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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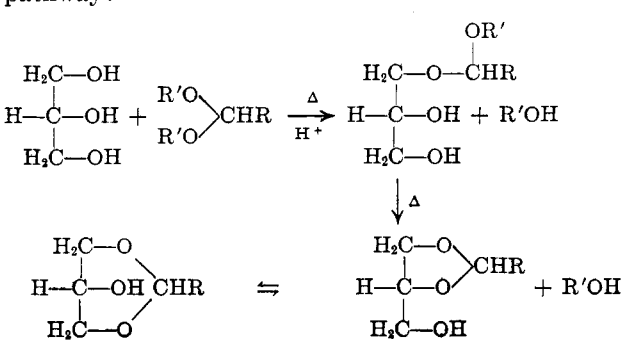
A previous report[3] showed that primary alcohols in acetal linkage may be exchanged with glycerol leading to the formation of 1,2-cyclic glycerol acetals. During the synthesis of the 1,2-benzylidene glycerol acetal (2-phenyl-4-hydroxymethyl-1,3-dioxolane) by transacetalation from the diethylacetal of 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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(3) C. Piantadosi, Carl E. Anderson, E. A. Brecht, and C. L. Yarbro, *J. Am. Chem. Soc.*, **80**, 6613 (1958).

Experimental

Synthesis of the Mixed Ethyl-Glycerol Acetal.—In a three-necked flask equipped with a stirrer, a thermometer, and a condenser for the collection of alcohol were placed 55 g. of glycerol, 35 g. of diethyl acetal, and 50 mg. of sulfosalicylic acid. The reaction mixture was heated on an oil bath and ethanol began to evolve at 94°. The first step in the evolution of ethanol was complete at 104°; yield of ethanol was 102% as calculated for the mixed acetal. The reaction was stopped at this point by chilling in an ice bath. After chilling, the reaction mixture was extracted three times with 125-ml. portions of ether. The combined extracts were washed with 50 ml. of a 0.1 *N* sodium hydroxide and then with distilled water and dried over anhydrous potassium carbonate. The ether was removed under reduced pressure leaving a yellowish oil which had an odor distinctly different from that of diethyl acetal, acetaldehyde or 1,2-ethylideneglycerol. This oil was further purified by fractional distillation at 3 mm. Two fractions were obtained: Fraction I, b.p. 53–55° (3 mm.); $n^{25}D$ 1.4395; yield was 21% as calculated for the mixed ethyl-glycerol acetal. Fraction II, b.p. 65–66° (3 mm.); $n^{25}D$ 1.4405 (These constants are identical with those reported earlier for 1,2-ethylideneglycerol acetal.[3]); yield was 3.1% as calculated for 1,2-ethylideneglycerol acetal.

Preparation of 1-2-Dimyristin from the Mixed Ethyl-Glycerol Acetal.—In a glass-stoppered Erlenmeyer flask were placed 9.6 g. of the product from fraction I, 12 ml. of pyridine, and 10 ml. of purified chloroform. This mixture was chilled thoroughly in an ice bath. To the chilled mixture were added in a dropwise manner 29 g. of myristoyl chloride. A crop of white crystals appeared and the solution became yellow in color. After the reaction was completed, 150 ml. of ether was added and a voluminous precipitate appeared which went back into solution upon addition of 150 ml. of ice–water. The ether layer was removed, washed with 10% sodium bicarbonate, then with ice–water, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure leaving a waxy solid. Yield of crude material was 99% as calculated for the dimyristoyl derivative of the mixed acetal.

