Novel Insertion, Rearrangement and Addition Products from Dihalogenocarbene Reactions with 5(10)-Unsaturated Steroids

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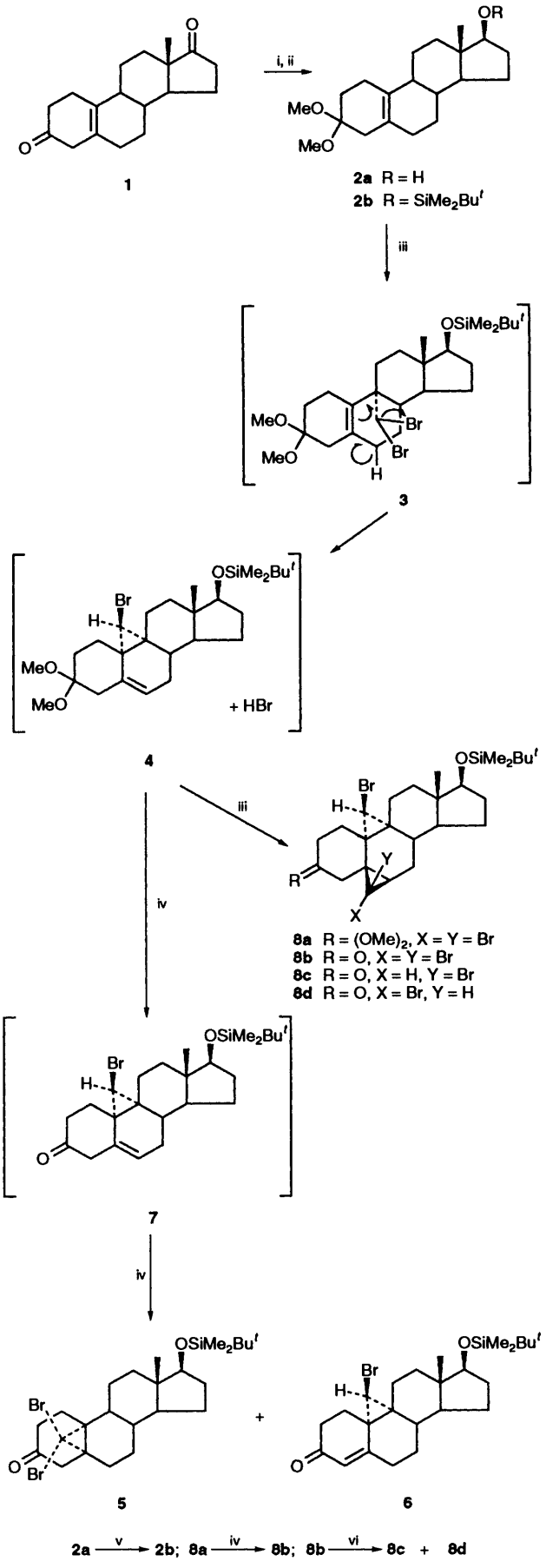
Novel insertion, rearrangement and addition products from dibromocarbene and dichlorocarbene reactions with 5(10)-unsaturated steroids have been identified. The dihalogenocarbenes were prepared under phase-transfer conditions ($CHBr_3$– or $CHCl_3$–NaOH), and from $CHBr_3$–$KOBu^t$–Et_2O, phenyl(trichloromethyl)mercury and sodium trichloroacetate. Evidence that the major products arise from an initial dihalogenocarbene reaction on the α face of the molecule is reported. The major products obtained from addition of CBr_2 to 3,17-disubstituted estr-5(10)-enes, after ketal hydrolysis, were 19(*S*)-bromo-9α,19-cyclo-10α-androst-4-en-3-one and 3,'3',19(*S*)-tribromo-3'*H*-9α,19-cyclocyclopropa[5,6]-5β, 10α-androstan-3-one derivatives together with the 19,19-dibromo-5α,19-cyclo-10α-steroid adduct. No products from addition of CBr_2 to the β face of the double bond, as previously reported, were identified. Reactions of CCl_2 gave, besides rearrangement products analogous to those obtained from CBr_2, a 5α-hydroxy-9α,19α-cycloandrostane derivative, the 9α-$CHCl_2$ insertion derivative and both α- and β-face addition products to the double bond. Structures were established by homonuclear and heteronuclear correlation and nuclear Overhauser effect NMR measurements and X-ray crystallography.

The addition of dihalogenocarbenes to steroid double bonds has been studied extensively.[1,2] Dibromocarbene addition to the 5(10)-double bond was employed in an early synthesis of the androstane structure[3] and with retrosteroids[4,5] to introduce the angular 19-methyl group. This dibromocarbene adduct was required as an intermediate in the synthesis of potential steroid enzyme inhibitors. Various reagents have been utilised to prepare dihalogenocarbenes in such reactions. Difluorocarbene, prepared from thermolysis of CF_2ClCO_2Na in refluxing diglyme [$(MeOCH_2CH_2)_2O$], has been reported to add to both the α- and the β-face of 3α,17β-diacetoxyestr-5(10)-ene, with β-face addition as the major product.[2] Dibromocarbene, prepared from $CHBr_3$–$KOBu^t$–Et_2O, has been reported[3a] to give, on addition to 17,17-ethylenedioxy-3,3-dimethoxyestr-5(10)-ene followed by acid hydrolysis, 19,19-dibromo-5β,19-cycloandrostane-3,17-dione (11% yield), which was converted *via* 5β,19-cycloandrostane-3,17-dione into androst-4-ene-3,17-dione. Dichlorocarbene insertion into steroid C–H bonds has been reported to take place at C-6 in the steroid 4-en-3-one[6] and at C-7 in the steroid 5-ene.[7] Dichlorocarbene-insertion reactions[8] are favoured in tertiary[9] and allylic[10] positions.

Results and Discussion

19-Hydroxyandrost-4-ene-3,17-dione was converted by modification of the method described by Ueberwasser *et al.*,[11] *via* estr-5(10)-ene-3,17-dione **1**, into the ketal alcohol **2a**, which yielded 17β-(*tert*-butyldimethylsiloxy)-3,3-dimethoxyestr-5(10)-ene **2b** (Scheme 1). Treatment of the 5(10)-ene **2b** with dibromocarbene, prepared from $CHBr_3$–NaOH under phase-transfer catalysis (PTC) with cetyltrimethylammonium bromide (CTAB), gave multiple products but the expected addition product to the β face of the 5(10)-double bond[3a] was not isolated. From this reaction the tribromo derivative **8a** was obtained in 37% yield, which on hydrolysis with acetone and aq. HCl gave the corresponding ketone **8b**. Initial treatment of the crude product from the dibromocarbene reaction with acetone and HCl, followed by chromatography, yielded the tribromo derivative **8a** together with a lesser amount of the monobromo *exo* (*S*)-isomer **6**. When the reaction was carried out for a longer time the α-face dibromo adduct **5** was isolated in low yield also.

Scheme 1 shows the proposed intermediates **3**, **4** and **7** in the formation of compounds **6**, **8a** and **8b**. Rearrangement of the initially formed insertion product **3** to intermediate **4** led, after hydrolysis of the ketal, to compounds **6** and **8b**. Dibromocarbene insertion into the 9α C–H bond to give the 9α-$CHBr_2$ derivative **3** (see the analogous 9α-$CHCl_2$ products **21** and **22** below) followed by loss of the 6β-H, either as $H^\cdot$ or H^+, with concomitant introduction of the C-5 double bond formed the 9α,19-cyclo-10α-derivative **4** with the less sterically hindered *endo* H. The intermediate **4** on acidic hydrolysis of the ketal to intermediate **7** followed by double-bond conjugation gave the monobromo derivative **6** (see also compounds **13** and **17**). This reaction may be driven by relief of steric strain. This rearrangement is consistent with the observation that no incorporation of deuterium occurred when $CDCl_3$–NaOD–D_2O was used with PTC (see below). A second addition of dibromocarbene to the less sterically hindered β face of the 5,6-double bond gave the tribromo derivative **8a**, which on acid hydrolysis yielded the tribromo ketone **8b**. Reduction of the tribromo ketone **8b** with tributyltin hydride gave two isomeric products identified as the *endo* (*R*)-isomer **8c** and the *exo* (*S*)-isomer **8d**. Formation of the 5,6- rather than the 4,5-double bond, shown by formation of the 5,6-dibromocyclopropano derivative, is consistent with the greater stability of the 5,6-double bond, *e.g.* preferential formation of the C-5 unsaturated ketal from the steroid 4-en-3-one.[12] A minor component from this reaction proved to be 19,19-dibromo-17β-(*tert*-butyldimethylsiloxy)-5α,19-cyclo-10α-androstan-3-one **5**. When the PTC reaction was carried out for 18 h, followed by acid hydrolysis of the ketal, compounds **6** and **8b** were isolated; however, when the reaction was continued for 48 h compounds **5** and **8b** were obtained. The longer reaction time would allow the intermediate **4** to be more completely converted into



