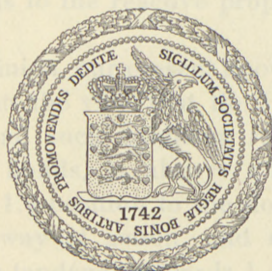


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REACTIONS OF
THE FURAN NUCLEUS; 2.5-DIALKOXY-
2.5-DIHYDROFURANS AND 2.5-
DIACETOXY-2.5-DIHYDROFURAN

BY

N. CLAUSON-KAAS



KØBENHAVN

I KOMMISSION HOS EJNAR MUNKSGAARD

1947

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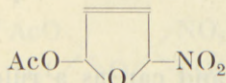


KØBENHAVN
I KOMMISSION HOS HANS WILKESGAARD

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I. Introduction.

It has recently¹ been proved that MARQUIS' nitroacetin,² the compound prepared by nitration of furan with nitric acid in acetic anhydride, is a 1.4-addition product of furan. The radicals added are the nitro and the acetic acid group, presumably formed by cleavage of a mixed anhydride of nitric and acetic acid.



Nitroacetin.

The theory of 1.4-addition has proved extremely useful to explain the structure of compounds obtained from oxidation of furans. Already before THIELE'S exposition (1899), the hypothesis was employed by HILL³ in his classic investigations in the furan series. Later it has been repeatedly discussed, especially by GILMAN, JOHNSON, LUTZ, WRIGHT, MILAS, and their co-workers. However, other reaction mechanisms are often suggested and among chemists working on this subject there still seems to be some disagreement as to the reactive properties of furan and its derivatives.

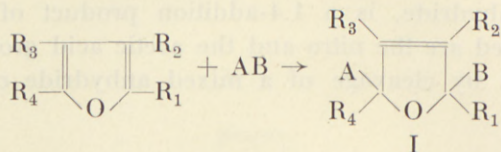
In the author's opinion, our present knowledge of the chemistry of the furans warrants the view that the initial reaction between the furan nucleus and such oxidizing reagents as usually add to aliphatic double bonds, is always one of two. First, the reagent may add in 1.4-position to the double bonds; this is by far the commonest way of action, and no other diene system exhibits so marked a tendency towards 1.4-addition as the furan nucleus. Secondly, in some cases a β -substituted furan may be formed by what is usually called direct substitution. It shall be stressed that it is apparently an inherent property of the furan nucleus to react with oxidizing reagents

exclusively as described. So far no experimental evidence which demonstrates a 1.2-addition, a direct α -substitution, or any alternative mode of action has been given.

In Part II the different aspects of 1.4-addition are discussed. β -substitution will not be considered in this communication.

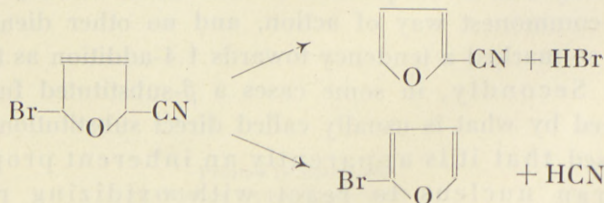
II. 1.4-Addition.

1.4-addition leads to the formation of a 2.5-dihydrofuran (I). The stability of such compounds depends largely upon the nature

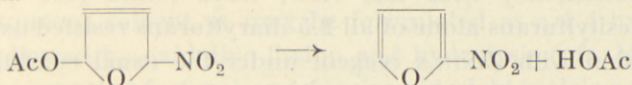


of the radicals added, and can as a rule be deduced from the structural formula. In general the dihydrofurans in question are very reactive at ordinary temperatures and only a small number have actually been isolated in a pure state.^{2, 4-6} They decompose into smaller molecules or react with the reagent or the solvent. Many different ways of further reaction are possible and by selecting the proper experimental conditions, simple furans may be used for the synthesis of several compounds which are otherwise difficult of accession or not accessible at all. To exemplify this, a number of typical reactions will be cited below.

