0.86 g. (0.01 mole) of vinyl ether, 0.098 g. (0.001 mole) of potassium acetate and 0.5 ml. of glacial acetic acid (0.01 mole) dissolved in 100 ml. of 80% dioxane. The solutions were sealed in Carius tubes and heated on a steam-bath for 64.5 hours. Distillation of the contents of one of the tubes into a 25-ml. portion of 2,4-dinitrophenylhydrazine reagent yielded no precipitate even on standing. Dilution of this same solution with water did yield a small amount of precipitate (less than 0.1 g.) melting point 174–177°, mixed m.p. with isobutyraldehyde 2,4-dinitrophenylhydrazone, 175–180°. The contents of the second tube were distilled into freshly prepared Fehling solution. No precipitate developed.

Rate Measurements.—The rate measurements in anhydrous acetic acid and in "80%" dioxane were carried out as in previous work.[3,5] The "80%" dioxane was the same solvent described previously.[3] Good first order kinetics were observed.

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[CONTRIBUTION FROM THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH AND THE DIVISION OF PURE CHEMISTRY OF THE NATIONAL RESEARCH COUNCIL OF CANADA[1]]

The Infrared Absorption Spectra of the Steroid Sapogenins

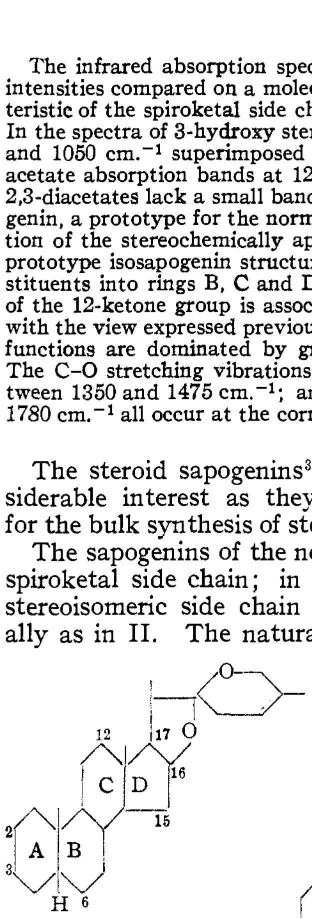
BY R. NORMAN JONES, E. KATZENELLENBOGEN AND KONRAD DOBRINER[2]

RECEIVED AUGUST 22, 1952

The infrared absorption spectra of thirty-five steroid sapogenins and derivatives have been investigated and the band intensities compared on a molecular extinction coefficient basis. Between 875 and 1350 cm.$^{-1}$ several strong bands characteristic of the spiroketal side chain are observed and these are distinctive for the sapogenins of the normal and iso-series. In the spectra of 3-hydroxy steroid sapogenins bands characteristic of the 3-hydroxyl group can be recognized between 1000 and 1050 cm.$^{-1}$ superimposed on the side chain absorption. The 3-acetoxy and 2,3-diacetoxy steroid sapogenins exhibit acetate absorption bands at 1240–1250 cm.$^{-1}$ and 1020–1040 cm.$^{-1}$ in addition to the side chain absorption bands. The 2,3-diacetates lack a small band at 956–961 cm.$^{-1}$ present in the simpler compounds. The spectrum of 3-desoxysarsasapogenin, a prototype for the normal sapogenin side chain structure, can be simulated quite closely by subtracting the absorption of the stereochemically appropriate 3-hydroxy steroid from that of the 3-hydroxy sapogenin. The spectrum of the prototype isosapogenin structure is predicted by a similar method. The introduction of additional oxygen containing substituents into rings B, C and D of the steroid nucleus induces minor but significant changes in the spectra. The presence of the 12-ketone group is associated with increased absorption near 1040 and 1075 cm.$^{-1}$. These observations are in accord with the view expressed previously that the infrared spectra of steroids substituted only at C_3 and C_{17} by oxygen containing functions are dominated by group absorptions localized in these substituents which act independently of one another. The C–O stretching vibrations of the 3-acetate group near 1240 cm.$^{-1}$; the methyl and methylene bending vibrations between 1350 and 1475 cm.$^{-1}$; and the C=O stretching vibrations of the sapogenin acetates and ketones between 1670 and 1780 cm.$^{-1}$ all occur at the correct positions for the accepted structures of these compounds.

The steroid sapogenins[3] are compounds of considerable interest as they are starting materials for the bulk synthesis of steroid hormones.

The sapogenins of the normal series (I) possess a spiroketal side chain; in the iso-series there is a stereoisomeric side chain represented conventionally as in II. The natural sapogenins of simplest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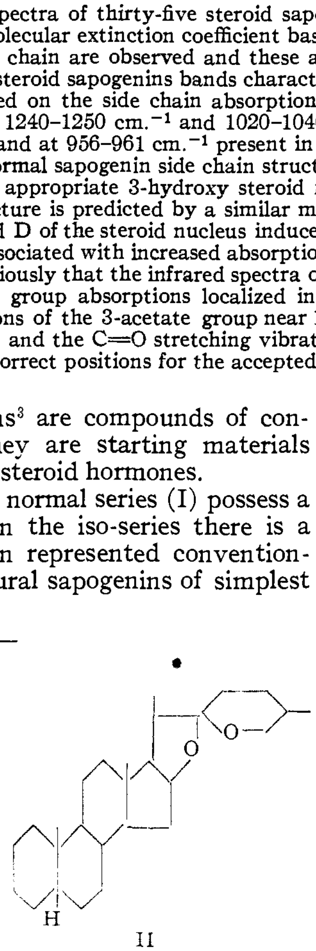
II

structure also contain a 3β-hydroxyl group; the A and B rings may be *cis* or *trans* linked or a Δ^5-double bond may occur. A more complex family of sapogenins contains a 2,3-dihydroxyl group, and others are known with oxygen functions at C_6, C_{12}, C_{15}, C_{16} and C_{17}.

Through the kind collaboration of Professor R. E. Marker we have had access to the extensive collection of these compounds and their derivatives isolated in his laboratory, and this paper is concerned with a comparison of their infrared absorption spectra. Some sapogenins obtained from other sources are also included in this survey.

The sapogenin spectra exhibit unusual features in the region between 850 and 1350 cm.$^{-1}$. In addition to their interest to steroid chemists they provide a good example of the independence of strong skeletal vibrations, when the groups concerned are well separated in the molecule. The spectra of the more highly substituted sapogenins also show how this skeletal group specificity diminishes as more oxygen-containing functional groups are introduced into the molecule.

Experimental Methods of Results

The curves reproduced in this paper have been selected to demonstrate certain features of the sapogenin spectra. The positions and intensities of the absorption maxima for the whole series of compounds are listed in Tables I–III and reproductions of the complete collection of spectra may be obtained on application.[5]

The compounds were used as received, without further purification, and most of the spectra were measured from

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(2) Died March 10, 1952.

(3) In this paper the term *sapogenin* will henceforth be used to designate *steroid sapogenin*. The nomenclature employed is the same as that used by Fieser and Fieser (ref. 4).

(4) "Natural Products Related to Phenanthrene," by L. F. Fieser and M. Fieser, Third Edition, Reinhold Publ. Corp., New York, N. Y., 1949. A concise summary of the structures of the principal steroid sapogenins is given on p. 591 of this monograph.

(5) "Collected Infrared Absorption Spectra of the Steroid Sapogenins," by R. N. Jones, E. Katzenellenbogen and K. Dobriner, Division of Information Services, National Research Council, Ottawa, Canada, and Sloan-Kettering Institute for Cancer Research, New York, N. Y.

