The Reactions of N-Substituted Thioamides with α-Halonitriles[*,1]

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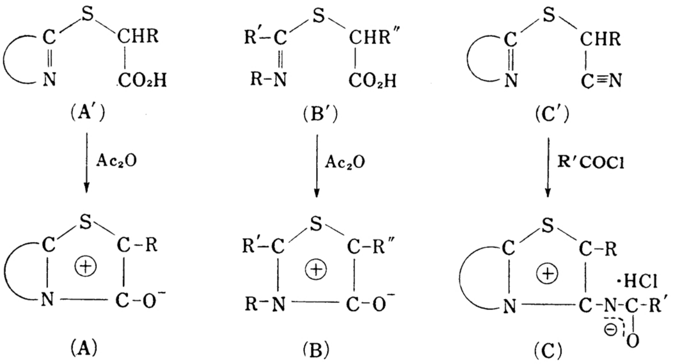
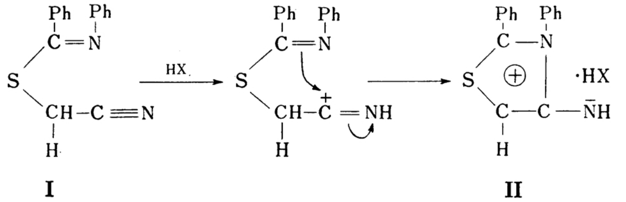
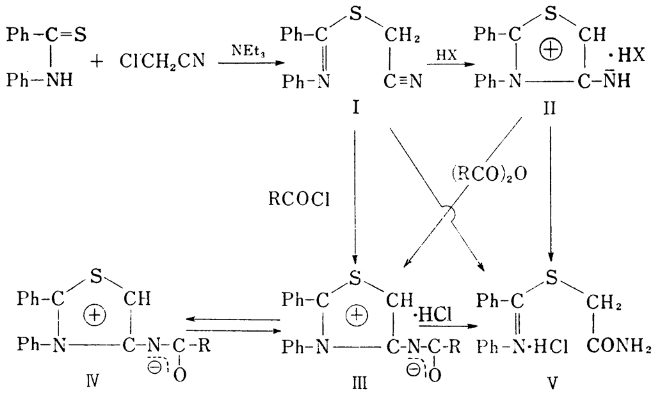
(Received May 25, 1964)

In the previous papers of this series, it has been described how the meso-ionic compounds A and B are obtained by the treatment of carboxymethylmercapto derivatives (A′ and B′) with acetic anhydride,[2,3] and how the treatment of cyanomethylmercapto derivatives of heterocyclic nitrogen compounds (C′) with acyl chloride gives compounds of the type C.[2] The present paper will report the synthesis of non-condensed compounds of the type C by the reaction of *N*-substituted thioamides with α-halonitriles, since it is interesting to investigate the properties and the reactivities of this ring system.

As a preliminary stage in the formation of this ring system, thiobenzanilide was condensed







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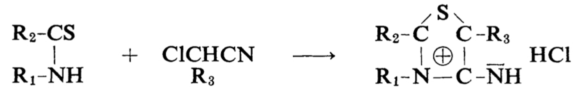
[*] Presented at the 17th Annual Meeting of the Chemical Society of Japan, Tokyo, March, 1964.

[1] Studies of Meso-ionic Compounds. Part XIX.

[2] H. Kato, K. Tanaka and M. Ohta, This Bulletin, 35, 1901 (1962).

[3] Part XVIII: M. Ohta, H. Chosho, C. Shin and K. Ichimura, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), 85, 440 (1964).

