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STUDIES ON 1,4-DIOXO-STEROIDS*

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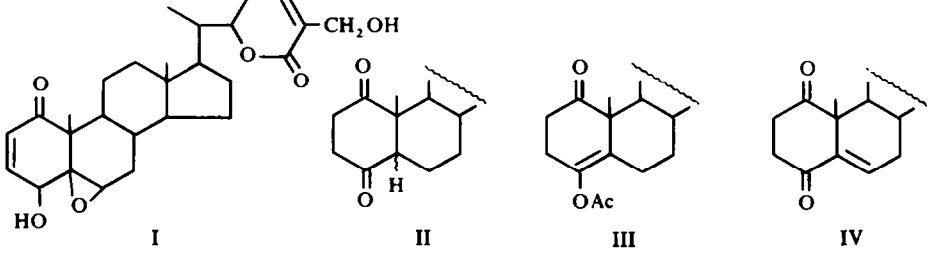
Abstract—Cholestan-1,4-diones as well as cholest-2-en-1,4-diones in the 5α and 5β series have been synthesized in several steps from 1α-hydroxy-5α-cholest-2-ene and 1β-hydroxy-5β-cholest-2-ene. The conformation of ring A in these compounds has been analysed by NMR solvent shifts. Equilibration studies have shown that the 1,4-diones are more stable with rings A/B in the *cis* arrangement. In the case of the unsaturated 1,4-diones, epimerization of the 5α-isomer takes place to an extent of 95%. The increased stability of the *cis* A/B system is attributed to a decrease of the nonbonded interaction of the 1-carbonyl with the 11α-H. The thioketalization of some of the above ketones has also been investigated; 4-thioketals in the 5β series have been obtained and their behaviour in acidic conditions studied.

IN THE course of our studies on the stereochemistry of withaferin A (I), a steroidal lactone isolated from the leaves of *Withania somnifera* (Solanaceae), an unseparable mixture (3:7 ratio) of C-5 epimeric 1,4-diketones (II) has been obtained by base treatment of the corresponding enol-acetate (III), or alternatively by zinc reduction in mild acidic conditions of the enone (IV).[1c-e] The configuration at C-5 of the two constituents of the mixture (II) of diketones has been studied by NMR solvent shifts measurements ($\Delta^{CDCl_3}_{C_6H_6}$)[1d] leading to the conclusion that the major component has a *cis* A/B rings stereochemistry†. The predominant formation, under equilibrating conditions of a steroidal 1,4-dione in the 5β-series, in contrast with the known smooth epimerization of steroidal 4-ones from the A/B *cis* to the *trans* series,[2] prompted us to investigate the problem of the relative stabilities of 1,4-dioxo steroids.



I II III IV

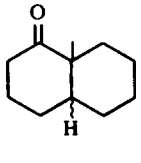
Extensive studies perfomed in the decaline series have shown that equilibration of *cis*-decaline at high temperature[3a] and in the presence of a Pd catalyst[3b] leads to the formation in high yield of the *trans*-decaline, in agreement with the lower enthalpy of the latter[4]. This tendency of isomerization is even stronger with 1-decalones, the equilibrium

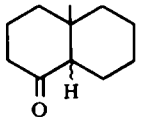
* Preliminary reports of this work have been presented at the 35th and the 38th Meetings of the Israel Chemical Society[1a,b]

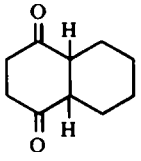
† Prof. E. R. H. Jones kindly informed us at the time that he and his collaborators have observed a similar behaviour with steroidal 1,6-diones[3a].

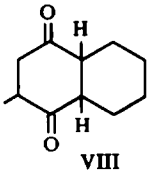
mixture containing at least 95% of the *trans* isomer.[5] The energy difference is however considerably decreased after introduction of an angular Me, the *cis* and *trans* 9-methyldecalones being of comparable stability (~55% *trans*)[6]. The same tendency is maintained with the decalones, the equilibrium mixture of the two 9-methyl-1-decalones (V) obtained by heating at 250° over a Pd catalyst, contained the *cis* and *trans* isomers in a 6:4 ratio;[7a] the 10-methyl-1-decalones (VI) require milder conditions of equilibration since the CO is next to the epimerizable centre, and the equilibrium mixture contained the *cis*:*trans* isomers in a 4:6 ratio.[7b] The energy differences calculated for decalones are in good agreement with the relative stability values determined experimentally, except for the pair of 10-methyl-1-decalones (VI), in which the energy calculated for the *cis* isomer was slightly lower than that of the *trans* isomer.[8] This system (VI) is actually present in the steroidal 4-ones and 6-ones, however, there is an extremely large difference of stability between the corresponding bicyclic and tetracyclic ketones.[9] The *cis* steroidal ketones are converted to an extent of 99% (4-ones) and 88% (6-ones) to the corresponding *trans* stereoisomers in mild equilibrating conditions. In both cases the free energies for the isomerization of the *cis* to the *trans* steroids are in agreement with the experimental values[2d]. This drastic change in stability from the bicyclic to the tetracyclic ketones has been attributed to the additional rings favoring the *trans* arrangement for the A/B system[7b].

Although, with the bicyclic 1,4-diones the *trans* isomers may be expected to be less stable than the *cis* counterparts due to additional nonbonded interactions of the CO groups,[10] the *cis*-decalin-1,4-dione (VII) can smoothly be isomerised in various conditions.[11] In the case of the *cis* decalin-dione VIII, the extent of alkali induced isomerization is 88%.[11a] In the octaline series, compound IX has been converted by


V


VI


VII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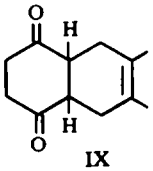
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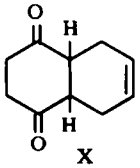
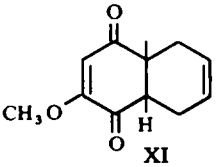
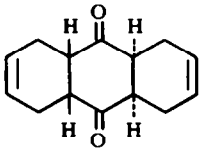

X



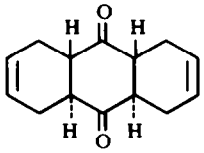
XI

alkaline treatment to the *trans* stereoisomer in 91% yield, whereas in similar conditions compound X gave only a low yield (20%) of the *trans* counterpart, no explanation being, however, advanced for this contradictory behavior.[12] In a bicyclic enedione (with an angular Me group) such as the hexaline derivative XI obtained in an early step of the Harvard total steroid synthesis, equilibration of the *cis* isomer in alkaline conditions yielded comparable amounts of the *trans* isomer, the conversion being almost complete only in conditions under which the latter stereoisomer could be induced to crystallize out of the reaction mixture.[13]

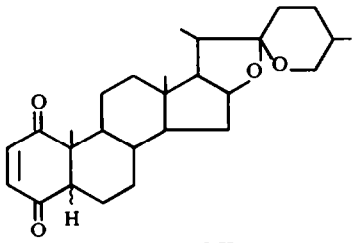
In the tricyclic series compound XIIa (*cis-anti-cis* configuration) has been isomerised in basic conditions to an extent of ~67% to the *trans-syn-trans* compound XIIb[14], whereas in acid medium 40% of XIIb has been obtained.[11b]



XIIa



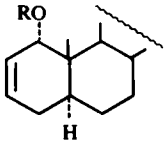
XIIb



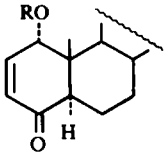
XIII

In the steroid series, with the exception of the mixture of 1,4-diones (II) described earlier,[1] compound XIII is to our knowledge the only steroidal 1,4-dione obtained so far during a sequence of reactions directed towards the structure elucidation of kitigenine.[15] This compound XIII, obtained by hydrolysis of the corresponding 4-enol acetate on alumina (i.e. in equilibrating conditions), was assigned a 5α configuration,[15] however no proof has been advanced to support this assignment, which is not in agreement with our results for similar systems (*vide infra*).