875 to 1350 cm.$^{-1}$ on Perkin–Elmer model 21 double beam spectrophotometers. The compound (1.5–3.0 mg.) was weighed on an analytical balance and dissolved in 300–1000 mg. of carbon disulfide. The solution was weighed immediately before transfer to a 1-mm. micro absorption cell[6] and the molar concentration evaluated; a density of 1.26 was assumed for the solution at room temperature.

The spectra were corrected for non-linearity in the I_0 background and the apparent molecular extinction coefficient (E_A) calculated[7] for all absorption maxima, minima and prominent points of inflection. The curves were plotted on a linear scale of apparent molecular extinction coefficients. Some of the more highly oxygenated sapogenins were soluble only with difficulty in carbon disulfide, and for these quantitative spectra could not be obtained.

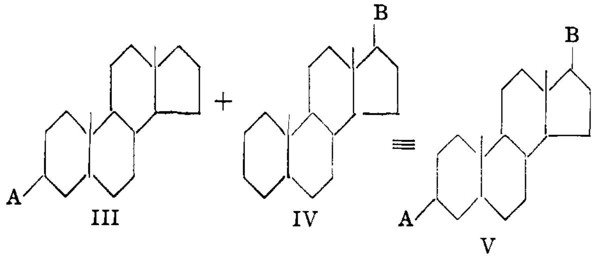
A smaller number of the sapogenins were measured also between 1300 and 3700 cm.$^{-1}$ on a Perkin–Elmer model 12C single beam spectrometer using a calcium fluoride prism and carbon tetrachloride solution. These spectra were computed directly as apparent molecular extinction coefficients.

Accuracy of the Intensity Measurements.—If *macro* absorption cells of conventional design are used and a total volume of 1–2 ml. of solution is prepared, it is possible to obtain E_A values reproducible to within $\pm 3\%$ on the same or different spectrometers provided the absorption lies between 20 and 80%. The curves for the steroids of the C_{19} series included in this paper satisfy these conditions.[9] Most of the sapogenins were available in small quantities only, necessitating the use of micro cells, and the preparation of minimal volumes of solution. Errors in sample concentration are larger under these conditions and in some instances the variation in the observed band intensities exceeded 10%; this can be seen from duplicate measurements on several sapogenins included in Table I. These E_A measurements, however, are used only to demonstrate the general uniformity of the intensities of corresponding bands in different compounds and their accuracy is quite adequate for this purpose.

Discussion

Absorption of Sapogenins and Other Steroids between 1350 and 850 Cm.$^{-1}$.—The absorption of steroids at frequencies between 1350 and 650 cm.$^{-1}$ is determined by C–C and C–O stretching vibrations and C–H deformation vibrations. It is usually considered that strong couplings occur among these vibrations and that the absorption in this region of the spectrum is modified considerably by small changes in chemical structure.

Under certain conditions it is possible for the absorption in this region of the spectrum to be dominated by local structural groups in the molecule. It has been noted[10] that the spectrum of androstanol-3β-one-17 can be simulated quite closely in this region of the spectrum by the summation at each frequency of the spectra of androstanol-3β and androstanone-17, when the curves are plotted on a scale of apparent molecule extinction coefficients. The possibility must be considered that the spectra of other 3,17-disubstituted steroids (V) might also be approximated by addition of the spectra of monosubstituted steroids (III, IV). In these A and B are oxygen



containing substituents or other groups which confer bands of high intensity on the spectrum ($E_A > 100$) and so submerge the weaker absorption ($E_A < 30$) associated with the saturated hydrocarbon vibrations seen in the spectra of androstane and etiocholane.

Such an hypothesis involves the assumption that the strongly infrared active vibrations associated with these substituent groups act as independent absorbing systems when spaced sufficiently far apart in the molecule. The conditions of molecular structure under which such a principle may be validly applied have yet to be worked out, and the steroid sapogenins offer a favorable group of compounds for such an investigation. Conversely, the comparative study of the sapogenin spectra is facilitated by the coördination of the data in terms of a systematizing principle of this kind.

The Normal Sapogenins.—Comparison of the spectra of 3-desoxysarsasapogenin (I) (Fig. 1A) and etiocholane (Fig. 2A) clearly demonstrates the intense absorption between 1350 and 850 cm.$^{-1}$ conferred on the steroid by the introduction of the spiroketal side chain. The most intense band in this region of the spectrum of etiocholane does not exceed 25 units while the bands designated by Greek letters in the spectrum of 3-desoxysarsasapogenin rise to 375 units (band τ). All of the bands, α–ω, may be attributed to vibrations associated with the side chain structure.

In Fig. 2 are shown the spectra of three sapogenins which contain a 3-hydroxyl group as well as the normal sapogenin side chain. Accompanying each is the spectrum of the 3-hydroxy C_{19}-

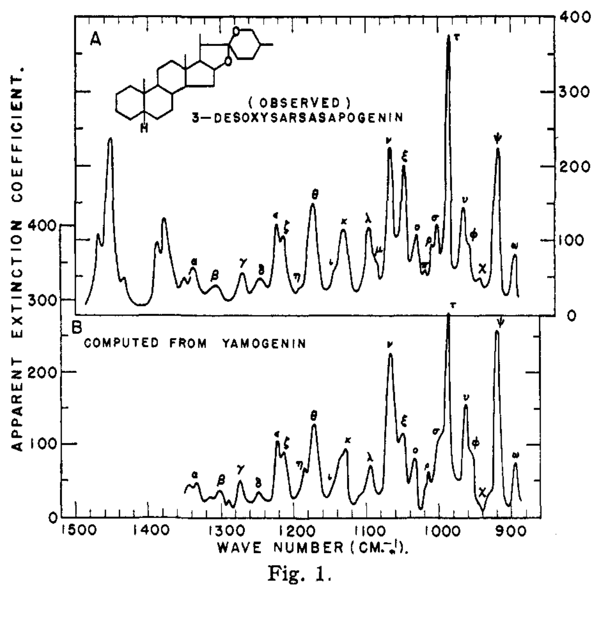


Fig. 1.

(6) A description of this cell, designed by Dr. J. Hardy, Cornell Medical School, will be published.

(7) R. N. Jones, D. A. Ramsay, D. S. Keir and K. Dobriner, THIS JOURNAL, **74**, 80 (1952). The spectral slit widths employed diminished from 6 cm.$^{-1}$ at 1350 cm.$^{-1}$ to 2 cm.$^{-1}$ at 850 cm.$^{-1}$ For an apparent band width at half maximal intensity of 15 cm.$^{-1}$ the true maximal molecular extinction coefficients would be expected to exceed the apparent ones by about 12% at 1350 cm.$^{-1}$ and 3% at 850 cm.$^{-1}$ (see Table I of ref. 8).

(8) D. A. Ramsay, *ibid.*, **74**, 72 (1952).

(9) These spectra will be discussed more fully in a separate publication.

(10) A. R. H. Cole, R. N. Jones and K. Dobriner, THIS JOURNAL, **74**, 5571 (1952).

