A mixture of 27 g. (0.15 mole) of 2-(2-chloroethyl)-piperidine hydrochloride, 50 g. (0.84 mole) of anhydrous trimethylamine, and 100 ml. of absolute methanol was heated in a steel bomb at 125° for 12 hours. After the bomb was opened, the excess trimethylamine and methanol were removed by heating on a steam-bath under vacuum. The resulting yellow viscous sirup was insoluble in ether and acetone and very soluble in alcohol. It was dissolved in 50 ml. of water and stirred for one hour with freshly precipitated silver oxide made from 100 g. of silver nitrate. The silver salts were filtered, and the filtrate was distilled to dryness. The portion of the distillate which was alkaline was saturated with potassium carbonate, extracted with ether, and the combined ether extracts were dried over potassium carbonate. After removal of the ether, distillation gave 3.4 g. (20%) of 2-vinylpiperidine, boiling at 138–142°. The picrate melted at 143–144° and showed no depression on mixing with the picrate obtained by using method A.

4-Vinylpiperidine (X) (Method A).—4-Vinylpiperidine was prepared from 2-[4-(1-acetopiperidyl)]-ethyltrimethylammonium iodide in the manner described; yield of 4-vinylpiperidine, 45%, b.p. 75.5–76.1° at 54 mm.; 54.5–55° at 18 mm.; n_D^{25} 1.4674.

Anal. Calcd. for $C_7H_{13}N$: C, 75.63; H, 11.78; N, 12.60. Found: C, 76.0; H, 11.8; N, 12.8.

Picrate, m.p. 136.5–137.5° (from ethanol). Calcd. for $C_{13}H_{16}N_4O_7$: C, 45.88; H, 4.74; N, 16.47. Found: C, 45.9; H, 4.9; N, 16.6.

There was also isolated 4-(2-dimethylaminoethyl)-piperidine, b.p. 99–103° at 18 mm., representing a 27% recovery of this material. The melting point of picrate was 187–189°; mixed m.p. with known sample, 188–189°.

Method B.—4-(2-Chloroethyl)-piperidine was obtained in a 75% yield from 4-(2-hydroxyethyl)-piperidine by the method described for 2-(2-chloroethyl)-piperidine. It melted at 149–150°.

Anal. Calcd. for $C_7H_{14}NCl$: C, 45.76; H, 8.22; N, 7.61; Cl, 38.52. Found: C, 45.9; H, 8.3; N, 7.8; Cl, 38.5.

This was converted in 35% yield to 4-vinylpiperidine by the method already described for IX; melting point of the picrate, 135–137°, undepressed admixture with a sample prepared by method A.

Preparation of N-Methyl-2-vinylpiperidine (XI).—A mixture of 22.2 g. (0.2 mole) of 2-vinylpiperidine, 26 g. (0.5 mole) of 90% formic acid and 26 g. of 37% formaldehyde solution was heated 8 hours on a steam-bath. After the solution was cooled, 40 ml. of 6 *N* hydrochloric acid was added. The excess acid was then removed by heating on a steam-bath under vacuum. The residue was treated carefully with 20 ml. of 50% sodium hydroxide and cooled with ice to keep the temperature below 30°. The mixture was then extracted with ether, and the combined ether extracts were dried over potassium carbonate, and distilled. There was obtained 14 g. of material, b.p. 59–59.6° at 40 mm.

Anal. Calcd. for $C_8H_{15}N$: C, 76.73; H, 12.09; N, 11.19. Found: C, 76.9; H, 11.9; N, 11.3.

Heating at 160–170° for 6 hours in a sealed tube caused no change in the compound. Picrate, m.p. 150–151° (from alcohol). Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.45; H, 5.12; N, 15.82. Found: C, 47.6; H, 4.7; N, 16.1.

Preparation of N-Methyl-4-vinylpiperidine (XII).—This was prepared in 60% yield from 4-vinylpiperidine by the method described for XI; b.p. 62–62.2° at 40 mm.

Anal. Calcd. for $C_8H_{15}N$: C, 76.73; H, 12.09; N, 11.19. Found: C, 76.6; H, 12.2; N, 11.25.

Picrate, m.p. 143–144° (from alcohol). Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.45; H, 5.12; N, 15.82. Found: C, 47.3; H, 5.0; N, 15.9.

ROCHESTER 4, NEW YORK

COMMUNICATIONS TO THE EDITOR

RAPID DEUTERIUM EXCHANGE IN THIAZOLIUM SALTS[1]

Sir:

In the course of work on a model system for thiamine action we have been led to investigate the stability of an anion at C-2 of thiazolium salts (I). Such a species is formally analogous to a cyanide ion, in that both are anions on a carbon atom which is multiply bonded to nitrogen,[2] and (I) might be expected to catalyze benzoin condensation and similar reactions in the same fashion as does cyanide ion. This is of special interest since thiazolium salts are known to be catalysts for the benzoin condensation,[3] and since thiamine, a thiazolium salt, is involved in biological catalysis of reactions formally analogous to the benzoin condensation.

