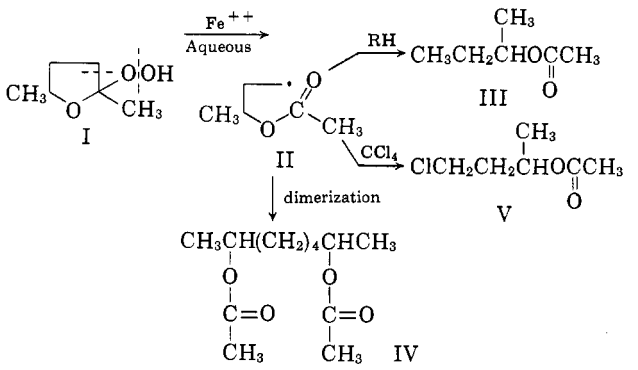
volving 2,5-dimethyltetrahydrofuran hydroperoxide[3] (I) apparently proceeds through free radical II, when aqueous ferrous ion is the reducing agent, to give *sec*-butyl acetate (III) by hydrogen abstraction from the solvent molecules, or 2,7-octanediol diacetate (IV) by dimerization of II as the principal products.



We have checked the work done by previous investigators on 2,5-dimethyltetrahydrofuran hydroperoxide with aqueous ferrous ion[3] and have extended this work by accomplishing the decomposition of I in the presence of carbon tetrachloride to produce 4-chloro-2-butyl acetate (V) along with IV. The production of V apparently proceeds by a reaction sequence similar to that for the formation of III except that in the presence of carbon tetrachloride the radical II reacts by extracting a chlorine atom to form V rather than by extracting a hydrogen atom from a solvent molecule as is the case with aqueous ferrous ion alone.

The extent of dimerization of II to produce IV when the reaction was done with aqueous ferrous ion along with carbon tetrachloride was comparable to that observed when the decomposition was done with aqueous ferrous ion alone (46 and 36%, respectively). In the experiment with carbon tetrachloride no III resulted but the yield of V with carbon tetrachloride approaches the yield of III in the absence of carbon tetrachloride (see Table I).

TABLE I

YIELD[a] OF VARIOUS ESTERS FROM DECOMPOSITION OF 2,5-DIMETHYLTETRAHYDROFURAN HYDROPEROXIDE

Compounds	Aqueous Fe^{++} only	Aqueous Fe^{++} with CCl_4
4-Chloro-2-butyl acetate	..	19
sec-Butyl acetate	32	..
2,7-Octanediol diacetate	46	36

[a] The yields given are in mole per cent in terms of the moles of hydroperoxide appearing as a particular product.

In addition to the ester-like material characterized in the reaction with carbon tetrachloride, a dark, viscous residue was recovered which amounted to 32 weight % of the starting hydroperoxide. This residue was not characterized.

Experimenta

Production of Hydroperoxide.—A sample of 2,5-dimethyltetrahydrofuran was allowed to stand in a glass reaction flask in contact with oxygen for a period of 6 weeks. Intermittent stirring was used to assure saturation with oxygen at all times. At the end of the 6-week period, analysis by the method of Wagner, Smith, and Peters[6] for hydroperoxide content indicated that the sample consisted of 38.6 g. of 2,5-dimethyltetrahydrofuran hydroperoxide and 139.4 g. of 2,5-dimethyltetrahydrofuran.

Decomposition of Hydroperoxide in the Presence of Carbon Tetrachloride.—The mixture described above was added, dropwise, to a mixture consisting of a saturated solution of ferrous sulfate heptahydrate, 1 l. of methanol, and 500 ml. of carbon tetrachloride. The methanol was added in an attempt to produce a homogeneous reaction medium but did not accomplish this end as two phases were present all during the reaction. The reaction mixture was contained in a 3-l., three-neck, round-bottom flask, equipped with an efficient stirrer, a condenser, and a dropping funnel from which the hydroperoxide was added. The reaction mixture was maintained at 30° by use of an ice bath as the reaction was quite exothermic. After the reaction was complete the resulting organic and water layers were separated and investigated individually.

