Tetrahedron Vol. 33, pp. 341 to 343 Pergamon Press 1977 Printed in Great Britain

DERIVATIVES AND REACTIONS OF GLUTACONDIALDEHYDE IV 1-SUBSTITUTED-3-FORMYL-2(1H)-PYRIDINETHIONES

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(*Received in the UK* 13 *July* 1976; *Accepted for publication* 7 *September* 1976)

Abstract—The reaction of the glutacondialdehyde anion with alkyl and acyl isothiocyanates has been investigated. Whereas alkyl isothiocyanates give rise to 1-alkyl-3-formyl-2(1H)-pyridinethiones, O-acylated glutacondialdehyde derivatives are formed from acyl isothiocyanates in most cases. The reaction courses may be understood on the basis of the principle of hard and soft acids and bases.

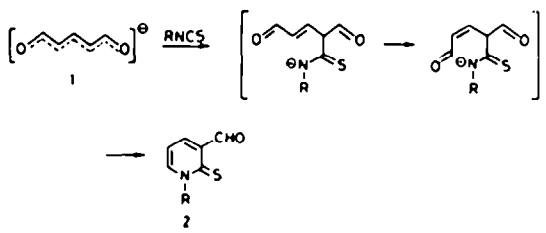
Recently we have reported[1] the preparation of 1 - aryl - 3 - formyl - 2(1H) - pyridinethiones from the glutacondialdehyde anion **1**[2] and aryl isothiocyanates. In order to investigate the generality of this reaction **1** was reacted with a number of alkyl and acyl isothiocyanates. Whereas the alkyl isothiocyanates gave rise to 1 - alkyl - 3 - formyl - 2(1H) - pyridinethiones **2**, the acyl isothiocyanates in most cases yielded O-acylated glutacondialdehyde derivatives (see Schemes 1 and 2).

These new and potentially useful pyridine derivatives seem inaccessible by known procedures,[3] e.g. alkylation of 2(1H)-pyridinethiones gives rise to 2-alkylthio substituted compounds and arylation is generally not possible.

RESULTS AND DISCUSSION

1 - Alkyl - 3 - formyl - 2(1H) - pyridinethiones **2**. The reaction of the glutacondialdehyde anion (**1**, sodium or potassium salt) with alkyl isothiocyanates gave rise to 1 - alkyl - 3 - formyl - 2(1H) - pyridinethiones (**2**, cf. Scheme 1).

Due to the low solubility of the salt **1** in organic solvents of low polarity, the reactions were run in *N,N*-dimethylformamide or dimethyl sulfoxide. In the aromatic series[1] the exothermic reaction took place at room temperature, whereas an elevated temperature (*ca.* 80°C) was necessary to complete the reaction in the aliphatic series. The yields were in some cases quantitative and with exception of **2g** (R = tert-butyl) in the other cases satisfactory (cf. Table 1 and Ref. 1). In **2g** strong steric interaction between the thiono sulfur atom and the 1 - tert - butyl group is present in any conformation of the substituent and this may be the reason for the low yields of this derivative.



	R (alkyl)		R (aryl)*
2a	methyl	2j	phenyl
2b	ethyl	2k	3 - methylphenyl
2c	propyl	2l	3 - fluorophenyl
2d	*iso* - propyl	2m	4 - fluorophenyl
2e	*iso* - butyl	2n	1 - napthyl
2f	*sec* - butyl	2o	2 - napthyl
2g	*tert* - butyl		
2h	cyclohexyl		
2i	allyl		

*The synthesis of **2j** to **2o** was reported elsewhere.

Scheme 1.