TABLE I. THIAZONE IMINE HYDROCHLORIDES PREPARED FROM *N*-SUBSTITUTED THIOAMIDES WITH α-HALONITRILES



Substituent			Color of crystal	Yield %	M. p. (decomp.) °C	Analysis Found, %			Analysis Calcd., %		
						C	H	N	C	H	N
R_1	R_2	R_3									
Ph	Ph	H	Yellow	96	207	61.88	4.74	9.78	62.38	4.50	9.71
CH_3	Ph	H	Pale yellow	67	201	53.16	5.03	12.49	52.98	4.86	12.36
Ph	CH_3	H	Colorless	80	173	52.92	5.10	12.60	52.98	4.86	12.36
$PhCH_2$	Ph	H	Yellow	50	192	63.18	5.00	9.49	63.47	4.96	9.26
Ph	$PhCH_2$	H	Yellow	86	190	—	—	9.05	—	—	9.26
$PhCH_2$	Ph	Ph	Orange	60	176	69.90	5.01	7.39	69.70	5.05	7.39
Ph	Ph	Ph	Yellow*	14	155	58.33	3.62	12.66	58.17	3.41	12.57

* This was identified as picrate.

with chloroacetonitrile in the presence of triethylamine to afford *S*-cyanomethylisothiobenzanilide (I). The treatment of this intermediate with hydrogen chloride in benzene or 2-propanol gave the expected product, " thiazone imine hydrochloride "[4] (II ; $X=Cl$), the structure of which was deduced by an elementary analysis, by the absence of absorption due to the nitrile group in its infrared spectrum, and by the appearance of a band at $3250\,cm^{-1}$ which may be due to the nitrogen-hydrogen stretching frequency. In addition, the hydrochloride (II ; $X=Cl$) showed a characteristic band at $360\,m\mu$ ($\varepsilon=6.55\times10^3$) in its ultraviolet spectrum suggestive of the heterocyclic system. This ring formation seems to proceed as a result of the interaction of two polar groups, by a mechanism similar to that of sydnone imine salts.[5] The hydrochloride (II ; $X=Cl$) was converted into the nitrate (II ; $X=NO_3$) by the treatment with silver nitrate. On the treatment of I with a strong organic acid such as picric acid and *p*-toluenesulfonic acid, the ring formation took place to produce the thiazone imine salts of corresponding acid. The structure was confirmed by infrared spectra and by the fact that this picrate was identical with that obtained by the treatment of the thiazone imine hydrochloride (II ; $X=Cl$) with picric acid.

Thiazone imine hydrochloride was converted into *N*-acyl derivatives III by the treatment with acid anhydride. The hydrochlorides of these *N*-acyl derivatives were also yielded by the treatment of I with the corresponding acyl chloride, as in the case of the compound C. The neutralization of the hydrochlorides of *N*-acyl compounds III gave free bases with high melting points, which could then be readily reconverted into the original hydrogen chlorides by the action of hydrogen chloride.

We attempted to prepare *S*-(α-cyanobenzyl)-isothiobenzanilide from thiobenzanilide and α-chlorophenylacetonitrile in the presence of triethylamine, which would be expected to form a 2, 3, 5-triphenylthiazone imine derivative, but only α, α′-dicyanostilbene resulted ; this must be a condensation product of two moles of α-chlorophenylacetonitrile. It was, however, found that the hydrochloride (II ; $X=Cl$) was also obtained by heating thiobenzanilide and chloroacetonitrile without a solvent or in biphenyl. This fact suggested that the other thiazone imine derivatives could also be obtained from the corresponding *N*-substituted thioamides and α-chloronitriles without isolating the intermediates. Actually, in a similar manner, some thiazone imine hydrochlorides were prepared from both components, as is shown in Table I. On the other hand, the reaction of thiopyrrolidone with chloroacetonitrile did not afford the expected heterocyclic compound, but alternatively formed *S*-cyanomethylisothiopyrrolidone hydrochloride (VI), the structural evidence for which is based on the elementary analysis and on its infrared spectrum.

