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PYRIDINETHIONES†—II

PREPARATION OF CONDENSED PYRIDINES RELATED TO 3-FORMYL-2(1H)-PYRIDINETHIONE

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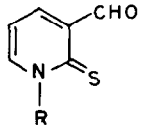
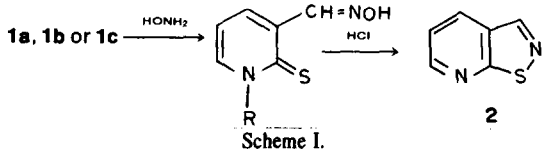
Abstract—Some condensed pyridines, isothiazolo[4,5-b]pyridine, 2-oxo-2H-thiopyranyl[5,6-b]pyridines, and thieno[3,2-b]pyridines, have been prepared from 3-formyl-2(1H)-pyridinethione or the 1-substituted precursors for this compound.

We have reported[1] a high yield synthesis of 1 - substituted - 3 - formyl - 2(1H) - pyridinethiones from the glutaconaldehyde anion and organic isothiocyanates. The parent compound 3 - formyl - 2(1H) - pyridinethione (**1a**) was prepared from the 1 - t - butyl- and R,S - 1 - methylbenzyl derivatives (**1b** and **1c**) by pyrolysis or acidic hydrolysis. The present paper deals with the synthesis of some condensed pyridines, isothiazolo(4,5-b]pyridine (**2**), 2 - oxo - 2H - thiopyranyl[5,6 - b]pyridines (**3**) and thieno[3,2-b]pyridines (**4**) with **1a**, **1b** or **1c** as starting material. The ring system **3** has hitherto not been reported, whereas more laborious synthetic routes are known to the systems **2** and **4**.



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



Scheme I.

†Part I: Ref. 2.

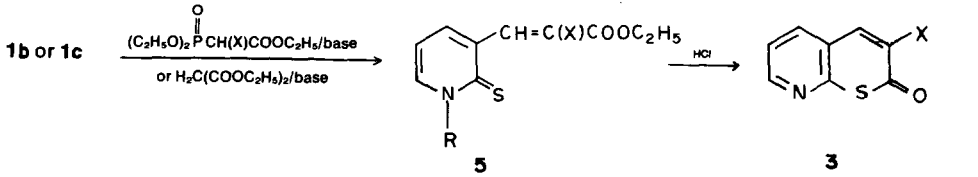
RESULTS AND DISCUSSION

Isothiazolo[4,5-b]*pyridine* (**2**). Reflux of **1a**, **1b** or **1c** with hydroxylammonium hydrochloride in hydrochloric acid yielded isothiazolo[4,5-b]pyridine (**2**, Scheme 1). This heterocycle was also obtained when the oxime of **1c** was refluxed in hydrochloric acid. Recently, Taurins and Khow[3] have prepared **2** in a five step reaction sequence, with a low overall yield.

2-Oxo-2H-thiopyranyl[5,6-b]*pyridines* (**3**). The derivatives **5a–5e** were prepared from **1b** or **1c**, by reaction with either organic phosphonate carbanions (**5a–5c**, Whittig–Horner reaction) or diethyl malonate and base (**5d–5e**), Scheme 2. The ^{1}H NMR spectrum of **5a** showed the configuration of the double bond ($J_{H,H}$ = 16 Hz) to be *trans* (E). **5b** was a mixture of the Z and E isomers. These observations on the stereochemistry of the products are in accordance with previous reports[4] on the Wittig–Horner reaction.

Reflux of compounds **5a–5e** in conc. hydrochloric acid yielded in all cases the corresponding derivatives of **3**. The yields depended on the reaction conditions (Experimental). As a poor yield of **3a** was obtained when **5a** was heated in polyphosphoric acid, it can be concluded that cyclization to **3** is best carried out in a strong acid.

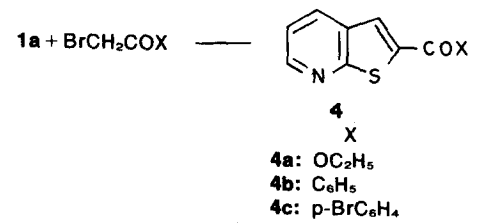
Thieno[3,2-b]*pyridines* (**4**). The thieno[3,2-b]pyridines (**4a–4c**) were prepared in a one step synthesis from **1a** and an α-bromocarbonyl compound, in the presence of a strong base such as potassium hydroxide (Scheme 3). The reactions probably proceed *via* the S-alkylated derivatives, followed by an intramolecular aldol condensation. It is well known that 2(1H)-pyridinethiones are



	X	R
5a:	hydrogen	*t*-butyl
5b:	hydrogen	*R,S*-methylbenzyl
5c:	methyl	*R,S*-methylbenzyl
5d:	ethoxycarbonyl	*t*-butyl
5e:	ethoxycarbonyl	*R,S*-methylbenzyl

	X
3a:	hydrogen
3b:	methyl
3c:	carboxy
3d:	ethoxycarbonyl

Scheme II.



