Pyridinethiones. XI. Diastereoselective Aldol Condensations with 2(1*H*)-Pyridones, 2(1*H*)-Pyridinethiones, and the Crystal Structure of 3-(1-Hydroxy-2-methyl-3-oxo-3-(4-chlorophenyl)propyl-1-isopropyl-2(1*H*)-pyridinethione.

Jan Becher*, Fahmy M. Asaad [1], Tea Johansen and Jesper Hansen

Department of Chemistry, Odense University,
DK-5230 Odense M, Denmark

Sine Larsen and Flemming Hansen

Chemistry Laboratory IV, The H. C. Ørsted Institute, Universitetsparken 5,
University of Copenhagen, DK-2100 Copenhagen Ø, Denmark

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Aldol condensation of 3-formyl-2(1*H*)-pyridinethiones and the corresponding pyridones with ketones such as acetophenones in aqueous base yields 3-hydroxy-1-propanones in high yields. Reaction with propiophenone showed this reaction to be highly diastereoselective as only the *erythro*-isomer is formed at room temperature. This assignment was based on an X-ray crystallographic investigation of the compound given in the title. Aldol condensations of a number of related 3-acetyl-2(1*H*)-pyridinethiones with benzaldehyde yielded the corresponding *trans*-vinyl ketones.

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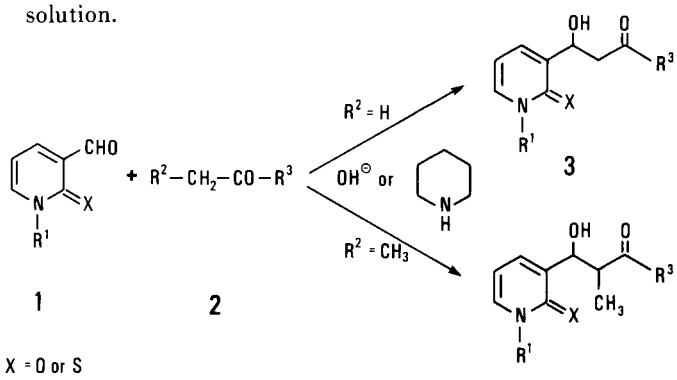
In previous papers [2] in this series we have described condensation reactions of the formyl group in the 3-formyl-2(1*H*)-pyridinethiones **1**. Normally such reactions give vinyl compounds, the dominant product was in all cases the one with the smallest group close to sulfur, reflecting the steric requirements of the relatively large sulfur atom. Generally the aldol condensation is an effective method for carbon-carbon bond formation. This reaction has therefore been studied [3] in order to design methods giving high stereoselectivity. Usually high selectivity cannot be obtained in aqueous solution as the aldol condensation in a protic solvent takes place through a rapid sequence of equlibriae, resulting in the formation of a mixture of diasteroisomers. High selectivity can only be obtained using metal enolates [4] at low temperature.

In a preliminary account [5] we described the aldol condensation of 1 and propiophenone $R_2 = CH_3$, $R_3 = C_6H_5$; we have now found that this reaction is quite general and highly stereoselective when carried out in basic aqueous solution.



As it was not possible to obtain absolutely decisive structural information from the ^1H nmr spectra [5] of these compounds (*vide infra*), a crystal structure determination was undertaken for a representative **3q** ($R_1 = CH(CH_3)_2$, $R_2 = CH_3$, $R_3 = 4\text{-Cl-}C_6H_4$) of the hydroxy ketones formed by this stereoselective reaction, in order to elucidate the stereochemistry.

X-Ray Crystallographic Results.

The final positional and isotropic thermal parameters are listed in Table 1. Bond lengths, bond angles, and selected torsion angles are listed in Table 2. The C-H bond lengths are all in the range 0.91 to 0.99 Å. The over-all geometry and the atomic labelling of the molecule are illustrated by the ORTEP drawing in Fig. 1. Least squares planes have been calculated for selected groups of atoms in the molecule. The two six membered rings are planar within the experimental accuracy, the interplanar angle between the two least squares planes is 29.5°. The sulfur atom is in the plane of the pyridine ring, but the other substituents, C6 and C9, are displaced significantly from the mean plane −0.13 Å and 0.10 Å, respectively.

Both the S1-C6 distance (3.039 Å) and the S1-C9 distance (3.113 Å) are significantly shorter than the sum of the van der Waals radii [6] for these atoms, 3.5 Å.

The structure of unsubstituted 2-thiopyridone has previously been studied by X-ray and neutron diffraction [7]. A comparison of the latter structure with the results from the present structure determination reveals some obvious differences. Both the C1-N1 and C1-C2 bond lengths are significantly larger in the present structure than in the unsubstituted compound, 1.391(2) Å and 1.365(2) Å, compared with 1.352(1) Å and 1.355(1) Å. The other molecular

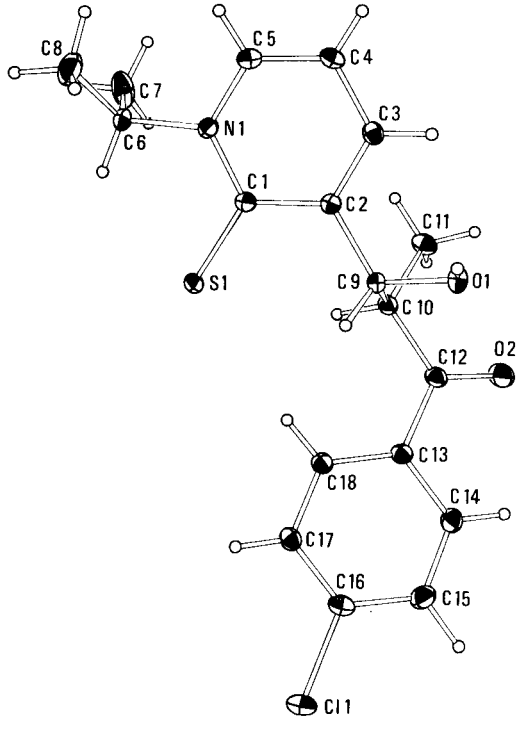


Figure 1. An ORTEP drawing of the molecule **3q** showing the atomic labelling.

dimensions in the pyridine ring are very similar in the two structures, making it likely that the differences are caused by the specific substitution of the pyridine ring. In the structure of ethyl-α-dimethylaminocroconate the substituted pyridine ring exhibits similar variations of the bond lengths [8]. From Fig. 1, as well as the torsion angles, it is obvious that the isopropyl group takes a conformation that minimizes steric interactions between the sulfur and the isopropyl group. A similar conformation of the isopropyl group is observed in the structure of diisopropyl-3,4-Δ^4-thiazolinethione-2 [9]. The C-S bond length in the latter structure, 1.678(1)Å, is significantly shorter than the C1-S1 distance of 1.702(1)Å found in the present structure which is slightly longer than the value for a C-S double bond [10], but still considerably shorter than the C-S single bonds, 1.769(2)Å and 1.790(2)Å, observed in 2-(2′-pyridylthio)-3-nitropyridine [11]. The remaining bond lengths and angles agree well with the expected values.

