The Nitrous-Acid Deamination of 2-[p-(2'-Hydroxyethoxy)phenyl] ethylamine

Research Report for Ch 80

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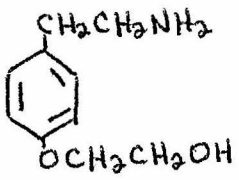
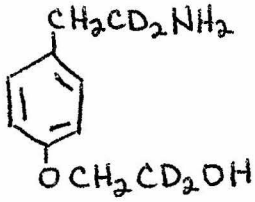
ABSTRACT

The synthesis of 2-[p-(2'-hydroxyethoxy)phenyl]ethylamine (I) and the subsequent aqueous nitrous acid deamination has been carried out and the major products identified. The deuterium-labeled amine (Ia) has been similarly deaminated and the extent of rearrangement of the methylene groups has been determined to be 40% by means of nuclear magnetic resonance spectroscopy.

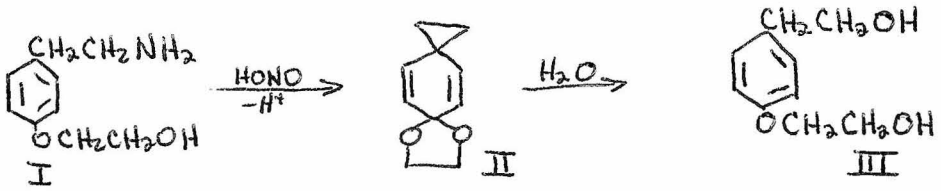


(I)



(Ia)

In the continuing controversy over the existence of non-classical intermediates, the nitrous acid deamination of 2-[p-(2'-hydroxyethoxy)phenyl]ethylamine was undertaken in an attempt to analyze the products (III), and possibly to isolate the proposed intermediate (II). Through this, it should be possible to distinguish the ions formed as intermediates as such rather than as transition states.



To detect the formation of (II), barring isolation itself, the synthesis of the α- and α'- deuterium-labeled amine (Ia) was undertaken. Deamination of this would result in products which could be analyzed with n.m.r., for deuterium shows no resonance signal at the proton resonance frequency. The extent of rearrangement of the labeled methylene groups at both ends of the aromatic ring could demonstrate the existence of (IIa), even if the intermediate itself was not isolated. This is shown in Chart I, below:

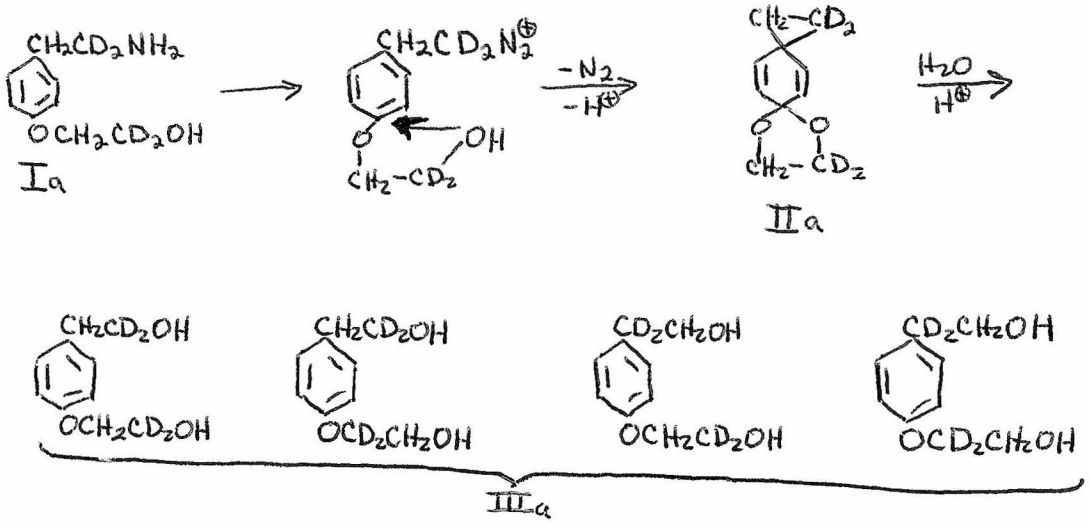


CHART I

The synthesis of (I) and (Ia) was carried out according to the scheme in Chart II. The n.m.r. spectra of (I) and (Ia), with the assigned resonance peaks, is shown in Figure 1.

