68. *Infrared Absorption of Halogeno-steroids.*

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An examination of the infrared absorption spectra of 2-, 3-, 5-, 6-, and 7-chloro-steroids and 2-, 3-, 4-, 5-, 6-, and 7-bromo-steroids, in which the stereochemical configurations of the carbon–halogen linkages are known, has revealed that the stretching frequency for an equatorial carbon–halogen linkage is greater than that for the corresponding axial linkage.

THE absorption frequencies of carbon–halogen linkages in simple alkyl halides [1] and halogeno*cyclo*hexanes [2] have received considerable attention and have been used in studies of internal rotation in these compounds. No information on the absorption of carbon–halogen linkages in halogeno-steroids has been published; Corey, Sneen, Danaher,

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[1] Brown and Sheppard, *Trans. Faraday Soc.*, 1954, **50**, 1164; Mizushima, " Structure of Molecules and Internal Rotation," Academic Press, New York, 1954, and references there cited.

[2] (*a*) Larnaudie, *Compt. rend.*, 1952, **235**, 154; 1953, **236**, 909; *J. Phys. Radium*, 1954, **15**, 650; (*b*) Kozima, Sakashita, and Maeda, *J. Amer. Chem. Soc.*, 1954, **76**, 1965.

Young, and Rutledge [3] reported that an equatorial carbon–chlorine linkage absorbs at a higher frequency than an axial, but did not provide supporting evidence. We believe that infrared spectroscopy is of value for assigning the conformations of carbon–halogen linkages in halogeno-steroids and that therefore the spectra of such compounds deserve more attention.

Jones, Ramsay, Herling, and Dobriner [4] (see also Corey [5]) developed a carbonyl stretching frequency method for assigning the conformations of carbon–bromine linkages in α-bromoketo-steroids; the method is, however, limited to α-halogenoketo-steroids. A method that is dependent on the carbon–halogen stretching frequency would have a much wider application.

One of us [6] has postulated that in general the stretching frequency for an equatorial substituent in ring A of a steroid is slightly greater than that for an axial substituent. In order to extend the possible applications of such a generalisation we have examined the infrared spectra of several pairs of epimeric bromo- and chloro-steroids and have been able to show that an equatorial carbon–halogen linkage absorbs at a higher frequency than an axial. The carbon–chlorine and carbon–bromine bands are fairly strong and, since they appear in a spectral region in which alicyclic compounds do not absorb strongly, the bands can be readily identified.

Since axial carbon–bromine linkages absorb below 650 cm.$^{-1}$, it was necessary to examine the halogeno-steroids over the 1000—400 cm.$^{-1}$ region by means of a spectrophotometer fitted with a potassium bromide prism. No information on the infrared absorption of steroids at frequencies below 650 cm.$^{-1}$ has so far been published. In view of the importance of the carbon–halogen bands, it is recommended that all reference spectra of chloro- and bromo-steroids should be recorded over the 1000—400 cm.$^{-1}$ region.

Certain simple alkyl halides [1] and halogeno*cyclo*hexanes [2] exhibit internal rotation and in the solid and the liquid state yield different infrared and Raman spectra. Thus the infrared spectrum of a liquid *n*-propyl halide has two carbon–halogen stretching bands (*gauche* and *trans* forms of the molecule) and that of the solid, one band (*trans* form). The halogeno-steroids would not be expected to show internal rotation and both their carbon disulphide solutions and Nujol mulls yield similar spectra. Nevertheless, many chloro- and bromo-steroids exhibited more than one band in the carbon–halogen stretching region, the stronger band, which is listed in the Tables, usually appearing at a slightly higher frequency than the weaker band.