An important aspect of the structure determination was to establish the absolute configuration of the two chiral carbon atoms, C9 and C10. It is apparent from Fig. 1 that the atoms have opposite absolute configuration, *R* and *S*, which corresponds to the *erythro* form of the molecule.

In the crystal intermolecular hydrogen bonds are formed between the hydroxo group and the thione sulfur of an adjacent molecule related by the inversion symmetry. The

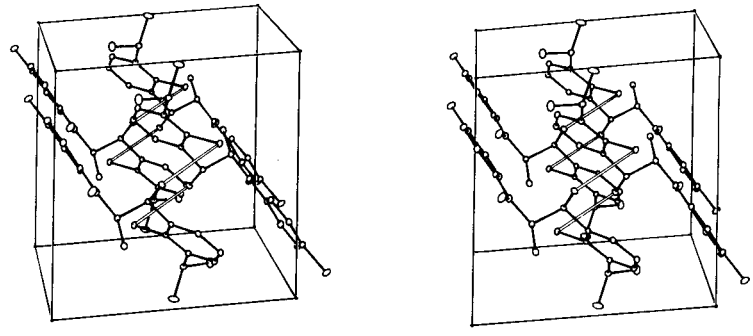


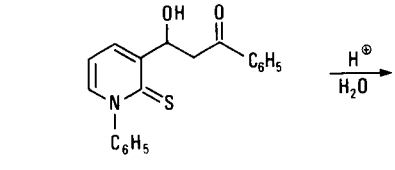
Figure 2. A stereo pair illustrating the packing in the crystal viewed along a*. The hydrogen bonds are drawn as the open bonds, compound **3q**.

two molecules form a hydrogen bonded dimer as the hydroxy group of the latter molecule is hydrogen bonded to the thione sulfur of the first. The hydrogen bonds are almost linear, the O1-H1-S1 angle is 169° and the S1-O1 distance 3.312(3)Å. This packing arrangement is illustrated in Fig. 2 which is a stereo pair with the hydrogen bonds indicated.

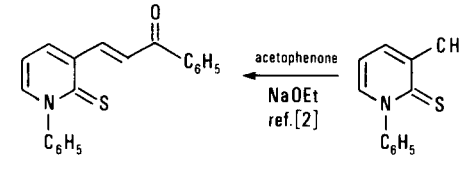
Reaction of **1** with Acetophenones and Propiophenones.

Preparation of the hydroxy ketones **3** was carried out in basic solution (0.2 *M* sodium hydroxide), these syntheses usually give high yields, Table 4.

The hydroxy ketones **3** are stable, pale yellow crystalline compounds. Heating with acid (4 *M* hydrochloric acid) results in rapid loss at water with formation of the expected vinyl ketones [5] in nearly quantitative yield, for example:



3a



5a **1**

Prolonged heating of the hydroxy ketones **3** in solvents with high boiling points such as methoxyethanol also leads to elimination of water and formation of the vinyl ketones [5], [12]. Recrystallization of the hydroxyketones **3** was found to be efficient in ethylacetate or benzene. When the aldol condensation was carried out with halogen substituted acetophenones (see Table 4), simultaneous forma-

Table 1

Fractional Coordinates and Equivalent* Isotropic Thermal Parameters in Units of Å²

Atom	x	y	z	B_{eq}
C1	0.0460(2)	0.4664(1)	0.7108(1)	0.89(2)
C2	−0.1332(2)	0.4637(1)	0.6162(1)	0.84(2)
C3	−0.2365(2)	0.5579(1)	0.6310(1)	1.01(3)
C4	−0.1684(2)	0.6601(1)	0.7352(2)	1.13(3)
C5	0.0038(2)	0.6632(1)	0.8229(2)	1.17(3)
C6	0.2875(2)	0.5762(2)	0.9224(2)	1.09(3)
C7	0.2549(2)	0.5324(2)	1.0433(2)	2.16(4)
C8	0.3989(2)	0.7067(2)	0.9518(2)	2.10(4)
C9	−0.2080(2)	0.3597(1)	0.4960(1)	0.88(2)
C10	−0.2773(2)	0.2309(1)	0.5303(1)	0.99(3)
C11	−0.4157(2)	0.2435(2)	0.5992(2)	1.30(3)
C12	−0.3591(1)	0.1378(1)	0.4005(2)	1.13(3)
C13	−0.2379(2)	0.0833(1)	0.3345(1)	1.01(3)
C14	−0.3200(2)	0.0081(2)	0.2088(2)	1.28(3)
C15	−0.2162(2)	−0.0477(2)	0.1435(2)	1.41(3)
C16	−0.0291(2)	−0.0290(2)	0.2059(2)	1.22(3)
C17	0.0568(2)	0.0449(1)	0.3293(2)	1.08(3)
C18	−0.0492(2)	0.1015(1)	0.3931(1)	1.03(3)
N1	0.1075(2)	0.5696(1)	0.8127(1)	0.94(2)
O1	−0.3574(4)	0.3948(1)	0.3931(1)	1.11(2)
O2	−0.5222(2)	0.1065(1)	0.3500(1)	2.01(2)
S1	0.17954(5)	0.35218(4)	0.69915(4)	1.054(6)
Cl1	0.10252(5)	−0.10232(4)	0.12673(4)	1.844(7)

$B_{eq} = \frac{1}{3} \cdot \sum_{ij} \tilde{a}_i \tilde{a}_j a_i^* a_j^* b_{ij}$

Table 2

Bond lengths (Å), bond angles (deg) and selected torsion angles (deg)

