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OPTICAL ROTATORY DISPERSION STUDIES—CXII[1] THIOSTEROIDS[2] (20)

AN OCTANT RULE FOR THE THIOCYANATE CHROMOPHORE AND ITS APPLICATION TO ROTAMERIC EQUILIBRIUM STUDIES IN THE STEROID SERIES

CARL DJERASSI, D. A. LIGHTNER and D. A. SCHOOLEY
Department of Chemistry, Stanford University, Stanford, California 94305

and

KEN'ICHI TAKEDA, T. KOMENO and K. KURIYAMA
Shionogi Research Laboratory, Shionogi & Co. Ltd., Fukushima-ku, Osaka, Japan

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Abstract—Optical rotatory dispersion and circular dichroism measurements of a number of steroidal thiocyanates have demonstrated that a low intensity absorption near 250 nm is optically active. On the assumption that this transition of thiocyanates is qualitatively similar to the $n \rightarrow \pi^*$ transition of azides, an octant rule is proposed for thiocyanates, which leads to the prediction of the sign of the Cotton effect. Its potential utility is demonstrated by analyzing rotameric contributions of various steroidal thiocyanates.

PREVIOUS discussion[3] of the optical activity associated with the azide chromophore (—N—$\overset{+}{N}\equiv$N), which has been classified as "inherently symmetric",[4] suggests that similar arguments might apply to the isoelectronic thiocyanate chromophore (—S—C≡N)† and that it too should be designated as "inherently symmetric" in local symmetry. Accordingly, any optical activity associated with these chromophores follows as a consequence of their being located in a dissymmetric molecular environment, and the signed magnitude of the activity will be determined by the nature and location of the atoms in the extrachromophoric environment. Similarly as in the case for the acide 280 nm transition ($\varepsilon \sim 30$), the thiocyanate 245 nm transition ($\varepsilon \sim 100$)[6] may be attributed to the promotion of an electron from a nonbonding $3p_y$ orbital situated mainly on sulfur to an anti-bonding π_x^* orbital determined largely by the carbon and nitrogen $2p_x$ atomic orbitals. The schematic representation of the pertinent orbitals is shown in Fig. 1.

The considerations which led to an octant rule for azides[3] apply also to thiocyanates insofar as the basic symmetry in the nature of the electronic transitions holds for these two chromophores. It should be pointed out that although the chromophores have been called isoelectronic, the sulfur atom contributes bonding and nonbonding electrons from a higher energy level ($n = 3$) in thiocyanates than does the correspond-

† The C—S—C bond angle of CH_3SCN is 99° 52′ and the S—C bond length 1·684 Å, (microwave), assuming the bond lengths are C—H = 1·093 Å, H_3C—S = 1·820 Å, and C—N = 1·21 Å, with the H—C—H angle having the normal tetrahedral value of 109° 28′.[5] Therefore for octant projections with Dreiding models a sulfide sulfur atom connected to an acetylene was used to visualize the thiocyanate chromophore.

ing nitrogen atom ($n = 2$) in azides. This distinction may lead to certain quantitative differences; however, it is unlikely to lead to qualitative discrepancies. With the latter thought in mind, we assume that thiocyanates should follow the Azide Octant Rule.[3] An octant diagram is described for the thiocyanate chromophore in Fig. 2.

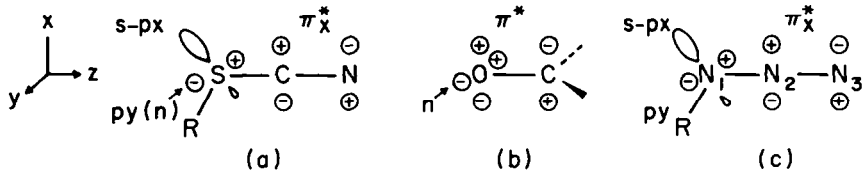


FIG. 1 Orbitals involved in the 245 nm transition of thiocyanates (a), in the 290 nm transition of ketones (b) and in the 280 nm transition of azides (c).

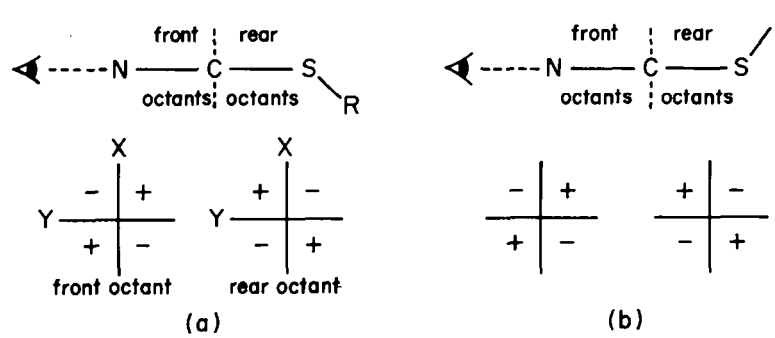


FIG. 2 Octant diagram of the thiocyanate chromophore.

A consideration of two possible orientations leads (a and b in Fig. 2) to the same result. In fact, the thiocyanate-azide octants are signed the same as the carbonyl octants.[7] Looking along the axis from nitrogen through carbon to sulfur, the symmetry planes are: (1) the XZ-plane containing the S,C and N atoms and the carbon of R attached to sulfur; (2) the YZ-plane orthogonal to the XZ-plane and containing the S,C and N atoms; and (3) an as yet poorly defined surface which we approximate by a third plane (XY) orthogonal to the other planes and passing through the carbon of the S—C≡N group.

RESULTS AND DISCUSSION

As in the case of the azide chromophore,[3] the rotational strength of the thiocyanate chromophore is weaker than that of the carbonyl group and, in a number of instances, the Cotton effect in the 250 nm region was discernible only with difficulty by ORD measurements because of the relatively strong background rotation upon which it is superimposed. A typical example is given in Fig. 3, and for that reason CD measurements were performed for all of the thiocyanates. The relevant data are summarized in Table 1 using the conventional ORD and CD notations[8] in terms of molecular rotation $[\phi]$ and molecular ellipticity $[\theta]$.

The stereochemical factor which needs to be taken into consideration in a thiocyanate octant rule analysis is complicated since the chromophore is subject to

rotation about the R—S bond. The technique of variable-temperature circular dichroism has been introduced to study conformational equilibria,[9] including the effect of free rotation.[10]

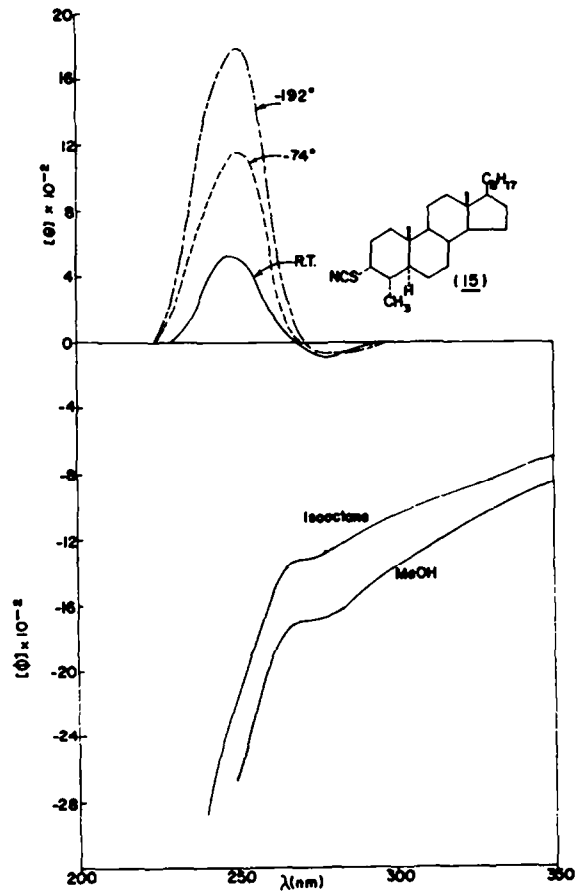


FIG. 3 ORD (isooctane and methanol) and variable-temperature CD (EPA) of 3α-thiocyanato-4α-methyl-5α-cholestane (15).

