Pyridinethiones. IX Preparation of Ricinidine, Thioricinidine and Other 2(1*H*)-Pyridones and -thiones Related to Nicotinic acid

Jan Becher* [1], Tea Johansen and Maged Aziz Michael [2]

Department of Chemistry, Odense University, Campusvej 55, DK5230
Odense M, Denmark

Received April 18, 1983

2(1*H*)-Pyridones and -thiones related to 1-substituted nicotinic acid derivatives have been prepared *via* the corresponding 1-substituted-3-formyl-2(1*H*)-pyridones and -thiones. A number of synthetic procedures for the interconversion of functional groups in these nicotinic acid derivatives are given *i.e.* preparation of the aldoximes, nitriles, carboxamides and carboxylic acids as well as the 3- hydroxyalkyl derivatives. The course of the basic peroxide oxidation of the 1-substituted-3-formyl-2(1*H*)-pyridinethiones is found to be very dependent upon the electronegativity of the 1-substituent. A preparation of ricinidine is also described.

J. Heterocyclic Chem., **21**, 41 (1984).

During our work on the chemistry of 2(1*H*)-pyridinethiones, [3] it became clear that we had an excellent starting material for preparation of a number of simple 2(1*H*)-pyridones related to the alkaloid ricinidine, and hence access to potentially biologically active compounds. In view of the current interest in simple pyridones [4], this paper reports a study of the redox reactions of 3-formyl-2(1*H*)-pyridinethiones, including preparation of a number of new pyridines related to the alkaloid ricinidine and to nicotinic acid by reactions of the 3-formyl group.

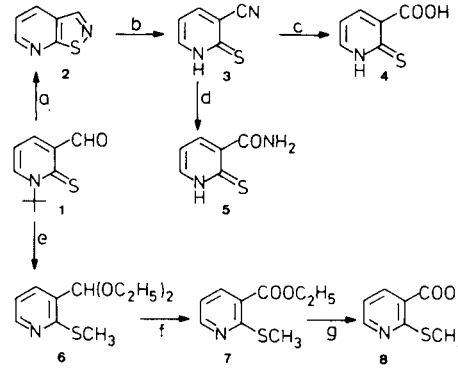
Results.

Nicotinic Acid Derivatives.

Scheme 1 describes the preparation of nicotinic acid derivatives from 3-formyl-2(1*H*)-pyridinethiones:

Scheme 1

a) Ref 3, b) $NaOCH_3$, c) H_3PO_4, d) H_2SO_4, e) Ref 4, f) hv, NBS, g) HCl



Preparation of 3-cyano-2(1*H*)-pyridinethione **(3)** was ac-

Table 1

3-Aldoximido-2(1*H*)-pyridinethiones **12**

Compound	Molecular formula	Yield %	mp °C (Solvent)	Analyses Found/(Calcd). C	H	N	Mass spectra m/e (%)
12a	$C_{12}H_{10}N_2OS$	83	163-164	62.75	4.34	12.17	230 (0.61, M^+)
	(230.28)		(Methanol-water)	(62.59)	(4.38)	(12.16)	213 (100)
12b	$C_{12}H_8Cl_2N_2OS$	81	195-196	48.47	2.63	9.42	299 (0.18, M^+)
	(299.17)		(Ethanol)	(48.18)	(2.70)	(9.36)	281 (100)
12c	$C_{12}H_9N_3O_3S$	72	205-206	52.46	3.59	15.55	275 (0.8, M^+)
	(275.28)		(Ethanol)	(52.36)	(3.30)	(15.26)	258 (100)
12d	$C_{14}H_{15}N_3OS$	68	184-185	61.60	5.42	15.66	273 (4, M^+)
	(273.35)		(Ethanol)	(61.52)	(5.53)	(15.37)	256 (100)
12e	$C_{12}H_9FN_2OS$	76	160-162	58.16	3.53	11.35	248 (0.53, M^+)
	(248.27)		(Benzene)	(58.05)	(3.65)	(11.28)	231 (100)
12f	$C_{13}H_{12}N_2OS$	73	180-181	63.71	4.91	11.28	244 (0.47, M^+)
	(244.31)		(Ethanol)	(63.91)	(4.95)	(11.47)	227 (100)
12g	$C_9H_{12}N_2OS$	61	130-131	55.22	6.18	14.06	196 (0.88, M^+)
	(196.27)		(Methanol-water)	(55.08)	(6.16)	(14.27)	179 (56), 137 (100)
12h	$C_8H_{10}N_2OS$	60	114-115	52.79	5.56	15.48	182 (0.58, M^+)
	(182.24)		(Cyclohexane)	(52.73)	(5.53)	(15.37)	165 (100)
12i	$C_7H_8N_2OS$	65	178-179	49.95	4.89	15.93	168 (0.95, M^+)
	(168.21)		(Ethanol)	(49.98)	(4.79)	(16.65)	151 (100)

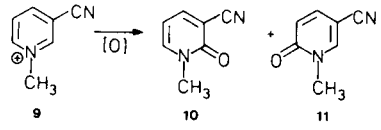
ir (potassium bromide): 3500-3100 cm^{-1} br (OH) for compounds **12a-12i**

complished starting [6] from the isothiazolo[5,4-*b*]pyridine (**2**). The acid **4** and the amide **5** was then obtained by standard methods. The 2-methylthionicotinic acid (**8**) was obtained from the acetal **6** [5] by irradiation in the presence of *N*-bromosuccinimide (NBS). This method, previously described by Marvell and Joncick [7] has, to our knowledge not been used for the oxidation of heterocyclic acetals. It is important to note that the sulfide moiety is not oxidized under these reaction conditions.

Preparation of Pyridines Related to Ricinidine.

