Pyridinethiones. I.* Preparation of 3-Formyl-2(1H)-pyridinethione and 5,11-Epoxydipyrido[2,3-b:2',3'-f]-[1,5]dithioocene

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Hull and coworkers have reported the formation of 3-formyl-2(1H)-quinolinethione by cyclization of o-isothiocyanatoacrynamaldehyde. However, attempts to prepare 3-formyl-2(1H)-pyridinethione (1a) from 5-isothiocyanatopenta-2,4-dienal failed.\[1\]

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We have recently described a general preparation procedure for 1-alkyl- and 1-aryl-3-formyl-2(1H)-pyridinethiones (cf. Scheme 1). In order to synthesize 1a we have investigated the thermolytic and hydrolytic behaviour of the 1-\text{ tert}-butyl- and (R,S)-1-methylbenzyl-substituted derivatives (1b and 1c, respectively). Previously, Jensen et al.\[2\] have reported the elimination of a 4-\text{ tert}-butyl- and a (R,S)-4-methylbenzyl group from thiosemicarbazides by reflux in concentrated hydrochloric acid.

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1a \( R = \text{hydrogen} \)
1b \( R = \text{ tert}-\text{butyl} \)
1c \( R = \text{R.S.}-\text{methylbenzyl} \)

Scheme 1.

Results and discussion. Thermolysis. When 1-\text{ tert}-butyl-3-formyl-2(1H)-pyridinethione (1b) was heated to ca. 190 °C, evolution of isobutene took place and 3-formyl-2(1H)-pyridinethione (1a) was formed (cf. Scheme 2). Analogous thermal syn-elimination of alkene from corresponding structural arrangements have been reported (e.g., Chugaev reaction). (R,S)-1-Methylbenzyl-3-formyl-2(1H)-pyridinethione (1c) distilled unchanged at ca. 200 °C (1 bar). As the thermolytic elimination of alkenes proceeds through a cyclic transition state, the difference in reactivity of 1b and 1c can be expected since in each conformation of the tert-butyl group a hydrogen atom fulfills the geometrical requirements of the transition state and elimination can take place, whereas the preferred conformations of the methylbenzyl group do not have a hydrogen atom in the right position.

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1b and 1c

Scheme 2.

Structure 1a was assigned to the reaction product on the basis of the way of synthesis and the spectroscopic properties (cf. Experimental section and Ref. 2).

3-Formyl-2(1H)-pyridinethione may exist in two tautomeric forms, 1a and 1c (Scheme 2). By comparing the UV spectrum of the reaction product with the spectrum of 1-methyl-3-formyl-2(1H)-pyridinethione it can be concluded that the same chromophore is present in both compounds, and consequently, the thioamide form (1a) is the principal one. This conclusion is in accordance with results reported for other α and γ-thionoaza-aromatic compounds.\[3\]

Hydrolysis. Reflux with concentrated hydrochloric acid converted 1c to the dihydrochloride of 5,11-epoxydipyrido[2,3-b:2',3'-f]-[1,5]dithioocene (2a, Scheme 3). The free base (2) was obtained in almost quantitative yield by neutralization.

Heating 1b for ca. 0.5 min in concentrated hydrochloric acid gave rise to 3-formyl-2(1H)-pyridinethione (1a). Prolonged reaction time led to the formation of 2a.

Structure of 2. In the mass spectrum of 2 a relative abundant molecular ion was observed [m/e = 260 (34 %)]. The base peak in the simple spectrum was situated at m/e = 154. By ac-

Scheme 3.

curate mass measurements the elemental composition of the corresponding ion was determined to C₃H₄NS₂⁺.

2

\[ \text{C}=\text{S} \quad \text{H} \quad \text{SH} \quad \text{and/or} \quad \text{C}=\text{S} \quad \text{H} \]

The UV spectrum of the product showed absorptions at 294 and 238 nm. These values are in accordance with results reported for simple 2-alkyliothioquinoxalines; e.g. 2-methylthiopyridine absorbs at 292 and 247 nm. Further evidence for the depicted structure (2) of the reaction product was obtained from the ¹H and ¹³C NMR spectra. The ¹H NMR spectrum showed four resonances with the integrals 1:1:1:1. The H₄, H₅, and H₆ pyridineproton rings had the expected shifts and couplings. The remaining singlet could be attributed to a CH-group with electronegative substituents. In the ¹³C NMR spectrum (cf. Fig. 1) six signals were observed. The shift values are in agreement with values reported for substituted pyridines.

The geometry of 2 permits the existence of one pair of enantiomers. However, attempts to resolve it have been unsuccessful.

Other 1-substituted-3-formyl-2(1H)-pyridinethiones [including the 1-(2'-phenylethyl)-derivative (cf. Experimental section)] did not react under the thermolytic and hydrolytic reaction conditions described in this paper.

Experimental. Microanalyses were carried out by the Microanalytical Department of the University of Copenhagen.

Instrumentation. IR: Perkin Elmer 457. UV: Beckmann ACTA III. ¹H NMR: JEOL C-60 HL and Bruker HX-60. MS: AEI-MS 902. ¹³C NMR: Varian XL-100-15FT. The melting points are uncorrected.

