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CONFORMATION OF RING A IN ACETONIDES OF 2β,3α-MERCAPTOCHOLESTANOLS EVIDENCED BY NMR SPECTROSCOPY[1,2]

(BILE ACIDS AND STEROIDS. XXX: THIOSTEROIDS. 15)

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Abstract—Conformations of ring A in five 4,5-disubstituted 2,2-dimethyl[1,3]oxathiolanes fused at the 2- and 3-positions of 5α-cholestane (I–V) and two at the 3- and 4-positions (VI and VII) are studied by NMR spectroscopy in connection with the oxathiolano-ring closure of 2β,3α-*trans*-diaxial mercapto-ols with acetone. Evidence was obtained for skewed-boat conformations of ring A in the former two 2β,3α-derivatives (I and II) and for slightly distorted-chair conformations of ring A in the latter derivatives (V–VII).

INTRODUCTION

IN OUR previous[3] paper it was reported that two *trans*-diaxial 2β,3α-mercapto-ols and 2β,3α-dimercaptans of cholestane were easily condensed with acetone to afford the corresponding 2,2-dimethyl[1,3]oxathiolano and 2,2-dimethyl[1,3]dithiolano derivatives, respectively, and also with N,N'-thiocarbonylbis(2-methylimidazol) to yield the corresponding 2-thioxo[1,3]oxathiolano and trithiocarbonate derivatives, respectively, whereas no acetonide formation was observed with a *trans*-diaxial 2β,3α-diol under the same conditions. Inspection of Dreiding models suggested that these ring formations is only possible for ring A in a boat conformation. However, it remains to confirm the conformation of ring A in these cyclized compounds. In this connection, we present in this report NMR spectroscopic evidence for the conformation of ring A in acetonides of the two 2β,3α-mercaptocholestanols, I and II, together with those for the conformation of ring A in other five oxathiolanocholestanes, III–VII, for comparison.

RESULTS AND DISCUSSION

The two *cis*-derivatives, III and IV, were synthesized from 2β-hydroxycholestan-3β-ethylxanthate and 3α-hydroxycholestan-2α-ethylxanthate.[4,5] Thus among the possible eight isomers of oxathiolanocholestanes the five derivatives were subjected to NMR spectroscopy. As stated previously[3] attempts to synthesize an acetonide of *trans*-diaxial 3α,4β-mercapto-ol were unsuccessful. Only the two compounds VI and VII were available to this study. These examined compounds can be classified under three types in regard to the signal patterns of the *gem*-dimethyl groups and of the

[1] Part CII (Thiosteroids. 14) see K. Takeda, K. Kauriyma T. Komeno, D. A. Lightner, R. Records and C. Djerassi, *Tetrahedron* **21**, 1203 (1965).

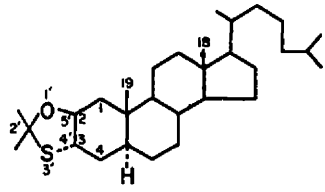
[2] NMR studies on steroids. IX. For Part VIII, see K. Tori and K. Kuriyama, *Tetrahedron Letters* in press.

[3] K. Takeda, T. Komeno, J. Kawanami, S. Ishihara, H. Kadokawa, H. Tokura and H. Itani, *Tetrahedron* **21**, 329 (1965).

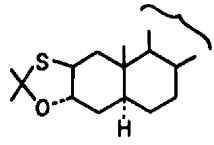
[4] D. A. Lightner and C. Djerassi, *Chem. & Ind.* 1236 (1962).