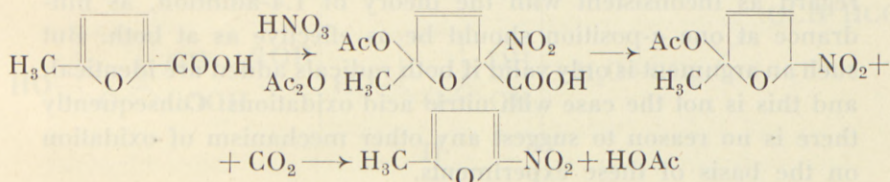
(a) 1.4-elimination; formation of an α -substitution product. KLOPP and WRIGHT⁷ have shown that furan and bromocyanogen yield a mixture of 2-furonitrile and 2-bromofuran. It is evident, as pointed out by these authors, that 1.4-elimination of hydrogen bromide and hydrogen cyanide from the preliminarily formed 1.4-addition product has occurred.



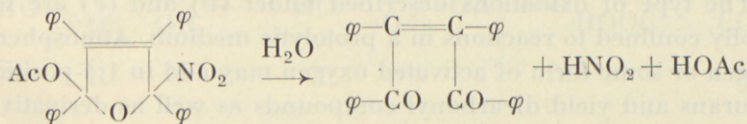
Often only one of the two possible ways of 1.4-elimination takes place; so the nitroacetates, formed by nitration of furans with MARQUIS' reagent,² only yield acetic acid and an α -nitrofuran when heated alone or with pyridine. No α -acetoxyfurans are obtained.



In some cases replaceable groups, such as carboxylic or sulphonic acid groups, are split off before 1.4-elimination (see FREURE and JOHNSON⁵). E. g. 2-methyl-5-furoic acid among other products yields 2-methyl-5-nitrofuran by nitration in acetic anhydride (RINKES⁸).



(b) Formation of unsaturated 1.4-dicarbonyl compounds. When the addition reactions are performed in acetic acid or in an aqueous solvent, unsaturated 1.4-dicarbonyl compounds may come into existence. In order to obtain good yields, the reaction must usually proceed at low temperature. Already ZININ⁹ prepared 1.2.3.4-tetraphenyl-2-butene-1.4-dione by oxidation of tetraphenylfuran with nitric acid in glacial acetic acid. The method has later been employed by LUTZ and co-workers in numerous oxidation experiments on 2.5-diarylfurans. The reaction may be formulated as a 1.4-addition of the nitro and the acetic acid group, followed by hydrolysis or acetolysis to the dicarbonyl compound (see LUTZ et. al.^{10, 11}).



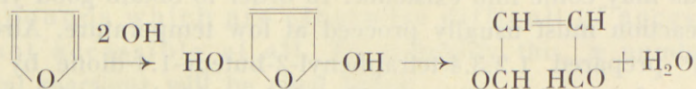
As in most 1.4-oxidations in a protolytic medium, where the addition product is not isolated, nothing is known with certainty

about the nature of the radicals actually added or about the way in which the dihydrofurans are transformed into carbonyl compounds, but it is evident that the reaction proceeds through a 1.4-addition.

In consistency with this view, LUTZ found (see 11) that 2.5-dimesitylfurans alone of all 2.5-diarylfurans resisted oxydative ring fission with ZININ's reagent under the usual conditions. If they reacted at all, only β -nitration or decomposition occurred. The failure to furnish unsaturated 1.4-diketones is readily understandable, if one assumes that the mesityl groups offer hindrance to addition at the α -carbons.

Later LUTZ and BOYER¹² found that α -mesitylfurans with only one mesityl group are easily oxidized to 1.4-diketones. This they regard as inconsistent with the theory of 1.4-addition, as hindrance at one α -position should be as effective as at both. But such an argument is only valid if both radicals added are identical, and this is not the case with nitric acid oxidations. Consequently there is no reason to suggest any other mechanism of oxidation on the basis of these experiments.