The first model compound employed in the present study was 2β-thiocyanato-5α-cholestane (1), for which the high-temperature CD curves are shown in Fig. 4. In this compound, inspection of Stuart (space-filled) models shows that free rotation about the C(2)—S single bond is considerably restricted due to steric interaction of the thiocyanate grouping with the C(19) angular Me substituent. It is, therefore, sufficient to consider three rotamers in which the thiocyanate substituent is rotated around the C(2)—S bond in 60° increments. These rotamers are most conveniently depicted in terms of octant projections (A–C) by looking from the S atom toward C-2 of the steroid nucleus. The Cotton effect sign predicted by the thiocyanate octant rule is indicated under each projection. In rotamer A, the 18 and 19 Me groups are

TABLE 1. ORD AND CD PROPERTIES (DIOXANE SOLUTION) OF THIOCYANATO-STEROIDS

Compound No.	Position of thiocyanate	R	Other subst.	CD maximum	ORD	
					Peak	Trough
1	2β	C_8H_{17}	—	$[\theta]_{272}$ +2657 (R.T.)[a] $[\theta]_{273}$ +2088 (+64°)[a] $[\theta]_{272}$ +1740 (+94°)[a] $[\theta]_{272}$ +1479 (+128°)[a] $[\theta]_{273}$ +1044 (+166°)[a]		
2	2β	C_8H_{17}	3α-OH	$[\theta]_{251}$ +1750	$[\phi]_{264}$ +2150	$[\phi]_{239}$ +810
3	2β	C_8H_{17}	3α-OAc	$[\theta]_{249}$ +3680	$[\phi]_{263}$ +4680	$[\phi]_{239}$ +2890
4	2β	C_8H_{17}	3α-OH 5α-OH	$[\theta]_{250}$ +1592	$[\phi]_{264}$ +1955	$[\phi]_{235}$ +316
5	2β	C_8H_{17}	3α-OAc 5α-OH	$[\theta]_{248}$ +3296[b]	$[\phi]_{263}$ +5220[b]	$[\phi]_{234}$ +1484[b]
6	2β	OH	3β-CH_3 3α-OH	$[\theta]_{250}$ +1367[b]	$[\phi]_{265}$ +2223[b]	$[\phi]_{241}$ +1235[b]
7	2β	OAc	3β-CH_3 3α-OAc	$[\theta]_{248}$ +2300	$[\phi]_{263}$ +4780	$[\phi]_{240}$ +3480
8	2β	OH	2α-CH_3 3α-OH	$[\theta]_{259}$ +1620[b] $[\theta]_{257}$ +1090	$[\phi]_{271}$ +2023[b] $[\phi]_{270}$ +2325	$[\phi]_{244}$ +629[b] $[\phi]_{246}$ +1500
9	2β	OAc	2α-CH_3 3α-OMs	$[\theta]_{255}$ +3731[b] $[\theta]_{254}$ +2930	$[\phi]_{270}$ +4408[b] $[\phi]_{270}$ +4910	$[\phi]_{243}$ +1429[b] $[\phi]_{243}$ +2410
10	2β	OAc	2α,3β-di-CH_3 3α-OH	$[\theta]_{255}$ +1617[b] $[\theta]_{256}$ +1530	$[\phi]_{270}$ +2930[b] $[\phi]_{270}$ +3030	$[\phi]_{250}$ +1520[b] $[\phi]_{244}$ +1610

11	2β	C_8H_{17}	3α-OAc Δ^5	$[\theta]_{249}$ +3580[b]	$[\phi]_{263}$ +4700	$[\phi]_{240}$ +2250
12	3α	C_8H_{17}	—	$[\theta]_{255}$ +446[d] $[\theta]_{255}$ +368 $[\theta]_{255}$ +573[b] $[\theta]_{255}$ +413 (R.T.)[e] $[\theta]_{255}$ +334 (+66°)[e] $[\theta]_{255}$ +360 (+92°)[e] $[\theta]_{255}$ +377 (+130°)[e] $[\theta]_{255}$ +465 (R.T.)[c] $[\theta]_{251}$ +490 (−74°)[c] $[\theta]_{252}$ +475 (−192°)[c]	$[\phi]_{244}$ +1027[d] $[\phi]_{260}$ +1218 $[\phi]_{262}$ +1352[b]	$[\phi]_{245}$ +891[d] $[\phi]_{245}$ +1053 $[\phi]_{242}$ +1118[b]
13	3α	C_8H_{17}	2β-Me	$[\theta]_{253}$ +1403[b] $[\theta]_{253}$ +1172[d] $[\theta]_{252}$ +1100 (R.T.)[c] $[\theta]_{252}$ +1230 (−74°)[c] $[\theta]_{253}$ +1120 (−192°)[c]	$[\phi]_{260}$ +795[d]	$[\phi]_{239}$ +514[d]
14	3α	C_8H_{17}	2α-Me	$[\theta]_{253-255}$ +196[d] $[\theta]_{255-260}$ +157 $[\theta]_{254-255}$ +398[b] $[\theta]_{253}$ +288 (R.T.)[c] $[\theta]_{253}$ +210 (−74°)[c] $[\theta]_{255}$ −51 (−192°)[c]	Plain dispersion curves	
15	3α	C_8H_{17}	4α-Me	$[\theta]_{250}$ +696[d] $[\theta]_{248}$ +606 $[\theta]_{249}$ +545[b] $[\theta]_{250}$ +510, $[\theta]_{278}$ −90 (R.T.)[c] $[\theta]_{250}$ +1152, $[\theta]_{280}$ −78 (−74°)[c] $[\theta]_{250}$ +1772, $[\theta]_{280}$ −96 (−192°)[c]	$[\phi]_{275-270}$ −1320, shoulder[d] $[\phi]_{280-275}$ −1700, −1748 shoulder $[\phi]_{280-270}$ −1670, −1705 shoulder[b]	

TABLE 1—*continued*

Compound No.	Position of thiocyanate	R	Other subst.	CD maximum	ORD	
					Peak	Trough
16	3β	C_8H_{17}	—	$[\theta]_{250}$ +80[d] $[\theta]_{255}$ +66 $[\theta]_{250}$ −56[b] $[\theta]_{260}$ +24 (R.T.)[c] $[\theta]_{245}$ −218 (−74°)[c] $[\theta]_{242}$ −420 (−192°)[c]	Plain dispersion curve	
17	3β	C_8H_{17}	2β-Me	$[\theta]_{248}$ +382[d] $[\theta]_{250}$ +306 $[\theta]_{248}$ +367[b] $[\theta]_{247}$ +468 (R.T.)[c] $[\theta]_{247}$ +470 (−74°)[c] $[\theta]_{247}$ +518 (−192°)[c]	$[\phi]_{245}$ +1854[d] tail $[\phi]_{250}$ +1750 tail $[\phi]_{250}$ +1950[b] tail	
18	3β	C_8H_{17}	2α-Me	$[\theta]_{250}$ −1200[d] $[\theta]_{248}$ −1130 $[\theta]_{248}$ −1415[b] $[\theta]_{249}$ −1406 (R.T.)[c] $[\theta]_{246}$ −2120 (−74°)[c] $[\theta]_{245}$ −3018 (−192°)[c]	$[\phi]_{235}$ −1952[d] $[\phi]_{235}$ −1274 $[\phi]_{246}$ −2650[b]	$[\phi]_{267}$ −390[d] $[\phi]_{265}$ −340 $[\phi]_{280}$ −300[b]
19	3β	C_8H_{17}	4α-Me	$[\theta]_{253}$ +1400[d] $[\theta]_{253}$ +1301 $[\theta]_{250}$ +1356[b] $[\theta]_{250}$ +1304 (R.T.)[c] $[\theta]_{249}$ +1922 (−74°)[c] $[\theta]_{248}$ +1950 (−192°)[c]	$[\phi]_{264}$ +1880[d] $[\phi]_{263}$ +1815 $[\phi]_{263}$ +1920[b]	$[\phi]_{235}$ +1130[d] $[\phi]_{240}$ +1122 $[\phi]_{237}$ +924[b]
20	3α	C_8H_{17}	2β-OH	$[\theta]_{252}$ +1430	$[\phi]_{263}$ +2200	$[\phi]_{244}$ +1630
21	3α	OH	2β-OH	$[\theta]_{251}$ +1574	$[\phi]_{265}$ +1822	$[\phi]_{240}$ +841

