with an excess of concentrated HCl, followed by dilution with H_2O and basification with 2 *N* NaOH. The product was extracted into $CHCl_3$, dried briefly over $MgSO_4$ and evaporated. The free base thus obtained was converted to its hydrochloride by treatment with ethanolic HCl. In the work-up of the reduction of **6**, methanolic rather than aqueous HCl was used.

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Registry No.—**1a**, 28341-73-3; **1b**, 4597-81-3; **1c**, 53746-37-5; **2a** HCl, 53746-38-6; **2b** 2 HCl, 53746-39-7; **2c** 2 HCl, 53746-40-0; **4**, 53746-41-1; **5** HCl, 53746-42-2.

References and Notes

(1) H.-W. Wanzlick and W. Löchel, *Chem. Ber.*, **86**, 1463 (1963).
(2) H. C. Brown, P. Heim, and N. M. Yoon, *J. Amer. Chem. Soc.*, **92**, 1637 (1970).
(3) A. J. Birch and K. P. Dastur, *Aust. J. Chem.*, **26**, 1363 (1973).
(4) M. A. Spielman, *J. Amer. Chem. Soc.*, **57**, 583 (1935).
(5) R. J. Ferm and J. L. Riebsomer, *Chem. Rev.*, **54**, 593 (1954).
(6) F. Korte, A. K. Bocz, and K. H. Buchel, *Chem. Ber.*, **99**, 736 (1966).
(7) J. W. Lown, J. P. Moser, and R. Westwood, *Can. J. Chem.*, **47**, 4335 (1969).

Borohydride Reduction of Pyridinium Salts. V. Thermal Dimerization of 1,6-Dihydro-1-methylpyridine-2-carbonitrile

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The 1,6-dihydropyridine **2**, obtained by $NaBH_4$ reduction of 2-cyano-1-methylpyridinium iodide, smoothly undergoes a thermal dimerization to the head to head [2 + 2] cycloadduct **6**. The cyclobutane derivative **6** rearranges, by heating, to the isomeric ethenonaphtyridine **9**. Label scrambling observed at 110° in the monodeuteriated derivative, **13**, reveals a degenerate thermal [3.3] sigmatropic shift.

Some time ago we started an investigation on the reduction with $NaBH_4$ of substituted pyridinium salts containing electron-attracting groups. In a number of reports already published,[1] we have clarified some aspects of the reduction of 3-cyano- and 4-cyano-1-methylpyridinium iodides; in particular, it was shown that in the reduction of 4-cyano-1-methylpyridinium iodide, dimerization of the intermediate 1,2-dihydropyridine occurs with formation of [2 + 2] and [4 + 2] cycloadducts. The investigation has now been extended to 2-cyano-1-methylpyridinium iodide (**1**), and the results are reported in the present paper.

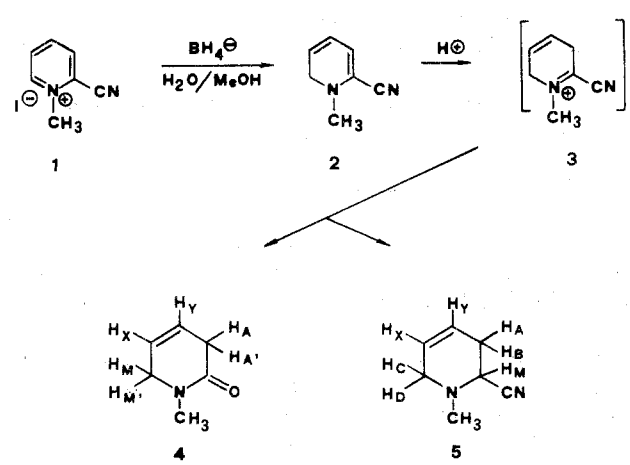
On treatment of **1** with $NaBH_4$ in methanol–water (4:1) at −20°, the initial formation of a dihydropyridine **2** is shown from the changes in the uv spectrum; a maximum appears at 365 nm, and its intensity increases as the reduction proceeds, with simultaneous disappearance of the maximum at 273 nm, which is characteristic of the pyridinium salt.

It is also possible to extract the dihydropyridine with $CHCl_3$ at a low temperature and to record the ir spectrum of the chloroform solution (1660 and 1625 cm^{-1}, C=C; 2210 cm^{-1}, C≡N), but the attempted isolation of the product was unsuccessful, since evaporation of the solvent leads to a new compound **6**, which has spectroscopic characteristics different from those of **2** (see below).

When the reaction was carried out in an nmr tube (CH_3OD–D_2O 9:1) at 30°, it was possible first to detect the formation of the dihydropyridine (δ 6.0–5.3 vinyl protons; 3.8, N–CH_2; 2.7 ppm, N–CH_3) and then to follow its conversion into the compound **6**: the dihydropyridine peaks slowly disappear, while the peaks of **6** gradually become more intense. After 1 hr, 30% of **6** has been formed.

