a conventional potentiostat[31] and cells described elsewhere.[4,5] Potentials are referred to the aqueous saturated calomel electrode. Working electrodes were fabricated from platinum foil (cyclic voltammetry) and platinum gauze (coulometry).

Spectra and kinetic transients were recorded on a Beckman Acta III spectrophotometer. The procedure employed for kinetic determinations consisted of pipetting 3.0 ml of Py or Py/acetonitrile solution into each of two matched cuvettes. The experiment was initiated by injection of a 10–20-μl volume of a stock $PH^{\cdot+}ClO_4^-$ solution (butyronitrile) into the sample cell, followed by rapid mixing. The molar absorptivity of $PH^{\cdot+}ClO_4^-$ in Py [8.32 ($\pm$.0.05) $\times 10^3$ M^{-1} cm^{-1}, 523 nm] was determined by extrapolation of the absorbance transient to zero time and comparison of the initial absorbance with that obtained from addition of an identical volume of the stock solution to 3.0 ml of butyronitrile [λ_{max} 515.5 nm, ϵ 8.70 ($\pm$0.07) $\times 10^3$ M^{-1} cm^{-1}]. All kinetic determinations were performed at 24.7 ($\pm$0.3) °C.

Registry No.—$PH^{\cdot+}ClO_4^-$, 52156-15-7; Py, 110-86-1; *N*-[3-(10-phenylphenothiazinyl)]pyridinium ClO_4^-, 61047-42-5; $PH^{\cdot+}$, 38130-02-8.

References and Notes

(1) (a) Part 5: J. F. Evans and H. N. Blount, *J. Org. Chem.*, preceding paper in this issue. (b) Part 4: J. F. Evans and H. N. Blount, *J. Phys. Chem.*, **80**, 1011 (1976).
(2) C. Barry, G. Cauquis, and M. Maurey, *Bull. Soc. Chim. Fr.*, 2510 (1966).
(3) H. J. Shine, J. J. Silber, R. J. Bussey, and T. Okuyama, *J. Org. Chem.*, **37**, 2691 (1972).
(4) H. N. Blount, *J. Electroanal. Chem.*, **42**, 271 (1973), and references cited therein.
(5) D. T. Shang and H. N. Blount, *J. Electroanal. Chem.*, **54**, 305 (1974).
(6) Aqueous pK_a ca. 4–5; see S. A. Alkaitis, G. Beck, and M. Grätzel, *J. Am. Chem. Soc.*, **97**, 5723 (1975).
(7) (a) Y. Tsujino, *Tetrahedron Lett.*, 2445 (1968); (b) *ibid.*, 411 (1968); (c) *ibid.*, 763 (1969).
(8) P. Hanson and R. O. C. Norman, *J. Chem. Soc., Perkin Trans. 2*, 264 (1973).
(9) G. Cauquis, A. Deronzier, and D. Serve, *J. Electroanal. Chem.*, **47**, 193 (1973).
(10) Most probably, PH^{2+} reacts with residual nucleophilic impurities (e.g., H_2O) which escape removal during solvent pretreatment. This reaction is much slower than the analogous reactions of thianthrene dication (Th^{2+}) and 9,10-diphenylanthracene dication (DPA^{2+}) since Th^{2+} may be electrochemically detected only in the presence of added nucleophile scavengers[11] while DPA^{2+} is not observed even under these conditions.
(11) O. Hammerich and V. D. Parker, *Electrochim. Acta*, **18**, 537 (1973).
(12) The site of substitution by Py at the ring system is assigned by analogy to the corresponding product from reaction of Py with phenothiazine cation radical.[3]
(13) The presence of an electron-withdrawing substituent (e.g., pyridinium) renders oxidation more difficult.[14] Although a 135-mV shift is noted in this case, a shift of 200 mV is noted for the analogous *N*-(2-thianthrenyl)pyridinium ion compared to its precursor.[1a]
(14) P. Zuman, "Substituent Effects in Organic Polarography", Plenum Press, New York, N.Y., 1967.
(15) H. Gilman and R. O. Ranck, *J. Org. Chem.*, **23**, 1903 (1958).
(16) For an EE system involving two reversible couples

$$A \rightarrow A^{\cdot+} + e^- \quad (E_1)$$

$$A^{\cdot+} \rightarrow A^{2+} + e^- \quad (E_2)$$

the equilibrium constant for disproportionation, K_{dis}, may be calculated by[4]

