TABLE I

QUATERNARY AMMONIUM SALTS

Compd	R^1	R^2	R^3	R^4	Yield, %[a]	Mol formula	Mp, °C	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
					Propargylic, $R^1R^2C(\overset{+}{N}R^3R^4CH_3)C{\equiv}CH$ (Cl^-)								
I	CH_3	CH_3	CH_3	C_2H_5	53	$C_9H_{18}NCl$	181–183	61.52	61.52	10.32	10.42	7.97	7.77
II	CH_3	CH_3	CH_3	$CH_2C{\equiv}CH$	30[b]	$C_{10}H_{16}NCl$	177–178	64.68	64.97	8.69	8.93	7.54	7.48
III[c]	CH_3	CH_3	CH_3	$CH_2CH{=}CH_2$	56	$C_{10}H_{18}NCl$	142–145	62.00	62.15	9.71	9.66	7.23	7.21
IV	CH_3	CH_3	CH_3	$CH_2CH_2CH_3$	84	$C_{10}H_{20}NCl$	199–201	63.30	63.21	10.63	10.70	7.38	7.35
V	CH_3	CH_3	$-(CH_2)_4-$		67	$C_{10}H_{18}NCl$	182–183	63.98	63.76	9.66	9.80	7.46	7.24
VI	CH_3	CH_3	CH_3	CH_2CH_2OH	82	$C_9H_{18}NOCl$	168–170	56.39	55.89	9.46	9.70	7.31	7.19
VII	CH_3	CH_3	CH_3	$CH_2CH_2OCOCH_3$	65	$C_{11}H_{20}NO_2Cl$	166–167	56.52	56.27	8.63	8.80	5.99	6.00
VIII	$-(CH_2)_5-$		CH_3	C_2H_5	48	$C_{12}H_{22}NCl$	214–215	66.79	66.86	10.28	10.42	6.49	5.94
IX	$-(CH_2)_5-$		CH_3	$CH_2CH{=}CH_2$	43	$C_{13}H_{22}NCl$	194–195	68.55	68.83	9.73	9.83	6.15	6.03
X	$-(CH_2)_5-$		CH_3	$CH_2CH_2CH_3$	61	$C_{13}H_{24}NCl$	210–211	67.95	68.05	10.53	10.69	6.10	6.27
XI[d]	$-(CH_2)_5-$		CH_3	$CH_2C_6H_5$	32[b]	$C_{17}H_{24}NCl$	175–176	71.85	71.83	9.05	8.98	4.66	4.50
XII	$-(CH_2)_5-$		$-(CH_2)_4-$		57	$C_{13}H_{22}NCl$	197–198	68.55	68.96	9.74	9.98	6.15	5.82
XIII	$-(CH_2)_5-$		CH_3	CH_2CH_2OH	61	$C_{12}H_{22}NOCl$	181–182	62.18	62.30	9.57	9.63	6.04	6.09
					Allenic, $R^1R^2C{=}C{=}CH{-}\overset{+}{N}(NR^3R^4CH_3)(Cl^-)$								
XIV[e]	CH_3	CH_3	CH_3	$CH_2C{\equiv}CH$	30[b]	$C_{10}H_{16}NCl$	119–120	63.14	63.06	8.75	8.79	7.36	7.16
XV	CH_3	CH_3	$-(CH_2)_5-$		90	$C_{11}H_{20}NCl$	151–153	65.49	64.76	9.99	10.32	6.94	6.36
XVI	CH_3	C_2H_5	CH_3	$CH_2C_6H_5$	58	$C_{16}H_{22}NCl$	146–148	71.55	71.65	8.81	9.09	5.56	5.44
XVII	C_2H_5	C_2H_5	CH_3	$CH_2C_6H_5$	52	$C_{16}H_{24}NCl$	112–114	72.29	72.40	9.10	9.22	5.27	5.18
XVIII	$-(CH_2)_5-$		CH_3	$CH_2C{\equiv}CH$	50	$C_{13}H_{20}NCl$	133–135	69.16	69.02	8.93	8.99	6.20	5.94
XIX	$-(CH_2)_5-$		CH_3	$CH_2C_6H_5$	32[b]	$C_{17}H_{24}NCl$	149–151	73.49	73.39	8.71	8.82	5.04	4.84
XX	$-(CH_2)_5-$		$-(CH_2)_5-$		55	$C_{14}H_{24}NCl$	144–147	69.54	69.18	10.01	10.34	5.79	5.52

[a] Yield of crude material. [b] 50% of total product. [c] Analysis for $C_{10}H_{18}NCl \cdot {}^1/_3H_2O$. [d] Analysis for $C_{10}H_{16}NCl \cdot {}^1/_4H_2O$. [e] Analysis for $C_{17}H_{24}NCl \cdot {}^1/_2C_2H_5OH$.

