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CONFIGURATION AND REACTIVITY OF TEN-MEMBERED 5,10-SECO-COMPOUNDS OBTAINED BY FRAGMENTATION OF 5-HYDROXY-STEROIDS

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Abstract—Assignment of configuration to the 1,10-double bond in the *cis-trans* isomeric 3β-acetoxy-5,10-seco-1,10-cholesten-5-ones has been achieved by means of NMR spectrometry. Some reactions of these new compounds have been studied and, as expected from conformational analysis, it was found that only the *trans*-isomer readily undergoes transannular cyclizations.

5,10-Seco-steroids, containing a ten-membered ring instead of the two fused cyclohexane rings A and B, were obtained,[4] by applying the lead tetra-acetate oxidation to 5-hydroxy-steroids. Thus, by treating 3β-acetoxycholestan-5α-ol (I) with one molar equivalent of lead tetraacetate in the presence of anhydrous calcium carbonate, fragmentation occurred[5,6] between the C_5-carbinol carbon atom and the adjacent quarternary C_{10}-carbon atom. Besides unchanged starting alcohol (about 30%), compound "B" (yield 15–17%) and compound "M" (yield 27–32%), which, according to analytical data and physical evidence (IR and NMR spectra), are the *cis-trans* isomers of 3β-acetoxy-5,10-seco-1,10-cholesten-5-one (III and IV), were obtained.[7] In some runs small amounts of cholestan-3β-ol acetate and cholesterol acetate were isolated as well (in a total yield not exceeding 6%).[8] Similarly, 3β-acetoxycholestan-5β-ol (II) afforded the 5, 10-seco-compounds "B" and "M" (III and IV) in comparable yields.

In this paper further evidence is presented for the proposed[4] constitution and

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[4] M. Lj. Mihailović, M. Stefanović, Lj. Lorenc and M. Gašić, *Tetrahedron Letters* No. 28, 1867 (1964).

[5] G. Cainelli, B. Kamber, J. Keller, M. Lj. Mihailović, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **44**, 518 (1961); M. Amorosa, L. Caglioti, G. Cainelli, H. Immer, G. Keller, H. Wehrli, M. Lj. Mihailović, K. Schaffner, D. Arigoni and O. Jeger, *Ibid.* **45**, 1674 (1962); see also K. Heusler and J. Kalvoda, *Angew. Chem.* **76**, 518 (1964); *Ibid.* (Intern. English Ed.) **3**, 525 (1964), and Refs therein.

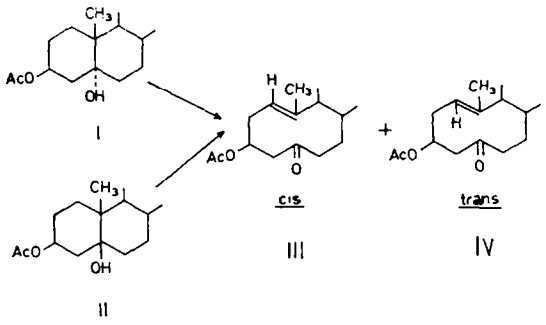
[6] M. Stefanović, M. Gašić, Lj. Lorenc and M. Lj. Mihailović, *Tetrahedron* **20**, 2289 (1964).

[7] M. Akhtar and S. Marsh, *Tetrahedron Letters* No. 36, 2475 (1964), have subsequently reported the preparation of what appears to be the same 5,10-seco-steroids (III and IV) with slightly different physical constants, by light-induced reaction of I with mercuric oxide and iodine. The position of the double bond in their products was not clearly established.

[8] Possible pathways leading to dehydroxylated products of these types[6,9,10] were discussed previously.[6,9]

[9] M. Lj. Mihailović, Z. Maksimović, D. Jeremić, Ž. Čeković, A. Milovanović and Lj. Lorenc, *Tetrahedron* **21**, 1395 (1965).

[10] M. Lj. Mihailović, Ž. Čeković and D. Jeremić, *Tetrahedron* **21**, 2813 (1965).



configurations of the two stereo-isomeric 3β-acetoxy-5,10-seco-1,10-cholesten-5-ones (III and IV), and some reactions of these compounds are described.

RESULTS AND DISCUSSION

Position and configuration of the double bond in isomers "B" and "M"

The double bond in compounds "B" and "M" is located at the 1,10- rather than at the 9,10-position (III and IV) in accordance with the NMR spectra (Figs. 1 and 2), which establish the presence of an olefinic proton in both isomers. The 100 Mc/s spectrum of acetoxy-seco-ketone "M" (Fig. 2) shows a broadened quartet at $\delta = 4{\cdot}81$ (one proton), and a complex multiplet at $\delta = 5{\cdot}35$ (one proton). Double irradiation[11] at the frequency of the C_{19}-methyl group (doublet at $\delta = 1{\cdot}73$; $J_{(1-CH)} \sim 1$ c/s, $J_{(2-CH_2)} \sim 0{\cdot}5$ c/s) removes the allylic coupling to the proton at $\delta = 4{\cdot}81$, causing a sharpening of the latter into a well resolved quartet; accordingly, irradiation of the $\delta = 4{\cdot}81$ signal transforms the $\delta = 1{\cdot}73$ methyl doublet into a sharp singlet. Consequently, the signal at $\delta = 4{\cdot}81$ may be attributed to the olefinic proton at C_1, and the signal at $\delta = 5{\cdot}35$ must hence be due to the C_3–H proton. The 100 Mc/s spectrum of acetoxy-seco-ketone "B" (Fig 1) shows a multiplet at $\delta = 5{\cdot}39$, a broadened quartet at $\delta = 5{\cdot}25$ (partially overlapped with the previous multiplet) and a quartet at $\delta = 3{\cdot}17$ (M part of an AMX spectrum), each signal being due to a single proton. By means of double irradiation it was again possible to attribute the signal at $\delta = 5{\cdot}25$ to the olefinic proton at C_1, and it was also shown that the proton at $\delta = 3{\cdot}17$ (no corresponding signals below 2·6 ppm are observed in the spectrum of compound "M" (Fig. 2)) is only coupled to the C_3–H at $\delta = 5{\cdot}39$, but not to the olefinic proton, and hence it must be one of the two protons at C_4.

Since both spectra with double resonance (Figs. 1 and 2) indicate that the C_{19}-methyl group is coupled with an olefinic proton (the order of allylic coupling being about 1 c/s), it follows, therefore, that the grouping $-\overset{1}{C}H=\overset{10}{C}(-)\overset{19}{C}H_3$ must be present in both isomers "B" and "M" (III) and IV).

In the preceding paper[4] the tentative assignment of configuration to the 1,10-double bond in the acetoxy-seco-ketones "B" and "M" was based on the assumption that the NMR spectrum showing the olefinic proton at a higher field (Fig. 2) should belong to the stereoisomer with the *trans*-substituted double bond (compound "M" = IV). To verify this assumption, we have now studied the NMR spectra

[11] R. Freeman and D. H. Whiffen, *Mol. Phys.* **4**, 321 (1961); L. F. Johnson, *Varian TI Bulletin* Vol. III, No. 3, p. 5 (1964).

