Oxidation of Enamino-ketones. Formation of a New Ring System, Furo[2,3-*b*; 5,4-*b*′]dipyridine

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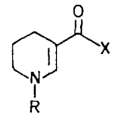
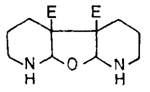
Summary The oxidation of 3-acetyl-, 3-carboxamido-, and 3-ethoxycarbonyl-1,4,5,6-tetrahydropyridines occurs readily, resulting in the formation of dimeric products based on the furo[2,3-*b*;5,4-*b*′]dipyridine ring system.

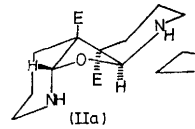
Although the nucleophilic[1] and photochemical[2] reactivity of enamino-ketones has been extensively studied, little work has been reported on their oxidation. We have found that the enamino-ketones (Ia—If), prepared in the usual manner,[3] are readily and rapidly oxidised in aqueous solution by Ag^I or Ce^{IV} salts. This ready oxidation is of interest not only because of the novel nature of the products, but also because these enamino-ketones bear a close structural relationship to those of the dihydropyridine series, the reduced pyridine nucleotides (NADH).



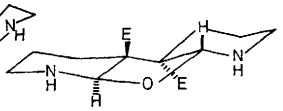
(Ia) R = H, X = OEt
(Ib) R = Me, X = OEt
(Ic) R = H, X = Me
(Id) R = Me, X = Me
(Ie) R = H, X = NH_2
(If) R = Me, X = NH_2



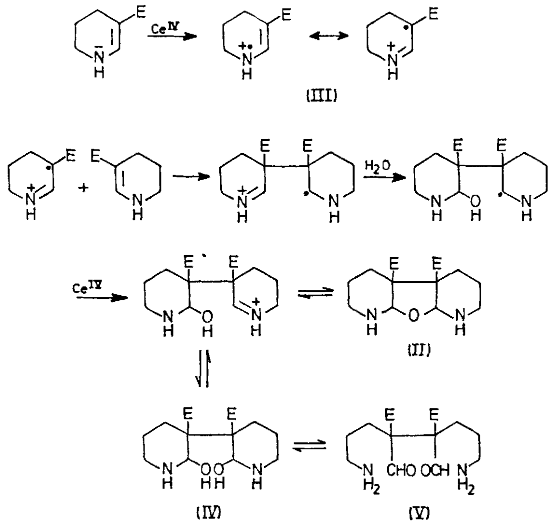
(II)



(IIa)



(IIb)



E = CO_2Et

Treatment of an aqueous solution of enamino-ketone (Ia—If) with aqueous $AgNO_3$ causes a rapid deposition of silver metal, even in the absence of oxygen and light. As difficulties were encountered in isolation of the products, a two-phase oxidation system was adopted, using aqueous cerium(IV)ammonium nitrate with a chloroform solution of the enamino-ketone. When ethyl 1,4,5,6-tetrahydronicotinate (used as a model compound in large-scale reactions for reasons of product stability and solubility) was treated with cerium(IV)ammonium nitrate, the orange colour of the Ce^{IV} ion disappeared immediately, and the products were isolated from the aqueous layer after addition of base. The major product (30%) was identified by high resolution mass spectrometry as having the molecular formula $C_{16}H_{26}N_2O_3$ (*m/e* 326·191); two equivalent non-conjugated ethoxycarbonyl groups [ν_{max} 1735 cm^{-1} (film); δ (90 MHz) 1·28 (6H, t) and 2·37 (4H, q)] and two secondary amino-groups [ν_{max} 3360 cm^{-1}; δ 2·37 (2H, s, D_2O exchangeable)] are evident. The vinyl proton signal is absent from the n.m.r. spectrum and has been replaced by a 2H singlet at δ 5·58 assigned to a methine proton adjacent to nitrogen and another similar deshielding group.[4] Because of the high degree of symmetry apparent in the n.m.r. spectrum structure (II) is proposed for this oxidation product. Two stereoisomeric forms, the *cis,anti,cis-isomer* (IIa), and the *trans,anti,trans-isomer* (IIb), each possessing a rotational axis of symmetry, are possible. This ring system has been assigned previously[5] to a reaction product of the 2,6-dihydroxypyridine-4-carboxylic acid series, but recent work[6] has shown that this assignment is most likely in error. Products analogous to (II) have been identified from the oxidation of other enamino-ketones (I); the yields are comparable to those observed with ethyl 1,4,5,6-tetrahydronicotinate.

Oxidation of the enamino-ketone probably proceeds *via* a cation-radical species (*e.g.* III), which, after dimerisation and subsequent hydration and oxidation, could lead to the furodipyridine (Scheme). The dihydroxy-compound (IV) and its aldehydic counterpart (V) are likely to be less stable, and thus isolable only with difficulty.

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