The water layer contained no organic material boiling above 100°.

The organic layer was washed with three 100-ml. portions of potassium carbonate solution, then dried overnight with anhydrous magnesium sulfate. The dry organic layer was subjected to a simple distillation and separated into three large fractions. The first fraction boiled 59–78° and contained chloroform, methyl alcohol, carbon tetrachloride, 2,5-dimethyltetrahydrofuran, and water. The second fraction was collected at 78–81° was mainly carbon tetrachloride. The remaining material was charged to a fractionation column (about 30 theoretical plates, glass-packed) and fractionally distilled. Additional chloroform, methanol, carbon tetrachloride, 2,5-dimethyltetrahydrofuran, and water were obtained. After the material boiling below 100° was removed, the pressure was reduced and distillation was continued. Two significant fractions were subsequently distilled. One fraction, which was eventually found to be 4-chloro-2-butyl acetate, possessed the following properties: b.p. 59–64°/13 mm. (lit.,[7] 71–72°/16 mm.), $n^{20}D$ 1.4280 (lit.,[7] 1.4273), m.p. of 3,5-dinitrobenzoate 113–114° (lit.,[7] 113–114°), sapon. equiv. 80.7 (corresponding to elimination of hydrogen chloride).

Anal. Calcd. for $C_6H_{11}ClO_2$: C, 48.6; H, 7.97; Cl, 23.5; O, 20.6. Found: C, 48.6; H, 7.55; Cl, 22.2; O, 21.7.

Qualitative infrared analysis indicated carbon–chlorine bonding in the material.

The other fraction, b.p. 71–115°/10 mm., $n^{20}D$ 1.4285, sapon. equiv. 115, was water-white and did not contain chlorine. This fraction was not rigorously characterized but on the basis of work by previous investigators[3] plus the information cited above was assumed to be a diol diacetate, possibly 2,7-octanediol diacetate.

Decomposition of Hydroperoxide with Ferrous Ion Alone.—The decomposition and work-up of the hydroperoxide accomplished in the presence of aqueous ferrous ion alone was similar to that described for the carbon tetrachloride experiment. The principal products were *sec*-butyl acetate and 2,7-octanediol diacetate (see Table I) as had been established previously.[3]

Acknowledgment.—The authors are indebted to Dr. J. H. Jones of the Petroleum Refining Laboratory at The Pennsylvania State University for supplying the 2,5-dimethyltetrahydrofuran used in this investigation.

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The Synthesis of the β-D-Glucoside of Medicagenic Acid, an Alfalfa Root Saponin[1]

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The β-D-glucoside of medicagenic acid has been synthesized by a four-step procedure. Crystalline

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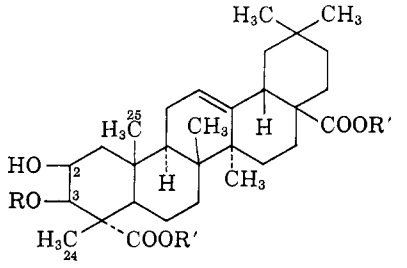
medicagenic acid, obtained by hydrolysis of an alfalfa root saponin concentrate, was transformed into the dibenzohydryl ester by reaction with diphenyldiazomethane. This derivative was condensed with acetobromoglucose by the Koenigs–Knorr reaction. Deacetylation of the reaction product produced the β-D-glucoside of dibenzohydryl medicagenate. Hydrogenolysis of this compound afforded the β-D-glucoside of medicagenic acid. The principal intermediates in the synthesis were carefully purified and identified from chemical constants and elemental analysis. The glucoside prepared by this procedure was identical in all respects to a naturally occurring root saponin reported earlier from this laboratory[2] which was characterized as 2β-hydroxy-3β-(β-D-glucopyranosyl)-Δ^{12}-oleanene-23, 28-dioic acid. The equivalence of the two compounds was established by melting point determinations, optical rotation, elemental analyses, and infrared spectra.

