4. The corresponding free energies have also been calculated. It appears that with increased branching in this group of heptane isomers the free energy level is raised by an average of 600 cal. for each side branch.

STANFORD UNIVERSITY, CALIFORNIA

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE RICE INSTITUTE]

ALPHA-TETRAHYDROFURFURYL CHLORIDE AND ALPHA-TETRAHYDROFURFURYL ETHERS

BY W. R. KIRNER

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In a recent paper from this Laboratory[1] the synthesis of α-furfuryl chloride and a few α-furfuryl ethers was described. The preparation of tetrahydrofurfuryl chloride has now been accomplished by a similar application of the Darzens reaction to tetrahydrofurfuryl alcohol. This alcohol is now available in quantity from the Miner Laboratories of Chicago. Furfuryl chloride was found to be a relatively unstable substance having a sharp odor and exhibiting lachrymatory properties and possessing an extremely reactive chlorine atom. Tetrahydrofurfuryl chloride, on the other hand, is a relatively stable substance with a mildly pleasant odor, exhibits no lachrymatory properties and has an extremely unreactive chlorine atom.

The synthesis of the tetrahydrofurfuryl ethers was first attempted by the method which was successfully used for the preparation of the furfuryl ethers, namely, treatment of the chloride with the desired alcohol in the presence of pulverized potassium hydroxide. Treatment of furfuryl chloride under these conditions gave high yields of ethers with the reaction occurring very rapidly. In the case of the tetrahydrofurfuryl chloride this method failed. It was found that the chlorine atom in tetrahydrofurfuryl chloride was very much less reactive than the chlorine atom in furfuryl chloride. Thus, in an attempt to prepare tetrahydrofurfuryl methyl ether, tetrahydrofurfuryl chloride was treated with pulverized potassium hydroxide and absolute methyl alcohol and refluxed for a considerable period of time at the boiling point of the alcohol. The reaction occurred extremely slowly and only to a slight extent. It is possible that this reaction might be used for the preparation of the higher ethers for then the reaction could be carried out at a much higher temperature than is possible when methyl alcohol is used. However, this proposed method of preparation of the tetrahydrofurfuryl ethers has the disadvantage that an unsaturated tetrahydrofuran derivative can be formed simultaneously due to the elimination of halogen acid by the basic reagent used, a reaction which was not possible in the case of furfuryl chloride. Thus

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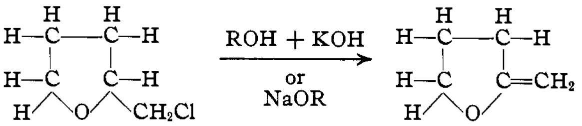
[1] Kirner, THIS JOURNAL, **50**, 1955 (1928).



In fact, the small amount of impure ether which was isolated in the above mentioned experiment showed strong reducing action to both bromine and potassium permanganate and obviously contained an unsaturated compound. Work on this phase of the reaction is being continued with the object of isolating the unsaturated compound in a pure state.

The synthesis of the ethers was satisfactorily accomplished using the method described by Wissell and Tollens[2] for the synthesis of the furfuryl ethers. This consisted in treating tetrahydrofurfuryl alcohol with the desired alkyl halide in the presence of pulverized potassium hydroxide. The reaction took place smoothly and rapidly and gave excellent yields. The tetrahydrofurfuryl ethers are much more stable than the simple furfuryl ethers and remain practically colorless when merely placed in glass-stoppered bottles under atmospheric pressure and in the absence of a stabilizing agent such as hydroquinone. Table I lists the physical properties, yields and analytical data of the· chloride and the ethers which were prepared.

