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NOVEL HETEROCYCLIC SYSTEMS, PART 4[1]: A SIMPLE, CONVENIENT SYNTHESIS OF 3-HYDROXYPYRIDINE-2-THIONE, AND THE PREPARATION OF TWO NOVEL TRICYCLIC BETAINES.

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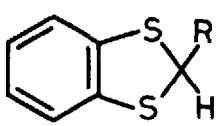
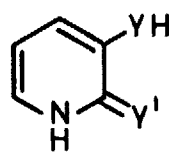
SUMMARY. Fusion of P_4S_{10} with 3-hydroxy-2-pyridone gives 3-hydroxypyridine-2-thione as the major product, along with significant amounts of two isomeric tricyclic betaines - the first examples of their class.

We have recently developed[2] a convenient synthesis of 2-substituted benzo-1,3-dithioles (I), compounds which are useful precursors of acyl carbanion equivalents.[3] As part of a wider plan to synthesize their heterocyclic analogues, we undertook to explore simple direct approaches to 3-mercaptopyridine-2-thione (II) and related heterocyclic compounds.



(I)



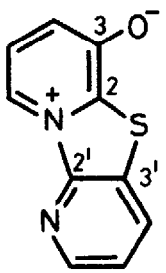
(II) Y = Y' = S
(III) Y = Y' = O
(IV) Y = O; Y' = S

3-Hydroxy-2-pyridone (III) is one of the few readily available disubstituted pyridines; hence it is attractive as a potential precursor for (II). A direct, forceful treatment of (III) with P_4S_{10} was attempted, but (perhaps predictably) this gave (IV) rather than the desired product. Compound (IV) was readily isolated in approximately 50% yield, and this method therefore presents distinct advantages over the previously published route.[4]

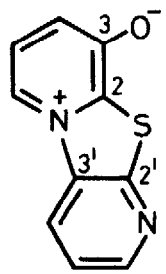
Smaller quantities of two other compounds could also be obtained from this reaction. Both were photosensitive, and could only be isolated pure and in reasonable yield when care was taken to exclude light during their isolation and purification. Their physical data (outlined below) indicate that they have structures (V) and (VI); they are

the first members of this interesting new class of tricyclic betaines.

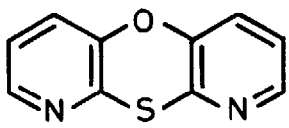
Field desorption mass spectrometry indicates that the compounds are isomeric, with molecular mass 202. Accurate mass determination of the molecular ion (electron impact) indicates the formula $C_{10}H_6N_2OS$, but the possibility that the compounds are diazaphenoxathiins has been ruled out by synthesis of (VII).[1]



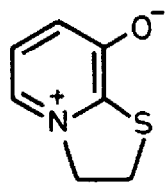
(V)



(VI)



(VII)



(VIII)

(VII) has properties which are quite different from those of (V) and (VI), which behave as much more polar molecules (soluble in H_2O and MeOH, much less so in less polar solvents; high m.p. with decomposition). The suspicion that (V) and (VI) might be betaines was investigated by synthesis of (VIII), a known analogue,[4] and indeed they were quite similar. All three were intensely fluorescent in solution, exhibited a marked solvatochromism, and gave similar (and characteristic) resonances in their n.m.r. spectra.

At this stage, only four possibilities exist for (V) and (VI); the two structures assigned to them, and their isomers with the nitrogen atom of the "bottom" ring in the alternative positions. The 100 MHz p.m.r. spectra of (V) and (VI) are too complex, due to overlapping signals, to allow clear distinction of these isomers. Hence spectra were recorded at 360 MHz,[5] giving complete separation of all signals and thereby permitting unequivocal assignments of all protons in (V) and (VI) (see table). Coupling patterns rule out the alternative isomers, confirming that the two isomers are indeed (V) and (VI). Distinction between these two is based on careful examination of the N.M.R. data.