(II), mp 177–178°. The pmr spectrum of each product and of the original crude material indicated that the latter contained the two products in nearly equal amounts.

3-(N-Methyl-β-acetoxyethylamino)-3-methyl-1-butyne methochloride (VII) was prepared by esterification of the hydroxy compound (VI) by heating with acetic anhydride (steam bath, 1 hr). The product, crystallized from acetonitrile, had mp 166–167° dec and showed infrared bands at 5.7 μ (ester carbonyl) and at 3.0 and 4.7 μ (ethynyl group).

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Characterization of an Intermediate in the Dithionite Reduction of a Diphosphopyridine Nucleotide Model as a 1,4-Addition Product by Nuclear Magnetic Resonance Spectroscopy[1]

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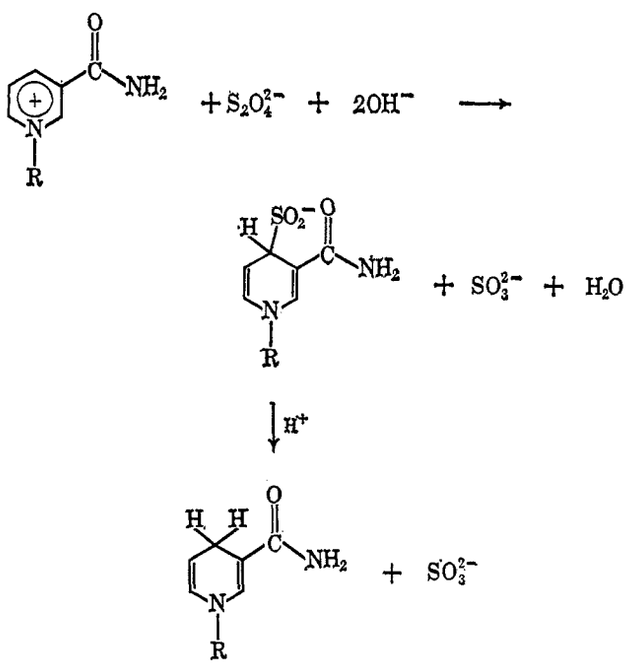
The yellow intermediate formed during the reduction of diphosphopyridine nucleotide (DPN) or its analogs was shown by Yarmolinsky and Colowick to decompose readily into the fully reduced compound ($DPNH_2$) and sulfite.[4] The reduction could thus be represented

SCHEME I



as shown in Scheme I. Here R could be adenosyldiphosphoribosyl, benzyl, or methyl. The yellow complex was studied only in solution where it was labile to air and neutralization, being stable only in strongly alkaline solution. Mauzerall and Westheimer[5] subsequently demonstrated the absence of paramagnetism associated with the intermediate.

The intermediate obtained from DPN exhibits a broad absorption band with λ_{max} at 357 mμ (ϵ 3200).[4] This absorption band is broader than that of other addition products of DPN. Unlike the labile alkali, cyanide, or acetone complexes,[6] the dithionite complex is not fluorescent.[4] Kosower and Bauer suggested that

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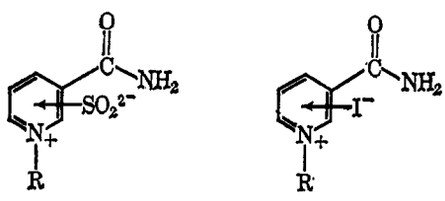
TABLE I

NMR DATA FOR PYRIDINIUM, 1,4-DIHYDRO, AND "YELLOW DITHIONITE INTERMEDIATE" SPECIES OF N¹-BENZYLNICOTINAMIDE

Compd	Chemical shifts[a] H_4	H_5	H_6	Spin–spin splittings, cps 4,5	5,6
N¹-Benzylnicotinamide chloride[b]	8.84	8.13	9.02	8.5	6.3
N¹-Benzyl-1,4-dihydronicotinamide[c]	3.15	4.72	5.72	3.3	7.9
Dithionite intermediate[d] (1,4-addition product)	3.97	4.92	6.19	5.5	7.8

[a] Parts per million from tetramethylsilane (see text). [b] In D_2O. [c] In $CDCl_3$. [d] In D_2O with 1 *M* NaOD.

the intermediate was not an addition product but a π complex (II) analogous to similar complexes of the pyridinium iodides (III).[7] That changes in substituents on the pyridine ring affected the ultraviolet spectra of the dithionite products and of the iodides similarly was considered by these authors to constitute a basis for their suggestion.