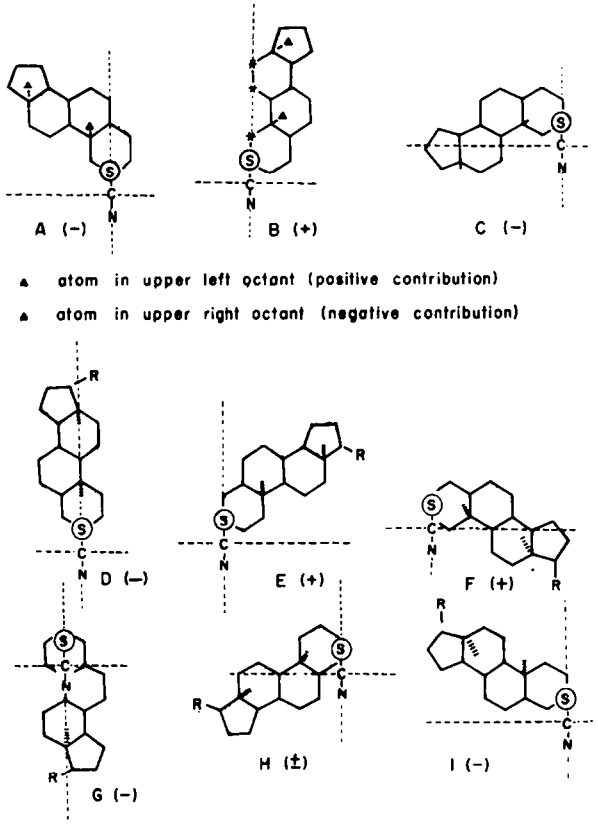
22	3α	OH	2β-OH 2α-CH_3	$[\theta]_{250}$ +1158	$[\phi]_{260}$ +3901	$[\phi]_{245}$ +3867
23	3α	OH	2β-OH 3β-CH_3	$[\theta]_{254}$ +1894	$[\phi]_{269}$ +2909	$[\phi]_{245}$ +1927
24	3α	OAc	2β-OH 2α,3β-di-CH_3	$[\theta]_{254}$ +3120	$[\phi]_{267}$ +5890	$[\phi]_{243}$ +3940
25	3α	OAc	2β-OAc 2α,3β-di-CH_3	$[\theta]_{254}$ +2553[b] $[\theta]_{254}$ +2160	$[\phi]_{270}$ +3558[b] $[\phi]_{269}$ +4280	$[\phi]_{241}$ +1143[b] $[\phi]_{242}$ +2190
26	3α	C_8H_{17}	2β,5α-di-OH	$[\theta]_{266}$ +240[b] $[\theta]_{242}$ −180[b] $[\theta]_{245}$ −870	$[\phi]_{274}$ +134[b] $[\phi]_{259}$ −580	$[\phi]_{263}$ 0[b] $[\phi]_{225}$ +1130
27	3α	C_8H_{17}	2β-OAc	$[\theta]_{250}$ +3510[b] $[\theta]_{249}$ +2980 $[\theta]_{248}$ +2890[d]	$[\phi]_{265}$ +4020[b] $[\phi]_{264}$ +4120 $[\phi]_{262}$ +3890[d]	$[\phi]_{241}$ +1970[b] $[\phi]_{240}$ +2480 $[\phi]_{240}$ +2050[d]
28	3α	C_8H_{17}	2β-OAc	$[\theta]_{247}$ +2330[b] $[\theta]_{248}$ +1170[d]	$[\phi]_{263}$ +1357 $[\phi]_{269}$ +240	$[\phi]_{235}$ −689 $[\phi]_{236}$ −1050
29	3α	C_8H_{17}	2β-OAc Δ^5	$[\theta]_{247}$ +12210	$[\phi]_{262}$ +8670	$[\phi]_{236}$ −3840
30	3α	C_8H_{17}	4β-OAc	$[\theta]_{250}$ −1904 (R.T.)[c] $[\theta]_{250}$ −2261 (−74°)[c] $[\theta]_{240}$ −2495 (−192°)[c] $[\theta]_{250}$ −1800 (R.T.)[e] $[\theta]_{250}$ −1800 (68°)[e]		
31	4β	C_8H_{17}	3α-OH	$[\theta]_{244}$ −1630	$[\phi]^{inf.}_{230}$ +2530	$[\phi]_{262}$ 0
32	4β	C_8H_{17}	3α-OAc	$[\theta]_{242}$ −930	$[\phi]_{220}$ +4280	$[\phi]_{260}$ +1610
33	4β	C_8H_{17}	5α-OH	$[\theta]_{249}$ −1210 (R.T.)[c] $[\theta]_{250}$ −1632 (−74°)[c] $[\theta]_{245}$ −2220 (−192°)[c] $[\theta]_{245}$ −945	$[\phi]_{245}$ +2660	$[\phi]_{267}$ +1620
34	5α	C_8H_{17}	3β-OAc 6β-OH	$[\theta]_{256}$ −3290	$[\phi]_{245}$ −890	$[\phi]_{274}$ −3240

TABLE 1—*continued*

Compound No.	Position of thiocyanate	R	Other subst.	CD maximum	ORD	
					Peak	Trough
35	6β	C_8H_{17}	3β-OAc 5α-OH	$[\theta]_{265}$ −180 $[\theta]_{273}$ −58 $[\theta]_{250}$ +290 (−29°)[c] $[\theta]_{275}$ −57 $[\theta]_{250}$ +313 (−41°)[c] $[\theta]_{250}$ +442 (−74°)[c] $[\theta]_{248}$ +936 (−192°)[c] $[\theta]_{255}$ +132 (R.T.)[a] $[\theta]_{255}$ +132 (+66°)[a] $[\theta]_{255}$ +290 (+83°)[a] $[\theta]_{255}$ +320 (+135°)[a] $[\theta]_{255}$ +390 (+162°)[a] no maximum	$[\phi]^{sh}_{265}$ −3710[b]	
36	11β	CH_3—CH(OAc)—	3β-OAc 12α-OH	$[\theta]_{261}$ +640	$[\phi]^{inf.}_{265}$ +2420	
37	12α	CH_3—CH(OAc)—	3β-OAc 11β-OH	$[\theta]_{256}$ +1090	$[\phi]^{inf.}_{259}$ +5260	
38	16β	17α-OH	3β-OAc	$[\theta]_{260}$ +397	$[\phi]^{inf.}_{275}$ −310	
39	17α	—	3β-OAc 16β-OH	$[\theta]_{265}$ −471	$[\phi]_{245}$ +290	$[\phi]_{270}$ −220

[a] Decalin. [b] Methanol. [c] EPA. [d] Isooctane.

in a positive upper rear octant, whereas the rest of the molecule is in a negative lower rear octant;† a negative Cotton effect is therefore expected. In rotamer B, all of the atoms except for the 18 and 19 Me groups are in a positive lower rear octant, and, therefore, a positive Cotton effect is assumed. In rotamer C, there are substituents in



both negative rear and positive front octants, but the latter are much more distant from the thiocyanate chromophore and a negative Cotton effect is expected. An increase in the magnitude of the rotational strength upon lowering the temperature from +166° to ca. 25° (Fig. 4) is indicative of the preponderance of rotamer B.

Because the introduction of substituents adjacent to the thiocyanate function might change the conformational equilibrium it seems pointless to speculate at this time about all such thiocyanates, especially those containing acetates or other groups having rotameric equilibria or electronic effects of their own. Me groups, lacking rotameric equilibria or the electronic effect of an OH function, are more easily understandable. In the 2β-thiocyanates (**2**–**11**) which were available, the 2α-Me group, when it occurs, has little influence on the observed Cotton effect (cf. **2** vs. **8**

† see footnote on page 6913.

or **6** vs. **10** in Table 1). It is therefore pertinent to examine the contribution of a 2α-Me group to the predicted sign of the Cotton effects of the various rotamers. In rotamer A, the Me group lies in a nodal plane, causing no change in rotatory contribution, but creating a slight steric hindrance to this rotamer. A less positive Cotton effect is predicted for B and a less negative one for C. The observed positive Cotton effect for **8**

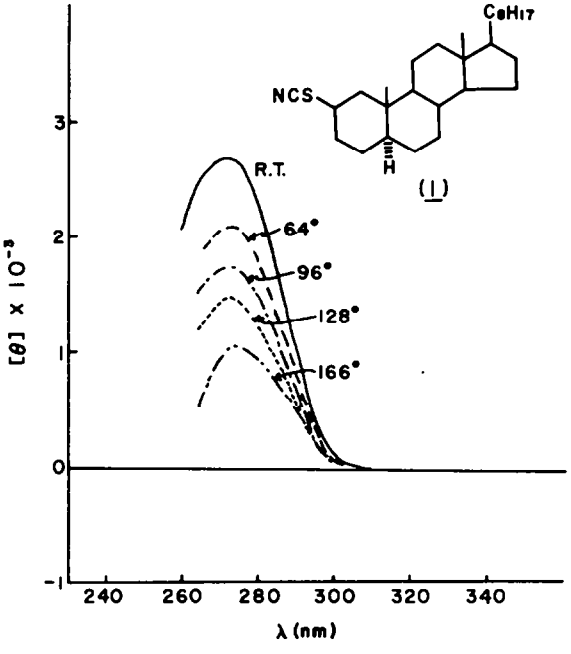


FIG. 4 Variable-temperature CD (decalin) of 2β-thiocyanato-5α-cholestane (**1**).

again points to a preponderance of rotamer B. Perhaps the *changes* in Cotton effect of rotamers B and C just offset one another, but this assumes a similarity in population for B and C which would be a coincidence at best. Also the observation that the Δ^5-double bond in comparing compounds **3** and **11** has little influence on the Cotton effect suggests that the energy difference between rotamers A, B and C is very small. It must, however, be remembered that the rotatory contribution of each rotamer has no reason to be identical.

Introduction of a 3β-Me group does lower the observed Cotton effect slightly (cf. **2** vs. **6** or **3** vs. **7** in Table 1), but since the group **R** and the solvents are different in the two this change has little statistical meaning. Just as in the case of a 2α-Me function, analysis of the effect of the added substituent led to no conclusive results.

Six probable low-energy rotamers of 3α-thiocyanato-5α-cholestane (**12**) are represented by octant projections D–I. On conformational grounds, rotamers F, G and H appear to be less favored since each of them contains at least one 1,3-diaxial hydrogen-thiocyanate interaction. The observed small positive Cotton effect, which remains constant between 130° and −192°, within experimental error, suggests that E

is the preferred rotamer but at least the energy difference between E, D and I is apparently very small.