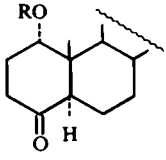
In order to study the relative stabilities of steroidal 1,4-diones and the corresponding enediones, procedures for the preparation of the pure stereoisomers in the cholestane series have been devised. The sequence of reactions designed for the preparation of 5α-cholestan-1,4-dione (XVII) and the Δ^2-1,4-dione (XVIII) starts with the allylic oxidation of the known 1α-acetoxy-cholest-2-ene XIVb which in turn has been prepared by the hydrazine hydrate reduction procedure[16] of 1α,2α-epoxy-5α-cholestan-3-one, and the subsequent acetylation of the corresponding allylic alcohol.[17]



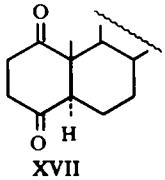
XIV



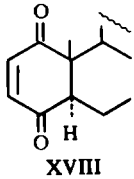
XV



XVI



XVII



XVIII

a: R = H
b: R = Ac

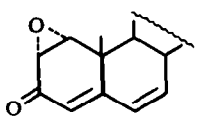
The only satisfactory procedure for the introduction of a CO at C-4 proved to be allylic oxidation of XIVb with sodium chromate,[18] leading to XVb in ~30% yield. Other agents known to perform allylic oxidation, such as selenium dioxide, gave complex and unseparable mixtures of products, while mercuric acetate, chromic acid in acetic acid solution and t-butyl chromate, left the starting material unreacted. Compound XVb displayed in the NMR spectrum a characteristic ABX pattern reminiscent of that featured by steroids possessing the reverse substitution pattern in ring A (4β-acetoxy-Δ^2-1-one, the 4 substituent being axial oriented), well known from our studies on the withanolides[1c]. The two vinylic hydrogen atoms at C-2 and C-3 exhibited a double doublet centered at δ 6·87 (J = 10 and 5·5 Hz) and a doublet at δ 6·05 (J = 10 Hz) respectively, whereas the quasiequatorial hydrogen at C-1 gave rise to a doublet

(J = 5·5 Hz) at δ 5·15. The structure assigned to XVb was supported by its UV absorption band, λ_{max} 213 nm (ε 9900) as well as by the IR absorption in the CO region, ν_{max} 1730 and 1683 cm^{-1}, and by the molr wt of the compound determined by mass spectrometry. Further reactions performed on XVb, in the sequence directed towards the diketones XVII and XVIII, constituted also a well documented support for the structure of XVb. Catalytic hydrogenation of the latter proceeded smoothly to give a quantitative yield of the saturated 1α-acetoxy-4-one derivative XVIb, which did not exhibit the signals of the two vinylic protons present in XV but displayed a narrow triplet for the 1-H (δ 5·07), confirming thereby the axial orientation of the adjacent acetate. Hydrolysis of the acetate function producing XVIa, followed by the smooth oxidation of the OH group (Jones method[19]) afforded almost quantitatively the crystalline diketone XVII. Conversely, mild hydrolysis of the acetate group in XVb yielded the corresponding allylic alcohol XVa, characterized by the expected shift of the 1-H from δ 5·15 in XVb to δ 4·07 in XVa. The oxidation of XVa to XVIII was again performed with Jones' reagent. The use of manganese dioxide which oxidized in excellent yield a 4-hydroxy-Δ^2-1-one derivative to the corresponding enedione[1c], left compound XVa largely unaffected. Mention may be made that attempted oxidation of the allylic alcohol XIVa with either manganese dioxide[20] or dichloro-dicyanoquinone[20, 21] failed to yield the corresponding enone, showing that the 1-hydroxy-Δ^2 system in steroids does not exhibit the typical behaviour of an allylic system.

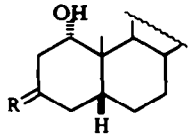
The next task was to devise a rather similar set of reactions leading to the 1,4-dione and the corresponding enedione in the 5β-series. Epoxidation of cholesta-1,4,6-trien-3-one to the 1α,2α-epoxide XIX followed by catalytic hydrogenation of the latter according to Pelc[22a] afforded the 1α-hydroxy-5β-cholestan-3-one (XXa) which was then dehydrated to 5β-cholest-1-en-3-one (XXI) in an overall yield of 45% (calculated on the trienone).

The 1-H in XXa gave rise to a double doublet at δ 3·57 and 3·70 with almost equal coupling constants (~8 Hz). The configuration at C-1 and C-5 in XXa was determined by reduction of the corresponding tosyl-hydrazone (XXb) with sodium borohydride to 1α-hydroxy-5β-cholestane (XXIIa), according to the procedure used for related systems[23a]. Although neither XXIIa, nor the acetate XXIIb could be induced to crystallize, the equatorial orientation of the hydroxyl group at C-1 was confirmed by the NMR pattern of the adjacent hydrogen, multiplet at δ 3·33 (XXIIa) and 4·57 (XXIIb). This configurational assignment was supported by comparison with the epimeric 1β-acetoxy-5β-cholestane XXVIIa, which exhibited a narrow triplet at δ 5·05 for the 1-H, in agreement with its equatorial orientation. Oxidation of both XXIIa and XXVIIa afforded the same monoketone identified as 5β-cholestan-1-one (XXIII) by its strong negative Cotton effect[24] and by the slightly negative solvent shift ($\Delta^{CDCl_3}_{C_6H_6}$ −7 Hz) experienced by the C-10 methyl, as expected for a steroidal 1-one in the 5β series.[1d, 25]

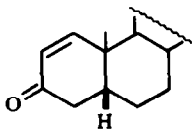
It is noteworthy to compare now the behaviour of the two hydroxy-ketones XXa and XXXII in the reaction with tosyl-hydrazine. Whereas XXa (C-1 OH equatorial) afforded the corresponding tosyl-hydrazone (XXb) without any difficulty, compound XXXII (C-1 OH axial, prepared by catalytic hydrogenation of 1α,2α-epoxy-5α-cholestan-3-one), afforded in similar conditions the unsaturated tosyl-hydrazone XXXIII, the OH group being eliminated during the reaction of the carbonyl at position 3. The structure of XXXIII was substantiated by the analysis of its NMR spectrum featuring the characteristic AA'BB' pattern of the four aromatic protons, doublets



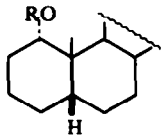
XIX



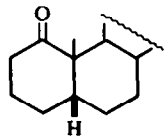
XX a: R = O
b: R = Tosyl-hydrazone



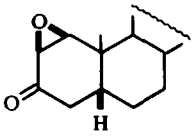
XXI



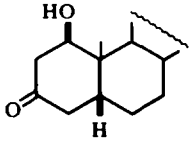
XXII



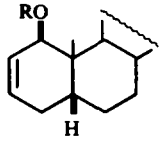
XXIII



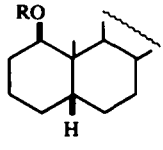
XXIV



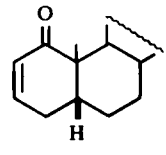
XXV



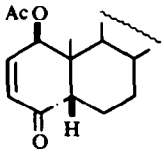
XXVI



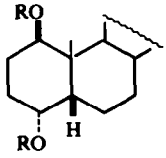
XXVII



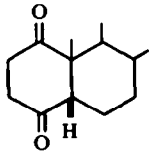
XXVIII



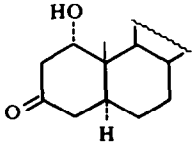
XXIX



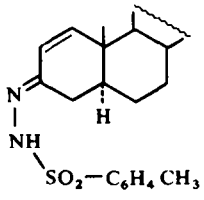
XXX



XXXI



XXXII



XXXIII
a: R = H
b: R = Ac

centered at δ 7·29 and 7·87 ($J = 8$ hz), an AB pattern for the vinylic 1-H and 2-H, doublets at δ 5·95 and 6·42 ($J = 10$ Hz) and a three proton singlet at δ 2·40 for the aromatic methyl group. This structure was confirmed by direct comparison with the corresponding tosyl-hydrazone of 5α-cholest-1-en-3-one.[23b] Furthermore, the tosyl-hydrazone moiety in XXXIII could not be cleaved by reduction with sodium borohydride in contrast with the smooth reduction of this group in the saturated tosyl-hydrazone XXb.

