Acid-catalysed Rearrangements of Steroid Alkenes. Part 2.[1] A Re-investigation of the Backbone Rearrangement of Cholest-5-ene

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Backbone rearrangement of cholest-5-ene (**1**) with boron trifluoride–diethyl ether gives, in addition to the well known diacholest-13(17)-enes (**4a,b**), their 10β counterparts (**6a,b**) as minor products. With anhydrous toluene-*p*-sulphonic acid–acetic acid, additional products include components also isomeric at C-10 and C-20 and having a spiro C/D ring junction. A proposed scheme for the rearrangement is given.

The backbone rearrangement of cholest-5-ene (**1**) and cholest-4-ene (**2**), first observed by Turner *et al.*,[2] has been the subject of several investigations.[3–11] It is now clear that the rearrangement occurs *via* a series of carbocation–alkene interconversions[9] and gives rise initially to 5β,14β-dimethyl-18,19-dinor-8α,9β,10α-cholest-13(17)-ene [diacholest-13(17)-ene, (**4a**)][3] which then undergoes isomerisation at C-20 with increasing reaction time, giving the diacholestene (**4b**).[4,5] The rearrangement also occurs naturally in sediments,[6] being a major pathway of steroid diagenesis.[12] Several studies[3,7,13] have indicated the presence of minor products but only in one study has a structure for one of these been suggested.[7] There is also mass spectral evidence for the presence of some of these minor products in sediments.[14]

In the present study, treatment of cholest-5-ene (**1**) with boron trifluoride–diethyl ether (BF_3–OEt_2) gave, in addition to the expected diacholest-13(17)-enes [(**4a**) (51%) and (**4b**) (46.5%)], two minor products [(**6a**) (1.5%) and (**6b**) (1%)] (see below), all with almost identical mass spectra. With anhydrous toluene-*p*-sulphonic acid–acetic acid, several other minor products are, however, formed as illustrated in the Figure. The mass spectra of these additional compounds suggested the presence of *abeo*-cholest-13(17)-ene-type structures (major ions at *m/z* 121 and 206) by comparison with 12(13 ⟶ 14) *abeo*-5α-cholest-13(17)-enes (**8a,b**)[1] and structures arising from partial backbone rearrangement (major ions at *m/z* 215 and 257). The product distributions are summarised in Table 1. The 1-day reaction (*cf.* Figure *d*) was repeated on a large scale. The products were separated initially by silver ion-impregnated t.l.c. into 3 fractions and each was then fractionated further by h.p.l.c.

The ^{1}H n.m.r. data for the diacholestenes (**4a,b**) (Table 2) were in agreement with those given previously.[5] In the ^{13}C n.m.r. spectra, the chemical shift of C-5 (δ 33.8) was, however, somewhat different from that reported (δ 38.3).[15] The value of δ 33.8 is in accord with an independent study[16] and with that given (δ 34.2) for 13α, 17β (H)-diacholestane.[17] The mass spectrum of compound (**4b**) did not show an ion at *m/z* 206, as reported previously.[6] The presence of this ion results from co-elution with component (**5a**) on g.l.c. (*cf.* the Figure) and t.l.c.

Component (**6a**) had an almost identical mass spectrum to that of compound (**4a**) but its ^{1}H n.m.r. spectrum (Table 2) showed a 0.13 p.p.m. deshielding of the 5β-Me. This effect is in accord with a change in the stereochemistry of the A/B ring junction from *trans* [as in compound (**4a**)] to *cis*.[18] Component (**6a**) is, therefore, 10β-diacholest-13(17)-ene. This assignment was confirmed by the ^{13}C n.m.r. spectrum [*cf.* chemical shifts of 5β-Me for compounds (**4a**) and (**6a**) in Table 3].

Component (**7a**) had an almost identical mass spectrum to that of the cholestene (**8a**)[1] although it had a shorter g.l.c. retention time. The ^{1}H n.m.r. spectrum was very similar to that of compound (**8a**)[1] (Table 2) with the exception of a 0.21 p.p.m. deshielding of the ring A/B methyl. This indicates a rearranged A/B ring junction, and comparison with the chemical shifts of the 5β-Me of the diacholestenes (**4a**) and (**6a**) indicates a rearranged *cis* A/B ring junction. Component (**7a**) is, therefore, 5β-methyl-19-nor-12(13 ⟶ 14) *abeo*-8α,9β,10β-cholest-13(17)-ene, an assignment supported by comparison of the ^{13}C n.m.r. spectrum (Table 3) with those of the diacholestene (**6a**) (for C-1 to C-7, C-9, C-10, and 5β-Me) and the cholestene (**8a**)[1] (for C-14, C-18, and C-20 to C-27), respectively.

