The Reactions of 4-Thiazone Imine Hydrochlorides with Amines[1]

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In the preceding paper of this series,[2] it was reported that mesoionic compounds with an exocyclic imino group such as thiazone imine and sydone imine are stable only in the forms of salts or of *N*-acyl derivatives and do not exist in the form of free bases.

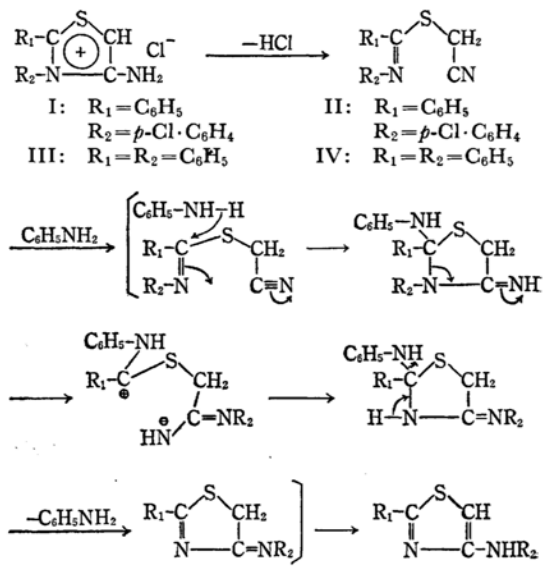
The treatment of 2-phenyl-3-*p*-chlorophenyl-4-thiazone imine hydrochloride (I) with sodium bicarbonate afforded cyanomethyl *N*-(*p*-chlorophenyl)benzthioimidate (II), which could then be converted back into I by treating it with hydrogen chloride, while the treatment of 2,3-diphenylthiazone imine hydrochloride (III) with sodium bicarbonate gave only tarry substances, from which neither the expected cyanomethyl *N*-phenylbenzthioimidate (IV) nor the free base of the corresponding thiazone imine hydrochloride could be obtained. It seems that the nucleophilic attack of a base upon thiazone imine hydrochloride might not be simple; therefore we investigated the behavior of thiazone imine hydrochloride towards the nucleophilic attack of amines.

Results and Discussion

The treatment of III with triethylamine, pyridine, and sodium alkoxide afforded tarry substances in all cases. When the solution of III in aniline was allowed to stand overnight, and was then neutralized with hydrochloric acid, colorless needles (V) were separated out; the results of an elemental analysis of them were consistent with the formula resulting from the removal of hydrogen chloride from III. In the infrared spectrum of V a band at 3300 cm^{-1}, which may be due to an NH stretching vibration, and a band at 1540 cm^{-1}, due to an N=C stretching vibration, appeared. V showed characteristic absorptions at 275 mμ, (ε=36000) and 362 mμ, (ε=4800) in its ultraviolet spectrum, absorptions suggestive of an aromatic heterocyclic system. These spectral analyses suggest that Compound V may be 2-phenyl-4-anilinothiazole. In addition, in the NMR spectrum V had an absorption at 3.85 τ. On the basis that the proton of the 5-position of 2,4-dimethylthiazole exhibits a singlet at 3.34τ,[3] this absorption was attributed to the proton of the 5-position of the above structure for V. Very few 4-aminothiazole derivatives have been found in the literature,[4] and no 4-anilinothiazole derivatives have been known. Although the structure of V was not confirmed by an independent sythesis, it may possibly be supported by the elemental and spectral analyses.

The consideration that the formation of V might proceed through the intermediate IV led us to examine the reaction of IV with aniline. When IV was treated with aniline under the same reaction conditions as in the case of the reaction of III with aniline, V was obtained in a good yield. In order to investigate the role of aniline, other bases were used in the reaction with IV. The treatment of IV with *o*-toluidine also gave V; this fact showed that the anilino group of the 4-position of V was not derived from the aniline used as the solvent, but was rather derived by the rearrangement of IV. When dimethylaniline was used instead of aniline, the starting material was recovered. This fact suggests, further, that aniline participates in the rearrangement by forming an adduct with IV.

As a consequence, the mechanism of the formation of V may be formulated in the way pictured in Scheme I.

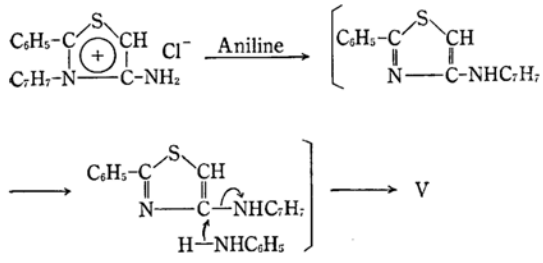


Scheme I

1) Studies on Mesoionic Compounds. XXXI.
2) M. Ohta, K. Yoshida and S. Sato, This Bulletin, **39**, 1269 (1966).
3) "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif.
4) E. C. Taylor, J. A. Anderson and G. A. Berchtold, *J. Am. Chem. Soc.*, **77**, 5444 (1955).