Scheme III.

easily S-alkylated.[5] One of the compounds (**4a**) has recently been prepared by Schneller *et al.*[6] in a multistep reaction sequence.

Structure of the products. The assignment of the structures **2**, **3** and **4** to the reaction products follows from the analytical and spectral data as well as by synthesis. From the ^{1}H NMR spectra it is seen that the chemical shift value of the proton originating from the aldehyde group is strongly influenced by the nature of the ring.

EXPERIMENTAL

Microanalyses were carried out in the Microanalytical Department of the University of Copenhagen by Mr. Preben Hansen. *Instrumentation.* UV; Beckman Acta III. ^{1}H NMR at 60 MHz, Jeol FX-60 or C-60 HL. The m.ps are uncorrected.

Isothiazolo[4,5-b]*pyridine* (**2**)

Method A. A mixture of R,S-**1c** (4.86 g), hydroxylammonium hydrochloride (1.6 g), 10 M NaOH (3 ml), water (5 ml) and EtOH (150 ml) was heated at 50° for 15 min. Addition of water (600 ml) and extraction with $CHCl_3$ and work up yielded the oxime of (R,S) - 1 - methylbenzyl - 3 - formyl - 2(1H) - pyridinethione which crystallized slowly, yield 3.5 g (67%). Recrystallization from MeOH gave yellow needles, m.p. 125–8°. ^{1}H NMR (DMSO-d_6): δppm 11.49 (s, 1H), 8.79 (s, 1H), 8.01 (d, J = 9 Hz, 1H), 7.78 (d, J = 9 Hz, 1H), (*ca.* 7.6 q, 1H), 7.42 (s, 5H), 6.81 (t, J = 9 Hz, 1H), 1.79 (d, J = 8 Hz, 3H). (Found: C, 65.10; H, 5.47; N, 10.83. $C_{14}H_{14}N_2SO$ requires: C, 65.11; H, 5.43; N, 10.84%).

The oxime (1.56 g) and conc. HCl (10 ml) were refluxed for 3 hr. Extraction with CCl_4 (20 ml) and neutralization of the water phase with Na_2CO_3 followed by extraction with methylene chloride (150 ml), drying of the extract, filtration and concentration *in vacuo* gave pale yellow needles. Sublimation (30°/0.05 mmHg) gave **2** as white crystals 0.7 g (85%) m.p. 50–2°; Ref. 3 gives the m.p. 55°. ^{1}H NMR ($CDCl_3$): 8.93 (s, 1H), 8.75 (dd, J = 4.4 and 1.6 Hz), 8.32 (dd, J = 8.4 and 1.6 Hz), 7.37 (dd, J = 8.4 and 4.4 Hz). UV [EtOH (log ε)]: 226 (4.24), 295 (3.53), 306 (3.46) nm. (Found: C, 53.00; H, 3.03; N, 20.58; S, 23.52. $C_6H_4N_2S$ requires: C, 52.92; H, 2.96; N, 20.57; S, 23.52%).

Method B. A mixture of **1c** (4.86 g), hydroxylammonium hydrochloride (1.6 g), abs EtOH (30 ml), and conc. HCl (25 ml) was refluxed for 5.5 hr. Evaporation of solvent addition of $NaHCO_3$aq and steam distillation gave after extraction of the distillate with $CHCl_3$ **2** as pale yellow needles 1.3 g (48%).

Method C. A mixture of **1b** (1.95 g), hydroxylammonium hydrochloride (1.0 g) and EtOH (30 ml) was stirred for 12 hr at room temp., followed by reflux for 2 min. Concentration *in vacuo*, addition of $NaHCO_3$aq and extraction with $CHCl_3$ yielded after work up 0.6 g (41%) of **2**.

