TITLE Cyclic Acetals

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CYCLIC ACETALS

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Floyd E. Anderson

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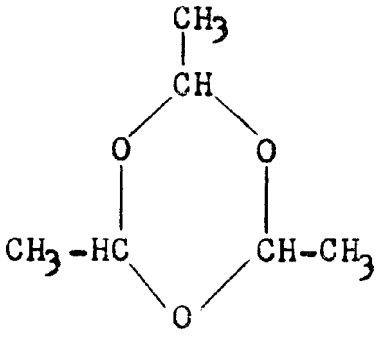
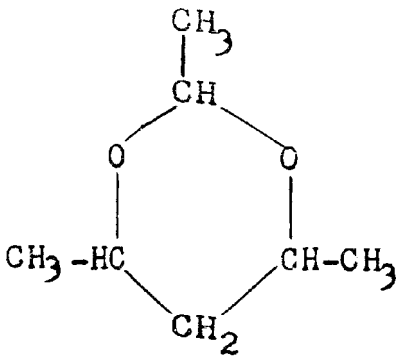
OBJECT OF THIS INVESTIGATION AND HISTORICAL INTRODUCTION

Paraldehyde has been described as one of the best and least toxic hypnotics, however, its use is restricted due to its burning, disagreeable taste and the odor which it imparts to the breath.

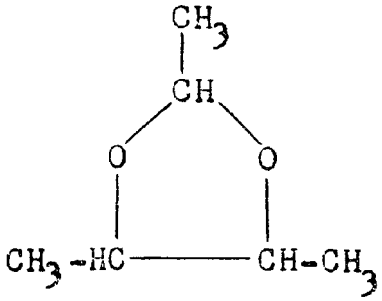
Since the structures of certain cyclic acetals, for example 2,4,6-trimethyl-1,3-dioxane and 2,4,5-trimethyl-1,3-dioxolane, are closely related to the structure of paraldehyde, it seemed desirable to prepare a series of such acetals in the hope that compounds might be found which would possess the hypnotic activity of paraldehyde but be free from its undesirable properties.



Paraldehyde



2,4,6-Trimethyl-1,3-dioxane



2,4,5-Trimethyl-1,3-dioxolane

Consequently, a number of cyclic acetals were synthesized, and examined for hypnotic activity in another laboratory; some of compounds proved to be active products.

Inasmuch as a large number of pharmacologically active compounds are basic substances, it was of interest to determine the manner in which the presence of a basic group might affect the activity of an acetal or a ketal. A group of basic ketals were synthesized and, upon pharmacological examination, it was found these products possessed antihistamine properties. As far as we are aware, such properties had not been observed hitherto in a cyclic acetal.

The information concerning acetals and ketals which is found in most textbooks tends to create the impression that these substances are of relatively little importance and, consequently, may not have been investigated to any great extent. A study of the chemical literature shows, however, that acetals, which were among the earliest organic compounds synthesized, are of academic interest in a number of respects, and find important commercial applications. Ever since their discovery, acetals and ketals have been the subject of a surprisingly large number of articles in the literature.

Although a complete discussion of acetals and ketals is beyond the scope of this dissertation, general information on certain phases of acetal and ketal chemistry, and on several subjects which are especially pertinent to this investigation are dealt with under the following headings:

Discovery of Acetals and Ketals
Nomenclature and Structures of Cyclic Acetals
Preparative Methods
General Properties of Acetals and Ketals
Uses of Cyclic Acetals and Ketals
Pharmacological Activity of non-Basic Acetals and Ketals
Cyclic Aminoacetals and Aminoketals
Pharmacological Activity of Basic Acetals and Ketals
Antihistamine Drugs

Discovery of Acetals and Ketals

During the summer of 1836, Robert Kane, Professor of Chemistry in Dublin, went to Giessen in order that he might continue his study of wood alcohol and its derivatives under the supervision of Justus Liebig. In the report of this investigation[1] he described the preparation and properties of a new substance which was obtained by the action of manganese dioxide and sulfuric acid on wood alcohol. The new product, described as a colorless, water-soluble liquid which boiled at 38° and possessed a pleasant "aromatic" odor, was named formal.

In 1858 Wurtz and Frapolli[2] discovered that acetaldehyde reacts with phosphorus pentachloride to form ethylidene chloride. In conformity with their expectations, they found that this substance condensed with ethyl alcohol to produce an acetal, the diethyl acetal of acetaldehyde, commonly called merely acetal.*

$$CH_3CHO \xrightarrow{PCl_5} CH_3CHCl_2 \xrightarrow{2\ C_2H_5OH} CH_3CH(OC_2H_5)_2$$

They stated also that alpha-chloroethers react with a sodium alcoholate to produce an acetal:

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(1) Kane, Ann. Pharm., 19, 164 (1836). It seems that Kane was also a pioneer in the development of chemical theory. Independent of Berzelius and Liebig, he pointed out the analogy between the ethyl and the ammonium radicals (Kane, The Dublin Journal of Medical and Chemical Science, 2, 348 (1833).

(2) Wurtz and Frapolli, Ann., 108, 223 (1858).

* It was found that this type of reaction can be used successfully for the preparation of ketals; for example, benzophenone dimethyl ketal (Mackenzie, J. Chem. Soc., 69, 987 (1896) and fluorenone diethyl ketal (Smedley, ibid., 87, 1252 (1905).

$$R_2CO \xrightarrow{PCl_5} R_2CCl_2 \xrightarrow{2\ NaOR'} R_2C(OR')_2$$

$$CH_3CHO + C_2H_5OH + HCl \longrightarrow CH_3CH(Cl)OC_2H_5 + H_2O$$

$$CH_3CH(Cl)OC_2H_5 + NaOC_2H_5 \longrightarrow CH_3CH(OC_2H_5)_2 + NaCl$$

A few years later, in 1863, Geuther[3] observed that acetal is produced by interaction of acetaldehyde and ethyl alcohol. This reaction accounts for the formation of formal

$$CH_3CHO + 2\,C_2H_5OH \longrightarrow CH_3CH(OC_2H_5)_2 + H_2O$$

in Kane's experiment; the wood alcohol was oxidized to formaldehyde which then combined with unoxidized alcohol to produce formaldehyde dimethyl acetal (formal).*

In 1887 Arnhold[4] obtained a liquid, which possessed a pleasant odor and all of the other properties of formal which Kane mentioned, by the action of sodium methylate on methylene chloride. This method of preparation indicated very clearly that formal might be dimethoxymethane.

$$CH_2Cl_2 + 2\,NaOCH_3 \longrightarrow CH_2(OCH_3)_2 + 2\,NaCl$$

Claisen[5] discovered the first satisfactory method for the preparation of ketals in 1896. He found that acetone, as well as other ketones, reacts with ethyl orthoformate in the following manner:

$$(CH_3)_2CO + HC(OC_2H_5)_3 \longrightarrow (CH_3)_2C(OC_2H_5)_2 + HCOOC_2H_5$$

This reaction may be used also for the synthesis of acetals.

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(3) Geuther, ibid., 126, 621 (1863).

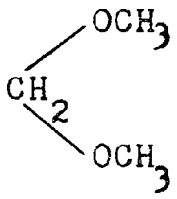
* After long periods of time, alcoholic solutions undergo oxidation with the formation of acetals, a reaction which plays an important role in the aging of wine.

(4) Arnhold, Ann., 240, 197 (1887).

(5) Claisen, Ber., 29, 1007 (1896); ibid., 31, 1010 (1898); ibid., 40, 3903 (1907).

Nomenclature and Structure

The nomenclature of acyclic and cyclic acetals is somewhat involved because of the variety of names which have been assigned to these compounds. For example, the acetal obtained from formaldehyde and methanol is known under the following names:



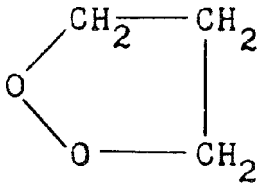
Formal
Formaldehyde dimethyl acetal
Dimethoxymethane
Methyleneglycol dimethyl ether
Methylal

Cyclic acetals, prepared from an aldehyde and a 1,2-glycol are known as 1,3-dioxolanes (five-membered rings), and those formed from an aldehyde and a 1,3-glycol are called 1,3-dioxanes (six-membered rings). In a few instances larger rings, composed of carbon atoms and two oxygen atoms, have been described.[6,7]

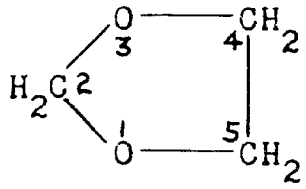
In this investigation we were interested especially in the preparation and properties of 1,3-dioxolanes, and to a lesser extent in 1,3-dioxanes.

Dioxolanes are five-membered rings composed of three carbon and two oxygen atoms. Only two such rings are possible-a 1,2- and a 1,3-dioxolane. A 1,4-dioxolane is identical with the 1,3 compound. These compounds are formulated below.

(6) Hill and Hibbert, J. Am. Chem. Soc., 45, 3124 (1923).
(7) Hill and Carothers, ibid., 57, 925 (1935).



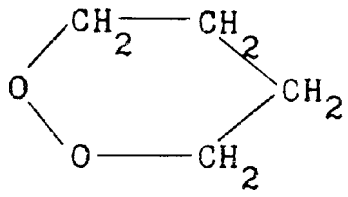
1,2-dioxolane



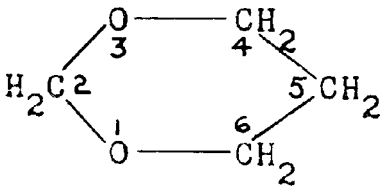
1,3-dioxolane
1,3-dioxacyclopentane
Ethylene methylene dioxide
Methylenedioxyethane
Ethylenemethylal
Formal of ethylene glycol

A 1,2-dioxolane, obviously, is a peroxide; this specific compound does not appear to be recorded in the literature.

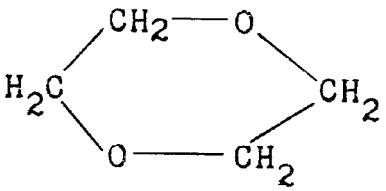
Six-membered rings which contain four carbon atoms and two oxygen atoms are known as dioxanes. The three possible rings are shown below.



1,2-Dioxane



1,3-Dioxane



1,4-Dioxane

1,3- and 1,4-Dioxanes, as well as many of their derivatives, are well known. Neither 1,2-dioxane or any of its simple derivatives seem to have been prepared.

A dioxolane or dioxane which, upon hydrolyses, yields a ketone is designated as a ketal; if an aldehyde is obtained, the compound is designated as an acetal.*

Preparative Methods

The various procedures which can be employed for the preparation of acyclic and cyclic acetals and ketals are indicated by the following formulations:

1 $RCHO + ROH \rightleftharpoons RCH(OH)(OR)$

$RCH(OH)(OR) + ROH \rightleftharpoons RCH(OR)_2 + H_2O$

$R_2CO + 2\ ROH \rightleftharpoons R_2C(OR)_2 + H_2O$

2 $HC\equiv CH + 2\ ROH \xrightarrow[\text{Catalyst}]{HgSO_4} CH_3CH(OR)_2$

3 $R'CH(OR)_2 + R''OH \longrightarrow R'CH(OR)(OR'') + ROH$

$R'CH(OR)(OR'') + R''OH \longrightarrow R'CH(OR'')_2 + ROH$

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* The term acetal is frequently used to indicate the ether-like derivatives of both aldehydes and ketones. But the discussion in this thesis is facilitated if a distinction is made between acetals and ketals. In recent recommendations (Chem. Eng. News, 26, 1623 (1948)) concerning carbohydrate nomenclature, sugar acetals and sugar ketals, both are designated as acetals. Ketals are called acetals in many textbooks and in articles in the chemical literature.

4 $RCH(Cl)OR + NaOR' \longrightarrow RCH(OR)(OR') + NaCl$

5 $R_2CO + PCl_5 \longrightarrow R_2CCl_2 + POCl_3$

$R_2CCl_2 + 2R'OH \longrightarrow R_2C(OR')_2 + 2\ HCl$

6 $RCHO + HC(OR)_3 \overset{H^+}{\rightleftharpoons} RCH(OR)_2 + HCOOR$

$R_2CO + HC(OR)_3 \overset{H^+}{\rightleftharpoons} R_2C(OR)_2 + HCOOR$

7 $RMgX + HC(OR)_3 \longrightarrow RCH(OR)_2 + Mg(OR)X$

8 $R_2CO + (RO)_2SO \xrightarrow{H^+} R_2C(OR)_2 + SO_2$

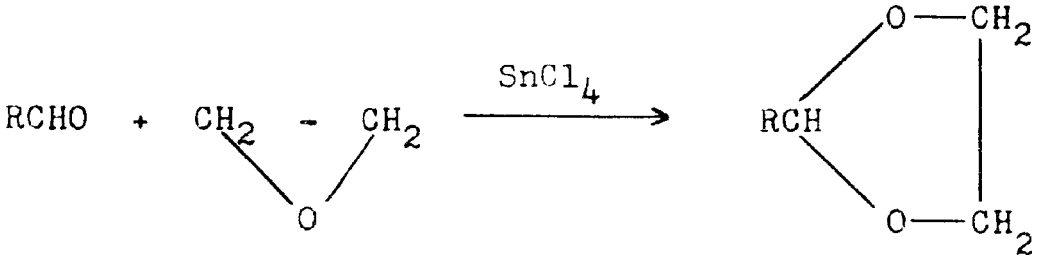
$RCHO + (RO)_2SO \xrightarrow{H^+} RCH(OR)_2 + SO_2$

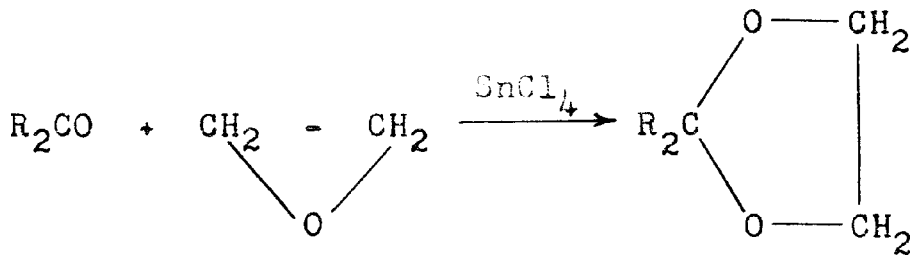
9 $RCHO + Si(OR')_4 \xrightarrow{H^+} RCH(OR')_2 + SiO(OR')_2$

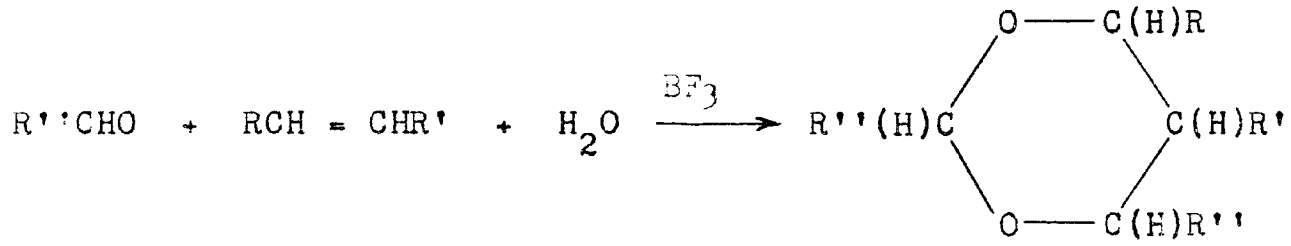
$R_2CHO + Si(OR')_4 \xrightarrow{H^+} R_2CH(OR')_2 + SiO(OR')_2$

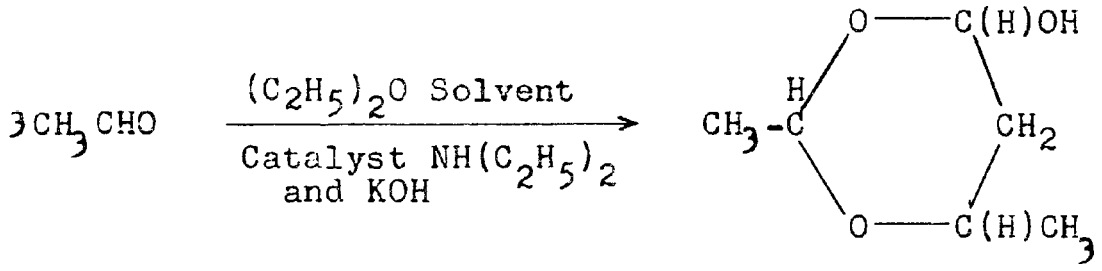
The methods represented by equations 1, 2 and 3 have been used to prepare both cyclic and acyclic acetals and ketals; 4, 5, 6, 7, 8 and 9 have, to date, yielded only the acyclic compounds.

The following methods have been applied only to the preparation of cyclic acetals and ketals:





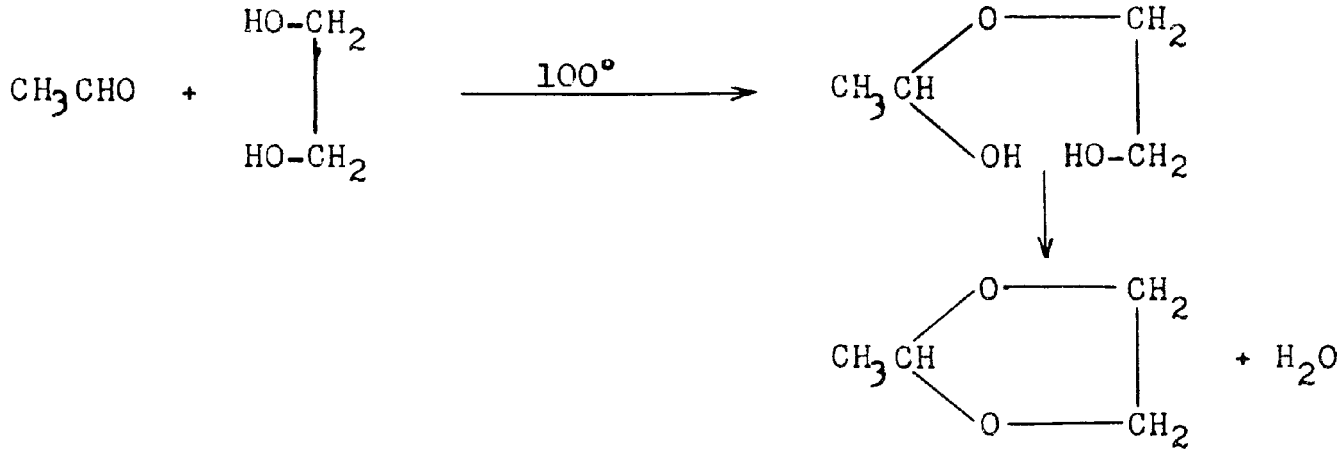




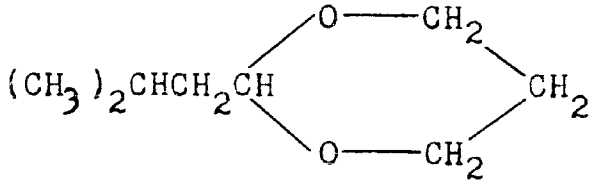
Since this dissertation deals only with the preparation of cyclic acetals and ketals, the following discussion is limited chiefly to reactions which yield cyclic types. However, since an acyclic acetal or ketal can be converted to a corresponding cyclic compound by an exchange (or replacement) reaction with a glycol the preparation of certain acyclic compounds will be discussed briefly in appropriate places.

Numerous cyclic acetals have been made by the direct reaction of an aldehyde and a 1,2 or a 1,3-glycol without the

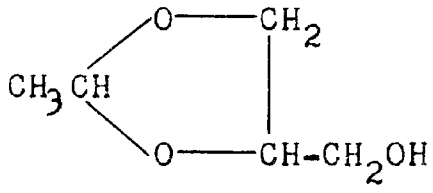
use of a catalyst. Wurtz[8] prepared 2-methyl-1,3-dioxolane by heating a mixture of acetaldehyde and ethylene glycol at 100°.*



Similarly, 2-isobutyl-1,3-dioxane (I) was prepared by heating an uncatalyzed mixture of isovaleraldehyde and trimethylene glycol[9].



(I)



(II)

(8) A. Wurtz, Ann., 120, 328 (1861).

* The experiments of Adkins and Broderick (J. Am. Chem. Soc., 50, 499 (1928)) indicate that the formation of a half acetal is the first stage in the formation of an acetal.

(9) Lochert, Ann. chim. et phys., (6) 16, 26 (1889).

When acetaldehyde was heated with anhydrous glycerol in a sealed tube at 180°, 2-methyl-4-hydroxymethyl-1,3-dioxolane (II) was obtained[10]. In a like manner, 2-isobutyl-4-hydroxymethyl-1,3-dioxolane was produced from isovaleraldehyde and glycerol.

Only a small yield of an impure acetal was obtained when benzaldehyde and glycerol were heated to 180-200° in a sealed tube. However, the yield increased to 50% when the reactants were heated, and the water produced by the reaction was allowed to escape[10].

Gerhardt[11] found that cyclic acetals could be prepared in good yield from an aromatic aldehyde and a glycol by heating the mixture until the calculated amount of water had been removed by distillation. A catalyst was not used during the distillation, but he declared that the compounds were more easily obtained in a crystalline state if the crude products had been treated with hydrogen chloride. Products were obtained from the reaction of such aldehydes as benzaldehyde, anisaldehyde and piperonal, and glycols such as glycerol-alpha-monochlorohydrin, trimethylene glycol and glycerol.

The effect of an acid catalyst in acetal formation is illustrated by the preparation of 2-phenyl-1,3-dioxane from

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(10) Harnitsky and Menschutkin, Ann., 136, 126 (1865).
(11) Gerhardt, Ger. Pat. 253,083 (Chem. Zentr., 83, II, 1953 (1912).

benzaldehyde and trimethylene glycol. If the reactants are heated to 105-120°, the reaction proceeds readily; however, the same yield of product may be obtained when the reaction is carried out at room temperature in the presence of hydrogen chloride[12].

Numerous acidic and water-avid substances, such as hydrogen chloride, sulfuric acid[13], phosphoric acid[14], phosphorous pentoxide[15], $SnCl_4$, $FeCl_3$, BF_3, SiF_4, p-toluene sulfonic acid, and camphor-sulfonic acid[16] have been used successfully as catalysts.

Cyclic ketals are very readily produced by the reaction of acetone with polyhydroxy compounds. This reaction is widely employed in sugar chemistry. It was found that acetone condensed readily with glycerol in the presence of an acid or anhydrous copper sulfate to form a five-membered cyclic compound[17]. Ketals were produced in yields of about 30% when methyl alkyl ketones and 1,2-butandiol were heated in the presence of concentrated sulfuric or hydrochloric acids[13]. Not a trace of the ketal of acetophenone was found when the ketone was reacted with ethylene glycol in the presence of 40% sulfuric acid[18]. Böeseken and Tellegen[19] were unable to obtain the cyclic ketals of either acetophenone or benzophenone when phosphorous pentoxide was used as a catalyst.

(12) E. Fischer, Ber., 27, 1527 (1894).
(13) Neish and MacDonald, Can. J. Research, 25, 75 (1947).
(14) H. T. Clarke, J. Chem. Soc., 101, 1804 (1912).
(15) Smith and Lundberg, Ber., 64, 505 (1931).
(16) H. Meyer, Synthese der Kohlenstoffverbindungen, p. 384, Zweiter Teil, Heterocyclen, I Hälfte.
(17) Hibbert and Morazain, Can. J. Research, 2, 35, 214 (1930).
(18) Froschl and Heuberger, Monatsh., 59, 289 (1932).
(19) Böeseken and Tellegen, Rec. trav. chim., 57, 133 (1938).

Gerhardt[11] effected the cyclization of acetophenone and glycerol by heating a mixture of the two compounds at 130-180° for two days.

Salmi[20] prepared cyclic ketals in 70-90% yields by removing the water produced in the reaction as an azeotrope with benzene or toluene. In this interesting method equivalent amounts of a ketone, a glycol and a small amount of an acid catalyst were refluxed with benzene or toluene. By means of a Dean and Stark tube[21], or another suitable arrangement[22], the water formed in the reaction was removed. In this way, the equilibrium of the ketalization reaction was constantly displaced, and yields approached the theoretical value. In addition to simple aliphatic ketones, other ketones which have been employed in this reaction are acetoacetic ester, cyclopentanone, menthone, camphor, pinacone and mesityl oxide. The polyhydroxy compounds which were reacted with the above mentioned ketones are propylene glycol, trimethylene glycol, hexahydrocatechol, tartaric acid, and 1,3-butandiol.