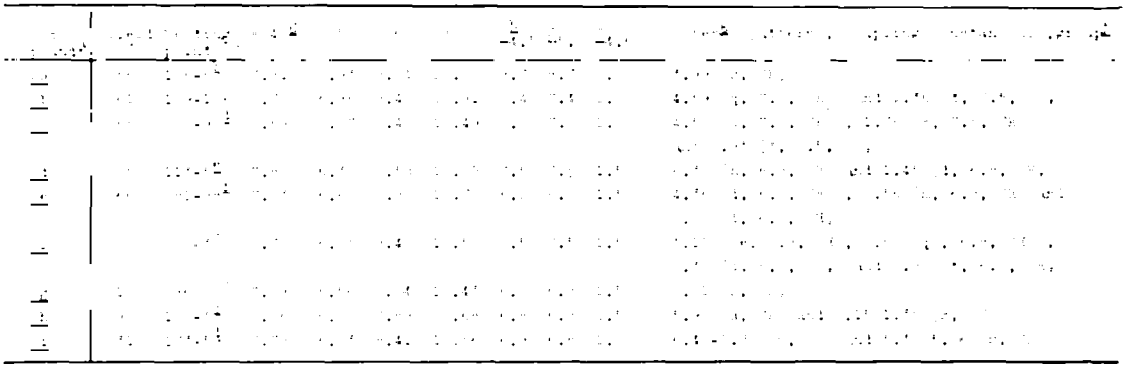
Structure of **2**. In the mass spectra relatively abundant molecular ions were observed. The fragmentation modes were as expected for 1 - substituted - 3 - formyl - 2(1H) - pyridinethiones.[4] The IR spectra exhibited bands at 1671–1691 cm^{-1} (C=O), 1600–1630 cm^{-1} (C=C) and 1073–1120 cm^{-1} (N–C=S). In the ^{1}H NMR spectra of **2** the ring protons gave rise to an ABX system (cf. Table 1). However, as $J_{4,5}$ is equal to $J_{5,6}$ the pattern from these protons was very simple with H(4) and H(6) as doublets of doublets at δ = 7.66–7.99 and 7.88–8.58 ppm, respectively, and H(5) as a triplet at δ = 6.30–6.94 ppm. The chemical shifts and the magnitudes of the coupling constants were as expected for a 3 - substituted - 2(1H) - pyridinethione or -one.[5]

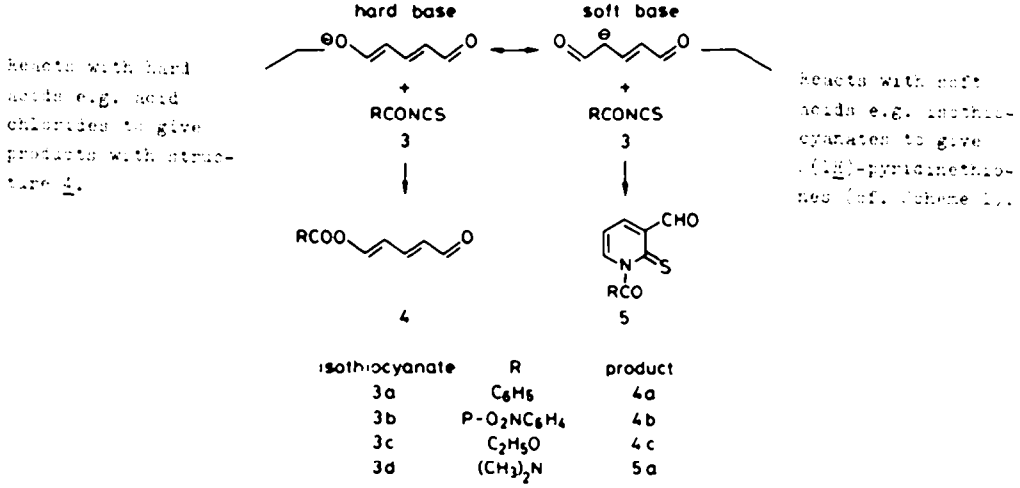
Reaction of **1** *with acyl isothiocyanates* **3**. According to the principle of hard and soft acids and bases (HSAB)[6] the carbanion center (C(2)) in **1** is a softer base than the oxygen anion center (RO , cf. Scheme 2). When only one electrophilic center is present in the other reagent as in acid chlorides (hard acid) and alkyl or aryl isothiocyanates (soft acid) the reaction course may be predicted on basis of the HSAB principle. The subsequent cyclization of the intermediate from the reaction of **1** and isothiocyanates forming the quasiaromatic 2(1H)-pyridinethione ring system is expectable (cf. Scheme 1).