Elimination of the 1α-OH in XXa could be performed in acidic conditions leading to the enone XXI in quantitative yield. This compound has been previously obtained in poor yield as byproduct in various reactions.[26]

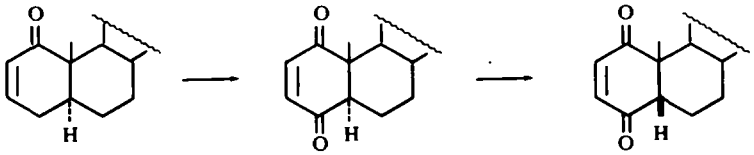
Epoxidation of XXI with alkaline hydrogen peroxide afforded the 1β,2β-epoxy-5β-cholestan-3-one (XXIV) characterized by the NMR signals of the two epoxidic protons, two sets of doublets at δ 3·47 and 3·30 ($J = 4$ Hz). The β orientation of the epoxide ring was confirmed by catalytic hydrogenation to the hydroxy-ketone XXV possessing the 1β-OH axial oriented (NMR signal of the adjacent 1-H, narrow triplet at δ 4·18). The axial orientation of the OH group in XXV was further confirmed by its smooth dehydration over neutral alumina to reform the enone XXI, in contrast to the epimeric hydroxy-ketone XXa (equatorial 1α-OH) which could be securely chromatographed under similar conditions, no trace of elimination product being detected.

The allylic alcohol XXVIa which was obtained by the hydrazine hydrate reduction[16] of the epoxy-ketone XXIV was characterized by two sets of NMR signals, a doublet ($J = 3·0$ Hz) at δ 3·87 for the 1-H (shifted downfield at δ 5·16 in the corresponding acetate XXVIb) and a narrow multiplet at δ 5·88 for the two vinylic protons. The structure of XXVIa was substantiated by catalytic hydrogenation to 1β-hydroxy-5β-cholestane (XXVIIa) and by direct oxidation (chromium trioxide in pyridine[27]) to 5β-cholest-2-en-1-one (XXVIII). The oxidation at position 4 in XXVIb was again

attempted by the sodium chromate procedure[18] resulting in the 4-one derivative XXIX. As expected, the crude compound obtained in this reaction could not be purified by chromatography on alumina due to rapid isomerisation at C-5; for the same reasons the sequences XVb→XVa→XVIII and XVb→XVIb→XVIa→XVII performed in the 5α series could not be used in the 5β series. Attempted alkaline hydrolysis of the acetate function in XXIX led to mixtures of 5α and 5β epimers. Compound XXIX could be obtained, however, in pure form for characterisation purposes by chromatography on silicagel; it showed the expected absorption band in the ultraviolet, λ_{max} 220 nm (ε 9800) and three sets of signals in the NMR spectrum, doublet at δ 5·36 (J = 6 Hz) for the 1-H, double doublet at δ 6·90 (J = 10 and 6 Hz) for the 2-H and doublet at δ 6·11 (J = 10 Hz) for the 3-H, paralleling the corresponding set of signals in XVb.

To overcome the tendency of epimerization at C-5, it was thought to change the symmetry of the C-4 atom from trigonal to tetrahedral by reduction of the CO to an alcohol, thus enabling the hydrolysis of the 1-acetate without affecting the stereochemistry at C-5. The hydride reduction of XXIX ($NaBH_4$ as well as LAH) proceeded, however, with the quantitative reduction of the double bond* leading (in the case of LAH as reducing agent) to the crystalline saturated diaxial diol, 1β, 4α-dihydroxy-5β-cholestane (XXXa) characterized together with its diacetate XXXb. The two equatorial H atoms adjacent to the respective acetate groups showed the expected multiplicity, two overlapped narrow signals at δ 5·21. The LAH reduction was thereafter performed on the crude product obtained following allylic oxidation of XXVIb, leading to an overall yield of 23% of XXXa (calculated on XXVIb). Oxidation of this diol led to a 1,4-dione XXXI different from XVII as shown by inspection of their NMR spectra (signals of the C-10 Me at δ 1·09 and 1·25 respectively). Since the 2–3 double bond was reduced, the enedione in the 5β series could not be obtained by an independent way, but only following epimerisation of the 5α-enedione (XVIII).

The 1,4-diones XVII and XXXI yielded by equilibration (over neutral, acidic or basic alumina, as well as by use of a dilute solution of potassium hydroxide in methanol) the same crystalline mixture in a ratio of ~3:7 (5α:5β), as evaluated from the relative intensities of the signals of the C-10 Me groups. The conversion of the enedione XVIII (5α) into the epimeric enedione XXXIV (5β) proceeded in similar conditions to an extent of ~95%. The two equivalent vinylic protons in XVIII gave rise to a singlet at δ 6·62, whereas in XXXIV the protons were equivalent as well, but their signal was at δ 6·66. A corresponding shift could be noted in the position of the C-10 Me, from δ 1·18 in XVIII to δ 1·31 in XXXIV. Alternatively, the enedione XVIII could be reached in



XXXV XVIII XXXIV

rather poor yield by direct allylic oxidation with sodium chromate of the known[28] 5α-cholest-2-en-1-one (XXXV). The crude product shows the signal of the two vinylic

* This reaction is in complete contrast with the hydride reduction of XVb; the problem will be discussed in a forthcoming publication.

protons at the same position as XVIII, however, epimerisation to XXXIV occurs during chromatography, the above signal being displaced to δ 6·66.

In view of these results, the 5α stereochemistry attributed[15] to the enedione XIII obtained by hydrolysis of an enol acetate on alumina seems highly improbable.

The solvent shift measured for the C-10 Me in XXXI (Table) fits the value calculated by summation of the shifts in 5β-cholestan-1-one (XXIII) and 5β-cholestan-4-one (XXXIX); concerning the corresponding shift in XVII, there is a difference of 4·5 Hz between the experimental value and that calculated by summation of the shifts in 5α-cholestan-1-one (XLIII) and 5α-cholestan-4-one (XXXVIII). Agreement between the calculated and the measured solvent shifts implies that in the two diketones XVII and XXXI ring A possesses a chair conformation as the corresponding monoketones. Although the chair conformation of ring A is well documented only for 5α-cholestan-1-one[29] and for the 3-ones[30], there are no data to support a different conformation in the 4-ones and the 5β-1-one. The small difference between the calculated and measured value for the 5α-diketone (XVII) may well reflect a slight distortion of ring A from the chair conformation. The solvent shifts of the C-10 Me in the enediones XVIII and XXXIV in perfect agreement with the values deduced from additivity considerations. Subtraction of the solvent shift of XIVb from XVb yields the contribution of a 4-one in a system having an sp^2 hybridized 2–3 bond. The obtained value added to that of XXXV leads to the same value as measured in the enedione XVIII (19 Hz); similarly, subtraction of the solvent shifts of XXVIb from XXIX and adding the obtained value to the shift of XXVIII gives 10 Hz, as measured for the enedione XXXIV.

