Studies on Organic Sulfur Comqounds. I. Thioformyl Phenylhydrazine

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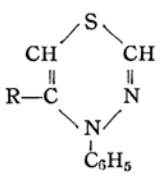
Thioformylation of amine by dithioformic acid or its potassium salt was first reported by Todd.[1] He suggested that thioformamino derivatives are useful for identification of amines because of their good crystallizability and sharp melting point. He also suggested that thioacylamino derivatives could be used for the synthesis of heterocyclic compounds.

Some kinds of thioformamino- or thioformhydrazino-derivatives have been reported by one of us as intermediates for the synthesis of thiazole- or thiadiazole-derivatives.[2] Concerning our research on the synthesis of 1,3,4-thiadiazine derivatives (I) from, β-thioformyl phenylhydrazine (II), we found it necessary to investigate the properties of thioformyl phenylhydrazine.



(I)

$$\underset{\alpha\ \beta}{C_6H_5NHNHCHS} \rightleftarrows C_6H_5NHN{=}CHSH$$

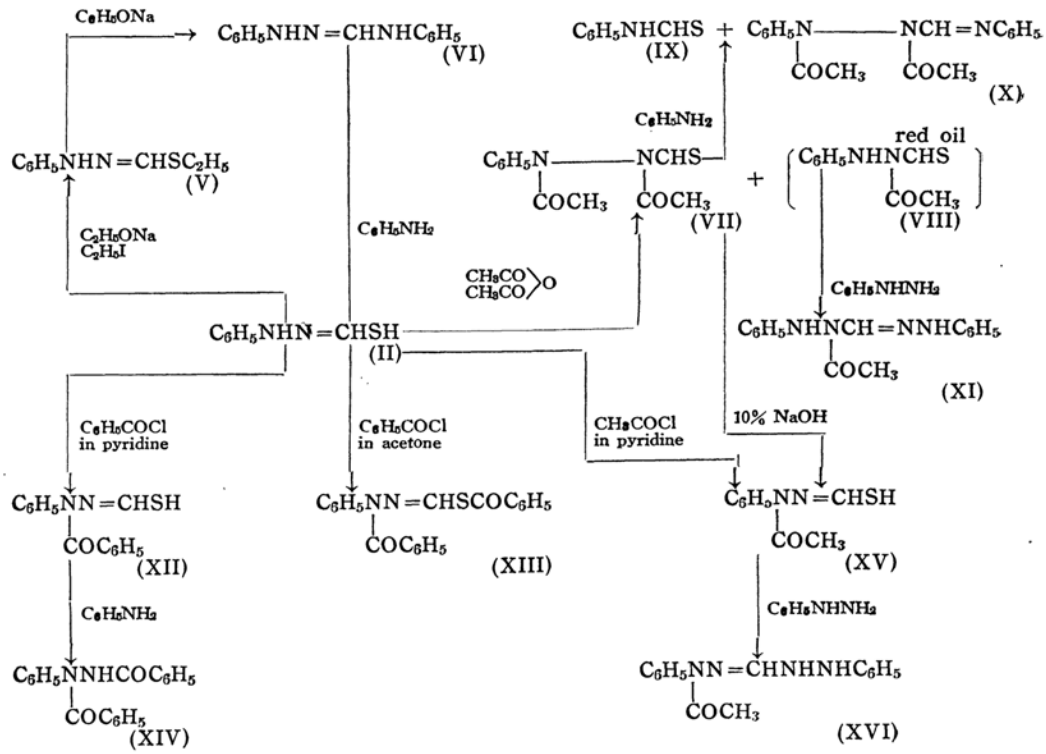
(II)

Baker et al.[3] reported the preparation of thioformyl arylhydrazine derivatives from sodium dithioformate and arylhydrazines.

1) A. R. Todd et al., *J. Chem. Soc.*, **1937**, 361.
2) M. Ohta, *J. Pharm. Soc. Japan*, **71**, 869 (1951); ibid., **73**, 701 (1953).
3) W. Baker et al., *J. Chem. Soc.*, **1950**, 3389.

They obtained (II) as an oil in a crude state and only a small portion of it became crystalline (m.p. 39-41°). They used the crude product in subsequent reactions, and concluded its structure to be (II) by analysis and several reactions. We obtained a compound (m.p. 102°) from phenylhydrazine and potassium dithioformate in a good yield. From various properties described in this report, no doubt remains that the product we obtained has a structure of (II). It is the purpose of this report to determine which hydrogen of two replaceable hydrogens of (II) is replaced, when (II) is submitted to alkylation or acylation.