The hydrochlorides of thiazone imines (II ; $X=Cl$) decomposed in alkaline conditions, showing themselves incapable of existence as

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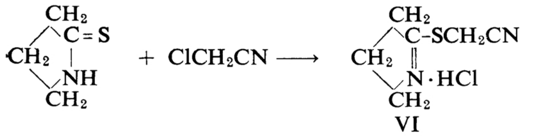
[4] This heterocyclic compound can be named " Ψ-4-imino-2, 3-diphenyl-3, 4-dihydrothiazole hydrochloride, " according to Baker's proposal (*J. Chem. Soc.*, **1949**, 311), the symbol Ψ indicating the hybrid ionic structure. In the preceding paper the meso-ionic compound B was provisionally named " thiazone " ; in the present paper the authors will refer to II derived from " thiazone " as salts of " thiazone imine " for the sake of simplification in naming.

[5] P. Brookes and J. Walker, *J. Chem. Soc.*, **1957**, 4409.



VI

a free base in contrast with the *N*-acylated free base IV. An acidic hydrolysis of the thiazone imine hydrochloride afforded an amide V, which was also produced by the acidic hydrolysis of the *N*-acetyl salt (III; R=CH_3) and *S*-cyanomethylisothiobenzanilide (I).

The reactivities of the compounds obtained above and the related derivatives containing other functional groups will be reported shortly.

Experimental

***S*-Cyanomethylisothiobenzanilide (I).** — Triethylamine (5 cc.) was added to a solution of thiobenzanilide (5 g.) and chloroacetonitrile (1.8 g.) in benzene (25 cc.), and the mixture was heated at 50°C for nine hours. After the mixture had stood overnight, the separated triethylamine hydrochloride was filtered off. The filtrate was evaporated to dryness under reduced pressure, and the residual crystals were collected. Recrystallization from ether-petroleum ether gave 3 g. of *S*-cyanomethylisothiobenzanilide as colorless needles; m. p. 68~69°C.

Found: C, 71.05; H, 4.83; N, 11.24. Calcd. for $C_{15}H_{12}N_2S$: C, 71.42; H, 4.76; N, 11.11%.

The Action of Hydrogen Chloride on I.—a) A 2-propanol solution of I (1 g.) was treated with 2-propanol saturated with hydrogen chloride. After the solution had stood, 2, 3-diphenylthiazone imine hydrochloride (II; X=Cl) precipitated; this was collected and washed with acetone. The yield was 0.8 g. It was purified by reprecipitation from an ethanolic solution with ether (see Table I).

b) The same hydrochloride was also obtained by passing dry hydrogen chloride into a benzene solution of I.

The Action of Picric Acid on I.—An ethanolic solution of I was treated with a solution of picric acid in ethanol to yield picrate (II; HX=picric acid) as yellow needles, which were recrystallized from 2-propanol, m. p. 177°C (decomp.).

Found: C, 52.23; H, 2.81; N, 14.47. Calcd. for $C_{21}H_{15}N_5O_7S$: C, 52.40; H, 3.21; N, 14.55%.

The Action of *p*-Toluenesulfonic Acid on I.—*p*-Toluenesulfonic acid (0.2 g.) in benzene was added to a benzene solution of I (0.1 g.). A yellow oil separated out. After the removal of the solvent, it was dissolved in methanol, and *p*-toluenesulfonate (II; HX=*p*-toluenesulfonic acid) was precipitated by adding ether drop by drop. This yellow needles (0.15 g.) melted at 197°C with decomposition.

Found: C, 62.28; H, 4.99; N, 6.60. Calcd. for $C_{22}H_{20}N_2O_3S_2$: C, 62.27; H, 4.75; N, 6.60%.

The Conversion of 2, 3-Diphenylthiazone Imine Hydrochloride (II; X=Cl) to Other Salts.—*Nitrate.*—Ten per cent aqueous silver nitrate was added to an aqueous solution of the hydrochloride (II; X=Cl) (1 g.). After the silver chloride had been filtered off, the filtrate was evaporated under reduced pressure and the residual crystals were collected by filtration. The yield was 0.9 g. Recrystallization from 2-propanol gave pure nitrate (II; X=NO_3) as yellow needles; m. p. 173.5°C (decomp.).

Found: C, 56.89; H, 4.19; N, 13.49. Calcd., for $C_{15}H_{13}N_3O_3S$: C, 57.14; H, 4.16; N, 13.33%.

