CONDENSATION PRODUCTS OF GLYCEROL WITH ALDEHYDES AND KETONES. 2-SUBSTITUTED *m*-DIOXAN-5-OLS AND 1,3-DIOXOLANE-4-METHANOLS

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I. INTRODUCTION

A. GENERAL

Until recently little systematic study had been made of the series of compounds which can be obtained by condensing glycerol with aldehydes and ketones, even though over 70 years has elapsed since the first experiments were carried out. Perhaps this was due to the successful use of the products obtained by condensing glycerol with either benzaldehyde or acetone in the synthesis of glycerides. Since for many years these compounds were regarded merely as very satisfactory intermediates in such syntheses, only a passing interest was shown in them. No other similar compounds among the few prepared proved any better; thus there was little point in preparing long series.

In addition to this, although it was recognized that certain derivatives could not be prepared, the stereochemical and conformational reasons for this were not at the time understood, so progress came to a temporary halt. With these difficulties overcome and with the development of physical-chemical methods of structural and conformational analysis, rapid advances were made.

The compounds under review are similar to, but simpler than, the carbohydrates and carbohydrate derivatives, so they were investigated in the initial work on the stereochemistry of the latter. At about the same time their value as drugs was recognized so that in recent years a large number of derivatives have been prepared and their physiological effects studied and evaluated. Other work has led to the introduction of related compounds into commercial fields.

This review deals with the original work of preparation and the newer methods and recent developments in connection with structure, conformation, and uses. It is restricted to those compounds derived from glycerol; no attempt is made to deal with the condensation products of the carbohydrates and carbohydrate derivatives.

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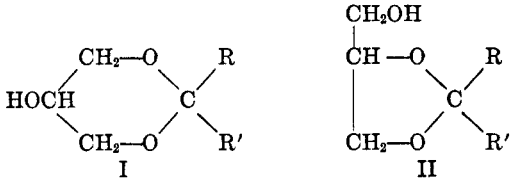
B. NOMENCLATURE

Nomenclature presents difficulties, since many names have been used for the same compounds. Thus I (R′ = H), obtained by condensing an aldehyde with glycerol, now referred to in *Chemical Abstracts* as 2-alkyl- (or aryl-) *m*-dioxan-5-ol (the name which will be used throughout this review), was known in the First to Fifth Decennial Indexes as 2-alkyl-5-*m*-dioxanol. A not infrequently used alternative is 2-alkyl-5-hydroxy-*m*-dioxan, and in many publications *m*- is replaced by 1,3- and/or dioxan replaced by dioxane. Early papers and some recent ones, especially if concerned with glyceride synthesis, often use the simpler term 1,3-alkylidene- (or arylidene-) glycerol.

The structural isomer II, obtained by the same reaction, is currently called 2-alkyl- (or aryl-) 1,3-dioxolane-4-methanol (and this name too is used throughout). Here the name differs from that used in the first three Decennial Indexes, which is 2-alkyl-1,3-dioxolane-4-carbinol, and the commonly employed 2-alkyl-4-hydroxymethyl-1,3-dioxolane. Here again there are minor variations, and dioxolan is frequently substituted for dioxolane, while as a derivative of glycerol it becomes 1,2-alkylideneglycerol.



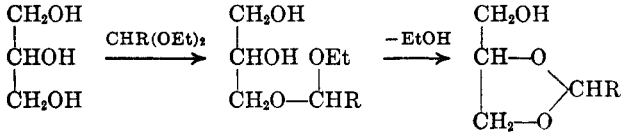
When ketones are condensed (R and R′ = alkyl and/or aryl) 2,2-disubstituted products are obtained, and the nomenclature is similar, but 1,2-acetoneglycerol is a very commonly used alternative to 1,2-isopropylideneglycerol.

II. CONDENSATION PRODUCTS OF GLYCEROL AND ALDEHYDES

A. PREPARATION

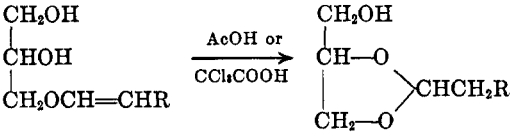
The reaction of formaldehyde and glycerol was first studied in 1893, and two isomers of the benzoates corresponding to the 1,2- and 1,3-condensation products (of glycerol) were isolated (104). When the work was repeated using benzaldehyde, however, only the 1,2 isomer was obtained (62), though it was later shown that the 1,3 isomer is also formed (20). It was claimed (111) that all aldehydes give both the 1,2- and 1,3-condensation products, *viz.*, 2-substituted 1,3-dioxolane-4-methanols and 2-substituted *m*-dioxan-5-ols, respectively, but that the latter is favored by a low temperature (below 0°) and the former by the presence of electron-withdrawing groups, *e.g.*, dibromomethyl, by using dibromoacetaldehyde. Azeotropic distillation gives both products (37), the former in the larger quantity, but the use of acid catalysts was finally shown to be the factor which prevents the formation of the *m*-dioxan derivatives (55).

More recently, transacetalation reactions (89, 93) have been shown to give only 2-substituted 1,3-dioxolane-4-methanols when aliphatic acetals and glycerol are condensed in the presence of sulfosalicylic acid. However, by modifying the reaction conditions, benzaldehyde yielded three isomers, 2-phenyl-1,3-dioxolane-4-methanol and *cis*- and *trans*-2-phenyl-*m*-dioxan-5-ol, though the equilibrium constant in acid solution still favored the dioxolane (93). The reaction has been shown to proceed *via* a mixed acetal linked to C_1 of the glycerol (94), *e.g.*



A similar type of reaction occurs with the esters of ortho acids (33); thus, on heating ethyl orthoformate with glycerol, two molecules of ethanol distil off, leaving a mixture of *cis* and *trans* isomers of both 2-ethoxy-1,3-dioxolane-4-methanol (88%) and 2-ethoxy-*m*-dioxan-5-ol (12%), all of which have been characterized by nmr studies (33).

Another method used to prepare the dioxolanes is by isomerization of unsaturated glycerol ethers (plasmalogens), and this reaction may explain why cyclic acetals are often found as artifacts when working with these compounds (95).



R = hexyl, octyl, or decyl

Both 2-methyl-1,3-dioxolane-4-methanol and *m*-dioxan-5-ol are produced by reacting acetylene with glycerol (45), but since this is done in the presence of mercuric sulfate and sulfuric acid there can be little doubt that acetaldehyde is formed as an intermediate. If the reaction is carried out in the liquid phase without these catalysts, only the former compound and 2-methyl-4-vinyloxy-1,3-dioxolane are obtained (90).

Chloroacetaldehyde has been condensed to give the two corresponding chloromethyl derivatives, subsequently converted to the 2-diethylaminomethyl derivative by reacting with diethylamine (116). The use of KU-1, a sulfonated polystyrene resin, as catalyst is claimed to give only the dioxolane derivative (117).

