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DEUTERIUM EXCHANGE IN ALKYLPYRIDINES[1]

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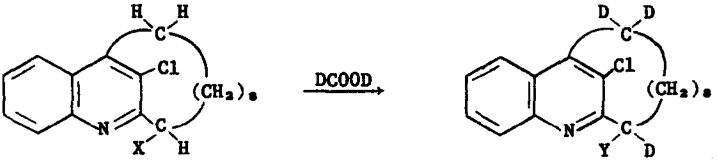
In experiments designed to elucidate the stereochemical course of reduction occurring during the solvolysis of <u>syn</u>- **1**[2] in formic acid[3], we have observed complete exchange of all benzylic hydrogen atoms by deuterium, both in recovered **1** and in products (**2**), when **1** was heated (reflux, 240 hr) in formic acid-d_2. While it is well known that benzylic hydrogen atoms in the 2- and/or 4-position of the pyridine (and related) ring systems undergo deuterium exchange readily in alkaline medium[4], there have been no previous reports of such exchange in organic acids. In this regard, Katritsky[5] and co-workers observed no deuterium exchange at the 2- or 4-alkyl groups when various pyridine derivatives were caused to undergo electrophilic aromatic substitution by deuterium with deuteriosulfuric acid, while Shatenshtein, et al[6] observed exchange in ethanol containing small amounts of mineral acid (DCl). Since HBr is formed during solvolysis of **1**, we were uncertain whether such exchange could be effected by organic acids alone or whether mineral acids are required.

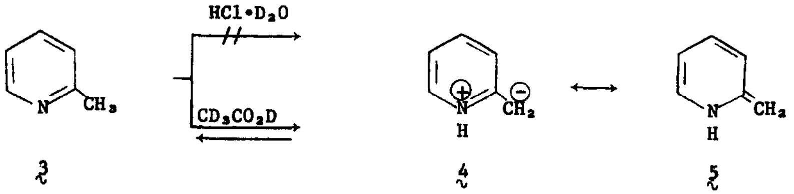


1 a; X=Br
b; X=H

2

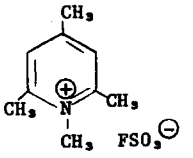
In initial studies we observed that alkyl pyridines do not undergo deuterium exchange in D_2O containing excess DCl. Thus, no exchange was observed when 2,4,6-trimethylpyridine was heated for 76 hr with hot (100°) 38% deuterium chloride in deuterium oxide or when 2-methyl pyridine hydrochloride was treated for 144 hr in hot (100°) deuterium oxide. Under these conditions we assume the pyridine base is largely protonated and that water, chloride ion in water, and sulfate ion in the case of sulfuric acid[5], are not sufficiently strong bases to lead to the anion **4** (enol or anhydrobase **5**) as shown in Scheme I.

Scheme I

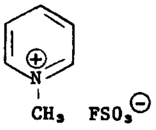


We have observed, however, that deuterium exchange occurs readily at the 2- and 4-benzylic positions in alkylpyridines in deuterioacetic acid. Thus, when 2,5-lutidine was treated for 21 hr in hot boiling acetic acid-d_4, approximately 67% of the hydrogen atoms were exchanged on the 2-methyl group, while little or no exchange occurred at the 5-methyl group. When 2,4,6-collidine was treated in the same manner (24 hr), all three methyl groups underwent exchange (70-71%). Under these conditions either acetate ion associated with the salt of **3**, or free nitrogen base **3**, could serve as base to give **4**(**5**), a probable intermediate in exchange.

The quaternary salt **6** [nmr (D_2O) δ 7.44 (2, s, aromatic H); 3.87 (3, s, N-CH_3); 2.56 (6, s, 2- and 6-CH_3); 2.36 (3, s, 4-CH_3); Calcd: C, 45.94; H, 5.99; N, 5.95. Found: C, 46.21; H, 6.00; N, 5.92], prepared from 2,4,6-collidine and methyl fluorosulfonate, does not undergo exchange when heated (reflux) for 87 hr in acetic acid-OD. It is assumed that lack of exchange under these conditions is a consequence of the fact that neither FSO_3^- or acetic acid is sufficiently basic to remove a proton from **6**. Exchange[7] was observed when **6** was treated



6

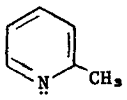


7

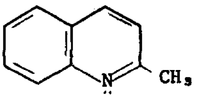
similarly but in the presence of 0.36M sodium acetate (2- and 6-CH_3, 22%; 4-CH_3, 15%; N-CH_3, 0%).

