahydrofuran (100 c.c.) was added with stirring to lithium (1·2 g.) in liquid ammonia (500 c.c.). The stirring was continued for 15 min. and ethanol (10 c.c.) was added dropwise. After the reaction was complete, water was added and the mixture was extracted with ether. The gummy product, on trituration with ether, gave crystals (3·1 g.) [evidently the alcohol (25)], m. p. 106—111°, $\nu_{max.}$(e) 3350, 1695, 1220, 1147, 1038, and 786 cm.$^{-1}$. The crystals (5 g.) were kept at reflux for 5 min. in methanol (100 c.c.)–glacial acetic acid (8·8 c.c.). Water (800 c.c.) was added to the cooled solution, the product was extracted with ether, and the ether solution washed with water and brine, and dried. Evaporation gave a gum which, on trituration with ether, gave crystals (3·76 g.), evidently the diol (26), m. p. 67—70°, $\nu_{max.}$(e) 3350, 1697, 1056, and 1034 cm.$^{-1}$, which could not be purified by recrystallisation from benzene–ethyl acetate or benzene–chloroform, possibly owing to some conversion into the ketones (28). A portion (1·5 g.) was kept in methanol (30 c.c.)–10N-hydrochloric acid (1·8 c.c.)–water (1·2 c.c.) for 1 hr. The crystalline product (0·78 g.) had m. p. 141—149°. A

portion in benzene was percolated through neutral alumina to give the products, m. p. 150—171° (from benzene–light petroleum) (Found: C, 74·5; H, 9·7. Calc. for $C_{19}H_{30}O_3$: C, 74·5; H, 9·9%). Fractional crystallisation from benzene gave an *isomer*, m. p. 178—180°, $\nu_{max.}$(e) 3433. 1704, 1378, 1239, 1127, 1119, 1068, 1056, 1039, 960, and 939 cm.$^{-1}$ (Found: C, 74·65, 74·6; H, 9·65, 9·7%). The *acetate*, from ethanol, had m. p. 186·5—189° (Found: C, 72·4; H, 9·25; COMe, 10·6. $C_{21}H_{32}O_4$ requires C, 72·35; H, 9·3; 1COMe, 12·4%). A second fraction had m. p. 165—169°, depressed to 147—169° on admixture with the above isomer, but the amount was too small for further examination.

9β-*Methyl*-5-(2-5′-*oxocyclohex*-1-*enylethyl*)-trans-*decalin*-1,6-*dione* (31).—The crude diol (26) (0·67 g., prepared as in the previous experiment) in acetone (80 c.c.) was oxidised with 8N-chromic acid as before to give a product (0·56 g.). Recrystallisation from light petroleum containing a little ethyl acetate, and further recrystallisation followed by evaporative distillation at 200° (bath)/0·1 mm., gave the *product*, m. p. 68—71°, $\nu_{max.}$ (b) 1715 cm.$^{-1}$ (Found: C, 75·5; H, 8·7. $C_{19}H_{30}O_3$ requires C, 75·5; H, 8·7%).

9ξ-*Hydroxy*-10ξ-D-*homo-œstr*-4-ene-3,17a-*dione* (32).—The crude trione (31) (0·53 g.) in light petroleum (9 c.c.)–benzene (1 c.c.) was adsorbed on Florex (20 g.). Elution with benzene and benzene–ether gave crystals (0·22 g.) of the *product*, m. p. 205—207·5° (from chloroform–benzene), $\lambda_{max.}$ 243 mμ (ε 15,500), $\nu_{max.}$(e) 3390, 1700, 1685, 1628, 1260, 1209, 1186, 1104, 1071, 925, and 871 cm.$^{-1}$ (Found: C, 75·65; H, 8·7. $C_{19}H_{26}O_3$ requires C, 75·5; H, 8·7%).

9ξ,17aξ-*Dihydroxy*-10ξ-D-*homo-œstr*-4-*en*-3-*one*.—The dione (35) (0·1 g.) in ethanol (12 c.c.) was reduced with sodium borohydride (0·01 g.) in the usual way. The *product* (0·056 g.) had m. p. 200—204° (from benzene–chloroform), $\lambda_{max.}$ 243 mμ (ε 15,800), $\nu_{max.}$(e) 3390, 1684, 1627, 1269, 1208, 1179, 1106, 1072, 925, and 871 cm.$^{-1}$ (Found: C, 75·3; H, 8·9. $C_{19}H_{28}O_3$ requires C, 75·0; H, 9·3%).

