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A STUDY OF THE REARRANGEMENT OF HECOGENIN DERIVATIVES INTO C-NOR-D-HOMO STEROIDS

J. M. COXON and M. P. HARTSHORN
Chemistry Department, University of Canterbury, Christchurch, New Zealand

and

D. N. KIRK and M. A. WILSON
Chemistry Department, Westfield College, Hampstead, London, N.W.3

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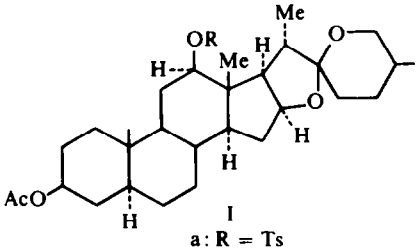
Abstract—Base-catalysed decomposition of the 12-tosylhydrazone (II) of hecogenin acetate under aprotic conditions occurs without rearrangement, to give the Δ^{11}-olefin (III). Hydroxylic solvents favour the formation of the C-nor-D-homo-$\Delta^{13(17a)}$-olefin (VI). The tosylate (Ia) of the 12β-alcohol derived from hecogenin acetate undergoes solvolysis to give mixtures containing varying proportions of the C-nor-D-homo-$\Delta^{13(17a)}$-olefin (VI) and the $\Delta^{17a(18)}$-isomer (IV), depending upon the reaction conditions. Polar solvents and elevated temperatures favour the endocyclic ($\Delta^{13(17a)}$)-olefin, but the exocyclic ($\Delta^{17a(18)}$)-olefin predominates in solvents of low polarity. The mechanisms of these reactions are discussed. Detailed NMR evidence is presented in support of the $\Delta^{13(17a)}$-structure for the endocyclic olefin. Rearrangements of the 12-tosylhydrazone (XVIb) and 12β-tosyloxy (XVIa) derivatives in the pregnane series gave only the endocyclic $\Delta^{13(17a)}$- and $\Delta^{17(17a)}$-olefins.

THE rearrangements of hecogenin derivatives (Ia, Ib, and II) to give products with the C-nor-D-homo skeleton was discovered in the early 1950's,[1, 2] during abortive attempts to find a good route to the Δ^{11}-derivative (III), as a step in the synthesis of cortisone. Other and better ways of converting hecogenin into cortisone were soon developed,[3] but the C-nor-D-homo rearrangement has received considerable study, both for its intrinsic interest, and because the products have the modified steroid skeleton found in the alkaloids jervine and veratramine.[4]



I
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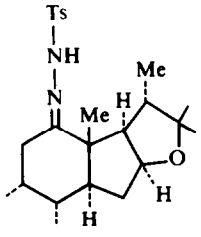
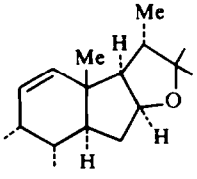
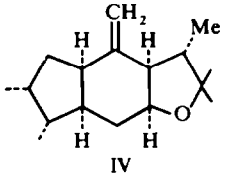
b: R = Ms
c: R = H



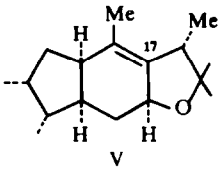
II



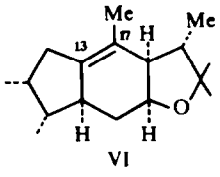
III



IV



V



VI

TABLE 1. PRODUCTS FROM DECOMPOSITION OF $C_{(12)}$-DERIVATIVES RELATED TO HECOGENIN (ANALYSED BY GLC AND NMR—SEE EXP)

Expt.	$C_{(12)}$-derivative	Reaction conditions	Products %[a]		
			C-nor-D-homo-olefins		Un-rearranged Δ^{11}-olefin
			$\Delta^{13(17a)}_{(endo)}$	$\Delta^{17a(18)}_{(exo)}$	
1	12-Tosylhydrazone (II)	KOH, "digol"[b], 140°	60–75[c]	~5	35–20[c]
2	12-Tosylhydrazone (II)	Na, "digol", 110–125°	90	trace	~10
3	12-Tosylhydrazone (II)	NaOH, digol/H_2O (4:1), 110°	90	trace	~10
4	12-Tosylhydrazone (II)	NaOH, digol/H_2O (1:1), 108°	86	trace	~14
5	12-Tosylhydrazone (II)	KO'Am, HO'Am, 105°	25	trace	~75
6	12-Tosylhydrazone (II)	$KOCMe_2Bu$, $HOCMe_2Bu$, 108°	19	—	81
7	12-Tosylhydrazone (II)	NaOMe, "diglyme"[d] 155°	—	—	60[c]
8	12-Tosylhydrazone (II)	NaH, "diglyme", 140°	8	—	92
9	12β-NH_2 (VII)	$NaNO_2$, aq HOAc, 20°	78	22	—
10	12β-Tosylate (Ia)	KOH, "digol", 80°	42	58	—
11	12β-Tosylate (Ia)	KOH, "digol", 104°	83	17	—
12	12β-Tosylate (Ia)	KOH, "digol", 120°	96	4	—
13	12β-Tosylate (Ia)	KOH, "digol", 140°	98	2	—

14	12β-Tosylate (Ia)	NaOAc, "digol", 140°	86	14	—
15	12β-Tosylate (Ia)	NaOMe, MeOH, 65°	75	25	—
16	12β-Tosylate (Ia)	NaO^{i}Pr, ^{i}PrOH, 65°	46	54	—
17	12β-Tosylate (Ia)	KO^{t}Bu, ^{t}BuOH, 83°	40	60	—
18	12β-Tosylate (Ia)	KO^{t}Am, ^{t}AmOH, 102°	36	64	—
19	12β-Tosylate (Ia)	KOH, 80% aq acetone, reflux	77	23	—
20	12β-Tosylate (Ia)	$CaCO_3$, 80% aq acetone, reflux	76	24	—
21	12β-Tosylate (Ia)	$CaCO_3$, EtOH, 80°	50	50	—
22	12β-Tosylate (Ia)	$CaCO_3$, ^{t}AmOH, 80°	40	60	—
23	12β-Tosylate (Ia)	Pyridine (anhyd.) reflux	10	90	—
24	12β-Tosylate (Ia)	80% aq Pyridine, reflux	42	58	—
25	12β-Tosylate (Ia)	HOAc, 5% pyridine	26	74	—
26	12β-Tosylate (Ia)	silica-gel column in benzene	58	42	—
27	12β-OH (Ic)	$POCl_3$, pyridine 25°	50	50	—
28	12β-OH (Ic)	TsCl, pyridine, reflux	47	53	—

[a] Percentage distribution among the three products indicated. Other minor components from certain experiments are not included. See Experimental section for full details.

[b] "digol" = diethylene glycol.

