The Reaction of "4-Thiazone Imine" Derivatives with Acetic and Benzoic Anhydride[1]

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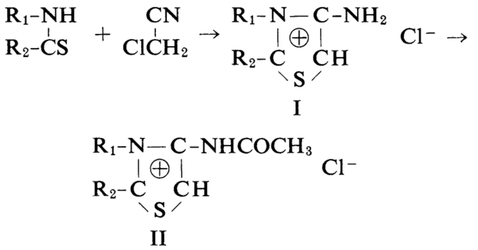
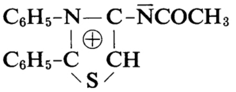
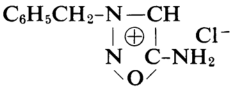
In a previous paper of this series, the synthesis of some new meso-ionic compounds, 4-thiazone imine hydrochlorides (Ia), by the condensation of thioamides with α-halonitriles was reported.[2] The acetylation of Ia by acetic anhydride at 100°C afforded hydrochlorides of an acetyl derivative IIa, which in turn gave a free acetyl derivative III when treated with an aqueous solution of sodium hydrogen carbonate.[2]


I

II

Ia : $R_1=C_6H_5$, $R_2=C_6H_5$
b : $R_1=C_6H_5$, $R_2=CH_3$
c : $R_1=CH_3$, $R_2=C_6H_5$
d : $R_1=p\text{-}ClC_6H_4$, $R_2=C_6H_5$
IIa : $R_1=C_6H_5$, $R_2=C_6H_5$
b : $R_1=C_6H_5$, $R_2=CH_3$
c : $R_1=CH_3$, $R_2=C_6H_5$
d : $R_1=p\text{-}ClC_6H_4$, $R_2=C_6H_5$


III


IV

Recently, the thermal instability of sydnone imine hydrochlorides possessing an aralkyl group, such as the benzyl group in the 3-position (IV), has been reported by Daeniker and Druey,[3] but the structures of the decomposition products have not yet been described.

In the course of our studies of the acylation of 4-thiazone imine salts, the present authors

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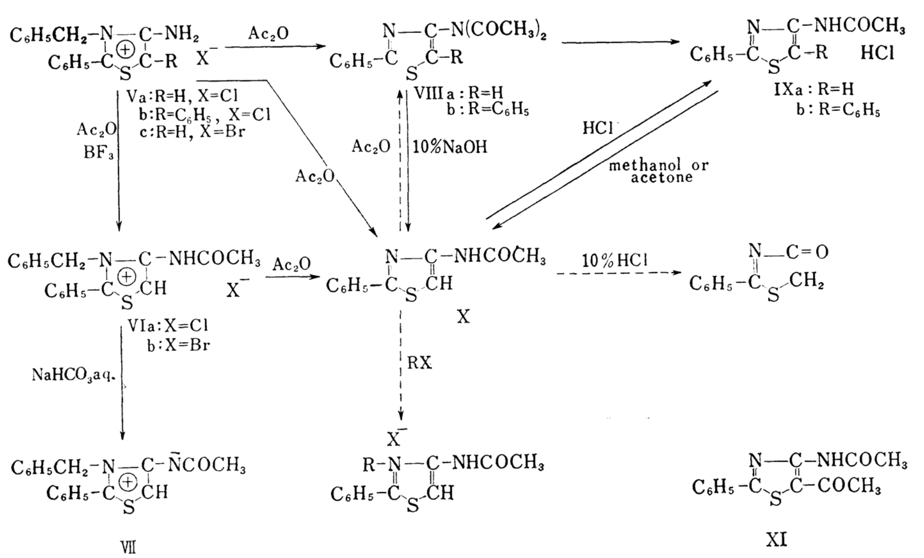
[1] This paper is the part XXIII of "Studies on Meso-ionic Compounds."

[2] H. Chosho, K. Ichimura and M. Ohta, This Bulletin, 35, 1670 (1964).