D-*Homo-œstra*-4,9-*diene*-3,17a-*dione* (33).—(a) The dione (32) (0·42 g.) was refluxed for 30 min. in benzene (70 c.c.) containing a small crystal of iodine. The *product* (0·27 g.) (from methanol), after sublimation and recrystallisation from methanol, had m. p. 165·5—167°, $\lambda_{max.}$ 306 mμ (ε 20,000), $\nu_{max.}$(b) 1715 and 1672 cm.$^{-1}$ (Found: C, 80·05; H, 8·55. $C_{19}H_{24}O_2$ requires C, 80·2; H, 8·5%).

(b) The dione (32) (0·25 g.) was refluxed for 2 hr. in benzene (20 c.c.)–acetic acid (2 c.c.) containing toluene-*p*-sulphonic acid (0·12 g.). The product (from light petroleum–ether) had m. p. 164—166°, undepressed by the material prepared as in (a).

17aξ-*Hydroxy*-D-*homo-œstra*-4,9-*dien*-3-*one* (34).—The dione (33) (0·23 g.) in ethanol (25 c.c.) at 8° was reduced with sodium borohydride (20 mg.) in the usual way, and the *product* (0·157 g.), had m. p. 137—139·5° (from light petroleum–ether), $\lambda_{max.}$ 310 mμ (ε 20,800) (Found: C, 79·5; H, 9·0. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·15%).

D-*Homo-œstra*-1,3,5(10)-*triene*-3,17aξ-*diol* (35).—(a) The ketol (34) (0·157 g.) was refluxed for 5 hr. in ethanol (50 c.c.) containing 30% palladised charcoal. The gummy product was percolated in benzene through Magnesol (5 g.) to give crystals (0·039 g.) of the *product* which, after two recrystallisations from light petroleum–ether, had m. p. 210—210·5°, $\lambda_{max.}$ 280 mμ (ε 1600) (Found: C, 79·75; H, 9·3. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·15%).

(b) 3-Methoxy-D-homo-œstra-1,3,5(10)-trien-17a-one (6a) (0·22 g.) was kept in molten pyridine hydrochloride (2·2 g.) at 210° for 40 min. The product was reduced with lithium aluminium hydride in tetrahydrofuran and recrystallised twice from ether to give the *product*, m. p. 209·5—211°, undepressed by the material prepared as in (a).

6-*Phenylhex*-1-*en*-3-*one* (36).—1-Diethylamino-6-phenylhex-2-yne (27·1 g.) was kept under nitrogen at 70° for 1·5 hr. in water (76·6 c.c.)–sulphuric acid (7·6 c.c.) containing mercuric sulphate (1·62 g.). The product was worked up in the usual way to give an oil, $\nu_{max.}$(d) 1705 cm.$^{-1}$, which on distillation gave what was evidently a mixture of 6-phenylhex-1-en-3-one and 1-diethylamino-6-phenylhexan-3-one (18·9 g.), b. p. 96—99°/0·3 mm., $\nu_{max.}$(a) 1705 and 1680 cm.$^{-1}$. This mixture was used in subsequent reactions. A portion, in ether, was washed with 3N-hydrochloric acid, aqueous sodium hydrogen carbonate, water, and brine, and dried. The product was distilled to give 6-*phenylhex*-1-*en*-3-*one*, b. p. 76°/0·3 mm., $\nu_{max.}$(a) 1680, 700, and 745 cm.$^{-1}$ (Found: C, 83·1; H, 8·1. $C_{12}H_{14}O$ requires C, 82·7; H, 8·1%).

9-*Methyl*-5-*phenethyl*-Δ$^{5(10)}$-*octalin*-1,6-*dione* (38).—The foregoing mixture of 6-phenyl-hex-1-en-3-one and 1-diethylamino-6-phenylhexan-3-one (19 g.) was refluxed for 15 hr. with 2-methylcyclohexane-1,3-dione (8·45 g.) in benzene (97·1 c.c.)–pyridine (7·4 c.c.). Working up in the usual way gave a gum, *C* (28 g.), which was refluxed for 24 hr. in xylene (162·4 c.c.)

containing benzoic acid (11·9 g.) and triethylamine (9·9 g.) (Dean–Stark water-separator). The *product* was a viscous oil, b. p. 164—168°/0·05 mm., $\lambda_{max.}$ 249 mμ (ε 9500), $\nu_{max.}$(a) 1705, 1660, 745, and 700 cm.$^{-1}$ (Found: C, 80·5; H, 7·55. $C_{19}H_{22}O$ requires C, 80·8; H, 7·9%). The same dione was produced when the gum *C* was refluxed for 2 hr. in benzene containing toluene-*p*-sulphonic acid (Dean–Stark water-separator).

