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THIOSTEROIDS—XXXIII[1]

10β-METHYLSULFONYL AND 10β-PHENYLSULFONYL DES-A-ESTR-9(11)-ENE DERIVATIVES AND THEIR ALKYLATION REACTION: SYNTHESIS OF A-FURANOSTEROIDS

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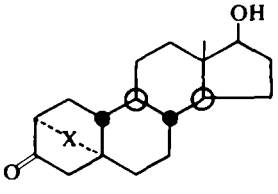
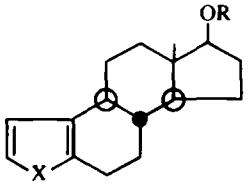
Abstract—The titled compounds, **12a**, 12b, 21a and **21b**, were synthesized by the reaction of the α-sulfonyl carbanion generated from dimethyl sulfone or phenyl methyl sulfone with the bisketal **9** of methyl 7a-methyl-1,5-dioxo-3aα,7aβ-hexahydroindan-4α-yl propionate prepared by fermentation of **5** and the subsequent oxidation of the product. Desulfurization of ketals of **21a** and **21b** gave the des-A-steroid **3a**. Michael addition of **12a**, **12b** and **21b** to methyl vinyl ketone led to the corresponding adducts with configurationally retained sulfonyl groups which were converted to 10β-methylsulfonyl and 10β-phenylsulfonyl steroids **27a**, **27b** and **27c** respectively. On the other hand, reaction of **21b** with methyl α-bromoacetate yielded **29**, desulfurization of which gave **30** identical with the product of alkylation of the enamine **28** of **3a**. A-Furanosteroids **1a** and **37a** were prepared from **30** and its 1-methyl derivative. The β axial configuration of the sulfonyl groups in the compounds was evidenced by the PMR and CD spectral data.

SYNTHESIS of A-furano- and A-thieno-steroids, **1a** and **1c**, has been achieved in this laboratory, though only in low yields, by photo-induced fragmentation reaction of the transannular 2α,5-epoxide and 2α,5-episulfide of 17β-hydroxy-19-nor-5α-androstan-3-one, **2a** and **2b** respectively.[2] Lednicer and Emmert[3] have recently reported an alternative route to the racemic A-furanosteroid **1a** starting with 17β-hydroxy-des-A-estr-9(10)-en-5-one **3a**, a familiar tricyclic enone;[4] and their successful results prompted us to present our studies in this field, which were carried out before their publication appeared. This paper deals with the synthesis of intermediates which are more convenient than the des-A-steroid **3a**, namely 10β-methylsulfonyl and 10β-phenylsulfonyl tricyclic enones, and with synthesis of optically active derivatives of A-furanosteroids with or without a methyl substituent at the β position in the furan ring.

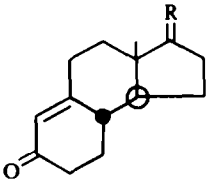
As the starting material leading to the tricyclic enone **3a**, we first chose optically active 7a-methyl-1,5-dioxo-3aα,7aβ-hexahydroindan-4α-yl propionic acid **4**[5] having



2a X = O
b: X = S

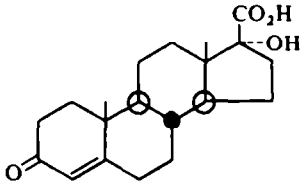


1a: X = O, R = H
b: X = O, R = Ac
c: X = S, R = H



3a: R = β-OH, α-H
b: R = β-OAc, α-H
17: R = O

natural configuration, since this compound can be readily prepared from 2-methylcyclopenta-1,3-dione and methyl 5-oxohept-6-enoate in a totally synthetic manner as described by Velluz *et al.*[6] In this work however, we prepared the acid **4** from 17α-hydroxy-3-oxoandrost-4-ene-17β-carboxylic acid **5**, which is readily available by the oxidation of "substance S" with periodic acid. Hayakawa *et al.*[7] have investigated the microbiological oxidation of a series of bile acid derivatives, which can be converted into the corresponding 1-substituted 7a-methyl-5-oxo-3aα,7aβ-hexahydroindan-4α-yl propionic acids in high yields, by Arthrobacter simplex, an organism requiring these substrates as the sole carbon source. By this method the acid **5** was transformed into the des-A-5,9-seco acid **6**, which in turn was converted in good yield to the acid **4** by oxidation with sodium bismuthate in aqueous acetic acid.



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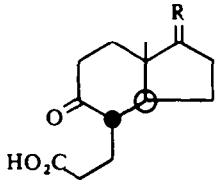
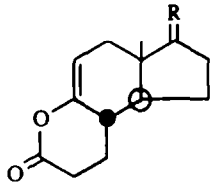


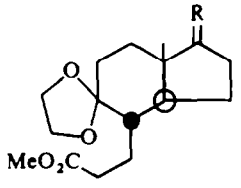
6: R = β-CO_2H, α-OH
4: R = O



7: R = O
8: R = β-OAc, α-H

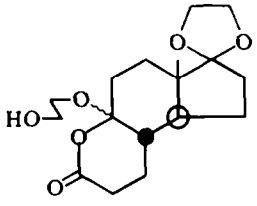
Initially our efforts were devoted to the partial reduction of the 5-membered ring ketone in the acid **4**, since the presence of the two active keto moieties in the molecule was considered to be unsuitable in a later step for the construction of the B-ring. This was attempted by partial reduction under various conditions of the oxo enol lactone **7**, easily obtainable from the acid **4**.[8] Sodium borohydride reduction of **7** in dimethylformamide at 0°, followed successively by acetylation and crystallization of the product, afforded 30–40% yield of the acetoxyenol lactone **8** in a pure state, the physical constants of which were in good agreement with those described in the literature.[6,8] However, as we could not attain an improvement in the yield of **8** even by several modifications of the reaction conditions, we gave up the scheme involving Grignard or intramolecular Wittig reaction[9] of the acetoxyenol lactone **8** to lead to the tricyclic enone **3a**, and instead we undertook an alternative route to **3a** directly from the acid **4** using the carbanion generated from dimethyl sulfone or phenyl methyl sulfone as the methylene source to be introduced into **4**. The former of these carbanions is known to be a highly effective reagent for condensation with a carboxylate[10] and even with a lactone.[11] Moreover, the β-ketosulfones produced still contain a highly active methylene moiety which may be condensed with the 6-membered ketone in the molecule to yield a methylsulfonyl or a phenylsulfonyl tricyclic enone. Prior to the condensation reaction, protection of the keto moieties in the methyl ester derived from the acid **4** was carried out by the usual ketalization with ethylene glycol in boiling benzene in the presence of *p*-toluenesulfonic acid; this gave a mixture of the bisketal **9**, the monoketal **10** and the hydroxyethylacetal **11** in ratios depending upon the conditions employed, **9** being the major product. The IR spectrum of **10** exhibited an absorption band due to a 5-membered ring ketone. The compound **11**, whose structure was assumed from the indication in the IR spectrum of the presence

of a hydroxyl group, was also obtained exclusively by direct ketalization of the acid **4** or the oxo-enol lactone **7** and gave the bisketal **9** on treatment with dry methanol in the presence of a catalytic amount of anhydrous *p*-toluenesulfonic acid. When the concentration of the acid catalyst and the reaction time were limited, ketalization of the methyl ester of **4** afforded mainly the bisketal **9** accompanied by very small amounts of **10** and **11**. This mixture was subjected to the following condensation reaction without further purification. Thus, the mixture reacted smoothly in monoglyme with an α-sulfonyl carbanion, generated either from dimethyl sulfone or from phenyl methyl sulfone by treatment with methylsulfinyl carbanion,[10] and subsequent hydrolysis of the ketal moieties with acid, followed by cyclization with alkali in methanol afforded crystalline 10β-methylsulfonyl and 10β-phenylsulfonyl des-A-estr-9(11)-ene-5,17-dione, **12a** and **12b** respectively, in 65–75% overall yield based on the acid **4**. The presence of the deconjugated 9(11)-double bond in these compounds



9: R =

10: R = O



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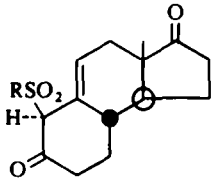
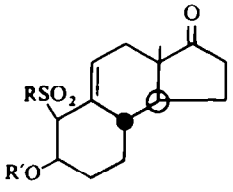
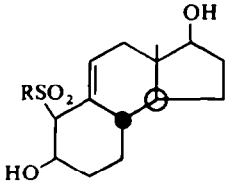


12a: R = Me
b: R = Ph

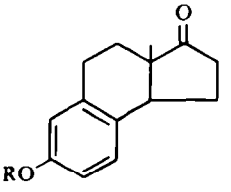
was supported by their PMR spectras' showing doublet-triplet patterns due to the vinyl proton characteristic of the double bond.* The configuration of the sulfonyl groups at C_{10} was assigned as β axial from the PMR spectra of their partial reduction products. By analogy with the reactivity of an α-haloketone, the keto function adjacent to the carbon bearing the electron-withdrawing sulfonyl moiety in **12a** and **12b** would be expected to be reduced with metal hydride to the corresponding alcohol faster than the unsubstituted keto group in the same molecule. Sodium borohydride reduction of **12a** and **12b** in dimethylformamide at 0° gave mixtures



13a: R = Me, R′ = H
b: R = Ph, R′ = H
c: R = Me, R′ = Ac
d: R = Ph, R′ = Ac



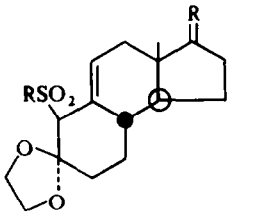
14a: R = Me
b: R = Ph

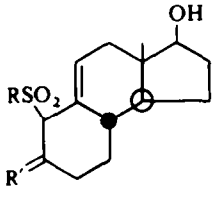


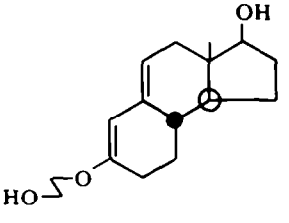
15a: R = H
b: R = Ac

* The C_{11}-vinyl protons in these compounds are considered to be coupled both to the C_{12}-methylene hydrogens ($J_{11,12\alpha} = J_{11,12\beta} = 3{\cdot}5$ Hz) and to the C_8-hydrogen in terms of allylic coupling ($J_{11,8} = 1{\cdot}5$ Hz). A similar triplet pattern due to a C_{11}-vinyl hydrogen has been observed in the spectra of $\Delta^{9(11)}$-olefinic steroids. See, also G. M. L. Cragg, C. W. Davey, D. N. Hall, G. D. Meakins, E. E. Richards and T. L. Whateley, *J. Chem. Soc.* (C), 1266 (1966).

of the monool, **13a** and **13b**, and the diol, **14a** and **14b**, in ratios of about 2 to 1 respectively. Although the PMR spectra of the monools showed overlapping of the C_{10}-proton signals with the C_5-proton signals, these signals were well separated in the spectra of the acetylation products, **13c** and **13d**. The C_{10}-proton signal was observed as a doublet (J = 5·0–5·5 Hz) and the C_5-proton signal as a doublet-triplet (J = 12·0 and 5·0–5·5 Hz) in each compound. This indicates that the configuration of the C_{10}-hydrogen is α equatorial and that of the C_5-hydrogen α axial; hence the compounds should have 10β-sulfonyl and the 5β-hydroxyl groups. It should be noted that on purification of the 10β-methylsulfonyl compound **12a**, prolonged treatment with basic alumina resulted in aromatization of the B-ring yielding a phenol **15a**. The mass spectra of **15a** and its acetate **15b** showed fragment peaks typical for a general phenol derivative (Experimental). Desulfurization of both **12a** and **12b** with usually employed aluminium amalgam[10] gave a deconjugated enedione in a low yield besides many other unidentified products. A more effective desulfurization method was therefore needed. Thus, after protection of the keto groups by conversion to the bisketals, **16a** and **16b**, by means of ethylene glycol in the presence of *p*-toluenesulfonic acid, the sulfonyl compounds were desulfurized with sodium in liquid ammonia. After hydrolysis of the product with acid, there was obtained in good yield a tricyclic enedione **17**, an α,β-unsaturated ketone whose physical constants were in good agreement with those described in the literature.[4, 12, 13] Moreover, these ketals offered the advantage of the ease with which their monoketals could be obtained by partial hydrolysis, as described below. It is well known that an α-haloketone