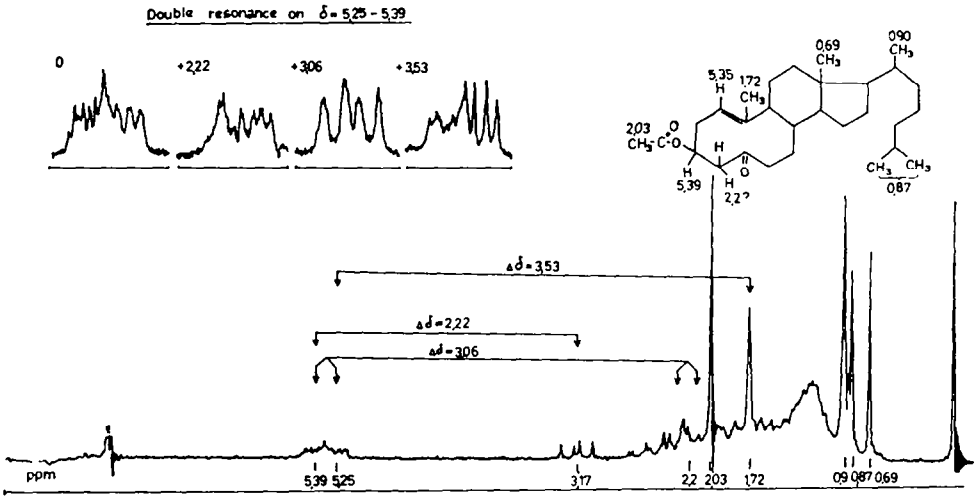


FIG. 1. NMR spectrum (at 100 Mc/s) of *cis*-3β-acetoxy-5,10-seco-1,10-cholesten-5-one (compound "B" = III).

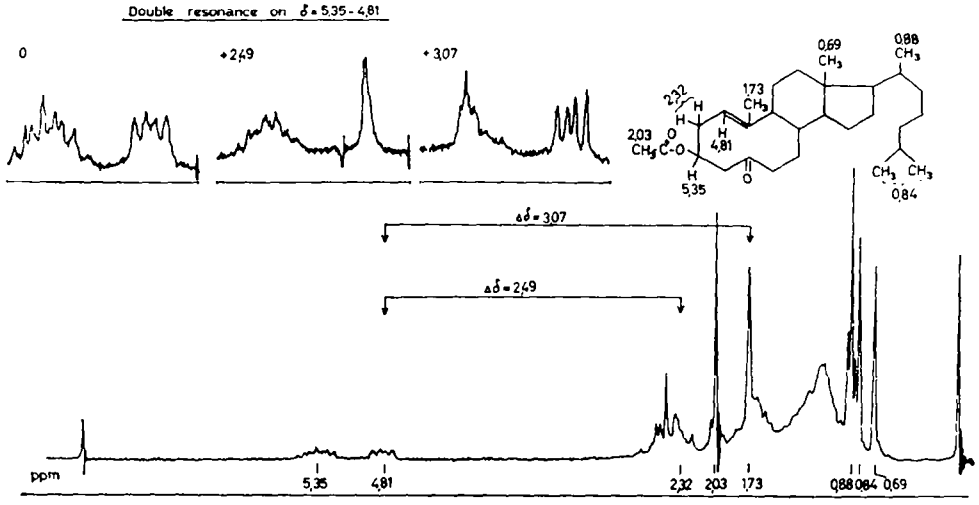


FIG. 2. NMR spectrum (at 100 Mc/s) of *trans*-3β-acetoxy-5,10-seco-1,10-cholesten-5-one (compound "M" = IV).

(Figs 3 and 4) of model compounds, i.e. of the known *cis*- and *trans*-5-cyclodecenones (V and VI).[12]

The 100 Mc/s spectrum (Fig. 4) of *trans*-5-cyclodecenone (VI) shows two olefinic protons in the region of 5·0–5·6 ppm, in the form of overlapping multiplets. Irradiation with a strong RF field at 1·9 ppm gives a well resolved AB system with $J_{AB} = 16$ c/s ($\delta_A = 5{\cdot}36$, $\delta_B = 5{\cdot}13$; $\Delta\delta = 0{\cdot}23$). Contrary to the *trans*-isomer, *cis*-5-cyclodecenone (V) shows two protons (Fig. 3) as a multiplet, centered at 5·35 ppm (XX′

[12] We are indebted to Prof. S. Wharton and Prof. H. Goering, of the University of Wisconsin, Madison, Wisconsin, USA, for generously supplying samples of these unsaturated ten-membered cyclic ketones.

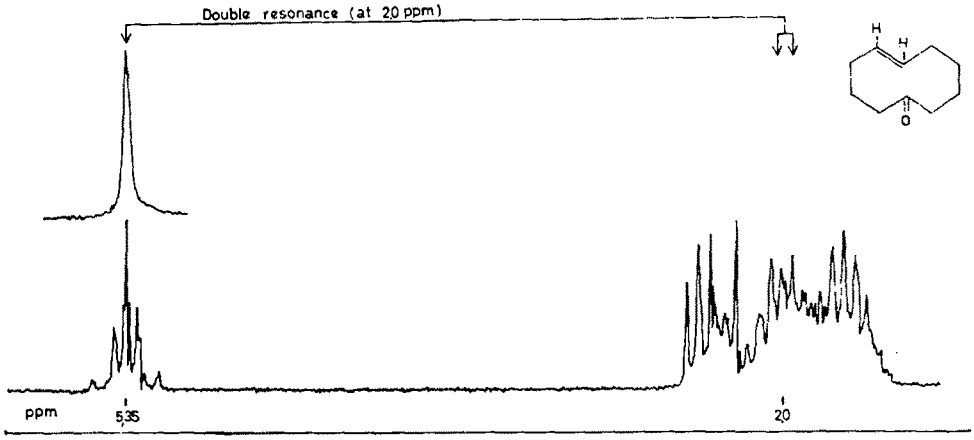


FIG. 3. NMR spectrum (at 100 Mc/s) of *cis*-5-cyclodecenone (V).

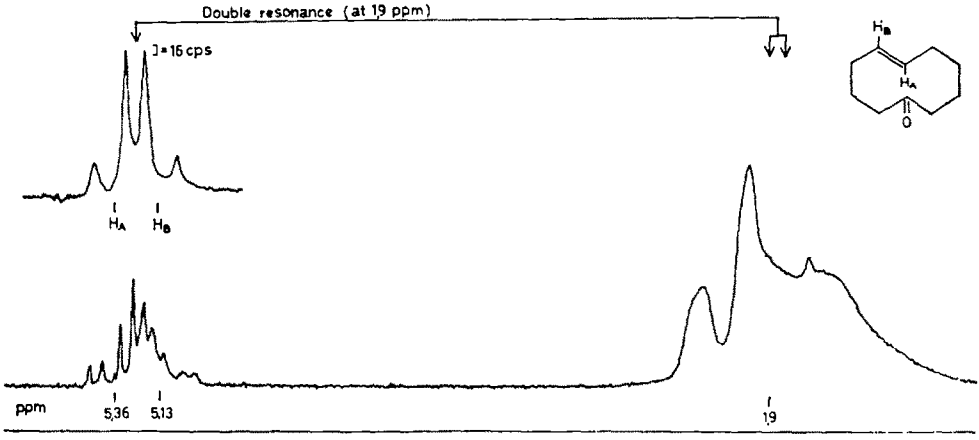


FIG. 4. NMR spectrum (at 100 Mc/s) of *trans*-5-cyclodecenone (VI).

part of an AA'BB'XX' system), which after irradiation at 2·0 ppm collapses to a single peak, thus indicating the equivalency of both olefinic protons.