Exchange was also observed when **6** was heated (24 hr) in acetic acid-OD containing 0.027M 2,4,6-collidine as added base (2,6-CH_3, 41%; 4-CH_3, 41%; N-CH_3, 0%). The possibility that exchange in this case occurred with the collidine, which underwent transmethylation with **6**, was not supported by the observation that **6** does not undergo transmethylation with pyridine and **7** does not undergo transmethylation with collidine under these conditions.

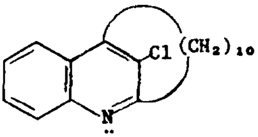
It is interesting to note that hydrogen chloride in acetic acid, in contrast to hydrogen chloride in water, does not prevent exchange. When 2-methylpyridine hydrochloride was treated (96 hr) with hot (reflux) acetic acid-d_4, 53% of the hydrogen atoms on the 2-methyl group were exchanged. Similarly, when the bases **3**, **8** and **9** were treated for 26 hr, 98 hr and 24 hr, respectively, with hot acetic acid-OD[7] containing >1 eq of DCl per eq of base (except **3** which contained .3 eq of DCl) exchange was observed to the extent shown under the formulas.



3
(CH_3, 45%)



8
(CH_3, 65%)



9
(all benzylic H, 65%)

Hydrogen chloride is a weak acid[8] in glacial acetic acid with $pK_a = 8.55$, and the hydrochloride and acetate salts of the free bases would consequently be in equilibrium with the free bases in acetic acid; either acetate ion or free nitrogen base would be present to assist in proton removal and exchange.

Interestingly, 2-alkylpyridines undergo hydrogen deuterium exchange, though quite slowly, in boiling deuterium oxide. Analysis of 2-methylpyridine (**3**) recovered after 144 hr reflux in deuterium oxide showed approximately 10% of hydrogen-deuterium exchange at the methyl group (by nmr). Mass spectral analysis showed $d_0 = 76\%$, $d_1 = 24\%$, $d_2 = d_3 = 0\%$. When 2-methylpyridium hydrochloride was treated similarly, essentially no exchange occurred (∿2% by nmr).

The materials used in these experiments were either prepared (acetic acid-OD by reaction of acetic anhydride and D_2O, compound **9** as reported[2]) or were available commercially (acetic acid-d_4, Stohler Isotope Chemicals, Inc.; 3% DCl in acetic acid-OD, Stohler Chemicals labeled acetic acid-OD).

Analysis of exchange was normally calculated by nmr by comparing total aromatic protons to the methyl or methylene protons in recovered product with unlabeled samples used as blanks. Exchanges of 2,4,6-collidine with acetic acid-OD and reaction of 2,5-lutidine with acetic acid-d_4 were checked by nmr using methylene chloride as internal standard. In no case did we observe any exchange of aromatic protons. 2-Methylpyridine from acetic acid-OD[7] showed by mass spectral analysis: 46.5% d_0, 31% d_1, 16% d_2 and 6% d_3 (27% total exchange); from its reaction as the hydrochloride in acetic acid-d_4: 10.3% d_0, 41% d_1; 38% d_2; 11.2% d_3 (50.2% total exchange).

References

1. Supported by the National Science Foundation, Grant No. GP 35429.
2. W. E. Parham, R. W. Davenport and J. B. Biasotti, J. Org. Chem., **35**, 3775 (1970).
3. W. E. Parham, P. E. Olson, K. R. Reddy, K. B. Sloan, J. Org. Chem. (In Press).
4. K. Schofield, "Hetero-Aromatic Nitrogen Compounds-Pyrroles and Pyridines", Butterworths and Co. Publishers, London (1967) pp. 324-327 and references cited therein.
5. A. R. Katritsky and B. J. Ridgewell, J. Chem. Soc., **1963**, 3753.
6. a) A. I. Shatenshtein and E. N. Zvyagintsera, Doklady Akad. Nauk SSSR, **117**, 852-5 (1957); acid exchange not abstracted C.A. **52**, 17912c (1958).
   b) A. I. Shatenshtein, translated by C. N. Turton and T. I. Turton, "Isotopic Exchange and the Replacement of Hydrogen in Organic Compounds", Consultant's Bureau, New York (1962) pp. 35-36.
7. It was shown that the smaller degree of exchange observed when **6**, as well as when the alkylpyridines, were treated with acetic acid-OD was a result of exchange on the methyl group in acetic acid which dilutes the label. Thus, when acetic acid-OD which was 0.58M in pyridine was refluxed for 46 hr nearly complete scrambling of the label in acetic acid was observed. In the presence of mineral acid, acetic acid-OD appears to be more comparable in effectiveness to acetic acid-d_4.
8. a) I. M. Kolthoff and S. Bruckenstein, J. Am. Chem. Soc., **78**, 1 (1956).
   b) I. M. Kolthoff and S. Bruckenstein, J. Am. Chem. Soc., **78**, 2974 (1956).