[5] For the syntheses of the compounds, I, II, V, VI and VII, see Ref. 3.

protons on the C_2 and C_3. In the *cis*-compound having $2\alpha,3\alpha$-, $2\beta,3\beta$- or $3\alpha,4\alpha$-substituents (III, IV and VI), the signals of the *gem*-dimethyl groups appear as two peaks ($\Delta\delta = 8$ c/s), and the signals of the protons on the C_2 and C_3 appear fairly separated (about 60 c/s), whose patterns can be analysed by the first order treatment. In the second class having *trans*-diequatorial, $2\alpha,3\beta$- or $3\beta,4\alpha$-substituents (V and



I



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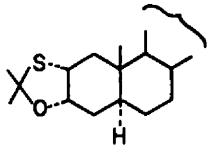
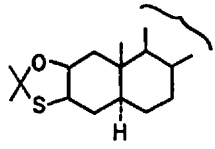
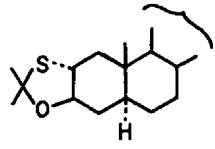


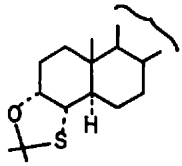
III



IV



V



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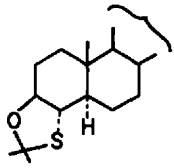
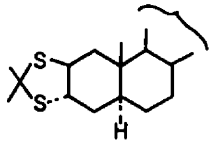


VII



VIII

VII), the signals of the *gem*-dimethyl protons also appear as two peaks ($\Delta\delta = 2$ c/s), and the signals of the protons on the C_2 and C_3 appear close together; the patterns were analysed by the quasi-first order approximation. In the last class having *trans*-diaxial $2\beta,3\alpha$-substituents (I and II), the signals of the *gem*-dimethyl groups appear as a single peak, and the signals of the protons on the C_2 and C_3 appear relatively separated (about 40 c/s), whose patterns were analysed by the quasi-first order treatment. Here it should be noted that the signal patterns under discussion belong in reality to the XX′ part of an ABXX′A′B′ and an ABXX′A′ system. However, the quasi-first order treatment on the analyses of the XX′ parts seems vindicable because these parts of the spectra observed were essentially unaltered when observed in benzene where the chemical shift differences $\Delta\delta_{AB}$, $\Delta\delta_{A'B'}$ and $\Delta\delta_{XX'}$ are anticipated to be changed, and because fairly large $\Delta\delta_{AB}$ values in I–V (more than 20–30 c/s) can be assumed from appearances of the 1β-proton signals in deuteriochloroform at relatively lower fields (at about 7·8–8·1 τ) apart from other signals.

Thus in Table 1 are summarized the NMR data obtained, and in Fig. 1 are reproduced the signal patterns of protons on the sulphur- or oxygen-bearing carbon atoms in these compounds.

The theoretically derived Karplus equation[6] which correlates the coupling constant

[6] M. Karplus, *J. Chem. Phys.* **30**, 11 (1959).

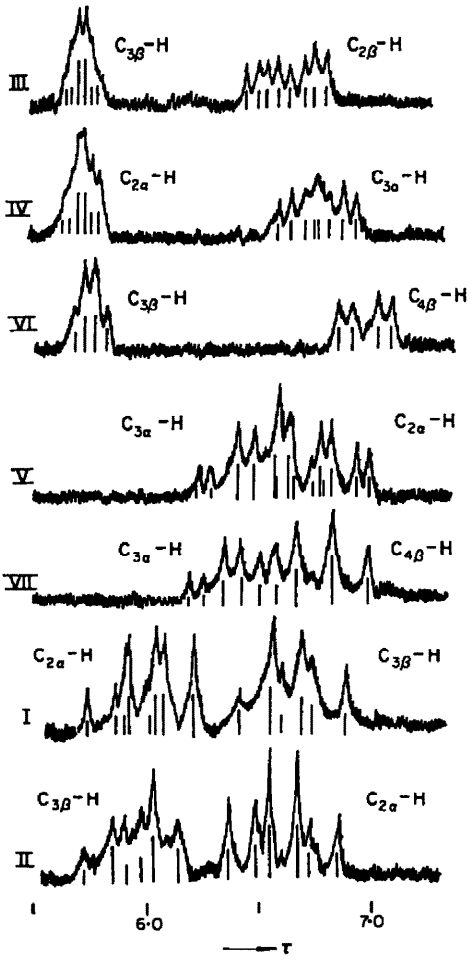


FIG. 1. NMR signal patterns of sulphur- or oxygen-bearing carbon atoms in the compounds I–VII in deuteriochloroform at 60 Mc/s.