The alkaloid 1-methyl-3-cyano-2(1*H*)-pyridone (ricinidine) (**10**) has been isolated from *Trewia nudiflora* L. by Ganguly [8]. Späth and Koller [9] obtained **10** by degradation of the alkaloid ricinine, and later Robinson and Cepurnek [10] reported the synthesis of ricinidine (**10**) in 31% yield by oxidation of nicotinonitrile methiodide, **10** was later obtained by Mukherjee and Chatterjee [11] by the same method. Möhrle and Weber [12] then reinvestigated this oxidation in detail. They concluded that normally a hexacyanoferrate(III) oxidation of 3-substituted-1-methylpyridinium compounds yields the two isomeric 2(1*H*)-pyridones, **10** and **11** (ricinidine and nudiflorin):

Scheme 2

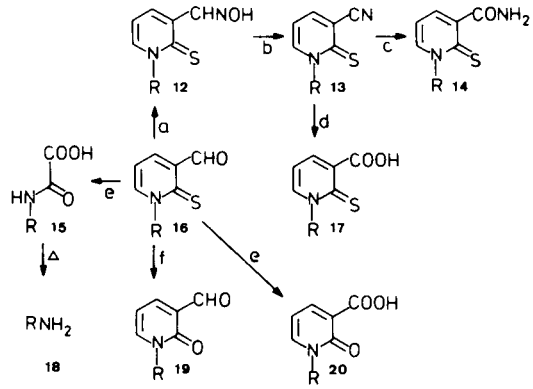


Furthermore they found that hydrolyses of nitriles such as **10** and **11** often gave rise to mixtures of the corresponding amides and acids [13]. Consequently it may be concluded, that better methods for the preparation of amides of this type are of interest.

Scheme 3 describes the preparation of ricinidine and thioricinidine derivatives and other related hitherto inaccessible 2(1*H*)-pyridones and -thiones:

Scheme 3

a) H_2NOH, b) $Al_2O_3/C_6H_5CH_3$, c) conc H_2SO_4, d) H_3PO_4, e) H_2O_2/OH f) $DMSO/H_2SO_4$



Starting Compounds **16**.

	R
16a	Phenyl [20a]
16b	2,6-Dichlorophenyl [20a]
16c	4-Nitrophenyl
16d	4-*N*,*N*-Dimethylaminophenyl
16e	2-Fluorophenyl
16f	2-Methylphenyl
16g	1-Naphthyl [20a]
16h	2-Naphthyl [20a]
16i	2,6-Dimethylphenyl [20a]
16j	Isopropyl [20c]
16k	Ethyl [20c]
16l	Methyl [20c]
16m	α-Methylbenzyl [20b]
16n	Cyclohexyl [20c]

1-Substituted-3-aldoximido-2(1*H*)-pyridinethiones **12**.

	R
12a	Phenyl
12b	2,6-Dichlorophenyl
12d	4-Nitrophenyl
12d	4-*N*,*N*-Dimethylaminophenyl
12e	2-Fluorophenyl
12f	2-Methylphenyl
12g	Isopropyl
12h	Ethyl
12i	Methyl

1-Substituted-3-cyano-2(1*H*)-pyridinethiones **13**.

	R
13a	Phenyl
13b	2,6-Dichlorophenyl
13c	4-Nitrophenyl
13d	4-*N*,*N*-Dimethylaminophenyl
13e	2-Fluorophenyl
13f	2-Methylphenyl
13g	Isopropyl
13h	Ethyl
13i	Methyl (thioricinidine)

1-Substituted-3-carbamyl-2(1*H*)-pyridinethiones **14**.

	R
14a	Phenyl
14b	2,6-Dichlorophenyl
14c	4-*N*,*N*-Dimethylaminophenyl
14d	2-Methylphenyl
14e	Isopropyl

1-Substituted-3-carboxy-2(1*H*)-pyridinethiones **17**.

	R
17a	Phenyl
17b	2,6-Dichlorophenyl
17c	4-Nitrophenyl
17d	4-*N*,*N*-Dimethylaminophenyl
17e	Isopropyl

1-Substituted-3-formyl-2(1*H*)-pyridones **19**.

	R
19a	Methyl
19b	Isopropyl
19c	α-Methylbenzyl
19d	Cyclohexyl
19e	Phenyl
19f	1-Naphthyl
19g	2-Naphthyl

1-Substituted-3-carboxy-2(1*H*)-pyridones **20**.

	R
20a	Methyl
20b	Isopropyl
20c	α-Methylbenzyl
20d	Cyclohexyl
20e	2,6-Dimethylphenyl

1-Substituted-3-aldoximido-2(1*H*)-pyridone **21**.

	R
21	Methyl

1-Substituted-3-cyano-2(1*H*)-pyridone **22**.

	R
22	Methyl (ricinidine)

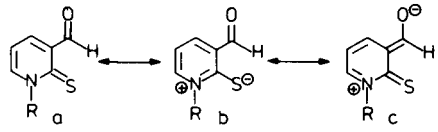
Other Oxidation Products, **15** and **18**.

	R
15a	Phenyl
15b	1-Naphthyl
18	4-Nitroaniline

In the thione series the nitriles **13** could in all cases be prepared in a clean reaction from the corresponding oximes by dehydration with aluminum oxide in refluxing toluene, dehydration by other methods such as acetic anhydride etc. did not work. Hydrolyses to the acids **17** was carried out with concentrated sulfuric acid while the amides **14** were obtained by reflux of the required nitriles in phosphoric acid. Preparation of ricinidin (**22**) from the oxime **21** by dehydration with aluminum oxide in refluxing toluene required longer reaction time than for the thione **13** in a less clean reaction, this reaction was not further investigated in the pyridone series.

