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THE TOTAL SYNTHESIS OF 7(8→11α)*ABEO*ESTROGENS*

DELINEATION OF THE ROLE OF STERIC EFFECTS IN THE BIOCHEMISTRY OF STEROIDS

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Abstract—The ambiguity concerning the relative importance of the spatial configuration and the electronic characteristics in determining the biological activity of steroids is reviewed. A novel approach to the resolution of this ambiguity, involving determination of the activity of model compounds, is presented. The total synthesis of some of these compounds, which are based on the 7(8→11α)*abeo*estrane ring system, is described. The biological activity of this class of compounds is found to provide evidence of the importance of the spatial characteristics of estrogens.

INTRODUCTION

"IN STEROID chemistry there is some uncertainty as to whether the molecule's electronic characteristics or the spatial configuration of each feature of the ring system influence biological activity." This introduction to a recent article[2] probably understates the paucity of unambiguous information in this area of biochemistry, where the detailed mechanisms of the varied physiological activity of steroid hormones still remain speculative.[3] In this paper we will describe how the synthesis and activity of some model compounds have provided us with a different approach to the evaluation of the role of steric and electronic effects. In order to properly present the rationale of this approach it is first helpful to review briefly the current understanding of structure-activity relationships in steroids.

Previous work[4] on the biological activity of steroids as a function of their structure has led to the generalization that ease of access to the α and β faces of the molecule can significantly influence physiological activity. In fact, progestational and androgenic activity have been associated with approach to the β and α faces, respectively, of the steroidal ring system.[5] This hypothesis is of practical value; for example, the removal of the 19(β) Me group and the introduction of an axial alkyl substituent on the α-face (*eg* 17α) is an established procedure for enhancing progestational activity. The importance of steric effects is also suggested by recent work[6] which has shown that 2-thio-A-nor-androstanes are biologically active. That is, substitution of sulfur for the C=C group, an isosteric exchange, does not remove the androgenic activity despite the drastic electronic differences between the two groups. On the other hand, hormonal activity is also very dependent on the electronic properties of the (oxygen) functions at C-3, C-17, and other positions,[5] and may be modified by introduction of suitable electronegative substituents proximate to these functions. For example, halogenated steroids have been extensively

* Meaning cleavage of the 7,8 bond of the estrane skeleton and formation of a new 7-11α bond. The numbering of the intermediates is based on the steroid system.

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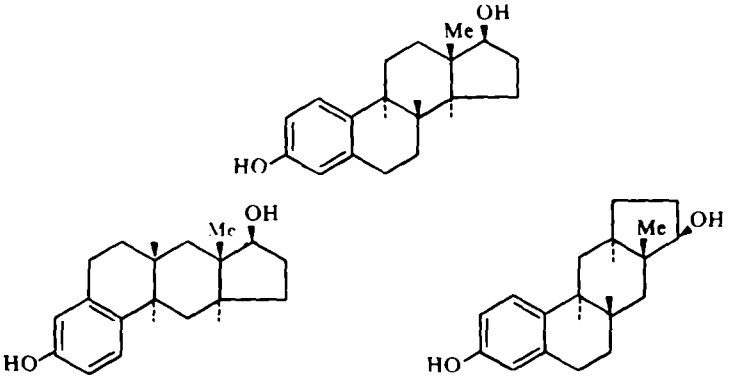
studied because of the enhanced hormonal activity of compounds such as the 9-halo-11-keto-progesterones.[7] Expansion or contraction of one or more rings in the skeleton generally effects an alteration in hormonal activity,[8] which may be attributed either to modification of the hydrocarbon template or to a change in the relative spatial orientation of the two or more functional groups in the molecule. The importance of relative spatial orientations is also implied by conformational analysis of the *anti-inflammatory* corticosteroids, which has shown[9] that the relative geometry of the functional groups in these molecules is the same as that in *inflammatory* agents such as histamine and serotonin.



d and *l*-3-hydroxy-7(8→11α)*abeo*estra-$\Delta^{1,3,5(10)}$-trien-17β-ol

FIG. 1. Stereochemical relationships between *d*-estradiol and *d*- and *l*-3-hydroxy-7(8→11α)*abeo*estra-$\Delta^{1,3,5(10)}$-trien-17β-ol

However, the important question of whether and why the 1:2-cyclo-pentenophenanthrene ring system of the steroid molecule is unique remains unanswered. Interaction of this tetracyclic hydrocarbon skeleton with the hydrophobic region of the receptor may well be very important. Alternatively, as noted in the preceding paragraph, the effect of defining the geometry of two or more functional groups of the steroid, relative to each other and to the receptor site, must be considered a definite possibility.

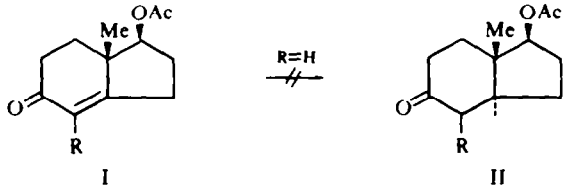
These questions may be probed by a comparison of the steroid with a molecule which retains the steroidal C-3 and C-17 functions *in exactly the same spatial relationship, yet possesses a different hydrocarbon skeleton connecting these functions.* The simplest molecule which possesses these requirements is based on the 2:3-cyclo-pentenophenanthrene ring system, which differs from the steroidal skeleton only in the displacement of rings B *or* D. This paper describes the synthesis and biological activity of two such derivates, *d*- and *l*-3-hydroxy-7(8→11α)*abeo*estra-$\Delta^{1,3,5(10)}$-trien-17β-ol.

In Fig 1 it can be seen that one antipode of this racemic pair differs from natural estradiol only in the placement of C-6 and C-7 (Ring B), while the other differs at C-15 and C-16 (Ring D). Apart from this, the stereochemistry of the functional groups and the ring systems of both antipodes is identical.

Synthetic procedures

5β-Acetoxy-10β-methyl-*trans*-2-decalone (III) was chosen as the starting material for the total synthesis. It may be obtained in substantial quantities by well documented

procedures[10] and its stereochemistry is established.[11, 12] While the envisaged synthesis (Figs 3–6) would be more efficiently accomplished starting with the analogous *trans*-hydrindanone II (Fig 2), the problem of effecting *trans* reduction[13] of the corresponding α,β-unsaturated ketone I negates the use of this compound. Velluz and others[13] have shown that *trans* reduction of the indanone I can be accomplished if the 4-position is first alkylated (*eg*, R = CH_2CH_2COOH): however, this approach is hardly applicable to the construction of the 2:3-cyclopentenonaphthalene skeleton.



I II

FIG 2

Annellation of the decalone III (Fig 3) with methyl vinyl ketone, using Stork's enamine procedure,[14] gave a 3:7 mixture of the α-β and β-γ unsaturated ketones V and VI in 50–60% yield, along with unchanged III and other minor products. The position of alkylation could be confidently assigned on the basis of earlier studies[15] of enolization dependent reactions of *trans*-β-decalones. The NMR spectrum of the pyrrolidine enamine IV also supported the proposed direction of alkylation. Only a small amount (~7%) of a tricyclic material, isomeric with V and VI, which may represent the alternate alkylation product VII, was formed in this reaction. As expected from the behavior of related systems,[14, 16] V and VI were labile in the presence of acids, both being transformed to an equilibrium mixture containing 57% of V and 43% of VI. This equilibrium, which involves the C-11 ring juncture, demonstrates that the C-11 hydrogen atom and the C-13 Me group of V must be in the stable syn configuration.