II III

The intermediate obtained from dithionite and N-benzylnicotinamide exhibits a similar broad absorption band although at somewhat longer wavelength, λ_{max} 372 mμ (ϵ 3200). The benzyldihydropyridine derivative also exhibits an absorption maximum shifted about 15 mμ to the red of the λ_{max} for $DPNH_2$ (N-benzyldihydronicotinamide, λ_{max} 355 mμ;[8] $DPNH_2$, λ_{max} 340 mμ).

Earlier Wallenfels and Schüly had prepared and characterized by elemental analysis and ultraviolet spectra the addition products of a DPN model (R = 2,6-dichlorobenzyl) with sulfite, sulfide, mercaptobenzothiazole, and benzyl mercaptan.[9] These adducts exhibited absorption bands with maxima at about 350 mμ, suggesting 1,4-addition products, and they dissociated into starting materials in dilute solution. Subsequently these authors isolated a crystalline addition product from a reaction with dithionite which they concluded was a 2-sulfinate.[10]

Proton nmr spectra of the alkali-stable yellow intermediate that is formed in the course of the dithionite reduction of N¹-benzylnicotinamide chloride indicate that the intermediate is a 1,4-addition product as would be the case with a sulfinate or sulfoxylate group attached to the 4 position of the pyridine ring. All proton chemical shifts have been unambiguously identified with the aid of suitably deuterated reactants, and by comparison with the corresponding chemical shift for protons of the analogous pyridinium and 1,4-dihydropyridine compounds. The chemical shifts and spin–spin splittings of the pyridine ring protons of the yellow intermediates resemble those of the fully reduced compounds rather than those of the fully oxidized compounds and are only compatible with a 1,4 adduct, and exclude 1,2 or 1,6 adducts, π complexes, or equilibrium mixtures of such postulated complexes (Figures 1 and 2 and Table I).

For the intermediate, H_2 and H_4 were shifted about 2 and 5 ppm, respectively, to high field compared with oxidized spectrum, whereas these protons were only about 0.1 and 0.8 ppm to low field from their position in the fully reduced species. Complexes of the type represented by II could be expected to exhibit nmr spectra which resemble the fully oxidized species far more closely than the fully reduced species[11] or, if a paramagnetic species resulted, broadening would be expected. Hanna and Ashbaugh have reported nmr spectra for a series of complexes between 7,7,8,8-tetracyanoquinodimethane and methyl-substituted benzenes.[11] In each case on molecular complex formation the acceptor protons were shifted to high field, but only to an extent far less than those shifts observed here in the intermediates produced with dithionite. The high-field shift which could result from charge neutralization in these intermediates (if regarded as charge-transfer complexes) would also be expected to be far too small to account for the shifts observed. On the other hand, the small shifts to low field in the spectrum of the intermediate compared with the fully reduced compound can be readily rationalized in terms of a 1,4-addition product. For example the low-field shift of 0.8 ppm for H_4 appears entirely consistent with the replacement of one of the 4 protons with a deshielding sulfinate or sulfoxylate group. Less marked deshielding effects are expected for the other positions as observed.

Solutions of the yellow intermediate and sodium hydroxide on cooling gave a crystalline, but unstable, yellow solid in good yield. The solid gave elemental analyses in accord with the presence of the sodium salt of either a sulfoxylate or a sulfinate group in the molecule. Solutions of the salt were yellow and exhibited an ultraviolet spectrum identical with the spectrum of the solution of yellow intermediate used in the nmr studies. A broad absorption band was found at about 372 mμ ($\epsilon \approx 3000$) for solutions which were prepared either by mixing dithionite and the oxidized species or by dissolving crystalline salt and also for solutions where concentrations of intermediate varied from 0.25 m*M* to 0.25 *M* or the concentrations of NaOH varied from 0.05 to 1 *M*. Furthermore, no intermediate other than the 1,4-addition product was detected in the nmr spectra. Thus the yellow color appears to be due to the 1,4-addition product.