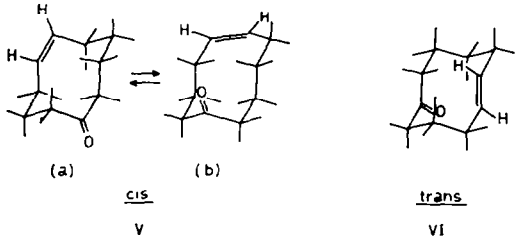
If the conformational concepts developed for compounds of the cyclodecane series[13] are extended to systems containing cyclodecene rings,[14] then, according to Dreiding models, in the stable conformations[15] of *cis*-5-cyclodecenone (Scheme 1,

[13] [a] V. Prelog, *Pure Appl. Chem.* **6**, 545 (1963); J. D. Dunitz and V. Prelog, *Angew. Chem.* **72**, 896 (1960). [b] See also E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis*. Interscience, New York (1965).

[14] The following discussion is based on the assumption that the conformation stabilities of 5-cyclodecenones (Scheme I, V and VI) and fused 5-cyclodecenone rings (Scheme 2, III and IV) are comparable to those of cyclodecane ring compounds,[15] i.e. that both saturated and unsaturated systems show an analogous stereochemical behaviour.

[15] It was established by X-ray analysis of solid derivatives that the cyclodecane ring skeleton has the boat–chair–boat (BCB) conformation;[16] calculations of minimum-energy conformations have also confirmed this result, showing that for cyclodecane the boat–chair–boat conformation is considerably more stable than the chair–chair–chair (CCC) and chair–chair–boat (CCB) conformations.[17]

Va and Vb) both olefinic protons are oriented in such a way as to lie outside of the region in which positive shielding of the carbonyl group could affect them.[18] The *trans*-isomer in its stable conformation (Scheme 1, VI) has also one olefinic proton situated outside of the positive shielding region of the carbonyl group, and this proton should therefore appear at the same field strength as the olefinic protons of the *cis*-ketone (V). Indeed, the lower-field olefinic proton of the *trans*-isomer (Fig. 4) does resonate at the same field strength as the protons of *cis*-5-cyclodecenone (Fig. 3), i.e. at 5·36 ppm. The other resonance signal in the NMR spectrum of *trans*-5-cyclodecenone (Fig. 4), being shifted upfield by 0·23 ppm, must be due to the olefinic proton (at C_5) which lies just above the carbonyl double bond of the keto group, i.e. in the region of positive shielding. It is interesting to note that the chemical shift between the two olefinic protons of *trans*-5-cyclodecenone (VI) does not appreciably change with temperature, being 0·23 ppm at 27° and 0·25 ppm at −40°. This suggests that the relative positions of the carbonyl group and the olefinic double bond in this compound remain practically unchanged during the flipping of the cyclodecene ring from one to another conformation. The presence of a rather slow flipping (of the order of a few cps) is indicated by the broadening of the CH_2 resonances at room temperature and a sharpening of these signals at −40°.



Scheme 1. Possible stable conformations of *cis*-(V) and *trans*-5-cyclodecenone (VI).

According to up to scale models and on the basis of conformational principles established for medium-sized ring compounds,[13–15] the *cis*-isomer of 3β-acetoxy-5,10-seco-1,10-cholesten-5-one (III) would be expected to have two stable conformations (Scheme 2, IIIa and IIIb), the olefinic hydrogen (at C_1) in both conformations being oriented as the corresponding olefinic hydrogen (at C_5) of *cis*-5-cyclodecenone (Scheme 1, V). The *trans*-isomer of the acetoxy-seco-ketone (IV) should exist mainly in conformation IVa (Scheme 2), the other, less stable conformation (IVb) being present, if at all, only to a minor extent; here also the olefinic hydrogen (at C_1) in the stable conformation (IVa) (and in IVb) has a similar orientation as the olefinic hydrogen at C_5 of *trans*-5-cyclodecenone (VI, Scheme 1).

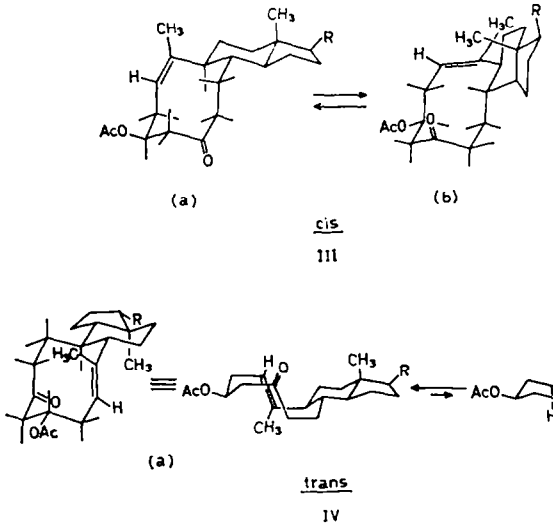
Therefore, since the resonance signal for the olefinic proton at 5·25 ppm in the NMR spectrum of acetoxy-seco-ketone "B" (Fig. 1) appears at the "normal" frequency, i.e. agrees with that observed ($\delta = 5{\cdot}35$) for the olefinic protons of *cis*-5-cyclodecenone (Fig. 3), and since in the NMR spectra of both acetoxy-seco-ketone "M" (Fig. 2) and

[16] E. Huber-Buser and J. D. Dunitz, *Helv. Chim. Acta* **43**, 760 (1960); **44**, 2027 (1961); J. D. Dunitz and K. Venkatesan, *Ibid.* **44**, 2033 (1961); W. Nowacki and M. H. Mladeck, *Chimia* (Switz.) **15**, 531 (1961); E. Huber-Buser, J. D. Dunitz and K. Venkatesan, *Proc. Chem. Soc.* 463 (1961).

[17] J. B. Hendrickson, *J. Amer. Chem. Soc.* **86**, 4854 (1964).

[18] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*. Pergamon Press, Oxford (1959).

trans-5-cyclodecenone (Fig. 4) the corresponding olefinic protons are shifted upfield (δ = 4·81 and 5·13, respectively), it may be concluded that the 1,10-double bond of 3β-acetoxy-5,10-seco-1,10-cholesten-5-one has the *cis*-configuration (III) in isomer "B", and the *trans*-configuration (IV) in isomer "M".[19]



Scheme 2. Possible stable conformations of *cis*-(III) and *trans*-3β-acetoxy-5,10-seco-1,10-cholesten-5-one (IV).

Reactions of isomers "B" (III) *and* "M" (IV)

Both unsaturated *cis*-(III) and *trans*-acetoxy-seco-ketones (IV) are converted, upon mild alkaline hydrolysis, to the corresponding hydroxy-seco-ketones (VII and VIII, respectively), which can, in turn, be reacetylated to the starting products.

In the stable conformation IVa (Scheme 2) and also in conformation IVb, the *trans*-acetoxy-seco-ketone would be expected to undergo readily transannular reactions[13b,21,22] with participation of the C=C double bond, because of the favourable position of the carbonyl group with respect to the olefinic bond. The ground-state stable conformations of the *cis*-isomer (IIIa and IIIb, Scheme 2), however, with the

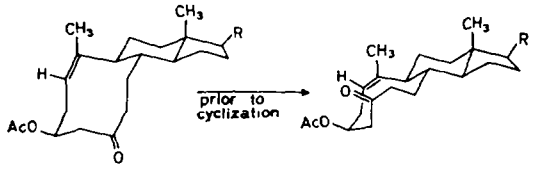
[19] The fact that the formed olefinic double bond in the fragmentation products "B" (III) and "M" (IV) is in position 1,10 rather than in position 9,10, may be interpreted by assuming that scission of the C_5–C_{10} bond in the tertiary alcohols (I and II) occurs with the assistance of the adjacent hydrogen which is in an *antiplanar* orientation with respect to the C_5–C_{10} bond, this being the equatorial hydrogen on C_1. The incipient tertiary (and therefore stable) C_{10}-carbonium ion (arising by an one-electron oxidation of the primarily formed radical[20]) will then eliminate this C_{10}-bridged C_1-hydrogen atom, either before or after changing its geometry, and thus produce both *cis-trans* isomers of 3β-acetoxy-5,10-seco-1,10-cholesten-5-one (III and IV).

