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TOTAL SYNTHESIS OF MODIFIED STEROIDS—1

8β-METHYL-D-HOMO-B-NORESTRANES

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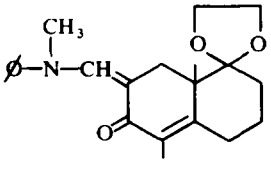
Abstract—The total synthesis of a variety of 8β-methyl-D-homo-B-norestranes is described. Reduction of the C-9 (11) double bond gives stereospecifically the 9β-isomer as determined by the complete X-ray analysis of a bromo derivative. Estranes differing only in their stereochemistry at C-14 can be prepared by initial reduction of tricyclic intermediates **5a** and **12** followed by cyclization to yield **26** and **27**.

MODIFICATION of the basic steroid nucleus has yielded an impressive list of products with high biological activities.[1] It is apparent that some derivatives might be more readily available by total synthesis rather than by the manipulation of intermediates derived from natural products. Thus, extension of the elegant Torgov synthesis[2] has yielded a wide variety of C-13 substituted steroids. Although several 8β-methyl steroids have been reported,[3-16] they were prepared from steroidal intermediates by rather lengthy methods. It was felt that this class of compound might be more readily prepared by total synthesis. At the same time it was anticipated that a wide variety of modifications of the basic steroid nucleus would be possible. This paper reports some of our work in this area.

The work of Kitahara[4] *et al.* on the total synthesis of dolabradiene showed that the bicyclic intermediate **1** added acrylonitrile stereospecifically from the α-face to give **2**.† The stereochemistry at the new asymmetric center is that to be expected based on findings of Wenkert[5] and Mazur[6] on the alkylation of αβ-unsaturated ketones. The anion of **1** could be most conveniently generated by the reaction of **1** with sodium



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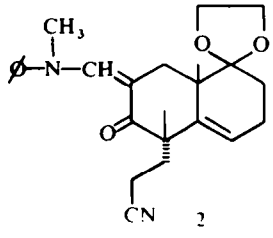

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hydride in dimethoxyethane. The anion is remarkably stable and can be stored for extended periods without appreciable decomposition. Alkylation of this anion with *m*-methoxybenzyl chloride gave in high yield **3a** assumed to have the stereochemistry as shown. The blocking group was then removed by the action of sodium hydroxide in

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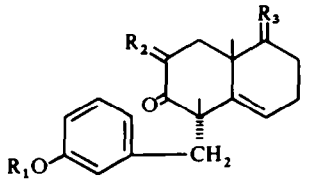
† Structural formulae containing one or more asymmetric carbon atoms depict one diasteroisomer but refer to racemic compounds throughout.

aqueous ethoxyethanol to give in excellent yield **4a**. Mild acid hydrolysis removed the ketal grouping to give **5a** in an overall yield of 79% based on **1**.

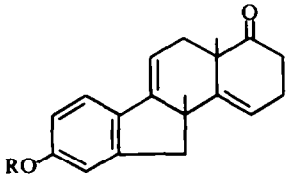


3a: $R_1 = CH_3$, $R_2 = CH{-}N(CH_3)(\phi)$, $R_3 = -OCH_2CH_2O-$

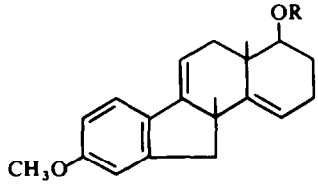
3b: $R_1 = CH_2\phi$, $R_2 = CH{-}N(CH_3)(\phi)$, $R_3 = -OCH_2CH_2O-$

4a: $R_1 = CH_3$, $R_2 = H_2$, $R_3 = -OCH_2CH_2O-$
4b: $R_1 = CH_2\phi$, $R_2 = H_2$, $R_3 = -OCH_2CH_2O-$
4c: $R_1 = H$, $R_2 = H_2$, $R_3 = -OCH_2CH_2O-$
5a: $R_1 = CH_3$, $R_2 = H_2$, $R_3 = O$
5b: $R_1 = H$, $R_2 = H_2$, $R_3 = O$

Polyphosphoric acid proved to be the most suitable reagent for the cyclodehydration of **5a** to **6a**. However, reaction times of more than 5 minutes and temperatures higher than room temperature caused drastic decreases in yield and made the purification of **6a** difficult. Liquid hydrogen fluoride also converted **5a** to **6a** but in somewhat lower yield.



6a: R = CH_3
6b: R = H

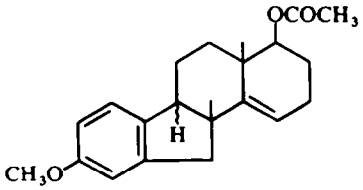


7a: R = H
7b: R = $COCH_3$

Many unsuccessful attempts were made with a wide variety of reagents to effect the cleavage of the OMe group in **6a**. In order to make available compounds related to **6b** a slightly modified synthesis was adopted in which **1** was alkylated with *m*-benzyloxybenzyl chloride to give **3b**. Strong base hydrolysis then gave **4b** which was catalytically reduced to **4c** in excellent yield. Mild acid hydrolysis of **4c** afforded **5b** which was cyclized by polyphosphoric acid or liquid hydrogen fluoride to the tetracyclic phenol **6b**.

Sodium borohydride reduction of **6a** gave the non-crystalline alcohol **7a** which was characterized as its acetate **7b**. Since **7a** was the sole product of the reduction and analogous systems are known to give the OH group *cis* to the angular Me group, it is reasonable to assume that the configuration of the OH group at C-17a is β. Further evidence for this assignment is presented below.