In comparing the boiling points of the furfuryl and tetrahydrofurfuryl compounds it is found that the tetrahydrofurfuryl compounds boil uniformly about 6° higher than the corresponding furfuryl compounds. The densities and refractive indices of the tetrahydro compounds are lower than those of the corresponding furfuryl compounds. In the case of the furfuryl compounds the molecular refraction showed a slight depression,

TABLE I

DATA ON TETRAHYDROFURFURYL COMPOUNDS

No.	Tetrahydrofurfuryl	B. p., °C.	Pressure, mm.	Yield, %
1	Chloride	149.0–149.5 38.5–39	721 10	75
2	Methyl ether (methyl iodide method)	140–141	715.5	73
2a	Methyl ether (dimethyl sulfate method)	140–141.5	723	74
3	Ethyl ether	152–154	726	85
4	*n*-Propyl ether	175–176.5	728	86
5	*n*-Butyl ether	194.5–196	721	79
6	Iso-amyl ether	86.5–87.5 209–210 (corr.)	10 718	69
7	*n*-Hexyl ether	107.5–108.5 231–233	10 708	63
8	Allyl ether	179.5–181	707	83
9	Benzyl ether	141.5–143	10	92

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[2] Wissell and Tollens, *Ann.*, **272**, 291 (1892).

TABLE I (*Concluded*)

No.	$n_D^{20°}$ (Abbé)	d_4^{20}	d_{20}^{20}	Mol. refr. (M_D) Calcd.	Obs.
1	1.4560	1.1102	1.1133	29.60	29.51
2	1.4292	0.9640	0.9667	30.99	31.06
2a	1.4300	.9625	.9653	30.99	31.16
3	1.4298	.9386	.9412	35.61	35.80
4	1.4313	.9248	.9274	40.23	40.36
5	1.4357	.9150	.9176	44.85	45.16
6	1.4370	.9040	.9065	49.47	49.89
7	1.4407	.9019	.9045	54.08	54.47
8	1.4498	.9571	.9598	39.76	39.89
9	1.5174	1.0484	1.0514	55.10	55.47

ANALYSES

No.	Sample, mg.	CO_2, mg.	H_2O, mg.	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
1	4.092	7.520	2.78	49.78	50.12	7.53	7.60
2	4.590	10.440	4.13	62.02	62.03	10.42	10.07
3	4.236	10.040	3.96	64.56	64.64	10.84	10.46
4	5.380	13.160	5.30	66.61	66.71	11.19	11.02
5	5.524	13.855	5.57	68.29	68.40	11.47	11.28
6	4.860	12.460	5.03	69.70	69.92	11.71	11.58
7	5.244	13.600	5.50	70.90	70.73	11.91	11.73
8	5.712	14.160	4.98	67.55	67.61	9.93	9.75
9	4.541	12.540	3.28	74.95	75.31	8.39	8.08

whereas with the tetrahydrofurfuryl compounds there appears to be a slight exaltation.

An attempt was made to prepare tetrahydrofurfuryl iodide by treatment of the chloride with sodium iodide in acetone solution. The mixture was refluxed for about thirty-five hours and allowed to stand for two and one-half months. Only a very small amount of sodium chloride precipitated and on working up the mixture practically all of the chloride was recovered unchanged; a small amount of higher-boiling residue remained which was possibly the iodide. This experiment confirms the non-reactivity of the chlorine atom previously mentioned.

Dr. Irvine Page, director of the Chemistry Division of the Deutsche Forschungsanstalt für Psychiatrie of the Kaiser Wilhelm Institut in Munich, kindly made a preliminary study of the physiological activity of the tetrahydrofurfuryl ethers on mice and guinea pigs. He reported the ethers moderately toxic, the M. L. D. for the ethyl and propyl compounds on both mice and guinea pigs being about 0.14 cc. per kilo body weight when injected intravenously and 1.4 cc. per kilo body weight when injected intraperitoneally, these values decreasing with the higher ethers. Subcutaneous injection seemed to produce little effect. Injection of the substances intraperitoneally first caused muscular incoördination and then complete muscular relaxation with a semi-anesthetic stage in which the animals showed diminished pain sensibility and reflexes, the condition somewhat resembling twilight sleep. After one to two hours the animals appeared quite normal. Autopsies after injection of toxic doses showed chemical peritonitis. The anesthetic action appeared to increase from the methyl to the butyl compound (in the latter compound 0.8 cc. in a guinea pig weighing 680 g. caused total anesthesia lasting for nine hours), and then decreased again in the higher ethers. The benzyl ether was found to be quite toxic and the animals showed signs of central nervous system irritation. In this case the anesthetic action was light. In many cases the animals recovered from the anesthetic action but died later, death being due to intestinal necrosis rather than to an inherent toxicity in the compounds themselves.

