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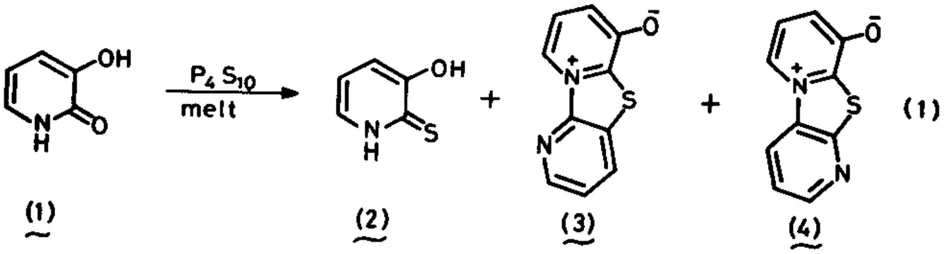
NOVEL HETEROCYCLIC SYSTEMS. PART 7[1]. NEW SPECIES CONTAINING TWO PYRIDINE RINGS BY DEHYDRATION OF 3-HYDROXY-2(1H)-PYRIDONE USING PHOSPHORUS PENTOXIDE.

Ian Matthews, Keith Smith* and John R. Turner[2]
Department of Chemistry, University College of Swansea, Swansea SA2 8PP, U.K.

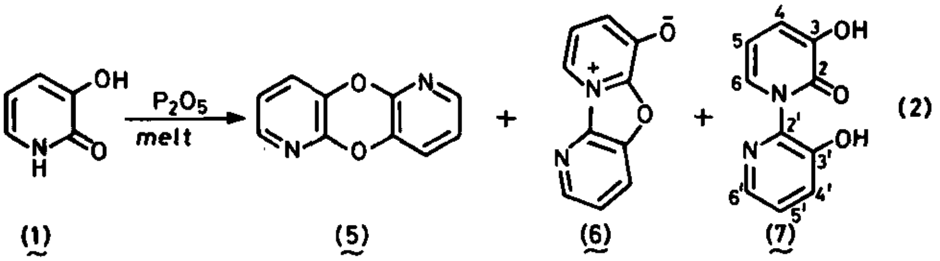
Gary E. Martin
Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy,
University of Houston, Houston, Texas 77004, U.S.A.

Abstract - Dimeric dehydration products of 3-hydroxy-2(1H)-pyridone (1) are obtained by melting a mixture of (1) and P_2O_5 at 250-290°C. The major product is 3-hydroxy-1-(3-hydroxy-2-pyridyl)-2(1H)-pyridone (7). Also obtained are 1,6-diazaphenodioxin (5) and a novel betaine, 6-oxidodipyrido-[2,1-b:2',3'-d]oxazolium (6).

When 3-hydroxy-2(1H)-pyridone (1) is melted together with P_4S_{10}, the major product, 3-hydroxy-pyridine-2(1H)-thione (2), is accompanied by two novel, light sensitive betaines, (3) and (4) (eq. 1).[3,4]



Previously, we have prepared[5] 1,6-diazaphenodioxin (5) by melting together a mixture of (1) and P_2O_5. Although this is a remarkably simple synthesis of (5), the yield is only ca. 15-25%. Following identification of the betaines (3) and (4) in the P_4S_{10} reaction, therefore, we investigated the P_2O_5 reaction in order to see if analogous oxygen-heterocyclic betaines were formed; such betaines may have been destroyed during previous studies because of failure to exclude light during work-up. One such betaine, (6), is indeed formed, though in low yield, but the main product of the reaction is another new type of compound, (7) (eq. 2).



(2)

An intimate mixture (1:2 mass ratio) of (1) and P_2O_5, under argon, was heated in a bath set at 250°C. The temperature of the bath was raised until the mixture began to bubble and form a viscous sludge, and then maintained for 1 h. Good results were obtained using 10g of (1) in a 250 ml flask.[6] Melting occurred at a bath temperature of ca. 280°C.

