[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

THE REACTION BETWEEN THIOCARBANILIDE AND MONOCHLORO-ACETIC ACID IN ALCOHOL AND IN ACETIC ACID SOLUTION[1,2]

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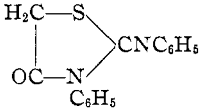
Following the general directions of Lange[3] for the preparation of diphenylisothiohydantoin from thiocarbanilide and monochloro-acetic acid, in order to study its condensation with aldehydes, Hann and Markley[4] and later Kingsbury and Markley[5] observed that the reaction conditions markedly affected not only the yield but also the compound which was formed. No explanation of these observations could be obtained from the papers of Lange, Andreasch,[6] Liebermann and Lange,[7] and Liebermann,[8] who previously prepared diphenylisothiohydantoin for the purpose of studying its constitution, since these authors failed to mention either the yields obtained or the effect of variations in the experimental conditions on the reaction. A number of experiments were therefore undertaken to determine what influence the concentration of reactants, time of reflux, solvent and catalyst had on the course of the reaction.

Results and Discussions.—As a result of this investigation it has been determined that, irrespective of solvent, the primary reaction between thiocarbanilide and monochloro-acetic acid is the formation of diphenylisothiohydantoin (I). From the results recorded in Table I it is evident that with alcohol as solvent the best yields are obtained with a short period of reflux, a small ratio of solvent to reactants, a slight excess of monochloro-acetic acid and the addition of sufficient anhydrous sodium acetate to remove the hydrochloric acid from the reaction as rapidly as it is formed. A high yield of diphenylisothiohydantoin may likewise

I



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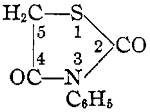

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[1] Presented in abstract before the Organic Division at the Columbus meeting of the American Chemical Society, April, 1929.

[2] From a part of the Ph.D. dissertation of Klare S. Markley, June, 1929. Parts II and III to follow.

[3] Lange, *Ber.*, **12**, 595 (1879).

[4] Hann and Markley, *J. Washington Acad. Sci.*, **16**, 169 (1926).

[5] Kingsbury and Markley, *ibid.*, **18**, 558 (1928).

[6] Andreasch, *Ber.*, **12**, 1385 (1879).

[7] Liebermann and Lange, *ibid.*, **12**, 1588 (1879).

[8] Liebermann, *Ann.*, **207**, 121 (1881).

be obtained with glacial acetic acid as solvent provided precautions are taken to remove the hydrogen chloride formed in the primary reaction.

TABLE I

EFFECT OF REACTION CONDITIONS UPON THE YIELD OF DIPHENYLISOTHIOHYDANTOIN

No.	$(C_6H_5$-$NH)_2CS$, g.	CH_2Cl-$COOH$, g.	Solvent used		Other reagents used		Time of reflux, hours	Crude diphenylisothiohydantoin		
			Kind	cc.	Kind	Amount		g.[a]	%	% N [b]
1	25	10.5	95% alc.	400	......	...	4.5	10.8	36.8	10.38
2	25	12.0	95% alc.	400	......	...	4.5	11.6	39.5	10.42
3	50	25.0	95% alc.	400	......	...	2.5	25.0	42.5	10.26
4	25	12.0	95% alc.	300	......	...	2.5	13.0	44.2	10.74
5	25	12.0	95% alc.	300	......	...	2.0	13.0	44.2	10.28
6	100	45.0	95% alc.	400	......	...	1.25	54.0	45.9	10.38
7	100	50.0	95% alc.	500	......	...	1.25	58.0	49.3	...
8	25	12.0	100% alc.	200	......	...	2.5	13.0	44.2	10.27
9	50	25.0	100% alc.	300	CH_3COONa	10 g.	3.5	45.0[c]	76.6	...
10	50	25.0	CH_3COOH	60	......	...	5.5	..	..	..
11	25	12.0	CH_3COOH	75	CH_3COONa	10 g.	2.0	24.0[c]	81.7	10.38
12	25	12.0	95% alc.	500	HCl	10 cc.	5.5	..	..	...

[a] The actual yields are somewhat higher due to the slight solubility of the compound in 95% alcohol. [b] Theoretical nitrogen: 10.45%. [c] Reaction mixture treated with water to separate the CH_3COONa.

When these precautions are not observed a mixture of diphenylisothiohydantoin and 3-phenyl-2,4-thiazolidione[9] (II) is formed in alcohol solution, whereas with glacial acetic acid (in proper proportion)[10] as the solvent and provided the time of reflux is sufficiently prolonged (five hours or more), practically quantitative yields of the latter compound are obtained, as indicated in Table II. It is apparent that the cyclic diketone results from the secondary hydrolysis of the diphenylisothiohydantoin under the influence of the hydrochloric acid formed in the primary reaction, as was suggested by Lange.