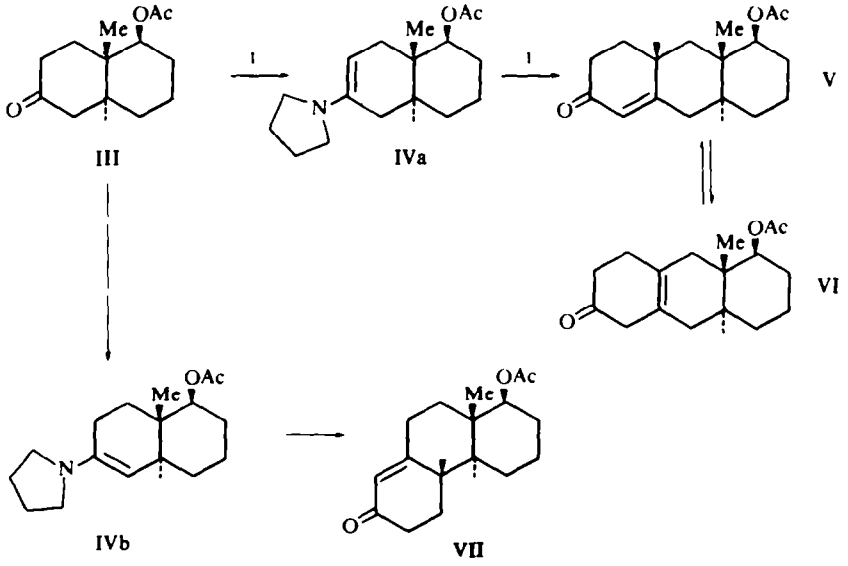


FIG 3

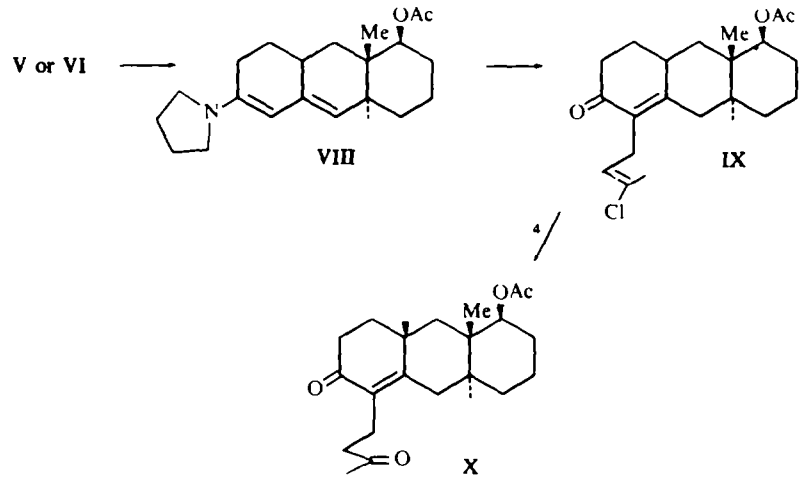


FIG 4

Both V and VI formed the same pyrrolidine enamine.* Alkylation of this enamine (VIII, Fig 4) with 1,3-dichlorobut-2-ene, followed by sulfuric acid hydrolysis, was used to attach the desired oxybutyl side chain at the 5-position of the hydroanthracene skeleton. The position of the side chain in IX and X was readily verified by NMR and UV spectroscopy.

Saturation of the double bond of the α-β unsaturated Ketone, to form the all-*trans* perhydroanthracene ring system, was first accomplished by selective ketalization of the side chain ketone group, followed by reduction with lithium in liquid ammonia (Fig 5).

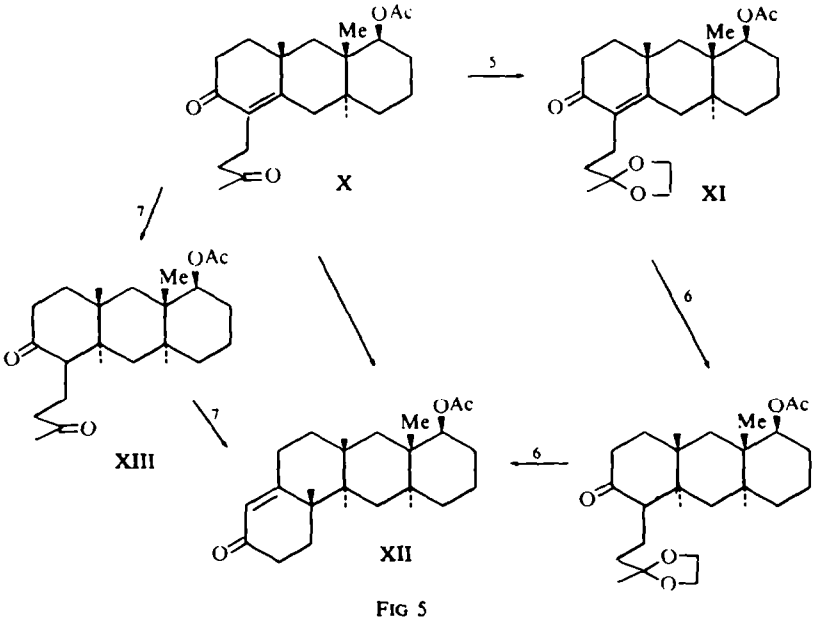


FIG 5

* In fact, a mixture of enamines may be formed, with the heteroannullar diene dominant;[17] because of its irrelevance to the synthetic outcome, this possibility was not explored.

Removal of the ketal group and aldol condensation to form XII were completed in a single step by treatment of the reduced product with hydrochloric acid in acetic acid. With regard to the stereochemistry of XII, the fact that the ketal XI was not isomerized by treatment with sodium methoxide demonstrated that the C-13 methyl group and the C-11 H-atom were still in the stable syn configuration[18] prior to reduction. With this knowledge, there is ample precedent[19] to believe that the Li/NH_3 reduction of an α,β-unsaturated ketone of the structure XI would produce the *trans* ring juncture. Furthermore, the transformations X→XI→XII are identical to the sequence used by Velluz *et al.*[20] to construct the all-*trans* natural steroidal ring system.

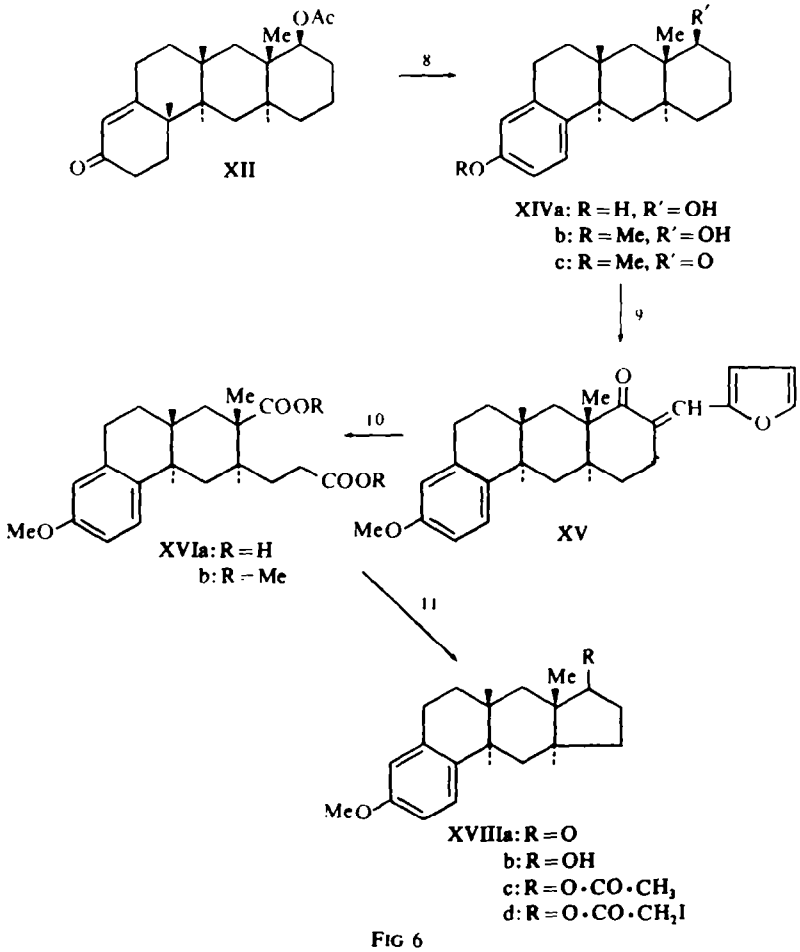


FIG 6

The stereochemistry of XII having been established, the transformation X→XII was carried out more conveniently by stereoselective catalytic hydrogenation, followed by aldol condensation of the intermediate XIII. Since no problems of stereochemistry were involved after this stage, the remaining transformations (Fig 6) could be simply accomplished by standard literature procedures. Aromatization of the A-ring was completed using N-bromosuccinimide.[21] The D-ring was then contracted by one of the standard methods developed by Johnson,[22] affording 3-methoxy-7(8→11α)*abeo*estra-

$\Delta^{1,3,5(10)}$-trien-17-one (XVIIIa) as the final product of the synthesis. An X-ray analysis,[23] carried out on the 17β-iodoacetate (XVIIId), confirmed the assigned structure.

