ACTA CHEMICA SCANDINAVICA 4 (1950) 1233–1240

The Preparation of 2,5-Diacetoxy-2,5-Dihydrofuran, 2,5-Diacetoxytetrahydrofuran and Pyridazine

NIELS CLAUSON-KAAS, SI-OH LI and NIELS ELMING

Centrallaboratoriet, Sadolin & Holmblad A/S, Copenhagen, Denmark

2,5-DIACETOXY-2,5-DIHYDROFURAN

It has previously been reported [1], that 2,5-diacetoxy-2,5-dihydrofuran may be obtained in a 70 per cent yield by oxidizing furan with bromine in acetic acid in the presence of potassium acetate. We have since observed that this method of preparation now and then fails totally because the diacetoxydihydrofuran, formed by the reaction, occasionally changes into a black insoluble mass. At the same time acetic acid is formed. This conversion either takes place during the final distillation, or on standing after the distillation has been completed. Sometimes it takes several days before the distillate turns black, but usually the black mass is formed during the distillation or immediately after, with the evolution of heat and with almost explosive violence. If the preparation of larger batches is attempted, decomposition *always* occurs. It thus became clear that the directions given previously for the synthesis of diacetoxydihydrofuran were insufficient, and that much more minute information than is usually necessary in synthetic organic chemistry, was required.

If a small amount of a strong acid (H_2SO_4, HCl, $SnCl_4$, BF_3, $AlCl_3$, $ZnCl_2$) is added to diacetoxydihydrofuran a transformation similar to the one described above takes place. We therefore believe, that the occasional destruction of diacetoxydihydrofuran during its preparation is due to the liberation of hydrobromic acid from certain bromo compounds, which are formed in small amounts together with diacetoxydihydrofuran by the action of bromine on furan. This was substantiated by the fact that all our samples of diacetoxydihydrofuran contained some bromine, usually 1—3 per cent.

After the sensitivity of diacetoxydihydrofuran towards acids had been observed, we modified the original procedure for its preparation. According

to the new method, a mixture of acetic acid and acetic anhydride is used as a solvent. The bromine is added first (at — 17°) and, immediately after, all the furan at once. Before the final distillation the reaction product is refluxed in vacuum over potassium acetate. In this way 0.8 mole of diacetoxydihydrofuran is obtained from 1.1 moles of furan and 2.0 moles of bromine. The product, which contains 0.5—2.0 per cent of bromine, is stable and sufficiently pure for most purposes.

Samples of diacetoxydihydrofuran, prepared according to the new method, as well as stable samples prepared after the original procedure, gradually turn yellowish-brown when kept at room temperature without any special precautions with regard to light, moisture or oxygen; but the refractive index remains almost constant and even two year old samples are apparently practically unchanged. If, however, such samples are redistilled, they decompose during the distillation or shortly after, which indicates that some hydrogen bromide has again been liberated.

This can be explained by assuming, that two different types of bromo-compounds are present as impurities in the diacetoxydihydrofuran. The first type are bromo-dihydro- or tetrahydrofurans, *e. g.* tetrabromotetrahydrofuran, which split off hydrogen bromide spontaneously on heating under regeneration of the double bonds of the furan nucleus. These compounds react when heated with potassium acetate, and they are thus not present in the stable samples of diacetoxydihydrofuran. The other type of bromo compounds are bromofurans like 2,5-dibromofuran or tetrabromofuran. Such compounds are autoxidized by atmospheric oxygen to substances, which either split off hydrogen bromide spontaneously or, like acyl bromides, by the action of water (*cf.* Hill and Hartshorn [2]; Torrey [3]). We think that these autoxidized bromofurans cause the decomposition of old samples of diacetoxydihydrofuran, as soon as a redistillation is attempted.

In agreement herewith we have found that bromine-free diacetoxydihydrofuran is obtained by redistilling old samples of ordinary diacetoxydihydrofuran from potassium or lithium acetate. Presumably the autoxidized bromofurans, when heated with the alkali acetate, react in such a way, that no bromo-compounds distil together with the diacetoxydihydrofuran. It was later found, that a bromine-free product could also be prepared by passing oxygen through the crude diacetoxydihydrofuran for one week and then refluxing and distilling from potassium acetate. Like the crude product, bromine-free diacetoxydihydrofuran slowly turns yellow on standing at room temperature for several months, but it can at any time be redistilled without decomposition.