with the dihedral angles between the vicinal protons in a >CH—CH< fragment, has frequently been applied to the problem on conformational analyses of many cyclic compounds. However, several recent studies[7–10] have pointed out that the values for the coefficients in the Karplus equation can be replaced with other values which vary with the nature of substituents on the >CH—CH< fragment. Furthermore, other factors dangerous to direct applications of this equation even in a revised form have been demonstrated.[11–13] Therefore, the coupling constants observed cannot strictly

[7] R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.* 806 (1963) and Refs. cited therein.
[8] R. J. Abraham and K. G. R. Pachler, *Mol. Phys.* **7**, 166 (1963–4).
[9] K. L. Williamson, *J. Amer. Chem. Soc.* **85**, 516 (1963).
[10] K. Tori, T. Komeno and T. Nakagawa, *J. Org. Chem.* **29**, 1136 (1964).
[11] M. Karplus, *J. Amer. Chem. Soc.* **85**, 2870 (1963).
[12] R. A. Wohl, *Chimia* **18**, 219 (1964).
[13] D. H. Williams and N. S. Bhacca, *J. Amer. Chem. Soc.* **86**, 2742 (1964).

be forced to correspond to the dihedral angles measured in Dreiding models at present. However, the dependence of the coupling constant upon the dihedral angle is believed to be still valid as long as we treat the equation in a qualitative sense.

In steroidal molecules having the normal chair conformation for rings A, B and C, reported values for the coupling constant between axial and axial protons on

TABLE 1. NMR SPECTRAL DATA ON SOME OXATHIOLANOCHOLESTANES IN DEUTERIOCHLOROFORM AND IN BENZENE (SHOWN IN PARENTHESES)

Compound	Chemical shift (τ)							Coupling constant (apparent) J (c/s)
	19-H	18-H	*gem*-dimethyl	1β-H	2-H	3-H	4-H	
Cholestane	9·23	9·35						
I	9·03 (9·23)	9·33 (9·37)	8·37 (8·30) (8·32)	8·08	5·93 (5·95)	6·60 (6·55)		$\lvert J_{1\alpha,1\beta}\rvert = 13{\cdot}8$ $\lvert J_{1\alpha,2\alpha}\rvert = 7{\cdot}3$, $J_{1\beta,2\alpha} = 9{\cdot}5$ $\lvert J_{2\alpha,3\beta}\rvert = 11{\cdot}0$ $\lvert J_{3\beta,4\alpha}\rvert = 8{\cdot}2$, $J_{3\beta,4\beta} = 8{\cdot}7$
II	9·09 (9·24)	9·33 (9·36)	8·37 (8·26) (8·35)	8·02	6·58 (6·58)	5·91 (5·85)		$\lvert J_{1\alpha,1\beta}\rvert = 14{\cdot}2$ $\lvert J_{1\alpha,2\alpha}\rvert = J_{2\alpha,3\beta} = 11{\cdot}0$ $\lvert J_{1\beta,2\alpha}\rvert = 7{\cdot}5$ $\lvert J_{3\beta,4\alpha}\rvert = J_{3\beta,4\beta} = 7{\cdot}2$
III	9·22	9·35	8·42 8·49	8·12	6·63	5·75		$\lvert J_{1\alpha,1\beta}\rvert = 13{\cdot}5$ $\lvert J_{1\alpha,2\beta}\rvert = 12{\cdot}0$ $\lvert J_{1\beta,2\beta}\rvert = 5{\cdot}7$ $\lvert J_{2\beta,3\beta}\rvert = J_{3\beta,4\beta} = 3{\cdot}5$ $\lvert J_{3\beta,4\alpha}\rvert = 1{\cdot}5$
IV	9·00	9·33	8·42 8·49	7·76	5·67	6·75		$\lvert J_{1\alpha,1\beta}\rvert = 14{\cdot}5$ $\lvert J_{1\alpha,2\alpha}\rvert = J_{2\alpha,3\alpha} = 3{\cdot}8$ $\lvert J_{1\beta,2\alpha}\rvert = 1{\cdot}5$ $\lvert J_{3\alpha,4\alpha}\rvert = 7{\cdot}2$, $J_{3\alpha,4\beta} = 10{\cdot}0$
V	9·13 (9·34)	9·33 (9·36)	8·34 8·37 (8·25) (8·31)	7·92	6·78 (6·71)	6·45 (6·42)		$\lvert J_{1\alpha,1\beta}\rvert = 13{\cdot}2$ $\lvert J_{1\alpha,2\beta}\rvert = 11{\cdot}8$ $\lvert J_{1\beta,2\beta}\rvert = 3{\cdot}5$, $J_{2\beta,3\alpha} = 9{\cdot}8$ $\lvert J_{3\alpha,4\alpha}\rvert = 4{\cdot}2$
VI	9·20	9·35	8·34 8·43			5·76	6·97	$\lvert J_{2\alpha,3\beta}\rvert = J_{2\beta,3\beta} = J_{3\beta,4\beta} = 3{\cdot}0$ $\lvert J_{4\beta,5\alpha}\rvert = 10{\cdot}5$
VII	9·11 (9·28)	9·35 (9·37)	8·33 8·36 (8·27) (8·32)			6·42 (6·35)	6·82 (6·73)	$\lvert J_{2\alpha,3\alpha}\rvert = 4{\cdot}5$ $\lvert J_{2\beta,3\alpha}\rvert = J_{3\alpha,4\beta} = J_{4\beta,5\alpha} = 10{\cdot}0$