Furans with free α -positions may under carefully controlled conditions give α,β -unsaturated aldehydes. Thus furan itself, when hydroxylated with hydrogen peroxide in aqueous methanol in the presence of osmiumtetroxide, yields malealdehyde.¹³

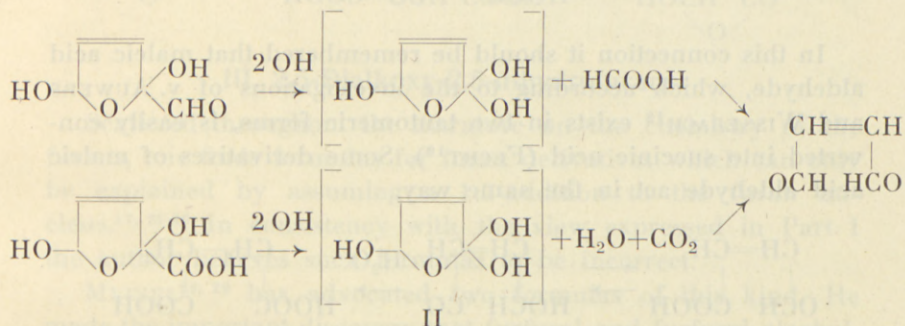


In such reactions the aldehyde groups may be oxidized further by the reagent to carboxylic acid groups; but some of the unsaturated aldehydes are so unstable, that polymerization or oxidation of other parts of the molecule occurs before the comparatively stable aldehyde groups are attacked.

The type of oxidations described under (b) and (c) are not wholly confined to reactions in a protolytic medium. Atmospheric oxygen or some form of activated oxygen may add in 1.4-position to furans and yield dicarbonyl compounds as well as derivatives of maleic acid. MILAS and WALSH¹⁴ were able to oxidize furan, furfural, furfuryl alcohol, and furoic acid in vapour phase with oxygen and a catalyst to maleic acid; and SCHENK¹⁵ oxidized

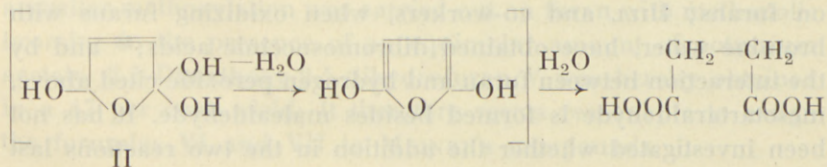
2.5-dimethylfuran with atmospheric oxygen to 1.2-diacetyl-ethylene.

(c) Oxidative elimination of α -substituents. This is a very common reaction, which has often been observed, e. g. when furfural or furoic acid are oxidized. If oxidation takes place in an aqueous solvent, it may be formulated as a 1.4-hydroxylation followed by oxidative fission and hydrolysis (cfr. MILAS¹⁶). It will be seen that furfural and furoic acid yield maleic acid alde-

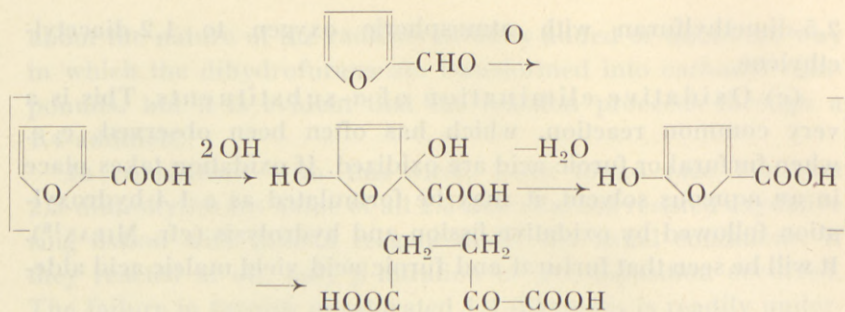


hyde together with formic acid and carbon dioxide, respectively. The maleic acid aldehyde, which has been isolated repeatedly, is easily oxidized to maleic acid, and the numerous preparations of maleic and fumaric acid from the common furans belong to this category of reaction.

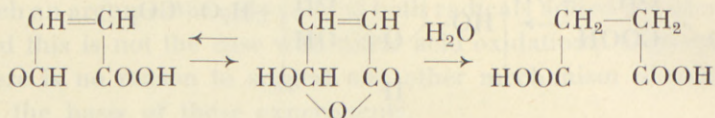
In one case, viz. when furfural was oxidized in water with CARO'S acid at about 20–35° C. (CROSS, BEVAN, BRIGGS¹⁷), a considerable amount of succinic acid was obtained. This may be explained by assuming a 1.4-elimination of water from the intermediate compound II.



Another compound isolated from the reaction mixture was the barium salt of a dicarboxylic acid $\text{C}_5\text{H}_6\text{O}_5$. This acid is probably α -ketoglutaric acid formed by a similar process.



