

The first addition product undergoes hydrolysis in the presence of hydrazine into methyl malonate monothioallylamide.

It forms addition products with halogens which through the loss of halogen hydride are immediately converted into penthiazolines.

Carbomethoxymethylmalonate monothioallylamide in the presence of sodium methylate forms a thiophene derivative with ethyl chloroacetate.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

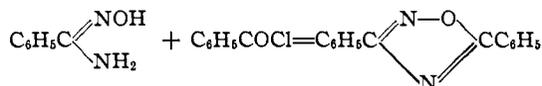
## THE FORMATION OF FURO- $\alpha,\beta'$ -DIAZOLES FROM ACYL IMIDOTHIOCARBONATES AND ACYL PSEUDOTHIUREAS<sup>1</sup>

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A review of the literature of the chemistry of furo- $\alpha,\beta'$ -diazoles or 1,2,4-oxdiazoles reveals the fact that there are essentially two different methods which are available for the synthesis of representatives of this type of heterocyclic compounds, namely, (1) by interaction of amidoximines with acyl chlorides or acid anhydrides according to Tiemann's well-known reaction expressed below, and which has been extensively studied and applied,<sup>3</sup> and (2) by the action of hydroxylamine on acyl imidothiocar-



bonates and acyl pseudoureas, or reactions which were reported by Johnson and Menge in 1904.<sup>4</sup> This latter method of synthesis has never been carefully studied since its discovery; furthermore, the structures of the resulting diazoles were by no means definitely settled in the original contribution. In this paper we shall describe experimental methods which permit us to decide definitely the constitution of the heterocyclic condensation products obtained by the application of Johnson and Menge's reaction.

Johnson and Menge described one experiment illustrating the behavior of hydroxylamine toward an acyl imidothiocarbonate. They observed that hydroxylamine interacted with diethyl benzoylimidothiocarbonate I at ordinary temperature with formation of a compound to which they as-

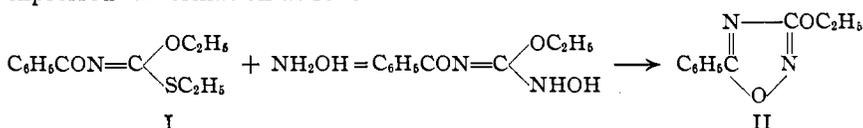
<sup>1</sup> Constructed from a dissertation presented by Shao Tseng Yang to the Faculty of the Graduate School of Yale University, June, 1931, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

<sup>2</sup> Holder of a Rockefeller Foundation foreign fellowship, 1929-1931.

<sup>3</sup> Tiemann and Krüger, *Ber.*, **17**, 1685 (1884); and many co-workers between 1884 and 1895.

<sup>4</sup> Johnson and Menge, *Am. Chem. J.*, **32**, 362 (1904).

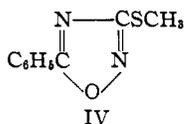
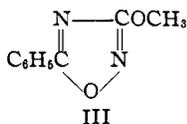
signed the constitution of  $\alpha'$ -phenyl- $\beta$ -ethoxyfuro- $\alpha,\beta'$ -diazole II, and expressed its formation as follows



In trying to reproduce the original experiment difficulty was at first encountered in establishing experimental conditions favoring the formation of this furo- $\alpha,\beta'$ -diazole. Unless a definite technique is applied benzamide is the major product of reaction. The formation of this amide is explained by the fact that the thiocarbonate I is very susceptible to the action of warm alkali and to add hydroxylamine hydrochloride simultaneously with the thiocarbonate I to an alcoholic solution of potassium hydroxide will invariably give benzamide. A free hydroxylamine solution must be first prepared in order to accomplish successfully the desired reaction.