3 - (2' - *Ethoxycarbonylvinyl*) - 1 - *t* - *butyl* - 2(1H) - *pyridinethione* (**5a**)

To sodium hydride (50% suspension, 0.48 g) in dry ether (50 ml) at 0° was added diethyl ethoxycarbonylmethyl phosphonate[7] (2.24 g) in ether (50 ml) followed by **1b** (1.95 g). This mixture was stirred at room temp. for 15 hr whereupon water (20 ml) was slowly added. After repeated washing with water (40 ml), the ether phase was dried (Na_2SO_4) and evaporated *in vacuo*. The residual orange oil was purified by PLC (silica, chloroform/acetone, 50/1). The main fraction was dark orange crystals 1.60 g (60%) of **5a**, m.p. 54–61°. ^{1}H NMR ($CDCl_3$): 8.35 (d, J = 16 Hz), 8.05 (dd, J = 7 and 2 Hz, 1H), 7.39 (dd, J = 7 and 2 Hz, 1H), 6.62 (t, J = 7 Hz, 1H), 6.07 (d, J = 16 Hz, 1H), 4.23 (q, J = 7 Hz, 2H), 2.02 (s, 9H), 1.32 (t, J = 7 Hz, 1H). (Found: C, 63.25; H, 7.27; N, 5.35; S, 12.19. $C_{14}H_{19}NO_2S$ requires: C, 63.40; H, 7.17; N, 5.28; S, 12.08%).

3 - (2' - *Ethoxycarbonylvinyl*) - 1 - (R,S) - *methylbenzyl* - 2(1H) - *pyridinethione* (**5b**)

To sodium hydride (50% suspension, 0.24 g) in dry ether (200 ml) at 0° were added diethyl ethoxycarbonylmethyl phosphonate[7] (1.12 g) in dry ether (50 ml) and R,S-**1c** (1.20 g). This mixture was stirred at room temp. for 15 hr, whereupon water (20 ml) was slowly added. Repeated washing with water (40 ml) and work up of the ether phase yielded a orange oil which crystallized on standing. Recrystallization from abs EtOH yielded 1.0 g (65%) orange crystals of **5b**, m.p. 110–2°. ^{1}H NMR ($CDCl_3$): 7.47–8.00 (m, 3H), 7.33 (s, 5H), 6.37–7.17 (m, 2H), 4.25 (q, J = 7 Hz, 2H), 2.13 (d, J = 1.5 Hz, 1H), 1.93 (d, J = 1.5 Hz, 2H, 2H), 1.78 (d, J = 7 Hz, 3H), 1.33 (t, J = 7 Hz, 3H). (Found: C, 69.10; H, 6.04; N, 4.42; S, 10.14. $C_{18}H_{19}NO_2S$ requires: C, 69.01; H, 6.07; N, 4.47; S, 10.22%).

Z *and* E - 3 - (2' - *Ethoxycarbonyl* - 2' - *methylvinyl*) - 1 - (R,S) - *methylbenzyl* - 2(1H) - *pyridinethione* (**5c**)

The method above was used, thus sodium hydride (50% suspension, 0.72 g), dry ether (650 ml), diethyl ethoxycarbonyl ethyl phosphonate and **1c** (3.6 g) were stirred at room temp. for 15 hr. Work up and purification by PLC (silica, chloroform) yielded an orange oil which slowly crystallized to give yellow crystals of **5c**, 4.22 g (86%), m.p. 75–96°. ^{1}H NMR ($CDCl_3$): 8.17 (s, 1H), 8.09 (d, J = 7 Hz, 1H), 7.37 (d, J = 7 Hz, 1H), 6.62 (t, J = 7 Hz, 1H), 4.27 (quintet, J = 7 Hz, 4H), 2.03 (s, 9H), 1.07–1.57 (m, 6H). (Found: C, 69.35; H, 6.40; N, 4.05; S, 10.15. $C_{19}H_{21}NO_2S$ requires: C, 69.72; H, 6.42; N, 4.28; S, 9.75%).

3 - (2',2' - *Diethoxycarbonyl*) - 1 - (R,S) - *methylbenzyl* - 2(1H) - *pyridinethione* (**5d**)

Compound **1b** (0.98 g), diethylmalonate (0.92 ml), piperidine (1 ml), gl AcOH (0.1 ml), and abs. EtOH (50 ml) were refluxed with a water separator for 8 hr. Concentration *in vacuo* and purification by PLC (silica, chloroform/methanol, 20/1) gave orange crystals of **5d**, 1.49 g (88%), m.p. 75–7°. ^{1}H NMR ($CDCl_3$): 8.28 (s, 1H), 7.32 (s, 5H), 7.13–7.77 (m, 3H), 6.57 (t, J = 7 Hz, 1H), 4.00–4.43 (m, 4H), 1.77 (d, J = 7 Hz, 3H), 1.03–1.50 (m, 6H). (Found: C, 60.00; H, 6.77; N, 4.07. $C_{17}H_{23}NSO_4$ requires: C, 60.51; H, 6.87, N, 4.15%).

