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Reactions of Thioamides with Haloacids*[1]

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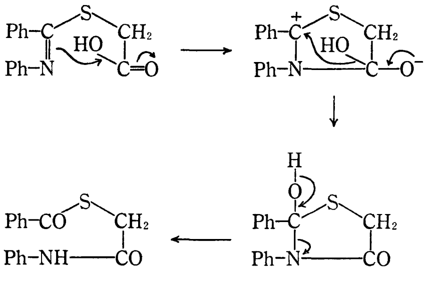
The reactions of *S*-carboxymethylisothioamide RC(=NR')SCHRCOOH with acetic anhydride proceeded through various courses depending on the reaction conditions and the structure of thioamides. When *S*-carboxymethylisothiobenzanilide (IIa) was treated with a mixture of acetic anhydride and triethylamine in the cold, an intermediate (A), presumably 2-hydroxy-2,3-diphenylthiazolidin-4-one (V), was isolated which was readily converted to benzoylthioacetanilide (IIIa). Attempts to convert A or IIIa to a mesoionic compound failed. Under the same reaction conditions as for IIa, *S*-carboxymethylisothiobenz-*p*-chloroanilide (IIb) afforded benz-*p*-chloroanilide, while corresponding *p*-anisidide (IIc) gave only tarry product. Attempts to obtain a mesoionic product from pyrrolidine-2-thione or thiocaprolactam and bromoacetic acid were unsuccessful. However, condensation of pyrrolidine-2-thione with α-chlorophenylacetic acid followed by treatment with a mixture of acetic anhydride and triethylamine gave eight-membered rearranged product (XII).

In previous papers,[1,2] we showed that the reaction of thiobenzanilide (Ia) with bromoacetic acid afforded three different products depending on the kinds of condensing agents and the reaction conditions. On refluxing a benzene solution of Ia and bromoacetic acid, benzoylthioglycolic acid anilide (IIIa) was obtained. It was proposed that the reaction proceeded *via* the pseudobase (V). Condensation of Ia with bromoacetic acid in the presence of triethylamine afforded *S*-carboxymethylisothiobenzanilide (IIa) which gave 5-acetyl-2,3-diphenyl-4-thiazone (IVb) by treatment with acetic anhydride, whereas treatment of Ia with a mixture of acetic anhydride and triethylamine gave 2,3-diphenyl-4-thiazone (IVa).

We found that when IIa was treated with a cold mixture of acetic anhydride and triethylamine, a new intermediate (A) of mp 143°C was obtained. When A was treated with ethanol, benzene or chloroform, benzoylthioglycolic acid anilide (IIIa) was obtained. Attempts to convert A or IIIa to IVa by treating with a mixture of acetic anhydride and triethylamine were unsuccessful. Elementary analysis indicated the composition of A to be $C_{15}H_{13}NO_2S$. Two structures having this composition may be taken into consideration, *viz.*, 2-hydroxy-2,3-diphenylthiazolidin-4-one (V) and 4-oxo-2,3-diphenylthiazolinium hydroxide (VI). Although we were unable to determine the structure of A unequivocally by IR or NMR spectra, pseudobase structure V seems to be more preferable to VI.

The mechanism of the formation of IVa from IIa by the action of acetic anhydride in the presence or absence of triethylamine was discussed in a previous paper.[2] The process was assumed to be similar to that proposed for the formation of sydnone from *N*-nitroso-*N*-phenylglycine, in which mixed acid anhydride is formed as an intermediate. From the present observation, it is clear that IVa is not derived from IIIa or A by internal dehydration. For the mechanism of the formation of IIIa, a probable scheme is shown below, which is quite similar to that proposed for the reaction of imidoyl chloride and glycolic acid.[3]



When *S*-carboxymethylisothiobenz-*p*-chloroanilide (IIb) was treated with a mixture of acetic anhydride and triethylamine in the cold, benz-*p*-chloroanilide was obtained instead of the rearranged product. When *S*-carboxymethylisothiobenz-*p*-anisidide (IIc) was treated with acetic anhydride in the presence or absence of triethylamine, only tarry matter was obtained.

