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2-CYANO-Δ³-PIPERIDEINES XIV : THE INVOLVEMENT OF SINGLE ELECTRON TRANSFER PROCESSES IN THE OXIDATION AND SUBSEQUENT REACTIONS OF THE AMBIDENT ANION OF 2-CYANO-3-ETHYL-1-METHYL-Δ³-PIPERIDEINE[1]

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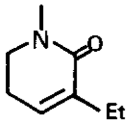
Abstract - The reaction of the ambident anion (2) derived from 2-cyano-3-ethyl-1-methyl-Δ³-piperideine (1) with trace quantities of O_2 leads to the formation of compounds (3) to (7), and in particular the interesting dimer (5). The formation of these products is interpretted in terms of single electron transfer processes.

2-Cyano-Δ³-piperideines such as (1) are a recently introduced class of 5,6-dihydropyridinium equivalents which have the combined capacity to react with nucleophiles as "potential" iminium salts and with electrophiles ("masked" reactivity) via the corresponding ambident anion (2) [2]. The dual reactivity of these synthons provides a multitude of possibilities in alkaloid synthesis.

In a study of the reaction of anion (2) with a series of alkyl halides [2,3] it was found that the products of substitutions at C-2 were formed regiospecifically under kinetic control. Interestingly this reaction appeared to be insensitive to the steric bulk of RX, the yields of the reaction of (2) with CH_3I, $C_6H_5CH_2Br$ and $(CH_3)_2CHBr$ being essentially equivalent to those observed in the reaction with t-butyl bromide and iodide, ie. > 80%. This result was surprizing and led us to suggest that the reaction of (2) with the very bulky tertiary alkyl halides occurred by a single electron transfer process rather than by the generally observed S_N2 mechanism [3].

There is now a considerable body of evidence in the literature to suggest that electron transfer from (2) to an external agent should be a favourable process as the resultant radical would be stabilized by both the electron withdrawing cyano group and the donating nitrogen atom (capto-dative substituent effect)[4].

In a continuation of our studies on the reactivity of the ambident anion (2) it was observed that in its reaction with poorly reactive electrophiles such as N_a-methyl gramine a number of side products, compounds (3)-(7) (diagram), could be detected [isolated in varying quantities by preparative layer chromatography on silica gel ; CH_2Cl_2 : CH_3OH (97:3)]. It was apparent from the presence of lactam (3) and the interesting dimer (5) in the product mixtures that in the absence of reaction with the added electrophile, anion (2) was oxidized by trace amounts of oxygen present in the solvent (THF)[5].



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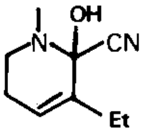

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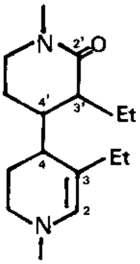

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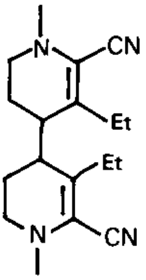

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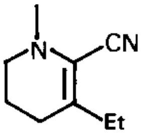

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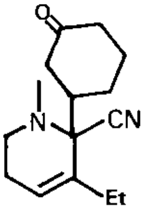
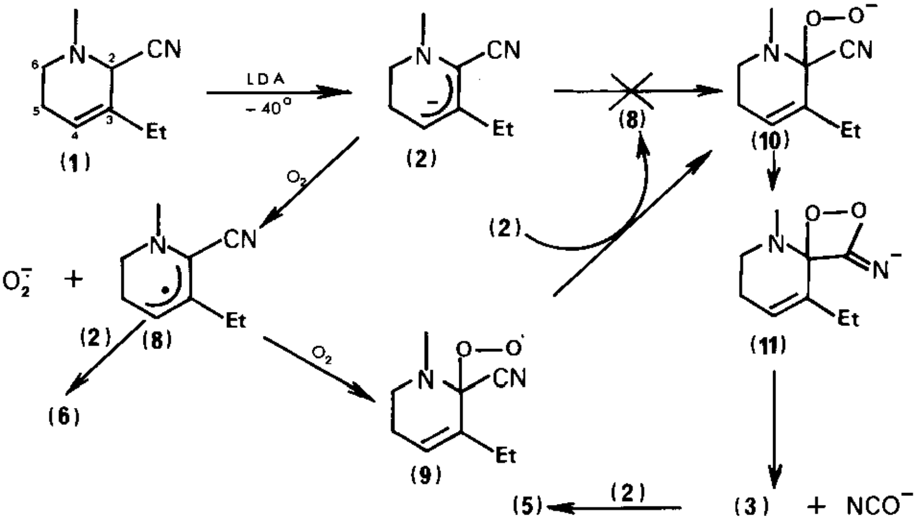


(12)

This was verified by simply stirring a solution of (2) in non degassed THF at room temperature under an argon atmosphere. Examination of the reaction mixture after 4.5 h showed that compounds (3) and (5) were indeed formed in 20% and 23% yields respectively[7]. The [4-4] dimer (6)[3] was also isolated in 8% yield along with aminonitrile (1) (20%). After 15 h at room temperature the starting anion (2) and lactam (3) were totally consumed and compound (5) was obtained in 28% yield. Secondary products were (6) (5%) and the cyanoenamine (7) (18%) (presumably formed by gradual deprotonation of the solvent and reprotonation of anion (2) at the C-4 position [2]).