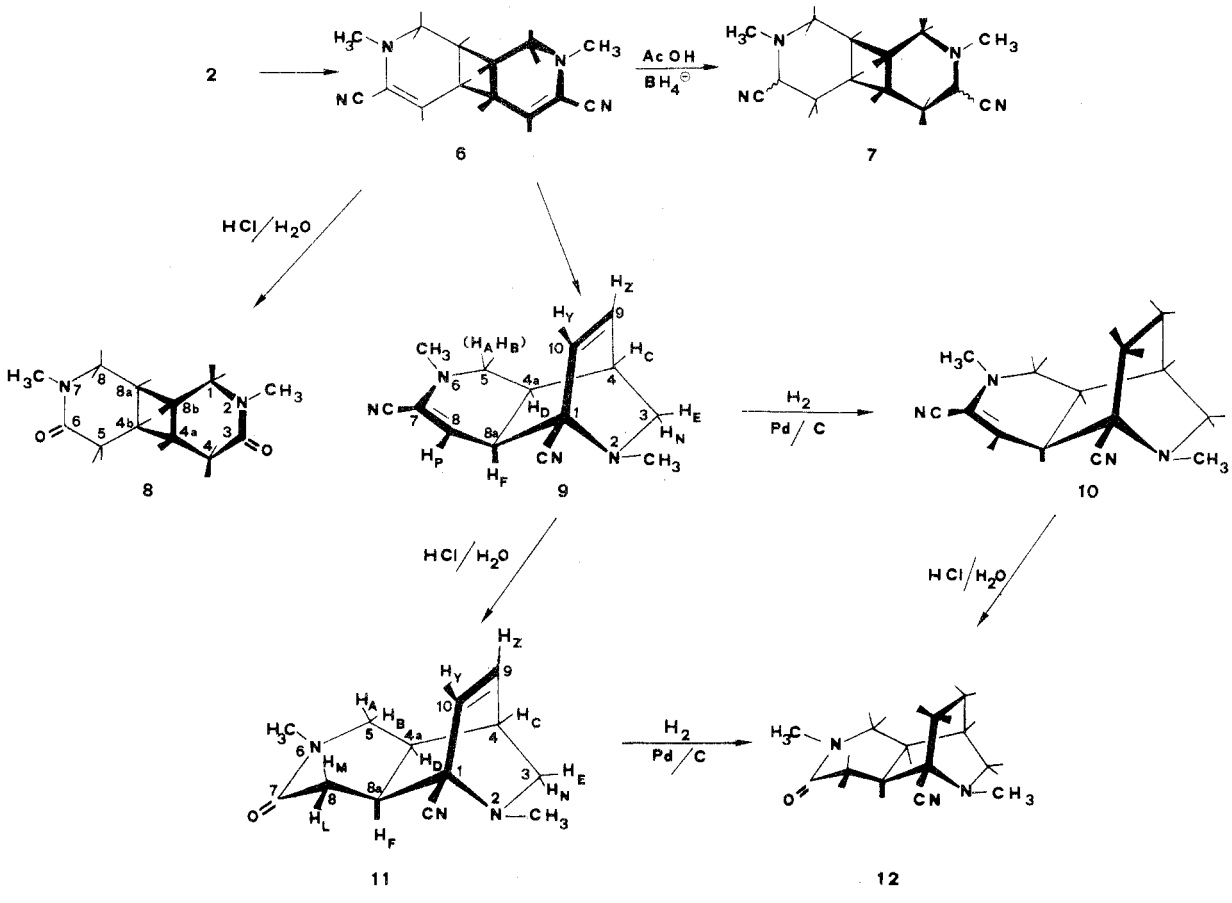
2 has the structure of 1,6-dihydro-1-methylpyridine-2-carbonitrile, as was shown by the formation of 3,6-dihydro-1-methylpyridin-2(1*H*)-one (**4**) and1,2,3,6-tetrahydro-1-methylpyridine-2-carbonitrile (**5**) on reduction of **1** in methanol–water (4:1) at −20° followed by treatment with 6 *N* hydrochloric acid (Scheme I).

Scheme I



It seems clear from the above that **1** undergoes attack in position 6 by the BH_4^- ion, with formation of the dihydropyridine **2**. Owing to the presence of the electron-attracting group in position 2, this dihydropyridine has little enamine character and consequently does not undergo protonation and further reduction in aqueous alcoholic media.[1a] Only the addition of acid can bring about the protonation in position 3 with formation of the iminium cation **3**, which can competitively undergo attack by the nucleophiles H_2O and BH_4^- to give **4** and **5**, respectively. Thus reactions carried out with a molar excess of sodium borohydride lead to a distinct increase in the quantity of tetrahydropyridine and a corresponding decrease in the quantity of pyridone.