TABLE 1. CHEMICAL AND SOLVENT SHIFTS OF 19-PROTONS

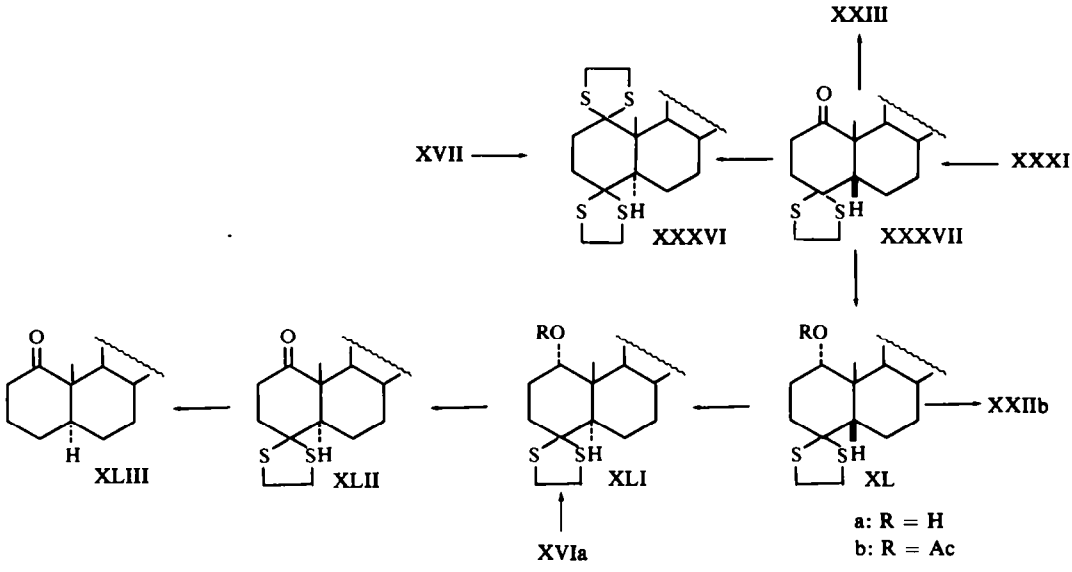
Compound	Cholestane derivative	19-H signal (ppm) (δ)		$CDCl_3$ ΔC_6H_6	
		$CDCl_3$	C_6H_6	ppm	Hz
XIVb	(5α)-Δ^2-1αOAc	0·78	0·70	+0·08	+5·0
XVb	(5α)-Δ^2-1αOAc-4-one	0·90	0·65	+0·25	+15·0
XVII	(5α)-1,4-dione	1·09	0·79	+0·30	+18·0
XVIII	(5α)-Δ^2-1,4-dione	1·18	0·86	+0·32	+19·0
XXIII	(5β)-1-one	1·13	1·25	−0·12	−7·0
XXVIb	(5β)-Δ^2-1βOAc	0·99	1·01	−0·02	−1·0
XXVIII	(5β)-Δ^2-1-one	1·18	1·24	−0·06	−3·5
XXIX	(5β)-Δ^2-1βOAc-4-one	1·15	0·94	+0·21	+12·5
XXXI	(5β)-1,4-dione	1·25	1·15	+0·10	+6·0
XXXIV	(5β)-Δ^2-1,4-dione	1·32	1·15	+0·17	+10·0
XXXV	(5α)-Δ^2-1-one	1·05	0·90	+0·15	+9·0
XXXVIII	(5α)-4-one[1d]	0·74	0·61	+0·13	+7·5
XXXIX	(5β)-4-one[1d]	1·12	0·89	+0·23	+14·0
XLIII	(5α)-1-one	1·14	0·89	+0·25	+15·0*

* Reported[31] +18·0 Hz. In the additivity calculations, the +15·0 Hz value has been used.

With the pure 1,4-diones XVII and XXXI prepared, the thioketalisation experiments previously performed [1a,e] on the mixture of diketones II were reinvestigated.

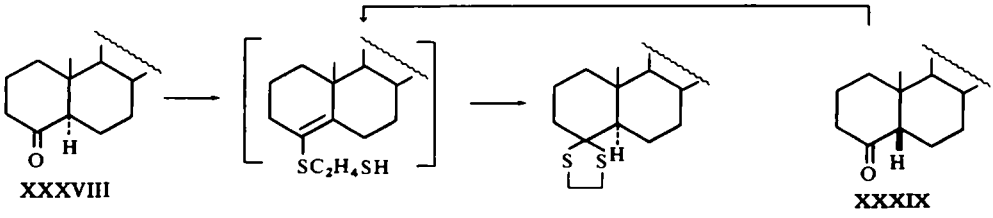
The reaction of XVII with ethanedithiol in presence of boron trifluoride proceeded at

a fast rate to yield the bis-dithioketal XXXVI in practically quantitative yield, The 5α-configuration in this compound was ascertained by hydrogenolysis over Raney Ni to 5α-cholestane. When submitted to the same reaction conditions the 1,4-diketone XXXI yielded mainly the 5β mono-dithioketal XXXVII (84%). The behaviour of XXXI is in contrast with that of 5β-cholestan-4-one (XXXIX) which leads to a dithioketal in the 5α series[2a].



Compound XXXVII was characterized by desulfurization with Raney Ni to 5β-cholestan-1-one (XXIII). The derivatization of the 1-CO in XXXVII with ethanedithiol and boron trifluoride proceeded at a much slower rate to yield again, as it has been already observed in the withanolide series,[1a,e] a bisdithioketal identical with XXXVI, i.e., in the 5α-series. When compound XXXVII was treated, however, with boron trifluoride only, no epimerization occured, the 1-CO stabilising the *cis* A/B system. The formation of the same 5α-4-dithioketal from both 5α and 5β-cholestan-4-one (XXXVIII and XXXIX) is explained[2a] by a common intermediate; it is noteworthy that boron trifluoride alone does not epimerize the 5β-4-one.

In the conversion of XXXVII to XXXVI, the epimerization at C-5 takes place, however, with a compound in which the dithioketal ring is already closed. To rationalise these results, it may be assumed that the reaction proceeds in two steps: (a) thioketalization of the 1-carbonyl, i.e. a change in the hydridization of C-1 from sp^2 to sp^3; (b)



opening and reclosing of the 4-dithioketal in the presence of boron trifluoride, leading to a 5α derivative (XXXVI), now favoured since C-1 is sp^3 hybridized. In order to check such an assumption, a 5β-4-dithioketal with an sp^3 hybridized C-1 was required. Since such a compound could not be prepared by the direct thioketalization of a 5β-4-ketosteroid,[2a] it has been obtained by stereoselective reduction with sodium borohydride of the CO function in XXXVII and subsequent acetylation (XLb). The α orientation assigned to the C-1 OAc in the latter is based on the NMR signal of the adjacent proton (multiplet, δ 4·58). The stereochemistry at C-5 was the same as in the starting ketone XXXVII, as shown by desulfurization with Raney Ni, yielding 1α-acetoxy-5β-cholestane (XXIIb). Upon treatment with boron trifluoride, overnight at room temperature, XLb was quantitatively epimerised at C-5 yielding a compound identical with XLIb, obtained in turn by treatment of 1α-hydroxy-5α-cholestan-4-one (XVIa) with ethanedithiol, and subsequent acetylation. The configurational change of the 1α-acetoxy substituent (XLb→XLIb) was clearly illustrated by the signal of the adjacent proton in each of these compounds: broad multiplet in the former (δ 4·58) and narrow triplet in the latter (δ 4·41). These experiments substantiate the increased stability of the *cis* A/B system in presence of a 1-CO. In this connection it seemed interesting to find out whether a 1-keto-4-dithioketal in the *trans* A/B series would be epimerized at C-5 in presence of an acidic reagent. Such a compound XLII has been prepared by oxidation with chromium trioxide-pyridine complex[27] of the C-1 OH in XLIa. The 5α-stereochemistry of XLII was proven by the positive solvent shift ($\Delta^{CDCl_3}_{C_6H_6}$ + 2·0 Hz) of the C-10 Me,* as well as by desulfurization to the known[28] 5α-cholestan-1-one (XLIII). Exposure of XLII to various reagents (boron trifluoride, toluene-*p*-sulphonic acid, acid alumina) failed, however, to bring about any inversion at C-5.

The reactions describing the behaviour of the 1,4-diones and the corresponding enediones lead to the conclusion that there is a tremendous increase in the relative stability of the A/B *cis* as compared to the *trans* junction in such systems. These results show that a CO group at C-1 renders the *cis* A/B rings system more stable than the *trans*. A directing effect of a 1-keto group has been also observed[33] in the reduction of a 5,6-double bond, leading predominantly to a *cis* A/B system. The increased stability of the *cis* A/B system in the related steroidal 1,6-diones series has been explained by Jones *et al.*[34] by a decrease of the non bonded repulsive interactions which exist in the 5α series between the 1-CO and the α hydrogen at C-11. The non-bonded repulsion between the 1-keto group and the 11α-hydrogen in the 5α-series seems more likely than the intramolecular hydrogen bridge between the same atoms, which was proposed in order to explain the stability of the keto form of 5α-cholestan-1,3-dione.[35] A recent alternative explanation for the impediment of enolization of the above 1,3-dione is that it may be due to a long-range effect of the side chain.[36]

EXPERIMENTAL

M.ps were determined with a Fisher–Johns apparatus and are uncorrected. Optical rotations were recorded with an automatic Perkin–Elmer 141 polarimeter and refer to $CHCl_3$ solns. Spectra were recorded on a Cary 14 spectrophotometer with EtOH solns (UV), a Perkin–Elmer Infracord 137 with $CHCl_3$ solns (IR) and a Varian A-60 spectrometer with $CDCl_3$ solns (NMR). The ORD measurements were done on a

* The contribution of the 1-CO to the solvent shift of the C-10 Me in XLII has been obtained by subtraction of the solvent shift of 5α-cholestan-4-dithioketal[32] ($\Delta^{CDCl_3}_{C_6H_6}$ −9·0 Hz) from that of XLII. This contribution is therefore + 11·0 Hz, in acceptable agreement with the value measured directly on 5α-cholestan-1-one (+15·0 Hz).