9β-*Methyl*-5-*phenethyl*-trans-*decalin*-1,6-*dione* (40).—(*a*) The dione (38) (3 g.) in ethanol (75 c.c.) containing 10% palladised charcoal (0·9 g.) was shaken with hydrogen until uptake ceased (5 hr.). Filtration and evaporation gave a gum which was kept at reflux in ethanol (300 c.c.)–4N-sulphuric acid (3 c.c.) for 2 hr. The *product* had m. p. 96—98° (from ethanol), $\nu_{max.}$(e) 1705, 745, and 700 cm.$^{-1}$ (Found: C, 80·1; H, 8·65. $C_{19}H_{24}O_2$ requires C, 80·2; H, 8·5%).

(*b*) The dione (38) (3 g.) was treated with sodium borohydride (0·55 g.) in ethanol (160 c.c.) at 8° for 12 min. The mixture was worked up as before to give a gum (2·8 g.), $\lambda_{max.}$ 249 mμ (ε 10,200), $\nu_{max.}$ 3450 and 1660 cm.$^{-1}$, which was taken up in tetrahydrofuran (30 c.c.) and added with stirring to lithium (0·35 g.) in liquid ammonia (300 c.c.). After 5 min., sodium nitrite was added and the mixture worked up in the usual way. The product, $\nu_{max.}$(e) 3400, 1700, 745, and 700 cm.$^{-1}$, was treated for 3 min. in acetone (30 c.c.) with 8N-chromic acid (1·65 c.c.) to give, after the usual working up, the product (2·0 g.), m. p. 96—98° (from ethanol).

The foregoing dione (0·25 g.) was kept with phosphoric acid (2·25 g.; *d* 1·8)–phosphoric anhydride (1·25 c.c.) at 60° under nitrogen for 45 min. The mixture was added to water and, after isolation with ether, the product was chromatographed on alumina. Benzene–light petroleum (2 : 3) eluted crystals of presumably, D-homo-œstra-1,3,5(10),6,8-pentaen-17-one (0·15 g.), m. p. 112—114° (from methanol), $\lambda_{max.}$ 229, 285, and 321 mμ (ε 72,300, 3900, and 1000), $\nu_{max.}$(e) 1695, 800, 750, and 730 cm.$^{-1}$, although a satisfactory elemental analysis was not obtained (Found: C, 85·25; H, 7·7. Calc. for $C_{19}H_{20}O_2$: C, 86·3; H, 7·6%). Johnson, Peterson, and Gutsche [75] report for an œstra-1,3,5(10),6,8-pentaen-17-one, $\lambda_{max.}$ 230·5, 282, and 321·5 mμ (ε 93,300, 5800, and 900).

5,5-*Ethylenedioxy*-10-*methyl*-1-*phenethyl*-$\Delta^{1(9)}$-*octalin*-2-*one* (39).—The dione (38) (6·3 g.) was kept at reflux in benzene (315 c.c.) containing ethylene glycol (1·47 c.c.) and toluene-*p*-sulphonic acid (0·63 g.) for 4 hr. Chromatography on neutral alumina gave the *product* (5·0 g.), b. p. 180—200° (bath)/0·1 mm., $\lambda_{max.}$ 249 mμ (ε 9000), $\nu_{max.}$(a) 1660, 1155, 1070, 745, and 700 cm.$^{-1}$ (Found: C, 77·2; H, 7·9. $C_{21}H_{26}O_3$ requires C, 77·2; H, 7·9%).

5,5-*Ethylenedioxy*-10β-*methyl*-1-*phenethyl*-trans-*decalin*-2-*one*.—The foregoing ketal (5 g.) in tetrahydrofuran (46·6 c.c.) was added with stirring to lithium (0·54 g.) in liquid ammonia (460 c.c.). After stirring for 5 min. sodium nitrite was added. The *product* (4·5 g.) had m. p. 81—82° (from methanol), $\nu_{max.}$(e) 1700, 1155, 1085, 750, and 700 cm.$^{-1}$ (Found: C, 77·0; H, 8·7. $C_{21}H_{28}O_3$ requires C, 76·8; H, 8·6%).

