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The Reaction of the Exo-cyclic Imino Group of "4-Thiazone Imine"[1)]

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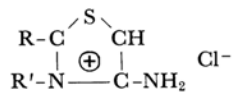
In order to accumulate further information about the properties of meso-ionic compounds with an exo-cyclic imino group, the reactivity of an exo-cyclic imino group of thiazone imine as compared with that of sydnone imine was investigated. Moreover, for the purpose of the pharmacological test, 2, 3-disubstituted thiazone imine hydrochlorides and their *N*-acetyl derivatives were prepared.

Meso-ionic compounds of various ring systems with an exo-cyclic imino group have been reported in the literatures; of these, sydnone imine has been most extensively investigated. The stabilities of the free bases of these meso-ionic compounds differ markedly, depending on the ring systems. In some

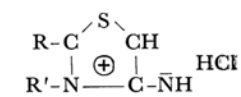
1) This paper is the Part XXVI of studies on meso-ionic compounds.

TABLE I. 2, 3-DISUBSTITUTED-4-THIAZONE IMINE HYDROCHLORIDES

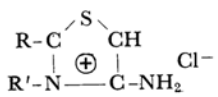


No.	R	R'	M. p., °C (decomp.)	Yield %	N, % Found	N, % Calcd.
1	C_6H_5	p-Cl-C_6H_4	200—201	86	8.84	8.66
2	C_6H_5	o-Cl-C_6H_4	245—247	75	8.74	8.66
3	C_6H_5	p-$CH_3OC_6H_4$	213—215	82	8.73	8.81
4	C_6H_5	o-$CH_3OC_6H_4$	207—208	65	8.89	8.81
5	p-CH_3O-C_6H_4	C_6H_5	220—223	75	8.92	8.81
6	C_6H_5	2-C_5H_4N	147—148	30	14.53	14.47

cases, as in "nitron", free bases can be obtained in a stable form, but sydnone imine or "thiazone imine", which we reported on previously,[2] is unstable and can not be obtained as a free base; it exists only in the form of a salt or an *N*-acyl derivative. Furthermore, the reactivity of the exo-cyclic imino group varies according to the ring system and appreciably differs from that of a usual imino group, which suggests the presence of intrinsic characteristics of the meso-ionic ring. The structure of meso-ionic compounds other than sydnone imine has scarcely been investigated; there remain many points for discussion concerning the representation of these compounds. In some cases, the representation of one specific polar structure might be satisfactory, although as a common feature the compounds can be regarded as resonance hybrids consisting of many polar structures. The structure of the hydrochloride of thiazone imine, which we considered as a meso-ionic compound, may be represented not only by formulae I and II, but also by the quaternary salt structure III, as will be shown below. The hydrochloride of an *N*-acyl derivative of thiazone imine may similarly be represented by IV, V, VI, etc.



(I)



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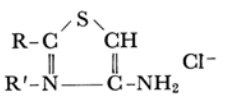

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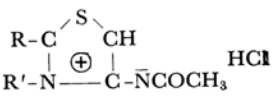

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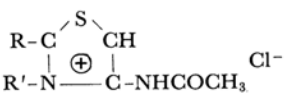

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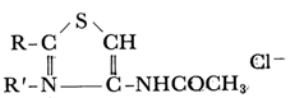
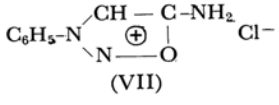
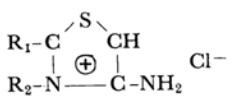


(VI)



(VII)



(VIIIa): $R_1=R_2=Ph$

(VIIIb): $R_1=CH_3O$-  -, $R_2=Ph$

(VIIIc): $R_1=Ph$, $R_2=Cl$-  -

Fig. 1.

