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FREE RADICAL OXIDATION OF DIHYDROPYRIDINES

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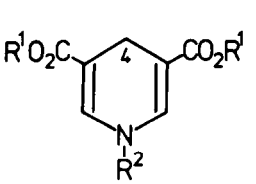
The important role of NADH in hydrogen transfer in biological systems has led to extensive work on the oxidation of dihydropyridines to pyridines.[3] Kinetic and mechanistic studies have revealed examples of both free radical and ionic mechanisms. However, there is only one report[4] of a direct comparison of the rates of oxidation of 1,2- and 1,4-dihydropyridines. Under the conditions employed oxidation took place by hydride ion transfer and, surprisingly, the 1,4-isomers reacted faster.

We have studied the oxidation of isomeric dihydropyridines under free radical conditions using diphenylpicrylhydrazyl (DPP·) to oxidise the dihydropyridines (I) - (IV)[6,7] and the 4,4-dideuterio derivative of (III).[5] The reactions, which were carried out under pseudo first-order conditions using excess of the dihydropyridine, showed second-order kinetics, being first-order with respect to each component. The results are listed in the Table.

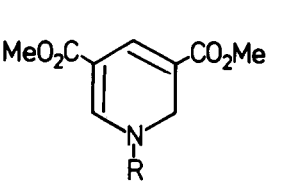
The use of benzoyl peroxide under pseudo first-order conditions (excess Bz_2O_2) did not give very accurate results owing to the limited solubility of the oxidant. Nevertheless, the reaction kinetics and relative rates are in line with those obtained for DPP· and the results are therefore included in the Table.



I; R^1 = Me, R^2 = H

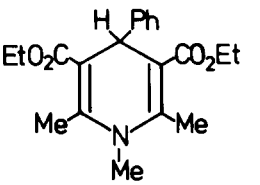
II; R^1 = Et, R^2 = H

III; R^1 = R^2 = Me

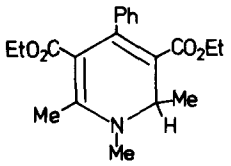


IV; R = H

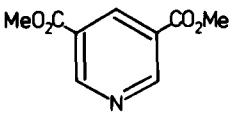
V; R = Me



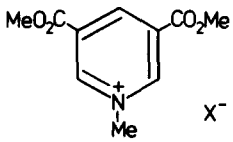
VI



VII



VIII



IX; X = $MeHSO_4$

X; X = $PtCl_6$

TABLE

Free Radical Oxidation of Dihydropyridines[a]

Dihydropyridine	Oxidant	k, M^{-1} sec^{-1} [b]
I	DPP·	0.54
II	DPP·	1.17
III	DPP·	0.52
III - d_2[c]	DPP·	0.24
IV	DPP·	5.00
I	Bz_2O_2	0.1
IV	Bz_2O_2	0.3
VI	Bz_2O_2	-[d]
VII	Bz_2O_2	0.1

[a] In MeCN at 27°; reaction monitored by following the absorbance of DPP· (or of the dihydropyridine in the case of Bz_2O_2) in a Durrum-Gibson stopped-flow spectrophotometer.

[b] Second order rate constants; average (for DPP·) of 3-4 determinations with standard deviations within 5%.

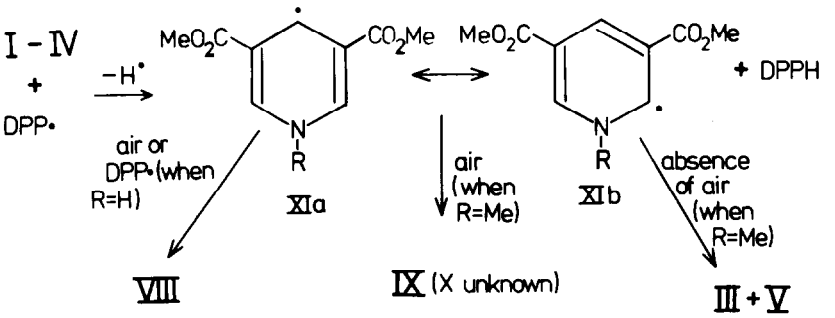
[c] 4,4-dideuterio derivative of (III).

[d] Reaction too slow to follow.

In preparative experiments reaction of (I) with DPP· (1.3 equiv.) in acetonitrile after one week afforded the expected pyridine (VIII) in 86% yield; under the same conditions, but in the absence of air, (I) and DPP· (2 equiv.) gave (VIII) in 80% yield.[8] The N-methyl derivative (III) and DPP· (1 equiv.) after two days yielded a pyridinium salt which was characterised as the

chloroplatinate (X),[7] m.p. 138-139° [λ_{max} (H_2O) 205, 260 nm; ε 44,100, 36,000; δ (DMSO) 9.8 (s, 2H, 2,6-H), 9.2 (s, 1H, 4-H), 4.6 (s, 3H, NCH_3), 4.2 (s, 6H, CO_2CH_3)], identical with an authentic sample prepared from (IX) and H_2PtCl_6. In the absence of air, however, (III) and DPP· (1.1 equiv.) after one week afforded a mixture which was separated by column chromatography[6] to give unchanged DPP· (92%), starting material (III) (33%), and a highly unstable yellow material (15%) which was identified by its spectral characteristics [λ_{max} (MeOH) 220, 280, 395 nm; δ ($CDCl_3$) 7.6 (s, 1H, 6-H), 7.5 (s, 1H, 4-H), 4.9 (s, 2H, 2-H), 3.7, 3.8 (2s, 6H, CO_2CH_3), 3.1 (s, 3H, NCH_3)] as the 1,2-dihydropyridine (V), identical with an authentic sample prepared by borohydride reduction of (IX).

The above results indicate the following mechanism for the reaction:



The rate determining step is the abstraction of an H atom by DPP· from the 2- or 4-position of the dihydropyridine as evidenced by the isotope effect for (III) (k_H/k_D = 2.17). The resultant mesomeric pyridinyl radicals can then undergo aerial oxidation to give (VIII) or (IX), or hydrogen abstraction by DPP· from (XI; R = H) with the formation of (VIII). In the absence of air the radicals (XI; R = Me) abstract hydrogen from the diphenylpicrylhydrazine (DPPH) formed in the first step to give the observed products (III) and (V).

Pyridinyl radicals have been postulated[9] to give isomeric dihydropyridines by halogen abstraction from halocarbons. The isolation of (III) and (V) in the present work provide the first example of the conversion of a pyridinyl radical into isomeric dihydropyridines; it is also the first example of a radical induced isomerisation.[10]

The similarity of the reactions of the dihydropyridines with DPP· and with Bz_2O_2 (see Table) indicate the operation of an analogous mechanism. The one proposed here is based essentially on that postulated by Huyser[11] for the reaction of structurally similar dihydropyridines with benzoyl peroxide, which has been conclusively established to proceed by a free radical pathway.

In accordance with expectation, free radical oxidation is faster for the 1,2-dihydropyridines (IV) and (VII) than for their 1,4-isomers. Replacing a hydrogen on the nitrogen in (I) by a methyl group in (III) does not affect the rate since the first step is abstraction of the hydrogen from the 4-position in both cases. The faster reaction of the ethyl ester (II) as compared to the methyl ester (I) is surprising but may involve steric factors. These may also account for the slower rates observed for Bz_2O_2 as compared to DPP·.

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7 All new compounds gave satisfactory elemental analyses and spectral data except (V) which was too unstable for analysis.

8 With one equiv. DPP· under the same conditions unreacted starting material (I) was still present.

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