Insertion of a 2α- or 4α-Me group has a most dramatic effect. As is the case with azides,[3] a 4α-Me substituent intensifies the already positive Cotton effect, while a 2α-Me function acts in the opposite way. Whereas the 2α-methyl-3α-azido-5α-cholestane Cotton effect was negative at room temperature,[3] that of the 2α-methyl 3α-thiocyanate (**14**) is positive at room temperature but becomes negative at −192°.

Inspection of space-filled models for this compound **14** shows that E is much less favorable. Use of the thiocyanate octant rule in conjunction with projections shows that a 2α-Me group in the molecule probably makes rotamer D positive, I slightly less negative, and the unfavorable E essentially unchanged, the Me being near the ill-defined XY plane. These factors tend to counteract one another and the preference for rotamer I is only seen at liquid nitrogen temperature.

Comparison of compounds **21** and **22** (Table 1) also verifies the effect of introduction of a 2α-Me group on lowering the rotational strength of the Cotton effect due to an alteration in rotameric population. Comparison of compounds **23** and **24** (Table 1) then presents a seemingly serious anomaly, since insertion of a 2α-Me group in **23** to give **24** causes a substantial increase in the rotational strength. This difference can be attributed to the 3β-Me function in these now tertiary thiocyanates and can be understood by considering three compounds. If we consider first the addition of a 3β-Me group to **21** to give **23**, we find from the thiocyanate octant rule that the predicted change in sign of the Cotton effect of the rotamers will be a positive enhancement for I (less negative), a smaller positive value for E, and no change for D, since the Me is now in a symmetry plane. Space-filled models show a slight hindrance for rotamer D only, and there is a slight increase in the Cotton effect observed for the 3β-methylated compound, so apparently the positive enhancement for I is the determining factor. Thus if we now compare the addition of a 2α-Me group to **23** to give **24**, we can see from the thiocyanate octant rule that the predicted Cotton effect of I again receives a positive enhancement, E will be little changed, and D becomes positive. Rotamer I appears to be favored (according to space-filled models), so the predicted positive increases in the Cotton effects of D and I apparently cause the observed positive increase in the Cotton effect of compound **24**.

Incorporation of a 4α-Me group (see **15** in Table 1 and Fig. 3) causes steric hindrance to rotamer I, while the predicted Cotton effect of I is essentially unchanged (Me group near the ill-defined XY plane), D becomes more negative and E less positive. The compound has a higher rotational strength than the unsubstituted 3α-thiocyanate, becoming much stronger at −192°, which clearly indicates E to be the preferred rotamer. However, there is evidence of asymmetric solvation effects[11] in the appearance of a small negative Cotton effect at 280 nm, which was seen only in EPA and not in the other solvents at room temperature.

In the 2β-methyl 3α-thiocyanate (**13**), the predicted Cotton effect of rotamer D will probably now be positive and that of E somewhat more positive, while in I the 2β-Me group lies in a nodal plane. Space-filled models show that the 2β-Me substituent exerts a negligible steric effect on the 3α-thiocyanate. One might expect the CD to be very similar to that of the unsubstituted 3α-thiocyanate but with a positive enhancement. This is indeed the case, with $[\theta]_{max}$ being 1320 for the methylated compound (**13**) and 446 for the unmethylated precursor (**12**), but this may only be a

coincidence since these predictions are based on octant projections with ring A in the chair form. However, it is quite likely that the axial 2β-Me group causes a deformation of ring A to a flexible form, which would defy analysis by our present models. Low temperature CD for this compound shows very little change in the rotational strength, indicating little change in rotameric population if ring A is indeed an intact chair.

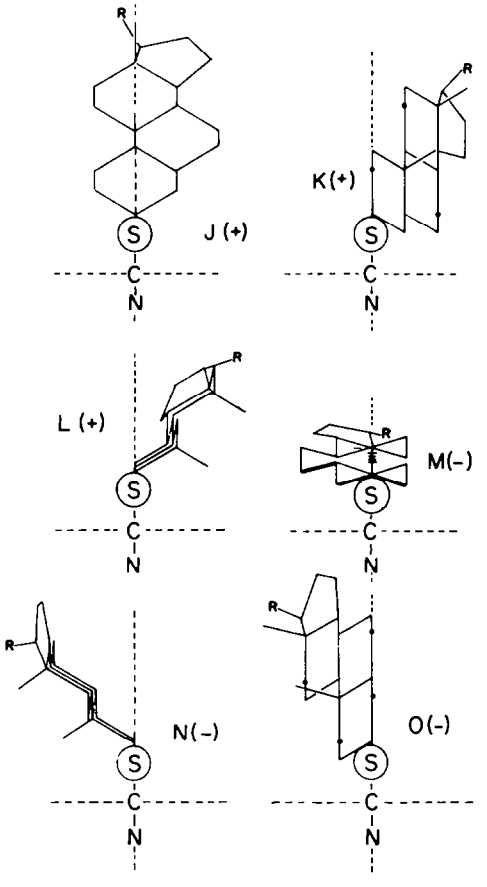
Introduction of a 2β-OH substituent to a 3α-thiocyanate has much the same effect on the amplitude of the Cotton effect at room temperature as introduction of a 2β-Me group (cf. **13** vs. **20** and **21** in Table 1), and for the same reasons as discussed for **13**. However, interpretation of the remaining 3α-thiocyanates is more dubious, since introduction of an acetoxyl function results in further rotameric complications, which is not the case with methylated compounds. Nevertheless, an interesting case is provided by 2β- and 4β-acetoxy-3α-thiocyanato-cholestanes (**27**) and (**30**), in which the rotatory contribution of the 2β-acetoxy group is opposite in sign and of smaller magnitude than that of the 4β-acetoxy group. Examination of the change in sign of the Cotton effects of rotamers D, E and I is now more difficult due to rotameric equilibria in the acetoxyl groups. Thus a prediction for change of signs in rotamers E and I is practically impossible, but the Cotton effect of rotamer D should become more negative for the 4β-acetoxy-isomer (**30**), corresponding to the observed Cotton effect; and positive for the 2β-acetoxy compound (**27**), also corresponding to its observed Cotton effect. Examination of variable-temperature CD data for **30** indicates no change in Cotton effect amplitude between room temperature and +68° and only a slight increase on going from room temperature to −192°. Thus again the energy barrier between rotamers D, E and I must be small.

A particularly interesting situation is presented by 2β-acetoxy-3α-thiocyanato cholest-5-ene (**29**). In rotamer E, the special relationship between the thiocyanate chromophore and the double bond is very much like the β,γ-unsaturated ketones and a large positive Cotton effect is expected. On the contrary, a strong negative Cotton effect is predicted for D and I. The observed strong positive Cotton effect for **29** suggests the preponderance of rotamer E, even though the energy difference between E, D and I is very small.

The double-humped CD curve of 3α-thiocyanato cholestane-2β,5α-diol (**26**) indicates the existence of several species. Although this is most likely attributable to asymmetric solvation,[11] there exists the possibility that some of these species represent rotameric variations of the thiocyanate group due to formation of a hydrogen bond between the 5α-OH group and the sulfur lone pair. This would probably tend to favor rotamer I with its predicted negative Cotton effect, which is indeed the sign of the observed lower wavelength Cotton effect for this compound. A negative contribution of a 5α-OH group is also seen in going from compound **27** to **28**. Use of the thiocyanate octant rule in comparing compounds **27** and **28** leads us to expect little change in the Cotton effect of rotamers, D, E and I, since in each the OH group lies very near symmetry planes. (Space filled models show that the 2β-acetoxy group may occupy the front lower right octant in E in both compounds, but this should effect **27** and **28** the same.) Thus to account for the observed lowering of the Cotton effect we can only postulate an increased population of rotamer I, tending to support the hydrogen bonding hypothesis. The fact that **28** shows a larger decrease in rotational strength on passing from methanol to isooctane than does **27** can also be taken as evidence for formation of a hydrogen bond. However, this evidence is rather tenuous,

as electronic interactions of the 5α-OH group with solvent could change the Cotton effects of rotamers.

The 3β-thiocyanates **16–19** present a more complicated situation than the 3α thiocyanates as in the absence of C-2 or C-4 substituents all six rotamers, represented by the octant projections J–O, are of about equal probability. Stuart models show that nonbonded interactions with the hydrogen atoms on carbons 3 or 4 are somewhat greater in rotamers L, M, and N; but this is not serious enough to preclude examination of these rotamers. Although the steroid skeleton is somewhat harder to visualize in these projections, the signs indicated by the thiocyanate octant rule are more straightforward in the equatorial thiocyanates as in no case is a plane cutting through the molecule and placing atoms in upper octants.



Since there are three positive contributing and three negative contributing rotamers, it is not surprising that the 3β-thiocyanate **16** shows a virtually plain dispersion curve in the ORD and very small rotational strength in the CD spectra. The effects of assymetric solvation are quite pronounced in this compound (see Table 1), with a weak Cotton effect ($[\theta]_{max} = +80$) in isooctane, a still lower value in dioxane (+66), finally becoming −56 in methanol. In EPA, $[\theta]_{max}$ went from +24 at room tem-

perature to −420 at liquid nitrogen temperature, with an accompanying blue shift. Therefore these results are best viewed as solvation effects[11] rather than rotameric preferences.

