The Syntheses and Properties of 5-Thiazones[1]

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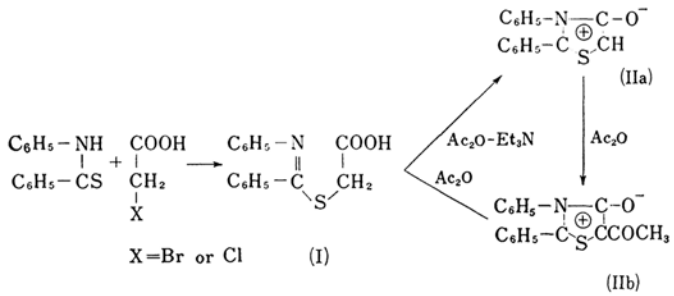
In a previous paper of this series,[2] it was reported that the treatment of *S*-carboxymethylisothiobenzanilide (I) with acetic anhydride in the presence or absence of triethylamine yielded new meso-ionic compounds, which we named 2, 3-diphenyl-4-thiazone (IIa) and 5-acetyl-2, 3-diphenyl-4-thiazone (IIb) respectively:

Syntheses of 5-thiazone derivatives by the ring-closure of *N*-substituted-*N*-thiobenzoylglycine with acetic anhydride or benzoyl chloride have already been reported by Lawson et al., but all of the compounds thus obtained have an acyl substituent in the 4-position which can not be removed by hydrolysis.[3,4]

The present paper will describe the syntheses and properties of 5-thiazones with neither acetyl nor benzoyl group in the 4-position. It has now been found that, as in the case of 4-thiazone, 2, 3-diphenyl- and 3-methyl-2-phenyl-5-thiazone (IV) can be readily obtained by treating *N*-thiobenzoylsarcosine (IIIa) or *N*-thiobenzoyl-*N*-phenylglycine (IIIb) with an acetic anhydride-triethylamine mixture at room temperature. When pyridine is used in place of triethylamine in these cyclization, only a small quantity of 4-acyl derivative (V) is obtained instead of IV. These new meso-ionic compounds, IVa and IVb, are readily soluble in such polar solvents as ethanol, but they are insoluble in such nonpolar solvents as ether. IVa is insoluble in 10% aqueous sodium hydroxide, and IVb is easily hydrolyzed by 10% aqueous hydrochloric acid to the corresponding parent acid. IVb is soluble in hot aqueous sodium hydroxide and insoluble in 10% aqueous hydrochloric acid. The structure of these new meso-ionic compounds is supported by elementary analysis and by their infrared spectra. The infrared spectra of IVa and IVb, in comparison with those of the parent acid, have a strong new absorption at 1620—1630 cm^{-1} and the band near 1700 cm^{-1} disappears as a result of the carbonyl vibration of the carboxy group. This characteristic change of the spectra due to the formation of a meso-ionic ring from III has been observed also in infrared spectra of meso-ionic compounds derived from 2-(carboxymethylmercapto)-pyridine,[5] and from azoles with a carboxymethylmercapto group.[6] Since the 5-thiazone derivatives obtained above should have an aromatic character because their structures are like sydnones, we examined several reactions of IV as in the case of sydnones.

The acetylation of IV with acetic anhydride gave V, which is identical with the *C*-acetyl derivatives prepared directly by the reaction of III with acetic anhydride. On the treatment of IVa with benzoyl chloride in the presence of pyridine, a benzoyl derivative was obtained; it is identical with the *C*-benzoyl derivative obtained by Lawson et al.[3,4] In order to prepare the halogen derivatives substituted at the 4-position, halogenation was carried out under several conditions; the hydrobromide



1) This paper is the part XXI of studies on meso-ionic compounds.

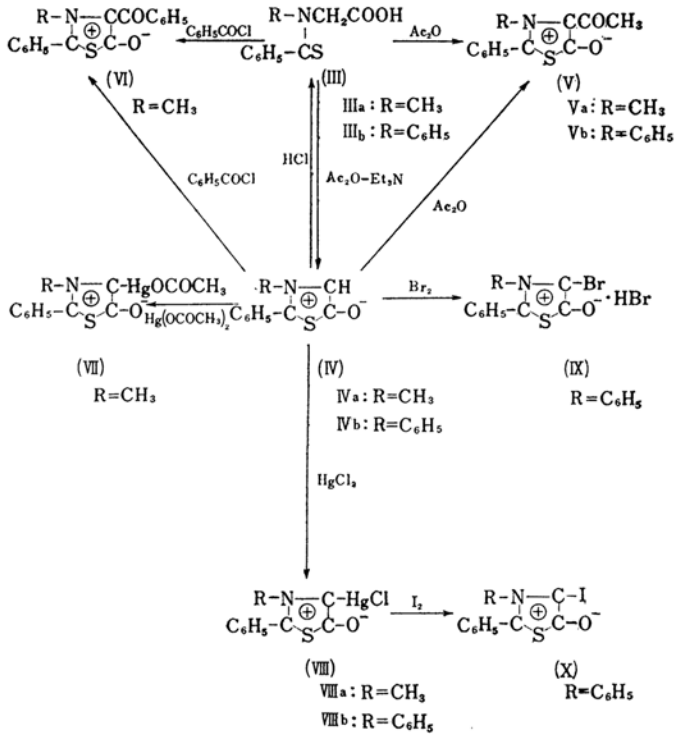
2) M. Ohta, H. Chosho, C. Shin and K. Ichimura, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **85**, 440 (1964).