Generally either *cis*- or an equilibrium mixture of *cis*- and *trans*-dioxan is obtained in the methods already discussed; *trans*-2-alkyl derivatives have only recently been prepared by inversion of the *cis*-2-alkyl-*m*-dioxan-5-methanesulfonates with sodium benzoate in dimethyl-

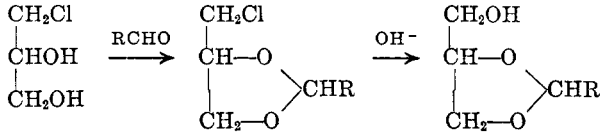
TABLE I

CONDENSATION PRODUCTS FROM ALDEHYDES AND GLYCEROL

2-Substituting group	Ref (2-substd 1,3-dioxolane-4-methanols)	Ref (2-substd *m*-dioxan-5-ols)
Hydrogen	11, 27, 53, 65, 75, 102–104, 115	27, 53, 65, 75, 79, 102–104, 115
Allyl	37	
Benzyl	18, 24, 63	63
Bromoalkyl (C_3–C_{10})	96	
Bromomethyl	42, 111	42, 111
Butyl	107	107
t-Butyl	111	111
7-Carboxyheptyl	89	
Chloromethyl	116, 117	116
p-Chlorophenyl		48
3-Cyclohex-1-enyl		16
Dibromomethyl	111	111
2,4- and 3,4-dichlorophenyl		48
Diethylaminomethyl	116	116
1,2-Dimercaptoethyl		91
2,6-Dimethylhepta-1,5-dienyl	63	63
2,6-Dimethylhepta-2,6-dienyl	93	
5,6-Epoxy-2-norbornyl		16
Ethoxy	33	33
Ethyl	13, 43, 111	9, 111
1-Ethylpentyl	48, 109	48, 59, 100, 109, 112
1-Ethylpropyl	59, 100	48, 59, 112
2-Furyl	18, 100	
Heptadecyl	93	
Heptyl	95	
Hexyl	18, 23, 24	48, 59, 100
Isopropyl	13, 111	9, 111
p-Methoxyphenyl	63	63, 94
Methyl	13, 43, 45, 46, 90, 93, 94, 101, 110	9, 45, 69, 108
6-Methylcyclohex-3-en-1-yl		16
3,4-Methylenedioxyphenyl		48
4-Methyl-7-oxabicyclo-[4.1.0]hept-3-yl		16
p-Nitrophenyl	53	36, 48, 53
Nonyl	95	
5-Norbornen-2-yl		16
7-Oxabicyclo[4.1.0]-hept-3-yl		16
Pentadecyl	38, 93	
Pentyl	59	59, 109
1-Pentylstyryl		48
Phenethyl	63, 93	63
Phenyl	1, 8, 13, 15, 18, 20, 37, 43, 48, 62, 93, 94, 113	8, 9, 20, 28, 36, 47, 48, 93, 113
Prop-1-enyl	37	
Propyl	23, 37	
Styryl	57	48, 57
2-Thienyl	18	
p-Tolyl		48
Trichloromethyl	11, 17, 29, 56, 110	
Tridecyl	93	
Undecyl	95	
Vinyl	41, 57, 60, 61, 77	60

formamide and hydrolysis of the resulting *trans* benzoates (9).

If one of the two structural isomers is required specifically, then it is usually prepared from a blocked glycerol. Thus glycerol monochlorohydrin, condensed with an aldehyde in the presence of concentrated hydrochloric acid and then submitted to alkaline hydrolysis, yields only a 1,3-dioxolane (1). Ester (38, 41)



and methyl ether groups (53) are frequently used to block either the 1 or 2 position of the glycerol and thereby yield 1,3-dioxolane or *m*-dioxan, respectively.

Table I lists the various compounds obtained by condensation of aldehydes by one or more of the methods outlined above.

B. SEPARATION OF *m*-DIOXANS AND 1,3-DIOXOLANES

Separation of 2-substituted 1,3-dioxolane-4-methanols from the corresponding 2-substituted *m*-dioxan-5-ols, if both are formed together, is generally achieved by fractional crystallization of the compounds themselves (53) or of their esters (104). Alternatively, dry hydrogen chloride passed into the cooled reaction mixture generally causes the separation of the six-membered *m*-dioxanol (113), probably due to the formation of a less soluble addition compound. Thin layer chromatography on silica gel has also been used (63). One of the commonest of these compounds, 2-phenyl-1,3-dioxolane-4-methanol, has only once been reported in the crystalline state (62), and other workers have subsequently relied on crystalline derivatives in their separations and purifications.

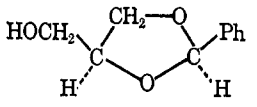
In many cases formation of one structural isomer proceeds to the exclusion of the other, and the same is often true of the formation of the geometrical isomers of each of these. If both *cis* and *trans* isomers are formed, this may be of no importance in certain syntheses in which the compounds are used (see sections IV and V) as intermediates. However, methods of obtaining the pure geometrical isomers are discussed later.

C. STRUCTURE

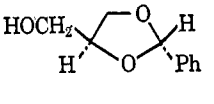
It has already been mentioned that the temperature and the nature of the substituent being introduced can influence the size of the ring formed when aldehydes condense with glycerol. Also, each of these isomers possesses stereochemical modifications, and it is useful therefore to indicate the various products obtainable as structural, geometrical, and optical isomers before embarking on a discussion of their stereochemistry. The products obtainable by condensing benzal-

dehyde and glycerol are typical and are summarized below.

5-Membered rings: 1,3-dioxolanes



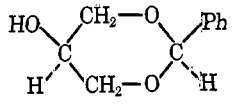
cis-2-phenyl-1,3-dioxolane-4-methanol
cis-1,2-benzylideneglycerol



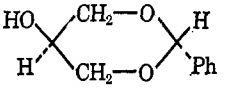
trans-2-phenyl-1,3-dioxolane-4-methanol
trans-1,2-benzylideneglycerol

Since both C_2 and C_4 are asymmetric, both *cis* and *trans* isomers possess (+) and (−) forms; *i.e.*, there are altogether four stereoisomers, two *cis* and two *trans*.

6-Membered rings: *m*-dioxans



cis-2-phenyl-*m*-dioxan-5-ol
cis-1,3-benzylideneglycerol

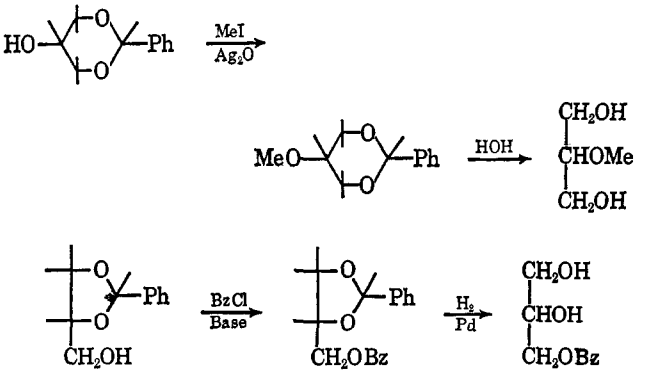


trans-2-phenyl-*m*-dioxan-5-ol
trans-1,3-benzylideneglycerol

There is a plane of symmetry in both the *cis* and *trans* forms so that no optical isomers exist.