It was decided that deuterium exchange would be the best way to demonstrate whether such an anion is indeed stable, since deuterium exchange at C-2 could only occur, under mild conditions, through the formation of (I), electrophilic attack by a deuteron on the positively charged thiazolium ring being of course quite improbable. It has been found that thiazolium salts do indeed exchange at C-2 with deuterium oxide very readily, and that *this occurs in the absence of any basic catalyst.*

3,4-Dimethylthiazolium bromide (II) incorporates one atom of deuterium (found,[4] 1.1 atoms[5]) on standing in D_2O at room temperature for 20 hours, and then vacuum drying. Similarly 3-benzyl-4-methylthiazolium bromide incorporates 1.2 atoms of deuterium under these conditions. Both compounds show a strong C–D stretching band[5] in the infrared (KBr pellet) at 4.5μ. The high intensity compared to that in a synthetic sample of 3-benzyl(α-d_2)-4-methylthiazolium bromide suggests that the deuterium is not located on a saturated carbon, and this is supported by the

(1) This is part II of the series "The Mechanism of Thiamine Action"; for part I see R. Breslow, *Chemistry and Industry*, R 28 (1956).

(2) A related species apparently is formed during the decarboxylation of pyridine-2-carboxylic acid (B. R. Brown and D. Ll. Hammick, *J. Chem. Soc.*, 659 (1949)).

(3) T. Ugai, S. Tanaka and S. Dokawa, *J. Pharm. Soc. Japan*, **63**, 269 (1943).

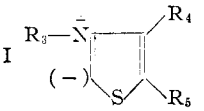
(4) The author wishes to acknowledge the assistance of Miss Laura Ponticorvo with these analyses, which were done by combustion and mass-spectral analysis after conversion of water to hydrogen gas.

(5) See, for instance, R. N. Jones and C. Sandorfy in A. Weissberger "Techniques of Organic Chemistry," Vol. IX, Interscience Publishers, New York, N. Y., 1956, Chap. IV.

loss of a band at 11.0μ which can be assigned to the out-of-plane bending of the H at C-2.[5] In addition, both substances are free of D_2O (no band at 4.0μ). Thiamine chloride hydrochloride itself incorporates 5.2 atoms of deuterium (including the OH and NH_3^+ groups), and also shows the new band at 4.5μ and the loss of a band at 11μ.

Confirmation of the conclusion that it is the hydrogen at C-2 which exchanges is found in nuclear magnetic resonance studies[6] on (II) in D_2O as solvent. The compound initially shows two small equal peaks, at -108 and -47 cycles/sec., and a larger pair at $+66$ and $+114$ cycles/sec. (Varian V-4012A magnet, 7050 gauss field, 30 megacycles/sec. probe; frequencies referred to benzene capillary and increasing field). These are assigned to the groups at C-2, C-5, N-3, and C-4, respectively. On standing, the peak at -108 cycles/sec. diminishes and disappears because of exchange with the solvent. *The half time for this disappearance is of the order of 20 minutes at 28°;* more accurate studies are in progress.

Thus the hydrogen at C-2 of thiazolium salts exchanges with D_2O more rapidly than almost any other "active" carbon-bound hydrogen so far reported,[7] and this is especially striking since its activity apparently is derived merely from attachment to a doubly-bonded carbon and proximity to two electronegative atoms. Such factors are, of



course, like the ones which stabilize cyanide ion, with its triple bond, but it is apparent that in suitable cases even a double bond is sufficient.[8]

(6) Performed by P. Corio and A. Okaya of this department.

(7) Most such exchanges require base or acid in order to proceed at an observable rate. As one example, it is reported that acetylene does not exchange with neutral D_2O after 36 hours (L. H. Reyerson and S. Yuster, THIS JOURNAL, **56**, 1426 (1934)).

(8) It seems that geometrical considerations rule out the possibility that sulfur assists ionization by valence expansion, as this would require a bent allenic carbon at C-2.

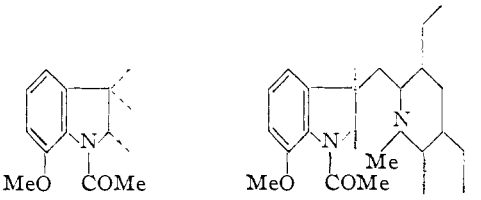
DEPARTMENT OF CHEMISTRY
COLUMBIA UNIVERSITY RONALD BRESLOW
NEW YORK, N. Y.