Two other components [(**6b**) and (**5a**)] were isolated in lower purity (*ca.* 60%). The near identity of the mass spectrum of

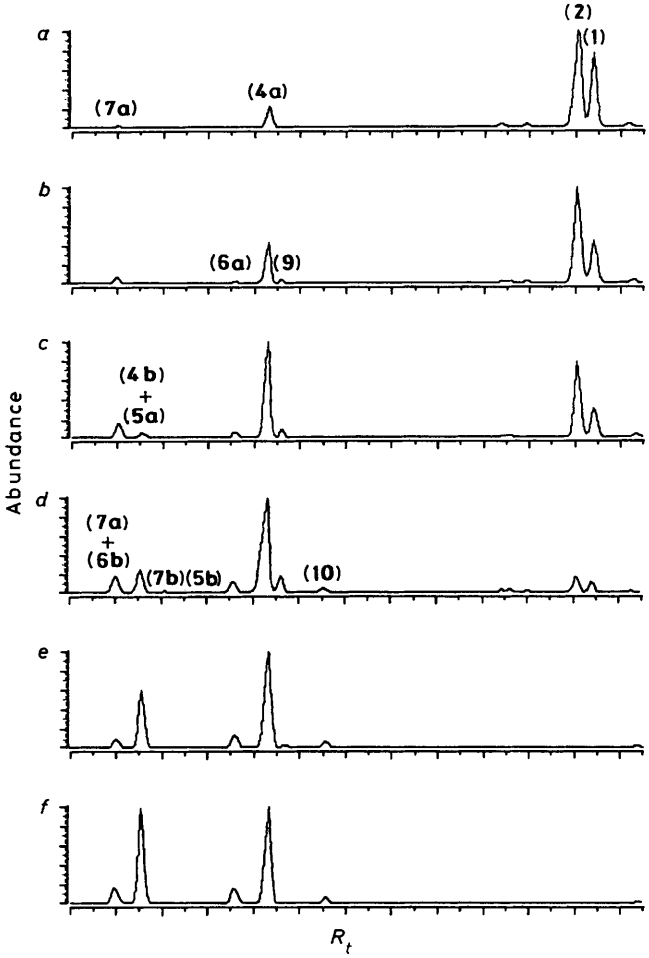


Figure. Reconstructed ion current chromatograms (g.l.c.–m.s. on 25 m OV-1 capillary column) of products from isomerisation of cholest-5-ene (**1**) with anhydrous TsOH–HOAc: *a*, 4 h; *b*, 8 h; *c*, 13 h; (*d*, 24 h; *e*, 3 days; and *f*, 7 days

Table 1. Product distributions (%)[a] from isomerisation[b] of cholest-5-ene (**1**)

Reaction time	(1)	(2)	(4a)	(4b)	(5a)	(5b)	(6a)	(6b)	(7a)	(7b)	(9)	(10)
0	100											
15 min	51.1	48.9										
30 min	41.4	58.6										
1 h	40.9	57.2	1.9									
4 h	33.4	51.7	9.6	0.1			0.4		1.0			
8 h	21.0	51.2	20.6	0.6	0.1		1.2		2.8		1.9	
13 h	12.6	31.5	41.5	2.4	0.4		2.1		5.7		3.7	
24 h	4.7	7.1	51.1	7.5	2.8	0.2	5.3	1.0	6.9	0.8	6.6	2.2
3 days			52.9	29.0	1.5	0.2	6.9	2.0	3.1	0.3	1.4	3.2
7 days			43.1	40.0	0.5	0.2	6.4	7.0	0.8	0.3		2.3
20 days			41.6	38.0	0.5	0.5	7.2	8.9	0.7	0.5		1.1

[a] Calculated from g.l.c. and g.l.c.–m.s. on 25 m OV-1 capillary column. [b] Anhydrous TsOH–HOAc at 70 °C.