TABLE I

POSITIONS AND INTENSITIES (E_A) OF ABSORPTION BANDS IN STEROID SAPOGENIN SPECTRA (1350–875 CM.$^{-1}$)

(Carbon Disulfide solution)

Normal sapogenins[a]	Principal bands associated with the spiroketal side chain[b] α 1340–1334	β 1308–1304	γ 1273–1266	δ 1250–1244	ε 1225–1220	ζ 1216–1211	η 1190–1185	θ 1175–1168	ι 1145–1142	κ 1131–1128	λ 1097–1092
3-Desoxysarsasapogenin (observed)	64	40	55	49	122	107	*38*	150	*60*	115	117
3-Desoxysarsasapogenin (computed from yamogenin)	48	37	50	36	105	90	66	118	*45*	94	72
3-Desoxysarsasapogenin (computed from 3-episarsasapogenin)	64	42	55	42	118	108	*60*	165	*60*	120	114
3-Desoxysarsasapogenin (computed from sarsasapogenone-3)	60	44	45	52	108	90	*50*	140	*45*	108	124
3-Desoxysarsasapogenin (computed from Δ⁴-sarsasapogenone-3)	90	45	97	..	152	110	*50*	190	..	150	130
3-Desoxyneotigogenin (computed from neotigogenin)	42	32	42	28	92	90	..	145	*50*	105	90
Sarsasapogenin	76	44	68	64	136	132	*60*	155	*70*	130	130
Sarsapogenin acetate	90	50	*140*	[f]	[f]	*170*	*80*	155	65	110	125
3-Episarsasapogenin	74	50	70	64	132	128	*60*	175	*80*	128	128
3-Episarsasapogenin[g]	60	40	60	52	110	100	*50*	140	*65*	106	106
3-Episarsasapogenin acetate	..	48	*100*	[f]	*190*	130	..	155	*60*	115	100
Sarsasapogenone-3	70	48	64	60	132	105	*55*	145	68	115	125
Δ⁴-Sarsasapogenone-3[h]	98	45	[j]	55	[j]	*125*	*55*	210	*55*	165	130
Neotigogenin	55	42	60	45	115	105	..	160	*65*	130	105
Yamogenin	64	42	66	50	120	108	85	132	..	118	92
Yamogenin[g]	68	42	59	43	117	100	73	123	..	116	95
Yamogenin acetate	50	50	80	[f]	*225*	*140*	70	115	..	120	98
Yamogenin acetate[g]	42	41	72	[f]	*223*	*138*	70	113	..	118	93

Isosapogenins[a]	A 1344–1338	B 1305–1295	E 1240–1237	F 1218–1208	G 1180–1173	H 1158–1152	J 1134–1126	K 1096–1090	L 1076–1070	M 1062–1056	N 1054–1048
3-Desoxytigogenin (computed from tigogenin)	62	32	150	70	160	110	46	94	152	*295*	354
3-Desoxytigogenin (computed from diogenin)	68	26	154	42	138	102	54	90	188	*365*	382
3-Desoxytigogenin (computed from tigogenone-3)	64	37	142	43	148	96	52	90	174	235	288
Tigogenin	80	44	165	86	180	126	73	113	206	*310*	384
Tigogenin acetate	70	44	[f]	*72*	152	112	98	115	180	*255*	345
Tigogenone-3	68	44	164	52	170	106	71	92	182	*236*	286
Tigogenone-3[g]	71	50	166	53	180	111	71	96	194	*240*	310
Tigogenone-3[g]	86	..	173	51	180	110	78	105	220	*270*	340
Diosgenin	92	46	165	58	156	120	74	112	212	*430*	[e]
Diosgenin acetate	78	43	[f]	[f]	132	90	80	104	177	*285*	346
Diosgenin acetate[g]	71	..	[f]	[f]	118	78	75	100	178	...	345
Gitogenin diacetate	*78*	80	[f]	*115*	140	108	...	113	194	...	420
Samogenin diacetate	*100*	75	[f]	[f]	162	137	...	132	217	*370*	520
Samogenin diacetate[g]	*108*	75	[f]	[f]	175	146	...	135	232	*375*	540
Yuccagenin diacetate	*80*	73	[f]	*140*	160	142	62	130	230	...	460
Chlorogenin diacetate	*85*	80	[f]	*200*	[k]	[k]	[k]	120	252	...	[f]
Pennogenin	92	..	144	58	123	140	...	*110*	156	...	[e]
Pennogenin acetate	94	60	[f]	103	150	167[k]	...	*110*	168	...	470
12-Dihydromanogenin diacetate-2,3	*100*	80	[f]	[f]	125	100	...	116	176	...	400
Hecogenin acetate	110	70	[f]	76	*138*	174	117	125	[k]	...	350
Manogenin diacetate	100	97	[f]	*145*	140	130	94	128	[k]	...	460

steroid of comparable stereochemistry. In all cases it is observed that outside of the region between 1050 and 1000 cm.$^{-1}$ the bands designated by Greek letters can be identified with their counterparts in the prototype spectrum in Fig. 1A. This agreement applies to the intensities as well as the positions of the bands as can be seen by glancing down the columns of Table I.

Between 1000 and 1050 cm.$^{-1}$ the 3-hydroxy steroids possess a strong absorption band (E_A 200–240),[10] and the presence of this band, superimposed on the absorption associated with the spiroketal group is readily recognized in Fig. 2. The spectrum of sarsasapogenone-3 shown in Fig. 3A agrees with that of 3-desoxysarsasapogenin even more closely, since the additive contribution of the 3-ketone group (as exemplified by etiocholanone-3) is smaller than that of the 3-hydroxyl group.

For this series of compounds the independence of the absorption bands contributed by the 3-hydroxyl and spiroketal side chain groups is clearly established qualitatively. If the specific absorptions associated with the remote ends of the molecule were truly independent it should be possible to compute the spectrum of 3-desoxysarsasapogenin by subtracting E_A for the appropriate 3-hydroxy C_{19}-steroid from that of the 3-hydroxy sapogenin and adding back E_A for the C_{19}-steroid hydrocarbon to weight for the weak absorption of the steroid ring structure.

Calculations of this kind have been carried out for the systems

i, yamogenin − Δ^5-androstenol-3β + etiocholane
ii, 3-episarsasapogenin − etiocholanol-3α + etiocholane
iii, sarsasapogenone-3 − etiocholanone-3 + etiocholane
iv, Δ^4-sarsasapogenone-3 − Δ^4-androstenone-3 + etiocholane
v, neotigogenin − androstanol-3β + androstane

The curves obtained for systems i and iii are shown in Figs. 1B and 3B and should be compared with the experimentally observed curve for 3-desoxysarsasapogenin in Fig. 1A. The results for systems ii, iv and v are given in curves 3, 5 and 6 of ref. 5. In all cases there is an excellent agreement between the positions and intensities of the observed and computed bands. Only two of the weakest bands observed in the spectrum of 3-

TABLE I (*Continued*)

ν 1068–1064	ξ 1052–1046	ο 1034–1028	ρ 1015–1006	σ 1005–998	τ 987–984	υ 965–960	φ 956–948	χ 950–936	ψ 920–915	ω 899–894	-Hydroxyl and acetate bands[c]	Other bands[d]
226	202	110	94	122	375	145	*95*	48	225	82		1085^{μ}, 1018^{π}
228	116	82	62	*110*	282	157	*95*	*20*	255	76		1290, *1020*$^{\pi}$
210	280	125	116	108	380	160	95	74	285	95		1085^{μ}, 1020^{π}
216	175	110	100	94	320	154	*85*	67	248	60		1112
260	185	150	80	140	375	140	112	42	365	97		1330, 1295, 1260, 1252, 1240, 908
210	170	100	75	120	290	96	95	*55*	295	62		
218	245	[e]	*85*	130	375	135	97	..	255	75	1028(240)	
235	255	[f]	*170*	145	425	165	84	..	240	82	1248, 1236, 1227, 1022(305)	1154
290	315	[e]	175	*140*	385	160	95	84	280	88	1035(240)	1082^{μ}
230	250	[e]	140	*115*	320	127	85	..	235	85	1035(210)	
240	245	[f]	122	125	350	135	*70*	65	260	90	1240, 1026(270)	1315, 1082
215	175	110	105	105	320	150	82	60	240	52		1318, 1295
255	185	145	90	135	380	150	130	64	370	90		1330, 1272,[k] 1260, 1232,[k] 1185[k], 906
230	195	[e]	105	140	310	105	125	60	300	60	1038(310)	1315, *1105*, *970*
250	[e]	142	110	140	285	160	135	37	250	62	1048(335)	1345, 1315, *1105*, 1004
250	[e]	148	126	137	280	153	134	..	270	79	1048(335)	1345, 1315, *1105*, 1004
260	205	[f]	*165*	132	346	158	110	..	212	76	1242, 1030(380)	1318, 1195, *1135*, *1105*, 902
233	185	[f]	*151*	123	325	153	115	..	210	74	1242, 1030(396)	1318, 1195, *1135*, *1105*, 902