The desired 7(8→11α)*abeo*estrane system having been obtained by a necessarily lengthy but stereochemically rigorous route, some attention was paid to an alternative and more efficient synthesis.* The basic scheme which was considered involves the Michael addition of 2-methylcyclopentane-1,3-dione (Ring D) to an α,β-unsaturated ketone which already contains the rudimentary components of rings A, "B" and C.† The synthesis of the α,β-unsaturated ketone (XX), which is the key intermediate in the

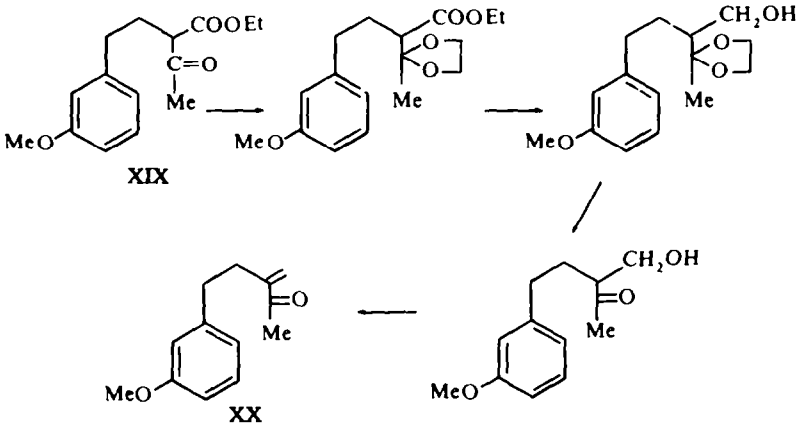


FIG 7

scheme, is shown in Fig 7. The base catalyzed Michael addition of 2-methylcyclopentane-1,3-dione to this olefinic ketone (Fig 8) was apparently hindered by the α-substituent on the double bond, but proceeded slowly in refluxing n-butanol. Aldol condensation of the adduct occurred in part under the same conditions, although refluxing in xylene with benzoic acid and triethylamine was used to complete this condensation. Ring closure of XXI to the tetracyclic ring system using polyphosphoric acid proceeded smoothly but was complicated by the formation of two isomeric products, shown to be interconvertible in the presence of acid and tentatively assigned the structures XXIV and XXV. This complication was avoided if the saturated keto group of XXI was first reduced with sodium borohydride, and the alcohol group acetylated prior to ring closure. Polyphosphoric acid treatment then afforded the desired heteroannular diene XXIII as the sole product. It appears that changing the hybridization at C-17 from sp^2 to sp^3 has a strong influence on which olefin is formed on cyclization, or alternatively it influences the rate of isomerization under these acidic conditions.

Catalytic reduction of the heteroannular diene XXIII gave a number of different products, depending on the catalyst and solvent used. Stepwise reduction could only be accomplished with difficulty using low catalyst to substrate ratios and dilute solutions.

* This only became feasible once an authentic sample of the 7(8→11α)-*abeo*estrane system was available.

† The synthetic scheme bears a formal resemblance to a previous steroid synthesis[24]. The most recent advances in steroid synthesis are not applicable to the 2,3-cyclopentenophenanthrene skeleton.

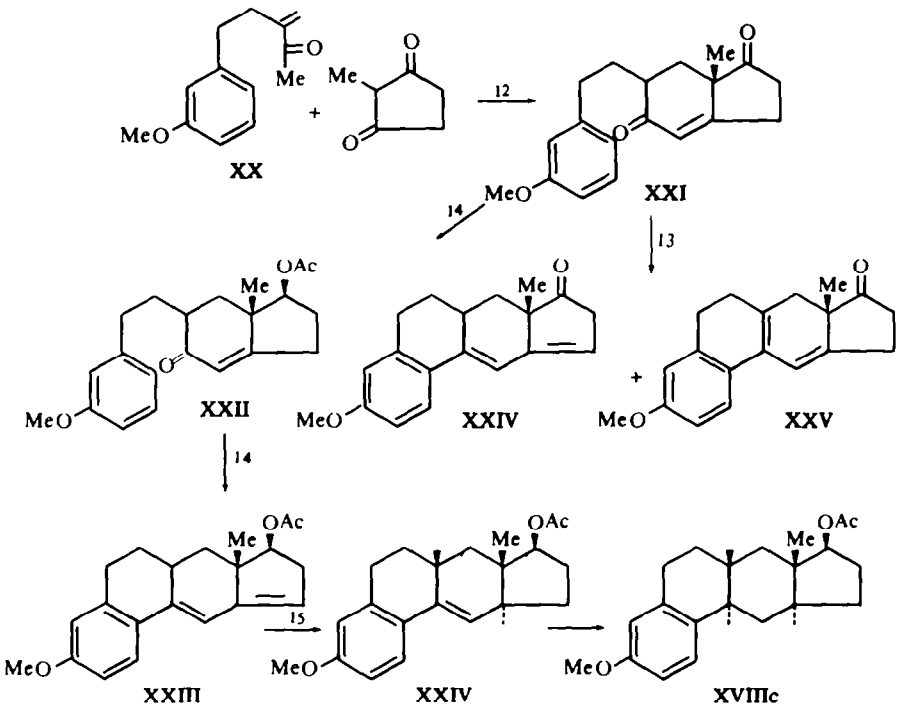


FIG 8

The optimum conditions involve the use of palladium on strontium carbonate in benzene, which caused both bonds to be reduced, and the all-*trans* product XVIIIc to be formed in 55% yield, along with two other isomers (5 and 40%). The all-*trans* product was readily separated by crystallization and proved identical in all respects with 3-methoxy-7(8→11α)*abeo*estra-$\Delta^{1,3,5(10)}$-trien-17β-ol acetate, obtained by the original synthetic procedure. Conversion to the 3,17β-diol was accomplished with pyridine hydrochloride. Birch reduction of XVIIIc gave 3-keto-7(8→11α)*abeo*estr-$\Delta^{5(10)}$-en-17β-ol.

The biological activity of the 7(8→11α)abeo*estrane system*

dl-3-Hydroxy-7(8→11α)*abeo*estra-$\Delta^{1,3,5(10)}$-trien-17β-ol and the corresponding 3-methoxy-17β-acetate (XVIIIc) are very weak estrogens, exhibiting between 2×10^{-2} and 10^{-3} of the activity* of estrone. 3-Keto-7(8→11α)*abeo*estr-$\Delta^{5(10)}$-en-17β-ol acetate is a moderate anti-estrogen.

The lack of estrogenic activity exhibited by the 7(8→11α)*abeo*estrane system is somewhat surprising, for it has long been thought that the structure-activity criteria for estrogenic molecular design are much less exacting than for other types of hormonal activity. For example, the derivatives of 1,2,5,6-dibenzanthracene and diphenylethane represent two of many classes of non-steroidal estrogens.[25] In the case of the 7(8→11α)*abeo*estrane skeleton, the ease of access to both the α and β faces, as well as the stereochemical relationship of the functional groups in rings A and D, is identical to that of estradiol, and cannot account for the substantially lower activity. We can only

* Determined by the uterine weight response in mice.

conclude that the edge-profile, as well as the faces of the molecule, must play a critical role in determining estrogenicity.

EXPERIMENTAL

IR spectra were measured with a Perkin–Elmer model 221 spectrophotometer. NMR spectra were obtained using a Varian A-60 spectrometer with samples dissolved in $CDCl_3$ and are reported downfield from TMS (internal standard). Signal intensities are reported to the nearest integer ratio. UV spectra were obtained using a Cary 14 spectrophotometer. TLC was run on plates coated with Silica Gel G, and developed with 5% phosphomolybdic acid in EtOH or 5% $CeSO_4$ in 10% H_2SO_4. M.ps are not corrected. The elemental analyses were performed by Micro-Tech Laboratories, Skokie, Illinois. Mass spectral analyses were obtained with an MS 9A mass spectrometer.

In the following experimental description, the reactions (Arabic numerals) and compounds (Roman numerals) are referenced with respect to the synthetic schemes depicted in Figs 3–9.

The reaction of III *with pyrrolidine and methyl vinyl ketone*

Reaction 1. A soln of III (32·6 g, 0·146 mole) in benzene (325 ml) was refluxed for several min, to remove water and dissolved O_2. Pyrrolidine (15·5 ml, 0·186 mole) was added to the cooled soln, which was then refluxed for 2·5 hr, removing water (2·8 ml) formed in the reaction by means of a Dean and Stark trap. GLC indicated less than 2% of unchanged III remained in the reaction mixture. The solvent was removed *in vacuo*, to leave the enamine as a yellow oil. The structure IVa, rather than structure IVb, was assigned to this product on the basis of its NMR spectrum which showed signals at 248 Hz (s, W$^+$ 7 Hz, 1H, CH_2—C$\underline{H}$=C), 54 Hz (s, 3H, CH_3—C), 122 Hz (s, 3H, O—CO—CH_3), 264–283 Hz (m, 1H, CH—OAc), 171–189 Hz (m, 4H, CH_2—C$\underline{H}_2$—N) in addition to the methylene envelope. Attempts to crystallize the enamine were without success.