16a: R = Me, R' = 

b: R = Ph, R' = 

18a: R = Me, R' = O

b: R = Ph, R' = O

19a: R = Me, R' = 

b: R = Ph, R' = 

21a: R = Me, R' = O

b R = Ph, R' = O

20

ketal resists hydrolysis of the ketal group under the conditions generally used. Similarly, treatment of these ketals with *p*-toluenesulfonic acid in acetone at room temperature for several hours afforded the corresponding monoketals, **18a** and **18b**, in quantitative yields. The monoketals were then quantitatively reduced with sodium borohydride to give the 17β-alcohols, **19a** and **19b** respectively. Desulfurization of both **19a** and **19b** with sodium in liquid ammonia, followed by acid-hydrolysis afforded the desired tricyclic enone **3a** in high yield, Jones oxidation of which gave the foregoing tricyclic enedione **17**. In these desulfurization reactions, the formation of an intervening carbanion at C_{10} was evidenced by isolation of the dienol ether **20**

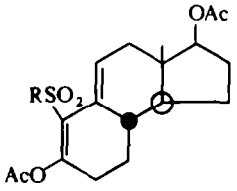
in the conversion of **19a** to **3a**. On the other hand, drastic acid-hydrolysis (refluxing in aqueous acetone in the presence of perchloric acid) of the sulfonyl monoketals **19a** and **19b** gave the corresponding sulfonyl enones **21a** and **21b** in *ca* 85% yields. The retained configuration of the sulfonyl substituents at C_{10} in these compounds was confirmed by chemical evidence based on their sodium borohydride reduction to give diols identical with those obtained by the same reduction of **12a** and **12b**, respectively. The tricyclic enone **3a** was also yielded simply by the reduction of **21a** with zinc dust in acetic acid.

It may be reasonably assumed that the β-ketosulfones **12a**, **12b**, **21a**, and **21b** each contain a stable sulfonyl moiety in the β axial orientation owing to the steric compression between the sulfonyl group and the vinyl hydrogen at C_{11}. Moreover, it is noteworthy that these compounds still have a reactive methyne group adjacent to the three functionalities; the double bond, sulfonyl and carbonyl groups. This is demonstrated by the reactions described below.

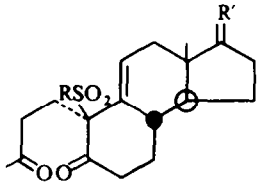
Although acylation of the β-ketosulfones **21a** and **21b** with benzoyl chloride in pyridine afforded intractable mixtures of the C- and O-acylated compounds which were not further studied, brief treatment with acetic anhydride in pyridine gave quantitatively yields of the dienol acetates, **22a** and **22b** respectively, in which serious repulsion between the sulfonyl groups and the vinyl hydrogens at C_{11} should be encountered. This is of interest in contrast to the lack of formation of the enol acetate on similar treatment of 10α-carbomethoxy-des-A-estrane-5,17-dione, the enol form of which contains a *trans*-Δ^1-octalin system unfavorable for energetic reasons.[14] Alkaline hydrolysis of the enol acetates gave the corresponding parent β-ketosulfones, **21a** and **21b**, indicating that protonation of the intervening enolate anions occurs from the α equatorial side in contrast to the axial protonation generally observed. These results are not surprising in view of both the steric effect discussed above and the stereoselective nature of the α-sulfonyl carbanion itself. A number of reactions of an α-sulfonyl carbanion yielding the configurationally retained product are known and their reaction mechanisms have been discussed.[15]

Such retention of configuration was also observed in the Michael addition reaction with β-ketosulfones **12a**, **12b** and **21b**. The reaction of methyl vinyl ketone with the compounds **12a** and **12b** in monoglyme in the presence of triethylamine gave high yields of the 1:1 adducts **23a** and **23b** respectively. The same reaction with **21b** was found to proceed very slowly and even after 160 hours *ca* 50% of the starting material was recovered. Use of pyridine as base instead of triethylamine gave a favorable result and a reasonable yield of the adduct **23c** was obtained. The structures of these adducts were deduced from PMR spectral evidence: Me signals due to the acetyl groups at 2·00–2·08 ppm and vinyl proton signals at 5·76–5·91 ppm. The vinyl proton signals for the enol acetates **22a** and **22b**, in which the vinyl hydrogens are in close proximity to the sulfonyl groups, were observed at the very low fields of 6·68 and 6·49 ppm respectively. In the methylsulfonyl derivatives prepared here, except **22a**, the vinyl proton resonance is at 5·75–5·85 ppm, while in the phenylsulfonyl compounds, except **22b**, it is in the range 5·00 to 5·68 ppm, such variation of the chemical shifts being reasonably accounted for by the anisotropic effect caused by restricted rotation of the phenyl moieties in the molecules. It can therefore be concluded from the chemical shift values for these vinyl protons that the Michael's adducts in question still contain the 10β-sulfonyl substituents. Regarding the stereochemical course in a

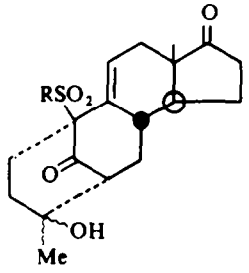
Michael reaction with methyl vinyl ketone, perpendicular attack by the electrophiles has been discussed by Velluz *et al.*[16] In keeping with this principle, 10-methyltricyclic enone and 10α-carbomethoxy saturated tricyclic ketone are known to be attacked by the reagent from β axial side.[14, 16, 17] Furthermore, the adducts **23a**, **23b** and **23c**, when treated in a homogeneous medium with acid or base under the conditions usually employed gave complex mixtures which were not further studied. However, the heterogeneous reaction of these adducts with sodium carbonate in dry methanol proceeded smoothly in a stepwise manner to afford good yields of the tetracyclic ketols **25a**, **25b** and **25c** respectively, although only the reaction of the methylsulfonyl compound **23a** was accompanied by aromatization of the ring A, yielding a considerable amount of 9(11)-dehydroestrone **26**. The bridged-ring ketol intermediates **24a** and **24b** formed in the course of the cyclization of **23a** and **23b**



22a: R = Me
b: R = Ph

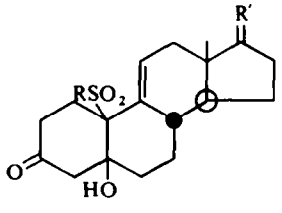


23a: R = Me, R′ = O
b: R = Ph, R′ = O
c: R = Ph, R′ = β-OH, α-H

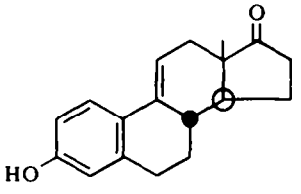


24a: R = Me
b: R = Ph

were isolated by preparative TLC and their structures were deduced from the PMR spectral data which showed methyl signals due to the methylcarbinol moieties at 1·18 and 1·31 ppm respectively. The ketols **25a**, **25b** and **25c**, in which the configuration of the formed hydroxyl groups was tentatively assumed to be β from consideration of the steric course of the cyclization reaction, gave upon treatment with hydrochloric acid in tetrahydrofuran high yields of the 10β-sulfonyl α,β-unsaturated



25a: R = Me, R′ = O
b: R = Ph, R′ = O
c: R = Ph, R′ = β-OH, α-H



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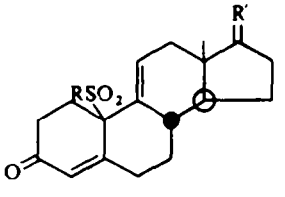


27a: R = Me, R′ = O
b: R = Ph, R′ = O
c: R = Ph, R′ = β-OH, α-H
d: R = Ph, R′ = β-OAc, α-H

ketones **27a**, **27b** and **27c** respectively. In the dehydration of **25b**, replacement of the solvent with acetone resulted in the formation of a mixture which consisted of 40% of **27b** and 50% of 9(11)-dehydroestrone **26**. Jones oxidation of **27c** afforded **27b** as expected. In Fig. 1, the CD curves of **27a** are shown together with those of the closely

related androsta-4,9(11)-diene-3,17-dione: they support the β-configuration of the methylsulfonyl group in **27a**.[18] The discrepancy observed at the shorter wave length is presumably interpreted as a result of the rotational contribution of the methylsulfonyl group to the π–π* transition of the 9(11)-double bond, since the CD curves of the methylsulfonyl bisketal **16a** also showed strong negative Cotton effect at the same wave length. This effect is considered to be very similar to that observed in an allylic alcohol system which is known as the Mills rule[19] and has been discussed by Scott and Wrixon.[20]

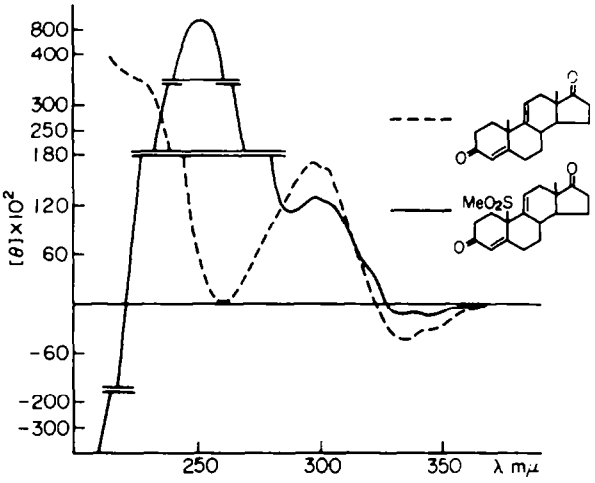
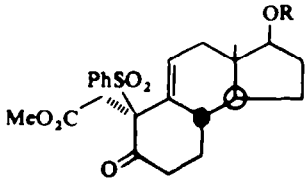
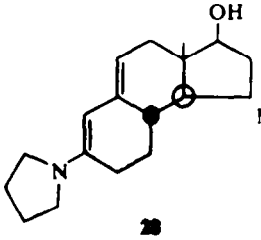


FIG 1. CD curves (dioxane) of 10β-methylsulfonylestra-4,9(11)-diene-3,17-dione **27a** and androsta-4,9(11)-diene-3,17-dione.

