The degree of dissociation of chloralethylalcoholate into its constituents has been determined in benzene for a wide range of concentrations, and in bromoform, ethylene bromide, and nitrobenzene in fewer concentrations. It is dissociated in dilute solutions, associated in more concentrated ones. There appears to be no relation between the degree of dissociation and the dielectric constant of the solvent.

We take pleasure in acknowledging our indebtedness to the Warren Fund of the American Academy of Arts and Sciences for the excellent polarimeter and spectroscope which were placed at our disposal for this work.

BRYN MAWR, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF KANSAS.]

ON THE REACTIONS OF THE FORMAMIDINES. VI. SOME THIAZOLE DERIVATIVES.

BY F. B. DAINS AND A. E. STEPHENSON.

Received June 24, 1916.

Owing to the inability of one of the authors to continue this investigation, it has been deemed best to publish the results already obtained as a preliminary paper in this special field.

It has already been pointed out[1] that compounds containing a methylene grouping react with ease with the substituted formamidines, giving a primary amine and the complex CHNHR in place of the H_2 of the methylene group, as follows:

$$>CH_2 + RN=CHNHR = >C=CHNHR + RNH_2$$

This occurs not only in the malonic ester, acetoacetic ester and benzyl cyanide type, but also with ring compounds like the pyrazolones and isoxazolones.

In the isothiohydantoins (ketotetrahydro-thiazoles), there is found the complex $—CO — CH_2 — S—$, which exhibits the general reactions characteristic of an acid methylene grouping, such as aldehyde, phthalic anhydride, nitroso derivatives, etc.

Such compounds should by analogy react with the formamidines; a supposition confirmed by the following experiments:

Diphenyl-isothiohydantoin (2-phenylimido-3-phenyl-4-keto-tetra-hydrothiazole) was readily obtained by heating in alcohol solution thiocarbanilide and chloroacetic acid. Small amounts of phenyl mustard oil glycollide and phenyl thiourethan were also formed.

Molar quantities of the isothiohydantoin and diphenylformamidine were heated at 140–50° for five hours. The reaction product contained

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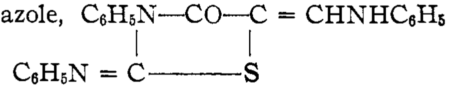
[1] *Ber.*, **35**, 2509 (1902); THIS JOURNAL, **31**, 1148 (1909); **35**, 959, 970 (1913).

aniline, and, in 78% yield, 2-phenylimido-3-phenyl-4-keto-5-anilidomethylene-tetrahydrothiazole,



$$\begin{array}{rl} & C_6H_5N\text{—}CO\text{—}C = CHNHC_6H_5 \\ & \qquad\qquad | \qquad\quad | \\ C_6H_5N = & C\text{————}S \end{array}$$

This crystallizes from alcohol in the form of short, pale yellow needles melting at 202°.

Calc. for $C_{22}H_{17}ON_3$: N, 11.32%. Found: 11.50%, 11.31%.

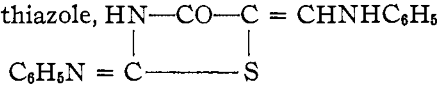
Hydrolysis of the Isothiohydantoin.—10 g. of the anilidomethylene derivative, 150 cc. alcohol and 15 cc. conc. hydrochloric acid, were heated under a reflux condenser for four hours. The products isolated were (1) diphenyl urea, (2) 2,4-diketo-5-anilidomethylene-tetrahydrothiazole (m. p. 192°), formed by the hydrolysis of the phenylimido group, obtained also, as will be described later, by the condensation of diphenylformamidine and the diketothiazole, (3) 3-phenyl-2,4-diketotetrahydrothiazole due to further loss of the anilidomethylene group, and (4) aniline hydrochloride. The results thus show a progressive hydrolysis of the molecule. It is of especial interest, however, in this fact that in all the investigations of the anilidomethylene derivatives, this is the first instance noted where that grouping could be split off without complete rupture of the entire molecule.

Di-*o*-tolyl-isothiohydantoin was prepared according to the method of Wheeler and Jamieson.[1] It melts at 153° and gives a benzal derivative melting at 182.5°. It should be noted here that these benzal substitution products can be formed by the direct heating of the aldehyde and hydantoin without the use of any solvent or condensing agent.

Molar quantities of the thiazole and diphenylformamidine, when heated at 140–50° for three hours gave a 75% yield of 2-*o*-tolylimido-3-*o*-tolyl-4-keto-5-anilidomethylenetetrahydrothiazole. From alcohol, this crystallizes in pale yellow, silky needles with a melting point of 200–1°.

Calc. for $C_{24}H_{21}ON_3S$: N, 10.53%. Found: 10.44%, 10.65%.

The monosubstituted thiazoles containing a methylene group react in an analogous manner. Thus diphenylformamidine and phenylisothiohydantoin at 150° yielded almost quantitatively 2-phenylimido-4-keto-5-anilidomethylene-tetrahydrothiazole,



$$\begin{array}{rl} & HN\text{—}CO\text{—}C = CHNHC_6H_5 \\ & \quad | \qquad\quad | \\ C_6H_5N = & C\text{————}S \end{array}$$

It is almost insoluble in alcohol, chloroform, gasoline and benzene, soluble in hot glacial acetic acid, pyridine and nitrobenzene. From the latter solvent it crystallizes in lemon yellow needles melting at 266.5°.

Calc. for $C_{16}H_{13}ON_3S$: N, 14.24%. Found: 14.12%, 13.90%.