adjacent carbon atoms, J_{aa}, range from 9·5 to 13·4 c/s, values for the coupling constant between axial and equatorial protons on adjacent carbon atoms bearing an equatorial substituent, J_{ae}, from 4·5 to 6·5 c/s, and values for the coupling constant between equatorial and axial protons on adjacent carbon atoms bearing an axial substituent, J_{ea} as well as J_{ee} from 2 to 3·5 c/s.[13,14] In a previous paper,[15] we reported the NMR

[14] For example, see A. C. Huitric, J. B. Carr, W. F. Trager and B. J. Nist, *Tetrahedron* **19**, 2145 (1963).

[15] K. Tori and T. Komeno, *Tetrahedron* **21**, 309 (1965).

spectra of many 5α-steroids having oxygen- or sulphur-containing substituents at the 2-, 3-, 4- and (or) 5-positions. The coupling constants obtained from the spectra of such compounds having hydroxyl, acetoxyl, mercapto and (or) acetylthio groups were 10–12 c/s for J_{aa}, 4·5–5 c/s for J_{ae}, and 2–3 c/s for J_{ea} and J_{ee}. Similar magnitudes of coupling constants could be reasonably expected in the present cases, if the A-ring of the examined compounds were of the normal chair form.

In the first and second type of the compounds, their A-ring is anticipated to be a distorted (or flattened) chair form owing to compression caused by the fused oxathiolano ring, as shown by examination of Dreiding models. As listed in Table 1, in the compound III, $J_{1\beta,2\beta}$ (5·7 c/s) and $J_{3\beta,4\beta}$ (3·5 c/s) are somewhat larger for J_{ae} and J_{ee}, respectively, whereas $J_{3\beta,4\alpha}$ (1·5 c/s) is somewhat smaller for J_{ee}; in the compounds IV, $J_{1\alpha,2\alpha}$ (3·8 c/s) and $J_{3\alpha,4\alpha}$ (7·2 c/s) are evidently larger for J_{ea} and J_{ae}, respectively, whereas $J_{1\beta,2\alpha}$ (1·5 c/s) and $J_{3\alpha,4\beta}$ (10·0 c/s) are smaller for J_{ee} and J_{aa}, respectively; in the compound V, $J_{1\beta,2\beta}$ (3·5 c/s) is smaller than the normal magnitude of J_{ae}. Therefore, the A-ring in III, IV and V is thought to be at any rate, distorted from the normal chair form. In the compounds VI and VII, the observed coupling constants rather fall in the normal range. Therefore, the A-ring in VI and VII seems to suffer no distortion, or even if the distortion were caused it might be to a slight extent.

