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NOVEL PRODUCTS FROM ATTEMPTED MICHAEL ADDITION TO 1-METHYL-1,2,5,6-TETRAHYDROPYRIDINE-4-CARBONITRILE

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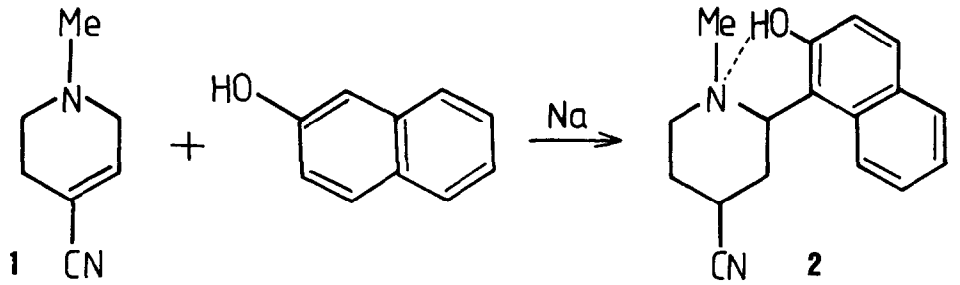
Summary: The reaction of some phenols with the title compound, in the presence of sodium, gives 2-(2-hydroxyaryl)piperidine derivatives. Geometrical isomers have been separated, which differ in having an equatorial (A) or axial (B) cyano group on the piperidine chair (the methyl and aryl groups are equatorial in both forms). The x-ray crystallographic structures of an example of each of A and B are reported and the proton NMR spectra are assigned.

Nucleophilic addition to the double bond of acrylonitrile is a particularly facile reaction[1] and we wished to investigate the possibility of achieving such reactions when the double bond of this grouping formed part of a heterocycle. The readily prepared[2] 1-methyl-1,2,5,6-tetrahydropyridine-4-carbonitrile, 1, was selected as a suitable substrate. We have indeed obtained addition products, but where the nucleophile is attached to C2 of the piperidine ring, rather than to C3 as expected. Thus, reaction of 1 with an excess of 2-naphthol and a little sodium at 100° for 2h (conditions under which acrylonitrile gives the Michael addition product with linkage through the naphthol oxygen[3]) gives 2. The same result can be obtained by preforming sodium naphthoxide.



The product was isolated by stirring the glassy residue with chloroform and 5% sodium hydroxide. The aqueous layer was extracted with more chloroform and the combined extracts gave crude 2 after washing with dilute hydroxide and water.

The crude product was a mixture of 2 isomers, denoted as A and B on the basis of the NMR chemical shift and splitting pattern for the low field heterocyclic ring proton signal. This signal is a doublet of doublets with J = 10, 4Hz for A and J = 8.5, 6Hz for B, with the B signal at lower field by c 0.4ppm. The N-Me signals also have slightly different shifts [2.25(A), 2.38(B)] and a ratio of A:B of 1.8 was obtained for the 2-naphthol compounds. Reactions with m- p-cresol and 4-t-butylphenol have given essentially the same results, though the ratio of A:B differs. Yields, after one crystallisation from light petroleum, are in the range 30-40%.

Repeated crystallization from ethanol gave pure samples of 2-naphthol A and p-cresol B and proof of the addition of the aryl function to the 2-position and the assignment of the A and B stereochemistry was provided by x-ray crystallographic structure determination on these samples.

Isolation of the other isomer of a pair has proved more difficult. Evaporation of the filtrate from the crystallization of 2-naphthol A followed by extraction with hot ligroin, evaporation of the extract, and TLC of the residue [alumina, 4% ethanol in light petroleum (b.p. 40-70°) eluent] did provide a sample of 2-naphthol B (leading edge of band, with rf 0.4). Isomers A and B are readily interconverted. Thus, if either 2-naphthol A or B was heated to melting and then cooled, the same product mixture was formed from each and the ratio was the same as that observed in the original crude mixture. Some isomerization was also suspected during preparative TLC and certain recrystallizations.

The isomers A and B proved to be geometrical isomers. Isomer A (2-naphthol) forms monoclinic crystals belonging to space group $\underline{P}2_1/\underline{c}$ with $\underline{a}$ = 10.359(1) Å, $\underline{b}$ = 12.919(1) Å, $\underline{c}$ = 11.410(2) Å, β = 108.61(1)°; isomer B (p-cresol) forms monoclinic crystals belonging to space group $\underline{C}2/\underline{c}$, with a = 18.583(3), b = 11.824(2), c = 12.010(1) Å, β = 99.00(1)°. The structures were solved by direct methods with *SHELX76*[4], from intensity data measured on a Rigaku-*AFC* four-circle diffractometer with CuKα radiation. Anisotropic refinement of the C,N and O atoms by full-matrix least-squares, in which the positional parameters of the H atoms were varied, converged at $R = \Sigma\Delta F/\Sigma F_o$ of 0.055 for 2103 terms (A) and 0.054 for 1601 terms (B). *ORTEP* drawings of the compounds are shown in Figure 1.