3 - (2',2' - *Diethoxycarbonyl* - 1 - (R,S) - *methylbenzyl* - 2(1H) - *pyridinethione* (**5e**)

Compound **1c** (0.61 g), diethyl malonate (0.46 g), piperidine (0.30 ml), and CCl_4 (25 ml) were refluxed for 8 hr. PLC (silica, chloroform) gave **5e** as an orange semicrystalline oil, 0.67 g (70%) which was used without further purification. ^{1}H NMR (DMSO-d_6): 8.43 (d, J = 16 Hz, 1H), 7.98 (t, J = 7 Hz, 2H), 7.66 (q, J = 7 Hz, H), 7.37 (s, 5H), 6.82 (t, J = 7 Hz, 1H), 6.47 (d, J = 16 Hz, 1H), 4.22 (q, J = 7 Hz, 2H), 1.80 (d, J = 7 Hz, 3H), 1.27 (t, J = 7 Hz, 3H).

2 - *Oxo* - 2H - *thiopyranyl*[5,6-b]*pyridine* (**3a**)

Method A—from **5d** (3.37 g) was refluxed for 4.5 hr in conc. HCl (15 ml). Cooling and neutralization with sat. Na_2CO_3 aq gave **5a** as a white ppt. The white crystals of **5a** was obtained analytically pure, yield 0.85 g (52%) with m.p. 142–144°. ^{1}H NMR (DMSO-d_6): 8.73 (dd, J = 5 and 1.5 Hz, 1H), 8.30 (dd, J = 8 and 1.5 Hz, 1H), 8.12 (d, J = 11 Hz, 1H), 7.55 (dd, J = 8 and 5 Hz, 1 H), 6.68 (d, J = 11 Hz, 1H). UV [EtOH (log ε)]: 228 (4.42), 256 (3.82), 278 (3.46), 288 (3.43), 313 (3.76) nm. (Found: C, 58.90; H, 3.09; N, 8.59; S, 19.61. C_8H_5NOS requires: C, 58.90; H, 3.25; N, 8.55; S, 19.50%).

Method B—from **5e**: **5e** (2.39 g) was refluxed for 30 hr in conc. HCl, cooling, washing with $CHCl_3$ and neutralization yielded 0.49 g (49%) of **3a**.

Method C—**5a** and **5b** gave in conc. HCl as above, 50% and 44% respectively, of **3a**.

3 - *Methyl* - 2 - *oxo* - 2H - *thiopyranyl*[5,6 - b]*pyridine* (**3b**)

Compound **5c** (0.65 g) was refluxed in conc. HCl (10 ml) for 2 days. The cold mixture was washed with CCl_4 (to remove the byproducts), addition of Na_2CO_3 and extraction with $CHCl_3$ (3 × 100 ml) yielded 0.35 g (100%) of **3b** as colourless crystals, m.p. 127–130° (cyclohexane). ^{1}H NMR ($CDCl_3$): 8.63 (d, J = 5 Hz, 1H), 7.85 (d, J = 8 Hz, 1H), 7.57 (s, 1H), 7.30 (dd, J = 8 and 5 Hz, 1H), 2.23 (s, 3H). UV [EtOH (log ε)]: 227 (4.26), 258 (3.77), 292 (3.60), 319 (3.75). (Found: C, 61.25; H, 4.09; N, 7.89. C_9H_7NOS requires: C, 61.01; H, 3.98; N, 7.91%).

2 - *Oxo* - 2H - *thiopyranyl*[5,6 - b]*pyridine* - 3 - *carboxylic acid* (**3c**)

The procedure described above was used, thus **5e** (1.92 g) in conc. HCl (20 ml) was refluxed for 4 hr, washed with $CHCl_3$ and neutralized. PLC (silica, chloroform/acetone, 14/1) yielded 0.38 g (47%) of **3c** as white crystals, m.p. 196–7°. ^{1}H NMR (DMSO-d_6): 8.80 (dd, J = 5 and 2 Hz, 1H), 8.66 (s, 1H), 8.48 (dd, J = 8 and 2 Hz, 1H), 7.62 (dd, J = 8 and 5 Hz, 1H). UV [EtOH (log ε)]: 230 (4.38), 261 (3.82), 301 (3.64), 335 (3.86) nm. (Found: C, 52.10; H, 2.34; N, 6.58; S, 15.46. $C_9H_5NO_3S$ requires: C, 52.17; H, 2.43; N, 6.76; S, 15.47%).