During the last decade a number of investigators have made valuable contributions leading to a better understanding of the molecular structure of aglycones occurring in water soluble saponins found in alfalfa.[3–8] Of particular interest to this research has been the establishment of the structure of medicagenic acid, since a saponin containing this aglycone has been found to be quite abundant in the roots of the alfalfa plant. In an earlier communication the isolation and characterization of this saponin was reported. Because this compound presented a simple glucose side chain, it appeared ideal as a compound for synthetic duplication.

The method of synthesis was similar to that previously found successful for the preparation of the β-D-glucoside[9] and the β-D-quinovoside[10] of oleanolic acid. The acid functions were protected by esterification with diphenyldiazomethane, since the benzohydryl groups may be conveniently removed later by catalytic hydrogenolysis without reduction of the carboxylic acid.[11] The glucoside of the diester was produced by the method of Koenigs and Knorr[12] as modified by Miescher and Mystre,[13] using silver carbonate as the catalyst. Following deacetylation of the glucoside, the diester was subjected to hydrogenolysis using a palladium catalyst, resulting in the formation of the β-D-glucoside of medicagenic acid.

No attempt was made to block the axial 2β-hydroxy group as the greater reactivity toward substitution at an equatorial position (3β) has been well substantiated by a number of investigators.[14] Further, a scale model of ring A of medicagenic acid indicated that considerable steric interference to 2β substitution would arise from the axial C-24 and C-25 methyls. These considerations, coupled with the bulky nature of the attacking species (tetra-O-acetyl-β-D-glucopyranosyl), would make substitution at the axial position virtually impossible and thus the 3β-glucoside was the expected product. Since the saponin thus obtained is identical to the natural alfalfa root saponin, it appears that the enzymatic synthesis conducted in the plant also favors the 3β-glycosidic position.

A repetition of this synthesis using C^{14}-labeled glucose is being considered in this laboratory. The saponin so prepared could be of value for determining the role of such compounds in plant and animal physiology.



I. R, R′ = H
II. R = H, R′ = $(C_6H_5)_2CH$
III. R = Tetra-O-acetyl-β-D-glucopyranosyl, R′ = $(C_6H_5)_2CH$
IV. R = β-D-glucopyranosyl, R′ = $(C_6H_5)_2CH$
V. R = β-D-glucopyranosyl, R′ = H

Experimental[15]

Isolation and Purification of Medicagenic Acid (I).—The isolation of the alfalfa root saponin followed the procedure previously described in the literature.[2] Nine kilograms of the dried root powder yielded approximately 120 g. of crude light brown saponin. This was not purified further but was hydrolyzed directly by refluxing with 8 l. of 1 *N* ethanolic-hydrochloric acid (1:1) for a period of 72 hr.[5] The crude acid was precipitated by addition of an equal volume of water and then dissolved in a minimum of hot dioxane, the solution decolorized with activated carbon and allowed to cool. The medicagenic acid crystallized from the solution in the form of needles, two recrystallizations from dioxane affording a pure product with the same constants as published earlier.[3] The needles exhibit parallel extinction between crossed nicols and have a negative sign of elongation.

Dibenzohydryl Medicagenate (II).—Dry medicagenic acid (15.06 g., 0.03 mole) was dissolved in 500 ml. of dioxane contained in a 1-l. three-necked flask equipped with a stirrer, thermometer, and gas delivery tube. The flask was placed in a water bath maintained at 60°,[16] a solution of 19.4 g. (0.10 mole) of diphenyldiazomethane in 100 ml. dioxane added, and the stirrer started. The nitrogen evolved was measured by displacement of water and in this manner the course of the reaction could be followed. At the end of 60 hr. the theoretical amount of nitrogen had been evolved and the color of the reaction mixture had changed from deep red to straw yellow. The solution was removed from the flask and evaporated to dryness in a rotary film evaporator. The resulting gummy yellow residue was kneaded with small quantities of hot ethanol until no more color could be removed. A white solid remained which crystallized without difficulty from acetone-water, a single recrystallization resulting in 15.3 g. (61.2%) of the dibenzohydryl ester. The product crystallized as broad needles melting sharply at 235° which exhibited a positive sign of elongation; $[\alpha]^{25}D$ +46.7° in chloroform (*c*, 0.0190 g./ml.).

