Ammonolysis of 3-Hydroxypicolinic Acids. A Correction and Illustration of the Use of ^{13}C Nmr OH/OD Isotope Shifts

George G. I. Moore, and Alan R. Kirk

Riker Laboratories

and

Richard A. Newmark

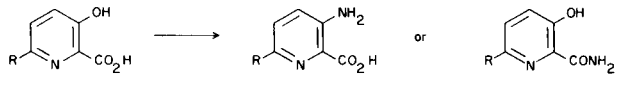
Central Research Laboratories, 3M Company, St. Paul, Minn. 55101

Received September 18, 1978

Ammonolysis of 3-hydroxy-6-methylpicolinic acid (**1a**) has been reported to give 3-amino-6-methylpicolinic acid. However, on heating 3-hydroxypicolinic acid with ammonia at 200°, the product proved to be the known 3-hydroxypicolinamide. ^{13}C Nmr OH/OD isotope shifts in DMSO show that ammonolysis of **1a** gives not **2a**, but instead 3-hydroxy-6-methylpicolinamide.

J. Heterocyclic Chem., **16**, 789 (1979).

Recently in this journal, Mutterer and Weis reported the direct synthesis of 3-amino-6-methylpicolinic acid (**2a**) from the corresponding hydroxy acid (**1a**), simply by heating at 200° in liquid ammonia (1). We required large quantities of the parent amino acid (**2b**), made previously from quinolinic acid imide (2) and from 2,6-lutidine (3) by laborious routes, and decided to apply this surprising reaction to 3-hydroxypicolinic acid (**1b**). The product had m.p. 191-194°, quite different from the 217° reported (2,3) for **2b** but quite suggestive of the isomeric amide **3b**, (m.p. 192-194°) (4). Comparison with authentic **3b** (5) confirmed this structure. Formation of **3b** is far more reasonable than formation of **2b**, since nicotinic acid under similar conditions yielded nicotinamide (6).



1a R = Me
1b H

2a Me
2b H

3a Me
3b H

Mutterer and Weis did not mention **3a** as a possibility. We repeated their reaction and obtained the same substance. Attempts at acidic and basic hydrolysis were not successful. Neither H nmr nor ir can distinguish between **2** and **3**.

^{13}C Nmr likewise was not expected to be useful since the shielding constants of hydroxy and amino groups are similar, as are the chemical shifts induced by a carboxy or carboxamide group. However, use of ^{13}C nmr OH/OD isotope shifts (7) led to unambiguous identification of the product as the amide **3a**. The ^{13}C spectrum of **3a** (see spectrum (a) in the Figure) shows 5 different aromatic ring carbon atoms and the carbonyl carbon as sharp singlets. The exchangeable protons in **3a** and **3b** (or **2a** and **2b**) were 50% deuterated by addition of 3 equivalents of deuterium oxide (3 are needed since there are 2 exchangeable amino protons in addition to the OH or CO_2H). The ^{13}C spectrum then showed doublets for 3 of the ring carbon singlets

