903. 8-*Azasteroids. Part I. The Synthesis of* 8-*Azaœstrone*

By R. Clarkson

A convenient stereospecific synthesis of (±)-8-azaœstrone is described using, as the key step, a Michael reaction between 1-(β-dimethylaminoethyl)-3,4-dihydro-6-methoxyisoquinoline and 2-methylcyclopentane-1,3-dione. Syntheses of corresponding 18-alkyl and D-homo-compounds are also described.

The synthesis of isosteres of biologically active molecules has attracted considerable interest in most fields. That steroids are no exception is illustrated by the rapidly growing number of publications on aza- and oxa-derivatives.[1] Much of this work has been concerned with partially synthetic routes from naturally derived starting materials, and these have mainly led to homosteroids or steroids in which a normal oxygen function (say at C-3) has become amidic or, in one case, lost altogether.[2] Much information concerning the effect of a basic group on the biological properties of steroids could be obtained if the introduced nitrogen atom neither markedly altered the stereochemistry, nor added extra active hydrogen atoms, nor modified the functional groups present in the original carbocyclic compound. Substitution of nitrogen for C-8 is one of the few changes that would meet these criteria. We have now prepared a range of 8-azasteroids,[3] and this Paper describes our initial experiments in the field.

Perhaps the major problem in steroid synthesis involves the stereospecific production of the *trans* C/D ring junction. The recent, very convenient, syntheses of œstrone [4] depend upon the hydrogenation of a Δ^{14}-intermediate for selective formation of 14α-compounds, presumably because the methyl group at C-13 directs absorption on to the catalyst from the α-face. As we could anticipate no complications from the presence of a tertiary nitrogen atom in a similar hydrogenation we concentrated on the synthesis of the appropriate 8-aza-Δ^{14}-compound. Although all structural formulæ are drawn to represent one enantiomer this is for convenience only and it is to be understood that all compounds are racemic. We have omitted the (±) sign also except in the summary and in the Experimental section.

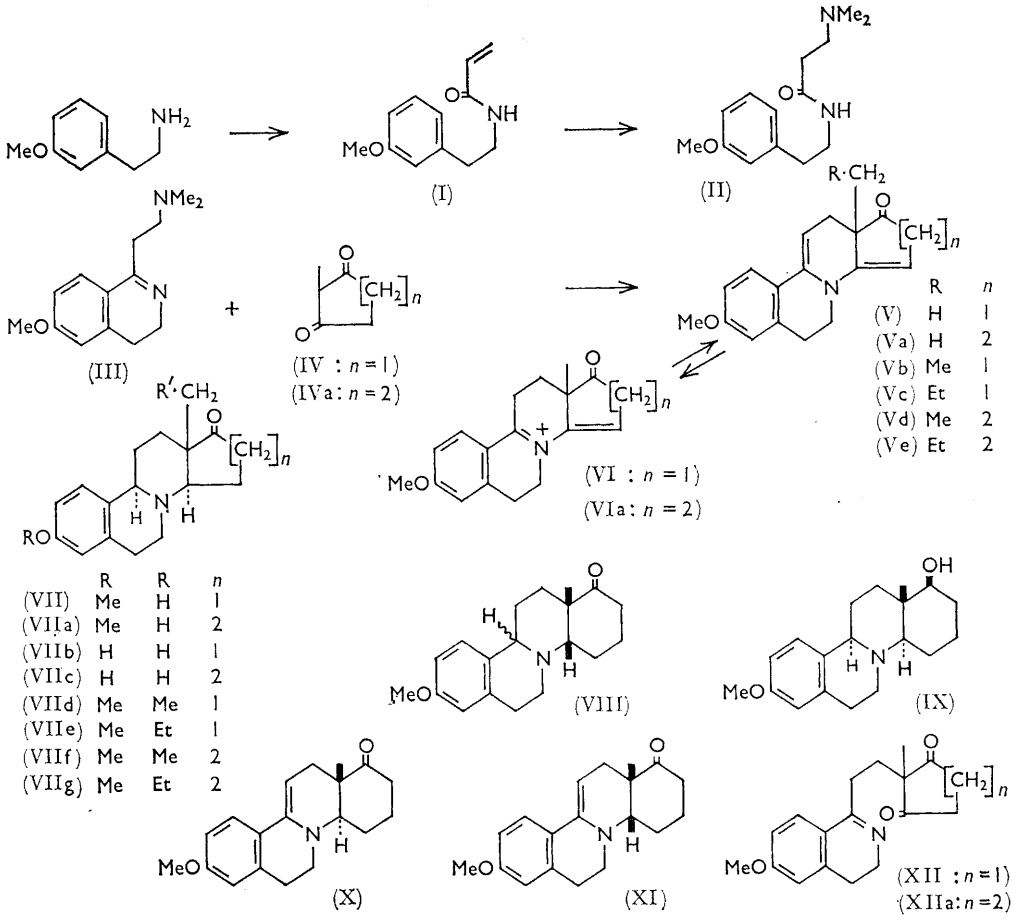
The addition of carbanions to the azomethine link of 3,4-dihydroisoquinolines is well known.[5] It therefore seemed reasonable to expect a 1-vinyl-3,4-dihydroisoquinoline to undergo a Michael reaction with 2-methylcyclohexane-1,3-dione (IVa) to give the dione (XIIa). We elected to work with the D-homo-series first because the cyclopentanedione (IV) is neither as readily accessible nor in general as reactive (see later) as the cyclohexane compound. Also, because of the predicted instability of a 1-vinyldihydroisoquinoline, it was decided to synthesise the β-dimethylaminoethyl compound (III) and use it in the Michael reaction.