Azeotropic distillation may not be employed in the preparation of ketals (or acetals) when the carbonyl compound or the alcohol boils so low that it forms the main part of the distillate, or when the boiling point of the product and the solvent are so close that separation is impossible. The advantages of this

(20) Salmi, Ber., 71, 1803 (1938); Salmi and Ranikko, Ber., 72, 600 (1939).
(21) Dean and Stark, J. Ind. Eng. Chem., 12, 486 (1920).
(22) Meyer, Ann., 433, 327 (1923).

method have been summarized as follows:

(1) The reaction may be carried almost to completion.

(2) The calculated amounts of reactant are sufficient.

(3) Only a very small amount of catalyst is necessary.

(4) The residue is water-free therefore the product is very easily isolated.

Senkus[23] utilized the azeotropic distillation method to prepare acetals from hitroglycols, such as 2-nitro-2-methyl-1,3-propandiol, and aldehydes such as butyraldehyde, heptaldehyde and lauraldehyde. A series of acyclic acetals, the formal, the benzal, and the isobutyral of 2-nitro-2-methyl-1-propanol, was also obtained by this method[24].

Dioxolanes have been prepared from glycerol and such carbonyl compounds as cyclohexanone, butyraldehyde and crotonaldehyde by azeotropic distillation with benzene[25]. The preparation of several of these compounds was stated to have occurred with almost explosive violence.

The displacement of one alkoxy group by another in an acetal appears to have been first investigated by Geuther and Bachmann[26]. Diethyl acetal and propyl alcohol had been heated in a sealed tube for several hours at 120°. Upon examination of the products there was found, in addition to considerable unchanged diethyl acetal, small amounts of ethyl

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(23) Senkus, J. Am. Chem. Soc., 63, 2635 (1941). See also Kühn, J. prakt. Chem., 156, 103 (1940).
(24) Senkus, J. Am. Chem. Soc., 69, 1381 (1947).
(25) Dupire, Compt. rend., 214, 359 (1942).

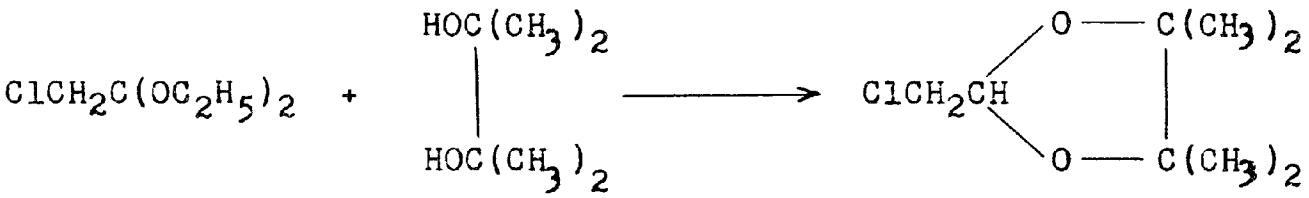
propyl acetal and dipropyl acetal.

$$CH_3CH(OC_2H_5)_2 + C_3H_7OH \rightleftharpoons CH_3CH(OC_2H_5)(OC_3H_7) + C_2H_5OH$$

$$CH_3CH(OC_2H_5)_2 + 2\ C_3H_7OH \rightleftharpoons CH_3CH(OC_3H_7)_2 + 2\ C_2H_5OH$$

Recently this method has been used in the preparation of mixed acyclic acetals which are of interest because of their pleasant odors[27]. For instance, when beta-phenylethyl alcohol is heated with the dimethyl acetal of enanthaldehyde, a mixed acetal is obtained which has a "musk-like odor with a rose note". Other fragrant mixed acetals derived from the diethyl acetal and rhodinyl, terpineyl, anisyl, santalyl and cinnamyl alcohols were reported.

Delepine[28] found that better yields were obtained if an acid was present, and if the lower, displaced alcohol was distilled from the reaction mixture. He further demonstrated the use of this method in the preparation of cyclic acetals. For example, when a mixture of chloroacetal and pinacol was heated, 2-chloromethyl-4,4,5,5-tetramethyl-1,3-dioxolane was formed.

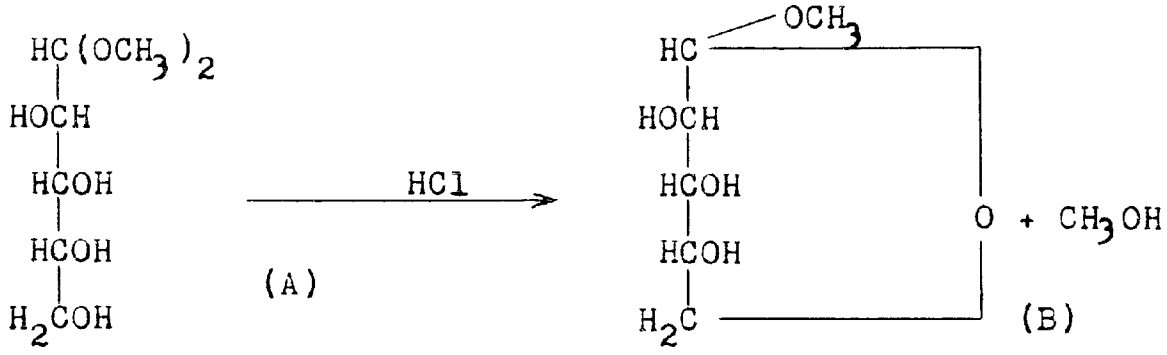


(27) R. Alquier, Bull. soc. chim., 10, 197 (1943); C.A., 38, 3953 (1944).

(28) Delepine, Bull. soc. chim., (3) 25, 574 (1901); cf. also Hallenquist and Hibbert, Can. J. Research, 8, 129 (1933).

Good yields of cyclic acetals were obtained when either glycerol or glycerol-alpha-monochlorohydrin was heated with the dimethyl acetal of benzaldehyde[29]. A single instance in which this reaction has been applied to the preparation of a cyclic ketal of an alkyl aryl ketone has been found[11]. When a mixture of dimethyl ketal of acetophenone and glycerol was heated, the cyclic ketal isolated was identical with that produced by prolonged heating of a mixture of acetophenone and glycerol. In this dissertation we have shown that the dimethyl ketal of diaryl ketones react in the same manner as a ketal of acetophenone.

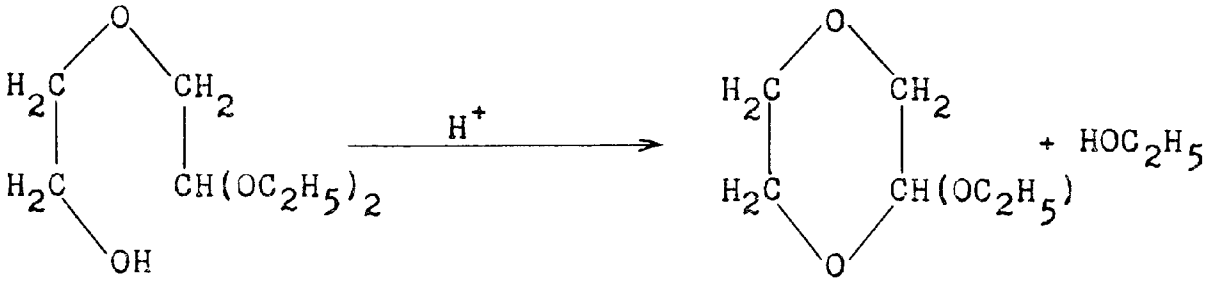
Intramolecular interchange of acetals was reported by Montgomery, Hann and Hudson[30]. They prepared a mixture of methyl-d-arabinosides (B) by the action of hydrogen chloride in methanol upon d-arabinose dimethyl acetal (A).



(29) Halberkan in Abderhalden's Handbuch der Biologischen Arbeitsmethoden, p. 1137, Abt. 1 Chemische Methoden, Teil 2, 1 Hälfte

(30) Montgomery, Hann and Hudson, J. Am. Chem. Soc., 59, 1124 (1937).

This type of reaction has been applied by Parham[31] who showed that simple delta-hydroxyacetals underwent an acid-catalyzed cyclization to produce mixed cyclic acetals by the elimination of a mole of alcohol. Thus, from diethyl(2-hydroxy-ethyloxy) acetal there was obtained 2-ethoxy-1,4-dioxane in 76% yield.



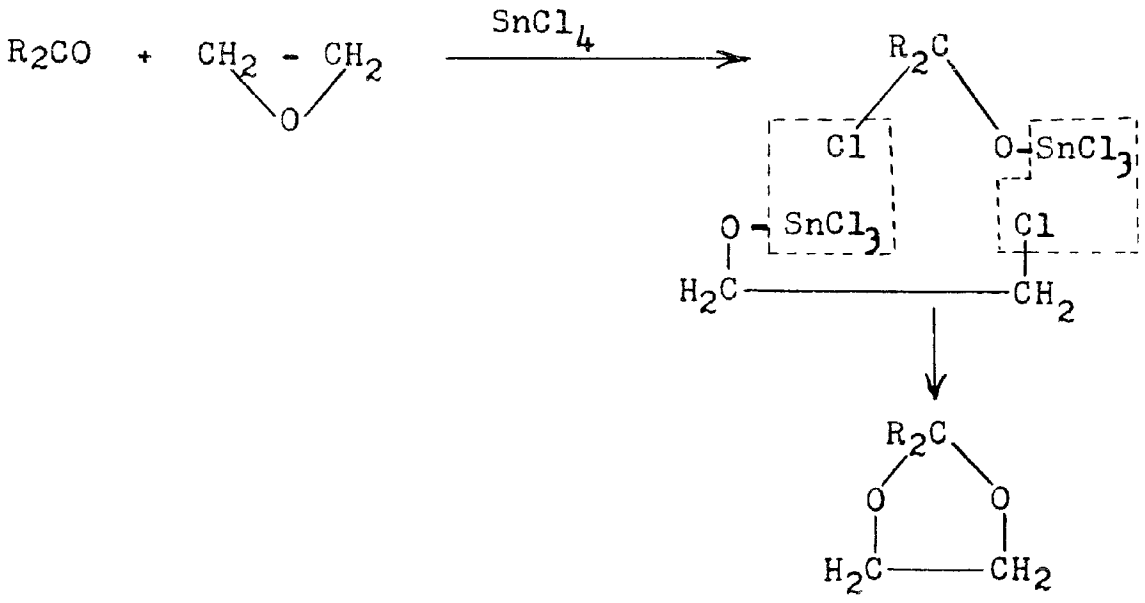
Compounds similar to the above were produced by Villani and Nord[32] who treated a cold ethereal solution of an aldehyde with a few drops of diethylamine; then a 10% aqueous solution of potassium hydroxide was added, dropwise, until the exothermal reaction ceased. From acetaldehyde they obtained a 47% yield of 2,6-dimethyl-4-hydroxy-1,3-dioxane; when isobutyraldehyde was treated in this manner a yield of 33.5% of 2,6-diisopropyl-5,5-dimethyl-4-hydroxy-1,3-dioxane resulted.

Wurtz[8] attempted to condense ethylene oxide directly with acetaldehyde without success. Lochert[33] also was unsuccessful when he tried to react both ethylene and propylene

(31) Parham, J. Am. Chem. Soc., 69, 2449 (1947).
(32) Villani and Nord, J. Am. Chem. Soc., 68, 1674 (1946).
(33) Lochert, Ann. chim. phys., (6) 16, 56 (1889).

oxides with acetaldehyde. Attempts to obtain a cyclic acetal by the use of benzylethylene oxide, in the presence of 40% sulfuric acid, also failed[34].

Bogert and Roblin, Jr.[35] seem to have been the first investigators to effect reaction between ethylene oxides and aldehydes or ketones with the formation of cyclic acetals. This was accomplished by the use of stannic chloride. The mechanism of the reaction is not known but they suggested that the complexes formed from both the ethylene oxide and the carbonyl compound with stannic chloride may play a part in the reaction. The highest yield of any cyclic acetal or ketal prepared by them was 35%. This relatively low yield was due to the fact that a considerable amount of high boiling material, the nature of which was unknown, was obtained as a by-product. In their experiments, the use of a solvent such as benzene or carbon tetrachloride, did not increase the yield of the cyclic acetal. This reaction, in the case of a ketone, may be formulated as follows:



(34) Read, Lathrop and Chandler, J. Am. Chem. Soc., 49, 3116 (1927).

(35) Bogert and Roblin, Jr., J. Am. Chem. Soc., 55, 3741 (1933).

They obtained yields of 22-35% from ethylene and propylene oxides and such carbonyl compounds as benzaldehyde, methyl hexyl ketone and acetophenone.

Bersin and Willfang[36] obtained dioxolanes in yields of 60-80% by the use of ethylene oxides with carbon tetrachloride as a solvent. The high yields obtained by these investigators seem to be due to the fact that the reactions were carried out at temperatures lower than those employed by Bogert and Roblin, Jr. 4-Chloromethyldioxolanes were obtained from epichlorohydrin and carbonyl compounds such as butyraldehyde, octylaldehyde, dodecylaldehyde, crotonaldehyde, chloral, diethyl ketone and benzophenone. Boron trifluoride has been shown to be equally effective as a catalyst in the reaction[37].

The synthesis of acetals by alcoholysis of acetylenes has been studied quite extensively[38]. In these reactions boron fluoride complexes are used as catalysts. Acetylene and methanol, under the influence of such a catalyst, react to yield the dimethyl acetal of acetaldehyde[39]. Acetylene has been condensed

$$HC{\equiv}CH + 2\ CH_3OH \xrightarrow[(CH_3OH)_2.BF_3]{Hg(OCH_3.BF_3)_2} CH_3CH(OCH_3)_2$$

(36) Bersin and Willfang, Ber., 70, 2167 (1937); see also Willfang, ibid., 74, 145 (1941).

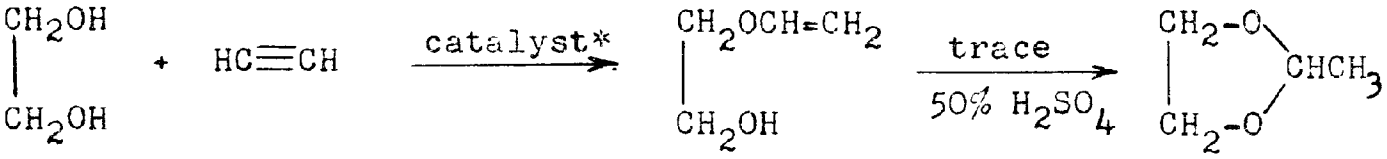
(37) A. A. Petrov, J. Gen. Chem. (U.S.S.R.), 10, 981 (1940); C.A., 35, 3604 (1941).

(38) The clue for this method came from the process of Kutscherow (Ber., 14, 1540 (1881); ibid., 42, 2759 (1909)) by means of which he obtained acetaldehyde from acetylene in the presence of water and a mercury catalyst. Early procedures which describe the preparation of ethers of ethylidene glycol from acetylene and alcohols by the use of mercury salts are disclosed in British Patents 14,246 (1913), 15,806 (1914) and 15,919 (1914).

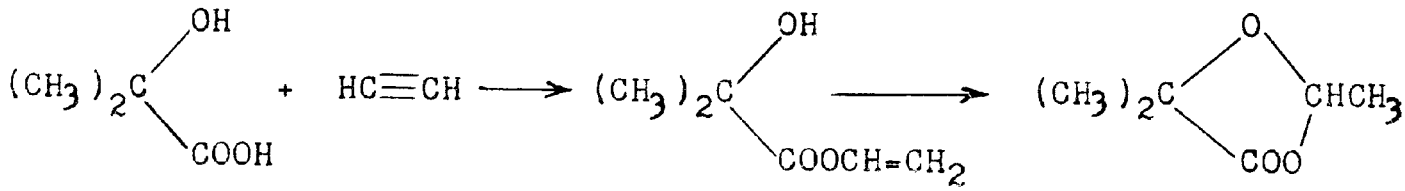
A survey of reactions of this type is found in "Newer Methods of Preparative Organic Chemistry", pp. 256-263, Interscience Publishers, Inc. (1948).

with primary alcohols as high as amyl alcohol, with tertiary alcohols up to nonyl alcohol and with various other alcohols such as benzyl and tetrahydrofurfuryl alcohol. Borneol, terpineol and cyclohexanol proved to be unsuitable in this reaction. Amino alcohols cannot be used since they form coordination complexes with boron trifluoride.

In addition to monohydroxy alcohols, polyhydroxy alcohols[40] and other polyhydroxy compounds condense with acetylene to form



cyclic acetals. alpha-Hydroxy acids and their derivatives may also be used. From glycerol a mixture of the 1,2-acetal (78%) and the 1,3-acetal (22%) was obtained. Each of these compounds can react further with acetylene to form a diglycerol triethylidene ether. Both pentaerythritol and mannitol react with more than one molecular equivalent of acetylene. When alpha-hydroxyisobutyric acid is employed, a cyclic ether-ester is obtained. Among the numerous other compounds which react with acetylene



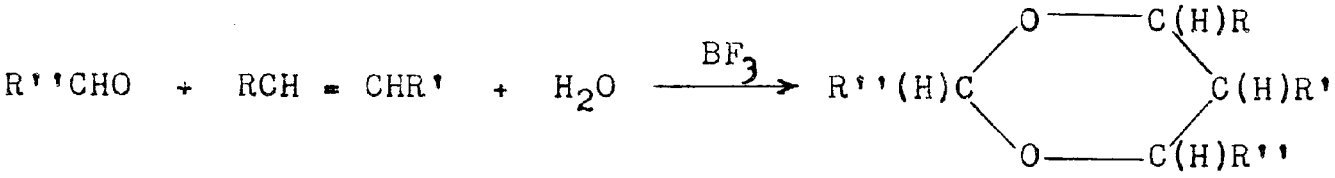
(40) Hill and Pidgeon, J. Am. Chem. Soc., 50, 2718 (1928).
* Hill and Hibbert, J. Am. Chem. Soc., 45, 3128 (1923).

are pinacol, glycerol phenyl ether, glycerol chlorohydrin, diethyl tartrate, mandelic and benzilic acid[41]. Glycolic acid and glycerol bromohydrin were found to be unreactive.

Alkylacetylenes, hydroxyalkylacetylenes and vinylacetylene have been used in place of acetylene. Butylacetylene reacts with mannitol to form a compound which contains three dioxolane rings.

It has been stated that many acetals, for example those of benzyl alcohol, cannot be obtained by the use of any catalyst except boron fluoride, and that the latter catalyst is superior to sulfuric acid since fewer by-products are formed.

1,3-Dioxanes are produced by causing a olefin to react with an aldehyde in the presence of boron trifluoride and water. In this manner, formaldehyde and propylene yield 4-methyl-1,3-dioxane. This general reaction[42] between an aldehyde and an olefin is represented below.

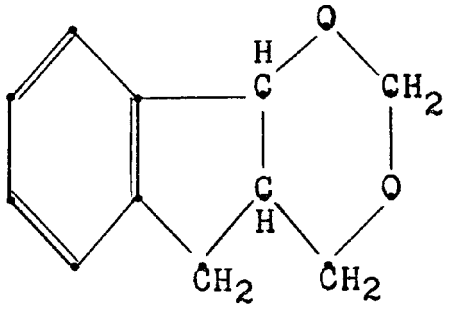


R,R' and R'' = alkyl, aryl or aralkyl groups.

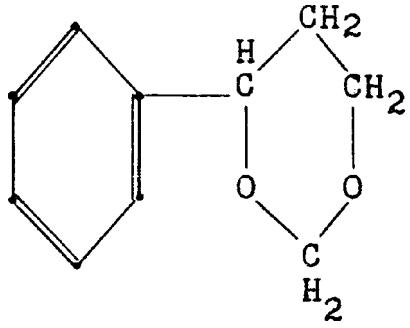
(41) Nieuwland, Vogt and Fooley, J. Am. Chem. Soc., 52, 1018 (1930).

(42) British Pat. 483, 828 (1938); C. A., 32, 7167 (1938). U.S.Pat. 2,325,760 (1944); C.A. 38, 380 (1944).

Indene, styrene, and coumarone have been condensed with formaldehyde in the presence of a mineral acid catalyst to prepare compounds which are regarded as 1,3-dioxanes[43]. A mixture of indene, 37% aqueous formaldehyde, toluene and a small amount of sulfuric acid was refluxed for five hours to produce indeno-1,3-dioxane (I). In similar manner, styrene yielded 4-phenyl-1,3-dioxane (II).



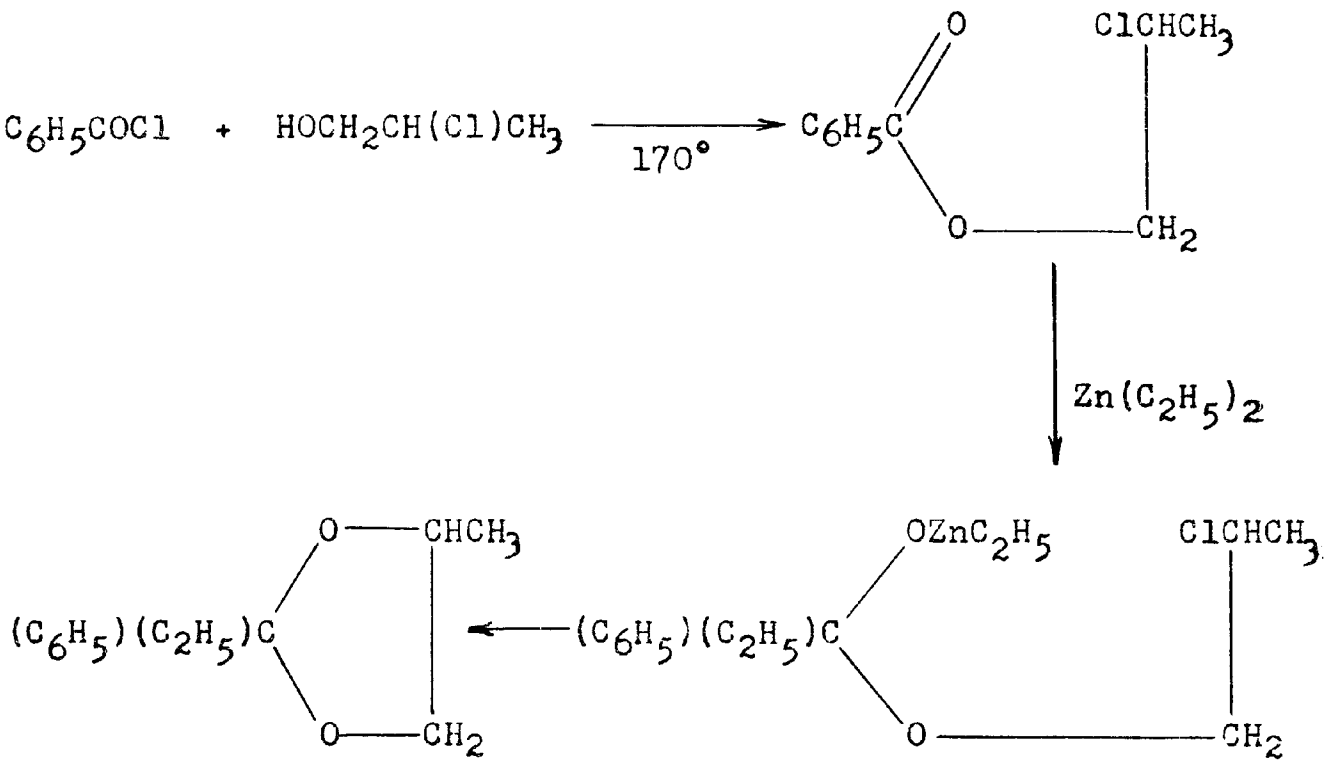
(I)



(II)

A very old and unusual procedure, which does not seem to have been used since its discovery[44], is the interaction of an acid chloride with a chlorohydrin, and subsequent treatment of the ester produced with a zinc alkyl. The reaction mechanism probably is that indicated below:

(43) U. S. Pat. 2,417,548 (1947); C. A., 41, 3493 (1947).
(44) Morley and Green, Ber., 17, 3016 (1884).



Several methods for the preparation of acyclic acetals and ketals, because of their general importance, are discussed below.

