of crude alcohol. Distillation of the crude product through a short Vigreux column yielded 7.3 g. (0.048 mole, 54.6%) of pure alcohol, b.p. 120–125° (5 mm.), m.p. 27–28°, and 1.0 g. of residue, a light brown oil. Tests of the crude product and purified alcohol with aqueous potassium permanganate (2% in water) and ferric chloride solution were negative.

Rate Measurements.—Dry acetic acid,[5,28] absolute ethanol, 0.05% water, and dry formic acid,[9] b.p. 30–31° (50 mm.), 0.01–0.18% water by Karl Fischer titration, were employed. Aqueous dioxane, 80.78% dioxane by volume, was prepared by addition of purified dioxane, freshly distilled from sodium, to 20 volumes of water up to a total of 100 volumes of solution.

The methods employed for the rate measurements were essentially those previously employed.[5,6,9] Titration of aliquots in the ethanolyses was carried out with standard sodium methylate in methanol using the mixed indicator, methyl red and brom cresol green. For the solvolyses in aqueous dioxane, aliquots were titrated with standard aqueous base to the phenolphthalein end-point.

(28) S. Winstein, C. Hanson and E. Grunwald, THIS JOURNAL, **70**, 812 (1948).

LOS ANGELES 24, CALIFORNIA

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Neighboring Carbon and Hydrogen. XV. Rearrangement as a Sequel to Neighboring Functional Group Participation. Solvolysis of 2-Methyl-2-methoxy-1-propyl *p*-Bromobenzenesulfonate

BY S. WINSTEIN, C. R. LINDEGREN AND L. L. INGRAHAM

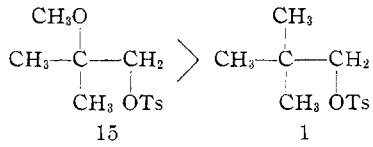
RECEIVED MAY 17, 1952

An exploratory study of the solvolysis of 2-methyl-2-methoxy-1-propyl *p*-bromobenzenesulfonate has shown isobutyraldehyde to be the chief product. The rate of solvolysis is relatively high, methoxyl participation in the rate-determining ionization step supplying a substantial driving force. Glycol monomethyl ether or vinyl ether are not intermediates for isobutyraldehyde formation, the present case illustrating pinacol type rearrangement by a chain of steps commencing with functional neighboring group participation.

It is possible for the pinacol type rearrangement to be associated with a sequence of events beginning with neighboring functional group participation, and we deal in the present article with an instructive case in point. This case is the solvolysis of 2-methyl-2-methoxy-1-propyl *p*-bromobenzenesulfonate (IV) which gives rise, at least largely, to isobutyraldehyde. An exploratory study of this solvolysis is the subject of this manuscript.

The bromobenzenesulfonate IV required for study was prepared from the corresponding alcohol III, this being available from the opening of isobutylene oxide with methanol under acidic conditions.[1] The isomeric alcohol I was prepared by the opening of isobutylene oxide with methanol under basic conditions analogous to the opening of trimethylethylene oxide.[2]

In spite of the high hindrance to nucleophilic attack on C_α by external reagents, the bromobenzenesulfonate IV was quite reactive in solvolysis, which disclosed at the very outset that some kind of anchimeric[3] assistance is involved in the rate-determining ionization step. The solvolysis rate constants of IV in glacial acetic acid and in the solvent used for product isolation, 80% dioxane, are given in Table I. The value of the rate constant in acetic acid, corrected by a factor[4] of 3 to bring the value down to that for the corresponding toluenesulfonate, relative to the value for neopentyl toluenesulfonate[4] gives the comparison which shows that the bromobenzenesulfonate IV is fifteen times as reactive in solvolysis as the neopentyl ester. If one allows for the fact that a β-methoxyl group would, in the absence of participation, reduce an ionization rate by a factor of



15 1

approximately[5] 10^2, it becomes clear that bromobenzenesulfonate IV ionizes at a rate at least 1500 times that which would prevail if no anchimeric assistance were involved. The value of 1500 represents a lower limit to the driving force due to participation in the rate-determining ionization step if neopentyl toluenesulfonate already has an enhanced rate due to carbon participation.[6] Of the two possible participations to be considered, namely, that due to the neighboring methoxyl group (IV) or that due to the neighboring methyl group (XV), the latter can be ruled out immediately on the basis of the final products. Methyl participation (XV) would result in methyl ethyl ketone as a product and, since the product is very largely isobutyraldehyde, methoxyl participation (IV) is therefore indicated. The large driving force associated with methoxyl participation in the bromobenzenesulfonate IV supports the previous