The amide (I), from acryloyl chloride and 3-methoxyphenethylamine, added dimethylamine readily to give the β-dimethylaminopropionamide (II). Phosphorus pentachloride in chloroform cyclised this amide to the moderately stable dihydroisoquinoline (III), which was isolated and stored as the dihydrochloride. The several attempts made to prepare 3,4-dihydro-6-methoxy-1-vinylisoquinoline, either by cyclisation of the acryloyl

[1] C. Djerassi, "Steroid Reactions," Holden Day Inc., San Francisco, 1963, p. 457.
[2] T. L. Jacobs and R. B. Brownfield, *J. Amer. Chem. Soc.*, 1960, **82**, 4033.
[3] B.P. 973,911—973,913.
[4] (*a*) G. A. Hughes and H. Smith, *Proc. Chem. Soc.*, 1960, 74; (*b*) *Chem. and Ind.*, 1960, 1022; (*c*) G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall, and H. Smith, *J.*, 1963, 5072; (*d*) A. V. Zakharychev, S. N. Ananchenko, and I. V. Torgov, *Steroids*, 1964, **4**, 31. (*e*) For a review of earlier work see I. V. Torgov, "The Chemistry of Natural Products," Butterworths, London, 1963, vol. 2, p. 525.
[5] J. H. Chapman, P. G. Holton, A. C. Ritchie, T. Walker, G. B. Webb, and K. D. E. Whiting, *J.*, 1962, 2471, and Papers following.

amide or by elimination reactions of the methiodide or *N*-oxide of the dimethylamino-compound (III), all gave polymeric products. However, condensation occurred readily between the dimethylaminoisoquinoline (III) and the dione (IVa) in benzene–pyridine to give, not the expected tricyclic dione (XIIa), but the slightly unstable tetracyclic dienamine (Va), the infrared spectrum of which showed bands at 1700 (C=O) and 1630 cm.$^{-1}$ (C=C); the absorption spectrum in cyclohexane and in methanol was of normal styrene type [6] (Figure) whereas in 0·1N-hydrochloric acid a marked hypsochromic shift was observed attributed to the fully conjugated cation (VIa). The C-11 and C-15 protons gave nuclear magnetic resonance signals at τ 4·75 (triplet) and 5·08 (multiplet), respectively.

It is interesting to compare the rate of this condensation, which is complete within 30 minutes, with that of the reaction between 2-methylcyclohexane-1,3-dione and the ketone



(XIII), which is incomplete even after 48 hours.[7] This probably means that in our reaction, the condensation and cyclisation steps are concerted.

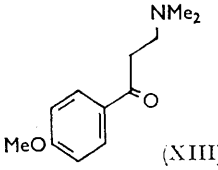
Hydrogenation of the dienamine (Va) over palladised charcoal gave, in high yield, the ketone (VIIa), which was pure after one crystallisation. Sodium borohydride reduction of the material from the mother-liquors from this crystallisation gave, in addition to the expected 17aβ-ol (IX), a ketone (VIII) [*ca.* 5% from compound (Va)] isomeric with compound (VIIa). The structure of this ketone (VIII), which is not reduced by ethanolic

[6] A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," Arnold, London, 1957, p. 141.