Claisen[5] found that acetone and ethyl orthoformate react as follows:

$$(CH_3)_2CO + HC(OC_2H_5)_3 \longrightarrow (CH_3)_2C(OC_2H_5)_2 + HCOOC_2H_5$$

In order to make the process cheaper, he decided to try "Nascent" ethyl orthoformate. Pinner[45] had discovered earlier that hydrogen cyanide, alcohol and hydrogen chloride react

(45) Pinner, Die Imidoather and ihre Derivate (1892).

readily to produce formimino ether hydrochloride which, in turn, may react with additional alcohol to produce ethyl orthoformate and ammonium chloride.

$$HCN + C_2H_5OH + HCl \longrightarrow HCl(=NH)OC_2H_5 \cdot HCl$$

$$HC(=NH)OC_2H_5 \cdot HCl + 2\ C_2H_5OH \longrightarrow HC(OC_2H_5)_3 + NH_4Cl$$

To prepare a ketal Claisen, therefore, let a mixture of ketone, alcohol and formimino ether hydrochloride remain in the cold for several days. The formimino ether method was used successfully in the preparation of such compounds as acetone dimethyl ketal, acetone diethyl ketal, acetoacetic ester diethyl ketal, acetophenone dimethyl ketal, and benzaldehyde diethyl acetal. This method failed in the case of benzophenone, and it was found necessary to use pure ethylorthoformate in a direct reaction with benzophenone to produce the ketal.

The extent of reaction of ethyl orthoformate and ketones to form ketals has been investigated by Pfeiffer and Adkins[46]. They found that the yields of ketal decreased in the following order: acetone (94.8%), acetophenone (86.2%), diisopropyl ketone (65.4%), methyl tert.-butyl ketone (50.1%), benzophenone (33.7%), di-tert.-butyl (17.2%). E. V. Lampiev[47] had reported earlier that the velocity of the reaction diminishes with increasing molecular weight of the ketone and that the velocity is greater in normal than in iso-compounds.

(46) Pfeiffer and Adkins, J. Am. Chem. Soc., 53, 1043 (1931).
(47) E. V. Lampiev, J. Russ. Phys. Chem. Soc., 54, 462 (1923).

Another related method which may be used to prepare acyclic acetals involves the Bodroux-Tschitschibabin reaction. In 1904, Bodroux[48] obtained low yields of triaryl methanes by the action of an aryl Grignard reagent upon chloroform or bromoform.

$$3RMgX + HCX_3 \longrightarrow R_3CH + 3MgX_2$$

He substituted ethylorthoformate for the haloform in an attempt to increase the yields and found that aldehydes were produced instead of the desired triaryl methanes.

$$RMgX + HC(OC_2H_5)_3 \longrightarrow RCH(OC_2H_5)_2 + MgXOC_2H_5$$

$$RCH(OC_2H_5)_2 + H_2O \xrightarrow{H^+} RCHO + 2\ C_2H_5OH$$

Independently, in the same year, Tschitschibabin[49] also discovered this reaction; he also found that the acetal could be isolated instead of the aldehyde by careful treatment of the reaction mixture with dilute acid. This reaction has been applied in the preparation of acyclic acetals or both aliphatic and aromatic aldehydes.[50]

Dimethyl sulfite has been employed[51] in the preparation of acyclic acetals and ketals. When a mixture of a ketone, dimethyl sulfite, methyl alcohol and a catalytic amount of hydrogen chloride is heated on a water bath, a rapid evolution

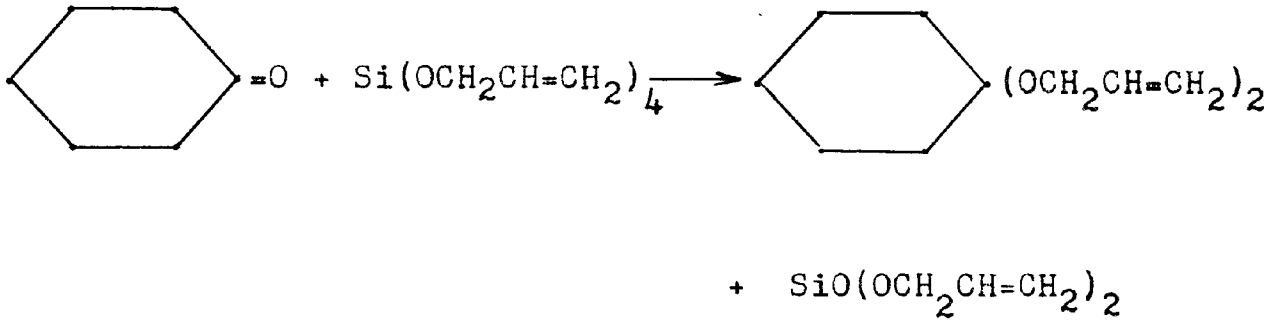
(49) Tschitschibabin, J. Russ. Phys. Chem. Soc., 35, 1284 (1903); Ber., 37, 186, 850 (1904).
(50) For leading references see L. I. Smith and M. Bayliss, J. Org. Chem., 6, 437 (1941).
(51) W. Voss, Ann., 485, 283 (1931).

of sulfur dioxide accompanies the formation of a ketal. The reaction is formulated below:

$$R_2CO + (CH_3O)_2SO \longrightarrow R_2C(OCH_3)_2 + SO_2$$

The dimethyl acetals of cyclohexanone, benzophenone and benzaldehyde have been obtained in this way.

Helferich and Hansen[52] introduced the use of orthosilicic esters in the preparation of acetals and ketals. Cyclohexanone diallyl ketal was prepared in 47% yield by treatment of cyclohexanone with tetraallylorthosilicate in the presence of an alcohol and a small amount of hydrogen chloride. This reaction may be formulated as follows:



Similarly, by the reaction of benzaldehyde with tetraallylorthosilicate in acetyl alcohol solution containing a trace of hydrogen chloride, benzaldehyde dicetyl acetal was prepared.

(52) Helferich and Hansen, Ber., 57, 795 (1924).

General Properties of Acetals and Ketals

A few general statements may be made with respect to the properties of acetals and ketals. Many of them are colorless liquids which possess pleasant odors. The compounds of low molecular weight are somewhat soluble in water, and may be "salted out" of solution with calcium chloride. They are slowly hydrolyzed by water, and are hydrolyzed almost instantly by dilute mineral acids, but they can be boiled with alkali without decomposition.

Some acetals form hydrates, for example, $CH_2(OC_2H_5)_2 \cdot H_2O$, which can be distilled. These hydrates also have characteristic odors; the one just mentioned has an odor of rum.

Acyclic acetals and ketals sometimes are used in place of the corresponding aldehyde or ketone for synthetic purposes because of their higher boiling points. (Acetaldehyde boils at 20°, diethyl acetal boils at 103°). In a condensation in which an acetal or ketal is employed, an alcohol instead of water is formed. This circumstance, in some cases, seems to be responsible for an increased yield. For example, in the preparation of vinyldiacetoneamine from acetaldehyde and diacetoneamine acid oxalate, the yield of the "vinyl" compound is poor, but when an acetal is used in place of the aldehyde, the yield is almost quantitative(53).

(53) Fischer, Ber., 17, 1793 (1884).
Heintz, Ann., 178, 326 (1875); ibid., 191, 122 (1878).
Harries, Ber., 29, 522 (1896).
King, Mason and Schryver, English Pat. 101,738.

In the preparation of a haloaldehyde, it may be advantageous to halogenate the acetal instead of the aldehyde, and then hydrolyze the haloacetal to the haloaldehyde.

Acetals will not reduce ammoniacal silver nitrate, nor will they react with alkali and iodine to form iodoform.

Aldehydes which are rapidly oxidized by air to the corresponding acid, thiophene-2-aldehyde for example, can be preserved in the form of their acetals which do not undergo oxidation by air.

Uses of Cyclic Acetals and Ketals

Acetals have long been used as ingredients in perfumes and as adjuncts to, or substitutes for, floral odors. Both cyclic and acyclic acetals have been employed, but the cyclic acetals frequently are preferred because their odors are less sharp(54). In a British patent(55) it is claimed that although known cyclic acetals prepared from dihydroxy alcohols, such as ethylene glycol, and aliphatic aldehydes or benzaldehyde have only faint or disagreeable odors, yet if dihydroxy alcohols are condensed with aryl-aliphatic aldehydes, such as phenylacetaldehyde, then cyclic acetals with enduring, agreeable odors are obtained. For example, if phenylacetaldehyde is condensed with

(54) Igolen, Soap, Perfumery and Cosmetics, 18, 372 (1945); Moncrieff, ibid., 18, 454 (1945).
(55) British Pat. 346,115 (1929); C. A., 26, 1941 (1932).

1,2-dihydroxypropane or with 1,2-dihydroxybutane, the acetals obtained smell like fresh roses and hyacinths, respectively. Natural extract of jasmine consists essentially of the formal of phenylglycol.

Weissenborn[56] describes how perfumes with odors similar to jasmine, honey and rose may be obtained from ketals which have six to nine carbons in the ketone residue. For example, diisobutyl ketone may be condensed with catechol to obtain a ketal useful as a honey flavoring agent. The less volatile and odorless cyclic acetals are often used as "fixatives" to diminish the volatility of the odorous principles, and thus to extend their period of fragrance. Hill and Carothers[57] reported the preparation of the cyclic formal of tetradecamethylene glycol; this compound has a musk-like odor and has possible use as a substitute for the expensive natural musk "fixative" used in perfumes.

Cyclic acetals prepared by reacting glycerol with aldehydes, such as formaldehyde, acetaldehyde and benzaldehyde, have been recommended as excellent solvents for cellulose esters, resins, gums, and organic substances.[58] Similar patent claims[59] are made for the mixture of the two acetal isomers prepared by reacting furfuraldehyde and glycerol. Acetals prepared from glycerol-alpha-monochlorohydrin and formaldehyde or acetaldehyde have been patented as solvents for cellulose esters[60].

(56) U. S. Patent, 2,169,984 (1940); C.A., 34, 228 (1940).
(57) Hill and Carothers, J. Am. Chem. Soc., 57, 925 (1935).
(58) Fairbourne, Gibson and Stephens, Chemistry and Industry, 49, 1069 (1930).
(59) U. S. Pat. 1,934,309 (1934); C.A., 28, 485 (1934).
(60) Ger. Pat. 288,267 (1915); Chem. Zentr., 86, II, 1037 (1915).

Acetals derived from piperonal have been tested as insecticides and were shown to be effective against the common housefly. The compound 2-(3,4-methylenedioxyphenyl)-4,4,6-trimethyl-1,3-dioxolane was among those derivatives found to be useful[61]. Ring acetals prepared from 3,5-dinitrosalicylaldehyde and polyhydroxy alcohols have been patented as parasiticides[62].

Polymeric cyclic acetals produced from polyvinyl alcohol and aldehydes find considerable industrial use here and abroad. Polyvinyl butyral resin has been widely used since 1936 in safety glass as the flexible mid-sheet in the glass sandwich[63]. Several patents cover the preparation of the resins[64]. Cyclic ketals obtained from aliphatic or cycloaliphatic ketones and trihydroxy alcohols have been patented as plasticizers for cellulose plastics[65].

The formals of 1,3-butylene glycol and of 1-butoxy-2,3-propandiol have been patented as fluids for hydraulic systems[66].

Substituted 5-amino-1,3-dioxanes, which have the general structure formula indicated below, have been claimed to be of especial use as non-foaming textile wetting agents usable in hard water and in solution containing appreciable quantities of alkali[67].

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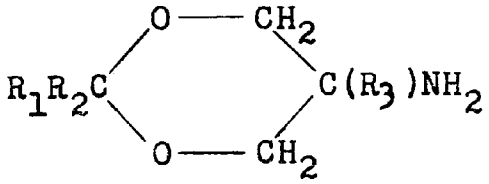
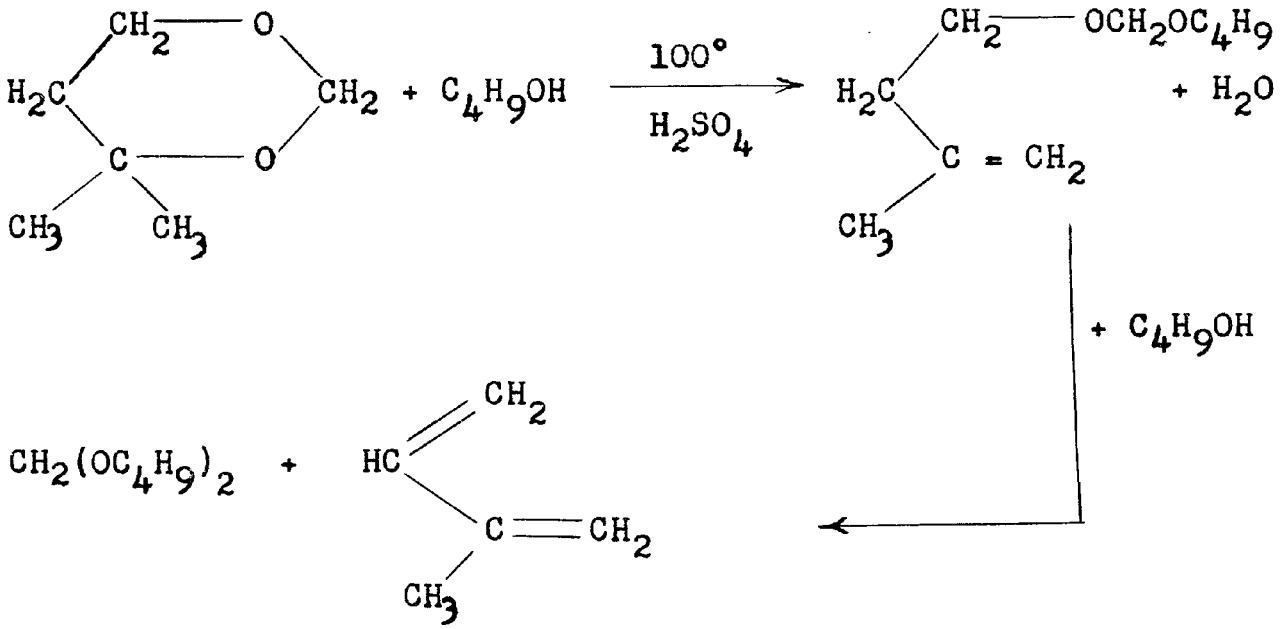
(61) Prill, Hartzell and Arthur, Contrib. Boyce Thompson Inst., 14, 397 (1947); C.A., 41, 7040.
(62) U.S. Pat., 2,272,153 (1942); C.A., 36, 3513.
(63) Simonds, Bigelow and Sherman, The New Plastics, p. 84, D. Van Nostrand Co. (1945).
(64) Fr. Pat. 850,891 (1939); Ger. Pat. 651,877 (1937); U.S. Pat. 2,360,477 (1944).
(65) British Pat. 557,238 (1943); C.A., 39, 2430 (1945)
(66) British Pat. 520,906 (1940); C.A., 36, 1120 (1942)
(67) U.S. Pat. 2,346,454 (1944) and 2,415,021 (1947).



R_1 and R_2 = Alkyl, aryl or aralkyl

R_3 = Alkyl

According to a patent of the Standard Oil Development Company[68], 1,3-dioxanes are converted to diolefins by treating the former substance with a primary alcohol in the presence of an acid catalyst at temperatures in the range 80 to 150°. The preparation of isoprene from 4,4-dimethyl-1,3-dioxolane is formulated as follows:



Conjugated diolefins are also produced[69] if a substituted 1,3-dioxane is treated with chlorine in the presence of water and sodium carbonate.

(68) British Pat. 578,438 (1946); C.A., 41, 3492 (1947).
(69) U.S. Pat. 2,367,234 (1945); C.A., 39, 2765 (1945).

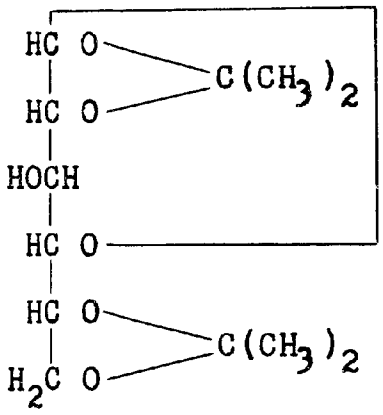
Cyclic acetals and ketals have been used to great advantage in synthetic processes wherein it is desirable to protect sensitive groups or to "block" reactive groups which may be uncovered in the further course of the synthesis. The preparation of vitamin C by Reichstein and Grüssner[70] may be given as a typical example of the use of cyclic acetal formation to protect sensitive groups. In their procedure, l-sorbose was oxidized by potassium permanganate to 2-keto-l-gulonic acid, a feat made possible by protecting the four other hydroxyl groups with two acetone residues.

Slooff[71] prepared pure 4-nitrocatechol in almost quantitative yield by protecting the hydroxyl groups of catechol with an acetone residue during nitration. The importance of such protection is clearly shown by the fact that direct nitration of catechol with nitric acid produces an impure product in low yield[72].

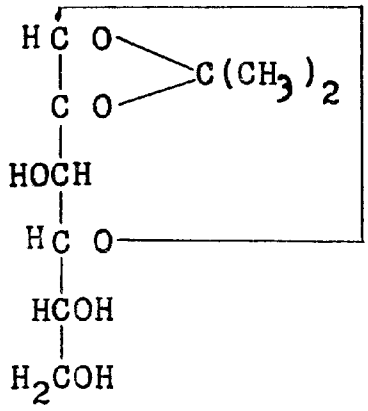
In working with sugar alcohols Meunier[73], in 1888, characterized them as their benzal derivatives in which the benzaldehyde had undergone acetal formation with the polyhydroxy sugar alcohol to form a cyclic acetal. In 1895, Emil Fischer[74] obtained a crystalline derivative of glucose in which two molecular equivalents of acetone had reacted with

(70) Reichstein and Grüssner, Helv. chim. Acta, 17, 311 (1934).
(71) Slooff, Rec. trav. chim., 54, 995 (1935).
(72) Welselsky and Benedict, Monatsh., 3, 386 (1882).
(73) Meunier, Compt. rend., 106, 1425 (1888).
(74) E. Fischer, Ber., 28, 1165 (1895).

the glucose. This substance is known as diacetoneglucose and, on graded acid hydrolysis, a crystalline monoacetoneglucose is formed. Subsequent work by a number of investigators proved that the acetone compounds are the cyclic ketals which possess the structures indicated below(75).



Diacetoneglucose



Monoacetoneglucose

These types of cyclic acetals and ketals played an important role in the synthetic methods and in the structure assignment of sugar chemistry(76).

Böeseken and his students have made extensive use of the formation of cyclic acetals to obtain an insight into the structure of some diols. From the ease with which a diol reacts with acetone, it is possible to draw conclusions about the positions and mobilities of both hydroxyl groups. The following is a simple example. Two 1,2-cyclopentandiols were known, a cis and

(75) The complex and lengthy evidence relative to their structures is treated in a review article by Wolfram in Gilman, Organic Chemistry, An Advanced Treatise, p. 1559, Second Edition.

(76) Fischer, Untersuchungen über Kohlenhydrate und Fermente, Vol. I (1884-1908); Vol. II (1908-1919); J. Springer, Berlin (1909, 1922).

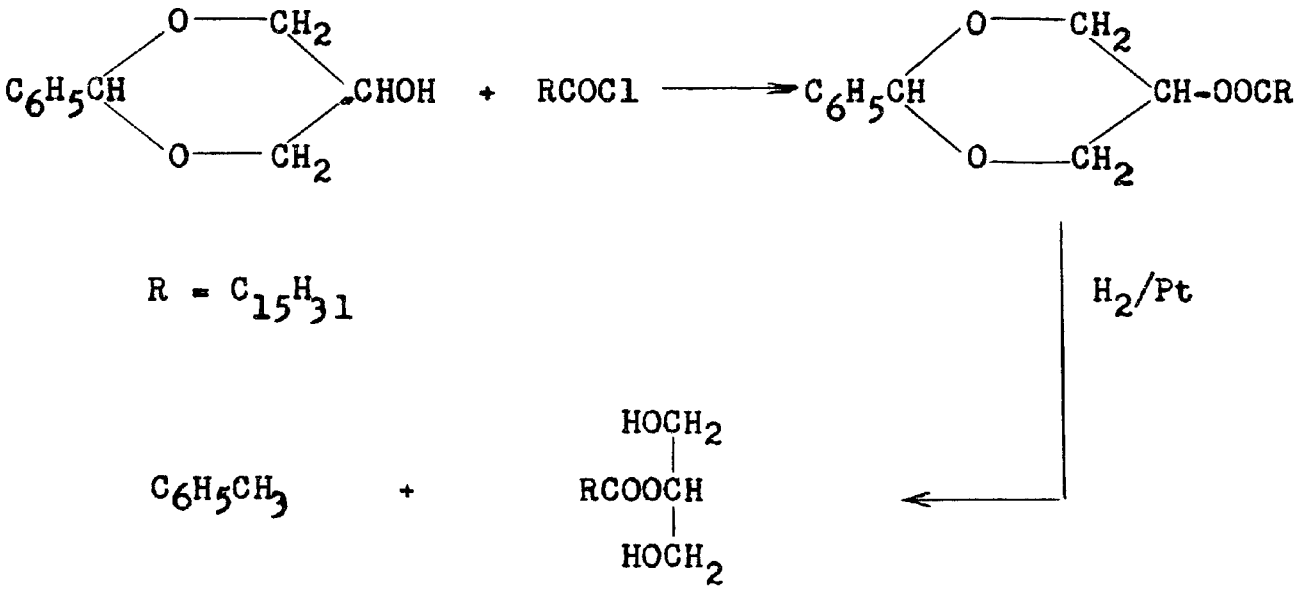
and a trans compound. From a consideration of the spacial configurations of these two compounds it was decided that the cis compound could react with acetone to form a cyclic ketal while the trans compound would not react. Experimentally it was found that one of the 1,2-cyclopentandiols reacted with acetone and that the other was unreactive. Based upon this and other confirming evidence, structure assignment for the two compounds was made possible(77).

A similar case occurred with the two stereoisomeric borneol carboxylic acids which have been known for a long time(78). One isomer melted at 178° and the other at 102°. The compound melting at 102° reacted quickly to form an acetone ketal, while the other isomer remained unchanged. Thus the compound melting at 102° was assigned the cis configuration(77).

Great difficulties were encountered in the preparation of beta-monoglycerides of fatty acids due to the tendency of an aliphatic acyl group to wander from the beta to the alpha position, a phenomenon described by E. Fischer(79). Bergman and Carter(80) found that the desired compounds could be obtained by the use of a cyclic acetal. They prepared beta-monopalmitin by treatment of 1,3-benzylidene glycerol (2-phenyl-5-hydroxy-1,3-dioxane) dissolved in pyridine, with palmityl chloride. The

(77) Böeseken, Slooff, Hoeffelman and Hirsch, Rec. trav. chim., 52, 881 (1933); Slooff, ibid., 57, 673 (1938).
(78) J. Bredt, Ann., 366, 1 (1909).
(79) E. Fischer, Ber., 53, 1621 (1920).
(80) Bergman and Carter, Z. physiol. chem., 191, 211 (1930).

"protecting" benzylidene moiety was then removed from the 2-palmityl-1,3-benzylidene glycerol by hydrogenation over platinum black in alcoholic solution. The reactions involved are represented below.



It is of interest here to mention the preparation of the intermediate, 1,3-benzylidene glycerol. When an acid-catalyzed mixture of benzaldehyde and glycerol is heated, the isomeric 1,2 and 1,3-benzylidene glycerols are formed in the approximate ratio of three to one[81]. The more nearly symmetrical 1,3 isomer separates in crystalline form (m.p. 84°) from a mixture of benzene and petroleum ether, while the oily 1,2 isomer remains dissolved in the mother liquor.