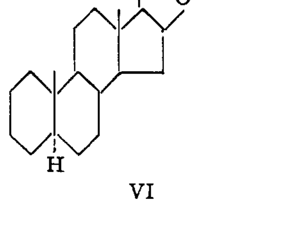
O 1024–1017	P 1008–1006	Q 981–976	R 961–956	S 952–948	T 920–916	U 899–897	Hydroxyl and acetate bands	Other bands
92	140	320	123	*50*	168	265		1285^{C}, 1275^{D}, 1257, *1147*^{I}, 940
96	146	330	160	*50*	146	250		1285^{C}, 1274^{D}, *1185*, 1140^{I}, 1110, *1068*, 935
85	90	304	107	*65*	130	180		1290^{C}, 1275^{D}, 1258, 1245^{I}, 1086, 935
137	160	330	148	*85*	170	246	1038(347)	1275^{D}, *1148*^{I}, 1110, 997, 937
[f]	176	320	130	*70*	158	226	1242, 1022(280)	*1275*^{D}, *1008*, *1034*, 990, 935
90	90	304	102	*70*	132	180		1270^{D}, 1255, 1226, 1145^{I}, 1086, 990, 938
100	96	332	112	*82*	148	216		1270^{D}, 1255, 1226, 1145^{I}, 1086, 990, 938
105	96	345	122	*86*	165	240		1270^{D}, 1255, 1226, 1145^{I}, 1086, 990, 938
155	182	350	170	95	145	260	1050(570)	1283^{C}, 1273^{D}, 1184, 1110, 994, 936
170	188	328	167	*62*	118	212	1240, 1032(334)	1314, *1278*, 1270^{D}, 1184, 1068, 938
174	188	320	155	*67*	125	235	1240, 1030(325)	1274^{D}, *930*, 908
220	160	354	[k]	70	136	226	1247, *1243*, 1230, *1038(394)*. *1030(325)*	1274^{D}, *930*, 908
210	*190*	404	[k]	80	110	198	1248, *1240*, 1225, 1030(320)	1185, 1133, 1087, 940, 923, 908
226	*190*	420	[k]	80	104	212	1248, *1240*, 1225, 1030(340)	1185, 1133, 1087, 940, 923, 908
250	186	416	85[k]	85	160	262	1248, 1238, *1230*, *1040(420)*, *1030*(320)	1326, 928
[f]	...	440	166	108	120	315	1245, 1058(505), 1030(600)	*1288*, 1200,[k] 1178,[k] 1160,[k] 1010
105	137	310	107	*60*	105	142	1050(505)	1288, 1280, 1265, 1122,[k] 1108, 997,[k] 884
[f]	*190*	385	115	*55*	140	162	1240, 1032(340)	1315, 1280, *1145*, 1122,[k] 1105, 998,[k] 888
...	186	330	[k]	72	138	200	1250, 1234, 1040(350), 1025(276)	*1270*, *1140*, 930
215	194	405	70[k]	56	160	305	1242, 1035(290)	1320, 1284, 1076[k] 1040,[k] 995, *930*
...	172	392	62[k]	60	180	286	1245, 1228, 1030(370)	*1110*, 1075,[k] 1040,[k] 930

[a] For sources of compounds see Table III. Qualitative spectra of the following sapogenins are also included in ref. 5: samogenin, β-chlorogenin diacetate, rockogenin, digitogenin triacetate, bethogenin, hexogenin, kammogenin diacetate. [b] The range of the band position in cm.$^{-1}$ is given at the head of each column. Points of inflection are italicized. [c] The band position is given first followed by the intensity in parentheses. For the acetate bands at 1250–1230 cm.$^{-1}$ no intensities are given. These were measured at absorptions in excess of 80% under which condition extinction coefficients are subject to large errors; they fall in the range between 500 and 1500 units. [d] These bands are all quite weak and only the position is listed. Bands μ, π, C, D, I which occur in the prototype spectra are identified by appropriate superscripts. [e] Region obscured by strong hydroxyl absorption. [f] Region obscured by strong acetate absorption. [g] Repeat determination on same batch of compound (includes preparation of new quantitative solution). [h] See footnote (*c*) to Table III. [i] Region obscured by strong Δ^4-3-ketone absorption. [k] For comment on this band see text.

desoxysarsasapogenin are lacking from the computed spectra (μ and π) and there are no medium or strong bands observed in the computed spectra which are not detected in the true spectrum.

A more detailed analysis of the band intensities indicates that the greatest variation occurs in band ξ. This lies very close to the strong hydroxyl vibration. In ii the intensity of this band exceeds that of ν. In such a region of rapidly changing absorption an error of 1 cm.$^{-1}$ in the measurement of the position of one of the component curves can have a very large effect on the differential curve and there can be no doubt that much of the variation noted in the intensity of this band in the computed spectra is attributable to experimental error.

The best agreement on intensity between the observed and computed curves is for the saturated 3-ketone system (iii) where the absorption associated with the A ring function is relatively weak. The



VI

TABLE II

ABSORPTION MAXIMA IN STEROID SAPOGENIN SPECTRA BETWEEN 1475 AND 1350 CM.$^{-1}$

(Carbon tetrachloride solution)

Compound[a]	Maxima[b]								
Normal series									
3-Desoxysarsasapogenin (obs.)	1468 (108)		1452 (240)	1434 (50)		1386 (98)	1378 (130)		
3-Episarsasapogenin	1468 (110)		1452 (245)	*1434 (45)*		1385 (110)	1378 (145)		
Yamogenin	1468 (112)		1454 (165)	*1438 (86)*		1387 (105)	1376 (145)		
Sarsasapogenin acetate	1468 (110)		1452 (250)	1435 (90)		*1385 (110)*	1376 (260)		1365 (176)
Iso series									
3-Desoxytigogenin (computed)	*1470 (60)*	*1460 (160)*	1452 (207)	1434 (56)		*1387 (56)*	1382 (110)	1378 (120)	
Diosgenin		*1462 (130)*	1456 (165)	1436 (74)		*1386 (90)*	1377 (140)	*1370 (90)*	
Tigogenone-3	*1470 (40)*	*1460 (160)*	1454 (186)	1430 (73)	1420 (65)	*1385 (80)*	1380 (106)	1377 (106)	
Diosgenin acetate		*1462 (130)*	1456 (185)	1436 (100)		*1386 (100)*	1376 (240)		1365 (210)
Samogenin diacetate		*1460 (185)*	1455 (225)	1435 (88)		*1388 (100)*	1378 (285)		1368 (350)

[a] For the sources of the compounds see Table III. [b] The band position is given first in cm.$^{-1}$ followed by the apparent molecular extinction coefficient in parentheses. Points of inflection are italicized.

introduction of the Δ^4-3-ketone group (system iv) introduces strong absorption bands at 1328 cm.$^{-1}$ (E_A 76); 1270 cm.$^{-1}$ (E_A 100) and 1232 cm.$^{-1}$ (E_A 142), although these subtract out satisfactorily.