Jasco model ORD/UV-5 instrument. Microanalyses were carried out in the microanalytical laboratory of our Institute under the direction of Mr. R. Heller. Molr Wts were determined with an Atlas CH4 mass spectrometer. TLC was done on chromatoplates of silicagel G (Merck) and spots were developed with I_2 vapour. For the chromatography, neutral Woelm alumina activity III was used, unless otherwise specified.

1α-*Acetoxy*-5α-*cholest*-2-*en*-4-*one* (XVb). To a soln of XIVb[17] (2·0 g) in AcOH (30 ml) and Ac_2O (15 ml), anhyd sodium chromate (3·0 g) was added and the resulting soln was allowed to stand overnight at 50°. Water was then added and the product extracted with ether, washed with water and $NaHCO_3$aq, dried over Na_2SO_4, and evaporated under reduced press to an oil which was chromatographed on alumina. Elution with hexane–ether (9·5:0·5) gave some unreacted starting material (110 mg), followed by a white crystalline product (600 mg, 33%), recrystallized from MeOH, m.p. 89–90°; $[\alpha]_D$ +178° (*c* 1·0); ν_{max} 1730 and 1683 cm^{-1}; λ_{max} 213 nm (ε 9900); NMR: δ 6·87 (2-H, d. d., J = 10·0 and 5·5 Hz), 6·05 (3-H, d., J = 10·0 Hz), 5·15 (1-H, d., J = 5·5 Hz), 2·10 (1α-OAc, s.), 0·90 (19-H, s.) and 0·66 (18-H, s.) (Found: C. 78·92; H, 10·34; M^+ 442; $C_{29}H_{46}O_3$ requires: C, 78·68; H, 10·47%; M. wt. 442·6).

1α-*Acetoxy*-5α-*cholestan*-4-*one* (XVIb). Compound XVb (500 mg) in EtOH (55 ml) was hydrogenated at room temp and atmic press over 10% Pd-C. When the H_2 uptake ceased, the soln was filtered, the solvent removed and the product recrystallized from MeOH (450 mg, 89%), m.p. 93–95°; $[\alpha]_D$ +52·5° (*c* 0·6), ν_{max} 1727 (shoulder) and 1706 cm^{-1}; NMR: δ 5·07 (1-H, narrow tr), 2·16 (1α-OAc, s), 0·91 (19-H, s) and 0·64 (18-H, s). (Found: C, 78·21; H, 10·95; M^+ 444; $C_{29}H_{48}O_3$ requires: C, 78·32; H, 10·88%; M. wt. 444·6).

1α-*Hydroxy*-5α-*cholestan*-4-*one* (XVIa). To a soln of XVIb (500 mg) in MeOH (60 ml), a 2% methanolic KOH (60 ml) was added; after ~16 hr at room temp, the soln was neutralized with dil HCl and most of the solvent removed. Water was added, the ppt filtered off, washed with water and recrystallized from MeOH (430 mg, 95%). Two recrystallizations from the same solvent afforded the analytical sample, m.p. 188–190°; $[\alpha]_D$ +45° (*c* 1·0); ν_{max} 1700 cm^{-1}; NMR: δ 3·90 (1-H, narrow tr.), 0·91 (19-H, s) and 0·66 (18-H, s). (Found: C, 80·24; H, 11·39; M^+ 402; $C_{27}H_{46}O_2$: C, 80·54; H, 11·52%; M. wt. 402·6).

5α-*Cholestan*-1,4-*dione* (XVII). A soln of XVIa (1·0 g) in acetone (170 ml) was treated with Jones reagent[19] for 20 min at 10°. The excess of oxidizing reagent was destroyed with MeOH and most of the solvent removed under reduced press. The product was extracted with ether, washed with water, dried over Na_2SO_4 and the solvent removed. Crystallization from MeOH yielded XVII (930 mg, 93%), M.p. 131–132°; $[\alpha]_D$ +43° (*c* 1·0); ν_{max} 1703 cm^{-1}; NMR: δ 1·09 (19-H, s) and 0·66 (18-H, s). (Found: C, 80·68; H, 10·96; M^+ 400; $C_{27}H_{44}O_2$ requires: C, 80·94; H, 11·07%; M. wt. 400·6).

1α-*Hydroxy*-5α-*cholest*-2-*en*-4-*one* (XVa). To a methanolic soln (60 ml) of XVb (250 mg), 5% methanolic $KHCO_3$ (60 ml) was added and the mixture left overnight at room temp. Following neutralization with dil HCl most of the solvent was removed and the product extracted with ether, washed with water, dried and evaporated to dryness. The residue was chromatographed on alumina; elution with hexane–ether 6:4 gave XVa (137 mg 60%), recrystallized from MeOH, m.p. 198–200°; $[\alpha]_D$ +87° (*c* 1·0); ν_{max} 1675 cm^{-1}; λ_{max} 215 nm (ε 7800); NMR: δ 6·85 (2-H, d.d., J = 10·0 and 5·5 Hz), 5·96 (3-H, d., J = 10·0 Hz), 4·07 (1-H, d., J = 5·5 Hz), 0·91 (19-H, s) and 0·67 (18-H, s). (Found: C, 80·72; H, 11·13; M^+ 400; $C_{27}H_{44}O_2$ requires: C, 80·94; H, 11·07%; M. wt. 400·6).

5α-*Cholest*-2-*en*-1,4-*dione* (XVIII). A solution of XVa (250 mg) in acetone (25 ml) was treated with Jones reagent[19] for 10 min at 10°. Following the usual work-up, the product (237 mg, 95%) which showed one spot on TLC, was recrystallized 3 times from MeOH to yield long, yellowish needles, m.p. 109–109·5°; $[\alpha]_D$ +15·5° (*c* 0·92); ν_{max} 1677 cm^{-1}; λ_{max} 226 (ε 10,700); NMR: δ 6·62 (2-H and 3-H, s), 1·18 (19-H, s) and 0·68 (18-H, s). (Found: C, 81·49; H, 10·76; M^+ 398; $C_{27}H_{42}O_2$ requires: C, 81·35; H, 10·68% M. wt. 398·6).

Preparation of cholesta-1,4,6-*trien*-3-*one*. This compound[37] can be prepared by dehydrogenation with DDQ of cholesta-4,6-dien-3-one, cholest-5-en-3-one or directly from cholesterol.[38] Cholesta-4,6-dien-3-one was prepared in our experiment by the dehydrobromination ($CaCO_3$-dimethyl acetamide)[39] of 6β-bromocholest-4-en-3-one. In a typical run 6β-bromocholest-4-en-3-one[40] (8·0 g) was added in small portions to a boiling suspension of $CaCO_3$ powder (6·4 g) in N,N-dimethylacetamide (80 ml) and the mixture was heated to reflux with stirring for 15 min. After cooling ether was added, the soln was filtered, washed with dil HCl and water, dried and evaporated under reduced press leaving a yellow oil, homogeneous on TLC; yield from 6·0 to 6·3 g (90–95%). The crude cholesta-4,6-dien-3-one thereby obtained was suitable for dehydrogenation with DDQ. The product was crystallized from methanol and compared with an authentic sample.[41]

1α,2α-*Epoxy*-*cholesta*-4,6-*dien*-3-*one* (XIX). A soln of cholesta-1,4,6-trien-3-one (1·0 g) in MeOH (35 ml) was treated with 10% methanolic NaOH (0·25 ml) and 30% H_2O_2 (1·6 ml) and left overnight at room

temp. The resulting crystalline epoxide was filtered off, washed with cold MeOH and dried (745 mg, 72%). This product was used as such for the subsequent reactions. An analytical sample was prepared by recrystallization from MeOH, m.p. 108–110°; $[\alpha]_D$ +195° (*c* 1·05); ν_{max} 1663 cm^{-1}; NMR: δ 6·05 (6-H and 7-H, s), 5·60 (4-H, d, J = 2 Hz), 3·57 (1-H, d, J = 4 Hz), 3·41 (2-H, d.d., J = 4 and 2 Hz), 1·17 (19-H, s) and 0·90 (18-H, s). (Found: C, 81·58; H, 9·97; M^+ 396; $C_{27}H_{40}O_2$ requires: C, 81·76; H, 10·17%; M. wt. 396·5).