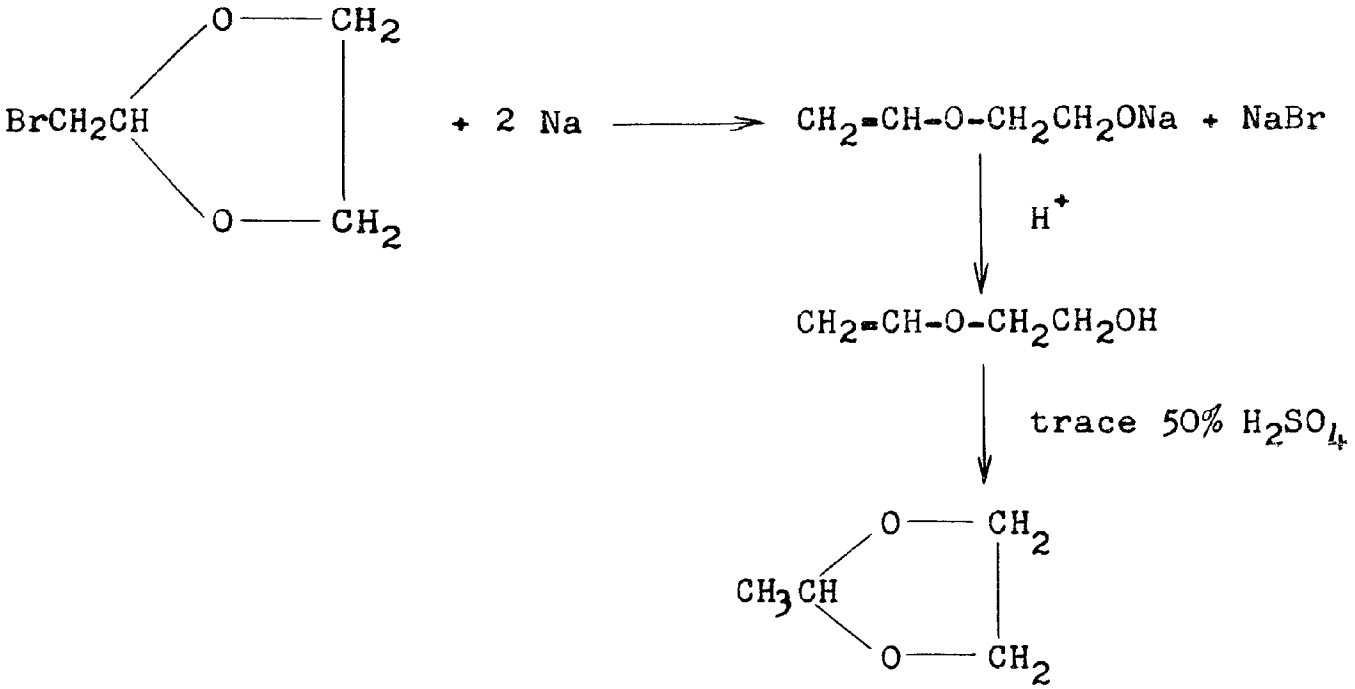
(81) Hill, Whelen and Hibbert, J. Am. Chem. Soc., 50, 2235 (1928).

The beta-monoglycerides of capric, lauric, myristic and stearic acids have also been prepared[82] by the method indicated above.

Certain vinyl omega-hydroxyalkyl ethers have been obtained by the action of sodium on a cyclic acetal. Bromoacetal reacts with sodium to form vinyl ethyl ether[83], and it was found[40] that the cyclic acetal, bromoethylidene glycol, will

$$BrCH_2CH(OC_2H_5)_2 + 2\ Na \longrightarrow CH_2{=}CH(OC_2H_5) + NaOC_2H_5 + NaBr$$

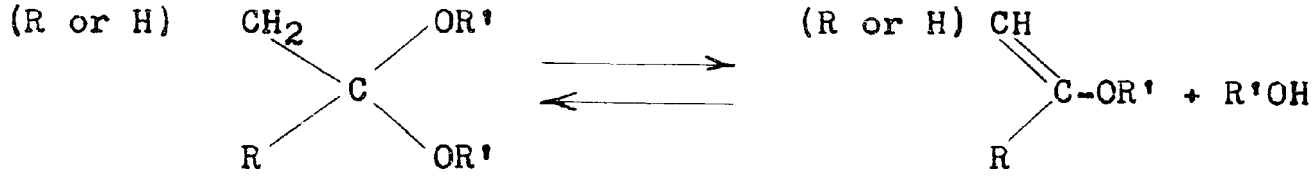
react with sodium to produce the sodium derivative of vinyl beta-hydroxyethyl ether. The ether itself, when treated with a trace of mineral acid, rearranges quantitatively, with explosive violence, to form the cyclic acetal ethylidene glycol.



(82) Stimmel and King, J. Am. Chem. Soc., 56, 1724 (1934).
(83) Wislicenus, Ann., 192, 112 (1878).
(40) Hill and Pidgeon, J. Am. Chem. Soc., 50, 2718 (1928).

The cyclic acetal, bromoethylidenetrimethylene glycol, behaves in an analogous manner[84], and has been converted into vinyl gamma-hydroxypropyl ether and ethylidenetrimethylene glycol, respectively.

The preparation of alpha-unsaturated ethers of the general formula $RC(OR')=CH_2$ from certain ketals (2,2-dimethoxy-alkanes) has been described by Killian, Hennion, and Nieuwland[85]. For example, a ketal of the type $R(CH_3)C(OCH_3)_2$ readily loses methyl alcohol when it is heated with a small amount of p-toluenesulfonic acid.



The vinyl ether thus prepared will react with the alcohol R'OH to form the original acetal, or with an unlike alcohol to produce a mixed acetal[85,86].

The ethylidene acetals, $RCH(OR')_2$, do not behave in this manner.

(84) Hill, J. Am. Chem. Soc., 50, 2725 (1928).
(85) Killian, Hennion and Nieuwland, J. Am. Chem. Soc., 57, 544 (1935).
(86) Shostakoviski and Gershtein, J. Gen. Chem. (U.S.S.R.), 16, 937 (1946); C.A., 41, 1999 (1947).

Pharmacological Activity of Non-Basic Acetals and Ketals

Formaldehyde dimethyl acetal, formaldehyde diethyl acetal, acetaldehyde dimethyl acetal, acetaldehyde diethyl acetal and acetone diethyl ketal exhibit hypnotic activity. Acetaldehyde is a very weak hypnotic.*

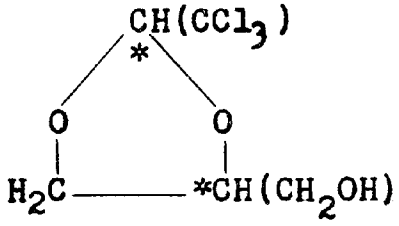
The diethylacetal of acetaldehyde was studied by v. Mering[87] and recommended as a hypnotic. Subsequent clinical trial[88] showed that large doses were required, and that the action was uncertain. Diethyl formal and dimethyl acetal were investigated as inhalation anesthetics[89], and found to possess no merit. The diethyl ketal of acetone[90] was shown to exhibit strong hypnotic properties but it affected adversely heart and respiration rates. Hess[91] mentioned the potential use of acyclic aliphatic acetals and ketals as hypnotic agents, but there appears to be no record of their subsequent clinical application. The half acetal 1-cyclohexoxy-2,2,2-trichloroethanol, obtained by spontaneous addition of cyclohexanol to chloral, produced narcosis in rats[92].

In a recent patent[93] it was claimed that 4-beta-hydroxyethoxymethyl-1,3-dioxolanes possess "therapeutic value".

(87) v. Mering, Berlin klin. Wochschr., 19, 648 (1882).
(88) Peretti, Der Irrenfreund, 25, 65 (1883).
(89) K. H. Meyer and H. Gottlieb-Billroth, Z. physiol. Chem., 112, 55 (1921).
(90) Brissmoret and Chavalier, Compt. rend., 148, 731 (1909).
(91) Hess, Ger. Pat. 197,804; Chem. Zentr., 79 I, 1863 (1908). See also Reitter and Hess, Ber., 40, 3023 (1907).
(92) Sumerford and Cronic, J. Am. Chem. Soc., 70, 448 (1948).
(93) U. S. Pat. 2,428,805 (1947). See Kharasch and Nordenberg, J. Org. Chem., 8, 189 (1943).

* For references see Houben, Fortschritte der Heilstoffchemie, Zweite Abteilung, I Band, I Hälfte, pp. 514, 515, 519, 525 and 574.

An interesting study has been made of trichloroethylidene glycerol (2-trichloromethyl-4-hydroxymethyl-1,3-dioxolane).

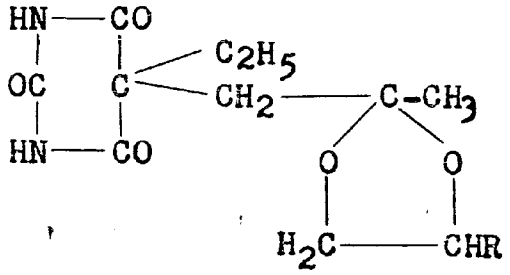


This substance was synthesized first by Yoder[94] and, subsequently, by a number of other investigators[95,96,97,98]. When trichloroethylidene glycerol is prepared, it is obtained in the form of a mixture of the cis and trans forms; each of these forms represents a racemic mixture. Hibbert et al.[16] found that if the alcoholic group in the compound is benzoylated, the two isomeric benzoates can be recognized, due to the difference in their crystalline structure, and separated mechanically. By a repetition of this process, and hydrolysis of the benzoates individually, Butler[98] obtained both the cis and the trans form of the dioxolane for pharmacological tests, although it was not determined whether the lower or the higher melting form represented the cis type.

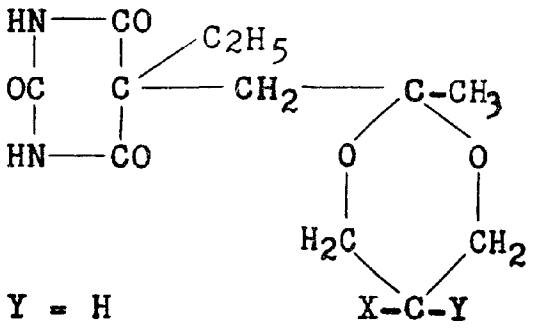
(94) Yoder, J. Am. Chem. Soc., 45, 475 (1923).
(95) Böeseken, Verlag Akad. Wetenschappen Amsterdam, 35, 1084 (1926).
(96) Hibbert, Morazain and Paquet, Canadian J. Research, Section B, 2, 131 (1930).
(97) Meldrum and Vad, J. Indian Chem. Soc., 13, 118 (1936).
(98) Butler, J. Pharmacol. Exp. Therap., 81, 72 (1944).

Yoder had already stated that this dioxolane exhibited "a marked and fleeting hypnotic action". The far more extensive study by Butler disclosed the following facts. Administered to mice by the intravenous and by the intraperitoneal route, both racemic isomers were shown to be about equally effective, and only a little less active than the potent anesthetic tribromoethanol (avertin). Their lethal doses, by both routes, are considerably higher than the lethal doses of tribromoethanol.

Very recently Hurd and McAuley[99] described the preparation and pharmacological properties of several 5,5 disubstituted barbituric acids. One of the 5 substituents was an ethyl group, the other was represented by a 1,3-dioxolane or a 1,3-dioxane residue. Formulas for these compounds are shown below.



R = H or CH_3



X = Y = H

X = NO_2 or NH_3

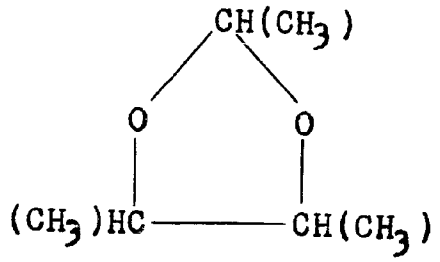
Y = CH_2OH

(99) Hurd and McAuley, J. Am. Chem. Soc., 70, 1650 (1948)

The products were prepared by condensation of 5-ethyl-5-acetonylbarbituric acid with the required ethylene or propylene or trimethylene glycol in the presence of p-toluenesulfonic acid. The water eliminated during the reaction was removed, as it was formed, by the slow distillation of toluene from the reaction mixture.

In non-toxic doses, the compounds produced no hypnotic effect in mice by intravenous injection, but they did exhibit some anticonvulsant activity.

Knoefel[100] examined a series of thirteen acyclic acetals which included the diethyl acetals of glycolaldehyde, ethoxy-acetaldehyde, glyoxal and ethyl orthoformate. Several of the compounds were found to be quite potent hypnotics but had a very narrow margin of safety. Then a group of cyclic acetals was studied by the same investigator[101], and he made this statement concerning them: "As the structure more closely approaches that of paraldehyde, so does the pharmacological activity". The product which Knoefel called butylene acetal (2,4,5-trimethyl-1,3-dioxolane) seemed to be the most active



Butylene Acetal

(100) Knoefel, J. Pharmacol. Exp. Therap., 50, 88 (1934).
(101) Knoefel, ibid., 53, 440 (1935).

substance. In addition to this trisubstituted dioxolane, Knoefel tested two dimethyl- and two monomethyl dioxolanes as well as the parent compound 1,3-dioxolane. He also studied the six-membered cyclic acetal 1,3-dioxane, a monomethyl derivative and the commercially-available 1,4-dioxane.

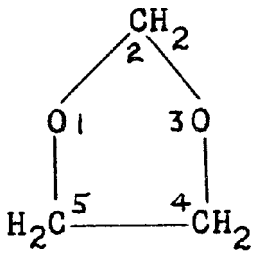
Since Knoefel had shown that the activity of a 1,3-dioxolane increases with the introduction of methyl groups, it seemed highly desirable that compounds should be prepared which are still more highly substituted than Knoefels most active product, the trimethyldioxolane. Consequently we prepared tetramethyl- and pentamethyldioxolane and several dioxolanes in which the substituents are both methyl and isopropyl groups. These compounds, which are listed in Table I, were tested for hypnotic activity by Dr. H. W. Werner and Miss Barbara B. Brown in the Wm. S. Merrell Company laboratories.

The pharmacological study proved to be highly disappointing since, with the exception of two slightly active compounds, all of the products failed to produce hypnosis.

Although several of the compounds reported in the table are known substances, as far as we are aware, they had not been tested hitherto for hypnotic potency. It was hardly expected that the first three compounds in the table would prove to be very active substances. They were tested merely because they had become available; they served as intermediates for the synthesis of compounds used in the latter part of this investigation.

TABLE I

1,3-Dioxolanes

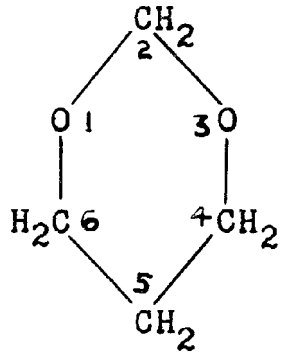


2	4	5	Hypnotic activity
- -	- - -	CH_2Cl	0
- -	- - -	$=CH_2$	Too toxic for tests
$CH(CH_3)_2$	- - -	CH_2Cl	Light narcosis
- -	CH_3, CH_3	CH_3, CH_3	0
CH_3	CH_3, CH_3	CH_3, CH_3	0
$CH(CH_3)_2$	CH_3, CH_3	CH_3, CH_3	0
$CH(CH_3)_2$	- - -	CH_2OCH_3	Light narcosis
$CH(CH_3)_2$	- - -	$CH_2OC_6H_5$	0
- -	CH_3, $CH(CH_3)_2$	$CH(CH_3)_2$	0
$CH(CH_3)_2$	CH_3, $CH(CH_3)_2$	$CH(CH_3)_2$	0

In the hope that more favorable results would be obtained with 1,3-dioxanes, five representatives of this class were prepared. It can be seen from Table II that all of these compounds were found to be inactive except the 4,6,6-trimethyl derivative. This substance proved to be active, and similar to paraldehyde, when administered orally to rats.

TABLE II

1,3-Dioxanes



2	4	6	Hypnotic activity
- -	CH_3	CH_3, CH_3	Active
- -	CH_3, CH_3	CH_3, CH_3	0
CH_3	CH_3, CH_3	CH_3, CH_3	0
$CH(CH_3)_2$	CH_3	CH_3, CH_3	0
$CH(CH_3)_2$	CH_3, CH_3	CH_3, CH_3	0

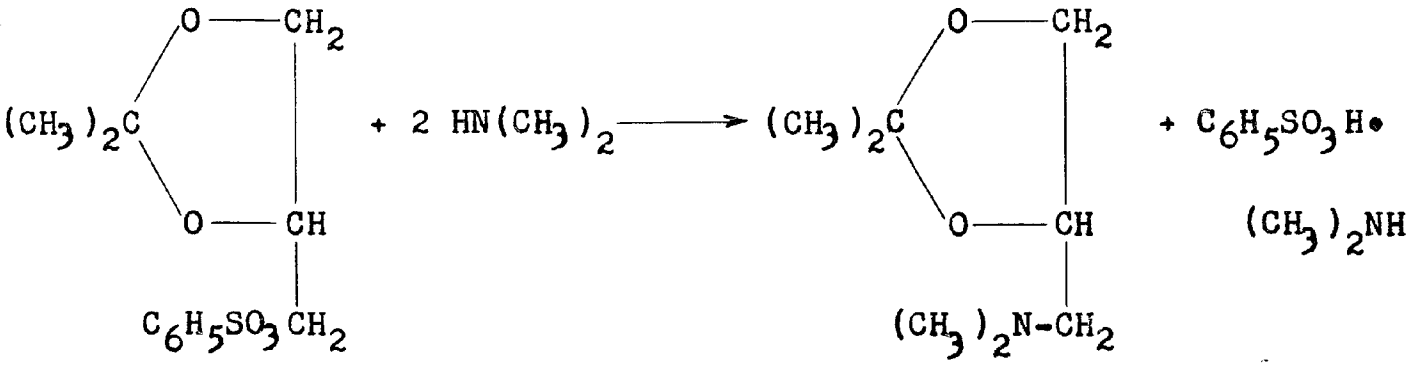
Although several of the cyclic acetals which we prepared did exhibit some activity, the degree of activity was not high enough to warrant detailed pharmacological studies and, furthermore, like paraldehyde, the active compounds produced a "bad breath".

Since the majority of pharmacologically active compounds are basic substances, we considered the preparation of basic cyclic acetals to be of interest. Pharmacological examination of the basic acetals which were synthesized led to the discovery that they possessed very interesting properties.

Cyclic Aminoacetals and Aminoketals

A number of basic acyclic acetals have been prepared by condensation of chloroacetal with ammonia[102], alkylamines[103], dialkylamines[104], benzylamine[105], and aniline[106] in the form of its sodium derivative.

Basic cyclic acetals and ketals, such as basic 1,3-dioxolanes, received no attention from investigators until recent times. The first compound of this type appears to have been made in 1926 by Freudenberg and Hess[107] while they were engaged in a study of lignin chemistry. They prepared 2,2-dimethyl-4-dimethylaminomethyl-1,3-dioxolane from the benzenesulfonic acid ester of acetoneglycerol and dimethylamine according to the following formulation:

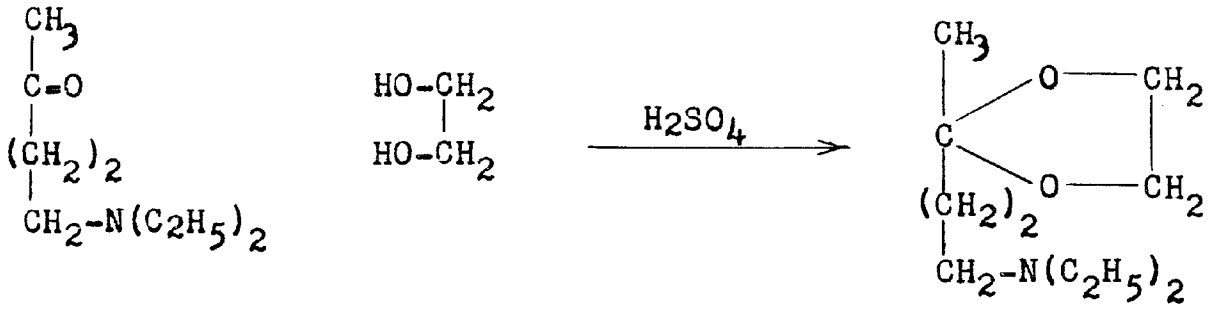


In a similar reaction, the para-toluenesulfonic acid ester of d(+) acetoneglycerol was treated with liquid ammonia to obtain

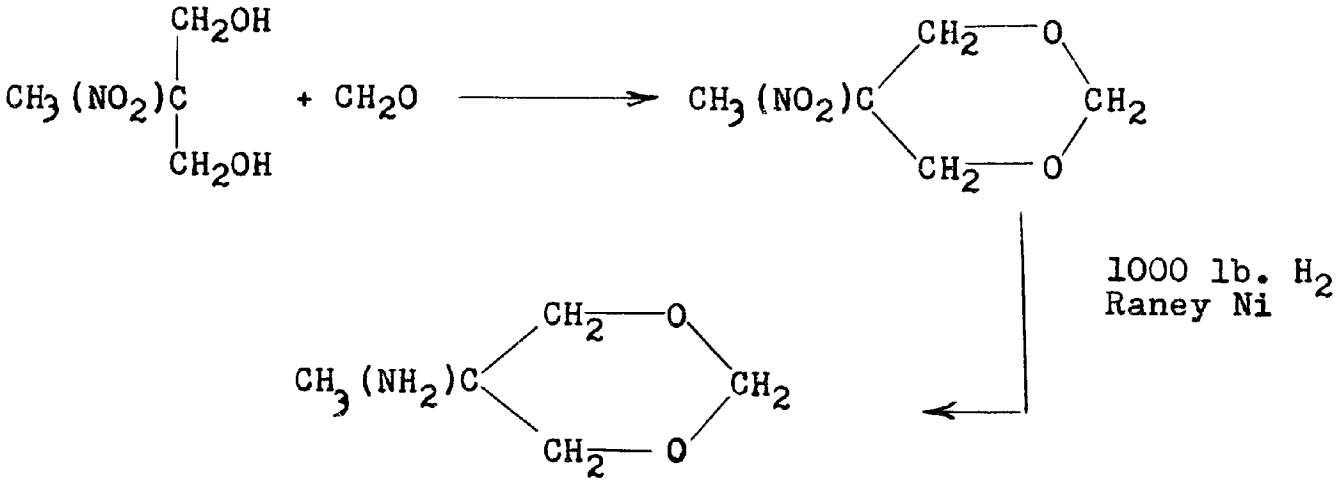
(102) Wohl, Ber., 21, 616 (1888).
(103) Paal and Van Gember, Arch. Pharm., 246, 306 (1908).
(104) Stoermer and Prall, Ber., 30, 1504 (1897).
(105) Rügheimer and Schön, Ber., 41, 17 (1908).
(106) Wohl and Lange, Ber., 40, 4727 (1907).
(107) Freudenberg and Hess, Ann., 448, 121 (1926).

1,2,2-dimethyl-4-aminomethyl-1,3-dioxolane;[108] this compound was made as an intermediate in the preparation of optically active mono-, di- and tri-glycerides.

Kühn[109] prepared a number of aminoketals from aminoketones and glycols by the azeotropic distillation procedure of Salmi[20]. The equation for his preparation of 2-methyl-2-(3'-diethylaminopropyl)-1,3-dioxolane is indicated below.

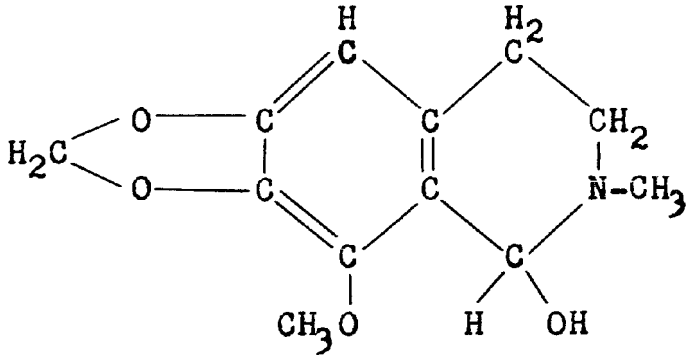


Senkus[23,24,110] synthesized a series of cyclic aminoacetals which contained an amino group in the 5 position, using the readily available nitroglycols. The preparation of 5-methyl-5-amino-1,3-dioxane is formulated below.



(108) Sowden and H.O.L. Fischer, J. Am. Chem. Soc., 64, 1291 (1942).
(109) Kühn, J. prakt. Chem., 156, 103 (1940).
(110) Senkus, J. Am. Chem. Soc., 65, 1656 (1943).
U.S.Pat. 2,247,256 (1941); C.A., 35, 6270 (1941).
U.S.Pat. 2,346,454 (1944); C.A., 38, 5028 (1944).
U.S.Pat. 2,370,586 (1945); C.A., 39, 4097 (1945).
U.S.Pat. 2,415,021 (1947); C.A., 41, 3132 (1947).