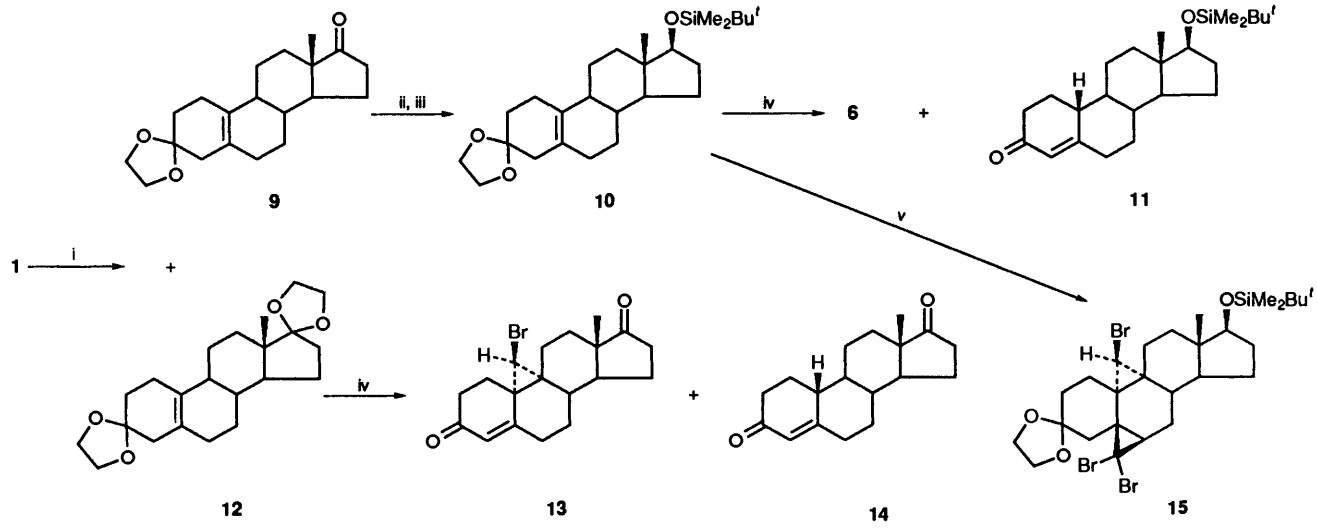
Scheme 1 *Reagents:* i, malonic acid–MeOH; ii, $NaBH_4$; iii, $CHBr_3$–NaOH–CTAB; iv, PTSA–acetone–water; v, Bu^tMe_2SiCl–imidazole–DMF; vi, Bu_3SnH–AIBN

compound **8a**, thus precluding formation of intermediate **7** to give enone **6**.

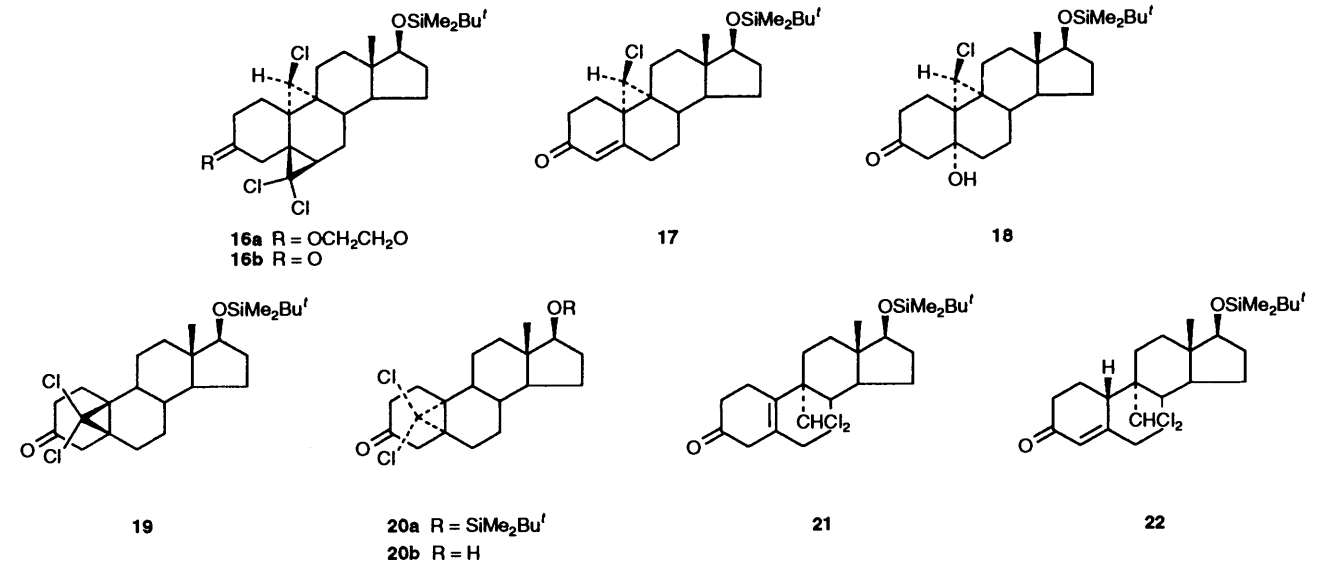
Selective C-3 ketalisation of the dione **1** by treatment with toluene-*p*-sulfonic acid (PTSA) and ethylene glycol in benzene at 50 °C for 1 h gave the monoketal **9**. Similar treatment (reflux using a Dean–Stark apparatus for 2 h gave a mixture of monoketal **9** and diketal **12** (**9**:**12**, 1:4), readily separable by chromatography. When reflux was continued for 16 h a mixture of the diketal **12** and the C-5 double-bond isomer, which proved difficult to separate, has been reported.[13]

17β-(*tert*-Butyldimethylsiloxy)-3,3-ethylenedioxyestr-5(10)-ene **10** was prepared from the ketal **9** by reduction ($NaBH_4$) of the C-17 ketone followed by silylation (Scheme 2). Treatment of the ketal **10** with dibromocarbene prepared from $CHBr_3$–$KOBu^t$–Et_2O gave mainly the monobromo derivative **6** together with the unsaturated ketone **11** after hydrolysis of the ketal with aqueous acid; the latter formed directly from the starting material. Ketal **10** under phase-transfer conditions with $CHBr_3$–NaOH–CTAB gave the tribromo derivative **15** as the major product isolated and this is consistent with addition of a second molecule of dibromocarbene to the intermediate C-5 double bond which is favoured under the more reactive phase-transfer conditions. Similarly, treatment of the diketal **12** with dibromocarbene prepared from $CHBr_3$–$KOBu^t$–Et_2O yielded, after acid hydrolysis, the monobromo derivative **13** (corresponding to the bromo derivative **6**) and the conjugated ketone **14** (corresponding to the unsaturated ketone **11**). The monobromo derivative **13** did not correspond to the expected 5β,19-cycloandrostane-3,17-dione previously reported by Birch *et al.*[3a]

In a series of reactions with 17β-(*tert*-butyldimethylsiloxy)-3,3-dimethoxyestr-5(10)-ene **2b** and 17β-(*tert*-butyldimethylsiloxy)-3,3-ethylenedioxyestr-5(10)-ene **10** the following products were identified after extensive chromatography (Scheme 3). Treatment of the ketal **10** with dichlorocarbene under PTC [$CHCl_3$–NaOH–benzyltriethylammonium chloride (BTEAC)] for 3 h at reflux, followed by acid hydrolysis of the ketal, gave fractions identified as the trichloro derivative **16a** (corresponding to the tribromo derivative **8a**), the monochloro derivative **17** (corresponding to the monobromo derivative **6**) and the 19,19-dichloro-5β,19-cycloandrostane **19**. Another fraction was identified as the unsaturated ketone **11** which can be derived directly from the ketal **10** on acid hydrolysis of the ketal followed by conjugation of the double bond. Repetition of this reaction using $CDCl_3$ and NaOD in D_2O with the ketal **10** showed no evidence for the incorporation of deuterium into the major products, **16a** and **17**, in the ^1H and ^{13}C NMR spectra; the singlet proton at δ_H 2.82 and 3.38 (19-H) in the ^1H NMR spectrum of the trichloro **16a** and monochloro **17** derivatives, respectively, was still present. This result is consistent with the rearrangement proposed in Scheme 1. A similar reaction with the dimethoxy ketal **2b**, using BTEAC at 25 °C, yielded fractions identified as follows. (i) 17β-(*tert*-Butyldimethylsiloxy)-19(*S*)-chloro-9α,19-cyclo-10α-androst-4-en-3-one **17** (corresponding to the bromo derivative **6**) and 17β-(*tert*-butyldimethylsiloxy)-19(*S*)-chloro-5β,6β-dichloromethylene-9α,19-cyclo-10α-androstan-3-one **16b**, the hydrolysis product from the dimethoxy ketal analogue of **16a**. The C-3 ethylenedioxy ketal in the trichloro derivative **16a** was resistant to PTSA–aq. acetone hydrolysis whereas similar treatment of the corresponding product from the dimethoxy ketal **2b** gave the trichloro ketone **16b**; (ii) the 19,19-dichloro-5α,19-cyclo-10α-androstane **20a**, also isolated as the 17β-alcohol **20b**, and 19,19-dichloro-5β,19-cycloandrostane **19**; (iii) The C(9α)–H insertion products, the unstable, non-crystalline, 9α-$CHCl_2$ **21** and its conjugated isomer **22**. Because dichlorocarbene-insertion reactions are favoured in tertiary and allylic positions, the axial C(9α)–H bond is the most favourable position for dichlorocarbene insertion to occur; (iv) the 19(*S*)-



Scheme 2 *Reagents:* i, $HOCH_2CH_2OH$–PTSA; ii, $NaBH_4$; iii, Bu^tMe_2SiCl–imidazole–DMF; iv, $CHBr_3$–$KOBu^t$–Et_2O; v, $CHBr_3$–NaOH–CTAB



2b —i, ii→ 11 + 16b + 17 + 18 + 19 + 20a + 20b + 21 + 22
10 —i, ii→ 11 + 16a + 17 + 19
10 —iii→ 11 + 16a
10 —iv→ 16a

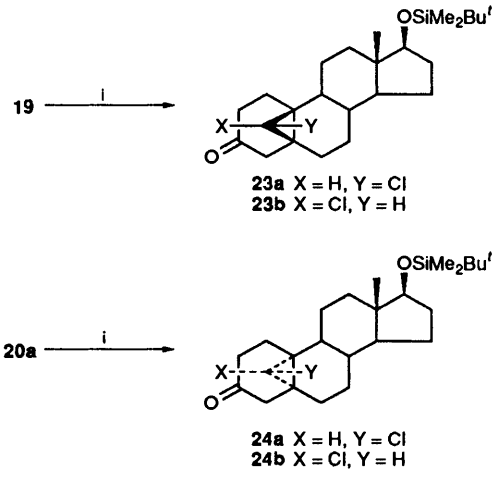
Scheme 3 *Reagents:* i, $CHCl_3$–NaOH–BTEAC; ii, PTSA–acetone–H_2O; iii, $PhHgCCl_3$; iv, CCl_3CO_2Na–diglyme

chloro-5α-hydroxy-9α,19-cyclo-10α-androstane derivative **18**, which may be formed by attack of water at C-5 and intramolecular rearrangement of the 9α-$CHCl_2$ derivative **21**; (v) the unsaturated ketone **11** was also isolated.

