Sulphur-mediated Five-membered Ring Expansions. Steroidal Examples

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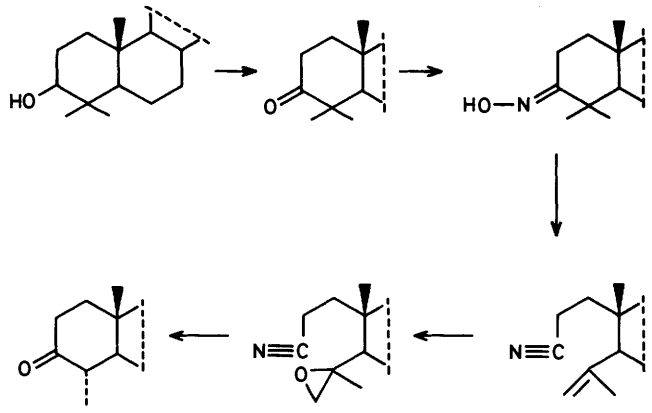
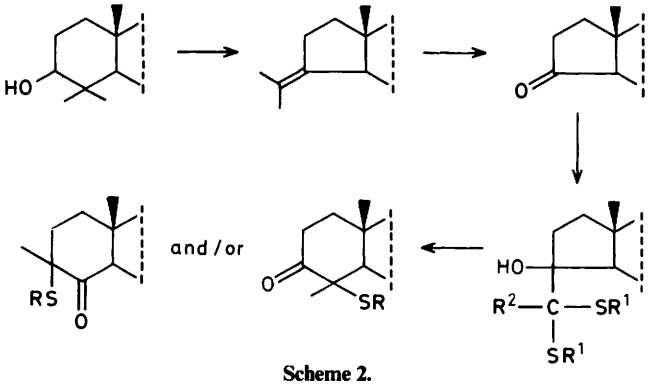
The acid-catalysed ring expansion reaction of α-hydroxy dithioacetals, derivatives of 3-hydroxy-3-acetyl-14α-methyl-4-nor-5α- and 5β-cholest-8-ene, resulted in the exclusive migration of a secondary carbon atom with formation of 3,14α-dimethyl-4-oxo steroids.

4-Demethyl-lanosterol is a postulated biosynthetic intermediate on the path from lanosterol to cholesterol.[1] Some important tetracyclic triterpenes, like helvolic acid,[2] fusidic acid,[3] steroidal cephalosporins,[4a] viridominic acids,[4b] and certain buxus alkaloids[4c] also lack one of the two geminal methyl groups usually present in position 4 of triterpenes. The chemical transformations of triterpenes to 4-demethyl compounds have been described.[5–7] From a synthetic point of view, the sequence described by Cohen *et al.*[5c] seems to be the best method for such a degradation. However, yields of 4-demethyl compounds obtained in this five-step syntheses (Scheme 1) varied and



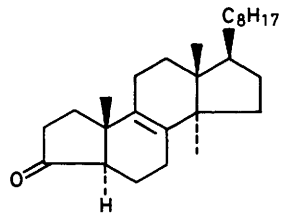
Scheme 1.

frequently were much lower than reported in the original investigation. Problems with selective epoxidation of the seco-nitrile[8] or with the isomerization of the double bond from the 8- to the 7-position[9] were encountered. As we required derivatives of 4-demethyl-lanosterol for further synthetic studies, the investigation of another approach to 31-nor-lanostanes was undertaken. The general sequence of reactions under investigation is shown in Scheme 2.



Scheme 2.

The salient feature of this approach, although unsuccessful as a method for the preparation of 4-methyl-3-ketones, was the investigation of sulphur-mediated ring expansion reactions, which have been reported only occasionally.[10,11] To the best of our knowledge, divalent sulphur-based cyclopentane ring expansions leading to α-substituted cyclohexanones have not been reported. Moreover, one-step ring expansions of the five-membered ring *A* in 4-nor steroids have not been investigated, in contrast to the wealth of work devoted to the ring expansion reactions of steroidal ring *D* acyloins, *i.e.* 17-acetyl-17-hydroxy steroids.[12]



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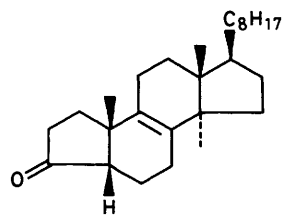

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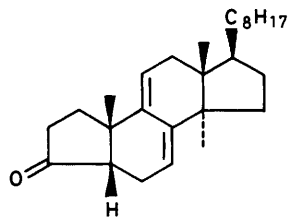
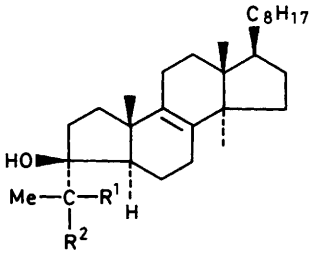


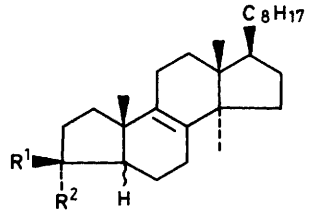
(3)

The 14α-methyl-4-nor-5α-cholest-8-en-3-one (**1**), prepared from lanosterol in three steps,[13] reacted with the lithium salt of 1,1-bisethylthioethane to give the hydroxy-dithioacetal (**4**) in 78% yield. In all additions of the above mentioned acyl anion equivalent to compound (**1**), the by-product (**6**) was formed. Its formation could not be avoided by changing the conditions or the ratio of reagents. Similar addition of the lithium salt of 1,1-bisphenylthioethane, an acyl anion equivalent obtained from acetaldehyde and benzenethiol, was unsuccessful, presumably for steric reasons.