[c] Range of figures from four runs. Relative proportions varied in "digol", possibly due to variations in water content.

[d] "diglyme" = diethylene glycol dimethyl ether.

[e] Isolated by crystallization—see Experimental.

The two groups of workers[1, 2] who originally studied these reactions found two rearranged olefinic products. One was identified as the $\Delta^{17a(18)}$-(exocyclic) olefin (IV). The other was thought to be the $\Delta^{17(17a)}$-(endocyclic) olefin (V) until we demonstrated, from chemical and NMR evidence not available to the original workers, that it is the $\Delta^{13(17a)}$-isomer (VI). This work has been reported briefly:[5] further details, especially of the significant NMR spectra, are given below.

Our work has now been extended in an attempt to explain the variations in relative yields of the rearranged olefinic products, as reported by different workers. Published work includes results in the spirostan,[1, 2, 6] pregnane,[7] cholane,[8a] and cholanic acid series.[8b] Bamford-Stevens decomposition of 12-tosyl-hydrazones always gave the endocyclic ($\Delta^{13(17a)}$) olefin as the major product, in yields varying between 30% (e.g. Ref 8*b*) and ca. 70%.[1, 6a] Small amounts of the Δ^{11}-olefins have also been reported.[2, 8a, 8b] Buffered solvolysis of 12β-mesyloxy- or tosyloxy-spirostan derivatives, in contrast, is said to afford mainly the exocyclic olefin (IV); yields 54%,[1] 66%,[6b] 73%,[2]) along with some endocyclic olefin (VI). The latter was, however, formed in "high yield"[2] when the solvolysis was performed in methanol without a buffer, and the authors commented[2] that the course of reaction seemed to be determined mainly by the polarity of the solvent. Rearrangement to give a similar mixture of C-nor-D-homo olefins has also been achieved by diazotization of the 12β-amino-spirostan (VII).[9]

In order to define more precisely the reaction conditions and mechanisms which lead to the three olefinic products in the spirostan series, we have studied the decomposition of the 12-tosylhydrazone (II) and the 12β-tosylate (Ia) under a variety of conditions. Products were analysed by GLC and NMR, in order to obtain greater precision than is possible by isolation techniques (Experimental). We find that the reactions of both $C_{(12)}$-derivatives can be controlled by appropriate choice of experimental conditions. Moreover the Δ^{11}-olefin (III), the unattained objective of the original workers, was formed almost exclusively when the 12-tosylhydrazone was decomposed by bases under *aprotic* conditions.

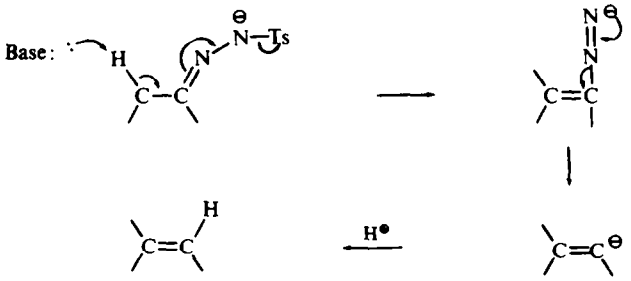
The 12-tosylhydrazone (II) was heated with bases in solvents of varying polarity and protic (or aprotic) character. In most cases decomposition was effected at the lowest practicable temperature by heating the mixture gradually, in a vessel connected to a gas burette. Nitrogen evolution became quite rapid at 105–110°. Table 1 records the outcome of these reactions.

The 12β-tosylate (Ia) was decomposed under a wider variety of conditions, including strongly basic and buffered solutions in solvents ranging from highly polar (e.g. aqueous acetone, methanol) to relatively low polarity (2-methylhexan-2-ol, pyridine, etc.) The effect of varying the reaction temperature was also studied with other factors being kept constant. The tosylate was stable in *anhydrous* benzene or "diglyme" at 80°, but decomposed readily in all the other systems used. Product analyses are included in Table 1, which records the relative yields of the $\Delta^{13(17a)}$- and $\Delta^{17a(18)}$-olefins. No detectable amount of the Δ^{11}-olefin (III) was formed from the 12β-tosylate. In a few cases, where the solvolyses were performed at low temperatures, GLC analysis revealed the presence of another product (maximum 20%—Experimental). This may have been a new olefinic compound, possibly the $\Delta^{17(17a)}$-isomer (V), but attempts to isolate it by column or TLC were unsuccessful. It was not found in significant amounts from solvolyses performed above 100°. Table 1 also records

an analysis of the olefins produced by deamination of the 12β-amine (VII). Only the two rearranged olefins were detected by GLC and NMR analysis.