C1 - S1	1.7022(14)	C13 - C14	1.405(2)
C1 - N1	1.391(2)	C14 - C15	1.385(2)
C1 - C2	1.432(2)	C15 - C16	1.387(2)
C2 - C3	1.378(1)	C16 - Cl1	1.7426(15)
C3 - C4	1.400(2)	C16 - C17	1.384(2)
C4 - C5	1.362(2)	C17 - C18	1.393(2)
C5 - N1	1.365(2)	C18 - C13	1.395(2)
N1 - C6	1.498(2)	C13 - C12	1.498(2)
C6 - C7	1.516(2)	C12 - O2	1.216(2)
C6 - C8	1.515(2)	C12 - C10	1.527(2)
C2 - C9	1.521(2)	C10 - C11	1.526(2)
C9 - O1	1.425(2)	C10 - C9	1.552(2)
C2 - C1 - N1	116.1(1)	C14 - C13 - C18	119.0(1)
C2 - C1 - S1	122.5(1)	C12 - C13 - C14	117.9(1)
N1 - C1 - S1	121.3(1)	C12 - C13 - C18	123.1(1)
C1 - C2 - C3	120.2(1)	C13 - C14 - C15	120.9(1)
C1 - C2 - C9	120.1(1)	C14 - C15 - C16	118.5(1)
C3 - C2 - C9	119.6(1)	C15 - C16 - C17	122.4(1)
C2 - C3 - C4	121.5(1)	C15 - C16 - Cl1	118.9(1)
C3 - C4 - C5	117.8(1)	Cl1 - C16 - C17	118.8(1)
C4 - C5 - N1	122.0(2)	C16 - C17 - C18	118.6(1)
C5 - N1 - C1	122.3(1)	C17 - C18 - C13	120.7(1)
C1 - N1 - C6	120.3(1)	C13 - C12 - C10	120.0(1)
C5 - N1 - C6	117.2(1)	C13 - C12 - O2	119.2(1)
N1 - C6 - C7	108.3(1)	C10 - C12 - O2	120.8(1)
N1 - C6 - C8	112.4(1)	C12 - C10 - C9	107.9(1)
C7 - C6 - C8	113.6(2)		
C2 - C9 - C10	113.1(1)	C12 - C10 - C11	110.4(1)
C2 - C9 - O1	111.7(1)	C11 - C10 - C9	113.2(1)
O1 - C9 - C10	106.3(1)		
C5 - N1 - C6 - C7	75.8	C13 - C12 - C10 - C9	72.0
C5 - N1 - C6 - C8	−50.6	C13 - C12 - C10 - C11	−163.8
S1 - C1 - N1 - C6	−5.7	C12 - C10 - C9 - O1	53.6
S1 - C1 - C2 - C9	−2.9	C12 - C10 - C9 - C2	176.5

Table 3

Summary of Crystal Data, Data Collection and Structure Refinement

Crystal data at 110K	
Space group	triclinic, P1
a:	7.917(4) Å
b:	10.616(3) Å
c:	10.749(3) Å
α,β,γ (deg)	95.74(3)°, 109.97(3)°, 95.25(3)°
V	837.1(12) Å³
Empirical formula	$C_{18}Cl H_{20} NO_2S$
Formula weight	349.88
Molecules/cell; Z	2
d_{calc} (110K)	1.388 g/cm³
Data Collection and Reduction	
Temperature	110K
Diffractometer	CAD-4
Radiation, wavelength	MoKα, 0.71073 Å
Crystal dimensions	0.05 × 0.10 × 0.28 mm³
Scan mode	$\omega - 2\theta$
Scan range	$\Delta\omega = 1.0° + 0.35° \cdot \tan\theta$
Maximum counting time	240 s
Scan rate, deg/min	0.39 - 5.49
θ - range	1° - 30°
Range in hkl	$-11<h<11;\ -14<k<14,\ -15<l<14$
Linear absorption coefficient, μ	3.54 cm⁻¹
Internal agreement factor, R_{int}	0.025
Structural Refinement	
Number of independent reflections	4863
Reflections used, $I/\sigma(I) \geq 3.0$	3082
Function minimized	$\Sigma\omega(\|F_o\| - \|F_c\|)^2$
Weights, w	$w^{-1} = \sigma^2(F) + 0.05\ \|F$
Number of variables	288
Final R, R_w	0.029, 0.037

tion of vinyl ketones **5** was seen. In such cases the use of piperidine as catalyst resulted in clean formation of the hydroxy ketones **3**. Furthermore we found that the total yields of **3** are relatively independent of substituents in the acetophenone part. However, the reaction times and stability of **3** were markedly influenced by such substituents. For example 4-cyanoacetophenone reacts much faster than acetophenone itself. The corresponding reaction of the thiones **1** with propiophenones was usually carried out in 50% ethanol-water in order to ensure a homogenous reaction mixture and in most cases the corresponding hydroxy ketones were the only reaction product. 1-Phenyl-3-formyl-2(1*H*)-pyridinethione and mesitylmethylketone only yielded the vinyl ketone **5**, reflecting the influence of a steric crowded ketone.

The hydroxy ketones obtained from the reaction with pyridones (**1**, X = O) eliminated water more easily than their sulfur analogues, resulting in mixtures of hydroxy ketones and vinyl ketones.

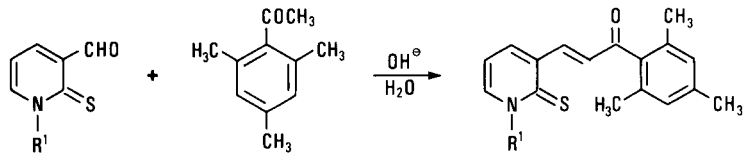


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Table 4

Hydroxy Ketones (**3** X = S) Prepared. 1-Substituted-3-hydroxy-(1-substituted-2(1*H*)-pyridinethione-3-yl)-1-propanones

Compound	X	R^1	R^2	R^3	Yield % (reaction time; hours, °C	mp °C (solvent)
3a	S	Phenyl	H	Phenyl	95 (12 h, 20 °C)	187-188 (ethyl acetate)
3b	S	4-*N,N*-dimethyl-aminophenyl	H	Phenyl	83 (5 h, 50 °C)	192-195 (ethyl acetate)
3c	S	4-Carbethoxy-phenyl	H	Phenyl	61 (12 h, 20 °C	186-188 (ethyl acetate)
3d	S	2-Propyl	H	Phenyl	97 (dissolved at 50°, then 12 h, 20 °C)	140-141 (2-propanol)
3e	S	*t*-Butyl	H	Phenyl	95 (dissolved at 50°, then 12 h, 20°	164-165 (ethanol)
3f	S	Phenyl	H	2-Hydroxy-phenyl	71 (dissolved at 50°, then 12 h, 20°) [a]	193-164
3g	S	Phenyl	H	4-Aminophenyl	91 (2h, 50°)	214-217d (ethyl acetate)
3h	S	4-Carbethoxy-phenyl	H	4-Aminophenyl	44 (2h, 50°)	210-215 (ethyl acetate)
3i	S	Phenyl	H	4-Cyanophenyl	84 (2h, 20°)	148-50 (ethyl acetate)
3j	S	2-Propyl	H	4-Cyanophenyl	90 (1h, 20°)	166-169 (ethyl acetate)
3k	S	4-Chlorophenyl	H	4-Fluorophenyl	80 (60 hours)	159-160 (benzene)
3ℓ	S	Phenyl	H	2-Hydroxy-4-chloro-phenyl	68 (3h, 20°) [a]	150-153° dec (ethanol)
3m	S	Phenyl	Methyl	Phenyl	89 (12 h, 20°)	163-165 (ethyl acetate)
3n	S	Methyl benzyl	Methyl	Phenyl	95 (12 h, 20°)	143-145 (ethyl acetate)
3o	S	2-Propyl	Methyl	Phenyl	87 (12 h, 20°)	118-121 (ethyl acetate)
3p	S	Phenyl	Methyl	4-Chlorophenyl	91 (12 h, 20°)	176-178 (ethyl acetate)
3q	S	2-Propyl	Methyl	4-Chlorophenyl	83 (12 h, 20°)	150-151 (ethyl acetate)
		1-Substituted-3-hydroxy-(1-substituted-2(1*H*)-pyridon-3-yl)-1-propanones (**3** X = O)				
3r	O	Phenyl	H	Phenyl	60 (12 h, 20°)	157-158 (2-propanol)
3s	O	2-Napthyl	H	Phenyl	93 (12 h, 20°)	137-140 (ethyl acetate)
3t	O	Methyl benzyl	Methyl	Phenyl	77 (5 h at 50° then 16 h at 20°)	173-176 (ethyl acetate)

