Studies in the Synthesis of Cortisone. Part XI. Infrared Absorption of Alkoxy- and Acetoxy-steroids.*

By J. E. PAGE.

[Reprint Order No. 6134.]

Absorption bands in the 1150—1000-cm.$^{-1}$ region may be used to identify the stereochemical configuration of 3-acetoxy- and 3-methoxy-steroids, the carbon–oxygen stretching frequency for an equatorial bond being slightly greater than that for an axial bond. The ether linkages in a *gem*-dialkoxy-steroid give four carbon–oxygen stretching bands.

FÜRST, KUHN, SCOTONI, and GÜNTHARD (*Helv. Chim. Acta*, 1952, **35**, 951; see also Cole, Jones, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 5571, and Rosenkrantz and Zablow, *ibid.*, 1953, **75**, 903) have shown that in 2-, 3-, and 4-hydroxy-steroids the carbon–oxygen stretching frequency for an equatorial (1044—1037 cm.$^{-1}$) is greater than that for an axial hydroxyl group (1036—996 cm.$^{-1}$), and Corey, Sneen, Danaher, Young, and Rutledge (*Chem. and Ind.*, 1954, 1294) have reported that the stretching frequency for carbon–deuterium and carbon–chlorine linkages is greater for the equatorial than for the axial arrangement. These findings are in harmony with our observations on the infrared absorption of 3-methoxy-steroids and suggest that *in general* the stretching frequency for an equatorial substituent in ring A is probably slightly greater than that for an axial substituent. This hypothesis may be explained qualitatively by an extension of the suggestion advanced for 3-hydroxy-steroids by Cole *et al.* (*loc. cit.*) that the stretching motion of an equatorial 3-substituent causes appreciable expansions and contractions of ring A, 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.

Our hypothesis does not conflict with the observations by Jones, Humphries, Herling, and Dobriner (*J. Amer. Chem. Soc.*, 1951, **73**, 3215) and by Fürst *et al.* (*loc. cit.*) that equatorial 2- and 3-acetoxy-steroids give single peaks and axial 2- and 3-acetoxy-steroids multiple absorption peaks at about 1240 cm.$^{-1}$; 4-acetoxycholestane is exceptional in that both stereoisomers yield complex absorption peaks. Thompson and Torkington (*J.*, 1945, 640) showed that a simple alkyl acetate gives two strong carbon–oxygen stretching bands in the 1250—1000-cm.$^{-1}$ region; the stronger band at about 1240 cm.$^{-1}$ is associated with the carbon–oxygen linkage contiguous to the carbonyl group and the second band at about 1050 cm.$^{-1}$ with the carbon–oxygen linkage of the alcohol residue. It is the absorption frequency for the latter band at about 1050 cm.$^{-1}$ that we should expect to be greater for an equatorial than for an axial acetoxy-group; previously the behaviour of this band has not been studied systematically (see Jones and Herling, *J. Org. Chem.*, 1954, **19**, 1252). The band can be readily identified in the spectra of simple steroids and steroidal sapogenins, but its precise frequency cannot always be assigned in the spectra of compounds containing two or more acetate groups and in those of acetoxy-steroids containing hydroxyl groups. The apparent molecular extinction coefficient of the band ranges from about 350 to 200 and is about one-third that of the corresponding 1240-cm.$^{-1}$ band.

An examination of the infrared spectra of the 3-acetoxy-steroids (in CS_2 solution) available to us, of the spectra reproduced by Dobriner, Katzenellenbogen, and Jones ("Infrared Absorption Spectra of Steroids. An Atlas," Interscience Publ. Ltd., London, 1953), and of the absorption frequency values reported by Rosenkrantz and Zablow (*loc. cit.*) revealed that the alcohol-residue carbon–oxygen linkage for an equatorial acetate yields a single peak at about 1031—1025 cm.$^{-1}$ and that for an axial acetate a single peak at about 1022—1013 cm.$^{-1}$ (see Table 1). The isomeric 2-, 3-, and 4-acetoxy-steroids studied by Fürst *et al.* (*loc. cit.*) appear to show a similar frequency displacement; it is noteworthy that the 4-acetoxycholestanes appear to conform to our generalisation. The

* Part X, *J.*, 1955, 447.

frequency differences are smaller than those reported for 2-, 3-, and 4-hydroxy-steroids, but can be detected in the spectra of CS_2 solutions; Nujol mull and potassium bromide disc spectra are less satisfactory for this purpose.