Scheme II



When the reduction of **1** with $NaBH_4$ in methanol–water (2:5) is carried out at 20° the product **6** precipitates out. **6** cannot be crystallized (see below), but can be purified by chromatography. Its ir spectrum shows a nitrile band at 2215 cm^{-1} and a double-bond absorption at 1610 cm^{-1}. The elemental analysis and the molecular weight (240) indicate a molecular formula $C_{14}H_{16}N_4$, which is exactly double than of **2**. Attempts to crystallize **6** from solvents such as ethanol or benzene lead to total conversion into a new compound **9**, which has the same molecular weight and the same elemental analysis, but different spectrographic characteristics. For example, the ir spectrum, among other things, shows an unconjugated nitrile absorption at 2230 cm^{-1}, a conjugated nitrile absorption at 2215 cm^{-1}, and two double-bond absorptions at 1620 and 1615 cm^{-1}, respectively.

The conversion of **6** into **9** can also be observed when **6** is heated as solid; for example, after heating at 85° the ratio **9**–**6** is 0.25, and this ratio tends to increase with rising temperature. At 107–110°, when the solid melts, **9** is practically the only species present. The nmr spectrum ($CDCl_3$) of **6** is not very significant, since the only identifications are two equivalent vinyl protons at δ 5.48 and two equivalent CH_3 groups at δ 2.86, all the other protons falling between δ 3.1 and 2.1. However, the spectroscopic properties and the molecular weight provide reasonable evidence of a symmetrical dimeric structure. The presence of two α-cyano-substituted enamine moieties in **6** is demonstrated by its reduction to **7** (mol wt = 244) on treatment with glacial CH_3COOH and $NaBH_4$ and by conversion into the dilactam **8** (mol wt = 222) on treatment with 6 *N* hydrochloric acid (Scheme II).

The ir spectrum of **7** shows a nitrile band at 2220 cm^{-1}, while the nmr spectrum shows the disappearance of the vinyl protons and confirms the symmetry of the dimeric structure. The ir spectrum of **8** shows a lactam band at 1630 cm^{-1}, while the nmr spectrum once again points to a symmetrical dimeric structure.

These experimental results lead us to postulate that **6** (and hence **7** and **8**) has a symmetrical cyclobutane structure resulting from the thermal dimerization[2] involving the 4–5 double bond of the dihydropyridine **2**. In fact, the only other conceivable symmetric dimeric structures, not containing the cyclobutane ring, are those arising from a [4 + 4] cycloaddition of the dihydropyridine **2**, but these must be excluded because they are largely inconsistent with the experimental results.

Theoretically several cyclobutanic dimers may be formed according to the mode of dimerization (head-to-head or head-to-tail) and the known possibilities for the stereochemistry around the cyclobutane ring. However, the structural symmetries of the compounds **6**, **7**, and **8**, which are clearly demonstrated by the nmr spectra, enable us to rule out the cyclodimers having a single 6–4 trans fusion; cyclodimers with a strained double 6–4 trans fusion, which is itself extremely improbable, can also be ruled out in view of the fact that a dihydropyridine such as **2**, in which the reactive cis olefinic moiety is blocked by the cyclic framework, cannot give cyclodimers with this configuration by thermal dimerization.

There are therefore four cis-fused isomers to be considered; these are the syn head-to-head, the syn head-to-tail, the anti head-to-head, and the anti head-to-tail cyclodimers (Scheme III). However, the easy conversion of **6** into **9**, which has all the features of an intramolecular rearrangement, seems to indicate a head-to-head structure, since only the 1,2-divinylcyclobutanes readily undergo intramolecular rearrangements.[3]

Table I
Nmr Data for 8

Protons	δ, ppm: Bz-d_5 δ (ppm)	δ, ppm: Bz-d_6 + Eu(DPM)$_3$	J,[a] Hz
$H_{8a} + H_{8b}$	1.60	5.68	$\lvert J_{8a,4b} + J_{8a,4a}\rvert = 7.5$
$H_{4a} + H_{4b}$	1.7–2.2	6.71	$J_{8b,1}$ (or $J_{8b,1'}$) = 3.0
H_1 (or $H_{1'}$) + H_8 (or $H_{8'}$)	2.81	6.39	$J_{8b,1'}$ (or $J_{8b,1}$)[b]
$H_{1'}$ (or H_1) + $H_{8'}$ (or H_8)	2.29	5.58	$J_{1,1'} = 13.0$
H_4 (or $H_{4'}$) + H_5 (or $H_{5'}$)	1.7–2.2	8.55	$J_{4,4a}$ (or $J_{4',4a}$)[b]
$H_{4'}$ (or H_4) + $H_{5'}$ (or H_5)	1.7–2.2	7.00	$J_{4',4a}$ (or $J_{4,4a}$) = 4.5
Me-2 + Me-7	2.78	7.72	$J_{4,4'} = 15.5$

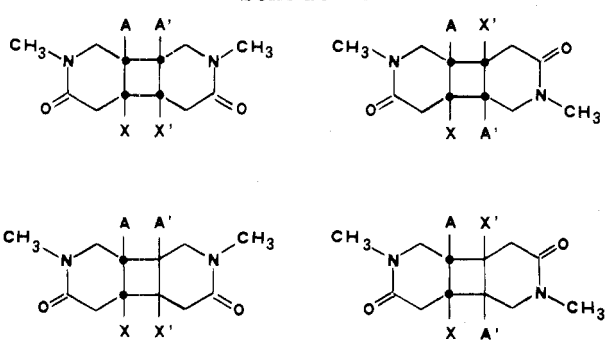
[a] Values obtained from solution added of Eu(DPM)$_3$. [b] This coupling cannot be detected because of the broadening by the shift reagent.

