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Polycarbonyl Heterocycles. Part III. Synthesis of 2,3-Furanodione Derivatives by Ring Transformations of Thiazolidine-4,5-dione Derivatives

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The base catalyzed isomerization of 2-(aroyl-methylene)-3-aryl-thiazolidine-4,5-dione derivatives **1** leads to salts of 1-aryl-3-aroyl-4-hydroxy-pyrroline-2-thio-5-one and aliphatic amines **2**. It was found that **2** undergo further transformation to 4-thioanilido-5-arylo-2,3-furanodione derivatives **4**. This series of reaction provides a convenient synthetic route to 2,3-furanodione derivatives **4**.

(Keywords: 2,3-Furanodiones; Thiazolidine-4,5-diones)

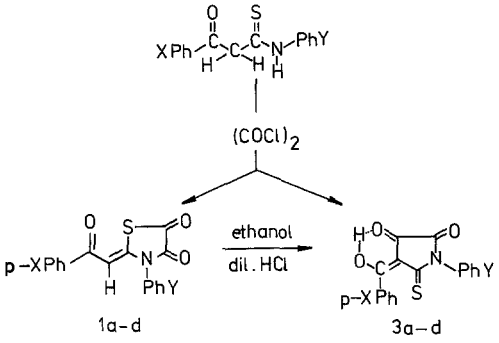
Polycarbonyl-Heterocyclen, 3. Mitt.: Synthese von 2,3-Furandion-Derivaten durch Ringtransformation von Thiazolidin-4,5-dion-Derivaten

Die basenkatalysierte Isomerisierung von 2-(Aroylmethylen)-3-aryl-thiazolidin-4,5-dionen **1** führt zu Salzen von 1-Aryl-3-aroyl-4-hydroxy-pyrrolin-2-thio-5-on und aliphatischen Aminen **2**. Die letzteren gehen in 4-Thioanilido-5-arylo-2,3-furandion-Derivate **4** über. Diese Reaktionsfolge stellte eine vorteilhafte synthetische Route zu 2,3-Furandionen dar.

In connection with our continued study[1,2] on synthesis and reactivity of polycarbonyl heterocycles we have investigated the influence of nucleophiles on the isomerization of 2-(aroyl-methylene)-3-aryl-thiazolidine-4,5-dione[3] derivatives (**1**) and 1-aryl-3-(aryl-hydroxy-methylene)-pyrrolidine-2-thio-4,5-trione[3] (**3**).

The compounds of type **1** and **3** were obtained by the known method[3] (Scheme 1). The condensation of appropriate thioanilides of β-ketoacids with oxalyl chloride led by two possible routes to the thiazolidinedione derivatives of type **1** (S and N acylation) and to pyrrolidinethiotrione system **3** (C and N acylation).

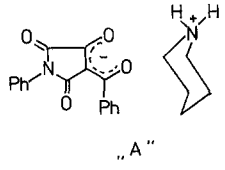
Scheme 1



1,3	a	b	c	d
X	H,	p-OCH_3,	p-Cl,	H
Y	H,	H,	H,	p-Cl

In a preceding paper[1] we reported that the interaction between 2,3,5-pyrrolidinetrione derivatives and 2° aliphatic amines (piperidine) led to the formation of a complex and finally of salts "A" (Scheme 2).

