

crude product which separated was then collected on a Büchner funnel, washed with water, dried and weighed. In the first case diphenylisothiohydantoin and 3-phenyl-2,4-thiazolidione equivalent to 49.4 and 17.5% and in the second case 42.5 and 26%, respectively, of the original thiocarbanilide were recovered.

Secondary Formation of 3-Phenyl-2,4-thiazolidione.—Since hydrochloric acid separated in molar proportions in the course of the reaction, its effect on diphenylisothiohydantoin and the original reactants was studied in this concentration. Two samples of 10 g. each of pure diphenylisothiohydantoin were dissolved in 60 cc. of glacial acetic acid and 1.35 g. of hydrochloric acid added in the form of its concentrated aqueous solution. To the second sample was added 5 g. of anhydrous sodium acetate. Both samples were boiled under a reflux condenser for four hours. Upon cooling, the reaction mixtures were poured into large volumes of cold water, the precipitates collected on Büchner funnels and washed to remove the acetic acid, hydrochloric acid and sodium acetate. After drying at 105°, the product from the first reaction, amounting to 7.0 g. (calcd. 7.2 g.), was identified by microscopic examination and nitrogen analysis as 3-phenyl-2,4-thiazolidione. The diphenylisothiohydantoin was quantitatively recovered in the second case.

Summary

The reaction between thiocarbanilide and monochloro-acetic acid has been studied in alcohol and in acetic acid under different experimental conditions and the probable mechanism of the reaction established. With anhydrous solvent containing sufficient anhydrous sodium acetate to remove both the water and hydrogen ions from the sphere of action, the maximum yield of diphenylisothiohydantoin is obtained. With acetic acid as solvent and a period of refluxing exceeding five hours, almost quantitative yields of 3-phenyl-2,4-thiazolidione are obtained.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

THE VESICANT ACTION OF CHLORO-ALKYL FURFURYL SULFIDES

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Introduction

In connection with studies concerned with furfural and its derivatives,¹ we have had occasion to synthesize β -chloro-ethyl furfuryl sulfide and γ -chloropropyl furfuryl sulfide. It was considered worth while to test these compounds for their vesicant action. This we have done. The β -chloro-ethyl sulfide has a marked vesicant action, which, however, is not so great as that of mustard gas ($(\text{ClCH}_2\text{CH}_2)_2\text{S}$). The γ -chloropropyl compound is without vesicant action. These results are in complete agreement with recent studies by Kirner.² He showed that in a

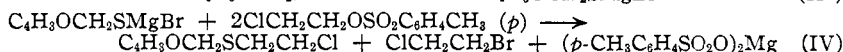
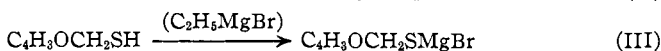
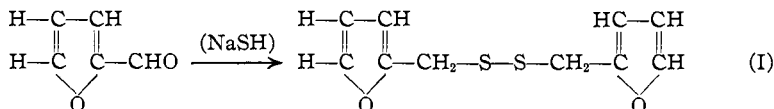
¹ See *Iowa State College J. of Science*, Vols. 2, 3, 4 (1928, 1929, 1930).

² Kirner, *THIS JOURNAL*, 50, 2446 (1928).

series of related chloro-alkyl sulfides only the β -chloro-ethyl (and not the α -chloro-methyl nor the γ -chloropropyl) sulfide had vesicant properties.

The following reactions were used for the preparation of our compounds in quite satisfactory yields.

The γ -chloropropyl furfuryl sulfide when applied to the skin in undiluted form produces no skin irritation.