It is a pleasure to acknowledge my thanks to Dr. Page for his kindness in carrying out the pharmacological investigation on these compounds as well as for the use of the refractometer with which the refractive indices were measured. I also wish to express my appreciation to Professor Heinrich Wieland for granting me permission to carry out this work in the Staats Laboratorium in Munich.

Experimental

I. Preparation of α-Tetrahydrofurfuryl Chloride.—A 200-cc. round-bottomed three-necked flask was fitted with a mechanical stirrer in the center neck; a 50-cc. dropping funnel (which had its delivery tube bent so as to deliver its contents near the center of the flask), was fitted into one side neck and a 50° thermometer was fitted into the remaining side neck. Fifty-one grams (0.5 mole) of freshly distilled tetrahydrofurfuryl alcohol and 43.5 g. (0.55 mole) of pyridine were placed in the flask; 65.5 g. (0.55 mole) of thionyl chloride (which was distilled from linseed oil and was perfectly water-white) was placed in the dropping funnel and added dropwise to the rapidly stirred alcohol–pyridine mixture. A vigorous reaction occurred with rise of temperature and darkening of the reaction mixture. The rate of addition of the thionyl chloride was such that addition was completed in approximately one and one-half hours; the temperature rose to between 50–55°. At the end of thirty to forty minutes a pasty, crystalline mass began to separate, which finally became so thick that the stirrer had difficulty in moving it. To avoid the thionyl chloride dropping on one spot of this mass, it was found that by gently tapping the flask with the hand the mass was loosened sufficiently so that it slowly rotated. At the end of about one and one-quarter hours this crystalline mass had redissolved leaving a dark brown liquid.

After the thionyl chloride was all added stirring was continued. As the temperature decreased crystallization again occurred and stirring was continued until this was complete and then the mixture was allowed to stand overnight. If crystallization occurred when the stirrer was not in motion it was found difficult to remove the stirrer from the hard crystalline mass which filled the flask the next morning.

The stirrer, dropping funnel and thermometer were removed and the liquid present in the flask was decanted off into an Erlenmeyer flask. The crystalline residue was then broken up, first with a sharp-pointed file and then with a glass rod having a button-shaped end; this treatment leaves a dark brown pasty mass of crystals. These were extracted by decantation seven times with 25-cc. portions of dry ether, the ether extracts being added to the solution originally decanted from the crystals. This combined solution was then washed three times with 50-cc. portions of water and allowed to dry over anhydrous sodium sulfate. The ethereal solution had a light brown color. The crystalline residue may be dissolved in water and treated with alkali to recover the pyridine.

The ether was distilled off and the residue fractionated in vacuum from a Claisen fractionating flask, the side arm of which was fitted with a short water condenser. The chloride distilled steadily at 41.5–42° at 11 mm. The boiling point observed at other pressures was 44–44.5° at 13 mm., and 45° at 14 mm. The yield of pure, distilled product was 75% and was duplicated many times. The remaining physical properties and analytical data are given in Table I. The chloride was a perfectly water-white liquid with a peculiar characteristic odor, but not at all lachrymatory as in the case of furfuryl chloride. It was found to be much more stable than furfuryl chloride and remained water-white for a long period when merely placed in a glass-stoppered bottle.

Attempts were also made to prepare the chloride by the use of phosphorus trichloride. The alcohol was dissolved in anhydrous ether and treated dropwise with a 10% excess of phosphorus trichloride, also dissolved in anhydrous ether. In one experiment the reaction mixture was kept cold; in another the reaction was run at the boiling point of the ether and in a third case a molecular quantity of pyridine was present. The yield by all of these methods was approximately 15% and in the fractional distillation there was always a considerable amount of high-boiling residue which was presumably unreacted alcohol. The chloride prepared by these methods always turned dark in a few days and gave off hydrogen chloride, the decomposition occurring more slowly, however, in the product obtained from the pyridine reaction. The phosphorus trichloride method is very much inferior to the thionyl chloride method both from the standpoint of yield and purity of the product obtained.