System v gives a computed spectrum for 3-desoxyneotigogenin (VI) where the A/B ring junction is *trans* linked. The curve does not differ significantly on this account and it would seem reasonable to predict that the spectrum of any saturated steroid with an oxygen substituent in the side chain and no substituent in the ring system will be little affected by stereochemical inversion at the A/B ring junction.

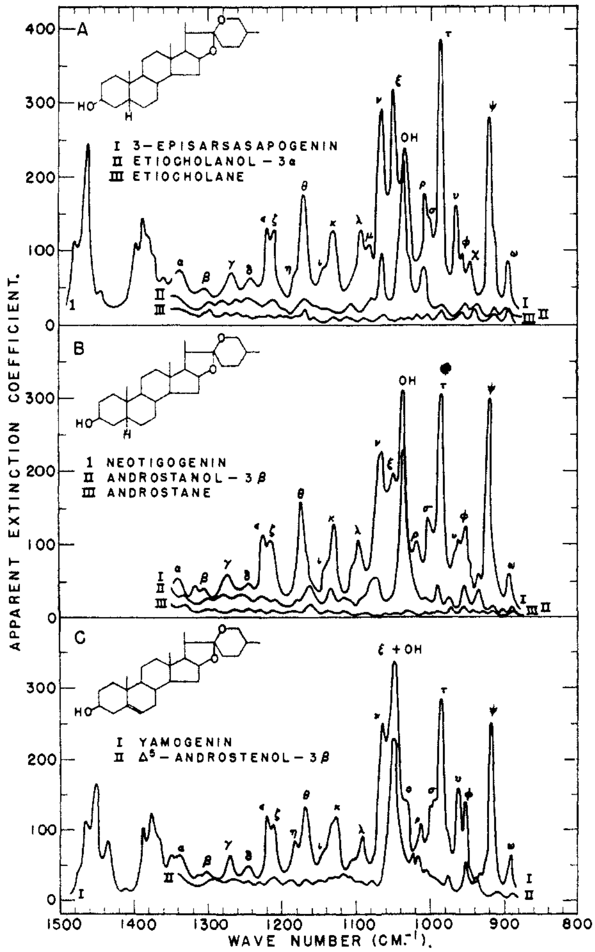


Fig. 2.

The Isosapogenins.—The spectra of the isosapogenins between 1350 and 850 cm.$^{-1}$ differ quite considerably from those of the normal series. The prototype isosapogenin (II) was not available to us, and there is no record in the literature of it ever having been prepared. In view of the agreement obtained between the computed and observed spectra for the prototype normal sapogenin (I) the spectrum of 3-desoxytigogenin (II) has been computed from the systems

(1) Tigogenin − androstanol-3β + androstane
(2) Diosgenin − Δ^5-androstenol-3β + androstane
(3) Tigogenone-3 − androstanone-3 + androstane

The curves obtained for (1) and (3) are shown in Figs. 4B and 5B and for system (2) in curve 14 of ref. 5. The computed prototype curves obtained by all three methods agree reasonably well and the bands A–U which are common to all the curves may be regarded as characterizing the side chain. For the absolute intensities of these bands the values derived from the ketonic system (3) are probably most acceptable for the reasons outlined in the preceding section.

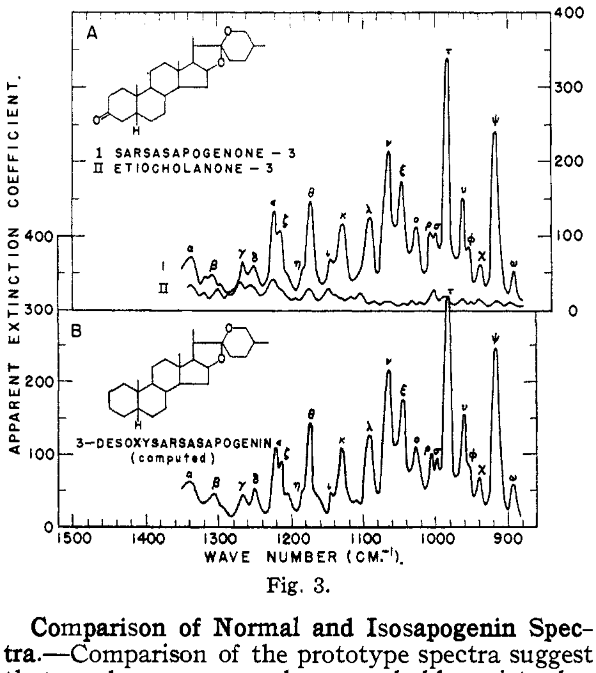


Fig. 3.

Comparison of Normal and Isosapogenin Spectra.—Comparison of the prototype spectra suggest that a close correspondence probably exists be-

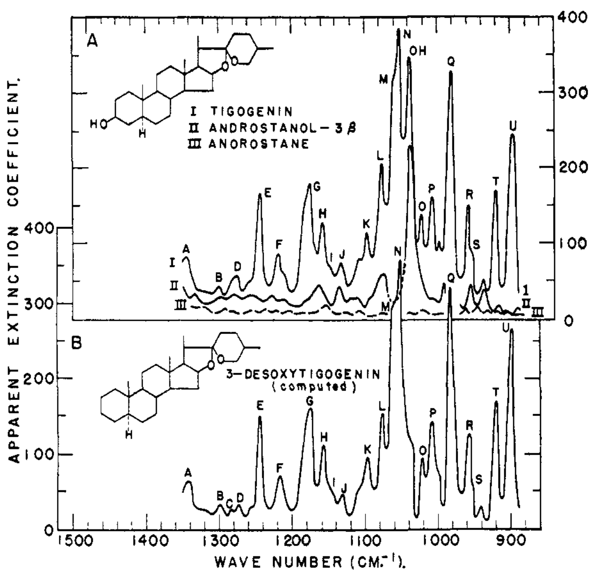


Fig. 4.

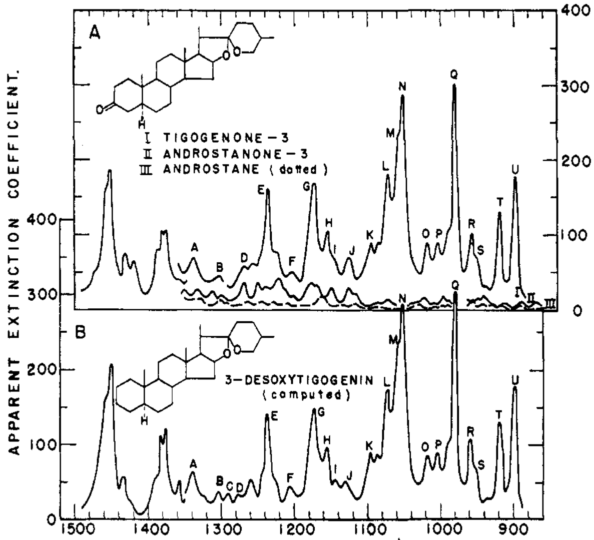


Fig. 5.

tween the pairs of bands α–A, β–B, θ–G, λ–K, o–O, τ–Q, ν–R, and ϕ–S as these bands agree both as to position and order of intensity. The most notable differences are in the region of the ν, ξ and M, N bands (1070–1040 cm.$^{-1}$) and also in the consistent reversal of the intensities of the low frequency bands ψ, ω and T, U.[11] Another difference between the spectra of normal and isosapogenins occurs near 1475 cm.$^{-1}$ (*vide infra*).