[20] See, for example, M. Lj. Mihailović, Ž. Čeković, Z. Maksimović, D. Jeremić, Lj. Lorenc and R. I. Mamuzić, *Tetrahedron* **21**, 2799 (1965).

[21] [a] E. L. Eliel, *Stereochemistry of Carbon Compounds* pp. 260–265. McGraw-Hill, New York (1962); [b] J. Sicher in *Progress in Stereochemistry* (Editors P. B. D. de la Mare and W. Klyne) Vol. 3; pp. 238–250. Butterworths, London (1962).

[22] For transannular reactions in the 5-cyclodecenyl system see, for example, H. L. Goering, W. D. Closson and A. C. Olson, *J. Amer. Chem. Soc.* **83**, 3507 (1961); H. L. Goering and W. D. Closson, *Ibid.* **83**, 3511 (1961), and Refs therein.

carbon-carbon double bond and carbonyl group on opposite parts of the ring, should not favour intramolecular cyclization. In order to undergo transannular reactions the molecule of the *cis*-acetoxy-seco-ketone would first have to change to the less stable, but for cyclization more suitable, conformation (IIIc).

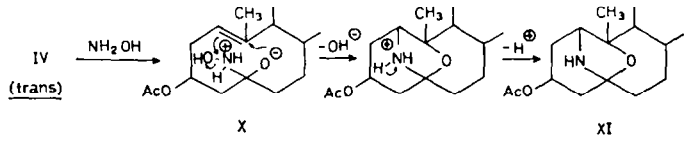


IIIa IIIc

On the basis of this reasoning, therefore, it was expected that the unsaturated *cis*- and *trans*-acetoxy-seco-ketones (III and IV, respectively) would behave differently towards reagents which might effect or participate in reactions involving bond formation across the ten-membered ring, and that the *trans*-isomer (IV) would be far more reactive in these transannular processes than the *cis*-isomer (III). This assumption was confirmed in reactions with hydroxylamine, acids and osmium tetroxide.

Treatment of the *cis*-acetoxy-seco-ketone (III) with hydroxylamine hydrochloride in the presence of pyridine afforded a product, m.p. 158–159°, which, according to analytical data ($C_{29}H_{49}O_3N$) and physical evidence (IR, NMR), is the "normal" oxime (IX). Moreover, the NMR spectrum indicates that the oxime is most probably a mixture of *syn*- and *anti*-isomers. Under similar experimental conditions, the *trans*-acetoxy-seco-ketone (IV) gives a product ("C"), m.p. 141–142°, which is isomeric with the *cis*-oxime (IX) ($C_{29}H_{49}O_3N$) and does not contain a keto-carbonyl group (IR spectrum). Its NMR spectrum in $CDCl_3$, however, indicates (a) that the 19-methyl group is now probably attached to a saturated C_{10}-carbon atom bearing an oxygen ($\overset{19}{C}H_3—\overset{10}{C}(—)—O—$) (singlet at 1·21 ppm);[18] (b) that the signal for the olefinic proton at C_1, which appears in the parent ketone (IV) at 4·81 ppm, is now absent and that the signal at $\delta = 5{\cdot}23$ corresponds to only one proton, this being the proton attached to the C_3-carbon atom; (c) that the characteristic resonance signal for the hydroxyl proton of the oxime grouping (>C=NO—H), in the region between 8 and 10 ppm, is absent; (d) that the quartet appearing at 2·84 ppm corresponds to one proton (X part of an ABXY system) and that it might be attributed to the tertiary hydrogen attached to the C_1-carbon atom bearing an amino group (—NH—C_1(—)—H).[18] Moreover, in the presence of trifluoroacetic acid ($CDCl_3$ + 10% CF_3COOH) the protons at C_1, C_3 and on the 19-methyl group are displaced to lower fields by 0·15–0·25 ppm and another proton at $\delta = 2{\cdot}00$ (probably the *e*-proton at C_4) is displaced by 0·84 ppm, suggesting the presence of a basic amino group.[18] Therefore, it appears that the nitrogen-containing compound "C", obtained from the *trans*-acetoxy-seco-ketone (IV) and hydroxylamine, is not an oxime,[23] but most probably an intramolecular cyclization product containing an amino group. Such a product could have the constitution (XI), resulting from attack of the proximate double bond on the primarily

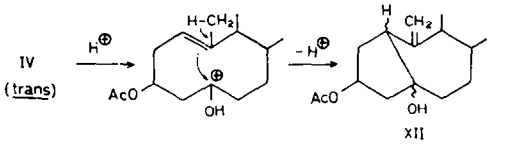
[23] In the preceding paper,[4] because of insufficient evidence, compound "C" was designated as an oxime.



X XI

formed hydroxylammonium ion (X). The "inverse" constitution, with the oxygen attached to C_1 and the nitrogen to C_{10}, is another possibility which might be envisaged.

When the *trans*-acetoxy-seco-ketone (IV) was treated with hydrochloric acid in chloroform solution at 0° or with *p*-toluenesulphonic acid in benzene solution at 40°, two isomeric cyclization products ("D" and "E") were obtained in about 70% yield, their ratio (D:E) being 89:11. According to chemical and physical evidence (which will be described elsewhere), the constitution of these compounds corresponds to formula XII.[24]



XII
(isomers "D" and "E")

If the conformations in the transition states for this acid catalysed process resemble geometrically the ground state conformations of the starting *trans*-acetoxy-seco-ketone (IVa and IVb, Scheme 3; see also Scheme 2), in both stereoisomeric cyclization products (XII, "D" and "E") the bridgehead hydrogen atom and hydroxyl group should be mutually *cis*-oriented (XIIa and XIIb, Scheme 3). Moreover, if the relative energies of the two transition states correspond to the stabilities of the starting ground-state conformations (IVa and IVb), product composition should reflect the relative population of these ground-state conformations (of IV), i.e. the major product ("D") should have the *cis*-1β-H, 5β-OH-configuration (XIIa) and the stereoisomer obtained in low yield ("E") the *cis*-1α-H, 5α-OH-configuration (XIIb).[25]

Under similar experimental conditions (HCl in $CHCl_3$ at 0° or *p*-toluenesulphonic acid in benzene at 40°), the *cis*-acetoxy-seco-ketone (III) did not react and was recovered unchanged; under more drastic conditions, a complex mixture of products was obtained, which could not be satisfactorily separated into well-defined components.[27]

Hydroxylation of the *trans*-acetoxy-seco-ketone (IV) with osmium tetroxide in benzene–pyridine afforded three main products, "F", "G" and "H", in about 6·5, 22 and 32% yield, respectively.