II. Preparation of α-Tetrahydrofurfuryl Ethers.—In general, about 0.3 mole of tetrahydrofurfuryl alcohol was mixed with a 200% excess of the desired bromide (except in case of the benzyl compound, where the chloride was used, and in case of the methyl compound, where the iodide was used), in a 250-cc. round-bottomed flask and then 100% excess of pulverized potassium hydroxide was added in small portions. Considerable heat was evolved, particularly in the case of the more reactive halides such as methyl iodide, ethyl and allyl bromide and benzyl chloride; when volatile halides were used the reaction mixture had to be cooled to avoid loss of the halide. The sodium halide precipitated voluminously during the addition of the alkali. When the potassium hydroxide was all added, the mixture was heated in a water-bath for three hours at such a temperature that the lower alkyl halides refluxed; for the higher alkyl halides a boiling water-bath was used. In the reactions involving the lower alkyl halides the excess alkyl halide was distilled off through a goose-neck tube at the end of the refluxing period, cooled, and 75 cc. of water added to the residue; in case of the higher alkyl halides water was added directly after being refluxed and cooled. The oily layer which separated was removed with a separatory funnel and the aqueous layer extracted three times with 25-cc. portions of ether. (The methyl ether is considerably soluble in water and no layer separated on adding water; therefore seven extractions with 25-cc. portions of ether were made.) The combined oily layer–ethereal solution was washed twice with 50-cc. portions of a saturated solution of sodium sulfate and the ethereal solution dried over anhydrous sodium sulfate. After standing overnight the solution was filtered from the sodium sulfate, the ether distilled off and the residue fractionated from a Claissen fractionating flask. In the case of the iso-amyl, *n*-hexyl and benzyl ethers the fractionation was performed in vacuum; in the other cases at atmospheric pressure. Before measuring the physical properties of the ethers they were allowed to stand over metallic sodium and then redistilled. All of the ethers showed considerable evidence of reaction with the sodium but without appreciable evolution of hydrogen. The tetrahydrofurfuryl ethers are all stable, water-white liquids with extremely pleasant odors. The physical constants, yields and analytical data are given in Table I.

The tetrahydrofurfuryl methyl ether was also made by methylation of the alcohol with dimethyl sulfate. A 100% excess of 40% sodium hydroxide solution was placed in a three-necked flask fitted with a stirrer and two dropping funnels and cooled in an ice-bath. The tetrahydrofurfuryl alcohol and a 50% excess of dimethyl sulfate were added simultaneously, dropwise, from the funnels, the reaction mixture being kept cold, and the temperature of the mixture not rising above 8°. After addition of the liquids was complete the mixture was stirred for three and one-half hours while cooled, and a further two and one-half hours with the ice-bath removed and then allowed to stand overnight at room temperature.

The reaction mixture consisted of two layers: an upper oily layer and the lower aqueous–alkaline layer. The mixture was transferred to a 250-cc. round-bottomed flask and steam distilled. The distillate at first contained two layers, but due to the solubility of the methyl ether in water, the insoluble layer gradually dissolved as more and more water distilled. The distillate was saturated with potassium carbonate, which caused an oily layer to separate, and was removed and then the aqueous layer was extracted three times with 25-cc. portions of ether. The combined solution was then dried over anhydrous potassium carbonate. The solution was filtered from the drying agent, the ether distilled off and the residue fractionated. The product obtained by this method, after being dried over metallic sodium and redistilled, agreed satisfactorily in its physical properties and in yield with that obtained by the methylation of tetrahydrofurfuryl alcohol with methyl iodide.

Summary

1. Tetrahydrofurfuryl chloride has been prepared using the Darzens reaction on tetrahydrofurfuryl alcohol and its physical properties determined. This chloride is much more stable and less reactive than furfuryl chloride.

2. The following tetrahydrofurfuryl ethers have been prepared by alkylation of tetrahydrofurfuryl alcohol, characterized and a preliminary study made of their physiological activity: methyl, ethyl, *n*-propyl, *n*-butyl, iso-amyl, *n*-hexyl, allyl and benzyl. The methyl ether was prepared by alkylation with both methyl iodide and dimethyl sulfate. These ethers are considerably more stable than the corresponding furfuryl ethers.

MUNICH, GERMANY