The Synthesis of 1,3-Thiazines by the Reaction of Non-isolable β-Imino(dithiocarboxylic) Acids with Aldehydes

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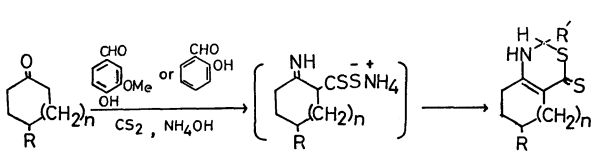
1,3-Thiazines, (**1**)—(**6**), were synthesized, in yields ranging from 2.9 to 43%, by the reaction of aldehyde with the intermediate β-iminodithiocarboxylic acids which are formed by the reaction of ketones with carbon disulfide in the presence of ammonia.

We have previously reported that a series of 1,3-thiazines were synthesized by means of the reaction of 2-iminocyclopentanedithiocarboxylic acid with carbonyl compounds.[1] This method, however, requires an isolated β-iminodithiocarboxylic acid as the starting material, and the preparation of the free acid is possible in only a few limited cases; thus, the scope of this method is restricted. Though there are many *N*-substituted β-iminodithiocarboxylic acids, they do not undergo the present reaction.

Only a few specific ketones, such as cyclopentanones and 4,5-dihydro-3-methyl-1-phenyl-1*H*-pyrazol-5-one, afforded the corresponding β-iminodithiocarboxylic acid when reacted with carbon disulfide in the presence of ammonia.[2-4] Other ketones, such as methyl ethyl ketone, cyclohexanone, cycloheptanone, and cyclooctanone, immediately give 1,3-thiazines, which are considered to be formed from the intermediate β-iminodithiocarboxylic acids by a reaction with the material ketones present.[5] All attempts to isolate the intermediate acids from the reaction products were unsuccessful. An attempt at the synthesis of the iminodithiocarboxylic acids from the corresponding β-ketodithiocarboxylic acids also failed.

The present investigation was undertaken in order to extend the method of preparing the 1,3-thiazines by making use of the supposed intermediate iminodithiocarboxylic acids mentioned above. Thus, a mixture of two kinds of carbonyl compounds, and carbon disulfide were allowed to react in the presence of ammonia to give the cross-reaction products. Cyclohexanone, 4-methylcyclohexanone, cycloheptanone, and cyclooctanone were chosen as the sources of the intermediate. Vanillin and salicylaldehyde were used as the other parts of the reactant because they gave easily crystallizable products. The yields of the present reaction ranged from 2.9 to 43%.

The limitation of the present reaction is that the use of two kinds of carbonyl compounds, both which have α-hydrogen atom, is unfavorable, because four kinds of 1,3-thiazines may be formed including the cross-reaction products.



(1) $n=1$, R=H, R′=*p*-hydroxy-*m*-methoxyphenyl
(2) $n=1$, R=H, R′=*o*-hydroxyphenyl
(3) $n=1$, R=Me, R′=*p*-hydroxy-*m*-methoxyphenyl
(4) $n=1$, R=Me, R′=*o*-hydroxyphenyl
(5) $n=2$, R=H, R′=*p*-hydroxy-*m*-methoxyphenyl
(6) $n=3$, R=H, R′=*p*-hydroxy-*m*-methoxyphenyl

Scheme

The products which were obtained here were identified on the basis of IR and UV spectra, and elemental analyses (see Experimental section). The spectra were similar to that of 4(1*H*)-thiono-5,6,7,8-tetrahydro-4*H*-3,1-cyclohexathiazine-2-spirocyclohexane.[5]

Experimental

2-(p-Hydroxy-m-methoxyphenyl)-4(1H)-thiono-5,6,7,8-tetrahydro-4H-3,1-cyclohexathiazine (1). A mixture of carbon disulfide (15.2 g, 0.20 mol) and cyclohexanone (1.5 g, 0.015 mol) was added to a solution of vanillin (3 g, 0.02 mol) in 28% aqueous ammonia (140 ml), and then the mixture was shaken at room temperature for 4 hr. The solid product was collected, washed with water, ether and ethanol, and dried (yield, *ca.* 2 g; 43%). Recrystallization from pyridine–ethanol gave yellow crystals; mp 222—224 °C (slow heating) and 240—242 °C (rapid heating). IR (KBr): 3290 (m, s NH), 3080 (m, br OH and aromatic CH), 1600 (m, aromatic C=C), and 1515 (s, br conj. C=C) cm^{-1}. UV: λ_{max}^{EtOH} 234 (log ε 4.19), 280 (3.37), 341 (3.79), 406 (4.26) nm.

Found: C, 58.73; H, 5.55; N, 4.71; S, 20.60%; mol wt (Mass), 307. Calcd for $C_{15}H_{17}NO_2S_2$: C, 58.63; H, 5.58; N, 4.56; S, 20.82%; mol wt, 307.3.

2-(o-Hydroxyphenyl)-4(1H)-thiono-5,6,7,8-tetrahydro-4H-3,1-cyclohexathiazine (2). A mixture of carbon disulfide (5 g, 0.066 mol) and cyclohexanone (3 g, 0.031 mol) was added to a solution of salicylaldehyde (5 g, 0.041 mol) in 28% aqueous ammonia (50 ml), and then the mixture was worked up as has been described for **1**. The crude product was washed with water and acetic acid, and dried (yield, *ca.* 3 g; 35%). Recrystallization from methanol gave orange crystals; mp 222—224 °C (slow heating) and 240—242 °C (rapid heating). IR (KBr): 3290 (s, NH), 3140 (s, br OH and aromatic CH), 1610 (w, NH), 1600 (s, aromatic C=C), 1500 (*vs.* conj. C=C) cm^{-1}. UV: λ_{max}^{EtOH} 275 (log ε 3.42), 343 (3.74), 406 (4.24) nm.