In this connection it should be remembered that maleic acid aldehyde, which according to the investigations of v. AUWERS and WISSEBACH¹⁸ exists in two tautomeric forms, is easily converted into succinic acid (FECHT¹⁹). Some derivatives of maleic acid aldehyde act in the same way.

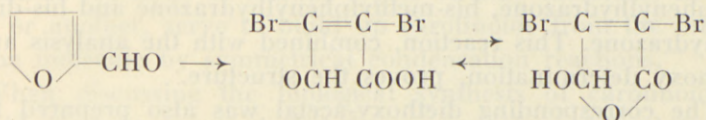


Possibly the above formulations involving a 1.4-elimination of water give no correct picture of what actually happens during the formation of the saturated acids, but all three reactions undoubtedly express the same tendency of similar dihydrofurans to rearrange in a similar manner.

(d) Reactions with the 3.4-double bond. In advance one would expect that reactions between the reagent and the 3.4-double bond of the dihydrofuran would frequently take place. Such reactions have also been observed. Tetrahalotetrahydrofurans may be isolated as the result of the action of halogens on furans; HILL and co-workers, when oxidizing furans with bromine water, have obtained dibromosuccinic acids;²⁰ and by the interaction between furan and hydrogen peroxide cited above, mesotartaraldehyde is formed besides malealdehyde. It has not been investigated whether the addition in the two reactions last mentioned takes place before or after the opening of the furan ring.

However, reactions of this type are rare because the double bond in the dihydrofurans or their products of hydrolysis is

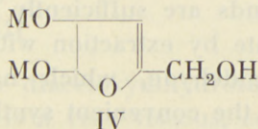
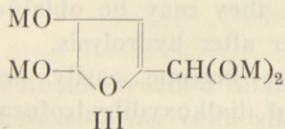
rather inert. As by other double bonds, which are inert towards addition reagents, substitution of the adjacent hydrogen atoms may take place instead of addition. A typical example is the well-known oxidation of furfural or furoic acid to mucobromic or mucochloric acid with warm bromine, respectively chlorine water.²¹



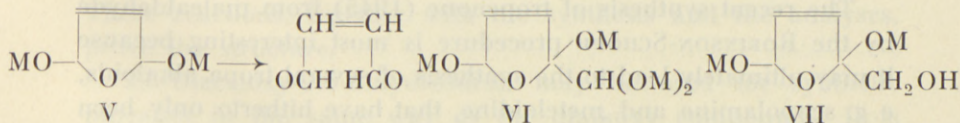
III. 2.5-Dialkoxy-2.5-dihydrofurans.

Scattered throughout the literature on the chemistry of the furans, one finds formulas for furan derivatives which can only be explained by assuming a 1.2-addition to the furan nucleus.^{17, 22-28} In consistency with the view expressed in Part I the author believes such formulas to be incorrect.

MEINEL^{28, 29} has advocated two formulas of this kind. He made the important discovery that furfural and furfuryl alcohol, when treated in methanolic solution with bromine or with compounds containing active bromine, e. g. N-bromophthalimide, add two methoxy groups. The aldehyde group of furfural is at the same time acetalized. MEINEL assigned the formulas III and IV to the addition products.



The experiments of MEINEL have not been repeated here, but a similar methoxylation was carried out on furan with methanolic bromine in the presence of an equimolar amount of potassium acetate. 2.5-Dimethoxy-2.5-dihydrofuran V was hereby obtained in a 47 per cent. yield. It therefore seems reasonable to assign the formulas VI and VII to MEINEL's compounds.



Dimethoxydihydrofuran is a cyclic acetal of malealdehyde. It has an odour similar to that of malealdehyde tetraethylacetal, prepared earlier by WOHL and MYLO,³⁰ and exhibits similar properties. It may be distilled in vacuum and is stable at ordinary temperature. It is rather soluble in water. In acid solution it is rapidly hydrolyzed to malealdehyde, which was identified as bis-phenylhydrazone, bis-methylphenylhydrazone and bis-diphenylhydrazone. This reaction, combined with the analysis and a methoxy determination, proves the structure.