$$2A^{\cdot+} \underset{}{\overset{K_{dis}}{\rightleftharpoons}} A^{2+} + A$$

$$K_{dis} = \exp\left(\frac{RT}{nF}|E_2 - E_1|\right)$$

From the data of Figure 1B, K_{dis} evaluates to be 2.2×10^{-12}.
(17) Calculated from the combined Stokes–Einstein and Smolunchousky equations:[18]

$$k_{diff} = \frac{8RT}{3000\eta}$$

For Py at 25 °, $\eta = 8.78 \times 10^{-3}$ P.[19]
(18) E. F. Caldin, "Fast Reactions in Solutions", Wiley, New York, N.Y., 1964, p 10.
(19) A. Cisak and P. J. Elving, *Electrochim. Acta*, **10**, 935 (1965).
(20) An analogous pathway involving rate-determining deprotonation of an oxidized cation radical/nucleophile intermediate has been proposed in the anisylation of thianthrene cation radical; see U. Svanholm, O. Hammerich, and V. D. Parker, *J. Am. Chem. Soc.*, **97**, 101 (1975).
(21) The dielectric constant of neat Py is considerably lower[22] than that of even the most concentrated solution of Py in acetonitrile used in this work. This lower dielectric solvent stabilizes the transition state (see Conclusion section) more so than the reactants, thereby affording a higher reaction rate. A comprehensive examination of solvent effects on reactions of radical cations of EE systems is in progress.[23]
(22) At 25°, ϵ 12.3 and 36.0 for P and acetonitrile, respectively. For 9.4 M Py in acetonitrile, ϵ 23.4.
(23) H. N. Blount et al., to be published.
(24) H. J. Shine and J. J. Silber, *J. Am. Chem. Soc.*, **94**, 1026 (1972).
(25) H. J. Shine and K. Kim, *Tetrahedron Lett.*, 99 (1974).
(26) B. K. Bandlish, A. G. Padilla, and H. J. Shine, *J. Org. Chem.*, **40**, 2590 (1975).
(27) T. Osa and T. Kuwana, *J. Electroanal. Chem.*, **22**, 389 (1969).
(28) J. F. . Evans and H. N. Blount, *J. Org. Chem.*, **41**, 516 (1976).
(29) H. Gilman, P. R. Van Ess, and D. A. Shirley, *J. Am. Chem. Soc.*, **66**, 1214 (1944).
(30) A. I. Popov and R. T. Pflaum, *J. Am. Chem. Soc.*, **79**, 570 (1957).
(31) A. A Pilla, *J. Electrochem. Soc.*, **118**, 702 (1971).

Structure and Rearrangement of the Reduction Dimers of *N*-Alkyl Pyridinium Cations[1]

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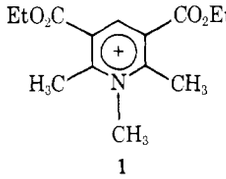
Reduction of the 1,2,6-trimethyl-3,5-dicarboethoxypyridinium cation (1) both chemically and electrochemically yields a mixture of isomeric reduction dimers. The less stable of these isomers, namely the 2,4′ dimer (8), undergoes rearrangement to yield the thermally more stable 4,4′ dimer **3** in a first-order reaction [$k = 1.1 \times 10^{12} \exp(-28.5/RT)$ s^{-1}]. A mechanism is proposed for the rearrangement that involves the thermal dissociation of the 2,4′ dimer 8 into two pyridinyl radicals (**5**) which recombine to yield the 4,4′ dimer **3**.

The reduction of the 1,2,6-trimethyl-3,5-dicarboethoxypyridinium cation **1** by sodium amalgam in aqueous acetic acid was reported by Mumm and his co-workers[2] to yield a dimeric reduction product that melted at 168 °C. Heating this material, which Mumm called "Primaester" ("primary ester"), resulted in its rearrangement to a higher melting isomer (mp 192 °C) referred to by Mumm as "Umwandlungester" ("transformation ester"). Mumm assigned the structure of the 2,2′ dimer **2** (1,1′,2,2′,6,6′-hexamethyl-3,3′,5,5′-tetracarboethoxy-1,1′,2,2′-tetrahydro-2,2′-bipyridine) to the "primary ester" and that of the 4,4′ dimer **3** (1,1′,2,2′,6,6′-hexamethyl-