The frequency of the alcohol-residue carbon–oxygen stretching linkage is affected by the introduction of substituents at the α-carbon atom to the acetate group and by the presence of an enol-acetate system; these frequency displacements may be of value for structure assignments, but they need further investigation.

TABLE 1. *Alcohol-residue carbon–oxygen stretching frequency assignments for 3-acetoxy-steroids in CS_2 solution.*

Compound	Type of steroid	Frequency ($cm.^{-1}$)	Confign. of C–O bond *
Androsterone acetate (3α-acetoxyandrostan-17-one) ...	3α-Acetoxy-5α-	1013 †	a
3α-Acetoxyandrost-16-ene	,,	1020 †	a
3α-Acetoxyandrost-11(?)-en-17-one	,,	1022 †	a
3α-Acetoxy*ætio*cholan-17-one	3α-Acetoxy-5β-	1029 †	e
3α : 17β-Diacetoxy*ætio*cholan-11-one	,,	1028 †	e
3α : 20α-Diacetoxypregnan-11-one	,,	1027 †	e
3α-Acetoxy-17α-hydroxypregnan-20-one	,,	1026 †	e
Sarsasapogenin acetate	3β-Acetoxy-5β-	1022	a
cyclo-ψ-Sarsasapogenin acetate	,,	1018	a
cyclo-ψ-Smilagenin acetate	,,	1020	a
Ergostanyl acetate (3β-acetoxyergostane)	3β-Acetoxy-5α-	1031 †	e
α-Ergostenyl acetate [3β-acetoxyergost-8(14)-ene]	,,	1028 †	e
γ-Ergostenyl acetate (3β-acetoxyergost-7-ene)	,,	1026 †	e
Tigogenin acetate	,,	1025	e
cyclo-ψ-Tigogenin acetate	,,	1026	e
*neo*Tigogenin acetate	,,	1026	e
cyclo-ψ-*neo*Tigogenin acetate	,,	1025	e
Diosgenin acetate	3β-Acetoxy-5-ene	1030	e
cyclo-ψ-Diosgenin acetate	,,	1030	e

* a = axial; e = equatorial. † From Rosenkrantz and Zablow (*loc. cit.*).

Although methoxy- and *gem*-dimethoxy-steroids are well-known compounds, little information on their infrared absorption has been published (cf. Jones and Herling, *loc. cit.*). The infrared spectrum of a simple ether is characterised by an intensely strong carbon–oxygen stretching band near 1100 $cm.^{-1}$, the exact frequency of which depends on the nature of the substituents on either side of the ether link (see Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 99).

TABLE 2. *Carbon–oxygen stretching frequency assignments for monomethoxy-steroids in CS_2 solution.*

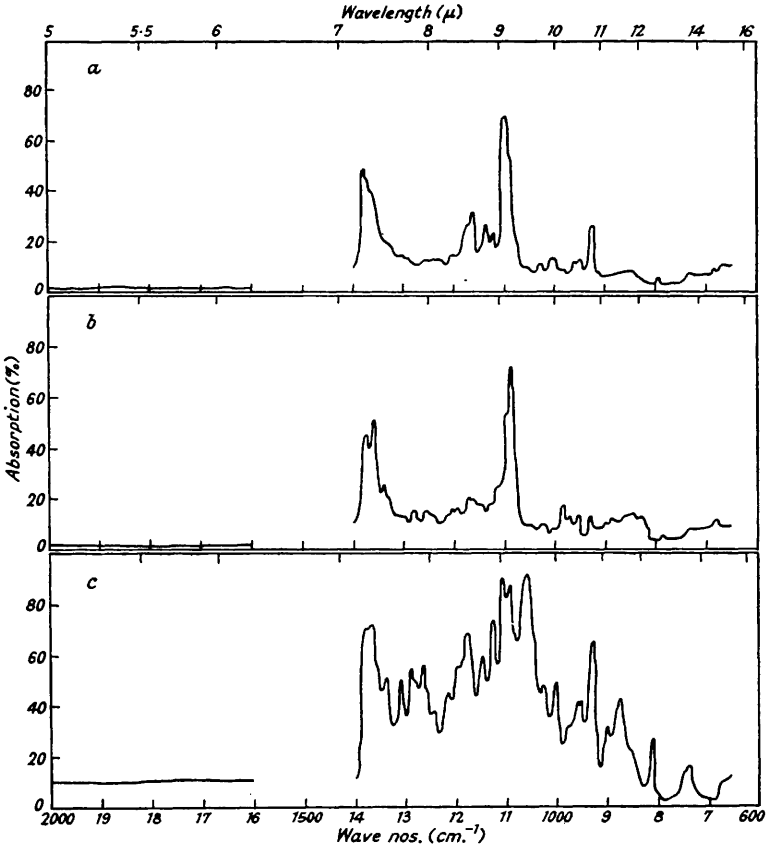
No.	Compound	Type of steroid	Frequency ($cm.^{-1}$)	Confign. of C–O bond
1	3α-Methoxycholestane	3α-Methoxy-5α-	1086	a
2	3α-Methoxycoprostane	3α-Methoxy-5β-	1100	e
3	3β-Methoxycoprostane	3β-Methoxy-5β-	1090	a
4	Sarsasapogenin methyl ether	,,	1088	a
5	3β-Methoxycholestane	3β-Methoxy-5α-	1100	e
6	3β-Methoxy-14-methylcholest-7-en-15-one	,,	1102	e
7	3β-Methoxy-14-methylergosta-7 : 22-diene	,,	1100	e
8	3β-Methoxy-14-methylergosta-7 : 22-dien-15-one	,,	1102	e
9	14-Acetoxy-3β-methoxyergosta-7 : 22-diene	,,	1100	e
10	3β-Methoxycholest-5-ene	3β-Methoxy-5-ene	1104	e
11	6β-Methoxy-3 : 5-*cyclo*ergosta-7 : 9(11) : 22-triene	3 : 5-*cyclo*-6β-Methoxy-	1090	a

