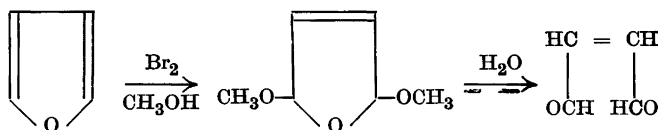


The Alkoxylation of Simple Furans and Related Reactions

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By the addition of alkoxy groups to the α -carbons of furans, stable 2,5-dialkoxy-2,5-dihydrofurans are obtained¹. These addition products may be hydrolyzed under very mild conditions to the corresponding unsaturated 1,4-dicarbonyl compounds, which often are unstable and therefore difficult of accession. The procedure can be illustrated by the methoxylation of furan.



In this article we report some experiments concerning the general applicability of the alkoxylation method. In conclusion, other methods for the preparation of dihydrofurans by oxidation of furans are discussed.

ALKOXYLATION

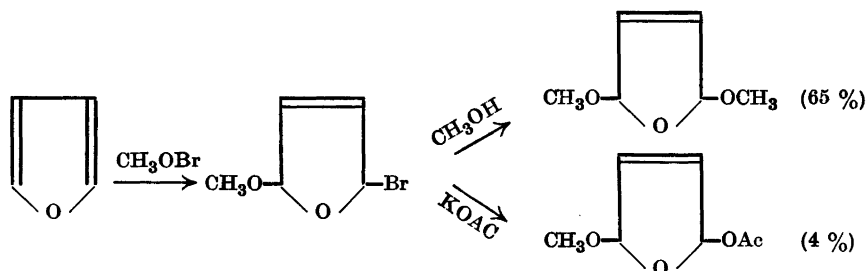
Alkoxylation of furans is accomplished with bromine in alcohol at low temperature in the presence of potassium acetate, which neutralizes the hydrogen bromide formed by the reaction. Furan¹, silvan², furfuryl alcohol³, furfuryl acetate², furfural³ and furfural diacetate⁴ have been methoxylated by this or a similar method. Furan has also been ethoxylated in the same way¹.

We have tried to methoxylate some furans with electronegative substituents in the α -positions, *viz.* furoic acid, ethyl furoate, ethyl furylacrylate, acetylfuran and 2,5-dibromofuran. None of the compounds yielded the corresponding dimethoxy derivatives. It therefore seems fairly safe to assume,

that α -substituted furans with substituents, which are known to decrease the reactivity of unsaturated systems towards the usual double bond reagents, as a rule do not yield addition products with bromine in methanol. The only furan derivative, with an electronegative α -substituent, which has been methoxylated, is furfural³. But in this case dimethoxydihydrofurfural dimethyl-acetal was formed, so that probably acetalization or semi-acetalization has taken place prior to methoxylation.

At present nothing is known about the applicability of the alkoxylation method on β -substituted furans.

It has previously been observed that a small amount of a higher boiling compound is obtained by the preparation of dimethoxydihydrofuran. This has now been identified as 2-methoxy-5-acetoxy-2,5-dihydrofuran. The structure was proved by analysis, methoxy, acetoxy and molecular weight determination, and by hydrolysis to malealdehyde. The formation of methoxy-acetoxy-dihydrofuran together with dimethoxydihydrofuran may be explained as follows:



We have also investigated the alkoxylation of furan with higher alcohols, *viz.* isopropyl, *n*-butyl and isoamyl alcohol. The reaction mixture was not poured into a solution of calcium chloride, but sodium alcoholate was added to neutralize the acetic acid formed by the reaction, after which the mixture was distilled through a column. In this way the major part of the alcohols could be recovered. The acetals were formed in good yields. They are stable liquids, which can be distilled in vacuum. The structure was confirmed by hydrolysis to malealdehyde.

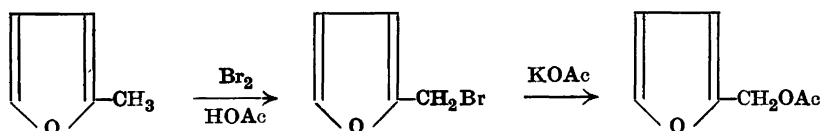
Dibutoxy- and diisoamyloxy-dihydrofuran have a pleasant odor, faintly resembling that of diisoamyl ether.