The nmr spectra of solutions of dithionite and N¹-benzylnicotinamide, the elemental analyses on the solid, and the correlation of ultraviolet spectra of solutions studied by nmr and of the solid all support the hypothesis that the yellow intermediate is the 1,4-sulfinate or -sulfoxylate and thereby provide strong experimental support for the original suggestion of Yarmolinsky and Colowick that the yellow intermediate

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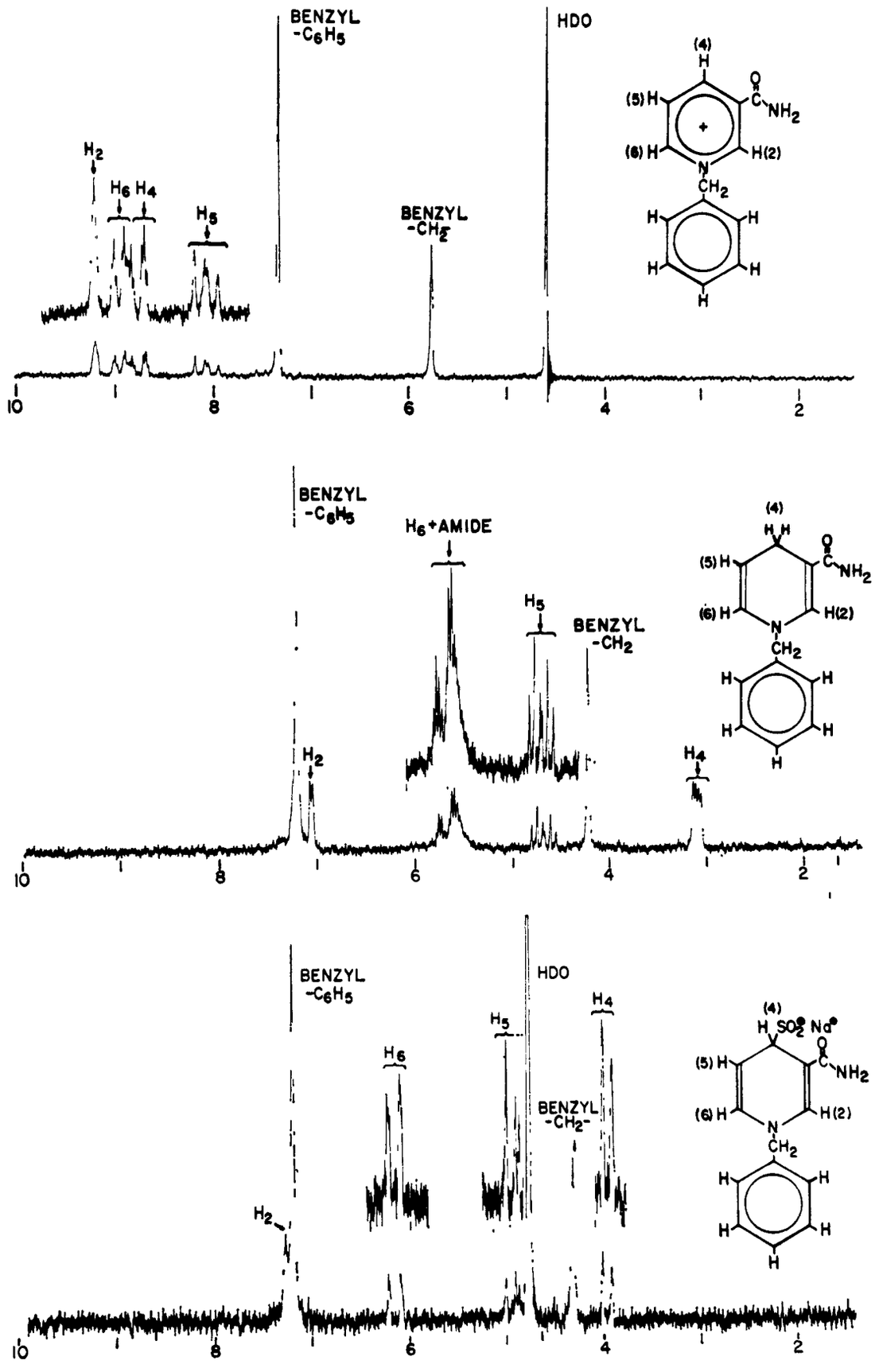

Figure 1.—Nmr spectra of 1-benzylnicotinamide derivatives. Upper and lower spectra in deuterium oxide; middle spectrum in deuteriochloroform.