Picrate.—The hydrochloride (II; X=Cl) in ethanol was treated with ethanol saturated with picric acid. Yellow needles; m. p. 177°C (unchanged by admixture with the picrate obtained above).

The Conversion of 2, 3-Diphenylthiazone Imine Hydrochloride (II; X=Cl) into *N*-Acetyl Derivatives (III and IV; R=CH_3).—When suspension of the hydrochloride (II; X=Cl) (2 g.) in acetic anhydride (10 cc.) was heated at 90°C for six hours, the reaction mixture turned into a clear solution. In about half an hour crystals precipitated, and the mixture was heated for a further two hours. The crystals were then filtered and washed with acetone. Yield, 2 g. Reprecipitation from an ethanolic solution with ether gave pure hydrochloride of *N*-acetyl-2, 3-diphenylthiazone imine (III; R=CH_3) as colorless needles; m. p. 290°C.

Found: C, 61.84; H, 4.76; N, 8.48. Calcd. for $C_{17}H_{15}N_2OSCl$: C, 61.50; H, 4.52; N, 8.47%.

This hydrochloride of the *N*-acetyl compound was treated with aqueous sodium hydrogen carbonate to yield 0.8 g. of its free base (IV; R=CH_3). Recrystallization from ethanol gave yellow needles; m. p. 198°C (decomp.).

Found: C, 69.55; H, 4.86; N, 9.59. Calcd. for $C_{17}H_{14}N_2OS$: C, 69.39; H, 4.76; N, 9.53%.

The Conversion of 2, 3-Diphenylthiazone Imine Hydrochloride (II; X=Cl) into an *N*-Benzoyl Derivative (IV; R=Ph).—A mixture of the hydrochloride (II; X=Cl) (2 g.) and the excess benzoic anhydride (4.9 g.) was heated at 150~160°C for one hour. The reaction mixture was then washed with hot benzene, and the crystals were collected. They were then suspended in water, treated with aqueous sodium hydrogen carbonate, filtered again, and washed with 2-propanol. Yield, 1.0 g. Recrystallization from ethanol gave a pure free base of an *N*-benzoyl compound (IV; R=Ph) as yellow needles; m. p. 211~212°C (decomp.).

Found: C, 73.95; H, 4.63; N, 7.87. Calcd. for $C_{22}H_{16}N_2OS$: C, 74.14; H, 4.53; N, 8.27%.

The Reaction of *S*-Cyanomethylisothiobenzanilide (I) with Acetyl Chloride.—*S*-Cyanomethylisothiobenzanilide (I) (1.0 g.) and acetyl chloride (0.32 g.) were heated in benzene at 60°C for three hours, and the precipitate was collected. An aqueous solution of the precipitate was treated with aqueous sodium hydrogen carbonate to yield yellow crystals. Recrystallization from ethanol gave the free base of an *N*-acetyl compound (IV; R=CH_3) as yellow needles; m. p. 198°C (decomp.), undepressed on admixture with a sample prepared from II with acetic anhydride.

The Reaction of *S*-Cyanomethylisothiobenzanilide (I) with Benzoyl Chloride.—The mixture of *S*-cyanomethylisothiobenzanilide (I) (1.0 g.) and the excess of benzoyl chloride was heated at 90°C for one hour, and crystals were precipitated. The precipitate was then filtered and washed with benzene. The treatment of this precipitate with aqueous sodium hydrogen carbonate gave yellow crystals, which were filtered, washed with 2-propanol, and recrystallized from ethanol. The yield of the free base of an *N*-benzoyl compound (IV; R=Ph), m. p. 211~212°C (undepressed on admixture with a sample prepared from II with benzoic anhydride), was 1.0 g.