Table II
Nmr Data for 9 and 11

	9		11	
Protons	Bz-d_6, δ (ppm)	J, Hz	$CDCl_3$, δ (ppm)	J, Hz
H_A (or H_B)	2.04	AB = 11.91[a]	3.05 (H_A)	AB = 13.06[a]
H_B (or H_A)	1.79	AD (or BD) = 5.55[a]	3.14 (H_B)	AD = 10.07[a]
H_C	1.60	BD (or AD) = 6.13[a]	2.49	BD = 6.33[a]
H_D	1.68	CD = 1.8[b]	2.40	CD = 2.0[b]
H_E	1.36	CE = 2.5	1.91	CE = 2.6
H_F	2.66	CN = 2.0	2.81	CN = 2.2
H_N	2.65	CY = 1.5	3.22	CY = 1.5
H_M		CZ = 7.0	2.14	CZ = 7.0
H_L		EN = 9.5	2.65	EN = 9.8
H_P	5.60	FD = 8.92[a]		FD = 10.52[a]
H_Y	5.69	FP = 3.7	6.29	FL = 6.15[a]
H_Z	5.76	YZ = 8.2	6.48	FM = 11.50[a]
Me	2.31		2.89	FY = 1.0
Me	2.16		2.38	ML = 14.63[a]
				YZ = 8.0
				ZD = 0.5
				ZN = 0.5

[a] Value obtained by iteration. [b] Value obtained only from spectrum with Eu(DPM)$_3$.

Scheme III



The structures and conformations of the compounds **6**, **7**, and **8** were established by the analysis of the nmr spectrum of the dilactam **8**, since the addition of Eu(DPM)$_3$ enables all the protons to be seen separately (Table I).

With regard to the cyclobutane protons H_{8a}, H_{8b}, H_{4a}, H_{4b}, which form an AA'XX' spin system further coupled with the protons of the adjacent methylene groups, only the sum $|J_{AX} + J_{AX'}| = 7.5$ Hz can be deduced from the spectrum.

According to the values and signs found for the vicinal[4] and diagonal[5] constants of the cyclobutane protons in similar systems, this result points to a vicinal cis J_{AX} and diagonal trans $J_{AX'}$; an anti head-to-head configuration thus seems the most probable for the compound **8**.

Since **7** and **8** are formed directly by an unambiguous path from **6**, it must be assumed that the geometry of all three compounds is the same.

The structure of **6** is compatible with a two-step biradical dimerization mechanism, which, in the light of recent work by Epiotis,[6] may be regarded as the most probable for the thermal dimerization ([2 + 2] AA cycloadditions).

As was mentioned above, **6** is thermally converted into **9**, whose nmr spectrum shows, among other things, three vinyl protons H_P, H_Y, H_Z respectively at δ 5.60, 5.69, and 5.76 (see below) and two methyl signals at δ 2.16 and 2.31. The experimental data clearly indicate that **9** no longer has the symmetrical structure characteristic of **6**. The presence of a single substituted α-cyanoenamine moiety is shown by the halving of the ε value (6,100) of the uv maximum at 278 nm with respect to the corresponding ε value (12,000) for compound **6**, and by conversion into the lactam **11** (mol wt 231; ir 1645 (C=O) and 2235 cm^{-1} (C≡N)) on treatment with 6 *N* hydrochloric acid. Furthermore, the catalytic reduction of **9** affords the dihydro derivative **10**. The nmr spectra show that H_P is the only vinyl proton present in **10**, whereas H_Y and H_Z are the only vinyl protons present in **11**. On catalytic reduction of **11**, 1 mol of hydrogen is absorbed with formation of the compound **12**; there are no vinyl proton signals in the nmr spectrum of **12**. **12** is also obtained from **10** on treatment with 6 *N* hydrochloric acid.

The structure of 1,4-etheno-3,4,4aα,5,6,8aα-hexahydro-2,6-dimethyl-2,6-naphtyridine-1,7(2*H*)-dicarbonitrile for the product **9** is proved by these experimental data and by the complete analysis of the nmr spectra of **9** and **11** (Table II).

This analysis was first carried out for the solution with added Eu(DMP)$_3$ to obtain a better first-order approximation. The coupling constants obtained were then used as the input for the second-order LAOCN 3 analysis of the spectra in the absence of the shift reagent.