The present investigation of the reactivity of the exo-cyclic imino group of thiazone imine, as compared with that of sydnone imine, was undertaken in order to accumulate further information about the structure of thiazone imine. Moreover, stimulated by the recent interest in pharmacological activities,[3] we synthesized 2, 3-disubstituted thiazone imine derivatives for the pharmacological test and also for the purpose of testing the applicability of the methods reported in a previous paper.[2]

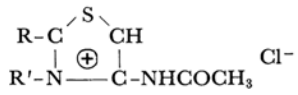
Two procedures for the synthesis of thiazone imine derivatives are available: the ring closure of intermediate nitriles prepared by refluxing a benzene solution of chloroacetonitrile and *N*-monosubstituted thioamides by treatment with hydrogen chloride (method A), and a one-step condensation of thioamides and chloroacetonitrile by heating, with or without diphenyl as a diluent (method B).

The data on the newly-synthesized thiazone imine hydrochlorides are summarized in Table I. Compounds No. 1 and No. 2 were prepared by both methods A and B, and the others, by only method B; an attempt to isolate the intermediates was in vain to give the starting materials. The reaction of thioformanilide and chloroacetonitrile to prepare 3-phenyl-thiazone imine hydrochloride could not be accomplished by method B. The reaction of thiocaprolactam with chloroacetonitrile by

2) H. Chosho, K. Ichimura and M. Ohta, This Bulletin, **37**, 1670 (1964).

3) H. V. Daeniker and J. Druey, *Helv. Chim. Acta*, **45**, 2426 (1962); L. B. Kier and D. Dhawan, *J. Pharm. Sci.*, **51**, 1058 (1962); V. G. Yashunskii and V. G. Ermolaeva, *J. Gen. Chem. U. S. S. R.*, **32**, 182 (1962).

TABLE II. *N*-ACETYL-4-THIAZONE IMINE HYDROCHLORIDES



R	R′	M. p., °C (decomp.)	Yield %	N, % Found	N, % Calcd.	Reaction time hr.
C_6H_5	*p*-Cl-C_6H_4	215—216	85	7.72	7.67	2
C_6H_5	*o*-Cl-C_6H_4	>300	82	7.76	7.67	12
C_6H_5	*p*-CH_3O-C_6H_4	194—195	87	7.80	7.78	2
C_6H_5	*o*-CH_3O-C_6H_4	248—250	85	7.96	7.78	2
p-CH_3O-C_6H_4	C_6H_5	232—233	75	7.50	7.78	1.5
C_6H_5	2-C_5H_4N	232—234	55	12.85	12.69	1

method B to prepare 2, 3-cyclopentamethylene thiazone imine salt gave *S*-acetoamido-isothiocaprolactam hydrochloride. These facts suggest that, in thiazone imine salt, the ring is stabilized by conjugation with aromatic substituents.

As a preliminary work for the subsequent experiments, the stability of the salt and bases of 2, 3-diphenyl thiazone imine was examined. Concerning the stability of sydnone imine, we[4] and Daeniker[3] have reported that its hydrochloride VII is quite stable when heated with water or dilute hydrochloric acid, while its free base can not be obtained by neutralization, which resulted only in decomposition yielding the nitrosoacetonitrile derivative. When an aqueous solution of sydnone imine hydrochloride is neutralized with sodium bicarbonate, a solution of bicarbonate of sydnone imine is formed; this solution, although it is decomposed on heating and carbon dioxide is evolved, can be used immediately for further experiments such as the preparation of *N*-acyl-derivatives. On the other hand, 2, 3-diphenyl-4-thiazone imine hydrochloride (VIIIa) is converted to the acid amide derivative by heating it in 10% hydrochloric acid at 100°C. When an aqueous solution of VIIIa was allowed to stand for a long period, heated at 100°C or neutralized with sodium bicarbonate, a tarry substance was separated out; from this substance nothing could be isolated in a pure state. However, an intermediate nitrile, *S*-cyanomethyl-isothiobenzoyl-*p*-chloroanilide, was isolated from the neutralization products of 2-phenyl-3-(*p*-chlorophenyl)-4-thiazone imine hydrochloride (VIIIc). The above facts indicate that the decomposition of VIIIa does not proceed through a simple reversed process of its formation and that VII is more sensitive to hydrolytic attack than is sydnone imine hydrochloride.