3-Acetoxy Sapogenins.—The spectra of the 3-acetoxy sapogenins conform excellently with the considerations described above for the free hydroxy compounds. As typical examples the acetates of yamogenin and diosgenin are compared with the spectrum of Δ^5-androstenol-3β acetate in Fig. 6.[12] Between 1200 and 1300 cm.$^{-1}$ these spectra are dominated by strong acetate absorption (E_A 500–1000) and a second strong acetate band (E_A 240–290) occurs at 1030–1040 cm.$^{-1}$ Outside of these regions the spectra of the 3-acetoxy sapogenins of both the normal and iso series resemble the prototype spectra of the 3-desoxy sapogenins.

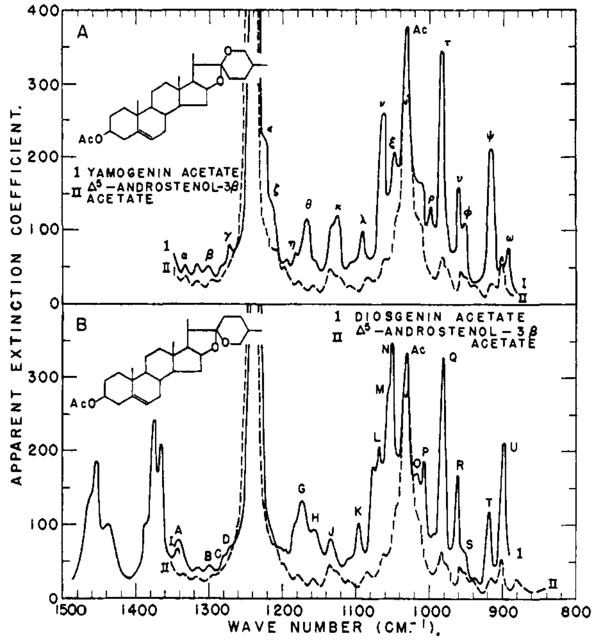


Fig 6.

The absorption of 3-acetoxy steroids near 1240 cm.$^{-1}$ has been shown to depend on the stereochemical configuration at C_3,[10,13] and the spectra of the 3-acetoxy sapogenins conform to the same rules. Where the 3-acetoxy group is attached to the ring by an equatorially directed bond[14] the band has a simple contour, but where the linkage is a polar one[15] the band is complex with two peaks or with one peak accompanied by prominent inflections.

Spectra of Sapogenins above 1350 Cm.$^{-1}$. Methyl and Methylene Bending Vibrations (1350–1500 Cm.$^{-1}$).—The absorption bands observed in steroid spectra between 1350 and 1500 cm.$^{-1}$ can be assigned to vibrations localized in individual methyl and methylene groups,[16,17] and this region of the spectrum of some representative sapogenins is included in Figs. 1A, 2A, 2C, 5A, 5B, 6B, 7A and 8B. The band positions and intensities are listed in Table II.

The free sapogenins show medium strong absorption (E_A 150–250) at 1452 cm.$^{-1}$ identified with "unperturbed" methylene bending vibrations in the rings. In addition the normal sapogenins possess a well resolved band at 1468 cm.$^{-1}$ (E_A 105) which is lacking from the spectra of the isosapogenins. The prototype sapogenin spectra of both stereochemical series also show a weak band

(11) This distinction has been noted also by Dr. C. R. Eddy of the Eastern Regional Laboratory, U. S. Dept. of Agriculture (private communication).

(12) The spectra of sarsasapogenin acetate, 3-episarsasapogenin acetate and tigogenin acetate are included in reference 5.

(13) R. N. Jones, P. Humphries and K. Dobriner, THIS JOURNAL, **73**, 3215 (1951).

(14) Acetates of 3-episarsasapogenin, neotigogenin, tigogenin, yamogenin, diosgenin, hecogenin, pennogenin, bethogenin, 5,6-dihydrobethogenin, 9,11-epoxytigogenin, Δ^{11}-tigogenin.

(15) Acetates of sarsasapogenin, smilagenin, 23-bromosarsasapogenin.

(16) R. N. Jones and A. R. H. Cole, THIS JOURNAL, **74**, 5648 (1952).

(17) R. N. Jones, A. R. H. Cole and B. Nolin, *ibid.*, **74**, 5662 (1952).

at 1435 cm.$^{-1}$ (E_A 50–60). This absorption is intensified in the acetates and the Δ^5-sapogenins and it has been shown previously[16] that both of these groups produce absorption near 1430 cm.$^{-1}$. Tigogenone-3 shows the asymmetric band at 1420 cm.$^{-1}$ characterizing methylene groups at C_2 and C_4 vicinal to a C_3-ketone.

Between 1350 and 1400 cm.$^{-1}$ the absorption bands are associated with methyl bending vibrations, and the free sapogenins of both stereochemical series have bands at 1385 cm.$^{-1}$ (E_A 90–110) and 1378 cm.$^{-1}$ (E_A 125–145). The "unperturbed" methyl groups at C_{18}, C_{19} and C_{21} absorb in this range and there is no indication of any band specific to the methyl group at C_{25} on the six-membered oxide ring.

In the spectra of the acetates the methyl bending absorption intensifies. The 1376 cm.$^{-1}$ band increases to E_A 190–260 and a new band characteristic of the acetate group[16] appears at 1365 cm.$^{-1}$ (E_A 275–260). In the diacetates E_A for these bands increases to about 300 and the other absorption is swamped.

TABLE III

CARBONYL STRETCHING BANDS IN STEROID SAPOGENINS[a]

Carbon tetrachloride or carbon disulfide solution

I. The following sapogenins contained no carbonyl groups and showed no significant absorption between 1660 and 1780 cm.$^{-1}$: 3-desoxysarsasapogenin, sarsasapogenin, 3-episarsasapogenin, neotigogenin, yamogenin, tigogenin,[1] diosgenin, gitogenin,[b] samogenin, chlorogenin,[b] rockogenin,[1] pennogenin, 5,6-dihydrobethogenin, bethogenin, yuccagenin,[b] digitogenin, dihydrosarsasapogenin, dihydro-3-episarsasapogenin, dihydrotigogenin.

II. The acetates of the following sapogenins exhibited a single maximum at 1735–1739 cm.$^{-1}$: sarsasapogenin, 3-episarsasapogenin, neotigogenin, yamogenin, smilagenin, tigogenin, 9,11-epoxytigogenin,[1] diosgenin, chlorogenin,[1] β-chlorogenin,[3] pennogenin, 5,6-dihydrobethogenin, bethogenin, digitogenin, dihydrosarsasapogenin, dihydro-3-episarsasapogenin, dihydrotigogenin. The 2,3-diacetates of the following sapogenins showed a maximum at 1742–1744 cm.$^{-1}$ and inflection at 1738 cm.$^{-1}$: gitogenin, samogenin, 12-dihydromannogenin. In yuccagenin diacetate the positions of the maximum and the inflection were reversed.

III. Ketones: Sarsasapogenone-3, 1719 cm.$^{-1}$; tigogenone-3,[2] 1719 cm.$^{-1}$; Δ^4-sarsasapogenone-3,[c] 1676 cm.$^{-1}$; hecogenin,[b] 1702 cm.$^{-1}$; mexogenin,[b] 1700 cm.$^{-1}$; 11-ketorockogenin[1]; 1706 cm.$^{-1}$.