As was pointed out earlier, the nmr spectrum of **9** shows three olefinic protons H_P, H_Y, and H_Z at δ 5.60, 5.69, and 5.76, respectively; the coupling constant (J_{YZ} = 8.2 Hz) indicates that H_Y and H_Z are situated on the same double bond.

The chemical couplings J_{EN} = 9.5 Hz and J_{AB} = 11.9 Hz in **9** indicate two methylene protons in the α position to an amine nitrogen and to an enamine nitrogen, respectively, whereas J_{LM} = 14.6 Hz in **11** indicates a methylene group α to a C=O group; J_{EN} and J_{AB} in **11** are similar to those in **9**. The sequences

$$\overset{AB}{N}\!-\!\overset{}{CH_2}\!-\!\overset{D}{CH}\!-\!\overset{C}{CH}\!-\!\overset{EN}{CH_2}\!-\!N, \quad \overset{C}{CH}\!-\!\overset{Z}{CH}\!-\!\overset{Y}{CH}$$

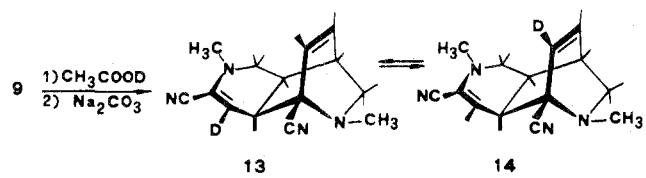
in both **9** and **11**,

$$\overset{P}{=CH}\!-\!\overset{F}{CH}\!-\!\overset{D}{CH}$$

in **9**, and

$$CH_2\!-\!\overset{F}{CH}\!-\!\overset{D}{CH}$$

Scheme IV



in **11** and their connections are clearly suggested by the coupling constants and by the values of the chemical shift. From the absence of coupling between H_D and H_E, the endo configuration can be assigned to **9** and **11** since the sequence H_D–C_{4a}–C_4–C_3–H_E should have perfectly coplanar zig–zag geometry in the exo configuration, and long-range coupling through four bonds should therefore be expected.[7] The low value ($\simeq$2 Hz) of J_{CD} in both **9** and **11** agrees with an angle of about 60° in such a fragment.

The structure and stereochemistry of **9** are consistent with a formation pathway from **6** implying a formal [1.3] sigmatropic shift, which involves the rupture of the C_{4a}–C_{4b} bond and the formation of the C_3–C_{4b} bond.

Treatment of the product **9** with D_1-acetic acid allows selective monodeuteration with formation of **13**, whose nmr spectrum is identical with that of **9** apart from the disappearance of β-enamine proton H_P and the corresponding decoupling of H_F. Heating of **13** to boiling in toluene leads to equilibration with the isomer **14** in which H_Y is replaced by deuterium (Scheme IV); in fact the nmr spectrum of the product, after heating, shows that it consists of an equimolar mixture of **13** and **14** since the areas for H_P and H_Y are halved.

The observed [3.3] sigmatropic shift provides unequivocal confirmation of the structure **9**, which is the only one showing the structural features necessary to undergo a degenerate rearrangement detectable after labeling with deuterium.

Experimental Section

All melting points were taken upon a Tottoli apparatus and are uncorrected; proton nmr spectra were recorded on Varian HA-100 and XL-100-15 spectrometers; chemical shifts are reported as δ units relative to TMS (δ 0) as internal standard. Decoupling experiments were performed in frequency sweep. All *m/e* values were determined on a AEI MS-12, 70 eV, low-resolution mass spectrometer. Ir spectra were recorded on a Perkin-Elmer 257 grating spectrophotometer as Nujol mulls or liquid films and uv spectra on a Perkin-Elmer 402 spectrophotometer. Column chromatography was performed on standardized Al_2O_3 Merck (activity II–III).

Reduction of 1 to 4 and 5. **1** (2.5 g, 0.01 mol) was added in small portions over a period of 30 min, with stirring, to a solution of $NaBH_4$ (0.4 g, 0.01 mol) in H_2O (2 ml) and CH_3OH (8 ml) cooled to −20°. Stirring was continued for 30 min more, and the resulting solution was poured dropwise into 6 *N* HCl (10 ml) previously cooled to −20°. The solution was concentrated under vacuum, H_2O (10 ml) was added, and the solution was extracted with $CHCl_3$. The chloroform extract was dried (Na_2SO_4), concentrated, and distilled, whereupon it gave **4** (0.35 g): bp 70–72° (0.8 mm); mp 30–32°; ir 1635 cm^{-1} (C=O); nmr (C_6D_6) δ 5.39 (1, H_Y), 5.28 (1, H_X, J_{XY} = 10.2 Hz), 3.3 (2, H_M + $H_{M'}$), 2.7 (2, H_A + $H_{A'}$, $\frac{1}{2}|J_{AM} + J_{AM}| = \frac{1}{2}|J_{A'M} + J_{A'M}| = 4.9$ Hz), and 2.7 ppm (3, Me, $J_{A'Me} = J_{A,Me} = 0.5$ Hz).