Scheme 2

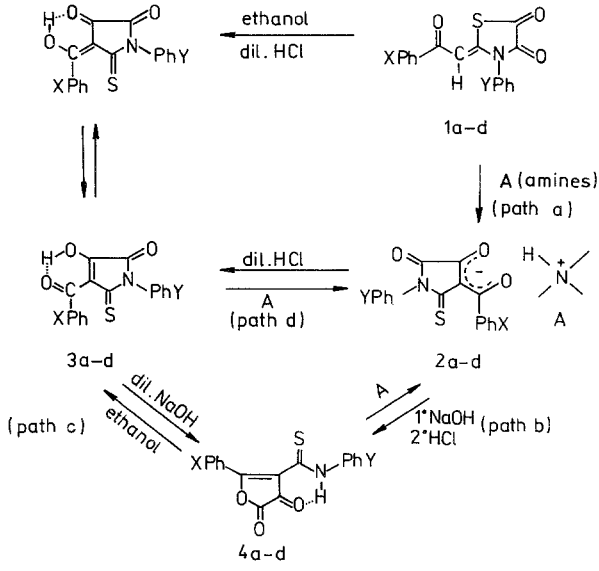


Direct treatment of **1** with an equimolar amount of aliphatic amine (1°, 2°, 3°) in ethanol gave almost immediately the red solution from which orange-red salts **2** were obtained (path a, as shown below in Scheme 3).

The structures of **2a–2d** were supported by their infrared, ^{1}H n.m.r., and MS spectra. The comparative study of the spectra of products **2** and compounds **1** and salts "A" (Scheme 2) suggested the structure of **2** as the salts of pyrroline derivatives and aliphatic amines.

The IR spectra of salts **2** showed a strong absorption in the CO region at 1 750 cm^{-1} due to the carbonyl group in position 5 of the pyrrolinethiodione system, and at ~ 1 650 cm^{-1} due to the aroyl carbonyl group stretching vibration; the band of the CO group in position 4 disappeared, because this group tautomerized to the hydroxy group and formed a salt with aliphatic amines

Scheme 3



A (amines): *n*-heptylamine, ethylenediamine, pyrrolidine, piperazine piperidine, morpholine, N-methylpiperazine, triethylamine.

(Scheme 2). The characteristic absorption of the NH^+ ion of amine[4] appeared at 2 450–2 550 cm^{-1}. The double bond (C = C) stretching vibrations of **2** appeared at 1 620 cm^{-1}.

The ^1H n.m.r. spectra of the salts **2** revealed as expected the signal due to NH^+ at δ 8.5 ppm. However, the characteristic signal of the vinyl proton of thiazolidinediones **1**[3] at 6.4 ppm disappeared. The remaining aromatic protons formed a multiplet at 6.5–7.5 ppm and multiplets of the aliphatic protons of amines appeared in the region of 1–4 ppm.

The mass spectra of salts **2** were in agreement with their proposed structure. Their basic fragmentation pathway was connected with elimination of amine ions[2]. Thr next peaks present in all spectra of salts **2** were characteristic for the fragmentation of the pyrrolinedione system[5]. The loss of the carbonyl group from the heterocyclic ring caused the formation of the ion $M\text{-}CO^{+\cdot}$, then this ion lost a second CO group forming ion $M\text{-}56^+$. The next intensive peak present in the spectra of all compounds was due to Ar_1CO^+.

The salts **2** were hydrolized in acidic ethanol solution to compounds **3** and corresponding aliphatic amine. The salts **2** were prepared directly by the reaction of **3** and appropriate aliphatic amines in ethanol (Scheme 3, path d).

With regard to the mechanism of formation of salts **2** (path a) it can be assumed that the nucleophilic attack of aliphatic amines cleaved the C—S bond of the thiazolidine ring (**1**). The unstable open-chain intermediate was formed, and then isomerized to the pyrrolidine system.

As a part of further exploration of the reactions of salts **2** we report now the rearrangement which was observed in reaction of the salts **2** with sodium hydroxide. In this reaction the nucleophilic attack of the base occurred at the amide carbon atom of pyrroline ring, and the intermediate open-chain product was formed. Subsequent treatment with the acid led to 4-aryl-5-thioanilido-2,3-furanodione derivatives **4**. This rearrangement occurred in good yields (ca. 90%) and at room temperature. When compounds **4** were refluxed in ethanol solution they rearranged to thermodynamically more stable pyrrolidine derivatives **3**. This rearrangement involved ring-opening and ring-closure steps.