D-*Homo*-8ξ,9ξ-*œstra*-1,3,5(10)-*trien*-17a-*one* (44).—Sodium (1 g.) was added to a boiling solution of the foregoing ketal (1 g.) in butanol (22 c.c.). Further metal (0·4 g.) was added after 10 min. After the reaction was complete, water was added to the cooled solution and the mixture was extracted with ether to give a product (0·8 g.), $\nu_{max.}$(a) 3450, 1185, 1085, 750, and 700 cm.$^{-1}$, which was kept in pyridine at 0° with methanesulphonyl chloride for 24 hr. The product (0·93 g.), m. p. 137—138°, $\nu_{max.}$(e) 1170, 1180, 750, and 700 cm.$^{-1}$, in benzene (30 c.c.) was adsorbed on alumina (75 g., Peter Spence, Grade 0). After 2 days, elution with benzene gave a gum (0·53 g.), $\nu_{max.}$(a) 750 and 700 cm.$^{-1}$. A portion (0·5 g.) was kept at 60° under nitrogen in phosphoric acid (4·05 g.)–phosphoric anhydride (2·25 g.) for 45 min. The mixture was poured into water and the product collected in ether. It was kept at reflux in t-pentyl alcohol (5 c.c.)–toluene (5 c.c.)–8N-hydrochloric acid (10 c.c.) for 10 min. Chromatography gave the *product* (0·083 g.), m. p. 95—96° (from methanol), $\nu_{max.}$(e) 1705 and 745 cm.$^{-1}$ (Found: C, 84·7; H, 9·0. $C_{19}H_{24}O$ requires C, 85·0; H, 9·0%).

Equilenin Methyl Ether, D-*Homoequilenin Methyl Ether, and their Analogues.*—*Equilenin methyl ether* (49). 3-Methoxyœstra-1,3,5(10),8-tetraen-17-one (0·2 g.) was refluxed for 1 hr. in t-butyl alcohol (15 c.c.) containing selenium dioxide (0·1 g.) and pyridine (2 drops). The cooled mixture was filtered and the product from the filtrate was chromatographed on alumina to give equilenin methyl ether (0·038 g.), m. p. 186—188° (from ethanol) (lit.,[71] 189—190·5°),

[75] Johnson, Peterson, and Gutsche, *J. Amer. Chem. Soc.*, 1947, **69**, 2942.

$\lambda_{max.}$ 268, 278, 289, 323, and 337 mμ (ε 4500, 4800, 3300, 2000, and 2400), identical with that determined under the same conditions for authentic (+)-equilenin methyl ether.

D-*Homoequilenin methyl ether.* The dione (4a) (1·12 g.) was kept in phosphoric acid (5 c.c.; d 1·8)–phosphoric anhydride (3·3 g.) at 90° for 45 min. The mixture was added to crushed ice and the product was collected with ether. Chromatography on alumina gave D-homo-equilenin methyl ether (0·114 g.), m. p. 209—212° (from chloroform–ether) (lit.,[57] 212—214°), $\lambda_{max.}$ 258, 268, 278, 308, 320, and 334 mμ (ε 7100, 7400, 5500, 3800, and 4800). The semi-carbazone had m. p. 245° (lit.,[57] 245°).

3-*Hydroxy-13α-œstra-1,3,5(10),6,8-pentaen-17-one* (48). The trione (12) (0·5 g.) was kept in molten pyridine hydrochloride (3 g.) at 210° for 40 min. under nitrogen. The product, recrystallised thrice from methanol, had m. p. 222—224° (0·162 g.) (lit.,[56] m. p. 223—224°), λ_{max} 267, 277, 289, 325, and 338 mμ (ε 6500, 6600, 4000, 2000, and 2350).

Stereoisomers of Œstrone and Œstrone Methyl Ether.—8α-*Œstrone methyl ether* (50; R = Me). 3-Methoxyœstra-1,3,5(10),8,14-pentaen-17-one (1 g.) in benzene (35 c.c.) containing 10% palladised charcoal (0·5 g.) was shaken with hydrogen until uptake ceased. Filtration and evaporation gave 8α-œstrone methyl ether (0·55 g.), m. p. 151—153° (from ethanol) (lit.,[60] 152·5—154·5°).