The enamine was redissolved in dry benzene (300 ml) and methyl vinyl ketone (10·2 g, 0·146 mole) was added to the stirred soln. GLC and NMR analyses showed that no reaction had occurred at room temp after 24 hr. The soln was therefore refluxed for 20 hr, before adding 75 ml of 1 : 2 : 2 mixture of NaOAc, AcOH and water, and refluxing for a further 4 hr. The aqueous phase was separated and extracted with benzene (3 × 50 ml). The combined organic phases were washed with 10% HCl aq (3 × 100 ml), $NaHCO_3$ aq (2 × 30 ml) and water (2 × 30 ml). The solvent was evaporated *in vacuo* and the semi-solid residue was shown by GLC to contain 10% of unchanged III, 24% of VI, 55% of V, as well as 7% of VII and 4% of a less volatile unidentified product. Fractional crystallization from ether afforded 6·605 g (16·4%) of V, melting at 121·5–124° (capill), and containing less than 2% of VI. The mother liquors were concentrated and the residual oil was dissolved in MeOH (200 ml) and pyrrolidine (15ml). This soln was refluxed under N_2 for 1 hr and cooled to −5°, to give 16·50 g (34·3%) of VIII, melting at 96–111° (evac. capill.).

In a separate experiment, the crude reaction product was fractionally crystallized from ether, and then various fractions were eluted from a florisil column with an ether/benzene mixture to provide pure samples of V: m.p. 128·5–129° (Kofler); $\nu_{max}^{CS_2}$ 3030, 1740, 1670, 1245 cm^{-1}; λ_{max}^{MeOH}240 nm (ε 17,400); NMR: 63·5 Hz (s, 3H, C—CH_3), 123·5 Hz (s, 3H, OCOCH_3), 350 Hz (s, W$^+$ 4·5 Hz, 1H, CH—C=C$\underline{H}$), 260–282 Hz (m, 1H, CHOAc). (Found: C, 74·05; H, 8·87. Calcd. for $C_{17}H_{24}O_3$: C, 73·88; H, 8·75%). VI: m.p. 107–107·5° (Kofler); $\nu_{max}^{CS_2}$ 1745, 1725, 1250 cm^{-1}; λ_{max}^{MeOH}286 nm (ε 30); NMR: 51·5 Hz (s, 3H, C—CH_3), 124 Hz (s, 3H, O—CO—CH_3), 164·5 Hz (s, W$^+$ 5 Hz, 2H, CO—CH_2—C=C), 266–289 Hz (m, 1H, CH—OAc). (Found: C, 73·97; H, 8·82. Calcd for $C_{17}H_{24}O_3$: C, 73·88; H, 8·75%). VII: m.p. 138·5–139·5° (Kofler); $\nu_{max}^{CS_2}$ 3030, 1735, 1670, 1245 cm^{-1}; λ_{max}^{MeOH}240 nm (ε 16,300); NMR: 64 Hz (s, 3H, C—CH_3), 123 Hz (s, 3H, O—CO—CH_3), 351·5 Hz (s, W$^+$ 4 Hz, 1H, CH—C=C$\underline{H}$), 260–281 Hz (m, 1H, CHOAc). (Found: C, 72·95, 73·00; H, 8·41, 8·44; *m/e* 276·174. Calcd. for $C_{17}H_{24}O_3$: C, 73·88; H, 8·75%; *m/e* 276·172).

The isomeric ketones V and VI (100 mg each) were separately dissolved in ether (2 ml) containing anhydrous HCl [from ether (190 ml), 37% HCl aq (10 ml) and an excess of anhyd $MgSO_4$]. After standing at room temp for 20 hr, the acid was neutralized by addition of $CaCO_3$. GLC and NMR analyses indicated that both solns had been converted into an equilibrium mixture of 43% of VI and 57% of V. In both experiments the GLC peak corresponding to V showed a shoulder of longer retention; however, the concentration of this material was not sufficient to allow detection in the NMR spectrum.

When the ketone VII was subjected to the above conditions, no isomerization to V and VI was observed,

confirming the different skeletal arrangement of this compound. A small amount of isomerization (≤5%) to a new compound, presumably the β,γ-isomer corresponding to VII, was observed.

Pyrrolidine enamine of V

Reaction 2. Pyrrolidine (0·2 ml) was added to a refluxing soln of V (200 mg) in MeOH (2 ml) under N_2. After refluxing for 15 min, the mixture was allowed to cool to −5°, when 179 mg of the product separated as white crystals, yield 75·1%; m.p. 110–112° (evac. capill.); $\nu_{max}^{CHCl_3}$ 1725, 1590 and 1260 cm^{-1}; λ_{max}^{ether} 298 nm (ε 12,500); NMR: 52 Hz (s, 3H, C—CH_3), 123 Hz (s, 3H, O—CO—CH_3), 265–295 Hz (m, 2H, CHOAc and C=C<u>H</u>—CH), 259 Hz (s, W ½ 3 Hz, 1H, N—C=CH), in addition to the Me envelope. (Found: C, 76·37; H, 9·48; N, 4·46. Calcd. for $C_{21}H_{31}NO_2$: C, 76·55; H, 9·48; N, 4·25%).

Repetition of this experiment using the β,γ-isomer VI gave a 49·2% yield of the pyrrolidine enamine identical in all respects (mixture m.p., IR, UV, NMR) with the enamine from V.

Reaction of VIII *with* trans-1,3-*dichlorobut-2-ene*

Reaction 3. A soln of VIII (12·41 g, 0·03768 mole) in dry benzene (75 ml), dry DMF (100 ml) and pyrrolidine (1·2 ml) was refluxed under N_2 for 2 hr, removing any water in the reaction mixture by means of a Dean and Stark trap. The benzene and pyrrolidine were then evaporated *in vacuo*. KI (6·255 g, 0·03768 mole) was added to the soln, which was stirred and cooled to 0–5° before adding *trans*-1,3-dichlorobut-2-ene (6·717 g, 1·4 mole equiv) dropwise. The slurry was stirred overnight, allowing the temp to rise to 23°, before adding water (20 ml) and stirring for a further 4 hr. The reaction mixture was diluted with water (150 ml) and extracted with ether (4 × 100 ml). The combined ether extracts were washed with 10% HCl aq (2 × 100 ml), $NaHCO_3$ aq (25 ml) and water (2 × 20 ml) before drying over $MgSO_4$. After evaporation of the ether, IR spectral analysis indicated the residual oil was a mixture of both saturated and α·β-unsaturated ketones. This oil was dissolved in ether (150 ml) containing HCl [from ether (190 ml), 37% HCl aq (10 ml) and an excess of anhyd $MgSO_4$] and allowed to stand at room temp for 24 hr before washing with $NaHCO_3$ aq (2 × 40 ml) and water (2 × 20 ml). The soln was dried over $MgSO_4$ and then the solvent was evaporated, to afford 11·570 g of a brown viscous oil. A portion (2·040 g) of the crude product was purified by elution from a florisil column with a benzene/ether mixture, yielding 813 mg of the desired product IX as a clear viscous oil. Attempts to crystallize the oil were without success.

The NMR spectrum showed signals at 63 Hz (s, 3H, C—CH_3), 123·5 Hz (s, 6H, C=C—CH_3 and O—CO—CH_3), 192 Hz (d, J = 7 Hz, 1H, C=C—C<u>H</u>$_2$—CH=C), and 264–285 Hz (m, 1H, CH—OAc). $\nu_{max}^{CH_2}$ 1745, 1670, 1255 cm^{-1}; λ_{max}^{MeOH} 249 nm (ε 13,600). (Found: C, 68·87; H, 7·95; Cl, 9·53. Calcd. for $C_{21}H_{29}ClO_3$: C, 69·12; H, 8·01; Cl, 9·72%).

Hydrolysis of IX *with sulfuric acid*

Reaction 4. A soln of IX (490 mg) in AcOH (1 ml) was added to conc H_2SO_4 (5 ml) at −10°. The soln turned a green to brown color and gas evolution was noted. The soln was allowed to warm to room temp over a period of 20 min, and then poured into sat Na_2CO_3 aq (50 ml). The product was extracted with chloroform (3 × 50 ml) and the combined organic extracts were washed with water (50 ml) and dried over $MgSO_4$. The solvent was evaporated and the residue was crystallized from hexane (50 ml) to give 358 mg (76·9%) of the desired product X as white prisms melting at 156–157.5°. Crystallization from MeOH afforded an analytical sample, 157–158·5° (evac. capill.); λ_{max}^{MeOH} 250 nm (ε 14,800); $\nu_{max}^{CHCl_3}$ 1720, 1660, 1605 and 1260 cm^{-1}. The NMR spectrum showed signals at 63·5 Hz (s, 3H, C—CH_3), 124 Hz (s, 3H, O—CO—CH_3), 128·5 Hz (s, 3H, C—CO—CH_3), 151 Hz (s, 4H, =C—CH_2—CH_2—C=), 263–282 Hz (m, 1H, CHOAc), in addition to the methylene envelope. (Found: C, 72·57; H, 8·77. Calcd. for $C_{21}H_{30}O_4$: C, 72·80; H, 8·73%).