IV. Keto acetates: hexogenin acetate, 1739, 1711 cm.$^{-1}$; manogenin diacetate, 1743, 1712, 1683[d] cm.$^{-1}$; mexogenin diacetate, 1745, 1713 cm.$^{-1}$; kammogenin diacetate, 1745, 1713 cm.$^{-1}$; kryptogenin diacetate, 1739, 1719 cm.$^{-1}$; 11,23-dibromohecogenin acetate,[1] 1736, 1722[e] cm.$^{-1}$.

[a] The sources of the compounds not obtained from the Marker collection are indicated by numeral superscripts: (1) C. Djerassi and G. Rosenkranz, Syntex S.A. Mexico City, Mexico; (2) C. R. Noller, Stanford University, Palo Alto, Calif.; (3) A. Solomon, Sloan-Kettering Institute, New York, N. Y. [b] Solvent chloroform. [c] This compound may also be designated Δ^4-neotigogenone-3. [d] This weak band is indicative of a trace of an α,β-unsaturated ketone impurity, the position of the band suggests a $\Delta^{9,11}$-12-ketone. [e] The normal position for the 11-ketone band in carbon disulfide or carbon tetrachloride solution is 1710–1716 cm.$^{-1}$ and the displacement in this compound to 1722 cm.$^{-1}$ may be attributed to the effect of the α-bromine atom.

Carbonyl Stretching Vibrations (1650–1800 Cm.$^{-1}$).—The sapogenin acetates and ketones all exhibit carbonyl stretching bands consistent with the accepted molecular structures.[18] The positions of these bands are summarized in Table III. The 3-monoacetates and 3,6-diacetates absorb at 1736 cm.$^{-1}$ (CS_2, CCl_4 solution). The 2,3-diacetates possess a single maximum of complex contour. For most compounds there is a peak at 1742–1744 cm.$^{-1}$ with an inflection at 1738 cm.,$^{-1}$ but for yuccagenin the positions of the peak and the inflection are reversed. The saturated 3-ketones absorb at 1719 cm.$^{-1}$ in CS_2 or CCl_4 solution and the 12-ketones at 1700–1702 cm.$^{-1}$ in $CHCl_3$ solution.

The absorption of the sapogenins above 1800 cm.$^{-1}$ and below 850 cm.$^{-1}$ has not been systematically studied but does not appear to show any unusual features.

More Complex Sapogenins.—On the introduction of additional oxygen functions into the ring system, the spectra intensify. A systematic comparison with the analogous C_{19}-steroids cannot be made, as the necessary C_{19}-compounds are not available. In many cases however the effect of the additional substituent can be observed by comparison with the spectrum of a simpler sapogenin.

Dihydroxy Sapogenins.—Most of the free dihydroxy sapogenins are too insoluble for investigation and have been examined as acetate derivatives. The effect of introducing the 2-acetoxy group is seen in Fig. 7 where the spectra of **samogenin diacetate** and tigogenin acetate are compared.[19] The increased contributions of the acetate absorption at 1240–1250 cm.$^{-1}$ and 1030–1050 cm.$^{-1}$ are immediately apparent. Through much of the spectrum the characteristic side chain bands are readily identified (G, H, Q, S, T, U) while bands K, L, N, O, P are also little effected except for an enhancement of intensity from the shoulders of the strong acetate bands.

A closer study of the spectra does show that for all of the 2,3-diacetates band R at 956–961 cm.$^{-1}$ is absent or very weak and there are also changes in the region of bands I and J. These cannot be explained by simple additivity of the A ring and side chain absorptions.

Chlorogenin diacetate contains acetate groups at the 3β- and 6α-positions. Its spectrum is compared with that of tigogenin acetate in Fig. 7B. The 6α-acetoxy group modifies the spectrum considerably between 1150 and 1200 cm.$^{-1}$ where bands G and H are replaced by three stronger bands at 1160, 1178 and 1200 cm.$^{-1}$ The spectrum of **β-chlorogenin diacetate** which contains 3β- and 6β-acetoxy groups resembles that of tigogenin acetate more closely[20] and bands G and H are normal.

(18) R. N. Jones, P. Humphries and K. Dobriner, THIS JOURNAL, 72, 956 (1950).

(19) Curves for the 2,3-diacetates of gitogenin, yuccagenin, 12-dihydromanogenin, manogenin and kammogenin are included in ref. 5.

(20) See curve 36 of ref. 5.

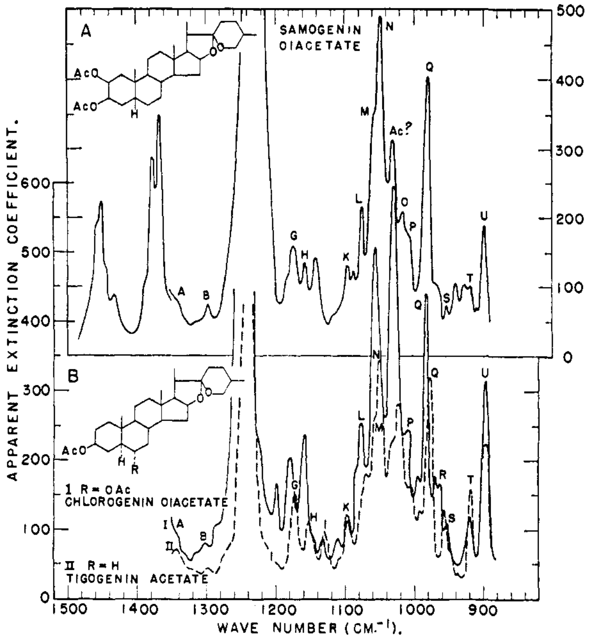


Fig. 7.

In Fig. 8 the spectra of **pennogenin** and diosgenin are compared. The introduction of the tertiary hydroxyl group at C_{16} enhances the intensity of band H, produces small new bands at 1120 and 994 cm.$^{-1}$ and shifts band Q down to 975 cm.$^{-1}$ Similar effects are observed in the spectrum of **pennogenin 3-monoacetate.**[21] In view of the proximity of the C_{17}-hydroxyl group to the side chain, these changes are comparatively minor.

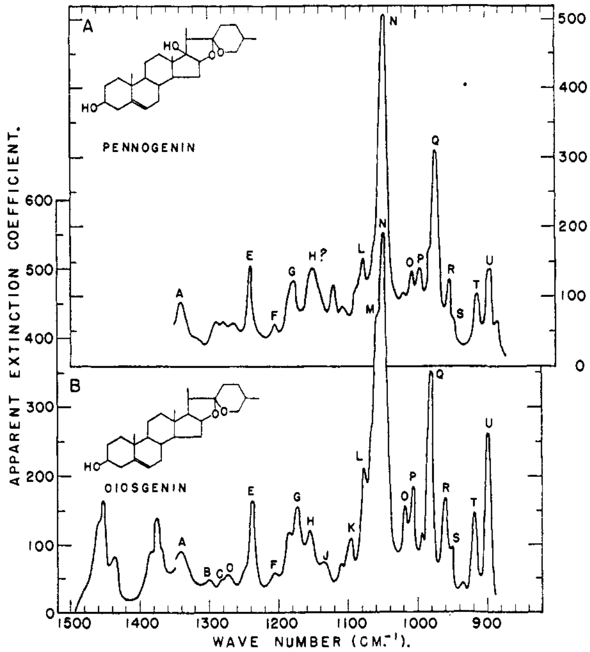


Fig. 8.

The C_{16}-methoxy group in **bethogenin**[22] produces much more profound changes. Medium strong bands are introduced at 1288, 1254 and 1245 cm.$^{-1}$ and weaker bands at 1150, 1120, 1103 and 1088 cm.$^{-1}$. Below this the spectrum conforms with that of the simpler isosapogenins.