Catalytic reduction of **7b** proceeded completely stereospecifically to give the tetraene **8**. In the NMR spectrum of **8** it was possible to see the tertiary benzylic proton at C-9 although partially obscured by the benzylic protons at C-6. It was possible that the question concerning the stereochemistry at C-9 could be answered by a study of the coupling constants of the C-9 hydrogen with the methylene protons at C-11. However, the dangers of utilizing only the X portion of an ABX system have been pointed out.[7] In order to simplify the NMR spectrum of **8**, the deuterated form **9**



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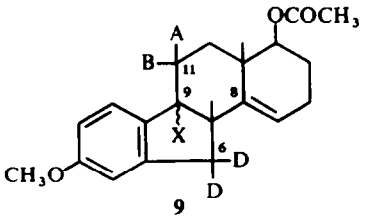

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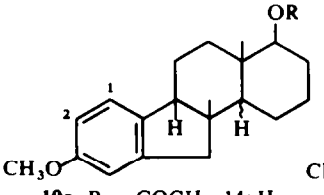
was synthesized. The deuterated *m*-methoxybenzyl chloride was readily prepared by the LAD reduction of methyl *m*-methoxybenzoate followed by reaction with thionyl chloride.

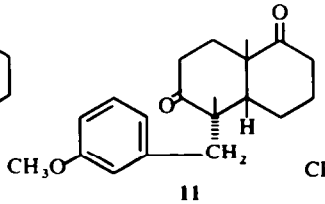
The X-portion of the ABX system of **9** was particularly well defined in the 100 mc NMR spectrum. The derived coupling constants for this portion were found to be 4·1 and 6·7 c/s. An examination of the Dreiding models of **8** in which the C-9 hydrogen is α shows that one dihedral angle must be 160–170° irrespective of the conformation of the rings. If the modified Karplus equaltion holds in this case then one coupling constant should be of the order of 14–15 c/s.[8] The observed values can be accommodated, however, if a β-orientation of the hydrogen at C-9 is assumed.

After completion of this work, the stereochemistry at C-9 was determined by a complete X-ray analysis of the 2-bromo derivative **10d**.* This material was readily prepared from **10a** by direct bromination. That substitution had occurred at the 2-position of **10d** was easily confirmed by its NMR spectrum which showed the two aromatic protons as singlets at 2·76 and 3·26 τ. The X-ray analysis showed that the C-9 hydrogen is indeed β and further confirmed the relative stereochemistry of the Me groups and OAc group as β and the C-14 hydrogen as α. It is remarkable that in this series of compounds, catalytic reduction of the C-9 (11) double bond occurs with such stereospecificity from the β-face in spite of the two axial Me groups on this face. This is in sharp contrast to the C-9 (11) unsaturated derivatives of estrone which reduce exclusively from the α-face.[9]

Further catalytic reduction of **8** required more vigorous conditions. Reduction under acidic conditions led to hydrogenation of the aromatic ring as well as the isolated double bond. Selective reduction of 8 was possible in ethanol at 75° and 3 atmospheres. The product was a mixture of the two C-14 isomers (**10a** and **10c**). These were separated and their configuration at C-14 established in an unequivocal manner by an alternative synthesis (see below). The lack of stereochemical control in the reduction of **8** prompted a study of the reduction of the 3-ring precursor **5a**.



10a: R = $COCH_3$, 14αH
10b: R = H, 14βH
10c: R = $COCH_3$, 14βH
10d: R = $COCH_3$, 14αH, 2-Br



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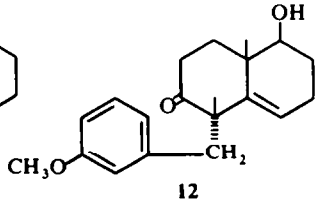

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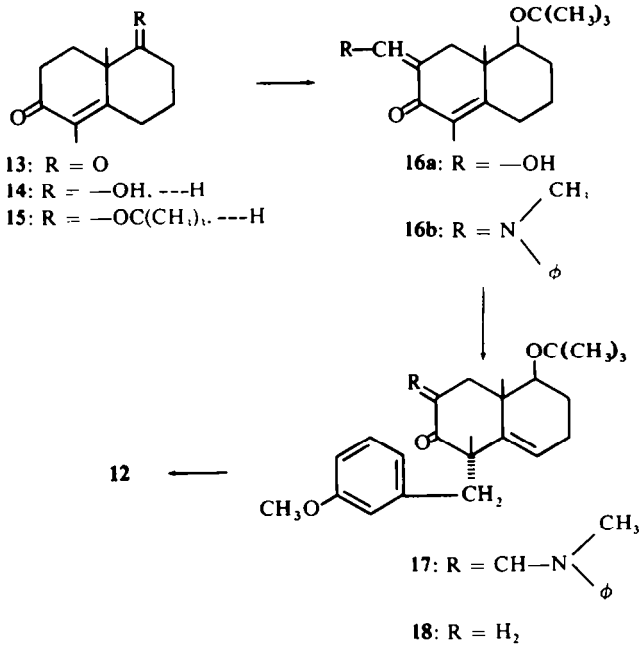
* We thank Dr. J. H. Van den Hende and Dr. D. B. Cosulich of Lederle Division, American Cyanamid Company for the results of their X-ray analysis. Details will be published later.

The reduction of **5a** in ethanol at 75° and 3 atmospheres gave a crystalline dihydro product later shown to be the *cis* compound **11**. The yield of crystalline **11** was variable and depended greatly on the activity of the Pd catalyst. Fresh catalyst invariably led to over reduction but this could be eliminated by the addition of small amounts of triethylamine and conditions could be found to give essentially quantitative yields of **11**.