[7] Emrys R. H. Jones, unpublished work.

sodium borohydride even after prolonged contact at room temperature, is discussed later.

Condensation of the isoquinoline (III) with 2-methylcyclopentan-1,3-dione (IV) using the benzene–pyridine conditions gave a poor yield (~15%) of the dienamine (V)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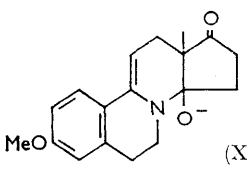
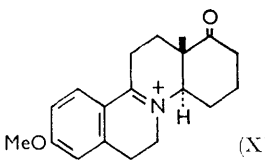

(XIV)

together with a considerable amount of tar. The dienamine had properties closely resembling those of the D-homo-analogue: $\nu_{max.}$ 1745 (C=O in 5-membered ring), and 1630 cm.$^{-1}$ (C=C); n.m.r. triplets at τ 4·75 (C-11 proton) and 5·29 (C-15); $\lambda_{max.}$ (MeOH) 260 mμ (ε 27,000) shifting to 367 mμ (22,000) in 0·1N-hydrochloric acid. It is known that products of Michael reactions with 2-methylcyclopentane-1,3-dione cleave readily, particularly with excess base.[8] The use of a catalytic amount of base (we used sodium hydride–benzene, successful in resolving analogous difficulties),[8] only marginally improved the yield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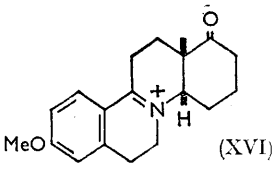
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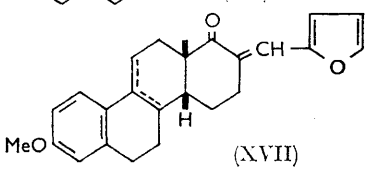
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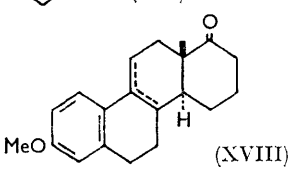

(XVIII)

in our condensation. Changing to dioxan as solvent and using "Hidrite" as desiccant improved the yield to 30—35%. If the condensation and cyclisation steps are concerted, the initial product should be the anion (XIV) which could protonate and dehydrate to give the dienamine or cleave to produce 3,4-dihydro-6-methoxy-1-vinylisoquinoline, previously shown to polymerise readily. In order to protonate the anion (XIV) rapidly and thus favour enamine formation, we added a molar proportion of *p*-methoxyphenol * which increased the yield to a readily reproducible 55—60%. Trace quantities of the phenol had previously been employed as a polymerisation inhibitor with only a slight effect on the overall yield.

Hydrogenation of the dienamine (V) was highly stereospecific and gave only 3-methoxy-8-azaœstrone (VII). This compound, and the D-homo-ketone (VIIa), were readily demethylated in fused pyridine hydrochloride [9] to 8-azaœstrone (VIIb) and 8-aza-D-homo-œstrone (VIIc), respectively.

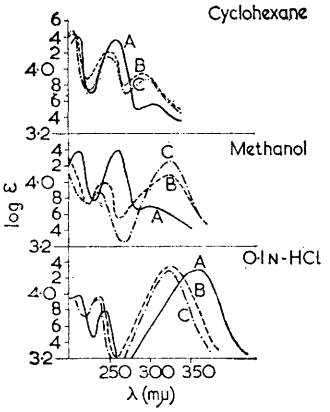
Stereochemistry of the D-*Homo-ketones* (VIIa and VIII).—These two ketones, when oxidised with mercuric acetate,[10] gave different enamines [(X) from (VIIa) and (XI) from (VIII)], and hence, if ketone (VIIa) has the 14α-configuration shown, then the ketone (VIII) will be 14β. A study of the basic strengths and ultraviolet spectra of the two enamines supports these assignments.