When phenyl-isothiohydantoic acid, $C_6H_5N = CNH_2 — S — CH_2$-COOH, is heated at 150–170° with diphenyl formamidine, the same

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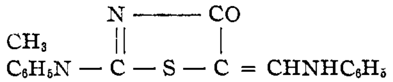
[1] This Journal, **25**, 369 (1903).

anilidomethylenephenylthiazole (m. p. 266°) is obtained. This involves both ring closure, due doubtless to the high temperature and reaction with the methylene hydrogen. Analogous results were obtained when the same thiohydantoic acid and benzaldehyde were allowed to react at a temperature of 140–50°, though for a few moments the thermometer rose to 200°. The ring was closed and there was formed 2-phenylimido-4-keto-5-benzaltetrahydrothiazole (m. p. 254°), a substance which had been previously obtained by condensing the aldehyde and thiazole in alcohol solution by means of sodium.[1] A similar reaction has been noted[2] in the case of the acetyl or benzoyl thiohydantoic acid, since when this is heated with benzaldehyde, there is formed 1-acyl-2-thio-4-benzalhydantoin.

Another type of thiazole containing a substituted amino group, the 2-methylphenylamido-4-keto-tetrahydrothiazole, was found to condense at 150° with diphenyl formamidine yielding the 2-methyl-phenylamido-4-keto-5-anilidomethylene-tetrahydrothiazole,



$$\begin{array}{lcccl} & N & \text{———} & CO & \\ CH_3 & \| & & | & \\ C_6H_5N\ - & C & -\ S\ - & C & = CHNHC_6H_5 \end{array}$$

This crystallizes from alcohol in reddish granules melting at 180°. It is soluble in hydrochloric acid and reprecipitated by alkalies.

Calc. for $C_{17}H_{15}ON_3S$: N, 13.60%. Found: 13.50%.

Diketo-thiazoles.—The presence of two keto groups in the ring seems to have little effect, either in diminishing or increasing the reactivity of the methylene hydrogen. Thus 3-phenyl-2,4-diketo-tetrahydrothiazole was heated with diphenylformamidine at 140–50° for three hours, giving an 80% yield of 3-phenyl-2,4-diketo-5-anilidomethylene-tetrahydrothiazole. This is difficultly soluble in alcohol from which it crystallizes in pale yellow glistening leaflets with a melting point of 192–3°.

Calc. for $C_{16}H_{12}O_2N_2S$: N, 9.46%. Found: 9.53%, 9.59%.

As has been noted in the early part of this article, this same compound was obtained by the partial hydrolysis of the 2-phenylimido-3-phenyl-anilidomethylene derivative.

While the above was the main reaction product obtained in heating the thiazole and formamidine, there was also formed a small amount of a compound, soluble in alcohol, melting at 237° and containing 13.11% nitrogen. The data corresponds to that demanded for diphenyl urea, which might readily be formed by the action of aniline on the original thiazole.

Condensation of an Unsubstituted Diketothiazole.—Under the same conditions as in previous experiments, a molar mixture of diphenyl formami-

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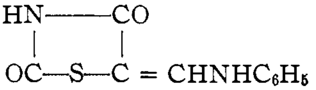
[1] Wheeler and Jamieson, THIS JOURNAL, **25**, 367 (1903).

[2] Wheeler, Nicolet and Johnson, *Am. Chem. J.*, **46**, 469 (1911).

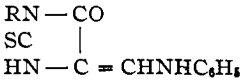
dine and the 2,4-diketo-tetrahydrothiazole gave the 2,4-diketo-5-anilidomethylene-tetrahydrothiazole,



This is very difficultly soluble in hot alcohol from which it crystallized in almost colorless plates melting at 233°.

Calc. for $C_{10}H_8O_2N_2S$: N, 12.73%. Found: 12.96%, 13.03%.

As a matter of interest it may be noted here that experiments show that the true thiohydantoins containing a methylene group condense with the formamidines giving substitued amino methylene derivatives of the type,



isomeric with the thiazole derivatives.

These investigations are being continued in this laboratory.

LAWRENCE, KANSAS.

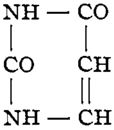
[CONTRIBUTIONS FROM THE SHEFFIELD CHEMICAL LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON PYRIMIDINES. LXXXI. SECONDARY-PYRIMIDINE-NUCLEOSIDES AND THEIR UNIQUE BEHAVIOR ON HYDROLYSIS.[1]

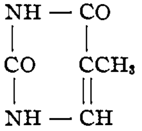
BY TREAT B. JOHNSON AND SIDNEY E. HADLEY.

Received June 28, 1916.

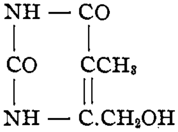
This is the fourth paper from this laboratory on pyrimidine nucleosides and, like those preceding it, deals with the chemistry of uracil and thymine combinations containing alcohol groupings in position 4 of the pyrimidine ring. The classification adopted namely, primary, secondary and tertiary



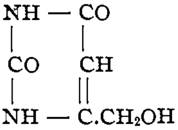
(Uracil)
(I).



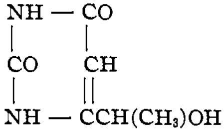
(Thymine)
(II).



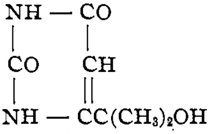
(III).



(IV).



(V).



(VI).

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[1] The observations recorded in this paper have developed from an investigation on nucleosides which was originally started in this laboratory by Dr. Lewis H. Chernoff in 1913. The paper has been constructed from a dissertation presented by Mr. Sidney Edward Hadley to the Faculty of the Graduate School of Yale University, 1916, in candidacy for the Degree of Doctor of Philosophy.