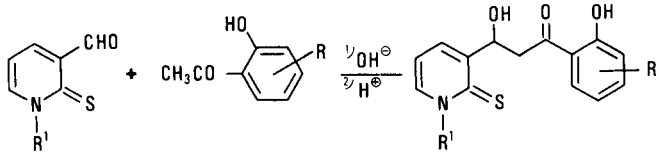
[a] Hydroxyketones **3f** and **3ℓ** prepared from *o*-hydroxyacetophenones were precipitated by ajusting the *p*H of the reaction mixture to *p*H = 4.

Table 5

Spectroscopic Data for Hydroxy Ketones **3**

Compound	Molecular formula	IR (KBr) cm^{-1} OH, C=O	UV (abs EtOH) λ max nm (log ε)	^{1}H-NMR H-5 J	H_a J_{ac}, J_{ab}	H_b J_{bc}, J_{ab}	H_c $J_{ac}J_{bc}$, J_{cd}	H_d = OH J_{cd}	[a] $CDCl_3$, [b] DMSO-d other protons
3a	$C_{20}H_{17}NO_2S$ (335.42)	3500 3420 1660	374 (3.74) 289 (3.98) 243 (4.25)	[a] 6.80 (t) 6.8	4.28 (dd) 4.2, 17.1	3.21 (dd) 7.8, 17.1	5.68 (ddd) 4.2, 7.8, 5.6	4.91 (d) 5.6	8.10-7.19 (m) H-4, H-6, 2 × phenyl
3b	$C_{22}H_{22}N_2O_2S$ (378.49)	3503 3420 1670	374 (3.74) 287 (4.12) 245 (4.34)	[a]	4.36 (dd) 4.3, 17.1	3.35 (dd) 7.6, 17.1	5.37 (m)	5.14 (d) 5.9	8.10-6.63 (m), H-4, H-5, H-6, phenyl 4H arom 3.10 (s) CH_3
3c	$C_{23}H_{21}NO_4S$ (407.49)	3495 3410 1710 1673 1660	374 (3.76) 285 (4.08) 237 (4.37) 224 (4.39)	[a] 7.0 (t) 7		3.3 (dd) 8,17	5.8 (m)		8.5-7.4 (m), H-4, H-6, phenyl, 4H arom 1.4 (t, 7 Hz) CH_3 4.7-4.1 (m) CH_2, OH, H_a
3d	$C_{17}H_{19}NO_2S$ (301.40)	3495 1667	362 (3.81) 273 (4.05) 241 (4.14)	[a] 6.81 (t) 6.8	4.26 (dd) 4.1, 17.1	3.19 (dd) 7.8, 17.1	5.71 (ddd) 4.1, 7.8, 5.4	4.89 (d) 5.4	8.10-7.32 (m) H-4, H-6 phenyl 6.67 (sept, 6.8 Hz) CH. 1.46 (d, 6.8 Hz) CH_3 1.44 (d, 6.8 Hz) CH_3
3e	$C_{18}H_{21}NO_2S$ (315.43)	3495 1668	371 (3.76) 289 (3.90) 241 (4.04)	[a] 6.68 (t) 6.8	4.19 (dd) 4.0, 17.1	3.20 (dd) 7.8, 17.1	5.75 (m) 4.0, 7.8	4.87 (d) 6 (90 MHz)	8.06-7.27 (m) H-4, phenyl 2.03 (s) CH_3
3f	$C_{20}H_{17}NO_3S$ (351.42)	3420 1630	372 (3.80) 341 (3.79) 289 (4.01) 250 (4.18)		[a] 4.26 (dd) 4.3, 16.8	3.31 (dd) 7.8, 16.8	5.64 (m) 4.3, 7.8	4.76 (d) 6.1	7.9-6.7 (m) H-4, H-5, 4H phenyl, 12.14 (s) phenol OH
3g	$C_{20}H_{18}N_2O_2S$ (350.44)	3470 3400 3320 3200 1640	373 (3.75) 321 (3.96) 294 (3.95)	[b] 6.96 (t) 6.8	3.52 (d) 15.4	2.60 (dd) 9.0, 15.4	5.59 (m)	5.40 (d) 4.9	8.06-7.25 (m) H-4, H-6, phenyl, 4H *p*-subst. phenyl, 5.99 (s, br) NH_2
3h	$C_{23}H_{22}N_2O_2S$ (422.50)	3450 3400 3360 3315 1705 1640	370 (3.76) 322 (4.26) 294 (4.24) 235 (4.03)		[a] 4.14 (dd) 3.7, 16.8	3.04 (dd) 7.6, 16.8	5.59 (m)	5.04 (d) 5.0	8.30-7.32 (m) H-4, H-6, 2 × phenyl, 6.93-6.54 (m) H-5, NH_2, 4.42 (q, 7.2 Hz) CH_2, 1.41 (t, 7.2 Hz) CH_3
3i	$C_{21}H_{16}N_2O_2S$ (360.43)	3420 3265 2220 (CN) 1680 (CO)	373 (3.78) 289 (4.04) 247 (4.42)	[a] 6.83 (t) 6.9	4.19 (dd) 3.6, 16.7	3.22 (dd) 8.2, 16.7	5.64 (m) 8.2	4.66 (d) 5.7	8.2-7.2 (m) H-4, H-6, phenyl, *p*-subst phenyl
3j	$C_{18}H_{18}N_2O_2S$ (326.42)	3400 3305 2220 (CN) 1680 (CO)	364 (3.83) 284 (4.08) 248 (4.33)	[a] 6.84 (t) 6.8	4.21 (dd) 3.8, 16.8	3.22 (dd) 8.2, 16.8	5.67 (ddd) 3.8, 8.2, 5.7	4.65 (d) 5.7	8.39-7.56 (m) H-4, H-6, *p*-subst phenyl, 6.52 (sept, 6.8 Hz) CH, 1.46 (d, 6.8 Hz) CH_3

When an *o*-hydroxyacetophenone was used, no vinyl ketone was formed as by-product (tlc). The hydroxy ketone formed in this case was soluble in base and could be precipitated upon acidification. These *o*-hydroxy condensation products **3f** and **3ℓ** are completely stable in acid in contrast to compounds **3** without an *o*-hydroxy moiety. This is probably a result of the formation of an intramolecular hydrogen bond, from the ketone oxygen to the more acidic phenolic hydroxy group.