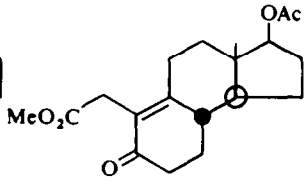
Next, we turned to an investigation of the alkylation of the phenylsulfonyl compound **21b** with alkyl halides containing functions suitable for the later construction of a furan ring and the results were compared with those obtained with the enamine **28**, which was readily derived from the tricyclic enone **3a**. When the α-sulfonyl carbanion generated from **21b** with methylsulfinyl carbanion was treated with methyl α-bromoacetate, there was obtained in 78% yield the alkylated compound **29a** as crystals, acetylation of which gave an oily acetate **29b**. Again, the PMR spectrum of **29a** showing the vinyl proton signal at 5·81 ppm indicates the presence of an α-equatorial alkyl group rather than that of the α-equatorial phenylsulfonyl group,



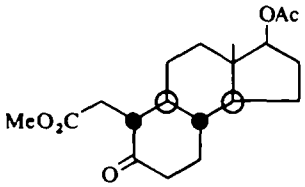
29a: R = H
b: R = Ac



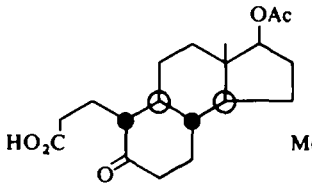
28



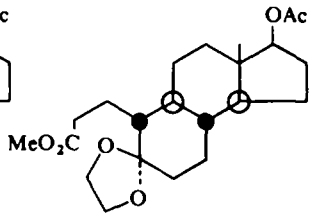
30



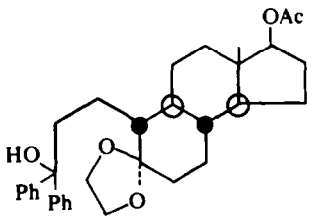
31



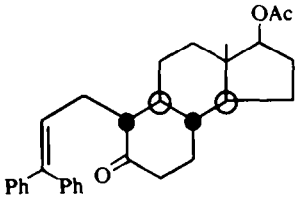
32



33

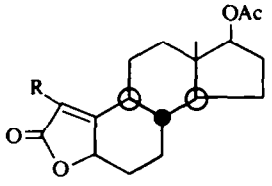


34

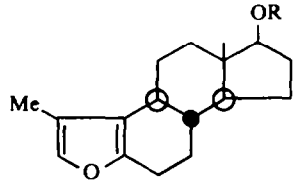


35

as mentioned above. Desulfurization of **29b** was effected by reduction with zinc dust in acetic acid. By this simple procedure **29b** was converted in 70% yield to the α,β-unsaturated ketone **30**, which was also obtained in 66% yield from the enamine **28** by alkylation with methyl α-bromoacetate. Hydrogenation of **30** over palladium on charcoal led to the saturated ketone **31**, which was also prepared independently from 19-nortestosterone acetate by a scheme similar to that described by Sondheimer *et al.*[14] This involved a series of reactions: oxidation of the steroid with ozone, Wieland degradation of the 3,5-seco-4-nor acid **32** produced (protection of the keto function at C_5 as the ketal **33**, Grignard reaction of **33** with phenyl magnesium bromide, treatment of the resulting diphenylcarbinol **34** with acid, and ruthenium tetroxide oxidation of the olefin **35** yielded), esterification of the resulting 2,5-seco-3,4-bisnor acid,* and subsequent acetylation. Hydrolysis of **31** so prepared with alkali, followed by heating with sodium acetate in acetic anhydride, afforded the α,β-unsaturated γ-lactone **36a** accompanied by small amounts of isomers of enol lactone, the latter being convertible to **36a** by treatment with sodium acetate. An attempted alkylation of the sulfonyl compound **21b** with methyl α-bromopropionate under the same conditions as employed in preparation of **29a** was unsuccessful and



36a: R = H
b: R = Me



37a: R = H
b: R = Ac

* This acid has been prepared by oxidation of 2-acetoxymethylene-19-nortestosterone acetate with ozone as described by Caspi *et al.* (ref 21).

21b was recovered. Alkylation of the enamine **28** with the reagent, successively followed by hydrolysis with alkali, hydrogenation, and treatment with sodium acetate afforded the 1-methyl homolog of α,β-unsaturated γ-lactone **36b** in a very low yield. These γ-lactones **36a** and **36b** were now subjected to aluminium diisobutylhydride reduction, which had been found by Minato and Nagasaki[22] to be highly effective for conversion of an α,β-unsaturated γ-lactone to a furan derivative. Thus, after the reduction, treatment with acid followed by reacetylation gave in moderate yields the desired A-furanosteroids **1b** and **37b**, these being hydrolyzed to **1a** and **37a** respectively. Assignment of the structures of these A-furanosteroids was based on their UV, PMR and mass spectral data.

EXPERIMENTAL

All m.ps were measured on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined in 1% EtOH–$CHCl_3$ with a Perkin-Elmer polarimeter, type 141. Unless otherwise stated, UV spectra were recorded in 95% EtOH with a Hitachi EPS-2 spectrophotometer and IR spectra were taken in Nujol mulls by use of a Koken DS-201B spectrophotometer. CD curves were determined with a Jasco Model ORD/UV-5 equipped with CD. All PMR spectra were taken in $CDCl_3$ solns with a Varian A-60 spectrophotometer, TMS serving as internal standard. Mass spectra were recorded with a Hitachi RMU-6 mass spectrometer (70 eV).

7a-Methyl-1,5-dioxo-3aα,7aβ-hexahydroindan-4α-yl propionic acid (**4**)

To a soln of **6**[7] (16 g), prepared by incubation of **5** with Arthrobacter simplex, in 500 ml of 50% AcOH, 24 g of $NaBiO_3$ was added. The resulting mixture was stirred for 48 hr at 28°. The excess $NaBiO_3$ was removed by filtration and washed with water and $CHCl_3$ repeatedly. The washings were combined with the filtrate and extracted with $CHCl_3$. The separated $CHCl_3$ layer was washed with NaCl aq and dried over Na_2SO_4. After evaporation of the solvent, the residue (13·1 g) was recrystallized from acetone–hexane to give 11·63 g (86·9%) of **4**, m.p. 112·5–113·5°: $[\alpha]_D^{24}$ +102·9 ± 1·5° (c = 0·991): ν_{max} 3190, 1755 sh, 1733, 1711, 1220 cm^{-1}: CD (in MeOH): $[\theta]_{293}$ +15,850, $[\theta]_{235}$ 0, $[\theta]_{210}$ +3820. (Found: C, 65·59; H, 7·71. $C_{13}H_{18}O_4$ requires: C, 65·53; H, 7·61%). Reported[5] m.p. 110–111·5°: $[\alpha]_D$ +121°.

Enol lactonization of **4**

A soln of **4** (6·664 g) in 660 ml of Reagent A (10^{-3} M, $HClO_4$–AcOEt) described by Edwards and Rao[8] was stirred for 15 min at room temp and poured into iced Na_2CO_3 aq. The separated AcOEt layer was washed with water and dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was crystallized from ether to yield 5·578 g (90·6%) of **7**, which upon recrystallization from acetone–hexane gave the pure sample, m.p. 136·5–137·5°: $[\alpha]_D^{24}$ +263·2 ± 30·2° (c = 1·000): ν_{max} 1761, 1728, 1667, 1244, 1195 cm^{-1}: λ_{max} 200 mμ (ε 9000): CD (in MeOH): $[\theta]_{295}$ +11,020, $[\theta]_{258}$ +1830, $[\theta]_{225·5}$ +26,100, $[\theta]_{210}$ +9660. (Found: C, 71·17; H, 7·33. $C_{13}H_{16}O_3$ requires: C, 70·89; H, 7·32%). Reported[5,8] m.p. 137–138·5°: $[\alpha]_D$ +286°.

Reducation of keto enol lactone (**7**)

A cooled solution of **7** (500 mg) in 4 ml of DMF was treated with 172 mg of $NaBH_4$ under stirring, then poured into NaCl aq and extracted with $CHCl_3$. The extract (484 mg) was acetylated with 1·5 ml of Ac_2O in 3·6 ml of pyridine at room temp overnight. Usual work-up gave the product (531 mg), which was recrystallized from isopropyl ether to yield 286 mg of pure **8**, m.p. 117·5–118·5: $[\alpha]_D^{22}$ +82·8 ± 1·5° (c = 0·832): ν_{max} 1730, 1243, 1051, 1020 (OAc), 1745, 1673, 1153, 1141 (enol lactone) cm^{-1}: $\lambda_{max}^{isooctane}$ 200 mμ (ε 11,800): CD (in isooctane): $[\theta]_{227}$ +28,700, $[\theta]_{215}$ +19,500, $[\theta]_{210}$ +17,040, $[\theta]_{205}$ +14,950: PMR (δ): 0·89 (s, 3, Me), 2·05 (s, 3, OAc), 4·75 (m, 1, AcOCH), 5·27 (m, 1, vinyl-H). (Found: C, 68·05; H, 7·56. $C_{15}H_{20}O_4$ requires: C, 68·16; H, 7·63%). Reported[6b] m.p. 118°: $[\alpha]_D$ +73°.

Methyl 7a-methyl-1,1,5,5-bisethylenedioxy-3aα,7aβ-hexahydroindan-4α-yl propionate (**9**)

(a) A soln of **4** (15·0 g) and 1 g *p*-TsOH·H_2O in 100 ml dry MeOH was allowed to stand at room temp overnight, then concentrated to a half its initial volume *in vacuo* and poured into ice water. Extraction with CH_2Cl_2 gave the methyl ester of **4** (16·0 g). A mixture of the ester, 25 ml ethylene glycol, 400 mg

p-TsOH·H_2O and 500 ml dry benzene was refluxed for 4 hr with continuous removal of water. After usual work-up, there was obtained 21·5 g of **9**, which could be used without further purification, though showing faint spots due to the by-products besides a main spot corresponding to **9** on TLC plate.

(b) Both a higher concentration of *p*-TsOH·H_2O and prolonged reaction time gave increased yields of the byproducts, as follows. The methyl ester prepared from 5·245 g of **4** was refluxed for 6 hr in a mixture of 180 mg *p*-TsOH·H_2O, 15 ml ethylene glycol and 90 ml dry benzene as described above. The product was chromatographed on 140 g of Al_2O_3. The eluates with light petroleum–benzene (4:1–1:2) gave 4·12 g of **9**; $\nu_{max}^{CCl_4}$ 1741, 1170, 1140, 1104 cm^{-1}. The fractions eluted with benzene and benzene–ether (9:1–1:1) yielded 490 mg of **10**; $\nu_{max}^{CCl_4}$ 1742, 1170–1110 cm^{-1}. The fractions eluted with ether and AcOEt afforded 900 mg of **11**, $\nu_{max}^{CCl_4}$ 3460, 1738, 1170, 1160, 1140, 1105 cm^{-1}. Compound **11** was also obtained in a pure state from the acid **4** and the enol lactone **7** by usual ketalization.

(c) A mixture of **4** (40·1 g), 1·5 g *p*-TsOH·H_2O, 100 ml ethylene glycol and 650 ml dry benzene was refluxed for 24 hr with continuous removal of water and worked up in the usual way to give **11**. A solution of **11** and 1·75 g anhydrous *p*-TsOH in 350 ml dry MeOH was stirred for 24 hr at room temp. Usual work-up gave 57·5 g of **9**, which could be used without further purification.

10β-*Methylsulfonyl-des-A-estr*-9(11)-*ene*-5,17-*dione* (**12a**)