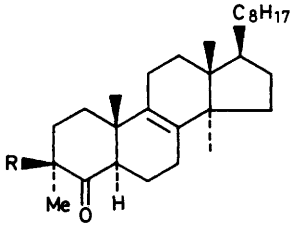
The change of configuration at C-5 in the 4-nor-ketones (**2**) and (**3**) was reflected in the reverse stereochemistry of their reaction with the carbanion obtained from 1,1-bisethyl-thioethane and butyl-lithium. Both addition products, (**13**) and (**17**) (65 and 72% yield), resulted from the attack of the nucleophile from the less hindered β-face of the five-membered ring *A*. The butyl-lithium addition products (**7**) and (**18**) were



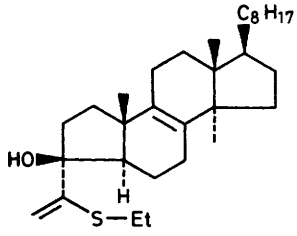
(4) $R^1 = R^2 = SEt$
(5) $R^1R^2 = O$



(6) $R^1 = OH$, $R^2 = Bu^n$, 5α
(7) $R^1 = Bu^n$, $R^2 = OH$, 5β



(8) R = OH
(9) R = SEt



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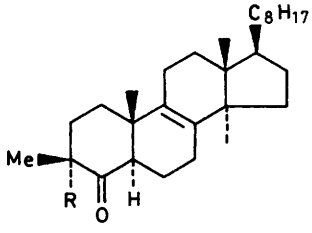
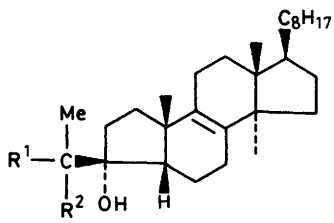
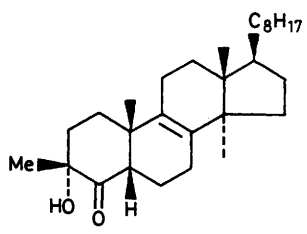


(11) R = SEt
(12) R = H



(13) $R^1 = R^2 = SEt$
(14) $R^1R^2 = O$



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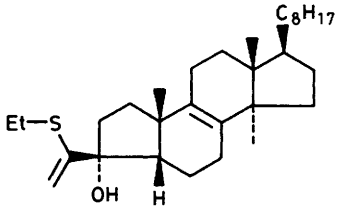

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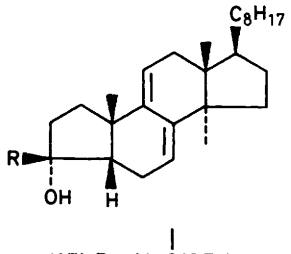
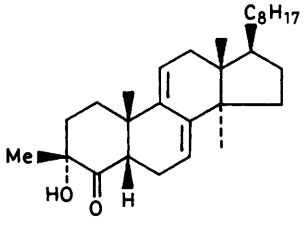


(17) R = $MeC(SEt)_2$
(18) R = Bu^n
(19) R = Ac



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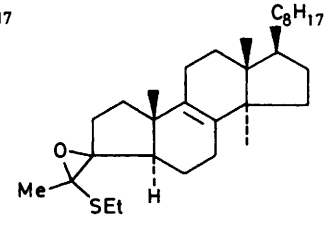


(21)

$[Cu(NCMe)_4]BF_4$

(22)

also isolated. When the carbanion was generated from 1,1-bisethylthioethane by the addition of three equivalents of lithium di-isopropylamide (LDA), its reaction with the ketone (2) afforded only (13), but the yield dropped to 39%. The same reaction with 1.5 equivalents of LDA gave (13) in 5% yield.

The ring-expansion reactions of the hydroxy-dithioacetals (4), (13), and (17) were catalysed by several Lewis acids. The best results were obtained when tetrakis(acetonitrile)copper(I) tetrafluoroborate (22) was used as a thiophile. Results of these reactions are summarized in Table 1.

In the course of an attempted hydrolysis of the dithioacetal group by a soft acid, copper(I) chloride, selective elimination of one molecule of ethanethiol from (4) occurred and the hydroxyenethiol thioether (10) was formed exclusively. This enabled the acid-catalysed ring-expansion reaction of this unusual, sulphur-containing substrate to be investigated. Indeed, when compound (10) was treated with trifluoroacetic acid in anhydrous benzene, ring expansion occurred. The two products isolated were the 6-membered α-ethylthio-ketones (9) and (11) obtained in 15 and 52% yields respectively.

The reductive removal of the ethylthio group from (9) and (11) by the action of tributyltin hydride gave the same α-methyl substituted ketone (12). The process required the temperature of boiling xylene and proceeded much faster for the isomer having the axial 3α-ethylthio group.

A very efficient elimination (97%) of ethanthiol occurred also upon treatment of (13) with copper(I) chloride in dimethylformamide. The resulting enethiolthioether (16) could be hydrolysed to give the acyloin (14) (89%) under the influence of trifluoroacetic acid in moist benzene.

Table 1. Reactions of the hydroxy dithioacetals (4), (13), and (17) with Lewis acids.

Substrate	Catalyst; conditions	Products (% yield)
(4)	(22); PhMe (moist), r.t.[a]	(8) (66)
		(9) (10)
		(11) (14)
(4)	(22); CH_2Cl_2 (anhyd.), −78 °C	(10) (9)
(4)	(22); CH_2Cl_2 (anhyd.), 40 °C	(8) (39)
		(9) (15)
		(11) (40)
(4)	(22) (2 equiv.); C_6H_6 (anhyd.), r.t. then 80 °C	(8) (33)
		(9) (10)
		(11) (43)
(4)	$TiCl_4$; CH_2Cl_2 (anhyd.), −78 °C	(5) (87)
(13)	(22); PhMe (moist), r.t.	(15) (83)
(17)	(22); PhMe (moist), r.t.	(20) (91)
(17)	$HgCl_2$–BF_3·Et_2O, DMF,[b] 70 °C	(19) (41)
		(20) (45)

[a] R.t. = room temperature. [b] DMF = dimethylformamide

Table 2. ^{13}C NMR chemical shifts for sulphur compounds and adducts (7) and (18)