When (II) was treated with sodium ethoxide and ethyl iodide, ethyl derivative (V) was obtained as an oil. (V) reacted with aniline at room temperature to afford formamidine derivative (VI) liberating ethyl mercaptan.



From this fact it is evident that the ethyl group is attached to the sulfur atom. (V) could be distilled under reduced pressure and was fairly stable compared with the ethyl derivative of thioformyl aniline which is unstable in the presence of moisture.[4]

As for the benzoylation of (II) with one mol. of benzoyl chloride, monobenzoyl derivative (XII) was formed exclusively in pyridine solution. But when the benzoylation of (II) was carried out in acetone solution in the presence of sodium bicarbonate, the principal product was dibenzoyl derivative (XIII), and the formation of monobenzoyl derivative (XII) was small in quantity. When two mols. of benzoyl chloride were reacted with one mol. of (II) in the presence of sodium bicarbonate, dibenzoyl derivative was the sole product. (XIII) did not react with aniline even on warming, which suggests that in dibenzoyl derivative (XIII), unlike in the case of diacetyl derivative (VII), one benzoyl group must be attached to α-nitrogen atom, and the other to sulfur atom.

Monobenzoyl derivative (XII) was soluble in aqueous sodium hydroxide solution, indicating the presence of the mercapto group, so that the benzoyl group should be attached to α-nitrogen. When (XII) was heated with aniline, hydrogen sulfide was liberated and a yellow oil was obtained. From this oil some amounts of colorless crystals (m.p.177°), were obtained. It was identified as α,β-dibenzoyl phenylhydrazine (XIV) from its analytical value, melting point and mixed melting point with an authentic sample. The mechanism by which dibenzoyl phenylhydrazine is formed from monobenzoyl derivative (XII) is unknown.

The reaction of (II) with acetyl chloride

4) O. Wallach and M. Wüster, *Ber.*, **16**, 145 (1883).

gave monoacetyl derivative (XV) in pyridine solution. In the reaction of two mols. of acetyl chloride with one mole of (II) in acetone in the presence of sodium bicarbonate, the formation of diacetyl derivative had been expected on the analogy of benzoylation in the same condition. But the reaction product was a red oil and crystallization or purification were unpossible. This red oil, unlike dibenzoyl derivative (XIII), reacted with aniline to liberate hydrogen sulfide, which is supposed to be due to some by-products.

Monoacetyl derivative (XV) was also soluble in aqueous sodium hydroxide solution, so that the acetyl group should be attached to α-nitrogen and when treated with aniline at room temperature in ethanol, hydrogen sulfide was liberated but the reaction product expected could not be isolated. (XV) reacted with phenylhydrazine to give orange crystals of (XVI), melting at 188°.

When (II) was treated with acetic anhydride at room temperature, diacetyl derivative (VII) was obtained, accompanied by small quantity of red oil (VIII). (VII) was insoluble in 10% sodium hydroxide solution, but on standing, it was hydrolyzed gradually and went into solution. On acidifying with acetic acid, monoacetyl derivative (XV) was obtained. (VII) reacted with aniline liberating hydrogen sulfide and gave thioformyl aniline and (X). This fact leads us to conclude that the two acetyl groups in (VII) must be attached to α-and β-nitrogen atoms of thioformyl phenylhydrazine. The isolation of α,β-diacetyl phenylhydrazine, which should be formed in this reaction, was impossible. The red oil (VIII) obtained as by-product in acetylation of (II) with acetic anhydride, reacted with phenylhydrazine to give colorless crystals, evolving a considerable amount of hydrogen sulfide and heat. This crystal was identified as monoacetyl derivative (XI), probably an isomer of (XVI), from its analytical value. This fact shows that (VIII) must also be monoacetyl derivative and an isomer of (XV). In (XV) as well as in (XVI), it is certain that the acetyl group is attached to α-nitrogen as explained before. Consequently, in (XI) or (VIII) the acetyl group is supposed to be attached to β-nitrogen. This was also confirmed by the insolubility of (VIII) in aqueous sodium hydroxide solution.

The authors are indebted to Mr. A. Kondo for the microanalytical results reported here.