Protonation of the enamines (X) and (XI) will occur at C-11 to give the immonium ions (XV) and (XVI), respectively. Thus, the stronger base will be that compound in

* Chosen because its acid strength (pK_a 10·21) lies half-way between that of the dione (IV) (pK_a 4·5) and the tertiary alcohol corresponding to (XIV) (pK_a >15).

[8] C. B. C. Boyce and J. S. Whitehurst, *J.*, 1959, 2022.
[9] W. S. Johnson, R. G. Christiansen, and R. E. Ireland, *J. Amer. Chem. Soc.*, 1957, **79**, 1995.
[10] N. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Amer. Chem. Soc.*, 1955, **77**, 439.

which the C/D ring junction stabilises the Δ^8-structure over the $\Delta^{9,11}$. In the carbocyclic series, much is known about the effect of ring-junction stereochemistry on the relative stability of double bonds in similar positions, for example: cholestanone enolises to the 2-position while coprostanone enolises to position 4, reflecting the fact that cholest-2-ene is more stable than cholest-3-ene whereas the reverse is true in the coprostane series.[11] A more direct analogy is found in the two pairs of olefins represented by structures (XVII) and (XVIII). In the C/D-*cis*-compounds (XVII) [12] the more stable Δ^8-olefin was formed on acid isomerisation of the $\Delta^{9,11}$, whilst the C/D-*trans* pair (XVIII) have equal stability since acid isomerisation of either isomer gives an equimolar mixture.[4c] We therefore expect the Δ^8-structure to be favoured by the C/D-*cis* ring junction and the enamine (XI) to be the stronger base, as was found; the pK_a values of (XI) and (X) were 12·25 and 10·85, respectively. In contrast, the saturated base (VIIa) is surprisingly weak (pK_a, 6·64) and, although one expects a tertiary base to be weaker than the enamine derived from it, this difference is much larger than usual.[13] A further feature we find difficult to explain is that the dienamine (Va) is a weaker base (pK_a 9·30) than either of the monoenamines even though the conjugate acid (VIa) must be highly stabilised by conjugation.



Ultraviolet spectra of (A) dienamine (Va), (B) *trans*-enamine (X), and (C) *cis*-enamine (XI)

The u.v. spectra of the two enamines (X) and (XI) and the dienamine (Va) (Figure) reflect the base strengths. In cyclohexanone the three exist as the neutral molecules (X), (XI), and (Va), whereas all exist as the cations (XV), (XVI), and (VIa), respectively, in 0·1N-hydrochloric acid. In methanol, the dienamine exists as the neutral molecule, the C/D-*cis*-enamine as the conjugate acid (XVI), whilst the C/D-*trans*-enamine exists as a mixture of both (X) and (XV). We have no direct evidence about the stereochemistry at C-9 but favour the 9β-assignment since an inspection of models shows that only in this isomer does the 17a-carbonyl group suffer sufficient steric hindrance to account for its failure to reduce with borohydride.

By using the appropriate 2-substituted cyclopentane-[14] or cyclohexane-1,3-dione,[15] the synthesis has been modified to prepare 18-methyl- and -ethyl-substituted 8-aza-œstrones and -D-homo-œstrones. The physical constants of these compounds are given in Tables 1 and 2.

[11] L. F. Fieser and M. Fieser, " Steroids," Reinhold, New York, 1959, p. 276.
[12] J. E. Cole, W. S. Johnson, P. A. Robins, and J. Walker, *J.*, 1962, 244.
[13] R. Adams and J. E. Makan, *J. Amer. Chem. Soc.*, 1942, **64**, 2588.
[14] H. Smith, G. A. Hughes, G. H. Douglas, G. R. Wenat, G. C. Buzby, R. A. Edgren, J. Fisher, T. Foell, B. Gadsby, P. Hartley, P. Herbst, A. B. A. Jansen, K. Ledig, B. J. McLoughlin, J. McMenamin, T. W. Pattison, P. C. Phillips, R. Rees, J. Siddall, J. Siuda, L. L. Smith, J. Tokolics, and P. H. P. Watson, *J.*, 1964, 4472.
[15] H. Stetter and W. Dierichs, *Chem. Ber.*, 1952, **85**, 61.