Insertion of a Me group in the 2 or 4 position simplifies matters somewhat by ruling out two rotamers on steric grounds. In 3β-thiocyanato-2α-methyl-5α-cholestane (**18**), N and O are no longer favorable energetically. Further, inspection of the projections reveals that a 2α-Me group will cause rotamers J and K to become negative (less positive), L to become more positive, and M to change sign to positive. The observed negative Cotton effect, becoming much more negative at low temperature, points to a definite preference for rotamers J and K.

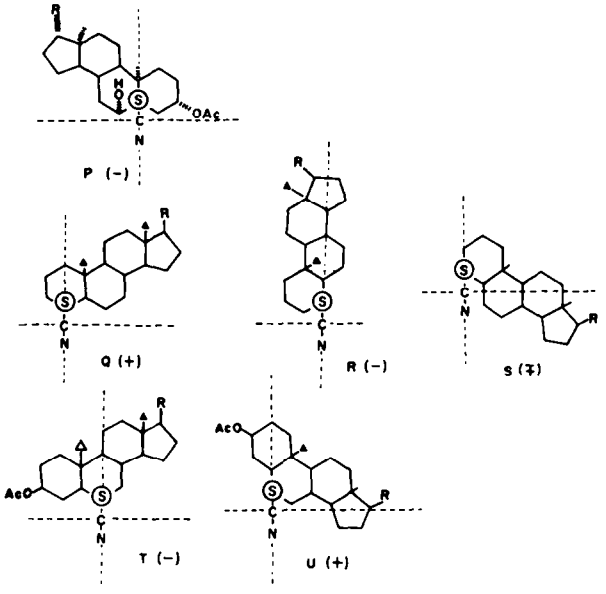
Stuart models rule out rotamers K and L for the 4α-methyl 3β-thiocyanate (**19**), while inspection of the effect of a 4α-Me substituent on the signs of the Cotton effects of the projected rotamers reveals that M and N will become more negative, J will become more positive, and O will become either positive or less negative. The positive Cotton effect points to a preference for J in particular, and O. The low temperature CD shows an increase in the Cotton effect at −74° but apparently little increase below that, indicating perhaps that the most favorable rotamer, J or O, is already "frozen out".

The 2β-methyl 3β-thiocyanate (**17**) has somewhat less hindrance to free rotation of the thiocyanate about the C—S—C bond than in **18** or **19**, but rotamers M and N will be unfavorable. The projections show that a 2β-Me group will make rotamer O more negative and rotamers K and L more positive, while it will make J less positive and probably negative. Thus the observed positive Cotton effect would tend to indicate that rotamers K and L are preferred. However, the relatively small change in the low temperature CD indicates that the energy difference between four accessible rotamers cannot be too great, and the possibility can again not be discounted that the 1–3 diaxial interaction of the two Me groups distorts ring A from a pure chair form, invalidating any thiocyanate octant rule projections.

Inspection of Stuart models of 5α-thiocyanato-cholestane 3β,6β-diol 3β-acetate (**34**) shows rotamer P to be by far the most favored. Application of thiocyanate octant projections to this rotamer shows that the 6β-OH group and carbons 11, 12, 19, the D-ring and the side chain lie in a negative lower rear octant, while the much closer 3β-acetoxyl function lies in a positive lower rear octant, all other atoms cancelling or lying in nodal planes. However, the acetoxyl group in its own rotameric variations can probably intrude into the negative front lower right octant. The prediction of a negative sign for this compound is therefore fairly safe and in agreement with the experimentally observed negative Cotton effect sign.

The three 4β-thiocyanates (**31**–**33**) all show negative Cotton effects (see Table 1). The thiocyanate octant projections reveal that rotamer Q will probably show a positive Cotton effect, rotamer R a negative Cotton effect, while a sign prediction for rotamer S is dubious because the molecule is split between a positive rear and a negative front octant. Fortunately, space-filled models show rotamer S to be least favored due to an interaction with the 6β-H atom. Consequently the observed negative Cotton effects for **31**–**33** suggest that R is the preferred rotamer in each. The observed small negative contribution of a 3α-OH function (as opposed to a 5α-OH function, cf. **31** vs. **33**, Table 1) is understandable since in the preferred rotamer R a 5α-OH group lies in a symmetry plane whereas a 3α-OH function would be expected to give a

negative contribution to the rotational strength. The low temperature CD data for **33** point to an increasing preference for R at low temperature. Finally it should be noted that the azide[3] corresponding to **33** showed a weak positive Cotton effect, which would seem anomalous except that the twenty degree difference in the chromophore-alkyl group bond angle[5] between azides and thiocyanates will make a large difference in the signs of various rotamers as seen by Dreiding models.



The two most favorable rotamers T and U for the 6β-thiocyanate **35** should probably show negative and positive signs respectively as revealed by thiocyanate octant projections. If the C and D rings and the 3β-acetoxyl group are ignored, the 6β-thiocyanate **35** is a mirror image of the 4β-thiocyanate **33**, and the corresponding favored "mirror image" rotamer is U, which with its predicted positive Cotton effect agrees with the positive Cotton effect observed for this compound at low temperature and in decalin solution (Table 1). However, solvation effects[11] for **35** are very marked, with large double humps in EPA even at −41°, rendering arguments for rotameric preferences dubious. Inspection of octant projections for the remaining thiocyanates (**36–39**) indicates great uncertainty in predicting Cotton effect signs, so further speculation on these compounds seems pointless.

In summary, the interpretations from an octant rule analysis of the ORD and particularly CD behavior of thiocyanato steroids are not completely conclusive because the very many accessible rotameric conformations introduce the complications noted. But when the chromophore has an obviously preferred orientation, which can most easily be seen with space-filled models, there is generally good coincidence between observed and predicted Cotton effect signs. Moreover, the thiocyanate chromophore, heretofore virtually neglected spectroscopically, offers another interesting example of a potential application of the octant rule to a non-carbonyl type chromophore.

EXPERIMENTAL

All measurements were performed using Spectrograde or purified solvents. ORD and CD measurements were performed partly at Stanford and partly at Osaka on a Jasco ORD/CD/5 spectropolarimeter. Variable temperature CD curves were obtained at Stanford.

Microanalyses were determined at Stanford by Messrs E. Meier and J. Consul and at Osaka by the members of the analysis room of Shionogi Research Laboratory. IR spectra were measured at Stanford on a Perkin–Elmer model 421 spectrophotometer, usually as KBr pellets, by Mrs. L. Carroll and Mr. J. Cawse and at Osaka on a Koken model DS-301 spectrophotometer by Mr. M. Takasuga, Optical rotation was determined in $CHCl_3$ solns at Stanford by Mrs. L. Carroll and Mr. J. Cawse and at Osaka by Messrs. T. Iwata and M. Moriyama. M.ps were determined on a Kofler block and are uncorrected.

The mass spectra were determined by Messrs. R. Ross and N. Garcia on an A.E.I. MS-9 or Atlas CH-4 mass spectrometers using direct inlet systems. Only the diagnostically most significant peaks are included. The NMR spectra were determined by Dr. T. Nishida on a Varian HA-100 spectrometer in $CDCl_3$ using TMS as internal standard. All thiocyanato steroids were shown by NMR to have the correct stereochemistry at C-3 and at the methylated carbon (for detailed analysis see Ref. 12).

General procedure for thiocyanate synthesis

While equatorial tosylates can be made by traditional methods, the following procedure had to be employed to obtain good yields of axial tosylates, especially those bearing Me groups at C-2 or C-4. The latter would not form in the presence of trace quantities of water and reaction at room temp gave olefin. Even analytical micro-slide TLC caused some decomposition to olefin of these sensitive tosylates.

To 0·2 g of the appropriate hydroxy cholestane in a vial with stirring bar was added 0·4 g of *p*-toluenesulfonyl chloride, m.p. 68·5–69°. After drying the vial at 56° and 0·1 torr until a little tosyl chloride had sublimed out, the vial was fitted with a septum, 1 ml of pyridine (distilled from BaO and stored over molecular sieves) injected, and placed in a desiccator. The reaction was stirred in a cold room (2°) for two days, after which time a crystal of ice was added. After stirring an additional 15 min, the mixture was partitioned between ether and 60 ml of ice-cold 1M HCl. The ether layer was washed successively with water, 5% $NaHCO_3$ aq, and water again, then dried ($MgSO_4$), filtered and evaporated. The crude tosylate was recrystallized, preferably from pentane.

The tosyloxycholestane (200 mg) was placed in a 5 ml long-necked conical flask with a 50% excess of KSCN and 2·5 ml 2-butanone, dried by distillation from P_2O_5 and stored over molecular sieves. The mixture was frozen (air excluded), the flask evacuated and the neck sealed with a torch. After heating in a steam bath for 24 hr, the flask was opened and the contents partitioned between ether and water. After washing twice with water, the ether layer was dried ($MgSO_4$), filtered and evaporated. The residue was separated on two silica gel GF_{254} chromatoplates (1:1 benzene–pet. ether) into thiocyanato cholestane and olefin.