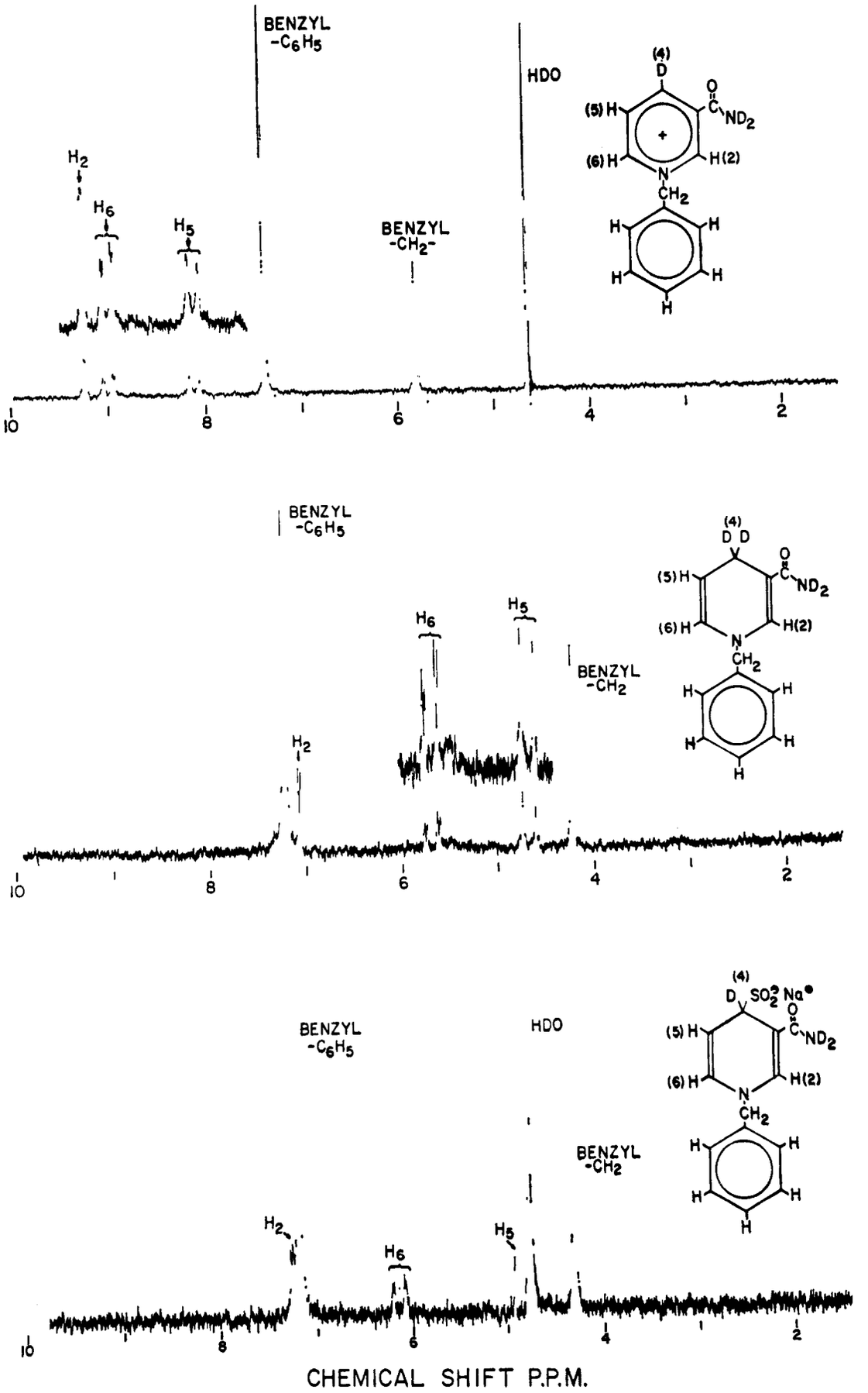

Figure 2.—Nmr spectra of 4-deuterated 1-benzylnicotinamide derivatives. Upper and lower spectra in deuterium oxide; middle spectrum in deuteriochloroform

formed during the dithionite reduction of DPN was an addition product.