A number of natural occuring alkaloids may be classified as basic cyclic acetals. Cotarnine is representative of the group.



Cotarnine

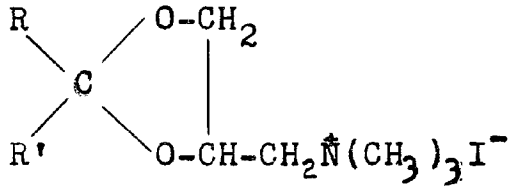
Although they have widely varying structures, other alkaloids such as narcotine, hydrocotarnine, hydrastine, narceine, bulbocapnine, and berberine also represent basic, cyclic formals.

Pharmacological Activity of Basic Cyclic Acetals and Ketals

Fourneau and associates[111,112,113,114,115] prepared a series of substituted 4-dialkylaminomethyl-1,3-dioxolanes by amination of the corresponding 4-chloromethyl compounds. The quaternary ammonium salts of these substances were shown to possess a powerful muscarinic and acetylcholine like type of

(111) Fourneau, D. Bovet, F. Bovet and Montezin, Bull. soc. chim. biol., 26, 516 (1944); C.A., 40, 3824 (1946).
(112) Fourneau and Bovet, Compt. rend. soc. biol., 138, 469 (1944).
(113) Fourneau and Chantalou, Bull. soc. chim., (5) 12, 845 (1945); C.A., 40, 6465 (1946).
(114) U.S.Pat. 2,439,969 (1948).
(115) British Pat. 595,963 (1948).

activity. The following table shows a few of the compounds which were described.



I	R = H, R' = H	0.5-2 (acetylcholine = 1)
II	R = H, R' = CH_3	10-50 times as active as I
III	R = H, R' = C_2H_5	0.1 as active as I
IV	R = CH_3, R' = CH_3	0.1 as active as I
V	R = H, R' = C_6H_5	0.001 as active as I

Since, as far as we could discover, basic 1,3-dioxolanes which contained two aryl groups in the 2 position had never been studied for pharmacological activity, we continued our investigation of cyclic ketals by the preparation of such compounds* .

The very significant discovery was made that 2,2-diphenyl-4-diethylaminomethyl-1,3-dioxolane, as well as a number of its analogs, exhibit antihistamine activity.

The compounds which we prepared and their relative activity is shown by the following table which we obtained from Dr. Werner and Miss Brown.

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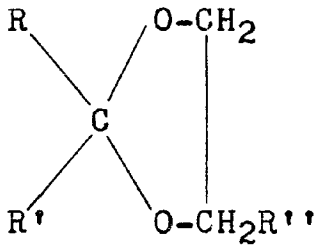
* It seems that, with one exception, compounds of this type have not been synthesized hitherto. 2,2-Diphenyl-5-methyl-5-amino-1,3-dioxolane has been described in the patent literature (U.S.Pat. 2,346,454; C.A., 38, 5028 (1944)) as a wetting agent.



R	R'	R''	Minimal Conc. required to antagonize 0.1 γ/cc. of histamine diphosphate
C_6H_5	C_6H_5	$N(CH_3)_2$	5
C_6H_5	C_6H_5	$N(CH_3)_2.CH_3I$	1
C_6H_5	C_6H_5	$N(C_2H_5)_2$	0.5
C_6H_5	C_6H_5	$N(C_3H_7)_2$	10
C_6H_5	C_6H_5	$N(C_4H_9)_2$	20
C_6H_5	C_6H_5	$NCH(CH_3)_2$	5
C_6H_5	C_6H_5	NC_5H_{10}*	1
C_6H_5	C_6H_5	$NC_5H_{10}.CH_3I$	5
C_6H_5	C_6H_5	NC_4H_8O**	20
C_6H_5	C_4H_3S***	$N(C_2H_5)_2$	0.1
C_4H_3S	C_4H_3S	$N(C_2H_5)_2$	5
p-$CH_3OC_6H_4$	p-$CH_3OC_6H_4$	$N(C_2H_5)_2$	
Biphenylene		$N(C_2H_5)_2$	10
Benadryl			0.05

* Piperidino

** Morpholino

*** 2-Thienyl

In view of the fact that benadryl (benzhydryl beta-dimethylaminoethyl ether hydrochloride) and a number of other antihistamine drugs are dimethylamino derivatives, it might have been expected that in our series, likewise, the dimethylamino derivative would be the most potent. However, the data shows that the diethylamino compound is ten times as active as the corresponding dimethylamino analog, and twenty times as active as the propyl homolog.

Especially noteworthy is the relatively high effectiveness of the 2-phenyl-2-thienyl compound.

From the general discussion of antihistamine drugs which is presented in the next chapter, it can be seen that although a number of active substances have been discovered, they are all derivatives of a very few parent compounds. In fact, it can be stated that all of the clinically useful compounds are either acyclic monoethers or derivatives of ethylenediamine. The 1,3-dioxanes can now be added to this small group of parent compounds which become active antihistaminic agents upon the introduction of suitable substituents.

ANTIHISTAMINE DRUGS*

Within the last few years the term allergy has become a household word. It is defined as "a condition of unusual or exaggerated specific susceptibility to a substance which is harmless in similar amounts for the majority of members of the same species."(116) Allergens are substances which are capable of inducing allergy or specific susceptibility; they may be a protein or a non-protein. Common allergens are pollen, the proteins of milk, wheat or egg, bacterial protein, dust, feathers and numerous chemical compounds.

The typical and recognized diseases of allergic origin (asthma, vasomotor rhinitis (hay fever), urticaria (hives), and certain eczematous conditions) appear to be based upon an hereditary transmission of capability for sensitization. These conditions affect some three to five percent of the entire population.

The peculiar reaction to drugs which some individuals experience has been termed "idiosyncrasy" to distinguish it from the toxic reactions which occur from overdosage; this phenomenon, as well as contact dermatitis, is now regarded as an allergic response. Today, allergic responses to sulfonamides, to atabrine and to penicillin, as well as many plastics, fabrics and dyes, are often encountered.

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* Material for this discussion has been taken freely from the following surveys of this subject:
1. S. M. Feinberg, J. Am. Med. Assn., 132, 702 (1946);
2. E. R. Loew, Physiol. Rev., 27, 542 (1947);
3. Amer. Profess. Pharmacist, 12, 140 (1946); ibid., 13, 551 (1947).

(116) Dorland, The American Illustrated Medical Dictionary, 17th ed., W. B. Saunders Co.

Koch[117] is believed to be the first to record an allergic reaction which was called the "Koch phenomenon". This term was applied to the inflammatory reaction which surrounded the needle puncture following a second injection of tubercle bacilli into the peritoneal cavity in guinea pigs.

von Pirquet[118] further studied this reaction and coined the word "allergic" which was derived from the Greek words allos (change) and ergon (reaction). He defined this word as an altered response of the tissues as a result of an infection or the introduction of various substances into the body by injection. Just prior to this, tissue hypersensitiveness to non-bacterial substances had been demonstrated.[119] It was discovered that although the first injection of a foreign protein substance elicits no significant reaction, a second injection of the same material, after an interval of ten days or more, may lead to profound shock or sudden death; this latter dramatic phenomenon was termed "anaphylaxis" by Richet who derived the term from the two Greek words ana (against) and phylaxis (protection), "against protection". He thus defined the hypersensitive state as the opposite of prophylaxis.

Attention was drawn to the fact that the symptoms of such allergic conditions as asthma and hay fever resembled closely

(117) R. Koch, Deut. med. Wochschr., 16, 1029 (1890).
(118) von Pirquet, Münch. med. Wochschr., 53, 1457 (1906).
(119) Partier and Richet, Compt. rend. soc. biol., 54, 170 (1902).

the anaphylactic symptoms in the quinea pig. In 1910 Dale and Laidlaw[120] pointed out the similarity of manifestations in the effect of injected histamine and in anaphylactic shock. This constituted the starting point for the progression of experimental evidence incriminating histamine as the mediator of anaphylactic and allergic symptoms. A good part of the evidence in favor of the histamine concept of allergy is based on the demonstration of the various points of resemblance between allergic and anaphylactic reactions, and on the fact that the effects of histamine administered to man are consistent with some of the phenomena of allergy.

Histamine has three major physiologic actions. It acts (1) on smooth muscle to produce contractions; (2) on capillaries to produce dilatation and increased permeability, which may lead to the formation of edema and (3) on secretory glands as a secretagogue. The acute phases of allergic reactions in many tissues seem adequately explained on the basis of liberation of histamine. In the lungs, for example, histamine acting on smooth muscle to produce bronchiolar constriction, on capillaries to produce edema and on the mucus glands to produce mucus, could quite accurately reproduce the findings of asthma.[121] In the skin, the urticaria and wheals of an acute reaction may also be duplicated by injection of histamine[122]. The large amount of evidence linking allergy and histamine is treated fully in several review articles[123,124].

(120) Dale and Laidlaw, J. Physiol., 41, 318 (1910).
(121) C. F. Code, Ann. Allergy. 2, 457 (1944).
(122) Lewis and Grant, Heart, 11, 209 (1924).
(123) S. M. Feinberg, J. Am. Med. Assn., 132, 702 (1946).
(124) E. R. Loew, Physiol. Rev., 27, 542 (1947).

Simultaneously, evidence accumulated which showed that the allergen-induced release of histamine was a complex immunological response. Early efforts to reduce the allergic symptoms were based on identifying the offending allergen and building up a tolerance to it by successive injections of minute but increasing amounts of the allergen. This type of treatment was named "active specific desensitization". In a second type of treatment, "passive specific desensitization", serum from animals was injected into the allergic person; the animals had been previously desensitized to the specific allergen which was held responsible for the allergic symptoms of the person. The existence of a transferable specific desensitization factor (antibody) was thus revealed.

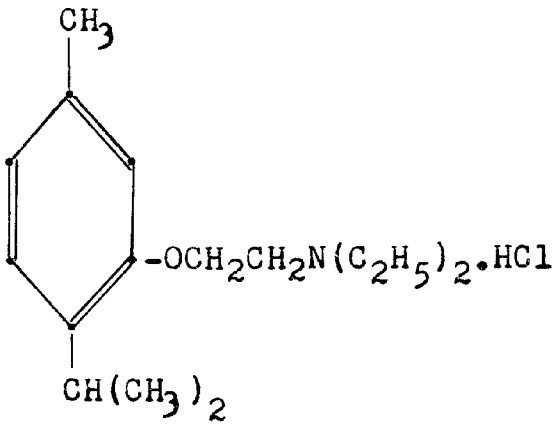
With the realization that histamine was at least in part responsible for the symptoms of allergy and anaphylaxis, non-specific antagonists to inhibit the physiological effects of histamine were sought.

Up to 1932, at least one hundred and sixty-five substances or methods aiming at non-specific inhibition of anaphylaxis had been reported[125]. Among these may be mentioned barium sulfate, barium chloride, atropine, ether, chloral hydrate, heparin, benzene in large doses, and reduction in barometric pressure. Although some of these methods possessed a degree of merit, on the whole they were impractical, too hazardous or insufficiently effective.

(125) J. H. Hill and L. Martin, Medicine, 11, 141 (1932).

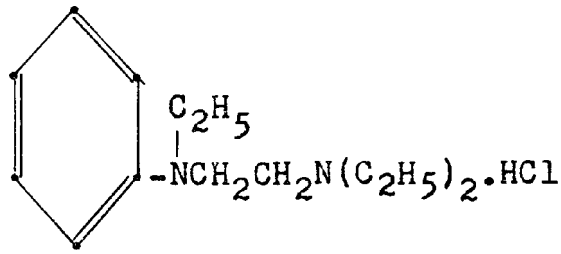
According to Loew[124], antihistamine drugs or histamine antagonists are "drugs which are capable of diminishing or preventing several of the pharmacological effects of histamine and which do so by a mechanism other than the production of pharmacological responses diametrically opposed to those produced by histamine."

The first publication, after the preliminary reports from Bovet's laboratory[126], which describes active substances of this type seems to be that of Anne-Marie Staub[127]. In this paper Staub mentions the antihistamine and antianaphylactic properties of a number of compounds which had been synthesized by Fourneau. The two most promising compounds, Fourneau 929 [128] and Fourneau 1571, were subjected to thorough pharmacological



929F

2-Isopropyl-5-methyl-phenoxyethyldiethylamine hydrochloride
Thymoxyethyldiethylamine hydrochloride



1571F

N-Phenyl-N,N',N'-triethylethylenediamine hydrochloride

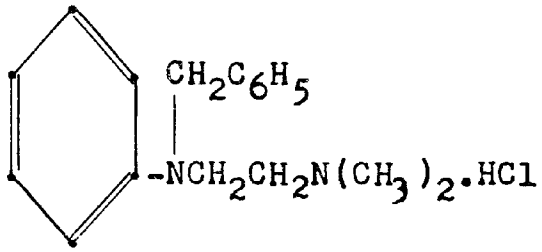
(126) Bovet and Staub, Compt. rend. soc. biol., 124, 547 (1937). Staub and Bovet, ibid., 125, 818 (1937).

(127) Anne-Marie Staub, Ann. Inst. Pasteur, 63, 400, 485 (1939).

(128) At an earlier date Fourneau and Bovet (Arch. intern. pharmacodynamie, 46, 178 (1933) had studied phenolic ethers with respect to their sympatholytic properties but they had not been tested as possible histamine antagonists.

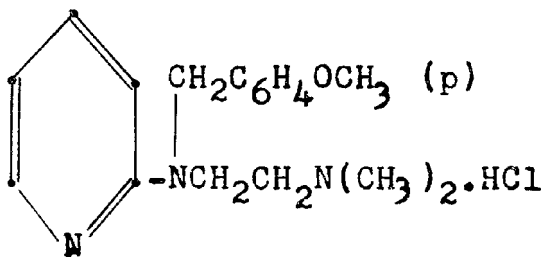
tests. Although these two compounds were found to be too toxic for therapeutic use, the fact that active substances had been discovered stimulated the search for antihistamine agents in a number of laboratories.

Halpern[129] studied a series of analogs of 1571F, which had been prepared by Mosnier in the Rhone-Poulenc laboratories, for antihistamine, antianaphylattic and antispasmodic activity. The dimethyl analog of 1571F (2325 Rhone-Poulenc, N-phenyl-N,N',N'-trimethylethylenediamine hydrochloride) and a product which became known as antergan (2339 Rhone-Poulenc) were tested extensively, and the latter substance was evaluated in human subjects.



Antergan

N-Phenyl-N-benzyl-N',N'-dimethylethylenediamine hydrochloride



Neoantergan

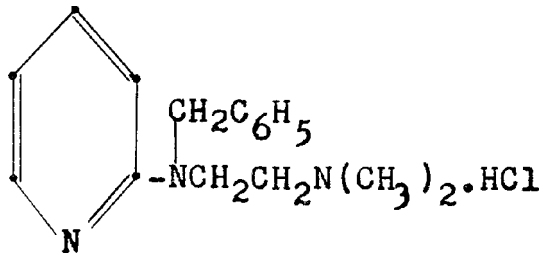
N-(alpha-Pyridyl)-N-(p-methoxybenzyl)-N',N'-dimethylethylenediamine hydrochloride

Horclois[130] prepared a compound similar to antergan except that an alpha-pyridyl radical was substituted for the

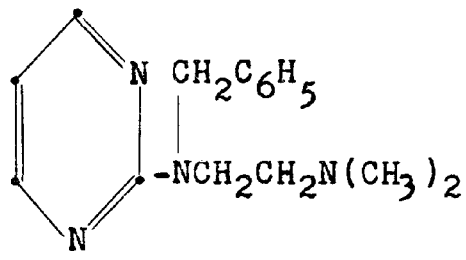
(129) Halpern, Arch. intern. pharmacodynamie 68, 339 (1942).
(130) Horclois. See Bovet and Walthert, Ann. pharmaceutiques francaises 2: suppl. to no. 4, 1 (1944).

phenyl group. Bovet and associates[131], in 1944, then found that neoantergan, a product which represents antergan in which the phenyl and benzyl groups have been replaced by alpha-pyridyl and p-methoxybenzyl, respectively, exhibits an unusually high degree of antihistamine activity.

The antihistamine and antianaphylactic properties of pyribenzamine hydrochloride were reported by Mayer, Huttrer, and Scholz[132] in 1945. This substance is neoantergan in which the methoxy group in the benzyl radical is replaced by hydrogen.



Pyribenzamine Hydrochloride



Hetramine
N-2-Pyrimidyl-N-benzyl-N',N'-dimethylethylenediamine

Hetramine[133], described in 1946, is the pyrimidine analog of pyribenzamine.

The activity of neohetramine[134] was announced in 1947. This substance differs from the hetramine only in that it contains a p-methoxybenzyl instead of a benzyl radical.

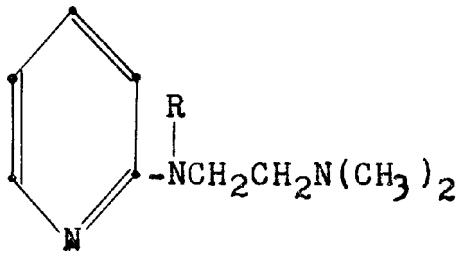
(131) Bovet, Horclois and Walthert, Compt. rend. soc. biol., 138, 99 (1944). Bovet, Horclois and Fournel, ibid., 138, 165 (1944).

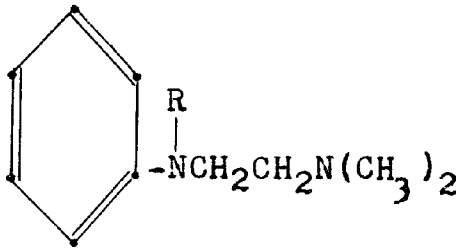
(132) Mayer, Huttrer and Scholz, Fed. Proc., 4, 129 (1945). Mayere, Huttrer and Scholz, Science, 102, 93 (1945). Huttrer, Djerassi, Beears, Mayer and Scholz, J. Am. Chem. Soc., 68 1999 (1946).

(133) Feinstone, Williams and Rubin, Proc. Soc. Exp. Biol. Med., 63, 158 (1946).

(134) Reinhard and Scudi, ibid., 66, 512 (1947). This product is made by the Nepera Chemical Company and is distributed by Wyeth Incorporated.

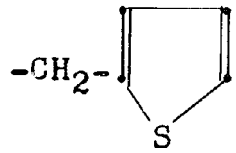
Especially interesting are several compounds which contain a thienyl or a substituted thienyl group. Three products of this type are known: thenylene (histadyl)[135], chlorothen[136], and diatrin[137].

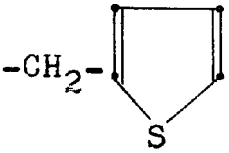


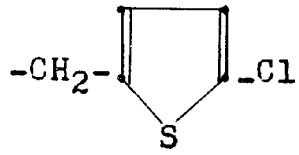


Thenylene (Abbott Laboratories)
Histadyl (Eli Lilly and Company)
Chlorothen (American Cyanamide)

Diatrin

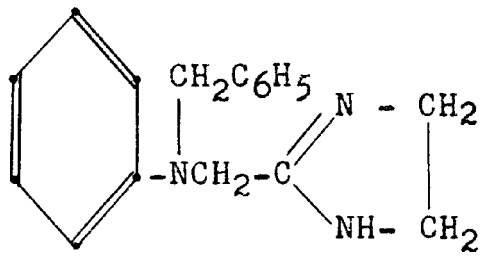
In thenylene R = 

In diatrin R = 

In chlorothen R = 

Antistin[138], although it is an imidazoline derivative, contains the structural unit common to many of the antihistamine drugs which have been mentioned, namely (phenyl)(benzyl)N-C-C-N.

(135) (a) Weston, J. Am. Chem. Soc., 69, 980 (1947).
(136) Clapp, Clark, Vaughan, English and Anderson, ibid., 69, 1549 (1947).
(137) Kyrides, Meyer and Zienty, ibid., 69, 2239 (1947). Leonard and Solmssen, ibid., 70, 2064 (1948).
(138) Bourquin, Schweiz. med. Wochsochr., 76, 294 (1946).



Antistin

2-(Phenylbenzylamino-
methyl)-imidazoline

With the exception of compound 929F, all of the drugs which have been described may be regarded as derivatives of ethylenediamine. Another group of substances which exhibit antihistaminic activity are ethers. Fourneau's thymoxyethyldiethylamine (929F) is a product of this type. At present, the most important representative of this class is benadryl(139).

$$(C_6H_5)_2CH\text{-}O\text{-}CH_2CH_2N(CH_3)_2.HCl$$

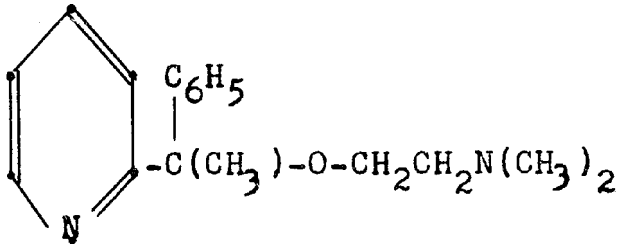
Benadryl

Benzyhydryl beta-dimethylamino-
ethyl ether hydrochloride

Benadryl was the first synthetic antihistaminic drug to find clinical application, and its highly successful use has motivated the search for other drugs of the ether type which might possess equal or greater activity yet produce fewer

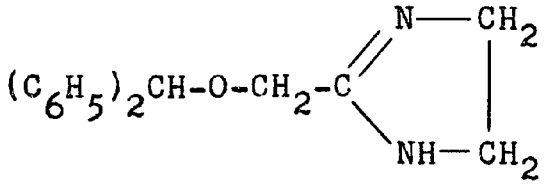
(139) Rieveschl, Jr. and Huber. See Loew, Kaiser and Moore, J. Pharmacol. Exp. Therap., 83, 120 (1945).

side effects. Three other drugs of this type which have been mentioned in the literature are decapryn[140,141], Mg 322[142] and C-5581-H[143].



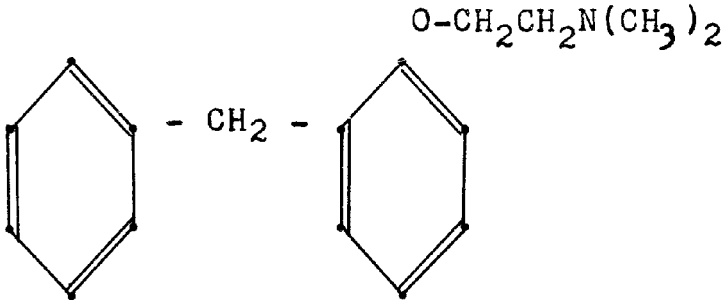
Decapryn

alpha-Phenyl-alpha-(alpha-pyridyl)-beta'-dimethylamino-diethyl ether



Mg 322

2-Benzhydryloxymethyl)-imidazoline



C-5581-H

2-(beta-Dimethylamino-ethoxy)-diphenylmethane

In addition to the products which may be classified as substituted ethylenediamines or ethers, other antihistamine

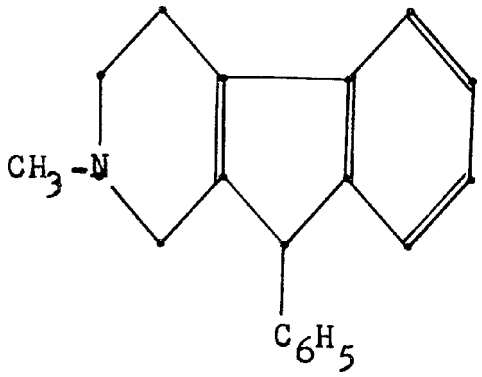
(140) Feinberg and Bernstein, J. Lab. Clin. Med., 33, 319 (1948).
(141) Sheldon, Weller, Haley and Fulton, Univ. of Mich. Hospital Bulletin, Vol. 14, No. 2, p. 13 (1948).
(142) Cavallini and Mazzucchi, Farm. sci. e. tec. (Pavia), 2, 273 (1947). C.A., 42, 1664 (1948).
(143) Feinberg et al., J. Allergy, 19, 90 (1948).

agents are known which, from the standpoint of chemical structure, can be referred to only as miscellaneous types:

The tertiary amine, ethyl-beta-bromoethyl-(alpha-naphthyl-methyl)-amine[144].