Table 2. ^{1}H N.m.r. (200 MHz) assignments for rearrangement products of cholest-5-ene (**1**)

	(4a)	(4b)	(5a)	(6a)	(6b)	(7a)	(8a)[1,a]	(9)	(10)
5β-Me	0.825, s	0.823, s	0.837, s	0.955, s	0.956, s	0.962, s		*b*	*c*
14β-Me	0.884, s	0.882, s		0.898, s	0.898, s				
12-H_{eq}	2.3, m	2.3, m	*d*	2.3, m	2.3, m	*d*	*d*	*d*	*d*
16-H_2	2.1, m	2.1, m	2.0, m	2.1, m	2.1, m	2.0, m	2.0, m	*d*	*d*
18-H_3			1.465, dd *J* 2 Hz			1.468, dd *J* 2 Hz	1.470, dd *J* 2 Hz	*b*	*c*
19-H_3							0.748, s		
20-H	2.4, m	2.4, m	2.5, m	2.4, m	2.4, m	2.5, m	2.5, m	*d*	*d*
21-H_3	0.945, d *J* 6.8 Hz	0.888, d *J* 6.8 Hz	0.934, d *J* 6.8 Hz	0.949, d *J* 6.8 Hz	0.900, d *J* 6.8 Hz	0.938, d *J* 6.8 Hz	0.932, d *J* 6.8 Hz	0.904, d *J* 6.7 Hz	0.821, d *J* 6.4 Hz
26-H_3	0.835, d *J* 6.4 Hz	0.857, d *J* 6.8 Hz	0.834, d *J* 6.3 Hz	0.836, d *J* 6.6 Hz	0.852, d *J* 6.3 Hz	0.835, d *J* 6.6 Hz	0.835, d *J* 6.4 Hz	0.868, d *J* 6.6 Hz	0.868, d *J* 6.6 Hz
27-H_3	0.830, d *J* 6.6 Hz	0.850, d *J* 6.7 Hz		0.831, d *J* 6.6 Hz	0.847, d *J* 6.6 Hz				

[a] Included for comparison. [b] 0.825, s or 0.862, s. [c] 0.816, s or 0.922, s. [d] Not directly observable.