In acyl isothiocyanates two electrophilic centers are present. The carbonyl carbon atom is classified as a hard acid, whereas the thiocarbonyl carbon atom is a soft acid. Consequently, a reaction is predicted to take place between either C(2) in the anion and the thiocarbonyl carbon atom or RO and the carbonyl carbon atom. On basis of the HSAB principle it seems impossible to decide, which of the two reaction paths will be the dominant one.

The reaction of the glutacondialdehyde anion **1** with acyl isothiocyanates (**3a** to **3c**) gave rise to the *O*-acylated glutacondialdehyde derivatives[2] (**4a** to **4c**), whereas **3d** yielded the 2(1H)-pyridinethione (**5a**) (cf. Scheme 2). An explanation for this difference in reaction course is that

Table 1. 1-Alkyl-3-formyl-2(1H)-pyridinethiones.





Scheme 2.

the electrophilic character of the carbonyl carbon atom in **3d** is decreased because of the lone-pair on the neighbouring nitrogen atom (cf. amides). As predicted from the HSAB principle the chloride corresponding to **3d** gave rise to a product of type **4**.

The spectroscopic properties of the products (**4a** to **4c** and **5a**) were in accordance with the proposed structures (cf. Experimental section).† To confirm the structure of **4c** the compound was also prepared from the corresponding chloride.

EXPERIMENTAL

Microanalyses were carried out in the Microanalytical Department of the University of Copenhagen.

Instrumentation. IR: Perkin Elmer 457. UV: Beckman ACTA III. ^{1}H NMR: Jeol C-60 HL and Bruker HX-60. MS: AEI MS-902. The melting points are uncorrected.

†Previously, the all-trans configuration was assigned to the glutacondialdehyde derivatives.[2]

General procedure for the preparation of 1 - alkyl - 3 - formyl - 2(1H) - pyridinethiones (2a to 2l)

The sodium salt of glutacondialdehyde[2] (**1**, 0.01 mole) and the appropriate isothiocyanate[3] (0.01 mole) in DMSO (10 ml) or DMF were heated at 70–80°C for 1 h. The dark reaction mixture was added to water (100 ml) and the resulting solution was continously extracted with ether for 20 h. The extract was dried and evaporated *in vacuo*, yielding the 2(1H)-pyridinethiones **2a** to **2l** (cf. Scheme 1 and Table 1).

Analyses: **2a** (Found: C, 54.90; H, 4.46; N, 9.18; S, 21.07. C_6H_5NOS requires: C, 54.88; H, 4.61; N, 9.14; S, 20.93), **2b** (Found: C, 57.50; H, 5.55; N, 8.41; S, 19.15. C_6H_6NOS requires: C, 57.49; H, 5.39; N, 8.38; S, 19.16), **2c** (Found: C, 59.70; H, 6.19; N, 7.75; S, 17.48. $C_8H_{11}NOS$ requires: C, 59.65; H, 6.08; N, 7.74; S, 17.68), **2d** (Found: C, 59.70; H, 6.19; N, 7.64; S, 17.52. $C_8H_{11}NOS$ requires: C, 59.65; H, 6.08; N, 7.74; S, 17.68), **2e** (Found: C, 61.50; H, 6.64; N, 7.05; S, 16.60. $C_{10}H_{13}NOS$ requires: C, 61.54; H, 6.67; N, 7.18; S, 16.41), **2f** (Found: C, 61.35; H, 6.83; N, 7.23; S, 16.20. $C_{10}H_{13}NOS$ requires: C, 61.54; H, 6.67; N, 7.18; S, 16.41), **2g** (Found: C, 61.50; H, 6.61; N, 7.15; S, 16.58. $C_{10}H_{13}NOS$ requires: C, 61.54; H, 6.67; N, 7.18; S, 16.41), **2h** (Found: C, 65.10; H, 6.94; N, 6.20; S, 14.35. $C_{12}H_{15}NOS$ requires: C, 65.16; H, 6.79; N, 6.34; S, 14.48) and **2i** (Found: C, 60.25; H, 5.11; N, 7.78; S, 17.64. C_8H_7NOS requires: C, 60.31; H, 5.06; N, 7.82; S, 17.89%).

