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Acid-catalysed Rearrangements of Steroid Alkenes-III[1]. Backbone Rearrangement of de-A-Steroid Alkenes and Preparation of an Aromatic de-A-Steroid.

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Abstract: *Backbone rearrangement of 10α(methyl)-de-A-cholest-5-ene (3c), 6-ene (3d), 9-ene (3a) and 5(10)-ene (3b) affords products isomeric at C-20 and with the C-10 methyl group in the more stable equatorial position (6a and 6b). 5-Methylene-10α(methyl)-de-A-cholestane (5) affords similar C-20 isomeric products with both the C-5 and C-10 methyls in the more stable equatorial positions (9a and 9b). The de-A-alkenes (3) provided a convenient starting point for preparation of de-A-cholesta-5,7,9-triene (7). Components (6a, 6b, 7, 9a and 9b) have been used to confirm the widespread occurrence of homologous series of de-A-steroids in marine shales with a mild thermal history.*

Ring A degraded steroids occur naturally in immature sedimentary rocks[2,3] where they are presumed to have arisen from degradation of the sterols of organisms living in the water column at the time of sediment deposition. The nature of the loss of ring A is not yet known although it may be initiated by a microbially induced, oxidative opening of ring A. Indeed, the conversion of cholesterol into the ring A-opened keto acid (2) is a known microbial transformation[4]. We reported recently the presence of three series of backbone rearranged and two series of aromatic ring A degraded steroids in immature marine shales[3]. The preparation and physical properties of selected members of certain of these series is described herein.

10α(Methyl)-de-A-cholestan-5-one (4), prepared from cholest-4-en-3-one (1) *via* the seco-keto acid (2)[5,6] was accompanied by a minor amount (5%) of four de-A-alkenes which were removed by column chromatography. The major alkene (70%), purified by h.p.l.c., was identified as de-A-cholest-5(10)-ene (3b) from its ^{1}H n.m.r. spectrum (vinylic methyl, δ 1.63, broad s; vinylic proton, δ 5.34, broad s). Mass spectral results (g.c.-m.s.) suggested that the other alkenes are double bond isomers [3a (3%), 3c (22%), 3d (5%)].

Elimination of the tosylhydrazone of 4 with methyllithium afforded, unexpectedly, a 1:1 mixture of two de-A-alkenes. An aliquot of the mixture was separated by h.p.l.c. and the components assigned as the 5-ene (3c; expected product) and 6-ene (3d) from the sizes of certain coupling constants for the olefinic protons in the ^{1}H n.m.r. spectra[7]. Thus, the 5-ene displayed basically a doublet ($J_{5,6}$ 10.7Hz) for the C-5 proton, showing second order characteristics, and a multiplet for the C-6 proton (additional couplings to the proton at C-10 and the protons at C-7). The olefinic protons of the 6-ene both displayed additional couplings in addition to that of the large olefinic coupling ($J_{6,7}$ 10.0 Hz). Thus, the C-7 proton showed allylic coupling to the axial C-5 proton and the C-6 proton allylic coupling to the C-8 proton (both J's *ca*, 4.5 Hz) although it was not possible to distinguish directly between the C-6 and C-7 protons. The formation of the 6-ene is not readily explicable in terms of the accepted mechanism of the elimination[8]; 3c and 3d were shown (g.c. co-injection) to be among the alkene components obtained from the preparation of 4. The other alkene (3a) may be the 9-ene, as suggested by the similarity in its mass spectrum to that of the 5(10)-ene (3b).

Isomerisation of the de-A-alkenes (3) with boron trifluoride-etherate (BF_3-OEt_2) gave rise to two major C-20 diastereomeric backbone rearranged products [(20R)- and (20S)-14β-methyl-18-nor-8α,9β,10β(methyl)-de-A-cholest-13(17)-ene; 6a (51%) and 6b (46%) respectively][9]. These were

separated by silver ion-impregnated t.l.c. Both components had almost identical mass spectra with the major ion at m/z 203 arising from loss of the side chain. Differences were apparent, however, in their ^1H and ^{13}C n.m.r. spectra, notably in the chemical shifts for C-21 H_3 and C-21 respectively (Tables 1 and 2). A COSY spectrum of **6a** (Fig. 1) clearly established that the C-10 methyl group (C-19) is equatorial since the C-5 axial hydrogen showed the presence of two axial-axial couplings and one geminal coupling (note the 40Hz wide pattern for the C-5 axial proton in Fig. 1). As indicated on Fig. 1 the COSY spectrum is fully assigned and the chemical shifts of the hydrogens (from the corresponding 2DJ spectrum) are given in Table 1. The ^{13}C n.m.r. spectra of both **6a** and **6b** were also assigned fully. The chemical shifts of diacholest-13(17)-enes[1(b)] were used as a reference for assignment of C-8, C-11 to C-27 and C-14 β-Me. The chemical shifts of C-5 to C-7, C-9, C-10 and C-19 were assigned by calculation using a published method[10] and are in agreement with the relevant carbons in 1β-methyl-*trans*-decalin[10]. The chemical shift of C-19 confirms the equatorial conformation for this methyl group at C-10. Also present in the isomerisation product mixture was a pair of minor components (both *ca.* 1%) with almost identical mass spectra to **6a** and **6b**. It is possible that they are C-10 isomers of **6a** and **6b**.