A study of the infrared absorption spectra of 3-methoxy-steroids of known stereochemical configuration has shown that in CS_2 solution (see Table 2) an equatorial methoxyl group absorbs strongly between 1100 and 1104 $cm.^{-1}$, and an axial methoxyl between 1086 and 1090 $cm.^{-1}$; the apparent molecular extinction coefficients of the bands range from about 400 to 300. The equatorial methoxyl groups in 3β-methoxycholestane (Fig. *a*, C.S. no. 204 *) and 3α-methoxycoprostane (C.S. no. 205) absorb at about 1100, and the

* Spectra thus designated have been deposited with the Society. Photocopies, price 3*s.* 0*d.* per copy per spectrum, may be obtained, on application quoting the C.S. no., from the General Secretary, the Chemical Society, Burlington House, Piccadilly, London, W.1.

axial groups in 3α-methoxycholestane (Fig. *b*, C.S. no. 206) and 3β-methoxycoprostane (C.S. no. 207) at about 1088 cm.$^{-1}$. These characteristic absorption frequencies are unaffected by other steroid nuclear substituents, such as double bonds at positions 5, 7, and 22 (cf. cholesteryl methyl ether and 3β-methoxy-14-methylergosta-7 : 22-diene) or a spirostan side-chain (cf. sarsasapogenin methyl ether). The spectra of the 3-methoxysteroids contained a band of medium intensity at about 1175 cm.$^{-1}$, which might also be associated with the ether linkage.

Infrared spectra of solutions in carbon disulphide of (*a*) 3β-*methoxycholestane* (1·0%), (*b*) 3α-*methoxycholestane* (1·0%), *and* (*c*) 3 : 3-*dimethoxycholestane* 2·0%).



Josien, Fuson, and Carey (*J. Amer. Chem. Soc.*, 1951, **73**, 4445) reported that 3β-methoxy-5-ene-steroids in CS_2 solution absorb at about 1103 cm.$^{-1}$ and 6-methoxy-3 : 5-*cyclo*-steroids at about 1098 cm.$^{-1}$; they suggested that the difference in carbon–oxygen stretching frequency could be used to distinguish between 3β-methoxy-5-ene- and 6β-methoxy-3 : 5-*cyclo*-steroids. We believe that the frequency displacement (cf. " *i*-dehydroergosteryl methyl ether ") is probably caused by the different configuration of the methoxyl groups rather than by the double-bond character of the 3 : 5-*cyclo*-group; the 3β-methoxyl group is equatorial and would be expected to absorb at a slightly higher frequency than the 6β-methoxyl, which is axial. Corey *et al.* (*loc. cit.*) observed similar displacements of the carbon–deuterium stretching bands for 6β-deutero-5α- and 6β-deutero-3 : 5-*cyclo*-steroids compared with those for 3β-deutero-5α- and 3β-deutero-5-ene-steroids.