TABLE 1

18-Substituted pentaenones

Compound	Yield (%)	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N
(Vb)	30	89—90°	77·0	7·1	4·6	$C_{19}H_{21}NO_2$	77·2	7·2	4·7
(Vc)	31	114—117	77·3	7·5	5·1	$C_{20}H_{23}NO_2$	77·6	7·5	4·5
(Vd)	45	125—129 (d.)	77·5	7·5	4·5	$C_{20}H_{23}NO_2$	77·6	7·5	4·5
(Ve)	38	85—90 (d.)	78·0	7·8	4·1	$C_{21}H_{25}NO_2$	78·0	7·8	4·3

TABLE 2

18-Substituted 8-azaœstrones

Compound	M. p.	Found (%) C	H	Formula	Required (%) C	H
(VIId)	129—130°	75·8	8·4	$C_{19}H_{25}NO_2$	76·2	8·4
(VIIe)	123—124	76·4	8·3	$C_{20}H_{27}NO_2$	76·6	8·7
(VIIf)	114—117	76·3	8·4	$C_{20}H_{27}NO_2$	76·6	8·7
(VIIg)	114—117	77·0	8·9	$C_{21}H_{29}NO_2$	77·0	8·9

Towards the completion of this work, Meltzer and his co-workers reported their synthesis of 8-azaœstrone.[16] However, although this route provides an excellent entry into the 14β-series, the preparation of compounds of the natural, 14α-series involves a separation of isomers. It would therefore be difficult to adapt this synthesis to the large-scale preparation of 8-aza-steroids which is necessary for full biological evaluation of the series.

EXPERIMENTAL

Light petroleum had b. p. 60—80° unless indicated otherwise; infrared spectra were measured on Nujol mulls; p*K* measurements were taken on 0·001M-aqueous solutions; n.m.r. spectra were run in deuterochloroform on a Varian A.60 spectrometer; thin-layer chromatography on alumina and/or silica was used to check the purity of all products.

N-(β-*Dimethylaminopropionyl*)-3-*methoxyphenethylamine* (II).—To 3-methoxyphenethylamine (30·2 g.) in benzene (200 c.c.) was added acryloyl chloride (18·2 g.) over 1 hr., the temperature being kept below 10° during the addition. Sodium hydroxide (105 c.c. of 2N) was then added to the solution which was stirred for a further hour. Separation of the benzene layer and evaporation *in vacuo* gave the amide (I) as a pale brown oil, which was dissolved in benzene (200 c.c.), containing 1·25 equivalents of dimethylamine, and the mixture was heated at 65° for 45 min. in a sealed tube. The residual oil, after evaporation of the benzene, was treated with an excess of oxalic acid in ethyl acetate to give the *ethylamine* (II) *oxalate*, m. p. 125—130° (61·2 g., 90%). An analytical sample, after crystallisation from ethyl acetate–methanol, had m. p. 132—134° (Found: C, 56·5; H, 7·2; N, 7·9. $C_{16}H_{24}N_2O_6$ requires C, 56·5; H, 7·1; N, 8·2%).

1-(β-*Dimethylaminoethyl*)-3,4-*dihydro*-6-*methoxyisoquinoline* (III).—The free base (II) (from 61·2 g. of oxalate) in ethanol-free chloroform (300 c.c.) was added to a finely divided suspension of phosphorus pentachloride (74·6 g.) in ethanol-free chloroform. The mixture was gently swirled until all the phosphorus pentachloride had dissolved then left overnight at room temperature, after which time a solid had separated. The residue, after evaporation of the chloroform, was dissolved in propan-2-ol and the *dihydroisoquinoline* (III) was precipitated, by addition of ether, as the crude hydrated dihydrochloride, m. p. 124—126° (46 g., 81%). An analytical sample purified by further precipitation had m. p. 114—116°, and proved to be the *dihydrochloride hemihydrate* [Found: C, 53·3; H, 7·3; Cl (ionic), 22·4. $C_{14}H_{20}N_2O,2HCl,\frac{1}{2}H_2O$ requires C, 53·5; H, 7·3; Cl, 22·6%].

(±)-3-*Methoxy*-8-*aza*-D-*homo*-*œstra*-1,3,5(10),9(11),14-*pentaen*-17a-*one* (Va).—The isoquinoline (III) free base was isolated from the dihydrochloride (31·4 g.) and added in benzene (100 c.c.) to a boiling suspension of 2-methylcyclohexane-1,3-dione (12·6 g.) in dry benzene (400 c.c.)