From treatment of the ketal **10** with phenyl(trichloromethyl)-mercury the trichloro derivative **16a** and the hydrolysis product from the starting material **11** were separated. The major product from treatment of the ketal **10** with dichlorocarbene, obtained from pyrolysis of CCl_3CO_2Na, was again the trichloro derivative **16a**.

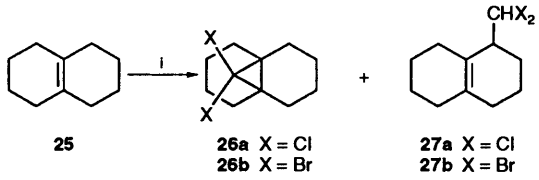
Tributyltin hydride reduction of the 19,19-dichloro-5β,19-cycloandrostane **19** gave two products identified as the monochloro 19(*R*)-isomer **23a** and the 19(*S*)-isomer **23b** (Scheme 4). Similarly, treatment of the 19,19-dichloro-5α,19-cyclo-10α-androstane **20a** gave the monochloro 19(*R*)-isomer **24b** and the 19(*S*)-isomer **24a**.

Anke *et al.*[14] reported that treatment of 9,10-octalin **25** with $CHCl_3$–NaOH–BTEAC for 3 h under reflux gave the dichloromethylene adduct **26a** in 96% yield on vacuum distillation.



Scheme 4 *Reagents:* i, Bu_3SnH–benzene

From this reaction under the same conditions we obtained the adduct **26a** in 51% yield together with the allylic dichloromethyl insertion product **27a** in 30% yield by flash chromatographic separation. The corresponding dibromo adducts **26b** and **27b** in 23 and 22% yield, respectively, were obtained when 9,10-octalin was treated with $CHBr_3$–NaOH–CTAB (Scheme 5).[15] This



25 **26a** X = Cl, **26b** X = Br **27a** X = Cl, **27b** X = Br

Scheme 5 *Reagents:* i, CHX_3–NaOH–BTEAC (Cl) or CTAB (Br)

result is consistent with the formation of the corresponding 9α-$CHBr_2$ insertion product **3** as an intermediate in the formation of compounds **6** and **8a**.

Nuclear Magnetic Resonance Analyses.—Steroid structures were established by ^1H NMR (Table 1) and ^{13}C NMR (Table 2) spectral analysis. ^{13}C NMR assignments are based on published data,[16] polarisation transfer[17] and internal consistency. Homonuclear[18] and heteronuclear[19,20] correlation and nuclear Overhauser effect (NOE)[21] measurements were performed as discussed below.

Homonuclear[18] (COSY) and heteronuclear[19] (HSQC) correlation spectra allowed a complete assignment of the carbon and proton spectra for compounds **6**, **8b**, **8c**, **8d**, **18**, **19**, **20a**, **22**, **23a**, **23b**, **24a** and **24b**. Because the cyclopropyl groups are located at quaternary sites, *i.e.* C-5, C-9 and C-10 and the dihalogeno carbons are quaternary themselves, the heteronuclear spectrum from the 2D heteronuclear multiple bond coherence (HMBC) experiment was critical in establishing the location of addition for products **8b**, **19** and **20a** and by analogy products **8a**, **15**, **16a**, **16b**, **18** and **20b**.

For the monobromo derivative **6** the COSY spectrum showed long-range (4-bond) coupling between the cyclopropyl proton and the 1β-H and 11β-H, consistent with the 9,10 location of the cyclopropyl group. These typical 'W' configuration couplings also suggest that the cyclopropyl group is located on the α face. NOE measurements observed from the cyclopropyl proton to the 7α-H (9.2%), 14-H (3.2%), 2α-H (0.5%) and 7β-H (−1.6%, *via* a 3-spin effect from the 7α-H) confirm that the cyclopropyl group is located on the α face. For compound **8b** the lack of unsaturation and the presence of three bromines was indicative of the addition of a second dibromocarbene. The location of the 9,10-cyclopropyl group was established by the presence of 4-bond couplings between the cyclopropyl proton and the 1β-H and 11β-H as seen in the monobromo derivative **6**. Furthermore these protons lacked the usual couplings to the 9α-H, and the expected cross-peaks were observed in the HMBC[20] spectrum. NOEs were observed from the (*S*)-C-19 cyclopropyl proton to the 7α-H (7.5%), 14-H (3.8%) and the 4α-H (4.8%) from which it was concluded that the cyclopropyl group is on the α side of the steroid with the hydrogen *endo*. While the HMBC[20] spectrum confirmed the location of the 5,6-cyclopropane ring the stereochemistry of addition could not be determined directly from the NMR data. However, the stereochemistry was established from the NOE data observed for compounds **8c** and **8d**. In compounds **8c** and **8d**, NOEs were observed from the 9,10-cyclopropyl proton to the 14-H and 7α-H. This confirmed the location of the cyclopropyl group on the α face of the steroid, with the hydrogen *endo* and the bromine *exo*, *i.e.* the (*S*)-isomer. In compound **8d** a strong NOE (12%) was observed from the 5,6-cyclopropyl proton to the 8-H. Therefore, the 5,6-cyclopropyl group is located on the β side of the molecule with the hydrogen *endo* and the bromine *exo*, *i.e.* the (*S*)-isomer. As further evidence for this conclusion, the coupling patterns clearly indicate that the 6-H is equatorial (and thus α) and has a *trans* cyclopropyl coupling (4.3 Hz) to the 5,6-cyclopropyl hydrogen. In compound **8c** the 5,6-cyclopropyl proton has an NOE to the 4β-H and a *cis* cyclopropyl coupling (8.1 Hz) to the 6α-H, clearly indicating that the 5,6-cyclopropyl group is β with the cyclopropyl proton *exo*, *i.e.* the (*R*)-isomer. The structure of the dimethoxy ketal **8a** followed from that of compound **8b**. The structure of compound **5** was determined by analogy with the ^1H and ^{13}C NMR spectra of the dichloro analogue **20a** (see below).

The structure of compound **18** was assigned on the following evidence. The location (9,10) of the cyclopropyl group was established by the observation, in the COSY spectrum, of a four-bond coupling between the cyclopropyl and 11β protons and from the 2- and 3-bond C–H couplings observed in the HMBC experiment. A 5.6% NOE was observed from the cyclopropyl proton to 7α-H, confirming that the cyclopropane ring is on the α face of the steroid with the H *endo*. The HMBC experiment confirmed a quaternary C-5 substituent. Based on the unequal geminal H–H couplings observed at C-2 (−18.5 Hz) and C-4 (−15.1 Hz), and from the NOEs observed from the 4β-H to the 1β-H and 6β-H, the stereochemistry at C-5 is most likely α with ring A in a conformation in which the 1β-H and 4β-H are both axial.

The location of the cyclopropyl group in compounds **19** and **20a** was established with the HMBC experiment. While it was not possible to determine the α- or β-face stereochemistry of these compounds directly the stereochemistry was determined from the reduction products **23a**, **23b**, **24a** and **24b**. For compound **23a**, NOEs were observed from the cyclopropyl proton to the 1β-H (2.3%), 2β-H (4.2%), and 4β-H (2.9%), establishing β-face addition with the cyclopropyl proton over ring A and 19(*R*) stereochemistry. Similarly, compound **23b** showed a 7.3% NOE between the cyclopropyl proton and the 8β-H, confirming that the cyclopropyl group is β with the cyclopropyl proton over ring B and the 19(*S*) configuration. In compound **24a** a 2.1% NOE was observed from the cyclopropyl proton to the 4α-H and a 4.2% NOE was observed to the 2α-H, confirming α-face addition and 19(*S*) stereochemistry at the cyclopropyl carbon. In compound **24b** a large (9.7%) NOE was observed from the cyclopropyl proton to the 9α-H, and a smaller (3.5%) NOE was observed from the cyclopropyl proton to the 7α-H, again establishing addition of the carbene to the α side of the steroid and 19(*R*) stereochemistry at the cyclopropyl carbon.

Comparison of the ^1H and ^{13}C NMR spectra of compounds **13** and **17** with those of compound **6**, compounds **15** and **16a** with compound **8a**, and compound **16b** with compound **8b** established their structures.