Methylenation of **4** afforded 5-methylene-10α(methyl)-de-A-cholestane (**5**). The double bond was readily isomerised into ring B with *p*-toluenesulphonic acid/acetic acid/cyclohexane (TsOH/HOAc/cyclohexane). The three major products were isolated by h.p.l.c. and characterised by ^1H n.m.r. spectroscopy as the 5-ene (**8c**; 56%; δ 1.63, broad s, vinylic methyl; δ 5.4, d, J 4.6Hz, vinylic proton); 5(10)-ene (**8b**; 37%; δ 1.595, s, overlapping vinylic methyls) and 9-ene (**8a**; 6%; δ 1.613, broad s, vinylic methyl). Their mass spectra were complementary to those of components **3**.

Isomerisation of **5** with BF_3OEt_2 gave two major C-20 diastereomeric rearranged compounds [(20R)- and (20S)-5α,14β-dimethyl-18-nor-8α,9β,10β(methyl)-de-A-cholest-13(17)-ene; **9a** (47%) and **9b** (43%) respectively]. As expected both components had almost identical mass spectra, with the major ion at m/z 217 corresponding to loss of the side chain. Again, differences were apparent in their ^1H and ^{13}C n.m.r. spectra, in particular for the chemical shifts of C-21 H_3 and C-21 respectively (Tables 1 and 2). A COSY spectrum of **9a** clearly indicated that the C-5 and C-10 methyls were equatorial since the C-10 hydrogen showed the presence of two axial-axial couplings and the C-6 axial hydrogen two axial-axial couplings and one geminal coupling. The ^{13}C n.m.r. spectra of **9a** and **9b** were again fully assigned by comparison with the chemical shifts of diacholest-13(17)-enes[1(b)] (for C-8, C-11 to C-27 and C-14 β-Me) and by calculation[10] (for C-5 to C-7, C-9, C-10, C-19 and C-5 α-Me). The chemical shifts of the carbons assigned by calculation were in agreement with those reported for the corresponding carbons in 1β,2α-dimethyl-*trans*-decalin[10]. As encountered earlier, another pair of components was present in the isomerisation product mixture but in higher abundance (both *ca.* 5%). They had almost identical mass spectra to **9a** and **9b** and may be isomers at C-5 and/or C-10.

The backbone rearrangement of **3** and **5** indicates, therefore, migration of the double bond in the general direction C-5, C-10, C-9, C-8, C-14, etc. and leaves the ring B methyl group(s) in the more stable equatorial conformation in the final backbone rearranged products (**6a**, **6b**, **9a** and **9b**).

Figure 1. 2-Dimensional spectrum (COSY) and the projection on to f_2 of (20R)-14β-methyl-18-nor-8α,9β,10β(methyl)-de-A-cholest-13(17)-ene (6a). Key: a = axial; e = equatorial.