Experimental Section

1-Benzylnicotinamide chloride was prepared according to Karrer and Stare.[12] Found in the nmr spectrum in D_2O were benzyl CH protons as a singlet at 5.81, phenyl protons as a singlet at 7.41, H_5 as a pair of doublets ($J_{4,5}$ = 8.5 cps, $J_{5,6}$ = 6.3 cps) at 8.13, H_4 as a pair of triplets ($J_{4,5}$ = 8.5 cps, $J_{4,6}$ and $J_{2,4}$ = 1.6 cps) at 8.84, H_6 as a pair of partially resolved triplets ($J_{5,6}$ = 6.5 cps, $J_{2,6}$ and $J_{4,6}$ = 1.6 cps) at 9.02, H_2 as a broad "singlet" at 9.27; HDO as a singlet at 4.65.

1-Benzyl-1,4-dihydronicotinamide was prepared by reduction of the nicotinamide chloride with dithionite according to Mauzerall and Westheimer.[8] Nmr spectra in $CDCl_3$ agreed closely with the data reported previously.[13,14] Found were H_4 as a pair of doublets ($J_{4,5}$ = 3.3 cps, $J_{4,6}$ = 1.7 cps) at 3.15, benzyl CH_2 as a singlet at 4.28, H_5 as a pair of triplets ($J_{4,5}$ = 3.3 cps, $J_{5,6}$ = 7.9 cps) at 4.72, H_6 as a pair of quarters ($J_{5,6}$ = 7.9 cps, $J_{4,6}$ and $J_{2,6}$ = 1.7 cps) at 5.72 with amide protons on high-field side, H_2 as a doublet ($J_{2,6}$ = 1.7 cps) at 7.13, phenyl protons as a singlet at 7.28.

1-Benzyl-1,4-dideuterionicotinamide and 1-Benzyl-4-deuterionicotinamide Chloride.—To a solution of 1-benzyl-1,4-dihydronicotinamide (0.76 g, 3.5 mmoles) in dimethylformamide (5 ml) was added chloranil (0.91 g, 3.7 mmoles) in dimethylformamide (20 ml).[15] After 10 sec while mixing thoroughly, 10 ml of 1 *M* HCl was added. The aqueous phase, which contained benzylnicotinamide chloride, was washed three times with ethyl acetate and evaporated to dryness. Crystals were obtained from ethanol in 70–90% yield, mp 229–232°. After three cycles of oxidation with chloranil in dimethylformamide and reduction with dithionite in deuterium oxide, the nmr spectra obtained for both the oxidized and reduced compounds were consistent with the presence of only deuterium at the 4 position.

In the nmr spectrum for the reduced compound in $CDCl_3$ were found benzyl CH_2 protons as a singlet at 4.28, H_5 as a doublet ($J_{5,6}$ = 8.0 cps) at 4.72, H_6 as a pair of doublets ($J_{5,6}$ = 7.9 cps, $J_{2,6}$ = 1.7 cps) at 5.73, H_2 as a doublet ($J_{2,6}$ = 1.8 cps) at 7.13, phenyl protons as a singlet at 7.28. In the nmr spectrum for the oxidized compound in D_2O were found benzyl CH_2 protons as a singlet at 5.83, phenyl protons as a singlet at 7.42, H_5 as a doublet ($J_{5,6}$ = 6.2 cps) at 8.14, H_6 as a pair of doublets ($J_{5,6}$ = 6.3 cps, $J_{2,6}$ = 1.2 cps) at 9.03, H_2 as a doublet ($J_{2,6}$ = 1.1 cps) at 9.28, HDO as a singlet at 4.65.