Experimental Part

Furfuryl Disulfide (See Reaction I).—The disulfide was prepared after recent patent directions.³ Dry hydrogen sulfide was added rapidly over a two-hour period to a mixture (cooled by ice and salt) made up of 288 g. (3.0 moles) of furfural in 1500 cc. of 95% alcohol and 250 g. (3.2 moles) of sodium sulfide. After permitting the mixture to stand at room temperature overnight, the liquid was separated from the undissolved sodium sulfide, refluxed for one hour and then distilled from a water-bath to remove one liter of the alcohol. The residue from the water-bath distillation was poured into four liters of water and extracted with two liters of ether. The ether layer was separated, dried over sodium sulfate, and then the ether was removed by distillation from a water-bath. The residue of disulfide was thereupon reduced without further purification. However, a small portion was found to distil with some decomposition and discoloration at 160–165° (5 mm.). The boiling point previously³ given is 112–115° (0.5 mm.), and the melting point 10–10.5°.

Furfuryl Mercaptan (See Reaction II).—To the crude disulfide dissolved in 500 cc. of alcohol and 25 cc. of acetic acid was added in small portions 130 g. (2 atoms) of powdered zinc. The time required for the addition of zinc was about one hour, during which period the mixture was refluxed on a water-bath and stirred vigorously. Subsequent to an additional two hours of refluxing, a saturated solution of oxalic acid containing 180 g. (1.43 moles) was added, and the whole subjected to steam distillation. The distillate was extracted with ether, dried over sodium sulfate and distilled. The yield of mercaptan distilling at 155° at atmospheric pressure was 250 g. or 73%. The boiling points reported previously are 45–47° (12 mm.)³ and 84° (65 mm.).⁴ The *p*-nitrobenzoate of the mercaptan was found to melt at 77°, which is in agreement with that reported elsewhere.³ Furfural mercaptan is a colorless liquid, very stable and with an extremely disagreeable odor.

³ Staudinger and Reichstein, Canadian Patent 283,765 (Oct. 2, 1928); *C. A.*, **22**, 4537 (1928); Internationale Nahrungs- und Genussmittel A.-G., Brit. Patent 286,152 (July 25, 1927); *C. A.*, **23**, 155 (1929).

⁴ Kirner, *THIS JOURNAL*, **51**, 3134 (1929), has just reported the preparation of furfuryl mercaptan in a 33% yield by hydrolysis, without isolation, of the product obtained by condensation of α -furfuryl chloride with thiourea.

β -Chloro-ethyl Furfuryl Sulfide (See Reactions III and IV).—The reactions used for the preparation of the chloro-alkyl furfuryl sulfides are applications of the alkylating action of alkyl sulfonates on organomagnesium halides reported previously from this Laboratory.⁵

An ethereal solution of ethylmagnesium bromide prepared from 24 g. (2.2 moles) of ethyl bromide in 250 cc. of ether was siphoned from unaltered magnesium into a one-liter, three-necked flask provided with a mercury-sealed mechanical stirrer, condenser and separatory funnel. To the Grignard solution, cooled by an ice-salt mixture, was added dropwise a solution of 22.8 g. (0.2 mole) of the furfuryl mercaptan dissolved in 250 cc. of ether. A vigorous reaction ensued, and because of the separation of the white heavy intermediate (see Reaction III), 100 cc. of ether was added. After allowing the mixture to come to room temperature, it was refluxed for three hours on a water-bath.

To the mixture, which was then permitted to come to room temperature, was added dropwise and with vigorous stirring, a solution of 93.8 g. (0.4 mole) of β -chloro-ethyl *p*-toluenesulfonate in 150 cc. of ether. The resulting mixture, subsequent to a two-hour period of refluxing on a water-bath, was cooled and then hydrolyzed by 250 cc. of water containing 30 cc. of sulfuric acid. The hydrolysate was transferred to a separatory funnel and 500 cc. of water was added to dissolve the magnesium *p*-toluenesulfonate. The ether layer (after washing with water and drying with sodium sulfate) was distilled at atmospheric pressure to remove the ether and most of the ethylene chlorobromide. The β -chloro-ethyl furfuryl sulfide was obtained by vacuum distillation as a colorless liquid boiling at 128° (5 mm.). The yield was 32 g. or 90%. It distills at 5 mm. without decomposition, but begins to darken after standing for a few days and decomposes on long standing. The chlorosulfide has a pronounced odor which is very disagreeable at high concentration, but in dilute form it is pleasant and resembles somewhat a mustard odor. A saturated solution in water at 30° contains 0.123% of the sulfide; d_{30}^{30} 1.1914; n_D^{30} 1.5200.