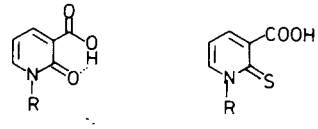
The course of oxidation with peroxide in sodium hydroxide was found to be very dependent upon the 1-substituent in the starting 3-formyl-2(1*H*)-pyridinethiones (**16**). Thus oxidation of the 1-alkylthiones **16** (R = alkyl) resulted in fair yields of the expected acids **20**. However in the aromatic series (R = aryl) oxidation of the thiones **16** yielded either the oxalic acid amides **15** or the amines **18** as a result of ring oxidation under these reaction conditions. This change in reactivity for different 1-substituents R is probably due to different electron distributions at the chalcogen atom and at the formyl group:

Scheme 4



An indication that this change is in fact due to a mesomeric effect was seen in the oxidation of 1-(2,6-dimethylphenyl)-3-formyl-2(1*H*)-pyridinethione (**16i**) which gave a fair yield of 1-(2,3-dimethylphenyl)-3-carboxy-2(1*H*)-pyridone (**20e**). In this case the 1-aryl group can not come into conjugation with the pyridine ring due to steric hindrance, and hence reacts as the compounds in the alkyl series. A similar change in the reactivity was seen in the formation of the oximes **12**; reaction of the aldehydes **16** with hydroxylamine was quite fast for R = aryl, while the same reaction in the alkyl series was very slow. A mesomer such as *c* in scheme 4 is stabilized by R = alkyl while the mesomer *a* corresponds to R = aryl. It may therefore be concluded that when R = an electron donating group, reactions occur according to *b* or *c*, while R = an electronegative group gives reactions according to the mesomer *a*.

We have previously described [15] preparation of some 3-formyl-2(1*H*)-pyridones *via* the acetals. The more effective and simple Mikolajczyk and Luczak [14] method was used in the present work for oxidation of the thiones **16** with dimethylsulfoxide/sulfuric acid. This method gave the required 3-formyl-2(1*H*)-pyridones **19** in fair yields; the method can easily be used for large scale preparations. The table gives the pk_a values for some of the nicotinic acid derivatives **17** and **20**:



Compound	pK_a	Compound	pK_a
20a	5.3	**4**	4.0
20b	5.4	**17a**	4.1
20d	5.5	**17c**	3.3
20e	5.1	**17e**	4.7

Values for the pyridones **20** corresponds to the pk_a = 5.30 found for 2(1*H*)-pyridone-3-carboxylic acid [16]. The missing hydrogen-bond in the thiones **17** gives a pk_a value similar to the pk_a = 4.85 found for nicotinic acid [16]. (All values determined by uv in water at *p*H = 2 and *p*H = 8.4.)

Reductions and Grignard Reactions.

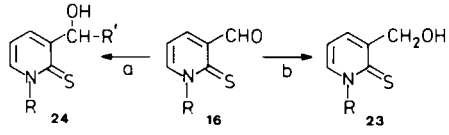
We have previously [20a] described the borohydride reduction of 1-substituted-3-formyl-2(1*H*)-pyridinethiones (**16**) to the corresponding primary alcohols **23**:

Scheme 5

a) R'MgX, b) Mo/H_2

Compounds **24** Compounds **23**

24a R = Phenyl, R' = methyl **23a** R = cyclohexyl
24b R = phenyl, R' = phenyl **23b** R = phenyl



This reduction can also be carried out by catalytic reduction with a molybdenum catalyst and hydrogen at high pressure, while catalytic reduction with Raney-nickel results in complete reduction to an *N*-substituted-3-methylpiperidine [17]. The secondary alcohols **24** were obtained *via* the Grignard reactions in fair yields.

EXPERIMENTAL

Microanalyses were carried out at NOVO A/S Bagsvaerd by Mr. Rolf Amsler. The instrumentation is the following: ^{1}H nmr, Jeol JNM-PMX60 ^{13}C nmr, Jeol FX60; mp Büchi apparatus (uncorrected); ir, Perkin Elmer 580; uv, Varian Cary 219. The aluminum oxide used was Woelm neutral. The mass spectra were determined on Varian MAT 311A. All yields are on recrystallized products.

3-Cyano-2(1*H*)-pyridinethione (**3**).

Isothiazolo[4,5-*b*]pyridine (**2**) (0.9 g) was added to a solution of sodium (0.2 g) in methanol (55 ml). This mixture was refluxed for four hours followed by evaporation *in vacuo*. The resulting white sodium salt was dissolved in water (15 ml) and the yellow precipitate filtered and dried. Recrystallization from 2-methyoxyethanol yielded **3** as yellow prisms, 0.65 g (72%) mp 234-236° dec (sealed tube); ir (potassium bromide): 2225 (CN) cm^{-1}; uv (absolute ethanol): 401 (3.50) 306 nm (4.30).

Anal. Calcd. for $C_6H_4N_2S$: C, 52.93; H, 2.96; N, 20.57. Found: C, 52.87; H, 2.78; N, 20.49.

3-Carboxy-2(1*H*)-pyridinethione (**4**).

3-Cyano-2(1*H*)-pyridinethione (**3**) (0.3 g) was refluxed in with sodium hydroxide (0.4 g) in 70% ethanol (5 ml) for fourteen hours, followed by evaporation *in vacuo*. Addition of water (3 ml) and hydrochloric acid (4*M*) precipitates the acid **4**, which was filtered and dried, 0.3 g (88%), mp 261-264° dec (water/ethanol), ref [19] gives mp 260-261°. Hydrolysis of the nitrile **6** may also be carried out with phosphoric acid. Thus **3** (1.36 g) was refluxed in 89% phosphoric acid for 10 minutes whereupon the reaction mixture was added to ice (10 g), filtered, washed with water and dried to yield 1.2 g (77%) mp 265-266° (methanol).

3-Carbamyl-2(1*H*)-pyridinethione (**5**).