3α-*Thiocyanato-5α-cholestane* (**12**)

5α-Cholestan-3β-ol tosylate[13] (200 mg, 0·368 mmole) and 54 mg (0·556 mmole, 51% excess) of KSCN were allowed to react in 2·5 ml 2-butanone according to the above procedure. After customary work-up and separation on chromatoplates 22 mg (16%) olefin, ν_{max} = 698 cm^{-1}, presumably Δ^2 cholestene, and 126 mg (80%) 3α-thiocyanato-5α-cholestane was obtained. Two crystallizations of the thiocyanate from MeOH gave platelets, m.p. 95–95·5°, $[\alpha]_D^{27}$ = 28° (*c* 1·5), ν_{max} = 2150 cm^{-1}. The mass spectrum showed *m/e* 429 (33%) (M^+), and *m/e* 370 (40%) (M^+—HSCN); with a metastable peak at 319 (calc. 319·1) being observed for loss of HSCN. (Found: C, 78·12; H, 10·91; N, 3·43; S, 7·73. $C_{28}H_{47}NS$ requires: C, 78·26; H, 11·02; N, 3·26, S, 7·46%). Lit.[14] m.p. 95·5–96°.

3β-*Thiocyanato-5α-cholestane* (**16**)

5α-Cholestan-3α-ol tosylate[13] (380 mg, 0·700 mmole) and 102 mg (50% excess) of KSCN were allowed to react in 5 ml 2-butanone as above. There was obtained after chromatography (3 plates) 121 mg (47%) olefin and 146 mg (49%) 3β-thiocyanato-5α-cholestane. The latter crystallized well from acetone to give prisms, m.p. 110–111°, $[\alpha]_D^{27}$ = 30° (*c* 1·0), ν_{max} = 2152 cm^{-1}, λ_{max} = 246 nm with ε_{max} = 42·9 (isooctane). The mass spectrum showed *m/e* 429 (63%) (M^+) and *m/e* 370 (33%) (M^+—HSCN). (Found: C, 78·11; H, 10·99; N, 3·38; S, 7·43. $C_{28}H_{47}NS$ requires: C, 78·26; H, 11·02; N, 3·26; S, 7·46%).

3α-Thiocyanato-2α-methyl-5α-cholestane (**14**)

2α-Methyl-5α-cholestan-3β-ol tosylate[15] (204 mg, 0·366 mmole) was displaced with 55 mg (50% excess) KSCN in 2·5 ml 2-butanone for 24 hr as usual. Following the standard work-up and chromatography gave 20 mg (14%) of predominantly 2-methyl-Δ^2-5α-cholestene with a smaller amount of more polar olefin (according to silica gel–10% $AgNO_3$ chromatography), presumably the Δ^3 isomer; and 114 mg (70%) 3α-thiocyanato-2α-methyl-5α-cholestane. Two crystallizations from acetone gave crystals which showed m.p. 90–91, $[\alpha]_D^{25} = 106°$ (*c* 1·0), $\nu_{max} = 2152\ cm^{-1}$. The mass spectrum showed *m/e* 443 (100%) (M^+) and *m/e* 384 (100%) (M^+—HSCN). (Found: C, 78·57; H, 11·20; N, 3·40; S, 7·10. $C_{29}H_{49}NS$ requires: C, 78·49; H, 11·13; N, 3·16; S, 7·22%).

2α-Methyl-5α-cholestan-3α-ol acetate

A mixture of 2α-methyl-5α-cholestan-3β-ol tosylate[15] (1·8 g, 3·23 mmole), 1·8 g freshly fused NaOAc, 18 ml glacial HOAc, and 1·8 ml Ac_2O was refluxed for 2·5 hr.[16] The reaction mixture was partitioned between water and $CHCl_3$, the aqueous layer washed with $CHCl_3$, and the organic layers conbined. The $CHCl_3$ solution was washed with 5% Na_2CO_3 aq and water, dried ($MgSO_4$), filtered and evaporated. The residue was chromatographed on 100 g of silica gel, the fractions eluted with pet. ether giving 725 mg (58%) of olefin. The fractions eluted with 1:1 benzene–pet. ether gave 487 mg (34%) 2α-methyl-5α-cholestan-3α-ol acetate which on crystallization from acetone had m.p. 135–137°, $\nu_{max} = 1720, 1250\ cm^{-1}$. The mass spectrum gave *m/e* 444 (13%) (M^+) and *m/e* 384 (97%) (M^+—HOAc). (Found: C, 80·80; H, 11·79. $C_{30}H_{52}O_2$ requires: C, 81·02; H, 11·79, O, 7·20%).

Analysis of the olefin fraction by silica gel–10% $AgNO_3$ TLC plates showed two widely separated spots. Column chromatography (30 g silica gel + 3 g $AgNO_3$) with hexane as eluent gave first 511 mg of 2-methyl-Δ^2-5α-cholestene, which after recrystallization from acetone had m.p. 97·5–98·5°, $[\alpha]_D^{27} = 71°$ (*c* 1·1), $\nu_{max} = 790\ cm^{-1}$; (Lit.[17] m.p. 97–97·5°, $[\alpha]_D = 75°$ (*c*, 0·74)).

Later fractions gave 198 mg 2α-methyl-Δ^3-5α-cholestene, which gave needles from acetone, m.p. 74·5–75·5°, $[\alpha]_D^{26} = 115°$ (*c*, 1·0), $\nu_{max} = 698\ cm^{-1}$. The mass spectrum showed *m/e* 384 (100%) (M^+) and *m/e* 316 (4%) ($M^+ - C_5H_8$ (retro-Diels–Alder)). [For comparison, in the mass spectrometer 2-methyl-Δ^2-5α-cholestene showed *m/e* 384 (100%) and *m/e* 316 (43%)]. The NMR showed, in addition to the side chain secondary Me groups, a secondary Me function, $\delta = 0{\cdot}969$, $J = 6{\cdot}9$ Hz and two (by integration) vinyl protons, centered at $\delta = 5{\cdot}3$. Upon epoxidation followed by LAH reduction, the compound also gave as the main product 2α-methyl-5α-cholestan-3α-ol, m.p. 109·5–111°, no mixture m.p. depression with an authentic sample (see below).

2α-Methyl-5α-cholestan-3α-ol

2α-Methyl-5α-cholestan-3α-ol acetate (400 mg, 0·899 mmole) dissolved in 10 ml ether was added to a suspension of 85 mg of LAH in 10 ml ether and the mixture refluxed for 30 min. After work-up by the Na_2SO_4 method 360 mg (99%) 2α-methyl-5α-cholestan-3α-ol was obtained, which after two recrystallizations from MeOH gave prisms, m.p. 110–111°, $[\alpha]_D^{27} = 29°$ (*c*, 1·1). (Found: C, 83·21; H, 12·44. $C_{28}H_{50}O$ requires: C, 83·51; H, 12·52; O, 3·97%); Lit.[17] m.p. 99–103° (not fully characterized).

2α-Methyl-5α-cholestan-3α-ol tosylate

2α-Methyl-5α-cholestan-3α-ol was converted to its tosyl ester by the above procedure scaled down for 150 mg (0·372 mmole) of compound. The crude tosylate (203 mg, 98%) was recrystallized from pentane-methylene chloride giving crystals, m.p. 104–104·5°, $\nu_{max} = 1170, 1185\ cm^{-1}$. (Found: C, 75·42; H, 9·93; S, 5·75. $C_{35}H_{56}O_3S$ requires: C, 75·49; H, 10·14; S, 5·76; O, 8·62%).

3β-Thiocyanato-2α-methyl-5α-cholestane (**18**)

2α-Methyl-5α-cholestan-3α-ol tosylate (148 mg, 0·266 mmole) and 39 mg (50% excess) KSCN were subjected to the usual displacement reaction in 2·5 ml 2-butanone. However, a ppt of potassium tosylate was noticed much earlier than usual so the reaction was allowed to proceed only 4 hr. After the usual work-up and chromatography there was obtained 69 mg (67%) of presumably mainly 2-methyl-Δ^2-5α-cholestene, $\nu_{max} = 790\ cm^{-1}$, and 18 mg (15%) of 3β-thiocyanato-2α-methyl-5α-cholestane, which gave crystals from acetone, m.p. 125–126°, $\nu_{max} = 2156\ cm^{-1}$. The mass spectrum showed *m/e* 443 (38%) (M^+) and *m/e* 384 (11%) (M^+ − HSCN). (Found: C, 78·23; H, 11·05. $C_{29}H_{49}NS$ requires: C, 78·49; H, 11·13; N, 3·16; S, 7·22%).