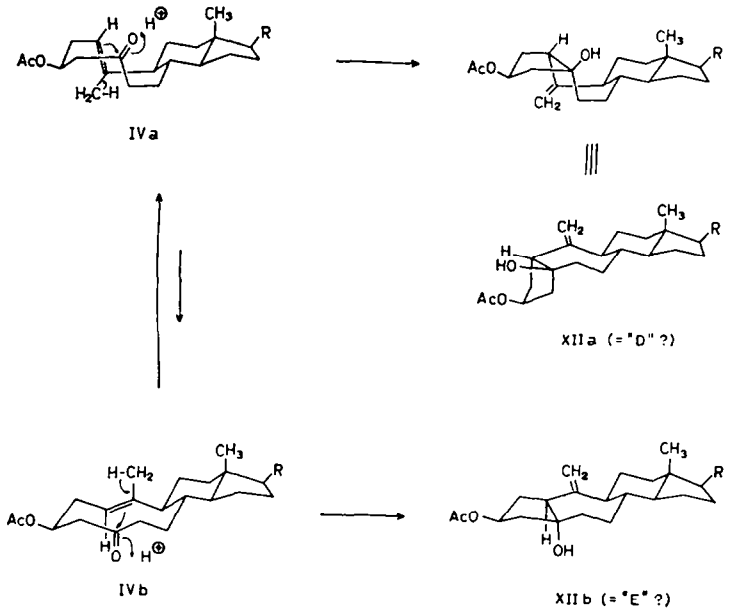
[24] One of these products ("D"), resulting from acid catalysed cyclization of IV, was also described by Akhtar and Marsh.[7]

[25] It is not possible to tell whether in this case the Curtin-Hammett principle[26] is obeyed or not, since the energy barrier between conformations IVa and IVb is not known.

[26] D. Y. Curtin, *Record Chem. Progr.* (*Kresge-Hooker Sci. Lib.*) **15**, 111 (1954), and other papers by this author; see also Ref. 21*a*, pp. 151 and 237.

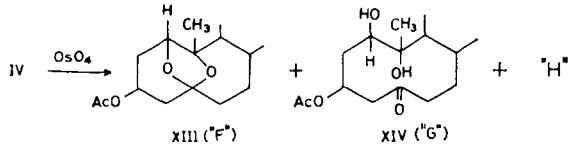
[27] As already pointed out, the *cis*-acetoxy-seco-ketone (III) in its stable conformations (IIIa and IIIb, Scheme 2) would not be expected to undergo facile transannular reactions, because of unfavourable orientations of the reacting centers with respect to one another. However, if the acid-catalysed intramolecular cyclization does occur, it should take place *via* the less stable conformation (IIIc), and in that case one would expect the product with the *cis*-1β-H,5β-OH-configuration (XIIa, Scheme 3) to be predominantly formed.

Substance "F", m.p. 124°, corresponds to $C_{29}H_{48}O_4$. According to its IR spectrum this compound has no hydroxyl groups, no keto-carbonyl group and no double bond (confirmed also by the negative tetranitromethane test), but contains an acetate group (bands at 1739 and 1238 cm^{-1}) and ether oxygens (C—O—C), probably in the form of a ketal group (five absorption bands in the region 1000–1200 cm^{-1}). A further indication as to the intramolecular ketal structure of product "F" is given by the NMR spectrum. The C_{19}-methyl group produces a sharp signal at $\delta = 1{\cdot}32$, a region



Scheme 3. Stereoisomeric *cis*-5-alcohols (XIIa and XIIb) which might be formed by acid-catalysed cyclization of *trans*-3β-acetoxy-5,10-seco-1,10-cholesten-5-one (IV).

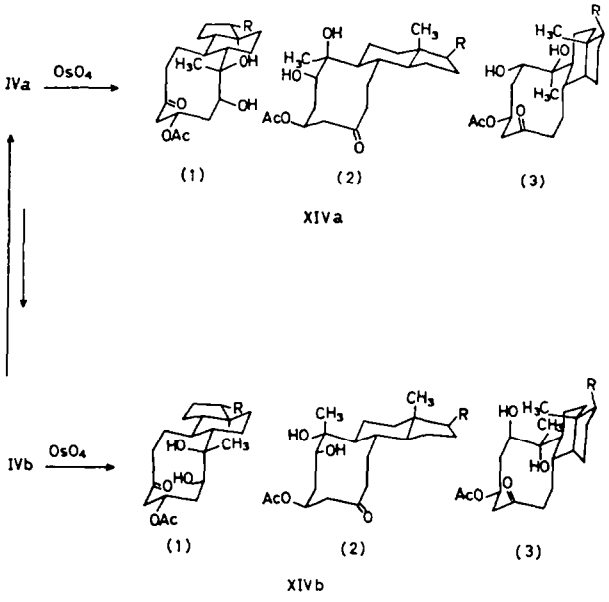
typical for a methyl group attached to a carbon atom bearing an oxygen ($\overset{19}{C}H_3—\overset{10}{C}—O—$); one also finds a quintuplet at $\delta = 5{\cdot}36$ ($J_{app.} \sim 7{\cdot}0$ c/s) due to the C_3-proton and a doublet at $\delta = 4{\cdot}19$ ($J = 4{\cdot}6$ c/s; $\Delta\delta/2 = 3$ c/s), attributable to the C_1-proton ($—O—\overset{1}{C}—H$). All these findings, therefore, suggest for compound "F" the intramolecular ketal constitution (XIII).



The second reaction product "G", m.p. 182°, according to analytical data ($C_{29}H_{50}O_5$); and physical evidence (IR spectrum: presence of hydroxyl, acetate and keto-carbonyl groups, absence of double bond; NMR spectrum: characteristic signals at 1·23 ppm

for the 19-methyl group ($CH_3^{19}—C^{10}—OH$), at 3·86 ppm for the C_1-proton ($H—C^{1}—OH$), at 5·34 ppm for the C_3-proton), is the expected *trans*-1,10-diol (XIV). The third product "H", m.p. 202–203° (probably $C_{29}H_{52}O_5$), contains hydroxyl groups and possibly a keto-carbonyl group, but, surprisingly enough, does not show (in its IR spectrum) bands characteristic for the acetate group. It appears to be a rearrangement product, and further work is in progress in order to establish its constitution.

The formation and some configurational aspects of the ketal "F" (XIII) and *trans*-1,10-diol "G" (XIV) may be accounted for by an inspection of models of the starting *trans*-acetoxy-seco-ketone conformations (IVa and IVb, Scheme 2) and of the possible stable conformations of products (XIV, Scheme 4). Since approach of osmium tetroxide to the double bond of IV may take place only from outside of the ring system,[28] and assuming, as above, that IV exists as an equilibrium mixture of conformations IVa and IVb in which IVa predominates, or that it reacts through these two conformations, hydroxylation with osmium tetroxide would be expected to afford two stereoisomeric *trans*-1,10-diols, the *trans*-1α,10β-diol (XIVa, Scheme 4) resulting from conformation IVa, and the *trans*-1β,10α-diol (XIVb, Scheme 4) resulting from

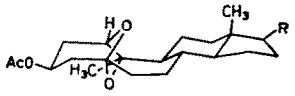


Scheme 4. Possible conformations of *trans*-5,10-seco-1α,10β-diol (XIVa) and *trans*-5,10-seco-1β,10α-diol (XIVb).

conformation IVb. Each of these diols can in turn exist as an equilibrium mixture of several conformations (Scheme 4). Only the *trans*-1β,10α-diol (XIVb) in conformation (1) can easily react intramolecularly to give the corresponding ketal, since in this formation (XIVb, 1) the two hydroxyl groups and the keto group are close enough

[28] Approach of the reagent from inside of the ring seems improbable, since it would result in a very strained transition state controlling the formation of the intermediate osmium tetroxide complex.

to permit ketalization.[29] Therefore, the ketal (XIII) being a derivative of the diol (XIVb), should have the configuration XIIIb. Ketal XIII is very stable and cannot be hydrolysed with hydrochloric acid in methanol ar room temperature, *p*-toluenesulphonic acid in benzene at 40° or acetic acid–acetic anhydride at 100°.[30] In the presence of hydrochloric acid, only the 3β-acetoxy group of XIII undergoes hydrolysis, and the resulting 3β-hydroxy-ketal can again be reacetylated (with acetic anhydride–pyridine) to the starting product (XIII).