TABLE

Compound	Chemical shift (ppm) at specified positions. Coupling patterns and coupling constants (Hz) are in parentheses.									
	2	3	4	5	6	2'	3'	4'	5'	6'
^{1}H nmr†	-	-	6.61	7.30	8.31	-	-	8.58	7.59	8.54
V			(dd; 0.8, 8.6)	(dd; 6.0, 8.5)	(dd; 0.7, 6.0)			(dd; 1.5, 8.1)	(dd; 4.8, 8.0)	(dd; 1.6 4.6)
^{13}C nmr#	148.8*A	164.3*	125.0B	125.5B	125.9B	146.3*A	125.2*	116.1C	135.4C	149.1
^{1}H nmr†	-	-	6.61	7.33	8.47	-	-	8.79	7.60	8.65
VI			(dd; ca 1, 8.5)	(ddd; 0.7 6.0, 8.7)	(dd; ca 1, 6.0)			(dd; 1.3, 8.6)	(ddd; 0.8, 4.7, 8.5)	(dd; 1.3, 4.7)
^{13}C nmr#	152.5*D	164.5*	124.5E	125.8E	125.9E	146.7*D	134.6*	118.7F	123.7F	152.7

† ^{1}H n.m.r. were run at 360 MHz in d_6-DMSO.

^{13}C n.m.r. were run at 25.2 MHz in d_4-methanol; ^{13}C assignments were made by comparison of resonances with those for (VIII), ^{13}C - ^{1}H coupling patterns, and general expectations. Where several signals are relatively close, assignments are arbitrary. In these cases, and in other cases where assignments are not unequivocal, the signals which may be interchanged are marked with a superscript capital.

* Weak singlets; ^{13}C signals not marked with an asterisk are doublets in the off-resonance spectra.

The following factors have particularly influenced our assignments:-

(a) the 4' and 6' protons in (VI) are at lower field than those in (V), suggesting that they are located ortho and para to the most electron-withdrawing group i.e. the pyridinium nitrogen;

(b) the 2' and 3' carbons in (VI) are much closer in chemical shift than those in (V) (even if the signals are wrongly assigned this would have to be so). This is expected on electronic grounds only for the given structures.

Other features of the n.m.r. spectra support these conclusions, but since ^{13}C assignments are not unequivocal, we do not list them here. Hence, the distinction between (V) and (VI) must still be considered tentative, although strongly favoured.

We are currently investigating the preparation of related heterocycles and of substituted derivatives of these interesting new ring systems, and we are also attempting to make the final assignments unequivocal. Additionally, the physicochemical and biological properties of the compounds should be of interest.

The procedure below outlines the preparation of the compounds.

3-Hydroxy-2-pyridone (10g) was finely ground with P_4S_{10} (20g), and then heated under nitrogen for 1 h. at 200°C. The solid produced was pulverized, and extracted with distilled water (300 ml) in a Soxhlet apparatus in a fume cupboard; the aqueous portion was then cooled, and continuously extracted with CH_2Cl_2 (approximately 1 litre) to give 7g of crude 3-hydroxypyridine-2-thione on removal of the CH_2Cl_2. Light was excluded with black plastic. Basification (pH>11) of the remaining aqueous layer and further continuous extraction with CH_2Cl_2 gave approx. 2.5g crude mixture of (V) and (VI). Column chromatography on silica with MeOH as eluent separated the two isomers; further purification by recrystallization from H_2O or Pr^iOH gave the pure compounds as monohydrates, melting respectively at 220°C and 290°C. In both cases decomposition begins before melting has been completed, thereby broadening the melting point. Satisfactory microanalyses were obtained for the monohydrates of (V) and (VI).

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References

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4. K. Undheim, V. Nordal, K. Tjønneland: Acta Chem.Scand., 1969, 23, 1704.
5. We thank Miss Betty Rather of the Purdue University Biological NMR Laboratory for running the spectra on a Nicolet 360 instrument, supported by NIH grant RR01077. We also thank Prof. J.B. Grutzner of Purdue University Chemistry Department for useful discussions concerning the NMR data.

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