Since commercially available NaH contains 50% mineral oil, in these experiments the oil was removed by washing with dry light petroleum before use. A mixture of NaH obtained from 9·32 g of commercial NaH, 39 ml DMSO, 16·6 g dimethyl sulfone and 134 ml monoglyme was stirred under N_2 and warmed at 65–70° for 2 hr. To the mixture cooled to room temp, a soln of **9** (23·8 g) in 190 ml monoglyme was added over a 30 min period. The resulting mixtire was stirred for 1·5 hr at room temp then warmed at 55–60° for 30 min. The cooled mixture was acidified with aqueous AcOH and extracted with CH_2Cl_2. The CH_2Cl_2 soln was washed with Na_2CO_3aq, dried over Na_2SO_4 and concentrated *in vacuo*. The residue (36 g) was dissolved into a mixture of 120 ml 90% acetone and 6 ml 70% $HClO_4$. After being stirred for 4·5 hr at room temp, the mixture was neutralized with Na_2CO_3aq, concentrated to a half its initial volume and poured into ice water. Extraction with CH_2Cl_2, followed by usual work-up, gave 27·1 g of an oily substance, which was further treated with 40 ml 2·5% KOH–MeOH under stirring. The mixture, from which crystals were deposited, was poured into ice water and extracted with CH_2Cl_2. Crystallization of the product from cold MeOH afforded 19·8 g of **12a**, which was recrystallized from MeOH to give 18·00 g (71·7% from **4**) of the pure sample, m.p. 198–200°; $[\alpha]_D^{24}$ +174·3 ± 2·1° (*c* = 1·009); ν_{max} 3032, 3004 (Δ), 1740, 1714 (C=O), 1308, 1299, 1126, 1118 (SO_2) cm^{-1}, CD (in MeOH): $[\theta]_{337}$ −320, $[\theta]_{257}$ +1683, $[\theta]_{225}$ +11,340; PMR (δ): 1·03 (s, 3, Me), 2·97 (s, 3, SO_2Me), 4·27 (s, $W_{h.2}$ = 3·0 Hz, 1, 10α-H), 5·83 (m, 1, 11-H); MS (*m/e*): 296 (M·, 5%), 281 (M·−Me, 7%), 217 (M·−SO_2Me, 100%). (Found: C, 60·83; H, 6·86; S, 10·78. $C_{15}H_{20}O_4S$ requires: C, 60·78; H, 6·80; S, 10·82%). In another run, the product in the reaction of **9** derived from **4** (10·155 g) with dimethyl sulfone (as described above except that mineral oil was not removed from the NaH used) was chromatographed over 280 g of Al_2O_3. The oil was eluted with light petroleum–benzene (1:1). The fractions eluted with benzene and benzene–CH_2Cl_2 (9:1–1:1) afforded 5·263 g of **12a**. The eluates with CH_2Cl_2 yielded 511 mg of **15a**, which was recrystallized from acetone–hexane to give the pure sample, m.p. 198–199°; $[\alpha]_D^{23}$ +91·4 ± 1·4° (*c* = 0·970, $CHCl_3$–EtOH = 1:1); ν_{max} 3390 (OH), 3019, 1622, 1585, 1580, 1506 (Ph), 1717 (C=O), 874, 820, 778 cm^{-1}; λ_{max}^{MeOH} 282 mμ (ε 2140); CD (in MeOH): $[\theta]_{280}$ +5830, $[\theta]_{240}$ +6310, $[\theta]_{223}$ −6500; MS (*m/e*): 216 (M·, 100%), 188 (M·−CO, 12%), 187 (M·−COH, 11%). (Found: C, 77·49; H, 7·47. $C_{14}H_{16}O_2$ requires: C, 77·75; H, 7·46%). After acetylation of **15a** with Ac_2O in pyridine, recrystallization from acetone–hexane gave the acetate **15b**, m.p. 92–93°; $[\alpha]_D^{23}$ +88·7 ± 1·4° (*c* = 0·955); ν_{max} 1751, 1205, 1186 (OAc), 3033, 1608, 1582, 1490, 925, 895 (Ph), 1728 (C=O) cm^{-1}; $\lambda_{max}^{isooctane}$ mμ (ε): 276 (690), 269 (740), 265 (610); CD (in isooctane): $[\theta]_{315}$ +2910, $[\theta]_{300}$ +5000, $[\theta]_{275}$ +2270; PMR (ε): 0·72 (s, 3, Me), 2·27 (s, 3, OAc), 6·80–7·20 (m, 3, Ph-H). MS (*m/e*): 258 (M·, 23%), 216 (M·−CH_2CO, 100%). (Found: C, 74·26; H, 7·09. $C_{16}H_{18}O_3$ requires: C, 74·39; H, 7·02%).

10β-*Phenylsulfonyl-des-A estr*-9(11)-*ene*-5,17-*dione* (**12b**)

To a soln of α-phenylsulfonyl carbanion, prepared from 2·0 g NaH, 6 ml DMSO and 5·26 g phenyl methyl sulfone in 35 ml monoglyme, a soln of **9** (5·734 g) in 45 ml monoglyme was added dropwise. The resulting mixture was stirred and warmed at 55° for 3 hr. The product extracted with CH_2Cl_2 was treated with acid and then with 2% KOH–MeOH as described above. Purification of the product was carried out by chromatography over Florisil (30 g). The product obtained from the fractions eluted with benzene–

CH_2Cl_2 was recrystallized from acetone–hexane to afford 4·919 g (81·3% from **4**) of **12b**, m.p. 198–200°: $[\alpha]_D^{27}$ +225·4 ± 2·9° (*c* = 0·9154): ν_{max} 3088, 3075, 3031, 1585, 674 (Ph), 1740, 1725 (C=O), 1326, 1319, 1303, 1172, 1148 (SO_2) cm^{-1}: CD (in $CHCl_3$): $[\theta]_{302}$ +10,340, $[\theta]_{281}$ +6620, $[\theta]_{268}$ +10,340, $[\theta]_{235}$ +22,300: PMR (δ): 1·07 (s, 3, Me), 4·30 (s, $W_{h/2}$ = 3·8 Hz, 1, 10α-H), 5·43 (m, 1, 11-H), 7·67 (m, 5, Ph–H): MS (*m/e*): 358 (M^+, 9%), 217 (M^+–SO_2Ph, 100%). (Found: C, 66·80: H, 6·26: S, 8·77. $C_{20}O_{22}O_4S$ requires: C, 67·02: H, 6·19: S, 8·93%).

$NaBH_4$ *Reduction of* **12a**

Compound **12a** (201 mg) was reduced with 25·3 mg $NaBH_4$ in 8 ml DMF at 0·3° for 50 min. The product, exhibiting two spots on TLC plate, was purified by preparative TLC ($CHCl_3$–AcOEt = 3:2). The more mobile fraction was recrystallized from acetone–hexane to give 120 mg (59·3%) of **13a**, m.p. 178–180°: $[\alpha]_D^{24}$ +116·9 ± 2·9° (*c* = 0·531): $\nu_{max}^{CHCl_3}$ 3505, 1065 (OH), 1737 (C=O), 1310, 1303, 1125 (SO_2) cm^{-1}: PMR (δ): 0·97 (s, 3, Me), 3·02 (s, 3, SO_2Me), 4·00 (m, 2, 10α-H and 5α-H), 5·80 (m, 1, 11-H). (Found: C, 60·41: H, 7·37: S, 10·82. $C_{15}H_{22}O_4S$ requires: C, 60·37: H, 7·43: S, 10·75%). This compound upon treatment with Ac_2O in pyridine afforded the oily **13c**: PMR (δ): 0·97 (s, 3, Me), 2·15 (s, 3, OAc), 2·98 (s, 3, SO_2Me), 4·10 (d, *J* = 5·5 Hz, 1, 10α-H), 5·07 (dt, *J* = 12·0 and 5·5 Hz, 1, 5α-H), 5·85 (m, 1, 11-H).

The less mobile fraction was recrystallized from acetone–hexane to yield 68 mg (33·5%) of the diol **14a** m.p. 215–217°: $[\alpha]_D^{24}$ +12·8 ± 0·9° (*c* = 0·592): $\nu_{max}^{CHCl_3}$ 3606, 3502, 1063 (OH), 1309, 1273, 1120 (SO_2) cm^{-1}: CD (in MeOH): $[\theta]_{210}$ −12,370. (Found: C, 59·87: H, 8·03: S, 10·95. $C_{15}H_{24}O_4S$ requires: C, 59·95: H, 8·05: S, 10·67%).

$NaBH_4$ *Reduction of* **12b**

Compound **12b** (431 mg) was treated with 46·7 mg of $NaBH_4$ in 8 ml DMF at 0° and the product was separated by preparative TLC (CH_2Cl_2–AcOEt = 2:1). The more polar fraction was recrystallized from acetone–hexane to give 143 mg (32·7%) of **14b**, m.p. 212–213°: $[\alpha]_D^{24.5}$ +81·6 ± 1·1° (*c* = 1·064): ν_{max} 3498, 1065, 1043 (OH), 1643 (Δ), 3050, 1582, 766, 734, 693 (Ph), 1285, 1138 (SO_2) cm^{-1}, CD (in dioxane): $[\theta]_{265}$ −780, $[\theta]_{218}$ +26,300: PMR (δ): 0·82 (s, 3, Me), 3·60–4·30 (m, 3, 5α-H, 10α-H and 17α-H), 5·00 (m, 1, 11-H), 7·58 (m, 3, Ph–H), 7·88 (m, 2, Ph–H). (Found: C, 66·57: H, 7·16: S, 9·14. $C_{20}H_{26}O_4S$ requires: C, 66·27: H, 7·23: S, 8·85%). The less polar fraction was recrystallized from MeOH to yield 249 mg (57·4%) of **13b**, m.p. 193–195°: $[\alpha]_D^{23}$ +166·8 ± 12·6° (*c* = 0·4497): ν_{max} 3536 (OH), 1736 (C=O), 1638 (Δ), 3091, 3068, 3028, 1585, 765, 725, 705, 690 (Ph), 1296, 1277, 1143 (SO_2) cm^{-1}: CD (in MeOH): $[\theta]_{296}$ +11,320, $[\theta]_{245}$ +640, $[\theta]_{218}$ +39,270, $[\theta]_{208}$ +42,740: PMR (δ): 0·97 (s, 3, Me), 3·70–4·20 (m, 2, 10α-H and 5α-H), 5·06 (m, 1, 11-H), 7·60 (m, 3, Ph–H), 7·86 (m, 2, Ph–H). (Found: C, 66·49: H, 6·78: S, 9·11. $C_{20}H_{24}O_4S$ requires: C, 66·64: H, 6·71: S, 8·90%). Acetylation of this compound gave **13d**, which was recrystallized from acetone–hexane, m.p. 185·5–187·5°: $[\alpha]_D^{23}$ +240·7 ± 11·6° (*c* = 0·619): ν_{max} 1749 sh, 1739, 1233, 1226, 1213 (OAc and C=O), 1307, 1142 (SO_2), 1640 (Δ), 3046, 1588, 757, 753, 733, 711, 682 (Ph) cm^{-1}: PMR (δ): 0·93 (s, 3, Me), 4·38) d, *J* = 5·0 Hz, 1, 10α-H), 4·97 (dt, *J* = 12·0 and 5·0 Hz, 1, 5α-H), 5·60 (m, 1, 11-H), 7·61 (m, 3, Ph–H), 7·91 (m, 2, Ph–H). (Found: C, 65·58: H, 6·48: S, 7·98. $C_{22}H_{26}O_5S$ requires: C, 65·65: H, 6·51: S, 7·97%).

10β-*Methylsulfonyl*-5,5,17,17-*bisethylenedioxy*-*des*-*A*-*estr*-9(11)-*ene* (**16a**)

A mixture of **12a** (3·633 g), 110 mg of *p*-TsOH·H_2O, 15 ml of ethylene glycol and 100 ml of dry benzene was refluxed for 22 hr with continuous removal of water. The product extracted with CH_2Cl_2 was recrystallized from acetone–hexane to yield 4·568 g (96·9%) of **16a**, m.p. 245–247°: $[\alpha]_D^{23}$ −9·3 ± 0·5° (*c* = 0·981): ν_{max} 3030 (Δ), 1305, 1291, 1119 (SO_2), 1096, 1060 (ketal) cm^{-1}: CD (in MeOH): $[\theta]_{215}$ −21,440, $[\theta]_{200}$ −70,000: PMR (δ): 0·94 (s, 3, Me), 3·07 (s, 3, SO_2Me), *ca* 3·97 (m, 9, ketal-CH_2 and 10α-H), 5·75 (m, 1, 11-H). (Found: C, 59·38: H, 7·16: S, 8·23. $C_{19}H_{28}O_6S$ requires: C, 59·35: H, 7·34: S, 8·34%).

10β-*Phenylsulfonyl*-5,5,17,17-*bisethylenedioxy*-*des*-*A*-*estr*-9(11)-*ene* (**16b**)

Compound **12b** (14·273 g) was treated with 70 ml ethylene glycol and 630 mg *p*-TsOH·H_2O in 350 ml dry benzene as described. Recrystallization of the product from acetone gave 17·257 g (97·1%) of **16b**, m.p. 184–186°: $[\alpha]_D^{23}$ +99·6 ± 7·0° (*c* = 0·994): ν_{max} 3064, 1590, 753, 730, 702, 685 (Ph), 1653 (Δ), 1306, 1141 (SO_2), 1068 (ketal) cm^{-1}: CD (in MeOH): $[\theta]_{273}$ +2420, $[\theta]_{259.5}$ +2440, $[\theta]_{227}$ +17,200, $[\theta]_{205}$ 33,720: PMR (δ): 0·90 (s, 3, Me), *ca* 3·85 (m, 9, ketal-CH_2 and 10α-H), 5·65 (m, 1, 11-H), 7·57 (m, 3, Ph–H), 7·95 (m, 2, Ph–H). (Found: C, 64·75: H, 6·85: S, 7·31. $C_{24}H_{30}O_6S$ requires: C, 64·55: H, 6·77: S, 7·18%).

