TABLE III
PHOTOLYSIS OF p-CHLOROPHENYL ETHYL CARBONATE

Compd	Gc retention time, sec	Column temp, °C	%	Deviation ±
Pinacol[a]	120	100	10.3	0.5
Phenol (3)	65	150	1.2	0.1
Phenyl ethyl carbonate (2)	216	150	29.0	0.2
Ethyl salicylate (4)	264	150	1.3	0.1
p-Chlorophenyl ethyl carbonate (1c)[b]	360	150	55.9	0.1
p-Isopropenylphenyl ethyl carbonate (7c)[c]	900	150	1.2	0.2

[a] Separate run. [b] An unknown peak follows this peak very closely. It represents 1.1% (±0.1) of the mixture and is believed to be ethyl p-hydroxybenzoate (5). [c] Using gas chromatography-mass spectroscopy an additional peak was observed after this peak and was identified as p-isopropoxyphenyl ethyl carbonate (6c) from its mass spectrum.

A control reaction was carried out for each of the chlorophenyl ethyl carbonates and gc analysis showed that no dark reaction had occurred. The photolyses were monitored by gc and were stopped when it appeared that new products were not being formed. When the photolysis was ended, the solvent was evaporated under vacuum and the remaining solution analyzed by gc and by gc–mass spectroscopy. The principle products of the photolysis were collected as they eluted from the gas chromatograph and analyzed further by nuclear magnetic resonance (nmr) and by infrared (ir) spectroscopy.

Product Identification.—**Pinacol** was identified by comparing its retention time with that of an authentic sample.

Phenol (3) was identified by comparing its retention time and mass spectrum with those of an authentic sample.

Phenyl Ethyl Carbonate (2).—The retention time and mass spectrum of this compound were identical with those of an authentic sample. A pure sample of the material was obtained using preparative gc. The ir and nmr spectra of the material confirmed its identity as phenyl ethyl carbonate.

Ethyl Salicylate (4).—This compound was identified by comparing its retention time and mass spectrum with those of an authentic sample.

Ethyl p-hydroxybenzoate (5) was identified by its retention time. The identification is certain in the m-chlorophenyl ethyl carbonate reaction mixture and its reasonably certain in the other two reaction mixtures.

Isopropenylphenyl Ethyl Carbonate (7).—Identification was made from the mass spectra obtained by gc–mass spectroscopy. The mass spectral data in the case of the meta isomer are given in Table IV.

TABLE IV

m/e	% of base	m/e	% of base
m-Isopropenyl Ethyl Carbonate			
207	2.5	162	7.5
206	11.0	135	11.8
134	100.0	115	14.2
133	32.0	94	58.0
119	24.0	91	34.2
117	14.2		
m-Isopropoxyphenyl Ethyl Carbonate			
225	1.8	138	6.0
224	7.5	137	2.5
183	1.0	110	100.0
182	3.5	109	9.5
152	3.5		

Isopropoxyphenyl Ethyl Carbonate (6).—Identification was made from mass spectra obtained by means of gc–mass spectroscopy. The mass spectral data are given in Table IV in the case of the meta isomer.

Registry No.—**1a**, 1847-88-7; **1b**, 1847-87-6; **1c**, 22719-87-5.

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The Reaction of Organometallic Reagents with Pyridinium Ions[1]

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The products of the reactions of methyl Grignard reagent with 1-methyl- and 1-benzyl-3-cyanopyridinium ions were shown to be mixtures of 1,2- and 1,6-dihydropyridines[3] resulting from nucleophilic addition at the ring carbons. From the reaction of these salts with aryl Grignards, only 6-aryl-1,6-dihydropyridines were detected. Comparable results were obtained from the reaction of methyl- and phenylcadmium reagents with 1-methyl- and 1-benzyl-3-methoxycarbonylpyridinium ions except that the phenylcadmium reagent with the 1-benzyl salt gave a mixture of products. The product of the reaction of 1-triphenylmethylpyridinium tetrafluoroborate with phenylmagnesium bromide gave 4-phenylpyridine on thermal decomposition. The structures of the products were based on spectral data.

The reactions of nucleophiles with pyridines occur to give 2- or 6-substituted pyridines presumably *via* 1,2- or 1,6-dihydropyridines[3] as intermediates.[4] The generality of this conclusion has been supported by the recent characterization of the organolithium adduct to pyridine.[5] In a few isolated examples, organometallic

(1) This research was presented in part before the Organic Division at the 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 1970. The research was supported in part by a grant from the National Cancer Institute of the National Institutes of Health, CA-04143.

(2) The research was abstracted from the thesis of E. White V presented to the Graduate Faculty of the University of New Hampshire in partial fulfillment of the requirements of the Ph.D. Degree.

(3) The correct numbering system for these dihydropyridines would require that they both be 1,2-dihydropyridine; however, to facilitate the understanding of the results and to be in keeping with earlier papers, the 1,2- and 1,6-dihydropyridine convention will be used throughout this paper.

(4) R. A. Abramovitch and J. G. Saha, *Advan. Heterocycl. Chem.*, **6**, 229 (1966).

(5) (a) R. A. Abramovitch and G. A. Poulton, *J. Chem. Soc. B*, 901 (1969); (b) C. S. Giam and J. L. Strout, *Chem. Commun.*, 142 (1969); (c) G. Fraenkel and J. C. Cooper, *Tetrahedron Lett.*, 1825 (1968).

reagents[6] or complex metal hydrides[7] have given products of nucleophilic addition at the 4 position of the pyridine ring. These examples have all been with pyridines having one electron-withdrawing substituent at the 3 position or two such substituents at the 3 and 5 position.