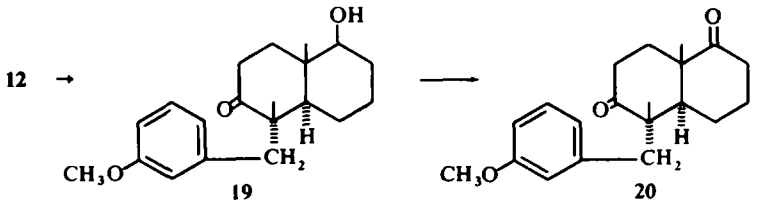
When **5a** was reduced in ethanol in the presence of a Pt catalyst, one carbonyl group was selectively reduced to give **12** in good yield. That it was the indicated CO group which was reduced was proven by the following reactions:



Selective reduction of **13** with sodium borohydride gave the alcohol **14** which was converted to the t-butyl ether **15** by reaction with isobutylene using a phosphoric acid-boron trifluoride catalyst.[10] Formylation followed by condensation with N-methylaniline afforded the blocked ketone **16b**. Alkylation and hydrolysis as before gave **17** and **18**. Finally, cleavage of the t-butyl ether with hydrogen bromide in chloroform yielded **12** indentical to the product of direct reduction of **5a**.

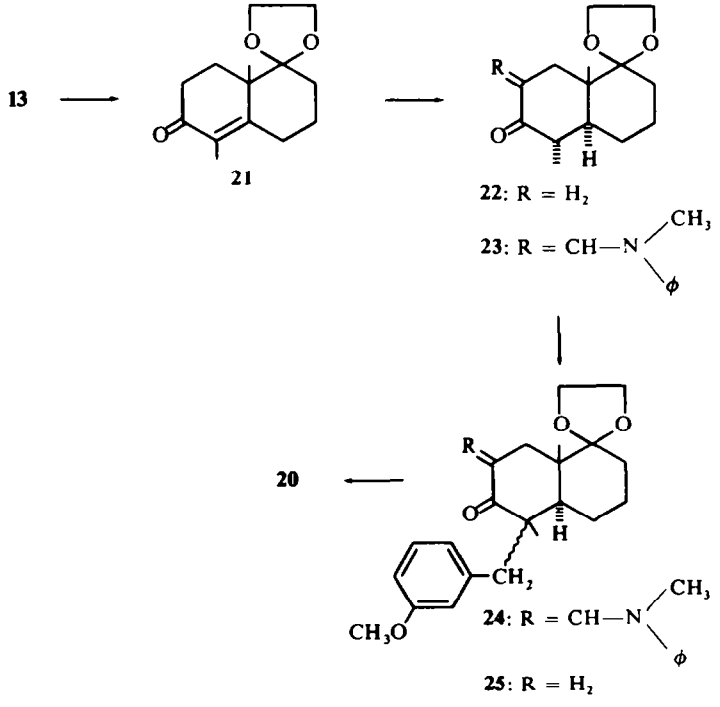
The borohydride reduction of **13** to the alcohol **14** has already been described. The alcohol has been assigned the β-stereochemistry *cis* to the angular Me group.[11] Cyclization of **12** by polyphosphoric acid followed by acetylation gave a product in excellent yield which was shown to be identical to **7b** derived from **6a**. This then established the stereochemistry of the C-17a OH group as β.

Further reduction of the alcohol **12** in ethanol at 75° gave a crude dihydro product **19** which was oxidized directly to the crystalline diketone **20** shown below to have a *trans* ring fusion.



The recent work of Spencer[12] *et al.* suggested that the question as to the stereochemistry of **11** and **20** might be answered by inspection of their NMR spectra. These authors showed that measurement of the width at half peak height of the Me signals would establish the nature of the ring fusion in **11** and **20**. They found that this band width was consistently greater in the *trans* than in the corresponding *cis* compounds. Application of this method gave equivocal results for two reasons. The difference being measured are small—in the order of 0·7 c/s—and secondly, **11** and **20** each has two Me groups the signals for which could not be confidently assigned.

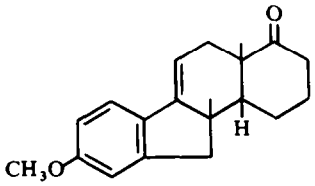
An alternative method was therefore devised which allowed the *trans* stereochemistry to be assigned unambiguously to **20**. Selective ketalization[4] of **13** gave **21**. Reduction of **21** by lithium in liquid ammonia gave **22** in which the former of the *trans* ring fusion may be assumed.[13] The secondary Me group is assigned the equatorial configuration since the compound is recovered unchanged on treatment with base. Formylation of **22** followed by reaction with N-methylaniline then afforded **23**. There



was no reason to expect that alkylation of **23** would be as stereospecific as found in the case of **1**. In fact it would be surprising.[14] It was hoped nevertheless that if a mixture were obtained, the presence of either **11** or **20** could be demonstrated thereby esta-

blishing the *trans* ring fusion in one of them. Alkylation of **23** with *m*-methoxybenzyl chloride yielded **24** which was converted by strong base to **25**. Mild acid hydrolysis of **25** then gave, in an over-all yield of 29% from **23**, a product identical in all respects with **20**.

Both **11** and **20** were cyclized by polyphosphoric acid to yield the tetracyclic products **26** and **27** respectively. It now became possible to relate **27** with one of the



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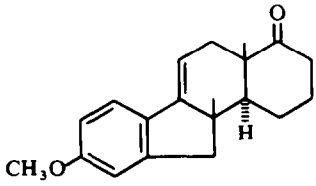

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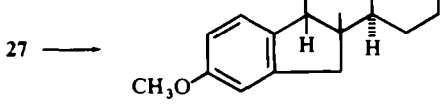
products obtained from the reduction of **8**. Catalytic reduction of **27** gave **28**. Further reduction of **28** by sodium borohydride followed by acetylation gave **10a** identical with one of the compounds derived from **8**.



