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THE EFFECT OF THE SIZE OF A RING ANNELATED ONTO 2-HYDROXYPYRIDINE ON THE PYRIDONE - PYRIDOL TAUTOMERIC EQUILIBRIUM.

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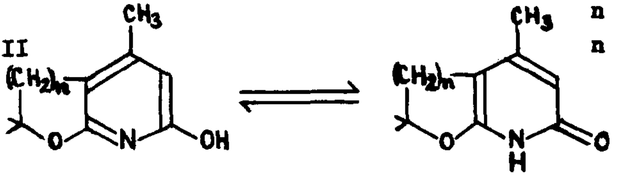
Unsubstituted 2-hydroxypyridine[1] and many of its 3- and 5-substituted derivatives[2,3] exist predominantly or wholly in the pyridone tautomeric form, and not in the pyridol form, in all phases examined, but for highly fluorinated[4], some 6-substituted[5], and very highly substituted[6] derivatives the pyridol tautomer tends to be favoured, especially in solvents of low polarity.

2,3-Dihydro-6-hydroxy-4-methylfuro[2,3-b]pyridine, long known to exist largely in the pyridol tautomeric form I in ethanol[7,5b], contains a five-membered ring. By virtue of the Mills-Nixon effect[8] (i.e. the tendency to minimize ring strain) a double bond outside a five-membered ring is energetically preferred to one inside, but with six-membered rings endocyclic double bonds are preferred.[9] In II the five-membered ring contains an endocyclic double bond, but in one of the Kekule structures of I there are only exocyclic double bonds; this factor will favour the tautomer I. In the corresponding sixmembered-ring system[3] III ⇌ IV any energetic preference of this type will favour the tautomer IV, which has an endocyclic double bond.

The tautomerism of compounds I-IV and of the "cleaved-ring" reference compounds 6-methoxy-2-hydroxypyridine (V) and 2,6-dihydroxypyridine (VI) has

n = 1 : I
n = 2 : III



n = 1 : II
n = 2 : IV

n = 1 : Basic pK_a, 1.95
n = 2 : 1.94

n = 1 with OMe in place of OH, 1.85. n = 1 with NMe in place of NH, 1.54
n = 2 with OMe in place of OH, 3.04. n = 2 with NMe in place of NH, 1.65

been examined by careful comparison of their ultraviolet spectra[3] with those of their *O*- and *N*-methyl derivatives; in cases of band overlap full allowance was made for the submerged wing and for band asymmetry. Special care was given to the minor tautomeric form if present only in small amount.

The change from a five to a six-membered annelated ring causes the ratio [pyridol]/[pyridone] to drop by a factor of ∼20 to 30. V is intermediate between the two ring systems, VI contains less pyridol tautomer than either. The approximate percentages of pyridol tautomer found are: In water: I ⇌ II, 14% V, III ⇌ IV, and VI, no detectable amount; in 99% ethanol: I ⇌ II, 75%; V, 53%; III ⇌ IV, 10%; VI, no detectable amount; in cyclohexane: I ⇌ II, 98%; V, 96%; III ⇌ IV, 73%.

Some ionization constants are listed; via the oversimplified relations sometimes used[5a] they are a treacherous guide to tautomeric equilibrium constants; 2-*O*-methylation in the pyridine is sometimes more base-weakening than *N*-methylation in the 2-pyridone; the amount of pyridol form is then overestimated (e.g. for the system I ⇌ II). Strain in the annelated ring destabilizes the pyridinium ion more than the neutral pyridine.

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