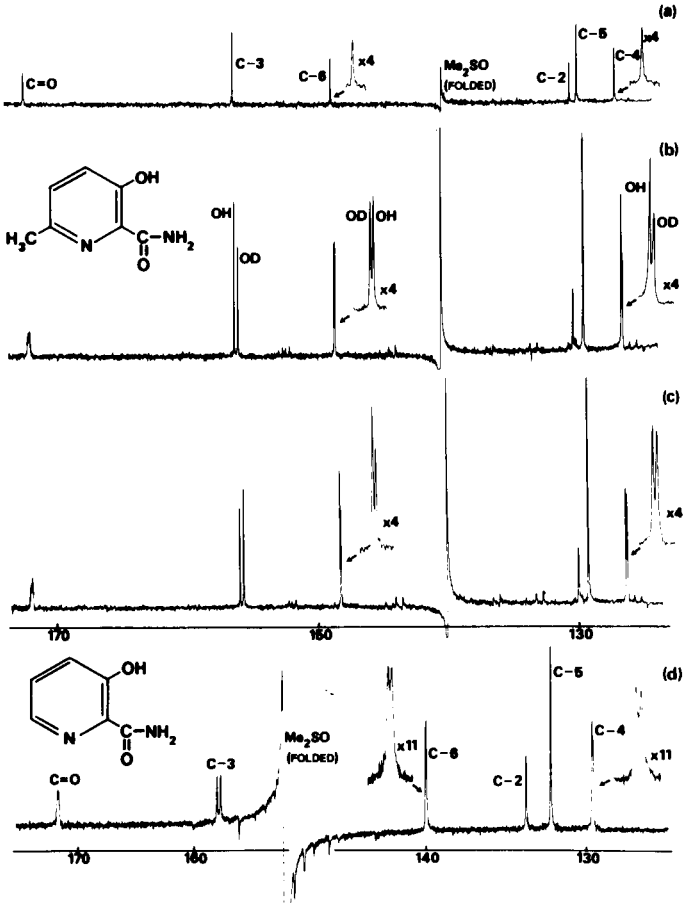


Figure. ^{13}C spectra of partially deuterated (OH/OD) **3a** and **3b**: (a)-(c) **3a** 0% (a), 50% (b), and 60% (c) deuterated, all at a 1221 Hz sweep width (0.31 Hz/point) with no pulse delay and a 48 μ second (35°) pulse width; (d) **3b** 50% deuterated with a 1370 Hz sweep width (0.34 Hz/point). The x11 expansions of (d) are from a spectrum obtained on a 491 Hz sweep (0.12 Hz/point).

(spectrum (b) of **3a** in the Figure). Since acid and amino protons undergo rapid exchange, doublets (or triplets) for

0022-152X/79/040789-03$02.25

the different isotopic species would not occur in **2a** or **2b**. Furthermore, in **2**, even if exchange were slow, the ring carbons would be isotopic triplets due to the $NH_2/NHD/ND_2$ isotopic forms (8). However, in amides and phenols exchange is slow and doublets are expected for the *ipso* and *ortho* carbons (7,8). Observation of such doublets in the products proves they are the hydroxy species **3a** and **3b**.

The nmr spectra were investigated in detail in order to assign the spectra and determine the isotope shifts since an isotopic doublet was not expected for the carbons *para* to the hydroxy group. The ^{13}C spectra were assigned from a consideration of the substituent chemical shifts (SCS) for quaternary carbons and single frequency off-resonance proton spin decoupling (SFOSR) for the methine carbons. The carbon atoms in picolinic acid were first assigned by SFOSR. The chemical shifts in 3-hydroxypicolinic acid (**1b**) were predicted from these data, using the known SCS of a 3-OH in a pyridine ring (9). This corresponded to the observed spectrum of **1b**, thus identifying C-2 and C-3. Since the shielding effects of $-CO_2H$ and $-CONH_2$ are very similar (see the Table), the quaternary atoms of 3-hydroxypicolinamide (**3b**) are unambiguously assigned by comparison to **1b**. The three methine carbons of **1b** and **3b** were assigned by SFOSR since $J_{5,6}$ is much less than $J_{4,5}$ in the proton spectra of pyridines. The chemical shifts of **3a** were calculated using the SCS of a 2-methyl group on a pyridine ring (9) and the observed shifts in **3b**. The observed spectrum of **3a** fits within 1.3 ppm. There is no ambiguity in the assignment of C-2 and C-5, since the former is quaternary and the latter a methine. This assignment shows that the doublets observed in the partially deuterated spectra of **3a** and **3b** are assigned to C-3, C-4, and C-6. The isotope shifts are -0.29, -0.07, and +0.06 in **3a** and -0.31, -0.08, and +0.05 in **3b**, respectively. The shift for C-3 is over twice as large as those typically observed for phenols (7), but a shift of -0.39 has been observed in a 5,4′-dihydroxyflavone (10) in which a strong intramolecular hydrogen bond is possible similar to that expected in **3a** or **3b**. The signs of the isotope shifts were determined from spectra obtained under identical spectrometer conditions with varying amounts of added deuterium oxide (see spectra (b) and (c) in the Figure). The intensities for the three doublets are not identical because the relaxation times for the carbons in the deuterated isomer are longer and the quaternary carbons were partially saturated under the experimental conditions employed. Finally, the carbonyl should be a triplet and C-2 should show a doublet of triplets from the long range effect of the OH/OD and the splittings expected for a carboxamide (8). These splittings were not resolved, but these carbons are clearly broadened in the 50% deuterated samples compared to the normal sample (see Figure).