The acetal group was removed by acid hydrolysis. The crude material was dissolved in 40 ml. of ether and 40 ml. of concentrated hydrochloric acid was added in a dropwise manner to the constantly shaken ether solution cooled in an ice–salt mixture. After the addition of acid was complete, the ether layer was separated and washed repeatedly with 100-ml. portions of ice–water. After each wash a troublesome emulsion occurred. Each water wash was extracted with three 100-ml. portions of ether, these extracts being added to the original ether solution. The combined ether fractions were dried over anhydrous sodium sulfate and placed in the cold room at 5° overnight, where a small amount of white precipitate formed. The ether solution was concentrated to a volume of 50–75 ml. by evaporation and the precipitate filtered on a Büchner funnel. The precipitate was shown to be mostly the soap of myristic acid, although repeated crystallization from ethanol at 5° produced a few milligrams of a white crystalline material melting at 71–72°. This melting point compared favorably with that reported for β-monomyristin.[7]

The ether filtrate from the above procedure was evaporated to dryness under reduced pressure. The residue obtained was dissolved in 50 ml. of acetone, and 50 ml. of water was added. This mixture was placed in the cold room overnight at 5° where a light yellow precipitate formed. This precipitate was recrystallized repeatedly from acetone until a white crystalline material melting sharply at 59° was obtained and which showed no change in melting point upon subsequent recrystallizations. This melting point corresponded exactly with that reported for 1,2-dimyristin.[7]

Investigation of Conditions for Ring Closure in the Synthesis of 1,2-Glycerol Acetals.—The synthesis of 1,2-benzylideneglycerol acetal from 0.1 *M* diethyl acetal of benzaldehyde and 0.1 *M* glycerol was carried out by the procedure previously described[3] with the following modification. After evolution of one-half of the theoretical quantity of alcohol, the reaction was stopped and the product extracted with ether and base in the usual manner. The ether was removed under reduced pressure and the oil which remained was heated to temperatures of 110–135° where evolution of the second half of the alcohol occurred. Distillation of the reaction mixture gave an 80% yield, b.p. 130–131° (3 mm.); $n^{30}D$ 1.5350. These constants compare with those reported earlier for 1,2-benzylideneglycerol acetal.

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Reaction of Chloral Hydrate with Aliphatic Amines in Water

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It has been shown by Blicke and Lu that chloral hydrate reacted with N-methyl-α-methylhomopiperonylamine or piperidine to form the N-formyl derivative in almost quantitative yield.[1] More detailed investigation with a number of amines showed that formylation with the aid of chloral in chloroform under anhydrous conditions is an excellent general procedure for the acylation of a strong organic base.

The purpose of this work was to establish whether the formylation could be performed in water (equation 1) at the same time differentiating between formamide synthesis through chloral hydrolysis followed by ammonium formate dehydration (equation 2).

$$RNH_2 + CCl_3CH(OH)_2 \xrightarrow{H_2O} RNHCHO + CHCl_3 \quad (1)$$

$$\downarrow H_2O$$

$$[R\overset{+}{N}H_3\ HCOO^-] + CHCl_3 \longrightarrow RNHCHO + H_2O \quad (2)$$

Four aliphatic amines representing various degrees of steric hindrance and one aliphatic diamine were studied (Table I).

TABLE I

REACTION OF AMINES WITH CHLORAL HYDRATE

$$RNHR' + CCl_3CH(OH)_2 \longrightarrow RNR'CHO + [RNH_2R'\ HCOO^-]$$

R	R′	Yield, % RNR′CHO	Yield, % [RNH₂R′HCOO⁻]
n-C₄H₉—	H	78.5	...
t-C₄H₉—	H	6.0	92.0
Cyclohexyl—	H	72.5	2.1
(CH₃)₂N(CH₂)₃—	H	73.5	8.3[a]
C₂H₅—	C₂H₅	41.5	19.7[b]

[a] Isolated as an N,N-Dimethylpropanediammonium formate–formic acid (3:1) azeotrope. [b] Isolated as a diethylammonium-formate–formic acid (3:2) azeotrope.

Hydrolysis to an ammonium formate was evident with *t*-butylamine and to a much lesser extent with all the other amines except the *n*-butyl analog. Ammonium formate dehydration was eliminated as a major route to formamides in this investigation on the basis of a comparison of conditions employed and those required for dehydration. The conditions for dehydration were determined previously in the course of distilling mixtures containing excess amine and 89% formic acid. The appropriate ammonium formates were isolated as solids, binary azeotropes with formic

(1) F. F. Blicke and C.-J. Lu, *J. Am. Chem. Soc.*, **74**, 3933 (1952).