1α-*Hydroxy*-5β-*cholestan*-3-*one* (XXa). Compound XIX (250 mg) dissolved in THF (8 ml) and EtOH (4 ml) was hydrogenated over 5% Pd–$CaCO_3$ (120 mg)[22a] until absorption ceased. The solvent was removed and the residue chromatographed on alumina; elution with hexane–ether 8:2 yielded XXa (165 mg, 65%), which was recrystallized from hexane, m.p. 114–115°; $[\alpha]_D$ +7° (*c* 1·0); ν_{max} 1709 cm^{-1}; NMR: δ 3·61 (1-H, tr, J = 8·0 Hz), 1·20 (19-H, s) and 0·68 (18-H, s). (Found: C, 80·33; H, 11·20; M^+ 402; $C_{27}H_{46}O_2$ requires: C, 80·54; H, 11·52%; M. wt. 402·6).

5β-*Cholest*-1-*en*-3-*one* (XXI). A soln of XXa (2·0 g) and toluene-*p*-sulphonic acid (120 mg) in benzene (50 ml) was heated to reflux for 2 hr with continuous removal of water. The benzene soln was washed with $NaHCO_3$ aq and water then dried and the solvent evaporated. The crude product, homogeneous on TLC, was passed over alumina (1·89 g, 97%) and recrystallized from MeOH, m.p. 105–106°; $[\alpha]_D$ +129·5° (*c* 1·0) (lit.: m.p. 105·5–106·5°; $[\alpha]_D$ +107·6° [26d]; m.p. 107–108°; $[\alpha]_D$ +135·9° [26b]).

5β-*Cholestan*-1α-*ol* (XXIIa). A methanolic (100 ml) soln of XXa (1·0 g) and of tosyl-hydrazine (750 mg) was left overnight at room temp; $NaBH_4$ (2·0 g) was then added and the reaction mixture heated to reflux for 8 hr and left again overnight at room temp. The resulting colourless soln was concentrated to a small volume, water was added and the product extracted with ether; the ethereal layer was washed with $NaHCO_3$ aq and water, dried and evaporated in vacuum to an oily residue. Chromatography on alumina (elution with hexane–ether 9·8:0·2) gave a colourless oil (475 mg; 49%), which could not be induced to crystallize; NMR: δ 3·28 (1-H, m), 1·12 (19-H, s) and 0·64 (18-H, s). The *acetate* (XXIIb) was obtained by acetylation with Ac_2O and pyridine, overnight at room temp. Chromatography of the crude product on alumina (elution with hexane–ether 9·5:0·5) gave in 87% yield a colourless oil, which could not be induced to crystallize; ν_{max} 1721 and 1250 cm^{-1}; NMR: δ 4·57 (1-H, m), 2·03 (1α-OAc, s), 1·0 (19-H, s) and 0·65 (18-H, s).

5β-*Cholestan*-1-*one* (XXIII). An acetone (20 ml) soln of XXIIa (250 mg) was treated with Jones reagent[19] for 20 min at 10°. Following the usual work-up the product (227 mg, 91%) was recrystallized from MeOH, m.p. 101–102°, $[\alpha]_D$ −73·5° (*c* 1·0); ORD (*c*, 0·133; trifluoroacetic acid), 21°; $[\phi]_{400}$ −1010; $[\phi]_{310}$ −7550; $[\phi]_{292}$ 0; $[\phi]_{273}$ +6960; $[\phi]_{230}$ +3050; ν_{max} 1683 cm^{-1}; NMR: δ 1·13 (19-H, s) and 0·63 (18-H, s). (Found: C, 83·76; H, 11·89; M^+ 386; $C_{27}H_{46}O$ requires: C, 83·87; H, 11·99%; M. wt. 386·6).

1β,2β-*Epoxy*-5β-*cholestan*-3-*one* (XXIV). A soln of XXI (1·0 g) in MeOH (250 ml) was treated with 10% methanolic NaOH (1·3 ml) and 30% H_2O_2 (4·4 ml), then left overnight at room temp, diluted with water (70 ml) and left again overnight at ~−5°. The crystalline ppt was filtered off, washed with cold MeOH and dried (640 mg, 61%); it was found to be homogeneous on TLC. An analytical sample from MeOH had m.p. 107–109°; $[\alpha]_D$ −11° (*c* 1·0); ν_{max} 1712 cm^{-1}; NMR: δ 3·47 (1-H, d., J = 4·0 Hz), 3·30 (2-H, d, J = 4·0 Hz), 1·30 (19-H, s) and 0·67 (18-H, s). (Found: C, 81·27; H, 10·87; M^+ 400; $C_{27}H_{44}O_2$ requires: C, 80·94; H, 11·07%; M. wt. 400·6).

1β-*Hydroxy*-5β-*cholestan*-3-*one* (XXV). A soln of XXIV (200 mg) in THF (5 ml) and EtOH (10 ml) was overnight hydrogenated over 5% Pd–$CaCO_3$ (100 mg)[22a]. Following the usual work-up the residue was chromatographed on silicagel (Merck); elution with hexane–ether 9:1 give unreacted XXIV (50 mg), followed by XXI (35 mg); further elution with hexane–ether 4:6 gave pure XXV (52 mg) recrystallized from MeOH, m.p. 159–160°; $[\alpha]_D$ +32·5° (*c* 1·0); ν_{max} 1709 cm^{-1}; NMR: δ 4·18 (1-H, narrow tr), 1·15 (19-H, s) and 0·68 (18-H, s). (Found: C, 80·50; H, 11·40; M^+ 402; $C_{27}H_{46}O_2$ requires: C, 80·54; H, 11·52%; M. wt. 402·6). When the chromatography was attempted on alumina, only unreacted XXIV (50 mg) and the enone XXI (120 mg) were obtained.

1β-*Hydroxy*-5β-*cholest*-2-*ene* (XXVIa). A mixture of XXIV (250 mg) hydrazine sulphate (500 mg) and 100% hydrazine hydrate (1·5 ml) was stirred under reflux for 20 min. The reaction mixture was cooled, diluted with water (10 ml) and extracted with ether. After evaporation of the solvent, the residue was chromatographed on alumina; elution with hexane–ether 9:1 gave XXVIa (166 mg, 68%), which crystallized by trituration with MeOH, m.p. 98–99°; $[\alpha]_D$ −52° (*c* 1·0); NMR: δ 5·88 (2-H and 3-H, narrow m.), 3·87 (1-H, m), 1·10 (19-H, s) and 0·66 (18-H, s). (Found: C, 84·02; H, 11·80; M^+ 386; $C_{27}H_{46}O$ requires: C, 83·87; H, 11·99%; M. wt. 386·6). The *acetate* (XXVIb) was obtained by the usual method in 82% yield, it crystallized from MeOH, m.p. 110–112°; $[\alpha]_D$ −154·5° (*c* 1·0); ν_{max} 1715 cm^{-1}; NMR: δ5·85 (2-

H and 3-H, narrow m.), 5·16 (1-H, m), 2·01 (1β-OAc, s), 0·99 (19-H, s) and 0·65 (18-H, s). (Found: C, 81·13; H, 11·31; M^+ 428; $C_{29}H_{48}O_2$ requires: C, 81·25; H, 11·29% M. wt. 428·6).

5β-Cholestan-1β-ol (XXVIIa). Compound XXVIa (200 mg) in cyclohexane (15 ml) was hydrogenated over 10% Pd–C (150 mg). When the H_2 absorption ceased, the catalyst was filtered off and the solvent was removed leaving a colourless oil (150 mg, 74%) homogeneous on TLC, which could not be induced to crystallize; NMR: δ 3·80 (1-H, narrow tr), 1·05 (19-H, s), and 0·65 (18-H, s). The *acetate* (XXVIIb) was obtained in 79% yield by acetylation of XXVIIa for 48 hr at room temp with Ac_2O in pyridine; recrystallized from MeOH, m.p. 100–101°; $[\alpha]_D$ −11·0° (*c* 1·0), ν_{max} 1706 and 1250 cm^{-1}; NMR: δ 5·05 (1-H, Narrow tr), 2·05 (1β-OAc, s), 0·94 (19-H, s) and 0·65 (18-H, s). (Found: C, 80·90; H, 11·50; M^+ 430; $C_{29}H_{50}O_2$ requires: C, 80·87; H, 11·70%; M. wt. 430·6).