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



have found that 3-benzyl derivatives behave peculiarly towards acylation under special conditions. When 3-benzyl-2-phenylthiazone imine hydrochloride (Va) was treated with acetic anhydride in the presence of boron trifluoride in acetic acid at room temperature for about two weeks, until all of the solids dissolved, the monoacetyl derivative VIa was obtained in a good yield as colorless prisms. Compound VIa gave the free acetyl derivative VII upon treatment with an aqueous solution of sodium hydrogen carbonate. On the other hand, we found that when Va was refluxed with acetic anhydride, 4-diacetylamino-2-phenylthiazole (VIIIa) or a mixture of VIIIa and 4-acetylamino-2-phenylthiazole (X) was obtained, depending upon the reaction temparature and the duration of the heating. Thus, the benzyl group was eliminated and one or two acetyl groups were introduced in this reaction. The elimination of the benzyl group as benzyl chloride was confirmed by the gas chromatographic analysis of the mother liquor. The action of acetic anhydride on VIa under reflux for 45 min. gave X, also.

When an acetone solution of VIIIa was treated with 30% ethanolic hydrogen chloride at room temperature, the hydrochloride of the monoacetyl derivative IXa was obtained in an almost quantitative yield, while under a brief reflux in acetone or methanol, IXa gave the monoacetyl derivative X. This free base could also be obtained by boiling VIIIa with a 10% sodium hydroxide solution for a few minutes. Considering that 4-thiazone, with no substituent at the 5-position, is acetylated at the 5-position (XI) by heating it with acetic anhydride,[4] it is probable that one of the acetyl groups in VIIIa may be located at the 5-position, but when 3-benzyl-2,5-diphenylthiazone imine hydrochloride (Vb) was refluxed with acetic anhydride, a diacetyl derivative VIIIb was also obtained, and it in turn gave monoacetyl derivative IXb upon hydrolysis. Only a very few 4-aminothiazole derivatives can be found in the literature. In order to establish the structure of the new acetyl derivatives, VIII and X, we tried the synthesis of X using thiobenzamide and chloroacetonitrile under various conditions; however, these attempts resulted only in the formation of resinous matter. The acetylation of Ia was reported in our previous paper,[2] in which 4-thiazone imine hydrochloride was heated with acetic anhydride at 100°C for many hours. When Ia–d were refluxed with acetic anhydride for one hour, monoacetylated thiazone imine hydrochlorides IIa–d were obtained in a good yield without the elimination of the substituent at the 3-position. The facile elimination of the benzyl group at the 3-position is, of course, due to the stability of the benzyl cation.

An attempted preparation of the 5-bromo derivative of Va with bromine in chloroform at room temperature afforded, in a high yield, yellow tablets of 3-benzyl-2-phenylthiazone imine hydrobromide (Vc), the structure of which was indicated by elemental analysis and by its infrared absorption spectrum, which was essentially identical with that of Va. It shows the same reactivity as compounds Va and Vb. Thus, by the action of acetic anhydride as in the case of Ia, Vc gave the monoacetyl derivative VIb at room temperature, while under

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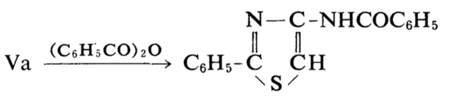
[4] Part XVIII: M. Ohta, H. Chosho, C. Shin and K. Ichimura, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **85**, 440 (1964).

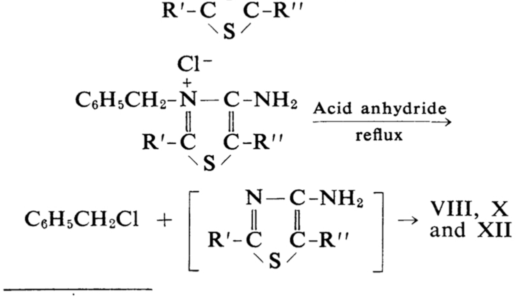
reflux, it gave X, also. An attempted preparation of VIIIa from X with acetic anhydride was not successful. Also not successful were the alkylation of X with benzyl chloride or methyl iodide and the hydrolysis of X with 10% hydrochloric acid. Moreover, we found that when Va was fused with benzoic anhydride in an oil bath for 10 min., 4-benzoylaminothiazole (XII) was obtained in a good yield.