Preparation of the mono-ethylenedioxy derivative of X

Reaction 5. A soln of X (502 mg) and *p*-toluenesulfonic acid monohydrate (10 mg) in 2,2-ethylmethyl-1,3-dioxolane (20 ml) was allowed to stand at room temp for 30 hr. TLC showed only a trace amount of unchanged X, and the presence of a single product. The soln was diluted with benzene (75 ml), washed with $NaHCO_3$ aq (2 × 10 ml) and water (3 × 10 ml), and dried over $MgSO_4$. The solvent was evaporated, and the residual oil was eluted from florisil with a benzene/ether mixture, to afford 239 mg of the desired product XI as a clear gum.

The NMR spectrum showed signals at 63·5 Hz (s, 3H, C—CH_3), 81·5 Hz (s, 3H, —C(O—)(O—)—CH_3), 124 Hz (s, 3H, O—CO—CH_3), 238 Hz, (s, 4H, O—CH_2—CH_2—O), 263–283 Hz (m, 1H, CHOAc), in addition

to the methylene envelope; $\nu_{max}^{CS_2}$ 1740, 1665, 1245, 1060 cm^{-1}; λ_{max}^{MeOH} 250 nm (12,700). (Found: C, 70·90; H, 8·58. Calcd. for $C_{23}H_{34}O_5$: C, 70·74; H, 8·78%).

Sodium methoxide treatment of XI. To a soln of Na metal (9 mg) in MeOH (10 ml) was added 40 mg of XI, and the mixture was refluxed overnight under N_2. The solvent was evaporated to leave a yellow gum, the IR spectrum of which showed absorption in the CO region at 1665 cm^{-1} (CS_2) only. The gum was redissolved in pyridine (2 ml) and Ac_2O (0·6 ml) and allowed to stand overnight. The soln was diluted with water (25 ml) and extracted with chloroform (4 × 20 ml). The combined organic extracts were washed with water (2 × 20 ml), dried over $MgSO_4$, and the solvent was evaporated. After removing residual solvent at 80° (0·1 mm) for 4·5 hr, the residual gum (41 mg) was shown by TLC and IR spectral analysis to be unchanged XI.

Reduction of XI *with lithium in ammonia*

Reaction 6. A soln of XI (80 mg) in dry THF (10 ml) was added to a stirred soln of Li metal (50 mg) in redistilled liquid ammonia. After 5 min, the excess of Li was destroyed with NH_4Cl and the ammonia was allowed to evaporate. The residue was diluted with benzene (75 ml) and washed with water (5 × 10 ml) before drying over $MgSO_4$. The solvent was evaporated, to leave 78 mg of a clear gum. TLC showed this reduction product was of greater than 90% purity. The IR spectrum showed absorption at 3620 cm^{-1} (OH), 1715 cm^{-1} (C=O) and 1060 cm^{-1}; there was no absorption at 1250 cm^{-1} (OAc).

The reduction product was dissolved in glacial AcOH (5 ml) containing 0·25 ml 37·5% HCl. After 6 hr, the soln was diluted with NaOH aq (50 ml) and extracted with benzene (4 × 50 ml). The combined benzene extracts were washed with water (3 × 25 ml) before drying over $MgSO_4$. The solvent was evaporated and the residue (72 mg) was eluted from a Florisil column with a benzene/ether mixture to afford 46 mg (68%) of a gum, which TLC indicated was homogeneous. Crystallization from ether (10 ml) gave 34 mg of crystals, melting at 184–185·5° (evac. capill.), identical (mixture m.p., IR, NMR, TLC) with the product obtained from acid catalyzed cyclization of XIII.

Catalytic hydrogenation of X

Reaction 7. A soln of X (200 mg) in EtOH containing 10% triethylamine (9 ml) was added to prehydrogenated 10% PdC in the same solvent (3 ml). The mixture was stirred under H_2 atmosphere until gas uptake had ceased. The reaction time was 40 min, and a total of 15·7 ml H_2 was consumed. (1 mole equiv = 14·1 ml). The catalyst was filtered off, and the filtrate was evaporated to afford a quantitative yield of XIII as a clear gum. While TLC indicated the product was virtually homogeneous, crystallization was not successful.

The NMR spectrum showed signals at 58 Hz (s, 3H, C—CH_3), 122 Hz (s, 3H, O—CO—CH_3), 127 Hz (s, 3H, c—CO—CH_3), 360–380 Hz (m, 1H, CHOAc); $\nu_{max}^{CS_2}$ 1735, 1715 (sh), 1710, 1245 cm^{-1}. (Found: C, 72·11; H, 9·24. Calcd. for $C_{21}H_{32}O_4$: C, 72·38; H, 9·26%). A soln of XIII (110 mg) in AcOH (5 ml) containing 0·25 ml 35% HCl aq was allowed to stand at room temp for 7 hr. The soln was diluted with water (25 ml) and the ppt was filtered off and dried *in vacuo*. Crystallization from ether (10 ml) at 0° afforded 70·3 mg (67%) of XII as white prisms, m.p. 184–184·5° (evac. capill.). An analytical sample melted at 185·5–186·5°. The NMR spectrum showed signals at 57·5 Hz (s, 3H, C—CH_3), 123 Hz (s, 3H, O—CO—CH_3), 262–282 Hz (m, 1H, CHOAc), 352 Hz (s, W ½ 3·5 Hz, 1H, CO—C<u>H</u>=C—CH); $\nu_{max}^{CS_2}$ 3030, 1740, 1675, 1250 cm^{-1}. λ_{max}^{MeOH} 242 nm (14,600). (Found: C, 76·27; H, 9·16. Calcd. for $C_{21}H_{30}O_3$: C, 76·32; H, 9·15%).

Aromatization of XII

Reaction 8. A mixture of XII (589 mg, 1·782 mmole) and N-bromosuccinimide (589 mg, 3·309 mmole) was dissolved in refluxing CCl_4 (150 ml) under N_2. The soln was irradiated using a sun lamp until a yellow color developed (5 min). After refluxing for 1·5 hr, the soln was allowed to cool and filtered to remove succinimide. The filtrate was washed with $NaHCO_3$ aq (2 × 10 ml), dried over $MgSO_4$ and then evaporated. The residue was redissolved in EtOH (80 ml) and added to prereduced PtO_2 (60 mg) in EtOH (10 ml) under H_2. After uptake of H_2 had ceased (10·9 ml, 2·5 hr), the catalyst was filtered off and the solvent evaporated. The solid residue was recrystallized from benzene to afford 171 mg (29·2%) of the desired product XIVa as off-white plates, m.p. 227–230° (Kofler). The mother liquors were concentrated, eluted from silica gel (16 g) with benzene containing 2·5% ether, and crystallized from benzene, to afford a further 196 mg (33·5%) of XIVa, m.p. 225·5–229·5° (Kofler).

The NMR spectrum (perdeuteriodimethylsulfoxide) showed signals at 53·5 Hz (s, 3H, C—CH_3), 120 Hz (s, 3H, O—CO—CH_3), 260–278 Hz (m, 1H, C<u>H</u>—OAc) and 385–443 Hz (m, 3H, aryl-H); ν_{max}^{KBr} 3425,

3025, 1730 sh (non-bonded OAc), 1705 (bonded OAc), 1620, 1280 (bonded OAc), 1225 (non-bonded OAc); λ_{max}^{EtOH} 281 nm (2,350), 288 nm (shoulder, 2130). (Found: C, 76·61; H, 8·70. Calcd. for $C_{21}H_{28}O_3$: C, 76·79; H, 8·59%).