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EXPERIMENTAL

M.ps were determined in open capillaries and are uncorrected. IR spectra were determined in mineral oil mulls on a Perkin–Elmer Infracord spectrometer. NMR Spectra were obtained in $CDCl_3$ on a Varian A-60A NMR Spectrometer using TMS as the internal standard. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

3′,7′,8′,8a′-*Tetrahydro*-5′α-(m-*methoxybenzyl*)-5′β,8′aβ-*dimethyl*-7′-(N-*methylanilinomethylene*)-*spiro*[1,3-*dioxolane*-2,1′(2′H)-*naphthalen*]-6′(5′H)-*one* (**3a**)

To a stirred solution of 223·5 g of **1** in 2·5 l. dry dimethoxy-ethane under N_2 was added 71·7 g of a 54% suspension of NaH in mineral oil. The mixture was refluxed for 2 hr. After cooling, 147·6 g of *m*-methoxybenzyl chloride was added in a slow stream and refluxing continued for 2 hr. Water was cautiously added to the cold mixture to destroy excess NaH. The mixture was diluted with water and extracted twice with CH_2Cl_2. The combined extracts were washed twice with water, then with sat NaCl aq, dried with Na_2SO_4, filtered and evaporated. The residue crystallized from ether to give 252·5 g (84%) of **3a**, m.p. 135–140° of sufficient purity for further preparative use. Three recrystallizations from acetone–hexane gave an analytical sample, m.p. 140·5–142°. (Found: C, 75·97; H, 7·59; N, 2·88. Calc. for $C_{10}H_{35}NO_4$: C, 76·08; H, 7·45; N, 2·96%).

3′,7′,8′,8′a-*Tetrahydro*-5′α-(m-*benzyloxybenzyl*)-5′β, 8′aβ-*dimethyl*-7′-(N-*methylanilinomethylene*)-*spiro*-[1,3-*dioxolane*-2,1′(2′H)-*naphthalene*]-6′(5′H)-*one* (**3b**)

Following the same procedure as described for the preparation of **3a**, 5·37 g of **1** was alkylated with 3·89 g. *m*-benzyloxybenzyl chloride in 50 ml dry dimethoxyethane using 1·72 g NaH (54% mineral oil suspension). Work up gave 9·4 g of crude **3b** which could not be crystallized and used directly for the preparation of **4b**.

3′,7′,8′,8′a-*Tetrahydro*-5′α-(m-*methoxybenzyl*)-5′β,8′aβ-*dimethyl-spiro*[1,3-*dioxolane*-2,1′(2′H)-*naphthalene*]-6′(5′H)-*one* (**4a**)

To a soln of 246·6 g of **3a** in 1·7 l. 2-ethoxyethanol was added a soln of 495 g KOH in 1·7 l. water. The mixture was refluxed for 7 hr under N_2. After standing overnight under N_2 the soln was diluted with an equal volume of water and extracted 3 times with ether. The combined extracts were washed with water, cold 2N HCl and twice with water, dried over Na_2SO_4 and evaporated. The residue, 176 g (95%) crystallized completely to a pale yellow solid, m.p. 85–86°. The analytical sample from n-propanol had m.p. 85·5–86·5°; ν_{max} 1710 (C=O), 1650 (C=C), 1600 (Ph). (Found: C, 73·83; H, 7·88. Calc. for $C_{22}H_{28}O_4$: C, 74·13; H, 7·92%).

3′,7′,8′,8′a-*Tetrahydro*-5′α-(m-*benzyloxybenzyl*]-5′β,8′aβ-*dimethyl-spiro*[1,3-*dioxolane*-2,1′(2′H)-*naphthalen*]-6′(5′H)-*one* (**4b**)

The crude alkylated product **3b** prepared as above from 0·68 mole of **1** was hydrolyzed by 644 g KOH in 2·2 l. 2-ethoxyethanol and 2·2 l water. Work up as for **4a** gave a crude product difficult to crystallize and normally used without purification for the preparation of **4c**. This lot of crude **4b** in a mixture of ether and hexane afforded 71·8 g of **4b**, m.p. 71–74·5°. Recrystallization from EtOH gave an analyical sample m.p. 79–80°; ν_{max} 1710 (C=O), 1650 (C=C), 1600 (phenyl). (Found: C, 77·98; H, 7·36. Calc. for $C_{28}H_{32}O_4$: C, 77·75; H, 7·46%).

3′,7′,8′,8′a-*Tetrahydro*-5′α-(m-*hydroxybenzyl*)-5′β,8′aβ-*dimethyl-spiro*[1,3-*dioxolane*-2,1′(2′H)-*naphthalen*]-6′(5′H)-*one* (**4c**)

A soln of 67·9 g of **4b** in 500 ml EtOH was reduced with H_2 in the presence of 8 g 5% Pd on C. After 42 hr the soln was filtered and the solvent evaporated. The residue was used without purification for the preparation of **5b**. Trituration of the product with ether and recrystallizing the product from 2-propanol gave an analytical sample, m.p. 155–156°; ν_{max} 3350 (OH), 1680 (C=O), 1650 (C=C), 1600 (Ph). (Found: C, 73·86; H, 7·82. Calc. for $C_{21}H_{26}O_4$: C, 73·66; H, 7·65%).

3,7,8,8a-*Tetrahydro*-5α-(m-*methoxybenzyl*)-5β,8aβ-*dimethyl*-1,6(2H,5H)-*naphthalenedione* (**5a**)

A soln of 85·7 g of **4a** in 600 ml EtOH and 360 ml 2N HCl was refluxed for 1 hr. The cold soln was diluted with water and extracted twice with ether. The combined ether layers were washed twice with water, dried and evaporated to give 74·0 g (98%) of **5a** as an oil. A small protion was distilled at 195° and 1 mm to give an analytical sample. (Found: C, 77·21; H, 8·05. Calc. for $C_{20}H_{24}O_3$: C, 76·89; H, 7·74%). Upon long standing it crystallized to give pure **5a** having m.p. 52–53°; ν_{max} 1710 (C=O), 1650 (C=C) 1610, 1590 (Ph); τ 4·15 (1H, tri), 6·28 (3H), 8·63 (3H), 8·86 (3H).