TABLE I

RATE CONSTANTS FOR REACTION OF 2-METHOXY-2-METHYL-1-PROPYL *p*-BROMOBENZENESULFONATE (IV)

Solvent	Concn., *M*	Other solute	Temp., °C.	*k*, sec.$^{-1}$
AcOH	0.047		74.73	$(3.55 \pm 0.08) \times 10^{-6}$
"80%" dioxane	.051	0.0587 *M* KOAc	99.73	$(3.89 \pm 0.08) \times 10^{-5}$

(1) K. R. Edlund, U. S. Patent 1,968,032, July 31, 1934.

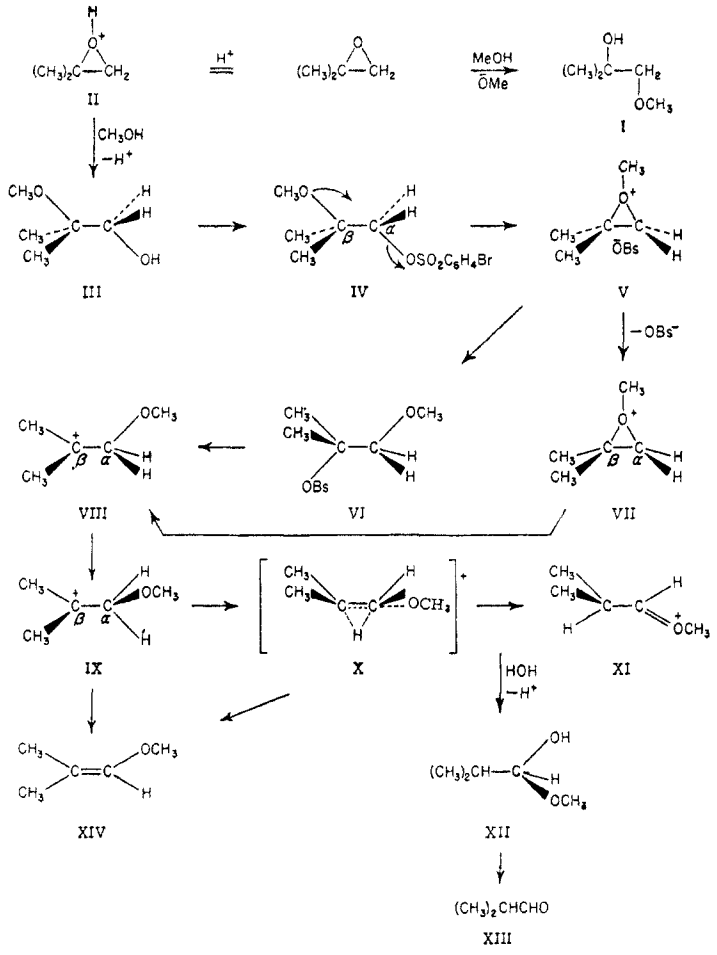
(2) (a) S. Winstein and L. L. Ingraham, THIS JOURNAL, **74**, 1160 (1952); (b) S. Winstein and R. B. Henderson, "Ethylene and Trimethylene Oxides," in Elderfield, "Heterocyclic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1950.

(3) S. Winstein, C. R. Lindegren, H. Marshall and L. L. Ingraham, THIS JOURNAL, **75**, 147 (1953).

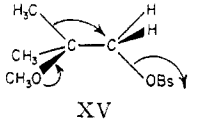
(4) S. Winstein, *et al.*, *ibid.*, **74**, 1113 (1952).

(5) S. Winstein, E. Grunwald and L. Ingraham, *ibid.*, **70**, 821 (1948).

(6) S. Winstein and H. Marshall, *ibid.*, **74**, 1120 (1952).



extrapolation[7] that a very substantial driving force due to methoxyl participation would be reached in a $T_\beta P_\alpha$ structure, with the leaving group primary and the neighboring methoxyl group tertiary.



XV

The solvolysis of the bromobenzenesulfonate IV in 80% dioxane buffered with potassium acetate gave rise to isobutyraldehyde (XIII), isolated as the dinitrophenylhydrazone. Based on the behavior of a control experiment on a known amount of isobutyraldehyde, the yield in the solvolysis of the bromobenzenesulfonate IV was 72%. Thus isobutyraldehyde is the major final product from the oxonium ion VII. The last steps of the chain of reactions through which VII disappears evidently involve X or XI[3] → hemiacetal XII → aldehyde XIII.