Reactions of nucleophiles with pyridinium ions occur with even greater ease. The addition is similarly directed to the centers of low electron density, the 2, 4, and 6 positions;[8] however, the common site of reaction is adjacent to the positive nitrogen except with reduction by hydrosulfite ion,[9] thermodynamically controlled cyanide addition,[10] or hydride additions to pyridinium ions having a bulky nitrogen substituent.[11] The reaction of organometallic reagents with pyridinium ions has been limited to the reaction of 1-methylpyridinium salts and their alkyl derivatives with benzyl Grignards in the synthesis of morphinans and benzomorphans.[12] It seemed of interest to explore the reactivity of a series of pyridinium ions, having electron-withdrawing groups attached, with the Grignard reagent and some related organometallic derivatives. In particular it was desirable to determine whether the aromatic ring *or* the electron-withdrawing group would undergo reaction more rapidly with the reagent and, if the ring suffered addition, whether orientation would be affected by the electron-withdrawing substituent.

The cyano group was chosen as the electron-withdrawing substituent since it is less reactive than the carbonyl derivatives with organometallic derivatives. Attack at the cyano function would be unlikely since 3,5-dicyanopyridine undergoes only ring addition[13] and 3-benzoylpyridine gives about 50% ring addition with Grignard reagents.[6b]

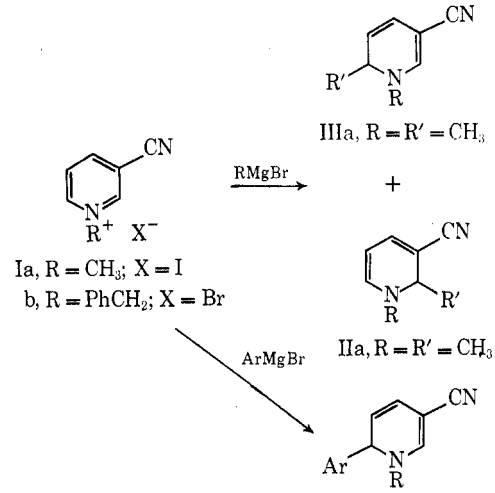
The reactions were carried out as heterogeneous processes in tetrahydrofuran. The reaction mixtures were decomposed with ammonium chloride solution, and the crude product was isolated by evaporation of the solvent. The dihydropyridines that were formed proved to be very unstable, and purification of the product by recrystallization, distillation, or chromatography was accompanied with great losses. In each instance a 1,6-dihydropyridine was isolated occasionally mixed with 1,2 isomer. Since the purification was accompanied by great losses, the presence of the 1,4-dihydropyridine could not be eliminated. It is worthy of note, however, in other series the 1,4-dihydropyridines have been shown to be more stable than the 1,2 or 1,6 isomers.[14]

The structures of the products were identified by ultraviolet, infrared, nuclear magnetic resonance, and mass spectroscopy.[15] The ultraviolet absorption spectra[16] provide the most reliable evidence for distinguishing between the three dihydro systems, for the 1,2-dihydropyridine with its conjugated cyano–dienamine system has a very low energy transition at about 400 nm while the 1,6-dihydropyridine has bands at 240 and 350 nm. The 1-methyl-3-cyano-1,4-dihydropyridine shows only a single absorption band at 340 nm, and this kind of spectrum was not observed in this study.

The nuclear magnetic resonance spectra were important for identification of the product but even more useful for quantitative analysis of the products which could not conveniently be separated. The distinction between the 1,2- and 1,6-dihydro system was immediately evident by noting whether or not the highest field signal was a doublet or singlet. This signal is from the proton attached to the sp^2 carbon adjacent to the nitrogen. If the product is the 1,2-dihydro derivative, this signal arises from the proton at the 6 position and will be split into a doublet by the proton at C-5. If the product is the 1,6-dihydropyridine, the proton at C-2 will be only weakly coupled with other hydrogens and appears as a singlet.

The infrared spectra also provided a means for the qualitative identification of the 3-cyano-1,2- and -1,6-dihydropyridines. These dihydropyridines have two bands due to vibrations of the dienamine function, one above and one below 1600 cm^{-1}. Both of these bands are at lower frequency in the 1,2-dihydropyridines near 1620 and 1525 cm^{-1} while the bands in the 1,6 isomer are near 1640 and 1585 cm^{-1}.

The reactions of 1-methyl-3-cyanopyridinium iodide (Ia) and 1-benzyl-3-cyanopyridinium bromide (Ib) with methylmagnesium bromide and *tert*-butylmagnesium chloride gave products which were very unstable and which failed to give correct analyses. The product from the methyl Grignard could be separated into two components which were shown by nmr, ir, and uv spectroscopy to be the 1,2-dimethyl-3-cyano-1,2-di-



IIIb, R = CH_3; Ar = C_6H_4
c, R = CH_3; Ar = p-$CH_3C_6H_4$
d, R = CH_3; Ar = o-$CH_3C_6H_4$
e, R = $PhCH_2$; Ar = C_6H_5
f, R = $PhCH_2$; Ar = p-$CH_3C_6H_4$

(6) (a) J. Kuthan, E. Janeckova, and M. Havel, *Collect. Czech. Chem. Commun.*, **29**, 143 (1964); (b) R. E. Lyle and D. A. Nelson, *J. Org. Chem.*, **28**, 169 (1963).

(7) J. Kuthan and E. Janeckova, *Collect. Czech. Chem. Commun.*, **30**, 3711 (1965).

(8) R. E. Lyle, *Chem. Eng. News*, **44**, 73 (1966).

(9) K. Wallenfels and H. Schüly, *Justus Liebigs Ann. Chem.*, **621**, 106, 215 (1959).

(10) R. E. Lyle and G. Gauthier, *Tetrahedron Lett.*, 4615 (1965).

(11) P. S. Anderson, W. E. Krueger, and R. E. Lyle, *ibid.*, 4011 (1965).

(12) (a) M. Freund and G. Bode, *Chem. Ber.*, **42**, 1746 (1909). (b) R. Grewe and A. Mondan, *ibid.*, **81**, 279 (1948). (c) A series by E. L. May and coworkers. See part XXXII: B. C. Joshi and E. L. May, *J. Med. Chem.*, **8**, 696 (1965). (d) J. Hellerbach, O. Schnider, H. Besendorf, and B. Pellmont, "Synthetic Analgesics," part IIa, Pergamon Press, Oxford, 1966; N. B. Eddy and E. L. May, *ibid.*, part IIb.