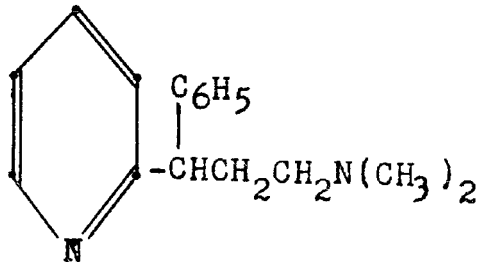
Certain N-dialkylaminoalkyl derivatives of thiodiphenyl-amine[145].

Theophorin[146] is reported to be 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene.



Theophorin (Hoffmann La-Roche)

Trimeton[147], 1-phenyl-1-(alpha-pyridyl)-3-dimethyl-aminopropane.



Trimeton (Schering)

(144) Stone, Achenbach and Loew, Fed. Proc., 7, 258 (1948).
(145) Halpern and Ducrot, Compt. rend. soc. biol., 140, 361 (1946). Halpern, ibid., 140, 363 (1946).
(146) Lehmann, J. Pharmacol. Exp. Therap., 92, 249 (1948).
(147) LaBelle and Tislow, Fed. Proc., 7, 236 (1948).

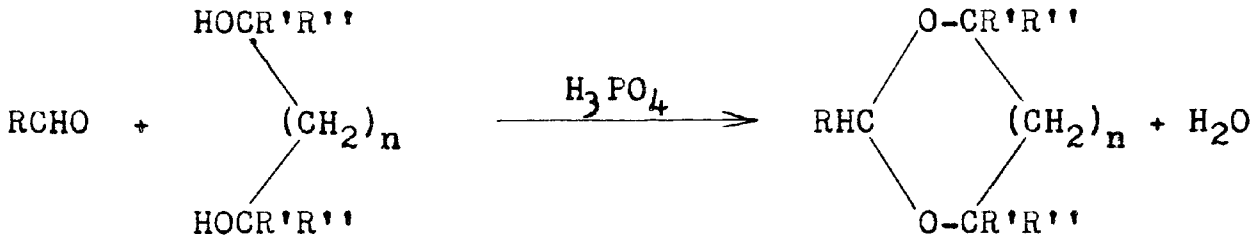
Doses of antihistamine agents which are effective therapeutically in allergic disturbances do not raise blood pressure. Most antihistamine drugs exhibit some degree of local anesthetic action. In animals, these drugs do not produce sedation or hypnosis, but in man sedation may be experienced in a degree which varies from person to person. A sedative effect is produced frequently with benadryl, less frequently with pyribenzamine, and has been known to occur after the administration of antergan or neoantergan.

Side effects, produced as the result of actions of antihistamine drugs on the gastrointestinal tract include gastric distress, nausea, emesis, colic and diarrhea. These effects are especially characteristic of those agents which are capable of inducing spasm of the intestinal muscle, but are seldom found in drugs such as benadryl which produce a slight degree of antispasmodic activity.

INTRODUCTION TO THE EXPERIMENTAL PART

The cyclic acetals and ketals, prepared during this investigation, may be arranged in three groups:

(a) Five-membered rings (1,3-dioxolanes) which were prepared from an aldehyde and a 1,2-glycol in the presence of a catalytic amount of 80% orthophosphoric acid.



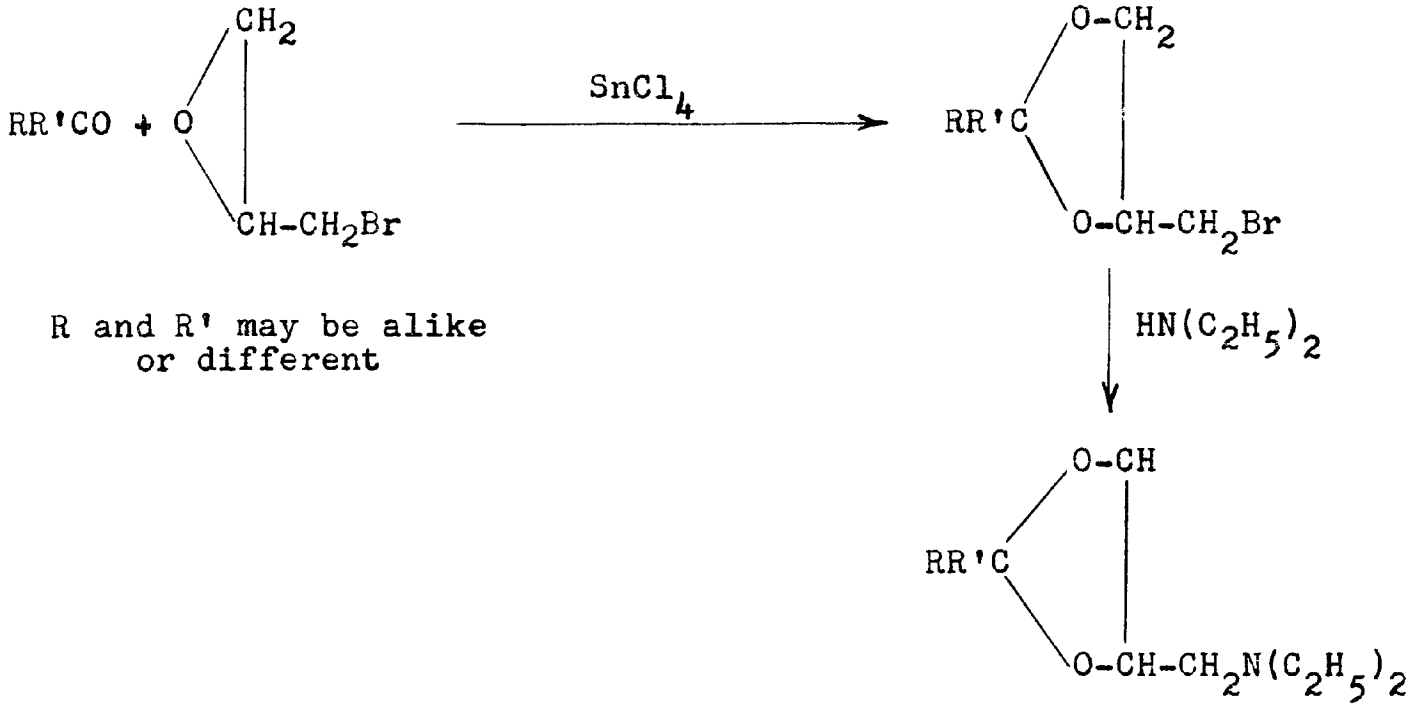
R, R' and R'' may be alike or different.

R' and R'' may represent hydrogen or alkyl.

n = 0 or 1.

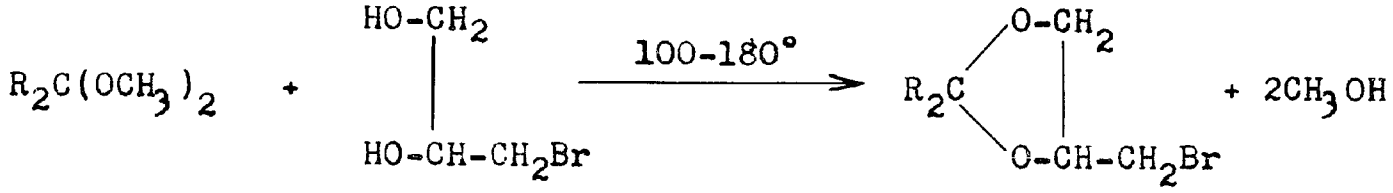
(b) Six-membered rings (1,3-dioxanes) obtained by interaction of an aldehyde with a 1,3-glycol; orthophosphoric acid was used as a catalyst in this reaction.

(c) Five-membered rings which contain a basic substituent such as a dialkylaminoalkyl radical. In order to obtain these compounds, a ketone was allowed to react with an epihalohydrin, in the presence of stannic chloride, and the haloalkyl-1,3-dioxolane obtained was then aminated to produce the corresponding basic-alkyl-1,3-dioxolane.



R and R' may be alike or different

Another useful procedure was an acetal exchange reaction[28,148] which is illustrated by the following scheme:



Although the dimethyl ketal of acetophenone had been condensed with glycerol to produce 2-methyl-2-phenyl-4-hydroxymethyl-1,3-dioxolane[11], we are not aware of any reported instance in which a dialkyl ketal of an aromatic ketone has been employed in this reaction. We have found that dimethoxydiphenylmethane can be used successfully.

(148) Halenquist and Hibbert, Can. J. Research, 8, 129 (1933).

In our first attempt to prepare 2,2-diphenyl-4-diethylaminomethyl-1,3-dioxolane, the corresponding 4-chloromethyl derivative was heated with an excess of diethylamine in a citrate bottle on a steam-bath. The 4-chloromethyl compound was recovered unchanged.* In order to obtain the more reaction 4-iodomethyl derivative, epoxyiodohydrin was allowed to react with benzophenone in the presence of stannic chloride. Since the oily reaction product could not be purified by distillation or recrystallization, the crude material was heated with diethylamine. The desired 4-diethylaminomethyl derivative was obtained, but the yield was very unsatisfactory. It was found then that by the use of epibromohydrin, the 4-bromomethyl dioxolane could be prepared, and that this easily purified halo derivative reacted satisfactorily with diethylamine to form the 4-diethylaminomethyl derivative in good yield.

Willfang(149), who had prepared 2,2-diphenyl-4-chloromethyl-1,3-dioxolane previously, stated that his chloro derivative would not form a Grignard reagent. He found also that other 4-chloromethyl-dioxolanes which he had synthesized would not react with pyridene or with silver nitrate. It was found by Kühn(109) that the chlorine was not removed from 2-phenyl-2-chloromethyl-1,3-dioxolane when this compound was boiled with alcoholic sodium hydroxide solution. These observations are in accord with

* Hurd and McAuley (J. Am. Chem. Soc., 70, 1650 (1948)) were unable to effect a condensation between 2-chloromethyl-2-methyl-1,3-dioxolane and sodio-5-ethylbarbiturate, even in the presence of sodium iodide. The dioxolane failed also to react with ethyl sodio-butylmalonate when the compounds were refluxed in alcoholic solution.

(149) Willfang, Ber., 74, 145 (1945).

others which have been made relative to the unreactivity of the halogen in beta-halo ethers[150].

Whenever epibromohydrin was employed for the preparation of a bromodioxolane, a certain amount of a by-product was obtained due to the polymerization of the epibromohydrin[151]. In all instances in which it was possible, the bromodioxolane was purified by recrystallization or distillation in order to separate it from the polymer. If this impurity was not removed, it was converted to a polymeric aminoether by subsequent amination. During the preparation of 2,2-di-(p-methoxyphenyl)-4-diethylaminomethyl-1,3-dioxolane, we have obtained a small amount of a product which we believe to be such a polymeric aminoether.

Attempts to condense 2-benzoylpyridine with epibromohydrin by the use of stannic chloride were unsuccessful since the basic ketone formed an insoluble complex with the inorganic chloride which prevented further reaction of the ketone. It should be noted, however, that basic ketones can be condensed to yield cyclic ketals by the azeotropic distillation procedure of Kühn.[109]

A dioxolane which contains two unlike substituents in the 2 position and a substituent in the 4 position is capable of existence in two racemic modifications. A compound of this type is 2-phenyl-2-(alpha-thienyl)-4-bromomethyl-1,3-dioxolane.

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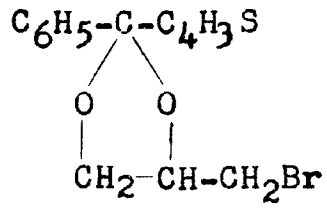
(150) Shriner and Fuson, Identification of Organic Compounds, p. 44, John Wiley and Sons (1940).

(151) Staudinger, (Die hochmolekularen Organischen Verbindungen, p. 288, J. Springer, Berlin (1932)) mentions similar products formed by ethylene oxide under the influence of stannic chloride. Bogert and Roblin (J. Am. Chem. Soc., 55, 3743 (1933)) obtained high boiling products when they used stannic chloride in the preparation of a cyclic acetal from ethylene oxide and benzaldehyde.



This dioxolane, in the crude state, proved to be an oil which could be distilled without decomposition. By refrigeration of the distillate, a crystalline compound was obtained from the oil which may have represented one of the stereoisomeric modifications. All attempts to convert the oily residue from which the crystals had been separated, into a crystalline product failed. Until further evidence has been obtained to the contrary, we have decided to consider the oily residue and crystalline product as isomeric racemates.

In many instances there is evidence of almost instant hydrolysis of an acetal or ketal upon contact with a dilute mineral acid(152). When 2,2-diphenyl-4-diethylaminomethyl-1,3-dioxolane was added to dilute hydrochloric acid, the basic compound dissolved immediately, and a clear solution was obtained. This solution rapidly became cloudy which indicated the formation of water-insoluble benzophenone. In one instance a ketal, 2,2-di-(p-methoxyphenyl)-4-diethylaminomethyl-1,3-dioxolane, was boiled with dilute hydrochloric acid, in order to ensure complete hydrolysis, and the products were then isolated; di-p-methoxybenzophenone was obtained in 95% yield, and 1-diethylamino-2,3-dihydroxypropane in 74% yield.

(152) Claisen (Ber., 31, 1010 (1898), footnote 2.) reported that when a turbid mixture of the diethyl ketal of acetone and water, which contained less than 0.01% of sulfuric acid, was shaken, the mixture became clear in a few seconds due to the decomposition of the ketal into acetone and alcohol.

The experimental procedures which are presented in the next section describe the preparation of ten substituted 1,3-dioxolanes five of which represent new compounds; five substituted 1,3-dioxanes, four of which are new products, and eleven new and one known basic 1,3-dioxolanes.

EXPERIMENTAL PART

General Methods

I. Cyclic Acetals from Acetaldehyde and Isobutyraldehyde

A mixture of 1.0 mole of the glycol, 1.1 mole of the aldehyde and two to five milliliters of 80% syrupy orthophosphoric acid (Baker and Adams Co.) were placed in a stoppered flask. The reaction mixture was allowed to remain at room temperature* for one to three days. If water separated, it was carefully aspirated from the mixture with a capillary pipette and measured since its volume may be used to calculate the extent of reaction. The product was extracted with ether, and the extract washed several times with water. After it had been dried over potassium hydroxide pellets or anhydrous potassium carbonate, the product was fractionated through an eight-inch Vigreaux column.

II. Cyclic Acetals from Formaldehyde

A mixture of 1.0 mole of the glycol, paraformaldehyde equivalent to two or three moles of formaldehyde, and twenty-five milliliters of syrupy phosphoric acid were heated under reflux on a steam-bath for twelve hours. The product was extracted

* Mild conditions are desirable to prevent polymerization of the aldehyde. Acetaldehyde is converted to metaldehyde and paraldehyde when it is heated with acids. (Kekule and Zincke, Ann., 162, 142 (1872); Weidenbusch, Ann., 66, 155 (1848). Isobutyraldehyde forms a crystalline trimer under similar conditions. (Fossek, Monatsh., 4, 660 (1883)).

with ether, washed with water several times and dried over potassium hydroxide pellets or anhydrous potassium carbonate. After removal of the ether, the residue was fractionated.

2-Isopropyl-4,4,5,5-tetramethyl-1,3-dioxolane (Isobutyral of Pinacol) (FA-102).- Dworzak and Lasch[153] prepared this compound in 68% yield by heating a mixture of pinacol and isobutyraldehyde in the presence of concentrated hydrochloric acid. The product contained a small amount of a halogen-containing compound which could not be removed; it boiled at 59° (13 mm.).

When this work was repeated, we found, likewise, that this method yielded a product which contained an appreciable amount of an organic halide and also some polymer of the aldehyde.

We obtained a pure, halogen-free product as follows: 113 g. (0.5 mole) pinacol hydrate, 108 g. (1.5 mole) of isobutyraldehyde and 30 ml. of syrupy phosphoric acid were placed in a stoppered flask and allowed to react for twelve hours at room temperature. The reaction mixture was then warmed on a steam-bath for an hour. Ether was added, and the ether extract washed several times with water. The extract was dried over Drierite and the product was fractionated; yield 81.7 g. (95%); b.p. 57.5° (15 mm.). This compound has a camphor-like odor.*

(153) Dworzak and Lasch, Monatsh., 51, 69 (1929).

* Unless otherwise specified, the odors of all other compounds are similar.

4,4,5,5-Tetramethyl-1,3-dioxolane (Formal of Pinacol) (FA-100).- This compound has been prepared[154] by displacing the methoxy groups of methyl formal with pinacol by heating a mixture of the two compounds in the presence of a small amount of hydrochloric acid. The boiling point was given as 124-125°.

The compound was prepared by us as follows: 190 g. (0.84 mole) pinacol hydrate, 77.5 g. paraformaldehyde (equivalent to 2.52 moles of formaldehyde) and 75 g. of 80% orthophosphoric acid were heated for twelve hours under reflux on a steam-bath. The product was extracted with ether, washed with water several times and dried over solid potassium hydroxide pellets. After removal of the ether, the residue was fractionated through an eight-inch Vigreaux column; yield 83.3 g. (76%); b.p. 123-125° (745 mm.).

2,4,4,5,5-Pentamethyl-1,3-dioxolane (Acetal of Pinacol) (FA-101).- Delepine[154] prepared this compound by heating dimethyl acetal with pinacol in the presence of an acid catalyst. He reported a boiling point of 134°. Hibbert and Hill[155], who prepared it in 61% yield by reacting pinacol and acetylene in the presence of a mercuric sulfate catalyst, reported a boiling point of 133-134°.

(154) Delepine, Bull. soc. chim., (3) 25, 581 (1901); Compt. rend., 132, 970 (1901).
(155) Hill and Hibbert, J. Am. Chem. Soc., 45, 3108 (1923).

We obtained the compound as follows: 113 g. (0.5 mole) of pinacol hydrate, 22 g. (0.5 mole) acetaldehyde, and 25 ml. of syrupy phosphoric acid were placed in a chilled citrate bottle. The reaction mixture was allowed to remain at room temperature for three days. It was then extracted with ether, the extract washed with water, and dried over potassium hydroxide pellets. To remove last traces of moisture and unreacted glycol, the extract was refluxed over metallic sodium for two hours. After removal of the ether, the residue was fractionated; yield 70.7 g. (98%); b.p. 133-135.5° (745 mm.).

2,4,4,6,6-Pentamethyl-1,3-dioxane (Acetal of 2,4-Dimethyl-2,4-pentandiol) (FA-104).- One hundred grams (0.76 mole) of 2,4-dimethyl-2,4-pentandiol,(156) 35 g. (0.76 mole) acetaldehyde and 1 ml. syrupy phosphoric acid were sealed in a chilled citrate bottle. After remaining at room temperature for three days, the lower aqueous layer which had separated measured 13.6 ml. Corrected for 1 ml. volume of the phosphoric acid, this volume corresponds to 92.5% of the theoretical amount of water.

The mixture was treated according to the general method (I); yield 100 g. (83.7%); b.p. 48° (14 mm.); 148.5-149° (740 mm.).

Anal. Calcd. for $C_9H_{18}O_2$: C, 68.32; H, 11.46
Found: C, 68.13; H, 11.40

(156) Lemaire, Bull. classe sci. Acad. roy. Belg., —, 146 (1909); Chem. Zentr., 80, I (1909). Franke and Konn, Ber., 37, 4731 (1904); Monatsh., 28, 1001 (1909).

4,4,6-Trimethyl-1,3-dioxane (Formal of 2-Methyl-2,4-pentandiol) (FA-108).- Fifty grams (0.42 mole) of 2-methyl-2,4-pentandiol*(157), 26.5 g. paraformaldehyde (0.84 mole formaldehyde), and 2 ml. syrupy phosphoric acid were reacted and treated according to the general method (II); yield 38.7 (71%); b.p. 139° (737 mm.).

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.84
Found: C, 64.68; H, 10.65

2-Isopropyl-4,4,6-trimethyl-1,3-dioxane (Isobutyral of 2-Methyl-2,4-pentandiol) (FA-109).- Forty-two grams (0.356 mole) of 2-methyl-2,4-pentandiol, 27 g. (0.375 mole) isobutyraldehyde and 1 ml. syrupy phosphoric acid were reacted and treated as indicated in the general method (I).

During the reaction an aqueous layer separated; after correction for the added phosphoric acid, it measured 7.0 ml. Assuming 100% reaction, the calculated volume of water should have been 6.4 ml. The yield of product was 58.2 g. (95%); b.p. 68.5 (25 mm.).

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70
Found: C, 69.84; H, 11.78

2,3,5-Trimethyl-3,4-hexandiol.- Methylmagnesium chloride was prepared by passing methyl chloride gas into 1500 ml. dry

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* This glycol has recently become commercially available - Shell Chemical Co.

(157) Zelinsky and Zelikow, Ber., 34, 2858 (1901); Monatsh., 22, 1070 (1901).

ether which contained 36.5 g. (1.50 mole) of magnesium turnings. A solution of 70 g. (0.485 mole) of isobutyroin[158] in 100 ml. dry ether was added. dropwise, to the Grignard reagent with stirring over a one and one-half hour period. The reaction mixture was allowed to stand overnight; it was then refluxed for two hours. To decompose the addition compound, 150 ml. of saturated aqueous ammonium chloride[159] was added, dropwise. The ether solution was filtered from the separated magnesium salts, the ether distilled. A residue of 74 g. crude glycol was obtained. The oily product was recrystallized from a mixture of 275 ml. ethanol and 500 ml. water (Norite) to obtain 46.8 g. (60.2%) of pure product; m.p. 94-95°.

Anal. Calcd. for $C_9H_{20}O_2$: C, 67.45; H, 12.58
Found: C, 67.35; H, 12.58

Monoxanthate* of 2,3,5-Trimethyl-3,4-hexandiol.- This derivative was prepared[160] and analyzed iodometrically[161] according to standard methods. This compound did not possess a sharp melting point.

Anal. Calcd. for $C_{10}H_{19}O_2S_2K$: equivalent wt. 274.46.
Found: 271.4

(158) Snell and McElvain, Organ. Syntheses, 13, 24 (1933); Col. Vol. II, 114.
(159) Fieser, Experiments in Organic Chemistry, p. 410, D. C. Heath and Co., (1941).
* Xanthates of tertiary alcohols are unstable and may decompose to yield an unsaturated hydrocarbon. It is apparent in this case that the tertiary alcohol in the glycol did not react. See H. Myer, Analyse u. Konstitutionsermittlung, p. 296, Julius Springer, (1931).
(160) Shupe, J. Assoc. Official Agri. Chem., 25, 485 (1942).
(161) Whitmore and Lieber, Ind. Eng. Chem., Anal. Ed., 7, 127 (1935).

4,5-Di-isopropyl-4-methyl-1,3-dioxolane (Formal of 2,3,5-Trimethyl-3,4-hexandiol (FA-111).- Twelve grams (0.075 mole) of 2,3,5-trimethyl-3,4-hexandiol, 27 ml. (ca. 0.22 mole) of aqueous 40% formaldehyde, and 1 ml. syrupy phosphoric acid were heated on a steam bath for four hours. The mixture was then treated as indicated in the general method (II); yield 11.0 g. (85%); b.p. 82° (20 mm.).

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70
Found: C, 69.70; H, 11.77

2,4,5-Tri-isopropyl-4-methyl-1,3-dioxolane (Isobutyral of 2,3,5-Trimethyl-3,4-hexandiol) (FA-112).- Twenty-five grams (0.156 mole) of 2,3,5-trimethyl-3,4-hexandiol, 15.1 g. (0.21 mole) of isobutyraldehyde and 1 ml. syrupy phosphoric acid are allowed to remain for three days at room temperature in a stoppered flask. An aqueous layer separated which measured 4.3 ml. Corrected for the added phosphoric acid the volume was 3.3 ml. Theoretical volume for 100% reaction: 2.80 ml.

The reaction mixture was treated as indicated in the general method (I); yield 30.5 g. (91%); b.p. 105° (23 mm.).

Anal. Calcd. for $C_{13}H_{26}O_2$: C, 72.85; H, 12.22.
Found: C, 73.12; H, 12.18

2-Isopropyl-4-methoxymethyl-1,3-dioxolane (Isobutyral of Glycerol-alpha-monomethyl Ether (FA-113).- Twenty-four

grams (0.226 mole) of glycerol-alpha-monomethyl ether[162], 19.5 g. (0.27 mole) of isobutyraldehyde and 2 ml. of phosphoric acid were mixed in a stoppered flask. The reaction was mildly exothermal and the solution became turbid within five minutes due to the separation of water. After the reaction mixture had remained at room temperature for three days, the separated water measured 4.1 ml. (corrected for added phosphoric acid). Theoretical volume: 4.0 ml.