The carbon–oxygen stretching bands for a 3 : 3-dialkoxy-steroid (see Table 3) do not appear, as might have been expected, at about 1102 and 1090 cm.$^{-1}$, but instead split into four components that absorb at about 1190—1175, 1155—1132, 1110—1100, and 1053—1050 cm.$^{-1}$, the absorption bands at 1190—1175 and 1155—1132 cm.$^{-1}$ being weaker

TABLE 3. *Carbon–oxygen stretching frequency assignments for* gem-*dialkoxy-steroids in* CS_2 *solution.*

No.	Compound	Frequency ($cm.^{-1}$)
12	3 : 3-Dimethoxycholestane	1175, 1136, 1107, 1050
13	3 : 3-Diethoxycholestane	1183, 1132, 1110, 1053
14*	17α : 21-Dihydroxy-3 .3-dimethoxy*allo*pregnane-11 : 20-dione	1182, 1155, 1101, 1050
15*	21-Acetoxy-17α-hydroxy-3 : 3-dimethoxy*allo*pregnane-11 : 20-dione	1190, 1135, 1100, 1052
16	3β-Acetoxy-22 : 22-dimethoxybisnor*allo*cholan-11-one	1185, 1143, 1095, 1064

* As Nujol mull.

than those at about 1110—1100 and 1053—1050 $cm.^{-1}$; these bands may be observed in the spectrum of 3 : 3-dimethoxycholestane (Fig. *c*, C.S. no. 208). Bergmann and Pinchas (*Rec. Trav. chim.*, 1952, **71**, 161) observed a splitting of carbon–oxygen stretching bands in the spectra of simple ketals in CCl_4 solution, the absorption peaks appearing at 1190—1158, 1143—1124, 1098—1063, and 1056—1038 $cm.^{-1}$; the apparent molecular extinction coefficient of the 1098—1063-$cm.^{-1}$ band ranged from 500 to 200 and was of the same order as that for the 1110—1100-$cm.^{-1}$ band in our compounds. The spectrum of the acetal, 3β-acetoxy-22 : 22-dimethoxybisnor*allo*cholan-11-one, has a similar group of absorption bands, but differs from that of a 3 : 3-dialkoxy-steroid in that the 1095-$cm.^{-1}$ band is weaker than the other bands in the group; it further contains a weak band at about 1108 $cm.^{-1}$, which might represent the carbon–hydrogen deformation band reported for simple acetals by Bergmann and Pinchas.

The splitting of the absorption band is attributed to repetition of an absorbing substituent on the same carbon atom (cf. Fox and Martin, *Proc. Roy. Soc.*, 1938, *A*, **167**, 257; Bergmann and Pinchas, *loc. cit.*). We have observed that the alcohol-residue carbon–oxygen stretching bands for the *gem*-diacetate group in 3β : 22 : 22-triacetoxybisnor*allo*cholan-11-one (C.S. no. 209) undergo a similar splitting. In this compound the 11-ketone and the 3-acetate group absorb normally at 1710 and at 1732 and 1240 $cm.^{-1}$, respectively, whereas the 22 : 22-diacetates absorb at 1760, 1240, and 1202 $cm.^{-1}$, the peaks at 1760 having twice and those at 1240 $cm.^{-1}$ three times the normal intensity. Interaction between the two carbonyl groups of the *gem*-diacetate [cf. 20-ketone 21-acetate grouping (Jones, Humphries, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2820) and 11-ketone 12-acetate grouping (Dickson and Page, *J.*, 1955, 447)] would account for displacement of the carbonyl stretching frequency from 1735 to 1760 $cm.^{-1}$. The carbon–oxygen stretching vibrations for the three acetate alcohol-residue linkages yield three characteristic peaks of approximately equal intensity at about 1026, 1004, and 972 $cm.^{-1}$; the peak at 1026 $cm.^{-1}$ is attributed to the 3β-acetate group and those at 1004 and 972 $cm.^{-1}$ to the *gem*-diacetate.

The spectra of the mono- and *gem*-di-alkoxy-steroids exhibited the expected absorption bands for other steroid nuclear substituents (cf. Jones and Herling, *loc. cit.*)

EXPERIMENTAL

The spectroscopic measurements were made with a Perkin-Elmer Corporation, model 21, double-beam, infrared spectrophotometer fitted with a sodium chloride prism (see Dickson, Page, and Rogers, *J.*, 1955, 443). Compounds sufficiently soluble in carbon disulphide and carbon tetrachloride were examined as 1·0% (w/v) solutions in 1·0-mm. sodium chloride cells. Compounds that were insoluble in carbon disulphide were examined as Nujol mulls. Bromoform and chloroform are unsuitable solvents for studying 3 : 3-dimethoxy-steroids; bromoform absorbs in the 1100-$cm.^{-1}$ region, and chloroform, which transmits between 1200 and 1000 $cm.^{-1}$ absorbs between 1270 and 1200 $cm.^{-1}$.