The observations summarised in Table 1 show that an equatorial carbon–chlorine linkage in 2- (755 cm.$^{-1}$), 3- (782—750 cm.$^{-1}$), and 7-chloro-steroids (749 cm.$^{-1}$) has a higher stretching frequency than the corresponding axial linkage (693, 730—617, and 588 cm.$^{-1}$, respectively). The absorption frequency differences for the epimeric pairs are greater than those reported for epimeric hydroxy-,[6b—d] methoxy-,[6a] acetoxy-,[6a, 6f] and deutero-steroids.[3] Unexpectedly strong bands at about 1258, 1275 and 1162, 1168, and 1275 cm.$^{-1}$ in the infrared spectra of 3α-chlorocholestane (Fig. *a*; C.S. No. 301), 3α-chlorocoprostane (Fig. *b*; C.S. No. 302), 3β-chlorocholestane (Fig. *c*; C.S. No. 303), and 3β-chlorocoprostane (Fig. *d*; C.S. No. 304), respectively, are also worthy of notice; similar bands appear in the spectra of the corresponding bromo-steroids.

The carbon–chlorine stretching frequencies for the dichloro-steroids (see Table 2) appear within, or close to, the ranges observed for monochloro-steroids. In compounds containing two equatorial or two axial chlorine atoms it is not possible to assign the equatorial or axial absorption bands to specific chlorine atoms; this is indicated in the Table by the insertion of " ? " after the frequency values for those bands whose assignment is uncertain.

The characteristic absorption bands for other substituents in the steroids listed appear at

[3] Corey, Sneen, Danaher, Young, and Rutledge, *Chem. and Ind.*, 1954, 1294.

[4] Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828.

[5] Corey, *ibid.*, 1953, **75**, 2301, 3297.

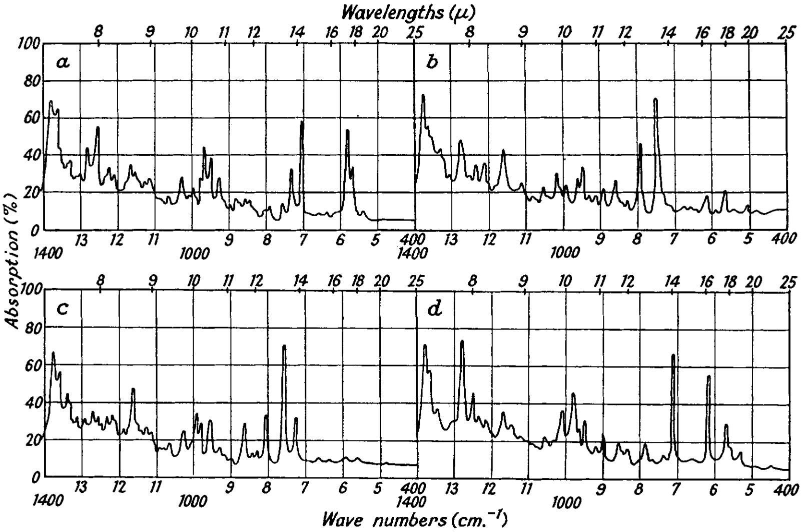
[6] (*a*) Page, *J.*, 1955, 2017; see also (*b*) Fürst, Kuhn, Scotoni, and Günthard, *Helv. Chim. Acta*, 1952, **35**, 951; (*c*) Cole, Jones, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 5571; (*d*) Rosenkrantz and and Zablow, *ibid.*, 1953, **75**, 903; (*e*) Ref. 3; (*f*) Stoll, Petrzilka, Rutschmann, Hofmann, and Günthard, *Helv. Chim. Acta*, 1954, **37**, 2039; (*g*) Rosenkrantz and Skogstrom, *J. Amer. Chem. Soc.*, 1955, **77**, 2237.

the expected frequencies. Thus the equatorial hydroxyl group in 2α-chlorocholestan-3β-ol absorbs at about 1056 cm.$^{-1}$, and the axial hydroxyl groups in 2β-chlorocholestan-3α-ol and 3α-chlorocholestan-2β-ol absorb at 1005 and 1012 cm.$^{-1}$, respectively.

The equatorial carbon–bromine linkages (see Table 3) for 2- and 3-bromo-steroids absorb at about 754—708 and 708—704 cm.$^{-1}$, respectively, and the corresponding axial linkages at about 662 and 692—591 cm.$^{-1}$, respectively. Equatorial and axial carbon–halogen linkages in dibromo- and bromochloro-steroids (see Tables 4 and 5) absorb in the same frequency ranges (see below) as the corresponding linkages in monohalogeno-steroids. It is possible to distinguish without difficulty between equatorial and axial halogen atoms.