XIII b

On the other hand, attempted ketalization (under various conditions) of the *trans*-1,10-diol "G" (XIV) and of compound "H" failed, suggesting that this diol is the hydroxylation product of conformation IVa of the starting *trans*-acetoxy-seco-ketone, i.e. that it represents *trans*-3β-acetoxy-1α,10β-dihydroxy-5,10-seco-cholestan-5-one (XIVa, Scheme 4), which, according to possible conformations on Scheme 4, cannot be readily converted (if at all) to an intramolecular ketal.[29] The ratio of diol (XIVa) and compound "H" to ketal XIII (similarly to the proportion of stereoisomeric products "D" (XIIa) and "E" (XIIb), resulting from acid-catalysed cyclization of IV), indicates that *trans*-acetoxy-seco-ketone (IV) exists or/and reacts predominantly in the form of only one conformation, this stable conformation being most probably IVa.[14]

In contrast to the *trans*-acetoxy-seco-ketone (IV), which reacts quantitatively with osmium tetroxide in benzene solution containing pyridine, the *cis*-acetoxy-seco-ketone (III), under identical conditions (10 days at room temp), remains mostly unchanged (over 80%), and the reacted part represents a complex mixture from which no defined products could be obtained.[31] This behaviour of the *cis*-acetoxy-seco-ketone (III) is not quite clear, since, according to models (conformations IIIa and IIIb on Scheme 2), approach of the reagent to the double bond from outside of the ring does not seem to be appreciably hindered.

It is also interesting to note that only the *trans*-hydroxy-seco-ketone (VIII) gives a digitonide (in 75% yield), while the *cis*-isomer (VII), upon treatment with digitonine, is not converted to the corresponding crystalline derivative.

EXPERIMENTAL[32]

M.ps (uncorrected) were determined on a micro-Kofler hot-stage apparatus. Optical rotations were measured in $CHCl_3$ unless mentioned otherwise. IR spectra were recorded on a Perkin–Elmer

[29] According to models, the *trans*-1α,10β-diol (XIVa, Scheme 4), in order to undergo ketalization, must first convert to a less favoured conformation of the ten-membered ring (chair–chair–chair conformation[13,15]), but even then, because of steric strain, ketal formation would be considerably more difficult (and the product less stable) than in the case of the *trans*-1β,10α-diol (XIVb) in conformation (1).

[30] A ketal of similar stability was described by H. R. Schenk, H. Gutmann, O. Jeger and L. Ružička, *Helv. Chim. Acta* **37**, 543 (1954); see also H. R. Schenk, Ph.D. Dissertation (ETH), Zürich (1952).

[31] However, after prolonged contact (30 days) with osmium tetroxide in pyridine solution, the *cis*-acetoxy-seco-ketone (III) reacts to a somewhat greater extent, but the products of this reaction have not yet been investigated.

[32] The authors wish to thank Mrs. R. Tasovac and Miss R. Dimitrijević, from the Microanalytical Laboratory of our Department, for the elemental microanalyses they carried out.

spectrophotometer, Model 421. NMR spectra were run in $CDCl_3$ solution at 100 Mc/s with a Varian HR-100 or HA-100 spectrometer, using tetramethylsilane as internal standard (signals reported in δ). Pet. ether refers to the fraction b.p. 40–60°. Alumina used for chromatography was of Brockmann grade II, neutral. The separation of products was controlled by TLC, which was carried out on silica gel G (Stahl) with benzene–AcOEt (9:1) or benzene–MeOH (4:1); the detection was effected with 50% H_2SO_4.

Oxidation of 3β-acetoxycholestan-5α-ol (I) *with lead tetraacetate.* Lead tetraacetate (25·0 g) dried *in vacuo* (P_2O_5 and KOH) and 10 g anhydrous thiophene-free benzene (dried over Na) were shortly heated under reflux. Upon cooling, 20 g of I[33] were added and the suspension heated under reflux with stirring. After 20 hr, the starch–iodine test for tetravalent lead was negative, indicating the end of the reaction. The cooled mixture was diluted with ether, filtered through a Celite mat and the insoluble precipitate thoroughly washed with ether. The combined filtrates were washed with water, $NaHCO_3$aq and water, and dried over $MgSO_4$. The solvents were evaporated under red. press. leaving 21·2 g of pale yellow oil, which was diluted with 100 ml pet. ether. Upon cooling at at 0°, 2·5 g of starting material (I) was precipitated (m.p. undepressed upon admixture with authentic sample).

The mother liquor was evaporated and the residue (about 18 g) was chromatographed on alumina (600 g). The first pet. ether–benzene (4:1) eluate contained (according to TLC) a mixture of products (0·27 g), which, upon separation, afforded cholestan-3β-ol acetate and some cholesterol acetate (identified by m.p. and mixed m.p. determination, and by comparison of their IR spectra with those of authentic samples).[34] The next pet. ether–benzene (4:1 and 3:2) eluates gave 2·45 g (12·25%) cis-*3β-acetoxy*-5,10-*seco*-1,10-*cholesten*-5-*one* (III, compound "B"), m.p. 138° (from acetone–MeOH); $[\alpha]_D^{23} = +38{\cdot}7°$ ($c = 0{\cdot}39$), $[\alpha]_D^{20} = +49°$ ($c = 0{\cdot}20$, dioxan). IR spectrum (KBr): $\nu_{max} = 1739$, 1709 and 1250 cm^{-1}; IR spectrum (CH_2Cl_2): $\nu_{max} = 1738$, 1706 and 1238 cm^{-1}. NMR spectrum (Fig. 1): $\delta = 0{\cdot}69$ (CH_3-18, singlet); 0·87 (CH_3-26 and CH_3-27, doublet); 0·90 (CH_3-21, doublet); 1·72 (CH_3-19, doublet; $J_{(1-CH)} = J_{(3-CH_2)} \sim 1$ c/s); 2·03 (OAc, singlet); 2·2 (C_4-*e* proton, multiplet); 3·17 (C_4-*a* proton, multiplet); 5·25 (C_1-proton, multiplet); 5·39 (C_3-proton, multiplet). (Found: C, 78·53; H, 10·81. $C_{29}H_{48}O_3$ requires: C, 78·32; H, 10·88%.)

Further elution with pet. ether–benzene (3:2 and 1:1) gave a mixture (3·9 g) of both isomeric *cis-trans* III and IV. By rechromatographying this mixture 0·6 g of III (total 3·06 g; 15·25%) and 1·8 g of IV were obtained. The next pet. ether–benzene (1:1) and benzene eluates afforded 3·6 g trans-*3β-acetoxy*-5,10-*seco*-1,10-*cholesten*-5-*one* (IV, compound "M") (total yield 5·4 g; 27%),[35] m.p. 136° (from acetone–MeOH); $[\alpha]_D^{23} = +4°$ ($c = 0{\cdot}50$), $[\alpha]_D^{20} = +13°$ ($c = 0{\cdot}20$, dioxan). IR spectrum (KBr): $\nu_{max} = 1733$, 1709 and 1238 cm^{-1}; IR spectrum (CH_2Cl_2): $\nu_{max} = 1738$, 1706 and 1238 cm^{-1}. NMR spectrum (Fig. 2): $\delta = 0{\cdot}69$ (CH_3-18, singlet); 0·84 (CH_3-26 and CH_3-27, doublet); 0·88 (CH_3-21, doublet); 1·73 (CH_3-19, doublet; $J_{(1-CH)} \sim 1$ c/s, $J_{(3-CH_2)} \sim 0{\cdot}5$ c/s); 2·03 (OAc, singlet); 4·81 (C_1-proton, multiplet); 5·35 (C_3-proton, multiplet). (Found: C, 78·46; H, 10·82. $C_{29}H_{48}O_3$ requires: C, 78·32; H, 10·88%.)