Dithionite Addition Products.—For the nmr studies the 4-hydrogen and 4-deuterio derivatives were both prepared in the same manner. Sodium dithionite (93% pure,[16] 87 mg, 0.5 mmole) was dissolved in 0.5 ml of 2 *M* NaOD in D_2O under nitrogen. The benzylnicotinamide chloride (63 mg, 0.25 mmole) in 0.5 ml of D_2O was added dropwise to the alkaline dithionite solution over a period of 1 min and the nmr spectrum was observed. In the nmr spectrum for the solution from the 4-deuterio derivative were found benzyl CH_2 protons as a singlet at 4.35, H_5 as a doublet with the low-field peak at 4.98 (the high-field peak was hidden under the HDO peak), H_6 as a doublet ($J_{2,6}$ = 1.2 cps, $J_{5,6}$ = 7.8 cps) at 6.19, phenyl protons as a singlet at 7.23, H_2 as a doublet ($J_{2,6}$ = 1.2 cps) at 7.30. In the nmr spectrum for the solution from the 4-hydrogen derivative were found H_4 as a doublet corresponding to one proton ($J_{4,5}$ = 5.4 cps) at 3.97, benzyl CH_2 protons as a singlet at 4.34 cps, H_5 as a pair of doublets partially under HDO peak ($J_{4,5}$ = 5.5 cps, $J_{5,6}$ = 7.5 cps) at 4.92, H_6 as a pair of doublets ($J_{2,6}$ about 1.0 cps, $J_{5,6}$ = 7.5 cps) at 6.19, phenyl protons as a singlet at 7.23, H_2 as a doublet ($J_{2,6}$ = 1.0 cps) at 7.30. A solution of the 4-hydrogen derivative was prepared in the same manner except for the use of ordinary water in place of D_2O. This solution was transferred while minimizing exposure to oxygen *via* a syringe to an absorption cell with a 0.025-mm path length (Perkin-Elmer ultraviolet short path length cell no. 220-0070). With a 10% transmission neutral density screen in the reference beam, it was possible to observe a broad absorption band with ϵ 2800 at 375 mμ on a Perkin-Elmer Model 202 spectrophotometer (dithionite absorption in the reference cell amounted to an ϵ of 110 at 375 mμ). The spectra of more dilute solutions in cells of longer path lengths gave similar spectra. Thus when the original solution was diluted 1000-fold with either 1 or 0.05 *M* NaOH, a broad absorption band was observed with λ_{max} 372 mμ (ϵ 3000–3200).

To obtain a sample for elemental analyses a preparation was carried out in nondeuterated solvent and with tenfold larger amounts. The intermediate spontaneously crystallized from such solutions on standing at 3–4° overnight. The crystals were isolated by centrifugation and pressed dry on unglazed porcelain followed by drying under vacuum at room temperatue for 12 hr. The yellow crystals turned brown on standing exposed to air and the material underwent decomposition during attempts at recrystallization. The yield was 53%.

Anal. Calcd for $C_{13}H_{13}N_2NaO_{13}S$: C, 51.99; H, 4.36; N, 9.33; Na, 7.66; S, 10.68. Found: C, 47.75; H, 4.67; N, 8.93; Na, 7.54; S, 10.74.

The low value for carbon could result from sodium carbonate formation during combustion (as is frequently encountered with sodium salts) or from lack of purity. The absorption spectra of a 0.25 m*M* solution of the crystalline material in 1 *M* NaOH exhibited a broad band with λ_{max} 372 mμ (ϵ 3100). The yellow crystals were insoluble in ethanol and freely soluble in water; a yellow oil, possibly the dihydropyridine, separated from the water solution a few minutes after mixing. When heated in a sealed evacuated capillary, the crystals shrank and turned brown at 114–117°; further heating (to 200°) did not result in melting. Both solubility and melting characteristics were consistent with the crystals being a salt. In contrast, the dihydropyridines were readily soluble in ethanol and sparingly soluble in water.

Nmr Spectra.—All nmr spectra were obtained with a Varian Model A-60 spectrometer. Data in $CDCl_3$ are reported as parts per million from tetramethylsilane as internal standard (δ values). Chemical shifts for the D_2O solutions were estimated by the method of tube replacement; these values are thus only approximate as no internal or external reference was used. More precise chemical shifts were not considered necessary to support the conclusions of this paper.

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Dihydropyran Derivatives of Secondary Aromatic Amines

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Although dihydropyran has been used in numerous synthetic sequences as a blocking group for alcohols and acids, recent reviews indicate its use has not been extended to amines.[2–4] The sole work in this area is that of Glacet, who prepared 2-tetrahydropyranylamines by the addition of aniline and N-methylaniline to dihydropyran.[5,6]

We have now extended the scope of this reaction to five secondary aromatic amines. Since the tetrahydropyranyl group can be easily removed to regenerate the original amine, it offers promise as a base-stable blocking group for these amines.

(1) To whom inquiries should be sent: Central Research Department, Experimental Station, E. I. du Pont de Nemours and Co., Wilmington, Del.

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