The observation that an equatorial carbon–halogen linkage absorbs at a higher frequency than an axial linkage may be explained qualitatively by an extension of the suggestion, advanced for 3-hydroxy-steroids by Cole, Jones, and Dobriner,[6c] that the stretching motion of an equatorial 3-substituent causes appreciable expansions and contractions of the *cyclo*hexane ring, whereas the stretching motion of an axial 3-substituent is largely normal to the plane of the ring and will have a smaller effect; the restoring force acting on $C_{(3)}$ should therefore be less for the axial than for the equatorial motion and should induce a lower vibration frequency. This hypothesis is supported by the spectra of α-substituted bromo-steroids.

Infrared spectra (1400—400 *cm.*$^{-1}$) *of* (*a*) 3α-*chlorocholestane,* (*b*) 3α-*chlorocoprostane,* (*c*) 3β-*chlorocholestane, and* (*d*) 3β-*chlorocoprostane in* CS_2.



The absorption frequencies observed for particular classes of equatorial or axial carbon–chlorine or carbon–bromine bands show close agreement with each other; the number of compounds examined with only one halogen atom and without unsaturation or neighbouring α-substituents was, however, small. Many of the halides examined were 1 : 2-dihalides or related halogenohydrins; it is of interest to examine the effect of neighbouring α-substitution on the carbon–halogen band frequency. So far as available data show, substitution of α-axial chlorine has a greater influence than α-axial hydroxyl on the absorption frequency for axial chlorine. The same applies to the effect of α-axial hydroxyl and bromine on the absorption frequency for axial bromine. The effect of neighbouring α-axial bromine on the frequency for axial bromine is profound, a shift of about 150 cm.$^{-1}$ towards lower frequencies being observed. On the other hand, α-equatorial bromine has no effect on the frequency for equatorial bromine. These effects are illustrated more specifically by the following examples. Cholestanyl bromide has an equatorial carbon–bromine frequency of 706 cm.$^{-1}$, and the stereoisomeric *epi*cholestanyl bromide an axial carbon–bromine frequency of 690 cm.$^{-1}$. The diequatorial 2α : 3β-dibromocholestane has carbon–bromine frequencies at 750 and 682 cm.$^{-1}$, frequencies only slightly displaced

TABLE 1. *Carbon–chlorine stretching frequency assignments (cm.$^{-1}$) for monochloro-steroids in* CS_2 *solution.*

			2-Chloro		3-Chloro		5-Chloro		6-Chloro		7-Chloro	
No.	Compound	Ref.	*e* *	*a* *	*e*	*a*	*e*	*a*	*e*	*a*	*e*	*a*
1	2α-Chlorocholestan-3β-ol	*a*	755	—	—	—	—	—	—	—	—	—
2	2β-Chlorocholestan-3α-ol	*b*	—	693	—	—	—	—	—	—	—	—
3	3α-Chlorocholestane	*c*	—	—	—	707	—	—	—	—	—	—
4	3α-Chlorocholestan-2β-ol	*b*	—	—	—	699	—	—	—	—	—	—
5	3α-Chlorocholestan-5-ene	*d*	—	—	—	617	—	—	—	—	—	—
6	3α-Chlorocoprostane	*e*	—	—	750	—	—	—	—	—	—	—
7	3β-Chlorocholestane	*c*	—	—	755	—	—	—	—	—	—	—
8	3β-Chloro-3α-methylcholestane	*f*	—	—	782	—	—	—	—	—	—	—
9	3β-Chlorocholest-5-ene	*g*	—	—	760	—	—	—	—	—	—	—
10	3β-Chlorostigmast-5-ene	*h*	—	—	760	—	—	—	—	—	—	—
11	3β-Chlorocoprostane	*i*	—	—	—	709	—	—	—	—	—	—
12	3β-Chlorocoprostan-6-one	*j*	—	—	—	711	—	—	—	—	—	—
13	3β-Chlorocoprostan-6β-ol	*j*	—	—	—	726	—	—	—	—	—	—
14	3β-Chlorocoprostan-6β-yl acetate	*j*	—	—	—	730	—	—	—	—	—	—
15	5α-Chloro-6β-hydroxycholestan-3β-yl benzoate	*k*	—	—	—	—	—	685	—	—	—	—
16	6β-Chlorocholestane-3β : 5α-diol	*l*	—	—	—	—	—	—	—	706	—	—
17	6β-Chloro-5α-hydroxycholestan-3β-yl acetate	*k*	—	—	—	—	—	—	—	706	—	—
18	6β-Chloro-5α-hydroxycholestan-3β-yl benzoate	*k*	—	—	—	—	—	—	—	707	—	—
19	7α-Chlorocholestane	*m*	—	—	—	—	—	—	—	—	—	588
20	7β-Chlorocholestane	*m*	—	—	—	—	—	—	—	—	749	—