N,N - *Dimethylcarbamoyl* - 3 - *formyl* - 2(1H) - *pyridinethione* **5a**

The potassium salt of glutacondialdehyde (2.72 g) in DMF (25 ml) was mixed with *N,N*-dimethylcarbamoyl isothiocyanate at 0° and stirred for 5 min. The red reaction mixture was poured on water (300 ml) and chloroform (300 ml). Isolation and work up of the chloroform phase yielded **5a** as orange crystals 1.97 g, (47%) mp 113–5°/benzene-ether. ^{1}H NMR (60 MHz, $CDCl_3$): 2.93 and 3.12 (6H two s), 6.79 (1H, t, *J* 6.8 Hz), 7.72 (1H, *J* 6.8 and 1.5 Hz), 7.80 (1H, dd, *J* 6.8 and 1.5), 10.61 (CHO, s). UV [abs. ethanol (log ε)]: 375 (3.38), 319 (3.70), 291 (3.69) nm. IR (KBr): 1687 (CHO), 1740 (CO) cm^{-1}. Found: C, 51.40; H, 4.71; N, 13.33; S, 15.18. $C_9H_{10}N_2O_2S$ requires: C, 51.41; H, 4.79; N, 13.32; S, 15.25%.

O - (N,N - *Dimethylcarbamoyl*) - 5 - *hydroxy* - trans - 2, trans - 4 - *pentadienal*

The potassium salt of glutacondialdehyde (7.8 g) and *N,N*-dimethylcarbamoyl chloride (5.4 g) were stirred in DMSO (20 ml) at 5° for ½ h. The reaction mixture was added to ice cold water (100 ml) and the precipitated crystals were collected, washed with water and dried (20°/1 mm Hg). Yield 2.94 g, nearly colourless unstable crystals. Recrystallization from ether-pentane (and activated carbon) gave colourless needles m.p. 88–91° d (stable when kept in the freezer). ^{1}H NMR (60 MHz, $CDCl_3$):† δ ppm 9.54 (H-1, d, *J* 7.6 Hz), 6.12 (H-2, dd, *J* 7.6 and 15.8 Hz), 7.15 (H-3, dd, *J* = 12.8 and 15.8 Hz), 6.16 (H-4, dd, *J* = 12.8 and 15.8 Hz), 7.81 (H-5, d, *J* = 12.8 Hz). UV [ethanol (log ε)] 282 (4.53), IR (KBr): 2830, 2760, 2710 (CHO), 975 (*trans*-CH=CH) cm^{-1}. Found: C, 56.90; H, 6.77; N, 8.16. $C_8H_{11}NO_3$ requires: C, 56.79; H, 6.55; N, 8.28%.