1. *Ring Size*

The substituted dioxolanes and dioxans are distinguished from each other by the products of either methylation and hydrolysis (54) or benzoylation and hydrogenolysis (20, 113). The former compounds give glyceryl-1-monomethyl ether and 1-monobenzoin, respectively, and the latter give the corresponding 2-substituted products, all of which have been synthesized unambiguously from derivatives of propane and propene. Nevertheless, when these and similar methods are used, great care must be taken where 2-monoglycerides are formed to use conditions which preclude acyl migration (to form the more stable 1-monoglycerides) (34).

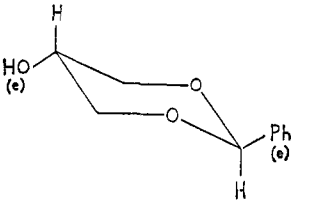


A further method of distinction is that any resolvable, or active compound, must be a dioxolane, but although active compounds have been prepared, resolution of racemates has proved such a difficult undertaking, with only incomplete separations recorded, that this method is not very practical.

2. *Stereochemistry and Conformation*

a. 2-Substituted *m*-Dioxan-5-ols

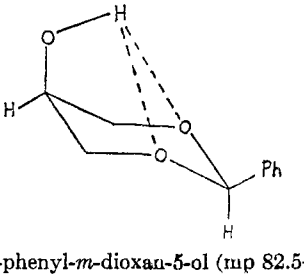
Until it was recognized that six-membered rings, including the dioxans, are puckered, and that any large group in the axial conformation renders the parent compound unstable, little progress was made in investigating the stability or otherwise of the geometrical isomers of 2-substituted *m*-dioxan-5-ols. However, once these findings had been reported, it became clear that, unless other factors are also involved, the *trans* isomer would be expected to be the more stable, since both substituent groups are equatorial, as in III.



III

Both isomers of 2-phenyl-*m*-dioxan-5-ol have been prepared. The more stable isomer, mp 82.5–83.5°, was first prepared by Gerhardt (47); it is easily obtained by heating glycerol and excess benzaldehyde at 145–170° in a stream of carbon dioxide and distilling out the water (113). By cooling the reaction mixture, rendering it slightly acidic, and seeding, the compound crystallizes. This may be converted to a second isomer, mp 63.5–64.5°, by acetylation and treatment with sodium methoxide (which causes inversion) (113) and, since this is the less stable isomer from the arguments already put forward, it was proposed as having the *cis* configuration.

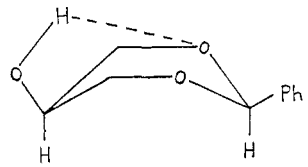
However, it was soon shown that this is not so, since the high-melting isomer shows infrared absorption only for hydrogen-bonded hydroxyl groups. These can only be axial, since hydrogen bonding is not possible in the equatorial conformation, but to stabilize the molecule the large phenyl group would be expected to be equatorial. Thus the more stable isomer is in fact that melting at the higher temperature, and it is *cis* in configuration (IV) (8). This is borne out by equilibration with aluminum isopropoxide, and, since



IV *cis*-2-phenyl-*m*-dioxan-5-ol (mp 82.5–83.5°)

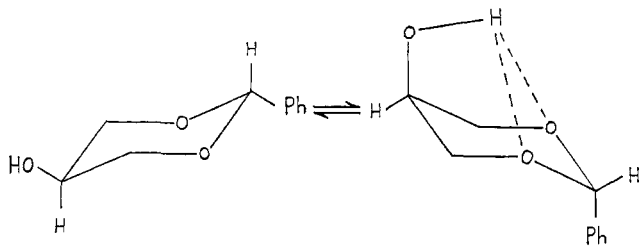
the results are the reverse of those obtained with cyclohexane derivatives, where the *trans*-1,4 isomers are the more stable (39), the stability of *cis*-2-phenyl-*m*-dioxan-5-ol (IV) must be due to hydrogen bonding.

If the ring were of the boat conformation, a hydrogen-bonded form such as V could be formed even with an equatorial hydroxyl group, but such conformations always appear to be less stable than the corresponding chair form, and so in fact do not occur.



V

Having recognized the stabilizing effect of hydrogen bonding, it becomes less certain whether the *trans* isomer should be represented by III or by an (*a*,*a*) conformation with the axial hydroxyl group hydrogen bonded. However, *trans*-2-methyl-, -2-ethyl-, and -2-isopropyl-*m*-dioxan-5-ols, first prepared from the *cis*-methanesulfonates by inversion with sodium benzoate in dimethylformamide and subsequent hydrolysis (9), and the well-known "*trans*"-2-phenyl-*m*-dioxan-5-ol (8) all showed infrared absorption at 3633–3634 and 3601–3604 cm^{-1}, indicating free and bonded –OH groups, respectively, whereas the *cis* isomers showed no absorption for free –OH. From the proportion of each, it was concluded that the *trans* isomers are best represented as being in a conformational equilibrium of III and VI, with most of the hydroxyl groups nonbonded, but, as might be expected, the reverse is true for unsubstituted *m*-dioxan-5-ol itself.

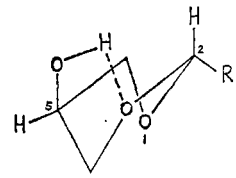


III VI

trans-2-phenyl-*m*-dioxan-5-ol (mp 63.5–64.5°)

Although the conclusions remained unaffected, it was later shown that the so-called "*trans*" isomer of the 2-phenyl compound (8) was a mixture of *cis* and *trans* isomers not separable even by chromatography. The pure *trans* isomer was prepared by lithium aluminum hydride reduction of 5-oxo-2-phenyl-*m*-dioxan (36). This casts considerable doubt on the claim that 2-*p*-nitrophenyl-*m*-dioxan-5-ol can be separated into its isomers by fractional crystallization of the methyl ethers (53).

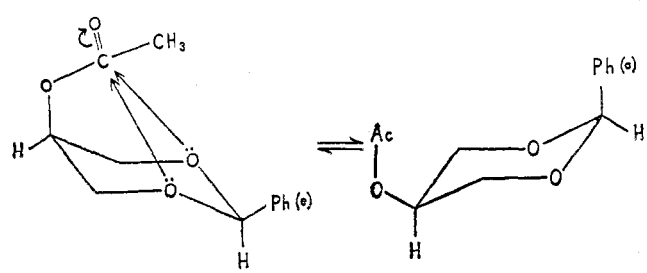
It is surprising to find little difference in the proportions of the two conformational isomers in the four compounds studied, since it might be expected that the larger the 2-substituent becomes, the less stable would be the bonded form in which the substituent is axial. As this is not so, it has been suggested that the smaller alkyl groups do not exert the maximum steric effect, or that a third conformation (VII) is taken up where the 2-substituent can exert little steric effect in any case (9).



VII

Even when groups are introduced into the 4 and 6 positions as in certain carbohydrate derivatives, the absorption spectra are still similar (14). Nevertheless, substituents in different positions in the ring must contribute something to the stability or otherwise of the system, and by nmr studies of the inner ring mobility of *m*-dioxans it has recently been shown that substituents in the 5 position render the molecule less flexible, and those in the 2 position make it more flexible (44). This has been done by calculating the free energy of activation from the observed temperature and that of maximum split for the parent compound and the 2,2- and 5,5-dimethyl derivatives. This lends support to the possibility of certain molecules taking up conformation VII.