In filling in the steps between oxonium ion VII and ion X or XI, tertiary alcohol I seemed a possible intermediate. The formation of alcohol I from oxonium ion VII would be analogous to the behavior of the similarly constituted oxonium ion XVI related to trimethylethylene. However, a control experiment on alcohol I, simulating the reaction conditions closely, gave no isobutyraldehyde detectable with a 2,4-dinitrophenylhydrazine reagent.

Thus tertiary alcohol I cannot be an intermediate for aldehyde formation in the present work. Another possible intermediate appeared to be vinyl ether XIV, whose formation could be conceived to involve VII → VIII → IX, the latter losing a proton, perhaps by way of X. At least under other conditions, it was, of course, clear that vinyl ether XIV could give isobutyraldehyde.[8] The behavior of the vinyl ether XIV suspected as a possible intermediate in the formation of isobutyraldehyde, prepared from the corresponding vinyl bromide, was scrutinized under the reaction conditions employed for the solvolysis of the bromobenzenesulfonate IV. This vinyl ether, which does give rise to isobutyraldehyde rapidly on treatment with dilute strong acid, failed to give appreciable amounts of isobutyraldehyde under the actual reaction conditions where the solvent was buffered with potassium acetate. Thus vinyl ether XIV is ruled out as an intermediate for isobutyraldehyde formation, the movement of hydrogen from C_α to C_β proceeding without proton loss.

The product of the solvolysis of IV in formic acid was also isobutyraldehyde, isolated as the 2,4-dinitrophenylhydrazone. However, in this solvent it is not possible to rule out intermediates such as was possible in the case of solvolysis in aqueous dioxane for it was found that alcohol I in formic acid gave rise to an 87% yield of isobutyraldehyde dinitrophenylhydrazone.

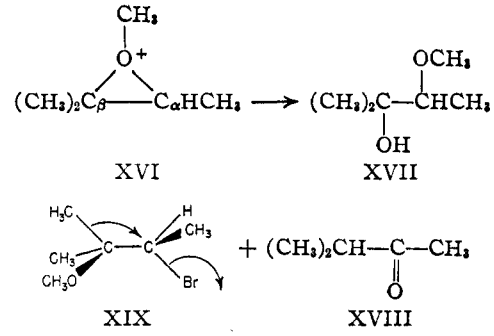
Ruling out I and XIV as intermediates, the most likely explanation for the conversion of oxonium ion VII to ion X or XI involves opening to give open ion VIII, which, after a little rotation around the C_β–C_α axis to configuration IX, is rearranged[7] to X and/or XI by hydride shift. In VIII, the ion first formed on opening of VII, the axis of the sp^3 orbital on C_α employed in formation of a bond to oxygen is in the same plane with the axis of the vacant p orbital on C_β. In IX, the axis of the vacant p orbital on C_β is in the same plane with the axis of the sp^3 orbital on C_α employed in formation of a bond to the hydrogen atom which is to shift. This is the rotational configuration stereoelectronically favorable to hydride shift, but how far must the changes, VII → VIII → IX, be completed before any substantial hydrogen participation can occur is an interesting question.

The above described behavior of oxonium ion VII would be in contrast with the behavior of the ion II in oxide opening and that of the ion XVI, previously observed[2a] to give mainly alcohol XVII. However, there are differences in the various cases, such as the higher temperature employed in the present work involving VII and the absence of the α-methyl group in VII which is present in XVI. These are just the kinds of variations which require systematic study. Even with the trimethylethyl-

(7) S. Winstein and E. Grunwald, THIS JOURNAL, 70, 828 (1948).

(8) A. Eltekoff, *Ber.*, 10, 705 (1877).

ene derivative XVI some methyl isopropyl ketone (XVIII) was observed.[2a] The latter may arise



XVI XVII

XIX XVIII

from XVI in the way it is suggested isobutyraldehyde arises from VII, although there is an ambiguity since methyl isopropyl ketone could also arise from methyl participation at a much earlier stage (XIX).

Another conceivable way VII becomes X or XI involves its conversion, while it is still in the ion-pair V, to rearranged ester VI by internal return.[9] Ester VI could give X or XI either by way of IX or more directly if ionization were to involve hydrogen participation. However, it is problematical how much rearranged ester VI is formed, since the indications are in other cases[10] that internal return is less important in 80% dioxane than, for example, in acetic acid.