The molar refraction of the various dihydrofurans was determined, and a small negative exaltation of approximately the same size (0.4—0.6) was found for all compounds. This is in agreement with the proposed similarity of structure.

RELATED REACTIONS

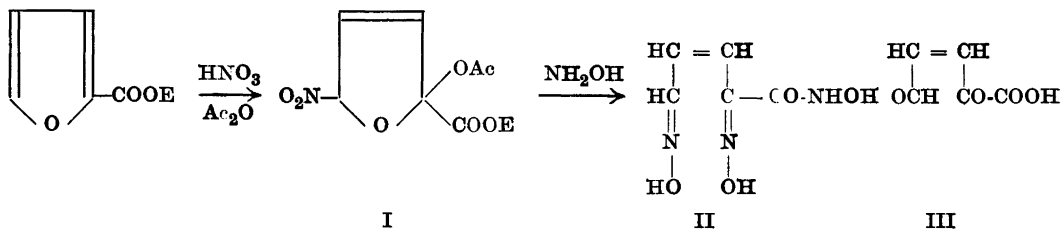
Acetoxylation. Addition of acetoxy groups to furan has been performed with lead tetraacetate,¹ and with bromine in acetic acid in the presence of potassium acetate⁵. No other furans have hitherto been acetoxyated.

It was to be expected that acetoxylation would be subject to the same limitation as alkoxylation. In agreement herewith, we were not able to add acetoxy groups to furoic acid or ethyl furoate by the above methods. But this is obviously not the only limitation of the methods, as silvan could not be acetoxyated with bromine in acetic acid either. The reaction product decomposed suddenly to a black mass when a distillation was attempted (at 1 mm). We believe that decomposition is due to the formation of furfuryl bromide. This suggestion was further strengthened by the isolation from the reaction mixture of a small amount of furfuryl acetate.

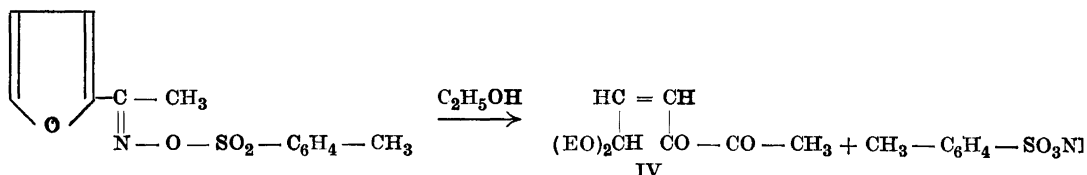


Buu-Hoï and Lecocq found, that silvan reacts with bromo succinimide in the same way⁶.

Marquis' method. Marquis found⁷, that a nitro and an acetoxy group are added to furan and ethyl furoate by the action of nitric acid in acetic anhydride. The procedure has later been extended to other furans. The resulting nitroacetates may in some cases be hydrolyzed to the corresponding unsaturated 1,4-dicarbonyl compounds, but these can, as a rule, be obtained much easier from dialkoxydihydrofurans, because the nitroacetates often are labile and difficult to hydrolyze. They also very easily split off acetic acid with the formation of an α -nitrofuran. However, Marquis' method is of importance for the preparation of unsaturated 1,4-dicarbonyl compounds from furans because *at present it is the only general way of obtaining 1,4-addition products of simple furans with an electronegative α -substituent.* *E. g.*, oxidation of ethyl furoate and addition of hydroxylamine to the nitroacetate (I) yields a derivative (II) of the acid III (Marquis⁷). This compound cannot be obtained by any other method.



Oxidation with hydroxylamine. It has recently been observed⁸, that *p*-toluenesulphonyl 2-acetofuran-oxime reacts with alcohol to form the acetal IV and toluenesulphonic acidic ammonium. No details of the reaction mechanism are known, but the net result of the reaction is that hydroxylamine



has oxidized acetofuran to the corresponding carbonyl compound. It is possible that the method is of general applicability for the oxidation of furans with a carbonyl group in the α -position.