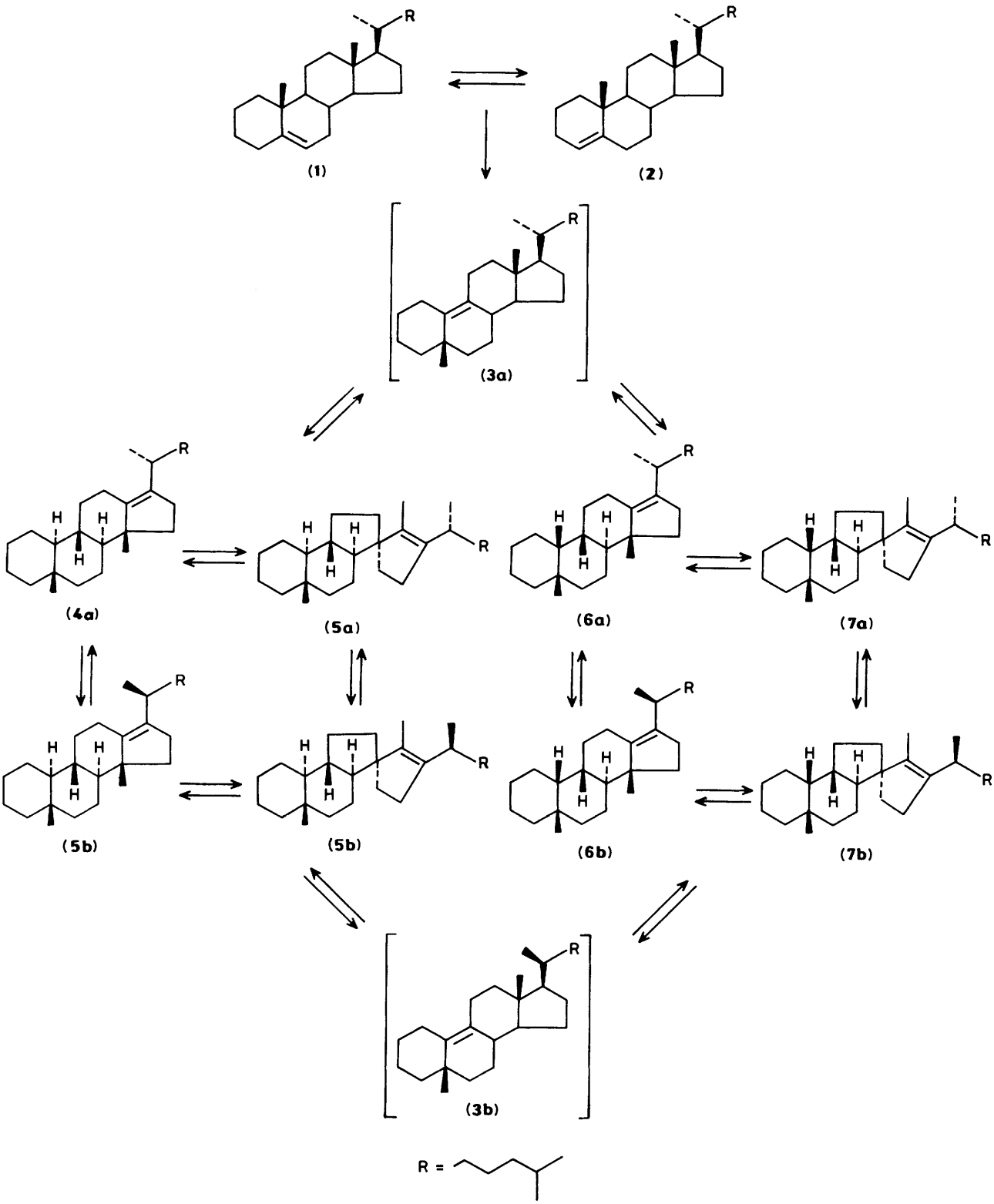
compound (**6b**) with those of the diacholestenes (**4a,b**) and (**6a**) showed that it has a diacholest-13(17)-ene-type structure, and it was assigned as (20*S*)-10β-diacholest-13(17)-ene on the basis of the following evidence: (i) it is partnered by (20*R*)-(**6a**) and by the [(20*R*)-(**4a**), (20*S*)-(**4b**)] pair on treatment of cholest-5-ene (**1**) with BF_3–OEt_2; (ii) the other 2 components present in the fraction were in sufficiently low abundance to allow interpretation of the ^{1}H n.m.r. features of the diacholestene (**6b**) (Table 2), *e.g.* deshielded 5β-Me, indicating a *cis* A/B ring junction [*cf.* (**6a**)], and shielded 21-H_3 doublet indicating (20*S*) stereochemistry [*cf.* (**4b**)]. The mass spectrum of compound (**5a**) showed that it has an *abeo*-cholest-13(17)-ene-type structure. Interpretation of the ^{1}H n.m.r. features of the cholestene (**5a**) (Table 2) was possible since the other 3 components present in the fraction were in low abundance. Thus, the chemical shift of the ring A/B methyl group is in accord with a rearranged *trans* A/B ring junction [*cf.* chemical shift of 5β-Me in the diacholestene (**4a**)] and the chemical shift of 21-H_3 indicates (20*R*) stereochemistry [*cf.* (**8a**)]. Component (**5a**) was assigned, therefore, as 5β-methyl-19-nor-*abeo*-8α,9β,10α-cholest-13(17)-ene.

Components (**5b**) and (**7b**) could not be obtained in sufficient purity for ^{1}H n.m.r. analysis. Given that their mass spectra are virtually identical to each other and to those of compounds (**5a**) and (**7a**), and that there are (20*R*), (20*S*) pairs of components (**4a,b**) and (**6a,b**), then it is likely that compounds (**5b**) and (**7b**) are the (20*S*) counterparts of compounds (**5a**) and (**7a**), respectively.

The mass spectra of components (**9**) and (**10**) showed major cleavage ions at *m/z* 215 and 257, indicative of a double bond in rings A, B, or C. The g.l.c. retention times[14] and ^{1}H n.m.r. spectra of both indicate a 5β-methyl-19-nor structure with a Δ^8 or $\Delta^{8(14)}$ double bond. Oxidation of compound (**9**) afforded an 8, 14-dione which displayed carbonyl bands in the i.r. spectrum at 1 695 and 1 730 cm^{-1} (6- and 5-membered ring ketones, respectively). Further studies are required to establish the stereochemistry at C-9 and C-10 in compound (**9**), and the position of the double bond and stereochemistry of the ring junctions in compound (**10**).