10β-*Methylsulfonyl*-5,5-*ethylenedioxy*-*des*-*A*-*estr*-9(11)-*en*-17-*one* (**18a**)

A mixture of **16a** (4·568 g) and 460 mg *p*-TsOH·H_2O in 200 ml acetone was stirred for 6 hr at room temp and poured into iced Na_2CO_3aq. The product extracted with CH_2Cl_2 was recrystallized from acetone–hexane to give 4·045 g (quantitative yield) of **18a**, m.p. 197·5–199·5°: $[\alpha]_D^{23}$ +112·0 ± 1·5° (*c* = 1·017): ν_{max} 3026, 1640 (Δ), 1736 (C=O), 1308, 1294, 1285, 1123 (SO_2), 1106, 1093 (ketal) cm^{-1}: CD (in MeOH): $[\theta]_{296}$ +10,630. (Found: C, 59·84: H, 7·22: S, 9·65. $C_{17}H_{24}O_5S$ requires: C, 59·97: H, 7·11: S, 9·42%).

10β-*Phenylsulfonyl*-5,5-*ethylenedioxy*-*des*-*A*-*estr*-9(11)-*en*-17-*one* (**18b**)

A mixture of **16b** (1·125 g) and 1·6 g *p*-TsOH·H_2O in 400 ml acetone was stirred for 8 hr at room temp. The product was recrystallized from acetone–hexane to afford a quantitative yield of **18b**, m.p. 203–205°: $[\alpha]_D^{23}$ +281·1 ± 11·0° (*c* = 0·530): ν_{max} 3061, 1587, 766, 735, 708, 688 (Ph), 1739 (C=O), 1646 (Δ), 1304, 1142 (SO_2), 1109, 1082 (ketal) cm^{-1}: PMR (δ): 0·98 (s, 3, Me), *ca* 3·78 (m, 5, ketal-CH_2 and 10α-H), 5·68 (m, 1, 11-H), 7·56 (m, 3, Ph-H), 7·92 (m, 2, Ph-H). (Found: C, 65·77: H, 6·60: S, 8·09. $C_{22}H_{26}O_5S$ requires: C, 65·65: H, 6·51: S, 7·97%).

10β-*Methylsulfonyl*-5,5-*ethylenedioxy*-*des*-*A*-*estr*-9(11)-*en*-17β-*ol* (**19a**)

The monketal **18a** (4·035 g) was reduced with 945 mg $NaBH_4$ in 80 ml MeOH for 2·5 hr. Recrystallization of the product isolated in the usual way from acetone–hexane gave 4·016 g (98·7%) of **19a**, m.p. 232–234°: $[\alpha]_D^{23}$ +21·6 ± 0·7° (*c* = 0·966): ν_{max} 3535 (OH), 3028 (Δ), 1308, 1298, 1134, 1124 (SO_2), 1108 (ketal) cm^{-1}. (Found: C, 59·62: H, 7·65: S, 9·38. $C_{17}H_{26}O_5S$ requires: C, 59·62: H, 7·65: S, 9·36%). Acetylation of this compound and recrystallization of the product from acetone–hexane gave the pure acetate, m.p. 219–220°: $[\alpha]_D^{23}$ −21·7 ± 0·6° (*c* = 1·035): ν_{max} 3047, 3030 (Δ), 1731, 1254, 1235 (OAc), 1296, 1133 (SO_2), 1107 (ketal) cm^{-1}. (Found: C, 59·16: H, 7·33: S, 8·48. $C_{19}H_{28}O_6S$ requires: C, 59·35: H, 7·34: S, 8·34%).

10β-*Phenylsulfonyl*-5,5-*ethylenedioxy*-*des*-*A*-*extr*-9(11)-17β-*ol* (**19b**)

The monketal **18b** (15·382 g) was reduced with 3·3 g $NaBH_4$ in 250 ml MeOH for 1·5 hr. Recrystallization of the product from acetone–hexane afforded a quantitative yield of **19b**, m.p. 181–183°: $[\alpha]_D^{23}$ +133·1 ± 5·1° (*c* = 1·044): ν_{max} 3510 (OH), 3048, 1584, 768, 738, 709, 691 (Ph), 1645 (Δ), 1297, 1285, 1139 (SO_2), 1082 (ketal) cm^{-1}: PMR (δ): 0·81 (s, 3, Me), *ca* 3·79 (m, 5, ketal-CH_2 and 10α-H), 5·65 (m, 1, 11-H), 7·57 (m, 3, Ph-H), 7·95 (m, 2, Ph-H). (Found: C, 65·39: H, 7·06: S, 8·09. $C_{22}H_{28}O_5S$: C, 65·32: H, 6·98: S, 7·93%).

10β-*Methylsulfonyl*-17β-*hydroxy*-*des*-*A*-*estr*-9(11)-*en*-5-*one* (**21a**)

A mixture of **19a** (10·870 g), 240 ml acetone, 80 ml water and 10 ml 70% $HClO_4$ was refluxed for 25·5 hr. After being neutralized with Na_2CO_3aq, the soln was concentrated and poured into ice water. The product extracted with CH_2Cl_2 was recrystallized from acetone–hexane to give 8·459 g (89·3%) of **21a**, m.p. 180·5–182·5°: $[\alpha]_D^{23}$ +81·2 ± 0·5° (*c* = 0·982): ν_{max} 3452 (OH), 1734 (C=O), 1307, 1144 (SO_2) cm^{-1} CD (in MeOH): $[\theta]_{335}$ −450, $[\theta]_{321}$ −1140, $[\theta]_{308}$ −1740, $[\theta]_{299}$ −2100, $[\theta]_{225}$ +11,200. PMR (δ): 0·89 (s, 3, Me), 1·77 (s, 1, OH), 2·95 (s, 3, SO_2Me), 3·78 (m, 1, 17α-H), 4·27 (s, 1, 10α-H), 5·77 (m, 1, 11-H): MS (*m/e*): 298 (M^+, 5%), 219 (M^+-SO_2Me, 43%), 201 (M^+-SO_2Me-H_2O, 100%). (Found: C, 60·37: H, 7·41: S, 10·78. $C_{15}H_{22}O_4S$ requires: C, 60·37: H, 7·43: S, 10·75%). Reduction of this compound with $NaBH_4$ in DMF gave a quantitative yield of the diol identical with **14a**.

10β-*Phenylsulfonyl*-17β-*hydroxy*-*des*-*A*-*estr*-9(11)-*en*-5-*one* (**21b**)

A mixture of **19b** (5·476 g), 120 ml acetone, 40 ml water and 5 ml 70% $HClO_4$ was refluxed for 18 hr. Recrystallization of the product from acetone–hexane yielded 4·860 g (99·6%) of **21b**, m.p. 176·5–177·5°: $[\alpha]_D^{23}$ +157·7 ± 5·5° (*c* = 1·021): ν_{max} 3554, 1080, 1040 (OH), 3056, 1587, 761, 722, 703, 686 (Ph), 1712 (C=O), 1317 sh, 1308, 1148, 1134 (SO_2) cm^{-1}: CD (in MeOH): $[\theta]_{341}$ −335, $[\theta]_{308}$ +10,400, $[\theta]_{268}$ +7460, $[\theta]_{261}$ +5990: PMR (δ): 0·92 (s, 3, Me), 1·55 (s, 1, OH), 3·78 (t, 1, 17α-H), 4·30 (s, $W_{h/2}$ = 3·4 Hz, 1, 10α-H), 5·39 (m, 1, 11-H), *ca* 7·78 (m, 5, Ph-H). (Found: C, 66·82: H, 6·78: S, 9·01. $C_{20}H_{24}O_4S$ requires: C, 66·64: H, 6·71: S, 8·90%). Reduction of this compound with $NaBH_4$ in DMF gave a quantitative yield of a diol identical with **14b**.

10-*Methylsulfonyl*-*des*-*A*-*estra*-5(10),9(11)-*diene*-5,17β-*diol diacetate* (**22a**)

The ketol **21a** (2·280 g) was acetylated with 5 ml Ac_2O in 10 ml pyridine at room temp overnight. Recrystallization from acetone–hexane gave 2·436 g (83·3%) of **22a**, m.p. 154·5–156·5°: $[\alpha]_D^{23}$ +114·2

± 1·5° (*c* = 1·006): ν_{max} 1775, 1601, 1194 (enol acetate), 1732, 1244 (OAc), 3023, 3006 (Δ), 1305, 1292, 1159, 1130 (SO_2) cm^{-1}, λ_{max} mμ (ε): 254 (10,800), 210 (7300): CD (in MeOH): $[\theta]_{245}$ +19,050, $[\theta]_{222}$ +24,430: PMR (δ): 0·82 (s, 3, Me), 2·05, 2·20 (each s, 3, OAc), 2·95 (s, 3, SO_2Me), 4·72 (t, 1, 17α-H), 6·68 (t, *J* = 3·5 Hz, 1, 11-H). (Found: C, 59·78; H, 6·86; S, 8·64. $C_{19}H_{26}O_6S$ requires: C, 59·66; H, 6·85; S, 8·38%). This acetate on treatment with 5% KOH–MeOH at room temp for 3 hr was hydrolysed to the parent **21a**.

10-*Phenylsulfonyl-des-A-estra*-5(10),9(11)-*diene*-5,17β-*diol diacetate* (**22b**)

Acetylation of **21b** as described afforded an oily **22b**, which could not be crystallized from any solvent: $\nu_{max}^{CCl_4}$ 3040, 682 (Ph), 1762, 1603, 1193 (enol acetate), 1740, 1240 (OAc), 1321, 1167, 1134 (SO_2) cm^{-1}: PMR (δ): 0·28 (s, 3, Me), 1·99, 2·24 (each s, 3, OAc), 4·65 (t, 1, 17α-H), 6·49 (m, 1, 11-H), 7·55 (m, 3, Ph–H), 7·89 (m, 2, Ph–H).

17β-*Hydroxy-des-A-estr*-9(10)-*en*-5-*one* (**3a**)

(a) *From methylsulfonyl ketal* (**19a**). To a stirred soln of 8·9 g Na in 1500 ml liquid ammonia, a soln of **19a** (25·263 g) in 650 ml anhydrous THF was added dropwise during 45 min. The resulting mixture was stirred for 2·5 hr and allowed to stand at room temp overnight. After addition of 10 ml EtOH and NaCl aq, extraction with CH_2Cl_2 gave 19·2 g (97·9%) of **20**, which was recrystallized from acetone–hexane to afford the pure sample, m.p 136·5–138·5°: $[\alpha]_D^{23}$ + 166·8 ± 2·1° (*c* = 0·991), ν_{max} 3405, 3322 (OH), 1642, 1613 (dienol ether) cm^{-1}: λ_{max}^{MeOH} 240 mμ (ε 18,830). CD (in MeOH): $[\theta]_{255.5}$ +9130, $[\theta]_{230}$ −14,170. (Found: C, 72·60; H, 9·11. $C_{16}H_{24}O_3$ requires: C, 72·69; H, 9·15%). A soln of the unpurified reduction product in a mixture of 430 ml acetone, 180 ml water and 20 ml 70% $HClO_4$ was stirred for 1·5 hr at room temp. After usual work-up, recrystallization of the product from ether gave 15·430 g (95·2%) of **3a**, m.p. 112–113°: $[\alpha]_D^{23}$ −38·2 ± 0·8° (*c* = 0·997): ν_{max} 3415, 3317 (OH), 1664, 1643, 1609 (enone) cm^{-1}: λ_{max} 240 mμ (ε 16,600): CD (in MeOH): $[\theta]_{366.5}$ −260, $[\theta]_{329}$ +1360, $[\theta]_{235}$ −26,600: PMR (δ): 0·93 (s, 3, Me), 1·70 (s, 1, OH), 3·78 (t, 1, 17α-H), 5·87 (s, 1, 10-H). (Found: C, 76·08; H, 9·03. $C_{14}H_{20}O_2$ requires: C, 76·32; H, 9·15%). Acetylation of this compound with Ac_2O in pyridine and recrystallization from i-Pr_2O–light petroleum afforded **3b**, m.p. 84–86°: $[\alpha]_D^{23}$ −27·5 ± 1·3° (*c* = 0·535): ν_{max} 1732, 1241, 1030 (OAc), 3013, 1671, 1615 (C=C—C=O) cm^{-1}: λ_{max} mμ (ε): 239·5 (17,140), 310 (71). (Found: C, 73·55; H, 8·17. $C_{16}H_{22}O_3$ requires: C, 73·25; H, 8·45%).