The IR spectra of compounds **4** showed medium intensity bands due to thioamide NH at 3 180 cm^{-1} and strong C=O bands at ~1 720 cm^{-1} and ~1 690 cm^{-1} as well as the strong C—O band at 1 180 cm^{-1}. **4** presumably exist in the form which is stabilized by an intramolecular hydrogen bond (Scheme 3).

The H^1 n.m.r. spectra of compounds **4** showed a singlet for one proton at 9.5 ppm (NH thioamide group) and a multiplet at 6.5–7.5 ppm (aromatic protons).

The fragmentation pathway in MS spectra, common to all compounds **4**, was initiated with the ring cleavage with loss of the CO group (ion $M\text{-}CO^+$). Another important fragmentation pathway led to the cation $XPhCO^+$ which appeared in all the spectra of compounds **4** as the base peak.

Finally, it is interesting to note, that the reaction paths a, b, c of the Scheme 3 are based on the *Dimroth* rearrangement[6]. An attractive feature of these rearrangements from synthetic point of view is that all the compounds were obtained in high yields. These rearrangements are especially interesting because they may be used for simple and convenient preparation of furano-2,3-dione derivatives **4**. The salts **2** under treatment with sodium hydroxide followed by acidification furnish compounds **4**. It is worth to note that the furano-2,3-dione derivatives **4** can not be obtained by methods described in the literature[7—10].

Experimental

Melting points are uncorrected. IR spectra were recorded on a UR-10 Carl Zeiss (Jena) spectrophotometer using KBr pellets. ^1H n.m.r. spectra were determined on a Jeol 100 MHz, in $CDCl_3$ or *DMSO-*d_6 with *TMS* as internal standard. Mass spectral molecular weights were determined with a LKB-9000 S spectrometer. Elemental Analyses were performed in the Regional Laboratory of Physico-Chemical Analyses and Structural Studies in Kraków.

Compounds **1 c, d** and **3 c, d** were synthesized according to Ref.[3], based on the condensation of β-ketothioanilides with oxalyl chloride in benzene solution.

2-(Benzoyl-methylene)-3-p-chlorophenyl-thiazolidine-4,5-dione (**1 c**)

M.p. 275 °C; $C_{17}H_{10}NO_3SCl$ (343.78).

Calcd. C 59.39 H 2.93 N 4.07 S 9.32 Cl 12.18.
Found. C 59.47 H 2.60 N 4.11 S 9.32 Cl 12.30.

IR (cm^{-1}): 1 740 s, 5 CO; 1 720 s, 4 CO; 1 630 s, COaryl; 1 615 s, C=C.
^1H n.m.r. (ppm): 7.8–7.5 m, 9 H arom.; 6.47 s, 1 H vinyl.
MS (*m*/e%): M^+ 343, 6.35; *M*-CO 315, 4.24; 299, 38.43; 298, 53.91; *M*-2 CO, 287.100; 286, 97.85; 176, 25.23; 141, 31.38; Cl*Ph*CO$^+$ 139, 99.73; Cl*Ph*$^+$ 111, 70.15; *Ph*$^+$ 77, 37.74; 76, 12.41; 75, 38.73; 51, 37.18.

2-(p-Chlorobenzoyl-methylene(-3-phenyl-thiazolidine-4,5-dione] (**1 d**)

M. p. 270°; $C_{17}H_{10}NO_3SCl$ (343.78).

Calcd. C 59.39 H 2.93 N 4.07 S 9.32 Cl 12.18.
Found. C 59.50 H 3.01 N 4.11 S 9.28 Cl 12.20.

IR (cm^{-1}): 1 740 s, 5 CO; 1 730 s, 4 CO; 1 635 s, COaryl; 1 610 s, C=C.
^1H n.m.r. (ppm): 7.7–7.4, m, 9 H arom.; 6.5, s, 1 H vinyl.
MS (*m*/e%): M^+ 343, 16.29; *M*-1 344, 5.72; *M*-CO 315, 10.6; *M*-2 CO 287, 18.2; Cl*Ph*CO$^+$ 139, 100; *Ph*NCO$^{+\cdot}$ 119, 10.2; Cl*Ph*$^+$ 111, 30.2; *Ph*$^+$ 77, 50.6.