EXPERIMENTAL

2,5-Dimethoxy-2,5-dihydrofuran and 2-methoxy-5-acetoxy-2,5-dihydrofuran

36 ml of freshly distilled furan (0.5 mole) and 100 g of anhydrous potassium acetate (1 mole) are dissolved in 600 ml of methanol. The mixture is cooled in an ice-salt bath and a solution of 25 ml of bromine in 500 ml of methanol is added under efficient stirring. The temperature must be kept below -7° . After all the bromine has been added (1 hour) stirring is continued for 5–10 minutes. Then the reaction mixture is poured into 1500 ml of a cooled, saturated, solution of calcium chloride. The acetal is extracted with 2000 ml of ether, and the ethereal layer shaken with 250 ml of a saturated solution of potassium carbonate and dried over 100 + 500 g of solid potassium carbonate. The ether is removed on the steam bath through a Vigreux column and the residue distilled in vacuum. Distillation begins at $54^\circ/13$ mm and the fraction boiling at $54\text{--}56^\circ$ is collected. It consists of dimethoxydihydrofuran, yield 42 g = 65 %. Distillation is continued, whereby about 4 g of higher boiling material is obtained (b. p. $56\text{--}106^\circ$). Redistillation of this fraction yields 3.2 g of a colourless liquid (b. p.₁₃ $96\text{--}99^\circ$) which is analytically pure methoxy-acetoxy-dihydrofuran. The compound turns yellow on prolonged standing but is otherwise stable.

$\text{C}_7\text{H}_{10}\text{O}_4$	Calc.	C 53.18	H 6.38	CH_3O 19.6	CH_3COO 37.4	Mol. wt.	158.2
	Found	» 53.63	» 6.22	» 19.5	» 35.9	» »	176

We have tried to carry out the synthesis of dimethoxydihydrofuran by adding sodium methoxide to the reaction mixture as described for the preparation of higher alkoxy derivatives, and also by substituting potassium acetate by pyridine. In both cases good yields of dimethoxydihydrofuran were obtained, but the method reported above was found to be more convenient.

Hydrolysis of methoxy-acetoxy-dihydrofuran; identification of malealdehyde. 189 mg of methoxy-acetoxy-dihydrofuran were boiled with 3 ml of 0.01 N hydrochloric acid and 2 ml of alcohol for one minute. After cooling, a solution of 0.3 ml of phenylhydrazine in diluted acetic acid (10 ml) was added and the bis-phenyl hydrazone of malealdehyde isolated in the usual manner¹. Yield of crude product 209 mg = 66 %. Yield after recrystallization from acetone-benzene 151 mg = 48 %. M. p. 168—69° (Kofler stage, corr.), previously found⁹ 171°.

$C_{16}H_{16}N_4$ (264) Calc. N 21.21 Found N 21.13

Higher dialkoxy-dihydrofurans

7.25 ml of furan (0.1 mole) and 20 g of potassium acetate (0.2 mole) are dissolved, or suspended, in 130 ml of the alcohol, (technical grade) and 5 ml of bromine in 100 ml of the alcohol are added at —7° during 20—30 minutes, as described above. The reaction mixture is heated to room temperature and allowed to stand for 30 minutes. Then a solution of sodium alkoxide from 4.60 g of sodium (0.2 mole) is added at 0° under stirring and efficient cooling. After 15 minutes 300 ml of ether are added, and the precipitated potassium bromide and sodium acetate filtered off and washed with 50 ml of ether. The ether is removed on the steam bath, and the residue distilled in vacuum through a Widmer column. Hereby the major part of the alcohol is recovered and may be employed in a subsequent run. The remaining acetal is distilled in vacuum without the column. It is sometimes necessary to remove traces of sodium acetate prior to distillation by renewed precipitation with ether.

Di-n-butoxy-dihydrofuran. B. p.₁₅ 127—128°, yield 16.0 g = 75 %.

$C_{12}H_{22}O_3$	Calc. C 67.26	H 10.35	Mol. wt. 214.3
	Found » 66.59	» 10.17	» » 190

188 mg of dibutoxy-dihydrofuran were boiled with 2 ml of 0.01 N sulfuric acid and 2 ml of alcohol for 2 minutes, and the bis-phenylhydrazone of malealdehyde prepared in the usual manner. Yield of crude product 164 mg = 71 %. Yield after recrystallization 94 mg = 41 %, m. p. 170—172°.

