Spontaneous Hydroxylation of a 1,5,7-Trisubstituted 4-Oxo-1,4,5,8-tetrahydro-1,8-naphthyridine

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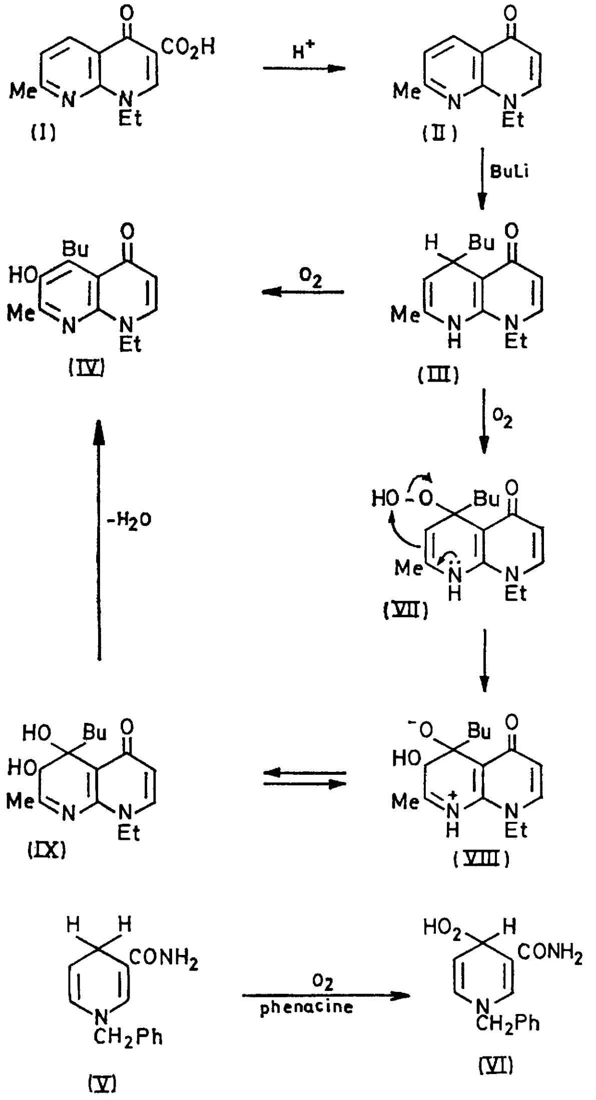
Summary Spontaneous hydroxylation, in the presence of air, of 5-butyl-1-ethyl-7-methyl-4-oxo-1,4,5,8-tetrahydro-1,8-naphthyridine (III) into 5-butyl-1-ethyl-6-hydroxy-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine (IV) is described.

In a programme designed to study the feasibility of the total synthesis of steroids containing a naphthyridine group by a reaction sequence related to the Torgov Synthesis,[1] we have investigated the reaction of n-butyl-lithium with the 1,8-naphthyridine (II). We report here the unexpected results of this model reaction.



Scheme

Compound (II) was obtained by decarboxylation of nalidixic acid (I), and identified by its physical constants[2] and spectroscopic data.[3] Reaction of (II) with BuLi at −70° gave a mixture of two products, plus starting material (*ca.* 22%), and traces of several minor impurities (*ca.* 10%), all of which were separated by SiO_2 chromatography. The major product (*ca.* 53%, m.p. 77—78°), was assigned structure (III).† The product was remarkably unstable to air.

The minor product could also be formed from pure (III) in fairly good yield and practically spontaneously in the presence of air. The analytical data for this new crystalline product (m.p. 170—172°) indicate structure (IV). It exhibited a u.v. absorption (EtOH) at λ_{max} 240 nm (ϵ = 10,200), 277 (shoulder) and 344 (ϵ = 5,800), typical of the related 4-oxo-1,4-dihydro-1,8-naphthyridines.[3]†

Compound (III) derives from a 1,4 addition to the pyridine ring, the α positions of which are occupied and the γ position is further activated by the neighbouring carbonyl group. Although we are not aware of any direct reference to the hydroxylation step, related properties of 1,4-dihydropyridines in biochemical redox systems are well known. For example, it has been reported[5] that phenacine catalyses the oxidation of (V) into the hydroperoxide (VI) in the presence of molecular oxygen. Other authors[6] describe the oxidation of cyclobutanone into γ-butyrolactone by O_2 in the presence of (V) and postulate the hydroperoxide (VI) as intermediate, by analogy to the Baeyer–Villiger oxidation. Here we consider a similar hydroperoxide (VII) as a possible intermediate in the formation of (IV) from (III) (*cf.* Scheme).

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† I.r., n.m.r., and mass spectral data support this structure.

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