The structure of the insertion product **22** was determined by the following NMR data. The ^1H and ^{13}C NMR data were consistent with the presence of the unsaturated 4-en-3-one group, and a singlet at δ_H 6.23 and a methine carbon at δ_C 76.59 were in agreement with the $CHCl_2$ group. The COSY spectrum showed long-range couplings assigned to coupling between the $CHCl_2$ proton and the 10β- and 11β-H. Similarly, NOEs were assigned between the $CHCl_2$ proton and the 14-H (19%), 12α-H (4.2%), 7α (1.9%), 11α-H (0.5%) and 17α-H (−1.0%), the last probably *via* a three-spin effect from the 14-H. These data clearly established that the $CHCl_2$ is attached to C-9 with α stereochemistry. The C-10β stereochemistry can be inferred from the axial coupling observed (13.5 Hz) between the 10β- and 1α-H. The structure of the non-crystalline dichloro product **21** is in agreement with its ^1H and ^{13}C NMR spectra.

^1H NMR and ^{13}C NMR spectra for the previously reported

Table 1 ^{1}H NMR chemical shifts (J in Hz)[a]

Compd.	13-Me	17α-H	$SiMe_2$	CMe_3	Others
2b[b]	0.74	3.64 (dd, *J* 7.6, 8.4)	0.02, 0.03	0.88	3.17, 3.20 (s, 2 × OMe)
5	0.73	3.58 (t, *J* 8.2)	0.00, 0.01	0.88	2.70 (d, *J* 16.4, 4α-H), 2.61 (ddd, *J* 1.7, 6.0, 14.8, 1β-H), 2.46 (d, *J* 16.4, 4β-H)
6[c]	0.83	3.66 (t, *J* 8.6)	0.019, 0.032	0.89	3.37 (s, 19-H), 2.66 (m, 2α-H), 6.18 (s, 4-H)
8a	0.74	3.61 (t *J* 8.5)	0.01, 0.02	0.87	3.25 (s, 2 × OMe), 2.79 (s, 19-H), 1.83 and 2.21 (each d, J_{AB} 13.4, 4-H_2), 2.52 (m, 2α-H)
8b[c]	0.76	3.65 (dd, *J* 7.6, 8.9)	0.013, 0.023	0.88	2.93 (s, 19-H), 2.81 (d, *J* 15.4, 4α-H), 2.57 (d, *J* 15.4, 4β-H)
8c[c]	0.78	3.65 (t, *J* 8.6)	0.02, 0.03	0.88	3.15 (s, 19-H), 2.91 (d, *J* 4.3, 20-H), 2.81 (d, *J* 15.3, 4α-H) 2.56 (m, 2α-H), 2.48 (m, 2β-H), 2.38 (dd, *J* 2.0, 15.4, 4β-H)
8d[c]	0.78	3.65 (dd, *J* 7.6, 8.7)	0.01, 0.02	0.88	3.06 (s, 19-H), 2.97 (d, *J* 8.1, 20-H), 2.92 (d, *J* 14.5, 4α-H) 2.63 (m, 2β-H), 2.54 (m, 8β-H), 2.45 (m, 2α-H), 2.34 (m, 1β-H), 1.62 (d, *J* 14.5, 4β-H)
10	0.71	3.59 (t, *J* 8.0)	−0.02, 0.01	0.88	3.96 (m, OCH_2CH_2O)
11	0.87	3.73 (t, *J* 7.4)	0.06, 0.07	0.90	5.74 (s, 4-H)
13	1.00				5.88 (s, 4-H), 3.37 (s, 19-H)
15	0.75	3.62 (t, *J* 8.5)	0.01, 0.02	0.87	4.10 (m, OCH_2CH_2O), 2.81 (s, 19-H), 2.60 (m, 2α-H)
16a	0.75	3.62 (t, *J* 7.4)	0.00, −0.01	0.87	4.00 (m, OCH_2CH_2O), 2.82 (s, 19-H), 2.35 (m, 2α-H)
16b	0.77	3.53 (t, *J* 8.0)	−0.01, −0.02	0.87	2.96 (s, 19-H), 2.80 and 2.48 (each d, J_{AB} 15.4, 4-H_2)
17	0.83	3.66 (t, *J* 8.5)	0.02, 0.03	0.89	5.86 (s, 4-H), 3.38 (19-H)
18[c]	0.81	3.67 (t, *J* 8.1)	0.02, 0.03	0.88	2.57 and 2.69 (each d, J_{AB} 15.2, 4-H_2), 3.55 (s, 19-H)
19[c]	0.74	3.56 (t, *J* 8.4)	0.00, 0.01	0.88	2.78 (d, *J* 17.2, 4β-H), 2.41 (d, *J* 17.3, 4α-H)
20a[c]	0.73	3.58 (t, *J* 8.3)	0.00, 0.01	0.88	2.70 (d, *J* 16.4, 4α-H), 2.52 (ddd, *J* 2.0, 5.7, 14.5, 1β-H), 2.37 (d, *J* 16.3. 4β-H), 2.16 (m, 2α-H)
20b[c]	0.78	3.67 (t, *J* 8.4)			2.70 (d, *J* 16.4, 4α-H), 2.52 (ddd, *J* 2.2, 5.0, 15.0, 1β-H), 2.37 (d, *J* 16.3, 4β-H)
21	0.78	3.67 (t, *J* 8.0)	0.00, 0.02	0.88	6.22 (s, 9α-$CHCl_2$), 2.76 and 2.88 (each d, J_{AB} *J* 20.9, 4-H_2)
22[c]	0.82	3.66 (t, *J* 8.60)	0.01, 0.02	0.88	6.23 (s, 9α-$CHCl_2$), 5.81 (s, 4-H)
23a[c]	0.74	3.58 (t, *J* 8.4)	0.00, 0.01	0.88	3.10 (s, 19-H), 2.57 (d, *J* 17.5, 4β-H), 2.48 (d, *J* 17.6, 4α-H)
23b[c]	0.74	3.56 (t, *J* 8.4)	0.00, 0.01	0.88	3.26 (s, 19-H), 2.57 (d, *J* 16.7, 4β-H), 2.26 (d, *J* 16.7, 4α-H)
24a[c]	0.74	3.58 (t, *J* 8.4)	0.00, 0.01	0.88	3.19 (s, 19-H), 2.55 (d, *J* 17.6, 4α-H), 2.44 (d, *J* 17.7, 4β-H)
24b[c]	0.71	3.53 (t, *J* 8.3)	0.00, 0.01	0.87	2.56 (d, *J* 16.1, 4α-H), 2.25 (d, *J* 16.1, 4β-H)

[a] For solution in $CDCl_3$ ($SiMe_4$ internal standard) unless otherwise indicated on a Bruker AM300 instrument. [b] In CD_3OD. [c] Determined by 2-D analysis on a Bruker AMX500 instrument.

dichloro **26a**[14] and dibromo **26b**[15] adducts were consistent with their structures. The dibromo **27b** and dichloro **27a** insertion products showed the presence of doublets at 6.19 (*J* 2.7 Hz) and 6.16 (*J* 2.8 Hz), respectively, assigned to the CHX_2 proton. The tetrasubstituted 9,10-double bond was observed in the ^{13}C spectra together with signals at δ_C 54.11 and 76.93 assigned to the CHX_2 carbon, respectively.

The structures of compounds **17** and **20a** have been confirmed by X-ray crystallographic analysis.

Experimental

Reactions were monitored by TLC which was carried out in the following solvent systems on silica gel (Merck type 60H): acetone–light petroleum (35–60 °C) (LP), diethyl ether–LP, ethyl acetate–LP; compounds were visualised by dipping the plates in 5% sulfuric acid–ethanol followed by heating at 120 °C. LP was used for compounds **26a/b** and **27a/b**, which were visualised in I_2 vapour. Flash chromatography was carried out on silica gel (Merck type 60 for column chromatography) unless otherwise stated. M.p.s were measured on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were performed by Mr. Baldeo, School of Pharmacy, University of London, England.

^{1}H and ^{13}C NMR spectra are reported in Tables 1 and 2. For compounds **26a,b** and **27a,b**, *J*-values are in Hz. Survey spectra were obtained on a Bruker AM300 instrument while two-dimensional and NOE spectra were recorded on a Bruker AMX500 spectrometer. Samples were measured in ~ 50 mmol dm^{-3} solutions in $CDCl_3$ in 5 mm sample tubes. The residual $CHCl_3$ peak in the solvent (δ_C 77.0, δ_H 7.26) was used as the internal reference for both proton and carbon spectra. Sample temperature was controlled at 300 K for all spectra. Carbon spectra were classified as to multiplicity with the DEPT technique.[17]

Homonuclear correlation (COSY) spectra,[18] were recorded with an F_1 time domain of 256 points. Zero-filling yielded a 1024 (real) by 1024 (real) matrix after transformation. A 45° mixing pulse was employed, and spectra were displayed and plotted in the magnitude mode.

Heteronuclear correlation spectra were recorded with the proton-detected single quantum coherence (HSQC) experiment,[21] with an F_2 time domain of 4096 points and an F_1 time domain of 256 points. Zero-filling in F_1 and F_2 resulted in a 4096 (real) by 512 (real) matrix after transformation.

Proton-detected multiple-bond heteronuclear correlation (HMBC) spectra[21] were recorded with a low-pass *J* filter to suppress correlations due to the one-bond couplings. The matrix dimensions were the same as for the HSQC spectra.

Difference NOE experiments were performed with a spectral width of ~ 2500 Hz and a real frequency domain data size of 32K points, resulting in a digital resolution of 0.08 Hz per point. Frequency-list cycling was employed to distribute long-term changes in homogeneity equally among all spectra. Multiplets were irradiated by stepping the decoupler frequency between each line of the multiplet at 200 ms intervals,[21] and each multiplet was irradiated for a total of 5 s. The irradiating field strength (calculated from the 90° pulse length and expressed as $\gamma B_2/2\pi$) was ~ 7 Hz. At least 512 transients (32 transients per irradiation point with 16 loops through the frequency list) were acquired for each irradiation point in order to ensure adequate signal-to-noise ratio and cancellation of unenhanced peaks. A control spectrum was subtracted from each spectrum, and NOE-values were determined by careful integration of the resulting difference spectrum. Using these techniques, NOE enhancements of less than 1% could be easily observed.