Experimental

N-Phenyl-N′-thioformylhydrazine (II). — A solution of potassium hydrosulfide was prepared by mixing a solution of potassium hydroxide (46 g. in 150 cc. of methanol) saturated with hydrogen sulfide, with a solution of 46 g. of potassium hydroxide in 150 cc. of methanol. The solution was heated to about 50° in a 3 l.-flask equipped with a long Dimroth condenser. Then 30 g. of chloroform was added and constantly shaken. An exothermic reaction occurred which led to violent boiling. After ten minutes the mixture was cooled and filtered. The filtrate was evaporated in vacuo to about 50 cc. The solution of crude potassium dithioformate thus obtained was mixed with a solution of 14 g. of phenylhydrazine in 30 cc. of methanol. The evolution of hydrogen sulfide was recognized at once. The mixture was allowed to stand overnight at room temperature, then diluted with water and acidified with acetic acid. The crystalline precipitates were collected by filtration, washed with water and dissolved in ethanol and filtered from a small amount of insoluble matter. The filtrate was diluted with water to precipitate thioformyl compounds. The crude product was purified by dissolving in dilute sodium hydroxide solution and reprecipitated by acidifying with acetic acid. Colorless leaflets resulted. m.p. 102°. Yield 17 g. (86%). Found: N, 18.21; calculated for $C_7H_8N_2S$: N, 18.41%.

N-Phenyl-N′-ethylmercaptomethylene-hydrazine (V).—To a solution of 5 g. of thioformyl phenylhydrazine in 15 cc. of ethanol were added 15 cc. of sodium ethylate solution (containing 0.8 g. of sodium) and then 5 g. of ethyl iodide at room temperature. After standing overnight at room temperature, most of the alcohol was evaporated under reduced pressure, water was added and extracted with ether. After drying over anhydrous sodium sulfate, ether was evaporated. A small portion of the residual oil was distilled under a pressure of 8 mmHg (bath temperature was 170—180°) and used for analysis. Found: C, 60.47; H, 6.36; calculated for $C_9H_{12}N_2S$: C, 60.00; H, 6.67%.

Benzoylation of (II). (*a*) *in pyridine.*—To a solution of 10 g. of thioformyl phenylhydrazine in 50 cc. of pyridine was added dropwise 9.5 g. of benzoyl chloride in a period of one hour, stirring continuously and cooling with ice-water. After standing overnight at room temperature, water was added, then the oil which soon solidified separated. Recrystallization from ethanol yielded 6 g. of light yellow crystals of N-phenyl-N-benzoyl-N′-mercaptomethylene-hydrazine (XII), melting at 140°. Found: C, 65.75; H, 4.91; N, 10.60; calculated for $C_{14}H_{12}N_2OS$: C, 65.63; H, 4.69; N, 10.93%.

(*b*) *In acetone with two mols. of benzoyl chloride.*—To a solution of 3 g. of thioformyl phenylhydrazine (1 mol.) in 30 cc. of acetone, 4 g. of sodium bicarbonate (2 mols.) were suspended, and 5.5 g. of benzoyl chloride (2 mols.) were added dropwise with constant stirring and cooling. During the addition, the product separated gradually. Stirring was continued for six hours at room temperature and the precipitates were collected by filtration, washed first with aqueous solution of sodium bicarbonate and then with water (yield, 6 g.). When recrystallized from ethanol, fine

needles of N-phenyl-N-benzoyl-N′-benzoylmercaptomethylene-hydrazine (XIII), melting at 137°, were obtained. Found: N, 7.64; calculated for $C_{21}H_{16}N_2O_2S$: N, 7.77%.

(c) *In acetone with one mole of benzoyl chloride.*—To a solution of 3 g. of thioformyl phenylhydrazine (1 mol.) in 30 cc. of acetone were added 2.5 g. of benzoyl chloride (1 mol.) in the presence of 1.7 g. of sodium bicarbonate (1 mol.) in the same manner as described above. After standing overnight the solid was collected and washed with 10% aqueous sodium hydroxide solution. The greater part of the solid was insoluble but when alkali washings were acidified with acetic acid some amounts of solid were obtained, which were identified as monobenzoyl derivative (XII) after the recrystallization from ethanol. The solid which was insoluble in alkali was dibenzoyl derivative (XIII).