The steroidal sapogenins and derivatives listed in Table 1 have been described by Callow, Dickson, Elks, Evans, James, Long, Oughton, and Page (*J.*, 1955, 1966). The monomethoxy-steroids, which had been provided by Professor D. H. R. Barton, F.R.S., and Professor C. W. Shoppee, and the dialkoxy- and 22 : 22-diacetoxy-steroids, which had been prepared in these laboratories (see previous and subsequent papers in the present series), had the properties given below, references below being (*a*) Lewis and Shoppee (*J.*, 1955, 1365, 1375,), (*b*) Nace (*J. Amer. Chem. Soc.*, 1952, **74**, 5937), (*c*) Babcock and Fieser (*ibid.*, p. 5472), (*d*) Barton, Ives, Kelly, Woodward, and Patchett (*J.*, in the press), (*e*) *idem* (*Chem. and Ind.*, 1954, 605), (*f*) Cameron,

Hunt, Oughton, Wilkinson, and Wilson (*J.*, 1953, 3864) (for names of compounds see Tables 2 and 3) :

(1) m. p. 63°, $[\alpha]_D$ +21° (*a*) {cf. m. p. 63°, $[\alpha]_D$ +18° (*b*)}.
(2) m. p. 88°, $[\alpha]_D$ +32° [prepared by methylation of coprostan-3α-ol (*a*)].
(3) m. p. 78°, $[\alpha]_D$ +28° (*a*) {cf. m. p. 63°, $[\alpha]_D$ +27° (*c*), double m. p. 64° and 79°, $[\alpha]_D$ +23° (Evans and Shoppee, *J.*, 1953, 540)}.
(4) (prepared by methylation of sarsasapogenin and hence probably 3β-methoxy-5β : 22*b*-spirostan), m. p. 155—158° [cf. 153—155° (Farmer and Kon, *J.*, 1937, 414)].
(5) m. p. 83°, $[\alpha]_D$ +20° (*a*) {cf. m. p. 82°, $[\alpha]_D$ +21° (*c*), m. p. 81—82°, $[\alpha]_D$ +20° (*b*)}.
(6) m. p. 86—87°, $[\alpha]_D$ +56° (*d*).
(7) m. p. 99—100°, $[\alpha]_D$ −24° (*e*).
(8) m. p. 124—126°, $[\alpha]_D$ +31° (*e*).
(9) m. p. 129—130°, $[\alpha]_D$ +14° (*d*).
(10) (cholesteryl methyl ether) m. p. 82°, $[\alpha]_D$ −41·5° {cf. m. p. 84·5—85°, $[\alpha]_D$ −46° (Müller and Page, *J. Biol. Chem.*, 1933, **101**, 127)}.
(11) ("*i*-dehydroergosteryl methyl ether") m. p. 53—54°, $[\alpha]_D$ +137° (Rees and Shoppee, *J.*, 1954, 3422).
(12) m. p. 81—82°, $[\alpha]_D$ +24°.
(13) m. p. 65—68°, $[\alpha]_D$ +22° {cf. 68—69·5°, $[\alpha]_D$ +26° (Serini and Köster, *Ber.*, 1938, **71**, 1766)}.
(14) m. p. 177—181°, $[\alpha]_D$ +52°.
(15) m. p. 205—212°, $[\alpha]_D$ +87°.
(16) m. p. 183—185°, $[\alpha]_D$ +28° (*f*).
(17) 3β : 22 : 22-Triacetoxybisnor*allo*cholan-11-one, m. p. 160—162°, $[\alpha]_D$ +9° (*f*).

We thank Professor C. W. Shoppee (University College, Swansea) for specimens of (1), (2), (3), (5), (10), and (11) and Professor D. H. R. Barton, F.R.S. (Birkbeck College), for specimens of (4), (6), (7), (8), and (9); the specimen of sarsasapogenin methyl ether (4) had been prepared by the late Professor G. A. R. Kon, F.R.S.

GLAXO LABORATORIES, LTD., GREENFORD, MIDDLESEX. [*Received, February 15th*, 1955.]