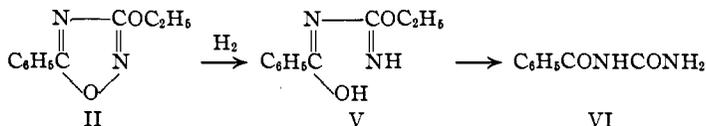
In the second place, the regulation of the temperature when applying the reaction is another very important factor as the change is an exothermic one leading to secondary reactions unless the reaction temperature is kept low. In this respect the dimethyl benzoylimidothiocarbonate is far more sensitive to temperature changes than the diethyl ester I.

The thiocarbonate I and its corresponding dimethyl ester react with hydroxylamine to form the respective furo- $\alpha,\beta'$ -diazoles represented by formulas II and III. In neither case does hydroxylamine interact with the imidothiocarbonate with formation of a mercaptofuro- $\alpha,\beta'$ -diazole derivative as represented by formula IV. Furthermore, the two imidothiocarbonates, dimethyl benzoylimidothiocarbonate and O-methyl-S-ethyl benzoylimidothiocarbonate, react with hydroxylamine to give the same furo- $\alpha,\beta'$ -diazole III. In other words, the mercapto group of the imidothiocarbonate is more readily eliminated by treatment with hydroxylamine than the alkyloxy group. A compound corresponding to formula IV was never detected as a product of this reaction. The formation of such mercapto derivatives of a furo- $\alpha,\beta'$ -diazole may be predicted by allowing hydroxylamine to interact with acyl imidothiocarbonates, a reaction which has not hitherto been studied.

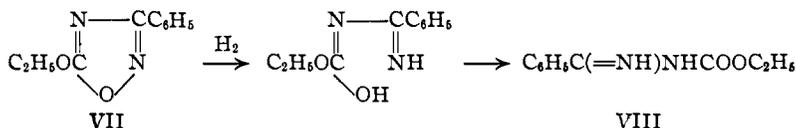


As to the structures of the furo- $\alpha,\beta'$ -diazoles formed in the above reactions, it was necessary to decide between the two possible isomeric constructions, namely, an  $\alpha'$ -phenyl- $\beta$ -alkoxyfuro- $\alpha,\beta'$ -diazole II or  $\alpha'$ -

alkoxy- $\beta$ -phenyl-furo- $\alpha,\beta'$ -diazole VII. This was accomplished by reduction of our respective furo- $\alpha,\beta'$ -diazoles with zinc dust and acetic acid. Both of our condensation products II and III were reduced practically quantitatively to benzoylurea VI as is expressed by the equation below. This change involves theoretically the intermediate formation of an acyl-imido ester V. These results confirm the original conclusions of

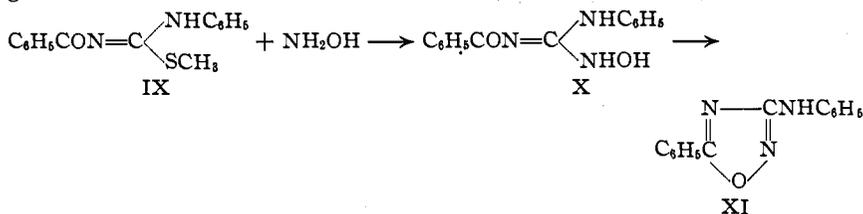


Johnson and Menge. An isomeric  $\alpha'$ -alkoxyl- $\beta$ -phenyl-furo- $\alpha,\beta'$ -diazole VII would be expected to give by reduction an entirely different product or a urethan derivative of benzamidine VIII as is illustrated by the equation



The behavior of our furo- $\alpha,\beta'$ -diazoles on reduction is entirely in accord with that of the anhydroximes on reduction, which were investigated by Rose and Scott.<sup>5</sup> This method of establishing structure is undoubtedly applicable to other heterocyclic constructions containing the furo- $\alpha,\beta'$ -diazole ring.

