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

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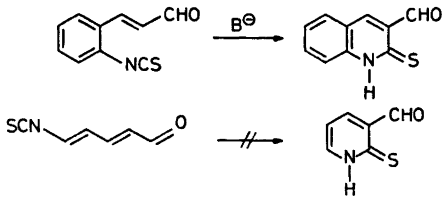
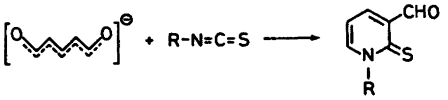
Hull [1a] has reported the formation of 3-formyl-2(1*H*)-quinolinethione by cyclization of *o*-isothiocyanatocinnamaldehyde. However, attempts to prepare 3-formyl-2(1*H*)-pyridinethione (*1a*) from 5-isothiocyanatopenta-2,4-dienal failed.[1b]



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

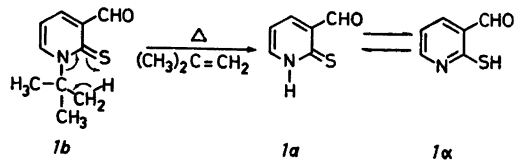


1a R = hydrogen
1b R = *tert*-butyl
1c R = *R,S*-methylbenzyl

Scheme 1.

Results and discussion. Thermolysis. When 1-*tert*-butyl-3-formyl-2(1*H*)-pyridinethione [2] (*1b*) was heated to *ca.* 190 °C, evolution of isobutene took place and 3-formyl-2(1*H*)-pyridinethione (*1a*) was formed (*cf.* Scheme 2). Analogous thermal *syn*-elimination of alkenes from corresponding structural arrangements have been reported (*e.g.* Chugaev reaction).

(*R,S*)-1-Methylbenzyl-3-formyl-2(1*H*)-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 fulfils 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.



1b *1a* *1α*

Scheme 2.

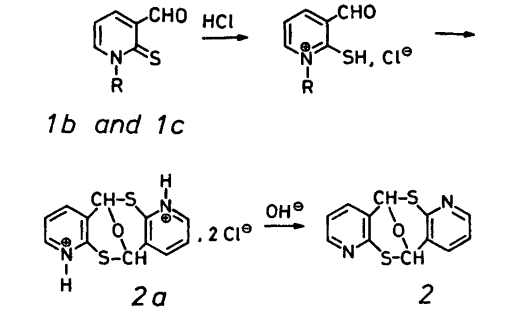
Structure *1a* was assigned to the reaction product on the basis of the way of synthesis and the spectroscopic properties (*cf.* Experimental section and Ref. 2).

3-Formyl-2(1*H*)-pyridinethione may exist in two tautomeric forms, *1a* and *1α* (Scheme 2). By comparing the UV spectrum of the reaction product with the spectrum of 1-methyl-3-formyl-2(1*H*)-pyridinethione [2] 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.[4]

Hydrolysis. Reflux with concentrated hydrochloric acid converted *1c* to the dihydrochloride of 5,11-epoxydipyrido[2,3-*b*:2′,3′-*f*]-[1,5]dithiocine (*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(1*H*)-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-

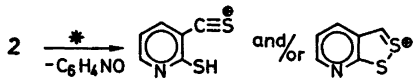


1b and 1c *2a* *2*

Scheme 3.

* This paper is a continuation of the series: Derivatives and Reactions of Glutacondialdehyde, see Ref. 2.

curate mass measurements the elemental composition of the corresponding ion was determined to $C_6H_4NS_2$:



The UV spectrum of the product showed absorptions at 294 and 238 nm. These values are in accordance with results reported for simple 2-alkylthiopyridines; *e.g.* 2-methylthiopyridine absorbs at 292 and 247 nm.[5]

Further evidence for the depicted structure (*2*) of the reaction product was obtained from the ^1H and ^{13}C NMR spectra. The ^1H NMR spectrum showed four resonances with the integrals 1:1:1:1. The H4, H5, and H6 pyridine-ring protons had the expected shifts and couplings.[3] The remaining singlet could be attributed to a CH-group with electronegative substituents. In the ^{13}C NMR spectrum (*cf.* Fig. 1) six signals were observed. The shift values are in agreement with values reported for substituted pyridines.[6]

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(1*H*)-pyridinethiones[3] [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: Bechmann ACTA III. ^1H NMR: JEOL C-60 HL and Bruker HX-60. MS: AEI-MS 902. ^{13}C NMR: Varian XL-100-15FT. The melting points are uncorrected.

3-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

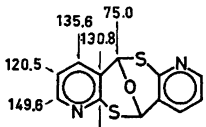


Fig. 1. ^{13}C NMR chemical shifts of 5,11-epoxydipyrido[2,3-*b*:2′,3′-*f*][1,5]dithiocine (*δ*, DMSO-d_6).

* Identified by MS.

respects identical to the product obtained by hydrolysis. *1a* was obtained analytically pure in quantitative yields.