The corresponding diethoxy-acetal was also prepared from furan and a solution of bromine in ethanol (yield 56 per cent.); the structure was proved in the same way as described for the dimethyl-acetal. The higher yield of the ethyl derivative is probably mainly due to its lesser solubility in water.

It is evident that the alkoxylation method is of general applicability in the furan series. The method makes it possible to synthesize stable acetals of labile unsaturated 1,4-dicarbonyl compounds, many of which, as pointed out in Part II, are of importance for synthetic purposes. It will as a rule be most convenient to prepare the ethyl acetals, which are easier to extract with ether than the methyl derivatives. In water or an aqueous solvent the acetals will react in the way of free carbonyl compounds when traces of acids are present. If the carbonyl compounds are sufficiently stable, they may be obtained in a pure state by extraction with ether after hydrolysis.

Malealdehyde, which has now become easily accessible through the convenient synthesis of dialkoxydihydrofurans, has so far only been employed for the synthesis of pyridazine (MARQUIS,² WOHL and BERNREUTHER³¹), of succinaldehyde and some of its derivatives (KEIMATSU and YOKOTA,³² WOHL and BERNREUTHER³¹) and of tropenone (PREOBRAZHENSKIJ, RUBTSOV, DANKOVA, and PAVLOV³³). However, this reactive dialdehyde will surely find a wider range of application when sufficient quantities are at hand.

The recent synthesis of tropenone (1945) from malealdehyde by the ROBINSON-SCHÖPF procedure is most interesting because it may ultimately lead to the synthesis of several tropa alkaloids, e. g. scopolamine and meteloidine, that have hitherto only been

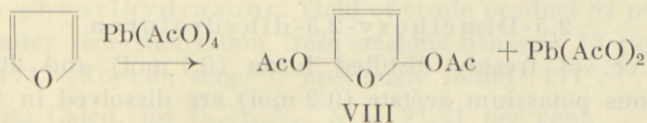
isolated from natural sources. The Russian authors seem to be working along this line. Unfortunately only an abstract of their paper has been available.

If malealdehyde yields tropenone in the ROBINSON-SCHÖPF procedure, it should also be capable of participating in condensation reactions of similar types. It may therefore, in one way or another, serve to build up carotinoids from the middle of the molecule by symmetrical condensation reactions.

When discussing the biological synthesis of carotinoids it should be kept in mind that furans may be oxidized to unsaturated 1.4-dicarbonyl compounds under biological conditions, e. g. with atmospheric oxygen (CIAMICIAN and SILBER,³⁴ MILAS and McALEVY,³⁵ SCHENK,¹⁵ SCHERING A.-G.,³⁶ and DUNLOP, STOUT, and SWADESH³⁷).

IV. 2.5-Diacetoxy-2.5-dihydrofuran.

In view of the stability of the dialkoxydihydrofurans it was highly probable that 2.5-diacetoxy-2.5-dihydrofuran (VIII) also would be a stable derivative of malealdehyde. In order to prepare this compound furan was treated with lead tetraacetate in acetic



acid. From the reaction mixture the diacetyldihydrofuran was isolated in a 45 per cent. yield. It is a very viscous, colourless oil boiling at about 130° C. in vacuum. The analysis and a molecular weight determination in benzene gave the correct values. Although almost insoluble in water, this mixed acetal-acetate is very easily hydrolyzed. The malealdehyde and the acetic acid formed by hydrolysis were identified as bis-phenylhydrazone and S-benzyl thiuronium salt, respectively. The acetic acid was further determined quantitatively by titration. These reactions, together with the synthesis and the analyses, prove the structure.

2.5-Diacetoxy-2.5-dihydrofuran may be used for synthetic purposes in the same way as the dialkoxy compounds. It is

possible that it will in some cases prove superior to the latter because it is easier to saponify in alkaline solution.

V. Summary.

The view is advanced, that reactions between the furan nucleus and what may be termed oxidizing double bond reagents only can be initiated by a β -substitution or a 1.4-addition. This mode of action seems to be an inherent property of the furan nucleus. The latter reaction is by far the most common and its different aspects are discussed.

In consistency with the conception of 1.4-addition, cyclic acetals of malealdehyde are obtained by alkoxylation of furan. The general applicability of this method for the synthesis of acetals of unsaturated 1.4-dicarbonyl compounds is suggested.