In the studies of reactions at the exo-cyclic imino group of thiazone imine hydrochloride, manipulations in an aqueous or alkaline media seem undesirable. Therefore, taking the results obtained here into consideration, several reactions of VIII under special conditions were examined.

VII can be acetylated with acetic anhydride or acyl chloride by usual methods. In contrast to sydnone imine, VIIIa can not be benzoylated with benzoyl chloride in pyridine, and VIII is recovered unchanged. The acetylation of VIIIa by heating it with acetic anhydride at 100°C for many hours in either the absence or the presence of pyridine gave an acetyl derivative, but the yield was not satisfactory. The use of boron trifluoride as a condensing agent shortened the reaction time considerably and gave a better yield. The data on newly synthesized *N*-acetyl-derivatives of 2, 3-disubstituted-4-thiazone imine hydrochlorides are summarized in Table II. However, the applicability of the method to the synthesis of various acyl-derivatives is extremely limited due to the necessity of using an acid anhydride. We have now found that acylation can be easily accomplished by the simple heating of VIIIa with acid chloride without a solvent or in an inert solvent; by this method various acyl derivatives are obtained in good yields. In a similar way, VII is easily acylated with aliphatic acid chloride, but not with aromatic acid chloride, presumably because of the high reaction temperature, which causes the decomposition of VII.

The carbamoylation and thiocarbamoylation of VII were also attempted. Phenylcarbamoyl and thiocarbamoyl derivatives are unknown. When VII was treated with potassium cyanate in water at room temperature overnight, the *N*-carbamoyl derivative (IX) of VII was obtained, along with a small quantity of *N*-nitroso-*N*-phenyl-glycinonitrile. Under similar conditions, VII and sodium thiocyanate gave only thiocyanate salts of sydnone imine X. All attempts to convert this into the thiocarbamoyl derivative (XI) were unsuccessful. In the case of VIIIa and VIIIb, the reaction with potassium cyanate in a chloroform solution under reflux produced the *N*-carbamoyl derivative, XIIa and XIIb. The reaction of VIIIa with sodium thiocyanate in water gave thiocyanate salts of thiazone imine XIII, which forms the same picrate

4) H. Kato, M. Hashimoto and M. Ohta, *J. Chem. Soc. Japan, Pure Chem. Sect.* (*Nippon kagaku Zassi*), **78**, 707 (1957).

as that obtained from VIII. Attempts to isomerize the thiocyanate of thiazone imine into a thiocarbamoyl derivative XIV were unsuccessful.

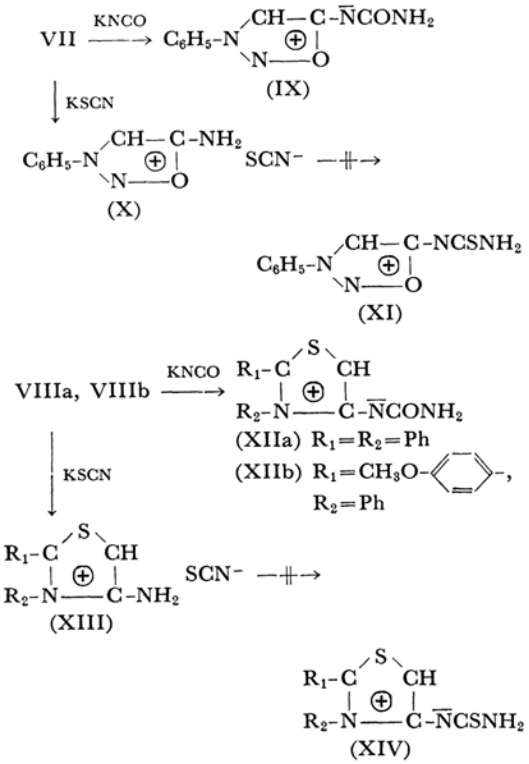


Fig. 2.