The hydrolysis of diphenylisothiohydantoin to form 3-phenyl-2,4-thiazolidione, however, is not the only factor which lowers the yield of diphenylisothiohydantoin as prepared in alcoholic solution, since the mother liquors from these preparations were found to contain, in addition to 3-phenyl-2,4-thiazolidione, urea, phenyl mustard oil and phenylthiourethan. The addition of hydrochloric acid to the original reaction mixture (Expt.

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[9] Liebermann and Völtzkow, *Ber.*, **13**, 276 (1880), obtained the same compound by heating phenylthiourethan, monochloro-acetic acid and absolute alcohol under pressure; P. Meyer, *Ber.*, **14**, 1659 (1881), by the hydrolysis of *o*-phenylthiohydantoic acid and *o*-phenylthiohydantoin; Evers, *ibid.*, **21**, 962 (1888), by the reaction of ethyl-, propyl- and allylphenyldithiourethan and monochloro-acetic acid; Wheeler and Barnes, *Am. Chem. J.*, **24**, 60 (1900), by melting together phenylthiourethan and monochloro-acetic acid.

[10] If the volume of glacial acetic acid is too large, diphenylisothiohydantoin is not completely converted into the cyclic diketone; if too small, partial decomposition ensues with the formation of phenyl mustard oil.

Table II

Effect of Reaction Conditions upon the Yield of 3-Phenyl-2,4-thiazolidione

No.	$(C_6H_5NH)_2CS$, g.	CH_2Cl-COOH, g.	CH_3-COOH, cc.	Time of reflux, hours	Yield of crude diketone g.	%	Solvent used for final crystallization	Purified compound, % N[a]
1	50	25	75	2.5	43[b]	..	......	..
2	25	12	25	2.0	16[c]	..	......	..
3	50	25	100	4.25	27[d]	..	......	..
4	25	12	40	4.0	18[e]	..	......	..
5	25	12	25	4.25	14	66.2	Not recryst.	7.27
6	50	25	65	4.5	36	85.1	CH_3COOH	7.35
7	25	12	25	4.0	18.3	86.5	CH_3COOH	7.23
8A	50	25	60	5.5	40	94.3	95% alc.	7.27[f]
8B	50	25	60	5.5	39	92.2	CH_3COOH	
9	25	12	30[g]	3.0	14	66.2	Not recryst.	7.28

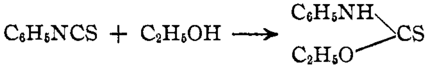
[a] Theoretical nitrogen, 7.25%. [b] 17.0 g. of diphenylisothiohydantoin separated from crude product. [c] 4.5 g. of diphenylisothiohydantoin isolated from crude product. [d] Analysis of crude compound gave 8.53% N; impurity found to be diphenylisothiohydantoin. [e] Nitrogen of crude product, 8.83%. Diphenylisothiohydantoin isolated from mixture. [f] After drying at 133°. [g] 10 cc. of concd. HCl added to reflux mixture; considerable phenyl mustard oil formed.

12, Table I) led to the formation of but small amounts of diphenylisothiohydantoin and 3-phenyl-2,4-thiazolidione and considerable quantities of phenyl mustard oil and phenylthiourethan, whereas the addition of hydrochloric acid to an alcoholic solution of diphenylisothiohydantoin led to its quantitative transformation into 3-phenyl-2,4-thiazolidione. Summarizing these results, the following reactions may be assumed to occur during the reaction of thiocarbanilide with monochloro-acetic acid in alcohol solution.

$$(C_6H_5NH)_2CS + CH_2ClCOOH \longrightarrow C_{15}H_{12}ON_2S + H_2O + HCl \qquad (I)$$

$$C_{15}H_{12}ON_2S + H_2O + HCl \longrightarrow C_9H_7O_2NS + C_6H_5NH_2 + HCl \qquad (II)$$

$$(C_6H_5NH)_2CS \longrightarrow C_6H_5NCS + C_6H_5NH_2 \qquad (III)$$



$$C_6H_5NCS + C_2H_5OH \longrightarrow \begin{matrix} C_6H_5NH \\ C_2H_5O \end{matrix}\!\!>\!CS \qquad (IV)$$