A suspension 3-cyano-2(1*H*)-pyridinethione (**3**) (1.36 g) in concentrated sulfuric acid (10 ml) was stirred 24 hours at 60°. The reaction mixture was added to ice (10 g) and continuously extracted with chloroform (10 hours). The extract was dried (magnesium sulfate), concentrated *in vacuo* and the product crystallized from ethanol to give yellow crystals of **5** 1.2 g (80%) mp 231-232°; ^{1}H nmr (in DMSO-d_6): 7.5-7.7 (m, 1H), 8.4-8.5 (dd, 1H), 8.9-9.0 (dd, 1H), 9.5 (s, br, NH_2) ppm from TMS; ms: 154 (2% M$^+$), 152 (100%); ir (potassium bromide): 1650 cm^{-1} ($CONH_2$).

Anal. Calcd. for $C_6H_6N_2OS$: C, 46.74; H, 3.92; N, 18.17; S, 20.79. Found: C, 46.47; H, 3.70; N, 18.06; S, 20.74.

2-Methylthionicotinic Acid Ethyl Ester (**7**).

A mixture of 2-methylthiopyridine-3-carboxaldehyde diethylacetal (**3**) (0.01 mole), *N*-bromosuccinimide (0.011 mole) and carbon tetrachloride (16 ml) was refluxed in a pyrex flask under a 250 W tungsten lamp for 3.25 hours and allowed to stand at room temperature overnight. Succinimide was filtered off and the filtrate concentrated *in vacuo* to give a yellow oil which was distilled in a "kuglerohr" still. The resulting colourless crystals of **7** were recrystallized from hexane, yield 64% mp 42-44°; ir (potassium bromide): 1700 (C=O) cm^{-1}; uv (absolute ethanol): 320 (3.51), 268 nm (4.11).

Anal. Calcd. for $C_9H_{11}NO_2S$: C, 54.80; H, 5.62; N, 7.10; S, 16.26. Found: C, 54.74; H, 5.89; N, 6.90; S, 15.92.

Table 2

3-Cyano-2(1*H*)-pyridinethiones **13**

Compound	Molecular formula	Yield %	mp °C (Solvent)	Analyses Found/(Calcd) C	H	N	Mass spectra m/e (%)
13a	$C_{12}H_8N_2S$ (212.27)	52	230-231 (Toluene)	67.75 (67.90)	3.69 (3.80)	13.14 (13.20)	212 (40, M$^+$) 211 (100)
13b	$C_{12}H_6Cl_2N_2S$ (281.16)	50	230-232 (Methanol)	51.34 (51.26)	2.12 (2.15)	9.86 (9.96)	281 (0.44, M$^+$) 247 (38), 245 (100)
13c	$C_{12}H_7N_3O_2S$ (257.27)	55	269-270 (Toluene)	56.07 (56.02)	2.66 (2.74)	16.31 (16.33)	257 (53, M$^+$) 256 (100), 210 (47)
13d	$C_{14}H_{13}N_3S$ (255.34)	58	271-272 (Toluene)	65.75 (65.86)	4.99 (5.13)	16.15 (16.46)	255 (99, M$^+$) 152 (100)
13e	$C_{12}H_7FN_2S$ (230.26)	52	184-185 (Ethanol)	62.55 (62.60)	2.99 (3.06)	12.15 (12.17)	230 (100, M$^+$)
13f	$C_{13}H_{10}N_2S$ (226.30)	52	130-132 (Methanol)	68.92 (69.00)	4.25 (4.45)	12.42 (12.38)	226 (49, M$^+$) 211 (100)
13g	$C_9H_{10}N_2S$ (178.25)	57	154-155 (Ethanol)	60.82 (60.64)	5.68 (5.65)	15.60 (15.72)	178 (45, M$^+$) 136 (100)
13h	$C_8H_8N_2S$ (164.23)	60	115-116 (Ethanol)	58.32 (58.51)	4.86 (4.90)	17.16 (17.06)	164 (89, M$^+$) 136 (100)
13i	$C_7H_6N_2S$ (150.20)	53	162-163 (Ethanol)	56.20 (55.98)	4.06 (4.03)	18.84 (18.65)	150 (46, M$^+$) 108 (100)

ir (potassium bromide): 2210 cm^{-1} s (CN) for compounds **13a-13i**

Table 3

3-Carbamyl-2(1*H*)-pyridinethiones **14**

Compound	Molecular formula	Yield %	mp °C (Solvent)	Analyses Found/(Calcd) C	H	N	Mass spectra m/e (%)
14a	$C_{14}H_{10}N_2OS$ (230.28)	81	228-229 (Ethanol)	62.45 (62.59)	4.35 (4.38)	12.07 (12.16)	230 (40, M^+) 229 (100)
14b	$C_{12}H_8Cl_2N_2OS$ (299.17)	71	279-280 (Ethanol)	47.92 (48.18)	2.60 (2.69)	9.00 (9.36)	299 (0.7, M^+) 263 (100)
14c	$C_{14}H_{15}N_3OS$ (273.35)	80	275-276 (Ethanol)	61.12 (61.52)	5.51 (5.53)	14.96 (15.37)	273 (100, M^+) 152 (78)
14d	$C_{13}H_{12}N_2OS$ (244.31)	80	226-227 (Ethanol)	63.85 (63.91)	4.97 (4.95)	11.42 (11.47)	244 (28, Me^+) 229 (100)
14e	$C_9H_{12}N_2OS$ (196.27)	68	142-143 (Ethanol)	55.33 (55.08)	6.03 (6.16)	13.96 (14.27)	196 (76, M^+) 154 (39), 137 (100)

ir (potassium bromide): 3450-3160 cm^{-1}s ($CONH_2$) and 1655-1670 cm^{-1}s (CO) for compounds **14a-14e**.