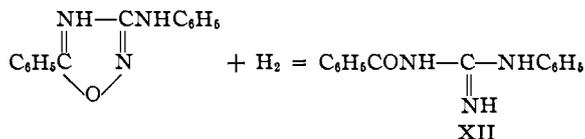
$\alpha'$ -Phenyl- $\beta$ -anilino-furo- $\alpha,\beta'$ -diazole XI is formed by the action of hydroxylamine on benzoylpseudomethylphenylthiourea in pyridine solution.<sup>6</sup> Johnson and Menge state in their original paper that this type of transformation is accomplished by interaction of hydroxylamine with an acylimidopseudourea, but no experimental evidence in support of this was presented. It has been our experience that the oxygen pseudoureas are not as reactive toward hydroxylamine as the corresponding sulfur analogs; therefore, we confined our work to the study of the sulfur derivatives. The reaction leading to the formation of an anilino-furo- $\alpha,\beta'$ -diazole is given below



<sup>5</sup> Rose and Scott, *THIS JOURNAL*, **39**, 273 (1917).

<sup>6</sup> Wheeler and Merriam, *ibid.*, **23**, 293 (1901).

The pseudothiourea IX used in this work, which was first prepared by Wheeler and Merriam<sup>6</sup> by the action of aniline on dimethyl benzoylimidothiocarbonate, was synthesized by the direct alkylation of *sym.*-benzoylphenylthiourea with methyl iodide. When the furo- $\alpha,\beta'$ -diazole XI was reduced with zinc and acetic acid it was converted smoothly into benzoylphenylguanidine XII, a change which establishes its constitution. The



free guanidine melted at 90–91°, and the picrate of the guanidine melted at 187–188°. These results, therefore, identify the reduction product as the guanidine derivative previously described by Wheeler and Johnson.<sup>7</sup> In other words, the acyl imidothiocarbonates and the corresponding pseudothioureas interact with hydroxylamine in a similar manner with evolution of mercaptan and formation of well characterized, crystalline furo- $\alpha,\beta'$ -diazole compounds.

### Experimental Part

**Preparation of Acylimidothiocarbonates.**—Dimethyl benzoylimidothiocarbonate,  $\text{C}_6\text{H}_5\text{CON}=\text{C}(\text{OCH}_3)\text{SCH}_3$ ,<sup>8</sup> was prepared by alkylation of methyl benzoylthiocarbonate<sup>9</sup> in alkaline solution with methyl iodide. It melted at 46° after recrystallization from ether. The corresponding diethyl imidothiocarbonate was prepared in an analogous manner by alkylation of ethyl benzoylthiocarbamate with ethyl bromide. It boiled at 200–203° at 16 mm. (Wheeler and Johnson reported the temperature of 209–212° at 19 mm.). The mixed ester O-methyl-S-ethyl benzoylimidothiocarbonate, which was prepared by the action of ethyl bromide on the potassium salt of methyl benzoylthiocarbamate, boiled at 195–205° at 14 mm.

**Preparation of Acyl Pseudothioureas.**—The pseudomethyl benzoylphenylthiourea,  $\text{C}_6\text{H}_5\text{CON}=\text{C}(\text{SCH}_3)\text{NHC}_6\text{H}_5$ , and the corresponding pseudoethyl compound used in this work were prepared by the direct alkylation of *sym.*-benzoylphenylthiourea in sodium alcoholate solution with methyl iodide and ethyl bromide, respectively. The pseudomethyl compound was obtained in a yield of 70% and melted at 104–105°,<sup>10</sup> and the pseudoethyl compound melted at the temperature of 88°, as originally reported by Wheeler and Merriam.

**$\alpha'$ -Phenyl- $\beta$ -methoxy-furo- $\alpha,\beta'$ -diazole,  $\text{C}_8\text{H}_8\text{O}_2\text{N}_2$  (III).**—This compound is easily prepared as follows: 56 g. of dimethyl benzoylimidothiocarbonate is dissolved in 50 cc. of 95% alcohol and the solution combined with an alcoholic solution of hydroxylamine, prepared by adding 19 g. of hydroxylamine hydrochloride to a solution of 15 g. of potassium hydroxide in 100 cc. of methyl alcohol. The solutions were mixed at a low

<sup>7</sup> Wheeler and Johnson, *Am. Chem. J.*, **26**, 417 (1901).