Anal. Calcd. for $C_{56}H_{66}O_6$: C, 80.54; H, 7.97. Found: C, 80.38; H, 8.03.

Tetra-O-acetyl-β-D-Glucopyranoside of Dibenzohydryl Medicagenate (III).—In a 500-ml. three-necked flask fitted with a stirrer, addition funnel, and distilling head was placed a solution of 8.35

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(15) All melting points are corrected. Analyses were performed by C. F. Geiger, Ontario, Calif.
(16) At significantly higher temperatures considerable amounts of bis(diphenylmethyl)ketazine were formed, while lower temperatures resulted in a prohibitively long reaction time.

g. (0.01 mole) of dibenzohydryl medicagenate in 200 ml. of dry benzene. Previously dried silver carbonate (10 g.) was added, the stirrer started, and a small fraction of benzene distilled to remove traces of water. A solution of 8.2 g. (0.02 mole) of acetobromoglucose in 100 ml. of benzene was then added slowly over a period of 2 hr., during which time the benzene–water azeotrope was continually removed by distillation. The reaction mixture was then filtered and the filtrate returned to the flask. Fresh silver carbonate (5 g.) was added and once more 4.1 g. (0.01 mole) of acetobromoglucose in 100 ml. benzene was added over a 2-hr. period, with continuous distillation. After addition was completed the mixture was warmed an hour on the water bath, cooled, filtered, and the filtrate evaporated to dryness. Attempts to crystallize the amorphous product were unsuccessful and it was considered expedient to attempt purification at a later stage of the synthesis.

β-D-Glucopyranoside of Dibenzohydryl Medicagenate (IV).—The dried residue (16.3 g.) from the Koenigs–Knorr reaction was deacetylated by solution in 100 ml. of absolute ethanol to which 1 g. of sodium had been added. This solution was boiled under reflux for 1 hr. and then poured into 100 ml. of cold water. The glucoside precipitated as a white amorphous solid which was filtered and washed with water on the filter. The product, which could not be crystallized, was chromatographed on 150 g. of activated alumina, elution being effected with methanol. Evaporation of the eluant yielded 4.10 g. (41%) of the amorphous β-D-glucopyranoside of dibenzohydryl medicagenate, m.p. 136–140° dec.

Anal. Calcd. for $C_{62}H_{76}O_{11}$: C, 74.67; H, 7.68. Found: C, 74.24; H, 7.64.

β-D-Glucopyranoside of Medicagenic Acid (V).—The glucoside of dibenzohydryl medicagenate (2.0 g., 0.002 mole) was dissolved in 60 ml. of absolute ethanol and 2.0 g. of 5% palladium on charcoal added. The mixture was shaken with hydrogen at room temperature and a pressure of 60 p.s.i. for 72 hr. At the end of this time the catalyst was removed and the filtrate evaporated to a white residue. The diphenylmethane formed by the reduction was removed by suspending this residue in water and steam distilling until no more of the hydrocarbon could be detected in the distillate. The glucoside was filtered and dissolved in ethanolic sodium hydroxide, diluted with water, and shaken with ether. Careful neutralization of the aqueous layer with hydrochloric acid resulted in the precipitation of the glucoside of medicagenic acid which was filtered and dried *in vacuo* for 4 hr. at 60°. The white amorphous product (0.75 g., 57%) melted at 253–255° and gave an $[\alpha]^{23}D$ of +71.4 in ethanol (*c*, 0.01793 g./ml.). Identity of this product with the naturally occurring alfalfa root saponin was demonstrated by infrared comparison and an undepressed mixture melting point.