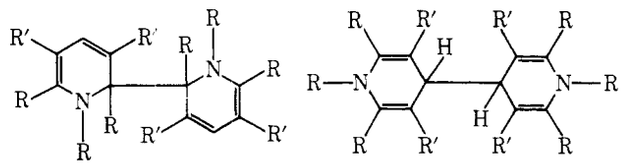


1

$\xrightarrow[AcOH]{Na(Hg)}$ $C_{28}H_{40}N_2O_8$ "primary ester" mp 168 °C

$\xrightarrow{Heat}$ $C_{28}H_{40}N_2O_8$ "transformation ester" mp 192 °C (1)

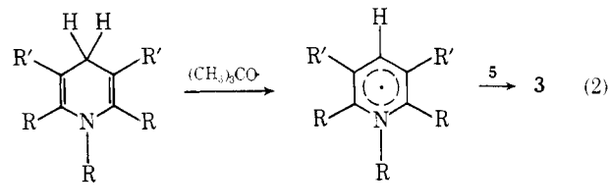
3,3′,5,5′-tetracarboethoxy-1,1′,4,4′-tetrahydro-4,4′-bipyridine) to the "transformation ester". Only the higher melting 4,4′



2 3

(R = CH_3; R′ = CO_2Et)

dimer **3** was obtained from the oxidation of 1,2,6-trimethyl-1,4-dihydro-3,5-dicarboethoxypyridine (**4**) with di-*tert*-butyl peroxide at 125 °C.[3] This reaction product was presumed to result from dimerization of two hybrid monohydropyridyl radicals **5** (1,2,6-trimethyl-3,5-dicarboethoxymonohydropyridyl) formed by abstraction of hydrogen atom from the 4 carbon of **4** by a *tert*-butoxyl radical obtained from the py-



4 5

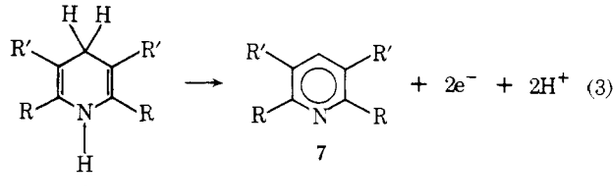
(R = CH_3; R′ = CO_2Et)

rolysis of the peroxide. The fact that no significant amounts of the lower melting "primary ester" were observed in this reaction, however, did not preclude its formation since the reaction temperature was sufficiently high and reaction time sufficiently long to have allowed for its rearrangement to the higher melting "transformation ester".

Our cyclic voltammetric studies of dihydropyridine derivatives reported in this article led to the observation that cathodic reduction of **1** yields the same reduction dimer obtained in its chemical reduction, namely the lower melting "primary ester". However, the NMR spectra of both the "primary ester" and "transformation ester" indicated that the structure assignment of the 2,2′ dimer **2** made previously for the "primary ester" was not correct. Determination of the correct composition of this lower melting reduction dimer made it possible to determine a mechanism for the rearrangement of the "primary ester" to the more stable "transformation ester" based on the kinetic parameters of the reaction.

Electrochemistry of Pyridine Derivatives in Acetonitrile. The anodic oxidation of various dihydropyridine derivatives to the corresponding pyridine and pyridinium derivatives has been the object of many investigations.[4] We have found that cyclic voltammograms of **4** and the corresponding dihydropyridine having no *N*-alkyl substituent, namely 2,6-dimethyl-1,4-dihydro-3,5-dicarboethoxypyridine (**6**), in acetonitrile at a platinum electrode to be informative, particularly with regard to the cathodic behavior of the anodic oxidation products of these dihydropyridine derivatives.

The dihydropyridine **6** undergoes anodic oxidation at a platinum electrode ($E_{p/2}$ = 0.81 V vs. SCE) to yield 2,6-dimethyl-3,5-dicarboethoxypyridine (**7**). Coulombic measure-



6 7

(R = CH_3; R′ = CO_2Et)

Table I. Summary of Electrochemical Data for Pyridine Derivatives[a]

Compd	$E_{p/2}$, V[b] Cathodic	$E_{p/2}$, V[b] Anodic	Coulometric measurement[c]
6		0.81	1.10
6 (+ γ-picoline)		0.81	1.99
4		0.75	1.05
4 (+ γ-picoline)		0.75	1.98
1 (ClO_4^-)	0.98		1.01
"Transformation ester"		0.20	2.05

[a] At a platinum electrode in acetonitrile, 0.10 M in tetraethylammonium perchlorate. [b] $E_{p/2}$ vs. a standard calomel electrode. [c] Number of faradays per mole of reagent initially present.