1-Phenyl-3-(p-chlorophenyl-hydroxy-methylene(-pyrrolidine-)2-thio)-4,5-trione (**3 c**)

M. p. 240 °C; $C_{17}H_{10}NO_3SCl$ (343.78).

Calcd. C 59.39 H 2.93 N 4.07 S 9.32 Cl 12.18.
Found. C 59.41 H 3.00 N 4.05 S 9.11 Cl 12.20.

IR (cm^{-1}): 2 800–2 500 OH enol; 1 750, 5 CO; 1 725, 4 CO; 1 590, C=C.
^1H n.m.r. (ppm): 7.7–7.4 m, 9 H aromat.; 15.6 w, OH enol.
MS (*m*/e%): M^+ 343, 50.92; *M* + 1 344, 13.9; *M* + 2 345, 21.38; *M*-COH 314, 10.46; *Ph*NCO$^{+\cdot}$ 119, 13.9; *Ph*NCS$^{+\cdot}$ 135, 7.3; *Ph*CO$^+$ 105, 100; Cl*Ph*$^+$ 111, 38.30; *Ph*$^+$ 77, 23.15.

1-p-Chlorophenyl-3-(phenyl-hydroxy-methylene)-pyrrolidine-(2-thio)-4,5-trione (**3 d**)

M.p. 210°; $C_{17}H_{10}NO_3SCl$ (343.78).

Calcd. C 59.39 H 2.93 N 4.07 S 9.32 Cl 12.18.
Found. C 59.43 H 2.81 N 4.13 S 9.33 Cl 12.15.

IR (cm^{-1}): 2 900–2 550 w, OH enol; 1 745, 5 CO; 1 730 s, 4 CO; 1 600, C=C.
^1H n.m.r. (ppm): 7.8–7.4 m, 9 H aromat.; 16 weak, OH enol.
MS (*m*/e%): M^+ 343, 57.72; *M* + 1 344, 14.32; *M* + 2 345, 23.64: *M*-COH 314, 8.76; *M*-2 COH 286, 9.61; Cl*Ph*CO$^+$ 141, 32.65; Cl*Ph*$^+$ 111, 38.26; *Ph*$^+$ 77, 25.67.

Synthesis of Salts **2 a–d**

1 g of compound **1** or **3** and the molar equivalent amount of an aliphatic amine (1°, 2°, 3°) were refluxed for 5–10 min in 20 ml of ethanol. The reaction mixture was cooled to room temperature. The crystalline product was filtered off. Analitically pure compounds were obtained after crystalllization from ethanol.

Yields 80–95%.

This reaction was carried out with *n*-heptylamine, ethylenediamine, pyrrolidine, piperidine, morpholine, piperazine, N-methylpiperazine, and triethylamine. As examples for analyses the following salts with piperidine were chosen:

Salt of 1-Phenyl-3-benzoyl-4-hydroxy-pyrroline-(2-thio)-5-one and Piperidine (**2 a**).

M. p. 162°; $C_{22}H_{22}N_2O_3S$ (394.41).

Calcd. C 66.99 H 5.62 N 7.10 S 8.12.
Found. C 66.89 H 5.70 N 7.11 S 8.15.

IR (cm^{-1}): 2 750–2 450 m, broad, NH_2^+; 1 745, 5 CO; 1 650, CO; 1 610, C=C.

^1H n.m.r. (ppm): 8.8 s, 2 H, NH_2^+; 7.8–7.2 m, 10 H arom; 3.2 m, 4 H, $(CH_2)_2$; 1.7 m, 6 H $(CH_2)_3$.

MS (*m*/e%): M^+ 309 (394–85), 100; *M*-CO 282, 17.9; *M*-2 CO; 252, 33.8; $PhCO^+$ 105, 56.5; $C_5H_{10}NH_2^+$ 85, 25.3; Ph^+ 77, 28.0.