Methyl ether of XIVa. A slurry of XIVa (1·0 g) in MeOH (10 ml) was treated with approx 5 ml 36% methanolic KOH. The resulting soln was cooled to 8°, and $MeSO_4$ (10 ml) and 20 ml 36% methanolic KOH was added simultaneously from separate addition funnels over a period of 1·5 hr, maintaining the temp at 5–12°. The mixture was then held at room temp for 16 hr before diluting with iced-water and extracting with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and evaporated. The residue (0·9 g) in 36% methanolic KOH (25 ml) was refluxed for 30 min, diluted with water (150 ml), and extracted with CH_2Cl_2. After drying over $MgSO_4$, the combined organic extracts were evaporated, and the residue was triturated with an ether–light petroleum, giving 0·50 g of the desired XIVb as a white solid, m.p. 138–140° (capill.). Recrystallization from MeOH afforded an anlytical sample, m.p. 139–140° (capill.); ν_{max}^{KBr} 3630 (OH), 2845 (OMe), 1610, 1500 (C=C) cm^{-1}; λ_{max} 278 nm (4070), 286·5 nm (3750). The NMR spectrum showed signals at 50 Hz (s, 3H, C—CH_3), 180–210 Hz (m, 1H, C<u>H</u>—OH), 225 Hz (s, 3H, OCH_3) and 390–440 Hz (m, 3H, aryl-<u>H</u>), in addition to the methylene envelope. (Found: C, 79·86; H, 9·38. Calcd. for $C_{20}H_{28}O_2$: C, 79·95; H, 9·39%).

Jones oxidation of XIVb. A soln of XIVb (130 mg) in acetone (7 ml) was treated with 0·11 ml Jones reagent [chromium trioxide (26·72 g), H_2SO_4 (23·0 ml), diluted with water to 100 ml] at room temp. Excess of the oxidant was destroyed with MeOH, and the mixture was filtered and concentrated *in vacuo*. The residual solid (130 mg) was crystallized from MeOH to give 80 mg of analytically pure XIVc as white crystals, m.p. 154–155° (capill.); $\nu_{max}^{CCl_4}$ 2845 (OMe), 1710 (C=O), 1610, 1500 (C=C) cm^{-1}. The NMR spectrum showed signals at 68 Hz (s, 3H, C—CH_3), 227 Hz (s, 3H, O—CH_3) and 290–440 Hz (m, 3H, aryl-<u>H</u>), in addition to the methylene envelope. (Found: C, 80·46; H, 8·90. Calcd. for $C_{20}H_{26}O_2$: C, 80·49; H, 8·78%).

Preparation of furfurylidene derivative XV

Reaction 9. The ketone (45 mg) in warm MeOH (10 ml) was treated with 33% NaOH aq (1 ml) and then with redistilled furfural (0·12 ml). The partially heterogeneous mixture was kept in the dark at room temp under N_2 for 18 hr. The mixture was cooled to ~0° before filtering, to give 60 mg of the desired product as an off-white powder, m.p. 158–160° (capill.). An analytical sample, crystallized from EtOH, melted at 158–159° (capill.); $\nu_{max}^{CCl_4}$ 1680 cm^{-1}; λ_{max}^{MeOH} 321 nm (24,400). The NMR spectrum showed signals at 64 Hz (s, 3H, C—CH_3), 227 Hz (s, 3H, OCH_3) and 386–456 (m, 3H, aryl-<u>H</u>), in addition to the methylene envelope. (Found: C, 79·63; H, 7·56. Calcd. for $C_{25}H_{28}O_3$: C, 79·75; H, 7·50%).

Oxidative cleavage of the furfurylidene derivative XV

Reaction 10. A soln of XV (350 mg) in EtOH (300 ml) containing NaOEt (from 0·2 g atom of Na) was treated with 30% H_2O_2 aq (40 ml). The resulting heterogeneous mixture was rapidly stirred in a capped Waring blender, the heat of stirring maintaining a temp of ~50°. After 28 hr, the still heterogeneous mixture was concentrated using a rotary evaporator, and then diluted with water (150 ml). The aqueous soln was extracted with ether to remove neutral materials, before acidifying with HCl and extracting with $CHCl_3$. The combined $CHCl_3$ extracts were washed with $FeSO_4$ aq, and water, and then dried over $MgSO_4$. After removing the solvent *in vacuo*, the residual crude XVIa was esterified with diazomethane in ether. Elution of the product from silica gel with $CHCl_3$ gave 280 mg (80·4%) of XVIb as an oil, $\nu_{max}^{CCl_4}$ 1730 cm^{-1}. The NMR spectrum showed signals at 68 Hz (s, 3H, C—CH_3), 221·5, 223 and 226 Hz (s, 3H, O—CH_3) and 400–430 Hz (m, 3H, aryl-<u>H</u>), in addition to the methylene envelope. (Found: *m/e*, 374·2086. Calcd. *m/e* for $C_{22}H_{30}O_5$: 374·2093).

Dieckmann condensation of XVIa

Reaction 11. K (0·3 g) was dissolved in dry t-BuOH (30 ml) under N_2. The excess of t-BuOH was evaporated *in vacuo*; dry benzene (30 ml) was added to the residue. The benzene was distilled in order to azeotropically remove the remaining t-BuOH. This process was twice repeated. The ester XVIa (226 mg) in dry benzene (60 ml) was added to the residual t-BuOK, and the mixture was stirred and refluxed for 4 hr, and then stirred overnight at room temp. The mixture was extracted with 5% H_2SO_4 aq, and water, and concentrated. A soln of the residual solid in AcOH (20 ml), 37% HCl aq (10 ml) and water (2 ml) was refluxed for 90 min, before evaporating the majority of the solvent. The residue was diluted with water and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with $NaHCO_3$ and water and dried over

$MgSO_4$. The soln was concentrated, and the residue (163 mg) was eluted from silica gel with $CHCl_3$ to give 124 mg of XVIIIa which after recrystallization from MeOH melted at 161–163° (Kofler); $\nu_{max}^{CCl_4}$ 1750 cm^{-1}. The NMR spectrum showed signals at 54 Hz (s, 3H, C—CH_3), 227 Hz (s, 3H, O—CH_3), and 390–445 (m, 3H, aryl-H), in addition to the methylene envelope. (Found: *m/e* 284·1781. Calcd. *m/e* for $C_{19}H_{24}O_2$: 284·1776).

Conversion of XVIIIa *to* 17β-*acetate and iodoacetate.* $NaBH_4$ (40 mg) in EtOH (5 ml) was added to XVIIIa (125 mg) in EtOH (15 ml). The mixture was stirred at room temp overnight, when TLC indicated the absence of starting material. The solvent was evaporated, and the residue treated with 5% HCl aq, and extracted with ether. The combined ether extracts were washed with water and dried over $MgSO_4$. The solvent was evaporated, and the residual XVIIIb was treated with pyridine (10 ml) and chloroacetic anhydride (2 g). After 6 hr at room temp, the mixture was diluted with 15% HCl aq (60 ml) and extracted with ether (3 × 50 ml). The combined ether extracts were washed with $NaHCO_3$ (2 × 25 ml), and dried over $MgSO_4$. The solvent was evaporated, and the residual chloroacetate of XVIIIb (pure by TLC and GLC analysis) in acetone (15 ml) was treated with NaI (1·0 g). The soln was stirred overnight at room temp, and then at reflux for 2 hr. The acetone was evaporated, and the residue treated with water (20 ml) and extracted with $CHCl_3$ (3 × 30 ml). The combined organic extracts were washed with $Na_2S_2O_3$ aq and water, dried over $MgSO_4$ and concentrated. The residual XVIIId (100 mg) crystallized from ether, m.p. 140–142° (Kofler); $\nu_{max}^{CS_2}$ 1735,1275 cm^{-1}. The NMR spectrum showed signals at 52 Hz (s, 3H, C—CH_3); 221·5 Hz (s, 2H, CO—CH_2—I), 226 Hz (s, 3H, OCH_3), 275–295 Hz (m, 1H, CHO—$COCH_2I$) and 395–445 Hz (m, 3H, aryl-H), in addition to the methylene envelope. (Found: *m/e* 454·1009. Calcd. *m/e* for $C_{21}H_{27}IO_3$: 454·1007).

The aqueous acidic portion from the preparation of the chloroacetate was saturated with salt and extracted with $CHCl_3$. The $CHCl_3$ extracts were concentrated, and the residue was heated on a steam bath with EtOH (9 ml), KOH (0·5 g), and water (0·5 g) for 1 hr. The base was neutralized with HCl aq, and the majority of the solvent was evaporated *in vacuo*. The residual slurry was extracted with ether, and the ether extracts were dried and concentrated to yield 70 mg of XVIIIb. The crude alcohol was acetylated with pyridine (5 ml) and Ac_2O (2 ml), allowing the mixture to stand overnight at room temp. Unchanged reagents were evaporated *in vacuo*, and the residue was eluted from alumina (Activity I, 7g), to give 50 mg of the pure XVIIIc, which crystallized from ether, m.p. 125–125° (Kofler), $\nu_{max}^{CS_2}$ 1740, 1240 cm^{-1}. The NMR spectrum showed signals at 50 Hz (s, 3H, C—CH_3), 123 Hz (s, 3H, —CO—CH_3), 226 Hz (s, 3H, OCH_3), 270–295 Hz (m, 1H, CH—OAc), 395–445 Hz (m, 3H, aryl-H), in addition to the methylene envelope. (Found: *m/e* 328·2043. Calcd. *m/e* for $C_{21}H_{28}O_3$: 328·2038).