3) A. Lawson and C. E. Searle, *J. Chem. Soc.*, **1957**, 1556.

4) A. Lawson and D. H. Miles, ibid., **1959**, 2865.

5) G. F. Duffin and J. D. Kendall, ibid., **1951**, 734; **1956**, 361.

6) M. Hashimoto and M. Ohta, This Bulletin, **33**, 1394 (1960).



(IX) was obtained in the presence of acetic anhydride. The corresponding free base, however, could not be obtained, even when IX was treated with a weak base, this fact might indicate its instability. Similar properties have been observed also in the case of 4-thiazone.[2] In a procedure similar to that used on sydnones,[7] IV reacted immediately with mercuric chloride in 50% methanol to give chloromercuri derivatives quantitatively, while only IVa reacted with mercuric acetate in methanol to give an acetoxymercuri derivative. These mercuri derivatives are insoluble in almost all organic solvents except ethanol and methanol. Though VIIIa and VIIIb are very stable, VII is unstable in the air and turned into a black material. When the chloromercuri derivative (VIIIb) was treated with iodine in methanol, an iodo derivative was obtained in a good yield ; this derivative was considered from elementary analysis to be X. Attempts to prepare the analogous iodo derivative from VIIIa and bromo derivatives from VIIIa and VIIIb were unsuccessful. These results make it seen likely that the reactivity at the 4-position of 5-thiazone with a phenyl group in the 3-position decreases as a result of the stabilization of the ring and that the halogen at the 4-position becomes reactive, as in the case of usual aromatic compounds.

7) K. Nakahara and M. Ohta, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zassi*), **77**, 1306 (1956).

Experimental

3-Methyl-2-phenyl-5-thiazone (IVa). — *N*-Thiobenzoylsarcosine (1 g.) was dissolved in a mixture of acetic anhydride and triethylamine (volume ratio 1 : 2) (3 ml.) at room temperature. The solution immediately turned brown, and after a few minutes yellowish prisms were crystallized out. After 2 hr. in an ice box, the crystals were filtered off and washed with ether. Recrystallization from acetone gave yellow needles, (m. p. 144—145°C (decomp.)). Yield, 0.8 g. λ_{max}^{EtOH} 362 mμ (ε, 10191)

Found : C, 63.91 ; H, 4.51 ; N, 7.43. Calcd. for $C_{10}H_9NOS$: C, 62.83 ; H, 4.71 ; N, 7.33%.

IVa is easily soluble in methanol and ethanol, soluble in hot benzene, ethyl acetate and acetone, and almost insoluble in ether, petroleum ether and 10% aqueous sodium hydroxide. When treated with 10% aqueous hydrochloric acid at room temperature, IVa was hydrolyzed to give the starting material, *N*-thiobenzoylsarcosine (IIIa).

2, 3-Diphenyl-5-thiazone (IVb).—*N*-Thiobenzoyl-*N*-phenylglycine (1 g.) was dissolved in a mixture of acetic anhydride and triethylamine (volume ratio 1 : 1) (4 ml.) at room temperature. The solution immediately turned brown, and after a few minutes yellow crystals were crystallized out. After the solution had stood overnight in an ice box, the crystals were filtered off and washed with ether. Recrystallization from ethyl acetate gave yellow needles, (m. p. 130—131°C (decomp.)). Yield, 0.8 g. λ_{max}^{EtOH} 382 mμ (ε, 10170).

Found : C, 70.90 ; H, 4.38 ; N, 5.61. Calcd. for $C_{15}H_{11}NOS$: C, 71.15 ; H, 4.35 ; N, 5.53%.

IVb is soluble in methanol, ethanol, acetone and hot 10% aqueous sodium hydroxide, and almost insoluble in ether and 10% aqueous hydrochloric acid.

4-Acetyl-3-methyl-2-phenyl-5-thiazone (Va).—IVa (0.5 g.) was heated with acetic anhydride at 100°C on a steam bath for 2 hr. The solution slowly darkened, and then the acetic anhydride was removed by evaporation under reduced pressure and by two subsequent evaporations with xylene. The recrystallization of the residual semi-solid from ethyl acetate-petroleum ether gave yellow needles, (m. p. 133—134°C (decomp.)). Yield, 0.6 g.