Experimental

Diphenylisothiohydantoin.—The general method used in preparing the diphenylisothiohydantoin was briefly as follows: 25 to 100 g. of thiocarbanilide and slightly more than the corresponding molar quantity of $CH_2ClCOOH$ were dissolved in 300 to 500 cc. of alcohol and heated under a reflux condenser for one and one-fourth to five hours. As long as the solid phase of the compound was absent, no crystals separated although the solution was enormously supersaturated with respect to diphenylisothiohydantoin. At the expiration of the time of refluxing, the hot solution was filtered with the aid of a hot water funnel. The diphenylisothiohydantoin separated from the hot filtrate in beautifully iridescent, very thin plates. When the volume of alcohol was sufficiently large the compound was found to separate in a very pure form as was shown by nitrogen analysis and melting point. When the compound was recrystallized, 3 to 5 times the volume of boiling alcohol was necessary to redissolve it as compared with the original volume of solvent from which it was obtained. Upon pouring the hot alcoholic solution into cold water, pure diphenylisothiohydantoin separated as a white microcrystalline powder and not as an oil as was reported by Lange. It did, however, separate as a red oil from the crude reaction mixture when the latter was treated with water in a similar manner. A solubility determination of diphenylisothiohydantoin in 95% alcohol at 27° gave a value of 0.35 g. per 100 g. of solvent, or 0.28 g. per 100 cc. The optical properties of diphenylisothiohydantoin as determined by Mr. G. L. Keenan of the Bureau of Chemistry and Soils were as follows. Recrystallized from 95% alcohol the compound consisted of thin, colorless, micaceous plates. The indices of refraction were found to be n_α 1.654, n_β 1.690, both ±0.003, $n_\gamma > 1.734$. In convergent polarized light, crossed nicols, biaxial interference figures were observed occasionally, particularly in plates perpendicular to an optic axis.

3-Phenyl-2,4-thiazolidione.—Since the condensation of diphenylisothiohydantoin with aromatic aldehydes is readily effected in glacial acetic acid, it was thought that this acid would prove to be an ideal solvent for its preparation. Nitrogen analysis, melting point and microscopic examination of the resulting product showed, however, that the compound formed was 3-phenyl-2,4-thiazolidione and not the expected diphenylisothiohydantoin. Almost quantitative yields were obtained when the following conditions were observed: 50 g. of $(C_6H_5NH)_2CS$, 25 g. of $CH_2ClCOOH$ and 60 cc. of glacial acetic acid were shaken together in a 300-cc. flask to form a paste. Partial solution occurred, accompanied by considerable cooling. The flask was connected with a reflux condenser and gentle heat applied to effect complete solution, after which vigorous boiling was maintained for five hours or more. On cooling, the contents of the flask solidified to a mass of star-shaped clusters of yellow needles quite unlike diphenylisothiohydantoin. Following the addition of water the mass was disintegrated by shaking, and the product washed first by decantation and then on a Büchner funnel. On recrystallization from alcohol it separated in the form of bushy rosets of long thin yellow needles.

Mother Liquors of Diphenylisothiohydantoin.—When the mother liquors from the alcohol series of preparations, which always possessed a typical phenyl mustard oil odor, were evaporated either by the aid of heat or spontaneously, crystallization continued with the separation of a compound which appeared to the casual view to be diphenylisothiohydantoin. When evaporation was continued to dryness it was observed that two different layers formed; an upper one which appeared like diphenylisothiohydantoin and a lower one composed of a dark red, oily material shot through with fine needle-like crystals. When heated to 100° or to an even lower temperature the whole mass melted to a clear red oil which solidified again on cooling. Examination of the mother liquors from Prepns. 3, 5, 7 and 8 (Table I) led to the isolation and identification of the following compounds: phenyl mustard oil, phenylthiourethan, diphenylisothiohydantoin, 3-phenyl-2,4-thiazolidione and diphenylthiourea. Although quantitative separations were impracticable, it appeared that phenyl mustard oil and phenylthiourethan comprised the bulk of the products contained in the mother liquors.

In addition to the experiments recorded in Tables I and II, two additional preparations were made by refluxing for two hours 25 g. of diphenylthiourea and 12 g. of $CH_2ClCOOH$ dissolved in 300 and 250 cc. of 95% alcohol, respectively. After separating the crystallized diphenylisothiohydantoin in the usual manner, the mother liquors and washings were evaporated until but 25 to 35 cc. of a red oil remained, which on cooling solidified to a light yellow crystalline mass. To the first residue there was added 5 g. of $CH_2ClCOOH$, 5 cc. of concd. hydrochloric acid and 60 cc. of acetic acid, and to the second 25 cc. of acetic acid only. Both mixtures were then refluxed for four hours. After cooling the reaction mixtures were poured into large volumes of cold water and allowed to stand for twenty-four hours to separate the crystalline material from the oil. The 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 (($(ClCH_2CH_2)_2S$). 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

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

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