If the 5-hydroxy group is substituted, hydrogen bonding is not possible, and so it is not surprising to find that the conformation in such compounds differs from that in the unsubstituted parent molecule. Thus the nmr spectrum of *trans*-5-acetoxy-2-phenyl-*m*-dioxan shows a complex coupling pattern suggesting a rigid molecule of chair form with the bulky groups *both equatorial* as in III (RCOO– replaces HO–). The *cis* isomer, however, gives a spectrum with only one peak for all the C_4 and C_6 protons, suggesting that they have lost their axial and equatorial characteristics, and that the compound is an equilibrium mixture of two conformations, VIII and IX (10). The



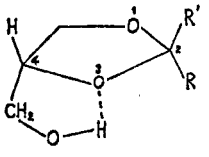
VIII IX

cis isomer is the more stable and formed by condensing benzaldehyde and 2-O-benzoylglycerol, and on this basis, structure VIII has been proposed, although it is not known how great a stabilizing effect "oxygen bonding" has on such a compound (20). The same observations are made for other 5-O-substituted derivatives, and it is rather surprisingly claimed for the unsubstituted compounds (10).

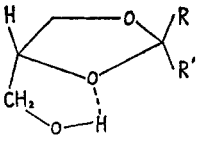
The complete separation of *cis*- and *trans*-2-substituted *m*-dioxan-5-ols has not yet been achieved, for although crystallization in the presence of acid yields the pure *cis* isomer (113) and chromatography on alumina does the same (*cis* is less strongly held) (36), the material remaining in both cases is an equimolecular mixture of *cis* and *trans* isomers. It seems that the only reliable method of obtaining the *trans* isomers at present is by synthesis (9, 36). Even so, although *cis* compounds give pure *cis* derivatives on acylation or etherification, when the *trans* isomers are similarly treated a mixture of *cis* and *trans* derivatives is obtained (36).

b. 2-Substituted 1,3-Dioxolane-4-methanols

Despite the puckered nature of the six-membered ring, a five-membered system, whether of cyclopentane or 1,3-dioxolane, is almost planar, as a study of Raman and infrared spectra of 1,3-dioxolane, 2,4-disubstituted derivatives, 2,2-dimethyl-1,3-dioxolane-4-methanol, and 4-deuterioxymethyl-2,2-dimethyl-1,3-dioxolane has shown. The puckering is so slight and the difference in energy levels of the two forms so small that, even though the rings possess limited flexibility, this has no steric consequence (11, 12). Substituent groups therefore occupy similar conformational positions no matter where placed in the ring, so that in all probability the other steric factors govern the relative stability of the *cis* (X) and *trans* (XI) isomers of the 2-substituted 1,3-dioxolane-4-methanols (R′ = H). Though not affecting the relative stability of the



X

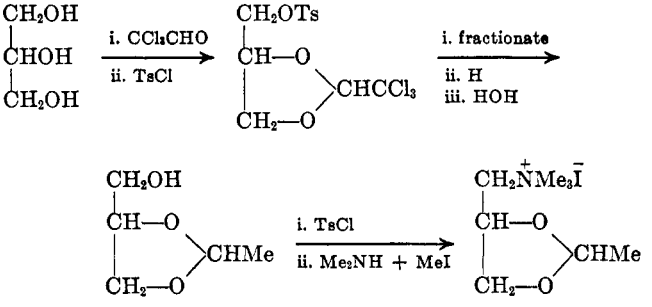


XI

two isomers, it would be expected that in both, hydrogen bonding would occur, either with O_1 to give a six-membered ring or with O_3 to give a five-membered one, and this has been confirmed. The bonding is not complete, even when there is no 2-substituent (27), and it is not understood why, since tetrahydrofurfuryl alcohol is fully bonded (13).

Since both C_2 and C_4 are asymmetric, there are four possible isomers of these compounds, D- and L-*cis* and D- and L-*trans*. The two geometric isomers of 2-*p*-nitrophenyl-1,3-dioxolane-4-methanol are claimed to have been separated as their methyl ethers (53), but it has been found that attempted separations of *cis* and *trans* isomers are in general unsuccessful, owing to the formation of intermolecular compounds. However, by reduction of the tosyl derivatives of 2-methyl-1,3-dioxolane-4-methanol to 2,4-dimethyl-1,3-dioxolane and subsequent gas chromatographic analysis, it was shown that there are about 63% *cis* and 37% *trans* isomers in the original compound as normally prepared. Other similar compounds have similar proportions of each isomer; *e.g.*, 4-ethyl-2-methyl-1,3-dioxolane, the most effective inhibitor of choline esterase activity in this class of compounds, has 60% *cis* and 40% *trans* isomers (110).

Nevertheless, the two geometrical isomers can be obtained. Chloral and glycerol are condensed and the tosyl derivative of the resulting *cis,trans*-2-trichloromethyl-1,3-dioxolane-4-methanol is prepared which is fractionated; each fraction is submitted to reductive hydrogenolysis and then hydrolyzed. By chromatography, pure *cis* and *trans* isomers are obtained (110). By reconverting these to tosyl derivatives and treatment with dimethylamine and methyl iodide, 4-



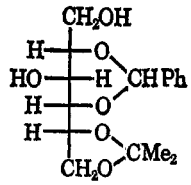
dimethylaminomethyl derivatives suitable for attempted resolutions were obtained. However, fractionation of the diastereoisomeric D- or L-dibenzoyltartrates of the DL-*trans* isomer gave final products of only 32% optical purity, while the DL-*cis* isomer proved unresolvable (110).

D. RELATED COMPOUNDS

1. *m*-Dioxans

Many 2-substituted *m*-dioxan-5-ols have been prepared by the methods already outlined and are listed in Table I; their properties and uses are discussed later.

Not many related compounds are known, except in carbohydrate chemistry where condensation of benzaldehyde with polyols can give rise to 4- and 4,6-substituted derivatives of 2-phenyl-*m*-dioxan-5-ol. "Double" compounds, such as 2,4-O-benzylidene-5,6-O-isopropylidene-D-glucitol (XII), can also be obtained and are best separated from each other chromatographically (15, 21).



XII

Sulfur analogs such as 2-phenyl-*m*-dithian-5-ol and the corresponding 5-sulfonate have been prepared (92), and sulfur has been introduced into the substituent group in 2-(1,2-dimercaptoethyl)-*m*-dioxan-5-ol (91). 2-Substituents in *m*-dithian have been shown by nmr studies to render the ring more flexible and 5-substituents to make it more rigid, as is the case with the dioxans (44).

2. 1,3-Dioxolanes

The 2-substituted 1,3-dioxolane-4-methanols are also listed in Table I; those related compounds not included in this list differ mainly by possessing a group other than $-CH_2OH$ at the 4 position.

2,4-Dimethyl-1,3-dioxolane has been prepared and partially separated into its isomers by fractional distillation (68); it has already been mentioned that these are also separable by gas chromatography, and, in the course of the same investigation into the activity of compounds related to muscarine (110), similar separations were achieved with $-CH_2Cl$, $-CH_2Br$, and $-CH_2NMe_2$ groups in the 4 position of 2-methyl-1,3-dioxolane. All of these compounds were shown to contain about 60% of the *cis* isomer.