The mixture was treated as indicated in the general method (I). After it was fractionated twice, the product weighed 20 g. (55%); b.p. 181-183° (745 mm.); 67° (11 mm.). It possessed a pleasant fruity odor.

Anal. Calcd. for $C_8H_{16}O_3$: C, 59.97; H, 10.07
Found: C, 59.85; H, 10.20

4-Chloromethyl-1,3-dioxolane (Formal of Glycerol-alpha-monochlorohydrin (FA-114).- This compound has been prepared by several investigators, but several boiling points have been indicated. Verley[163] gave a boiling point of 126° (750 mm.). Henry[164] gave the value 150°.

We repeated the work of Verley as follows: 55.3 g. (0.50 mole) glycerol-alpha-monochlorohydrin[165], 100 g. aqueous 40% formaldehyde (ca. 1.33 moles) and 50 g. of syrupy phosphoric

(162) Grün and Bockish, Ber., 41, 3471 (1908).
(163) Verley, Bull. soc. chim., (3) 21, 276 (1899).
(164) Henry, Bull. soc. chim., (3) 13, 384 (1895).
(165) Conant and Quale, Organic Syntheses, Col. vol. I, p. 294 (2nd ed.).

acid were mixed and distilled. The distillate (b.p. 96-97°) was an azotrope composed of one volume of the desired product and two volumes of water. The lower, insoluble, organic layer in the distillate weighed 47.5 g. It was washed with water, dried over Drierite, and redistilled; yield 40 g. (65.3%); b.p. 146-147° (745 mm.).

2-Isopropyl-4-phenoxymethyl-1,3-dioxolane (Isobutyral of alpha-Glyceryl Phenyl Ether) (FA-115).- A mixture of 16.8 g. (0.10 mole) of alpha-glyceryl phenyl ether[166], 10.8 g. (0.15 mole) isobutyraldehyde and 2 ml. phosphoric acid was allowed to remain at room temperature six days. The separated water layer, after correcting for the added phosphoric acid, measured 1.1 ml. Theoretical volume: 1.8 ml. The reaction mixture was treated as indicated in the general method (I); yield 17.5 g. (78.7%); b.p. 167-169° (19 mm.); 106-106.5° (2 mm.). The product had a mild floral odor.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16
Found: C, 69.86; H, 8.04

4-Diethylaminomethyl-1,3-dioxolane (FA-116).- This compound has been prepared by Fourneau and Chantalou[113]. It was prepared by us as follows: 25 g. (0.2 mole) of 4-chloromethyl-1,3-dioxolane, 73 g. (1.0 mole) diethylamine, and 30 g. (.2 mole)

(166) Wheeler and Willson, Organic Syntheses, Col. vol. I, p. 296.

sodium iodide* were heated in a citrate bottle on a steam-bath for three days. A dark brown oil continued to separate until it composed one-third the total volume. The mixture was poured into 250 ml. of cold aqueous 10% sodium hydroxide. The upper brown layer, composed of the desired product and excess diethyl amine, was separated and distilled at reduced pressure to obtain two distinct fractions.

Fraction I (b.p. 24-29°, 45-33 mm.). which composed the major amount of material, was diethyl amine.

Fraction II (b.p. 25-31°, 18 mm.) (wt. 45.5 g.) was an azotrope of the desired amino dioxolane and water. It boiled at 98.5° (742 mm.). The amine was obtained by saturating the solution with potassium carbonate. The organic layer which separated was dried over potassium carbonate and distilled; yield 6 g. (18.8%); b.p. 190-192 (748 mm.).

4-Methylene-1,3-dioxolane (Formal of Propene-2,3-diol) (FA-117).- A mixture of 60 g. (0.49 mole) of 4-chloromethyl-1,3-dioxolane and 112 g. (2.0 mole) of potassium hydroxide pellets was heated to reflux for four hours. Dry ether was added to the cool mixture and the ether solution of the product was filtered from the salt and excess alkali. After removal

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* The improved yields resulting from the temporary exchange of chlorine for the more reactive iodine in the preparation of amines and nitriles has been studied by A. Wohl, Ber., 39, (1906).

of the ether, the product was fractionated; yield 22.2 g. (52.7%); b.p. 89° (723 mm.).

Fischer et al.[167] obtained this product by a similar procedure. They reported a boiling point of 93-95° (758 mm.).

2-Isopropyl-4-chloromethyl-1,3-dioxolane (Isobutyral of Glycerol-alpha-monochlorohydrin) (FA-118).- A mixture of 111.0 g. (1.0 mole) of glycerol-alpha-monochlorohydrin, 87.0 g. (1.2 mole) of isobutyraldehyde and 5 ml. syrupy phosphoric acid was warmed for four hours on a steam-bath. The mixture was treated as indicated in the standard method (I). The water layer which formed (corrected for added phosphoric acid) measured 18.0 ml.; theoretical volume: 18.0 ml.; yield of product 132.2 g. (80.4%); b.p. 74-75° (17 mm.); n_D^{20} 1.4424.

Anal. Calcd. for $C_7H_{13}O_2Cl$: Cl, 21.54

Found: Cl, 21.67

Epibromohydrin.- Epibromohydrin was prepared by treatment of alpha, beta-dibromohydrin with aqueous calcium hydroxide. The procedure followed is exactly that described in Organic Syntheses[168] except that for alpha, gamma-dibromohydrin we substituted the more easily available alpha, beta-dibromohydrin[169] prepared from allyl alcohol and bromine.

(167) H.O.L. Fischer, Baer, Feldman, Ber., 63, 1732 (1930).
(168) Geza Braun, Organic Syntheses, Col. Vol. II, p. 256
(169) Biilmann, Monatsh., 61, 216 (1900).

The yield of epibromohydrin from either initial material is the same, 84-89%; b.p. 134-136° (750 mm.); 61-62° (50 mm.); n_D^{25} 1.4795.

2,2-Diphenyl-4-bromomethyl-1,3-dioxolane.- Fifty grams (0.275 mole) of benzophenone, 45.0 g. (0.328 mole) of epibromohydrin, and 250 ml. of dry carbon tetrachloride were placed in a 500 ml., three-necked flask fitted with a stirrer, dropping funnel and thermometer. The flask was surrounded by an ice-water bath. When the temperature of the flask contents had reached 5°, a solution of 10 g. (0.038 mole) of stannic chloride in 75 ml. of dry carbon tetrachloride (protected from atmospheric moisture) was added, dropwise, over a three hour period. Throughout this period the temperature was maintained at 3-6°. The solution became light yellow within the first hour, and turned orange-red shortly thereafter. A cold solution of 16 g. of sodium hydroxide in 40 ml. of water was added in one portion, and stirring was continued for five to ten minutes. The organic layer was separated, dried over anhydrous sodium carbonate, the solvent removed by distillation under reduced pressure, and the residue cooled in an ice-salt mixture. It was rubbed until it crystallized completely. The product was triturated with 50 ml. portions of dry isopropyl alcohol and then filtered; yield 57.9 g. From the mother liquors an additional 6.3 g. of product was obtained; total yield 64.3 g. (73%); m.p. 71-73°.

Anal. Calcd. for $C_{16}H_{15}O_2Br$: Br, 25.04

Found: Br, 25.09

This compound was also prepared by displacing the methoxyl groups of the acyclic acetal, dimethoxydiphenyl methane, with glycerol-alpha-monobromohydrin.

Seven grams (0.031 mole) of dimethoxydiphenylmethane[170] and 4.8 g. (0.031 mole) of glycerol-alpha-monobromohydrin[171] were placed in a small distillation flask and heated in an oil-bath at 140-180°. The methanol which distilled weighed 1.7 g.; the calculated amount is 1.98 g. The residue was cooled, and suspended in a very small amount of dry isopropyl alcohol; yield 8.1 g. (82.7%); m.p. 71-73°. The mixed melting point, with product obtained by the first method, was undepressed.

2,2-Diphenyl-4-dimethylaminomethyl-1,3-dioxolane (FA-120).- Thirty grams (0.094 mole) of 2,2-diphenyl-4-bromomethyl-1,3-dioxolane, 50 ml. benzene, and 20 g. (0.445 mole) of anhydrous dimethylamine were heated to 60° in a citrate bottle for forty-eight hours. The material was treated in the same manner as that described previously; yield 24.3 g. (91.4%); b.p. 121-123° (.01 mm.); n_D^{20} 1.5531.

Anal. Calcd. for $C_{18}H_{21}NO_2$: N, 4.94
Found: N, 4.88

2,2-Diphenyl-4-dimethylaminomethyl-1,3-dioxolane Hydrochloride (FA-122).- Four grams (0.014 mole) of the dioxolane in 100 ml. of dry ether was treated with 8.90 ml. of 1.75 N ethereal hydrogen chloride. The oily precipitate crystallized in the refrigerator; yield 3.8 g. (84.5%); m.p. 189-191°. The product

(170) J. E. MacKenzie, J. Chem. Soc., 69, II, 987 (1896).
(171) Fourneau and Marques, Bull. soc. chim., (4) 39, 699 (1926).

was recrystallized from dry 99% ethyl acetate; m.p. 190-191°.

Anal. Calcd. for $C_{18}H_{22}ClNO_2$: Cl, 11.09

Found: Cl, 11.15

2,2-Diphenyl-4-dimethylaminomethyl-1,3-dioxolane Methiodide (FA-123).- Four grams (0.014 mole) of the free amine was dissolved in 100 ml. of dry ether and 20 g. (0.141 mole) of methyl iodide was added. After twenty-four hours at room temperature, the crystalline precipitate of crude product weighed 5.5 g. After two recrystallizations from a mixture of 65 ml. of ethanol and 35 ml. of ether, a yield of 4.2 g. (70%) of pure product was obtained; m.p. 193-195°.

Anal. Calcd. for $C_{19}H_{24}INO_2$: I, 29.84

Found: I, 29.55

2,2-Diphenyl-4-dimethylaminomethyl-1,3-dioxolane Methobromide (FA-129).- Ten grams (0.031 mole) of 2,2-diphenyl-4-bromomethyl-1,3-dioxolane, 10 g. (0.169 mole) trimethylamine, and 50 ml. of dry chloroform were heated in a citrate bottle for forty-eight hours on a steam-bath. After the solvent had been removed under reduced pressure, the residue weighed 16.7 g. It was triturated with 75 ml. of dry acetone, and then recrystallized from a mixture of 180 ml. isopropyl alcohol and 250 ml. of isopropyl ether; yield 6.5 g. (54.8%); m.p. 210-212° (dec.)*.

Anal. Calcd. for $C_{19}H_{24}BrNO_2$: Br, 21.12; N, 3.70.

Found: Br, 21.24; N, 3.72

* The melting point bath was preheated to 205°.

2,2-Diphenyl-4-diethylaminomethyl-1,3-dioxolane (FA-119).- Forty grams (0.125 mole) of 2,2-diphenyl-4-bromomethyl-1,3-dioxolane and 45.6 g. (0.625 mole) of diethylamine were heated in a citrate bottle on a steam-bath for twenty-six hours. Plate-like crystals of diethylamine hydrobromide precipitated. A solution of 10 g. sodium hydroxide in 50 ml. water was added. The mixture was extracted with ether, and the ether layer dried over solid potassium hydroxide. After removal of the solvent, the residue was fractionated through a three-inch Vigreaux column; yield 35.0 g. (90%); b.p. 129-132°(.01 mm.); n_D^{20} 1.5432.

Anal. Calcd. for $C_{20}H_{25}NO_2$: N, 4.50

Found: N, 4.44

2,2-Diphenyl-4-diethylaminomethyl-1,3-dioxolane Hydrochloride (FA-125).- Thirteen grams (0.042 mole) of the above dioxolane was dissolved in 225 ml. of dry ether. To the solution there was added 24.8 ml. of 1.85 N ethereal hydrogen chloride. The oily precipitate, which became crystalline after it had remained in a refrigerator for twelve hours, weighed 14.5 g. After two recrystallizations from dry ethyl acetate, the pure product weighed 9.0 g. (62%); m.p. 118-120°.

Anal. Calcd. for $C_{20}H_{26}ClNO_2$: Cl, 10.19

Found: Cl, 10.28

2,2-Diphenyl-4-di-n-propylaminomethyl-1,3-dioxolane.- Twenty-four grams (0.075 mole) of 2,2-diphenyl-4-bromomethyl-1,3-dioxolane,

25 g. (0.247 mole) of di-n-propylamine, and 30 ml. of dry benzene were placed in a citrate bottle and heated on a steam-bath for twenty-four hours. The product was obtained in the usual manner; yield 20.3 g. (79.6%); b.p. 172-176° (0.02 mm.).

2,2-Diphenyl-4-di-n-propylaminomethyl-1,3-dioxolane Hydrochloride (FA-131).- A solution of 10.3 g. (0.030 mole) of the above dioxolane in 200 ml. of ether was treated with 17.0 ml. of 1.84 N ethereal hydrogen chloride. After it had remained in a refrigerator for twelve hours, the product became crystalline; weight 10.5 g. When it was recrystallized from 200 ml. dry ethyl acerate 9.6 g. (84%) of pure product was obtained; m.p. 146-147°.

Anal. Calcd. for $C_{22}H_{30}ClNO_2$: Cl, 9.43; N, 3.72
Found: Cl, 9.31; N, 3.73

2,2-Diphenyl-4-di-n-butylaminomethyl-1,3-dioxolane.- Twenty grams (0.063 mole) of 2,2-diphenyl-4-bromomethyl-1,3-dioxolane, 81 g. (0.63 mole) of di-n-butylamine, and 50 ml. benzene were heated in a citrate bottle on a steam-bath for twenty-eight hours. The reaction mixture was treated in the usual manner; yield 19.7 g. (85.6%); b.p. 193-195° (.01 mm.).

Anal. Calcd. for $C_{24}H_{33}NO_2$: N, 3.81
Found: N, 3.81

2,2-Diphenyl-4-di-n-butylaminomethyl-1,3-dioxolane Hydrobromide (FA-134).- A solution of 5.66 g. (0.0154 mole) of the above dioxolane in 200 ml. dry ether was treated with 5.37 ml. of 2.83 N alcoholic hydrogen bromide. The crystals, which separated after the solution remained in a refrigerator for twelve hours, weighed 5.1 g. (73.8%); m.p. 101-103°.

Anal. Calcd. for $C_{24}H_{34}BrNO_2$: Br, 17.82
Found: Br, 17.91

2,2-Diphenyl-4-isopropylaminomethyl-1,3-dioxolane Hydrochloride (FA-127).- Thirty grams (0.094 mole) of 2,2-diphenyl-4-bromomethyl-1,3-dioxolane and 83 g. (1.40 moles) of isopropylamine were heated in a citrate bottle on a steam-bath for twenty-four hours. The product was obtained in the usual manner; yield, 25.18 g. (90%); b.p. 134-138° (.01 mm.).

A solution of 14.5 g. (0.049 mole) of the aminodioxolane in 400 ml. of ether was treated with 30 ml. of 1.80 N ethereal hydrogen chloride. The isolated hydrochloride weighed 14.0 g. (86%); m.p. 195-197°; recrystallized from acetone, m.p. 201-203°.

Anal. Calcd. for $C_{19}H_{24}ClNO_2$: Cl, 10.62; N, 4.19
Found: Cl, 10.80; N, 4.11

2,2-Diphenyl-4-piperidinomethyl-1,3-dioxolane.- Thirty grams (0.094 mole) of 2,2-diphenyl-4-bromomethyl-1,3-dioxolane and 37.8 g. (0.445 mole) of piperidine were heated in a citrate

bottle for twenty-four hours at 80°. The product was obtained in the usual manner; yield 28.7 g. (94.3%); b.p. 154-156° (.01 mm.).

Anal. Calcd. for $C_{21}H_{25}NO_2$: N, 4.33
Found: N, 4.10

2,2-Diphenyl-4-piperidinomethyl-1,3-dioxolane Hydrochloride (FA-121).- A solution of 4.7 g. (0.0145 mole) of the above amine in 100 ml. of dry ether was treated with 8.3 ml. of 1.75 N ethereal hydrogen chloride. The oily precipitate crystallized after remaining in a refrigerator for twelve hours; yield, 4.7 g. (90%); m.p. 202-204°; recrystallized from ethyl acetate; m.p. 203-204.5°.

Anal. Calcd. for $C_{21}H_{26}ClNO_2$: Cl, 9.85
Found: Cl, 9.77

2,2-Diphenyl-4-piperidinomethyl-1,3-dioxolane Methiodide (FA-124).- Twenty-two grams (0.155 mole) of methyl iodide was added to a solution of 5.0 g. (0.0155 mole) of the above dioxolane in 100 ml. ether. The mixture was allowed to remain at room temperature for twenty-four hours. The precipitate was recrystallized from a mixture of 150 ml. acetone and 150 ml. ether; yield 5.1 g. (70.7%); m.p. 157-159°.

Anal. Calcd. for $C_{22}H_{28}INO_2$: I, 27.27
Found: I, 27.49

2,2-Diphenyl-4-morpholinomethyl-1,3-dioxolane.- Seventeen grams (0.052 mole) of 2,2-diphenyl-4-bromomethyl-1,3-dioxolane,

38.0 g. (0.436 mole) of morpholine and 25 ml. benzene were heated in a citrate bottle for twenty-four hours on a steam-bath. The reaction mixture was treated in the usual manner. The product was a solid amine which weighed 17.5 g. After recrystallization from 75 ml. dry methanol, the pure product weighed 14.4 g. (84.6%); m.p. 92-93°. It may also be recrystallized from isopropanol or ethyl acetate.

Anal. Calcd. for $C_{20}H_{23}NO_3$: N, 4.30
Found: N, 4.20

2,2-Diphenyl-4-morpholinomethyl-1,3-dioxolane Hydrochloride (FA-126).- A solution of 7.0 g. (0.0215 mole) of the above dioxolane in 150 ml. of dry ether was treated with 13.0 ml. of 1.80 N ethereal hydrogen chloride. The crude precipitate weighed 7.6 g. After recrystallization from 250 ml. dry acetone, the pure weighed 5.85 g. (75.1%); m.p. 192-193°.

Anal. Calcd. for $C_{20}H_{24}ClNO_3$: Cl, 9.81; N, 3.87
Found: Cl, 9.83; N, 3.84

2-Phenyl-2-thienyl-4-bromomethyl-1,3-dioxolane.- 2-Benzoyl thiophene* (52.6 g.(0.280 mole)) and 44.5 g. (0.324 mole) of epibromohydrin were dissolved in 100 ml. of dry carbon tetrachloride. To the stirred solution maintained at 4-6° there was added, dropwise, over a four hour period, a solution of 10 g. (0.038 mole) of stannic chloride in 100 ml. carbon tetrachloride. A cold solution of 16 g. sodium hydroxide in 100 ml. water was added in one portion with vigorous stirring. The organic layer was

* Obtained from Socony Vacuum Oil Company

separated, dried over potassium carbonate, filtered, and the solvent removed at reduced pressure. The residue weighed 94 g. Because the molecule contained two unlike asymmetric carbon atoms, the product may have been a mixture of diastereoisomers. It could be distilled without decomposition. From 22 g. of the above residue 18 g. distillate was obtained; b.p. 127-130° (.01 mm.).

Anal. Calcd. for $C_{14}H_{13}BrO_2S$: Br, 24.57
Found: Br, 24.48

Until further evidence has been obtained to the contrary, we have decided to consider the oily and crystalline products described in the following experiments as isomeric racemates.

Separation of Diastereoisomeric Pairs of 2-Phenyl-2-thienyl-4-bromomethyl-1,3-dioxolane.- The mixture of diastereoisomers in the crude reaction product was separated by two different methods.

Procedure A.- Forty-eight grams of the mixture was covered with 20 ml. of dry methanol and allowed to stand in a refrigerator for one week. The crystals which formed were filtered by the use of a fritted-glass funnel surrounded by ice; yield 14 g. (29.2%); m.p. 42-48°. This product is hereafter referred to as the crystalline bromo racemate.

The methanol in the above filtrate was removed by distillation under pressure, and the residue fractionated; yield 11.7 g.;

b.p. 153-155° (.02 mm.). This product could not be obtained solid and is accordingly hereafter referred to as the oily bromo racemate. It is probably not a pure racemate but represents a concentrate of one racemic pair.

Procedure B.- Sixteen grams of the unseparated diastereoisomers (b.p. 127-130° (.01 mm.)) were seeded and allowed to remain in a refrigerator for ten days. The oily crystalline mixture was spread in a thin layer over pieces of unglazed porcelain plate, and allowed to remain in a desiccator for ten days. After the oily material had been absorbed by the plate, the crystals were removed; yield 5.5 g. (34.4%); m.p. 42-46°.

Fourteen grams of the crystals from Procedure A and 5.5 g. of the crystals from Procedure B were combined, triturated with 20 ml. methanol and allowed to remain in a refrigerator twenty-four hours. The crystals then weighed 15.5 g. (79.5% recovery); m.p. 49-51°.

Anal. Calcd. for $C_{14}H_{13}BrO_2S$: Br, 24.57; S, 9.86

Found: Br, 24.53; S, 9.63

Amination of the Crystalline Bromo-racemate (FA-132).- The above crystalline bromodioxolane (15.5 g. (0.048 mole)) and 27 g. (0.37 mole) of diethylamine were heated in a citrate bottle for forty-eight hours at 80°. A solution of 10 g. sodium hydroxide in 50 ml. water was added; the amine was extracted with ether, and the extract dried over solid potassium hydroxide. The residue

was distilled, after removal of the solvent, under reduced pressure; yield 9.2 g. (60.8%); b.p. 142-145° (.01 mm.).

Anal. Calcd. for $C_{18}H_{23}NO_2S$: N, 4.41
Found: N, 4.41

Amination of the Unseparated Bromo-racemate (FA-128).- Twenty grams (ca. 0.061 mole) of the crude, unseparated bromo diastereoisomers and 45 g. (0.62 mole) of diethylamine were heated in a citrate bottle for seventy-two hours at 80°. The product was obtained in the same manner as the previous amine; yield 14.8 g. (ca. 76%); b.p. 130-141° (.01 mm.).

Anal. Calcd. for $C_{18}H_{23}NO_2S$: N, 4.41; S, 10.10
Found: N, 4.25; S, 9.82

Amination of the Oily Bromo-racemate (FA-130).- The oily bromo-diastereoisomers (11.7 g. (0.036 mole)) obtained by separation procedure A and 26.3 g. (0.36 mole) diethylamine were heated in a citrate bottle for forty-eight hours at 80°. The product was obtained in the same manner as the previous amine; yield 10 g. (87.5%); b.p. 135-139° (.01 mm.).

Anal. Calcd. for $C_{18}H_{23}NO_2S$: N, 4.41; S, 10.10
Found: N, 4.24; S, 10.24

Dithienyl Ketone.- This compound has been made in small yield by reacting phosgene and thiophene in the presence of aluminum chloride[172], and by reaction of cyanogen chloride

(172) Gatterman, Ber., 18, 3013 (1885).

with alpha-thienylmagnesium bromide[173]. A 50% yield was obtained[174] by reacting alpha-thenoyl chloride with an excess of thiophene in the presence of aluminum chloride.

We have obtained the ketone in improved yield by the following procedure based on the preparation of 2-benzoyl thiophene[175]. In a one-liter, three-necked flask fitted with a stirrer, dropping funnel, and thermometer there were placed 100 g. (0.682 mole) of alpha-thenoyl chloride[176], 63 g. (0.75 mole) of thiophene, and 600 ml. of dry benzene. The solution was cooled to 0°, and 160 g. (0.615 mole) of stannic chloride was added, dropwise, with stirring over a two hour period. The temperature of the reaction mixture was maintained at 3-6°. The solution, bright yellow initially, became increasingly turbid and a suspension of dense orange-yellow crystals was formed. With stirring and cooling the reaction was allowed to continue for two additional hours. The reaction mixture was warmed to 60°, and this temperature was maintained for one half-hour. A solution of 25 ml. concentrated hydrochloric acid and 200 ml. water was then added, dropwise. The benzene layer was separated, extracted twice with 125 ml. of 12% sodium hydroxide solution, washed with water and dried over magnesium sulfate. After removal of the solvent at reduced pressure, the nearly pure ketone weighed 112.5 g. It was recrystallized from 300 ml. ethanol.