Anal. Calcd for C_6H_9NO: N, 12.60; mol wt, 111.14. Found: N, 12.35; *m/e* 111 (parent peak).

The acidic mother liquor was made alkaline with 2 *N* NaOH and extracted with $CHCl_3$. The chloroform extract was dried (Na_2SO_4) and concentrated. Chromatography of the oily residue (eluent, cyclohexane–AcOEt 1:1) gave **5** (0.25 g) and **4** (0.15 g). **5**: bp 65° (0.2 mm); ir 2220 (CN) and 1660 cm^{-1} (C=C); nmr (C_6D_6) δ 5.6–5.2 (2, H_X + H_Y), 3.06 (1, H_M), 2.76 (1, H_D) 2.72 (1, H_C, J_{CD} = 17.5 Hz), 2.14 (1, H_B, J_{BC} = 3.5 Hz, J_{BD} = 3.5 Hz, J_{BM} = 5.9 Hz), 2.02 (3, Me), and 1.77 ppm (1, H_A, J_{AB} = 17.2 Hz, J_{AC} = 2.0 Hz, J_{AD} = 2.0 Hz, J_{AM} = 2.0 Hz).

Anal. Calcd for $C_7H_{10}N_2$: C, 68.82; H, 8.25; N, 22.9; mol wt, 122.17. Found: C, 69.15; H, 8.24; N, 23.20; *m/e* 122 (parent peak).

1,2,4aα,4bβ,7,8,8aβ,8bα-Octahydro-2,7-dimethylcyclobuta[1,2-*c*:4,3-*c*']dipyridine-3,6-dicarbonitrile (6). **1** (8.5 g, 0.034 mol) was added in small portions over a period of 1 hr, with stirring, to a solution of $NaBH_4$ (1.3 g, 0.034 mol) in H_2O (25 ml) and CH_3OH (10 ml) at 20°. After the addition, stirring was continued for 2 hr. The precipitate was separated by filtration, washed with water, dried under vacuum, and chromatographed (eluent, light petroleum ether–AcOEt 9:1) to give **6** (3.4 g): uv max (95% EtOH) 278 nm (ϵ 12,000).

Anal. Calcd for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.31; mol wt, 240.30. Found: C, 69.70; H, 6.42; N, 23.79; *m/e* 240 (parent peak).

1,2,3,4,4aα,4bβ,5,6,7,8,8aβ,8bα-Dodecahydro-2,7-dimethylcyclobuta[1,2-*c*:4,3-*c*']dipyridine-3,6-dicarbonitrile (7). $NaBH_4$ (0.3 g) was added in small portions, with stirring, to a solution of **6** (0.3 g) in glacial CH_3COOH (5 ml) cooled to 5°. After the addition, stirring was continued for 30 min more; H_2O (5 ml) was then added, the solution was made alkaline with Na_2CO_3, and extracted with CH_2Cl_2. After drying (Na_2SO_4), evaporation of the extract gave **7** (0.28 g): mp 172–174° (EtOH).

Anal. Calcd for $C_{14}H_{20}N_4$: C, 68.82; H, 8.25; N, 22.93; mol wt, 244.33. Found: C, 68.76; H, 8.16; N, 23.32; *m/e* 244 (parent peak).

1,2,4,4aα,4bβ,5,7,8,8aβ,8bα-Decahydro-2,7-dimethylcyclobuta[1,2-*c*:4,3-*c*']dipyridine-3,6-dione (8). **6** (2.0 g) was added in small portions, with stirring, to 6 *N* HCl (20 ml) cooled to 0°. After standing for 1 hour the solution was extracted with $CHCl_3$. The dried chloroform extract, on evaporation, yielded a solid residue, which was crystallized from benzene to give **8** (0.7 g): mp 165–166°.

Anal. Calcd for $C_{12}H_{18}O_2N_2$: C, 64.84; H, 8.16; N, 12.60; mol wt; 222.28. Found: C, 64.60; H, 8.13; N, 12.53, *m/e* 222 (parent peak).

Conversion of 6 into 9. **6** (4 g) was heated under reflux in C_2H_5OH (50 ml) for 3 hr. Evaporation of the solvent gave **9**: mp 110–112° (EtOH); uv max (95% EtOH) 278 nm (ϵ 6100).

Anal. Calcd for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.31; mol wt, 240.30. Found: C, 69.72; H, 6.90; N, 23.57; *m/e* 240 (parent peak).