A rearrangement analogous to this was observed in that of *N*-acetyl-sydnone imine hydrochloride into a 5-hydroxytriazole derivative.[5] When 2-*p*-methoxyphenyl-3-phenyl-thiazone imine hydrochloride was treated with aniline, 2-*p*-methoxyphenyl-4-anilinothiazole was obtained, but in the case of II, the corresponding thiazole was not obtained by the treatment of II with aniline. When 2-phenyl-3-benzyl-thiazone imine hydrochloride was treated with aniline, V was obtained. The isolation of this unexpected product may be explained on the assumption that there was an exchange of the benzylamino group of the first-formed 2-phenyl-4-benzylaminothiazole with aniline.

When IV was treated with benzylamine, two substances were obtained; one was *N*-phenyl-*N'*-benzyl-benzamidine, but the structure of the other



Scheme II

was not clear. When IV was allowed to stand in liquid ammonia, thiobenzanilide was isolated.

V formed the hydrochloride and picrate; the former was so unstable that it was converted into polymeric substances within one or two days. When an ethanolic solution of V was boiled with hydrochloric acid, a tarry substance was formed, from which nothing was obtained in a pure state, but when it was boiled with sodium hydroxide for eight hours, V was almost quantitatively recovered unchanged. V was acetylated with acetyl chloride to form 2-phenyl-4-anilino-*N*-acetyl-thiazole. Attempts to form the quaternary salt with benzyl chloride and the *N*-nitroso derivative were not successful. By the treatment of 2-phenylsydnone imine hydrochloride with aniline, an analogous rearrangement product was not obtained, in contrast with the case of thiazone imine hydrochloride, but *N*-nitroso-*N*-phenyl-glycinonitrile was obtained.

Experimental[6]

The Reaction of 2,3-Diphenyl-thiazone Imine Hydrochloride(III) with Aniline. A solution of 1 g of III in 10 m*l* of aniline was allowed to stand overnight at room temperature, and then it was neutralized with 10% hydrochloric acid under ice cooling. The precipitates were collected and recrystallized from ethanol to give colorless needles; mp 102—102.5°C. Yield, 0.4 g. UV: λ_{max}^{EtOH} 275 mμ (ε=36300), 362 mμ (ε=4800). IR: 3200, 1600, 1530 cm^{-1}. Found: C, 71.14; H, 4.59; N, 11.08%. Calcd for $C_{15}H_{12}N_2S$: C, 71.42; H, 4.76; N, 11.11%.

The treatment of 2-*p*-methoxyphenyl-3-phenyl-thiazone imine hydrochloride with aniline gave the corresponding thiazole under the same experimental conditions as have been described. Mp 120—121°C. The yield was 70%. Found: N, 10.23%. Calcd for $C_{16}H_{14}N_2OS$: N, 9.93%.

The Reaction of Cyanomethyl *N*-Phenylbenzthioimidate (IV) with Amines. *With Aniline.* A solution of 1 g of IV in 10 m*l* of aniline was allowed to stand overnight at room temperature, and then it was neutralized with 10% hydrochloric acid under ice cooling. After collection by filtration, the precipitates were recrystallized from ethanol to give colorless needles; mp 102—103°C. No depression of the melting point was observed on admixture with V. The yield was 0.7 g.

With o-Toluidine. The treatment of IV with *o*-toluidine instead of aniline under the above experimental conditions afforded V. The yield was 15%.

With Dimethylaniline. A solution of 1 g of IV in 10 m*l* of dimethylaniline was allowed to stand for a week, and then it was neutralized with 10% hydrochloric acid under ice cooling. The precipitates which separated out were collected and recrystallized from methanol to give colorless needles; mp 65—67°C. No depression of the melting point was observed on admixture with the starting material.

With Liquid Ammonia. A solution of 1 g of IV in liquid ammonia was allowed to stand for four days at room temperature. After the removal of the ammonia, the residue was collected and recrystallized from ethanol to give yellow prisms; mp 96—97°C.

No depression of the melting point was observed on admixture with thiobenzanilide.

With Benzylamine. A solution of 1 g of IV in 10 m*l* of benzylamine was allowed to stand overnight and was then neutralized with 10% hydrochloric acid under ice cooling. From the precipitates which separated out, *N*-phenyl-*N'*-benzyl-benzamidine was isolated by fractional recrystallization from ethanol.

The Reaction of 2-Phenyl-3-benzyl-thiazone Imine Hydrochloride with Aniline. A solution of 1 g of 2-phenyl-3-benzyl-thiazone imine hydrochloride in 10 m*l* of aniline was allowed to stand overnight, and was then neutralized with 10% hydrochloric acid under ice cooling. The precipitates were collected and recrystallized from ethanol to give colorless needles; mp 102—103°C. No depression of the melting point was observed on admixture with V.

The Acetylation of 2-Phenyl-4-anilinothiazole (V). In 20 m*l* of acetyl chloride 0.2 g of V was dissolved, and then the solution was refluxed for one hour. After the removal of the excess acetyl chloride, ether was added to the oily residue. The precipitates were collected and recrystallized from ethanol to give colorless prisms; mp 107—109°C. The yield was 0.2 g. Found: C, 69.51; H, 4.90; N, 10.06%. Calcd for $C_{17}H_{14}N_2OS$: C, 69.39; H, 4.76; N, 9.52%.

5) H. U. Daeniker and J. Druey, *Helv. Chim. Acta*, **45**, 2426 (1962).

6) All melting points were determined on a micro hot stage, and are not corrected.