(13) J. Kuthan, *Collect. Czech. Chem. Commun.*, **30**, 2609 (1965); **31**, 3593 (1966).

(14) U. Eisner, *Chem. Commun.*, 1348 (1969).

(15) R. E. Lyle and E. White, *Tetrahedron Lett.*, 1871 (1970).

(16) R. E. Lyle and P. S. Anderson, *Advan. Heterocycl. Chem.*, **6**, 45 (1966).

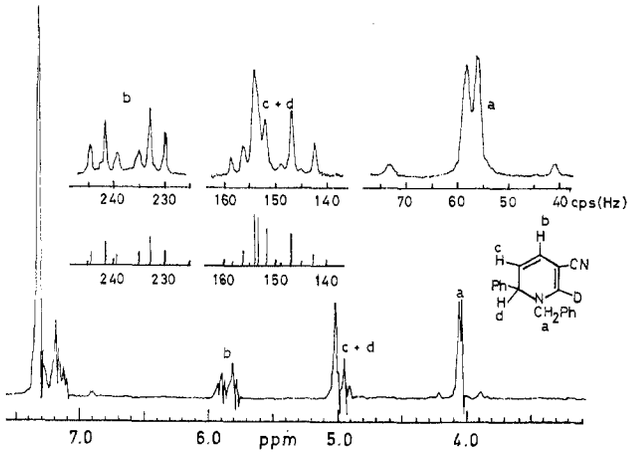
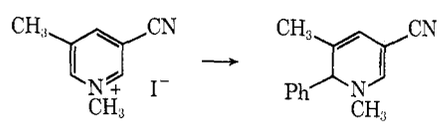


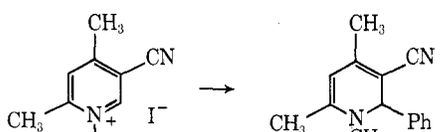
Figure 1.—The nmr spectrum of 1-benzyl-2-deuterio-6-phenyl-3-cyano-1,6-dihydropyridine (2-deuterio-IIIe). The calculated spectrum for the ABC pattern for the 4, 5, and 6 protons is shown under the observed signals.

hydropyridine (IIa) and 1,6-dimethyl-3-cyano-1,6-dihydropyridine (IIIa).

The products from the reactions of arylmagnesium halides were somewhat more stable and could be obtained in analytical purity, but only with great losses in yield. The reaction of Ia with phenyl Grignard reagent gave a product in which only 1-methyl-6-phenyl-3-cyano-1,6-dihydropyridine (IIIb) could be detected by nmr or glc or isolated. Similar results were obtained with a series of aromatic Grignard reagents with Ia and Ib. The major product in each case seems to result from addition of the Grignard reagent at the 6 position. This was true even when the steric interference to approach to this position was increased by introduction of a methyl substituent at the 5 position, for 1,5-dimethyl-3-cyanopyridinium iodide (IV) also gave the 1,6-dihydro derivative V. The 2 position was shown to be reactive to addition by blocking the 4 and 6 positions with methyl substituents. The reaction of 1,4,6-trimethyl-3-cyanopyridinium iodide (VI) with phenyl Grignard gave an addition product which was clearly the 1,2-dihydropyridine (VII) in view of the ultraviolet absorption at 404 nm.



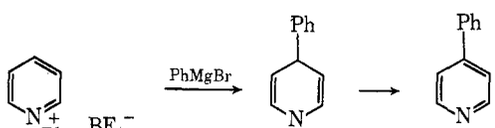
IV V



VI VII

The identification of the 6-aryl-1,6-dihydropyridines (IIIb–f) was confused by the nmr spectra which showed complex multiplets for the ring hydrogens. Only in the case of the *o*-tolyl adduct IIId did the complex pattern approach a first-order pattern. In order to support the structural assignment based on the ultraviolet absorption spectrum, a complete analysis of the nmr spectrum of 1-benzyl-6-phenyl-3-cyano-1,6-dihydropyridine was made.[17] The 100-MHz spectrum clearly indicated the diastereotopic nature of the benzyl protons which appeared as an AB quartet. This probably provided evidence for ruling out the 1,4-dihydropyridine, since the element of dissymmetry is too far removed from the benzyl substituent to be effective in causing magnetic anisotropy.[18] It was apparent that the ring hydrogens formed a four-spin system of the ABCM type. This conclusion was confirmed by double resonance experiments. To simplify the analysis to a three-spin system, the 2-deuterio-IIIe was prepared. This approximated a three-spin system involving the 4, 5, and 6 protons. The spectrum is shown in Figure 1. Following the method of Wiberg[19] and obtaining trial values for the chemical shifts and coupling constants as described by Bible[20] the resonance pattern was calculated. After making small variations in the spectral parameters, the calculated spectrum shown in Figure 1 was obtained using the following δ values: 4-H, 236.8 Hz; 5-H, 150.4 Hz; 6-H, 153.0 Hz ($J_{4,5}$ = 9.8 Hz, $J_{5,6}$ = 4.4 Hz, $J_{4,6}$ = −1.0 Hz).

The reaction of complex metal hydrides with pyridinium ions showed a sensitivity to the steric size of the 1-substituent,[11] a large group directing some addition to the 4 position. A similar experiment was tried with the Grignard reagent by studying the reaction of phenylmagnesium bromide and 1-triphenylmethylpyridinium fluoroborate (VIII). The product, a dihydropyridine (IX), was decomposed thermally to give 4-phenylpyridine (X) in 35% yield, purified. This reaction could not have occurred by initial addition of the phenyl group at the 2 position with subsequent rearrangement to the 4 position for 1-triphenylmethyl-2-phenyl-1,2-dihydropyridine has been shown to give 2-phenylpyridine on decomposition.[21]



VIII IX X

The reaction of organocadmium reagents with pyridinium ions was studied to determine if the carbanion nature of the reagent would be sufficiently nucleophilic to add to the ring and to explore the possible uses of more reactive functional groups as the electron-withdrawing substituent. 1-Methyl- and 1-benzyl-3-methoxycarbonylpyridinium salts (XIa and b) were investigated with methyl- and phenylcadmium reagents; the results were very similar to those with the Grignard reactions. There was no evidence of addition to the carbonyl group of the ester, and addition of the organometallic carbanion occurred at the 6 position in all cases and

(17) The authors wish to express appreciation to Mrs. E. Richards of Dyson Perrins Laboratory, Oxford, England, and Dr. D. A. Nelson of the University of Wyoming for assistance with the double resonance experiments, and Dr. J. J. Uebel of the University of New Hampshire for assistance in calculating the spectrum of the three-spin system.