XII

The structures of these 4-aminothiazole derivatives, VIII, IX, X and XII, were assigned on the basis of elemental analyses and their infrared absorption spectra. The elemental analysis of VIIIa is consistent with either one of two structures, VIIIa or XI; the infrared absorption spectrum showed the sharp stretching bands of two carbonyl groups, at 1700 and 1650 cm^{-1}, as in the case of VIIIb, which showed bands at 1720 and 1700 cm^{-1}. The disappearance of the $-NH_2$ stretching band at 3250 cm^{-1} and the characteristic sharp absorptions of the 4-thiazone imine ring at about 1630, 1570 and 1500 cm^{-1} in the cases of VIIIa and VIIIb, however, suggest the formation of *N*-diacetylated 4-aminothiazole derivatives. Compounds X and XII showed typical secondary amide absorptions, the former at 3200, 1650 and 1290 cm^{-1}, and the latter at 3250, 1660 and 1265 cm^{-1}.

Daeniker et al.[3,5] have reported the facile removal of the benzyl group of *N*-acetyl-3-benzylsydnone imine by reduction and the formation of *N*-substituted diazoacetamide. They explained its formation in terms of an intermediate formation of the 1, 2, 3-oxadiazole derivative. The formation of VIII, X and XII by reaction with acid anhydride can very possibly be explained by a similar sequence of reactions, which can be shown as follows:



We expected the reaction of acid anhydride with *N*-acyl-3-benzylsydnone imine hydrochloride to be similar and we have found that the same type of reaction does indeed take place. The details of this will be the subject of a future report.

Experimental

3-Benzyl-2-phenyl-*N*-acetylthiazone Imine Hydrochloride (VIa).—A suspension of 1 g. of Va in 10 ml. of acetic anhydride and 3 drops of boron trifluoride in acetic acid was heated on a steam bath for 4—5 hr. and then kept standing for about two weeks until all the solid had dissolved. The color of the solution turned brown. The removal of acetic anhydride by evaporation under reduced pressure afforded a brown oil. Upon the addition of anhydrous acetone, colorless prisms crystallized out. Recrystallization from chloroform-ether also afforded colorless prisms. Yield, 0.7 g.; m. p. 150—151°C.

Found: C, 62.90; H, 5.01; N, 8.42. Calcd. for $C_{18}H_{17}ClN_2OS$: C, 62.70; H, 4.93; N, 8.13%.

2, 3-Diphenyl-*N*-acetylthiazone Imine Hydrochloride (IIa).—A suspension of 2 g. of Ia in 20 ml. of acetic anhydride was heated under reflux for one hour, until all of the solids had dissolved; the removal of half of the acetic anhydride by evaporation under reduced pressure then afforded colorless precipitates. The precipitates were collected by means of suction and washed with acetone (yield, about 1 g.). An additional 1 g. was obtained from the brown filtrate. Recrystallization from ethanol-ether gave colorless prismatic needles. The total yield of IIa was 1.6 g.; m. p. 291—292°C (decomp.). The melting point and the infrared spectrum of IIa were shown to the identical with those of an authentic sample. In exactly the same manner as in the case of IIa, *N*-monoacetylated 4-thiazone imine hydrochlorides, IIb, IIc and IId, were prepared from the corresponding thiazone imine hydrochlorides.

IIb: m. p. 228—229°C (decomp.), yellow needles.

Found: C, 53.42; H, 4.92; N, 10.74 Calcd. for $C_{12}H_{13}ClN_2OS$: C, 53.63; H, 4.84; N, 10.43%.

IIc: m. p. 215—216°C (decomp.), yellow needles.

Found: N, 10.54. Calcd. for $C_{12}H_{13}ClN_2OS$: N, 10.43%.

IId: m. p. 279—280°C (decomp.), colorless prisms.

Found: N, 7.76. Calcd. for $C_{17}H_{14}Cl_2N_2OS$: N, 7.67%.