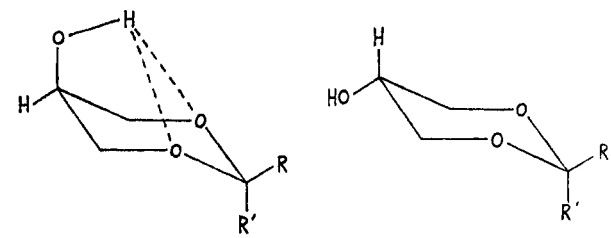
In studies on the formation of acetals with acrolein, 4-chloromethyl-2-vinyl-1,3-dioxolane was obtained in 75% yield from propylenechlorohydrin, while glycerol gave a 78.5% yield of 2-vinyl-1,3-dioxolane-4-methanol (41). When glycerol is vinylated with acetylene, the major product is 2-methyl-4-vinyloxymethyl-1,3-dioxolane, not the previously reported 1,2,3-trivinyloxypropane. 2-Methyl-1,3-dioxolane-4-methanol can be obtained in 30% yield by shortening the reaction time (101). Only 2-phenyl-4-sulfomethyl-1,3-dithiolane has been reported from other heterocyclic systems (92).

III. CONDENSATION PRODUCTS OF GLYCEROL AND KETONES

A. PREPARATION

Although the study of the condensation products of glycerol and ketones lagged behind that of the products obtained using aldehydes, once it had been demonstrated that glycerol and acetone condense to form 2,2-dimethyl-1,3-dioxolane-4-methanol (62), the two studies rapidly became one, with many workers using both aldehydes and ketones in the same series of experiments, thus posing problems for the reviewer. The use of ethyl ketal also yields 2,2-dimethyl-1,3-dioxolane-4-methanol (93), and ethyl acetoacetate gives 2-ethoxy-2-methyl-1,3-dioxolane-4-methanol (33). Both methods have general application, and in most cases condensation can be brought about by azeotropic distillation (37) or the use of catalysts such as hydrogen chloride (1, 71), *p*-toluenesulfonic acid (31, 114), iodine (50), phosphorus pentoxide (40), or calcium carbide and a sodium alkylsulfonate (69). The resins used in condensing the aldehydes (117) (see section IIA) would almost certainly prove just as useful with ketones, and, since acetone condenses with glycidol, $HOCH_2-\underline{CH-CH_2O}$, to give 2,2-dimethyl-1,3-dioxolane-4-methanol in the presence of boron trifluoride in ether (97), this latter catalyst would probably also catalyze the normal condensation.

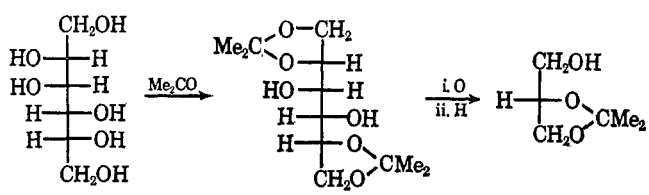
When a ketone condenses with glycerol two possible products may result, either the 2,2-disubstituted 1,3-dioxolane-4-methanol (X and XI) or the 2,2-disubstituted *m*-dioxan-5-ol (XIII and XIV). In XIII the hydroxyl group is axial and stabilized by hydrogen



XIII XIV

bonding, while in XIV it is stabilized by being in an equatorial conformation, but in both geometrical isomers and both conformations one of the substituent groups on the 2 position is always axial. Thus the whole structure is sterically unfavored relative to the dioxolane structures X and XI in which all groups occupy similar conformational positions (see section II) and are relatively more stable, so that when ketones condense with glycerol only the 2,2-disubstituted 1,3-dioxolane-4-methanols are obtained (see Table II).

These compounds exist as optical isomers and D-(−)-2,2-dimethyl-1,3-dioxolane-4-methanol has been synthesized from D-mannitol (3, 4, 6). The latter is condensed with acetone and the product cleaved oxidatively with lead tetraacetate or potassium periodate and reduced catalytically to the required compound.



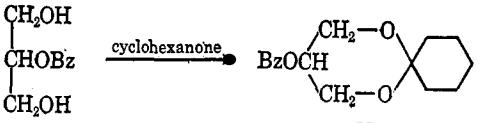
The enantiomer may be obtained in a similar manner from L-mannitol (5) or by inversion of the D-(−)-"acetoneglycerol." The D-*p*-nitrobenzyl ester is first

TABLE II
CONDENSATION PRODUCTS FROM KETONES AND GLYCEROL

2,2-Substituting groups	Reference: 2,2-Disubstituted 1,3-dioxolane-4-methanols	Reference: 2,2-Disubstituted *m*-dioxan-5-ols
Bisheptamethylene	27	
Bishexamethylene	27	
Bispentamethylene	27, 37, 50	20, 40, 66
Bistetramethylene	27	
Bromomethyl–methyl	114	
Butyl–ethyl	18, 23	
Butyl–methyl	18, 23	
t-Butyl–isopropyl	18	
t-Butyl–methyl	18, 58	
Chloroethyl–methyl	31	
Chloromethyl–methyl	18, 23	
p-Chlorophenyl–methyl	78–83, 85	
Cyclobutyl–methyl	58	
Cyclohexyl–methyl	18	
Cyclopropyl–methyl	58	
Dibutyl	18	
Di(chloromethyl)	23, 114	
Dicyclobutyl	58	
Diethyl	18, 23, 27	
Diisobutyl	18, 23, 48	
Diisopropyl	17, 18, 23, 43, 58, 64, 76	
Dimethyl	1, 3–7, 11, 15, 18, 27, 30, 43, 55, 58, 61, 62, 84, 87, 88, 93, 97, 110	20, 40
Diphenyl	22, 27, 58	
Dipropyl	18, 58	
Ethoxy–methyl	33	
Ethoxymethyl–methyl	114	
Ethyl–isopentyl	18	
Ethyl–methyl	19, 51, 58	20, 40
Ethyl–pentyl	18, 23	
Ethyl–phenyl	52, 78–83, 85	
Heptyl–methyl	18, 23	
Hexyl–methyl	18, 23, 50	
Isobutyl–methyl	18, 37, 48, 50	
Isopropyl–methyl	23, 58	
Isopropyl–phenyl	52	
2-Methylbispentamethylene	37	
Methyl–1-methylbutyl	18, 23	
Methyl–1-methylpentyl	18	
Methyl–nonyl	2, 79	
Methyl–pentyl	23, 37, 50, 58	
Methyl–phenyl	18, 48, 58, 59, 82, 100	20, 40
Methyl–propyl	18, 23, 58	
Methyl–*o*-tolyl	18, 23	

formed, then hydrolyzed and tritylated; at each stage inversion occurs to give D-glyceryl-1-trityl ether, and this on treatment with acetone and zinc chloride forms a compound which on hydrogenolysis gives L-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol, but only in an over-all 6.6% yield (7).