Experimental

The Preparation of 2-Phenyl-3-*p*-chlorophenyl-4-thiazone Imine Hydrochloride (VIIIc) by Method A.—A solution of 45 g. of thiobenzoyl-*p*-chloroanilide, 14 g. of chloroacetonitrile and 23 g. of triethylamine in 300 ml. of benzene was refluxed for 3 hr. After the solution had cooled, the precipitated triethylamine hydrochloride was filtered off, and benzene was removed by evaporating it under reduced pressure. The oily residue crystallized after the solution had then stood overnight. The recrystallization from methanol gave *S*-cyanomethyl-isothiobenzoyl-*p*-chloroanilide as white prisms; m. p. 118°C. The yield was 55 g.

Found: C, 62.82; H, 4.01; N, 9.82. Calcd. for $C_{15}H_{11}ClN_2S$: C, 62.94; H, 3.85; N, 9.79%.

Into the solution of 55 g. of *S*-cyanomethyl-isothiobenzoyl-*p*-chloroanilide in 300 ml. of dry acetone, 30 ml. of 30% alcoholic hydrogen chloride was added under cooling in an ice-water bath. The yellow crystals of VIIIc which precipitated were recrystallized from ethanol. *S*-Cyanomethyl-isothiobenzoyl-*o*-chloroanilide (m. p. 80°C) and 2-phenyl-3-*o*-chlorophenylthizaone imine hydrochloride were prepared in the same way.

The Preparation of 2, 3-Disubstituted-4-thiazone Imine Hydrochloride by Method B.—In order to avoid needless repetition, the experimental conditions for carrying out these reactions have been generalized. A mixture of *N*-substituted thioamides, a slight excess over the calculated amount of chloroacetonitrile and an equal amount of diphenyl was heated at 100—120°C in an oil bath. First the reaction mixture melted to a clear solution, and then, as the reaction proceeded, the hydrochloride began to crystallize out. Usually, the reaction is accompanied by a considerable temperature elevation which must be controlled by cooling. After ten to twenty minutes heating, acetone was added to the cooled mixture, and the insoluble crystals were collected by filtration and washed with an acetone-ether mixture. The products can be recrystallized from an ethanolic solution by gradually adding ether.

The Preparation of *N*-Acetyl-2, 3-disubstituted-4-thiazone Imine Hydrochloride.—The experimental conditions for carrying out these reactions have been generalized.

A suspension of 2, 3-disubstituted-4-thiazone imine hydrochloride in about ten times as much acetic anhydride by weight containing a small amount of boron trifluoride etherate was heated at 100°C while being stirred. The reaction times are shown in Table I.

Into the cooled solution, ether was added and the precipitates were collected by filtration and recrystallized from ethanol.

The Reaction of VIIIc and Sodium Bicarbonate.—Into the solution of 1 g. of VIIIc in 10 ml. of water, 5 ml. of 5% sodium bicarbonate solution was added. The solution was allowed to stand overnight. During this time a brown solid was separated out; it was then recrystallized from methanol. 0.3 g. of *S*-cyanomethyl-isothiobenzoyl-*p*-chloroanilide (m. p. 118°C) was thus obtained.

The Acylation of Sydnone- and Thiazone Imine Hydrochlorides with Acyl Chloride.—*General Procedure.* Sydnone- or thiazone imine hydrochloride was heated with an excess of acyl chloride without a solvent or in an inert solvent such as toluene, and the hydrochloride of the acyl derivative was collected by filtration, washed with benzene, and recrystallized from an appropriate solvent.

The following acyl derivatives were prepared by this method: Acetyl-: m. p. 290°C (decomp.). Free base: m. p. 198°C (decomp.). Propionyl-: m. p. 220°C (decomp.).

Found: N, 7.60; Calcd. for $C_{18}H_{17}ClN_2OS$: N, 8.10%.

Benzoyl-: m. p. 223°C (decomp.). Free base: m. p. 212°C (decomp.). Cinnamoyl-: m. p. 272°C (decomp.). Found: N, 6.70; Calcd. for $C_{23}H_{19}ClN_2OS$: N, 6.72%.