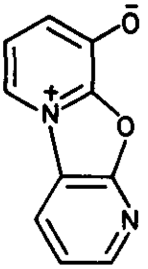
After cooling, the reaction mixture was carefully dissolved in water (ca. 250 ml for 10 g of (1)). Any insoluble matter was filtered and further extracted with water, and the combined aqueous layers (pH ca. 1) were extracted with dichloromethane (4 x 80 ml). Evaporation of the solvent gave crude (5) (15-25% yield), which has been characterized previously.[5]

The residual layer was continuously extracted, in the dark, with dichloromethane to remove any remaining (1), and then basified to pH 11 with concentrated NaOH solution.[7] Further exhaustive extraction gave material in which the main component was the betaine (6). This was purified by chromatography on silica in the dark, using methanol as eluent. Yields were typcially 1-5%. Recrystallisation was from isopropanol; m.p. 215-217°C, with decomposition.

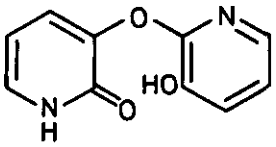
Finally, after neutralization of the aqueous layer to pH 7 using conc. HCl, further continuous extraction gave a large amount (typically 50-55% yield) of substantially pure (7). Further purification involved sublimation (150°C, 5 mmHg) and recrystallization from chloroform (containing a few drops of methanol) - m.p. 203.5-205.5°C (crystals appear to change shape, possibly via sublimation, ca. 30°C below the melting temperature).

The betaine (6) was distinguished from its possible isomer (8) by use of a europium shift reagent, as previously described[4] for betaines (3) and (4). The relative changes in chemical shift on addition of $EuCl_3$ are given in the Table. The assumed molecular structure (10) (all C-H bonds 1.05 Å and bisecting the CCC angles) was used to provide values of Eu-H distances (r) and off-axis angles (θ). Calculated relative changes in chemical shift (Δ_{calc}) were then obtained using the McConnell-Robertson equation.[8]

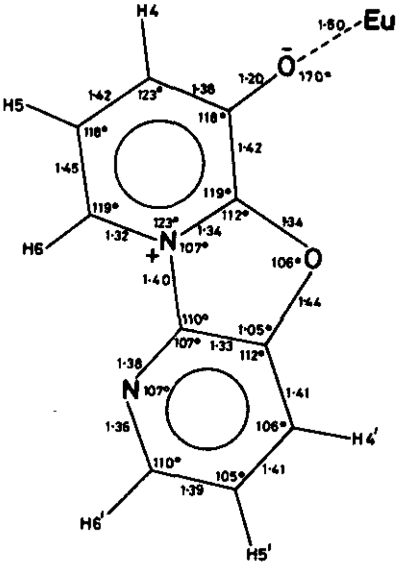
$$\Delta_{calc} = Kr^{-3}(\cos^2\theta-1)$$



(8)



(9)



(10)

The fit for structure (6) was quite good (see Table), but there was no fit for structure (8).

Table

Hydrogen atom	H4	H5	H6	H4'	H5'	H6'
Δ_{obs} (relative to H6)	5.14	1.75	1.00	-0.54	-0.16	0.13
r (Å)	3.69	5.80	6.51	6.25	8.37	8.88
θ(deg.)	19	3.5	19	75	65.5	49.5
Δ_{calc} (relative to H6)	5.49	1.67	1.00	-0.54	-0.14	0.06

In order to distinguish (7) from its possible isomer (9), 1 g of the compound was heated with P_2O_5 under conditions comparable with those used for the reaction of (1) with P_2O_5. Compound (9) would be expected to give a mixture of (5) and (6) in approximately the proportions found in the reaction of (1), i.e. with (5) vastly predominant, whereas (7) should give (6) but no (5). In fact, after work-up much of the compound was recovered, along with up to ca. 50 mg of (6), but only 2-3 mg of (5). The trace of (5) could have resulted via some hydrolysis of the compound to give (1), but the production of a relatively large quantity of (6), comparable to that obtained in the reaction of (1), argues strongly in favour of structure (7) rather than (9).