Experimental Part

2-Methoxy-2-methyl-1-propanol.[11]—To a cooled solution of 72.1 g. of isobutylene oxide in 350 ml. of methanol was added in portions a solution of 2 drops of concd. sulfuric acid in 50 ml. of methanol. After the reaction had subsided, the mixture was brought to the reflux point and held there one hour. On distillation there was obtained 72.1 g. (69%) of material, b.p. 140–141° (753 mm.).

The 3,5-dinitrobenzoate of the alcohol was prepared in the usual way; m.p. 60.3–60.7° after several recrystallizations.

Anal. Calcd. for $C_{12}H_{14}N_2O_7$: C, 48.32; H, 4.73. Found: C, 48.18; H, 4.95.

2-Methoxy-2-methyl-1-propyl *p*-Bromobenzenesulfonate.—This material, m.p. 49–50°, was prepared in the usual way in 52% yield, using a two-day reaction period.

Anal. Calcd. for $C_{11}H_{15}O_4SBr$: C, 40.87; H, 4.68. Found: C, 41.10; H, 4.80.

1-Methoxy-2-methyl-2-propanol.—A mixture of a solution of 5.1 g. (0.22 gram atom) of sodium in 85 ml. of anhydrous methanol and 21.7 g. (0.20 mole) of isobutylene chlorohydrin was held under reflux for 2.5 hours. Working up in the usual way gave 12.79 g. (0.123 mole), 61.4%, of material, b.p. 116.1–116.5°, $n^{25}D$ 1.4023 (reported[12] b.p. 116.6°, $n^{20}D$ 1.4047).

The 3,5-dinitrobenzoate, m.p. 73.6–74.3°, was prepared in the usual way.

Anal. Calcd. for $C_{12}H_{14}N_2O_7$: C, 48.32; H, 4.73. Found: C, 48.20; H, 4.68.

Solvolysis of 2-Methoxy-2-methyl-1-propyl *p*-Bromobenzenesulfonate in Aqueous Dioxane.—A 0.050 *M* solution of the bromobenzenesulfonate in 80% dioxane, also 0.055 *M* in potassium acetate was refluxed for 113 hours. The solution was poured into 2 l. of water and extracted with ether. The ether extract was dried over anhydrous potassium carbonate and then it was distilled through a 35-cm. column. Addition of a 2,4-dinitrophenylhydrazine reagent solution to the fraction, b.p. 34–84°, yielded a derivative, m.p. 176–178°, m.p. 179–180° after recrystallization from ethanol, mixed m.p. with isobutyraldehyde 2,4-dinitrophenylhydrazone (m.p. 180–182°) 179–181°.

A solution of 3.24 g. (0.010 mole) of bromobenzenesulfonate and 1.16 g. (0.011 mole) of potassium acetate in 100 ml. aqueous dioxane was heated in a sealed tube 66 hours on the steam-bath. The mixture was then distilled through a short Vigreux column into 25-ml. portions of 2,4-dinitrophenylhydrazine reagent until no more precipitate appeared.

After allowing the solutions to stand overnight, the precipitate was filtered, washed and dried to give 1.10 g. of product, m.p. 156.0–165.0°. Addition of water to the filtrate gave an additional 0.14 g. of solid, m.p. 145.0–161.0°. Recrystallization from ethanol raised the m.p. of both fractions to 175–178°, mixed m.p. with isobutyraldehyde dinitrophenylhydrazone (m.p. 178.6–180.5°) 176–178°.

A solution of 0.724 g. (0.010 mole) of isobutyraldehyde, b.p. 60–63°, in 100 ml. of aqueous dioxane was distilled as in the above procedure into 25-ml. portions of 2,4-dinitrophenylhydrazine reagent to give a total yield of 1.71 g. (67.8%) of derivative, m.p. 154–173°, m.p. after recrystallization from ethanol, 178.6–180.5°. Based on the yield of 2,4-dinitrophenylhydrazone derivative isolated from the known quantity of isobutyraldehyde, the yield of isobutyraldehyde obtained in the solvolysis of bromobenzenesulfonate was 72.3%.