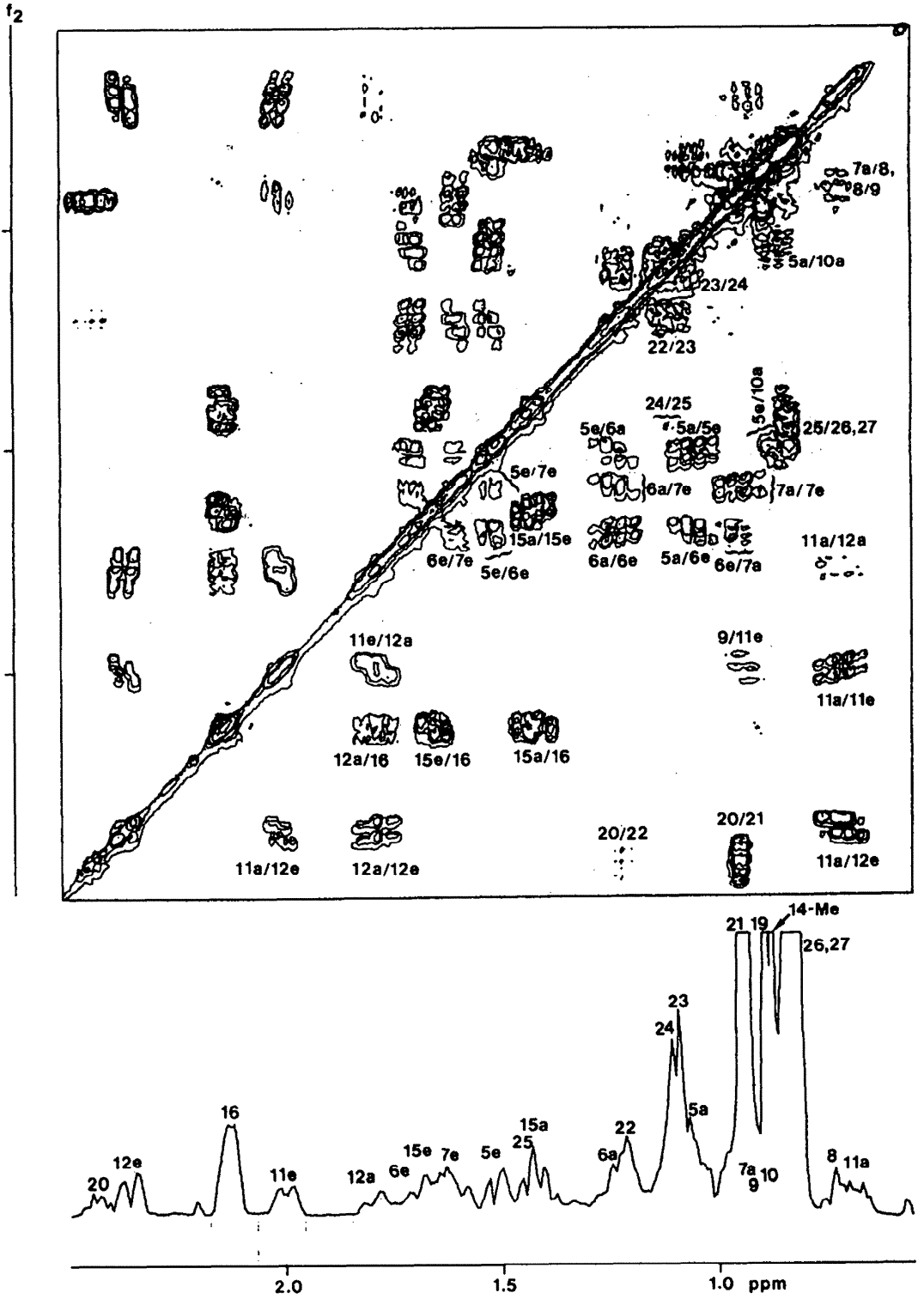

Table 1. ^1H n.m.r. assignments for **6a** **6b**, **9a** and **9b**.

C no.	hydrogens		6a*	6b+	hydrogens		9a*	9b+
C-5	α-H	(eq)	1.52, m		α-CH_3	(eq)	0.833, d J 5.8Hz	0.884, d J 5.8Hz
	β-H	(ax)	1.05, m					
C-6	α-H	(ax)	1.23, m					
	β-H	(eq)	1.70, m					
C-7	α-H	(eq)	1.59, m					
	β-H	(ax)	0.95, m					
C-8	α-H	(ax)	0.70, m					
C-9	β-H	(ax)	0.93, m					
C-10	α-H	(ax)	0.89, m					
	β-CH_3	(eq)	0.889, d J 5.8Hz	0.890, d J 5.8Hz	β-CH_3	(eq)	0.921, d J 6.4Hz	0.921, d J 6.4Hz
C-11	α-H	(ax)	0.71, m					
	β-H	(eq)	2.00, m		β-H	(eq)	2.06, m	
C-12	α-H	(eq)	2.36, m	2.36, m	α-H	(eq)	2.38, m	2.38, m
	β-H	(ax)	1.78, m					
C-14	β-CH_3	(ax)	0.847, s	0.850, s	β-CH_3	(ax)	0.847, s	0.838, s
C-15	H		1.42, m					
	H		1.65, m					
C-16	H_2		2.14, m		H_2		2.15, m	
C-20	H		2.43, m	2.43, m	H		2.44, m	2.44, m
C-21	H_3		0.946, m J 6.8Hz	0.903, m J 6.8Hz	H_3		0.953, m J 6.8Hz	0.903, m J 6.8Hz
C-22	H_2		1.28, m					
C-23	H_2		1.08, m					
C-24	H_2		1.10, m					
C-25	H		1.47, m					
C-26	H_3		0.832, d J 6.6Hz	0.855, d J 6.6Hz	H_3		0.839, d J 6.6Hz	0.855, d J 6.6Hz
C-27	H_3		0.829, d J 6.6Hz	0.850, d J 6.6Hz	H_3		0.833, d J 6.6Hz	0.848, d J 6.6Hz

* 400 MHz (inc. 2DJ for **6a**).
\+ 200 MHz.

Table 2. ^{13}C n.m.r. assignments for **6a**, **6b**, **9a**, **9b** and reference compound [(20R)-diacholest-13(17)-ene[1(b)]].

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