^1H NMR (DMSO-d_6): *δ* 7.85 [dd, H(4)], 6.89 [t, H(5)], 7.96 [dd, H(6)], 10.64 (sCHO), 7.90 (broad, s, NH); $J_{4,5}=6.1$, $J_{5,6}=6.1$, $J_{4,6}=1.5$ Hz. UV [abs. ethanol (log *ε*)]: 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. C_6H_5NOS: 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(1*H*)-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 d. Titration of *2a* with sodium hydroxide gave the equivalent weight 172 g/mol (calc. 167 g/mol). ^1H NMR (60 MHz, DMSO-d_6): *δ* 7.20 (4, H, s), 7.33 (2 H, dd, *J* 8.3 and 5.3 Hz) 8.03 (2 H, dd, *J* 8.3 and 1.5 Hz) 8.45 (2 H, dd, *J* 5.3 and 1.5 Hz). UV [abs. ethanol (log *ε*)]: 298 (3.97) 242 (4.36) nm. Anal. $C_{12}H_{10}N_2OS_2Cl_2$: 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, $n_D^{24}=1.5876$). 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 mmHg).[7] ^1H NMR (60 MHz, CCl_4): *δ* 1.44 (3H, d, *J* 9.0 Hz), 3.30–3.70 (1 H, m), 6.25 (1 H, d, *J* 2.3), 7.16 (11 H, m, CH and aryl H). UV [abs. ethanol (log *ε*)]: 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.[7]

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 (99 %) analytically pure *2*.

Method 2. (*R,S*)-1-Methylbenzyl-3-formyl-2(1*H*)-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(1*H*)-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.

260 g/mol) by titration with perchloric acid (the monoperchlorate separated as crystals) ^{1}H NMR (60 MHz, DMSO-d_6): δ 7.06 (2 H, s), 7. 25 (2 H, dd, J 8.1 and 5.3 Hz), 7.87 (2 H, dd, J 8.1 and 1.5 Hz), 8.40 (2 H, dd, J 5.3 and 1.5 Hz). UV [abs. ethanol (log ε)]: 298 (3.75) 243 (4.14) nm. IR (KBr): 1095 s (C–O–C) cm^{-1}. Anal. $C_{12}H_6N_2OS_2$: C, H, N, S.

(R,S)-1-Methylbenzyl-3-formyl-2(1H)-pyridinethione (*1c*). Glutacondialdehyde sodium salt (120 g) and (*R,S*)-methylbenzyl isothiocyanate (110 g) in dimethyl sulfoxide (500 ml) were heated to 80 °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 °C. ^{1}H NMR (60 MHz, DMSO-d_6): δ 1.81 (3 H, d, J 6.2 Hz), 7.40 (5 H, s), 7.46 (1 H, q, J 6.8 Hz), 7.78 (1 H, dd, J 6.2 and 1.5 Hz), 8.30 (1 H, dd, J 6.2 and 1.5 Hz), 10.65 (CHO, s). UV [abs. ethanol (log ε)]: 388 (3.49) 3.18 (4.06) 294 sh (3.77) nm. IR (KBr): 1685 (CHO) cm^{-1}. Anal. $C_{14}H_{13}NOS$: C, H, N, S.

1-(2'-Phenylethyl)-3-formyl-2(1H)-pyridinethione. Glutacondialdehyde potassium salt (2.72 g) and 2-phenylethyl isothiocyanate (3.26 g) in *N,N*-dimethylformamide were heated to 100 °C for 4 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 °C. ^{1}H NMR (60 MHz, $CDCl_3$); δ 3.28 (2 H, t, J 7.5 Hz), 4.97 (2 H, t, J 7.5 Hz), 6.59 (1 H, t, J 6.9 Hz), 7.35 (5 H, s), 7.53 (1 H, dd, J 6.9 and 1.5 Hz), 7.88 (1 H, dd, J 6.9 and 1.5 Hz), 11.00 (CHO, s). UV [abs. ethanol (log ε)]: 377 (3.36) 320 (4.01) 294 sh (3.72) nm. IR (KBr): 1682 (CHO) cm^{-1}. Anal. $C_{14}H_{13}NOS$: C, H, N, S.

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Studies on the Kolbe Electrolysis. XII.* Complete Racemization of Optically Active Radicals from (—)-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.[1–4] Previous experiments to test this idea have, however, resulted in completely racemized coupling products and hence not proved to be conclusive on this point.[5,6] 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 [7] 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 D-(–)-2-methyloctadecanoic acid (*1*) and methyl hydrogen malonate (eqn. 1). Both *1* and the product, methyl 3-methylnonadecanoate (*2*), were known with respect to their maximal optical rotation and configuration.[8,9]

$$\underset{1}{RCH(CH_3)COO^-} + MeOCOCH_2COO^- \xrightarrow[R=C_{16}H_{33}]{\text{Pt anode}} \underset{2}{RCH(CH_3)CH_2COOCH_3} \quad (1)$$

After initial experiments with the (+)-isomer to establish the proper reaction conditions, the crucial experiment was run with (–)-*1* and methyl hydrogen malonate in a 1:8 molar ratio in methanol (total salt concentration ~1 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.[10] The temperature of the electrolyte solution

* Part XI. See Ref. 6.

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