Ring formation to the last type of the compounds derived from *trans*-diaxial 2β,3α-mercapto-ols is only possible when ring A changes from the chair to a boat form because the two adjacent axial bonds in the chair form are incapable of a five-membered ring formation. Inspection of Dreiding models shows that it is possible for ring A to have a boat conformation: one of the two classical boat forms with C_2–C_5 and C_3–C_{10} at the bow-stern position, or an intermediate of these two conformations, a skewed (or twisted) boat form. It can be expected that a skewed form is more preferred for such a situation[16] because the dihedral angle of 2β-C_2–C_3-3α and the distance between the 2β- and 3α-substituents are mininum in this form. If the compounds I and II would have a classical boat form for the A-ring, one of $J_{1,2}$ or $J_{3,4}$ should have a small value, about 2–3 c/s, for J_{ae} because the 2α- or 3β-proton is placed at the boat-pole position and therefore, staggered against the adjacent methylene group. However, all the observed coupling constants shown in Table 1 are fairly large. Hence the A-ring of these compounds is believed to take a skewed boat conformation or to be equilibrated at this conformation. Examination of Dreiding models suggests the given assignment of each coupling constant in I and II, which is consistent with the skewed boat form and the Karplus equation.

It is reasonable to assume that the difference in the chemical shifts of the *gem*-dimethyl groups in the examined compounds is governed only by the long-range shielding effect of the steroidal nucleus because the shielding effect arising from the oxathiolano ring seems equal upon each methyl group in all types of the compounds. The single signal for the *gem*-dimethyl protons in the last type of the compounds implies that each methyl group is equally shielded and hence the oxathiolano ring and the steroidal nucleus are situated almost in the same plane which bisects the *gem*-dimethyl groups. Dreiding models shows that the above situation is realized when the A-ring has a skewed boat conformation. In the spectra of the isopropylidene

[16] J. B. Hendrickson, *J. Amer. Chem. Soc.* **83**, 4537 (1961).

derivative of the 2β,3α-dimercaptan reported earlier,[3] VIII, the signal of the *gem*-dimethyl groups appears as a single peak at 8·22τ. Although the signals of the 2α- and 3β-protons were not resolved, this compound VIII can be assumed to have a skewed boat form for the A-ring also.

It is interesting to note that in the spectra of benzene solutions, the *gem*-dimethyl signals are shifted to lower fields than those in chloroform probably because of anisotropic shielding effects of benzene molecules coordinating to the oxygen and sulphur atoms.[13] Even the single peak of the *gem*-dimethyl groups in I and II are separated to two peaks in benzene. Plausibly, the coordinating benzene molecules might exert different shielding effects on each methyl group.

EXPERIMENTAL

The NMR spectra were taken with a Varian A-60 spectrometer on about 10% (w/v) solutions in $CDCl_3$ and benzene containing tetramethylsilane as an internal standard. Calibration of the spectrometer was checked by the usual side-band technique. Accuracies of the measurements are within about ±0·02τ for chemical shifts and about ±0·3 c/s for coupling constants.

All m.ps were determined on a Kofler block and uncorrected. Optical rotations were measured in $CHCl_3$ using a Rudolf photoelectronic polarimeter, model 200, and the IR spectra were taken with a Koken IR spectrophotometer, model DS-301.