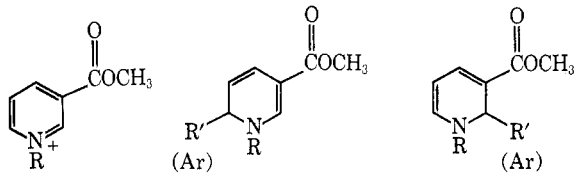
(18) R. E. Lyle and J. J. Thomas, *Tetrahedron Lett.*, 897 (1969).

(19) K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, p 551.

(20) R. H. Bible, Jr., "Interpretation of NMR Spectra—An Empirical Approach," Plenum Press, New York, N. Y., 1965, p 89.

(21) R. Grashey and R. Huisgen, *Chem. Ber.*, **92**, 2641 (1959).

also at the 2 position with the methyl reagent and with the phenyl reagent on reaction with XIb. The success of the addition with organocadmium reagents provide a means for synthesis of otherwise difficultly prepared pyridines.



XIa, R = CH_3 IIIg, R = R′ = Me IIi, R = $PhCH_2$; Ar = Ph
b, R = $PhCH_2$ h, R = Me; Ar = Ph
i, R = $PhCH_2$; Ar = Ph

The reaction of phenyllithium with 1-benzyl-3-cyanopyridinium bromide (Ib) was very vigorous and gave no isolable product. On the other hand diphenylmercury was found to be unreactive with a pyridinium salt even at the reflux temperature of tetrahydrofuran. Alkylation with ethyl cyanoacetate and ethyl acetoacetate occurred, but the highly colored solutions probably resulted from "anhydro bases" which were not isolated. Using an anion which could not form an "anhydro base," diethyl ethylmalonate, a product (XIII) could be isolated on reaction with 1-(2,6-dichlorobenzyl)-3-cyanopyridinium chloride (XII). The product appeared to be the 1,6-dihydropyridine based on the nmr spectrum.

Experimental Section[22]

General.—The preparation of organometallic compounds and operations involving dihydropyridines were conducted under an atmosphere of dry nitrogen. Dry tetrahydrofuran (THF) was prepared by distillation from calcium hydride and was stored over sodium. Evaporations were carried out under reduced pressure at temperatures below 40°.

1,2-Dimethyl-3-cyano-1,2-dihydropyridine (IIa) and 1,6-Dimethyl-3-cyano-1,6-dihydropyridine (IIIa).—A solution of the Grignard prepared from 5.84 g (0.240 g-atom) of magnesium and excess methyl bromide in a mixture of 150 ml of THF and 50 ml of ether was added dropwise in 3 hr to a stirred suspension of 49.4 g (0.200 mol) of 1-methyl-3-cyanopyridinium iodide (Ia)[23] in 300 ml of THF with cooling in an ice bath. After 1 hr the solid was collected and washed with benzene. The filter cake and the filtrate were hydrolyzed separately with aqueous ammonium chloride, and the resulting solutions were extracted with benzene and methylene chloride. The extracts were dried (K_2CO_3) and evaporated to give 10.0 and 8.6 g, respectively, of dark red oils which were mixtures of II and III in each case.

Distillation of the 8.6 g of material obtained from the filtrate gave 3.8 g (14%) of IIa as a yellow air-sensitive liquid, bp 130–139° (9.5 mm). The purity was 87% as determined by nmr spectroscopy and gas–liquid chromatographic analysis on Carbowax 20M on Chromosorb W at 150°. Correct elemental analyses could not be obtained since the material decomposed rapidly. The structure IIa was confirmed by the spectral data: uv λ_{max}^{EtOH} 397 nm; ir (film) ν 2185, 1620, and 1525 cm^{-1}; pmr δ 1.23 (CCH_3, d, J = 6.2 Hz), 3.00 (NCH_3, s), 4.20 [2 H, q (additional small coupling) J = 6.2 Hz], 4.76 (5 H, t, J = 6.5 Hz), 6.37 (C-4, d of d, J = 6.5, 1.0 Hz), 6.63 (6 H, d, J = 6.5 Hz).

The material obtained from the filter cake was distilled to give 7.6 g (26%) of IIIa, of 92% purity, bp 119–126° (1.25 mm), as a yellow liquid which darkened immediately on contact with air. A center cut, bp 122–124° (1.25 mm), mp 29–31°, was shown to be 98% pure by gas–liquid chromatography; however, the material underwent decomposition too rapidly to obtain an elemental analysis. The structure was evident from the spectral data: uv λ_{max}^{MeOH} 242.5 nm (log ϵ 3.90), 341.5 (3.72); ir (film) ν 2185, 1638, 1580 cm^{-1}; pmr δ 1.17 (CCH_3, d, J = 6.1 Hz), 2.97 (NCH_3, s), 4.17 (6 H, quintet, $J \cong 5.9$ Hz), 4.98 (5 H, d of d, J = 10.0 Hz, *ca.* 4.7), 5.78 (4 H, d with additional small coupling, J = 10 Hz), 6.83 (2 H, s, with additional coupling).