Salt of 1-Phenyl-3-p-methoxybenzoyl-4-hydroxy-pyrroline-(2-thio)-5-one and Piperidine (**2 b**)

M. p. 155 °C; $C_{23}H_{24}N_2O_4S$ (424.51).

Calcd. C 65.07 H 5.69 N 6.60 S 7.55.
Found. C 65.11 H 6.00 N 5.56 S 7.45.

IR (cm^{-1}): 2 850–2 450 m, broad NH_2^+; 1 740, 5 CO; 1 640, CO; 1 620, C=C.

^1H n.m.r. (ppm): 8.8, 2 H, NH_2^+; 7.8–6.8 m, 9 H arom.; 3.9, 3 H OCH_3; 3.2, 4 H $(CH_2)_2$; 1.7, 6 H$(CH_2)_3$.

MS (*m*/e%): M^+ 339 (424–v85), 57.35; *M*-1 340, 13.25; *M*-COH 311, 12.7; *M*-2 CO 282, 8.44; CH_3OPhCO^+ 135, 100; 92, 14.22; $C_5H_{10}NH^+$ 85, 36.84; Ph^+ 77, 43.1.

Salt of 1-Phenyl-3-p-chlorobenzoyl-4-hydroxy pyrroline-(2-thio)-5-one and Piperidine (**2 c**)

M. p. 201 °C; $C_{22}H_{21}N_2O_3SCl$ (428.85).

Calcd. C 61.61 H 4.93 N 6.53 S 7.47 Cl 8.26.
Found. C 61.62 H 4.85 N 6.49 S 7.51 Cl 8.30.

IR (cm^{-1}): 2 550–2 450 cm^{-1}, broad NH_2^+; 1 720, 5 CO; 1 630, CO; 1 610, C=C.

^1H n.m.r. (ppm): 8.6 s, 2 H, NH_2^+; 7.3–6.9 m, 9 H aromat.; 3.2 m, 4 H $(CH_2)_2$; 1.7 m, 6 H $(CH_2)_3$.

MS (*m*/e%): M^+ 343 (428–85), 42.72; $M+1$ 344, 9.14; $M+2$ 345, 14.74; *M*-CO 315, 6.27; 141, 32.70; $ClPhCO^+$ 139, 100; $ClPh^+$ 111, 40.63; $C_5H_{10}NH^+$ 85, 43.50; $C_5H_{10}N^+$ 84, 80.82; Ph^+ 77, 51.63.

Salt of 1-p-Chlorophenyl-3-benzoyl-4-hydroxy-pyrroline-(2-thio)-5-one and Piperidine (**2 d**)

M. p. 205 °C; $C_{22}H_{21}N_2O_3SCl$ (428.85).

Calcd. C 61.61 H 4.93 N 6.53 S 7.47 Cl 8.26.
Found. C 61.55 H 4.89 N 6.58 S 7.51 Cl 8.32.

IR (cm^{-1}): 2 500–2 450 m, broad NH_2^+; 1 745, 5 CO; 1 650, CO; 1 610, C=C.

^1H n.m.r. (ppm): 8.75 s, 2 H, NH_2^+; 7.8–6.9 m, 9 H aromat.; 3.2 m, 4 H $(CH_2)_2$; 1.7 m, 6 H $(CH_2)_3$.

MS (*m*/e%): M^+ 343 (428–85), 39.65; $M+1$ 344, 10.65; $M+2$ 345, 16.34; $ClPh^+$ 111, 6.99; $PhCO^+$ 105, 100; $C_5H_{10}NH^+$ 85, 34.33; $C_5H_{10}N^+$ 84, 79.52; Ph^+ 77, 56.04.

Isomerization of **2** *to* **4**

A solution of 0.5 g of **2a–d** in 10 ml of ethanol was treated with 5 ml of 5% NaOH aqueous solution at room temperature. After 10 min the light yellow mixture was acidified (*pH* 3), compound **4a–d** was precipitated, filtered off and crystallized from cyclohexane. Yields (80–95%).