Table 2 ^{13}C NMR chemical shifts[a]

Carbon	Compound											
	2b[b–d]	**5**[b]	**6**[b,e]	**8a**[b,c]	**8b**[b,e]	**8c**[b,e]	**8d**[b,e]	**10**[b,c]	**11**[b]	**13**	**15**[b,c]	**16a**[b,c]
1	26.24	25.58	26.86	24.61	24.49	25.97	25.46	23.15	27.49	26.85	24.66	22.80
2	38.86	37.20	35.44	40.25	39.13	39.22	39.21	37.58	37.08	35.37	34.73	34.15
3	101.20	210.36	198.83	100.10	207.76	208.36	209.08	108.32	198.43	198.51	108.30	108.14
4	40.36	48.06	126.41	48.79	48.31	45.78	49.90	40.70	124.83	126.72	41.23	39.34
5	125.63	31.28[g]	162.47	33.94	32.40	27.33	25.50	125.59	166.51	161.27	33.42	33.80
6	31.91	28.30	29.60	34.70	33.95	27.63	21.27	31.40	35.88	29.60	34.33	33.05
7	27.86	25.92[f]	21.03	22.04	21.94	22.17	21.87	26.62	31.58	21.19	21.98	21.48
8	40.54	35.48	36.50	29.78	30.08	32.24	31.85	38.93	41.21	36.00	29.81	30.18
9	47.78	41.82	33.61	33.45	33.96	32.06	33.17	46.52	50.09	33.34	31.54	31.84
10	130.76	31.37[g]	29.71	30.75	29.51	29.15	28.44	129.58	43.10	29.88	30.31	29.73
11	26.24	25.24[f]	24.33	24.61	25.04	25.24	25.20	26.07	26.84	23.91	23.21	22.80
12	30.00	36.80	34.95	34.76	34.77	34.85	34.96	30.85	37.69	35.66	34.73	35.26
13	45.07	43.28	43.77	43.89	44.05	43.68	43.94	43.90	44.13	47.93	43.90	43.89
14	50.69	50.56	48.30	48.79	48.81	48.31	49.00	49.56	50.64	49.02	48.82	49.14
15	24.15	23.51	22.88	22.73	22.75	23.01	22.81	25.15	23.95	20.45	22.72	22.11
16	32.18	30.69	30.91	30.93	30.93	30.84	30.96	31.06	31.58	29.37	30.94	30.96
17	83.20	81.43	81.31	81.25	81.15	81.39	81.29	81.76	82.45	219.29	81.24	81.27
18	12.17	11.51	11.17	11.42	11.51	11.20	11.47	11.60	11.78	13.64	11.43	11.42
19		61.24	34.21	32.80	32.52	32.92	32.65			33.34	32.48	40.75
5′				40.79	37.71	26.81	31.71				40.38	69.24
9′												
	16b[b]	**17**[b]	**18**[b,e]	**19**[b,e]	**20a**[b,e]	**20b**[e]	**21**[b]	**22**[b,e]	**23a**[b,e]	**23b**[b,e]	**24a**[b,e]	**24b**[b,e]
1	23.34	24.87	21.58	28.12	23.34	23.35	29.64[f]	24.17	28.75	23.12	23.53	20.57
2	39.47	35.36	37.15	35.98	37.10	37.10	38.89	38.21	36.06	36.02	36.22	37.51
3	207.83	198.86	210.88	210.30	210.56	210.49	211.20	198.74	210.79	212.62	210.32	212.77
4	46.23	126.33	54.18	46.95	45.62	45.66	45.14	125.00	48.15	45.09	46.27	43.73
5	34.33	162.66	71.03	30.85	30.94	30.89	131.32[g]	166.31	22.48	24.76[f]	22.42[f]	26.27[f]
6	32.90	29.69	38.52	29.90	25.37[f]	25.38	31.05	33.62	27.25	32.64	25.23	29.35
7	21.40	20.97	19.30	26.28	26.73[f]	26.72	20.52	22.94	26.51	26.50	25.44	25.39
8	30.34	36.50	37.39	35.98	36.08	36.09	42.13[h]	44.24	36.71	35.86	35.23	38.67
9	32.68	33.97	34.19	47.76	39.37	39.25	48.09	47.78	50.46	45.21	38.00	47.96
10	28.91	30.34	33.78	32.19	31.62	31.57	132.49[g]	50.75	26.07	29.57[f]	24.98[f]	27.21[f]
11	23.15	24.87	23.35	22.27	25.82	25.79	30.43[f]	34.87	22.97	24.55	24.56	26.38
12	35.26	35.92	35.44	37.67	36.88	36.52	33.29	33.40	37.69	36.98	37.00	37.14
13	44.01	43.78	43.91	44.55	43.24	42.89	44.04	43.78	44.34	44.00	43.31	43.29
14	49.07	48.39	48.60	50.38	50.53	50.89	43.30[h]	43.56	47.62	49.35	50.36	49.95
15	22.80	22.37	22.84	23.09	23.48	23.33	23.51	23.67	23.29	23.19	23.66	23.29
16	30.93	30.91	30.99	30.92	30.71	30.35	31.05[f]	30.84	30.95	30.86	30.76	30.80
17	81.17	81.30	81.33	81.43	81.47	81.53	81.32	81.26	81.61	81.56	81.58	81.54
18	11.48	11.17	11.32	11.90	11.49	11.25	11.50	11.56	11.75	11.62	11.36	11.45
19	40.88	43.18	42.00	77.93	79.04	78.95			48.48	48.82	46.39	52.82
5′	67.65											
9′							78.47	76.59				

[a] For solution in $CDCl_3$ ($SiMe_4$ internal standard) on a Bruker AM300 instrument unless otherwise indicated. [b] The Bu^tMe_2Si group resonates at $\sim\delta_C$ −4.48 s and 4.81 s ($SiMe_2$), 18.07 (CMe_3) and 2.84 (CMe_3). [c] The ketal signals occur in compound **2b** at δ_C 48.06, 48.15; in compound **8a** at δ_C 47.92, 47.97; in compound **10** at δ_C 64.21, 64.47; compound **15** at δ_C 65.12, 64.36; and compound **16a** at δ_C 64.89, 64.36. [d] In CD_3OD. [e] Determined by 2-D analysis on a Bruker AMX500 instrument. [f–h] Numbers in columns are interchangeable.

The mass spectrum of compound **27b** was recorded on a VG-7070E instrument at 70 eV.

X-Ray crystallographic data collection was on a Rigaku AFC6S diffractometer with a graphite monochromator with **17** Mo-Kα (λ = 0.710 69 Å) or **20a** Cu-Kα (λ = 1.541 78 Å) radiation. Crystallographic data are summarised in Table 3. Cell constants and an orientation matrix for data collection were obtained by least squares using the setting angles for **17** 25 or **20a** 22 reflections in the 2θ ranges **17** 8.85–33.33° or **20a** 46.67–49.57°. Data collection used the ω–2θ scan technique. Omega scans of several intense reflections, made before data collection, had an average scan width at half-height of **17** 0.48° or **20a** 0.30° with a take off angle of 6°. Scans of **17** (1.47 + 0.30 tan ω°) or **20a** (0.89 + 0.30 tan θ°) were made at a speed of **17** 4° min^{-1} or **20a** 8° min^{-1} (in ω). The weak reflections $I < 10.0\sigma(I)$ were rescanned (maximum of 2 rescans), and the counts accumulated to assure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. Three reference reflections, measured every 150 reflections, remained constant for **20a** but declined by 1.6% for **17** and a linear decay correction was applied. Intensities were corrected for Lorentz and polarization effects; a correction for absorption was applied based on azimuthal scans of several reflections **17** or by application of the program DIFABS[22] **20a**. The structure was solved using direct methods. Full-matrix least-squares refinement with anisotropic factors given to all non-H atoms converged to **17** (R = 0.080, R_w = 0.059, S = 2.78) or **20a** (R = 0.058, R_w = 0.065, S = 2.93). The weighting scheme was based on counting statistics. The maximum shift/error in the final cycle was **17** 0.01 or **20a** 0.00. The largest peaks in the final difference map were **17** 0.025 and −0.25 or **20a** 0.23 and −0.23 e $Å^{-1}$. Atomic scattering factors were from International Tables for X-ray crystallography;[23] anomalous dispersion effects were included in F.[23] All calculations were made with the TEXSAN crystallographic software package.[24] Figs. 1 and 2 were prepared using PLUTO.[25] The silyl group in **17** exhibits conformational disorder (details in supplementary material). Tables of atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.*

Estr-5(10)-*ene*-3,17-*dione* **1**.—A solution of 19-hydroxyandrost-4-ene-3,17-dione (10 g) in acetone (150 cm^3) at 10 °C was treated with Jones reagent (30 cm^3) for 30 min at 10–15 °C. CH_2Cl_2 (350 cm^3) was added, the organic layer was washed successively with water and 43% aq. $(NH_4)_2SO_4$ and the residue was stirred with saturated aq. $NaHCO_3$ (100 cm^3) for 30 min. The aqueous layer was washed with EtOAc, the EtOAc was back-extracted with aq. $NaHCO_3$ (20 cm^3) and the combined water layers were acidified with 10% HCl to give, on filtration, 3,17-dioxoandrost-4-en-19-oic acid (7.3 g), m.p. 145–147 °C (decomp.) (lit.,[11] 146 °C).