(b) *From phenylsulfonyl ketal* (**19b**). A soln of **19b** (24·780 g) in 550 ml THF was added dropwise to a stirred soln of 15·9 g Na in 2000 ml liquid ammonia during 40 min. The resulting mixture was further stirred for 2·5 hr and allowed to stand for 18 hr at room temp. After addition of 5 ml EtOH, extraction with CH_2Cl_2 gave 16·1 g of a crystalline material, which was stirred in a mixture of 500 ml of 70% acetone aq and 17·5 ml 70% $HClO_4$ for 2·5 hr. The product extracted with CH_2Cl_2 was purified by chromatograhy over 100 g Al_2O_3. The fractions eluted with benzene and benzene–ether (9:1) were crystallized from ether yielding 9·564 g (70·8%) of **3a**, m.p. 112–113°, identified with an authentic sample by mixed m.p. and comparison of the IR spectra.

(c) *From methylsulfonyl ketone* (**21a**). A mixture of **21a** (200 mg), 2 g of Zn dust and 7·5 ml 70% AcOH was stirred under reflux for 3 hr. Extraction with CH_2Cl_2 and acetylation with 0·3 ml of Ac_2O in 0·6 ml pyridine gave a crude material, which was purified by preparative TLC affording 130 mg of **3b**, m.p. 84–86°. This compound was identified with an authentic sample by mixed m.p. and comparison of the IR spectra.

Des-A-estr-9(10)-*ene*-5,17-*dione* (**17**)

(a) Phenylsulfonyl ketal **16b** (2·44 g) dissolved in 70 ml THF was desulfurized by treatment with 1 g Na in 200 ml liquid ammonia. After heating in 45 ml 70% AcOH, the product was chromatographed over 8 g Al_2O_3. The fractions eluted with benzene were recrystallized from acetone–hexane affording 700 mg **17**, m.p. 137–138°: $[\alpha]_D^{26.5}$ +87·8 ± 1·2° (*c* = 1·074): ν_{max} 3023, 1740, 1665, 1613 cm^{-1}: λ_{max} 238·5 mμ (ε 15,270): CD (in $CHCl_3$): $[\theta]_{352}$ −370, $[\theta]_{300}$ +11,570. (Found: C, 77·03; H, 8·24. $C_{14}H_{18}O_2$ requires: C, 77·03; H, 8·31%). Reported[4,12,13] m.p. 137°: $[\alpha]_D$ +85·5°: λ_{max} 237 mμ (ε 14,850).

(b) Oxidation of **3a** (40 mg) with 0·065 ml 8N Jones reagent in 1 ml acetone gave 34 mg (86%) of **3b**, m.p. 137–138°, which was identified with an authentic sample by mixed m.p. and comparison of the IR spectra.

Michael addition of methylsulfonyl diketone (**12a**) *to methyl vinyl ketone* (*MVK*)

To a soln of **12a** (551 mg) in 20 ml monoglyme, 6·35 ml Et_3N and 9·16 ml freshly distilled MVK were

added. The resulting mixture was allowed to stand for 182 hr then concentrated to dryness under reduced pressure. The residue was crystallized from acetone–ether to afford 303 mg crude **23a**. The mother liquor was subjected to preparative TLC (CH_2Cl_2–AcOEt = 1:1). The less polar fraction (241 mg) was combined with the above material and recrystallized from acetone yielding 383 mg (56·2%) pure **23a**, m.p. 194·5–196·5°; $[\alpha]_D^{22}$ +205·7 ± 3·5° (c = 0·6934); ν_{max} 3048, 3020 (Δ), 1738, 1713 (C=O), 1302, 1135 (SO_2) cm^{-1}; PMR (δ): 0·97 (s, 3, Me), 2·08 (s, 3, Ac), 2·83 (s, 3, SO_2Me), 5·91 (m, 1, 11-H); MS (m/e): 366 (M^+, 1%), 287 ($M^+ - SO_2Me$, 100%). (Found: C, 62·19; H, 7·04; S, 9·06. $C_{19}H_{26}O_5S$ requires: C, 62·27; H, 7·15; S, 8·75%). The polar fraction gave 62 mg of a mixture of **24a** (R_f = 0·25) and **25a** (R_f = 0·34), which could not be separated to each component.

Cyclization of **23a**

(a) A suspension of **23a** (1·458 g) and 1·5 g Na_2CO_3 in MeOH (22 ml) was stirred for 91 hr at room temp then poured into ice water. After extraction with CH_2Cl_2, recrystallization of the product from acetone–hexane gave 499 mg of **25a**, m.p. 163–164° (dec); $[\alpha]_D^{22}$ +99·2 ± 1·6° (c = 0·852); ν_{max} 3531 (OH), 3060, 3042, 3020, 1629, (Δ), 1732, 1724 (C=O), 1286, 1124 (SO_2) cm^{-1}. PMR (δ): 0·95 (s, 3, Me), 2·97 (s, 3, SO_2Me), 3·58 (s, 1, OH), 6·10 (m, 1, 11-H). (Found: C, 62·33; H, 7·20; S, 8·89. $C_{19}H_{26}O_5S$ requires: C, 62·27; H, 7·15; S, 8·75%). The mother liquor was chromatographed over 18 g of Florisil. The fractions eluted with CH_2Cl_2 gave 150 mg of **26**, m.p. 256–258° (dec); $[\alpha]_D^{25}$ +290·2 ± 3·2° (c = 1·034); ν_{max} 3260 (OH), 1722 (C=O), 3017, 1616, 1606, 1582, 730 (Ph) cm^{-1}. (Found: C, 80·64; H, 7·61. $C_{18}H_{20}O_2$ requires: C, 80·56; H, 7·51%). This compound was identified with an authentic sample by mixed m.p. and comparison of the IR spectra. The fraction eluted with CH_2Cl_2–AcOEt (9:1) was three times recrystallized from acetone–hexane yielding an additional 129 mg of **25a**: combined yield of **25a** was 628 mg (43·1%).

(b) A suspension of **23a** (170 mg) and 80 mg of Na_2CO_3 in 2 ml MeOH was stirred for 30 min at room temp and worked up as described above. Purification by preparative TLC gave the bridged ketol **24a**, which could not be crystallized from any solvent: PMR (δ): 0·91 (s, 3, Me), 1·31 (s, 3, Me), 1·81 (s, 1, OH), 3·07 (s, 3, SO_2Me), 6·48 (m, 1, 11-H).

10β-*Methylsulfonylestra*-4,9(11)-*diene*-3,17-*dione* (**27a**)

A mixture of **25a** (397 mg), 4 ml of THF and 0·1 ml of 10% HCl was stirred for 5·5 hr at room temp then poured into ice water. The product extracted with CH_2Cl_2 was recrystallized from acetone–hexane to give 334 mg (88·5%) of **27a**, m.p. 122·5–123·5° (dec); $[\alpha]_D^{22}$ +296·3 ± 2·2° (c = 1·035); ν_{max} 3047, 1613 (Δ), 1734 (C=O), 1676, 1627 (C=C–C=O), 1302, 1295, 1135 (SO_2) cm^{-1}; CD (in dioxane): $[\theta]_{385}$ +249, $[\theta]_{370}$ +149, $[\theta]_{358}$ −607, $[\theta]_{343}$ −1393, $[\theta]_{332·5}$ −1284, $[\theta]_{315}$ +7588, $[\theta]_{304}$ +12,810, $[\theta]_{297}$ +13,435, $[\theta]_{287}$ +11,570, $[\theta]_{251}$ +83,850, $[\theta]_{210}$ −34,085; PMR (δ): 0·95 (s, 3, Me), 2·93 (s, 3, SO_2Me), 6·05 (m, 1, 11-H), 6·22 (d, J = 2·0 Hz, 1, 4-H). (Found: C, 65·51; H, 7·03; S, 9·43. $C_{19}H_{24}O_4S$ requires: C, 65·49; H, 6·94; S, 9·20%).

Michael addition of phenylsulfonyl diketone (**12b**) *to MVK*

A mixture of **12b** (3·281 g), 60 ml monoglyme, 21·4 ml of MVK and 13·1 ml of Et_3N was stirred for 17 hr at room temp and concentrated to dryness *in vacuo*. The residue was crystallized from ether to yield 3·546 g (90·4%) of **23b**, which upon recrystallization from acetone–hexane gave the pure sample, m.p. 136·5–138·5°; $[\alpha]_D^{28}$ + 191·5 ± 2·7° (c = 0·852); ν_{max} 1740, 1717 (C = O), 1310, 1140 (SO_2), 1651, 1627, 1584, 760, 712, 693 (Ph) cm^{-1}; PMR (δ): 1·09 (s, 3, Me), 2·00 (s, 3, Ac), 5·83 (m, 1, 11-H), 7·68 (m, 5, Ph–H). MS (m/e): 428 (M^+, 1%), 287 ($M^+ - SO_2Ph$, 100%). (Found: C, 67·00; H, 6·67; S, 7·45. $C_{24}H_{28}O_5S$ requires: C, 67·26; H, 6·59; S, 7·48%).

Cyclization of **23b**

(a) A suspension of **23b** (614 mg) and Na_2CO_3 (600 mg) in 25 ml MeOH was stirred for 3 hr at room temp. After usual work-up the product was separated into three components by preparative TLC (CH_2Cl_2–AcOEt = 3:1). The most mobile fraction gave 109 mg (21·2%) of unchanged **23b** and the middle fraction yielded 246 mg (40·0%) of **25b**, recrystallization of which from CH_2Cl_2–acetone gave the pure sample, m.p. 159–161° (dec), $[\alpha]_D^{28}$ +76·6 ± 1·1° (c = 1·033); ν_{max} 3463 (OH), 1737 (C=O), 1308, 1283, 1145, 1127 (SO_2), 3072, 3030, 1621, 1586, 770, 720, 696 (Ph and Δ) cm^{-1}; CD (in dioxane): $[\theta]_{303}$ +9700 $[\theta]_{244}$ −6760, $[\theta]_{221}$ +20,290; PMR (δ): 1·13 (s, 3, Me), 1·65 (s, 1, OH), 5·63 (m, 1, 11-H), 7·72 (m, 5, Ph–H). (Found: C, 67·37; 6·55; S, 7·64. $C_{24}H_{28}O_5S$ requires: C, 67·26; H, 6·59; S, 7·48%). The most polar fraction

afforded 189 mg (30·8%) of the bridged-ring ketol **24b** as an oily substance, which was found to be a mixture of epimers in a ratio of 4 to 1 from the PMR spectrum; $\nu_{max}^{CHCl_3}$ 3430 (OH), 1737 (C=O), 1302, 1146 (SO_2) cm^{-1}; CD (in dioxane): $[\theta]_{304.5}$ +7180, $[\theta]_{274.5}$ −2720, $[\theta]_{271}$ +1330, $[\theta]_{268}$ −180, $[\theta]_{271}$ +1325, $[\theta]_{224}$ −34,220. PMR (δ): 0·68 (0·62) (each s, Me), 1·26 (1·18) (each s, Me), 6·55 (m, 1, 11-H), 7·57 (m, 3, Ph-H), 8·12 (m, 2, Ph-H). This compound upon treatment with Na_2CO_3 in MeOH yielded the crystalline ketol **25b**.

(b) A mixture of **23b** (3·431 g) in 80 ml MeOH and 1·7 g Na_2CO_3 was stirred for 20 hr. The product extracted with Na_2CO_3 was stirred for 20 hr. The product extracted with CH_2Cl_2 was crystallized from ether to give 2·373 g (69·2%) of **25b**, m.p. 159–161° (dec.).