[16] R. I. Meltzer, D. M. Lustgarten, R. J. Stanaback, and R. E. Brown, *Tetrahedron Letters*, 1963, 1581.

and pyridine (16 c.c.) under nitrogen. The water liberated in the process was separated using a Dean and Stark trap. The solution was heated under reflux for 30 min., when the theoretical amount of water had been collected and evolution of dimethylamine had ceased, and evaporated *in vacuo*. Absolute ethanol (70 c.c.) was added to the residual brown syrup which then crystallised. The crystals were collected and washed well with ice-cold ethanol * to give the crude *dienamine* (Va), m. p. 117—118° (21·0 g., 71%), suitable for hydrogenation. The analytical sample, after two crystallisations from ethanol, had the same m. p. and showed $\lambda_{max.}$ (MeOH) 261 and 306 mμ (ε 24,200 and 4800), $\lambda_{max.}$ (0·1N-HCl) 245 and 358 mμ (ε 6300 and 20,000); $\nu_{max.}$ 1700 (C=O) and 1630 cm.$^{-1}$ (C=C's) (Found: C, 76·9; H, 6·9. $C_{19}H_{21}NO_2$ requires C, 77·2; H, 7·2%). The n.m.r. spectrum ($CDCl_3$) showed the C-11 and C-15 protons as a triplet and multiplet centred at τ 4·86 and 5·08, respectively.

(±)-3-*Methoxy*-8-*aza*-D-*homo*-*œstra*-1,3,5(10)-*trien*-17a-*one* (VIIa).—The above pentaenone (21 g.) in ethyl acetate (400 c.c.) was shaken with 5% palladium–carbon (6 g.) in an atmosphere of hydrogen until the uptake ceased. The product was isolated and crystallised from light petroleum (b. p. 80—100°) to give the *trienone* (15·1 g., 71%), m. p. 126—128°, $\lambda_{max.}$ (MeOH) 280 and 287 mμ (ε 2150 and 2060), $\nu_{max.}$ 1710 cm.$^{-1}$ (C=O) (Found: C, 75·9; H, 8·3; N, 4·9. $C_{19}H_{25}NO_2$ requires C, 76·2; H, 8·4; N, 4·7%). The mother-liquors from this crystallisation contain the isomeric ketone (VIII).

(±)-3-*Methoxy*-8-*aza*-D-*homo*-*œstra*-1,3,5(10)-*trien*-17aβ-*ol* (IX).—The foregoing ketone (VIIa) (2·10 g.), suspended in absolute ethanol (100 c.c.), was reduced with sodium borohydride (200 mg.) for 30 min. at room temperature. The excess of sodium borohydride was decomposed with acid, water was added, and the mixture was extracted with ethyl acetate, to give the *alcohol* (IX) (1·33 g.), m. p. 128—130° (Found: C, 75·5; H, 8·9. $C_{19}H_{27}NO_2$ requires C, 75·7; H, 9·0%).

(±)-3-*Methoxy*-8-*aza*-D-*homo*-9ξ-14β-*œstra*-1,3,5(10)-*trien*-17a-*one* (VIII).—The material (0·600 g.) from the mother-liquors after crystallisation of the ketone (VIIa) was reduced with sodium borohydride as above. The product was chromatographed on alumina. Elution with benzene–ethyl acetate (30 : 1) gave the *ketone* (VIII) (0·122 g.), m. p. 136—137° (from light petroleum) (Found: C, 76·0; H, 8·3; N, 4·7. $C_{19}H_{25}NO_2$ requires C, 76·2; H, 8·4; N, 4·7%). Elution with benzene–ethyl acetate (1 : 1) gave the 17a-alcohol (VII) (0·100 g.), m. p. 128—130°.