EXPERIMENTAL

Proton noise decoupled ^{13}C spectra were run in the Fourier transform mode on a Varian XL-100 NMR spectrometer. Spectra of **3a** and **3b** were obtained on 200 mg. samples in 2.0 ml. DMSO to which 0.5 ml. DMSO-d_6 was added for a lock. Much higher concentrations were used for references picolinic acid, **1b**, benzoic acid, and benzamide. The amount of deuterium oxide added to observe isotopic doublets in **3a** and **3b** was equal to the number of equivalents of exchangeable protons in the solute plus 10μl. to compensate for residual water in the solvent. Three pellets (about 200 mg.) of nonindicating Drierite® (calcium sulfate) were than added and the sample allowed to stand overnight in the nmr tube. All chemical shifts reported are for DMSO solutions in the absence of water.

Peaks were referenced to internal DMSO (40.48 ppm relative to TMS) because of the low solubility of TMS in DMSO, but chemical shifts are reported relative to TMS.

Spectra were obtained on 8K data points at sweep widths of 5000 Hz (1.25 Hz/point) for chemical shifts and at sweep widths under 1220 Hz (0.31 Hz/point) for isotopic splittings.

3-Hydroxypicolinamide (**3b**).

A mixture of 139.1 g. (1.0 mole) of **1b** and 500 ml. (17 moles) of liquid ammonia (1) was heated at 200° in a 1 liter steel autoclave for 5 hours. The resulting grey solid was dissolved in 5% aqueous sodium hydroxide, filtered with charcoal, and the solution brought to *p*H 6 with concentrated hydrochloric acid. The tan precipitate was collected and dried to give 72.0 g. (52%) of **3b**, m.p. 185-190°. A sample was purified by recrystallization from ethanol-water to give a white solid, m.p. 191-194°. This product proved identical by ir and mixed m.p. with authentic **3b** (5).

3-Hydroxy-6-methylpicolinamide (**3a**).

6-Methyl-3-pyridinol was carbonated as reported (1) to give **1a** (52%,

Table 1

Chemical Shifts (Ppm from TMS)

Sample	C-1	C-2	C-3	C-4	C-5	C-6	C=O
Benzoic Acid, Obsd.	132.0	130.6	129.4	133.7	129.4	130.6	168.9
Benzamide, Obsd.	134.4	127.7	128.4	131.5	128.4	127.7	168.6
Picolinic Acid, Obsd.		148.4	124.8	137.6	127.2	149.5	166.2
1b, **3b**, Calcd. (a)		136.4	154.8	124.2	126.8	139.6	
1b, Obsd.		129.5	160.3	132.2	129.8	133.5	165.5
3b, Obsd.		131.4	157.8	125.8	129.3	139.9	171.8
3a, Calcd. (b)		130.6	155.3	125.0	128.3	149.0	
3a, Obsd. (c)		129.9	155.8	126.3	129.1	147.9	171.8

(a) Calcd. from SCS of OH on picolinic acid. (b) Calcd. from SCS of CH_3 on **3b**. (c) The methyl carbon is at 23.0 ppm.

m.p. 237-239°). Heating 16.0 g. (0.10 mole) of **1a** with 100 ml. of liquid ammonia (1) for 5 hours at 200° gave 11.5 g. (76% crude) of **3a**, m.p. 150-156°. Recrystallization from water gave pure **3a**, m.p. 160-162° (lit. m.p. 157-158°), possessing the same ir and proton nmr features as reported by Mutterer and Weis (1).

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.2; H, 5.3; N, 18.4. Found: C, 54.8; H, 5.4; N, 18.3.

REFERENCES AND NOTES

(1) F. Mutterer and C. D. Weis, *J. Heterocyclic Chem.*, **13**, 1103 (1976).

(2) E. Sucharda, *Chem. Ber.*, **58**, 1727 (1925).

(3) E. V. Brown and R. H. Neil, *J. Org. Chem.*, **26**, 3546 (1961).

(4) R. B. Arnold, A. W. Johnson and A. B. Mauger, *J. Chem. Soc., 4466 (1958).*

(5) Aldrich Chemical Co., Milwaukee, Wisconsin.

(6) E. P. Oliveto, in "Pyridine and its Derivatives", E. Klingsberg, Ed., Interscience, New York, N. Y., Part 3, 1962, p. 218.

(7) R. A. Newmark and J. R. Hill, 18th Experimental NMR Conference, Asilomar, California, Poster Session II-10; to be published in Org. Magn. Reson.

(8) R. A. Newmark and J. R. Hill, *J. Magn. Reson.*, **21**, 1 (1976).

(9) C. J. Turner and G. W. H. Cheeseman, *Org. Magn. Reson.*, **6** 663 (1974).

(10) F. W. Wehrli, *J. Chem. Soc., Chem. Commun.*, 663 (1975).