If compounds such as XIII or XIV are required, they are obtainable by reacting a ketone with glycerol blocked in the 2 position. Thus when 2-O-benzoylglycerol is treated with acetone, methyl ethyl ketone, acetophenone, or cyclohexanone, the appropriate 2,2-disubstituted 5-benzoyloxy-*m*-dioxan, such as XV, is obtained (20, 40).



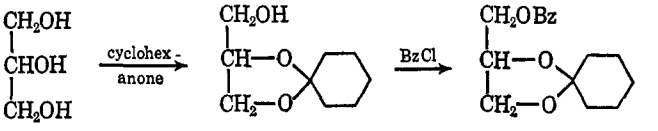
XV

The separation of structural isomers was discussed in connection with the 2-monosubstituted compounds, but clearly in the case of the 2,2-disubstituted derivatives, since only the dioxolanes are formed, no separation is necessary.

B. STRUCTURE

1. *Ring Size*

The methods of determining the size of the ring have already been discussed in section IIC1 and are applicable to the 2,2-disubstituted *m*-dioxans and 1,3-dioxolanes (20, 113), but, since the former are only obtained by blocking the 2 position of glycerol, their structure is fairly obvious in any case. This is supported by the fact that the product of condensing a ketone with 2-benzoylglycerol differs from that obtained by benzoylation of the condensation product of the same ketone with glycerol, thus suggesting that the latter has a five-membered ring. In this way it was shown that cyclohexanone and glycerol give 2,2-bispentamethylene-1,3-dioxolane-4-methanol (XVa) since the benzoyl derivative XVb, mp 37° (66), was clearly different from that obtained by earlier workers by condensing cyclohexanone and 2-O-benzoylglycerol; they obtained 5-benzoyloxy-2,2-bispentamethylene-*m*-dioxan (XV), mp 88° (40).



XVa XVb

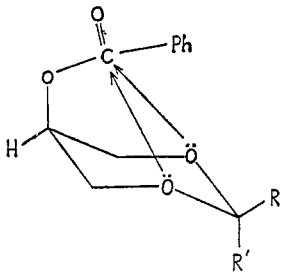
2. *Stereochemistry and Conformation*

a. 2,2-Disubstituted *m*-Dioxan-5-ols

As has already been mentioned, these compounds have only been obtained as the 5-O-substituted derivatives. They are not optically active, but geometrical isomers will exist if an asymmetric ketone is condensed with a 2-substituted glycerol.

It has been suggested (40) that since 2-O-benzoylglycerol reacts with benzaldehyde to give a *cis* compound with the phenyl group equatorial and the benzoyloxy group axial (20), unsymmetric ketones

will give a similar conformation, with the larger 2-substituent equatorial as in XVI. However, since



XVI

the bonding between the oxygen atoms and the carbonyl group must be comparatively weak, it seems possible that, while an equatorial phenyl group might hold the ring in this conformation, the additional strain introduced by an axial alkyl group (especially if the equatorial phenyl is replaced by a smaller group) could easily favor the formation of the *trans* isomer with the 5-benzoyloxy group equatorial, and the evidence already presented suggests that a less rigid molecule results when a second 2-substituent is introduced (44). Thus if the short series of compounds so far prepared (10) are *cis* (and this may need confirmation since all the other work has been carried out using aldehydes), it seems very possible that they exist in the conformational equilibrium of the two chair forms.

No methods have yet been suggested for the separation of geometrical isomers of this group of compounds; possibly the *cis* esters and ethers can be obtained in a pure state by chromatography on alumina as for the 2-monosubstituted compounds, but the other component obtained would need very careful examination before it could be assumed to be the pure *trans* form (8, 36).

b. 2,2-Disubstituted 1,3-Dioxolane-4-methanols

Compounds of this type resemble those discussed in section IIC2. If unsymmetric ketones are used in their preparation, R and R′ in X and XI are dissimilar and there are still four isomers, each geometrical isomer possessing D and L forms. If R′ is larger than R, then X is probably the preferred configuration, since XI with the two large groups *cis* would be less favored sterically. If R and R′ are identical, then only one D and one L isomer exist.

The commonest compound of this group is undoubtedly 2,2-dimethyl-1,3-dioxolane-4-methanol (1,2-acetoneglycerol), and this has been partially resolved by fractional crystallization of D- and L-dibenzoyltartrates of the 4-trimethylammonium methyl iodide derivative, prepared in the same manner as in section IIC2, but an optical purity of more than 33% was never obtained for either isomer (110). It was found better therefore to synthesize pure D-(−)-2,2-dimethyl-1,3-dioxolane-4-methanol (3, 4, 6), and this was then converted to D-(−)-2,2-dimethyl-4-trimethylammonium methyl-1,3-dioxolane iodide and used as a standard in other experiments (110).

2-Methyl-2-nonyl-1,3-dioxolane-4-methanol has been separated into two racemates by fractional crystallization of the carbamate, and these presumably correspond to the geometrical isomers (2).

c. Related Compounds

Since the 2,2-disubstituted *m*-dioxan-5-ols are only known as esters and ethers, there is little recorded on compounds related to them, but a number of compounds related to the 2,2-disubstituted 1,3-dioxolane-4-methanols listed in Table II are known, mostly with a different substituent in the 4 position.

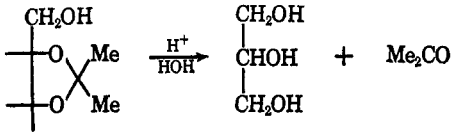
Thus in a study on fluorine compounds, 2,2-dimethyl- and 2-ethyl-2-methyl-4-fluoromethyl-1,3-dioxolane were prepared (19); 2,2-diisopropyl-4-*o*-cresyloxy-1,3-dioxolane was synthesized with other compounds for evaluation as a tranquilizer (64); 2-isobutyl-2-methyl-4-trimethylacetoxymethyl-1,3-dioxolane was prepared in order to study its reaction with phosphoric acid (25). In a search for central nervous system depressants, 2-methyl-2-(3-hydroxy-3-ethylpentyl)-1,3-dioxolane was found to be the most active, but in almost all the compounds prepared there was no substituent at the 4 position of a 1,3-dioxolane nor at the 5 position of a *m*-dioxan (86). 2,2-Disubstituted-4-vinyloxy-1,3-dioxolanes have been treated with carboxylic acids to give a series of compounds with –O–CH(Me)–O–CO–R as a side chain; all were mobile liquids immiscible with water, but no use was proposed for them (105). 2,2-Diphenyl-1,3-dioxolanes with basic groups in the 4 position have also been prepared (22).

Of the sulfur analogs, 2-methyl-2-phenyl-4-sulfomethyl-1,3-dioxolane has been reported (92), and nmr spectra of some 2,2- and 5,5-disubstituted *m*-dithians have been studied. The same conclusions have been reached as for the *m*-dioxans concerning the rigidity of the ring system in the presence of these groups (44).