5β-Cholest-2-en-1-one (XXVIII). To an ice cold slurry of CrO_3 (150 mg) in pyridine (3 ml), a soln of XXVIa (100 mg) in pyridine (4 ml) was added and stirred for 30 min in the ice bath, then overnight at room temp. Water was added, the product extracted with ether, washed with dil HCl and with water until neutral, then dried. The solvent was removed and the slightly yellowish residue chromatographed on alumina, elution with hexane–ether 9·5:0·5 gave pure XXVIII (81 mg, 82%), recrystallized from MeOH, m.p. 99·100°; $[\alpha]_D$ −39·5° (*c* 1·0); ν_{max} 1661 cm^{-1}; λ_{max} 223 nm (ε 8200); NMR: δ 6·87 (3-H, d.q., $J_{2\text{-}3}$ = 10 Hz), 5·94 (2-H, narrow d.q., $J_{2\text{-}3}$ = 10 Hz), 1·18 (19-H, s) and 0·65 (18-H, s). (Found: C, 83·78; H, 11·49; M^+ 384; $C_{27}H_{44}O$ requires: C, 84·31; H, 11·53%; M. wt. 384·6).

Catalytic hydrogenation of 5β-cholest-2-en-1-one (XXVIII). Compound XXVIII (50 mg) in cyclohexane (25 ml) was hydrogenated over 5% Pd–C (50 mg). When the H_2 absorption ceased, the solvent was removed leaving a colourless oil (48 mg, 96%), homogeneous on TLC, which recrystallized from MeOH; it was found identical with XXIII.

1β-Acetoxy-5β-cholest-2-en-4-one (XXIX). The oxidation of XXVIb (500 mg) in AcOH (30 ml) and Ac_2O (15 ml) with anhyd sodium chromate (1·0 g) was performed as described for XIVb→XVb. The crude product was chromatographed on silicagel (Merck); elution with hexane–ether 9:1 gave crystalline XXIX (200 mg, 30%), recrystallized from MeOH, m.p. 97–98°; $[\alpha]_D$ −140° (*c* 1·0); ν_{max} 1736, 1672 and 1250 cm−1; λ_{max} 220 nm (ε 9800), NMR: δ 6·90 (2-H, d.d., J = 10·0 and 6·0 Hz), 6·11 (3-H, d., J = 10·0 Hz), 5·36 (1-H, d., J = 6·0 Hz), 2·07 (1β-OAc, s) 1·15 (19-H, s) and 0·66 (18-H, s). (Found: C, 78·89; H, 10·65; M^+ 442; $C_{29}H_{46}O_3$ requires: C, 78·68; H, 10·47%; M. wt. 442·6). When the chromatography of the crude product was attempted on alumina, a mixture of C_5-epimers was obtained.

5β-Cholestan-1β,4α-diol (XXXa). A soln of XXIX (100 mg) in dry THF (10 ml) was added dropwise to a stirred slurry of LAH (120 mg) in dry THF (10 ml), and heated to reflux for 2·5 hr. The work up was done with EtOAc and a sat Na_2SO_4 aq. Following filtration and evaporation of the solvent, the residue was dissolved in $CHCl_3$, dried and the solvent removed. Chromatography on alumina (elution with hexane–ether 7·5:2·5) gave XXXa (69 mg; 75%), which crystallized by trituration with MeOH, m.p. 158–159°; $[\alpha]_D$ +14·5° (*c* 0·6); NMR: δ 3·96 (1-H and 4-H, narrow signal, $W_{\frac{1}{2}}$ 5·5 Hz), 1·20 (19-H, s) and 0·64 (18-H, s). (Found: C, 80·16; H, 11·70; $C_{27}H_{48}O_2$ requires: C, 80·14; H, 11·96%). The *diacetate* (XXXb) was prepared by the usual method in 70% yield and recrystallized from MeOH, m.p. 103–105°; $[\alpha]_D$ −8° (*c* 1·0); ν_{max} 1715, 1692 and 1250 cm^{-1}; NMR: δ 5·21 (1-H and 4-H, two overlapping narrow tr), 2·12 (1β-OAc and 4α-OAc, s), 1·10 (19-H, s) and 0·64 (18-H, s). (Found: M^+ 488; $C_{31}H_{52}O_4$ requires: M. wt. 488·7).

5β-Cholestan-1,4-dione (XXXI). The diol XXXa (100 mg) in acetone (30 ml) soln was treated with Jones reagent[19] for 20 min at 10°. Following the usual work-up the dione XXXI was obtained and recrystallized from MeOH (75 mg, 76%). A second recrystallization afforded an analytical sample, m.p. 124–125°; $[\alpha]_D$ −23° (*c* 1·0; ν_{max} 1706 cm^{-1}; NMR: δ 1·25 (19-H, s) and 0·65 (18-H, s). (Found: C, 80·82; H, 11·10; M^+ 400; $C_{27}H_{44}O_2$ requires: C, 80·94; H, 11·07%; M. wt. 400·6).

1α-Hydroxy-5α-cholestan-3-one (XXXII). 1α,2α-Epoxy-5α-cholestan-3-one[28] (250 mg) in THF (8 ml) and EtOH (4 ml) was overnight hydrogenated over 5% Pd–$CaCO_3$ (125 mg)[22b]. The crude product (245 mg, 97%), homogeneous on TLC, recrystallized from MeOH, m.p. 173–175° (dec); $[\alpha]_D$ +43° (*c* 1·0); ν_{max} 1712 cm^{-1}; NMR: δ 4·15 (1-H, narrow tr.), 0·98 (19-H) and 0·68 (18-H, s). (Found: C, 80·61; H, 11·63; M^+ 402; $C_{27}H_{46}O_2$ requires: C, 80·54; H, 11·52%; M. wt. 402·6).

5α-Cholest-1-en-3-one-tosyl hydrazone (XXXIII). The reaction was done with XXXII (100 mg) and tosyl-hydrazine (75 mg) in MeOH (15 ml) as described for XXIIa. Following the work up the crude product (97 mg, 71%), homogeneous on TLC, was recrystallized from MeOH; it was found identical with an authentic sample prepared by the reaction of 5α-cholest-1-en-3-one with tosyl hydrazine[23b]; NMR: δ 7·87 (d., J = 8·0 Hz) and 7·29 (d., J = 8·0 Hz) (4 aromatic protons), 6·42 (1-H, d., J = 10·0 Hz), 5·95 (2-H, d., J = 10·0 Hz), 2·40 (aromatic Me, s), 0·89 (19-H, s) and 0·66 (18-H, s).

Equilibration experiments

(a) To a methanolic soln (15 ml) of XVII (50 mg), 1·5% ethanolic KOH (7·5 ml) was added and the soln was allowed to stand overnight at room temp. After neutralization with dil HCl the product was extracted with ether. After removal of the solvent a mixture of the two epimeric diketones (XVII and XXXI) was obtained; NMR: δ 1·25 (19-H in XXXI, s, stronger signal) and 1·09 (19-H in XVII, s, weaker signal). The integrated areas of these signals indicated a 3:7 ratio of XVII:XXXI.

(b) Compounds XVII and XXXI (50 mg each) were separately stored over-night on an alumina column (20 g) in benzene. Similar mixtures of XVII and XXXI were obtained from each column, in the same ratio as above (according to NMR data).

(c) *Preparation of 5β-cholest-2-en-1,4-dione* (XXXIV). Compound XVIII (50 mg) was stored overnight on alumina as described above. Elution with $CHCl_3$ gave a yellow crystalline product (47 mg); NMR: δ 1·31 (19-H for the 5β-epimer, the signal at δ 1·18 for the 19-H in the starting material has almost completely disappeared), δ 6·66 (s. for the C-2 and C-3 vinylic protons in the 5β-enedione XXXIV; the corresponding signal in the 5α-enedione XVIII appeared at 6·62). The ratio of the integrated areas is 95:5 (XXXIV:XVIII); three recrystallizations from MeOH afforded the pure XXXIV as yellow crystals, m.p. 103–105°; $[\alpha]_D$ +59° (*c* 1·0); ν_{max} 1677 cm^{-1}; λ_{max} 227 nm (ε 10,000); NMR: δ 6·66 (2-H and 3-H, s), 1·31 (19-H, s) and 0·65 (18-H, s). (Found: C, 81·46; H, 10·55; M^+ 398; $C_{27}H_{42}O_2$ requires: C, 81·35; H, 10·62%; M. wt. 398·6).