4-Thioanilido-5-phenyl-2,3-furanodione (**4a**)

M. p. 140 °C; $C_{17}H_{11}NO_3S$ (309.33).

Calcd. C 66.00 H 3.58 N 4.52 S 10.36.
Found. C 66.05 H 3.70 N 4.49 S 10.28.

IR (cm^{-1}): 3170, NH amid.; 1760, CO; 1690, CO; 1600, C=C.
^1H n.m.r. (ppm): 9.4 s, 1 H, NH amid; 7.75–6.85 m, 9 H aromat.
MS (*m*/e%): M^+-CO 281, 26.9; 255, 10.4; *M*-2 COH, 252, 13.5; 222, 13.5; *Ph*$NCS^{+\cdot}$ 136, 3.9; *Ph*CO^+ 105, 100; *Ph*$^+$ 77, 93.9.

4-Thioanilido-5-p-methoxyphenyl-2,3-furanodione (**4b**)

M. p. 138 °C; $C_{18}H_{13}NO_4S$ (339.36).

Calcd. C 63.70 H 3.86 N 4.12 S 9.44.
Found. C 63.65 H 3.76 N 4.10 S 9.32.

IR (cm^{-1}): 3190, NH amid; 1745, CO; 1690, CO; 1610, C=C.
^1H n.m.r. (ppm): 9.45, s, 1 H, NH amid; 7.7–6.8 m, 9 H aromat.; 3.9 s, 3 H, OCH_3.
MS (*m*/e%): *M*-CO 311, 26.93; *M*-2 CO 293, 8.3; 251, 11.66; OCH_3*Ph*CO^+ 135, 100; OCH_3*Ph*$^+$ 107, 9.27; *Ph*NH^+ 92, 17.17; *Ph*$^+$ 77, 32.10.

4-Thioanilido-5-p-chlorophenyl-2,3-furanodione (**4c**)

M.p. 135°; $C_{17}H_{10}NO_3SCl$ (343.78).

Calcd. C 59.39 H 2.93 N 4.07 S 9.32 Cl 12.18.
Found. C 59.41 H 2.81 N 4.11 S 9.33 Cl 12.17.

IR (cm^{-1}): 3180, NH amid; 1770, CO; 1690, CO; 1610, C=C.
^1H n.m.r. (ppm): 9.45 s, 1 H, amid; 7.9–7.25 m, 9 H aromat.
MS (*m*/e%): *M*-CO 315, 7.3; 288, 10.7; 289, 27.49; *M*-2 CO 275, 6.3; 256, 28.83; Cl*Ph*CO^+ 139, 100; Cl*Ph*$^+$ 111, 30.59; *Ph*NH_2^+ 93, 25.26; *Ph*$^+$ 77, 18.93.

4-Thio-p-chloroanilido-5-phenyl-2,3-furanodione (**4d**)

M.p. 150°; $C_{17}H_{10}NO_3SCl$ (343.78).

Calcd. C 59.39 H 2.93 N 4.07 S 9.32 Cl 12.18.
Found. C 59.23 H 2.84 N 4.10 S 9.34 Cl 12.20.

IR (cm^{-1}): 3190, NH amid; 1770, CO; 1690, CO; 1610, C=C.
^1H n.m.r. (ppm): 9.45 s, 1 H, NH amid; 7.9–7.2 m, 9 H aromat.
MS (*m*/e%): M^+ 343, 12.74; *M*-CO 315, 14.69; 255, 8.87; 162, 14.52; *Ph*NCS^+ 135, 13.68; *Ph*NCS^+ 105, 100; *Ph*$^+$ 77, 65.3.

Isomerization of **4** *to* **3**

A sample of **4a–d** ethanol was refluxed for 10 min. After cooling a crystalline compound **3a–d** was filtered off.

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