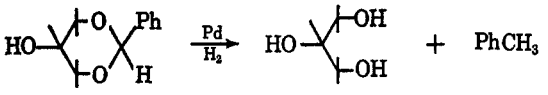
IV. Reactions

In many ways the reactions of both *m*-dioxans and 1,3-dioxolanes are similar. Both are easily hydrolyzed with dilute acid to glycerol and the appropriate aldehyde or ketone. When the 2-substituent is trichloromethyl, only a little chloral is liberated, even on treatment of the parent compound with concentrated acid (56). Except in this one case, estimation of the aldehyde or ketone liberated on hydrolysis provides a useful method of estimating the original compounds (83), and in thin-layer chromatographic separations the compounds are usually hydrolyzed on the plate and

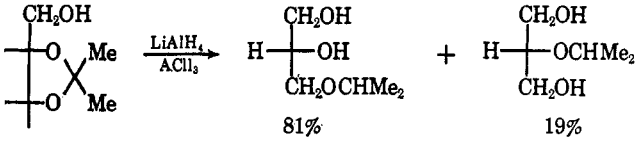
detected as the aldehyde or ketone by use of a suitable reagent (15)



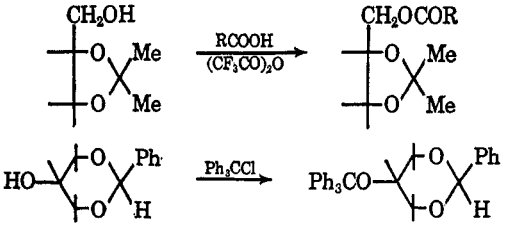
Catalytic hydrogenolysis will remove the 2-substituent and C_2 as a hydrocarbon (20), but they resist attack by metal hydrides. However, if an electron



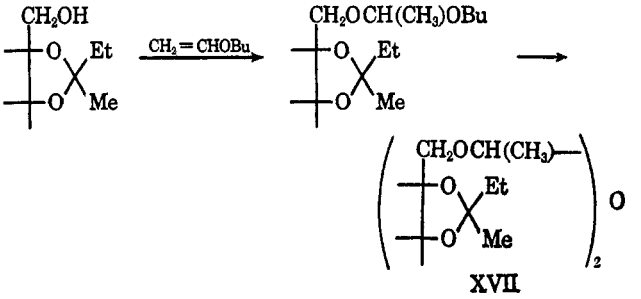
acceptor is present this is not so, and it is found that lithium aluminum hydride, in the presence of aluminum chloride or boron trifluoride, causes reduction even at room temperature. In the case of the 1,3-dioxolanes, electron-donor groups on C_2 accelerate the reaction and electron acceptors slow it down, and a similar but less marked effect is observed for substituents at C_4 or C_5. In addition, however, donor groups at C_4 favor cleavage of the C_2–O bond remote from C_4, while acceptor groups tend to cause cleavage at the other C_2–O bond, *i.e.*, C_2–O_3, so that different proportions of primary and secondary alcohols are obtained depending on the 4-substituent (67).



The hydroxyl group in both types of compound can be reacted with acid halides, generally in pyridine (74) or directly with acids in trifluoroacetic anhydride (32) to yield esters, and with alkyl halides to form ethers, which often form useful blocking groups (see section VA).

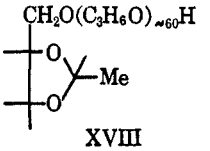


Ethers can also be formed with unsaturated compounds, such as butyl vinyl ether, but in this case the initial product disproportionates to a symmetrical bis compound (XVII) (106). An ether (XVIII) also results



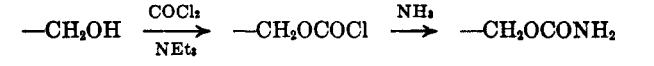
XVII

when 2-methyl-1,3-dioxolane-4-methanol and propylene oxide are heated at 130° for 17 hr (46).

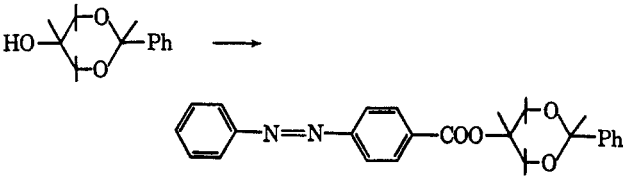


XVIII

In recent years the carbamates of a large number of the dioxolanes and a lesser number of the dioxans have been prepared, usually by treatment of the starting compound with carbonyl chloride in triethylamine, and then with ammonia (58). A number of these derivatives are used as drugs.



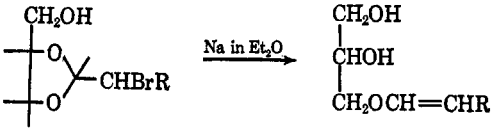
The rate of reaction of the hydroxy groups in the nonplanar *m*-dioxan-5-ols has been shown to differ for the two isomers; *p*-phenylazobenzoyl chloride reacts 5.6 times faster with *cis*-2-phenyl-*m*-dioxan-5-ol (with an axial –OH) than with the *trans* form (28). The resulting "azoates" (XIX) are readily crystallizable and valuable as derivatives (see ref 27). The same



XIX

effect is probably observable in other reactions involving the hydroxyl group, but both 2-phenyl isomers are hydrolyzed at the same rate with 0.02 *N* sulfuric acid (8).

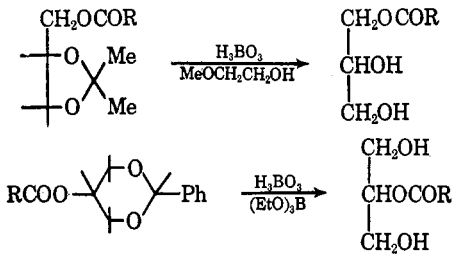
The 2-(1-bromoalkyl)-1,3-dioxolane-4-methanols undergo an interesting reaction when treated with sodium, all (from C_3 to C_{10} inclusive) yielding 3-(alk-1-enyloxy)-propane-1,2-diols (96).



V. USES

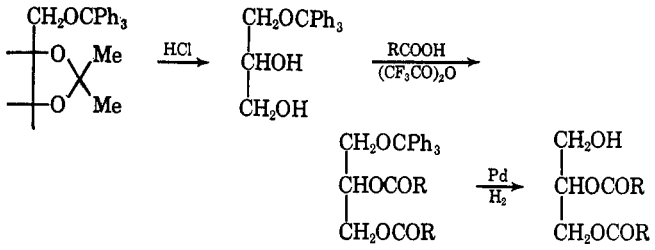
A. SYNTHESIS

The most important use of the 1,3-dioxolanes and *m*-dioxans is in the synthesis of glycerides. The esterified compounds, prepared as in section IV, can be carefully hydrolyzed with cold, dilute acid. To avoid any risk of acyl migration or of removal of the ester group as well, it is best to use boric acid in 2-methoxyethanol (49) or in triethyl borate (73), respectively. The product is washed with water to hydrolyze the borate esters and the 1- or 2-monoglyceride extracted. Removal of the benzylidene or isopropylidene group by



catalytic reduction (20) is also satisfactory, provided that R is not unsaturated; if it is, then it becomes saturated by this procedure.

If ether derivatives are hydrolyzed, two free hydroxyl groups are obtained so that on esterification of these and hydrogenolysis of the ether group, 1,2- or 1,3-diglycerides are obtained. By a combination of these



and other methods almost any glyceride may be synthesized, and for further details the reader is referred to the various reviews on this field of chemistry (70, 72, 98).