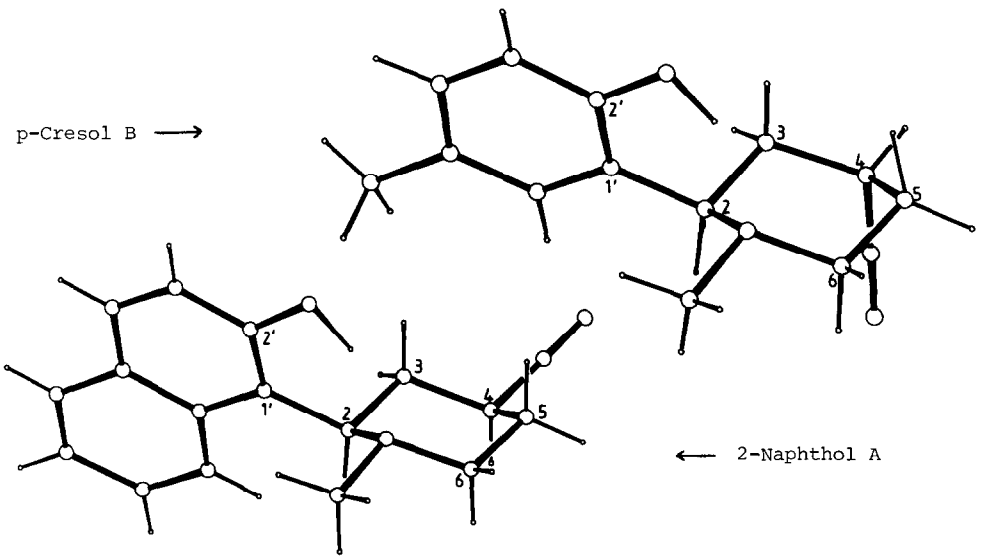


Figure 1

In both compounds studied, the piperidine ring adopts a chair conformation. In isomer A, the methyl, cyano, and aryl substituents are equatorial, while in B the cyano group is axial. The aryl ring is twisted out of the "plane" of the piperidine ring, as defined by the torsional angle N1-C2-C1'-C2' [37.4(3)° (A); 44.8(3)° (B)], so that the hydroxyl group is adjacent to the ring nitrogen with which it forms an intramolecular hydrogen bond [O-H = 1.00(3) Å (A); 0.99(3)

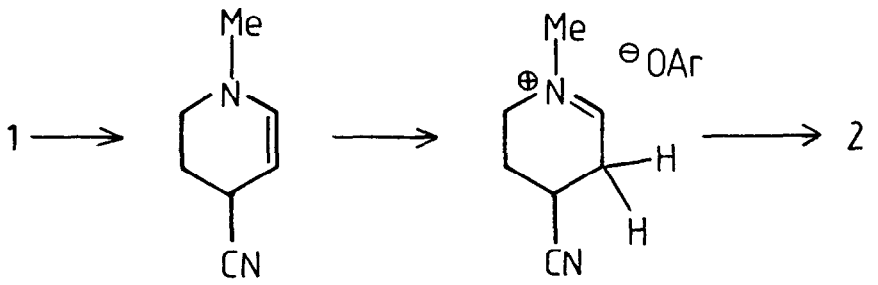
Å (B); N----H = 1.67(3) Å (A), 1.79(3) Å (B); angle NHO = 155(1)° (A), 148(1)°. The NMR spectra in carbon tetrachloride had a broad peak at 11.1 (A) and 9.75ppm (B), attributable to this hydrogen bonded proton.

For A, atoms C2, C3, C5, C6 of the piperidine ring are coplanar within ±0.009(2) Å and the plane makes an angle of 129.7(3)° with the C2, N1, C6 plane and an angle of 129.6(3)° with the C3, C4, C5 plane. Atoms C2, C3, C5, C6 in B are again coplanar within ± 0.010(3) Å, but the plane angles corresponding to those of A are 128.5(4)° and 132.5(4)° respectively.

With the structures known it is now possible to assign the proton NMR signals of the distinguishable piperidine ring protons. For isomer A there are three of these, well resolved at 200MHz. The characteristic low field dd (part of a 3-spin system) at 3.94 (J = 10, 4Hz) is H-2a, the dt (4-spin) at 3.22 (J = 12, 3Hz) is H-6c, and the tt (5-spin) at 2.68 (J = 12, 4Hz) is H-4a. The remaining ring proton signals comprise a multiplet centred at 2.2ppm. For isomer B there are four resolved signals. The low field dd at 4.34 (J = 8.5, 6Hz) is again assigned as H-2a, and a dt at 3.2 (J = 13, 3Hz) is H-6e, as for A. A relatively narrow peak at 3.1, with no large coupling is H-4e; the chemical shift difference of 0.4ppm with respect to H-4a in A is consistent with that observed for H-1a and H-1e in 4-t-butylcyclohexanecarbonitrile[5]. The qd at 2.75 (J = 13, 10, 5.5Hz) is H-6a (with J_{gem} fitting that in H-6e). The signals for H-3,5 are a multiplet centred at 2.15ppm. The downfield shift of 0.4 - 0.5ppm for H-2a and H-6a in B with respect to A is attributable to the 1,3-diaxial relationship of these protons with the cyano substituent in B.[6] The 'fixed' cyano geometry in these compounds provides an interesting spectroscopic example of the differential effect of axial and equatorial cyano groups on proton chemical shifts.

The characteristic difference in coupling constants for the H-2a signal in A with respect to B, is a consequence of the more flattened ring in the latter. This results in a reduced H-2a H-3a dihedral angle and smaller J_{aa} value, and reduced H-2a H-3e dihedral angle and larger J_{ae} value than in the more regular A chair.

The key to the formation of these unexpected products is proposed to be a rearrangement of 1 under the basic reaction conditions to an enamine. In the presence of the excess of phenol such an enamine could form an imminium salt, with subsequent nucleophilic attack by the phenoxide, apparently only at the position ortho to the oxide function.



Further investigation of the scope and mechanism of this reaction is underway.

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