Further confirmation of the structure of (7) is provided from the assignment of the ^{13}C n.m.r. spectrum of the compound and the measurement of the T_1 relaxation times of the protonated carbon atoms. Thus, the molecule has two carbons (C4 and C5') with short relaxation times (T_1) which is consistent with a system undergoing rotation about an axis coincident with the N1-C2' bond axis. In contrast, if (9) had been the correct structure the axis of rotation would be analogous to that described for the case of pyrrolo[3,2,1-kl]phenothiazine,[9] which in the case of (9) leads to the expectation of four carbons (C5, C6, C5', and C6') with short relaxation times and only two carbons with long relaxation times, this expectation being a function of the altered orientation of the C-H bond vectors relative to the axis of anisotropic reorientation.

The production of a single betaine, (6), in the P_2O_5 reaction, compared with the production of two isomeric betaines in the P_4S_{10} reaction, may indicate different mechanisms for the two reactions. We are investigating this possibility.

Properties of compound (6): soluble in water, methanol; almost insoluble in ether, chloroform; light sensitive; λ_{max} 227, 268, 292, 352 nm; ^{1}H n.m.r. (d_4-methanol), δ = 8.71 p.p.m. (1H, d, J = 4Hz), 8.45 (1H, d, J = 8.5Hz), 8.29 (1H, d, J = 6Hz), 7.87 (1H, dd, J = 4.5Hz, 8Hz), 7.69-7.39 (2H, overlapping m); ^{13}C n.m.r. (d_4-methanol), δ = 155.5 p.p.m. (singlet in the off-resonance decoupled spectrum), 151.2(s), 148.1(d), 142.7(s), 142.1(s), 131.6(d), 126.9(d), 124.5(d), 123.6(d), 110.4(d).

Properties of compound (7): soluble in water, methanol; moderately soluble in chloroform; λ_{max} (0.64 mM in MeOH) 245, 285, 310(sh)nm; ^{1}H n.m.r. (d_6-DMSO), 9.7 p.p.m. (2H, broad, exchangeable 7.98(1H, dd, J = 4Hz, 2Hz), 7.35 (2H, m), 6.97 (1H, dd, J = 7Hz, 2Hz), 6.75(1H, dd, J = 7Hz, 2Hz), 6.14 (1H, t, J = 7Hz); ^{13}C n.m.r. ($CDCl_3$), δ(T_1 sec); 158.46-C2; 147.93-C3; 145.97-C3'; 141.94-C2'; 140.89(2.17)-C6'; 129.86(2.17)-C4'; 127.35(2.01)-C6; 125.54(1.72)-C4; 115.98(1.71)-C5'; 109.41(2.18)-C5; the i.r. spectrum (KBr disc) varies according to the way in which the solid is prepared but always contains broad O-H bands, sometimes with peaks, in the 3500-2400 cm^{-1} region, a band around 1650 cm^{-1}, and several bands in the 1600-1500 cm^{-1} region; the $CHCl_3$ solution spectrum shows bands at 1660 cm^{-1} (medium), 1610 cm^{-1} (strong), 1550 cm^{-1} (weak) and

1445 cm^{-1} (strong); m/e 204.0535 (calculated for $C_{10}H_8N_2O_3$, 204.05348); found, C = 58.72%, H = 4.23%, N = 13.56%; expected, C = 58.82%, H = 3.92%, N = 13.73%.

ACKNOWLEDGEMENT We thank the S.R.C. for a studentship to J.R.T. and N.A.T.O for collaborative grant 019.81 to K.S. and G.E.M.

DEDICATION We should like to dedicate this publication to Professor H.C. Brown for his outstanding contributions to organic chemistry, on the occasion of his seventieth birthday.

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