1-Methyl-3-cyano-6-phenyl-1,6-dihydropyridine (IIIb).—The Grignard reagent prepared from 37.7 g (0.240 mol) of bromobenzene and 5.59 g (0.230 g-atom) of magnesium in 180 ml of THF was added in 2.5 hr to a stirred suspension of 49.4 g (0.200 mol) of 1-methyl-3-cyanopyridinium iodide (Ia)[23] in 300 ml of THF in an ice bath. After the mixture was stirred for 2 hr, it was hydrolyzed by the addition of aqueous ammonium chloride. The THF was removed by evaporation and the mixture was diluted with 250 ml of water and extracted with a total of 550 ml of ether. The combined ether extracts were washed with an equal volume of water, dried (K_2CO_3), treated with charcoal, and evaporated to give 33.4 g of red oil. Distillation of the residual oil gave a fraction, bp 142–193° (0.05–0.1 mm), which on redistillation gave 9.55 g (25%) of IIIb as a yellow liquid, bp 182–186° (0.03 mm). From one reaction the product crystallized to give an yellow solid, mp 55–58°. The spectral data for IIIb: uv λ_{max}^{MeOH} 222 nm (log ϵ 4.23), 250 (sh, 3.85), 352 (3.65); ir ν 2185, 1645, 1575 cm^{-1}; pmr δ 2.7 (NCH_3, s), 5.0 (C-5 and C-6, multiplet), 5.9 (multiplet), 6.8 (C-2 broad singlet), 7.4 (Ph, s).

Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.28. Found: C, 79.76; H, 5.96; N, 14.29.

1-Methyl-3-cyano-6-*p*-tolyl-1,6-dihydropyridine (IIIc).—The reaction of the Grignard reagent prepared from 41.1 g (0.240 mol) of *p*-bromotoluene and 5.59 g (0.230 g-atom) of magnesium with 49.4 g (0.200 mol) of 1-methyl-3-cyanopyridinium iodide (Ia)[23] in a manner analogous to that for the preparation of IIIb was followed by a similar work-up. The residual oil was treated with hexane to give 39.5 g (94%) of crude IIIc, mp 85–93°. Two distillations gave 16.9 g (40%) of IIIc as a yellow liquid, bp 160–162° (0.03 mm), which slowly solidified on standing. The spectral data provide support for the structure: ir ν 2185, 1640, 1580 cm^{-1}; nmr δ 2.31 (CCH_3, s), 2.71 (NCH_3, s), *ca.* 5.0 (C-5 + C-6, m), *ca.* 5.8 (C-4, m), 6.80 (C-2, broad s), 7.22 (Ph, s).

Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71. Found: C, 79.97; H, 6.70.

1-Methyl-3-cyano-6-*o*-tolyl-1,6-dihydropyridine (IIId).—The reaction of the Grignard reagent prepared from 37.6 g (0.220 mol) of *o*-bromotoluene and 5.59 g (0.230 g-atom) of magnesium with 49.4 g (0.200 mol) of 1-methyl-3-cyanopyridinium iodide (Ia)[23] as above for the preparation of IIIb was followed by a similar work-up. The residue was washed with hexane to give 21.3 g (51%) of crude IIId, mp 124–145°. Recrystallization from ethanol and then from methanol gave 14.2 g (34%) of yellow crystals: mp 148–150.5° (open capillary), 149–150.5° (evacuated capillary); ir ν 2180, 1640, 1580 cm^{-1}; nmr δ 2.38 (CCH_3, s), 2.70 (NCH_3, s), 4.88 (C-5, d of d, J = 10, 3.8 Hz), 5.49 (C-6, d of d, J = 3.8, 1.5 Hz), 5.80 (C-4, d of m, J = 10 Hz), 6.88 (C-2, broad s), *ca.* 7.2 (Ph, m).

Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71; N, 13.32. Found: C, 79.91; H, 6.66, N, 13.50.

1-Benzyl-3-cyano-6-phenyl-1,6-dihydropyridine (IIIe).—The Grignard reagent from 37.7 g (0.240 mol) of bromobenzene and 5.6 g (0.23 g-atom) of magnesium was added to 55.0 g (0.200 mol) of 1-benzyl-3-cyanopyridinium bromide (Ib).[24] The reaction was run as for IIIb to give 25.1 g (46%) of IIIe, mp 142–145.5°, after two recrystallizations from methanol. Chromatography on Florisil with methylene chloride as eluent followed by crystallization from methanol gave an analytical sample: mp 144.5–146°; uv λ_{max}^{MeOH} 225 nm (sh, log ϵ 4.23), 252 (sh, 3.83), 353 (3.74); ir ν 2190, 1640, 1575 cm^{-1}; for nmr, see discussion.

(22) Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are corrected. Boiling points are uncorrected. The infrared spectra of all compounds were recorded on a Perkin-Elmer Model 337 spectrophotometer. Complete spectra are shown in the thesis from which the material is drawn.[2] Ultraviolet spectra were recorded on a Cary Model 15 spectrophotometer. Proton nuclear magnetic resonance spectra were determined in deuteriochloroform on a Varian Model A-60 nmr spectrometer. The chemical shifts are reported in parts per million shift downfield from tetramethylsilane as an internal standard. The coupling constants J are reported in hertz. Analytical gas chromatography was performed with a Perkin-Elmer Model 154 "Vapor fractometer." Microanalyses were determined by Drs. Weiler and Strauss, Oxford, England, and in these laboratories using an F & M Model 180 or Model 185 carbon, hydrogen, and nitrogen analyzer.

(23) K. Schenker and J. Druey, *Helv. Chim. Acta*, **42**, 1960 (1959).

(24) J. H. Supple, Ph.D. Thesis, University of New Hampshire, 1963.

Anal. Calcd for $C_{19}H_{16}N_2$: C, 83.78; H, 5.92. Found: C, 83.78; H, 5.77.

1-Benzyl-2-deuterio-3-cyano-6-phenyl-1,6-dihydropyridine (2-deuterio-IIIe).—This material was prepared in the same manner as IIIe. From 7.7 g (0.021 mol) of 1-benzyl-2-deuterio-3-cyanopyridinium bromide[25] was obtained 3.0 g (52%) of the 1,6-dihydropyridine (2-deuterio-IIIe), mp 142–147°. Purification as above gave 2.7 g (47%) of pure 1,6-dihydropyridine, mp 144–146°.[15]

1-Benzyl-3-cyano-6-*p*-tolyl-1,6-dihydropyridine (IIIf).—The procedure followed was the same as that used for the preparation of IIIb. Addition of the Grignard reagent from 30.3 g of *p*-bromotoluene (0.230 mol) and 5.34 g (0.220 g-atom) of magnesium to 55.0 g (0.200 mol) of 1-benzyl-3-cyanopyridinium bromide (IIIb)[24] gave 28.8 g (50%) of crude IIIf, mp 89.5–98° after crystallization from methanol–hexane (1:1). Two further recrystallizations from methanol gave 23.8 g (42%) of IIIf, mp 96.5–98°.