Acetonide of 2α-mercapto-5α-cholestan-3α-ol (V). To a suspension of 3-oxocholestan-2α-ethylxanthate (2·8 g) in a mixture of EtOH (60 ml) and ether (30 ml), $NaBH_4$ (500 mg) was added. After agitation for 2 hr at room temp, H_2O was added to the solution and the product was extracted with ether. The ethereal extract was acetylated with pyridine (10 ml) and Ac_2O (5 ml). The product was chromatographed over Al_2O_3 (70 g). The eluate with pet. ether afforded 5α-cholestan-2α,3α-episulphide (1·159 g, m.p. 121–123°). The material eluted with pet. ether–benzene (9:1–4:1) was recrystallized from pentane to yield 3α-acetoxy-5α-cholestan-2α-ethylxanthate (152 mg, m.p. 156–159°) (lit.[4] m.p. 160–161°), which was further reduced with $LiAlH_4$ (100 mg) in abs. ether (20 ml) to give a mercapto-ol. The mercapto-ol was heated under reflux in acetone (15 ml) in the presence of *p*-TsOH (30 mg) for 6 hr. The material isolated with ether was purified by passing through Al_2O_3 column (4·5 g) to give an acetonide (V, 112 mg), m.p. 129–131°, which was recrystallized from acetone to an analytical sample as leaflets, m.p. 132–134°, $[\alpha]_D^{24.5}$ +85·6 ± 2° (c = 1·120), ν_{max}^{Nujol} 1367 cm^{-1}. (Found: C, 78·37; H, 11·43; S, 7·17. $C_{30}H_{52}OS$ requires: C, 78·19; H, 11·38; S, 6·96%).

3β-Mercapto-5α-cholestan-2β-ol. 3α-Bromo-5α-cholestan-2-one (m.p. 155–156°, lit.[17] m.p. 151–153°) (1·110 g) was treated with KSC(=S)OEt (760 mg) in acetone (30 ml) for 2·5 hr. The oily ethylxanthate (1·333 g) was reduced with $LiAlH_4$ (450 mg) in abs. ether (70 ml) for 1 hr. The product was chromatographed over Florisil (25 g). The material eluted with pet. ether and benzene (4:1–1:1) was recrystallized from acetone–MeOH to yield 3β-mercapto-5α-cholestan-2β-ol (766 mg) as leaflets, m.p. 119–120°, $[\alpha]_D^{24.5}$ +52·9 ± 2° (c = 1·030), ν_{max}^{Nujol} 3404, 2532, 1242, 1133, 1030, 1010, 971, 723 cm^{-1}. (Found: C, 76·84; H, 11·60; S, 7·59. $C_{27}H_{46}OS$ requires: C, 77·08; H, 11·50; S, 7·62%). This compound (219 mg) was acetylated with pyridine (2 ml) and Ac_2O (1 ml), followed by recrystallization from CH_2Cl_2–MeOH, to yield a diacetate (174 mg) as leaflets, m.p. 154–156°. $[\alpha]_D^{26}$ +60·3 ± 2° (c = 0·980), ν_{max}^{Nujol} 1738, 1696, 1242, 1137 cm^{-1}. (Found: C, 74·02; H, 10·48; S, 6·30. $C_{31}H_{50}O_2S$ requires: C, 73·96; H, 10·30; S, 6·30%).

Acetonide of 3β-mercapto-5α-cholestan-2β-ol (IV). The foregoing mercapto-ol (383 mg) was heated under reflux for 4 hr in acetone (30 ml) in the presence of *p*-TsOH (60 mg). The product was chromatographed over Florisil (8 g). The material eluted with pet. ether and with pet. ether–benzene (9:1) was recrystallized from ether–acetone to give an acetonide (IV, 378 mg) as needles, m.p. 136–137°, $[\alpha]_D^{24.5}$ +71·8 ± 2° (c = 1·087), ν_{max}^{Nujol} 1370 cm^{-1}. (Found: C, 78·45; H, 11·41; S, 7·09. $C_{30}H_{52}OS$ requires: C, 78·19; H, 11·38; S, 6·96%).

[17] G. H. Alt and D. H. R. Barton, *J. Chem. Soc.* 4284 (1954); C. Djerassi and T. Nakano, *Chem. & Ind.* 1385 (1960).