Table 4

3-Carboxy-2(1*H*)-pyridinethiones **17**

Compound	Molecular formula	Yield %	mp °C (Solvent)	Analyses Found/(Calcd) C	H	N	Mass spectra m/e (%)
17a	$C_{12}H_9N_2OS$ (231.27)	83	255-256 (Ethanol)	62.23 (62.32)	3.78 (3.92)	5.93 (6.06)	231 (42, M^+) 230 (100) 186 (22)
17b	$C_{12}H_7Cl_2NO_2S$ (300.16)	72	253-255 (Ethanol)	48.22 (48.02)	2.35 (2.35)	4.55 (4.67)	264 (100) 220 (135)
17c	$C_{12}H_8N_2O_4S$ (276.27)	78	218-220 (Ethanol)	52.23 (52.17)	2.89 (2.91)	10.21 (10.14)	276 (40, M^+) 275 (100) 232 (19)
17d	$C_{14}H_{14}N_2O_2S$ (274.34)	72	258-260 (Ethanol)	61.25 (61.29)	5.17 (5.14)	10.33 (10.21)	274 (100, M^+) 273 (42) 230 (4)
17e	$C_9H_{11}NO_2S$ (197.25)	74	145-146 (Methanol)	54.72 (54.80)	5.65 (5.62)	6.98 (7.10)	197 (100, M^+) 149 (29) 153 (5)

ir (potassium bromide): 1705-1715 cm^{-1} s (CO) for compounds **17a-17e**.

Compound	UV Spectra (Absolute Ethanol): λ max nm (log ε)			
17a	390 (3.64)	304 (4.22)		
17b	347 (3.73)	300 (3.76)	267 (4.05)	243 (4.29)
17c		300 (4.16)	238 (4.17)	
17d	384 (3.58)	302 (4.17)	260 (4.29)	
17e	378 (3.50)	300 (4.11)		

2-Methylthiopyridine-3-carboxylic Acid (**8**).

2-Methylthionicotinic acid ethyl ester (**7**) (0.5 g) was refluxed in concentrated hydrochloric acid (25 ml) for six hours and evaporated to dryness *in vacuo*. The resulting hydrochloride was washed with sodium acetate solution and the product recrystallized from ethanol yielding 2-methylthionicotinic acid (**8**) as colourless crystals, 0.2 g (67%) mp 217-218°; ir (potassium bromide): 1670 cm^{-1} (CO); uv (absolute ethanol): 314 (3.50, 265 nm (4.10).

Anal. Calcd. for $C_7H_7NO_2S$: C, 49.68; H, 4.17; N, 8.28. Found: C, 49.58; H, 4.15; N, 8.29.

Synthesis of 1-Substituted-3-aldoximido-2(1*H*)-pyridinethiones **12**.

General Procedure.

Saturated sodium carbonate (10 ml) was added to a solution of the 1-substituted-3-formyl-2(1*H*)-pyridinethione **16** (0.01 mole) and hydroxylamine hydrochloride (0.02 mole) in ethanol (100 ml). The reaction mixture was heated under reflux for one hour and allowed to cool. The inorganic material was separated by filtration and washed several times with dry ether. The filterate was concentrated *in vacuo* and the product recrystallized from a suitable solvent to give **12** (Table 1).

Synthesis of 1-Substituted-3-cyano-2(1*H*)-pyridinethiones **13**.

General Procedure.

Neutral aluminum oxide (5 g) was added to a solution of the 1-substi-

Table 5

3-Formyl-2(1*H*)-pyridones **19**

Compound	Molecular formula	Yield %	mp °C (Solvent)	Analyses Found/(Calcd) C	H	N	Mass spectra m/e (%)
19a	$C_7H_7NO_2$	66	102-103	61.40	5.21	10.16	137 (2, M^+)
	(137.17)		(Cyclohexane)	(61.31)	(5.15)	(10.21)	109 (100)
19b	$C_9H_{11}NO_2$	63	115-117	65.27	6.69	8.42	165 (18, M^+)
	(165.19)		(Toluene)	(65.44)	(6.71)	(8.48)	95 (100)
19c	$C_{14}H_{13}NO_2$	61	126-131	see ref [15]			127 (12, M^+)
	(227.26)		(Cyclohexane)				105 (100)
19d	$C_{12}H_{15}NO_3$	69	99-101	70.07	7.65	6.90	224 (26, M^+)
	(205.26)		(Toluene)	(70.22)	(7.33)	(6.82)	56 (100)
19e	$C_{12}H_9NO_2$	66	153-157	see ref [15]			199 (11, M^+)
	(199.21)		(Toluene)				161 (100)
19f	$C_{16}H_{11}NO_2$	89	151-153	see ref [15]			249 (25, M^+)
	(249.26)		(Methyl-cyclohexane)				121 (100)
19g	$C_{16}H_{11}NO_2$	63	191-192	77.02	4.43	5.63	249 (33, M^+)
	(249.26)		(Methyl-cyclohexane)	(77.09)	(4.45)	(5.62)	221 (100)

ir (potassium bromide): 1680-1700 cm^{-1}s (CHO),, 1645-1660 cm^{-1}s (CO) for compounds **19a-19g**

Table 6

3-Carboxy-2(1*H*)-pyridones **20**

Compound	Molecular formula	Yield %	mp °C (Solvent)	Analyses Found/(Calcd) C	H	N	Mass spectra m/e (%)
20a	$C_7H_7NO_3$	61	182-184		see refs [8], [9]		153 (57, M^+)
	(153.14)		(2-Propanol)		and [21]		109 (100)
20b	$C_9H_{11}NO_3$	65	116-117	59.63	6.15	7.53	181 (23, M^+)
	(121.19)		(Water)	(59.66)	(6.12)	(7.73)	95 (100)
20c	$C_{14}H_{13}NO_3$	24	129-130	69.02	5.36	5.72	243 (19, M^+)
	(243.26)		(Ethanol-water)	(69.12)	(5.39)	(5.76)	105 (100)
20d	$C_{12}H_{15}NO_3$	39	181-183	64.98	6.81	6.28	221 (11, M^+)
	(221.26)		(2-Propanol)	(65.14)	(6.83)	(6.33)	122 (100)
20e	$C_{14}H_{13}NO_3$	55	147-149	68.78	5.34	5.90	243 (100, M^+)
	(243.26)		(2-Propanol)	(69.12)	(5.39)	(5.76)	

ir (potassium bromide): 3430-3440 cm^{-1}s (CO) for compounds **17a-17e**.