3,7,8,8a-*Tetrahydro*-5α-(m-*hydroxybenzyl*)-5β,8aβ-*dimethyl* 1,6(2H,5H)-*naphthalenedione* (**5b**)

A soln containing 51·6 g of **4c** in 300 ml EtOH and 100 ml 2N HCl was refluxed for 2 hr. Work up as for **5a** gave 45·7 g (100%) of **5b**, m.p. 119–122°. Recrystallization from toluene gave an analytical sample m.p. 120·5–121·5°; ν_{max} 3350 (OH), 1700, 1680 (C=O) 1650 (C=C), 1600 (Ph). (Found: C, 76·32; H, 7·40. Calc. for $C_{19}H_{22}O_3$: C, 76·48; H, 7·43%).

3-*Methoxy*-8β-*methyl*-D-*homo*-B-*nor-estra*-1,3,5(10),9(11), 14-*pentaen*-17a-*one* (**6a**)

To about 350 ml polyphosphoric acid was added 30 g of **5a** in 19 ml benzene. The mixture was stirred gently until it became very viscous and red in color. After stirring briskly for 5 min a large amount of ice was added. Stirring was continued until all the acid had dissolved. The mixture was diluted with water and extracted twice with ether. The combined extracts were washed twice with water, dried (Na_2SO_4) and evaporated. The residue crystallized from EtOH to give 20·0 g of **6a**, m.p. 113·5–115°. A second crop, 3·3 g, m.p. 108–111 was obtained from the mother liquors. The analytical sample obtained from ether-hexane had m.p. 114–115°; ν_{max} 1720; τ 4·16 (2H,), 6·25 (3H), 8·59 (3H), 8·72 (3H). (Found: C, 81·69; H, 7·34. Calc. for $C_{20}H_{22}O_2$: C, 81·60; H, 7·53%).

3-*Hydroxy*-8β-*methyl*-D-*homo*-B-*nor-estra*-1,3,5(10),9(11),14-*pentaen*-17a-*one* (6b)

A. To about 25 g polyphosphoric acid was added 1·0 g of **5b** in 2 ml warm benzene. After stirring vigorously for 5 min, excess ice was added followed by water and CH_2Cl_2. The organic phase was washed with water, dried (Na_2SO_4) and evaporated. The residue was triturated with ether to give 300 mg of **6b**, m.p. 169–173°. Two recrystallizations from n-propanol gave an analytical sample m.p. 175–177°; $\nu_{max}^{AsCl_3}$ 3600 (OH), 1700 (C=O), 1600 (Ph); τ 4·13 (2H), 8·61 (3H), 8·72 (3H). (Found: C, 81·04; H, 7·17. Calc. for $C_{19}H_{20}O_2$: C, 81·39; H, 7·19%).

B. To about 2 ml liquid HF, stirred and cooled in an ice-water bath, was added 1 g of **5b**. After 5 min the mixture was diluted with CH_2Cl_2 and water. The organic phase was washed with water, sat $NaHCO_3$ aq, dried (Na_2SO_4) and evaporated. The residue was crystallized from MeCN to give 600 mg of **6b**, identical with the product prepared in A.

This material often crystallizes in two distinct crystalline forms from the same soln. These have different liquid paraffin mull IR spectra. The soln IR spectra (in $AsCl_3$) and NMR spectra of the two forms are identical.

3-*Methoxy*-8β-*methyl*-D-*homo*-B-*nor*-*estra*-1,3,5(10),9(11),14-*pentaen*-17aβ-*ol*(**7a**) and *acetate* **7b**

To a soln of 3·5 g of **6a** in 55 ml 95% EtOH was added 1·0 g $NaBH_4$. After ¾ hr a further 1·0 g $NaBH_4$ was added. The mixture was warmed intermittently on the steam bath for 2 hr. The soln was diluted with water, acidified with conc HCl and extracted with ether. The extract was washed twice with water, sat $NaHCO_3$ aq, dried (Na_2SO_4) and the solvent evaporated. The IR spectrum of the residue, **7a**, showed complete reduction. This material could not be crystallized.

The crude alcohol **7a** was dissolved in 25 ml Ac_2O and 6 ml pyridine. After standing overnight at room temp, the solvents were removed *in vacuo*. The residue was dissolved in ether and the ether washed successively with 2N HCl, water and sat $NaHCO_3$ aq. The ether soln was dried (Na_2SO_4) and evaporated. The residue in 1:1 benzene–hexane was filtered through a plug of magnesium silicate. The solvents were removed under reduced press and the residue crystallized from hexane to give 2·75 g of **7b**, m.p. 93–99°. Two further crystallizations from hexane gave an analytical sample, m.p. 98–99·5°; ν_{max} 1730, 1250; τ 4·22 (1H, tri), 4·45 (1H, tri), 5·13 (1H, qu), 6·18 (3H), 7·8 (3H), 8·62 (3H), 8·69 (3H). Found: C, 77·98; H, 7·91. Calc. for $C_{22}H_{26}O_3$: C, 78·07; H, 7·74%).

3-*Methoxy*-8β-*methyl*-D-*homo*-B-*nor*-9β-*estra*-1,3,5(10),14-*tetraen*-17aβ-*ol acetate* (**8**)

A soln of 5·0 g of **7b** in 100 ml AcOH was reduced with H_2 at atmospheric press and room temp in the presence of 400 mg 5% Pd on C. Reduction stopped after 21 min. The catalyst was removed by filtration and the solvent evaporated. The residue was filtered through a plug of magnesium silicate in 1:1 benzene–hexane. After removing the solvents, the residue was crystallized from hexane to give 4·4 g of **8**, m.p. 99–101°. The analytical sample had m.p. 102·5–103·5°; λ_{max}^{MeOH} 280 (ε 2,780); ν_{max} 1730, 1250; τ 4·38 (1H, tri), 5·39 (1H, qu), 6·25 (3H), 7·98 (3H), 8·65 (3H), 8·75 (3H). (Found: C, 77·75, H, 8·16. Calc. for $C_{22}H_{28}O_3$: C, 77·61; H, 8·29%).