1,4-Ethano-3,4,4aα,5,6,8aα-hexahydro-2,6-dimethyl-2,6-naphtyridine-1,7(2*H*)-dicarbonitrile (10). A solution of **9** (0.240 g, 0.001 mol) in C_2H_5OH (50 ml) was hydrogenated at 20° (3 atm) over 10% Pd/C catalyst (0.1 g) until 0.001 mol of H_2 was absorbed. The reaction mixture was filtered, concentrated, and chromatographed (eluent, light petroleum–AcOEt 95:5) to give **10** (0.15 g): mp 50–51° (light petroleum); uv max (95% C_2H_5OH) 277 nm (ϵ 6200); ir 2235, 2225 (CN), 1615 cm^{-1} (C=C); nmr ($CDCl_3$) δ 5.56 (1, H_P), 2.98 (1, H_F, $J_{P,F}$ = 1 Hz), 2.85 (3, Me), and 2.56 ppm (3, Me).

Anal. Calcd for $C_{14}H_{18}N_4$: C, 69.39; H, 7.49; N, 23.12; mol wt, 242.32. Found: C, 69.67; H, 7.55; N, 23.77; *m/e* 242 (parent peak).

1,4-Ethano-3,4,4aα,5,6,7,8,8aα-octahydro-2,6-dimethyl-7-oxo-2,6-naphtyridine-1(2*H*)-carbonitrile (12). A solution of **11** (1 g, 0.004 mol) in AcOEt (60 ml) was hydrogenated at 20° (1 atm) over 10% Pd/C catalyst (0.2 g) until 0.004 mol of H_2 was absorbed. The reaction mixture was filtered and concentrated to give **12**: mp 117–118° (benzene); ir 2240 (CN), 1645 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01; mol wt, 233.31. Found: C, 67.17; H, 8.40; N, 18.38; *m/e* 233 (parent peak).

12 was also obtained in 75% yield from **10** by treatment with 6 *N* hydrochloric acid (see procedure for compound **11**).

1,4-Etheno-3,4,4aα,5,6,7,8,8aα-octahydro-2,6-dimethyl-7-oxo-2,6-naphtyridine-1(2*H*)-carbonitrile (11). **9** (3 g) was added in small portions, with stirring, to 6 *N* HCl solution (15 ml) cooled to 0°. The solution was made alkaline with concentrated NaOH, saturated with Na_2CO_3, and extracted with $CHCl_3$; evaporation of the solvent yielded a solid residue (**11**) which was crystallized from benzene (1.4 g): mp 87–89°.

Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.50; H, 7.41; N, 18.17; mol wt, 231.29. Found: C, 67.48; H, 7.46; N, 18.44; *m/e* 231 (parent peak).

Labeling of 9. A solution of **9** (0.45 g) in CH_3COOD (5 ml) containing Ac_2O (0.5 ml) was allowed to stand for 30 min at 20°. The solvent was distilled off under reduced pressure, and anhydrous Na_2CO_3 (5 g) and anhydrous benzene (50 ml) were added to the residue. The mixture was stirred for 6 hr and filtered, the solvent was evaporated off, and the residue was chromatographed (eluent, cyclohexane–AcOEt 1:1) to give **13** (0.35 g), which was crystallized from cyclohexane.

Thermal Equilibration of 13 with 14. A solution of **13** (0.25 g) in toluene (30 ml) was refluxed for 2 hr. The solvent was evaporated off and the residue was chromatographed (eluent, cyclohexane–AcOEt 9:1). The product obtained (0.20 g) was examined by nmr spectroscopy and found to be an equimolar mixture of **13** and **14**.

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Registry No.—**1,** 3785-03-3; **4,** 53516-28-2; **5,** 53516-29-3; **6,** 53516-30-6; **7,** 53516-31-7; **8,** 53516-32-8; **9,** 53516-33-9; **10,** 53516-34-0; **11,** 53516-35-1; **12,** 53516-36-2; sodium borohydride, 16940-66-2.

References and Notes

(1) (a) F. Liberatore, V. Carelli, and M. Cardellini, *Tetrahedron Lett.*, 4735 (1968); (b) *Chim. Ind. (Milan)*, **51**, 55 (1969); (c) F. Liberatore, A. Casini, V. Carelli, A. Arnone, and R. Mondelli, *Tetrahedron Lett.*, 2381 (1971); (d) *ibid.*, 3829 (1971).
(2) This reaction gave the same results when carried out in the dark; it must therefore be concluded that it is not a photosensitized reaction but a thermal reaction.
(3) D. Valentine, N. J. Turro, and G. S. Hammond, *J. Amer. Chem. Soc.*, **86**, 5202 (1964).
(4) (a) I. Fleming and D. H. Williams, *Tetrahedron*, **23**, 2747 (1967); (b) L. Paolillo, H. Ziffer, and O. Buchard, *J. Org. Chem.*, **35**, 38 (1970).
(5) (a) A. Gamba and R. Mondelli, *Tetrahedron Lett.*, 2133 (1971); (b) *Org. Magn. Resonance*, **5**, 101 (1973).
(6) N. D. Epiotis, *J. Amer. Chem. Soc.*, **94**, 1924 (1972).
(7) M. Barfield and B. Chakrabarti, *Chem. Rev.*, **69**, 757 (1969).