	(4)	(6)	(7)	(9)	(10)	(11)	(13)	(16)	(17)	(18)
C-1	36.2	35.6	35.9	33.4	36.3	32.6	35.6	36.3	39.8	38.8
C-2	38.7	39.1	38.7	36.4	41.2	36.7	36.7	36.6	40.0	40.1
C-3	86.2	80.3	83.2	56.8	83.1	52.8	88.4	85.8	89.2	82.4
C-4				211.1		210.9				
C-5	51.3	55.3	54.5	51.8	54.6	49.3	51.7	54.0	49.0	52.6
C-6	19.9	17.3	24.1	17.5	16.4	17.3	23.8	24.1	23.1	21.3
C-7	26.0	25.9	19.9	24.5	25.7	24.4	27.0	19.7	120.1	120.3
C-8	133.9	134.0	137.9	132.4	134.0	132.4	137.5	137.8	145.4	145.4
C-9	135.5	135.3	131.7	135.9	135.2	135.6	131.9	132.3	137.8	137.7
C-10	45.3	44.6	44.3	42.3	44.7	42.4	45.9	43.9	45.8	45.0
C-11	22.6	22.5	22.3	22.0	22.6	21.9	22.3	22.6	119.8	120.3
C-12	30.7	30.7	30.3[a]	31.0[a]	30.7	30.9	30.2[a]	30.4[a]	38.3	38.2
C-13	45.1	45.1	44.6	44.6	45.1	44.6	44.5	44.6	44.3	44.2
C-14	49.3	49.4	50.3	50.0	49.4	50.1	50.2	50.3	50.4	50.4
C-15	30.7	30.7	31.1[a]	30.9[a]	30.7	30.9	30.9[a]	31.0[a]	31.4	31.3
C-16	28.3	28.3	28.2	28.1	28.3	28.1	28.2	28.2	27.8	27.8
C-17	50.5	50.5	50.6	50.6	50.4	50.6	50.5	50.6	51.0	50.9
C-18	15.6	15.6	15.7	15.8	15.6	15.8	15.7	15.7	15.8	15.7
C-19	20.5	19.8	27.4	18.8	19.9	18.5	25.6	28.0	30.2	30.4
C-20	36.6	36.6	36.5	36.5	36.6	36.5	36.5	36.5	36.5	36.4
C-21	18.9	18.8	18.8	18.8	18.8	18.8	18.8	18.8	18.5	18.5
C-22	36.5	36.5	36.5	36.5	36.5	36.5	36.5	36.5	36.2	36.2
C-23	24.1	24.2	24.1	24.1	24.1	24.1	24.1	24.1	24.1	24.1
C-24	39.6	39.6	39.5	39.6	39.6	39.6	39.6	39.6	39.6	39.5
C-25	28.0	28.0	28.0	28.0	28.0	28.0	28.0	28.0	28.0	28.0
C-26	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5
C-27	22.8	22.8	22.8	22.8	22.8	22.8	22.8	22.8	22.8	22.8
C-28	24.5[a]	24.5	24.3	24.6	24.5	24.5	24.4[b]	24.4	24.9[a]	24.9
C-29				25.3		24.1				
C-30										
C-1′	71.2	42.5	41.6		153.5	24.1	69.9	151.2	69.0	42.0
C-2′	24.7[a]	26.6	26.5		104.6		24.5[b]	105.1	23.8[a]	26.2
C-3′		23.4	23.4							23.4
C-4′		14.1	14.1							14.1
CH_3CH_2S	25.6			22.4	26.7	22.8	25.6	26.4	25.2	
	24.9						25.1		24.9	
CH_3CH_2S	14.1			14.3	13.2	14.4	14.1	13.2	14.0	
	14.3						14.1		14.1	

[a,b] These signals may be interchanged.

Discussion

In the reactions described, the ethylthio substituent was preserved to various extents in the reaction product, when the hydroxydithioacetals (**4**), (**13**), and (**17**) reacted with acids. This seems to depend on some water content of the solvent and the catalyst used. When strictly anhydrous solvents and the nonhydrated catalyst (**22**) were used the formation of the 6-membered acyloin (**8**) from (**4**) was still observed. Similar difficulties were encountered before.[10] The best yield (67%) of the ring *A* expanded products having an ethylthio substituent was obtained when the vinyl sulphide (**10**) was treated with trifluoroacetic acid in anhydrous benzene. The reaction of the hydroxy-dithioacetals (**4**), (**13**), and (**17**) with complex (**22**) gave the ring-expanded hydroxyketones (**8**), (**15**), and (**20**) *via* the intermediate 5-membered acyloins (**5**), (**14**), and (**19**), respectively.

The structure of the new compounds described in this work follows from their spectral properties (see Experimental section). Full assignment of the ^{13}C NMR spectra is presented in Table 2. These spectra supported the proposed structures of new compounds. The configuration of C-3 in compound (**4**) is assigned on the basis of the assumption that the bulky sulphur-stabilized anion approaches the 3-carbonyl group from the less hindered α-side of the ring *A*. A β-approach is favourable in the case of the *A*/*B cis* ketones (**2**) and (**3**). The configuration of C-3 in the acyloin (**8**) was assigned on the basis of the following assumptions: (i) the acyloin (**5**) is an intermediate on the way from (**1**) to (**8**); (ii) in the transition state leading from (**5**) to (**8**) the 3-hydroxy and the carbonyl of the 3-acetyl group are *cis*[12c] to each other. Similar arguments apply to the stereochemistry of the acyloin (**15**). The structures of compounds (**9**), (**10**), and (**11**) follow from their spectral data. They were confirmed when it was found that physical and spectral properties of their transformation product, the α-methyl ketone (**12**), were distinct from those of the known 4α,14α-dimethyl-5α-cholest-8-en-3-one.[5c] The configuration at C-3 in (**9**) and (**11**) was assigned on the basis of CD and ^{13}C NMR spectra. A large negative Cotton effect ($\Delta\varepsilon$ − 9.29 at 290 nm) is observed for compound (**11**) having the ethylthio substituent in the α-axial position to the C-4 carbonyl chromophore. In ^{13}C NMR spectra of (**9**) and (**11**), characteristic upfield shifts are observed for C-1 and C-5, resulting from the more pronounced γ-*gauche* effects of the ethylthio substituent at C-3. Also, a substantial downfield shift[10] of the 5α-proton was observed in the ^1H NMR spectrum of the 3α-ethylthio-4-ketone (**11**).

In the 5α- and 5β-series of dithioacetals studied, the two possible migrations are depicted in Figure 1. In each case the appropriate orbital alignments are possible for both tertiary (C-5) and secondary (C-2) carbon migrations. However, the electronically favoured migration of C-5 would require a boat-like arrangement of atoms in the transition state (Figure 1, case a).