A sample of IIIf was further purified by chromatography on Florisil using ether as eluent followed by crystallization from ether to give pure IIIf as large yellow crystals: mp 97.5–99°; uv λ_{max}^{MeOH} 232 nm (log ϵ 4.24), 352 (3.75); ir ν 2185, 1645, 1575 cm^{-1}; nmr δ 2.33 (CCH_3, s), 4.05 (CH_2, broad s), *ca.* 4.9 (C-5,6, m), *ca.* 5.8 (C-4, m), 6.88 (C-2, broad s), 7.19 (Ph, s), *ca.* 7.25 (Ar, m).

Anal. Calcd for $C_{20}H_{18}N_2$: C, 83.88; H, 6.33; N, 9.78. Found: C, 84.15; H, 6.18; N, 9.67.

1,5-Dimethyl-3-cyano-6-phenyl-1,6-dihydropyridine (V).—The Grignard reagent from 17.3 g (0.110 mol) of bromobenzene and 2.82 g (0.120 g-atom) of magnesium was added to 26.0 g (0.100 mol) of 1,5-dimethyl-3-cyanopyridinium iodide (IV).[26] Hydrolysis and work-up as above for IIIb gave 14.7 g (70%) of crude V as a solid, mp 105–120°. The solid was distilled twice to give 9.4 g (45%) of clear yellow liquid, bp 148–152° (0.02 mm), which solidified on standing: mp 118–124.5° (open capillary), mp 120–124.5° (evacuated capillary); uv λ_{max}^{MeOH} 220 nm (sh, log ϵ 3.85), 251 (3.85), 353 (3.69); ir ν 2180, 1650 (m), 1590 cm^{-1}; nmr δ 1.45 (CCH_3, d, $J \leqq 2$ Hz), 2.72 (NCH_3, s), 4.80 (C-6, broad s), 5.70 (C-4, m), 6.75 (C-2, broad s), 7.34 (Ph, s).

Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71; N, 13.32. Found: C, 80.07; H, 6.63; N, 13.45.

1,4,6-Trimethyl-2-phenyl-3-cyano-1,2-dihydropyridine (VII).—The reaction of the Grignard reagent prepared from 18.8 g (0.120 mol) of bromobenzene and 3.16 g (0.130 g-atom) of magnesium with 27.4 g of 1,4,6-trimethyl-3-cyanopyridinium iodide (VI)[27] was conducted in the same manner as for the preparation of IIIb. Two distillations through a short Vigreux column gave 5.35 g (24%) of VII as a deep yellow oil: bp 133–134° (0.02 mm); uv λ_{max}^{MeOH} 404 nm (log ϵ 3.88); ir ν 2180, 1615 (m), 1525 cm^{-1}; nmr δ 1.90 (CCH_3, s), 2.79 (NCH_3, s), 4.61 (C-5, s), 5.01 (C-2, s), 7.31 (Ph, s).

Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.39; H, 7.18; N, 12.56.

4-Phenylpyridine (X) from Phenylmagnesium Bromide and 1-Triphenylmethylpyridinium Fluoroborate (VIII).—The Grignard reagent prepared from 17.3 g (0.110 mol) of bromobenzene and 2.92 g (0.120 g-atom) of magnesium in 75 ml of THF was added in 0.4 hr to a stirred suspension of 37.5 g (0.0918 mol) of VIII[28] in 100 ml of THF cooled with an ice bath. The mixture was stirred at room temperature for 0.3 hr and hydrolyzed by the addition of aqueous ammonium chloride.

The mixture was diluted with 500 ml of water and extracted with 250 ml of ether. The ether extract was washed twice with 500-ml portions of water, diluted with 100 ml of methylene chloride, dried (K_2CO_3), and evaporated to give a sticky yellow solid.

The solid was pyrolyzed at 8 mm under a water-cooled condenser in an air bath held at 200° for 1 hr. The material in the condenser and in the pot was dissolved in 200 ml of ether. Hydrogen bromide gas was bubbled into the ether solution until precipitation was complete. The precipitate was collected, washed with ether, and dried to give 16.2 g of brown powder. This solid was suspended in a mixture of 200 ml of ether and 20 ml of water. Solid potassium carbonate was added in large excess and the ether layer was decanted, dried (K_2CO_3), treated with charcoal, and evaporated to give a brown solid. Crystallization from 6 l. of water gave 5.03 g (35%) of X as white plates, mp 73–75.5°. The melting point was not depressed on mixing with authentic 4-phenylpyridine.

1,2-Dimethyl-3-carbomethoxy-1,2-dihydropyridine (IIg) and 1,6-Dimethyl-3-carbomethoxy-1,6-dihydropyridine (IIIg).—The Grignard reagent prepared from 11.63 g (0.480 g-atom) of magnesium and excess methyl bromide in 500 ml of THF was converted to the cadmium reagent by the addition of 87.8 g (0.480 mol) of dry cadmium chloride and 150 ml of THF and heating the mixture under reflux for 1 hr. To the stirred cadmium reagent, cooled by an ice bath, was added 92.8 g (0.400 mol) of 1-methyl-3-carbomethoxypyridinium bromide (XIa)[29] all at once. The mixture was stirred with cooling for 1 hr and then at room temperature for 16 hr. Hydrolysis with 200 ml of saturated aqueous ammonium chloride and dilution with 800 ml of water was followed by extraction with 1700 ml of methylene chloride. The organic layer was washed with water and dried (K_2CO_3), and the solvent was evaporated to give 32.8 g of a red liquid shown by glc to contain nearly equal amounts of IIg and IIIg.