In the same manner as in the case of Va, the acetyl derivative (Vb) was obtained from IVb (0.5 g.) and recrystallized from benzene-petroleum ether as yellow needles, (m. p. 192—193°C (decomp.)). Yield, 0.4 g. Lawson et al., however, reported the melting point as 170—172°C.

Va and Vb showed no depression on admixture with the compounds by the ring-closure of IIIa and IIIb respectively.

4-Benzoyl-3-methyl-2-phenyl-5-thiazone (VI).—Into a solution of IVa (0.8 g.) in pyridine (5 ml.) benzoyl chloride (0.6 g.) was stirred at room temperature. The resultant brown mixture was warmed at 50°C on a water bath for 10 min.; then pyridine was evaporated under reduced pressure, and the green residual oil was washed twice with 10% aqueous hydrochloric acid and water. Recrystallization from benzene gave yellow needles, (m. p. 219—220°C (decomp.)). This compound showed no depression on admixture with an authentic specimen prepared by the ring-closure of IIIa with benzoyl chloride.

4-Chloromercuri-3-methyl-2-phenyl-5-thiazone (VIIIa).—A solution of mercuric chloride (1.2 g.) in 50% aqueous methanol (60 ml.) was stirred into a solution of IVa (0.7 g.) and sodium acetate (1.2 g.) in the same solvent at room temperature. Yellow precipitates were immediately separated, collected by filtration, and washed successively with ether, acetone and methanol. This compound did not melt below 300°C. Yield, 1.4 g.

Found: N, 3.41. Calcd. for $C_{10}H_8NOSHgCl$: N, 3.32%.

VIIIa is insoluble in usual organic solvents. In the same manner as in the case of VIIIa, the chloromercuri derivative (VIIIb) was obtained from IVb (0.5 g.) and recrystallized from 50% aqueous ethanol to give yellow needles, (m. p. 187—189°C (decomp.)). Yield, 0.85 g.

Found: N, 2.90. Calcd. for $C_{15}H_8NOSHgCl$: N, 2.89%.

VIIIa is soluble in methanol and ethanol, insoluble in benzene and ether.

4-Acetomercuri-3-methyl-2-phenyl-5-thiazone (VII).—A solution of mercuric acetate (0.9 g.) in methanol (30 ml.) was stirred into a solution of IVa (0.5 g) in methanol (10 ml.) at room temperature. The solution immediately turned yellow, and after a few minutes yellow precipitates separated. Recrystallization from ethanol gave small yellow needles, (m. p. 158—159°C (decomp.)). Yield, 1.1 g.

When this compound was kept standing for several days in the air at room temperature, it turned black.

Found: N, 3.12. Calcd. for $C_{12}H_{11}NO_3SHg$: N, 3.11%.

VIIIa is soluble in hot ethanol, and insoluble in methanol, chloroform, ethyl acetate and ether.

4-Bromo-2,3-diphenyl-5-thiazone Hydrobromide (IX).—When a solution of bromine (0.3 g.) in acetic anhydride (3 ml.) was stirred, portion by portion, into a solution of IVb (0.5 g.) in acetic anhydride (5 ml.) below 0°C, orange precipitates were gradually separated. After the solution had stood overnight in an ice box, the precipitates were collected by filtration and washed with ether. Recrystallization from acetone gave pale yellow small needles, (m. p. 163—164°C (decomp.)) Yield, 0.4 g. These crystals are deliquescent.

Found: C, 42.89; H, 3.46; N, 3.24. Calcd. for $C_{15}H_{11}NOSBr$: C, 43.58; H, 2.66; N, 3.39%.

IX is easily soluble in water and methanol, soluble in hot ethanol and acetone, and almost insoluble in ether and benzene.

2,3-Diphenyl-4-iodo-5-thiazone (X).—A solution of iodine (0.42 g.) in methanol (30 ml.) was stirred, portion by portion, into a solution of VIIIb (0.8 g.) in methanol (40 ml.) below 0°C over a 10 min. The color of the iodine immediately disappeared, and yellow precipitates were gradually separated. After the solution had stood overnight in an ice box, the precipitates were collected by filtration and recrystallized from ethanol as yellow needles, (m. p. 168—169°C (decomp.)) Yield, 0.4 g. λ_{max}^{EtOH} 405 mμ (ε, 38596).

Found: C, 47.45; H, 2.66; N, 3.72. Calcd. for $C_{15}H_{10}NOSI$: C, 47.49; H, 2.64; N, 3.70%.

X is soluble in hot ethanol, methanol and benzene, but almost insoluble in acetone, ether and ethyl acetate.

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