Compound	UV Spectra (Absolute Ethanol): λ max nm (log ε)	
20a	329 (3.99)	232 (3.70)
20b	331 (4.66)	234 (4.37)
20c	331 (3.94)	232 (3.66)
20d	332 (5.08)	231 (4.74)
20e	331 (3.63)	232 (3.44)

tuted-3-aldoximido-2(1*H*)-pyridinethione **12** (0.01 mole) in dry toluene. The mixture was heated under reflux for 1-2 hours. When all starting material was consumed (controlled by tlc), the reaction mixture was filtered and the toluene filterate was concentrated *in vacuo*. The crude product was crystallized from a suitable solvent to give **13** (Table 2).

Synthesis of 1-Substituted-3-carbamyl-2(1*H*)-pyridinthiones **14**.

A suspension of the 1-substituted-3-cyano-2(1*H*)-pyridinethione (**13**) (0.01 mole) in concentrated sulfuric acid (10 ml) was stirred for 24 hours at 60°. The reaction mixture was ice-cooled and added to crushed ice (10 g). The product was filtered, washed with water and dried. The product was crystallized from ethanol to give analytically pure **14** (Table 3).

Special Procedure, Compound **14c**.

The product did not precipitate. The solution was therefore extracted with chloroform (10 ml) dried (magnesium sulfate) and concentrated *in vacuo*, and the product recrystallized from ethanol to give analytically pure **14c**.

Synthesis of 1-Substituted-3-carboxy-2(1*H*)-pyridinethiones (**17**).

General Procedure.

A suspension of the 1-substituted-3-cyano-2(1*H*)-pyridinethione (**13**) (0.01 mole) in 10 ml of phosphoric acid 89% (10 ml) was heated until a clear solution was achieved in about 10-20 minutes at 128-135°. The reaction mixture was cooled and added to crushed ice (10 g). The product was then collected by filtration, washed with water, dried and recrystallized from a suitable solvent to give **17** (Table 4).

Synthesis of 1-Substituted-3-formyl-2(1*H*)-pyridones (**19**).

The required 2-formyl-2(1*H*)-pyridinethione (**19**) (0.01 mole) was dissolved in DMSO (15 ml) whereupon concentrated sulfuric acid (1 ml) was added dropwise and stirring was continued at 80° for 12 hours. The reaction mixture was cooled to 20° and poured in ice-water (25 ml), neutralized with ammonia, filtered and the precipitate washed with a small amount of water followed by drying *in vacuo* to yield the pyridones **19**. Recrystallization from a suitable solvent gave analytically pure 3-formyl-2(1*H*)-pyridones (Table 5).

Special Procedures.

1-Methyl-3-formyl-2(1*H*)-pyridone (**19a**).

With a reaction time of 5 hours at 70°, a small amount of precipitate was filtered off, whereupon the product was extracted with ether (continuous extraction, 50 hours). Evaporation *in vacuo* gave **19a** 66% mp 102-103° (cyclohexane).

1-Isopropyl-3-formyl-2(1*H*)-pyridone (**19b**).

After precipation of the reaction product an additional amount was isolated by extraction of the filtrate with ether, total yield after recrystallization 63% mp 115-117° (toluene).

1-Cyclohexyl-3-formyl-2(1*H*)-pyridone **19d**.

The crude product was extracted with chloroform, dried (magnesium sulfate) and evaporated to dryness *in vacuo*, yield, 69%. This product was purified by ptlc on silica (eluent ether), yield of **19d**, 37%, mp 99-101°.

Synthesis of 1-Substituted-3-carboxy-2(1*H*)-pyridones (**20**).

General Procedure.

The required 3-formyl-2(1*H*)-pyridinethione (**16**) (0.015 mole) was suspended in sodium hydroxide (200 ml, 1*M*), and hydrogen peroxide (9 ml, 50%) was slowly added. Cooling was in some cases necessary to keep the temperature at 45°. Stirring was continued at 35° for 16 hours. The reaction mixture was then neutralized with hydrochloric acid (4*M*), and excess peroxide destroyed with saturated sodium sulfite. Acidification (*p*H = 2) with hydrochloric acid (4*M*) and cooling precipitated the product which was filtered and washed with ice-water. Drying *in vacuo* and recrystallization from a suitable solvent gave the pyridones **20** (Table 6).

Special Procedure.

1-Methyl-3-carboxy-2(1*H*)-pyridone (**20a**).

The product was isolated by continuous extraction for 48 hours (ether). Drying (magnesium sulfate) and evaporation *in vacuo* gave **20a** 61% mp 182-184° (2-propanol), ref [9] mp 184°, see also ref [8] and [21].

2-Phenylamino-2-oxoacetic Acid (Oxanilic Acid) (**15a**).