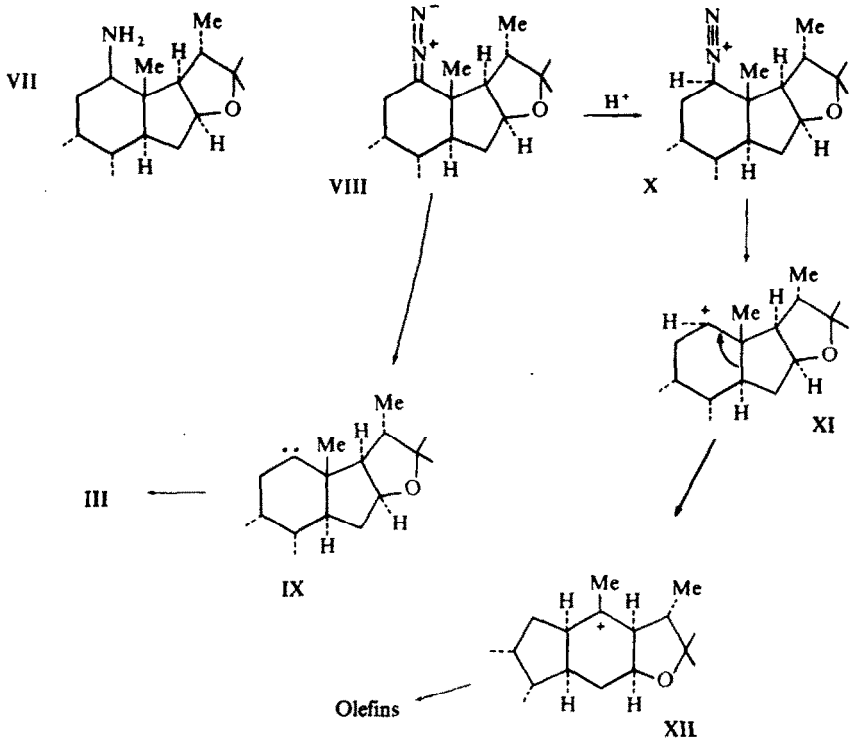
DISCUSSION

It is recognized[10] that tosylhydrazone anions may decompose by at least two distinct mechanisms, involving carbenes and carbonium ions respectively as intermediates. Carbenes arise by thermal decomposition of diazo-intermediates (e.g. VIII), in aprotic solvents. They afford either normal or rearranged olefinic compounds, and frequently also "insertion" products. Carbonium ions are formed in hydroxylic solvents, probably by C-protonation of the diazo-compounds and expulsion of nitrogen from the diazonium ion (e.g. X). Products derived from carbonium ions generally differ from those formed via carbenes; rearrangements of Wagner–Meerwein type are common although some "hot carbonium-ion" insertion reactions have also been reported.[11] A third possible reaction path, described recently,[12] involves synchronous removal of a vicinal proton with expulsion of toluene-*p*-sulphinate ion from the sulphonylhydrazone anion. This elimination reaction requires a very strong base (e.g. sodium hydride,[12a] butyl lithium,[12b] or in the special case of $C_{(17)}$-tosylhydrazones, the BH_4^- or AlH_4^- ion[12c]) and gives the least-substituted ("Hofmann-type") olefinic product.



The decomposition of hecogenin tosylhydrazone in the aprotic solvent "diglyme" seems most likely to involve the $C_{(12)}$-carbene (IX), leading to the Δ^{11}-olefin (III). In hydroxylic solvents the sequence; $C_{(12)}$-diazonium ion (X) → $C_{(12)}$-carbonium ion (XI) → rearranged products is probable. Solvents of low "protic" character (e.g. tertiary alcohols, Table 1) permit both types of reaction to proceed simultaneously. The alternative 1,2-elimination mechanism (above) for formation of the Δ^{11}-olefin cannot be decisively ruled out by present evidence, but seems improbable in view of the steric hindrance at the $C_{(11)}$-position, the relatively weak basicity of sodium methoxide, and the observed similarity of decomposition temperature for the tosylhydrazone whatever solvent/base system is used. The reaction paths *via* a carbene or a carbonium ion probably share a common rate-controlling thermal fission of the tosylhydrazone anion to give the diazo-compound (VIII). This fission involves no change in the number of ionic particles so should be relatively insensitive to solvent character, which only becomes important in determining the fate of the highly reactive diazo-compound once it is formed.

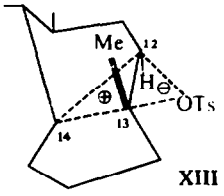
The involvement of a more-or-less-free carbonium ion in the skeletal rearrangement is strongly supported by other data in Table 1. The 12β-amine (VII) would be



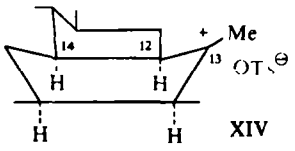
expected to react with aqueous nitrous acid to give the 12β-diazonium ion (X), or an equivalent covalent species.[13] Rapid expulsion of a nitrogen molecule would give an intermediate (XI) with carbonium-ion character at $C_{(12)}$, leading to immediate (probably concerted) migration of the $C_{(13)}$—$C_{(14)}$ bond, as described elsewhere.[1] The fate of the relatively stable rearranged $C_{(17a)}$-carbonium ion (XII) will then be decided in the Saytzeff sense, mainly according to the relative stabilities of the $\Delta^{13(17a)}$- and $\Delta^{17a(18)}$-olefins.[14] The endocyclic olefin (VI) predominates, being more stable than the exocyclic isomer (IV) from which it has been obtained by the action for formic acid.[1] The non-appearance of the third possible rearranged olefin, the $\Delta^{17(17a)}$-isomer (V), is probably due to the inductive effect of the 16β-oxygen function, which would have a specific destabilizing effect on a transition state for de-protonation of the $C_{(17a)}$–carbonium ion involving a shift of positive charge towards $C_{(17)}$.*

Exactly similar arguments will explain the composition of olefin mixtures derived by solvolysis of the 12β-tosylate (Ia) in aqueous or other highly polar media. Here the ionic fragments should be readily solvated and separated, so that the carbonium ion can follow the same path as the ion derived from the 12β-amine. A contrasting situation exists, however, in solvents of low polarity, where the carbonium ion and tosylate anion would be expected to remain in intimate contact.[16] We envisage a transition state of the type (XIII) for skeletal rearrangement, leading to a stereospecifically associated ion-pair (XIV). It is even possible that this ion-pair undergoes transient

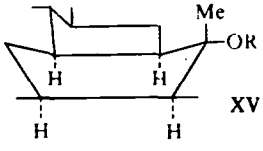
* Similar control over olefin formation from a carbonium ion adjacent to an electronegative substituent has recently been discussed in relation to the acid-catalysed dehydration of 3β,6α-diacetoxy-5-hydroxy-5α-cholestane, which gave the Δ^4-unsaturated derivative as the sole product.[15]



XIII



XIV



XV a: R = Ts
b: R = H

collapse to a covalent tertiary tosyloxy-derivative (XVa), although this step is not required to explain the preference for formation of the exocyclic olefin under these conditions. Inspection of models of the rearranged ion-pair (XIV), or its covalent equivalent (XVa), shows that the only proton available for elimination *trans* to the tosylate group is one at $C_{(18)}$. There is a close parallel here with our earlier finding[17] that the 17aα-hydroxy-17aβ-methyl compound (XVb) is dehydrated cleanly by thionyl chloride–pyridine to give the exocyclic olefin, whereas the epimeric 17aβ-alcohol, which has a suitably placed *trans* hydrogen at $C_{(13)}$, gave the $\Delta^{13(17a)}$-olefin (VI).

The results listed in Table 1 substantiate the two mechanisms proposed for solvolysis of the 12β-tosylate, and show trends which imply the simultaneous operation of both mechanisms in proportions depending upon (a) the reaction temperature, and (b) the solvent. They also confirm the opinion[2] that these reactions are true solvolyses, and are not strongly influenced by the basic species present. Increasing yields of endocyclic olefin with higher temperatures accord with the greater probability that the ion-pair will become separated by the solvent. The influence of solvent polarity and ion-solvating power is revealed in the sequence of results obtained in primary, secondary and tertiary alcohols and in the figures for anhydrous and aqueous pyridine. The negligible influence of the basic species present is clear from a comparison of reactions where solid calcium carbonate and dissolved potassium hydroxide, respectively, were used to prevent solutions in aqueous acetone from becoming acidic. The size of the basic species also seems to have little influence, for *tert*-butoxide and *tert*-amyloxide ions should be much more subject to steric effects than pyridine, yet were less efficient in producing the exocyclic olefin.