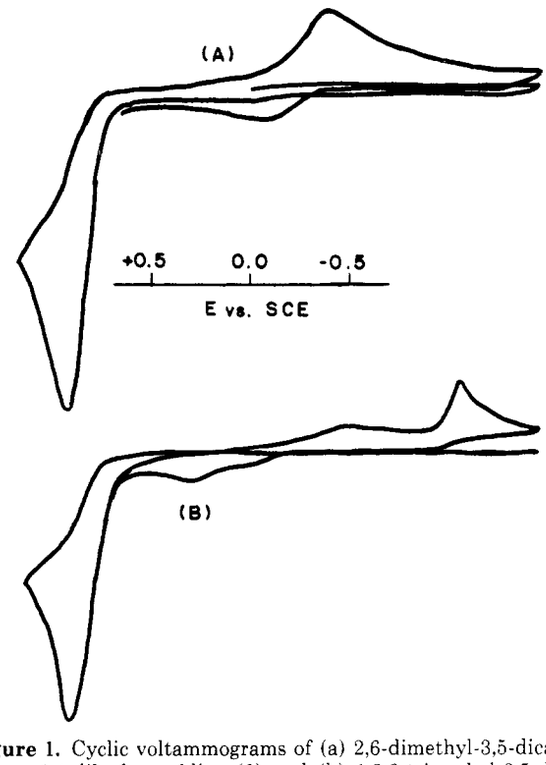


Figure 1. Cyclic voltammograms of (a) 2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine (**6**) and (b) 1,2,6-trimethyl-3,5-dicarboethoxy-1,4-dihydropyridine (**4**) in acetonitrile (0.1 M TEAP).

ment of the oxidation of **6** (Table I) indicated that only half of the dihydropyridine was reduced because the protons formed in the oxidation interact with **6** to yield the protonated amine which is not oxidized at this potential. However, in the presence of an excess of the base γ-picoline, the reduction proved to be a 1.99-electron process (see Table I). The cyclic voltammogram of **6** (Figure 1a) shows a cathodic peak ($E_{p/2}$ = −0.23) that corresponds to the reduction of the protonated amine to yield molecular hydrogen. The reversible character of this peak as well as the appearance of a peak at the same potential observed in the cathodic sweep of **6** in the presence of a small amount of perchloric acid supports the assignment of reaction 4 for the cathodic peak in the cyclic voltammogram **6**. A cathodic sweep of **6** in acetonitrile in the absence of acid shows no peaks.

$$6\,H^+ + e^- \rightarrow 6 + \tfrac{1}{2}H_2 \qquad (4)$$

Anodic oxidation of the *N*-alkyl dihydropyridine derivative **4** occurs at $E_{p/2}$ = 0.75 V. Coulombic measurements show the oxidation is a two-electron process if γ-picoline is present to react with the protons formed in the reaction. The cyclic

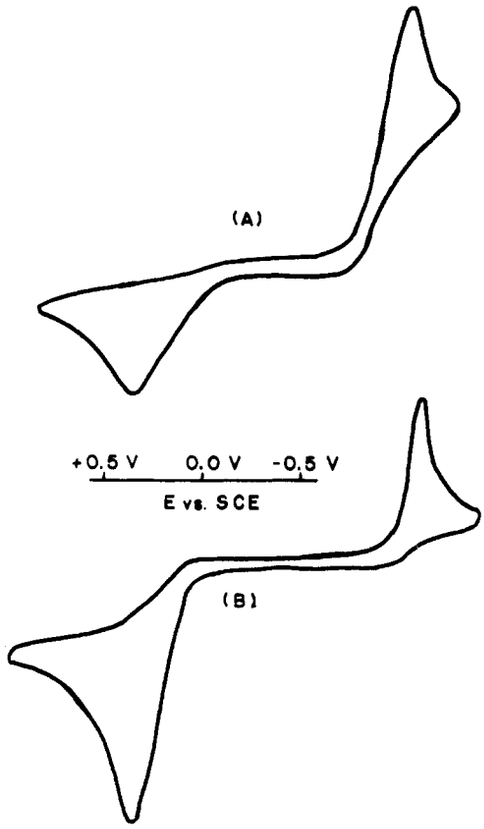


Figure 2. Cyclic voltammograms of (a) 1,2,6-trimethyl-3,5-dicarboethoxypyridinium perchlorate (1) and (b) the 4,4′-bipyridine 3 in acetonitrile (0.1 M TEAP).