Saponification of XVIIId with ethanolic KOH aq, and acetylation of the resulting crude XVIIIb with Ac_2O in pyridine gave a quantitative yield of XVIIIc.

3-(m-*Methoxyphenethyl*)*but*-3-*en*-2-*one* (XX). The K salt of ethyl acetoacetate was alkylated with *m*-methoxyphenethyl iodide by the procedure of Robinson,[29] to give XIX in 81% yield.

A soln of XIX (91·0 g, 0·345 mole), ethylene glycol (27·2 g, 0·438 mole), and *p*-toluenesulfonic acid (0·8 g) in toluene (400 ml) was refluxed, collecting water in a Dean and Stark trap. After water evolution had ceased (5 hr), the cooled mixture was washed with $NaHCO_3$ aq, water, and dried over $MgSO_4$. The crude ketal (100·5 g, 94·5%) showed a single IR CO stretching band at 1740 cm^{-1}. The NMR spectrum exhibited signals at 83 Hz (s, 3H, C—CO—CH_3), 76 Hz (t, $J = 7$ Hz, 3H, O—CH_2—CH_3), 225 Hz (s, 3H, OCH_3), 251 Hz (q, $J = 7$ Hz, 2H, O—CH_2—CH_3), and multiplets attributable to aromatic, aliphatic and O—CH_2—CH_2—O groupings. The latter was a partially split singlet, the adjacent asymmetric center creating an A_2B_2 pattern. Although prolonged heat caused decomposition, a small sample (<5 g) distilled at 130–132° (0·07 mm). (Found: *m/e* 308·1622. Calcd. *m/e* for $C_{17}H_{24}O_5$: 308·1624).

The crude ketal of XIX (94·0 g, 0·305 mole) in dry THF (150 ml) was added dropwise to a stirred slurry of LAH (12·9 g, 0·340 mole) in THF (500 ml), and the mixture was then heated at reflux for 18 hr. Water was added to the mixture until the Al salts separated from the organic phase as a coagulated solid. Filtration through celite, washing the ppt thoroughly with $CHCl_3$, and concentration gave 71·0 g (87%) of the crude hydroxyketal. The IR spectrum (film) showed maxima at 3450 (OH), 2840 (OCH_3), 1605 and 1495 (Ar) cm^{-1}, but no absorption in the CO stretching region. (Found: *m/e* 266·1518. Calcd. *m/e* for $C_{15}H_{22}O_4$: 266·1518)

The hydroxyketal (71·0 g) was dissolved in 90% MeOH aq (710 ml) containing 37·5% HCl (7·1 ml). After 1 hr at room temp, TLC indicated the reaction was complete. The solvent was evaporated *in vacuo*, and the residue extracted with CH_2Cl_2. After drying and concentrating, the crude β-hydroxyketone (59 g, 100%) remained as an oil; ν_{max}^{film} 3445, 1705 cm^{-1}. The NMR spectrum showed signals at 129 Hz (s, 3H,

C—CO—CH_3), 224 Hz (d, J=5 Hz, 2H, CH—CH_2—OH) and 226 Hz (s, 3H, OCH_3), as well as multiplets associated with the remaining aromatic and aliphatic protons. (Found: *m/e* 222·1252. Calcd. *m/e* for $C_{13}H_{18}O_3$: 222·1256).

Small scale experiments (~1 g) indicated the β-hydroxyketone was not dehydrated to XX with iodine, but could be converted to XX in refluxing pyridine. Duplication on a large scale was unsuccessful although conversion to XX occurred during distillation.

A soln of the β-hydroxyketone (59 g) in pyridine (450 ml) was refluxed for 15 hr under N_2. TLC indicated minimum conversion to XX. Concentration and distillation through a 12 mm Vigreaux column at 0·15 mm afforded 25·4 g (46·5%) of XX boiling at 113–116°. The IR spectrum (film) showed absorption at 1675 (C=C—C=O), 1600 and 1485 (Ar) cm^{-1}, and no maxima attributable to OH or saturated CO groups. The NMR spectrum showed signals at 136 Hz (s, 3H, C—CO—CH_3), 158 Hz (s, 4H, CO—CH_2—CH_2—C=C), 224 Hz (s, 3H, OCH_3), 343 Hz (s, 1H, C=C—H), 358 Hz (s, 1H, C=C—H), 295–445 Hz (m, 4H, aryl-H). (Found: C, 76·42; H, 7·81; *m/e* 204·1144. Calcd. for $C_{13}H_{16}O_2$: C, 76·44; H, 7·90%; *m/e*: 204·1150).

p-Toluenesulfonic acid treatment of the β-hydroxyketone in benzene did not lead to XX but to a single product identified as 1-acetyl-6-methoxy-tetralin on the basis of NMR, IR, and mass spectral analyses.

Michael addition of 2-methylcyclopentan-1,3-dione to XX

Reaction 12. The ketone XX (6·12 g), 2-methylcyclopentane-1,3-dione (5·04 g, 1·5 mole equiv) and a half of a pellet of KOH in n-BuOH (10 ml) were stirred and refluxed under N_2 for 40 hr when TLC showed the virtual absence of starting material. The mixture was diluted with benzene and filtered to remove unchanged dione. The filtrate was washed with $NaHCO_3$ aq and the washings back-washed with benzene. The combined organic phase was washed with 10% HCl aq, water, and then dried and concentrated *in vacuo*. The residual oil in xylene (50 ml) containing benzoic acid (1·9 g) and triethylamine (1·85 ml), was refluxed under N_2 for 4 days, collecting water evolved in a Dean and Stark trap. The mixture was then diluted with benzene and washed with 10% HCl aq, $NaHCO_3$ aq and water. After drying and concentrating, the residual oil was crystallized from ether (50 ml) to give 2·0 g (22%) of XXI as off-white crystals, m.p. 125–127·5° (capill.). Recrystallization from MeOH raised the m.p. to 128·5–130°; $\nu_{max}^{CHCl_3}$ 2840, 1745, 1665, 1600, 1485 cm^{-1}; λ_{max}^{EtOH} 279 (2310), 272 (2430), 235 sh (11000), 221 (15900) nm. The NMR spectrum showed signals at 76 Hz (s, 3H, C—CH_3), 227 Hz (s, 3H, OCH_3), 358 Hz (s, W½ 3·5 Hz, 1H, C=CH—C=O), and 395–440 Hz (m, 4H, aryl-H), in addition to the methylene envelope. (Found: C, 76·33; H, 7·47; *m/e* 298. Calcd. for $C_{12}H_{22}O_3$: C, 76·48; H, 7·43%; *m/e* 298).

Cyclization of XXI *with polyphosphoric acid*

Reaction 13. A soln of XXI (500 mg) in benzene (20 ml) was added to P_2O_5 (1·2 g) and H_3PO_4 (s.g. 1·7, 1·75 ml) and the mixture was stirred and refluxed under N_2 for 30 min. The mixture was washed with water, $NaHCO_3$, dried over $MgSO_4$, and then concentrated. Although TLC showed only one spot, the NMR spectrum indicated two components (ratio 2:1) with angular Me groups resonating at 69·5 and 63·5 Hz respectively. Crystallization from MeOH (20 ml) at 0° afforded 145 mg of the predominant component XXIV, m.p. 104–108°, containing approximately 20% of the minor component XXV; ν_{max} 1750 cm^{-1}; λ_{max}^{EtOH} 302, 296 (inf), 312 (inf) nm. The NMR spectrum showed signals attributable to XXIV at 69·5 Hz (s, C—CH_3), 227·5 Hz (s, OCH_3), 347 Hz (s, W½ 7 Hz, C=CH—CH_2), 401 Hz (s, C=CH—C=C), in addition to the aromatic and methylenic protons. (Found: C, 81·24; H, 7·16. Calcd. for $C_{19}H_{20}O_2$: C, 81·39; H, 7·19%).

A mixture of XXV (1 part) and XXIV (2 parts), when dissolved in $CDCl_3$ saturated with HCl, was converted within 15 min to an equilibrium mixture of XXV (1 part) and XXIV (1 part), as judged by NMR. This interconversion, and the presence of only a single olefinic signal at 380 Hz (W½ 4 cps) in the NMR spectrum (apart from those attributed to XXIV) is the only evidence for the structure assigned to XXV.