Further elution with benzene alone afforded a mixture (1 g) of IV and starting alcohol (I). Elution with benzene–ether (in various ratios) gave 5·7 g of unchanged I (total 8·2 g; 41%).

Oxidation of 3β-acetoxycholestan-5β-ol (II) *with lead tetraacetate.* Alcohol II[36] (2·0 g) was oxidized similarly with lead tetraacetate (2·8 g), the reaction being completed after 22 hr. The oily product was dissolved in 10 ml pet. ether and treated with the same volume of EtOH, whereby 365 mg of unchanged alcohol (II) precipitated (m.p., mixed m.p. and IR spectrum).

The residue upon evaporation of the mother liquor was chromatographed on alumina (80 g). Elution with pet. ether gave a mixture (23 mg) which was not investigated. The first pet. ether–benzene

[33] Pl. A. Plattner, Th. Petrzilka and W. Lang, *Helv. Chim. Acta* **27**, 513 (1944).

[34] In some runs the total yield of these two products amounted to 6%.

[35] The yields of the acetoxy-seco-ketones (III and IV) varied considerably from run to run. It appears that they are particularly dependent on the content of acetic acid in lead tetraacetate, the best yields being obtained (up to 17% for III and 32% for IV) when the oxidizing agent (after recrystallization from glacial acetic acid) was dried at 20–30 mm over KOH and P_2O_5 for several days.

[36] Pl. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta* **31**, 1885 (1948); **32**, 265 (1949).

(9:1) eluate afforded 192 mg (9·6%) *cis*-III, this product being identical in every respect with that obtained from I.

Further elution with pet. ether–benzene (9:1) afforded a mixture of both isomeric *cis-trans*-III and IV. With pet. ether–benzene (4:1) 235 mg (11·75%)[35] of *trans*-IV was obtained which was identical with IV obtained from I (m.p., mixed m.p., IR spectrum, NMR spectrum). Elution with pet. ether–benzene (in various ratios) and with benzene alone gave first a mixture of IV and II (292 mg) and then pure II (297 mg; total 662 mg; 33·1%).

Hydrolysis of cis-3β-*acetoxy*-5,10-*seco*-1,10-*cholesten*-5-*one* (III). A solution of *cis*-III (100 mg) in 10 ml 5% methanolic KOH, after standing overnight at room temp, was poured into water and extracted with ether. The solution was washed with water, dried (Na_2SO_4) and evaporated. The residue was chromatographed on alumina, whereby the benzene–ether (9:1) eluate afforded 82 mg of cis-3β-*hydroxy*-5,10-*seco*-1,10-*cholesten*-5-*one* (VII), m.p. 116–118° (from MeOH); $[\alpha]_D^{23} = +38°$ ($c = 0·49$). IR spectrum (KBr): $\nu_{max} = 3279$ and 1695 cm^{-1}. (Found: C, 80·38; H, 11·60. $C_{27}H_{46}O_2$ requires: C, 80·59; H, 11·44%.)

Hydrolysis of trans-3β-*acetoxy*-5,10-*seco*-1,10-*cholesten*-5-*one* (IV). *trans*-IV (100 mg) was hydrolysed in the same way as III, to give 87 mg of trans-3β-*hydroxy*-5,10-*seco*-1,10-*cholesten*-5-*one* (VIII), m.p. 158° (from MeOH); $[\alpha]_D^{23} = +27°$ ($c = 0·38$). IR spectrum (KBr): $\nu_{max} = 3448$ and 1698 cm^{-1}. (Found: C, 80·81; H, 11·50. $C_{27}H_{46}O_2$ requires: C, 80·59; H, 11·44%.)

Treatment of cis-3β-*acetoxy*-5,10-*seco*-1,10-*cholesten*-5-*one* (III) *with hydroxylamine hydrochloride.* To a solution of III (150 mg) in EtOH (6 ml) and pyridine (0·1 ml), hydroxylamine hydrochloride (150 mg) was added and the mixture gently refluxed for 5 hr. The solution was poured into water, the separated crystals filtered off and thoroughly washed with water containing traces of acetic acid. The product was crystallized from aqueous MeOH to give 140 mg of the *oxime of* cis-3β-*acetoxy*-5,10-*seco*-1,10-*cholesten*-5-*one* (IX), m.p. 158–159°;[37] $[\alpha]_D^{23} = +65·2°$ ($c = 0·27$). IR spectrum (KBr): $\nu_{max} = 3390$, 1745 and 1250 cm^{-1}. NMR spectrum:[38] $\delta = 0·69$ (CH_3-18, singlet); 0·86 (CH_3-26 and CH_3-27, doublet); 0·89 (CH_3-21, doublet); 1·69 (CH_3-19, singlet); 2·01 (OAc, singlet); 5·30 (C_3-proton and C_3-proton, multiplet); 8·34 (=N—O—H). (Found: C, 76·83; H, 10·84; N, 3·24. $C_{29}H_{49}O_3N$ requires: C, 76·77; H, 10·74; N, 3·05%.)

Treatment of trans-3β-*acetoxy*-5,10-*seco*-1,10-*cholesten*-5-*one* (IV) *with hydroxylamine hydrochloride.* A solution of IV (200 mg) and hydroxylamine hydrochloride (200 ml) in EtOH (10 ml) and pyridine (0·13 ml) was refluxed for 5 hr. The crystalline *product* "*C*" (probably XI; 200 mg) after recrystallization from aqueous methanol, melted at 141–142°; $[\alpha]_D^{23} = +66·5°$ ($c = 0·34$). IR spectrum (KBr): $\nu_{max} = 3448$, 3241, 1739 and 1248 cm^{-1}. NMR spectrum: $\delta = 0·72$ (CH_3-18, singlet); 0·84 (CH_3-26 and CH_3-27, doublet); 0·87 (CH_3-21, doublet); 1·21 (CH_3-19, singlet); 2·06 (OAc, singlet); 2·00 (C_4-*e* proton (?), multiplet); 2·84 (C_1-proton, quartet); 5·23 (C_3-proton, multiplet). (Found: C, 76·88; H, 10·91; N, 3·44. $C_{29}H_{49}O_3N$ requires: C, 76·77; H, 10·74; N, 3·05%.)

Digitonide of trans-3β-*hydroxy*-5,10-*seco*-1,10-*cholesten*-5-*one.* A saturated 50% ethanolic solution of digitonine (24·59 mg) was slowly added to an ethanolic solution of *trans*-VIII (8·04 mg), whereby a precipitate appeared slowly. After the mixture was allowed to stand overnight at room temp, the digitonide was filtered off and washed successively with acetone–ether (1:2) and ether yielding 24·3 mg (74·5%) of trans-3β-*hydroxy*-5,10-*seco*-1,10-*cholesten*-5-*one digitonide*, m.p. about 210°. (Found: C, 60·68; H, 8·80. $C_{83}H_{138}O_{31}$ requires: C, 61·10; H, 8·50%.)

Similar treatment of the *cis*-VII did not afford the corresponding crystalline digitonide.