<sup>8</sup> Wheeler and Johnson, *ibid.*, **24**, 200 (1900); Johnson and Menge, *ibid.*, **32**, 364 (1904).

<sup>9</sup> Miquel, *Ann. chim.*, [5] **11**, 330 (1877). Wheeler and Johnson, *Am. Chem. J.*, **24**, 200 (1900).

<sup>10</sup> See Wheeler and Merriam, *THIS JOURNAL*, **23**, 290 (1901).

temperature and then allowed to stand in an ice chest for forty-eight hours. The alcohol solution was then poured into cold water when the furo- $\alpha,\beta'$ -diazole separated as an oil which soon solidified. It was purified by crystallization from dilute alcohol and separated in the form of prisms. Some of these crystals were more than one inch in length. The yield of purified furo- $\alpha,\beta'$ -diazole was 31 g. It melted at 58–59°.

*Anal.* Calcd. for  $C_6H_8O_2N_2$ : C, 61.36; H, 4.54; N, 15.90. Found: C, 61.28; H, 4.60; N, 16.05.

The furo- $\alpha,\beta'$ -diazole is insoluble in water, moderately so in ligroin and very soluble in alcohol, ethyl acetate, chloroform, ether and benzene.

$\alpha'$ -Phenyl- $\beta$ -ethoxy-furo- $\alpha,\beta'$ -diazole,  $C_{10}H_{10}O_2N_2$  (II).—This furo- $\alpha,\beta'$ -diazole was prepared according to the same technique described in the previous experiment by allowing hydroxylamine to interact with diethyl benzoylimidothiocarbonate at ordinary temperature. After standing in an ice chest for thirty-six hours, the alcohol solution was poured into water, when the furo- $\alpha,\beta'$ -diazole separated as an oil which solidified almost immediately. It was purified by recrystallization from 95% alcohol and separated in the form of stout prisms melting at 49–50°. The solubility of this compound is similar to that of the corresponding methoxy compound.

*Anal.* Calcd. for  $C_{10}H_{10}O_2N_2$ : N, 14.73. Found: N, 14.83.

These two furo- $\alpha,\beta'$ -diazoles are characterized by their great stability and extreme inertness. Notwithstanding the fact that they contain an imido ester grouping they do not form salts with the acids—hydrochloric, nitric and sulfuric. In concentrated hydrochloric acid they remain undissolved in the cold and on warming the acid the furo- $\alpha,\beta'$ -diazoles melt without alteration. In concentrated sulfuric and nitric acids both furo- $\alpha,\beta'$ -diazoles dissolve in the cold and are reprecipitated unchanged by dilution of the acid solutions with water. They are not attacked by concentrated nitric acid when the acid solution is heated at the boiling point for several minutes. They can be heated to 250° without decomposition. They do not react with aniline at its boiling point, and can be heated with alcoholic ammonia at 200–250° for hours without alteration. We obtained no evidence that Wieland and Bauer's<sup>11</sup>  $\alpha'$ -phenyl- $\beta$ -amino-furo- $\alpha,\beta'$ -diazole is formed by interaction with ammonia. Neither of the two furo- $\alpha,\beta'$ -diazoles responds favorably to the experimental conditions employed in applying a Zeisel reaction. The furodiazole nucleus is completely destroyed by hydriodic acid at 100° with the formation of benzoic acid.

**Reduction of  $\alpha'$ -Phenyl- $\beta$ -methoxy-furo- $\alpha,\beta'$ -diazole with Zinc and Glacial Acetic Acid.**—Five grams of this furo- $\alpha,\beta'$ -diazole was dissolved in 25 cc. of cold glacial acetic acid and ten grams of zinc dust added. The mixture was then heated at 85–90° for one hour and finally allowed to stand for three hours, when the unchanged zinc was removed by filtration and the excess of acetic acid evaporated on a water-bath. A crystalline residue was obtained. This was identified as a mixture of the unaltered furo- $\alpha,\beta'$ -diazole and benzoylurea. About one-half of the furo- $\alpha,\beta'$ -diazole was recovered unchanged. On recrystallizing the crude reduction product from alcohol the urea was obtained in pure form melting at 208°.