The regiochemistry of carbon migration in five-membered ring-expansion reactions depends largely on electronic and

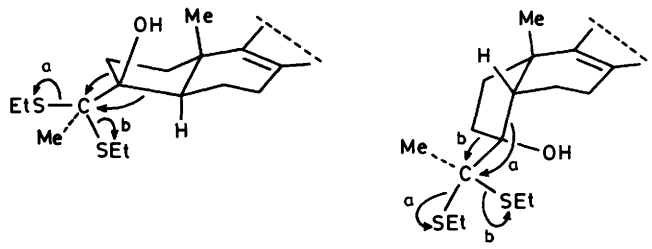
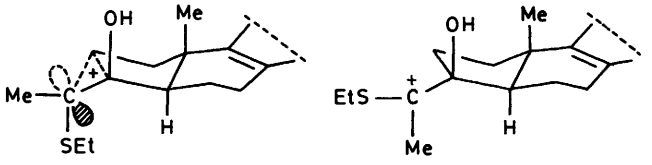


Figure 1. Possible migrations of (a) tertiary and (b) secondary carbon atoms in the hydroxydithioacetals (**4**) and (**13**) with the 5α- and 5β-configuration

conformational factors. It has been found[11] that the most highly substituted carbon atom migrates preferentially in sulphur-mediated ring expansions of conformationally flexible cyclic molecules. The regioselectivity was the same for similar expansions carried out with bicyclic systems.[10] A strong preference for the quaternary over secondary carbon migration was observed in ring expansions of 17-hydroxy-20-oxo steroids[12] including a case in which a boat-like transition state was required.[12c,14,15] However, a methylene rather than bridgehead carbon migration was observed in diazomethane ring expansions of bridged bicyclic ketones.[16] The regiochemistry observed in reactions reported in this study depends primarily upon conformational, rather than electronic, factors. The preference for a chair-like transition state was observed in all cases studied. Migration of the C(2)–C(3) bond proceeds predominantly *via* a least crowded transition state in which the SEt group is in a *cis* 1,3-relationship with the 5α-hydrogen, as in part structure (**23a**). For such a conformation the least-motion



(**23a**) (**23b**)

principle seems also be be fulfilled. In this arrangement the electron pair of the migrating bond is colinear with the empty orbital of the electron-poor C-4 atom and minor displacements of C-4 and C-5 atoms are required. A ring-expansion product resulting from the migration of the more heavily substituted C(3)–C(5) bond has not been observed in the reactions studied. Migration of this bond would require a boat-like transition state leading to the product. Consequently, a deep reorganization of atoms involved on the way to the transition state and further to the six-membered ring *A* of chair conformation should take place.

The similar distribution of the ring-expansion products obtained from (**4**) (co-ordination with a Lewis acid) and (**10**) (protonation with the formation of a carbocationic species) suggests that in the case of (**4**) the migration of the C(2)–C(3) bond follows the cleavage of the bond between C-4 and the co-ordinated ethylthio group. The common intermediate is then of carbocation-type and it may be stabilized by an electron pair of the adjacent hydroxy group. The population of both rotamers (**23a**) and (**23b**) is reflected in the proportion of the ethylthio-ketones (**9**) and (**11**) formed in the rearrangement. Formation of the epoxysulphide (**21**), a possible intermediate in the course of acid-catalysed ring expansions of (**4**) or (**10**) was not observed. However, it cannot be excluded as a short-lived intermediate.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer 580 grating spectrophotometer for solutions in chloroform. UV spectra were recorded with a Shimadzu 160 spectrophotometer for solutions in ethanol. ^1H and ^{13}C NMR spectra were recorded with a JEOL FX 90 Q spectrometer operating in the Fourier transform mode using solutions in deuteriochloroform. The chemical shifts (δ) are expressed in ppm relative to tetramethylsilane. The SFORD technique along with extensive substituent effect comparison in the lanostane series[17] was used for ^{13}C signal assignments. Mass spectra were recorded with a JEOL JMS-D 100 spectrometer using electron impact. CD spectra were recorded with a Jobin-Yvon Dichrograph Mark III for solutions in dioxane. Column chromatography was performed by using Merck 70–230 mesh silica gel 60. The progress of reactions was monitored by TLC using precoated aluminium-backed silica plates (Merck, type 5554). The work-up, chromatography, and crystallization procedures in the case of acid-sensitive sulphur compounds were greatly facilitated by the use of 'protective' admixtures of *ca.* 20 ppm of pyridine.

3α-(1,1-*Bisethylthioethyl*)-3β-*hydroxy*-14α-*methyl*-4-*nor*-5α-*cholest*-8-*ene* (**4**).—1,1-Bisethylthioethane[18] (1.500 g, 10 mmol) was dissolved in dry tetrahydrofuran (15 ml) and the solution was cooled to −78 °C. Butyl-lithium solution (8.0 ml, 10 mmol) was then added and the temperature was raised to 0 °C. After being stirred for 2 h the mixture was again cooled to −78 °C and a solution of the ketone (**1**) (1.300 g, 3.385 mmol) in dry tetrahydrofuran (4 ml) was added to the rapidly stirred carbanion solution during 3 min. After an additional 2 h of stirring at −78 °C the reaction was complete; 10 drops of water were added. The mixture was allowed to warm to room temperature, diluted with diethyl ether (80 ml), washed with water, dried, and concentrated *in vacuo* to give a pale yellow oil. The oil was purified by column chromatography on silica gel (85 g). Elution with benzene–light petroleum (3:1) afforded: the substrate; acetaldehyde diethyldithioacetal (710 mg); the *bisethylthio derivative* (**4**) (1.404 g, 78%) as a colourless, thick oil (needles from methanol–acetone, m.p. 54–56 °C); ν_{max} 3 520, 3 430, 1 330, 1 118, 1 047, and 995 cm^{-1}; δ 2.71 (2 H, q, *J* 7.3 Hz), 2.69 (2 H, q, *J* 7.3 Hz), 2.62 (1 H, br s, OH), 1.62 (3 H, s), 1.24 (6 H, t, *J* 7.3 Hz, Me), 1.11, 0.73, 0.90, and 0.83; *m/z* 472, 457, 411, and 43 (Found: C, 74.2; H, 11.0. $C_{33}H_{58}OS_2$ requires C, 74.1; H, 10.9%); and 3α-*butyl*-3β-*hydroxy*-14α-*methyl*-4-*nor*-5α-*cholest*-8-*ene* (**6**) (141 mg, 9.5%) as a thick colourless oil which could not be induced to crystallize; ν_{max} 3 605, 1 338, 1 285, 1 160, 1 140, 1 040, 994, and 968 cm^{-1}; δ 2.16 (2 H, m), 1.08, 0.73, 0.90, and 0.83; *m/z* 442 (M^+), 427, 409, 369, and 43 (Found: C, 84.3; H, 12.4. $C_{31}H_{54}O$ requires C, 84.1; H, 12.3%).