Formyl-2(1H)-pyridinethione (1a). Hydrolysis. 1b (0.3 g) in conc. hydrochloric acid (5 ml) was refluxed for ca. 0.5 min. Evaporation (in vacuo) of the turbid reaction mixture, addition of water (20 ml) and filtration yielded 0.140 g (66%) of analytically pure 1a, yellow crystals, m.p. 214–216°C.

Thermolysis. When 1b was heated to ca. 190°C (1 bar) isobutene * was evolved, whereupon the residue crystallized. The resulting orange crystals melted at 214–216°C and were in all respects identical to the product obtained by hydrolysis. 1a was obtained analytically pure in quantitative yields.

¹H NMR (DMSO-d₆): δ 7.85 [dd, H(4)], 6.89 [t, H(5)], 7.96 [dd, H(6)], 10.64 (sCHO), 7.90 (broad, s, NH); J₆₇ = 6.1, J₆₈ = 6.1, J₆₉ = 1.5 Hz. UV [abs. ethanol (log e)]; 375 (3.82), 320 (4.02) 293 sh (3.75), 216 (4.02) nm IR (KBr); 1678 (CHO) cm⁻¹. MS; m/e = 139 (44 %, M⁺), 67 (100 %). Anal. C₃H₄NOS: C, H, N, S.

5,11-Epoxydipyrido[2,3-b:2',3'-f][1,5]dithiocine dihydrochloride (2a). (R,S)-1-Methylbenzyl-3-formyl-2(1H)-pyridinethione (10 g) was refluxed in concentrated hydrochloric acid (100 ml) for 8 h. The turbid reaction mixture was extracted with carbon tetrachloride and the resulting water phase evaporated in vacuo. Washing of the residue with acetone yielded colourless needles of analytically pure 2a [4.5 g (74%), m.p. 248–250°C. Titration of 2a with sodium hydroxide gave the equivalent weight 172 g/mol (calc. 167 g/mol). ¹H NMR (60 MHz, DMSO-d₆): δ 7.20 (4H, s), 7.33 (2H, dd, J 8.3 and 5.3 Hz) 8.03 (2H, dd, J 8.3 and 1.5 Hz) 8.45 (2H, dd, J 5.3 and 1.5 Hz). UV [abs. ethanol (log e)]; 298 (3.97) 242 (4.36) nm. Anal. C₂₉H₂₃NO₂S₄Cl₂: C, H, N, S, Cl.

The carbon tetrachloride phase was dried (sodium sulfate) and evaporated in vacuo. The resulting oil was distilled (1.0 g, main fraction b.p. 138–141°C/1.5 mmHg, n₂₀<sub>5</sub> = 1.5876). By refluxing (R,S)-1-phenylethyl alcohol and 4 M hydrochloric acid an identical mixture of isomers of 1,3-diphenylbutene was obtained (b.p. 140–145°C/1.0 mmHg). ¹H NMR (60 MHz, CCl₄): δ 1.44 (3H, d, J 9.0 Hz), 3.30–3.70 (1H, m), 6.25 (1H, d, J 2.3), 7.16 (11H, m, CH and aroyl H). UV [abs. ethanol (log e)]; 252 (3.93) 213 (3.93) nm. MS m/e (% rel. int.): M⁺ at 208 (100 %).

Bromination of a sample gave white crystals (m.p. 99–112°C (methanol)). This mixture of stereoisomeric 1,2-dibromo-1,3-diphenylbutanes has previously been identified by Marion.

5,11-Epoxydipyrido[2,3-b:2',3'-f][1,5]dithiocine (2). Method 1. 2a (4.0 g) was dissolved in water (20 ml) and pH was adjusted to 9 with 2 M sodium hydroxide. The precipitated crystals were collected and dried. Yield: 3.1 g (96 %) analytically pure 2.

Method 2. (R,S)-1-Methylbenzyl-3-formyl-2(1H)-pyridinethione (4.5 g) was refluxed in concentrated hydrochloric acid (50 ml) for 10 h. After cooling and extraction, with carbon tetrachloride, pH was adjusted to 7 with 10 M sodium hydroxide. The precipitated crystals were collected and dried [3.9 g (81 %)]. Recrystallization from methanol yielded white needles m.p. = 242–244°C.

Method 3. 3-Formyl-2(1H)-pyridinethione was refluxed in concentrated hydrochloric acid, pH was adjusted to 7 and the white crystals of analytically pure 2 were isolated. The equivalent weight was found to 260 g/mol (calc.

Fig. 1. ¹³C NMR chemical shifts of 5,11-epoxydipyrido[2,3-b:2',3'-f][1,5]dithiocine (δ, DMSO-d₆).

* Identified by MS.