* *a* = axial; *e* = equatorial.

[a] Beereboom, Djerassi, Ginsburg, and Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 3500; [b] Alt and Barton, *J.*, 1954, 4284; [c] Shoppee, *J.*, 1946, 1138; [d] Shoppee and Summers, *J.*, 1952, 1790; [e] Lewis and Shoppee, *J.*, 1955, 1365; [f] Barton, Campos-Neves, and Cookson, unpublished work; [g] Diels and Blumberg, *Ber.*, 1911, **44**, 2847; [h] Windaus and Hauth, *Ber.*, 1906, **39**, 4378; [i] Bridgewater and Shoppee, *J.*, 1953, 1709; [j] Jones, Shoppee, and Summers, unpublished work; [k] Spring and Swain, *J.*, 1939, 1356; [l] Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 370, and references there cited; [m] Cremlyn and Shoppee, *J.*, 1954, 3794.

TABLE 2. *Carbon–chlorine stretching frequency assignments (cm.$^{-1}$) for dichloro-steroids in* CS_2 *solution.*

			2-Chloro		3-Chloro		5-Chloro		6-Chloro	
No.	Compound	Ref.	*e*	*a*	*e*	*a*	*e*	*a*	*e*	*a*
21	2α : 3β-Dichlorocholestane	*b*	784 ?	—	738 ?	—	—	—	—	—
22	2β : 3α-Dichlorocholestane	*b*	—	639	—	639	—	—	—	—
23	5α : 6α-Dichlorocholestan-3β-ol	*l*	—	—	—	—	—	684	777	—
24	5α : 6β-Dichlorocholestane	*l*	—	—	—	—	—	652	—	652
25	5α : 6β-Dichlorocholestan-3β-ol	*l*	—	—	—	—	—	650	—	650
26	5α : 6β-Dichlorocholestan-3β-yl acetate	*l*	—	—	—	—	—	648	—	648
27	5α : 6β-Dichlorocholestan-3β-yl benzoate	*l*	—	—	—	—	—	652	—	652

TABLE 3. *Carbon–bromine stretching frequency assignments* (*cm.*$^{-1}$) *for monobromo-steroids in* CS$_2$ *solution.*

			2-Bromo		3-Bromo		5-Bromo		7-Bromo	
No.	Compound	Ref.	*e*	*a*	*e*	*a*	*e*	*a*	*e*	*a*
28	2α-Bromocholestan-3α-ol	*n*	754	—	—	—	—	—	—	—
29	2α-Bromocholestan-3β-ol	*n*	708	—	—	—	—	—	—	—
30	2β-Bromocholestan-3α-ol	*b*	—	662	—	—	—	—	—	—
31	3α-Bromocholestane	*o*	—	—	—	690	—	—	—	—
32	3α-Bromocholest-5-ene	*d*	—	—	—	591	—	—	—	—
33	3α-Bromocoprostane	*e*	—	—	708	—	—	—	—	—
34	3β-Bromocholestane	*o*	—	—	706	—	—	—	—	—
35	3β-Bromocholest-5-ene	*o*	—	—	704	—	—	—	—	—
36	3β-Bromocoprostane	*i*	—	—	—	692	—	—	—	—
37	5α-Bromo-6β-hydroxycholestan-3β-yl benzoate	*p*	—	—	—	—	—	668	—	—
38	7β-Bromocholestane	*m*	—	—	—	—	—	—	710	—