2β-Methyl-5α-cholestan-3α-ol

2-Methyl-Δ^2-5α-cholestene[17] (1·50 g, 3·90 mmole) was dissolved in 50 ml THF (freshly distilled from LAH) and cooled to 0° in a flask, which was flushed with N_2 and fitted with a septum. After injecting 3·9 ml of 1M BH_3 in THF (3-fold excess), the soln was stirred for 4 hr, at the end of which time 5 ml 10% NaOH aq was added cautiously. After several minutes 4 ml 30% H_2O_2 was added slowly and the mixture stirred vigorously for 90 min at 0°. The reaction mixture was then partitioned between ether and water, and the ether layer washed with 10% $NaHSO_3$ aq followed by water, then dried over $MgSO_4$, filtered, and evaporated Chromatography on 100 g alumina (benzene eluent) gave first 71 mg of ketonic (ν_{max} = 1700 cm^{-1}) impurities followed by 1·38 g (88%) 2β-methyl-5α-cholestan-3α-ol, and finally 92 mg (5·9%) 2α-methyl-5α-cholestan-3β-ol, m.p. 137–139° (crystallized from EtOH, no mixture m.p. depression with an authentic sample). Three crystallizations from EtOH gave an analytical sample of 2β-methyl-5α-cholestan-3α-ol, m.p. 119–120°, $[\alpha]_D^{27}$ = 44° (*c*, 1·0). (Found: C, 83·26; H, 12·40. $C_{28}H_{50}O$ requires: C, 83·51; H, 12·52; O, 3·97%); Lit.[17] m.p. 122–128°. Chromatographic examination (chromatoplate eluted 5 times with benzene) of the literature sample showed it to contain 2 mg of 2α-methyl-5α-cholestan-3α-ol (based on comparative R_f value only) and 12 mg of an alcohol, m.p. 128–130°. M^+ *m/e* 400, of yet unknown structure.

2β-Methyl-5α-cholestan-3α-ol tosylate

2β-Methyl-5α-cholestan-3α-ol (200 mg, 0·497 mmole) was converted to the 3α-tosylate by the above procedure, giving 210 mg (76%) 2β-methyl-5α-cholestan-3α-ol tosylate after recrystallization from pentane. The compound had m.p. 88·5–89·5°, ν_{max} = 1157, 1176, 1188 cm^{-1}. (Found: C, 75·40; H, 10·16; S, 5·79. $C_{35}H_{56}O_3S$ requires: C, 75·49; H, 10·14; S, 5·76; O, 8·62%).

3β-Thiocyanato-2β-methyl-5α-cholestane (17)

2β-Methyl-5α-cholestan-3α-ol tosylate (108 mg, 0·194 mmole) and 28 mg (50% excess) KSCN were allowed to react in 1·5 ml 2-butanone. Work-up and separation as usual gave 35 mg (47%) presumed Δ^2- and Δ^3-2-methyl-5α-cholestenes and 20 mg (23%) 3β-thiocyanato-2β-methyl-5α-cholestane, which on crystallization from acetone was found to have m.p. 94·5–96°, ν_{max} = 2152 cm^{-1}. The mass spectrum showed *m/e* 443 (93%) (M^+) and *m/e* 384 (54%) (M^+—HSCN). (Found: C, 78·39; H, 11·16. $C_{29}H_{49}NS$ requires: C, 78·49; H, 11·13; N, 3·16; S, 7·22%).

2β-Methyl-5α-cholestan-3β-ol

To 100 ml of distilled acetone was added 520 mg (1·292 mmole) 2β-methyl-5α-cholestan-3α-ol, while cooling the soln to 15° with stirring under a N_2 atm. A 30% excess (0·42 ml) 8N CrO_3–H_2SO_4–water soln[18] was added and stirring continued for 15 min; then a few drops 2-propanol was added and stirring continued several min. The reaction mixture was then partitioned between ether and water, the ether layer washed with water, dried briefly (Na_2SO_4), filtered and evaporated. The residue, crude 2β-methyl-5α-cholestan-3-one, was not purified but dried at room temp under vacuum (10^{-3} torr). The dried material was taken up in 20 ml dry ether and added slowly to a suspension of LAH (160 mg) in 15 ml ether. After refluxing for 30 min, the reaction was worked up in the usual way and the residue separated on 5 chromatoplates. The least polar fraction gave 28 mg (5%) presumed 2β-methyl-5α-cholestan-3α-ol (identical R_f to authentic material), while the main fraction gave 380 mg (73%) 2β-methyl-5α-cholestan-3β-ol, which after crystallization (EtOH) gave m.p. 136·5–137·5°, $[\alpha]_D^{27}$ = 45° (*c*, 1·0). Analytical TLC (eluted 5 times with benzene) showed essentially no contamination by the 2α-methyl epimer (pure compounds compared on the same plate with a mixture of the two). The NMR spectrum gave a more convincing demonstration of the absence of the 2α-methyl epimer. The literature constants on this substance prepared by different methods are contradictory: m.p. 121–124°, $[\alpha]_D$ = 30°[17] (examination of this sample by NMR showed it to contain about $\frac{1}{3}$ of the 2α-Me epimer); m.p. 142–145°, $[\alpha]_D$ = 26° (*c*, 0·9), and m.p. 145–147°, $[\alpha]_D$ = 23° (*c*, 0·7)[19]; and m.p. 134–135°, $[\alpha]_D$ = 42°.[20]

2β-Methyl-5α-cholestan-3β-ol tosylate

2β-Methyl-5α-cholestan-3β-ol (200 mg, 0·497 mmole) was converted to the tosylate with 400 mg tosyl chloride and 1·5 ml pyridine in the usual way. The crude 2β-methyl-5α-cholestan-3β-ol tosylate (238 mg, 86%) was recrystallized from pentane to give a microcrystalline mass, m.p. 95–96·5°, ν_{max} = 1176 cm^{-1}. (Found: C, 75·67; H, 10·02; S, 5·75. $C_{35}H_{56}O_3S$ requires: C, 75·49; H, 10·14; S, 5·76; O, 8·62%).

3α-Thiocyanato-2β-methyl-5α-cholestane (**13**)

According to the usual procedure 158 mg (0·284 mmole) 2β-methyl-5α-cholestan-3β-ol tosylate was displaced with 42 mg (52% excess) KSCN in 2·5 ml 2-butanone, but a ppt of potassium tosylate appeared after only 10 min, so the reaction was stopped after 4 hr. Work-up and chromatography gave 104 mg (95%) presumably mainly 2-methyl-Δ^2-5α-cholestene, ν_{max} = 790 cm^{-1}, and 1·1 mg (0·9%) 3α-thiocyanato-2β-methyl-5α-cholestane, which crystallized from 3 drops of EtOH to give m.p. 79–86°, $\nu_{max}^{CHCl_3}$ = 2150 cm^{-1}. The mass spectrum showed *m/e* 443 (100%) (M^+) and *m/e* 384 (75%) (M^+—HSCN) with a strong metastable peak at *m/e* 333 (calc. 333·4 for 443 → 384). High resolution measurements on the molecular ion gave an observed mass of 443·35832, $C_{29}H_{49}NS$ requires 443·35856 ($C_{12}F_{27}N$ as reference).

4α-Methyl-5α-cholestan-3β-ol tosylate

4α-Methyl-5α-cholestan-3β-ol[21] (1·3 g, 3·23 mmole), treated with 2·6 g tosyl chloride in 10 ml dry pyridine as usual gave a crude yield of 1·75 g (97%) 4α-methyl-5α-cholestan-3β-ol tosylate which on recrystallization from $CHCl_3$–EtOH gave platelets, m.p. 139–140°, ν_{max} = 1173, 1186 cm^{-1}. (Found: C, 75·49; H, 9·97; S, 6·01. $C_{35}H_{56}O_3S$ requires: C, 75·49; H, 10·14; S, 5·76; O, 8·62%).

3α-Thiocyanato-4α-methyl-5α-cholestane (**15**)

4α-Methyl-5α-cholestan-3β-ol tosylate (200 mg, 0·359 mmole) was treated with 55 mg (50% excess) KSCN in 2·5 ml 2-butanone as above. Customary work-up and chromatography gave 21 mg olefin, presumably mixed Δ^2- and Δ^3-4-methyl-5α-cholestenes, and 127 mg (80%) 3α-thiocyanato-4α-methyl-5α-cholestane, which after recrystallization from acetone had m.p. 120·5–121·5°, ν_{max} = 2150 cm^{-1}. The mass spectrum showed *m/e* 443 (52%) (M^+) and *m/e* 384 (48%) (M^+—HSCN), with a strong metastable ion at *m/e* 333 (calculated 333·4 for loss of HSCN) being observed. (Found: C, 78·68; H, 11·17; N, 3·29; S, 7·10. $C_{29}H_{49}NS$ requires: C, 78·49; H, 11·13; N, 3·16; S, 7·22%).