A solution of the acid (1.0 g) in pyridine (1 cm^3) was heated and stirred at 50 °C for 1 h, poured into ice–water, and filtered to give the unsaturated dione **1** (700 mg), m.p. 140–145 °C (from benzene–LP) (lit.,[11] 144–146 °C).

3,3-*Dimethoxyestr*-5(10)-*en*-17β-*ol* **2a**.—The dione **1** (6 g) and malonic acid (3 g) were stirred in MeOH (90 cm^3) for 19 h, then the mixture was cooled in an ice-bath, adjusted to pH 8 (Universal indicator paper) with saturated aq. $NaHCO_3$, and the product was filtered off to give 3,3-dimethoxyestr-5(10)-en-17-one (5.1 g), m.p. 114–117 °C (lit.,[11] 115–116 °C).

* For details of the deposition scheme, see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1994, Issue.

Table 3 Crystallographic data

Compound	**17**	**20a**
Formula	$C_{25}H_{39}ClO_2Si$	$C_{25}H_{40}Cl_2O_2Si{\cdot}0.3H_2O$
Formula wt.	435.12	477.54
T/K	299	299
Crystal system	monoclinic	hexagonal
Space group	$P2_1$	$P6_3$
Cell dimensions a/Å	12.680(2)[a]	26.465(3)
b/Å	6.720(3)	—
c/Å	15.272(2)	6.772(3)
β/°	93.63(1)	—
Z	2	6
Cell volume/$Å^3$	1298.7(7)	4108(3)
F(000)	472	1543
D_c/g cm^{-3}	1.113	1.548
μ/mm^{-1}	2.07 (Mo-Kα)	27.34 (Cu-Kα)
Crystal dimensions/mm	0.35 × 0.35 × 0.08	0.4 × 2 × 0.1
2θ max/°	45	119.9
Independent reflections	1878	2246
Acceptance ($I/\sigma I$ >)	2.00	2.00
Observed reflections	949	1504

[a] Estimated standard deviations in parentheses refer to the last digit.

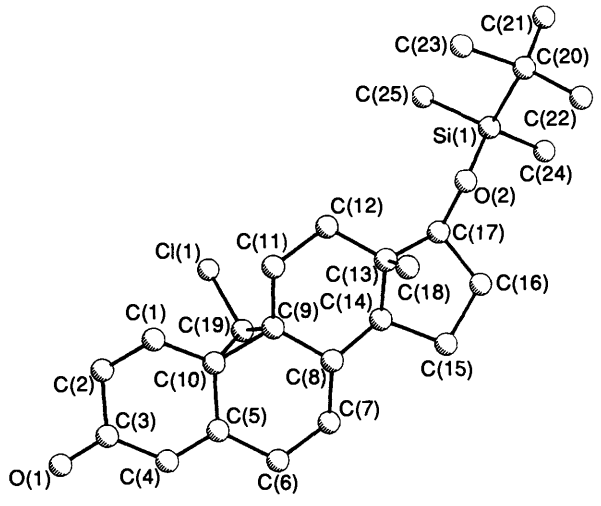


Fig. 1 PLUTO view of the major conformation of 9α,19α-chlorocycloandrostane **17**

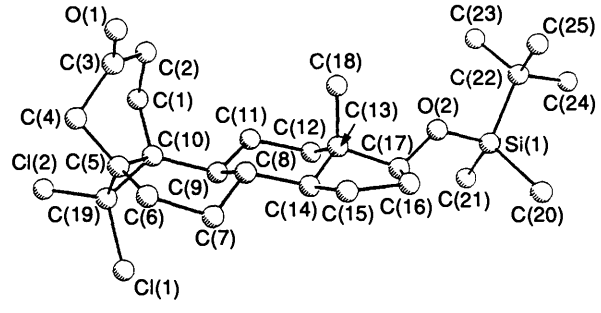


Fig. 2 PLUTO view of the 5α,19α-dichlorocycloandrostane **20a**

To a solution of the dimethoxy ketal (5.5 g) in MeOH (50 cm^3) was added $NaBH_4$ (1.3 g) and the mixture was stirred for 1 h. The reaction mixture was poured into ice–water and extracted with diethyl ether to give the 17-alcohol **2a** (5.2 g), m.p. 90–95 °C (from Et_2O–LP), sufficiently pure for the next reaction, which on recrystallisation had m.p. 110–112 °C (lit.,[11] 112–113 °C).

19(S)-*Bromo*-17β-(tert-*butyldimethylsiloxy*)-5β,6β-*dibromomethylene*-3,3-*dimethoxy*-9α,19-*cyclo*-10α-*androst*-5(10)-*ene* **8a**.—To a mixture of imidazole (1.4 g) in dimethylformamide (DMF) (40 cm^3) were added the 17-alcohol **2a** (1.6 g) and Bu^tMe_2SiCl (1.5 g) and the mixture was stirred at 50 °C for 1 h, poured into water, and extracted with diethyl ether to give a residue which, on flash chromatography and elution with 5% diethyl ether–LP, yielded the non-crystalline dimethoxy ketal **2b** (1.7 g).

To a solution of the dimethoxy ketal **2b** (1.1 g) in bromoform (5 cm^3) were added CTAB (200 mg) and 50% aq. NaOH (5 cm^3) and the mixture was stirred vigorously at room temperature under Ar for 18 h. The reaction mixture was diluted with diethyl ether and washed with 3% aq. HCl to give a residue which, on flash chromatography and elution with 4% Et_2O–LP, yielded the *tribromo derivative* **8a** (650 mg), m.p. 148–152 °C (from Et_2O–LP) (Found: C, 48.5; H, 6.6; Br, 34.1. $C_{28}H_{45}Br_3O_3Si$ requires C, 48.2; H, 6.5; Br, 34.4%).

19(S)-*Bromo*-17β-(tert-*butyldimethylsiloxy*)-5β,6β-*dibromomethylene*-9α,19-*cyclo*-10α-*androstan*-3-*one* **8b**.—The tribromo derivative **8a** (300 mg) was dissolved in acetone (10 cm^3) containing 3% aq. HCl (1 cm^3) and the mixture was stirred for 30 min at room temperature. The solution was adjusted to pH 8 with saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2 to give, on flash chromatography and elution with 5% EtOAc–LP, the *tribromo ketone* **8b** (200 mg), m.p. 217–218 °C (from Et_2O–LP) (Found: C, 47.8; H, 6.0; Br, 36.5. $C_{26}H_{39}Br_3O_2Si$ requires C, 47.9; H, 6.0; Br, 36.8%).

19(S)-*Bromo*-17β-(tert-*butyldimethylsiloxy*)-5β,6β-*dibromomethylene*-9α,19-*cyclo*-10α-*androstan*-3-*one* **8b** *and* 17β-(tert-*Butyldimethylsiloxy*)-19,19-*dibromo*-5,19-*cyclo*-10α-*androstan*-3-*one* **5**.—To a solution of the dimethoxy ketal **2b** (see preparation of compound **8a** above) (1.45 g) in bromoform (5 cm^3) were added CTAB (300 mg) and 50% aq. NaOH (5 cm^3) and the mixture was stirred vigorously under Ar for 48 h. The mixture was diluted with Et_2O, washed with 3% aq. HCl and extracted with Et_2O to give a residue, which was passed through silica gel in 5% Et_2O–LP to remove bromoform. The steroidal fractions (1.13 g) were dissolved in acetone (30 cm^3), PTSA (150 mg) was added, and the mixture was stirred for 1 h, diluted with water and extracted with CH_2Cl_2. The organic layer was washed successively with aq. $NaHCO_3$ and water to give a residue which, on flash chromatography and elution with 8% acetone–LP, gave the tribromo derivative **8b** (300 mg), m.p. 217–218 °C (from CH_2Cl_2–Et_2O) and the 19,19-*dibromo adduct* **5** (21 mg), m.p. 173–176 °C (from CH_2Cl_2–Et_2O) (Found: C, 53.8; H, 7.0; Br, 28.8. $C_{25}H_{40}Br_2O_2Si$ requires C, 53.6; H, 7.2; Br, 28.5%).

19(S)-*Bromo*-17β-(tert-*butyldimethylsiloxy*)-5β,6β-*dibromomethylene*-9α,19-*cyclo*-10α-*androstan*-3-*one* **8b** *and* 19(S)-*Bromo*-17β-(tert-*butyldimethylsiloxy*)-9α,19-*cyclo*-10α-*androst*-4-*en*-3-*one* **6**.—To a solution of the dimethoxy ketal **2b** (see preparation of compound **8a** above) (1.1 g) in bromoform (5 cm^3) were added CTAB (200 mg) and 50% aq. NaOH (5 cm^3) and the mixture was stirred vigorously under Ar for 18 h. After extraction (Et_2O) the stirred residue was treated with 3% aq. HCl (3.5 cm^3) in acetone (35 cm^3) for 30 min, and the mixture was then adjusted to pH 8 with aq. $NaHCO_3$ and extracted with CH_2Cl_2 to give, on flash chromatography and elution with 5% acetone–LP, the tribromo derivative **8b** (215 mg), m.p. 210–215 °C and the bromo derivative **6** (53 mg), m.p. 182–185 °C (from CH_2Cl_2–Et_2O) (Found: C, 62.4; H, 8.1; Br, 16.35. $C_{25}H_{39}BrO_2Si$ requires C, 62.6; H, 8.2; Br, 16.7%).