Backbone rearrangement of cholest-5-ene (**1**) with anhydrous TsOH–HOAc, therefore, gives rise to a variety of products, some of which are not detected when the rearrangement is carried out with BF_3–OEt_2 [*i.e.* compounds (**5a,b**), (**7a,b**), (**9**), and (**10**)]. Components (**6a,b**) were also obtained in higher relative abundance with anhydrous TsOH–HOAc. Rearrangement with BF_3–OEt_2 gives rise to the most thermodynamically stable products (**4a,b**) (>97%). Formation of the minor 10β rearrangement products [(**6a,b**) and (**7a,b**)] requires protonation from the more hindred β-face of a Δ^9 intermediate (**3**) during the course of the rearrangement. The 'spiro' components [(**5a,b**) and (**7a,b**)] are formed from C-ring contraction to a C-14 carbonium ion. The presence of these 'spiro' components indicates that ring C/D cationic spiran intermediates are present when the rearrangement is carried out in anhydrous TsOH–HOAc, a hypothesis which was doubted earlier.[9]

When the diacholestene (**6a**) was treated with BF_3–OEt_2, components (**4a,b**) were also obtained in addition to compound (**6b**). This indicates that the double bond can migrate back to C-9 as in compounds (**3a,b**). Such a 'long-distance' isomerisation



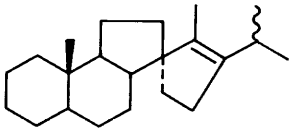
Scheme. Acid-catalysed rearrangement of cholest-5-ene (**1**). Square brackets indicate putative transient alkenes (**3a,b**)

has also been observed whereby 19-norandrost-4-ene-3,17-dione was converted into 19-nor-14β-androst-4-ene-3,17-dione by the action of hydrogen fluoride–antimony pentafluoride.[20] The proposed transformation pathways resulting from cholest-5-ene (**1**) are summarised in the Scheme. Although we suggested[21] that 12(13 ⟶ 14)*abeo*-5α-cholest-13(17)-enes (**8a,b**) might be rearrangement products of cholest-5-ene (**1**), it is now clear that this is not so.

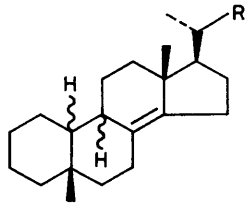
Table 3. ^{13}C N.m.r. (50 MHz) assignments for rearrangement products of cholest-5-ene (**1**)

Carbon	(**4a**)	(**4b**)	(**6a**)[a]	(**6a**)	(**7a**)	(**8a**)[1,b]
1	24.4	24.4	22.2	23.5	24.4	39.9
2	27.3	27.3	26.7	27.1	28.5	21.8
3	21.6	21.6	22.2	21.7	21.5	27.2
4	42.2	42.1	42.2	41.9	42.5	28.4
5	33.8	33.8	33.9	33.7	29.7	47.3
5β-Me	16.9	16.8	25.6	27.8	27.4	
6	42.4	42.3	33.1	29.6	31.2	29.5
7	22.1	22.1	22.2	22.0	22.3	32.8
8	55.4	55.7	43.4	46.5	52.1	45.1
9	36.5	36.4	37.0	35.1	40.1	54.6
10	50.7	50.7	47.9	46.9	48.1	36.5
11	31.3	31.4		31.9	*c*	*c*
12	23.0	22.8		22.7	*c*	*c*
13	141.5	141.2		141.9	*d*	*d*
14	50.2	50.2		50.3	60.5	60.0
14β-Me	18.3	18.1		18.4		
15	37.9	37.9		38.1	*c*	*c*
16	27.8	28.0		27.9	*c*	*c*
17	133.9	133.7		133.9	*d*	*d*
18					9.5	9.5
19						11.4
20	31.4	31.6		31.4	32.6	32.6
22	35.8	35.6		35.8	35.8	35.9
23	25.5	25.6		25.4	25.6	25.6
24	39.0	39.0		39.0	39.1	39.2
25	28.0	28.0		28.0	28.0	28.0
26	22.7	22.8		22.7	22.6	22.6
27	22.6	22.6		22.6	22.6	22.6