The Reaction of Thiocaprolactam with Chloroacetonitrile.—Two grams of thiocaprolactam with 1.2 g. of chloroacetonitrile was heated at 100°C on a water bath. The reaction was completed in several minutes, yielding a viscous oil which solidified when left standing at room temperature. Acetone was added, and the insoluble products were collected by filtration. Recrystallization from benzene-ethanol gave *S*-carbamoylmethyl-isothiocaprolactam hydrochloride as colorless prisms. Yield, 1.6 g; m. p. 158—159°C.

Found: C, 43.54; H, 6.52; N, 12.57. Calcd. for $C_{18}H_{13}ClN_2S$: C, 43.14; H. 6.74; N, 12.48%.

***N*-Carbamoyl-3-phenyl-sydnone Imine (IX).**—One gram of VII was dissolved in water, and then an aqueous solution of 0.4 g. of potassium cyanate was added. After the solution had been allowed to stand

overnight, the pale yellow precipitates were collected by filtration and recrystallized from ethanol to give IX as yellow crystals, m. p. 153°C (decomp.).

Found: C, 52.91; H, 4.17; N, 27.38. Calcd. for $C_8H_8N_4O_2$: C, 52.94; H, 3.95; N, 27.44.%

3-Phenylsydnone Imine Thiocyanate (X).—Into an aqueous solution of 1 g. of VII, a solution of 0.42 g. of sodium thiocyanate was added. The precipitate was immediately separated out and recrystallized from ethanol to give pale yellow needles, m. p. 155°C (decomp.).

Found: C, 49.57; H, 3.66; N, 25.30. Calcd. for $C_8H_8N_4OS$: C, 49.09; H, 3.66; N, 25.45%.

This was not converted into *N*-thiocarbamoyl-3-phenylsydnone imine when heated.

***N*-Carbamoyl-2,3-diphenylthiazone Imine (XIIa).**—One gram of VIIIa and 0.9 g. of pulverized potassium cyanate were refluxed in 80 ml. of chloroform for 5 hr. After the solvent had been removed under reduced pressure, the residue was recrystallized from ethanol to give XIIa as yellow crystals, m. p. 275°C (decomp.).

Found: C, 65.02; H, 4.48; N, 14.38. Calcd. for $C_{16}H_{13}N_3OS$: C, 65.08; H, 4.44; N, 14.23%.

2,3-Diphenylthiazone Imine Thiocyanate (XIIIa).—To an aqueous solution of 1 g. of VIIIa, a solution of 0.3 g. of sodium thiocyanate was added. The yellow precipitate which was immediately separated out was collected and recrystallized from 70% aqueous ethanol to give yellow needles, m. p. 113°C (decomp.).

Found: C, 65.02; H, 4.48; N, 14.38. Calcd. for $C_{16}H_{13}N_3S_2$: C, 65.08; H, 4.34; N, 13.49%.

This thiocyanate could not be converted into *N*-thiocarbamoyl-2,3-diphenylthiazone imine by heating it.

***N*-Carbamoyl-2-(*o*-methoxyphenyl)-3-phenylthiazone Imine (XIIb).**—One gram of VIIIb was dissolved in chloroform, and then 0.75 g. of powdered potassium cyanate was added. After the mixture had been allowed to stand overnight at room temperature, it was evaporated under reduced pressure to yield a crystalline residue. The residue was recrystallized from ethanol to give yellow scales, m.p. 287°C (decomp.).

Found: N, 14.41. Calcd. for $C_{17}H_{15}N_3O_2S$: N, 13.59%.

2-(*p*-Methoxyphenyl)-3-phenylthiazone Imine Thiocyanate (XIIIb).—When an aqueous solution of 1 g. of VIIIb, a solution of 0.3 g. of sodium thiocyanate was added, yellow crystals were crystallized out immediately. Recrystallization from ethanol gave yellow needles, m. p. 163°C (decomp.).

Found: N, 12.39. Calcd. for $C_{17}H_{15}N_3OS_2$: N, 12.30%.