4α-Methyl-5α-cholestan-3α-ol acetate

4α-Methyl-5α-cholestan-3β-ol tosylate (1·3 g, 2·33 mmole) was subjected to acetolysis in an identical manner to the 2α-methyl-3β-tosylate (see above) except that the reaction was scaled down accordingly. Chromatography of the residue, after work-up, on 40 g silica gel with pet. ether at eluent gave 619 mg (69%) of olefin. Elution with 90% pet. ether–10% ether gave 298 mg (29%) 4α-methyl-5α-cholestan-3α-ol acetate, which crystallized from EtOH, m.p. 112–113°, ν_{max} = 1740, 1240 cm^{-1}. The mass spectrum showed *m/e* 444 (22%) (M^+) and *m/e* 384 (100%) (M^+—HOAc). (Found: C, 81·09; H, 11·80. $C_{30}H_{52}O_2$ requires: C, 81·02; H, 11·79; O, 7·20%). The olefin fraction was found to contain three olefins by silver nitrate TLC. Separation of the mixture on 6 silica gel G–10% $AgNO_3$ chromatoplates (hexane) gave 245 mg of least polar olefin (R_f 0·5) m.p. 85–87° (acetone); 191 mg olefin (R_f 0·2), m.p. 90–91° (acetone); and 89 mg olefin (R_f 0·1), m.p. 84–86° (acetone). All three olefins showed *m/e* 384 (M^+) as the base peak, but all had distinctly different NMR and IR spectra. The least polar olefin, m.p. 85–87°, showed 1 vinyl proton at δ = 5·35 and a vinyl Me at δ = 1·62. Therefore it can be assigned the structure 4-methyl-Δ^3-5α-cholestene. (Found: C, 87·52; H, 12·58. $C_{28}H_{48}$ requires: C, 87·42; H, 12·58%). For speculations on structure of the other two olefins see Ref. 12.

4α-Methyl-5α-cholestan-3α-ol

4α-Methyl-5α-cholestan-3α-ol acetate (250 mg, 0·562 mmole) dissolved in 10 ml dry ether was added to a suspension of 50 mg of LAH in 10 ml ether. After refluxing for 30 min, the reaction was worked up in the usual way to give 221 mg (98%) 4α-methyl-5α-cholestan-3α-ol, which after 3 crystallizations from EtOH showed m.p. 116–117°, $[\alpha]_D^{27}$ = 10° (*c*, 1·0). (Found: C, 83·63; H, 12·45. $C_{28}H_{50}O$ requires: C, 83·51; H, 12·52; O, 3·97%).

4α-Methyl-5α-cholestan-3α-ol tosylate

4α-Methyl-5α-cholestan-3α-ol (124 mg, 0·308 mmole) was treated with 300 mg tosyl chloride and 1 ml pyridine according to the usual procedure to give 149 mg (87%) crude 4α-methyl-5α-cholestan-3α-ol tosylate, which on recrystallization from pentane–methylene chloride gave platelets, m.p. 104–106°, ν_{max} = 1160, 1170, 1186 cm^{-1}. (Found: C, 75·54; H, 10·14; S, 5·58. $C_{35}H_{56}O_3S$ requires: C, 75·49; H, 10·14; S, 5·76; O, 8·62%).

3β-*Thiocyanato*-4α-*methyl*-5α-*cholestane* (**19**)

4α-Methyl-5α-cholestan-3α-ol tosylate (120 mg, 0·215 mmole) was displaced with 31 mg (50% excess KSCN in 2 ml 2-butanone in the usual way, except for 12 hr. The usual work-up and chromatography gave 46 mg (55%) olefin and 22 mg (23%) 3β-thiocyanato-4α-methyl-5α-cholestane which crystallized from acetone to give m.p. 134–135°, ν_{max} = 2150 cm^{-1}. The mass spectrum showed *m/e* 443 (100%) (M^+) and *m/e* 384 (15%) (M^+—HSCN). (Found: C, 78·22; H, 11·10. $C_{29}H_{49}NS$ requires: C, 78·49; H, 11·13; N, 3·16; S, 7·22%).

4β-*Thiocyanato*-5α-*cholestan*-5α-*ol* (**33**)

To a mixture of KSCN (3 g) dissolved in a small volume of ice water and ether (10 ml), 4·5 g of H_3PO_4 was added in small portions and shaken to extract HSCN formed into ether layer. The pink colored HSCN–ether soln was dried (Na_2SO_4) and added to 393 mg 5α-cholestan-4α,5α-oxide.[22] The reaction mixture was allowed to stand at room temp overnight. The soln was washed with Na_2CO_3 aq and water, dried (Na_2SO_4), and evaporated to dryness. Recrystallization with ether–EtOH afforded 178 mg of needles, m.p. 162–164°, ν_{max}^{Nujol} 3556 (OH), 2162 (SCN) cm^{-1}. (Found: C, 75·81; H, 10·70; N, 3·04; S, 7·45. $C_{28}H_{47}ONS$ requires: C, 75·44; H, 10·63; N, 3·14; S, 7·19%).

11β-*Thiocyanato*-5α-*pregnane*-3β,12α,20β-*triol* 3,20-*diacetate* (**36**)

3β,20β-Diacetoxy-5α-pregnan-11α,12α-oxide † (1·470 g) was treated with HSCN-soln, prepared from 10·1 g KSCN, 12·5 g H_3PO_4, and 30 ml ether, at room temp for 3 days. After work-up as mentioned above, recrystallization from $CHCl_3$–hexane afforded 1·522 g (90·8%) cubes, m.p. 94–96°, $[\alpha]_D^{25}$ +46·0 ± 2° (*c*, ν_{max}^{Nujol} 3452 (OH), 2150 (SCN), 1729, 1246 (OAc) cm^{-1}. (Found: C, 64·47; H, 8·30; N, 2·70; S, 6·40. $C_{26}H_{39}O_5NS \cdot \frac{1}{2}H_2O$ requires: C, 64·56; H, 8·27; N, 2·90; S, 6·63%).

12α-*Thiocyanato*-5α-*pregnane*-3β,11β,20β-*triol* 3,20-*diacetate* (**37**)

3β,20β-Diacetoxy-5α-pregnan-11β,12β-oxide[23] (557 mg) was treated with HSCN–ether soln, prepared from 3·8 g KSCN, 4·7 g H_3PO_4, and 20 ml ether, at room temp for 3 days. After work-up as mentioned above, recrystallization from $CHCl_3$–hexane gave 596 mg (93·8%) needles, m.p. 213–215°, $[\alpha]_D^{26}$ +104·7 ± 4° (*c*, 0·550), ν_{max}^{Nujol} 3467 (OH), 2172 (SCN), 1730, 1261, 1239 (OAc) cm^{-1}. (Found: C, 65·38; H, 8·29; N, 2·82; S, 6·81. $C_{26}H_{39}O_5NS$ requires: C, 65·38; H, 8·23; N, 2·93; S, 6·70%).

16β-*Thiocyanato*-5α-*androstane*-3β,17α-*diol* 3-*monoacetate* (**38**)

3β-Acetoxy-5α-androstan-16α,17α-oxide[24] (5·00 g) was treated with HSCN–ether soln, prepared from 30 g KSCN, 45 g H_3PO_4, and 150 ml ether, at room temp overnight. The soln was washed with Na_2CO_3 aq and water, dried (Na_2SO_4) and evaporated to dryness. The crystalline residue was recrystallized from acetone–hexane to give 5·32 g (90·5%) rods, m.p. 193–195°, $[\alpha]_D^{27}$ −27·8 ± 2° (*c*, 1·054), ν_{max}^{Nujol} 3458 (OH), 2164 (SCN), 1715, 1268, 1058, 1030 (OAc) cm^{-1}. (Found: C, 67·64; H, 8·61; N, 3·57; S, 8·10. $C_{22}H_{33}O_3NS$ requires: C, 67·48; H, 8·50; N, 3·58; S, 8·19%).

17α-*Thiocyanato*-5α-*androstane*-3β,16β-*diol* 3-*monoacetate* (**39**)

3β-Acetoxy-5α-androstan-16β,17β-oxide[24] (m.p. 127–128°, $[\alpha]_D^{22.5}$ +13·4 ± 2° (*c*, 0·976), ν_{max}^{Nujol} 1731, 1269, 1249 (OAc) cm^{-1}), (2·097 g) was treated with HSCN–ether soln, prepared from 12 g KSCN, 18 g H_3PO_4, and 60 ml ether, at room temp overnight. After work-up as mentioned above recrystallization from ether–pet. ether and further from acetone–hexane afforded 695 mg (28·1%) prisms, m.p. 167–168°, $[\alpha]_D^{23}$ −45·2 ± 2° (*c*, 1·011), ν_{max}^{Nujol} 3458 (OH), 2170 (SCN), 1730, 1244, 1027 (OAc) cm^{-1}.

The synthesis of compounds **5**–**11**, **22**–**26**, **28** and **29** will be published elsewhere by the Shionogi authors.

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† This compound was prepared from 3β,20β-diacetoxy-5α-pregn-11-ene, m.p. 97–98°, by epoxidation with monoperphathalic acid and showed m.p. 162–163°, $[\alpha]_D^{27}$ +32·9 ± 2° (*c*, 1·00) and ν_{max}^{Nujol} 1729, 1260, 1244 (OAc), 879 cm^{-1}.

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