3β-(1,1-*Bisethylthioethyl*)-3α-*hydroxy*-14α-*methyl*-4-*nor*-5β-*cholest*-8-*ene* (**13**).—The reaction of the ketone (**2**) (786 mg, 2.05 mmol) under conditions similar to those applied for the synthesis of compound (**4**) (*vide supra*), after work-up and chromatography, afforded the 3α-*hydroxy derivative* (**13**) (710 mg, 65%), m.p. 71–73 °C (from acetone); ν_{max} 3 510, 3 430, 1 350, 1 270, 1 085, 1 025, and 985 cm^{-1}; δ 2.72 (2 H, q, *J* 7 Hz, CH_2), 2.69 (2 H, q, *J* 7 Hz, CH_2), 1.61 (3 H, s, 10-Me), 0.72 (3 H, s, 13-Me), 0.90, and 0.82 (other methyl signals); *m/z* 473, 472, and 54 (Found: C, 74.3; H, 10.9. $C_{33}H_{58}OS_2$ requires C, 74.1; H, 10.9%); and 3β-*butyl*-3α-*hydroxy*-14α-*methyl*-4-*nor*-5β-*cholest*-8-*ene* (**7**) (147 mg, 16%) as a thick oil; ν_{max} 3 570, 1 290, 1 220, 1 160, 1 050, 985, and 915 cm^{-1}; δ 1.98 (4 H, m), 1.62 (1 H, br s, OH), 1.06 (3 H, s, 10-Me), 0.72 (3 H, s, 13-Me), 0.91, and 0.82 (other methyl signals); *m/z* 442 (M^+), 424, 409, 57, and 43 (Found: C, 83.9; H, 12.3. $C_{31}H_{54}O$ requires C, 84.1; H, 12.3%).

Synthesis of Compound (**13**) (*LDA Method*).—Lithium di-isopropylamide was prepared by the dropwise addition of butyl-lithium (7.0 ml, 9.1 mmol) to a rapidly stirred solution of di-isopropylamine (1.28 ml, 9.1 mmol) in tetrahydrofuran (15 ml) at 0 °C. The mixture was stirred at 0 °C for 30 min. To this solution was added acetaldehyde diethyl dithioacetal (0.336 ml, 2.15 mmol) and stirring at 0 °C was continued for 1.5 h followed by cooling to −78 °C and stirring for a further 10 min. A solution of the ketone (**2**) (700 mg, 1.82 mmol) in dry tetrahydrofuran (3 ml) was added dropwise over 2 min to the stirred LDA solution at −78 °C, resulting in a yellow solution. After the mixture had been stirred for 2 h, the reaction was quenched by addition of (1 ml) brine and the mixture allowed to warm to room temperature. After dilution with diethyl ether (50 ml), the mixture was washed (×2) with brine, and then with water. The organic layer was dried (K_2CO_3), filtered, and concentrated *in vacuo* to an oil. Purification by column chromatography on silica gel (50 g) with benzene as eluant afforded compound (**13**) (thick oil; 383 mg, 39%) and the unchanged ketone (**2**). No trace of compound (**7**) was detected throughout the reaction and chromatography.

3β-(1,1-*Bisethylthioethyl*)-3α-*hydroxy*-14α-*methyl*-4-*nor*-5β-*cholesta*-7,9(11)-*diene* (**17**).—Reaction of the ketone (**3**) (470, 1.23 mmol) under conditions similar to those applied for the synthesis of compound (**4**), after work-up and chromatography, gave the *diene* (**17**) (472 mg, 72%) as a white solid, m.p. 52–54 °C (needles from methanol); ν_{max} 3 540, 1 283, 1 210, 1 148, 1 131, 1 058, 972, and 862, cm^{-1}; δ 5.66 (2 H, m, $w_{\frac{1}{2}}$ 12 Hz), 2.76 (2 H, q, *J* 7.3 Hz, CH_2), 2.73 (2 H, q, *J* 7.3 Hz, CH_2), 2.51 (4 H, m), 1.58 (3 H, s, Me), 1.22 (6 H, t, *J* 7.3 Hz, Me), 1.19 (3 H, s, 10-Me), 0.57 (3 H, s, 13-Me), 0.91, and 0.83 (other methyl signals); *m/z* 470, 452, 422, 390, 338, and 44 (Found: C, 74.15; H, 10.5. $C_{33}H_{56}OS_2$ requires C, 74.4; H, 10.6%); and 3β-*butyl*-3α-*hydroxy*-14α-*methyl*-4-*nor*-5β-*cholesta*-7,9(11)-*diene* (**18**) (46 mg, 8.5%), m.p. 97–99 °C (from ether–methanol); ν_{max} 3 560, 1 348, 1 150, 1 120, 1 105, 1 088, 1 047, and 1 030 cm^{-1}; δ 5.62 (2 H, m, $w_{\frac{1}{2}}$ 14 Hz), 2.23 (4 H, m), 1.16 (3 H, s, 10-Me), 0.92 (3 H, t, *J* 8 Hz), 0.58 (3 H, s, 13-Me), 0.90, and 0.83 (other methyl signals); *m/z* 440 (M^+), 422, 407, 365, and 43 (Found: C, 84.35; H, 12.0. $C_{31}H_{52}O$ requires C, 84.5; H, 11.9%).