(173) Thomas and Couderc, Bull. soc. chim., (4) 23, 290 (1918).
(174) Steinkopf and Hempel, Ann., 495, 162 (1932).
(175) Stadnikoff and Goldfarb, Ber., 61, 2341 (1928).
(176) Jones and Hurd, J. Am. Chem. Soc., 43, 2444 (1921).

The first crop of characteristic needle-like crystals weighed 75.5 g. From the mother liquors an additional 26.5 g. was obtained; total yield 102 g. (77%); m.p. 87-89°.

2,2-Di(alpha-thienyl)-4-bromomethyl-1,3-dioxolane.- A solution of 20 g. (0.103 mole) of dithienyl ketone in 100 ml. of warm benzene was poured into a 500 ml., three-necked flask, fitted with a stirrer, two dropping funnels and thermometer, which contained 200 ml. of dry carbon tetrachloride. The solution was then cooled to 3°; and a solution of 3.6 g. (0.014 mole) of stannic chloride in 50 ml. of carbon tetrachloride was added dropwise; simultaneously, a solution of 17 g. (0.124 mole) of epibromohydrin in 50 ml. of carbon tetrachloride was added, dropwise. The addition of both solutions was regulated at such a rate so that the addition of both solutions required ten hours. During this interval the temperature was maintained at 3-5°. A cold solution of 10 g. sodium hydroxide in 40 ml. of water was then added with vigorous stirring. The organic layer was separated, dried over potassium carbonate, and distilled under reduced pressure to remove the solvent. The brown residue weighed 30.0 g. (88% theoretical weight). It decomposed on attempted distillation at 0.01 mm. pressure, and it could not be obtained crystalline; therefore it was aminated directly.

2,2-Di-(alpha-thienyl)-4-diethylaminomethyl-1,3-dioxolane Oxalate (FA-136).- Thirty grams (ca. .09 mole) of impure 2,2-dithienyl-4-bromomethyl-1,3-dioxolane, 75 g. (1.02 moles)

of diethylamine, and 80 ml. of benzene were heated in a citrate bottle at 65° for forty-eight hours. The crystalline plates of diethylamine hydrobromide which formed weighed 10.67 g. (0.069 mole); m.p. 210-213°. This corresponds to 76% amination. Further heating of the filtrate did not cause additional precipitation. The filtrate was treated with a solution of 8 g. sodium hydroxide in 50 ml. of water, and the product was extracted with benzene. After the extract had been dried over anhydrous potassium carbonate, the solvent and excess diethylamine were removed under reduced pressure. The residue of crude, free amine was not distilled since previous efforts showed it decomposed at 185-190° (.01 mm.). The crude amine was dissolved in 600 ml. of dry ether and precipitated as the oxalate by treatment with a solution of 6.3 g. (0.07 mole) of anhydrous oxalic acid in 150 ml. of ether. The light tan product weighed 24.0 g. (64.5%). After it was recrystallized twice from 75 ml. n-butanol (Norite), washed with acetone, and dried in vacuo, the product weighed 10.3 g. (27.7%); m.p. 146-148°.

Anal. Calcd. for $C_{16}H_{21}NO_2S_2 \cdot C_2H_2O_4$: N, 3.39; S, 15.51

Found: N, 3.47; S, 15.20

2,2-Di-(alpha-thienyl)-4-diethylaminomethyl-1,3-dioxolane Hydrochloride (FA-137).- The above amine oxalate (3.94 g. (0.0095 mole)) was treated with a solution of 2 g. sodium hydroxide in 200 ml. of water. The free amine was

extracted with four 75 ml. portions of benzene and the benzene removed by distillation under reduced pressure. The amine residue was dissolved in 300 ml. of dry ether and treated with 5.3 ml. of 1.80 N ethereal hydrogen chloride. After it had been recrystallized from a mixture of 13 ml. n-butanol and 15 ml. isopropyl ether, the product weighed 1.95 g. (56.8%); m.p. 124-126°.

Anal. Calcd. for $C_{16}H_{22}ClNO_2S_2$: Cl, 9.85; N, 3.89; S, 17.82
Found: Cl, 9.81; N, 3.89; S, 17.51

2,2-Di-(para-methoxyphenyl)-4-bromomethyl-1,3-dioxolane.- Forty grams (0.165 mole) of p,p'-dimethoxybenzophenone(177) and 26.2 g. (0.191 mole) of epibromohydrin were dissolved in a mixture of 100 ml. carbon tetrachloride and 150 ml. chloroform. A solution of 6.0 g. (0.023 mole) stannic chloride in 75 ml. of chloroform was added, dropwise, with stirring over a four hour period. The temperature of the reaction mixture was maintained at 2-5° during this interval. A solution of 15 g. sodium hydroxide in 70 ml. of water was added to decompose the catalyst, and to render the solution alkaline. The organic layer was separated, dried over anhydrous potassium carbonate, and the solvent removed under reduced pressure. The residue weighed 66.5 g. This product could not be obtained crystalline, and it decomposes on attempted distillation at 0.01 mm. pressure. It was therefore aminated directly as indicated below.

(177) Schnackenberg and Scholl, Ber., 36, 654 (1903).

2,2-Di-(para-methoxyphenyl)-4-diethylaminomethyl-1,3-dioxolane (FA-133).- A mixture of 15.8 g. (0.041 mole) of the above dioxolane and 25 g. (0.334 mole) of diethylamine was heated in a citrate bottle at 100° for eight hours. The reaction mixture was treated in the usual manner; yield, 14.6 g. (96%); b.p. 175-180° (.01 mm.).

Anal. Calcd. for $C_{22}H_{29}NO_4$: N, 3.77
Found: N, 3.85

2,2-Di-(para-methoxyphenyl)-4-diethylaminomethyl-1,3-dioxolane Oxalate (FA-138)*.- Two grams (0.0054 mole) of the above dioxolane was dissolved in 250 ml. of dry ether and treated with a solution of 0.485 g. (0.0054 mole) of anhydrous oxalic acid in 50 ml. of dry ether. The voluminous precipitate which formed immediately weighed 2.48 g. (100%); m.p. 116-118°. After it had been recrystallized from a mixture of 40 ml. of n-butanol and 20 ml. isopropyl ether, the product weighed 2.05 g. (81%); m.p. 118-120°.

Anal. Calcd. for $C_{22}H_{29}NO_2 \cdot C_2H_2O_4$: N, 3.04
Found: N, 3.08

Structure Proof of 2,2-Di(para-methoxyphenyl)-4-diethylaminomethyl-1,3-dioxolane.

A. Isolation of p,p'-dimethoxybenzophenone.- The purified oxalate of the above aminodioxolane (13.85 g. (0.030 mole))

* The hydrochloride and hydrobromide were hydroscopic

was added to a solution of 20 ml. of concentrated hydrochloric acid in 100 ml. water. The mixture was heated on a steam-bath for three hours, and then extracted several times with benzene. The aqueous acid layer which contained the aminoglycol fragment was set aside for later examination. The combined benzene extracts were washed with aqueous 5% sodium hydroxide to remove the oxalic acid. After the benzene was removed, the residue of ketone weighed 6.9 g. (95% recovery); m.p. 141-144°. After recrystallization from ethanol, it weighed 6.0 g. (82.5% recovery); m.p. 143-144°. A mixed melting point with the known pure ketone showed no depression.

B. Isolation of 1-diethylamino-2,3-propandiol.- The aqueous acid layer from above experiment was rendered alkaline by addition of a 50% solution of sodium hydroxide. The solution was extracted twelve times with 75 ml. portions of ether and five times with 50 ml. portions of chloroform. After the extracts had been combined and the solvent removed, the residue was fractionated under reduced pressure; yield 3.26 g. (74%)*; b.p. 120-122 (15 mm.).

Derivatives were made of this product following the procedures given in the next section. From 1.00 g. (0.0068 mole) of this distillate there was obtained 2.49 g. (97%) of the potassium dixanthate with a melting point and an iodine titre corresponding exactly to the reference compound, (see next section).

* The unfavorable coefficient of distribution of the aminoglycol between water and the organic solvent could account for the incomplete isolation of the product. When 4.42 g. (0.03 mole) of pure 1-diethylamino-2,3-propandiol was extracted from 100 ml. of water in an identical manner, only 3.10 g. (70%) of the compound was recovered.

The hydrochloride of the monophenylurethane melted at 133-135° and showed no depression when mixed with the pure reference compound.

Finally the oxalate prepared from the isolated amine-diol melted at 105-107° and showed no depression when mixed with the reference oxalate.

Reference Compounds

A. 1-Diethylamino-2,3-propandiol.- This compound was prepared from 55.2 g. (0.50 mole) of glycerol-alpha-monochlorohydrin and 105 g. (1.43 moles) of diethylamine according to the method of Roth[178]; yield 52.6 g. (71.5%); b.p. 131-132° (21 mm.).

B. Monophenylurethane of 1-Diethylamino-2,3-propandiol Hydrochloride.- 1-Diethylamino-2,3-propandiol (2.10 g. (0.014 mole)) and 1.70 g. (0.014 mole) of phenyl isocyanate, in 150 ml. of dry ether, were refluxed for three hours. The solution was cooled, and treated with 8.0 ml. of 1.80 N ethereal hydrogen chloride. After the precipitate had been recrystallized twice from dry acetone, it weighed 1.8 g. (47%); m.p. 133-135°. Rider[179] reported the melting point as 135°.

C. Dixanthate of 1-Diethylamino-2,3-propandiol.- 1-Diethylamino-2,3-propandiol (0.86 g. (0.0058 mole)), 5 ml. (ca. 0.08 mole) of carbon disulfide and 5 ml. of acetone were added to a solution of 20 g. potassium hydroxide in 15 ml. water. The

(178) Roth, Ber., 15, 1153 (1882).
(179) Rider, J. Am. Chem. Soc., 52, 2116 (1930).

mixture was allowed to remain at room temperature for twelve hours. The organic layer was then separated and filtered. Ether was added to precipitate the potassium xanthate; yield, 2.15 g. (98%). After recrystallization from a mixture of 20 ml. ethanol and 75 ml. ether, the product weighed 1.99 g. (91%); m.p. 150-153° (dec.)*.

Anal. Calcd. for $C_9H_{15}O_2NS_4K_2$: N, 3.73

Found: N, 3.70

Iodometric titration**: Calcd. Equivalent wt. 187.84

Found: 161.7

D. Oxalate of 1-Diethylamino-2,3-propandiol.- A solution of 0.72 g. (0.008 moles) of anhydrous oxalic acid in 75 ml. ether was added to 1.18 g. (0.008 mole) of 1-diethylamino-2,3-propandiol dissolved in 100 ml. of dry ether. The initial oily precipitate became crystalline after it had remained in a refrigerator for ten days. The hydroscopic crystals became non-hydroscopic after they had been triturated twice with 10 ml. portions isopropyl alcohol; yield 0.40 g. (25%); m.p. 105.5-107.5°.

Anal. Calcd. for $2C_7H_{17}NO_2 \cdot H_2C_2O_4$: N, 7.29

Found: N, 7.10

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* The melting point bath was preheated to 143°.

** The end-point fades rapidly and is ascribable to the reaction of free iodine with the diethylamino group. A competitive reaction which consumes iodine would explain the low value for the equivalent weight as well as the fleeting end-point. A similar result has been observed in the iodometric titration of the trixanthate of triethanol amine by Shupe (Assoc. Offic. Agric. Chem., 25, 495 (1942)).

Isolation of a Polymeric Impurity.- 2,2-Di-(para-Methoxyphenyl)-4-diethylaminomethyl-1,3-dioxolane (8.33 g. (0.022 mole)) (b.p. 175-180° (.01 mm.)) was treated with aqueous hydrochloric acid and the products of the ring fission were isolated as indicated previously. The ketone fragment weighed 4.86 g. (89.5% recovery). The amino-glycol fragment yielded two fractions when distilled. The first fraction was the pure compound, 1-diethylamino-2,3-propandiol; yield 1.99 g. (60%); b.p. 120-122° (15 mm.). The second fraction weighed 0.62 g.; b.p. 148-184 (2-3 mm.).

Calculated for the polymeric unit structure $C_7H_{15}NO$: N, 10.83

Found: N, 9.77

2-(Biphenylene)-4-bromomethyl-1,3-dioxolane.- Forty grams (0.222 mole) of fluorenone and 35 g. (0.255 mole) of epibromohydrin in 100 ml. dry carbon tetrachloride was treated, dropwise, with a solution of 8 g. (0.031 mole) of stannic chloride in 100 ml. of dry carbon tetrachloride during a four hour period. During this interval the reaction mixture was maintained at 4-6°. A cold solution of 14 g. sodium hydroxide in 100 ml. water was then added, in one portion, with vigorous stirring. The organic layer was separated, dried over potassium carbonate, filtered, and the solvent removed at reduced pressure. The oily residue weighed 67 g. It could not be obtained crystalline, and it decomposed during attempts to distill it at .01 mm. The compound was therefore aminated directly.

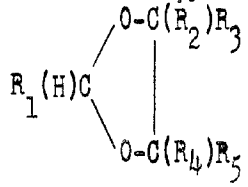
2-(Biphenylene)-4-diethylaminomethyl-1,3-dioxolane.- Fifty-one grams (ca. 0.161 moles) of the above impure bromodioxolane and 100 g. (1.37 moles) of diethylamine were heated in a citrate bottle for forty-eight hours at 80°. The mixture was rendered alkaline with a solution of 15 g. sodium hydroxide in 100 ml. of water. The amine was extracted with ether and the extract dried over solid potassium hydroxide. After removal of ether and excess diethylamine, the residue was twice distilled; yield 14.1 g. (28%); b.p. 163-168 (.01 mm.).

2-(Biphenylene)-4-diethylaminomethyl-1,3-dioxolane Hydrobromide.- The above dioxolane amine (5.25 g. (0.017 mole)) in 450 ml. of dry ether was treated with 5.85 ml. of 2.83 N alcoholic hydrogen bromide. The crystalline precipitate, which weighed 5.7 g., was a light tan color. After digesting it with 15 ml. of hot isopropyl alcohol, the nearly white residue weighed 2.0 g. It was then recrystallized from a mixture of 33 ml. n-butanol and 40 ml. isopropyl ether; yield 1.48 g. (22.3%); m.p. 191-193°.

Anal. Calcd. for $C_{20}H_{24}BrNO_2$: Br, 20.48; N, 3.59

Found: Br, 20.41; N, 3.58

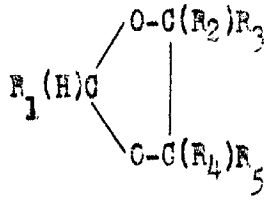
TABLE III. Substituted 1,3-Dioxolanes



CODE #	R_1	R_2	R_3	R_4	R_5	% Yield	B.p., °C.	Mm.	Formulas	Analyses, % Calcd. C	Calcd. H	Found C	Found H
FA-114	H	H	H	H	CH_2Cl	63	146-147 (a)	745	- - - -				
FA-117	H	H	H	H	$=CH_2$	52	89 (b)	723	- - - -				
FA-118	$CH(CH_3)_2$	H	H	H	CH_2Cl (c)	80	74-75	17	$C_7H_{13}ClO_2$				
FA-113	$CH(CH_3)_2$	H	H	H	CH_2OCH_3	55	181-183	745	$C_8H_{16}O_3$	59.97	10.07	59.85	10.20
FA-115	$CH(CH_3)_2$	H	H	H	$CH_2OC_6H_5$	78	167-169	19	$C_{13}H_{18}O_3$	70.24	8.16	69.86	8.04
FA-111	H	$CH(CH_3)_2$	CH_3	H	$CH(CH_3)_2$	85	82	20	$C_{10}H_{20}O_2$	69.72	11.70	69.70	11.77
FA-112	$CH(CH_3)_2$	$CH(CH_3)_2$	CH_3	H	$CH(CH_3)_2$	91	105	23	$C_{13}H_{26}O_2$	72.85	12.22	73.12	12.18
FA-100	H	CH_3	CH_3	CH_3	CH_3	76	124-125 (d)	745	- - - -				
FA-101	CH_3	CH_3	CH_3	CH_3	CH_3	98	133 (e)	745	- - - -				
FA-102	$CH(CH_3)_2$	CH_3	CH_3	CH_3	CH_3	95	57 (f)	15	- - - -				

(a) Henry, Bull. soc. chim., (3) 13, 384 (1895), reported 150°; German Pat. 271,381 (Chem Zentr., 85, I, 1316 (1914), b.p. 148°.
(b) Fischer et al., Ber., 63, 1732 (1930), reported 93-95° (758 mm.).
(c) Anal., Calcd. for $C_7H_{13}ClO_2$: Cl, 21.54. Found: Cl, 21.67.
(d) Delepine, Bull. soc. chim., (3) 25, 581 (1901), reported 124-125°.
(e) Hibbert and Hill, J. Am. Chem. Soc., 45, 3115 (1923), found 133-134°.
(f) Dworzak and Lasch, Monatsh., 51, 69 (1929), reported 59° (13 mm.).

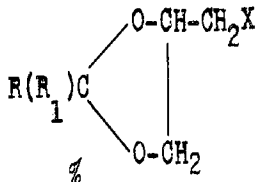
TABLE IV. Substituted 1,3-Dioxanes



CODE #	R_1	R_2	R_3	R_4	R_5	% Yield	B.p., °C.	Mm.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
FA-108	H	H	CH_3	CH_3	CH_3	71	139	743	$C_7H_{14}O_2$	64.58	10.84	64.68	10.65
FA-109	$CH(CH_3)_2$	H	CH_3	CH_3	CH_3	95	68	25	$C_{10}H_{20}O_2$	69.72	11.70	69.84	11.78
FA-103	H	CH_3	CH_3	CH_3	CH_3	80	52 152	18 733	$C_8H_{16}O_2$	66.62	11.19	66.51	10.82
FA-104	CH_3	CH_3	CH_3	CH_3	CH_3	83	48 148	14 740	$C_9H_{18}O_2$	68.32	11.46	68.13	11.40
FA-105	$CH(CH_3)_2$	CH_3	CH_3	CH_3	CH_3	80	67 (a)	17	$C_{11}H_{22}O_2$	70.92	11.90	70.97	11.70

(a) Dworsak and Lasch, Monatsh., 51, 69 (1929), reported 67-73 (21 mm.).

TABLE V . Basic 1,3-Dioxolanes



CODE #	No.	R	R	X	% Yield	B.p., °C.	Mm.	Formula	Nitrogen, % Calcd.	Found
FA-116	1	H	H	$N(C_2H_5)_2$	18	190-192	748 (a)	- - -	- -	- -
FA-120	2	C_6H_5	C_6H_5	$N(CH_3)_2$ (b)	91	121-123	0.01	$C_{18}H_{21}NO_2$	4.94	4.88
FA-119	3	C_6H_5	C_6H_5	$N(C_2H_5)_2$	90	129-132	0.01	$C_{20}H_{25}NO_2$	4.50	4.44
--	4	C_6H_5	C_6H_5	$N(C_3H_7)_2$	79	172-176	0.02	- - -	- -	- -
--	5	C_6H_5	C_6H_5	$N(C_4H_9)_2$	85	193-195	0.01	$C_{24}H_{33}NO_2$	3.81	3.81
--	6	C_6H_5	C_6H_5	$NHCH(CH_3)_2$	90	134-138	0.01	- - -	- -	- -
--	7	C_6H_5	C_6H_5	NC_5H_{10} (c,d)	94	154-156	0.01	$C_{21}H_{25}NO_2$	4.33	4.10
--	8	C_6H_5	C_6H_5	NC_4H_8O (e)	84	- - (f)	- -	$C_{20}H_{23}NO_3$	4.30	4.20
FA-128	9	C_6H_5	C_4H_3S (g)	$N(C_2H_5)_2$	76	130-147	0.01	$C_{18}H_{23}NO_2S$ (h)	4.41	4.25
--	10	C_4H_3S	C_4H_3S	$N(C_2H_5)_2$	27 (i)	- - -	- -	- - - -	- -	- -
FA-133	11	p-$CH_3OC_6H_4$	p-$CH_3OC_6H_4$	$N(C_2H_5)_2$	96	175-180	0.01	$C_{22}H_{29}NO_4$	3.77	3.85
--	12	Biphenylene		$N(C_2H_5)_2$	28	163-168	0.01	- - -	- -	- -

(a) Fourneau and Chantalou, Bull. soc. chim., (5) 12, 845 (1945) found 106° (60 mm.).
(b) Methiodide, m.p. 193-195° (from ethanol-ether). Anal. Calcd. for $C_{19}H_{24}INO_2$: I, 29.84. Found:I, 29.55. Methobromide, m.p. 210-212° (dec.) (from isopropyl alcohol-isopropyl ether. Anal. Calcd. for $C_{19}H_{24}BrNO_2$: Br, 21.12; N, 3.70. Found: Br, 21.24: N, 3.72. (c) Piperidino. (d) Methiodide, m.p. 157-159° (from acetone-ether). Anal. Calcd. for $C_{22}H_{28}INO_2$: I, 27.27. Found: I, 27.49.
(e) Morpholino. (f) M.p. 92-93° (from methanol). (g) 2-Thienyl. (h) Anal. Calcd. for $C_{18}H_{23}NO_2S$: S, 10.10. Found: S, 9.82. (i) This product was isolated and purified as the oxalate. The yield is based on the pure oxalate. The oxalate (from butanol) melted at 145-147°. Anal. Calcd. for $C_{16}H_{21}NO_2S_2C_2H_2O_4$:N, 3.39; S, 15.5 . Found: N,3.47: S, 15.20.

TABLE VI. Basic 1,3-Dioxolanes

Hydrochlorides and Hydrobromides

Code #	No*	M. p., °C.	Formulas	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
FA-122	2*	190-191 (a)	$C_{18}H_{22}ClNO_2$	11.09	11.15	- -	- -
FA-125	3	118-120	$C_{20}H_{26}ClNO_2$	10.19	10.28	- -	- -
FA-131	4	146-147	$C_{22}H_{30}ClNO_2$	9.43	9.31	3.72	3.73
FA-134	5	101-103	$C_{24}H_{34}BrNO_2$	17.82 (Br)	17.91	- -	- -
FA-127	6	201-203	$C_{19}H_{24}ClNO_2$	10.62	10.80	4.19	4.11
FA-121	7	203-204	$C_{21}H_{26}ClNO_2$	9.85	9.77	- -	- -
FA-126	8	192-193	$C_{20}H_{24}ClNO_3$	9.81	9.83	3.87	3.84
FA-137	10	124-126	$C_{16}H_{22}ClNO_2S_2$ (b)	9.85	9.81	3.89	3.89
FA-138	11	116-118	$C_{22}H_{29}NO_4.C_2H_2O_4$ (c)	- -	- -	3.04	3.08
FA-135	12	191-193	$C_{20}H_{24}BrNO_2$	20.48 (Br)	20.41	3.59	3.58

* These numbers refer to like-numbered compounds in Table V.
(a) In all instances the melting point bath was preheated to 5° below the melting point of the compound. Compounds 2,3,4 and 7 were recrystallized from ethyl acetate; compounds 6 and 8 from acetone; compounds 10, 11 and 12 from butanol-isopropyl ether.
(b) Anal. Calcd. for $C_{16}H_{22}ClNO_2S_2$: S, 17.82. Found: S, 17.51.
(c) Oxalate.

SUMMARY

The object of this investigation was the preparation of cyclic acetals and ketals - 1,3-dioxolanes and 1,3-dioxanes. Compounds of these types are very similar in structure to paraldehyde, and it was hoped that products might be obtained which would possess the excellent hypnotic properties of paraldehyde but lack its undesirable side effects.

Ten dioxolanes and five dioxanes were synthesized, and examined for hypnotic potency in another laboratory. It was found that most of the compounds were inactive as hypnotics, and that several of them which were active, like paraldehyde, produced a "bad breath".

Twelve dioxolanes which contained a basic substituent, such as a diethylaminomethyl group, were then prepared and tested pharmacologically. A typical example of this group, namely 2,2-diphenyl-4-diethylaminomethyl-1,3-dioxolane, was shown to be devoid of hypnotic properties, however, the important discovery was made that this compound, as well as other members of the series, exhibits antihistamine activity.

Practically all of the clinically important antihistamine agents known at the present time are basic acyclic, monoethers or derivatives of ethylenediamine. A further study of basic dioxolanes may show that these compounds are clinically-useful antihistamine drugs.

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