Anal. Calcd. for C_7H_9OClS : S, 18.13; Cl, 20.11. Found: S, 17.41, 17.49; Cl, 20.26, 20.09.

γ -Chloropropyl Furfuryl Sulfide, $C_4H_3OCH_2S(CH_2)_3Cl$.—This chlorosulfide was prepared after the method just described for the synthesis of the β -chloro-ethyl homolog. From a 0.1-mole run using 3 g. of magnesium, 11 g. of ethyl bromide, 11.4 g. of furfuryl mercaptan and 49.6 g. of γ -chloropropyl *p*-toluenesulfonate, the yield of γ -chloropropyl furfuryl sulfide distilling at 135° (5 mm.) was 15 g. or 79%. It is a colorless liquid with an odor similar to that of β -chloro-ethyl sulfide, and although it darkens on standing it is more stable than the β -chloro-ethyl sulfide; d_{30}^{30} 1.1687; n_D^{25} 1.4740.

Anal. Calcd. for $C_8H_{11}OClS$: S, 16.80; Cl, 18.63. Found: S, 16.38, 16.26; Cl, 18.59, 18.59.

Physiological Tests

The γ -chloropropyl furfuryl sulfide when applied to the skin in undiluted form produces no skin irritation.

Several preliminary qualitative tests were carried out with the β -chloro-ethyl furfuryl sulfide. When applied to the skin in undiluted form a red spot appeared in two to three hours, and with some men, large deep blisters developed in five to eight hours. Of the five who were tested in this Laboratory, three developed burns very like those of mustard gas, whereas

⁵ The most recent reference is that of Gilman and Heck, *Ber.*, 62, 1379 (1929). From this all previous references may be traced.

the other two had deep red blotches which persisted for several months.⁶

In a more exact study, six men were selected for the test which was run with a 0.5% mustard gas control. The mustard gas caused a blister on all subjects, while our chlorosulfide was negative up to 2%. A 3% solution caused redness and slight itching. A 5% solution caused a blister which was equal in nearly every case to the blister caused by a 0.5% solution of mustard gas. It also caused itching comparable to mustard gas. Carbon tetrachloride was used as a solvent for both compounds. It is quite probable that the furfuryl sulfide is more effective than these results indicate, because the tests were carried out with a sample that had undergone partial decomposition. Because of this decomposition no toxicity tests were made.

The authors wish to thank the Miner Laboratories of Chicago for liberal supplies of furfural, and those who helped carry out the several tests.

Summary

Directions are given for the preparation of β -chloro-ethyl furfuryl sulfide and γ -chloropropyl furfuryl sulfide in good yields. The β -compound in agreement with other results has a pronounced vesicant action, whereas the γ -chlorosulfide is without vesicant action.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

ALPHA-METHYL-GAMMA-TETRAHYDRO-2-FURYLPROPYLMAGNESIUM BROMIDE

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Introduction

In extension of studies concerned with furan compounds, it was quite natural for us to turn to the preparation of organomagnesium halides synthesized from furan types, primarily with a view to an interpretation of other furan reactions. An astonishingly small number of such investigations has been made, undoubtedly because of the inaccessibility of halogen furan compounds and the relative inertness of the halogen in many of these compounds. Moureu, Dufraisse and Johnson¹ prepared furylace-tenylmagnesium bromide $C_4H_3OC\equiv CMgBr$, by an indirect method in-

⁶ Some tests were carried out with the assistance of Professor M. D. Helser (to whom grateful acknowledgments are made) on hogs, in connection with the possible utility of these and other compounds for the marking of hogs. When applied in undiluted form to the skin of hogs twelve hours before killing, intense red spots remained on the skin of the animals after removal from the depilatory bath. However, no blisters developed.

¹ Moureu, Dufraisse and Johnson, *Ann. chim.*, **7**, 1 (1927).