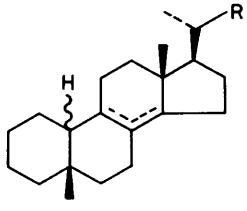
[a] Calculated using a published method.[19] [b] Included for comparison. [c] (**7a**): 20.5, 28.5, 33.7 or 35.0. (**8a**): 22.2, 26.4, 28.6 or 35.2. [d] (**7a**): 134.1 or 139.7. (**8a**): 134.0 or 139.7.



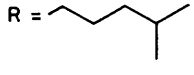
(20*R*)-(**8a**)
(20*S*) (**8b**)



(**9**)



(**10**)



All of the rearrangement products described also occur naturally in sediments, sometimes in almost exactly the same relative abundances as observed in the Figure (*cf.* Table 1).[22]

Experimental

The techniques and instrumentation were basically as described earlier.[1]

Isomerisation of Cholest-5-ene (**1**).—(*a*) *With* BF_3–OEt_2. BF_3–OEt_2 (0.25 ml) was added to cholest-5-ene (**1**) (50 mg) in dry toluene (5 ml). The mixture was shaken, left for 24 h in the dark and then worked up.[1]

(*b*) *With anhydrous* TsOH–HOAc. A series of 1-ml reacti-vials containing cholest-5-ene (**1**) (5 mg) and anhydrous TsOH–HOAc (0.5 ml)[1] were heated for various times. Each vial was worked up. The 24-h reaction was repeated on a large scale using cholest-5-ene (**1**) (1 g) in anhydrous TsOH–HOAc (100 ml). After work-up, the alkene products were initially separated by silver ion-impregnated t.l.c. (hexane development) into 3 fractions. The uppermost band (R_F 0.81—0.90) contained compounds (**9**) and (**10**); the middle (R_F 0.57—0.73) compounds (**4b**), (**5a**,**b**), (**6b**), and (**7a**,**b**) and the lowest (R_F 0.35—0.52) compounds (**1**), (**2**), (**4a**), and (**6a**). Each fraction was then further fractionated by h.p.l.c. The uppermost band afforded 2 peaks (mobile phase 5% water–acetone): R_t 15.5 min [(**9**) (99%)] and 16.5 [(**10**) (99%)]. The middle band afforded 4 peaks (mobile phase 7% water–acetone): R_t 28.5 min [(**7a**) (95%)]; 30 [(**5a**) (60%), (**6b**) (15%), (**7a**) (9%), and (**7b**) (14%)]; 32 [(**5a**) (21%), (**5b**) (12%), and (**6b**) (60%)]; and 33 [(**4b**) (99%)]. The lowest band afforded 4 peaks (mobile phase 5% water in acetone): R_t 16 min [(**4a**) (5%) and (**6a**) (94%)]; 17.5 [(**4a**) (99%)]; 21 [(**2**) (99%)]; and 22 [(**1**) (99%)]. The diacholest-13(17)-ene-type components [(**4a**,**b**) and (**6a**,**b**)] typically had: *m*/*z* 370 ($M^{+\bullet}$, 8%), 355 ($M^{+\bullet}$ – Me, 20), and 257 (cleavage through C_{17}–C_{20}, 100) and the 'spiro' components [(**5a**,**b**) and (**7a**,**b**)] typically had [*cf.* (**8a**)][1]: *m*/*z* 370 (3%), 219 (19), 206 (100), and 121 (40). Component (**9**) had: *m*/*z* 370 ($M^{+\bullet}$, 56%), 355 ($M^{+\bullet}$ – Me, 32), 274 (cleavage through C_5–C_6 and C_9–C_{10}, 22), 257 (cleavage through C_{17}–C_{20}, 64), and 215 (cleavage through C_{13}–C_{17} and C_{14}–C_{15}, 100). Component (**10**) had [*cf.* (**9**)]: *m*/*z* 370 (78%), 355 (52), 274 (23), 257 (37), and 215 (100).