Reaction of Compound (**4**) *with* (**22**) *in Toluene*.—The α-hydroxy-dithioacetal (**4**) (311 mg, 0.582 mmol) was dissolved in toluene (15 ml) and water (120 μl) was added. The mixture was stirred at room temperature for 10 min. Tetrakis-(acetonitrile)copper(I) tetrafluoroborate (**22**)[19] (300 mg, 0.95 mmol) was added in one portion and the stirring was continued. After being stirred for 3.5 h the reaction was complete and the mixture was diluted with benzene (30 ml), and washed successively with 10% NH_4Cl–aq. NH_3 (2 × 50 ml), and with water. The organic layer was dried, filtered, and concentrated *in vacuo* to a pale yellow solid that was purified by column chromatography on silica gel (15 g). Elution with benzene afforded three pure substances in order of increasing polarity: 3α-*ethylthio*-3β,14α-*dimethyl*-5α-*cholest*-8-*en*-4-*one* (**11**) (39 mg, 14%), m.p. 64–64.5 °C (from MeOH–CH_2Cl_2); ν_{max} 1 695, 1 305, 1 295, 1 179, 1 133, 1 050, 1 005, and 977 cm^{-1}; CD Δε (λ) −9.29 (308 nm); δ 3.38 (1 H, dd, *J* 11.7 and 3.6 Hz, 5α-H), 2.32 (2 H, m), 1.38 (3 H, s), 1.15 (3 H, t, *J* 7.3 Hz), 0.93, 0.84, 0.68, 0.90, and 0.83; *m/z* 472 (M^+), 457, 411, and 395 (Found: C, 78.6; H, 11.05. $C_{31}H_{52}OS$ requires C, 78.75; H, 11.1%); 3β-*ethylthio*-3α,14α-*dimethyl*-5α-*cholest*-8-*en*-4-*one* (**9**) (28 mg, 10%), white solid, m.p. 130–131 °C (from methanol); ν_{max} 1 707, 1 282, 1 255, 1 137, 1 108, 1 005, and 957 cm^{-1}; CD Δε (λ) −2.79 (296 nm); δ 2.62 (2 H, q, *J* 7.3 Hz), 2.55 (1 H, m, 5α-H), 1.56 (3 H, s), 1.25 (3 H, t, *J* 7.3 Hz), 0.92 (3 H, s, 10-Me), 0.88, 0.69, 0.90, and 0.83; *m/z* 472 (M^+), 457, 412, 411, 410, 397, and 357 (Found: C, 78.6; H, 11.1%); and 3β-*hydroxy*-3α,14α-*dimethyl*-5α-*cholest*-8-*en*-4-*one* (**8**) (144 mg, 66%), m.p. 107–108 °C (from methanol); ν_{max} 3 490, 1 705, 1 310, 1 277, 1 180, 1 130, 1 025, 1 010, 960, and 923 cm^{-1}; CD Δε (λ) −2.70 (287 nm); δ 4.05 (1 H, br s, OH), 2.58 (1 H, dd, *J* 10 and 4.5 Hz, 5α-H), 1.41 (3 H, s), 0.93, 0.87, 0.69, 0.90, and 0.83; *m/z* 428 (M^+), 413, 395, and 259 (Found: C, 81.1; H, 11.4. $C_{29}H_{48}O_2$ requires C, 81.25; H, 11.3%).

3α-*Hydroxy*-3β,14α-*dimethyl*-5β-*cholest*-8-*en*-4-*one* (**15**).—The α-hydroxy-dithioacetal (**13**) (280 mg, 0.524 mmol) reacted with (**22**)(300 mg, 0.95 mmol) in moist toluene in the same manner as described for the reaction of (**4**) with (**22**) (*vide supra*). After 40 min, TLC monitoring indicated complete conversion to a single product. After work-up the crude product was purified by column chromatography on silica gel (10 g). Elution with benzene afforded the *ketone* (**15**) (186 mg, 83%), m.p. 101–102 °C (from methanol); ν_{max} 3 490, 1 702, 1 305, 1 290, 1 172, 1 141, 1 015, 975, and 955 cm^{-1}; CD Δε (λ) +2.25 (290 nm); δ 4.01 (1 H, br s, OH), 2.40 (1 H, $w_{\frac{1}{2}}$ 8 Hz, 5β-H), 1.37 (3 H, s), 1.21, 0.77, 0.70, 0.90, and 0.83; *m/z* 428 (M^+), 413, 410, 395, and 385 (Found: C, 81.0; H, 11.3. $C_{29}H_{48}O_2$ requires C, 81.25; H, 11.3%).

3α-*Hydroxy*-3β,14α-*dimethyl*-5β-*cholesta*-7,9(11)-*dien*-4-*one* (**20**).—The α-hydroxy-dithioacetal (**17**) (40 mg, 0.075 mmol) reacted with tetrakis(acetonitrile)copper(I) tetrafluoroborate (**22**) (25 mg, 0.079 mmol) in moist toluene (10 ml) in the same manner as described for the reaction of compound (**4**) with (**22**). TLC monitoring indicated after 15 min of reaction only traces of the substrate and of compound (**20**), the α-ketol (**19**) being the major product; after 45 min the amount of α-ketols (**19**) and (**20**) was approximately the same and after 80 min the reaction was almost complete. The mixture was then diluted with benzene (10 ml), and washed with 10% NH_4Cl–aq. NH_3 (2 × 10 ml) and with water (×2). The organic layer was dried, filtered, and concentrated *in vacuo* to give a solid; column chromatography on silica gel (2 g) with benzene as eluant afforded, as a colourless thick oil, the ketol (**19**) (1.5 mg), identified by TLC, and the dienone (**20**) (29 mg, 90.6%) as a semi-solid which could not be induced to crystallize from a number of solvents; ν_{max} 3 480, 1 715, 1 330, 1 300, 1 282, 1 170, 1 145, 1 080, 1 030, and 980 cm^{-1}; λ_{max} (ε) 242 nm (10 600); δ 5.45 (2 H, m, $w_{\frac{1}{2}}$ 15 Hz), 3.96 (1 H, br s, OH), 2.56 (1 H, m, 5β-H), 1.39. 0.90, and 0.83; *m/z* 462 (M^+), 411, 408, 393, 365, 325, and 55 (Found: M^+ 426.3492. $C_{29}H_{46}O_2$ requires *M*, 426.3498).

Reaction of Compound (**4**) *with* (**22**) *in Methylene Chloride* (*at* +40 °C).—The α-hydroxy-dithioacetal (**4**) (327 mg, 0.612 mmol) was dissolved in dry methylene chloride (100 ml) and 80 ml of the solvent was distilled off. To the residue boiling under reflux a similarly evaporated suspension of (**22**) (360 mg, 1.14 mmol) in methylene chloride (10 ml) was added. The reaction was complete within 15 min and no change was observed upon boiling an aliquot for an additional 2 h. The mixture was diluted with methylene chloride (50 ml), and washed with 10% NH_4Cl–aq.NH_3 (×2) and with water (×2). The organic layer was dried, filtered, and concentrated *in vacuo* to give a white solid which was separated by column chromatography on silica gel (16 g). Elution with benzene–light petroleum (5:1) afforded two pure compounds: (**11**) (116.5 mg, 40%) and (**9**) (42 mg, 14.5%). Further elution with methylene chloride afforded the α-ketol (**8**) (102 mg, 39%). The identity of these samples was proved by m.p. measurements, and ^1H NMR and mass spectra.