Cyclization of trans-3β-*acetoxy*-5,10-*seco*-1,10-*cholesten*-5-*one* (IV). (a) *p*-Toluenesulphonic acid (100 mg) was added to IV (2·0 g) in 600 ml dry benzene and the resulting solution heated at 40° for 20 hr. The mixture was washed with $NaHCO_3$aq and water, dried (Na_2SO_4) and evaporated under red. press. The residue was chromatographed on alumina (60 g). Elution with pet. ether–benzene (4:1) afforded unchanged IV (150 mg), m.p. and mixed m.p. 136°. Elution with pet. ether–benzene (1:1) gave a mixture of IV and product "D" (XII). The next pet. ether–benzene (1:1) and benzene eluates yielded 1·34 g (67%) of pure *cyclization product* "*D*" (XII, possible configuration XIIa), m.p. 109° (from MeOH); $[\alpha]_D^{20} = +46°$ ($c = 0·67$).[7] IR spectrum (CH_2Cl_2): $\nu_{max} = 3540$, 1735, 1630 and 1238 cm^{-1}. NMR spectrum: $\delta = 0·73$ (CH_3-18, singlet); 0·85 (CH_3-26 and CH_3-27, doublet); 0·88 (CH_3-21, doublet); 2·03 (OAc, singlet); 2·25 (C_3-proton, multiplet); 2·49 (C_4-proton,

[37] According to the NMR spectrum this product is a mixture of *syn* and *anti* isomeric forms.
[38] The given values refer to the predominant form (*syn* or *anti*).

multiplet); 2·99 (C_1-proton, multiplet); 4·98 and 5·17 (exocyclic > C=CH_2 protons); 5·22 (C_3-proton, multiplet). (Found: C, 78·16; H, 10·88. $C_{29}H_{48}O_2$ requires: C, 78·32; H, 10·88%.)

Fractions eluted with benzene–ether (1:2) were a mixture of both isomeric products "D" and "E" (XII; 38 mg). Further elution with benzene–ether (1:2) gave the pure *cyclization product "E"* (XII, possible configuration XIIb) (163 mg; 8%), m.p. 135–136° (from MeOH); $[\alpha]_D^{20} = -6°$ ($c = 0·421$). IR spectrum (CH_2Cl_2): $\nu_{max} = 3600$, 1738, 1640 and 1240 cm^{-1}. NMR spectrum: $\delta = 0·73$ (CH_3-18, singlet); 0·86 (CH_3-26 and CH_3-27, doublet); 0·89 (CH_3-21, doublet); 2·03 (OAc, singlet); 4·90 and 4·95 (exocyclic >C=CH_2 protons); 5·28 (C_3-proton, multiplet). (Found: C, 78·28; H, 11·08. $C_{29}H_{48}O_2$ requires: C, 78·32; H, 10·88%.)

(b) A saturated solution of HCl in $CHCl_3$ (5 ml) was slowly added at 0° to IV (200 mg) in 5 ml $CHCl_3$ and the resulting solution was kept at 0° for 2 hr. It was then diluted with ether, washed with $NaHCO_3$aq and water, dried (Na_2SO_4) and evaporated. The residue was crystallized from MeOH to give 140 mg (70%) of a product, which was identical with the cyclization product "D" obtained according to (a) (m.p., mixed m.p. and IR spectrum). According to TLC the isomeric cyclization product "E" was also formed (in low yield) under these conditions.

The attempted cyclization of *cis*-III was unsuccessful, giving either unchanged starting material (under the above given conditions) or (under more vigorous conditions) a complex mixture of products, which was not further investigated.

Hydroxylation of trans-3*β-acetoxy*-5,10-*seco*-1,10-*cholesten*-5-*one* (IV) *with osmium tetroxide. trans*-IV (600 mg), dissolved in dry benzene (20 ml) containing pyridine (2 ml), was treated with osmium tetroxide (500 mg). The mixture was allowed to stand at room temp for 10 days, after which time it was diluted with AcOEt. H_2S was bubbled through the solution for 1 hr, and the insoluble salts were removed by filtration. Evaporation of the solvents gave a residue which was chromatographed on alumina (18 g).

Fractions eluted with benzene gave the *intramolecular ketal "F"* (XIII), which is possibly the *ketal of* trans-3*β-acetoxy*-5,10-*seco*-1*β*,10*α-dihydroxycholesten*-5-*one* (XIIIb; 40 mg; 6·4%), m.p. 124° (from MeOH); $[\alpha]_D^{20} = +84°$ ($c = 0·475$). IR spectrum (KBr): $\nu_{max} = 1739$ and 1238, five peaks in the region 1000–1200 cm^{-1}. NMR spectrum: $\delta = 0·70$ (CH_3-18, singlet); 0·87 (CH_3-26 and CH_3-27, doublet); 0·89 (CH_3-21, doublet); 1·32 (CH_3-19, singlet); 2·01 (OAc, singlet); 4·19 (C_1-proton, doublet); 5·36 (C_3-proton, multiplet). (Found: C, 75·84; H, 10·25. $C_{29}H_{46}O_4$ requires: C, 75·60; H, 10·50%.)

The oily product (210 mg) obtained by elution with benzene–ether (9:1 and 4:1), upon crystallization from pet. ether, afforded 140 mg (21·8%) of trans-3*β-acetoxy*-5,10-*seco*-1*ξ*,10*ξ-dihydroxy-cholestan*-5-*one* (XIV, compound "G"), which has probably the 1*α*,10*β*-configuration (XIVa), m.p. 182° (from pet. ether); $[\alpha]_D^{20} = +2°$ ($c = 0·471$). IR spectrum (KBr): $\nu_{max} = 3460$, 3540, 1735, 1704 and 1250 cm^{-1}. (Found: C, 72·90; H, 10·56. $C_{29}H_{50}O_5$ requires: C, 72·76; H, 10·53%.)

Further fractions eluted with benzene–ether (in various ratios) and ether alone contained a mixture (70 mg) which was not further investigated. Elution with MeOH yielded *product "H"* (211 mg, 32·5%), m.p. 202°, of unknown constitution; $[\alpha]_D^{20} = -6°$ ($c = 0·42$, EtOH–$CHCl_3$ 1:1). IR spectrum (Nujol): $\nu_{max} = 3540$ and 3380 cm^{-1}. (Found: C, 72·50; H, 10·93. $C_{29}H_{52}O_5$ requires: C, 72·45; H, 10·90%.) This product (60 mg) was acetylated in 3 ml pyridine with 3 ml Ac_2O (at room temp for 14 hr), to give 54 mg of a *diacetylated product*, m.p. 143–144° (from pet. ether); $[\alpha]_D^{20} = -6°$ ($c = 0·235$). IR spectrum (CH_2Cl_2): $\nu_{max} = 3670$, 3620, 1735 and 1250 cm^{-1}. (Found: C, 69·87; H, 9·96. $C_{33}H_{56}O_7$ requires: C, 70·17; H, 9·99%.)

Attempted hydroxylation of cis-3*β-acetoxy*-5,10-*seco*-1,10-*cholesten*-5-*one* (III) *with osmium tetroxide. cis*-III (222 mg) was dissolved in dry benzene (5 ml) containing pyridine (0·5 ml), and then treated with osmium tetroxide (165 mg). The mixture was allowed to stand at room temp for 10 days, after which time it was worked up as described above. Chromatography on alumina (8 g) with benzene gave 160 mg (72%) of recrystallized unreacted starting *cis*-III, m.p. and mixed m.p. 138°. Fractions eluted with benzene–ether (in various ratios), ether and MeOH were complex mixtures, from which no well-defined products could be isolated.

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