Found: C, 60.63; H, 5.43; N, 5.03; S, 22.99%; mol wt (Mass), 277. Calcd for $C_{14}H_{15}NOS_2$: C, 60.64; H, 5.45; N, 5.05; S, 23.08%; mol wt, 277.3.

2-(p-Hydroxy-m-methoxyphenyl)-6-methyl-4(1H)-thiono-5,6,7,8-tetrahydro-4H-3,1-cyclohexathiazine (3). A mixture of 4-methylcyclohexanone (1 g, 0.009 mol), carbon disulfide (2 g, 0.026 mol), vanillin (1.5 g, 0.01 mol), and 28% aqueous ammonia (15 ml) was shaken at room temperature for 5 hr and then kept overnight in an ice box. The solid product was collected, washed with ethanol, and dried (yield, 0.48 g; 17%). Recrystallization from pyridine–water gave yellow crystals; mp 247—248 °C (in a sealed tube, slow heating) and

263—265 °C (decomp.) (in a sealed tube, rapid heating). IR (KBr): 3270 (s, br NH), 3200 (br, sh OH), 3040 (sh aromatic CH), 1615 (w, NH), 1605 (m, aromatic C=C), 1520 (s, br conj. C=C) cm^{-1}. UV: λ_{max}^{EtOH} 235 (log ε 4.15), 285 (3.29), 338 (3.74), 350 (3.79), 406 (4.26) nm.

Found: C, 59.99; H, 5.98; N, 4.49; S, 19.74%; mol wt (Mass), 321. Calcd for $C_{16}H_{19}NO_2S_2$: C, 59.80; H, 5.96; N, 4.36; S, 19.92%; mol wt, 321.3.

2-(o-Hydroxyphenyl)-6-methyl-4(1H)-thiono-5,6,7,8-tetrahydro-4H-3,1-cyclohexathiazine (4). A mixture of 4-methylcyclohexanone (10 g, 0.089 mol), carbon disulfide (20 g, 0.26 mol), salicylaldehyde (15 g, 0.12 mol), and 28% aqueous ammonia (100 ml) was worked up as has been described for **1**. The reaction mixture was then shaken with some ether and filtered. The filtrate was evaporated under reduced pressure, and to this chloroform was added. The solid product was collected and recrystallized from ethanol to give yellow crystals (yield, 0.75 g; 2.9%); mp 222—223 °C (decomp.) (slow heating) and 238—240 °C (decomp.) (rapid heating). IR (KBr): 3270 (s, NH), 3100 (s, br OH and aromatic CH), 1605 (w, NH), 1595 (s aromatic C=C), 1500 (*vs.* conj. C=C) cm^{-1}. UV: λ_{max}^{EtOH} 343 (log ε 3.78), 405 (4.24) nm.

Found: C, 61.71; H, 5.67; N, 4.94; S, 21.93%; mol wt (Mass), 291. Calcd for $C_{15}H_{17}NOS_2$: C, 61.85; H, 5.88; N, 4.81; S, 21.97%; mol wt, 291.3.

2-(p-Hydroxy-m-methoxyphenyl)-4(1H)-thiono-5,6,7,8-tetrahydro-4H-3,1-cycloheptathiazine (5). A mixture of cycloheptanone (1 g, 0.009 mol), carbon disulfide (2 g, 0.026 mol), vanillin (1.5 g, 0.01 mol), and 28% aqueous ammonia (20 ml) was worked up as has been described for **1**. Recrystallization from pyridine–methanol gave yellow crystals (yield, 0.57 g; 19%); mp 225—226 °C (decomp.) (slow heating) and 241—243 °C (rapid heating). IR (KBr): 3240 (s, NH), 3090 (m, br OH and aromatic CH), 1610 (w, NH), 1595 (s, aromatic C=C), 1510 (s, br conj. C=C) cm^{-1}. UV: λ_{max}^{EtOH} 233 (log ε 4.22), 282 (3.62), 336 (3.77), 404 (4.22) nm.

Found: C, 59.82; H, 5.84; N, 4.67; S, 19.63%; mol wt (Mass), 321. Calcd for $C_{16}H_{19}NO_2S_2$: C, 59.80; H, 5.96; N, 4.36; S, 19.92%; mol wt, 321.3.

2-(p-Hydroxy-m-methoxyphenyl)-4(1H)-thiono-5,6,7,8,9,10-hexahydro-4H-3,1-cyclooctathiazine (6). A mixture of cyclooctanone (1 g, 0.008 mol), carbon disulfide (2.5 g, 0.33 mol), vanillin (1.5 g, 0.01 mol), and 28% aqueous ammonia (20 ml) was worked up as has been described for **1**. The solid product was collected and recrystallized from ethanol–ether (yield, 0.65 g; 26%) and then from acetone–ethanol to give yellow crystals; mp *ca.* 135 °C. IR (KBr): 3270 (s, NH), 3140 (m, sh OH), 3040 (w, aromatic CH), 1600 (m, aromatic C=C), 1510 (*vs.* conj. C=C) cm^{-1}. UV: λ_{max}^{EtOH} 235 (sh) (log ε 4.15), 290 (3.53), 340 (3.77), 412 (4.23) nm.

Found: C, 60.80; H, 6.51; N, 3.90; S, 18.92%; mol wt (Mass), 335. Calcd for $C_{17}H_{21}NO_2S_2$: C, 60.88; H, 6.31; N, 4.18; S, 19.09%; mol wt, 335.4.

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