8α-*Œstrone* (50; R = H). (*a*) 8α-Œstrone methyl ether (0·05 g.) was kept in molten pyridine hydrochloride at 210° for 40 min. under nitrogen. 1·5N-Hydrochloric acid (25 c.c.) was added to the cooled mass and the product was extracted with chloroform and recrystallised from methanol to give 8α-œstrone (0·011 g.), m. p. 253—255° (lit.,[60] 253·6—254·8°).

(*b*) 3-Hydroxyœstra-1,3,5(10),8,14-pentaen-17-one (9) (0·1 g.) in ethanol (25 c.c.) containing 10% palladised charcoal (0·05 g.) was shaken with hydrogen until uptake was complete. The gummy product crystallised (0·086 g.) on trituration with ether, to give 8α-œstrone, m. p. 253—255° (from methanol), $\lambda_{max.}$ 281 mμ (ε 2150).

8α,14β-*Œstrone methyl ether* (52) *and* 13α-*œstrone methyl ether* (54). The ketol (14) (1·4 g.) in tetrahydrofuran (30 c.c.) was added dropwise with stirring to lithium (0·02 g.) in liquid ammonia (200 c.c., distilled from sodium) just to discharge the blue colour. More lithium (0·02 g.) was then added and the procedure was repeated until only a faint permanent blue colour remained after complete addition of the solution. Sodium nitrite (0·01 g.) was added and the mixture was worked up in the usual way. The gummy product (1·3 g.), $\lambda_{max.}$ 272 and 279 mμ (ε 2100 and 1900) was kept in pyridine (50 c.c.) with chromium trioxide (1·4 g.) for 16 hr. and the resulting gum was cyclised in methanolic hydrochloric acid as before to give a mixture of 3-methoxyœstra-1,3,5(10),8- and -1,3,5(10),9(11)-tetraen-17-one stereoisomers (51) (1·0 g.), m. p. 80—120°, $\lambda_{max.}$ 274 mμ (ε 16,000), $\nu_{max.}$(e) 1735 and 810 cm.$^{-1}$ (Found: C, 80·5; H, 7·8. Calc. for $C_{19}H_{22}O_2$: C, 80·8; H, 7·85%). This mixture in tetrahydrofuran (30 c.c.) was added with stirring to lithium in liquid ammonia. After 5 min. more metal (0·25 g.) was added, the stirring was continued for 2 hr., and ammonium chloride (0·5 g.) was added. The gummy product was dissolved in benzene and chromatographed on alumina (80 g.). Light petroleum–benzene (1 : 1) eluted crystals (0·45 g.) of 8α,14β-œstrone methyl ether, m. p. 113—116° (from methanol) (lit.,[60] 115—116°) identical in infrared absorption * with authentic material. Light petroleum–benzene (1 : 4) eluted crystals (0·34 g.) of 13α-œstrone methyl ether, m. p. 105—108° (from methanol) (lit.,[60] 109—110°) depressed to 80—104° on admixture with 8α,14β-œstrone methyl ether, and identical in infrared absorption * with authentic material.

8α,13α-*Œstrone methyl ether* (55) *and* 8α,14β-*œstrone methyl ether* (52). The dione (3) (3·45 g.) was refluxed for 4 hr. in benzene (25 c.c.) containing ethylene glycol (0·765 c.c.) and toluene-*p*-sulphonic acid (0·173 g.) (Dean–Stark water-separator). The product, $\lambda_{max.}$ 249 mμ (ε 9700), $\nu_{max.}$(d) 1665, 1155, 1070, 790, and 700 cm.$^{-1}$, in ethanol (80 c.c.) containing 10% palladised charcoal (1 g.) was shaken with hydrogen until uptake was complete (2 days). Filtration and evaporation gave a gum (2·8 g.), $\nu_{max.}$(a) 1710, 780, and 690 cm.$^{-1}$. A portion (0·288 g.) was refluxed for 2 hr. in methanol (9·3 c.c.)–10N-hydrochloric acid (1·5 c.c.). The product, recrystall-ised from methanol, gave a mixture of 3-methoxyœstra-1,3,5(10),8- and -1,3,5(10),9(11)-tetraen-17-one stereoisomers (0·14 g.), m. p. 85—89°, $\lambda_{max.}$ 272 mμ (ε 16,100), $\nu_{max.}$(e) 1740 and 805 cm.$^{-1}$ (Found: C, 80·8; H, 7·8. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·8%). The mixture (0·44 g.) in methanol (20 c.c.) containing 10% palladised charcoal (0·3 g.) was shaken with hydrogen until