Reduction of 3-*methoxy*-8β-*methyl*-D-*homo*-B-*nor*-9β-*estra*-1,3,5(10),14-*tetraen*-17aβ-*ol acetate* (**8**)

A soln containing 1·02 g of **7b** in 54 ml EtOH was hydrogenated at 75° and 3 atmospheres in the presence of 300 mg 5% Pd on C. After 3 days, the mixture was cooled, the catalyst removed and the solvent evaporated. The residue in ether was filtered through a plug of magnesium silicate to remove colloidal catalyst. The ether was evaporated and the residue crystallized from hexane to give 223 mg (22%) of the *trans* isomer **10a**, m.p. 158–159·5. The analytical sample from the same solvent had m.p. 162–162·5°; ν_{max} 1740, 1240 (acetate); τ 5·75 (1H), 6·19 (3H), 8·02 (3H) 8·77 (3H), 8·94 (3H). (Found: C, 77·37; H, 8·66. Calc. for $C_{22}H_{30}O_3$: C, 77·15; H, 8·83%).

The mother liquors from the isolation of **10a** were evaporated and the residue refluxed in 25 ml EtOH and 25 ml 2N KOH for 2 hr. The mixture was cooled, diluted with water and extracted with ether. The ether extract was washed twice with water, dried (Na_2SO_4) and evaporated. Crystallization of the residue from pentane gave 444 mg (49%) of **10b**, m.p. 95–96°. The analytical sample had m.p. 95–96°; ν_{max} 3500 (OH); τ 6·18 (3H), 8·96 (3H), 9·02 (3H). (Found: C, 80.05; H, 9·73. Calc. for $C_{20}H_{28}O_2$: C, 79·95; H, 9·39%).

A sample of **10b**, was acetylated by means of Ac_2O-pyridine. The usual work up gave the crystalline **10c**, m.p. 114–115°. The analytical sample from hexane had m.p. 114·5–115·5°; ν_{max} 1740, 1260 (acetate); τ 4·6 (1H, m), 6·2 (3H), 8·01 (3H), 8·88 (3H), 9·01 (3H). (Found: C, 77·04; H, 8·98. Calc. for $C_{22}H_{30}O_3$: C, 77·15; H, 8·83%).

3,4,4aβ,7,8,8a-*Hexahydro*-5α-(m-*methoxybenzyl*)-5β,8aβ-*dimethyl*-1,6,(2H,5H)-*naphthalenedione* (**11**)

The yield in this reduction varied considerably. The best results were obtained with an old, rather inactive catalyst. Alternatively, catalytic activity was reduced by the addition of triethylamine to the soln.

The reduction of 31·2 g of **5a** in 250 ml EtOH was carried out at 70° and 3 atmospheres in the presence of 5 g of 5% Pd on C. After 48 hr, the soln was cooled, the catalyst removed and the solvent evaporated. The residue was crystallized from hexane–acetone to give 20·15 g (64%) of **11**, m.p. 98–102°. Two further crystallizations from the same solvents gave an analytical sample, m.p. 102–103·5°; ν_{max} 1710 (C=O), 1610, 1590 (Ph); τ 6·28 (3H), 8·67 (3H), 8·89 (3H). (Found: C, 76·53; H, 8·29. Calc. for $C_{20}H_{26}O_3$: C, 76·40; H, 8·35%).

3,4,4a,5,6,7-*Hexahydro*-5β-*hydroxy*-1α-(m-*methoxybenzyl*)-1β,4aβ- *dimethyl*-2(1H)-*naphalenone* (**12**)

Reduction of 2 g of **5a** in 50 ml EtOH was carried out at 75° and 3 atmospheres in the presence of 150 mg PtO_2. After 16 hr, the catalyst was removed and the solvent evaporated. The residue was crystallized from ether–hexane to give 1·45 g of **12**, m.p. 99–101°. The analytical sample had m.p. 103·5–104°; ν_{max} 3600 (OH), 1700 (C=O), 1600 (Ph); τ 4·48 (1H, tri), 6·24 (3H), 8·69 (3H) 9·10 (3H). (Found: C, 76·47; H, 8·30. Calc. for $C_{20}H_{26}O_3$: C, 76·40; H, 8·34%).

3-*Methoxy*-8β-*methyl*-D-*homo*-B-*nor-estra*-1,3,5(10), 9(11), 14-*pentaen*-17aβ-*ol acetate* (**7b**) *via cyclization of* **12**

Cyclization of 0·5 g of **12** with polyphosphoric acid as described for **5a** gave crude **7a** which on acetylation yielded 290 mg **7b** identical with that prepared from **6a**.

5β-*t-Butoxy*-4,4a,5,6,7,8-*hexahydro*-1,4aβ-*dimethyl*-2(3H)-*naphthalenone* (**15**)

Selective $NaBH_4$ reduction of **13** gave **14**, m.p. 79–80°. (Found: C, 74·19; H, 9·34. Calc. for $C_{12}H_{18}O_2$: C, 74·17; H, 9·24%).

To a soln of 4·0 g of **14** in 20 ml dry CH_2Cl_2 at −20° in pressure bottle was added 20 ml isobutylene followed by 0·5 ml catalyst (100% phosphoric acid saturated with BF_3). The bottle was closed and the mixture shaken overnight at room temp. After cooling to −20°, the bottle was opened and excess isobutylene removed by a stream of N_2. The residue was diluted with CH_2Cl_2 and thoroughly washed with sat $NaHCO_3$ aq. The organic phase was dried (Na_4SO_4) and evaporated. The residue from four such experiments was combined to give 24·1 g of oil. A soln of this oil in hexane was passed through a short column of neutral alumina. Evaporation of the hexane gave 20·85 g of **15** of sufficient purity for further use. Short-path distillation of a small aliquot gave an analytical sample of **15**, b.p. 120–122 at 0·3 mm, n_D^{25} 1·5073 (Found: C, 76·72; H, 10·65. Calc. for $C_{16}H_{26}O_2$: C, 76·75; H, 10·47%).