The crude, as well as the purified diacetoxydihydrofuran, usually crystallizes after standing for some weeks at — 20°. At room temperature, only about 2/3 of the samples remain crystalline. This may be due to the presence of impurities, but it is also possible, that the diacetoxydihydrofuran is a mixture of the *cis* and the *trans* isomer.

2,5-DIACETOXYTETRAHYDROFURAN

Diacetoxydihydrofuran may, similar to 2,5-dialkoxy-2,5-dihydrofurans [4,5], be hydrogenated catalytically to the corresponding tetrahydrofuran with Raney nickel. The rate of hydrogenation is much lower than the rate of

hydrogenation of the dialkoxycompounds so there is no sudden evolution of heat when the reaction is started. We also found, that the course of the reaction depends largely on the purity of the diacetoxydihydrofuran. With the crude, bromine-containing diacetoxydihydrofuran good yields of diacetoxytetrahydrofuran were obtained in some experiments, while other experiments, which were carried out under what one would normally call identical conditions, only led to the formation of lower boiling compounds such as acetic acid and succinaldehyde. Sometimes no hydrogenation at all took place. It was evident that during the hydrogenation varying amounts of hydrogen bromide were liberated, which interfered with the hydrogenation reaction as well as with the isolation of the tetrahydrofuran. We therefore tried to change the hydrogen pressure, the solvent, the time of hydrogenation and the amount of catalyst. We also tried adding substances such as pyridine or potassium acetate before or after the hydrogenation, but it was not possible to find any way of preparation, which gave reproducible results.

This was first achieved, when bromine-free diacetoxydihydrofuran was used for the hydrogenation. With alcohol as a solvent about 80 per cent of diacetoxytetrahydrofuran may then be obtained regularly. Hydrogenation also takes place in acetic acid but not in ethyl acetate.

Diacetoxytetrahydrofuran is a new compound. After hydrolysis with dilute hydrochloric acid and addition of phenylhydrazine to the hydrolysate a perfectly white precipitate (succinaldehyde bis-phenylhydrazone) is formed. This indicates, that no traces of the original dihydrofuran are present, since diacetoxydihydrofuran gives a yellow precipitate (malealdehyde bis-phenylhydrazone) after hydrolysis.

PYRIDAZINE

The easiest way to prepare pyridazine is by condensing malealdehyde or a derivative of malealdehyde with hydrazine. This method was first employed by Marquis [6], who added a large excess of hydrazine to nitroacetin (2-nitro-5-acetoxy-2,5-dihydrofuran) in methanol (yield of pyridazine 60 %). Later Wohl and Bernreuther [7] used malealdehyde, obtained by hydrolysis of the tetraethylacetal, and an aqueous solution of hydrazine (yield 80 %). Recently malealdehyde has become easily accessible through hydrolysis of 2,5-dialkoxy-2,5-dihydrofurans or 2,5-diacetoxy-2,5-dihydrofuran [8,9]. Of these derivatives of malealdehyde, diacetoxydihydrofuran is the easiest to prepare in large amounts in the laboratory. We have therefore worked out directions for a synthesis of pyridazine from diacetoxydihydrofuran. The diacetoxydihydrofuran is first hydrolyzed at room temperature with $N/10$ sulfuric acid, then the

acetic acid formed is neutralized and an aqueous solution of hydrazine added. The yield of pyridazine is about 85 per cent.

EXPERIMENTAL

(Microanalyses by G. Cornali)

Preparation of 2,5-diacetoxy-2,5-dihydrofuran*

205 g of anhydrous potassium acetate (2.09 moles) are placed in a 2 liter three-necked flask fitted with a calcium chloride tube, a thermometer and a stirrer of the Hershberg type [10]. 600 ml of acetic anhydride and 400 ml of acetic acid are added, the mixture is heated until the potassium acetate has dissolved, and then cooled with stirring to about − 17° in a cooling-bath of − 22°. Part of the potassium acetate precipitates, and care should be taken that no cakes of potassium acetate are formed on the walls of the flask. It is desirable that some acetic acid crystallizes, but not so much as to slow down the speed of the stirrer. Now 160 g of bromine (2.00 moles) are added and − as soon as the solution has become homogenous − 80 ml of furan (1.10 moles) (note 1) are quickly poured into the mixture with efficient stirring. The addition of furan should take 6—7 seconds. The temperature rises to about 12° and then after 1 minute begins to fall again. The major part of the bromine has disappeared after 20—30 seconds and after 2—5 minutes the reaction mixture is perfectly white. When the temperature has fallen to zero, the flask is placed in an ice-water-bath and kept there for 30 minutes. Then the mixture is heated in a water-bath to 80° in the course of 15 minutes, kept at 80° for 10 minutes and cooled with water to room temperature. During these operations stirring is continued. The potassium bromide is removed by filtration and washed with 200 ml of acetic acid containing 10 per cent of acetic anhydride. The yield of potassium bromide may, if desired, be determined by washing with ether and drying. Yield: 224 g = 94 %.