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uptake ceased (5 hr.). The product was dissolved in benzene and chromatographed on alumina. Benzene–light petroleum (4 : 1 and 9 : 1) eluted crystals of 8α,14β-œstrone methyl ether, m. p. 116—117° (from methanol) (0·212 g.) undepressed by material made as previously described, $\lambda_{max.}$ 278 mμ (ε 2100) (Found: C, 79·9; H, 8·5. Calc. for $C_{19}H_{24}O_2$: C, 80·2; H, 8·5%). Benzene–ether (19 : 1) eluted crystals of 8α,13α-œstrone methyl ether (0·035 g.), m. p. 104—105° (from methanol) (lit.,[60] 105—106°), $\lambda_{max.}$ 279 mμ (ε 1900), $\nu_{max.}$(c) (10% solution in $CHCl_3$) 1727, 1615, 1508, 1475, 1415, 1388, 1336, 1288, 1272, 1240, 1158, 1137, 1093, and 1042 cm.$^{-1}$ (Found: C, 80·1; H, 8·5. Calc. for $C_{19}H_{24}O_2$: C, 80·2; H, 8·5%).

8α,14β-Œstrone. 8α,14β-Œstrone methyl ether (0·8 g.) was kept under nitrogen in molten pyridine hydrochloride (10 g.) at 210° for 40 min. 8α,14β-Œstrone had m. p. 181—182° (0·6 g.) (from methanol) (lit.,[60] 180·5—181·5°) (Found: C, 80·1; H, 8·3. Calc. for $C_{18}H_{22}O_2$: C, 80·0; H, 8·15%).

9β-Œstrone methyl ether (56). The ketal (21) (3·5 g.) in acetic acid (180 c.c.)–acetic anhydride (20 c.c.) containing palladised charcoal (1·4 g.) was shaken with hydrogen until uptake had ceased (5 min.). The mixture was filtered and added to crushed ice, the product extracted with ether, and the ether solution washed with water, aqueous sodium hydrogen carbonate, and water, and dried. The gummy product was refluxed for 45 min. in methanol (100 c.c.)–10N-hydrochloric acid (10 c.c.). Œstrone methyl ether (1·5 g.) had m. p. 135—140° (from methanol). Evaporation of the mother-liquors gave a gum (1·46 g.) closely similar in infrared absorption to 9β-œstrone methyl ether.[60] An aliquot (0·98 g.) was refluxed in ethanol (60 c.c.) with sodium borohydride (0·24 g.) for 20 min., to give 3-*methoxy*-9β-*œstra*-1,3,5(10)-*trien*-17ξ-*ol* (58) (0·719 g.), m. p. 140—141° (from light petroleum), $\nu_{max.}$(e) 3305 and 1612 cm.$^{-1}$ (Found: C, 80·0; H, 9·2. $C_{19}H_{26}O_2$ requires C, 79·7; H, 8·95%). A portion was oxidised in the usual way with 8N-chromic acid, to give 9β-œstrone methyl ether, m. p. 67—68° (from methanol) (lit.,[60] 67—68°), $\lambda_{max.}$ 278 mμ (ε 1700), $\nu_{max.}$(c) (10% solution in $CHCl_3$) 1730, 1612, 1505, 1473, 1462, 1412, 1380, 1355, 1322, 1301, 1293, 1273, 1256, 1111, and 1038 cm.$^{-1}$.

9β-Œstrone (57). 9β-Œstrone methyl ether (0·117 g., the crude gum from the previous experiment) was demethylated with pyridine hydrochloride (1 g.) at 210° for 40 min. and the product was chromatographed on magnesol (10 g.). Benzene and benzene–ether (9 : 1) eluted crystals of 9β-œstrone (0·06 g.), m. p. 195—197° (from methanol) (lit.,[60] 197—198°), $\nu_{max.}$ 3370, 1725, 1615, and 819 cm.$^{-1}$ (Found: C, 80·1; H, 8·2. Calc. for $C_{18}H_{22}O_2$: C, 80·0; H, 8·15%).

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