12-Keto Sapogenins.—The principal effect of introducing the 12-ketone group is to produce a strong band at 1075 cm.$^{-1}$. This is seen in Fig. 9A in the spectrum of **hecogenin acetate.** It is also noted in the spectra of **hecogenin, mannogenin diacetate** and **kammogenin diacetate.**[23] There is also some enhancement of the intensity near 1040 cm.$^{-1}$ and some displacement of the acetate band from 1023 to 1030–1040 cm.$^{-1}$. Bands R and S are also depressed in intensity. The spectrum of pregnanone-12 is also included in Fig. 9A. Allopregnanone-12, a closer analog, was not available but from the weakness of the absorption it would seem unlikely that any simple additive effect of the 12-ketone group would account for the differences between the spectra of hecogenin acetate and tigogenin acetate.

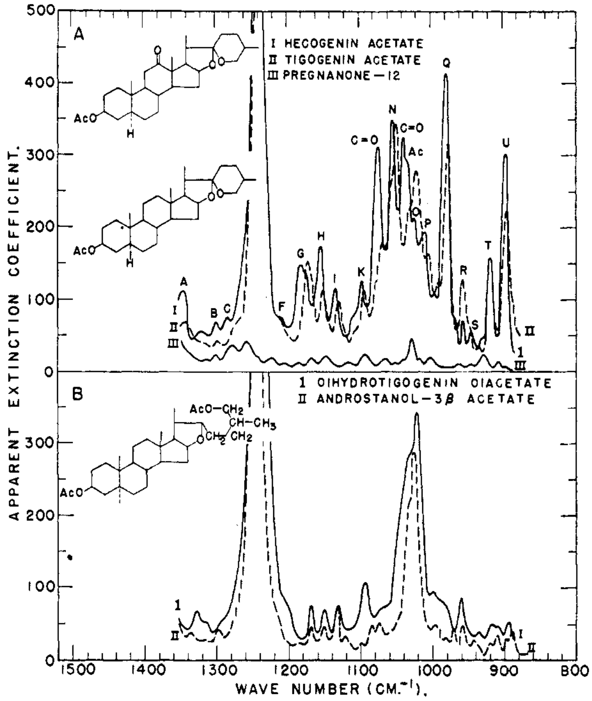
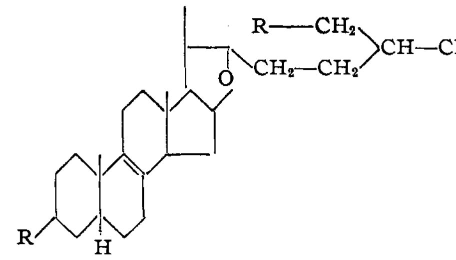


Fig. 9.

Effects of Opening the Side Chain Rings.—On hydrogenation of the normal sapogenins in acid solution the six-membered ring opens to yield a dihydrosapogenin (VII). These compounds are poorly soluble in carbon disulfide, but in Fig. 9B the



VII, R = OH
VIII, R = $OCOCH_3$

(21) See curve 29 of ref. 5.

(22) See curve 39 of ref. 5.

(23) See curves 33, 40 and 41 of ref. 5.

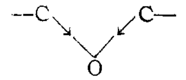
spectrum of dihydrotigogenin diacetate (VIII) is compared with the spectrum of androstanol-3β acetate. All of the characteristic side chain bands are lost and if allowance is made for the absorption of the terminal acetate group it is clear that the five-membered oxide ring contributes little to the spectrum.

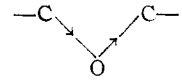
Conclusions

It is evident from the foregoing analysis, that provided the steroid ring is substituted only at position 3, the absorption of these compounds between 850 and 1350 cm.$^{-1}$ can be treated in quite good approximation as the sum of two independent absorbing systems; one is associated with the A ring and is determined by the nature of the substituent at C_3 and the stereochemical configuration at C_3 and C_5; the second, predominating, system is centered in the spiroketal side chain and is determined by the stereochemistry at the spirane ring junction.

On the introduction of addition hydroxyl, acetoxy or ketone groups small but significant changes are noted. The spectra can no longer be reconciled with the above hypothesis and some interaction effects involving the two centers of absorption apparently occur. The effect is more notable for the 12-ketones than for the sapogenins containing acetate or hydroxyl groups at 2, 6, 12 or 16. Even in these more highly substituted sapogenins, however, the interaction effects are comparatively small and the more prominent characteristic side chain bands (N, Q, T, U) are little affected.

The association of the side chain bands α–ω and A–U with specific modes of vibration in the spiroketal ring system cannot be made at present. It may be surmised that some of the stronger bands arise from symmetrical and antisymmetrical stretching vibrations of the C–O bonds (IX, X) since these motions should be associated with fairly large changes in dipole moment. From the fact that these bands all disappear in the spectra of the dihydrosapogenins it seems that the six-membered oxide ring rather than the five-membered oxide ring is most concerned in the active vibrations.


IX


X

Acknowledgments.—The authors wish to thank Professor R. E. Marker and the other investigators, listed individually in a footnote to Table III, who provided the compounds on which this study is based. The technical assistance of Mr. D. S. Keir of the National Research Council of Canada and Mr. R. Cohen, Miss F. Herling, and Miss Rita Conolly of the Sloan–Kettering Institute is also gratefully acknowledged.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY, TOKYO INSTITUTE OF TECHNOLOGY]

Molecular Structures of *trans*-1,4-Dihalogenocyclohexanes

BY KUNIO KÔZIMA AND TSUNEO YOSHINO

RECEIVED JULY 11, 1952

From the studies on the Raman spectra of *trans*-1,4-dihalogenocyclohexanes in various states, it has been concluded: (1) that they stand in the dynamic equilibrium of the two isomers (1p,4p) $\rightleftarrows$ (1e,4e) in solutions; (2) that the molecules, which have the structure (1e,4e), become more stable in the dilute carbon tetrachloride or cyclohexane solution than in the dilute benzene, ethyl alcohol or diethyl ether solution; and (3) that in the solid state, they take only the configuration (1e, 4e). The differences in the potential energy of the both configurations in various solvents were approximately estimated by measuring the relative intensities of the Raman lines.

It has been well established by means of various methods that the only form of the molecule of cyclohexane is the "chair-form" of D_{3d} symmetry. Hence, investigation of the molecular structure of these derivatives has now become a very interesting subject of study.

Supposing the valency angle of each carbon atom of the cyclohexane ring to be tetrahedral, one of the two remaining bonds of each carbon atom of the ring runs parallel to the threefold axis of symmetry and the other bond is not very far from being horizontal to the ring. According to the designation proposed by Pitzer, *et al.*,[1] the position of atoms combined with the former bonds was called p and that of those combined with the latter was called e. Using this designation and numbering the carbon atoms as usual from 1 to 6, a full and yet concise description of halogen derivatives can be given by symbols which indicate positions of only the halogen atoms combined to the ring.

At first sight it would seem that because of the difference in position of the halogens combined to the ring 1,4-dihalogenocyclohexane has the four configurations represented by the following symbols: (1p, 4p), (1p, 4e), (1e, 4p) and (1e, 4e). However, since (1p, 4e) and (1e, 4p) represent the same configuration, three configurations remain to be considered. If by the torsional and deformation vibration in the ring, one chair configuration is converted into the other chair configuration—which is identical, so far as the carbon ring is con-

(1) K. S. Pitzer and C. W. Beckett, THIS JOURNAL, **69**, 977 (1947).