Anal. Calcd. for $C_{36}H_{56}O_{11}$: C, 65.04; H, 8.49. Found: C, 65.55; H, 8.60.

Transacetalation. The Reaction Pathway[1]

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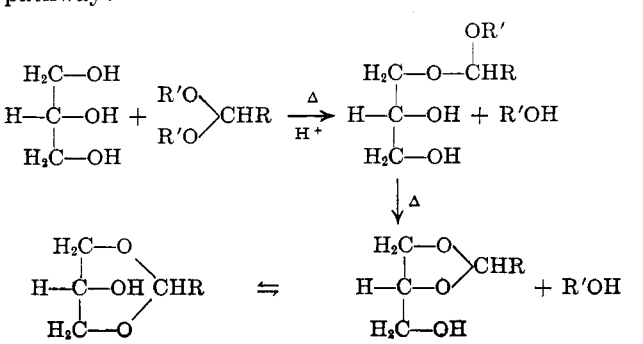
A previous report[3] showed that primary alcohols in acetal linkage may be exchanged with glycerol leading to the formation of 1,2-cyclic glycerol acetals. During the synthesis of the 1,2-benzylidene glycerol acetal (2-phenyl-4-hydroxymethyl-1,3-dioxolane) by transacetalation from the diethylacetal of benzaldehyde a stepwise evolution of alcohol was noted. The same phenomenon was noted in the synthesis of other low molecular weight glycerol acetals. This stepwise evolution of alcohol suggested the occurrence of an intermediate in the synthesis of 1,2-glycerol acetals by this reaction. Such an intermediate could be either the mixed ethyl–glycerol acetal or possibly a hemiacetal. Of these two possibilities the mixed acetal would appear to be the more likely, particularly in view of the demonstrated success in the syntheses of open structure type mixed acetals.[3-5]

With the above possibilities in mind, the synthesis of the ethylidene glycerol acetal (2-methyl-4-hydroxymethyl-1,3-dioxolane) by transacetalation from diethyl acetal was stopped after the evolution of one-half the theoretical quantity of alcohol and the products in the reaction mixture were isolated. Two fractions were obtained. One fraction, isolated in a very low yield, had physical constants identical with the 1,2-ethylidene glycerol acetal reported earlier.[3] The other fraction in much higher yield had entirely different physical constants. Acylation of this latter fraction with tetradecanoyl chloride followed by subsequent cleavage of the acetal linkage led to the isolation of 1,2-dimyristin whose melting point agreed with that reported by Daubert and King.[6] These data show that the transacetalation reaction progressed *via* the mixed acetal stage.

The fraction, subsequently shown to be 1,2-ethylideneglycerol, could have arisen during the initial reaction or during the distillation procedure. The latter possibility would suggest that ring closure took place under the influence of heat alone and did not require an acid catalyst. This was subsequently shown to be the case by stopping the synthesis of benzylideneglycerol acetal by the transacetalation reaction after evolution of one-half the theoretical amount of alcohol, neutralizing the catalyst, and again heating the reaction mixture. The 1,2-benzylideneglycerol acetal was obtained in good yield. Subsequently the synthesis of the 1,2-ethylideneglycerol acetal was achieved by heating the isolated mixed ethyl–glycerol acetal to a temperature of 115–120°. Attempts at the isolation of the mixed acetal where palmital dimethyl acetal was used in the transacetalation reaction were unsuccessful. This finding may be explained by the high temperature (130°) needed in this case for initiating the first step in the reaction. This temperature was apparently high enough to cause immediate ring closure.

The findings reported in this investigation and those reported earlier on the interconversion of benzylidene glycerols[3] show that the transacetalation reaction for the preparation of cyclic glycerol acetals follows the pathway:



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(2) Biology Branch, Research and Development Division, U. S. Atomic Energy Commission, Oak Ridge, Tenn.

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