Distillation of the crude mixture through a short Vigreux column gave 6.8 g (10%) of IIg as a yellow liquid (96% IIg by glc), bp 126–138° (9 mm), and 17.3 g (26%) of IIIg as a yellow liquid (92% IIIg by glc), bp 140–149° (9 mm).

Redistillation of IIg gave 3.6 g of pure IIg as a yellow air-sensitive liquid: bp 115–116.5° (8 mm); uv λ_{max}^{MeOH} 416 nm (log ϵ 3.92); ir ν 1685, 1620 (m), 1525 cm^{-1}; nmr δ 1.03 (CCH_3, d, J = 6.5 Hz), 3.00 (NCH_3, s), 3.63 (OCH_3, s), 4.50 q (2 H, q, J = 6.5 Hz), 4.71 (C-5, t, J = 6.5 Hz), 6.37 (C-4, d of t, J = 6.5 Hz), 6.97 (C-6, d, J = 6.5 Hz).

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.66; H, 7.62; N, 8.74.

Redistillation of IIIg gave an 11.5-g sample of IIIg, bp 140.5–142° (8 mm), as a yellow, air-sensitive material with a purity of about 92% (estimated from the nmr since variable results arising from pyrolysis were obtained by glc). The sample for the ultraviolet spectrum and for analysis was redistilled immediately before use: uv λ_{max}^{MeOH} 257 nm (sh, log ϵ 3.95), 263 (4.00), 271 (sh, 3.90), 324 (3.83), 345 (sh, 3.77); ir ν 1680, 1640, 1575 cm^{-1}; nmr δ 1.15 (CCH_3, d, J = 5 Hz, 2.97 (NCH_3, s), 3.58 (OCH_3, s), 4.13 (C-6, quintet, $J \leqq 5.5$ Hz), 4.90 (C-5, d of d, J = 10, 5.0 Hz), 6.29 (C-4, d of d, J = 10, *ca.* 1 Hz), 7.24 (C-2, broad s).

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Foupd: C, 64.46; H, 7.96; N, 8.29.

1-Methyl-3-carbomethoxy-6-phenyl-1,6-dihydropyridine (IIIh).—To the Grignard reagent prepared from 18.82 g (0.120 mol) of bromobenzene and 2.92 g (0.120 g-atom) of magnesium in 150 ml THF was added 22.0 g (0.120 mol) of dry cadmium chloride and 50 ml of THF. The mixture was heated under reflux for 0.7 hr. The cadmium reagent was cooled to room temperature and, with stirring, 23.2 g (0.100 mol) of 1-methyl-3-carbomethoxypyridinium bromide (XIa)[29] was added all at once. The reaction mixture was stirred for 12 hr, cooled in an ice bath, and hydrolyzed by the addition of 50 ml of a saturated solution of ammonium chloride and 150 ml of water. The THF was evaporated and the residue was extracted with four 100-ml portions of ether. The combined ether extracts were washed with water, dried (K_2CO_3), and treated with charcoal. The ether was removed to leave an oil which solidified. Two recrystallizations from methanol gave 10.4 g (45%) of IIIh as light yellow crystals: mp 101–106°; ir ν 1670, 1630, 1565 cm^{-1}; nmr δ 2.73 (NCH_3, s), 3.68 (OCH_3, s), *ca.* 5.0 (C-5,6, m), 6.48 (C-4, m), 7.32 (Ph, s).

Samples of IIIh showed no improvement in melting point after either chromatography on Florisil or sublimation. Thin layer chromatography on silica gel gave no evidence for the presence of impurities.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.64; H, 6.80; N, 6.22.

Mixture of 1-Benzyl-2-phenyl-3-carbomethoxy-1,2-dihydropyridine (IIi) and 1-Benzyl-3-carbomethoxy-6-phenyl-1,6-dihydropyridine (IIIi).—To the cadmium reagent prepared from 9.89 g (0.0630 mol) of bromobenzene, 1.46 g (0.0600 g-atom) of magnesium, and 11.0 g (0.0600 mol) of dry cadmium chloride was added to 15.4 g (0.050 mol) of 1-benzyl-3-carbomethoxy-

(25) The 1-benzyl-2-deuterio-3-cyanopyridinium bromide was prepared from the undeuterated salt Ib by repeated exchange with deuterium oxide at 100° in the presence of small amounts of potassium cyanide. The deuterium incorporation was determined by nmr and mass spectral[15] analysis.

(26) G. J. Gauthier, Ph.D. Thesis, University of New Hampshire, 1966.

(27) T. Kametani and M. Sato, *Yakugaku Kenku*, **34**, 112 (1962); *Chem. Abstr.*, **58**, 13910 (1963).

(28) R. E. Lyle and C. B. Boyce, unpublished results.

(29) D. A. Nelson, Ph.D. Thesis, University of New Hampshire, 1960.

pyridinium bromide (XIb).[30] Work-up in a manner similar to that for IIIb gave an oil from which no crystalline material could be obtained. Distillation provided 6.2 g of viscous yellow oil, bp 210–245° (0.06–1.0 mm), subsequently chromatographed on neutral alumina using benzene as eluent and redistilled to give 1.4 g (9%) of viscous yellow oil [bp 198–202 (0.03 mm); uv λ_{max}^{MeOH} 267.5 nm, 353, 427] shown by nmr spectroscopy to be 21% of the 1,2-dihydropyridine IIi and 79% of the 1,6-dihydropyridine IIIi: nmr δ 3.47 (IIi, OCH_3, s), 3.66 (IIIi, OCH_3, s), 4.05 (IIIi, NCH_2, s), 4.30 (IIi, NCH_2, s), 7.53 (IIIi, C-2, s), and other multiplets to be expected from this mixture.

Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.66; H, 6.45; N, 4.69.