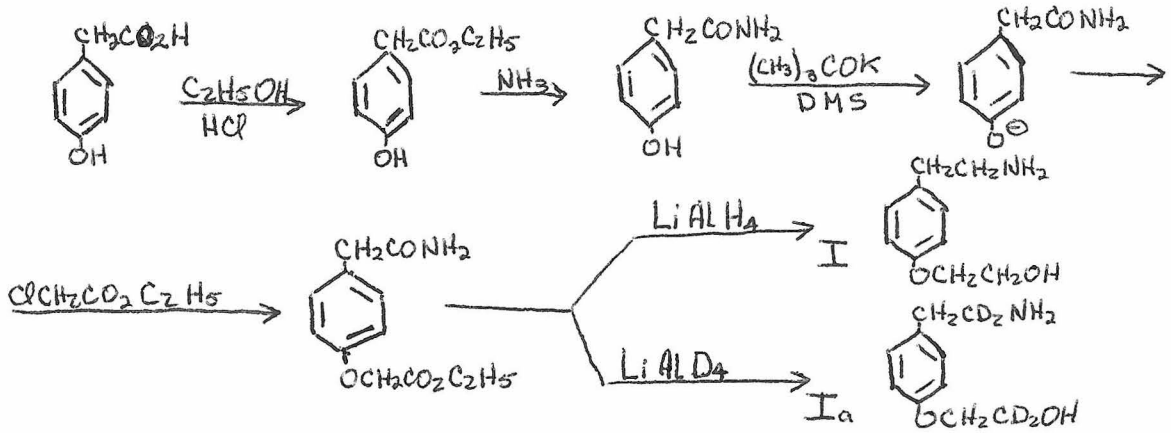


CHART II

Synthesis of (I) was also attempted starting with p-nitrophenyl acetonitrile according to the scheme of Chart III. However, the final reduction with lithium aluminum hydride could not be carried out satisfactorily.

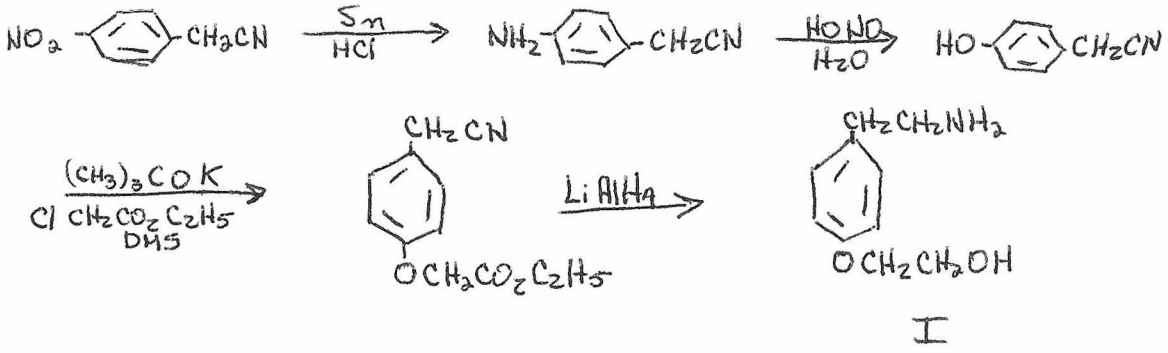


CHART III

Deamination of (I) was carried out in dilute aqueous fluoboric acid solution. The major products were identified from infrared and n.m.r. spectra as the diol (III) and the corresponding nitro compound, $HOCH_2CH_2O\text{-}C_6H_4\text{-}CH_2CH_2NO_2$. Trace amounts of the hydride shift product (IV) were detected, and no evidence of the formation of the elimination product or the tricyclic intermediate (II), was obtained.