Refluxing acetic acid converted the 12β-tosylate into a complex mixture of products (GLC) which included no detectable quantities of any of the known olefins. Acetic acid buffered by pyridine, however, gave mainly the *exo*-olefin, in agreement with the poor solvating character of acetic acid for anions. The *exo*-olefin, rather surprisingly, was unaffected by boiling for 2 hr. in acetic acid containing a trace of toluene-*p*-sulphonic acid. The olefin cannot, therefore, be an intermediate in the un-buffered acetolysis, which seems likely to involve some different mode of reaction of the rearranged 17a-carbonium ion in the absence of any effective base.

The 12β-alcohol (Ic) reacted with an excess of either tosyl chloride or phosphoryl

TABLE 2. NMR SPECTRA.* CHEMICAL SHIFTS AND APPARENT COUPLING CONSTANTS FOR 16α-H AND ADJACENT PROTONS

Proton	Chemical shift (δ, ppm from Me_4Si)	
	$\Delta^{13(17a)}$-(Endocyclic) olefin	$\Delta^{17a(18)}$-(exocyclic) olefin
16α-H	4·205 (octet)	4·09 (octet)
15β-H	0·86 (multiplet)	0·78 (multiplet)
15α-H	2·12 (multiplet)	1·96 (multiplet)
17α-H	2·55 (triplet)	2·54 (triplet, $J \sim 9{\cdot}5$, with additional fine structure)
13α-H	—	2·42 (triplet, $J \sim 9$)
20β-H	ca. 1·18	1·29
Methyl signals:		
18-CH_3	1·665 ($W_{\frac{1}{2}} = 5$–6)	(18 = CH_2; 4·86, 4·78)
19-CH_3	0·79 (sharp singlet)	0·77 (sharp singlet)
21-CH_3	1·14 (doublet, $J = 6{\cdot}5$)	1·08 (doublet, $J = 6{\cdot}5$)
27-CH_3	0·79 (doublet, $J \sim 6$)	0·80 (doublet, $J \sim 6$)
Spin–Spin coupling:	*Apparent coupling constants* (Hz)	
$J_{15\alpha,16\alpha}$	5	4·5
$J_{15\beta,16\alpha}$	11	12
$J_{16\alpha,17\alpha}$	8	9·5
$J_{17\alpha,20\beta}$	ca. 10	9·5
$J_{15\alpha,15\beta}$	—	11·5
$J_{14\alpha,15\alpha}$	—	4·5
$J_{14\alpha,15\beta}$	—	12

* Determined for $CDCl_3$ solutions at 100 MHz, by Dr. W. C. Jankowski, Varian NMR Spectroscopy Applications Laboratories, California. A 100 MHz spectrum of the endocyclic olefin, kindly determined by Dr. M. Takeuchi, Jeolco (Europe) S.A., provided virtually identical shifts for all the main signals, except 15β-H, which was not located.

chloride in pyridine (Table 1) to give comparable proportions of the *exo*- and *endo*-olefins. Possibly the increased ionic strength of these solutions promotes an unusually high degree of separation of the steroid carbonium ion from its anion, and so gives higher yields of *endo* olefins than when pyridine alone is used with the 12β-tosylate. Thionyl chloride/pyridine gave a mixture of unidentified products, but none of the known olefins.

NMR spectra. Our assignment of the $\Delta^{13(17a)}$-unsaturated structure to the endocyclic-olefin rested in part on the width and multiplicity of the signal due to the 16α-proton in the NMR spectrum. The spectrum has now been analysed in more detail by double-irradiation. The 16α-proton resonance, centred at $\delta = 4.20$ ppm, is a well-defined octet, due to spin–spin coupling with the 15α, 15β- and 17α-protons (Table 2). The 16α-H signal was reduced to a quartet, of different structure in each case, by simultaneously irradiating any one of the three vicinal protons.

The signal due to the 17α-H was clearly discernible as a broad triplet ($\delta = 2{\cdot}53$ ppm) resulting from coupling with both the 16α and 20β-protons, with similar J-values. The large chemical shift is a consequence of deshielding both by the double bond and by the 16β-oxygen. The 17α-H assignment was further confirmed when the 20β-H

signal was located by double resonance. The 17α-H triplet was reduced to a doublet by simultaneous irradiation of the 20β-H, the observed splitting ($J^{Apparent}_{17\alpha,20\beta}$ = 9·5 – 10 Hz) agreeing with the dihedral angle (ca. 140°) between these protons.

The 15α- and 15β-H signals were located only through the spin decoupling experiments, for they are further coupled with each other and with the 14α-H, resulting in a broad complex signal for each of the $C_{(15)}$-protons in regions of the spectrum already occupied by other signals. Assignments of chemical shifts to the $C_{(15)}$ protons are based on the splittings which they produce at the 16α-H; a Dreiding model showed a large 15β/16α-dihedral angle (ca. 160–180°) and a small 15α/16α-dihedral angle (ca. 40–60°).[18] The 15β-H signal occurs at unusually high field because of the proximity of this proton to the β-lobe of the π-orbital direction of the double bond.[19] The 15α-H, in contrast, is nearer the nodal plane of the olefinic bond, and is deshielded. The spectrum for 16α-H is reproduced very closely by a simple first-order treatment using the coupling constants given in Table 2 (cf. Fig. 1).

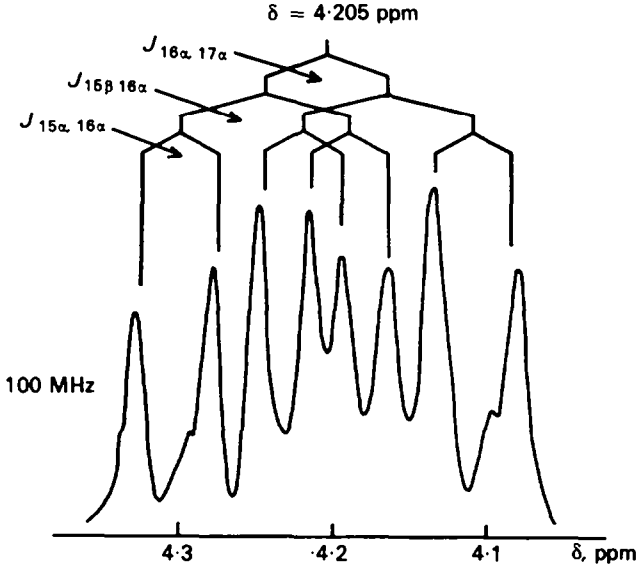


FIG. 1. NMR spectrum of 16α-H in the $\Delta^{13(17a)}$ endocyclic olefin (VI).