voltammogram (Figure 1b) reveals that in addition to the expected cathodic peak at $E_{p/2} = -0.28$ V for the protonated amine, a second cathodic peak ($E_{p/2} = -0.98$ V) appears, a peak not observed in a cathodic sweep of 4 prior to anodic oxidation. The half-potential of this peak is identical with that observed in the cyclic voltammogram of an authentic sample of the perchlorate salt of the pyridinium cation 1 (Figure 2a).

$$4 \rightarrow 2 + H^+ + 2e^- \quad (5)$$

An anodic sweep *after* reduction of the cation 1 reveals oxidation ($E_{p/2} = 0.20$ V) of a material that is not present in the initial anodic sweep of 4. The coulometric data obtained for the reduction of the pyridinium cation 1 at −1.1 V (see Table I) correspond to a one-electron process which would be consistent with the formation of a reductive dimer of the pyridinium cation 1. The cyclic voltammogram of an acetonitrile solution of an authentic sample of the "transformation ester" (Figure 2b) prepared by rearrangement of the "primary ester" obtained by sodium amalgam reduction of 1 gave a peak with the same $E_{p/2}$ ascribed to the reductive dimer observed in the cyclic voltammogram of 4 and, subsequent to the oxidation of the dimer, a cathodic peak that can be ascribed to 1. Coulometric measurement of the anodic oxidation of the reductive dimer indicated the reaction to be a two-electron process (Table I).

Several attempts were made to reduce the pyridine 7 cathodically to a reductive dimer in acetonitrile. In no case was there evidence of any current flow or of a yellow coloration at the electrode, a phenomenon characteristic of the cathodic reduction of the pyridinium cation 1 to the yellow reduction dimer. Cathodic reduction of the pyridine 7 in the presence of $HClO_4$ showed only a peak at −0.32 V corresponding to the reduction of the protonated pyridine to yield hydrogen.

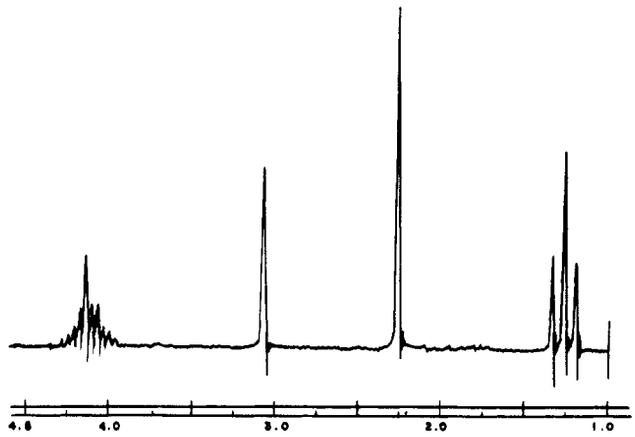


Figure 3. NMR spectrum of 1,1′,2,2′,6,6′-hexamethyl-3,3′,5,5′-tetracarboethoxy-1,1′,4,4′-tetrahydro-4,4′-bipyridine (3).

Structures of Reductive Dimers. We found that reduction of the sulfate salt of 1 by 3% sodium amalgam in acetic acid in the manner reported by Mumm and his co-workers yielded a material ("primary ester") that melted over a 3 °C range (162–165 °C). The same material could be isolated from the electrochemical reduction at a platinum electrode of the perchlorate salt of 1 in anhydrous acetonitrile at a potential of −1.1 V (vs. a standard calomel electrode). The "transformation ester" (mp 193 °C) was formed in 91% yield of recrystallized material by refluxing a toluene solution of the "primary ester" for about 24 h. A 40% yield of the "transformation ester" was obtained simply by heating the "primary ester" for 10 min at 180 °C.