Cyclization of XXII *with polyphosphoric acid*

Reaction 14. $NaBH_4$ (0·45 g, 11·9 mmole) in EtOH (100 ml) was added dropwise to a stirred soln of XXII (3·55 g, 11·9 mmole) in THF (50 ml). After TLC indicated the mixture was complete (~2 hr), excess of $NaBH_4$ was destroyed with AcOH. The mixture was then treated with $NaHCO_3$ (c 5 g) and water (20 ml) and concentrated *in vacuo*. The product was extracted with benzene and then $CHCl_3$, dried over $MgSO_4$, and concentrated to leave 3·829 g of the 17β-alcohol as a viscous non-crystallizable oil, essentially pure as judged by TLC; ν_{max}^{film} 3430, 1660. The NMR spectrum showed signals at 66·5 Hz (s, 3H, C—CH_3), 221 Hz

(s, 3H, OCH_3), 250 Hz (m, 1H, C<u>H</u>—OH), 347 Hz (s, 1H, C<u>H</u>=C—C=O) as well as those attributable to aromatic and methylenic protons. (Found: *m/e* 300·1723. Calcd. *m/e* for $C_{19}H_{24}O_3$: 300·1725).

The crude product in pyridine (5 ml) was treated with Ac_2O (5 ml) and, after standing overnight, the volatiles were evaporated *in vacuo*. TLC of the residual oil (4·04 g) showed that acetylation was complete; ν_{max}^{film} 1740, 1670 cm^{-1}. The NMR spectrum showed signals at 64 Hz (s, 3H, C—CH_3), 121 Hz (s, 3H, O—CO—CH_3), 221 Hz (s, 3H, OCH_3), 284 Hz (t, $J=8$ Hz, 1H, C<u>H</u>OAc), 343 Hz (s, 1H, C<u>H</u>=C), in addition to multiplets attributable to the remaining aromatic and aliphatic protons. (Found: *m/e* 342·184. Calcd. *m/e* for $C_{21}H_{26}O_4$: 342·183).

A soln of this acetate (2·019 g) in benzene (12 ml) was added to a stirred mixture of P_2O_5 (4·62 g) and H_3PO_4 (s.g. 1·7, 6·5 ml), and then refluxed under N_2 for 30 min. The mixture was diluted with more benzene, and washed with $NaHCO_3$ until neutral, before drying and concentrating *in vacuo*. Elution from silica gel with $CHCl_3$, followed by crystallization from acetone, afforded 1·495 g of XXIII, m.p. 131–133° (capill.), yield (based on XXII) 38%; $\nu_{max}^{CHCl_3}$ 1730, 1250 cm^{-1} (OAc), 1605, 1495 cm^{-1} (aromatic); λ_{max}^{EtOH} 315 nm (infl., 22,000), 302 nm (29,600), 295 nm (infl., 28,100). The NMR spectrum showed signals at 61 Hz (s, 3H, C—CH_3), 126 Hz (s, 3H, O—CO—CH_3), 228 Hz (s, 3H, OCH_3), 303 Hz (t, $J=8$ Hz, CHOAc), 326 Hz (m, W ' 7 Hz, 1H, —CH_2C<u>H</u>=C), 404 Hz (s, 1H, AR—C<u>H</u>=C), and the remaining aromatic protons (395–415 Hz) and aliphatic protons (70–190 Hz) as multiplets.

Catalytic reduction of XXIII

Reaction 15. (a) A mixture of 10% Pd on $BaCO_3$ (30 mg) and XXIII (300 mg) in benzene (300 ml) was stirred under H_2. When GLC analysis indicated conversion of XXIII to the dihydro product XXIV was optimum, relative to the formation of tetrahydro products (<10%), the hydrogenation was stopped (6 hr). The catalyst was filtered off, the solvent was evaporated, and the crude product was crystallized from MeOH, to give 148 mg of XXIV, m.p. 95–103° (capill.). The purity (~95% on the basis of GLC analysis, XXIII is major contaminant) was not improved by further recrystallization. The NMR spectrum showed signals at 51 Hz (s, 3H, C—CH_3), 123 Hz (s, 3H, O—CO—CH_3), 226 Hz (s, 3H, OCH_3), 287 Hz (t, $J=8$ Hz, 1H, C<u>H</u>—OAc), 351 Hz (s, W ' 3 Hz, 1H, =C<u>H</u>—CH), 395–460 Hz (m, 3H, aryl-H); $\nu_{max}^{CCl_4}$ 1740, 1245 cm^{-1}; λ_{max}^{EtOH} 265 nm (18,500).

When HCl was added to an ethanolic soln of XXIV the absorption maxima changed to 272 nm (15,600).

A mixture of XXIV (117 mg) and 5% Pt-C (100 mg) in benzene (100 ml) was stirred in a H_2 atmosphere until uptake of the gas was complete. The catalyst was filtered, and the solvent evaporated to leave a residual oil, which was shown by GLC to be a mixture of XVIII (87%) and a single isomeric impurity (13%).

(b) A soln of XXIII (225 mg) in benzene (20 ml) was added to a prehydrogenated suspension of 10% Pd on $BaCO_3$ (200 mg) in benzene (25 ml), and the mixture was stirred until gas uptake ceased (31·9 ml in 60 min, theory uptake 33·8 ml). GLC analysis showed the product was a mixture of XVIIIc (55%) and two isomeric impurities (5%, 40%). The catalyst was filtered, and the solvent evaporated. The mixture was partially separated by elution from alumina (Grade I, 50 g) with benzene, the desired product being eluted first. Fractional crystallization from ether at −10° afforded XVIIIc, m.p. 123–125° (Kofler). Mixture m.p., NMR and IR analysis showed the product to be identical with that obtained from Reaction 11.

The product distributions obtained from the catalytic reduction of XXIII were very sensitive to the concentration of substrate and catalyst, and the solvent employed. Dilution favored the formation of XVIIIc. More polar solvents and use of palladium chloride favored formation a (single) isomer of XVIIIc.

Birch reduction of XVIIIc. Li wire (120 mg) was added to a stirred mixture of XVIII (93 mg) in ether (25 ml) and redistilled ammonia (25 ml). After 15 min, EtOH (2 ml) was added in portions over a period of 15 min. After the ammonia had evaporated, water (30 ml) was added and the ether layer was separated. The aqueous layer was extracted with ether (3 × 50 ml), and the combined ethereal phase was washed with water and dried over $MgSO_4$. The ether was evaporated, and the residue was treated with MeOH (15 ml) and oxalic acid dihydrate (230 mg) in water (3 ml). After 1 hr, when TLC showed conversion to a new product was complete, the mixture was made basic with $NaHCO_3$, and the product was extracted with ether (3 × 50 ml). The combined ether extracts were washed with water and dried over $MgSO_4$. The solvent was evaporated and the residual oil was treated with Ac_2O (1 ml) and pyridine (2 ml). After 4 hr, GLC showed esterification was complete, and the reagents were evaporated *in vacuo*. The residue was eluted from silica gel with 2·5% EtOAc in CH_2Cl_2, to give 44 mg of 3-keto-7(8→11α)*abeo*estr-$\Delta^{5(10)}$-en-17β-ol acetate; m.p. (Evacuated capill.) 148·5–150°; $\nu_{max}^{CS_2}$ 1740–1730, 1255 cm^{-1}. The NMR spectrum showed signals at 50 Hz (s, 3H, C—CH_3), 122·5 Hz (s, 3H, O—CO—CH_3), 146·5 Hz (s, W ' 4 Hz, 4H, C=C—CH_2—CH_2—C=O),

165 Hz (s, W½ 6 Hz, 2H, C=C—CH_2—C=O), 282 Hz, (t, J=7 Hz, 1H, CHOAc). (Found: *m/e* 316·2037. Calcd. *m/e* for $C_{20}H_{28}O_3$: 316·2038).

3-Hydroxy-7(8→11α)abeo-$\Delta^{1,3,5(10)}$-trien-17β-ol. A mixture of XVIIIc (5 mg) and pyridine hydrochloride (200 mg) was heated at 210° under N_2 for 60 min. The mixture was cooled, diluted with water (1 ml) and the product extracted with ether. The combined ether extracts were dried over Na_2SO_4, and then concentrated. The residual product was purified by elution from ChromAR 500 (Mallinkrodt) with an acetone–hexane (1:4) mixture and then distilled *in vacuo* (200°, 0·05 mm) from bulb to bulb; ν_{max} 3595 cm^{-1} (broad); no absorption 1700–1750 cm^{-1}. The R_f of the product (GLC, TLC) was identical with that of estradiol. (Found: *m/e* 272·178. Calcd. *m/e* for $C_{18}H_{24}O_2$: 272·178).

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