*Anal.* Calcd. for  $C_6H_8O_2N_2$ : N, 17.07. Found: N, 17.00.

When the corresponding  $\alpha'$ -phenyl- $\beta$ -ethoxy-furo- $\alpha,\beta'$ -diazole was reduced with zinc dust and acetic acid under the same conditions it was also converted into benzoylurea. After digesting with zinc at 95–100° for three hours, about one-half of the furo- $\alpha,\beta'$ -diazole was still recovered unaltered.

$\alpha'$ -Phenyl- $\beta$ -anilino-furo- $\alpha,\beta'$ -diazole,  $C_{14}H_{11}ON_3$  (XI).—This furo- $\alpha,\beta'$ -diazole is

<sup>11</sup> Wieland and Bauer, *Ber.*, 40, 1691 (1907).

formed by the action of hydroxylamine on pseudomethyl benzoylphenylthiourea or pseudoethyl benzoylphenylthiourea. One experiment will be described in order to illustrate the technique employed. Ten grams of pseudomethyl benzoylphenylthiourea was dissolved in 25 cc. of pyridine and two molecular proportions of hydroxylamine hydrochloride added to the solution while cooling. After allowing to stand for about forty-eight hours the pyridine solution was diluted with water, when the above furo- $\alpha,\beta'$ -diazole separated in a crystalline condition. This crude reaction product was washed with dilute sulfuric acid to remove traces of pyridine and then recrystallized from benzene. It separated, on cooling, in the form of rectangular prisms melting at 139–140°. It did not respond to a test for sulfur and also crystallized from alcohol in prisms melting at 139–140°. For analysis the compound was dried at 110–120° to constant weight.

*Anal.* Calcd. for N, 17.72. Found: N, 17.62, 17.70.

The furo- $\alpha,\beta'$ -diazole did not interact with acetic anhydride by refluxing with this reagent for three hours. It dissolved in concentrated sulfuric acid in the cold, giving a red colored solution. On diluting the acid solution with water the furo- $\alpha,\beta'$ -diazole was precipitated unchanged.

**Behavior on Reduction.**—Two grams of the anilino-furo- $\alpha,\beta'$ -diazole was reduced with zinc dust and glacial acetic acid at 90–95° for three hours. After removing the excess of zinc and evaporating the acetic acid, a crystalline substance was obtained which was purified by crystallization from benzene. It was identified as benzoylphenylguanidine and melted at 90–91°. When picric acid was added to an alcoholic solution of the base, the picrate separated as reported previously by Wheeler and Johnson.<sup>7</sup>

*Anal.* (Picrate). Calcd. for  $C_{20}H_{16}O_8N_2$ : N, 17.94. Found: N, 17.80.

**$\beta$ -Chlorethyl Benzoylthioncarbamate**,  $C_6H_5CONHCSOCH_2CH_2Cl$ .—This compound is easily prepared by allowing freshly distilled benzoyl isothiocyanate to interact at ordinary temperature with ethylene chlorohydrin. The thioncarbamate was purified by crystallization from acetone or alcohol and crystallized in the form of needles melting at 179–180°.

*Anal.* Calcd. for  $C_{10}H_{10}O_2NSCl$ : N, 5.71. Found: N, 5.74, 5.83.

### Summary

1. Acylimidothiocarbonates react with hydroxylamine to form alkoxy furo- $\alpha,\beta'$ -diazoles.
2. Pseudoalkylacylphenylthioureas react with hydroxylamine to form anilino-furo- $\alpha,\beta'$ -diazoles.
3. The structures of heterocyclic combinations of the furo- $\alpha,\beta'$ -diazole type are established by their behavior on reduction with zinc and acetic acid. The alkoxy compounds are broken down with formation of acylureas while the anilino derivatives give acyl derivatives of substituted guanidines.

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