Isomerisation of 10β-*Diacholest*-13(17)-*ene* (**6a**).—A few drops of BF_3–OEt_2 were added to compound (**6a**) (5 mg) in dry toluene (1 ml). The mixture was shaken and left for 24 h in the dark and then worked up. G.l.c.–m.s. analysis indicated the presence of the diacholestenes (**4a**,**b**) and (**6a**,**b**) all in *ca.* 1:1:1:1 ratio.

Oxidation of Component (**9**).—Osmium tetroxide (35 mg) was added to component (**9**) (20 mg) in dry pyridine (5 ml) and the reaction left at ambient temperature (7 days). The resulting osmate ester was reduced with lithium aluminium hydride (15 mg) in refluxing ether (10 ml) for 2 h, which, after work-up afforded the slightly impure diol. The diol (10 mg) in t-butyl alcohol (1 ml) and HOAc (1 ml) was further oxidised with lead tetra-acetate (80 mg) for 18 h at ambient temperature. After addition of a few drops of ethanediol to destroy the excess of reagent, the reaction mixture was worked up to afford the slightly impure dione which had: δ_H(200 MHz) 0.860 (6 H, d, *J* 6.6 Hz, C-26 and -27), 0.878 (3 H, d, *J* 6.4 Hz, C-21), 0.946 (3 H, s, C-18 or 5β-Me), and 0.992 (3 H, s, C-18 or 5β-Me); $\nu_{max.}$ 1 695 and 1 730 cm^{-1} (C=O).

Acknowledgements

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References

1 Part 1, T. M. Peakman and J. R. Maxwell, *J. Chem. Soc., Perkin Trans. 1*, 1988, preceding paper.
2 R. B. Turner, W. R. Meador, and R. E. Winkler, *J. Am. Chem. Soc.*, 1957, **79**, 4122.

3 J. W. Blunt, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, 1969, **25**, 149.
4 D. N. Kirk and P. M. Shaw, *J. Chem. Soc., Chem. Commun.*, 1970, 806.
5 D. N. Kirk and P. M. Shaw, *J. Chem. Soc., Perkin Trans. 1*, 1975, 2284.
6 I. Rubinstein, O. Sieskind, and P. Albrecht, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1833.
7 R. U. Almaula, G. K. Trivedi, and S. C. Bhattacharyya, *Indian J. Chem.*, 1975, **16B**, 257.
8 D. M. Tal, E. Keinan, and Y. Mazur, *Tetrahedron*, 1981, **37**, 4327.
9 D. E. Akporiaye, R. D. Farrant, and D. N. Kirk, *J. Chem. Res.*, 1981, (*S*), 210.
10 N. A. Lamb, Ph.D. Thesis, University of Bristol, 1982.
11 O. Sieskind and P. Albrecht, *Tetrahadron Lett.*, 1985, **26**, 2135.
12 A. S. Mackenzie, S. C. Brassell, G. Eglinton, and J. R. Maxwell, *Science*, 1982, **217**, 491.
13 P. E. Bauer, D. A. Nelson, D. S. Watt, J. H. Reibenspies, O. P. Anderson. W. K. Seifert, and J. M. Moldowan, *J. Org. Chem.*, 1985, **50**, 5460.
14 S. C. Brassell, J. McEvoy, C. F. Hoffmann, N. A. Lamb, T. M. Peakman, and J. R. Maxwell, *Org. Geochem.*, 1984, **6**, 11.
15 D. M. Tal, H. E. Gottlieb, C. Ben-Ari, and Y. Mazur, *Tetrahedron*, 1981, **37**, 4331.
16 D. N. Kirk, personal communication.
17 T. Pehk, S. D. Pustil'nikova, N. N. Abryutina, G. P. Kayukova, and A. A. Petrov, *Neftekhimiya*, 1982, **22**, 21 (*Chem. Abstr.*, 1982, **97**, 39225e).
18 N. S. Bhacca and D. H. Williams, 'Applications of NMR Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964.
19 H. Beierbeck, J. K. Saunders, and J. W. ApSimon, *Can. J. Chem.*, 1977, **55**, 2813.
20 J. C. Jacquesy, R. Jacquesy, and G. Joly, *Tetrahedron Lett.*, 1972, 4739.
21 T. M. Peakman, N. A. Lamb, and J. R. Maxwell, *Tetrahedron Lett.*, 1984, **25**, 349.
22 T. M. Peakman and J. R. Maxwell, unpublished results.

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