The mass spectra of both the "primary ester" and "transformation ester" had parent peaks at *m/e* 532 and base peaks at *m/e* 266. The parent and the base peaks strongly support the suggested dimeric character of these reductive dimers of 1 (mol wt 266).

One apparent difference in the two materials is that the higher melting "transformation ester" can be isolated readily as crystalline material whereas the lower melting "primary ester" was obtained from reaction mixtures only as powder. However, on standing for several days at room temperature, a methanolic solution of the "primary ester" yielded a crop of crystals which melted sharply at 176.5–177 °C. These observations suggested that the "primary ester" formed in the reduction reactions is actually a mixture, the main component of which is the material that melts at 176.5–177 °C.

The NMR spectrum (Figure 3) of the "transformation ester" confirmed the assignment of 4,4′-tetrahydrobipyridine structure 3 for this compound made by Mumm and Beth.[2a] The triplet centered at 1.52 ppm (12 protons) can be assigned to the methyl protons of the four ethyl groups, the singlet at 2.52 ppm to the 3,3′,5,5′-methyl groups, and the singlet at 3.08 ppm (6 protons) to the two *N*-methyl groups. The multiplet centered at 4.20 ppm (10 protons) consists of a singlet at 4.25 ppm that can be assigned to the 4,4′ protons and a multiplet consisting of ten peaks resulting from the eight methylene protons of the four ethyl groups. The complexity of the signal (four overlapping quartets) is due to the nonequivalence of the two protons of each methylene group owing to the chiral character introduced in the molecule because of the restricted rotation at the 4,4′ linkage.[5]

The NMR spectrum of the crystalline material obtained from the "primary ester" is more complex (Figure 4) but is consistent with the assignment of the 2,4′ dimer 8 for this compound. The *N*-methyl groups appear as two singlets (unassigned) at 3.06 and 3.12 ppm, the 2-methyl as a singlet at 1.75 ppm, the 2′,6,6′-methyls as three singlets (unassigned)

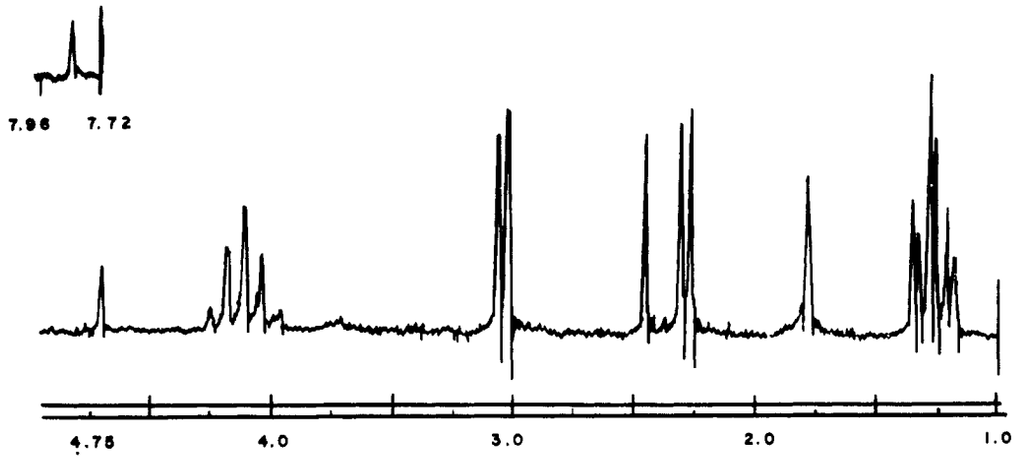
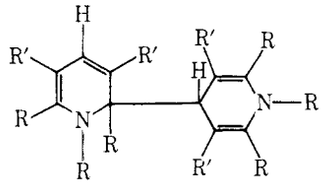


Figure 4. NMR spectrum of 1,1′,2,2′,6,6′-hexamethyl-3,3′,5,5′-tetracarboethoxy-1,1′,2,4′-tetrahydro-2,4′-bipyridine (8).

at 2.27, 2.32, and 2.45 ppm, the 4′ proton at 4.70 ppm, and the 4 proton at 7.85 ppm. The resonances centered at 1.50 and 4.15



8

(R = CH_3; R′ = CO_2ET)

ppm can be ascribed to the triplets and quartets of the four ethyl groups of the carboethoxy groups.