An Unequivocal Synthesis of N-Substituted 1,4-Dihydropyridines

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The cycloaddition of alkyl, aryl, and sulfonyl azides to 2,3-diazabicycloheptenes (**2**) leads to triazolines (**10**) and aziridino adducts (**3**). Hydrolysis of **3** followed by oxidation of the hydrazino derivatives (**4**) products the tricyclic azo compounds which spontaneously fragment with concomitant nitrogen extrusion producing N-substituted 1,4-dihydropyridines in 11–90% yields.

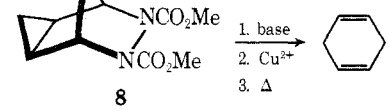
There has been considerable interest in recent years regarding the synthesis and properties of 1,4-dihydropyridines, particularly those possessing little or no substitution.[2] This interest stems from the synthetic utility[3,4] of this system, and in NADH models for biomimetic reductions.[5]

The inherent instability of simple dihydropyridines has deterred complete studies on their potential usefulness as well as synthetic approaches. The route most commonly taken to reach dihydropyridines involves either the Hantzsch synthesis or metal hydride reduction of *N*-substituted pyridinium salts.[2] Addition of cyanide ion to pyridinium salts has been reported to give several stable 4-cyano-1,4-dihydropyridines.[6] Cook and Lyons[7] showed that *N*-trimethylsilyl-1,4-dihydropyridines are among a multitude of products when pyridines are treated with trimethylsilane in the presence of palladium catalysts. Fowler has reported[3,8] the efficient preparation of *N*-carbethoxy-1,4- and -1,2-dihydropyridines by reduction of pyridinium salts.

In 1972, two brief reports appeared which described the synthesis of 1,4-dihydropyridines **1** arising from a retro-Diels–Alder reaction (Scheme I). Deyrup[9] reported the synthesis of *N*-phenyl-1,4-dihydropyridine **1c**, and we described[10] the preparation of the N-benzenesulfonyl derivative **1a**. Our studies were an outgrowth of the previously reported synthesis of divinyl carbamates **6** obtained from a retro-Diels–Alder reaction of the sulfolene derivative **7**.[11]

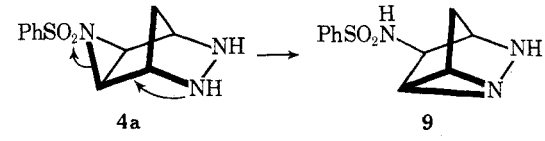
7 **6**

The failure of cyclopentadiene to form an adduct with sulfur dioxide led us to the more accessible system **2**[12] as a suitable precursor to our goal. This approach (Scheme I) was attractive in view of the symmetry-allowed extrusion of nitrogen from **5** which would lead solely to the 1,4-dihydropyridines. In an analogous sequence, Allred[13] showed that 1,4-cyclohexadiene was cleanly produced from **2** (R = Me) by initial transformation to the cyclopropano derivative **8.**



8

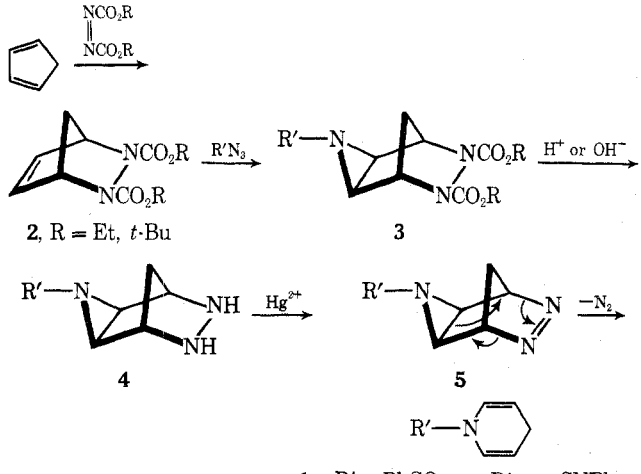
This report enumerates the scope of the synthesis in Scheme I and also describes some of the reactions and properties of the 1,4-dihydropyridines prepared. Heating a benzene solution of **2** (R = Et) with benzenesulfonyl azide produced the *N*-benzenesulfonyl aziridino compound **3a** in 97% yield. Alkaline hydrolysis of the carbamate groups led, not to the hydrazo compound **4a,** but to the tricyclene **9.** It was evident that the 1,3-elimination process (**4a** → **9**) was



4a **9**

kinetically a most favorable pathway and all attempts to intercept **4a** by oxidation to **5a** were fruitless. However, repeating the sequence using the *tert*-butyl ester of **2** gave the aziridine derivative **3** (R′ = $PhSO_2$; R = *t*-Bu) in good

Scheme I



2, R = Et, *t*-Bu **3** **4** **5**

1a, R′ = $PhSO_2$ **e**, R′ = *p*-CNPh
b, R′ = $MeSO_2$ **f**, R′ = *p*-MeOPh
c, R′ = Ph **g**, R′ = $PhCH_2CH_2$
d, R′ = *p*-BrPh **h**, R′ = Me