5β-*t-Butoxy*-4,4a,5,6,7,8-*hexahydro*-3-(*hydroxymethylene*)-1,4aβ-*dimethyl*-2(3H)-*naphthalenone* (**16a**)

To a stirred suspension of 111 g NaOMe in 1·9 l. benzene under N_2 was added 300 ml ethyl formate. After cooling the mixture to 12°, 150·5 g of **15** in 700 ml benzene was added dropwise. Stirring was then continued overnight at room temp. The mixture waw extracted with water followed by two 250 ml portions of 2N NaOH. The combined aqueous phases were acidified with 2·5M NaH_2PO_4 and extracted with ether. The extract was washed twice with water, dried and exaporated. The residue, 164·2 g of oil was used without further purification.

A sample crystallized from n-propanol had m.p. 76–77°. (Found: C, 73·26; H, 9·42. Calc. for $C_{17}H_{26}O_3$: C, 73·34, H, 9·41%).

5β-*t-Butoxy*-4,4a,5,6,7,8-*hexahydro*-1,4aβ-*dimethyl*-3-(N-*methylanilinomethylene*)-2(3H)-*naphthalenone* (16b)

To a soln of 2·78 g of crude **16b** in 10 ml MeOH was added 1·17 g N-methylaniline. After standing overnight, the solvent and excess aniline were removed *in vacuo* to leave 3·5 g of oil of sufficient purity for the preparation of **17**. It could be crystallized only with difficulty from nitromethane, m.p. 77·5–79°; ν_{max} 1640 (C=O), 1600 (Ph), 1550 (—N—C=C); τ (HoAc soln) 2·22 (1H), 6·53 (3H), 8·17 (3H), 9·05 (9H), 9·07 (3H).

5β-*t-Butoxy*-3,4,4a,5,6,7-*hexahydro*-1α-(m-*methoxybenzyl*)-1β,4aβ-*dimethyl*-3-(N-*methylanilinomethylene*) 2(1H)-*naphthalenone* (**17**)

Alkylation of 79·7g of **16b** with 51·1 g m-methoxybenzyl chloride in 850 ml dimethoxyethane using 24·6 g of 54% NaH mineral oil suspension exactly as described for the preparation of **3a** gave 77·4 g (73%) **17**, m.p. 119–121°.

Recrystallization from n-propanol gave an analytical sample m.p. 120·5–121·5°; ν_{max} 1670, 1650, 1600, 1570. (Found: C, 78·62; H, 8·63; N, 2·77. Calc. for $C_{32}H_{41}NO_3$: C, 78·81; H, 8·47; N, 2·87%).

5β-*tert-Butoxy*-3,4,4a,5,6,7-*hexahydro*-1α-(m-*methoxybenzyl*)-1β,4aβ-*dimethyl*-2(1H)-*naphthalenone* (**18**)

Hydrolysis of 74·9 g of **17** by 146 g KOH in 500 ml water and 500 ml 2-ethoxyethanol exactly as described for the preparation of **4a** gave 38·9 g (68%) of **18** as an oil [ν_{max} 1710 (C=O), 1650 (C=C), 1600 (Ph)] of sufficient purity for the preparation of **12**.

3,4,4a,5,6,7-*hexahydro*-5β-*hydroxy*-1α-(m-*methoxybenzyl*)-1β,4aβ-*dimethyl*-2(1H)- *naphthalenone* (**12**) *from the* t-*butyl ether* **18**

Gaseous HBr was passed into 300 ml $CHCl_3$ at 0° for 1 hr. A soln of 34·8 g of **18** in 200 ml $CHCl_3$ was added and the mixture left at 0° for 1 hr. The soln was then washed twice with water, sat $NaHCO_3$aq, dried and evaporated. The residue was crystallized from ether–hexane to give 25·0 g (84·6%) of 12, m.p. 103·5–104° identical with the product obtained from the catalytic reduction of **5**.

3,4,4aα,7,8,8a-*Hexahydro*-5α-(m-*methoxybenzyl*)-5β,8aβ-*dimethyl*-1,6(2H,5H)-*naphthalenedione* (**20**)

A soln containing 22·0 g of **12** in 240 ml EtOH was hydrogenated at 73° and 3 atmospheres in the pressence of 5 g of 5% on C. After 65 hr the mixture was cooled, the catalyst removed and the solvent evaporated. The residue in ether was filtered through a plug of magnesium silicate. Evaporation of the ether gave 21·5 g of crude **19** as an oil, ν_{max} 3500 (OH), 1700 (C=O), 1600 (Ph).

Crude **19** was oxidized in the usual way by Jones' reagent. Usual work up gave the crude dione **20** which was crystallized from ether–hexane to give 17·7 g (80·4%) of *trans* **20**, m.p. 84–88°. The analytical sample of **20** had m.p. 91–92°, ν_{max} 1700 (C=O), 1610, 1580 (Ph); τ 6·26 (3H), 8·76 (3H) 8·79 (3H). (Found: C, 76·32; H, 8·44. Calc. for $C_{20}H_{26}O_3$: C, 76·40; H, 34%).