$C_{16}H_{16}N_4$ Calc. N 21.21 Found N 21.34

Diisoamyloxy-dihydrofuran. B. p._{0.6} 101—103°, yield 15.5 g = 64 %.

$C_{14}H_{26}O_3$	Calc. C 69.39	H 10.82	Mol. wt. 242.3
	Found » 69.53	» 10.54	» » 230

169 mg of diisoamyloxy-dihydrofuran were boiled with 1 ml of N sulfuric acid and 1 ml of alcohol for one minute and the bis-phenylhydrazone of malealdehyde prepared in the usual manner. Yield of crude product 114 mg = 62 %. Yield after recrystallization 56 mg = 31 %, m. p. 169—170°.

$C_{16}H_{16}N_4$ (264) Calc. N 21.21 Found N 21.32

Diisopropoxy-dihydrofuran. In the preparation of this acetal, it was necessary to add the bromine in a solution of carbon tetrachloride because of the ease with which isopropyl alcohol is oxidized by bromine. Furthermore, the acetic acid was removed by shaking the reaction mixture with 300 ml of ether and two portions of potassium carbonate (each 50 g) for 10 and 30 minutes, respectively. B. p.₁₅ 85—90°, yield 13.0 g = 70 %.

$C_{10}H_{18}O_4$	Calc.	C 64.51	H 9.74	Mol. wt. 186.2
	Found	» 64.98	» 9.73	» » 188

Diisopropoxy-dihydrofuran turns yellow after some days. This may, however, be due to a small amount of an impurity.

209 mg of the acetal were hydrolyzed as described for the butoxy derivative. Yield of crude malealdehyde-bisphenylhydrazone 150 mg = 51 %. Yield after recrystallization 117 mg = 40 %, m. p. 169—170°.

$C_{16}H_{16}N_4$ (264)	Calc.	N 21.21	Found	N 21.25
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Molar refractions of dialkoxydihydrofurans

2 ml of the dialkoxydihydrofuran were redistilled carefully at 12 mm. The middle fraction (about 1 ml) was collected and employed for the determination of the density, and the refractive index. The results are tabulated below.

Dihydrofuran	B.p. ₁₂	d_4^{20}	n_D^{20}	M_D	M_D calc.	Δ
Dimethoxy-	51°	1.0713	1.4328	31.56	32.17	— 0.61
Diethoxy-	71— 73°	1.0019	1.4309	40.86	41.41	— 0.55
Diisopropoxy-	83— 84°	0.9539	1.4284	50.27	50.64	— 0.37
Di- <i>n</i> -butoxy-	118—120°	0.9436	1.4371	59.51	59.88	— 0.37
Diisoamyloxy-	130—131°	0.9267	1.4380	68.67	69.11	— 0.44

SUMMARY

The general applicability of the alkoxylation method in the furan series has been investigated. 2,5-Diisopropoxy-, 2,5-di-*n*-butoxy- and 2,5-diisoamyloxy-2,5-dihydrofuran were prepared. 2-methoxy-5-acetoxy-2,5-dihydrofuran was isolated as a by-product from the methoxylation of furan. Other methods for the preparation of dihydrofurans by oxidation of furans have been discussed.

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REFERENCES

1. Clauson-Kaas, N. *Kgl. Danske Videnskab. Selskab, Mat.-fys. Medd.* 24 (1947) (6).
2. Clauson-Kaas, N., and Limborg, F. *Acta Chem. Scand.* 1 (1947) 619.
3. Meinel, K. *Ann.* 516 (1935) 231.
4. Clauson-Kaas, N., and Fakstorp, J. *Acta Chem. Scand.* 1 (1947) 415.
5. Clauson-Kaas, N. *Acta Chem. Scand.* 1 (1947) 379.
6. Buu-Hoi, Ng., and Lecocq, J. *Compt. rend.* 222 (1946) 1441.
7. Marquis, R. *Ann. chim.* (8) 4 (1905) 196.
8. Vargha, L., Ramonczai, J. and Bite, P. *Nature* 159 (1947) 744.
9. Clauson-Kaas, N., and Fakstorp, J. *Acta Chem. Scand.* 1 (1947) 210.

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