The NMR spectrum of the "primary ester" is a composite of the spectra of the 4,4′ dimer **3** and the 2,4′ dimer **8.** Missing in the NMR spectrum of the "primary ester" is any evidence of the 2,2′ dimer **2,** the structure assigned by Mumm to the "primary ester". Although **2** would be expected to exist as a mixture of the meso and racemic diastereoisomers and therefore display the same number of singlet methyl group resonances (four singlets for the 2,2′,6,6′-methyls and two singlets for the *N*-methyls), the observed chemical shifts are not consistent with the assignment of the 2,2′ dimer to either the low-melting "primary ester" or the crystalline material obtained from it. The chemical shifts of the 2- and 2′-methyl groups of the two diastereomers of **2** would be expected to appear as singlets upfield relative to the singlets of the 6- and 6′-methyl groups. Furthermore, the signals of the 4 and 4′ protons would appear in the downfield region expected for vinyl protons. The absence of any observable amounts of the 2,2′ dimer **2** in the "primary ester" mixtures is discussed subsequently in this article.

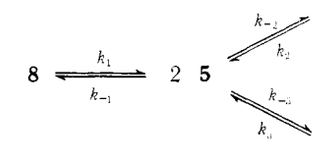
Integration of the resonance signal at 3.17 ppm for the *N*-methyl groups of **3** and those at 3.06 and 3.12 ppm for the *N*-methyl groups of **8** (see Experimental Section) allows for determination of the amounts of the two isomers that comprise the "primary ester" mixture. Employing this method, we found that the "primary ester" prepared by sodium amalgam reduction of **1** consisted of 81% of the 2,4′ dimer **8** and 19% of the 4,4′ dimer **3.**

Mechanism of the Rearrangement of the 2,4′ Dimer to the 4,4′ Dimer. The kinetics of the isomerization of the 2,4′ dimer **8** to the 4,4′ dimer **3** are informative of the mechanism of this rearrangement. The rates of the rearrangement in chlorobenzene were determined by measuring the NMR integrations of the *N*-methyl protons after appropriate intervals of heating. Chlorobenzene was used as the solvent for these reactions because it did not show any observable amounts of reaction with either **8** or **3** at the reaction temperatures used in our kinetic studies. Extensive coloration of the solution and formation of insoluble reaction products (not identified) were encountered when both **8** and **3** were heated for short times (10 min) in deuteriochloroform and 1,1,2,2-tetrachloroethane. Chlorobenzene was not a suitable solvent for the NMR determinations, however, because neither **3** nor **8** is sufficiently soluble in chlorobenzene at room temperature to allow for reliable NMR measurements. Therefore, after removal of the chlorobenzene under vacuum, solutions of the reaction mixtures in 1,1,2,2-tetrachloroethane were prepared for NMR analysis. Table II lists the first-order rate constants obtained for the rearrangement from which the rate constant $k = 1.1 \times 10^{12} \exp(-28.6/RT)\ s^{-1}$ can be calculated.

Table II. First-Order Rate Constants for Rearrangement of 8 to 3

Temp, °C	Rate constant $\times 10^5$, s^{-1}	Std dev $\times 10^5$
99.8	1.85	0.07
119.4	7.86	0.32
131.9	39.5	2.34

A mechanism consistent with the kinetic parameters for the rearrangement is one in which the 2,4′ dimer **8** undergoes unimolecular homolysis to form a pair of the hybrid radicals **5,** the same radical that is formed in the one-electron reduction of the pyridinium cation **1** or by abstraction of a 4-hydrogen atom from **4.** Two of the hybrid radicals **5** can recombine to form the 2,2′ dimer **2,** the 4,4′ dimer **3,** or the 2,4′ dimer **8.** Both **2** and **3** may also undergo homolysis to form the hybrid radi-



(6)

cals **5,** the former considerably faster than **8** ($k_2 \gg k_1$) because of greater steric crowding in the region of the bond undergoing cleavage and the latter more slowly than **8** ($k_3 \ll k_1$) because of less steric crowding. In the temperature region of our studies (100–130 °C), **3** apparently does not decompose to any significant extent whereas **2** does so rapidly. Indeed, our failure to observe any evidence of the 2,2′ dimer **2** in the "primary ester" mixture very likely arises from the fact that this isomer is not stable even at the temperatures used to "work up" the reaction mixtures (refluxing methanol) and rearranges to **3** and **8.**