3′,4′,4′aα,5′,8′,8,a-*Hexahydro*-5′α,8′aβ *Dimethyl*-7′-(N-*methylanilinomethylene*) -*spiro*[1,3 *dioxolane*-2,1′(2′H)-*naphthalen*]-6′(7′H)-*one* (**23**)

To a soln of 1·0 g Li in 200 ml distilled ammonia was added dropwise with stirring 2·36 g of **21** in 100 ml dry ether. After stirring for ½ hr, excess Li was destroyed by the addition of excess $NaNO_2$ and the ammonia evaporated. The residue was distributed between water and ether. The ether extract was thoroughly washed with water, dried and exaporated to give 2·15 g of crude **22** contaminated with some starting material. Purification of **22** is readily accomplished by the method of Counsell *et al.*[15] To crude **22** in 50 ml MeOH was added 8·5 g meta $NaHSO_3$ in 42 ml H_2O and the mixture stirred for 0·5 hr. The precipated solid (1·8 g) was filtered off and washed with MeOH. The addition compound was decomposed by 3N NaOH and the free ketone extracted into ether. The ether extract was washed with water, dried and evaporated. This gave 1·1 g of pure **22**:; ν_{max} 1710 cm^{-1} (sat. CO); τ 6·08 (4H), 8·75 (3H), 9·03 (3H, d, J = 6 c/s).

Using the procedure described for the preparation of **16b** from **15**, the saturated ketone **22** was converted to crystalline **23** in overall yield of 76%, m.p. 133–143°, τ 6·59 (3H), 8·82 (3H, d, J = 6 c/s), 9·12 (3H). (Found: C, 74·41; H, 8·24; N, 4·20. Calc. for $C_{22}H_{29}O_3N$: C, 74·33; H, 8·22; N, 3·94%).

Preparation of trans-*diketone* **20** *from* **23**

To 1·2 g of **23** in 130 ml dry dimethoxyethane under N_2 was added 0·37 g of 54% NaH in mineral oil followed by 1·05 g of *m*-methoxybenzyl chloride. The mixture was refluxed with stirring for 5 hr. After cooling, water was added cautiously followed by excess 2·5M NaH_2PO_4. The mixture was extracted twice with ether, the combined extracts washed twice with water, dried and evaporated.

The crude **24** was hydrolyzed as described for the hydrolysis of **17** using 14 ml ethylene glycol monoethyl ether and 14 ml water containing 4 g KOH. After a similar work up, the crude product was chromatographed on neutral alumina. The fractions eluted with hexane, 1:1 hexane–benzene and benzene were combined. The crude product **25** was then acid hydrolyzed to remove the ketal exactly as described for **5a**. Work up gave an oil which crystallized from hexane to give 307 mg (29% from **23**) of **20** m.p. 85–88°. When recrystallized from ether–hexane it had m.p. 91–92° and was identical in all respects with **20** prepared from **12**.

3-*Methoxy*-8β-*methyl*-D-*homo*-B-*nor*-*estra*-1,3,5(10), 9(11)-*tetraen*-17a-*one* (**27**)

Cyclization of 50 g of **20** in 60 ml benzene with approximately 600 ml polyphosphoric acid as

described for **6a** gave 38·1 g of **27** m.p. 149–151° from acetonitrile. The analytical sample from EtOH had m.p. 152·5–154°, ν_{max} 1710 (C=O), 1610, 1580 (Ph); τ 4·36 (1H, tr), 6·26 (3H), 8·73 (3H), 8·88 (3H). (Found: C, 80·78; H, 8·18. Calc. for $C_{20}H_{24}O_2$: C, 81·04; H, 8·16%).

3-*Methoxy*-8β-*methyl*-D-*homo*-B-*nor*-14β-*estra*-1,3,5(10), 9(11)-*tetraen*-17a-*one* (**26**)

Cyclization of 5 g of **11** in 10 ml benzene with 200 g polyphosphoric acid as described for **6a** gave 3·6 g (76%) of **26**, crystallized from ether–hexane, m.p. 81–91°. The analytical sample obtained from EtOH had m.p. 93–94°, ν_{max} 1700 (C=O), 1610, 1590 (Ph); τ 4·04 (1H, tr), 6·20 (3H), 8·63 (3H), 8·78 (3H). (Found: C, 80·88, H, 8·12. Calc. for $C_{20}H_{24}O_2$: C, 81·04; H, 8·16%).

m-*Benzyloxybenzyl chloride*

To a soln of 214 g of *m*-benzyloxybenzyl alcohol in 1·2 l. $CHCl_3$ containing 2 ml pyridine was added dropwise during 1 hr 87 ml $SOCl_2$. After the addition, the soln was refluxed for 1 hr. The mixture was poured onto ice, the organic phase separated, washed with sat $NaHCO_3$ aq, twice with water, dried and evaporated. The residue distilled at 143–149° at 0·2 mm. This was crystallized from MeOH to give 181 g (78%) *m*-benzyloxybenzyl chloride, m.p. 42–46°. The analytical sample was obtained from MeOH, m.p. 45–46°. (Found: C, 72·03; H, 5·64; C, 15·03. Calc. for $C_{14}H_{13}ClO$: C, 72·24; H, 5·63; Cl, 15·24%).

3-*Methoxy*-8β-*methyl*-D-*homo*-B-*nor*-9β-*estra*-1,3,5(10)-*trien*-17aβ-*ol acetate* (**10a**) *from* **27**

Hydrogenation of 296 mg of **27** was carried out in 20 ml EtOH in the presence of 100 mg 5% Pd on C at room temp and atm press. Reduction was complete in 15 min. The catalyst was removed, the solvent evaportated and the residue crystallized from acetone–hexane to give 185 mg of **28**, m.p. 130–134 used without further purification.

To a soln of 150 mg of **28** in 5 ml EtOH was added 150 mg $NaBH_4$. After standing overnight, the soln was diluted with water, acidified (conc HCl) and extracted into ether. The ether was washed twice with water, dried and evaporated. The crude alcohol was acetylated with Ac_2O-pyridine in the usual way. This yielded 95 mgs of **10a**, m.p. 158–160° identical in all respects with one of the reduction products derived from **8**.

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