A control run on 1-methoxy-2-methyl-2-propanol was carried out by holding a solution of 1.06 g. (0.0102 mole) of the alcohol, 0.098 g. (0.0010 mole) of potassium acetate and 0.5 ml. glacial acetic acid (0.01 mole) in 100 ml. of aqueous dioxane in a sealed tube on the steam-bath for 66 hours. Distillation of this solution into a 25-ml. portion of 2,4-dinitrophenylhydrazine reagent yielded no precipitate even upon standing overnight. A mixture of 25 ml. of the distillation residue and 25 ml. of the dinitrophenylhydrazine reagent likewise did not give a precipitate either upon standing overnight or upon subsequent addition of 10 ml. of water.

Formolysis of 2-Methoxy-2-methyl-1-propyl *p*-Bromobenzenesulfonate.—Ten ml. of a formic acid solution, 0.01835 *M* in bromobenzenesulfonate and 0.0588 *M* in potassium acetate was kept at 75° for 24 hours. After being cooled, it was added to 20 ml. of 2,4-dinitrophenylhydrazine reagent and the mixture was allowed to stand overnight. Dilution with 50 ml. of water gave a 58% yield of material, m.p. 150–169°, m.p. after recrystallization from ethanol, 172–176°, not depressed by mixture with isobutyraldehyde dinitrophenylhydrazone.

A control run on 1-methoxy-2-methyl-2-propanol was carried out by holding a solution of the alcohol (0.05014 *M*) and sodium formate (0.0543 *M*) in formic acid at 75° for 24 hours. To 10 ml. of this solution was added 20 ml. of the 2,4-dinitrophenylhydrazine reagent. After standing overnight, the solution was diluted with 50 ml. of water to give an 87% yield of derivative, m.p. 157–167°, m.p. after recrystallization from ethanol 171.5–176.5°, undepressed on mixing with isobutyraldehyde 2,4-dinitrophenylhydrazone.

Preparation of and Control Experiments with 1-Methoxy-2-methyl-1-propene.—Isobutylene dibromide was converted to 1-bromo-2-methyl-1-propene, b.p. 89–92°.[13] The 1-bromo-2-methyl-1-propene was converted in poor yield to 1-methoxy-2-methyl-1-propene by the method of Eltekoff.[8] The vinyl ether, b.p. 69–72°, displayed major absorption peaks in the infrared spectrum at 3.47, 6.92, 8.43, 9.05, 9.15 (twin peaks), 11.12 and very small peaks at 6.05 and 7.31 μ. Thus the infrared spectrum showed the presence of methyl groups and carbon–carbon unsaturation and indicated the presence of less than 1% aldehyde. Heating a sample of the vinyl ether on the steam-bath briefly with 6 *N* sulfuric acid, followed by the addition of 2,4-dinitrophenylhydrazine reagent, gave an immediate copious precipitate of isobutyraldehyde 2,4-dinitrophenylhydrazone, m.p. 181–182°, after recrystallization from alcohol, mixed m.p. with an authentic sample undepressed. The addition of the vinyl ether directly to the 2,4-dinitrophenylhydrazine reagent did not give any immediate precipitate. Upon standing for five minutes, however, a small amount of precipitate slowly formed. Two solutions were prepared, each containing

(9) S. Winstein and K. C. Schreiber, THIS JOURNAL, **74**, 2165 (1952).

(10) N. J. Holness, E. Kosower and E. Clippinger, unpublished work.

(11) We are indebted to Mr. Duane Gish for the preparation of this material.

(12) C. E. Sparks and R. E. Nelson, THIS JOURNAL, **58**, 671 (1936).

(13) J. K. Farrell and G. B. Bachman, *ibid.*, **57**, 1282 (1935).

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.

LOS ANGELES 24, CALIF.

[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

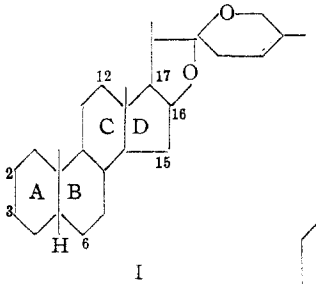
BY R. NORMAN JONES, E. KATZENELLENBOGEN AND KONRAD DOBRINER[2]

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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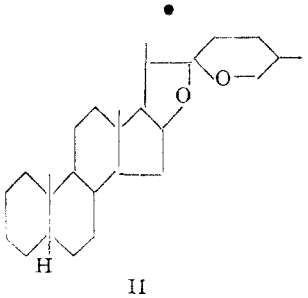

II

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

(1) Published as Contribution No. 2880 from The Laboratories of The National Research Council of Canada, and No. XVII in the series "Studies in Steroid Metabolism."

(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.