19(S)-*Bromo*-5β,6β-[(R)-*bromomethylene*]-17β-(tert-*butyldimethylsiloxy*)-9α,19-*cyclo*-10α-*androstan*-3-*one* **8c** *and* 19(S)-*Bromo*-5β-6β-[(S)-*bromomethylene*]-17β-(tert-*butyldimethylsiloxy*)-9α,19-*cyclo*-10α-*androstan*-3-*one* **8d**.—To a solution of the ketone **8b** (250 mg) in dry Et_2O (15 cm^3) containing azoisobutyronitrile (AIBN) (2 mg) under Ar at 0 °C was added slowly a solution of tributyltin hydride (150 mg) in Et_2O (15 cm^3) and the mixture was stirred for 2 h, at which time reaction was complete by TLC. The residue obtained after evaporation of the solvent was flash chromatographed. Elution with 2% acetone–LP gave the (R)-*isomer* **8c** (48 mg), m.p. 200–203 °C (from Et_2O–MeOH) (Found: C, 54.2; H, 7.2; Br, 28.1. $C_{26}H_{40}Br_2O_2Si$ requires C, 54.55; H, 7.0; Br, 27.9%) and the (S)-*isomer* **8d** (72 mg), m.p. 155–158 °C (from Et_2O–MeOH) (Found: C, 54.55; H, 7.1; Br, 27.8%).

19(S)-*Bromo*-17β-(tert-*butyldimethylsiloxy*)-9α,19-*cyclo*-10α-*androst*-4-*en*-3-*one* **6** *and* 17β-(tert-*Butyldimethylsiloxy*)*estr*-4-*en*-3-*one* **11**.—To a stirred solution of the ketal **10** (see below) (500 mg) and $KOBu^t$ [prepared by dissolution of K metal (0.5 g) in dry Bu^tOH, evaporation of excess of alcohol at reduced pressure, and drying of the residue at 150 °C for 1 h] in dry Et_2O (15 cm^3) at −30 °C was added a solution of $CHBr_3$ (3.5 cm^3) in dry Et_2O (15 cm^3) during 2 h and the mixture was stirred for a further 22 h, when it was poured into water and extracted with Et_2O; the extract was dried and evaporated, to give a residue, which was stirred in acetone (30 cm^3) containing PTSA (300 mg) for 2 h. Water was added and the mixture was extracted with CH_2Cl_2, which was washed with aq. $NaHCO_3$ to give the monobromo derivative **6** (65 mg), m.p. 182–185 °C (from CH_2Cl_2–Et_2O) and the *unsaturated ketone* **11** (45 mg), m.p. 134–136 °C (from Et_2O–MeOH) (Found: C, 74.0; H, 10.5. $C_{24}H_{40}O_2Si$ requires C, 74.2; H, 10.4%).

3,3-*Ethylenedioxyestr*-5(10)-*en*-17-*one* **9** *and* 3,3,17,17-*Bis*(*ethylenedioxy*)*estr*-5(10)-*ene* **12**.—The dione **1** (3.0 g), PTSA (125 mg) and ethylene glycol (42 cm^3) were refluxed in benzene (160 cm^3) in a Dean–Stark apparatus for 2 h. The organic layer was washed successively with aq. $NaHCO_3$ and water to give, after flash chromatography and elution with 20% EtOAc–LP, the diketal **12** (2.55 g), m.p. 84–86 °C (lit.,[13a] 79–80 °C) and the monoketal **9** (586 mg), m.p. 122–125 °C (lit.,[26] 130–131 °C).

17β-(tert-*Butyldimethylsiloxy*)-3,3-*ethylenedioxyestr*-5(10)-*ene* **10**.—A solution of the dione **1** (4 g), PTSA monohydrate (200 mg) and ethylene glycol (30 cm^3) in benzene (320 cm^3) was heated at 50 °C for 1 h. The reaction mixture was washed successively with 6% aq. $NaHCO_3$ and water to give a residue (**9**), which was dissolved in MeOH (50 cm^3) and $NaBH_4$ (2 g) was added slowly to the stirred solution for 1 h. The organic layer was separated and evaporated to give, after flash chromatography and elution with 20% EtOAc–LP, a residue (3.2 g), which was treated with imidazole (1.5 g), *tert*-butyldimethylsilyl chloride (3.0 g) and DMF (150 cm^3) at 50 °C for 2 h. Water was added and the mixture was extracted with CH_2Cl_2 to give the *ketal* **10** (3.76 g), m.p. 126–127 °C (from Et_2O–MeOH) (Found: C, 72.1; H, 10.4. $C_{26}H_{44}O_3Si$ requires C, 72.2; H, 10.25%).

19(S)-*Bromo*-9α,19-*cyclo*-10α-*androst*-4-*ene*-3,17-*dione* **13** *and Estr*-4-*ene*-3,17-*dione* **14**.—A mixture of the diketal **12** (1.0 g) and solid $KOBu^t$ [prepared as described from K metal (1 g) above and sublimed] in dry Et_2O (30 cm^3) was treated with $CHBr_3$ (6.7 cm^3) followed by acetone (50 cm^3) containing PTSA (500 mg) as described for the preparation of compound **6**. Flash chromatography and elution with 40% EtOAc–LP gave dione **14** (213 mg), m.p. 170–172 °C (from CH_2Cl_2–Et_2O) (lit.,[27] 171–173 °C) and the *monobromo androstane derivative* **13** (161 mg), m.p. 239–240 °C (from CH_2Cl_2–Et_2O) (Found: C, 62.6; H, 6.1; Br, 21.7. $C_{19}H_{23}BrO_2$ requires C, 62.8; H, 6.4; Br, 22.0%).

When the above dibromocarbene reaction was carried out on the diketal **12** (468 mg) for 2 h as reported by Birch *et al.*[3a] the unsaturated ketone **14** (53 mg), m.p. 166–170 °C and the monobromo derivative **13** (28 mg), m.p. 235–240 °C were obtained.

19(S)-*Bromo*-17β-(tert-*butyldimethylsiloxy*)-5β,6β-*dibromomethylene*-3,3-*ethylenedioxy*-9α,19-*cyclo*-10α-*androstane* **15**.—The ketal **10** (200 mg) was stirred vigorously with $CHBr_3$ (1 cm^3), 50% aq. NaOH (1 cm^3) and CTAB (40 mg) and under Ar for 18 h and was then treated with PTSA in acetone as described for compound **8b** to give the *tribromo derivative* **15** (40 mg), m.p. 245–248 °C (from Et_2O–CH_2Cl_2) (Found: C, 46.8; H, 6.2; Br, 33.25. $C_{28}H_{43}Br_3O_3Si$·1.5 H_2O requires C, 46.55; H, 6.4; Br, 33.2%).

17β-(tert-*Butyldimethylsiloxy*)-19(S)-*chloro*-5β,6β-*dichloromethylene*-3,3-*ethylenedioxy*-9α,19-*cyclo*-10α-*androstane* **16a**.—The ketal **10** (100 mg) was heated in bis-(2-methoxyethyl) ether (1 cm^3) to 120–130 °C, a mixture of CCl_3CO_2Na (2.5 g) in bis-(2-methoxyethyl) ether (15 cm^3) was added over a period of 30 min and the temperature was maintained for a further 3 h.[28] The mixture was cooled and filtered and the solvent was evaporated off to give, after flash chromatography and elution with 1% acetone–LP, the trichloro derivative **16a** (41 mg), m.p. 254–257 °C (from Et_2O–LP).

17β-(tert-*Butyldimethylsiloxy*)*estr*-4-*en*-3-*one* **11**, 17β-(tert-*Butyldimethylsiloxy*)-19(S)-*chloro*-5β,6β-*dichloromethylene*-3,3-*ethylenedioxy*-9α,19-*cyclo*-10α-*androstane* **16a**.—The ketal **10** (150 mg) and phenyl(trichloromethyl)mercury (207 mg) [m.p. 106–109 °C (lit.,[29] 110 °C) prepared as in ref. 29] in dry toluene (10 cm^3) was refluxed under Ar for 3 h, when a second portion of reagent (140 mg) was added and reflux was continued for a further 14 h. The mixture was cooled and filtered, and the residue obtained from evaporation was triturated with MeOH to remove insoluble mercury compounds, and the MeOH-soluble portion was evaporated, treated with PTSA (150 mg) in acetone (15 cm^3) and stirred at room temperature for 2 h. Work-up as described for compound **6** on flash chromatography and elution with 10% Et_2O–LP gave the trichloro derivative **16a** (17 mg), m.p. 250–254 °C (from Et_2O–LP) and the unsaturated ketone **11** (25 mg), m.p. 125–130 °C.

17β-(tert-*Butyldimethylsiloxy*)*estr*-4-*en*-3-*one* **11**, 17β-(tert-*Butyldimethylsiloxy*)-19(S)-*chloro*-5β,6β-*dichloromethylene*-3,3-*ethylenedioxy*-9α,19-*cyclo*-10α-*androstane* **16a**, 17β-(tert-*Butyldimethylsiloxy*)-19(S)-*chloro*-9α,19-*cyclo*-10α-*androst*-4-*en*-3-*one* **17** *and* 17β-(tert-*Butyldimethylsiloxy*)-19,19-*dichloro*-5β,19-*cyclo*-5β-*androstan*-3-*one* **19**.—The ketal **10** (200 mg), 50% aq. NaOH (1 cm^3), BTEAC (50 mg) and $CHCl_3$ (5 cm^3) were refluxed under Ar for 3 h. The reaction mixture was poured into water and extracted with diethyl ether to give a residue, which was treated at room temperature with PTSA (120 mg) in acetone (30 cm^3) for 2 h, diluted with water, and extracted with CH_2Cl_2. The extracts were washed with aq. $NaHCO_3$ to give a residue which, on flash chromatography and elution with 10% Et_2O–LP, gave the *trichloro derivative* **16a** (27 mg), m.p. 254–257 °C (from Et_2O–LP) (Found: C, 59.6; H, 7.7; Cl, 18.9. $C_{28}H_{43}Cl_3O_3Si$ requires C, 59.8; H, 7.7; Cl, 18.9%); the 5β,19-*cyclo derivative* **19** (11 mg), m.p. 154–157 °C (from MeOH–Et_2O) (Found: C, 63.9; H, 8.6; Cl, 15.0. $C_{25}H_{40}Cl_2O_2Si$ requires C, 63.7; H, 8.55; Cl, 15.0%); unsaturated ketone **11** (8 mg), m.p. 130–133 °C; and *monochloro unsaturated ketone* **17** (53 mg), m.p. 161–163 °C (from MeOH–Et_2O) (Found: C, 66.4; H, 9.0. $C_{25}H_{39}ClO_2Si$·H_2O requires C, 66.3; H, 9.1%).