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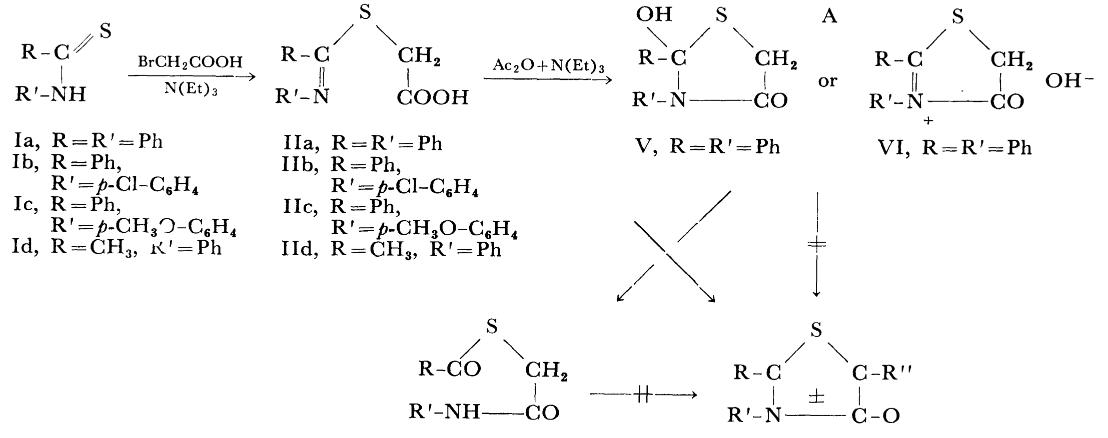
*[1] Studies on mesoionic compounds. XXXIII. Part XXXII; Ref. 3.

[1] M. Ohta, H. Chosho, C. Shin and K. Ichimura, *Nippon Kagaku Zasshi*, **85**, 440 (1964).

[2] M. Ohta and C. Shin, This Bulletin, **38**, 704 (1965).

[3] A. Chinone, S. Sato, T. Mase and M. Ohta, *ibid.*, **42**, 2310 (1969).



Ia, $R=R'=Ph$
Ib, $R=Ph$, $R'=p\text{-}Cl\text{-}C_6H_4$
Ic, $R=Ph$, $R'=p\text{-}CH_3O\text{-}C_6H_4$
Id, $R=CH_3$, $R'=Ph$

IIa, $R=R'=Ph$
IIb, $R=Ph$, $R'=p\text{-}Cl\text{-}C_6H_4$
IIc, $R=Ph$, $R'=p\text{-}CH_3O\text{-}C_6H_4$
IId, $R=CH_3$, $R'=Ph$

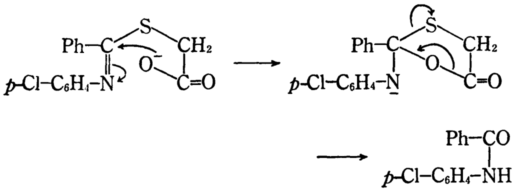
V, $R=R'=Ph$

VI, $R=R'=Ph$

IIIa, $R=R'=Ph$
IIIb, $R=CH_3$, $R'=Ph$

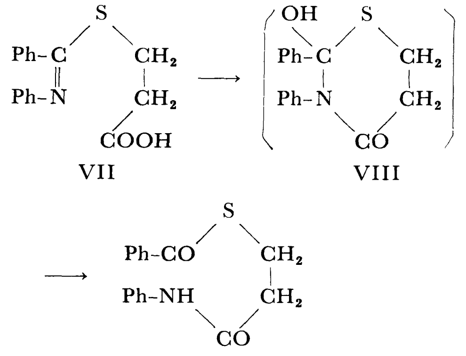
IVa, $R=R'=Ph$, $R''=H$
IVb, $R=R'=Ph$, $R''=COCH_3$

The mechanism for the formation of benz-*p*-chloroanilide may be explained by assuming that the electron attractive chlorine atom would lower the nucleophilicity of nitrogen atom and enhance the electrophilicity of carbon atom of $\rangle C=N-$ grouping. The latter effect would favor the attack of anion in preference to the attack of nitrogen on carbonyl carbon atom and the cleavage of C–S bond may ensue.



An unexpected result obtained in the case of thiobenz-*p*-anisidide, where the *p*-methoxy group would favor the formation of mesoionic compound by enhancing the nucleophilicity of nitrogen, may be ascribed to the instability of the mesoionic compound which would decompose if formed.