Alternative procedure for the preparation of the enediones XVIII *and* XXXIV. Compound XXXV[21, 28] (300 mg) was oxidized with anhyd sodium chromate (400 mg) in AcOH (9 ml) and Ac_2O (4·5 ml) as described above for XVb. A mixture of unreacted starting material and XVIII was obtained (NMR and TLC evidence). The product was chromatographed on alumina; elution with hexane gave unreacted enone (70 mg); further elution with hexane–ether (9·8:0·2) yielded XXXIV (70 mg, 23%), (epimerization of the 5α-isomer occurred on the column).

5α-Cholestan-1,4-dione-bisethylene-dithioketal (XXXVI). To a suspension of XVII (500 mg) in ethanedithiol (2 ml), BF_3 etherate (1 ml) was added. The diketone dissolved and the bisdithioketal precipitated in less than 1 min. After 30 min at room temp $CHCl_3$ was added, the excess reagent removed with dil NaOH aq and water. The crude product was chromatographed on alumina, it emerged with pentane (650 mg, 94%). Three recrystallizations from CH_2Cl_2–MeOH afforded the analytical sample, m.p. 204–205°; $[\alpha]_D$ +20° (*c* 1·0); NMR: δ 3·23 (1- and 4-ethylene dithioketal protons, m), 1·30 (19-H, s) and 0·65 (18-H, s). (Found: C, 67·50; H, 9·59; S, 23·10; M^+ 552; $C_{31}H_{52}S_4$ requires: C, 67·33; H, 9·48; S, 23·19%; M. wt. 552·9). By desulphurization with Raney Ni 5α-cholestane was obtained.

5β-Cholestan-1,4-dione-4-ethylene-dithioketal (XXXVII). The thioketalization reaction was carried out as reported above with XXXI (200 mg) for 15 min at room temp. Chromatography of the crude product on alumina (elution with hexane–ether 9·5:0·5) gave XXXVII (200 mg, 84%), which was recrystallized from acetone–MeOH, m.p. 164–166°; $[\alpha]_D$ −40° (*c* 0·74); ν_{max} 1697 cm^{-1}; NMR: δ 3·35 (4-ethylene dithioketal protons, m.), 1·16 (19-H, s) and 0·63 (18-H, s). (Found: C, 72·50; H, 9·86; S, 13·55; M^+ 476; $C_{29}H_{48}OS_2$ requires: C, 73·07; H, 10·15; S, 13·45%; M. wt. 476·6). When stored overnight in benzene soln in the presence of BF_3, XXXVII remained unchanged.

Raney Ni desulphurization of 5β-cholestan-1,4-dione-4-ethylene-dithioketal (XXXVII). To a soln of XXXVII (50 mg) in EtOH (15 ml), Raney Ni (one teaspoon) was added and the mixture was heated to reflux overnight under stirring. The product was isolated with $CHCl_3$ and filtered through alumina (38 mg, 94%). Recrystallization from MeOH afforded 5β-cholestan-1-one, identical with authentic XXIII.

Thioketalization of 5β-cholestan 1,4-*dione*-4 *ethylene-dithioketal* (XXXVII). Compound XXXVII (100 mg) in the presence of ethanedithiol (1 ml) and BF_3-etherate (1 ml) was allowed to stand at room temp for 70 hr. Following the usual work up, the crude product was chromatographed on alumina (elution with n-pentane) yielding XXXVI (83 mg, 72%) identical with an authentic sample.

1α-Hydroxy-5β-cholestan-4-one ethylene-dithioketal (XLa). To a soln of XXXVII (100 mg) in MeOH (25 ml), $NaBH_4$ (100 mg) was added over a few-min. The soln was stirred for 3 hr at room temp, then neutralized with dil HCl. Isolation with $CHCl_3$ gave a colourless oil (100 mg, quantitative yield), homogeneous on TLC, which could not be induced to crystallize. NMR: δ 3·26 (4-ethylene-dithioketal protons, m, overlapping the signal of the 1-H), 1·18 (19-H, s) and 0·65 (18-H, s). The *acetate* (XLb) obtained as usual in 94% yield, crystallized by trituration with EtOH, m.p. 105–107°; $[\alpha]_D$ +6° (*c* 0·62); ν_{max} 1724 and 1250 cm^{-1}; NMR: δ 4·58 (1-H, m), 3·26 (4-ethylenedithioketal protons, m), 2·03 (1α-OAc, s), 1·06 (19-H, s) and 0·66 (18-H, s). (Found: C, 71·48; H, 10·07; M^+ 520; $C_{31}H_{52}O_2S_2$ requires: C, 71·50; H, 10·07; M. wt. 520·7).

Raney Ni desulphurization of 1α-*acetoxy* 5β-*cholestan-4-one ethylenedithioketal* (XLb). Compound XLb (50 mg) was treated with Raney Ni as described for XXXVII. Chromatography of the crude product on alumina (elution with hexane–ether 9·5:0·5) gave a colourless oil (20 mg, 50%), which was found identical with an authentic sample of XXIIb.

1α-*Hydroxy*-5α-*cholestan-4-one ethylene dithioketal* (XLIa). Compound XVIa (100 mg) was treated with ethanedithiol and BF_3 etherate for 15 min as above. Chromatography on alumina (elution with hexane–ether 9·5 :0·5) afforded XLIa (88 mg, 74%), which recrystallized from MeOH, m.p. 152–153°; $[\alpha]_D$ +10° (*c* 1·0); NMR: δ 3·66 (1-H, narrow tr), 3·18 (4-ethylenedithioketal protons, narrow m), 0·93 (19-H, s) and 0·65 (18-H, s), (Found: C, 72·58; H, 10·31; S, 13·23; M⁺ 478; $C_{29}H_{50}OS_2$ requires: C, 72·76; H, 10·53; S, 13·39%; M. wt. 478·8). The *acetate* (XLIb) was obtained in 68% yield by acetylation for 48 hr with Ac_2O and pyridine at room temp; recrystallized from CH_2Cl_2–MeOH m.p. 133–134°; $[\alpha]_D$ +25·5° (*c* 0·63); ν_{max} 1724 and 1250 cm^{-1}; NMR: δ 4·41 (1-H, narrow tr.), 3·20 (4-ethylene dithioketal protons, narrow m), 2·06 (1-αOAc, s), 0·97 (19-H, s) and 0·62 (18-H, s). (Found: M⁺ 520; $C_{31}H_{52}O_2S_2$ requires: M. wt. 520·7).

Boron trifluoride epimerization of XLb *to* XLIb. Compound XLb (70 mg) in benzene (10 ml) was treated with boron trifluoride etherate (0·5 ml) and allowed to stand overnight at room temperature. The solution was washed with aqueous sodium hydrogen carbonate, and water, then the solvent was removed to yield an oil (64 mg, 91%) homogenous on TLC. Recrystallization from methylene chloride–methanol afforded XLIb identical with an authentic sample.

5α-*Cholestan*-1,4-*dione*-4 *ethylene-dithioketal* (XLII). Compound XLIa (500 mg) was oxidized with CrO_3–pyridine as described for XXVIII. Chromatography on alumina (elution with hexane–ether 9·5:0·5) gave XLII (445 mg, 89%), which was recrystallized from acetone–MeOH, m.p. 137–139°; $[\alpha]_D$ +69·5° (*c* 1·0); ν_{max} 1697 cm^{-1}; NMR: δ 3·25 (4-ethylenedithioketal protons, m), 1·29 (19-H, s) and 0·65 (18-H, s). (Found: C, 73·26; H, 9·91; S, 13·45; M⁺ 476; $C_{29}H_{48}OS_2$ requires: C, 73·07; H, 10·15; S, 13·45%; M. wt. 476·6).

This compound XLII remained unchanged in the following conditions: storage overnight on a column of acid washed alumina (Merck); exposure to BF_3 in benzene soln or heating to reflux during 5 hr in benzene soln, in the presence of toluene-*p*-sulphonic acid.

Raney Ni desulphurization of 5α-*cholestan*-1,4-*dione* 4-*ethylene-dithioketal* (XLII). Compound XLII (100 mg) was treated with Raney Ni as decribed for XXXVII. The product was isolated with $CHCl_3$ (74 mg, 91%), recrystallized from MeOH and found identical with an authentic sample of XLIII.[28]

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