3-Benzyl-2-phenyl-4-thiazone Imine Hydrobromide (Vc).—Into a solution of 10 g. of Ia in 100 ml. of chloroform, 5.3 g. of bromine in 30 ml. of chloroform were gradually added and stirred for 2 hr. at room temperature. When the chloroform was removed by evaporation under reduced pressure without heating, a brown residual oil was obtained. Yellow precipitates were crystallized out from the oil by the addition of acetone. Yield, 9.3 g.; m. p. 194—195°C (decomp.).

Found: C, 55.06; H, 4.64; N, 8.09. Calcd. for $C_{16}H_{15}BrN_2S$: C, 55.34; H, 4.32; N, 8.07%.

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[5] H. U. Daeniker and J. Druey, *Helv. Chim. Acta*, **46**, 805 (1963).

In the same manner as in the case of Ic, 2,3-diphenyl-4-thiazone imine hydrobromide was obtained from the corresponding hydrochloride (Ia) (2 g.) and recrystallized from ethanol-ether as yellow needles. Yield, 1.8 g.; m. p. 209—210°C (decomp.).

Found: C, 54.26; H, 3.29; N, 8.52. Calcd. for $C_{15}H_{13}BrN_2S$: C, 54.05; H, 3.90; N, 8.41%.

3-Benzyl-2-phenyl-*N*-acetylthiazone Imine Hydrobromide (VIb).—A suspension of 2 g. of Vc in 20 ml. of acetic anhydride and 1 ml. of boron trifluoride in acetic acid was swirled on a steam bath for 2 hr., by which time all of the solids had dissolved. The removal of the acetic anhydride of the solution by evaporation under reduced pressure afforded a brown oil. White precipitates were crystallized out from the oil by the addition of acetone. Recrystallization from ethyl acetate - ethanol gave colorless prismatic needles. Yield, 1.5 g.; m. p. 160—161°C.

Found: C, 55.85; H, 4.70; N, 7.40. Calcd. for $C_{18}H_{17}BrN_2OS$: C, 55.52; H, 4.37; N, 7.20%.

3-Benzyl-2-phenyl-*N*-acetylthiazone Imine (VII).—To 20 ml. of an aqueous solution of VIa (4.5 g.), 10 ml. of a saturated aqueous solution of sodium hydrogen carbonate was added, and the mixture was shaken with benzene. The benzene layer was then washed with water and dried with sodium sulfate. The removal of the benzene afforded 3.5 g. of yellow crystals, which were then recrystallized from acetone - petroleum ether. Yield, 2.8 g.; m. p. 155—156°C.

Found: C, 69.87; H, 5.02; N, 9.43. Calcd. for $C_{18}H_{16}N_2OS$: C, 70.13; H, 5.19; N, 9.25%.

2-Phenyl-4-diacetaminothiazone (VIIIa).—A suspension of 7 g. of Va in 50 ml. of acetic anhydride was heated gently under reflux for 30 min.; the subsequent removal of the acetic anhydride of the solution by evaporation under reduced pressure afforded colorless needles. Recrystallization from a small amount of methanol afforded colorless prismatic needles. Yield, 3.8 g.; m. p. 98—99°C. The crystals showed λ_{max}^{EtOH} 290 mμ (ε=11700) and 296 mμ (ε=21100).

Found: C, 60.00; H, 4.62; N, 10.77. Calcd. for $C_{13}H_{12}N_2O_2S$: C, 60.01; H, 4.55; N, 11.06%.

In the same manner as in the case of VIIIa, VIIIb was obtained from Vb (1 g.) and recrystallized from methanol as colorless needles. Yield, 0.5 g.; m. p. 108—109°C. The crystals showed λ_{max}^{EtOH} 230 mμ (ε=18700), 240 mμ (ε=18500), 285 mμ (ε=12600) and 304 mμ (ε=13500).

Found: C, 67.44; H, 4.77; N, 8.40. Calcd. for $C_{19}H_{16}N_2O_2S$: C, 67.85; H, 4.80; N, 8.33%.