10β-Phenylsulfonylestra-4,9(11)-diene-3,17-dione **27b**

(a) A mixture of **25b** (1·954 g), 40 ml of THF and 0·5 ml of 10% HCl was stirred for 15·5 hr at room temp. Recrystallization of the product from CH_2Cl_2–MeOH afforded 1·781 g (95·2%) of **27b**, m.p. 150·5–152·5°; $[\alpha]_D^{25}$ + 236·0 ± 4·8° (c = 0·572); ν_{max} 1734 (C=O), 1674, 1629 (C=C—C=O), 1297, 1136 (SO_2), 3097, 3041, 1582, 773, 720, 695 (Ph) cm^{-1}; $\lambda_{max}^{CHCl_3}$ 246 mμ (ε 16,700); CD (in dioxane): $[\theta]_{381}$ + 580, $[\theta]_{365}$ + 824, $[\theta]_{350}$ + 120, $[\theta]_{340}$ − 925, $[\theta]_{329}$ − 1030, $[\theta]_{300}$ + 12,340, $[\theta]_{290}$ + 15,420, $[\theta]_{260}$ + 58,210, $[\theta]_{235.5}$ − 31,610, $[\theta]_{222}$ + 73, 250; PMR (δ): 1·09 (s, 3, Me), 5·42 (m, 1, 11-H), 6·22 (d, J = 1·6 Hz, 4-H), 7·60 (m, 5, Ph-H). (Found: C, 70·03; H, 6·21; S, 7·96. $C_{24}H_{26}O_4S$ requires: C, 70.21; H, 6·38; S, 7·81%).

(b) A soln of **25b** (10 mg) in 1 ml acetone was treated with 2 drops 10% HCl for 24 hr as described. The product was separated by preparative TLC and there were obtained 5 mg of **26** and 4 mg of **27b**, which were identified with authentic samples by mixed mps and comparison of the IR spectra, respectively.

Michael addition of phenylsulfonyl ketol **21b** *to MVK*

A mixture of **21b** (3·645 g), 60 ml monoglyme, 7 ml pyridine and 7 ml MVK was stirred for 93 hr and concentrated to dryness *in vacuo*. The residue was crystallized from MeOH-ether giving 3·112 (71·5%) of **23c**, which was recrystallized from acetone-hexane to give 2·446 g of the pure sample, m.p. 157–159° (dec): $[\alpha]_D^{22}$ +116·2 ± 2·9° (c = 0·538); ν_{max} 3545, 1077 (OH), 3092, 3070, 1582, 769, 717, 692 (Ph), 1725, 1717 (C=O), 3036, 1629 (Δ), 1301, 1282, 1137 (SO_2) cm^{-1}; PMR (δ): 0·96 (s, 3, Me), 1·70 (s, 1, OH), 2·01 (s, 3, Ac), 3·79 (t, 1, 17α-H), 5·76 (m, 1, 11-H), 7·65 (m, 5, Ph-H). (Found: C, 67·07; H, 7·11; S, 7·72. $C_{24}H_{30}O_5S$ requires: C, 66·95; H, 7·02; S, 7·45%).

Cyclization of **23c**

A suspension of **23c** (2·170 g) and 2 g Na_2CO_3 in 30 ml MeOH was stirred for 20 hr at room temp. Recrystallization of the product from acetone gave 1·700 g (78·4%) of **25c**, m.p. 166–167° (dec): $[\alpha]_D^{22}$ − 4·8 ± 0·5° (c = 0·926); ν_{max} 3468, 1077, 1046 (OH), 3094, 3066, 1586, 767, 719, 696 (Ph), 1721 (C=O), 3030, 1627 (Δ), 1284, 1130 (SO_2) cm^{-1}. (Found: C, 66·83; H, 6·79; S, 7·71. $C_{24}H_{30}O_5S$ requires: C, 66·95; H, 7·02; S, 7·45%)

10β-Phenylsulfonyl-17β-hydroxyestra-4,9(11)-dien-3-one **27c**

A mixture of **25c** (1·860 g) in 40 ml THF and 0·6 ml 10% HCl was stirred for 20 hr at room temp. Recrystallization of the product from CH_2Cl_2–MeOH gave 1·657 g (92·8%) of **27c**, m.p. 150–152° (dec): $[\alpha]_D^{22}$ + 12·6 ± 0·7° (c = 0·232); ν_{max} 3510, 1078, 1050 (OH), 1676, 1629 (C=C—C=O), 1581, 770, 721, 695 (Ph), 1286, 1130 (SO_2) cm^{-1}; CD (in dioxane): $[\theta]_{382}$ + 454, $[\theta]_{366}$ + 597, $[\theta]_{341}$ − 1098, $[\theta]_{329}$ − 1767, $[\theta]_{316}$ − 1970, $[\theta]_{277}$ + 27,460, $[\theta]_{269}$ + 32,240, $[\theta]_{262.5}$ + 40,480, $[\theta]_{258}$ + 38,810, $[\theta]_{237.5}$ − 19,400, $[\theta]_{223}$ +46,570. (Found: C, 69·63; H, 6·68; S, 8·12. $C_{24}H_{28}O_4S$ requires: C, 69·87; H, 6·84; S, 7·77%). This compound was acetylated with Ac_2O in pyridine in the usual way and recrystallization from acetone-hexane yielded the acetate **27d**, m.p. 133–134° (dec): $[\alpha]_D^{22}$ +127·8 ± 2·1° (c = 0·791); ν_{max} 3087, 3045, 1582, 767, 712, 696 (Ph), 1736, 1237, 1044 (OAc), 1678, 1632 (C=C—C=O), 1618 (Δ), 1301, 1291, 1136 (SO_2) cm^{-1}; λ_{max} 245 mμ (ε 17,000). PMR (δ): 0·91 (s, 3, Me), 2·05 (s, 3, Ac), 4·70 (t, 1, 17α-H), 5·31 (m, 1, 11-H), 6·21 (br. s, 1, 4-H), 7·72 (m, 5, Ph-H). (Found: C, 68·43; H, 6·61; S, 7·15. $C_{26}H_{30}O_5S$ requires: C, 68·69; H, 6·65; S, 7·05G). Jones oxidation of **27c** afforded **27b** in quantitative yield.

Alkylation of phenylsulfonyl ketol **21b** *with methyl α-bromoacetate*

To a stirred soln of α-methylsulfinyl carbanion generated from 140 mg NaH and 0·622 ml DMSO in 6 ml monoglyme were added **21b** (1·052 g) and 6 ml monoglyme under N_2 and the mixture warmed at 50° for 15 min. To the cooled mixture was added 0·328 ml of $BrCH_2CO_2Me$. The resulting mixture was

stirred at room temp for 4 hr and then at 50° for 3 hr. The product extracted with CH_2Cl_2 was crystallized from ether to give 798 mg of **29a**. The mother liquor was purified by preparative TLC (cyclohexane–AcOEt = 1:1). The more mobile fraction yielded 365 mg of **29a**, which was combined with the above material and recrystallized from acetone–hexane to afford 953 mg (78·4%) of pure **29a**, m.p. 184–186°; $[\alpha]_D^{22}$ +111·8 ± 1·5° (c = 1·010); ν_{max} 3586 (OH), 1735, 1716 (C=O), 1628 (Δ), 1586, 760, 715, 688 (Ph), 1320, 1310, 1140 (SO_2), 1196 (C—O—C) cm^{-1}; CD (in dioxane): $[\theta]_{306}$ −11,040, $[\theta]_{297}$ −12,510, $[\theta]_{247.5}$ +15,450, $[\theta]_{235}$ +10,960, $[\theta]_{230}$ +11,040, $[\theta]_{219}$ +8167, $[\theta]_{210}$ +13,240; PMR (δ): 0·95 (s, 3, Me), 1·53 (s, 1, OH), 3·10 and 3·37 (AB-type q, J_{AB} = 13·2 Hz, 2, CH_2), 3·53 (s, 3, OMe), 3·80 (t, 1, 17α-H), 5·81 (m, 1, 11-H), 7·62 (m, 5, Ph-H). (Found: C, 63·98; H, 6·60; S, 7·68. $C_{23}H_{28}O_6S$ requires: C, 63·87; H, 6·53; S, 7·41%). This compound, when treated with Ac_2O in pyridine, gave the acetate **29b** as an oily substance in quantitative yield.

5-Pyrrolidyl-des-A-estra-5(10),9(11)-dien-17β-ol **28**

To a warmed soln of **3a** (15·43 g) in 10 ml anhydrous MeOH was added 7·6 ml pyrrolidine. On allowing the mixture to stand for 30 min, **28** was deposited as crystals which were collected by filtration, washed with cold isopropyl ether and dried. (Yield: 17·502 g, 91·5%), m.p. 146–148°; ν_{max} 3519 (OH), 1619, 1592, 827 cm^{-1}. This compound was used for the subsequent reactions without further purification.

Methyl 17β-acetoxy-5-oxo-2,5-seco-3,4-bisnorestr-9(10)-en-2-oate **30**

(a) *From the enamine* **28**. To a cooled and stirred soln of **28** (10·063 g) in 50 ml dry DMF was added 6·78 g methyl α-bromoacetate under N_2. The mixture was stirred for 17 hr at room temp then 25 ml water was added. The mixture was warmed on a steam bath for 3 hr and extracted with CH_2Cl_2 gave 10·35 g of the product, which was acetylated with 12 ml Ac_2O in 20 ml pyridine at room temp overnight. The product extracted with CH_2Cl_2–ether was crystallized from CH_2Cl_2–isopropyl ether, affording 7·55 g of **30**. The mother liquor (*ca* 4 g) dissolved in cyclohexane–AcOEt (= 1:1) was chromatographed over 400 g of silica gel and there was obtained an additional 547 mg of **30**: combined yield of **30** was 8·097 g (65·8%), m.p. 135–137°; $[\alpha]_D^{23}$ − 65·5 ± 1·0° (c = 1·078); $\nu_{max}^{CCl_4}$ 1745, 1244, 1169 (OAc and CO_2Me), 1676, 1616 (C=C—C=O) cm^{-1}; λ_{max}^{MeOH} 241·5 mμ (ε 14,320); CD (in MeOH): $[\theta]_{335}$ − 1456, $[\theta]_{296}$ + 714, $[\theta]_{238}$ − 16,480, $[\theta]_{205}$ + 10,440; PMR (δ): 0·94 (s, 3, Me), 2·04 (s, 3, OAc), 3·29 and 3·55 (AB-type q, J_{AB} = 16·5 Hz, 2, CH_2), 3·63 (s, 3, OMe), 4·64 (t, 1, 17α-H). (Found: C, 68·18; H, 7·87. $C_{19}H_{26}O_5$ requires: C, 68·24; H, 7·84%).

(b) *From the phenylsulfonyl compound* **29b**. A mixture of **29** (538 mg) and Zn dust (5 g) in 15 ml of 90% AcOH was stirred under reflux for 3·5 hr. After usual work-up, the product was reacetylated and purified by preparative TLC (cyclohexane–AcOEt = 1:1). Recrystallization from isopropyl ether gave 267 mg (70·2%) of **30**, m.p. 135–137°.

Methyl 17β-acetoxy-5-oxo-2,5-seco-3,4-bisnorestran-2-oate **31**

(a) *From the alkylated enone* **30**. A soln of **30** (10·71 g) in 300 ml AcOEt containing 6 ml Et_3N was hydrogenated over pre-reduced 10% Pd–C (2·5 g) until 1 equivalent of H_2 had been adsorbed. After removal of the catalyst, the filtrate was concentrated to dryness *in vacuo*. The residue was recrystallized from CH_2Cl_2–MeOH affording 8·018 g (74·3%) of **31**, m.p. 156–157°, $[\alpha]_D^{22}$ − 16·2° ± 2·0° (c = 1·059); ν_{max} 1730, 1258 cm^{-1}; CD (in $CHCl_3$): $[\theta]_{288}$ − 6720. (Found: C, 67·52; H, 8·49. $C_{19}H_{28}O_5$ requires: C, 67·83; H, 8·39%). Reported[21,23] m.p. 151–153°, $[\alpha]_D$ − 35·6° (dioxane).