Reaction of (XII) with Aniline.—To a solution of 2 g. of (XII) in 40 cc. of ethanol, 0.8 g. of aniline was added and refluxed for four hours. Addition of water to the cooled reaction mixture gave an oil, which was taken up in ether and after drying over anhydrous sodium sulfate, the ether was evaporated. From the residual oil small amounts of crystals were obtained. Recrystallization afforded colorless crystals, melting at 177°. The mixed melting point with authentic sample of N,N′-dibenzoyl phenylhydrazine (XIV) was also 177°. Found: N, 9.28, calculated for $C_{20}H_{16}N_2O_2$: N, 8.86%.

N - Phenyl - N - acetyl-N′-mercaptomethylene-hydrazine (XV).—To a solution of 5 g. of thioformyl phenylhydrazine in 30 cc. of pyridine was added dropwise 2.5 g. of acetyl chloride during a period of one hour, stirring continuously and cooling with ice-water. After standing overnight at room temperature, water was added, then the oil which soon solidified separated. Recrystallization from ethanol yielded 3 g. of light red rhombic crystals (XV), melting at 120–2° to red liquid. Found: N, 14.35; calculated for $C_9H_{10}N_2OS$: N, 14.43%.

N - Phenyl - N - acetyl - N′ - phenylhydrazino - methylene-hydrazine (XVI). — To a solution of 1 g. of (XV) in 20 cc. of ethanol 0.6 g. of phenylhydrazine was added at room temperature. The reaction proceeded with liberation of hydrogen sulfide. After an hour water was added and the crystalline precipitates which separated were recrystallized from ethanol. Orange crystals of (XVI), m.p. 188° resulted. Yield, 0.5 g. Found: N, 20,56; calculated for $C_{15}H_{16}N_4O$: N, 20.90%.

N - Phenyl - N,N′ - diacetyl-N′ - thioformylhydrazine (VII). — Five grams of thioformyl phenylhydrazine were dissolved in 30 cc. of acetic anhydride, the temperature of the solution being kept under 30° by external cooling with water. After standing overnight at room temperature, water was added to decompose the excess of acetic anhydride. A viscous oil which soon solidified was separated. The solid was collected on the filter, and washed with ether. The crude product weighed 7 g., and melted at 103–4°. Recrystallization from ethanol yielded 6 g. of (VII) as yellow rhombic crystals melting at 107°. Found: N, 11.85; calculated for $C_{11}H_{12}N_2O_2S$: N, 11.86%.

N^{α}-Acetyl-N^{β}, $N^{\beta'}$-diphenyl-formhydrazidine (XI).—From the ether washings in the above reaction, ether was evaporated. The ethanol solution of the residual red oil was treated with phenylhydrazine at room temperature. The reaction proceeded with evolution of hydrogen sulfide and heat. After a little while water was added and the separated solid was recrystallized from dilute ethanol. Colorless needles of (XI), melting at 173° resulted. Found: C, 66.89; H, 6.09; N, 20.41; calculated for $C_{15}H_{16}N_4O$: C, 67.16; H, 5.97; N, 20.90%.

Reaction of (VII) with Aniline.—To a solution of 1 g. of (VII) in a small volume of acetone 0.4 g. of aniline was added and the mixture was kept standing at room temperature for one hour. On addition of water a colorless solid was separated. Recrystallization from dilute ethanol gave 0.3 g. of thioformyl aniline, melting at 140°, which was confirmed by its mixed melting point with authentic sample and analytical value. (Found: N, 10.02, calculated for C_7H_7NS: N, 10.21%.) Addition of water to the mother liquor of the recrystallization gave still greater amounts of solid. This was washed witn 10% sodium hydroxide solution to remove thioformyl aniline, and the residue, on recrystallization from dilute ethanol afforded colorless crystals of N,N′-diacetyl-N′-phenyl-hydrazinomethyleneaniline (X), melting at 135°. Found: N, 14.2; calculated for $C_{17}H_{17}N_3O_2$: N, 14.23%.

Hydrolysis of Diacetyl derivative (VII) into Monoacetyl derivative (XV). — One gram of diacetyl derivative (VII) was suspended in 3.5 cc. of 10% sodium hydroxide solution, and stirring was continued until dissolution was completed. Decolorizing with charcoal and acidifying with acetic acid gave an oil which soon solidified. Recrystallization from ethanol yielded colorless rhombic crystals, melting at 120–1°. Mixed melting point with monoacetyl derivative (XV) showed no depression.

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