2-Phenyl-4-acetaminothiazole Hydrochloride (IXa).—To a solution of 0.5 g. of VIIIa in 6 ml. of anhydrous acetone, 3 ml. of a 30% ethanolic hydrogen chloride solution was added portion-by-portion at room temperature; small colorless needles were thereby crystallized out. The crystals were filtered and washed with acetone. Yield, 0.45 g.; m. p. 165—166°C (decomp.).

Found: C, 52.22; H, 4.59; N, 11.61. Calcd. for $C_{11}H_{10}ClN_2OS$: C, 51.87; H, 4.32; N, 11.01%.

In the same manner as in the case of IXa, IXb was obtained from VIII (1 g.) and recrystallized from acetone as yellow prisms. Yield, 0.6 g.; m. p. 182—183°C (decomp.).

Found: C, 61.94; H, 4.29; N, 8.75. Calcd. for $C_{17}H_{15}ClN_2OS$: C, 61.73; H, 4.54; N, 8.47%.

2-Phenyl-4-acetaminothiazole (X).—*a) From Va.*—A solution of 2 g. of Va in 50 ml. of acetic anhydride was heated under reflux for 1 hr.; the subsequent removal of the acetic anhydride from the solution by evaporation under reduced pressure afforded colorless precipitates, to which 8 ml. of acetone was then added and the solution filtered. To the filtrate was added, portion-by-portion, 10 ml. of a 30% ethanolic hydrogen chloride solution at room temperature. In a few minutes, small colorless needles began to separate out. After 20 min., the products were filtered and washed with acetone. Recrystallization from methanol afforded colorless tablets. Yield, 0.6 g.; m. p. 169—171°C. The crystals showed λ_{max}^{EtOH} 238 mμ (ε=24600) and 315 mμ (ε=10900).

Found: C, 60.36; H, 4.69; N, 12.99. Calcd. for $C_{11}H_{10}N_2OS$: C, 60.54; H, 4.62; N, 12.84%.

b) From Vc.—A suspension of 2 g. of Vc in 20 ml. of acetic anhydride was heated under reflux for 45 min., during which time Vc was gradually dissolved in it. The removal of the acetic anhydride by evaporation under reduced pressure afforded colorless tablets. Yield, 0.6 g.; m. p. 170—171°C. This material was shown, by mixed melting point determination and by a comparison of their infrared absorption spectra, to be identical with the X obtained from Va.

c) From VIa.—A solution of 1 g. of VIa in 10 ml. of acetic anhydride was heated under reflux for 45 min.; then the acetic anhydride was removed by evaporation under reduced pressure. Crude colorless precipitates were obtained. Recrystallization from benzene gave colorless tablets. Yield, 0.3 g. In the same manner as in the case of c), X was obtained from VIb.

d) From VIIIa.—A suspension of 2 g. of VIIIa in a 10% aqueous sodium hydroxide solution was heated under reflux for a few minutes, during which time the crystal form of Va was gradually changed. After cooling, the products were collected by filtration. Recrystallization from methanol afforded colorless tablets. Yield, 1.2 g.; m. p. 170—171°C.

e) From IXa.—A suspension of IXa (0.45 g.) in acetone was heated under reflux for 20 min.; crude crystals were crystallized out after the removal of the acetone. Recrystallization from methanol afforded colorless tablets. Yield, 0.25 g.; m. p. 170—171°C.

2-Phenyl-4-benzoylaminothiazole (XII).—Two grams of Va and 1.5 g. of benzoic anhydride were fused at 200—210°C in an oil bath for 10 min. The reaction mixture turned brown, and then in a few minutes, colorless prisms were separated out. After these had cooled, anhydrous ether was added, and the products were filtered and washed with anhydrous ether. Recrystallization from ethanol gave colorless needles. Yield, 0.8 g.; m. p. 128—129°C. The material showed λ_{max}^{EtOH} 315 mμ (ε=24100).

Found: C, 68.66; H, 4.43; N, 10.04. Calcd. for $C_{16}H_{12}N_2OS$: C, 68.58; H, 4.29; N, 10.00%.

The authors are indebted to Miss Toshiko Aoyagi for her elementary analysis.

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