One could envisage as the first step in this reaction the condensation of anion (2) with oxygen to produce the peroxide ion intermediate (10). However this process is spin forbidden[8], and does not account for the formation of the [4-4] dimer (6). In view of the fact that O_2 is an excellent electron acceptor a more plausible mechanism (scheme 1) would involve an electron transfer from (2) to oxygen forming the radical (8) and superoxide ion. Reaction of (8) could then occur either with anion (2) giving dimer (6) as previously described [3], or with a second molecule of oxygen to give the peroxy radical intermediate (9). Further reduction of (9) to (10) also serves to propagate the chain.

Although the subsequent decomposition of (10) to lactam (3) can take place during extractive work-up and/or purification[7], it appeared probable that the dimeric compound (5) was formed via conjugate addition of anion (2) to a molecule of (3) produced by an in situ reduction of (10). Such an internal reduction could occur through formation of an oxetane type intermediate (11) which rearranges intramolecularly to (3) with elimination of isocyanate ion [9].



Scheme 1

In order to determine whether compound (5) could be formed in this manner a THF solution of lactam (3) was added dropwise to a cooled solution of anion (2) (THF, -20°) and the resulting mixture was stirred for 30 min. From this experiment dimer (5) was isolated in 71% yield along with compound (6) (10%).

Two features concerning this result are particularly striking : i) this is the first example of a 1,4-addition of an ambident aminonitrile anion to an enone system involving attack at the γ-position of the aminonitrile component[10]. The corresponding reaction with cyclohexenone occurs uniquely at the α-position of (2) giving compound (12)[2] (70%). ii) the concomitant formation of the [4-4] dimer (6) is a good indication that the radical species (8) was generated at some point in the reaction pathway.

From this latter observation it is compelling to suggest that the difference in regiochemistries in the reactions leading to (5) and (12) may be the consequence of an electron transfer process in which an electron is transferred from (2) to (3) producing the radical (8) which then undergoes conjugate addition to the radical anion of lactam (3) giving the enolate anion corresponding to (5).

An alternative explanation is that of the amide enolate ion derived from bond formation to the α-position of (2) dissociates giving a radical + radical anion pair which recombines to give compound (5). Such a rearrangement of aminonitrile radicals has previously been proposed [3]. Unfortunately, at present we do not have any firm physical evidence which would confirm one or either of these mechanisms.

REFERENCES

1) For part XIII in this series see : R.J. Sundberg, D.S. Grierson and H.-P. Husson, J. Org. Chem. 1984, 49, 2400.

2) D.S. Grierson, M. Harris and H.-P. Husson, J. Am. Chem. Soc, 1980, 102, 1064.

3) D. Grierson, M. Urrea and H.-P. Husson, J. Chem. Soc. Chem. Commun., 1983, 891.

4) H.G. Viehe, R. Merenyi, H. Stella and Z. Janousek, Angew. Chem. Int. Ed. Engl., 1979, 18, 917.

5) In contrast, when O_2 was bubbled into a solution of (2) for 1 h at -70°C followed by addition of an acid solution of $SnCl_2$[6] at room temperature lactam (3) was obtained in 60% yield along with trace amounts of (6). When treatment with $SnCl_2$ was omitted lactam (3) was also obtained as an admixture with small quantities of cyanohydrin (4) (59%) (detected by M.S.). In this instance lactam formation may occur in part during reaction work-up via elimination of OOH^- from the hydroperoxide intermediate corresponding to (10) and addition of OH^- to the resulting iminium ion giving cyanohydrin (4) which decomposes to (3).

6) S.J. Selikson and D.S. Watt, J. Org. Chem., 1975, 40, 267.

7) (3) (colourless oil) ; IR (film) : 1666, 1623cm^{-1} ; ${}^1H$ NMR ($CDCl_3$) : δ 2.98 (s, NCH_3), 6.20 (s, H-4) ; ${}^{13}C$ NMR ($CDCl_3$) : δ 34.7 (NCH_3), 131.6 (C-4), 137.3 (C-3), 166.0 (C-2) ; MS (m/e) : 139 ($M^{+\cdot}$), 124, 96. (5) (colourless oil) ; IR (film) : 2220, 1640cm^{-1} ; UV λ_{max} (EtOH) 281nm ; ${}^1H$ NMR ($CDCl_3$) : δ 0.88, 1.10 (2 t, $CH_2C\underline{H}_3$), 2.75, 2.92 (2 s, NCH_3) ; ${}^{13}C$ NMR ($CDCl_3$) : δ 41.4 (NCH_3), 35.3 (C-4), 115.3 (CN), 121.2 (C-2), 133.2 (C-3), 34.21 (N'-CH_3), 35.0 (C-4'), 44.5 (C-3'), 172.06 (C-2') MS (m/e) : 289 ($M^{+\cdot}$), 149.

8) G.A. Hamilton, in "Molecular Mechanisms of Oxygen Activation", p. 407, Ed. O. Hayaishi, Academic Press 1974.

9) H.G. Aurich, Tetrahedron Lett., 1964, 657.

10) Similarly, the reaction of the analogous cyanohydrin derived anions with conjugated ketones and esters all involve attack at the α-position of the cyanohydrin component[8] ; see J.D. Albright, Tetrahedron, 1983, 39, 3207.

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