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Related compounds with *o*-hydroxy groups have been found in natural products [13].

Structure of Hydroxy Ketones **3**.

Only few hydroxy ketones of pyridinealdehydes are known [12], and the examples derived from pyridine-3-aldehydes are all prepared by reactions in polar solvents. Some natural products [13] from plants have been identified as compounds of the type R^1-CH(OH)-CH_2CO-R^2, where both R^1 and R^2 are cyclic groups, in the examples [14]:

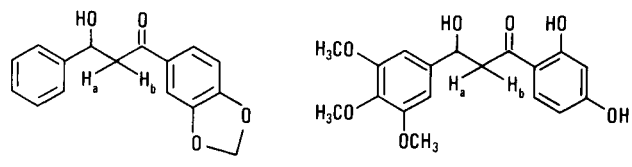
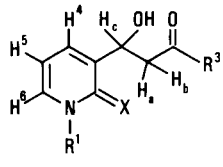


Table 5 continued

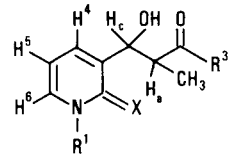
Compound	Molecular formula	IR (KBr) cm^{-1} OH, C=O	UV (abs EtOH) λ max nm (log ε)	^{1}H-NMR δ ppm j in Hz H-5 J	H_a J_{aCH_3}, J_{ac}	H_b J_{ac}, J_{ac}	CH_3 J_{aCH_3}	H_d = OH J_{cd}	[a] $CDCl_3$, [b] DMSO-d other protons
3k	$C_{20}H_{13}ClFNO_2S$ (387.86)	1688 (CO)	245 (4.23) 290 (3.92) 375 (3.71)	[a] 6.82 (t) 6.8	4.21 (dd) 4.0, 17.0	3.12 (dd) 8.1, 17.0	5.61 (ddd) 4.0, 8.1 5.3	4.73 (d) 5.3	8.17-6.96 (m) H-4, H-6, 2 × phenyl
3ℓ	$C_{20}H_{14}ClNO_3S$ (385.87)	1639 (CO)	261 (4.22) 290 (4.06) 330 (3.84) 367 (3.82)	[a] 6.83 (t) 7.1	4.16 (dd) 3.9, 16.6	3.28 (dd) 8.3, 16.6	5.62 (ddd) 3.9, 8.3	4.67 (broad)	7.88-6.98 (m) H-4, H-6, 8 aryl H, (11 H, incl phenol OH)
3m	$C_{21}H_{19}NO_2S$ (349.45)	3420 (OH) 1670 (CO)	374 (3.78) 289 (3.98) 242 (4.21)	[a] 6.75 (t) 7.0	4.78 (dq) 7.2, 4.1	5.47 (dd) 4.1, 4.6	1.06 (d) 7.2	4.82 (d) 4.6	8.2-7.3 (m) H-4, H-6 2 × phenyl
3n	$C_{23}H_{23}NO_2S$ (377.51)	3430 (OH) 1675 (CO)	367 3.86 285 4.03 239 4.24	[a] 6.58 (t) 7.0	4.87 (dq) 7.2, 4.4	5.48 (dd) 4.4,	1.15 (d) 7.2	4.94 (d) 5.0	8.2-7.3 (m) H-4, H-6, 2 × phenyl 7.83 (q, 7.0 Hz) CH, 1.68 (d, 7.0 Hz) CH_3
3o	$C_{18}H_{21}NO_2S$ (315.43)	3420 (OH) 1670 (CO)	367 3.85 284 4.03 241 4.13	[a] 6.76 (t) 7.0	4.78 (dq) 7.1, 4.0	5.48 (dd) 4.0, 4.8	1.11 (d) 7.1 (*threo*) 1.17 (d) 6.5 (*erythro*)	4.43 (d) 4.8	8.2-7.3 (m) H-4, H-6, phenyl 6.52 (sept 6.7 Hz) CH, 1.44 (d, 6.7 Hz) CH_3, 1.36 (d, 6.7 Hz) CH_3
3p	$C_{21}H_{18}ClNO_2S$ (383.89)	3430 (OH) 3300 (OH) 1675 (CO)	374 3.73 289 3.90 249 4.25	[a] 6.76 (t) 6.9	4.70 (dq) 7.1, 3.9	5.42 (dd) 3.9, 4.6	1.13 (d) 7.1	4.60 (d) 4.6	8.3-7.0 (m) H-4, H-6, phenyl, *p*subst phenyl
3q	$C_{18}H_{20}ClNO_2S$ (349.88)	3420 (OH) 3320 (OH) 1675 (CO)	362 3.82 283 3.99 252 4.26	[a] 6.78 (t) 7.0	4.75 (dq) 7.1, 4.1	5.42 (dd) 4.1, 5.0	1.11 (d) 7.1	4.70 (d) 5.0	8.1-7.2 (m) H-4, H-6 6.53 (sept, 6.7 Hz) CH, 1.47 (d, 6.7 Hz) CH_3, 1.39 (d, 6.7 Hz) CH_3
				H-5 J	H_a J_{ac}, J_{ab}	H_b J_{bc}, J_{ab}	H_c J_{ac}, J_{bc}, J_{cd}	H_d = OH J_{cd}	other protons
3r	$C_{20}H_{17}NO_3$ (319.35)	3510 (OH) 1662 (CO) 1649 (CO)		[a] 6.32 (t) 6.8	3.80 (dd) 4.5, 17.0	3.31 (dd) 7.8, 17.0	5.27 (m)	4.54 (d) 6.5	8.15-7.11 (m) H-4, H-6 phenyl
3s	$C_{24}H_{19}NO_3$ (369.42)	3320 (OH) 1670 (CO) 1655 (CO)	312 (3.94) 287 (3.96) 278 (3.94) 221 (4.87)	6.31 (t) 6.8	3.80 (dd) 4.3, 16.9	3.29 (dd) 7.9, 16.9	5.33 (m)	4.60 (d) 6.4	8.3-7.1 (m) H-4, H-6 naphthyl
				H-5 J	H_a $J_{ac}CH_3$, J_{ac}	H_c J_{ac}, J_{cd}	CH_3 J_aCH_3	H_d = OH	
3t	$C_{23}NO_3$ (361.44)	3380 (OH) 1685 (CO) 1640 (CO)	390 (3.83) 239 (4.06)	[a] 6.07 (t) 7.0	4.31 (dq) 7.0, 5.6	4.98 (dd) 5.6, 6.7	1.26 (d) 7.0	4.54 (d) 6.7	8.00 (dd, 2.5 Hz, 7.4 Hz) H-4, 7.6-7.3 (m), 2 × phenyl, 6.98 (dd, 2 5 Hz, 6 Hz) H-6, 6.42 (q, 7.1) CH, 1.62 (d, 7.0 Hz) CH_3