For reference purposes, a similar study was made of the exocyclic olefin, where the 16α-H again appeared as an octet, and the three vicinal protons were found at positions quite similar to those in the endocyclic olefin. The geometry of the part of the structure: $C_{(14)}$—$C_{(15)}$—$C_{(16)}$—$C_{(17)}$—: is similar in both olefinic compounds, so that corresponding *J*-values differ only slightly. It was additionally possible to locate the signal due to the allylic 13α-H in the exocyclic olefin (Table 2). Furthermore, a comparison of spectra at 100 MHz and 220 MHz revealed the detailed structure of the 15β-H signal in the exocyclic olefin, and probably also parts of the 15α-H signal (this was partly obscured by the $C_{(19)}$- and $C_{(27)}$ methyl peaks). The relevant

parts of these spectra are reproduced in Figs. 2 and 3, and correlate well with calculations using the first-order approximation, assuming the J-values listed in Table 2.

This NMR analysis confirms the assigned structures of the two olefins. Chemical evidence which substantiates the structure of the endocyclic olefin has been presented elsewhere.[5]

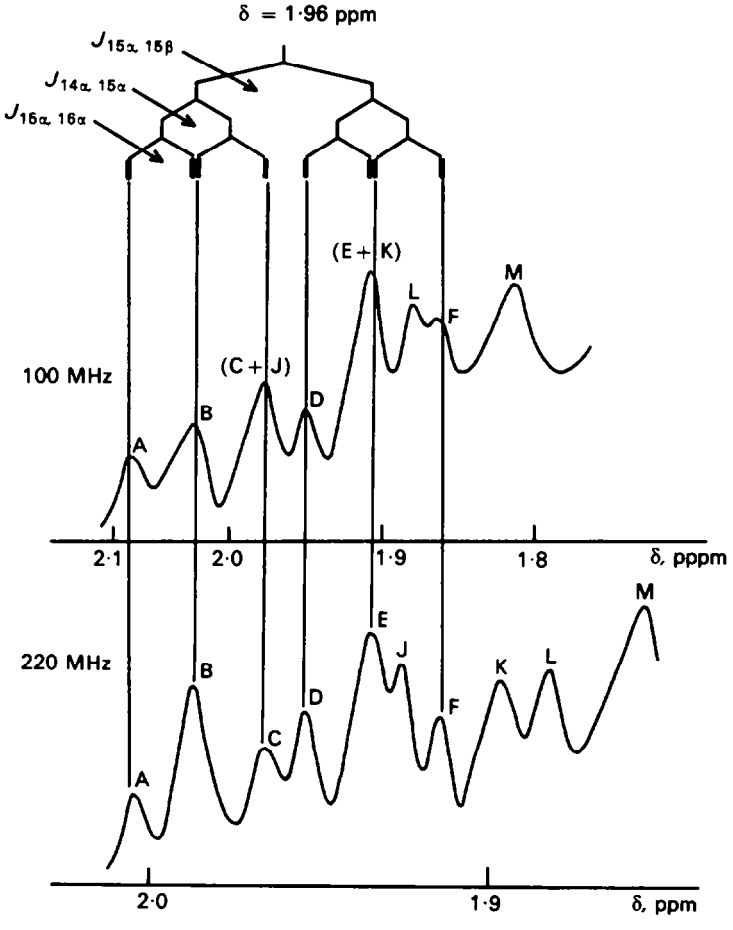


FIG. 2. NMR spectra of 15α-H in the $\Delta^{17a(18)}$-exocyclic olefin (IV). (Sextet, indicated by A–F; an overlapping quartet, marked J–M, appears to be due to an unidentified proton, $\delta \approx 1{\cdot}89$ ppm.)

Rearrangements in the pregnane series

In order to determine what influence, if any, is exerted by the relative rigidity imposed upon ring D in the spirostan series, we prepared the 12β-tosyloxy pregnane derivative (XVIa) and the corresponding 12-tosylhydrazone (XVIb), and rearranged

them by standard procedures. The absence of both $C_{(11)}$- and $C_{(20)}$-oxygen substituents is a novel feature, although there have been several reports of rearrangement of suitable 3,11,12- and 3,12,20-trisubstituted pregnanes to give C-nor-D-homo compounds. The preparation of these compounds from hecogenin followed well-established methods.[20] Reduction of the 12-ketone (XVIc) with lithium borohydride

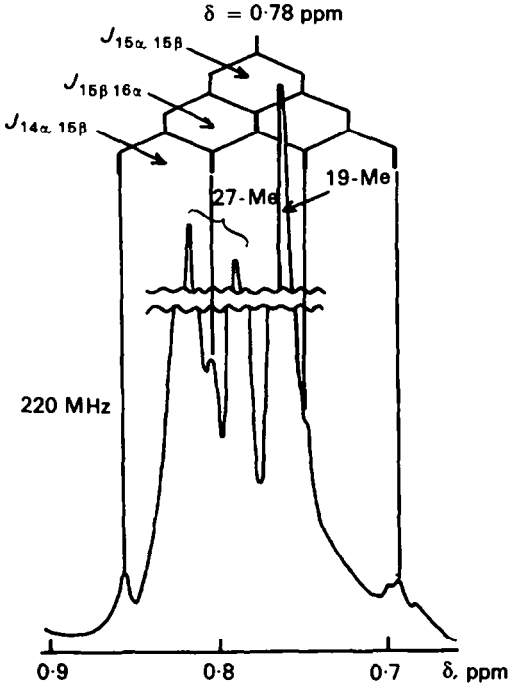
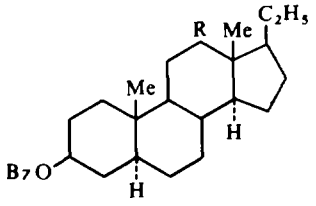


FIG. 3. NMR spectrum of 15β-H in the $\Delta^{17a(18)}$-exocyclic olefin (IV).

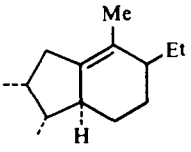
gave the 12β-hydroxy derivative as the major product (12β/12α = 3/2), recognized by the NMR signal due to the axial 12α—H (quartet, J = 5, J' = 10 Hz) centred at δ = 3·48 ppm. The lesser product, the 12α-alcohol, gave a triplet assigned to the equatorial 12β-H (δ = 3·80 ppm, $J = J'$ = 2·5 Hz).

Reaction of the 12-toluene-*p*-sulphonylhydrazone (XVIb) with a solution of sodium in ethane diol, followed by re-benzoylation at $C_{(3)}$, gave an unsaturated product, assigned the C-nor-D-homo-$\Delta^{13(17a)}$-structure (XVII). The NMR spectrum had a three-proton signal at δ = 1·53 ppm, assigned to the C_{18}-Me group. The location of the double bond was confirmed by oxidation with osmium tetroxide followed by lead tetra-acetate. The structure of the resulting dicarbonyl compound (XVIII) followed from its IR spectrum, (ν_{max} 1748, 1721 and 1360 cm^{-1}) indicating a five-membered ring ketone and an acetyl group. The presence of the acetyl group was confirmed by the NMR spectrum, showing a sharp 3-proton singlet at δ = 2·10 ppm.