260 g/mol) by titration with perchloric acid (the monoperochlorate separated as crystals) 

\[ ^1 \text{H NMR (60 MHz, DMSO-}d_6) : \delta 7.06 (2 \text{ H, s), 7.25 (2 \text{ H, dd, J 8.1 and 5.3 Hz), 7.87 (2 \text{ H, dd, J 8.1 and 1.5 Hz), 8.40 (2 \text{ H, dd, J 5.3 and 1.5 Hz), UV [abs. ethanol (log } \epsilon) : 298 (3.75) 243 (4.14) nm. IR (KBr) : 1095 s (C-\text{O-}C) \text{ cm}^{-1}. \text{ Anal. C}_{1}_3\text{H}_{1}_2\text{N}_3\text{O}_4\text{S}_2 : C, H, N, S.} \]

\((R,S)-1\text{-Methylbenzyl-3-formyl-2(1H)-pyridine-thione (1c). Glutaconaldehyde sodium salt (120 g) and (R,S)-methylbenzyl isothiocyanate (110 g) in dimethyl sulfoxide (500 ml) were heated to 80 \degree \text{C for 2 h. The reaction mixture was poured in ice-cold water (4 l). The precipitated orange crystals were collected [119 g (73 %)] and recrystallized from methanol/water (510/88). m.p. 103–105 \degree \text{C.} \text{H NMR (60 MHz, DMSO-}d_6) : \delta 1.81 (3 \text{ H, d, J 6.2 Hz), 7.40 (5 \text{ H, s), 7.46 (1 \text{ H, q, J 6.8 Hz), 7.78 (1 \text{ H, dd, J 6.2 and 1.5 Hz), 8.30 (1 \text{ H, dd, J 6.2 and 1.5 Hz), 10.65 (CHO, s). UV [abs. ethanol (log } \epsilon) : 388 (3.49) 3.18 (4.06) 294 sh (3.77) nm. IR (KBr) : 1685 (CHO) cm^{-1}. Anal. C_{1}_4\text{H}_{1}_3\text{NOS} : C, H, N, S.} \]

\((R,S)-2\text{-Phenylethyl-3-formyl-2(1H)-pyridine-thione. Glutaconaldehyde potassium salt (2.72 g) and 2-phenylethyl isothiocyanate (3.26 g) in } N,N\text{-dimethylformamide were heated to 100 \degree \text{C for 1 h. The reaction mixture was evaporated in vacuo, water (200 ml) was added and the dark crystals were collected. Trituration with cyclohexane gave orange crystals [2.8 g (50 %)]. Recrystallization from heptane yielded pale orange crystals with m.p. 132–135 \degree \text{C.} \text{H NMR (60 MHz, CDCl}_3) : \delta 3.28 (2 \text{ H, t, J 7.5 Hz), 4.97 (2 \text{ H, t, J 7.5 Hz), 6.59 (1 \text{ H, t, J 6.9 Hz), 7.35 (5 \text{ H, s), 7.53 (1 \text{ H, dd, J 6.9 and 1.5 Hz), 7.88 (1 \text{ H, dd, J 6.9 and 1.5 Hz), 11.00 (CHO, s). UV [abs. ethanol (log } \epsilon) : 377 (3.36) 320 (4.01) 294 sh (3.72) nm. IR (KBr) : 1682 (CHO) cm^{-1}. Anal. C_{1}_4\text{H}_{1}_3\text{NOS : C, H, N, S.} \)


Studies on the Kolbe Electrolysis. XII.* Complete Racemization of Optically Active Radicals from \((-\text{-2-Methyloctadecanoate in a Mixed Coupling Reaction}}

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The hypothesis that the Kolbe anodic coupling of carboxylates proceeds via adsorbed radicals would seem to demand at least partial retention of configuration in the coupling product from an initially optically active radical. Previous experiments to test this idea have, however, resulted in completely racemized coupling products and hence not proved to be conclusive on this point.* Only if retention is observed would adsorbed radicals be implicated in the mechanism with any degree of certainty.

The explanation put forward by Muck and Wilson for the remarkably selective Kolbe coupling of long-chain carboxylates, parallel stacking of the long alkyl chains perpendicular to the anode surface with concomitant very low mobility of the alkyl radicals formed, suggests yet another possibility to find a system with a maximal propensity toward retention of configuration, if it is indeed possible to find one at all. We now report a study on the mixed Kolbe coupling between \((-\text{-2-methyloctadecanoic acid (1) and methyl hydrogen malonate (eqn. 1). Both I and the product, methyl 3-methylmalonate (2), were known with respect to their maximal optical rotation and configuration.}**

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\begin{align*}
\text{RCH(CH}_3\text{)CO}^- + \text{MeOCOCOCH}_3\text{COO}^- & \rightarrow \text{Pt anode} \\
\text{RCH(CH}_3\text{)CH}_2\text{COOH}_2 & \rightarrow \text{2} \\
\end{align*}
\]

After initial experiments with the \((+\text{-})-\text{isoomer to establish the proper reaction conditions, the crucial experiment was run with \((-\text{-})-\text{I and methyl hydrogen malonate in a 1:8 molar ratio in methanol (total salt concentration } \sim 1 \text{ M). Both acids were fully neutralized in order to compensate for the difference in pK between them, and a large Hg cathode was used to avoid alkalinization (by amalgamation of the sodium discharged) during the run. The temperature of the electrolyte solution}

* Part XI. See Ref. 6.
** To whom inquiries should be addressed.