KBr (119.0) Calc. Br 67.2 Found Br 67.2

The filtrate is evaporated from a water-bath of 70°, first at 10—15 mm and then, after the removal of about 900 ml of the solvent, at 1—2 mm. When the distillation is complete, a dark, almost black oil, remains in the flask. This consists of diacetoxydihydrofuran and a small amount of acetic anhydride together with a precipitate of a mixture of potassium bromide and an acid potassium acetate. 200 ml of dry ether are added, and the precipitate (15—20 g) is removed by filtration and washed twice with 50 ml of ether. The etheral solution of diacetoxydihydrofuran is evaporated from a water-bath of 50° and the residue poured into a 250 ml distillation flask, which has previously been coated on the inside with 5 g of potassium acetate by melting the potassium acetate in the flask and letting it crystallize while the flask is swirled. The flask is now fitted to the distillation apparatus by a 40 cm long vertical air-condenser and the product refluxed in vacuum (10—15 mm) by heating with an infrared lamp. The temperature at the top of the condenser hereby rises to 60—80° and a fore-run (15—20 ml) is collected. After ½ hour the air-condenser is removed and the remaining diacetoxydihydrofuran is distilled under 10—15 mm. Distillation is continued until the temperature begins to fall in spite of continous heating. At this point the distillation flask is almost dry and only contains

a black mass. The boiling range from the first to the last drop is 4—5° at about 135°. Yield of diacetoxydihydrofuran 155 g = 83 %, $n_D^{25} = 1.4534 \pm 0.0005$. The product is not perfectly colourless, but has a yellowish-brown tinge. The time required for the synthesis is 6—7 hours.

$C_4H_4O_3$ $(CH_3CO)_2$ (186.2)	Calc.	CH_3CO	46.2	Br	0
	Found	»	45.4	»	0.9

After standing for one month at room temperature without any special precautions with regard to light, moisture or oxygen the colour is somewhat darker yellowish-brown, but the refractive index remains constant within 0.0005. If the product is stored at — 20° it usually crystallizes to a solid mass after some weeks. When these crystals are used to inocculate liquid samples kept at room temperature, about 2/3 of the sample will crystallize in the course of a few days with the formation of very large rhombic plates. After being filtered off and washed with petroleum ether, the melting point of the crystals is 29°—35° (Kofler hot stage), 35°—38° (Hershberg apparatus[10]). The refractive index of the crystals, when molten, as well as of the mother liquid is the same as of the original sample.

Note 1. The purity of the reagents does not seem to be essential. We used good technical grades of furan, bromine, acetic acid and potassium acetate and an analytical grade of acetic anhydride. The reagents were not purified in any way before use.

Purification of crude diacetoxydihydrofuran

Bromine-free diacetoxydihydrofuran was obtained in two ways. In one experiment various 6 months old samples of crude diacetoxydihydrofuran, containing 1—3 per cent of bromine, were redistilled in vacuum from potassium acetate and then from lithium acetate. In another experiment oxygen was passed through a sintered glass disk into the diacetoxydihydrofuran for one week at room temperature. Then the product was refluxed over potassium acetate with an air condenser and distilled as described above for the synthesis of diacetoxydihydrofuran. Both procedures yielded a distillate, which gave a negative Beilstein test for halogen during the major part of the distillation, while the last fractions gave a weak positive Beilstein test. The refractive index remained almost constant during the distillation, ($n_D^{25} = 1.4537—1.4541$).

When attempting the purification of a large amount of diacetoxydihydrofuran the product may decompose to some extent during the distillation with the formation of acetic acid. Probably the traces of hydrogen bromide formed on heating are not neutralized by the alkali acetate on the walls of the flask as rapidly in a large as in a small flask. Usually a second distillation from alkali acetate proceeds without decomposition.