IV

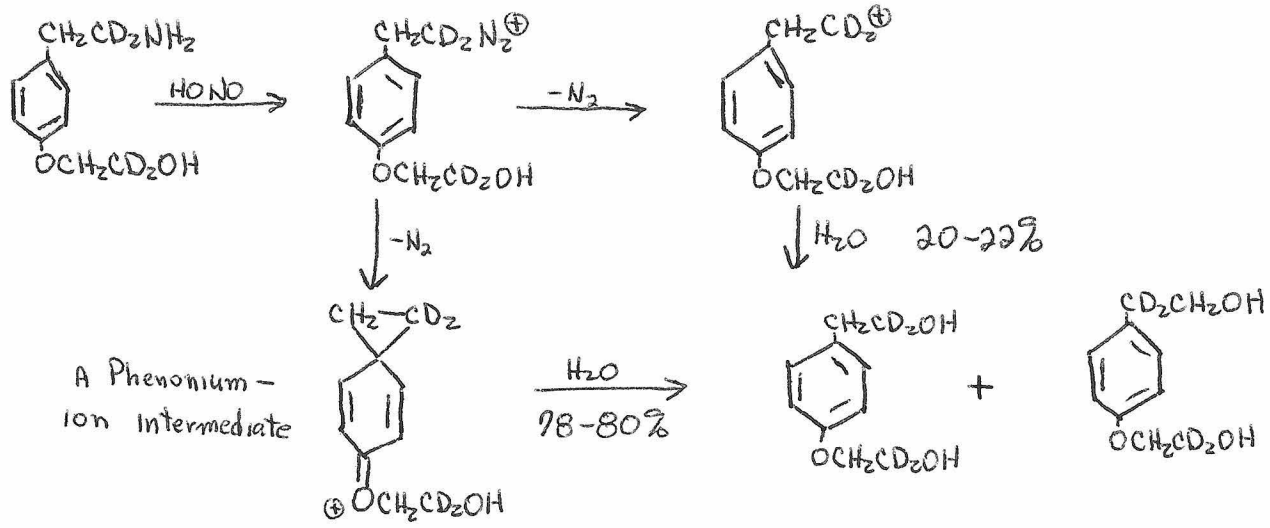
Deamination of the deuterium-labeled amine (Ia) was carried out exactly as for the unlabeled amine (I). The n.m.r. spectra of the diols (III) and (IIIa) are compared in Figure 2. The absence of a peak at 4.0 ppm denotes that rearrangement of the $-OCH_2CD_2OH$ group has not occurred. Further evidence for this is that the area of the peaks of α-CH_2 and β-CH_2 is equal to the area of the α'-CH_2 peak at 4.11 ppm.

These results seem to show that the tricyclic intermediate (II) did not form in the deamination of the aminoalcohol (I). The extent of rearrangement observed (39-40%) agrees well with that observed in the deamination of 2-(p-methoxy)-phenylethylamine-1-^{14}C (33-45%)*. With (I) as with anisylethylamine, the products cannot arise directly from a symmetrical phenonium-ion intermediate, for symmetrical ions should open with 50% rearrangement. At most then, 78-80% of the products of deamination could be derived from this phenonium-ion intermediate, and the remaining parts from an open, primary carbonium ion, such as would result if the carbonium ion

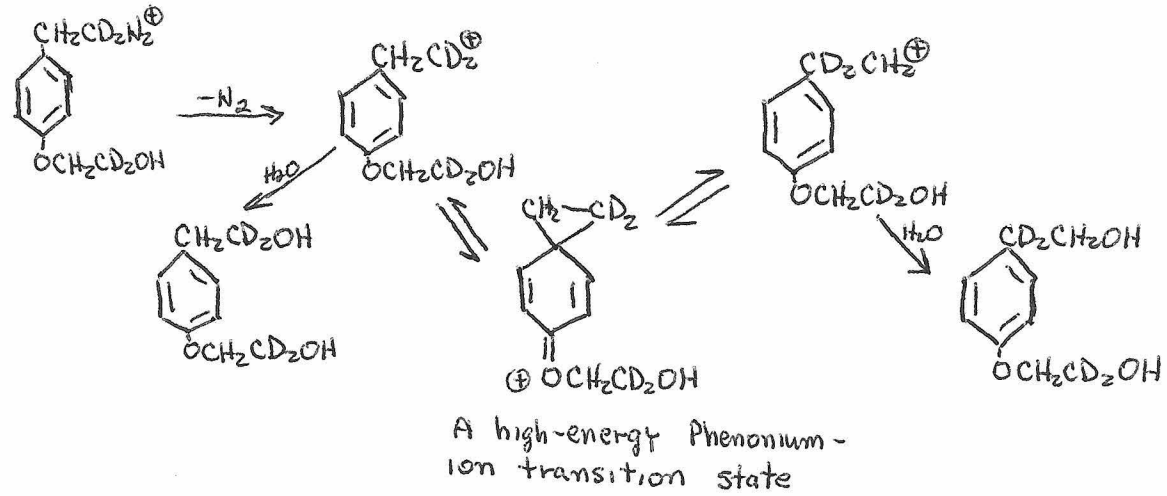
* J.D. Roberts and C.M. Regan, JACS 75, 2069 (1953).

were formed from the diazonium ion while in a rotational conformation unfavorable for phenyl participation.