[n] Fieser and Huang, *J. Amer. Chem. Soc.*, 1953, **75**, 4837; Corey, *ibid.*, p. 4832; [o] Roberts, Shoppee, and Stephenson, *J.*, 1954, 2705; [p] Barton, Miller, and Young, *J.*, 1951, 2598.

TABLE 4. *Carbon–bromine stretching frequency assignments* (*cm.*$^{-1}$) *for dibromo-steroids in* CS$_2$ *solution.*

			2-Bromo		3-Bromo		4-Bromo		5-Bromo		6-Bromo	
No.	Compound	Ref.	*e*	*a*	*e*	*a*	*e*	*a*	*e*	*a*	*e*	*a*
39	2α : 3β-Dibromocholestane	*b*	750 ?	—	682 ?	—	—	—	—	—	—	—
40	2β : 3α-Dibromocholestane	*b*	—	548	—	542	—	—	—	—	—	—
41	3α : 4β-Dibromocholestane	*b*	—	—	—	566 ?	—	547 ?	—	—	—	—
42	3β : 4α-Dibromocholestane	*b*	—	—	716 ?	—	693 ?	—	—	—	—	—
43	5α : 6β-Dibromocholestan-3β-yl benzoate	*q*	—	—	—	—	—	—	—	618 ?	—	566 ?
44	5β : 6α-Dibromocholestane	*q*	—	—	—	—	—	—	746 ?	—	707 ?	—
45	5β : 6α-Dibromocholestan-3β-yl benzoate	*q*	—	—	—	—	—	—	747 ?	—	722 ?	—

[q] Ref. 7 and references there cited.

TABLE 5. *Carbon–chlorine and carbon–bromine stretching frequency assignments* (*cm.*$^{-1}$) *for chlorobromo-steroids in* CS$_2$ *solution.*

			2-Chloro		3-Chloro		2-Bromo		3-Bromo	
No.	Compound	Ref.	*e*	*a*	*e*	*a*	*e*	*a*	*e*	*a*
46	3β-Bromo-2α-chlorocholestane	*b*	772	—	—	—	—	—	700	—
47	3α-Bromo-2β-chlorocholestane	*b*	—	601	—	—	—	—	—	601
48	2β-Bromo-3α-chlorocholestane	*b*	—	—	—	587	—	587	—	—
49	2α-Bromo-3β-chlorocholestane	*b*	—	—	772	—	703	—	—	—

TABLE 6. *Carbon–bromine stretching frequency assignments* (*cm.*$^{-1}$) *for 23-bromo-*isos*apogenins in* CS$_2$ *solution.*

No.	Compound	Ref.	*e*	*a*
50	23a-Bromo-12-oxo-5α : 22a-spirost-9(11)-en-3β-yl acetate	*r*	727	—
51	23b-Bromo-12-oxo-5α : 22a-spirost-9(11)-en-3β-yl acetate	*r*	—	655
52	11α : 23a-Dibromo-12-oxo-5α : 22a-spirostan-3β-yl acetate	*r*	728	—
53	11α : 23b-Dibromo-12-oxo-5α : 22a-spirostan-3β-yl acetate	*r*	—	652

[r] Ref. 10.

relative to that for cholestanyl bromide. In contrast the diaxial 2β : 3α-dibromocholestane shows carbon–bromine frequencies at 548 and 542 cm.$^{-1}$, frequencies greatly displaced relative to that for *epi*cholestanyl bromide. The simplest explanation for the difference in behaviour between 2α : 3β- and 2β : 3α-dibromocholestane is the importance of the weight of the neighbouring substituent and its coplanarity with the carbon–bromine and α-carbon atoms. As is well known,[7] diaxially substituted *cyclo*hexanes satisfy this requirement, whereas their diequatorial analogues do not.