2 - *Oxo* - 2H - *thiopyranyl*[5,6 - b]*pyridine* - 3 - *carboxylic acid ethylester* (**3d**)

Compound **5d** (3.37 g) was refluxed in a mixture of EtOH (10 ml) and conc. HCl (10 ml) for 1.5 hr, whereupon the reaction was evaporated *in vacuo*. This yielded 1.65 g (61%) of the hydrochloride of **3d**, from which **3d** was obtained by neutralization. White crystals m.p. 131–132° (MeOH). ^{1}H NMR (DMSO-d_6): 8.75 (dd, J = 5 and 2 Hz, 1H), 8.61 (s, 1H), 8.43 (dd, J = 8 and 2 Hz, 1H), 7.55 (dd, J = 8 and 5 Hz, 1H), 4.33 (q, J = 7 Hz, 2H), 1.32 (t, J = 7 HZ, 3H). UV [EtOH (log ε)]: 232 (4.38), 257 (3.88), 292 (3.60), 342 (3.76) nm. (Found: C, 56.00; H, 3.81; N, 6.05. $C_{11}H_9NO_3S$ requires: C, 56.16; H, 3.86; N, 5.96%).

Thieno[3,2 - b]*pyridine* - 2 - *carboxylic acid ethylester* (**4a**)

A mixture of **1a** (0.28 g), bromoacetic acid ethylester (0.34 g), KOH (0.16 g) and DMF (10 ml) was stirred at 20° for 4 days. Filtration, evaporation and PLC (silicagel, chloroform) yielded 0.34 g (81%) of **4a** as white crystals, m.p. 58–9°. Ref. 6 gives the m.p. 57–8°. ^{1}H NMR spectra identical to the spectra given in this ref. UV [EtOH (log ε)]: 239 (4.21), 286 (3.10). (Found: C, 57.75, H, 4.71, N, 6.48, S, 15.77. $C_{10}H_9NO_2S$ requires: C, 57.97, H, 4.35, N, 6.76, S, 15.46%).

2 - *Benzoylthieno*[2,3 - b]*pyridine* (**4b**)

To a soln of **1a** (0.28 g) and KOH (0.22 g) in DMF (10 ml) was added phenacylbromide (0.40 g). This mixture was heated to 50° for 2 hr. Addition of water (100 ml) gave 0.31 g (64%) of **4b** as cream coloured crystals. m.p. 96–98° (toluene/pentane). ^{1}H NMR (DMSO-d_6): 8.77 (dd, J = 4 and 2 Hz, 1H), 8.50 (dd, J = 8 and 2 Hz, 1H), 8.13 (S, 1H), 7.47–8.07 (m, 6H). UV [EtOH (log ε)]: 225 (4.14), 253 (3.99), 300 (4.25) nm. (Found C, 70.25, H, 3.73, N, 5.83, S, 13.45. $C_{14}H_9NOS$ requires: C, 70.29, H, 3.79, N, 5.86, S, 13.38%).

2 - (p - *Bromobenzoyl*)*thieno*[3,2 - b]*pyridine* (**4c**)

Prepared as above, **1a** (0.28 g), KOH (0.22 g) and *p*-bromophenacylbromide (0.40 g) in DMF at 60° for 0.5 hr. Work up gave 0.59 g (92%) of **4c** as white crystals. m.p. 180–181° (methylcyclohexane). ^{1}H NMR (DMSO-d_6): 8.77 (dd, J = 5 and 1.5 Hz, 1H), 8.48 (dd, J = 8 and 1.5 Hz, 1H), 8.15 (s, 1H), 7.87 (S, 4H), 7.58 (dd, J = 8 and 5 Hz, 1H). UV [EtOH (log ε)]: 225 (4.34), 302 (4.39) nm. (Found: C, 53.00, H, 2.68, N, 4.25, S, 9.91. $C_{14}H_8BrNOS$ requires C, 52.85, H, 2.53, N, 4.40, S, 10.07%).

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