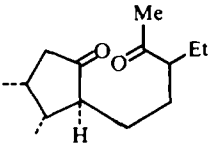
In analogous rearrangements, 3β,20β-dihydroxy-5α-pregnan-12-one and 3β,11β,20β-trihydroxy-5α-pregnan-12-one are reported to give the corresponding C-nor-D-homo-$\Delta^{13(17a)}$-olefins.[7]



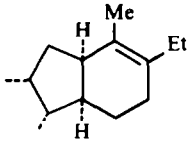
XVI a: R = β – OTs
b: R = :N – NHTs
c: R = :O
d: R = β – OH



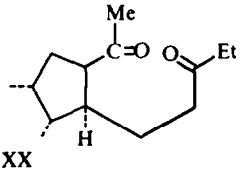
XVII



XVIII



XIX



XX

Reaction of the tosylate (XVIa) with potassium t-butoxide in t-butanol, followed by rebenzoylation, gave the $\Delta^{13(17a)}$-olefin (XVII) by direct crystallization. Chromatography of the mother liquors gave a solid, m.p. 92–93° which was a mixture of the $\Delta^{13(17a)}$- and $\Delta^{17(17a)}$-olefins. Oxidation of this mixture with osmium tetroxide followed by periodic acid gave a mixture of the D-seco-diones (XVIII and XX). The composition was revealed by the IR spectrum (Experimental) and by the NMR spectrum, which revealed two distinct acetyl signals, at $\delta = 2{\cdot}13$ and $\delta = 2{\cdot}09$ ppm, in the ratio 3:1. The minor component was assigned to the 13,17a-seco diketone (XVIII) derived from the $\Delta^{13(17a)}$-olefin, and the other to the 17,17a-seco compound, (XX) derived from the $\Delta^{17(17a)}$-olefin (XIX), which has not been isolated. The 17,17a-seco-compound showed the $C_{(20)}$-methylene, adjacent to the $C_{(17)}$-carbonyl, as a quartet (width 21 Hz) centred at $\delta = 2{\cdot}38$ ppm.

The IR and NMR spectra of the residual materials derived from the 12β-tosyloxy-pregnane and 12-tosylhydrazone derivatives were scrutinized carefully for evidence of traces of the corresponding Δ^{11}- or C-nor-D-homo-exocyclic olefin, but neither could be detected. Solvolysis of the 12β-tosylate in anhydrous pyridine surprisingly produced a similar result.* It seems that the exocyclic olefin arises only in the special stereochemical situation obtaining in the spirostan molecule, where ring D in the rearranged carbonium ion (or the intimate ion-pair) is constrained in the boat

* This phase of our work was completed in 1965.[21] A recent account of similar work in the 5β-cholane series[8e] reports that the 12β-tosylate gave 30% of C-nor-D-homo exocyclic olefin with collidine, and the 12-tosylhydrazone gave 24% of the Δ^{11}-olefin, along with the rearranged endocyclic olefins corresponding to XVII and XIX.

conformation (XIV). Inspection of Dreiding models shows that ring D in the pregnane series is quite flexible, and likely to "flip" into different conformations during rearrangements, so that the arguments given above for the spirostan series are not relevant here.

EXPERIMENTAL

Rotations were measured for $CHCl_3$ solns at room temp. IR spectra were recorded for CS_2 solns. NMR spectra [δ, ppm from TMS; multiplicity indicated by s (singlet), t (triplet), or q (quartet)] were recorded at 60 MHz for $CDCl_3$ solns. Alumina used for chromatography was P Spence, Grade H, deactivated by 5% of 10% AcOH. Silica gel M.F.C. was Hopkin & Williams Ltd. Light petroleum refers to the fraction of b.p. 40–60 or 50–70°.

Spirostan series

The derivative Ia was prepared from Ic[22] by reaction with toluene-*p*-sulphonyl chloride (2 mols) in anhyd pyridine for 3 days at room temp. Precipitation into water gave an amorphous solid which was washed thoroughly, dried in vacuum at 25°, and re-precipitated twice from acetone. The 12β-tosylate, which failed to crystallize, was obtained as a white powder, homogeneous by TLC on silica, m.p. ca. 140–150° (dec), ν_{max} 1740, 1236, 1189, and 1180 cm^{-1}. Attempted GLC analysis led to decomposition to give a characteristic set of peaks of short retention time. None of those peaks appeared in the same region as the olefinic products (III, IV and VI) formed by solvolysis of the tosylate.

The 12-tosylhydrazone II[1,2] and 12β-amine VIII[9] were prepared by published procedures.

Decomposition of tosylhydrazone II

Most of these reactions were performed by stirring, under N_2, a mixture of the tosylhydrazone (200 mg), and solvent containing the appropriate base (see below). The vessel was connected to a gas burette and the flow of N_2 from the cylinder was stopped. The mixture was warmed until N_2 evolution began (ca. 105°), and the temp was then allowed to rise very gradually until there was no further reaction (2–3 hr; final temp ca. 110° in most cases). Reactions at 140° were achieved by gradual addition of solid tosylhydrazone to the stirred solvent/base system at 140°, in N_2. Considerable frothing occurred in all cases. The cooled mixtures were poured into dil HCl, and the products were extracted with ether + benzene, and analysed either as trimethylsilyl ethers or as acetates, prepared in the usual way.

The following reagents were used (cf. Table 1):

Expt. 1: KOH (1 g) in diethylene glycol ("digol"; 5 ml).
2: Na Metal (90 mg) dissolved in anhyd "digol" (5 ml), (using 0·25 g 12-tosylhydrazone +0·125 g cholestanol as GLC reference).
3–4: NaOH (0·3 g) in aqueous "digol" (10 ml), with steroid quantities similar to Expt. 2.
5–6: K metal (0·2 g) dissolved in the anhyd alcohol (5 ml).
7: See preparation of 11:ene, below.
8: NaH (0·2 g) in diglyme (5 ml).

Preparation of 3β-*acetoxy*-5α, 25*R*-*spirost*-11-*ene* (III). The 12-tosylhydrazone II (2 g) was added to a stirred suspension of NaOMe (2·7 g) in anhyd diglyme (5 ml) and the mixture was heated to 155° for 2 hr in N_2. Isolation of the steroid as above, and acetylation with Ac_2O-pyridine, gave the 11-ene (865 mg), m.p. 204–208° from MeOH, $[\alpha]_D$ −38°. (Lit.[2] m.p. 206–210°, $[\alpha]_D$ −44°).