RECEIVED JANUARY 30, 1957

THE STRUCTURE OF ASPIDOSPERMINE

Sir:

Contrary to published reports, the alkaloid aspidospermine,[1] $C_{22}H_{30}O_2N_2$, contains an N-methyl grouping; this is shown by the presence of an intense singlet peak at 1164 cycles[2] in the nuclear magnetic resonance spectra of aspidospermine and of deacetylaspidospermine, and by a direct Herzig–Meyer determination upon aspidosine (calcd. for one N-methyl: 5.04; found: 4.72). Aspidospermine had been shown[1d] to contain the 7-methoxy-1-acetylindoline system (I), to give 3,5-diethylpyridine and, presumably, 3-ethylindole and/or skatole, upon zinc dust distillation[1c] and to contain one additional C-methyl grouping.[1b] The NMR spectra strongly suggest the presence of three aminomethine hydrogen atoms >CHN– and the absence of any methylene groups adjacent to nitrogen[3]; the latter conclusion is consistent with our failure to prepare any corresponding lactam in oxidation experiments. In consideration of the certain relationship to tryptamine we propose the part-structure (II) and from the evidence for the lack of additional unsaturation we note that the two C—C bonds are missing in II; one bond must



I II

join the alpha carbon of the piperidine ring to either the *alpha* or *beta* indolic positions.[4]

The von Braun degradation with aspidospermine leads to a bromocyanamide, m.p. 178° (calcd. for $C_{23}H_{30}O_2N_3Br$: C, 59.98; H, 6.57; N, 9.13; found: C, 59.35, 59.98; H, 6.67, 6.28; N, 8.55, 9.77) and not to loss of methyl bromide or to any other cyanamide; the bromocyanamide is converted to aspidospermine merely by reflux with hot aqueous ethanol or to deacetylaspidospermine by reflux with dilute acid. Clearly N_b is bonded to some center which can undergo displacement with extraordinary ease.[5] Zinc dust in methanolic ammonium chloride gave a cyanamide, m.p. 188° (calcd. for $C_{23}H_{31}O_2N_3$: N, 11.01, found:

(1) (a) A. J. Ewins, *J. Chem. Soc.*, **105**, 2738 (1914); (b) E. Schlittler and M. Rottenburg, *Helv. Chim. Acta*, **31**, 446 (1948); (c) B. Witkop, THIS JOURNAL, **70**, 3712 (1948); (d) B. Witkop and J. B. Patrick, *ibid.*, **76**, 5603 (1954).

(2) At 40.01 mc./sec. on an arbitrary scale wherein the toluene aromatic proton resonance peak is assigned a value of 1000 cycles and the toluene methyl proton peak assigned 1197 cycles. The proton resonance peak of water on this scale is at 1067 cycles. Spectra were examined in carbon tetrachloride or chloroform solution with an internal toluene reference capillary on a Varian Associates High Resolution Nuclear Magnetic Resonance Spectrometer with Superstabilizer.

(3) In our experience with NMR spectra of a number of compounds containing —CH_2—N< groupings taken in chloroform or carbon tetrachloride solution resonance fell within the range 1115–1150 cycles, usually within the range 1120–1140 cycles. While the NMR curve for aspidospermine showed a weak, broad peak at 1127 cycles, its integrated intensity corresponded to no more than one proton, so that it cannot represent a methylene group. A peak at 1097 cycles corresponding to two protons in area is ascribed to two tertiary hydrogens adjacent to nitrogen and another peak at 1086 cycles is assigned to a single tertiary hydrogen next to the acetylated N_a. Other features were: aromatic protons, 980; methoxyl, 1100; acetyl C-methyl, 1168; ethyl C-methyl, 1227 and miscellaneous methylene and methine protons, 1127–1210 cycles.

(4) We reject an eserine-like structure: (i) because of the difficulty in rationalization of formation of 3,5-diethylpyridine (ref. 1c), (ii) because aspidospermine methiodide, m.p. 268–272° (calcd. for $C_{23}H_{33}N_2O_2I$: C, 55.63; H, 6.70; N, 5.64; found: C, 55.14; H, 6.84, N, 5.63) gives upon acid hydrolysis a deacetyl methiodide which shows no tendency to revert to the expected indolenine-tertiary amine with alkali and is stable to sodium borohydride, (iii) because although deacetylaspidospermine is slowly degraded by lithium aluminum hydride at higher temperatures the product still contains a tertiary N_b and (iv) the change in pK at N_b upon acetylation at N_a is negligible (ref. 1d).

(5) The methiodide, in contrast, gave upon Hofmann degradation merely a mixture of deacetylaspidospermine and its N_a-methyl derivative substantially identical to that produced in a lithium aluminum hydride reduction of vallesine.