Reaction of Compound (**4**) *with* (**22**) *in Benzene*.—The α-hydroxy-dithioacetal (**4**) (231 mg, 0.433 mmol) was dissolved in dry benzene (70 ml) and 40 ml of the solvent was distilled off. The dried solution was added in one portion to a similarly evaporated suspension of (**22**) (200 mg, 0.637 mmol) in benzene (15 ml) refluxing under argon. The reaction was complete within 30 min. The mixture was cooled to room temperature, diluted with benzene (20 ml), and washed with 10% NH_4Cl–aq. NH_3 (2 × 30 ml) and with water (× 2). The organic layer was dried, filtered, and concentrated *in vacuo* to give a white solid, which was separated by column chromatography on silica gel (12 g). Elution with benzene–light petroleum (5:1) afforded compound (**11**) (88 mg, 43%) and compound (**9**) (21 mg, 10%). Further elution with methylene chloride afforded the α-ketol (**8**) (61 mg, 33%) as a solid. The structures of the products were evident from their m.p.s and ^1H NMR spectra, which were identical with those already presented for compounds (**8**), (**9**), and (**11**).

3α-*Acetyl*-3β-*hydroxy*-14α-*methyl*-4-*norcholest*-8-*ene* (**5**).—The α-hydroxy-dithioacetal (**4**) (70 mg, 0.131 mmol) was dissolved in dry methylene chloride (10 ml) and stirred at −78 °C. A solution of $TiCl_4$ in dry methylene chloride (0.5 ml of 5% v/v solution) was then added and stirring under argon was continued for 2 h, followed by quenching with 5% aqueous $NaHCO_3$ (5 ml). After usual work-up the resulting thick colourless oil was purified by column chromatography on silica gel (2.5 g) with benzene as eluant. The only substance obtained was a mixture of compound (**5**) and its Δ^7 isomer in a 1:1 ratio (49 mg, 87%), which was inseparable by chromatography or crystallization. This crystallized from methanol as needles, m.p. 112–114 °C: compound (**5**), δ 3.88 (1 H, br s, OH), 2.21 (3 H, s, Ac), 1.13, 0.73, 0.90, and 0.83; signals ascribe to Δ^7 isomer, δ 5.22 (m, $w_{\frac{1}{2}}$ 9 Hz, 7-H), 3.92 (br s, OH), 2.20 (3 H, s, Ac), 1.01, 0.67, 0.90, and 0.83. The ^1H NMR data of (**5**) are known from a spectrum of the pure compound obtained by an independent route. The isomer ratio is a mean value calculated from integration of the signals of the acetyl, C-10, and C-13 methyl groups.

3α-(1-*Ethylthioethenyl*)-3β-*hydroxy*-14α-*methyl*-4-*nor*-5α-*cholest*-8-*ene* (**10**).—A solution of the α-hydroxy-dithioacetal (**4**) (207 mg, 0.388 mmol) in dry dimethylformamide (20 ml) was stirred at +50 °C. Anhydrous copper(I) chloride powder (200 mg, 2.02 mmol) was added in one portion and stirring was continued for 15 min. The mixture was cooled to room temperature, diluted with benzene–light petroleum (1:1; 50 ml), and washed with 10% NH_4Cl–aq. NH_3 (2 × 50 ml), and water (3 × 50 ml). The organic layer was dried, filtered, and concentrated *in vacuo* to yield a white solid, which was purified by column chromatography on silica gel (10 g). Elution with benzene afforded the *ethylthioethenyl derivative* (**10**) (180 mg, 98%), m.p. 95–96 °C (from methanol); ν_{max} 3 590, 1 595, 1 335, 1 320, 1 263, 1 140, 1 120, 1 043, 965, and 860 cm^{-1}; δ 5.41 (1 H, br s), 4.81 (1 H, br s), 2.73 (2 H, q, *J* 7.3 Hz), 1.30 (3 H, t, *J* 7.3 Hz), 1.12, 0.73, 0.90, and 0.83; *m/z* 472 (M^+), 457, 439, 428, 413, 411, and 43 (Found: C, 78.5; H, 11.2. $C_{31}H_{52}OS$ requires C, 78.75; H, 11.1%).

Reaction of Compound (**4**) *with* (**22**) *in Methylene Chloride*.—A solution of the α-hydroxy-dithioacetal (**4**) (103 mg, 0.193 mmol) in dry methylene chloride (10 ml) was cooled under argon to −78 °C. A suspension of (**22**) (95 mg, 0.302 mmol) in dry methylene chloride (5 ml) was then added in one portion and stirring was continued for 30 min. After this time TLC analysis showed an almost pure single spot of a product identical with the α-ketol (**5**). That this was a TLC artefact was shown by the following. The cold (−78 °C) reaction mixture was quenched upon stirring with 10% NH_4Cl–aq. NH_3 (5 ml) and allowed to warm to room temperature. It was diluted with methylene chloride (20 ml), and washed with 10% NH_4Cl–aq. NH_3 (× 2) and with water (3 × 20 ml). The organic layer was dried, filtered, and concentrated *in vacuo* to give a colourless thick oil. Column chromatography on silica gel (5.5 g) with benzene as eluant afforded unchanged (**4**) (89 mg) along with compound (**10**), identical with an authentic sample.

Reaction of Compound (**10**) *with Trifluoroacetic Acid in Benzene* (*Ring Expansion*).—A solution of the dried crystalline hydroxy sulphide (**10**) (205 mg, 0.434 mmol) in dry benzene (20 ml) was stirred under argon and trifluoroacetic acid (TFA) (0.15 ml) added in one portion. Stirring was continued at room temperature for 10 min and pyridine (1 ml) was added. The mixture was diluted with light petroleum (20 ml) and washed with water (3 × 30 ml). The organic layer was dried, filtered, and concentrated *in vacuo* to give a thick colourless oil, which was separated by column chromatography on silica gel (12 g). Elution with benzene–light petroleum (4:1) gave compound (**11**) (107 mg, 52%) as a thick colourless oil and compound (**9**) (31 mg, 15%) as a solid, whose spectral data were in accordance with those for the original samples.