The absorption frequencies of equatorial and axial carbon–chlorine linkages in the monohalogeno-steroids examined are respectively 56—39 and 37—17 cm.$^{-1}$ higher than those for the corresponding carbon–bromine linkages. The frequencies for the equatorial linkages in 3β-chloro-, 3β-bromo-, and 3β-iodo-cholest-5-ene (the only simple iodo-steroid available) [8] are 760, 704, and 672 cm.$^{-1}$, respectively. These values are close to those reported for monohalogeno*cyclo*hexanes by Larnaudie [2a] (equatorial and axial chlorine, 742 and 688 cm.$^{-1}$., respectively; equatorial and axial bromine, 685 and 658 cm.$^{-1}$, respectively; equatorial and axial iodine, 654 and 639 cm.$^{-1}$, respectively), but the values for bromine and iodine linkages are considerably higher than those quoted for simpler compounds by Bellamy [9] (600—500 cm.$^{-1}$ and near 500 cm.$^{-1}$, respectively).

In monohalogeno-steroids, the apparent molecular extinction coefficient of an equatorial carbon–halogen absorption band (carbon–chlorine, 150—100; carbon–bromine, 135—70) was usually greater than that of the corresponding axial absorption band (carbon–chlorine, 110—70; carbon–bromine, 95—45); the axial bands sometimes split into several relatively weak components. The apparent molecular extinction coefficients for the carbon–halogen stretching bands listed in Tables 1 and 3 for 3α-chloro-, 3β-chloro-, 3α-bromo-, and 3β-bromo-cholestane were about 75, 150, 55, and 135, respectively.

Dickson and Page [10] originally believed that the absorption band at about 726 cm.$^{-1}$ in the absorption spectrum of a 23a-bromo-*iso*sapogenin [11] was associated with a carbon–bromine linkage, but they discounted the suggestion because of the lack of supporting infrared evidence. A re-examination of the spectra of 23a-bromo- and 23b-bromo-*iso*-sapogenins [11] over the 1000—400 cm.$^{-1}$ region (see Table 6) has revealed strong absorption bands at about 727 and 654 cm.$^{-1}$, respectively, suggesting in the light of the observations reported above that, provided the bromine atom in bromo*iso*sapogenins is actually at $C_{(23)}$, the carbon–bromine linkages at $C_{(23)}$ are equatorial and axial, respectively.

EXPERIMENTAL

The halogeno-steroids were examined over the 4000—650 cm.$^{-1}$ and 1000—400 cm.$^{-1}$ spectral regions by means of a Perkin-Elmer Corporation, Model 21, double-beam, infrared spectrophotometer fitted with a sodium chloride or potassium bromide prism, respectively. Measurements with the sodium chloride prism were made as described by Dickson, Page, and Rogers.[12]

For potassium bromide prism measurements the instrument was calibrated by reference to known bands in the absorption spectra of ammonia gas and of the atmosphere; [13] the accuracy of frequency measurements for sharp absorption bands was probably greater than ±2 cm.$^{-1}$ over the range 1000—400 cm.$^{-1}$. The halogeno-steroids were examined as 1·0% (w/v) carbon disulphide solutions in a 2·0 mm. potassium bromide cell; compensation for solvent absorption was achieved by passing the reference beam of the spectrophotometer through pure carbon disulphide in a matched cell. Carbon disulphide absorbs weakly at about 652 cm.$^{-1}$ and strongly at about 422 cm.$^{-1}$.

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[7] Barton and Miller, *ibid.*, 1950, **72**, 1066.
[8] Beynon, Heilbron, and Spring, *J.*, 1936, 907.
[9] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 269.
[10] Dickson and Page, *J.*, 1955, 447.
[11] Mueller and Norton, *J. Amer. Chem. Soc.*, 1954, **76**, 749.
[12] Dickson, Page, and Rogers, *J.*, 1955, 443.
[13] Roberts, *J. Sci. Instr.*, 1954, **31**, 226, and references there cited.