(±)-3-*Methoxy*-8-*azaœstra*-1,3,5(10),9(11),14-*pentaen*-17-*one* (V).—2-Methylcyclopentane-1,3-dione (11·2 g.), " Hidrite " (42 g.), and *p*-methoxyphenol (14 g.) were added successively to a suspension of sodium hydride (0·24 g. of 50%NaH in oil) in peroxide-free dioxan (450 c.c.). This suspension was stirred and refluxed under nitrogen while the isoquinoline (II) (from 31·4 g. of the dihydrochloride) was added dropwise during 30 min. The mixture was stirred and refluxed for a further 1·5 hr., then filtered, and the solvent evaporated from the filtrate at 10 mm. Ice-cold ethanol was added to the dark syrupy residue, which then crystallised to give the crude *dienamine* (V), m. p. 112—115° (16·3 g.). Crystallisation from light petroleum (b. p. 80—100°) gave the pure compound as colourless needles, m. p. 116—118°, $\lambda_{max.}$ (MeOH) 260 and 306 mμ (ε 27,000 and 5900), $\lambda_{max.}$ (0·1N-HCl) 246 and 367 mμ (ε 6700 and 22,000); $\nu_{max.}$ 1745 (C=O) and 1630 cm.$^{-1}$ (C=C) (Found: C, 76·6; H, 6·8; N, 4·9. $C_{18}H_{19}NO_2$ requires C, 76·8; H, 6·8; N, 5·0%). N.m.r. spectrum ($CDCl_3$) showed the C-11 and C-15 protons as triplets centred at τ 4·75 and 5·29, respectively.

(±)-3-*Methoxy*-8-*azaœstra*-1,3,5(10)-*trien*-17-*one*.—The dienamine (V) (8·4 g.) in ethyl acetate (200 c.c.) containing 5% palladium–charcoal (2 g.) was stirred in an atmosphere of hydrogen until the uptake ceased. The product crystallised from benzene–light petroleum to give the *methoxyazaœstrone* (VII), m. p. 169—172° (6·2 g.). The analytical sample after further crystallisation had m. p. 172—173° (Found: C, 76·1; H, 8·1. $C_{18}H_{23}NO_2$ requires C, 75·8; H, 8·1%).

(±)-3-*Hydroxy*-8-*aza*-D-*homo*-*œstra*-1,3,5(10)-*trien*-17a-*one* (VIIc).—A mixture of the methoxy-ketone (VIIa) (0·300 g.) and pyridine hydrochloride (6 g.) were heated under nitrogen at 210—215° for 40 min. Water was added to the cooled melt and the resulting solution was basified with sodium carbonate solution to precipitate the *phenol* (VIIc), m. p. 204—206° (decomp.) (from aqueous methanol) (Found: C, 75·2; H, 8·1. $C_{18}H_{23}NO_2$ requires: C, 75·8; H, 8·1%).

* Inadequate washing leads to catalyst poisoning at the next stage.

(±)-3-*Hydroxy*-8-*azaœstra*-1,3-5(10)-*trien*-17-*one* (VIIb).—Demethylation of the methyl-ether (VII) by fusing in pyridine hydrochloride as described previously for the D-homo-compound gave the 8-*azaœstrone* (VIIb), m. p. 235—241° (decomp.) (Found: C, 75·0; H, 7·7. $C_{17}H_{21}NO_2$ requires C, 75·2; H, 7·8%).

(±)-3-*Methoxy*-8-*aza*-D-*homo*-*œstra*-1,3,5(10),9(11)-*tetraen*-17a-*one* (X).—The ketone (VIIa) (0·300 g.) was added to a solution of mercuric acetate (0·638 g.) in acetic acid (6 c.c.) and the mixture was kept overnight at room temperature. The precipitated mercurous acetate was filtered off, water added, and the solution saturated with hydrogen sulphide to remove dissolved mercury salts. The mixture was filtered and the dissolved hydrogen sulphide was removed under reduced pressure. The resulting solution was basified with 2N-sodium hydroxide solution to precipitate the *enamine* (IX), m. p. 139—142° (from aqueous methanol), $\nu_{max.}$ 1710 (C=O) and 1630 cm.$^{-1}$ (C=C) (Found: C, 77·0; H, 7·9. $C_{19}H_{23}NO_2$ requires C, 76·7; H, 7·8%). N.m.r. ($CDCl_3$) showed the C-11 proton as a quartet centred at τ 4·70.

(±)-3-*Methoxy*-8-*aza*-D-*homo*-14β-*œstra*-1,3,5(10),9(11)-*tetraen*-17a-*one* (XI).—Mercuric acetate oxidation of the ketone (VIII) gave the *enamine* (XI), m. p. 113—116 (from aqueous methanol), $\nu_{max.}$ 1710 and 1630 cm.$^{-1}$ (Found: C, 76·3; H, 7·7%). N.m.r. showed the C-11 proton as a multiplet centred at τ 5·10.

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