Following the general procedure for preparation of the 3-carboxyl-2(1*H*)-pyridones (**20**) gave upon acidification to p*H* = 1 and continuous extraction (ether) **15a** (35%) mp 150-152° (water) identified as oxanolic acid (**15a**). Authentic oxanilic acid prepared by the method given by Tingle and Bates [18] had mp 151-153° (toluene); no depression was seen by mixed mp; ir (potassium bromide): 3355, 3285, (NH,OH), 2950 br (COOH), 1670, 1685 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): 10.66 (COOH, exchange with deuterium oxide), 6.9-7.9 m (phenyl, NH) in ppm from TMS; ms 165 (95%, M^+), 120 (100%), 93 (89%), 92 (47%), 77 (45%).

2-Naphthylamino-2-oxoacetic Acid (**15b**).

During the reaction carried out as before with **16h** a vigorous smell of isocyanide appears. Acidification and continuous extraction (ether) gave **15b** (40%) mp 160° dec (toluene), decomposes yielding isocyanide; ir (potassium bromide): 3360 (NH,OH), 2900 br (COOH), 1755, 1685 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) 10.79 s (COOH, exchanges with deuterium oxide), 8.5-9.1 m (NH, exchanges with deuterium oxide), 7.6-8.3 m (naphthyl), ppm from TMS; ms: 215 (100%, M^+), 170 (29%), 169 (60%), 154 (22%), 143 (65%) 127 (28%), 115 (74%). Peak match Found: 215.0593. Calcd. for $C_{12}H_9NO_3$: 215.0582.

4-Nitroaniline (**18**).

Following the general procedure for the oxidation, **16a** gave a product which precipitated when the reaction mixture was neutralized. Recrystallization from water gave 4-nitroaniline (**18**) (71%), mp 142-144° (water); ^1H nmr, ir and ms identical with 4-nitroaniline.

1-(4-Nitrophenyl)-3-formyl-2(1*H*)-pyridinethione (**16a**).

This compound was prepared according to ref [20a], pale yellow crystals, yield 81%, mp 236-237° (benzene).

Anal. Calcd. for $C_{12}H_8N_2O_3S$: C, 55.38; H, 3.10; N, 10.76; S, 12.32. Found: C, 55.45; H, 3.08; N, 10.61.

1-(*N,N*-Dimethylaminophenyl)-3-formyl-2(1*H*)-pyridinethione (**16d**).

This compound was prepared according to ref [20a], red crystals, yield 72% mp 216-217° (benzene).

Anal. Calcd. for $C_{14}H_{14}N_2OS$: C, 65.09; H, 5.46; N, 10.84; S, 12.41. Found: C, 65.36; H, 5.48; N, 10.69.

1-(2-Fluorophenyl)-3-formyl-2(1*H*)-pyridinthione (**16e**).

This compound was prepared according to ref [20a], yellow crystals, yield 75%,mp 137-138° (cyclohexane).

Table 7

3-Hydroxyalkyl-2(1*H*)-pyridinethiones **23** and **24**

Compound	Molecular formula	Yield %	mp °C (Solvent)	Analyses Found/(Calcd) C	H	N	Mass spectra m/e (%)
23a	$C_{12}H_{17}NOS$ (223.34)	47	110-112 (Toluene)	64.45 (64.54)	7.56 (7.67)	6.17 (6.27)	223 (62, M^+) 124 (100)
23b	$C_{12}H_{11}NOS$ (217.29)	74	140-142 (Toluene)	see ref [20a]			217 (59, M^+) 216 (100)
24a	$C_{13}H_{13}NOS$ (231.31)	80	115-118 (PLC)	67.60 (67.50)	5.73 (5.66)	6.15 (6.06)	231 (100, M^+) 198 (34)
24b	$C_{18}H_{15}NOS$ (293.38)	57	141-143 (Ethanol)	73.75 (73.69)	5.18 (5.15)	4.76 (4.77)	293 (100, M^+) 260 (46)

ir (potassium bromide): 3350 cm^{-1} s(OH) for compounds **23a-24b**.

Anal. Calcd. for $C_{12}H_8NOS$: C, 61.79; H, 3.46; N, 6.00; S, 13.74. Found: C, 61.64; H, 3.42; N, 5.83; S, 13.64.

1-(2-Methylphenyl)-3-formyl-2(1*H*)-pyridinethione (**16f**).

This compound was prepared according to ref [20a], yellow crystals, yield 67% mp 126-128° (methylcyclohexane).

Anal. Calcd. for $C_{13}H_{11}NOS$: C, 68.10; H, 4.83; N, 6.11; S, 13.98. Found: C, 67.95; H, 4.76; N, 6.21; S, 13.88.

1-Methyl-3-aldoximido-2(1*H*)-pyridone (**21**, R = CH_3).

The general procedure described above for the thiones **13** was used. The reaction time was 1½ hours, yield 83% mp 177-179° (cyclohexane-methanol); ir (potassium bromide): 3150-3450 br (OH), 1640 cm^{-1} (CO); ms: 152 (100%, M^+), 135 (50%), 122 (18%); ^1H nmr (DMSO-d_6): 3.48 (s, CH_3); 6.28 (t, J = 7 Hz, C-5); 7.80 (d, J = 7 Hz, C-4 and C-6); 8.15 (s, CH); 11.17 ppm from TMS (s, OH).

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.18; H, 5.36; N, 18.34.

1-Methyl-3-cyano-2(1*H*)-pyridone (**22**, R = CH_3, Ricinidine).

A mixture of 1-methyl-3-aldoximido-2(1*H*)-pyridone (**21**) and neutral aluminumoxide (Woelm) was refluxed for 50 hours in dry toluene (100 ml). Analysis by tlc indicated that the starting material was consumed. The mixture was filtered and the aluminum oxide was continuously extracted with ethyl acetate. The combined filtrate and extracts were concentrated *in vacuo* to give white crystals of **22**. Recrystallization from ethanol gave 0.37 g (49%) of ricinidine mp 146-147° (corrected), ref [12] mp 147°; uv (absolute ethanol): 233 (3.72), 334 nm (3.96); ^{13}C nmr (deuteriochloroform): 160.1 (C-2), 147.1 (C-6), 143.5 (C-4), 115.5 (CN) 105.3 (C-5 or C-3), 38.4 (CH_3) ppm from TMS; ms: m/e 134 (100%, M^+), 106 (34%), 105 (34%), 79 (16%), 64 (16%), 42 (22%). Alternatively crude ricinidine can be purified by plc on silica with chloroform-methanol, 19:1 as the eluent, followed by sublimation.