Preparation of 2,5-diacetoxytetrahydrofuran*

50 g of bromine-free diacetoxydihydrofuran and 200 ml of absolute ethanol (technical product) are hydrogenated with 4 g of Raney nickel under 100 atmospheres for 2 hours in a 1 liter flask. After hydrogenation the solvent is removed in vacuum and the reddish brown residue distilled under 10 mm. About 12 g of fore-run are collected, then

* Patent pending.

the main fraction distils at 125°—128°. There is no residue in the flask. Yield 39 g = 77 %; $n_D^{25} = 1.4390$.

$C_4H_6O_3$ $(CH_3CO)_2$ (188.2)	Calc.	C 51.1	H 6.43	CH_3CO	45.6
	Found	» 51.4	» 6.92	»	44.7

The product gives a pure white precipitate with phenylhydrazine after hydrolysis with N/10 hydrochloric acid.

Hydrogenation of 2,5-dialkoxy-2,5-dihydrofurans

For the sake of comparison we have hydrogenated dimethoxydihydrofuran and diethoxydihydrofuran with Raney nickel. The hydrogenation of dimethoxydihydrofuran to the tetrahydro compound has previously been reported in a patent by Jones [4] (yield 85 %) and the reaction conditions given below are almost identical with those of Jones. The hydrogenation of diethoxydihydrofuran was first described by Fakstorp, Raleigh and Schniepp [5] (yield 85 %).

50.0 g of analytically pure dimethoxydihydrofuran (commercial product from *Kemisk Værk Køge A/S*, Copenhagen) and 60 ml of methanol (technical product) were shaken with 1.5 g of Raney nickel under 100 atmospheres for 1 hour in a 1 liter flask. The temperature rose to about 80° during the first few minutes of shaking. After hydrogenation the methanol was removed through a packed column, and the residue distilled under ordinary pressure without the column.

Fractions	g	b. p.	n_D^{25}
1	2.6	145.2°—147.2°	1.4138
2	40.4	147.2°—149.6°	1.4160
3	3.3	148.0°—152.0°	1.4160
4	1.2	151.3°—160.2°	1.4160

There was no residue in the flask. All fractions gave a pure white precipitate with phenylhydrazine after hydrolysis with N/10 hydrochloric acid.

It will be seen, that the boiling point is not constant during the distillation, while the refractive index remains constant. We have in separate experiments found, that this is due to overheating, which always occurs, when the substance is distilled in the usual way without a column.

Fractions 2—4 (44.9 g) were mixed and analyzed.

C_4H_6O $(OCH_3)_2$ (132.2)	Calc.	C 54.6	H 9.16	CH_3O	47.0
	Found	» 55.4	» 9.57	»	46.1

The yield of analytically pure dimethoxytetrahydrofuran is thus 89 %.

50.0 g of analytically pure diethoxydihydrofuran (commercial product from *Kemisk Værk Køge A/S*, Copenhagen) and 60 ml of absolute ethanol were shaken with 1.5 g of Raney nickel under 50 atmospheres for 3 hours in a 1 liter flask. The temperature rose to about 60° during the first 10 minutes of shaking. After hydrogenation the ethanol was removed through a column and the residue distilled under ordinary pressure without the column. There was no residue. Since both fractions are analytically pure, the yield

Fractions	g	b. p.	n_D^{25}	C_2H_5O (calc. 56.2)
1	46.0	167°—174°	1.4170	56.6
2	3.0	174°—178°	1.4171	56.9

of pure diethoxytetrahydrofuran is 49.0 g = 97 %. The product gave a pure white precipitate with phenylhydrazine after hydrolysis with *N*/10 hydrochloric acid. The value for n_D^{25} given by Fakstorp, Raleigh and Schniepp[5] (1.4164) agrees with our values.

The rise in the boiling point towards the end of the distillation is due to overheating (see above).