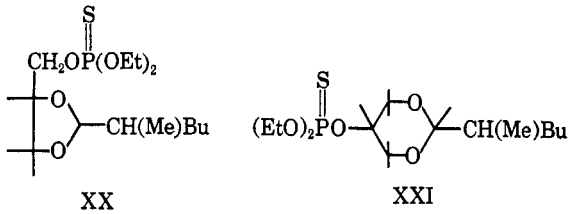
B. PHARMACEUTICALS

A mixture of *m*-dioxan-5-ol and 1,3-dioxolane-4-methanol obtained by condensing glycerol and formaldehyde in the presence of the acidic resin KU-1 is known as Glyphoral (115) and is used as a solvent for pharmaceuticals (75) since compounds such as these have been shown to be nontoxic to humans, and incidentally to rats (102, 103). 2,2-Dimethyl-1,3-dioxolane-4-methanol is also nontoxic to humans even though it is a bactericide (84), and it is partly for this latter reason that its use is recommended, under its trade name of Solketal, as a solvent for cosmetics and perfumes; it is also used for disinfectants and aerosols (87, 88).

C. PESTICIDES

As well as being bactericides, the 2-substituted derivatives of both types of compound have insecticidal properties, and a number have been prepared and evaluated (see tables) as repellants for mosquitoes (107, 109), beetles of the genus *Tribolium* (which feed on flour and grain) (112), and deerfly (rather unsuccessfully in this case) (100). Since such compounds were to be used in sprays of various types, their effect on paint and plastic surfaces has been studied (59).

The ring systems under discussion have been incorporated into dialkyl thiophosphates, for use as insecticides and acaricides, by reacting the crude condensation product of glycerol and an aldehyde with chlorodiethylphosphorothionate, $(EtO)_2$–PS–Cl, to give a mixture of compounds such as XX and XXI. If a ketone is condensed originally, only compounds such



XX XXI

as XX are obtained. In a few cases the 4 position (XX) or the 5 position (XXI) has been further substituted with a nitro group by the use of trimethylolnitromethane (48). All these compounds are closely related to the well-known pesticide Parathion, *p*-$NO_2C_6H_4O$-P(=S)$(OEt)_2$, where the toxicity is due to conversion by plant enzymes to the more toxic Paraoxon, where oxygen replaces sulfur (35). No doubt the toxicity of XX and XXI is due to the same cause, perhaps enhanced by the heterocyclic ring also present.

D. DRUGS

Many of the 2- and 2,2-substituted 1,3-dioxolane-4-methanols (but not the -*m*-dioxan-5-ols) are physiologically active. For this reason they have been used as antispasmodics (114), sedatives (52), and analgesics (78), and both they and the carbamate (58) and other (64) derivatives are used as tranquilizers. 2-Trichloromethyl-1,3-dioxolane-4-methanol causes anesthesia in mice (29), whereas many other compounds of this type give rise to muscular paralysis by a depressant effect on the central nervous system (18, 23) or by serving as interneural blocking agents (81). The 2-methyl-2-phenyl, 2-ethyl-2-phenyl, and 2-*p*-chlorophenyl-2-methyl derivatives all exert a paralyzing effect on the blood vessels and a phyllogenetic effect on the nerve tissue of frogs and rabbits (82). The

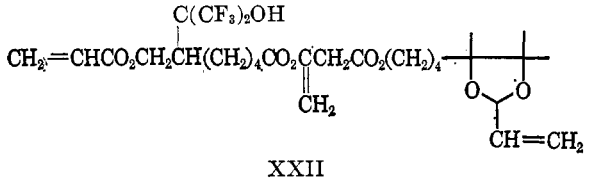
two last-mentioned compounds antagonize convulsive drugs but raise the potency of administered barbiturate during the duration of the effect (80) and stimulate guinea pigs under hexobarbital narcosis (85). Both they and 2-methyl-2-nonyl-1,3-dioxolane-4-methanol antagonize veratramine toxicity and can prevent death from this compound (79). The 2,2-diisopropyl compound has a significant antitremorine effect with carbamates (76). Little study has been made of the comparative effects of the different isomers, but *trans*-2-methyl-4-trimethylaminomethyl-1,3-dioxolane salts are six times more potent than acetylcholine as a cholineolytic agent, while the *cis* isomers have much less effect (17, 43, 110).

E. PAINTS, PLASTICS, AND OTHER USES

Solketal (see section VB) is used as a solvent for plastics, waxes, printing colors, and mordants (87, 88). This and related compounds have been proposed as dispersing and emulsifying agents for pigments, insecticides, and metals in varnishes, resins, and latex (30). Both *m*-dioxan-5-ol and 1,3-dioxolane-4-methanol have been used to prevent shrinkage of paper (65).

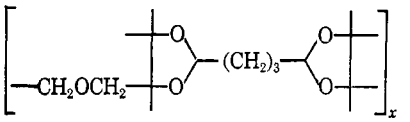
The polymeric ether XVIII, derived from 2-methyl-1,3-dioxolane-4-methanol (see section IV) after hydrolysis and reaction with tolylene diisocyanate, yields a polyurethan foam (46), and similar polyurethans are obtained by treating the 2-ethyl-2-methyl compound with trialkyl and triaryl phosphites, and the resultant bis- and trisphosphites with polyisocyanates (51).

2-Vinyl-1,3-dioxolane-4-alkylols are incorporated with acrylates to give film-forming plastics (77), and both 2-vinyl compounds as the undecylenate esters are used in film-forming paints (60). 2-Vinyl-1,3-dioxolane-4-methanol when heated in air at 70° forms a hydroperoxide which can be polymerized or serve as an initiator of polymerization (61), while the diitaconate ester when treated with hexafluoroacetone yields a compound (XXII) which has been used to coat metals (26).



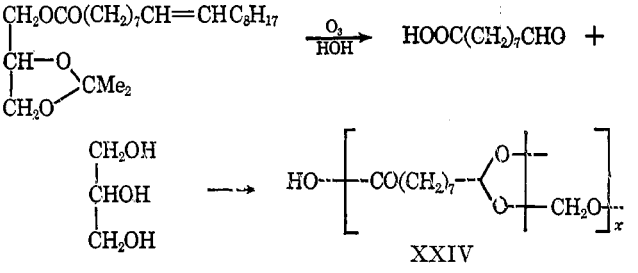
XXII

A large number of compounds with an unsaturated cyclic 2-substituent have been proposed as liquid active diluents for curing epoxide resins (16), while XXIII, prepared from divinylethylene glycol and 2,5-diethoxy-1,4-tetrahydropyran, has been proposed as a pressure-sensitive adhesive resin (99).



XXIII

A dark, rubbery polymer (XXIV) is produced by a rather unusual reaction involving ozonolysis. 2,2-Dimethyl-1,3-dioxolane-4-methanol is converted to the oleate ester and ozonized; on hydrolysis, acetone, glycerol, and azelaaldehyde are liberated and the two latter immediately combine to form a 1,3-dioxolane-4-methanol. The free hydroxyl of the compound then reacts with the carboxyl of the azelaaldehyde molecule and a polymeric ester is formed.



XXIV

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