The ^{1}H chemical shifts of the methylene protons in the compounds depicted above were found at δ (H_a) = 3.19 and δ (H_b) = 3.09; δ (H_a) = 3.01 and δ (H_b) = 2.77; δ (H_a) = 3.00 and δ (H_b) = 2.70 ppm, respectively [14]. The relatively large difference between these shift values corresponds to the values found for compounds **3**.

A numbering similar to the one used above has been used to label the protons in the hydroxy ketones **3**.



Hydroxyketone from an acetophenone



Hydroxyketone from a propiophenone

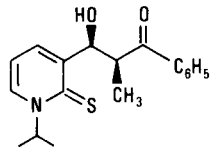
Table 6

Elementary Analyses

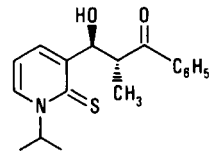
Compound	C Found Calcd.	H Found Calcd.	N Found Calcd.
3a	71.52	5.13	4.12
	71.62	5.11	4.18
3b	69.54	5.81	7.31
	69.81	5.86	7.40
3c	67.52	5.14	3.29
	67.79	5.19	3.44
3d	67.71	6.32	4.65
	67.77	6.31	4.65
3e	68.63	6.74	4.42
	68.57	6.67	4.44
3f	68.29	4.88	3.95
	68.38	4.84	3.99
3g	68.46	5.12	7.73
	68.55	5.17	7.99
3h	65.40	5.30	6.66
	65.39	5.25	6.63
3i	69.89	4.43	7.62
	69.98	4.47	7.77
3j	66.22	5.60	8.48
	66.23	5.56	8.58
3k	62.12	3.87	3.60
	61.93	3.87	3.61
3ℓ	62.61	4.16	3.56
	62.25	4.18	3.63
3m	72.10	5.44	3.89
	72.18	5.48	4.01
3n	73.20	6.15	3.68
	73.18	6.14	3.71
3o	68.31	6.78	4.61
	68.54	6.71	4.44
3p	65.76	4.72	3.64
	65.70	4.73	3.65
3q	61.92	5.77	3.99
	61.79	5.76	4.00
3r	75.10	5.36	4.39
	75.24	5.33	4.39
3s	77.77	5.14	3.72
	78.03	5.18	3.79
3t	76.48	6.40	3.78
	76.43	6.41	3.88

The ^{1}H nmr spectra of compounds **3b**, **3ℓ**, **3p**, and **3q** showed no change in the chemical shift values for the OH protons (H_d protons) when the concentrations were varied (0.25, 0.15, 0.08, and 0.04 *M* in deuteriochloroform). These results indicate the presence of intramolecular hydrogen bonds in solution for both types of hydroxy ketones (from acetophenones as well as propiophenones), or it may indicate the presence of dimers in solution, similar to the dimers found in the crystalline state for **3q**.

If the reaction between propiophenones and the pyridinethiones **1** is carried out in aqueous phase, two isomers are possible, namely



erythro



threo

Normally the ^{1}H nmr coupling constants in the staggered forms of related hydroxy ketones have been assigned the values; *erythro*: J_{bc} = 2.6 and J_{ac} = 8-12 Hz; *threo*: J_{bc} = 3.7 and J_{ac} = 1.8 Hz (14). The values found in the present compounds **3** give the values (Table 5) J_{bc} = 7.8 and J_{ac} = 4.2 Hz. Consequently, the geometry of the molecules **3** is different from the previously reported vinyl ketones [14]. If the present coupling constants J_{ac} and J_{bc} (Table 5) are used in the Karplus equation [15], the angle H_a-H_c ≃ 135° and the angle H_b-H_c ≃ 15 ° are suggested and these values seem to correspond best with the *threo* form which was therefore tentatively suggested in the preliminary note [5]. However, applications of the Karplus equation for quantitative work are frequently subject to errors because of uncertainty in the A term. Although there is some evidence of intramolecular hydrogen bonding in solution as described above, the presence of a second rotamer can hardly be ruled out, and if such a rotamer is populated, the ^{1}H nmr measurement of the torsion angle will be invalidated.

From the ^{1}H and ^{13}C nmr spectra it is clearly seen that only one isomer is formed in each case. As the crystal structure has confirmed that the isomer observed is the *erythro* form, it is tempting to conclude that this is also the isomer found in solution.

The crystallographic study clearly indicates that the sulfur atom influences the geometry of the entire molecule.

As described in the preliminary note [5], the reaction in THF with the *syn*-enolate of propiophenone yielded a mixture of isomers (82% yield, 1:1 mixture of *erythro* and *threo*). The transition states in THF leading from the *Z*-enolate to the *erythro* and *threo* products in this case could be:

As a 1:1 mixture was formed in THF, steric hindrance and stability of the two intermediates are probably equal [5].

The question can now be asked: Why is the reaction with propiophenones stereoselective in water? This selectivity reflects differences in the intermediates and is probably due to different solvatisation. An experiment was carried out in which piperidine was used as catalyst in the propiophenone reaction yielding exclusively the *erythro* form. The reaction is therefore independent of the metal ion and it is only the water of solvatisation which can be responsible for the selectivity. A mixture of the *erythro* and *threo* forms does not equilibrate at room temperature.