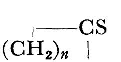
Our findings on the rearrangement of *S*-carboxymethylisothioamide prompted us to extend the reaction to the analogous *S*-(*β*-carboxyethyl)isothiobenzanilide (VII) obtained by condensing thiobenzanilide with *β*-bromopropionic acid in the presence of triethylamine. When VII was treated with a mixture of acetic anhydride and triethylamine in the cold, the intermediate analogous to A was not isolated and by working up the reaction mixture, *β*-benzoylthiopropionanilide (IX) was obtained. In this case, the rearrangement proceeds probably *via* the pseudobase (VIII).



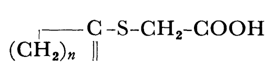
VII VIII

IX

Anticipating some information on the effect of substituents upon the reaction courses and the possibility of preparing 4-thiazone having an aliphatic substituent at 2 or 3 position, reaction of several other *N*-substituted thioamides with bromoacetic acid were attempted. Thioacetanilide (Id), when reacted with bromoacetic acid in the presence of triethylamine in benzene at room temperature, gave an oily intermediate (IId). Treatment of this intermediate with a mixture of acetic anhydride and triethylamine gave a rearranged product, acetylthioacetanilide (IIIb). Attempts to obtain mesoionic compound by cyclizing IId with a mixture of acetic anhydride and boron trifluoride or acetic anhydride and triethylamine were unsuccessful.



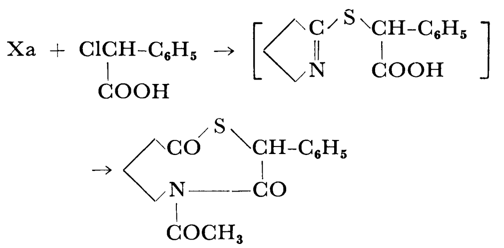
Xa, $n=3$
Xb, $n=5$



XIa, $n=3$, $R=H$
XIb, $n=5$, $R=H$

Reaction of pyrrolidine-2-thione (Xa) or thiocaprolactam (Xb) with bromoacetic acid in the presence or absence of triethylamine were also carried out and the intermediate (XIa and XIb or their hydrobromides) were obtained, which could not be cyclized to the mesoionic compounds either amine or with DCC in nitromethane.

The reaction of Xa with *α*-chlorophenylacetic acid in the presence of triethylamine, followed by treatment with a mixture of acetic anhydride and triethylamine, gave the acetylated rearranged product (XII) instead of the mesoionic compound. In a similar reaction, however, Xb did not react with α-chlorophenylacetic acid to give the rearranged product or the mesoionic compound and tarry substance was obtained.



XII

Experimental

Intermediate (A). A solution of 5.0 g of thiobenzanilide, 3.3 g of bromoacetic acid and 5.0 g of triethylamine in 25 m*l* of benzene was heated for 1 hr at 50°C. Triethylamine hydrobromide was filtered off and washed with benzene. The combined filtrates were concentrated in a vacuum to obtain reddish viscous oil, which was dissolved in a cold mixture of 7.5 m*l* of acetic anhydride and 7.5 m*l* of triethylamine. Within a few minutes, crystals separated out. After 10 min the crystals were collected by filtration, washed well with a mixture of petroleum ether and diethyl ether (5 : 1) and dried quickly to give 4 g of pale yellow crystals, mp 143°C.

Found: C, 66.16; H, 5.01; N, 5.44%. Calcd for $C_{15}H_{13}NO_2S$: C, 66.42; H, 4.79; N, 5.16%.

β-Benzoylthiopropionanilide (IX). A solution of 2.1 g of thiobenzanilide, 1.5 g of β-bromopropionic acid and 1.4 g of triethylamine in benzene (25 m*l*) was refluxed for 2 hr. After cooling, triethylamine hydrobromide was filtered off, washed with benzene, and the combined filtrate was concentrated in a vacuum to give reddish viscous oil, which was dissolved in a cold mixture of 3 m*l* of acetic anhydride and 3 m*l* of triethylamine. A small amount of triethylamine hydrobromide separated was filtered off and the filtrate was concentrated in a vacuum to remove acetic anhydride. The resulting reddish oil was allowed to stand for one week over sodium hydroxide in a desiccator. To a partly crystallized mass, a mixture of carbon tetrachloride and petroleum ether (1 : 1) was added, and the crystals were collected and recrystallized from chloroform solution by adding petroleum ether to give colorless crystals, mp 140—141°C. The yield was 1.15 g.