1-Cyclohexyl-3-hydroxymethyl-2(1*H*)-pyridinethione (**23a**).

1-Cyclohexyl-3-formyl-2(1*H*)-pyridinethione (**18c**) (4.75 g) was dissolved in absolute ethanol (250 ml) with a molybdenum catalyst (0.250 g, Girdler Südchemie T 306, Mo 7.5%) and hydrogen (72 atmospheres) for 24 hours at 100 °C in a Parr hydrogenation apparatus. Filtration and concentration *in vacuo* gave the title compound as pale yellow crystals 2.36 g (47%).

1-Phenyl-3-hydroxymethyl-2(1*H*)-pyridinthione (**23b**).

1-Phenyl-3-formyl-2(1*H*)-pyridinethione (**18a**) (1.08 g) was hydrogenated for 48 hours as described above to give **23b** (0.80 g, 74%) identical to **23b** described in ref [20a].

1-Phenyl-3-(1-hydroxyethyl)-2(1*H*)-pyridinethione (**24a**).

To a solution of 1-phenyl-3-formyl-2(1*H*)-pyridinethione (**18a**) (2.15 g) in ether (120 ml), a solution of methyl magnesium iodide (0.011 mole) in ether (30 ml) was slowly added (30 minutes) whereupon the mixture was refluxed for 3 hours. Addition of ice (50 g), adjusting to *p*H = 7 with 4*M* hydrochloric acid and extraction with chloroform, drying (magnesium sulfate) and concentration *in vacuo* yields 2.03 g product. This crude product was purified by ptlc (silica, chloroform:methanol 15:1), to give **24a**, 1.85 g (80%).

1-Phenyl-3-(1-hydroxybenzyl)-2(1*H*)-pyridinethione (**24b**).

1-Phenyl-3-formyl-2(1*H*)-pyridinethione (**18a**) (10.75 g) dissolved in THF (50 ml) was slowly added (20 minutes) to a solution of phenylmagnesium bromide (0.05 mole) in THF (25 ml) with stirring at 60°. After addition, stirring was continued at 60° for 2 hours whereupon the reaction mixture was added to ice-water (400 ml), and *p*H adjusted to *p*H = 7 with 4*M* hydrochloric acid. Extracted with chloroform drying ($MgSO_4$) and concentration *in vacuo*, gave **24b**, 8.3 g (57%); uv (absolute ethanol): 378 (3.68), 292 nm (3.96).

Acknowledgements.

We are grateful to cand. scient. C. Dreier and cand. scient. M. C. Christensen for some of the preparations.

REFERENCES AND NOTES

[1] Author to whom correspondence should be addressed.

[2] A DANIDA grant to M.A.M. is gratefully acknowledged.

[3] J. Becher, M. C. Christensen, J. Møller and J. Winckelmann, *Sulfur Letters*, **1**, 43 (1982), Pyridinethiones VII.

[4] H. D. H. Showalter and T. H. Haskell, *J. Heterocyclic Chem.*, **18**, 367 (1981); H. D. H. Showalter, J. M. Damagala and J. P. Sanchez, *ibid.*, **18**, 1609 (1981).

[5] M. C. Christensen, C. Dreier and J. Becher, *Synthesis*, 405 (1980).

[6] J. Becher, C. Dreier, E. G. Frandsen and A. S. Wengel, *Tetrahedron*, **34** 989 (1978).

[7] E. N. Marvell and M. J. Jonciek, *J. Am. Chem. Soc.*, **73**, 973 (1951).

[8] S. N. Ganguly, *Phytochemistry*, **9**; 1667 (1970).

[9] E. Späth and G. Koller, *Ber.*, **56**, 880 (1923).

[10] T. Robinson and C. Cepurneek, *Phytochemistry*, **4**, 75 (1965).

[11] R. Mukherjee and A. Chatterjee, *Tetrahedron*, **22**, 1461 (1966).

[12] H. Möhrle and H. Weber, *Chem. Ber.*, **104**, 1478 (1971).

[13] For hydrolyses to the carboxylic acid, see ref [8].

[14] M. Mikolajczyk and J. Luczak, *Chem. Ind.*, (London), 76 (1972).

[15] J. Becher, E. G. Frandsen, C. Dreier and L. Henriksen, *Acta Chem. Scand.*, **B31**, 843 (1977).

[16] W. Ostwald, *Z. Phys. Chem.*, **3**, 369 (1889).

[17] J. Becher unpublished results.

[18] J. Tingle and S. J. Bates, *J. Am. Chem. Soc.*, **31**, 1237 (1909).

[19] L. R. Fiebel and P. E. Spoerri, *ibid*, **70**, 3908 (1948).

[20a] J. Becher and E. G. Frandsen, *Acta Chem. Scand.*, **B30**, 863 (1976); [b] J. Becher and E. G. Frandsen, *ibid.*, **B30**, 904 (1976); [c] J. Becher and E. G. Frandsen, *Tetrahedron*.

[21a] W. I. M. Holman and C. Wiegand, *Biochem. J.*, **43**, 423 (1948). [b] H. W. Chambers and J. E. Casida, *Toxicol. Appl. Pharm.*, **10**, 105 (1967); [c] H. Tomisawa, R. Fujita, H. Hongo and H. Kato, *Chem. Pharm. Bull.*, **22**, 2091 (1974).