Another derivative of malealdehyde, viz. 2.5-diacetoxy-2.5-dihydrofuran, was obtained in a similar way by 1.4-addition of two acetoxy groups to furan. The acetoxylation was performed with lead tetraacetate.

VI. Experimental Part.

2.5-Dimethoxy-2.5-dihydrofuran.

7.25 cc. of freshly distilled furan (0.1 mol) and 20 g. of anhydrous potassium acetate (0.2 mol) are dissolved in 130 cc. of methanol. The mixture is cooled in an ice-salt bath and a solution of 5 cc. of bromine (0.1 mol) in 100 cc. of methanol is added under efficient stirring. The temperature must be kept below -7° C. After all the bromine has been added (20–30 min.) stirring is continued for 5 minutes. Then the reaction mixture is poured into 300 cc. of a cooled saturated solution of calcium chloride. The acetal is extracted with 400 cc. of ether and the ethereal layer shaken with 50 cc. of a saturated solution of potassium carbonate and dried over 20 + 50 g. of solid potassium carbonate. The ether is removed on the steam bath through an ordinary VIGREUX column and the residue distilled in vacuum. Distillation begins at $48^{\circ}/8$ mm. and the fraction boiling at $48-53^{\circ}$ was collected. A small amount (1.3 g.) of a higher boiling residue remained in the flask. The distillate consisted of pure

dimethoxydihydrofuran and boiled sharply at $47^{\circ}/8$ mm. when redistilled.

Yield 6.1 g. = 47 per cent.

Analysis: Calcd. for $C_6H_{10}O_3$: C = 55.36 per cent., H = 7.76 per cent., CH_3O = 47.7 per cent.
 found : C = 55.56 per cent., H = 7.73 per cent., CH_3O = 45.7 per cent.

The acetal is a colourless, stable liquid. It smells like other lower acetals and exhibits similar chemical properties.

Bis-hydrazones of malealdehyde.

About 150 mg. of the acetal were boiled with 3 cc. of centi-normal sulphuric acid for 45 seconds. After cooling, a solution of the corresponding hydrazine in diluted acetic acid (10 cc.) was added. The hydrazones precipitated immediately. The mixture was allowed to stand for some hours, then the precipitate was filtered off, washed thoroughly with water and dried in vacuum over calcium chloride. The crude products were recrystallized once and then proved to be identical with authentic specimens prepared from malealdehyde tetraethylacetal.¹

Bis-phenylhydrazone. Yield of crude product 82 per cent. Yield after recrystallization from acetone-benzene 73 per cent. M. p. 171° (KOFLEK stage*); previously found¹ 171° .

Analysis: Calcd. for $C_{16}H_{16}N_4$: N = 21.21 per cent.
 found : N = 21.13 per cent.

Bis-methylphenylhydrazone. Yield of crude product 98 per cent. Yield after recrystallization from acetone-benzene 67 per cent. M. p. 176° (KOFLEK); previously found¹ 176° .

Analysis: Calcd. for $C_{18}H_{20}N_4$: N = 19.18 per cent.
 found : N = 19.14 per cent.

Bis-diphenylhydrazone. Yield of crude product 82 per cent. Yield after recrystallization from acetone-methanol 60 per cent. M. p. 180° (KOFLEK); previously found¹ 177° .

Analysis: Calcd. for $C_{28}H_{24}N_4$: N = 13.46 per cent.
 found : N = 13.68 per cent.

* All melting points are corrected.

2.5-Diethoxy-2.5-dihydrofuran.

This acetal was prepared in the same way as the methyl derivative, using ethanol instead of methanol. The ethereal extract of the acetal contained a comparatively large amount of ethanol, which was removed by distillation through a small WIDMER column at ordinary pressure. An equal volume of ether was added to the residue and a crystalline precipitate filtered off. The acetal, when distilled in vacuum, boiled at 65–70°/10 mm. The first drops of the distillate had a strong yellow colour, due to some free malealdehyde. This could be removed by heating the distillate for some time on the steam bath. The malealdehyde was hereby destroyed and a colourless product obtained on redistillation.