Preparation of pyridazine

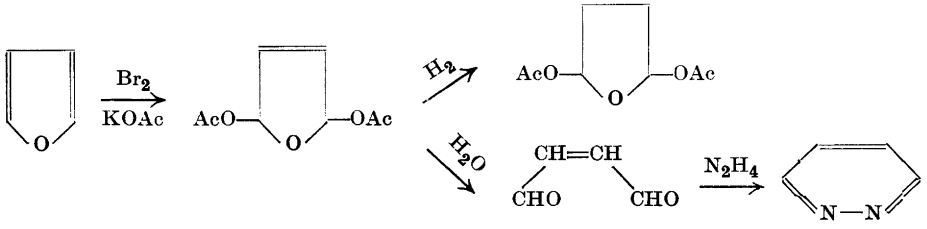
93 g of diacetoxydihydrofuran (0.50 mole) and 400 ml of N/10 sulfuric acid are placed in a 2 liter three-necked flask fitted with a separatory funnel, a thermometer and a stirrer of the Hershberg type. The mixture is stirred efficiently at room temperature until a homogeneous solution is obtained, which usually requires 20—30 minutes. After standing further for 30 minutes, the flask is placed in an ice-salt-bath, the solution cooled to zero and neutralized by adding a solution of 42 g of sodium hydroxide in 800 ml of water in the course of 15—20 minutes. When the major part of the sodium hydroxide has been added, the solution turns yellow. The addition is continued until the solution reacts neutral towards litmus paper. During the neutralization the temperature rises to 5°. Now a previously cooled solution of 98 g of hydrazine sulfate (note 1) (0.75 mole) and the equivalent amount of sodium hydroxide (61 g) in 300 ml of water is added within 2 minutes. The temperature of the reaction mixture hereby rises to 13°. Stirring is discontinued and the flask removed from the cooling-bath and left standing overnight at room temperature. In the first half hour after the addition of hydrazine the colour becomes a little darker. The next day the reaction mixture is refluxed for 30 minutes, then 168 ml of concentrated hydrochloric acid are added with stirring and the dark brown reaction mixture is evaporated in vacuum in a 3 liter round-bottomed flask until 1500 ml of water have been removed. Hereby a large amount of sodium chloride and sodium sulfate precipitates. The residue is cooled with ice-water, filtered and the precipitate washed with 500—600 ml of 60 % aqueous ethanol, which has first been cooled to zero. The filtrate is further evaporated in vacuum in a 2 liter flask till about 200 ml and another batch of salts is removed by filtration. After renewed evaporation to 200 ml 195 g of anhydrous potassium carbonate are added to liberate the pyridazine, and the reaction mixture is stirred or shaken until all the potassium carbonate has reacted or dissolved (30—60 minutes). Now the pasty mixture is shaken vigorously in the flask with 100 ml of ether and the etheral extract decanted. This is repeated about 10 times until no black oil drops remain. The combined etheral extracts are shaken for ½ hour with 30 g of

potassium carbonate and the ether is removed through a small packed column. The oily yellowish-brown residue is then distilled in vacuum. After 0.5—1 ml of fore-run, the fraction boiling within 1° at about 85° under 13 mm is collected. About 2 g of a dark red residue remains in the flask. Yield of pyridazine 34 g = 85 %. The product is slightly yellow. $n_D^{23,5} = 1.5231$ (Brühl [11] = 1.5231).

Note 1. The hydrazine sulfate, as well as the sodium hydroxide used in this synthesis were good technical grades.

SUMMARY

Detailed directions are given for the preparation of 2,5-diacetoxy-2,5-dihydrofuran, 2,5-diacetoxytetrahydrofuran and pyridazine by the following sequence of reactions.



During this investigation one of us (Si-Oh Li) received financial aid from *The Danish Committee on Training of Foreign Scientists in Danish Laboratories.*

LITERATURE

1. Clauson-Kaas, N. *Acta Chem. Scand.* **1** (1947) 379.
2. Hill, H. B., and Hartshorn, G. T. *Ber.* **18** (1885) 448.
3. Torrey, R. *Am. Chem. J.* **19** (1897) 168.
4. Jones, D. G., and Imperial Chemical Industries Ltd. Brit. 610876. *C. A.* **43** (1949) 2643.
5. Fakstorp, J., Raleigh, D., and Schniepp, L. E. *J. Am. Chem. Soc.* **72** (1950) 869.
6. Marquis, R. *Ann. chim. phys.* (8) **4** (1905) 196.
7. Wohl, A., and Bernreuther, E. *Ann.* **481** (1930) 1.
8. Jones, D. G., and Imperial Chemical Industries Ltd. Brit. 595041. *C. A.* **42** (1948) 2992.
9. Clauson-Kaas, N. *Kgl. Danske Videnskab. Selskab, Mat. fys. Medd.* **24** (1947) 6.
10. Fieser, L. F. *Experiments in organic chemistry.* Boston (1941) pp. 308, 327.
11. Brühl, I. W. *Z. phys. Chem.* **22** (1897) 373.

Received July 28, 1950.