Alternatively, the products could arise exclusively from open primary carbonium ions resulting from the rapid 1,2-migration of the phenyl group. These two schemes are summarized below:



OR



A complete discussion of the nitrous-acid deamination of 2-[p-(2'-hydroxyethoxy)phenyl] ethylamine is included in the Research Report of M.C. Caserio and R. D. Levin of December, 1964. Experimental details for the above aqueous deaminations are enumerated in this report, as well as results of some deaminations in acetic acid.

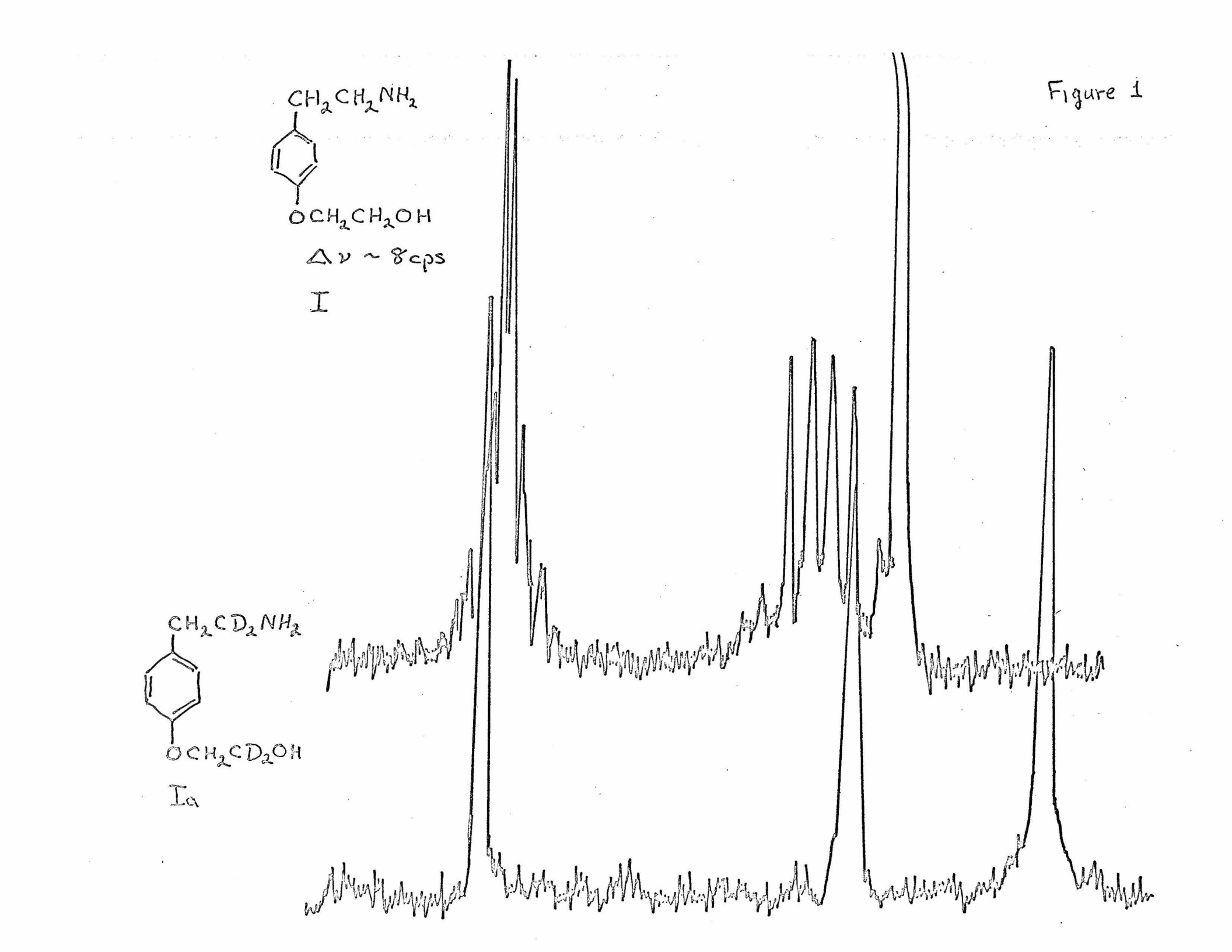

$CH_2CH_2NH_2$
OCH_2CH_2OH
$\Delta\nu \sim 8$ cps
I
$CH_2CD_2NH_2$
OCH_2CD_2OH
Ia

Figure 1

DEAMINATION IN WATER

Figure 2