3β,14α-*Dimethyl*-5α-*cholest*-8-*en*-4-*one* (**12**).—(a) To a solution of compound (**11**) (109 mg, 0.231 mmol) refluxing in dry *m*-xylene (20 ml), azoisobutyronitrile (AIBN) (10 mg) was added. The mixture was refluxed for 10 min and a solution of tributyltin hydride (TBTH) (0.15 ml) in dry *m*-xylene (3 ml) added in drops during 2 min. The reaction was complete in 15 min. The mixture was cooled to room temperature and washed with water (3 × 20 ml). The organic layer was dried and concentrated *in vacuo* to yield a white solid, which was purified by column chromatography on silica gel (5 g) with benzene as eluant. 3β,14α-*Dimethyl*-5α-*cholest*-8-*en*-4-*one* (**12**) (93 mg, 97.8%) was obtained as a white solid, m.p. 75–76 °C (from methanol); ν_{max} 1 705, 1 317, 1 288, 1 170, 1 160, 1 125, 1 005, and 947 cm^{-1}; CD Δε(λ) −0.21 (298 nm) and −0.14 (307 nm); δ 0.99 (3 H, d, *J* 6.4 Hz, 3β-Me), 0.91, 0.85, 0.69, 0.90, and 0.83; *m/z* 412 (M^+), 397, 243, and 231 (Found: C, 84.3; H, 11.6. $C_{29}H_{48}O$ requires C, 84.4; H, 11.7%).

(b) Compound (**9**) was treated with TBTH–AIBN under identical conditions as in the foregoing experiment. TLC monitoring of this reaction was ineffective because the substrate (**9**) and the product showed the same polarity in a number of solvents. Moreover, in the case of the equatorial ethylthio epimer (**9**) the reaction was dramatically slower than with (**11**) and after 4.5 h only *ca.* 40% of the ketone (**12**) could be detected along with unchanged substrate (^1H NMR).

3β-(1-*Ethylthioethenyl*)-3α-*hydroxy*-14α-*methyl*-4-*nor*-5β-*cholest*-8-*ene* (**16**).—A solution of the α-hydroxy-dithioacetal (**13**) (200 mg, 0.374 mmol) in dry dimethylformamide (20 ml) was stirred at 50 °C. Anhydrous copper(I) chloride powder (200 mg, 2.02 mmol) was added in one portion and stirring was continued for 20 min. The mixture was cooled to room temperature, diluted with benzene–light petroleum (1:1; 50 ml), and washed with 10% NH_4Cl–aq. NH_3 (× 2) and with water (2 × 50 ml). The organic layer was dried, filtered, and concentrated *in vacuo* to yield a colourless thick oil, which was purified by column chromatography on silica gel (10 g). Elution with benzene–light petroleum (3:1) afforded the *ethylthioethenyl* compound (**16**) as a thick colourless oil (171 mg, 96.7%) which could not be induced to crystallize; ν_{max} 3 590, 3 525, 1 595, 1 315, 1 290, 1 165, 1 040, 1 022, 1 010, 977, and 862 cm^{-1}; δ 5.48 (1 H, br s), 4.82 (1 H, br s), 2.47 (2 H, q, *J* 7.3 Hz), 2.10 (1 H, br s, OH), 1.31 (3 H, t, *J* 7.3 Hz), 1.14, 0.73, 0.90, and 0.83; *m/z* 472

(M^+), 454, 428, 413, 395, and 385 (Found: C, 78.8; H, 11.2. $C_{31}H_{52}OS$ requires C, 78.75; H, 11.1%).

3β-Acetyl-3α-hydroxy-14α-methyl-4-nor-5β-cholest-8-ene (**14**).—To a stirred solution of the sulphide (**16**) (122 mg, 0.258 mmol) in moist benzene (20 ml), trifluoroacetic acid (3 drops) was added at room temperature. After 5 min the reaction was complete. Pyridine (0.5 ml) was added and the mixture was washed with water (3 × 30 ml). The organic layer was dried, filtered, and concentrated *in vacuo* to yield a white solid, that was purified by column chromatography on silica gel (6 g). Elution with benzene afforded the pure *acetyl derivative* (**14**) (98 mg, 88.6%) as a white solid, m.p. 102–103 °C (from methanol); ν_{max} 3 490, 1 696, 1 356, 1 318, 1 290, 1 185, 1 120, 1 045, 1 020, and 973 cm^{-1}; CD $\Delta\varepsilon(\lambda)$ −1.15 (277 nm) and +0.19 (312 nm); δ 3.41 (1 H, br s, OH), 2.27 (3 H, s, Ac), 1.16, 0.73, 0.90, and 0.83; *m/z* 428 (M^+), 413, 395, and 367 (Found: C, 81.2; H, 11.2. $C_{29}H_{48}O_2$ requires C, 81.25; H, 11.3%).

Reaction of Compound (**17**) *with Mercury*(II) *Chloride and Boron Trifluoride*.—Mercury(II) chloride (28 mg, 0.103 mmol) was added in one portion to a solution of the α-hydroxydithioacetal (**17**) (50 mg, 0.094 mmol) in dimethylformamide (7 ml) stirred under argon at room temperature. The mixture was kept at room temperature for 1 h and at 70 °C for 1 h. Boron trifluoride–diethyl ether (0.018 ml) was added dropwise and the mixture was stirred at 70 °C for 6 h, cooled to room temperature, diluted with benzene (15 ml) and light petroleum (10 ml), and washed successively with brine, 5% aqueous sodium hydrogen carbonate, and water (× 2). The organic layer was dried, filtered, and concentrated *in vacuo* to yield a thick oil, column chromatography of which on silica gel (4 g) with benzene as eluant afforded the α-ketol (**19**) as a thick, colourless oil (16.5 mg, 41%); ν_{max} 3 560, 1 300, 1 145, 1 120, 1 050, 1 025, 980, 900, and 815 cm^{-1}; δ 5.62 (2 H, m, $w_{\frac{1}{2}}$ 20 Hz), 2.75 (1 H, br s, OH), 2.25 (3 H, s, Ac), 1.22, 0.95, 0.59, 0.90, and 0.84; *m/z* 426 (M^+), 411, 408, 393, and 383 (this compound decomposed easily upon storage in a refrigerator); and the ketol (**20**) (18 mg, 45%), the spectral data of which were in accordance with those already cited.

Acknowledgements

Financial support of the work from the program RP II.13.2 is gratefully acknowledged.

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Paper 9/02445J
Received 9*th June* 1989
Accepted 11*th September* 1989