(b) *From 19-nortestosterone acetate*. A soln of 19-nortestosterone acetate (2·004 g) in 50 ml AcOEt and 10 ml AcOH was ozonized for 4 hr by a stream of ozonized O_2 (20·3 mg O_3/260 ml O_2/min) at − 70°. After addition of 2 ml AcOH, 0·8 ml 30% H_2O_2aq and 4 ml water, the mixture was allowed to stand overnight at room temp. Extraction in the usual way of the 3,5-seco-4-nor acid formed, followed by crystallization from acetone–hexane gave 1·247 g (58·7%) of **32**, m.p. 114·5–116·5°, $[\alpha]_D^{22}$ − 5·1 ± 2·0° (c = 1·044); ν_{max} 3300–2640 (CO_2H), 1728, 1263, 1242 (OAc), 1710 (C=O) cm^{-1}; CD (in $CHCl_3$): $[\theta]_{292}$ − 7660. (Found: C, 67·95; H, 8·47. $C_{19}H_{28}O_5$ requires: C, 67·83; H, 8·39%). The acid (875 mg) was treated with an ethereal soln of diazomethane and then converted to **33** by refluxing in a mixture of 6 ml ethylene glycol and 100 mg *p*-TsOH·H_2O in 100 ml dry benzene for 14·5 hr. A soln of the ketal (1·023 g) so obtained in 35 ml of ether was refluxed for 4·5 hr with a soln of PhMgBr prepared from 610 mg of Mg and 4·0 g of PhBr in 20 ml ether. Crystallization of the product from ether gave 874 mg (70·5% from **32**) of **34**, m.p. 210–213; $[\alpha]_D^{22}$ + 67·1 ± 2·0° (c = 1·081); ν_{max} 3495, 3350 (OH), 1600, 748, 703, 695 (Ph) cm^{-1}. (Found: C, 77·95; H, 8·56. $C_{31}H_{40}O_4$ requires: C, 78·11; H, 8·46%). The compound **34** (22·894 g) was refluxed in

460 ml 90% AcOH for 4·5 hr. The product extracted with ether was acetylated with 40 ml Ac_2O in 120 ml pyridine. The acetate was purified by chromatography over 500 g of Al_2O_3. The fractions eluted with light petroleum–benzene (9:1–4:1) and with benzene were combined and recrystallization from acetone–hexane gave 13·571 g (67·3%) of **35**, m.p. 117–119°: $[\alpha]_D^{22}$ + 8·9 ± 2·0° (*c* = 1·040); ν_{max} 3063, 3025, 776, 760, 708, 697 (Ph), 1732, 1243 (OAc), 1716 (C=O) cm^{-1}; CD (in $CHCl_3$): $[\theta]_{295}$ −7610; PMR (δ): 0·82 (s, 3, Me), 2·00 (s, 3, OAc), 4·60 (t, 1, 17α-H), 6·07 (t, *J* = 7·0 Hz, 1, vinyl-H), 7·25 (m, 10, Ph-H). (Found: C, 81·33: H, 7·97. $C_{31}H_{36}O_3$ requires: C, 81·54: H, 7·95%). A soln of a part of this compound (4·701 g) dissolved in 285 ml acetone was added to RuO_4 reagent (prepared from 230 mg of RuO_2 and 3 g $NaIO_4$ in 100 ml water) and the mixture was stirred for 6·5 hr, during which time an additional 3 g $NaIO_4$ was added in 500 mg portions. After termination of the oxidation by addition of i-PrOH, the acid formed was extracted in the usual way. The crude material (2·859 g) was treated with CH_2N_2 in ether and acetylated with 5 ml Ac_2O in 15 ml pyridine. Recrystallization of the product from MeOH afforded 2·501 g (72·2%) of **31**, m.p. 156–157°, which was identified with the compound prepared in (a) by mixed m.p. and comparison of the IR spectra.

17β-*Acetoxy*-3-*oxa*-*A*-*norestr*-1(10)-*en*-2-*one* **36a**

A mixture of **31** (8·018 g) in 125 ml of MeOH and 8·24 g of K_2CO_3 in 58 ml of water was refluxed for 30 min then concentrated to a half its initial volume *in vacuo*. After acidification with AcOH, extraction with CH_2Cl_2 gave 6·60 g of the free acid, which was refluxed for 41 hr in 116 ml of Ac_2O containing 979 mg of AcONa. The mixture was concentrated to dryness *in vacuo* and the residue was extracted with CH_2Cl_2. The product was crystallized from ether–light petroleum to yield 4·06 g crude material. The mother liquor (3·56 g) was chromatographed over 360 g of SiO_2 (cyclohexane–AcOEt). The first elution gave 1·814 g of a mixture of enol lactone as an oily substance. The second elution afforded 823 mg crystals. These were combined with the first product and the whole was recrystallized from acetone–hexane to yield 3·946 g (54·4%) of pure **36a**, m.p. 180·5–182·5°: $[\alpha]_D^{22}$ − 164·8 ± 2° (*c* = 1·034); ν_{max} 1739, 1647, 1252 cm^{-1}; λ_{max} 215 mμ (ε 16,330); CD (in MeOH): $[\theta]_{240}$ −2720, $[\theta]_{225}$ −4490; PMR (δ): 0·83 (s, 3, Me), 2·04 (s, 3, OAc), 4·69 (t, 1, 17α-H), 5·64 (s, 1, 1-H). (Found: C, 71·28: H, 8·11. $C_{18}H_{24}O_4$ requires: C, 71·02: H, 7·95%). The mother liquor of the recrystallization was combined with the oily substance of the first eluate and treated with Ac_2O and AcONa as described above. Chromatography of the product over 250 g of SiO_2 afforded 10113 g of a mixture of enol lactone and 975 mg crystals. Recrystallization from acetone–hexane gave 848 mg (11·7%) of **39a**: combined yield, 4·794 g (66·1%).

17β-*Acetoxy*-1-*methyl*-3-*oxa*-*A*-*norestr*-1(10)-*en*-2-*one* **36b**

A mixture of **28** (4·43 g), 3·3 g methyl α-bromopropionate and 20 ml DMF was stirred for 65 hr at room temp. Work-up in the usual way, followed by hydrolysis with 60 ml 5% KOH–MeOH gave 2·158 g of an oily substance as an acid fraction, which was hydrogenated over 436 mg 10% Pd–C in 60 ml AcOEt containing 1·2 ml Et_3N. Heating the product in a soln of 390 mg AcONa in 46 ml Ac_2O for 39 hr, followed by chromatography over 200 g SiO_2 afforded 298 mg of **36b** as crystals, which were recrystallized from acetone–hexane to give the pure sample, m.p. 191·5–192·5°: $[\alpha]_D^{26}$ − 141·5 ± 2° (*c* = 0·930): ν_{max} 1744, 1665, 1256, 1239, 1069, 1044, 1021 cm^{-1}: λ_{max} 220 mμ (ε 15,550): CD (in MeOH): $[\theta]_{274}$ + 362, $[\theta]_{235}$ − 33,810: PMR (δ): 0·85 (s, 3, Me), 1·98 (s, $W_{h/2}$ = 3·5 Hz, 3, 1-Me), 2·04 (s, 3, OAc), 4·54 (m, 2, 5-H and 17α-H). (Found: C, 71·73: H, 8·29. $C_{19}H_{26}O_4$ requires: C, 71·67: H, 8·23%).

3-*Oxa*-*A*-*norestra*-1,5(10)-*dien*-17β-*ol* **1a**

To a stirred soln of **36a** (1·400 g) in 14 ml dry THF, cooled to − 30°, 9·61 ml of a soln of $Al(i\text{-}Bu)_2H$ (1.30 M) was added dropwise under N_2. The mixture was stirred for 2 hr at the same temp and 8·8 ml 10% H_2SO_4 was added. After agitation for 30 min, the product extracted with ether was acetylated with 1·2 ml Ac_2O in 3·6 ml pyridine at room temp overnight. The product was chromatographed over 140 g of SiO_2 (cyclohexane–AcOEt = 2:1). The first elution gave 896 mg (67·3%) of **1b**, which was recrystallized from hexane yielding the pure sample, m.p. 118–119°: $[\alpha]_D^{24}$ +28·7 ±0·7° (*c* = 0·951): ν_{max} 1734, 1241 (OAc), 1627, 1567, 1505, 725 cm^{-1}: CD (in MeOH): $[\theta]_{225}$ − 12,970: PMR (δ): 0·84 (s, 3, Me), 2·04 (s, 3, OAc), 4·68 (t, 1, 17α-H), 6·23 and 7·26 (AB-type q, *J* = 2·0 Hz, 2, 1-H and 2-H). (Found: C, 74·74: H, 8·37. $C_{18}H_{24}O_3$ requires: C, 74·97: H, 8·39%). The second elution gave 303 (21·6%) of recovered **36a**, m.p. 180–182°.

Reduction of **1b** (4·160 g) with 710 mg of LAH in 100 ml of dry ether at 0° for 30 min and recrystallization of the product from acetone–hexane yielded 3·254 g (86·5%) of **1a**, m.p. 137·5–139·5°: $[\alpha]_D^{20}$ + 47·4 ± 0·7° (*c* = 1·036): $\nu_{max}^{CCl_4}$ 3628, 1505, 902, 724 cm^{-1}: λ_{max} 222·5 mμ (ε 6290): CD (in MeOH): $[\theta]_{225}$ − 15,200:

PMR (δ): 0·78 (s, 3, Me), 3·75 (t, 1, 17α-H), 6·23 and 7·23 (AB-type q, J = 2·0 Hz, 2, 1-H and 2-H): MS (*m/e*): 246 (M^+: 100%). (Found: C, 78·01: H, 9·16. $C_{16}H_{22}O_2$ requires: C, 78·01: H, 9·00%).

1-*Methyl*-3-*oxa*-*A*-*norestra*-1,5(10)-*dien*-17β-*ol* **37a**

A soln of **36b** (380 mg) in 4 ml dry THF was reduced at − 30° with 1·8 ml of an Al(i-Bu)$_2$H soln (1·82 M) for 4·5 hr. After work-up as described above, the acetylated product was purified by preparative TLC (cyclohexane–AcOEt = 4:1). The more polar fraction gave 165 mg (45·7%) of recovered **36b**. The less polar fraction afforded 175 mg (46·1%) of **37b**, which was recrystallized from acetone–hexane to give the pure sample, m.p. 98–99°: $[\alpha]_D^{26}$ + 44·6 ± 2·2° (c = 0·390): ν_{max} 1734, 1239, 1041, 1031 (OAc), 1627, 795 cm^{-1}: $\lambda_{max}^{isooctane}$ 222 mμ (ε 6420): CD (in isooctane): $[\theta]_{233.5}$ − 9161, $[\theta]_{217}$ + 7048. (Found: C, 75·66: H, 8·52. $C_{19}H_{26}O_3$ requires: C, 75·46: H, 8·67%).

Reduction of **37b** (225 mg) with 34 mg of LAH in 5 ml dry ether at 0° for 45 min and recrystallization of the product from acetone gave 120 mg of **37a**, m.p. 103–105°: $[\alpha]_D^{26}$ +64·1 ±2·1° (c = 0·505): ν_{max} 3318, 1674, 1556, 1107, 1069, 1061, 759 cm^{-1}: λ_{max}^{MeOH} 222·5 mμ (ε 6180): CD (in MeOH): $[\theta]_{235}$ − 6845, $[\theta]_{217}$ + 4212: PMR (δ): 0·79 (s, 3, Me), 2·02 (d, J = 1·0 Hz, 3, 1-Me), 3·74 (m, 1, 17α-H), 7·01 (s, $W_{h/2}$ = 3·5 Hz, 1, 2-H): MS (*m/e*): 260 (M^+, 100%). (Found: C, 78·19: H, 9·26. $C_{17}H_{24}O_2$ requires: C, 78·42: H, 9·29%).

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