Found: C, 67.53; H, 5.27; N, 5.01%. Calcd for $C_{16}H_{15}NO_2S$: C, 67.36; H, 5.26; N, 4.91%. IR(KBr): 3290 and 1640 cm^{-1} (-CONH-)

Reaction of Thiobenz-*p*-chloroanilide with Bromoacetic Acid. A solution of 3.6 g of thiobenz-*p*-chloroanilide, 2.1 g of bromoacetic acid and 3.0 g of triethylamine in 25 m*l* of benzene was heated at 50°C for 3 hr. The precipitated triethylamine hydrobromide was filtered off and the solvent was removed by evaporation in a vacuum. This left a viscous oil, which was dissolved in 6 m*l* of acetic anhydride and left standing overnight. Acetic anhydride was removed by vacuum distillation. To the residual crystalline mass ether was added and the crystals were collected by filtration and washed with ether to obtain 0.9 g of *p*-chlorobenzanilide identified by its mp (195°C) and by comparison of IR spectrum with that of an authentic sample.

A similar experiment was carried out using a mixture of 5 m*l* of acetic anhydride and 5 m*l* of triethylamine instead of acetic anhydride. Only a minute amount of *p*-chlorobenzanilide was obtained as an identifiable product.

Acetylthioacetanilide (IIIb). To a solution of 3.0 g of Id and 2.8 g of bromoacetic acid in 40 m*l* of benzene, 4.0 g of triethylamine was added and stirred for 3 hr at room temperature. The precipitates were filtered off and the filtrate was concentrated in a vacuum to give reddish oil, which was dissolved in a mixture of 5 m*l* of acetic anhydride and 5 m*l* of triethylamine and left standing overnight. The reaction mixture was then poured into ice water and after several hours the brownish semi solid mass was recrystallized from water to give 1.6 g of colorless needles of mp 94—96°C.

Found: C, 57.70; H, 5.56; N, 7.03%. Calcd for $C_{10}H_{11}NO_2S$: C, 57.41; H, 5.30; N, 6.70%.

IR: 3230, 3185, 3060, 1705, 1650, 1690 cm^{-1}.

2-Carboxymethylthio-1-pyrroline Hydrobromide (XIa-HBr). A solution of 2.5 g of Xa and 3.5 g of bromoacetic acid in 30 m*l* of benzene was heated on a water bath for 1 hr. After cooling the solution, the precipitates were collected and recrystallized from acetonitrile to give 5.8 g of colorless crystals of the hydrobromide of XIa; mp 126—128°C.

Found: C, 30.23; H, 4.26; N, 5.82%. Calcd for $C_6H_{10}NO_2SBr$: C, 30.01; H, 4.16; N, 5.83%. IR: 3450, 3200, 1730, 1605 cm^{-1}.

7-Carboxymethylthio-3,4,5,6-tetrahydro-2*H*-azepine Hydrobromide (XIb-HBr). A solution of 1.2 g of thiocaprolactam and 1.4 g of bromoacetic acid in 30 m*l* of benzene was refluxed for 1 hr and after cooling, the precipitates were collected and recrystallized from acetonitrile to give 2.3 g of colorless crystals of the hydrobromide of XIb; mp 124—125°C.

Found: C, 35.91; H, 5.19; N, 5.47%. Calcd for $C_8H_{14}NO_2SBr$: C, 35.82; H, 5.22; N, 5.22%. IR: 3350, 2940, 1720, 1600 cm^{-1}.

***N*-Acetyl-2-phenyl-hexahydro-1,4-thiazocine-3,8-dione (XII).** A solution of 1.0 g of Xa, 1.7 g of α-chlorophenylacetic acid and 3 m*l* of triethylamine in 30 m*l* of benzene was heated on a water bath for 1 hr. The precipitates were filtered off and the filtrate was concentrated to give brownish oil, to which 5 m*l* of acetic anhydride and 5 m*l* of triethylamine were added and allowed to stand overnight. The precipitates were collected and recrystallized from ethanol to give 1.1 g of colorless crystals; mp 133—134°C.

Found: C, 60.54; H, 5.31; N, 5.04%. Calcd for $C_{14}H_{15}NO_3S$: C, 60.64; H, 5.45; N, 5.05%. IR: 2950, 1765, 1666, 1655 cm^{-1}.