Analysis: Calcd. for $C_8H_{14}O_3$: C = 60.76 per cent., H = 8.89 per cent., C_2H_5O = 56.9 per cent.
 found : C = 60.30 per cent., H = 8.66 per cent., C_2H_5O = 54.9 per cent.

The acetal was hydrolyzed as described above and the bis-phenylhydrazone of malealdehyde prepared. Yield of crude product 78 per cent. Yield after recrystallization 55 per cent. M. p. 167° (KOFER).

Analysis: Calcd. for $C_{16}H_{16}N_4$: N = 21.21 per cent.
 found : N = 21.27 per cent.

2.5-Diacetoxy-2.5-dihydrofuran.

Preparation. 3.4 g. of freshly distilled furan (0.05 mol), 22.2 g. of lead tetraacetate (0.05 mol) and 100 cc. of perfectly dry glacial acetic acid were placed in a 250 cc. round-bottomed flask fitted with a reflux condenser. The flask is heated over a flame under frequent shaking until the temperature of the mixture is about 100°. By this time all lead tetraacetate has dissolved. The temperature is kept at 90–100° for some minutes; then the flask is cooled with water. If crystals of lead tetraacetate appear on cooling, the reaction is not yet complete and heating must be repeated.

The acetic acid is evaporated under reduced pressure in a water bath. 100 cc. of water containing cracked ice and 200 cc. of ether is added, the mixture shaken vigorously and the aqueous

layer separated. The ethereal layer is dried with sodium sulphate and calcium chloride and the ether removed at ordinary pressure. The residue is distilled in vacuum. After a fore-run of acetic acid, a small amount of free malealdehyde distils at 50–60°. Distillation of the diacetoxydihydrofuran begins at 129°/10 mm. The first drops of the distillate are yellow, the main portion is colourless. Distillation is interrupted when the distillate begins to turn yellow again due to destruction of the residue. The temperature is now about 135°. Yield 4.2 g. = 45 per cent. Redistillation yields 3.9 g. of a slightly yellow product boiling at 128–129°/10 mm. Very viscous oil, almost insoluble in water.

Analysis: Calcd. for $C_8H_{10}O_5$: C = 51.60 per cent., H = 5.42 per cent.
 found : C = 52.01 per cent., H = 5.43 per cent.

Molecular weight determination. The freezing point depression of a benzene solution was measured. Calcd. $M = 186$, found $M = 188$.

Hydrolysis; identification of malealdehyde. Hydrolysis and preparation of the bis-phenylhydrazone of malealdehyde was performed as described for the dialkoxy compounds. Yield of crude product 68 per cent. Yield after recrystallization 58 per cent. M. p. 168–169° (KOFER).

Analysis: Calcd. for $C_{16}H_{16}N_4$: N = 21.21 per cent.
 found : N = 21.33 per cent.

Hydrolysis; titration of acetic acid. About 200 mg. were heated with 5 cc. of 0.02 normal hydrochloric acid to 100° for some minutes and the acetic acid formed by hydrolysis titrated with decinormal barium hydroxide. Found 98.5 per cent. of the theoretical amount.

Hydrolysis; identification of acetic acid. 186 mg. were boiled for one minute with 2 cc. of decinormal sulphuric acid. 3.1 cc. of normal sodium hydroxide were added and boiling continued for some minutes. Then 0.5 cc. of normal sulphuric acid and a solution of 420 mg. of S-benzyl thiuronium chloride

in 2 cc. of water was added and the mixture left in an ice bath for 10 minutes. The precipitate formed was filtered off, washed with 5 cc. of alcohol and dried in vacuum over calcium chloride. Yield 327 mg. = 72 per cent. Yield after recrystallization from 2 cc. of alcohol 180 mg. = 40 per cent. M. p. 132—133° (in a tube). Mixed melting point with an authentic specimen of S-benzyl thiuronium acetate 133°. (DONLEAVY³⁸ 134°; VEIBEL and LILLELUND³⁹ 135—136°).

Analysis: Calcd. for $C_{10}H_{14}O_2N_2S$: N = 12.39 per cent.
found : N = 12.32 per cent.

VII. Acknowledgements.

The analyses have been performed in a most careful way by my colleague Mr. O. ROSENLUND-HANSEN.

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Copenhagen, February 1947.
Universitetets kemiske Laboratorium.

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