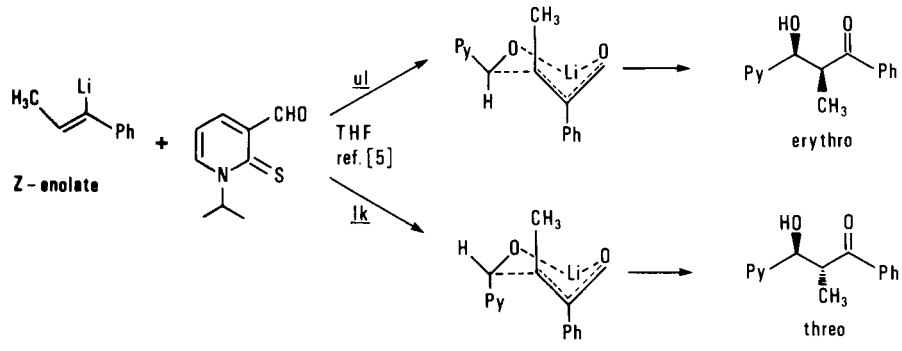


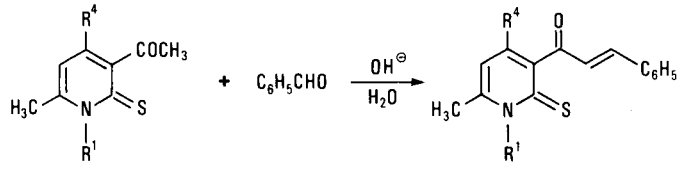
Table 7

Spectroscopical and Analytic Data for Vinyl Ketones **7**

Compound	Molecular formula [a]	IR (KBr) ν cm^{-1}	UV (abs EtOH) λ max nm (log ϵ)	^{1}H NMR (ppm) ($CDCl_3$)	mp °C (solvent)	Yield %
7a	$C_{22}H_{19}NOS$ (345.45)	1652 (CO)	370 (3.87) 287 (4.28)	6.9-7.8 (m, 5H, phenyl), 6.35 (s, 1H, C-5), 2.07 (s, 3H, CH_3), 2.16 (s, 3H, CH_3)	216-217 (benzene)	84
7b	$C_{22}H_{19}NO_2S$ (361.45)	1650 (CO)	355 (3.99) 287 (4.43) 229 (4.49)	7.1-7.5 (m, 5H, phenyl), 6.49 (s, 1H, C-5), 2.11 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3)	212-213 (toluene)	88
7c	$C_{20}H_{19}NOS$ (353.49)	1645 (CO)	370 (3.81) 288 (4.44)	7.1-7.6 (m, 5H, phenyl), 6.57 (s, 1H, C-5), 2.09 (s, 3H, CH_3), 2.45 (s, 3H, SCH_3)	205-206 (toluene)	85
7d	$C_{22}H_{18}ClNOS_2$ (411.96)	1643 (CO)	362 (3.76) 289 (4.29)	6.9-7.8 (m, 5H, phenyl), 6.57 (s, 1H, C-5), 2.11 (s, 3H, CH_3),2.46 (s, 3H, SCH_3)	240-241 (toluene)	85

[a] See experimental for elemental analyses.

The thermodynamic stability of the two forms may well be the reason for the selectivity in aqueous solution and we infer from this stereoselectivity that a ring is formed at one stage and that the substituents of the chiral carbon atoms take equatorial positions.



6 **7**

The thione sulfur atom in the 3-formyl-2(1*H*)-pyridinethiones **1** is necessary for formation of the hydroxy ketones. Thus, when the 3-acetyl-2(1*H*)-pyridinethiones **6** [16] were reacted with benzaldehyde, only the corresponding vinyl ketones **7** were formed under the reaction conditions which readily produced hydroxy ketones from the 3-formyl-2(1*H*)-pyridinethiones (**1**, X = S).

EXPERIMENTAL

Crystal Structure Determination.

The crystal data as well as a summary of the data collection and structure refinement are given in Table 3. The setting angles for 14 reflections were used to determine the cell parameters. The crystal was cooled with a conventional Enraf-Nonius low-temperature device, the temperature measured with a thermous couple was constant with ± 0.5 K. The intensities of three standard reflections which were recorded after every 10000 s. showed no systematic variations during the experiment. The data were corrected for Lorentz and polarization effects and symmetry related reflections were averaged.

The structure was solved by direct methods, the best solution from a standard MULTAN [18] run gave starting positions for 20 of the non-hydrogen atoms. The positions for remaining two non-hydrogen atoms were found after subsequent least squares and difference Fourier calculations. After an anisotropic refinement of the non-hydrogen atoms, the positions of all the hydrogen atoms in the structure were clearly found in the difference density. Both positional and isotropic thermal parameters for the hydrogen atoms were included in the final refinement cycles. In the final cycle the maximum shift was 0.29σ. The maximum peaks in the final difference density of 0.37 e/Å^3 are found in the bonds of the phenyl group.

The SDP (Structure Determination Package) [17] programs by Enraf-Nonius were used for all the computations. The atomic scattering factors and anamalous dispersion corrections were used as contained in the SDP programs.

List of observed and calculated structure amplitudes and anisotropic thermal parameters is available as supplementary material.

Microanalyses were carried out at NOVO A/S, Bagsvaerd, Denmark, by Mr. Rolf Amsler. The ^{1}H nmr and ^{13}C nmr spectra [12] were recorded on a JEOL-FX 60, ir spectra on a Perkin-Elmer 580 (potassium bromide used in all cases), uv spectra [12] on a Varian Cary 219 (abs. ethanol as solvent in all cases), and Mass spectra on a Varian MAT 311 A. Melting points were obtained on a Büchi apparatus (uncorrected).

General Procedure for the Preparation of Hydroxy Ketones **3a-3ℓ** and **3q-3v**. (The procedure for **3a** is given as an example.) 1-Phenyl-3-hydroxy-(1-phenyl-2(1*H*)-pyridinethion-3-yl)-1-propanone (**3a**).

1-Phenyl-3-formyl-2(1*H*)-pyridinethione [1] (21.5 g, 0.1 mole) was suspended in ethanol-water (400 ml, 50%), acetophenone (12.0 g, 0.1 mole) was added with stirring whereupon sodium hydroxide (50 ml, 2 *M*) was added. This suspension turned pale yellow after 15 minutes and was left with stirring overnight. Filtration and washing with water (50 ml), followed by drying (over phosphorus pentoxide *in vacuo*), yielded the product as pale yellow crystals 31.8 g (95%) mp 187-188°.

When analytically pure starting material is used, only one spot was seen by tlc (chloroform, silicagel). The title compound may be recrystallized from ethyl acetate or 2-methoxyethanol.

Alternatively the reaction can be carried out in a mixture of 900 ml of water and 100 ml 2 *M* sodium hydroxide.

General Procedure for the Preparation of Hydroxy Ketones **3m-3o**.

The required acetophenone (0.011 mole) was added to a suspension of the required 3-formyl-2(1*H*)-pyridinethione (0.010 mole) in ethanol (45 ml) and water (55 ml) whereupon piperidine was added (4 drops). The reaction mixture was stirred at room temperature as described in the table. The reaction was followed by tlc (silica gel, chloroform as eluent).

The precipitated yellow product was filtered off, washed with water, dried, and recrystallized from benzene.

General Procedure for the Preparation of Hydroxy Ketones **3x-3z**. (2(1*H*)-Pyridones).