Diazotization of the 12β-*amine* (VII) was carried out as previously described.[9]

Solvolysis of the 12β-*tosylate* (Ia). The solvent or reagent mixture (see below) was stirred at the required temp (Table 1) in N_2, under reflux where necessary, and the solid steroid tosylate (100 mg), was added all at once. The temp and stirring were maintained for 4–8 hr, then the mixture was poured into water, treated with a slight excess of dil HCl, and the products were extracted with ether–benzene for analysis.

The following reagent mixtures were used:

Expt. 10–13: KOH (1 g) in diethylene glycol (5 ml).
14: NaOAc (0·5 g) in diethylene glycol (5 ml).
15–18: a soln of Na or K metal (0·2 g) in the appropriate anhyd alcohol (10 ml).
19: KOH (1 g) in 80% aq acetone (37 ml).

20–22: $CaCO_3$ (ca. 1 g, freshly pptd and washed with the appropriate solvent), in the solvent (30 ml).
23–25: solvents as in Table 1 (5 ml).
26: the 12β-tosylate (0·5 g) in benzene (20 ml) was adsorbed on to a silica gel column (15 g in light petroleum) for 1 hr, then eluted with benzene.

Reactions using 3β-*acetoxy*-12β-*hydroxy*-5α, 25*R*-*spirostan* (Ic)

(a) *With* $POCl_3$-*pyridine* (expt. 27). The 12β-ol (200 mg) in anhyd pyridine (5 ml) was cooled in ice and treated with freshly distilled $POCl_3$ (0·5 ml). The mixture was allowed to stand at room temp for 2 hr, then poured into water. The products were isolated as above, and acetylated for GLC analysis.

(b) *With* TsCl-*pyridine* (expt. 28). The 12β-ol (200 mg), toluene *p*-sulphonyl chloride (500 mg) and pyridine (5 ml) were heated together under reflux for 2 hr, then the products were isolated as above.

Analysis of products

GLC results, other than those mentioned below, were obtained during 1966 using a Gas Chromatography Ltd. model S3A gas chromatograph, with a 4 ft column of 2·5% "Epikote" on Diatoport (100 mesh) at 260°. The olefinic products (either as 3-acetates or as free alcohols) gave two peaks. The first peak contained the *exo*-($\Delta^{17a(18)}$)-olefin (IV) and the Δ^{11}-compound III; the second was the *endo*-($\Delta^{13(17a)}$)-olefin (VI). Relative retention times for the two peaks were in the ratio 3 :4 approx. Analysis of synthetic mixtures of the olefins confirmed that peak areas were proportional to weights of material to within ±3%, which are considered to be the probable limits of error in Table 1. An unidentified product, probably olefinic, sometimes appeared as a shoulder on the side of the peak due to the *endo*-olefin, with retention time some 13% longer. This component was detectable only in experiments 10, 11, 12 and 20. At its maximum (expts 10 and 20) it was estimated as ca. 20% of the total olefinic material. Results in Table 1 exclude this peak.

Column chromatography of representative product mixtures on alumina showed that the combined weight of olefin products (which were not well separated under these conditions) generally accounted for >90% of the total steroidal material.

Product mixtures which gave a significant peak due to the *exo*- and/or Δ^{11}-olefins were examined by NMR to estimate the relative proportions of these two products. The Δ^{11}-olefin produced a well-defined AB-quartet, due to the two vinylic protons, $\delta_A = 5{\cdot}40$, $\delta_B = 5{\cdot}75$ ppm, $J_{AB} = 10$ Hz. The exocyclic methylene group appeared as a broad peak at $\delta = 4{\cdot}75$ ppm, ($W_{\frac{1}{2}} \sim 7$Hz). This was best seen in the un-acetylated product, since the very broad absorption due to 3α-H in the 3β-acetate occurred ca. 4.7 ppm, width ca. 25 Hz, and made integration of the $=CH_2$ protons unreliable. Analyses obtained in this way (expts 1–8) are only approximate, since the lesser of the two components in most cases hardly exceeded the noise level of the spectrum. No Δ^{11}-compound was detectable in any of the products from the 12β-tosylate.

Products 2–4, 21, 22, 25, 27 and 28 were analysed during 1968, using a Hewlett Packard 402 (Biomedical) Gas Chromatograph, with a 4 ft column of 3·8% UCW98 (SE30) on Diatoport S, 80–100 mesh, at 250–270°. The steroid samples were first converted to their trimethylsilyl ethers at $C_{(3)}$. Runs 2–4 were made strictly quantitative by adding a weighed amount of 5α-cholestan-3β-ol to the 12-tosylhydrazone before the alkaline decomposition. From the relative peak areas produced by mixtures containing known weights of 5α-cholestan-3β-ol and the product olefins, the actual percentages of olefins derived from the tosylhydrazone were calculated. The olefins totalled 90%, 92%, and 84%, respectively, for runs 2, 3 and 4, the remainder being very largely hecogenin in each case. (Minor shoulders on the main olefin peaks were again ignored in calculating olefin ratios, as these were not significantly affected.)

Pregnane series

3β-*Benzoyloxy*-5α-*pregnan*-12-*one*. 3β-Hydroxy-5α-pregnan-12-one[7] (25 g) in benzene (200 ml) and pyridine (30 ml) was treated with benzoyl chloride (26 ml) overnight. The product, isolated *via* dichloromethane, crystallized from MeOH to give the 3-*benzoate* (33 g) as needles, m.p. 215–217°, $[\alpha]_D$ +90° (*c* 1·125) ν_{max} 1712, 1274 cm^{-1} (Found: C, 79·3; H, 9·1. $C_{28}H_{38}O_3$ requires: C, 79·6; H, 9·1%).

Tosylhydrazone of 3β-*benzoyloxy*-5α-*pregnan*-12-*one* (XVIb). Toluene-*p*-sulphonyl hydrazide (2·5 g), was added to a soln of 3β-benzoyloxy-5α-pregnan-12-one (4 g) in glacial AcOH (240 ml) and the mixture was kept at 20° for 12 hr. The crystalline 12-tosylhydrazone (5 g) was washed with water and EtOH, and dried: m.p. 225–250°, $[\alpha]_D$ +27° (*c* 0·6), ν_{max} 3205 cm^{-1} (N—H), 1724, 1274, 1190 and 1180 cm^{-1}.