The Hydrolysis of *S*-Cyanomethylisothiobenzanilide (I).—A suspension of *S*-cyanomethylisothiobenzanilide (I) (0.5 g.) in 10% aqueous hydrochloric acid (5 cc.) was heated gently on a water bath for twenty minutes, and then the hydrolysate was crystallized by being left standing. The yield of hydrochloride of *S*-carbamoylisothiobenzanilide (V), m. p. 65~70°C, was 0.4 g. Recrystallization from chloroform raised the melting point to 85~88°C. Colorless crystals.

Found: C, 55.20; H, 5.38; N, 8.51. Calcd. for $C_{15}H_{15}N_2SOCl\cdot H_2O$: C, 55.46; H, 5.23; N, 8.62%.

The Hydrolysis of 2, 3-Diphenylthiazone Imine Hydrochloride (II; X=Cl).—The hydrochloride (II; X=Cl) (1 g.) in 10% aqueous hydrochloric acid was heated on a steam bath for a few minutes. Oil separated and solidified when the mixture was left standing. The solid was filtered and recrystallized from acetone. The yield was 1.0 g.; m. p. 85~88°C, undepressed by admixture with the above hydrolysate prepared from I.

The Hydrolysis of *N*-Acetyl-2, 3-Diphenylthiazone Imine Hydrochloride (III; X=CH_3)—The hydrochloride of the *N*-acetyl compound (1 g.) was hydrolysed with 10% aqueous hydrochloric acid in a manner similar to that above. The yield was 0.8 g.; m. p. 85~88°C, not depressed by admixture with the hydrolysate obtained above.

An Attempt to Prepare *S*-(α-Cyanobenzyl)-isothiobenzanilide. — Thiobenzanilide (5 g.) and α-chlorophenylacetonitrile (4 g.) were dissolved in benzene (40 cc.), triethylamine (10 cc.) was added, and the mixture was refluxed for two hours. After the mixture had stood overnight, triethylamine hydrochloride (3.5 g.) was filtered off, and the solvent was removed under reduced pressure from the filtrate. The residue crystallized by scratching. The crystals were collected and washed with methanol. Recrystallization from methanol gave *cis*-α, α-dicyanostilbene as colorless needles; m. p. 158°C (reported m. p. 160°C).⁽⁶⁾

Found: C, 83.46; H, 4.43; N, 11.87. Calcd. for $C_{16}H_{10}N_2$: C, 83.51; H, 4.35; N, 12.17%.

A General Procedure for Preparing Thiazone Imine Hydrochlorides.—a) *N*-Substituted thioamide and α-chloronitrile (a small excess) were heated on a steam bath, until the fused reaction mixture got more viscous with a rapid rise in the temperature. The cooled viscous product was then crystallized by rubbing it with acetone, filtered, and washed with acetone. Reprecipitation from an ethanolic solution with ether gave pure thiazone imine hydrochloride.

b) *N*-Substituted thioamide, α-chloronitrile, and biphenyl as a solvent were heated at about 120°C while being stirred. The reaction mixture was then cooled as soon as the temperature began to rise, and acetone was added in order to remove the biphenyl. The acetone-insoluble hydrochloride of the heterocyclic compound was then collected, washed with acetone, and purified by reprecipitation from an ethanolic solution with ether.

The Reaction of Thiopyrrolidone with Chloroacetonitrile.—A mixture of thiopyrrolidone (1 g.) and the excess chloroacetonitrile was heated. The reaction started suddenly in about fifteen minutes with the evolution of heat, but it was at once interrupted by cooling. The solid was washed with ethanol. Yield, 1.35 g. This *S*-cyanomethylisothiopyrrolidone hydrochloride (VI) was thoroughly washed with methanol in order to analyze it.

Found: C, 40.54; H, 5.23; N, 15.89. Calcd. for $C_6H_9N_2SCl$: C, 40.79; H, 5.10; N, 15.86%. IR: 2250 (-C≡N), 1610 ($>C=N\langle^{+}$) cm^{-1}.

The authors are grateful to the Kyorin Pharmaceutical Co., Ltd., for recording the ultraviolet spectra.

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(6) J. v. Braun, *Ber.*, **36**, 2652 (1903).