The starting 2(1*H*)-pyridones **1x-1z** (0.01 mole) were suspended in sodium hydroxide (0.2 *M*, 50 ml) and the appropriate aryl alkyl ketone **2** (0.01 mole) added. The mixture was stirred overnight, sometimes heating to maximum 50° was necessary to finish the reaction (tlc), the product filtered, washed with water, and dried.

Recrystallization from ethyl acetate gave the analytically pure ketones.

1-(2,4,6-Trimethylphenyl)-3-(1-phenyl-2(1*H*)-pyridinethion-3-yl)-2-propen-1-one (**5**).

Compound **5** was prepared by the general method given above. Reaction time 16 hours at 20° followed by 5 hours at 50° yielded yellow crystals of **5**, 82% mp 173-175° (absolute ethanol); ir (potassium bromide): 1637 cm^{-1} (CO); ^1H nmr (60 MHz, δ ppm from TMS in deuteriochloroform): 7.97 (d, 1H, J = 16.4 Hz, CH), 7.7-7.2 (m, 7H, H-4, H-6, phenyl), 6.8 (s, 2H, phenyl), 6.7 (d, 1H, 16.4 Hz, CH), 6.6 (t, 1H, 6.6 Hz, H-5), 2.3 (s, 3H, 4-CH_3), 2.2 (s, 6H, 2.6-CH_3); uv (absolute ethanol): 427 (3.74), 339 (4.03), 257 nm (log ϵ = 4.35).

Anal. Calcd. for $C_{23}H_{21}NOS$ (359.48): C, 76.85; H, 5.89; N, 3.90. Found: C, 76.67; H, 5.86; N, 3.78.

Low Temperature Preparation of a Mixture of Diastereomeric 1-Phenyl-3-hydroxy-2-methyl-(1-isopropyl-2(1*H*-pyridinethion-3-yl)-1-propanone (**3e**).

Dry tetrahydrofurane (15 ml), dry diisopropylamine (0.058 ml, 0.40 mmol), and *n*-butyllithium (1.5 *N* in hexane, 0.27 g, 0.40 mmol) was mixed under argon. After 15 minutes propiophenone was added (50 μl, 0.38 mmole) at −78° and the mixture stirred for one hour, whereupon 1-isopropyl-3-formyl-2(1*H*)-pyridinethione (66.3 mg, 0.37 mmole in tetrahydrofuran, 15 ml) was added at −78°. Stirring was continued for 15 minutes whereupon the reaction mixture was quenched with aqueous saturated ammonium chloride (5 ml). Extraction with ether, drying (magneisum sulfate), and concentration *in vacuo* followed by chromatography on a short column (silicagel-ether) and isolation of the yellow fraction yielded the product **3e**, 95.2 mg (82%) as a yellow oil. The hplc and ^1H nmr showed this to be a 1:1 mixture of diastereoisomers of **3e**.

General Procedure for the Preparation of Vinyl Ketones **7a-7d**. 3-Phenyl-1-(1-phenyl-2(1*H*)-pyridinethion-3-yl)-2-propen-1-one (**7**).

To a mixture of the appropriate 3-acetyl-2(1*H*)-pyridinethione [10] (0.01 mole) and a benzaldehyde (0.01 mole) in absolute ethanol (40 ml) was added sodium hydroxide (2 *M*, 6 ml) and the mixture stirred at room temperature for 48 hours. The precipitated orange crystals were filtered, washed with water, dried, and recrystallized.

Compounds **7a**, **7b**, **7c**, and **7d** have the following elemental analyses: **7a**, $R^1 = C_6H_5$, $R^4 = CH_3$; Calcd. (Found); C, 76.52 (76.63); H, 5.50 (5.58); N, 4.06 (3.98); **7b**, $R^1 = C_6H_5$, $R^4 = OCH_3$; C, 73.13 (73.48); H, 5.26; (5.40); N, 3.88 (3.81); **7c**, $R^1 = C_6H_5$, $R^4 = SCH_3$; C, 70.02 (70.98); H, 5.04 (5.17); N, 3.71 (3.61); **7d**, R^1 = 4-Cl-C_6H_4, $R^4 = SCH_3$; C, 64.15 (64.11); H, 4.37 (4.40); N, 3.40 (3.36).

REFERENCES AND NOTES

[1] DANIDA postdoctorate fellow 1983.

[2] M. A. Michael, J. Becher, and I. Winckelmann, *J. Heterocyclic Chem.*, **20**, 1651 (1983); Pyridinethiones IX.

[3a] T. Mukaiyama, *Org. React.*, **28**, 203 (1982). [b] A. T. Nielson and W. J. Houlihan, *Org. React.*, **16**, 1 (1968).

[4] C. J. Heatcock, "Asymmetric Organic Reactions" Vol 3, J. D. Morrison, ed, Academic Press, New York, 1984.

[5] J. Becher, T. Johansen, J. Hansen, and F. M. Asaad, *Sulfur Letters*, **2**, 189 (1984).

[6] A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964).

[7] V. Ohms, H. Greth, A. Kutogen, and C. Schemiger, *Acta Crystallogr.*, **B38**, 831 (1982).

[8] R. W. J. Carney, J. Wojtkunski, B. Fechtig, R. T. Puckett, B. Biffar, and G. Stevens, *J. Org. Chem.*, **36**, 2602 (1971).

[9] G. Pepé and M. Pierrot, *Acta Crystallogr.*, **B32**, 1317 (1976).

[10] D. R. Johnson, F. X. Powell, and W. H. Kirchhoff, *J. Mol. Spectrosc.*, **39**, 136 (1971).

[11] M. Kimura, S. H. Simonsen, S. R. Calawell, and G. E. Martin, *J. Heterocyclic Chem.*, **18**, 469 (1981).

[12] C. S. Marvel, L. E. Colemann, and G. P. Scott, *J. Org. Chem.*, **20**, 1785 (1955).

[13a] A. Corvaisier and J. Tirouflet, *Compt. Rend.*, **251**, 1641 (1960); [b] K. Samula, *Rocz. Chem.*, **45**, 1833 (1971).

[14a] F. Bohlmann, P. K. Mahanta, and C. Zdero, *Phytochem.*, **17**, 1935 (1978); [b] G. D. Manners and L. Jourd, *Phytochem.*, **18**, 1037 (1979).

[15] For the Karplus equation see: F.A . Bovey, "Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, 1969, p 135.

[16] F. M. Asaad and Jan Becher, *Synthesis*, 1025 (1983).

[17] B. A. Frenz, "SDP Users Guide", Enraf-Nonius, Delft, The Netherlands , 1982.

[18] P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, MULTAN 80. A system of computer programs for the automatic solution of crystal structures from X-Ray Diffraction Data. Univs. of York, England, and Louvain, Belgium.