When the above reaction was repeated with the ketal (200 mg) but with $CDCl_3$ and NaOD in D_2O [prepared by dissolution of Na metal (0.7 g) in D_2O (2.5 cm^3)] the products, **16a** (25 mg), m.p. 254–257 °C and **17** (41 mg), m.p. 160–163 °C showed the same ^1H and ^{13}C NMR signals obtained previously.

17β-(tert-*Butyldimethylsiloxy*)*estr*-4-*en*-3-*one* **11**; 17β-(tert-*Butyldimethylsiloxy*)-19(S)-*chloro*-5β,6β-*dichloromethylene*-9α,19-*cyclo*-10α-*androstan*-3-*one* **16b**, 17β-(tert-*Butyldimethylsiloxy*)-19(S)-*chloro*-9α-19-*cyclo*-10α-*androst*-4-*en*-3-*one* **17**, 17β-(tert-*Butyldimethylsiloxy*)-19(S)-*chloro*-5α-*hydroxy*-9α,19-*cyclo*-10α-*androstan*-3-*one* **18**, 17β-(tert-*Butyldimethylsiloxy*)-19,19-*dichloro*-5β,19-*cyclo*-5β-*androstan*-3-*one* **19**, 17β-(tert-*Butyldimethylsiloxy*)- **20a** *and* 17β-*Hydroxy*-19,19-*dichloro*-5α,19-*cyclo*-10α-*androstan*-3-*one* **20b**, 17β-(tert-*Butyldimethylsiloxy*)-9α-*dichloromethylandrost*-5(10)-*en*-3-*one* **21** *and* 4-*en*-3-*one* **22**.—A solution of the dimethoxy ketal **2b** (200 mg) in $CHCl_3$ (5 cm^3) was treated with 50% aq. NaOH (1 cm^3) and BTEAC (50 mg) under Ar and the mixture was stirred at room temperature for 16 h. Work-up and treatment with PTSA were as described in the previous procedure for the ketal **10** except that treatment with PTSA was for 30 min. Flash chromatographic separation and elution with 2% acetone–LP gave the *dichloro adduct* **20a** (8 mg), m.p. 160–163 °C (from acetone–MeOH) (Found: C, 63.9; H, 8.7; Cl, 14.9. $C_{25}H_{40}Cl_2O_2Si$ requires C, 63.7; H, 8.55; Cl, 15.0%); the non-crystalline dichloromethyl derivative **21** (24 mg); the dichloro adduct **19** (25 mg), m.p. 157–160 °C (from MeOH–Et_2O); the *trichloro ketone* **16b** (3 mg), m.p. 155–160 °C (from MeOH–acetone) (Found: C, 60.0; H, 7.7; Cl, 20.2. $C_{26}H_{39}Cl_3O_2Si$ requires C, 60.3; H, 7.6; Cl, 20.5%); the unsaturated ketone **11** (24 mg) m.p. 125–130 °C; and the monochloro derivative **17** (28 mg), m.p. 156–161 °C (from Et_2O–MeOH).

A larger-scale reaction with the dimethoxy ketal **2b** (1.2 g) gave, on elution with 5% acetone–LP, in addition to the above compounds, the *dichloromethyl* 4-*en*-3-*one* **22** (132 mg), m.p. 139–141 °C (from acetone–LP) (Found: C, 63.9; H, 8.75; Cl, 14.95. $C_{25}H_{40}Cl_2O_2Si$ requires C, 63.7; H, 8.55; Cl, 15.0%); the 5-*hydroxy derivative* **18** (20 mg), m.p. 181–184 °C (from Et_2O–LP) (Found: C, 65.8; H, 9.1; Cl, 8.2. $C_{25}H_{41}ClO_3Si$ requires C, 66.3; H, 9.1; Cl, 7.8%); and the 17-*alcohol* **20b** (100 mg), m.p. 203–205 °C (from Et_2O–MeOH) (Found: C, 63.8; H, 7.5; Cl, 20.0. $C_{19}H_{26}Cl_2O_2$ requires C, 63.9; H, 7.3; Cl, 19.8%) were isolated.

17β-(tert-*Butyldimethylsiloxy*)-19(R)-*chloro*- **23a** *and* 19(S)-*chloro*-5β,19-*cyclo*-5β-*androstan*-3-*one* **23b**.—To a solution of the dichloro adduct **19** (53 mg) in dry benzene (5 cm^3) containing AIBN (2 mg) under an inert atmosphere was added tributyltin hydride (49 mg) and the mixture was heated to reflux for 2 h. Evaporation of the solvent gave a residue, which was flash chromatographed and on elution with 4% EtOAc–LP yielded the (S)-*isomer* **23b** (16 mg), m.p. 139–142 °C (from MeOH–acetone) (Found: C, 68.4; H, 9.45; Cl, 8.4. $C_{25}H_{41}ClO_2Si$ requires C, 68.7; H, 9.45; Cl, 8.1%) and the (R)-*isomer* **23a** (12 mg), m.p. 105–109 °C (from MeOH–acetone) (Found: C, 69.0; H, 9.5; Cl, 8.0%).

17β-(tert-*Butyldimethylsiloxy*)-19(S)-*chloro*- **24a** *and* 19(R)-*chloro*-5α,19-*cyclo*-10α-*androstan*-3-*one* **24b**.—The dichloro adduct **20a** (70 mg) was refluxed with tributyltin hydride (64 mg) in benzene (5 cm^3) containing AIBN (2 mg) under Ar for 2 h. Flash chromatography of the residue obtained on evaporation of the reaction mixture gave, on elution with 2% acetone–LP, the (R)-*isomer* **24b** (15 mg), m.p. 83–85 °C (from MeOH–acetone) (Found: C, 68.9; H, 9.7; Cl, 8.3%) and the (S)-*isomer* **24a** (11 mg), m.p. 126–129 °C (from MeOH–acetone) (Found: C, 68.7; H, 9.4; Cl, 8.3%).

11,11-Dichloro- **26a** *and 11,11-Dibromo-tricyclo-*[4.4.1.$0^{1,6}$]-*undecane* **26b** *and 1-Dichloromethyl-* **27a** *and 1-Dibromomethyl-1,2,3,4,5,6,7,8-octahydronaphthalene* **27b**.—9,10-Octalin **25** (500 mg), chloroform (2.5 cm^3), CTAB (100 mg), and 50% aq. NaOH (2.5 cm^3) were stirred together under reflux for 3 h. After dilution with water and extraction with Et_2O the residue obtained from the extract was flash chromatographed; elution with cyclohexane gave the dichloro derivative **26a** (410 mg), m.p. 35–38 °C (from EtOH) (lit.,[14] 37–38 °C); $\delta_H(CDCl_3)$ 1.30 (4 H, m), 1.45 (4 H, m), 1.65 (4 H, m) and 1.80 (4 H, m); δ_C 27.41 (C-1, -6), 78.88 (CCl_2), 20.65 and 29.81; and the non-crystalline dichloromethyl derivative **27a** (237 mg), $\delta_H(CHCl_3)$ 6.16 (d, *J* 2.8, $CHCl_2$) and 2.65 (br s, 1-H); δ_C 134.28 (C-9), 125.38 (C-8), 76.93 ($CHCl_2$), 49.82 (C-1), 31.00, 30.64, 27.26, 23.07, 22.89, 22.57 and 21.05.

9,10-Octalin **25** (500 mg), bromoform (2.5 cm^3), CTAB (100 mg) and 50% aq. NaOH (2.5 cm^3) were stirred together at room temperature for 16 h and worked up as described above. TLC showed two components. Flash chromatographic separation gave, on elution with cyclohexane, the dibromo derivative **26b** (261 mg), m.p. 42–45 °C (from acetone–MeOH) (lit.,[30] 46–47 °C); $\delta_H(CDCl_3)$ 1.30 (4 H, m), 1.50 (4 H, m) and 1.80 (8 H, m); δ_C 27.98 (C-1, -6), 61.86 (CBr_2), 20.43 and 31.76; and the non-crystalline dibromomethyl derivative **27b** (249 mg), $\delta_H(CDCl_3)$ 6.19 (1 H, d, *J* 2.7, $CHBr_2$) and 2.65 (1 H, br s, 1-H); δ_C 134.51 (C-9), 126.39 (C-8), 54.11 ($CHBr_2$), 50.61 (C-1), 31.09, 30.84, 27.10, 25.65, 23.08, 22.55 and 21.28; *m/z* 306, 307 and 308 (M^+), 225 and 227 $(M - Br)^+$, 149 $(M + H - Br_2)^+$ and 135 $(M - CHBr_2)^+$.

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