5 - *Hydroxy* - trans - 2, trans - 4 - *pentadienal benzoate* **4a**

To **1** (1.56 g) in DMF (20 ml) at −15° was added benzoyl isothiocyanate (1.63 g). After 15 min the reaction mixture was added to ice cold water (100 ml) and the precipitated white crystals were isolated, yield 1.8 g. A sample recrystallized from ethanol-water had identical m.p. and spectra with authentic **3a** obtained from **1** and benzoyl chloride.[2a]

5 - *Hydroxy* - trans - 2, trans - 4 - *pentadienal* p - *nitrobenzoate* **4b**

Prepared as above (yield 79%). White needles m.p. 180–3°/abs. ethanol. ^{1}H NMR (60 MHz, DMSO-d_6): 9.51 (H-1, d, *J* 8 Hz), δ 6.40 (H-2, dd, *J* 8 and 15 Hz), 7.60 (H-3, dd, *J* 11 and 15 Hz), 6.72 (H-4, dd, *J* 11 and 12 Hz), 8.20 (H-5, d, *J* 12 Hz), 8.25 (C_6H_4, s). UV [abs. ethanol (log ε)]: 364 (4.14), 273 (4.39) nm. IR (KBr): 2835 (CHO) 981 (*trans*-C=C) cm^{-1}. Found: C, 58.10; H, 3.66; N, 5.97. $C_{12}H_9NO_5$ requires: C, 58.30; H, 3.67; N, 5.67%.

O - *Ethoxycarbonyl* - 5 - *hydroxy* - trans - 2, trans - 4 - *pentadienal* **4c**

Method A. **1** (8 g) and ethoxycarbonyl isothiocyanate[7] (6.5 g) were stirred in DMSO (15 ml) at 0°. After 15 min the reaction mixture was added to water (100 ml) and the precipitated brown crystals were isolated, yield 5.49 g. The physical and spectroscopic properties were in agreement with those of the product obtained by method B.

Method B. To **1** (7.8 g) in DMF (20 ml) at 5° was added chloroformic acid ethyl ester (5.5 g). After 5 min the reaction mixture was added to ice cold water (100 ml) and the precipitated white crystals were isolated, yield 6.31 g. Sublimation (50°/1 mm Hg) yielded **4c** as colourless unstable crystals m.p. 63–64°. A sample recrystallized from ether pentane had m.p. 67–69°. ^{1}H NMR (60 MHz, DMSO-d_6): δ 9.46 (H-1, d, *J* 7.5 Hz), 6.11 (H-2, dd, *J* 7.5 and 15.0 Hz), 7.36 (H-3, dd, *J* 12.0 and 15.0 Hz), 6.31 (H-4, dd, *J* 12.0 and 15.0 Hz), 7.71 (H-5, d, *J* 12.0 Hz). UV [abs. ethanol (log ε)]: 274 (4.57) nm. 112 (KBr): 2830, 2759, 2710 (CHO), 985 (*trans*-C=C) cm^{-1}. Found: C, 56.50; H, 6.07. $C_8H_{10}O_4$ requires: C, 56.46; H, 5.92%.

†The numbering of the glutacondialdehyde derivatives have been defined in Ref. 2a.

REFERENCES

[1] J. Becher and E. G. Frandsen, *Acta Chem. Scand.* **B30**, 0000 (1976).

[2a] J. Becher, *Acta Chem. Scand.* **26**, 3627 (1972); [b] J. Becher, N. Haunsø and T. Petersen, *Acta Chem. Scand.* **29**, 124 (1975).

[3a] H. L. Yale, In *Pyridine and Its Derivatives* Part Four. E. Klingsberg (A. Weissberger) ed., Interscience, NY. 1964; [b] H. L. Yale, In *Pyridine and Its Derivatives* (Suppl. Part Four) R. A. Abramovitch (A. Weissberger) ed., Interscience, NY. 1975.

[4] R. Lawrence and E. S. Waight, *J. Chem. Soc. B.* 1 (1968).

[5] W. E. Stewart and T. H. Siddall, *J. Phys. Chem.* **74**, 2027 (1970).

[6] R. G. Pearson, *Hard and Soft Acids and Bases*, Dowden, Hutchinson & Ross, Pennsylvania (1973).

[7] The isothiocyanates were prepared according to well-known procedures, see for example, *Methoden der Organischen Chemie, Houben–Weyl*, Vol. **9**, pp. 867–884, Georg Thieme, Stuttgart (1955).