Alkaline decomposition of the toluene-p-*sulphonyl hydrazone* (XVIb) *of* 3β-*benzoyloxy*-5α-*pregnan*-12-*one*. Sodium (4 g) was dissolved in diethylene glycol (160 ml) with warming. The soln was cooled to 50° and the tosylhydrazone (5 g) was added. The mixture was heated gradually to 165° and kept at that temp until no

further gas evolution was apparent (2 hr). After being cooled to 60°, the mixture was diluted with water and the steroidal material was isolated *via* ether. The crude product was treated with pyridine (100 ml) and benzoyl chloride (4 ml) at room temp for 30 min. Adsorption of the crude benzoate on alumina (150 g) and elution with light petroleum–benzene (9 : 1) gave 3β-*benzoyloxy*-C-*nor*-D-*homo*-5α-*pregn*-13 (17a)-*ene* (XVII; 2·4 g) as prisms (from acetone), m.p. 140–141°, $[\alpha]_D$ +17° (*c* 1·04), ν_{max} 1742 and 1274 cm^{-1}; NMR: δ 0·77 (s, 19-Me), 1·53 (s, 18-Me), 0·97 (t, 21-Me). (Found: C, 83·3; H, 9·8. $C_{28}H_{38}O_2$ requires: C, 82·7; H, 9·4%).

Hydroxylation of 3β-*hydroxy*-C-*nor*-D-*homo*-5α-*pregn*-13(17a)-*ene and cleavage of ring* D. A soln of 3β-benzoyloxy-C-nor-D-homo-5α-pregn-13(17a)-ene (500 mg) and KOH (1 g) in 90% aqueous EtOH (100 ml) was heated under reflux for 6 hr to hydrolyse the 3β-benzoyloxy group. The crude hydroxyolefin in pyridine (40 ml) was treated with osmium tetroxide (500 mg) and left at room temp for 9 days. H_2S was then passed through the soln and the precipitated osmium sulphide was removed by filtration. After removal of solvents *in vacuo* the black residue was heated under reflux for 6 hr in EtOH (200 ml) containing Na_2SO_3 (2·2 g) in water (50 ml). Isolation of the steroidal material *via* chloroform extraction gave the crude 3β,13,17a-triol as an oil, ν_{max} 3600 cm^{-1}.

A soln of the 3β,13,17a-triol (180 mg) in t-butanol (20 ml) and AcOH (20 ml) was stirred with lead tetraacetate (1 g) for 18 hr. Ethanediol (5 ml) was added, and the resulting clear soln was poured into water. The steroidal material was extracted with ether, which was washed successively with water, $NaHCO_3$ aq and water. The D-*seco*-*dione* (XVIII) was obtained as an oil (150 mg), ν_{max} 3610 cm^{-1} (OH), 1748 cm^{-1} (5-membered ring ketone), 1721 and 1360 cm^{-1} (COMe); NMR: δ 0·80 (s, 19-Me), 2·10 (s, 18-Me).

Reduction of 3β-*benzoyloxy*-5α-*pregnan*-12-*one* (XVIc). A suspension of 3β-benzoyloxy-5α-pregnan-12-one (15 g) and $LiBH_4$ (4 g) in THF (400 ml) was stirred at room temp for 3·5 hr. After isolation of the steroidal material *via* dichloromethane–ether, and removal of solvents, the residue was adsorbed onto deactivated alumina (1 kg). Elution with light petroleum–benzene (1 : 1), and crystallization from hexane, gave 3β-*benzoyloxy*-12β-*hydroxy*-5α-*pregnane* (7·9 g), m.p. 191–191·5°, $[\alpha]_D$ +20° (*c* 1·12), ν_{max} 3597, 1724 and 1274 cm^{-1}. (Found: C, 78·6; H, 9·6. $C_{28}H_{40}O_3$ requires: C, 79·2; H, 9·5%).

Further elution with the same solvent mixture gave 3β-*benzoyloxy*-12α-*hydroxy*-5α-*pregnane* (6·0 g), m.p. 165–166° from MeOH, $[\alpha]_D$ +27° (*c* 1·15), ν_{max} 3610, 1724 and 1274 cm^{-1}. (Found: C, 78·8; H, 9·6. $C_{28}H_{40}O_3$ requires: C, 79·2; H, 9·5%).

Tosylation of 3β-*benzoyloxy*-12β-*hydroxy*-5α-*pregnane* (XVId). 3β-Benzoyloxy-12β-hydroxy-5α-pregnane (7·1 g) in pyridine (36 ml) was treated with toluene-*p*-sulphonyl chloride (10 g) in pyridine (36 ml) at room temp for 4 days. The soln was poured into water and the product was isolated *via* ether, to give the 12β-*tosylate* (XVIa) as an oil, ν_{max} 1724, 1274, and 1175 cm^{-1}, homogeneous by TLC.

Base-catalysed rearrangement of 3β-*benzoyloxy*-12β-*tosyloxy*-5α-*pregnane* (XVIa). The 12β-tosylate (XVIa, 5 g) was heated in a soln prepared from K metal (3 g) in t-BuOH (400 ml) under reflux in N_2 for 18 hr. The crude product, after re-benzoylation with pyridine (100 ml) and benzoyl chloride (8 ml), crystallized from acetone to give 3β-benzoyloxy-C-nor-D-homo-5α-pregn-13(17a)-ene as chunks (1·6 g), m.p. 140–141°, identical with the sample prepared above.

The residue, after removal of solvents, was adsorbed onto silica gel (250 g). Elution with light petroleum and crystallization from MeOH gave a mixture (3 g) consisting mainly of XIX (ca. 75%), contaminated with the 13(17a)-ene (ca. 25%). This mixture, which resisted further separation, had m.p. 92–93°, $[\alpha]_D$ −16·5° (*c* 0·78), ν_{max} 1724 and 1274 cm^{-1}; NMR: δ 0·80 (s, 19-Me), 0·93 (t, 21-Me), 1·53 (s, 18-Me). (Found: C, 82·4; H, 9·6. $C_{28}H_{38}O_2$ requires: C, 82·7; H, 9·4%).

Cleavage of ring D *in the impure* 3β-*hydroxy*-C-*nor*-D-*homo*-5α-*pregnan*-17,17a-*ene* (XIX).

The olefin mixture above (400 mg) and KOH (600 mg) in aqueous EtOH (100 cc) were heated under reflux for 6 hr. The steroidal material, isolated in the usual manner, was dissolved in benzene (20 ml) and pyridine (3 ml), and treated with osmium tetroxide (500 mg) in benzene (10 ml) for 6 days. The osmate esters were decomposed with H_2S followed by Na_2SO_3 as described above, to give a mixture of triols as an oil, ν_{max} 3610 cm^{-1}. This mixture (175 mg) in MeOH (20 ml) was treated with periodic acid (100 mg) in water (5 ml) at room temp for 18 hr. The steroidal material, isolated in the usual manner, was an oil, containing XX and XVIII, ν_{max} 3610 (OH), 1748 (weak absorption, 5-membered ring ketone), 1721 (COMe and CO·Et) and 1360 cm^{-1} (CO·Me). The NMR spectrum showed this material to contain XX and XVIII in ratio 3 : 1. Features associated with XX were: δ 0·78 (s, 19-Me), 2·15 (s, 18-Me), 2·38 (q; W = 21 Hz, 20-CH_2).

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