1-(2,6-Dichlorobenzyl)-3-cyano-6-(1,1-dicarbethoxypropyl)-1,6-dihydropyridine (XIII).—Diethyl ethylmalonate, 1.87 ml, was added dropwise to a stirred suspension of 0.50 g of a 49.7% dispersion of sodium hydride in mineral oil in 20 ml of THF. The resulting solution was added dropwise to a stirred suspension of 3.0 g (0.010 mol) of 1-(2,6-dichlorophenyl)-3-cyanopyridinium chloride (XII)[26] in 20 ml of THF. The mixture was stirred for 0.5 hr, was filtered, and was concentrated. The residual oil was dissolved in ether and treated with charcoal. The solvent was removed and the residue crystallized on trituration with petroleum ether. Recrystallization from benzene–petroleum ether gave 0.8 g (18%) of crude XIII: mp 117–122° dec; uv λ_{max}^{MeOH} 363 nm, 310, 242 (sh). The nmr was consistent with the structure XIII. The triplets for two nonequivalent methyls of the ester and the methyl of the C-ethyl appear at about 1 ppm. The diastereotopic protons of the methylene of the C-ethyl give a multiplet at 2.0 ppm. The methylene protons of the ester groups appear at 4.1 ppm. The benzylmethylene appears at 4.64 ppm. The ring protons appear at 4.95 (C-5, d of d, J = 8.0, 4.5 Hz), 6.3 (C-4, d of d, J = 8.0, 1.5 Hz), 6.88 (C-2, d, J = 1.5 Hz). Recrystallization from 2-propanol and ether improved the melting point, 130.5–132.5°, but the nmr did not change.

Anal. Calcd for $C_{22}H_{24}Cl_2N_2O_4$: C, 58.54; H, 5.36; N, 6.21. Found: C, 58.28; H, 4.72; N, 6.25.

(30) G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *J. Amer. Chem. Soc.*, **88**, 3099 (1966).

Registry No.—IIa, 27531-36-8; IIg, 27531-37-9; IIi, 27531-38-0; IIIa, 27531-39-1; IIIb, 27531-40-4; IIIc, 27531-41-5; IIId, 27531-42-6; IIIe, 27531-43-7; IIIe (2-deuterio), 27531-44-8; IIIf, 27531-45-9; IIIg, 27531-46-0; IIIh, 27531-47-1; IIIi, 27531-48-2; V, 27531-49-3; VIII, 27531-54-0; XIII, 27531-55-1; methylmagnesium bromide, 75-16-1; *tert*-butylmagnesium chloride, 677-22-5; phenylmagnesium bromide, 100-58-3.

Quinazolines and 1,4-Benzodiazepines. XLVIII. Ring Enlargement of Some Chloromethylquinazolin-4-ones[1]

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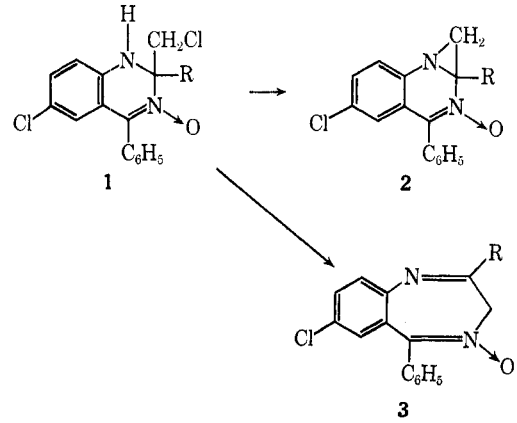
Treatment of 2-chloromethyl-1,2,3,4-tetrahydroquinazolin-4-ones with bases gives 1,4-benzodiazepin-5-ones. Aziridines are implicated as intermediates.

Reaction of 2-chloromethylquinazoline 3-oxide derivatives, such as **1**, with strong bases leads to ring expansion with formation of two types of compounds, benzodiazepines **3** and their structural isomers **2**.[2] One can consider this reaction to be an internal alkylation in which the chloromethyl group alkylates either the 1 nitrogen to produce **2** or the 3 nitrogen to produce ultimately **3**. Obviously, this reaction should be extendable to the synthesis of other heterocycles containing a seven-membered ring. However, since a change of the substituent R from hydrogen to methyl is enough to change the product from one type to the other, one might expect that other changes would also affect this delicate balance.[2] It therefore seemed of interest to study additional examples of this reaction.



We now report that 1,2,3,4-tetrahydro-4-oxoquinazolines,[3] *e.g.*, **5**, give only products derived by alkylation of the 1 nitrogen. The starting materials, **5**, **12**, and **17**, are easily prepared by the acid-catalyzed condensation of an anthranilamide with chloroacetone with azeotropic removal of the water formed. Treatment of **5** with potassium *tert*-butoxide in tetrahydrofuran, conditions which in the case discussed above favor formation of the aziridines **2**, yielded the benzodiazepinone **7**.

The nmr spectrum of **7** showed a singlet at δ 2.17 ppm for the methyl group, a band at δ 4.16 ppm for the methylene group, and a band at δ 8.5 for the NH. It absorbed 1 mol of hydrogen on hydrogenation over platinum to give the tetrahydrobenzodiazepinone **9**.[4] The structure of **7** was confirmed by its hydrolysis to an acetonyl anthranilamide (**8**) which on treatment with base gave 2-acetylindoxyl (**10**).[5] Alkylation of anthranilamide with chloroacetone in the presence of calcium carbonate also gave **8** (Scheme I).

Reaction of **5** with potassium methoxide in methanol, conditions which in the quinazoline 3-oxide series favor

(1) (a) Presented in part at the Middle Atlantic Regional Meeting of the American Chemical Society, New York, N. Y., Feb 1966. (b) Paper XLVII: R. Y. Ning, I. Douvan, and L. H. Sternbach, *J. Org. Chem.*, **35**, 2243 (1970).

(2) G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Amer. Chem. Soc.*, **89**, 332 (1967).

(3) H. Boehme and H. Boeing, *Arch. Pharm. (Weinheim)*, **293**, 1011 (1960); W. L. F. Armarego in "Fused Pyrimidines: Part I, Quinazolines," D. J. Brown, Ed., Interscience, New York, N. Y., 1967, pp 392–394.

(4) Similar compounds have been prepared by A. A. Santilli and T. S. Osdene, *J. Org. Chem.*, **31**, 4268 (1966).

(5) H. C. F. Su and K. C. Tsou, *J. Amer. Chem. Soc.*, **82**, 1187 (1960).