The steady-state concentration for the intermediate hybrid radical **5** is shown in eq 7.

$$\left(\frac{k_1[8] + k_2[2] + k_3[3]}{k_{-1} + k_{-2} + k_{-3}}\right)^{1/2} = 5 \quad (7)$$

If it is assumed that the 2,2′ dimer decomposes at the temperatures of our reactions essentially as fast as it is formed ($k_2[2] = k_{-2}[5]^2$), that $k_3 \ll k_1$, and that the rate of the formation of the 4,4′ dimer **3** by dimerization of two of the hybrid radicals **5** is given by $d[3]/dt = k_{-3}[5]^2$, then the rate law of rearrangement of **8** to **3** is that shown in eq 8, a rate law consistent with the first-order kinetics observed for the reaction.

$$\frac{d[3]}{dt} = \frac{k_1[8]}{1 + k_{-1}/k_{-3}} \quad (8)$$

The activation parameters for the rearrangement of **8** to **3** are determined by the rate-limiting step of the reaction sequence, namely the unimolecular decomposition of **8**. Although the activation energy is consistent for a reaction involving rupture of a single σ bond between two carbon atoms to yield two resonance stabilized radicals at the rates observed for the rearrangement, the preexponential (frequency) factor A (1.1×10^{12} s^{-1}) is unexpectedly low for such a reaction.[6] In general, unimolecular fragmentation reactions that involve breaking of a single σ bond (e.g., peroxide decompositions) have A values that are greater than 10^{13} ($\Delta S^{\ddagger} > 0$). A values less than 10^{13} ($\Delta S^{\ddagger} < 0$) are more often encountered in unimolecular decompositions that proceed by simultaneous bond breaking and bond making at two or more sites in the molecule (e.g., ester and anhydride pyrolyses). Severe conformational restrictions are encountered in the transition states of the latter reactions accounting for the low frequency factors or negative entropies of activation.

The low A values for the rearrangement of **8** to **3** must be ascribed to the decomposition of the 2,4′ dimer **8** and consequently reflect a conformational requirement for the transition state of the homolysis of the σ bond between the 2 and 4′ carbon atoms of this molecule. Since the resonance stabilization of the monohydropyridyl radicals (**5**) is the principal reason that homolysis of this carbon–carbon bond occurs at these moderate temperatures, the transition state likely has considerable productlike character, namely that of the resonance stabilized radicals. The bond breaking would therefore be expected to occur most readily if the p orbitals generated at the 2 and 4′ carbon atoms are parallel to those of the π bonds in the two ring systems in order to allow for maximum overlap of the p orbitals of the resonance stabilized radical. Such would be the case only if the fragmenting molecule assumes the proper conformation in the transition state of the homolysis, namely that in which the σ bond that is broken is in an axiallike position with respect to both rings. Although not the preferred conformation for **C** (the equatorial–equatorial, the equatorial–axial, and axial–equatorial all likely more stable), it is only in (he axial–axial conformation that the σ bond undergoes homolysis since it is only in this conformation that the resonance stabilization of the radicals being formed can lower the activation energy requirement for the reaction.

Homolysis of the σ bond between the two rings of other tetrahydrobipyridyls has been proposed for various thermal reactions of these compounds.[7] In gereral, the products of these reactions are pyridine derivatives or rearrangement products and can be accounted for in terms of reactions of the monohydropyridyl radicals formed in the fragmentation.

Experimental Section

2,6-Dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine (6) was prepared by the method of Singer and McElvain[8] and **2,6-dimethyl-3,5-dicarboethoxypyridine (7)** by oxidation of **6** with sodium nitrite.[9] The perchlorate salt of the **1,2,6-trimethyl-3,5-dicarboethoxypyridinium** cation **1** was obtained by reaction of **7** with dimethyl sulfate followed by precipitation of the perchlorate salt by addition of sodium perchlorate in the manner described by Brook and Karrer.[10] **1,2,6-Trimethyl-3,5-dicarboethoxy-1,4-dihydropyridine (4)** was prepared by sodium dithionite reduction of the perchlorate salt.[3]

Acetonitrile (Baker Analyzed reagent) was dried over calcium hydride for 24 h and distilled from phosphorus pentoxide according to the procedure described by Adams.[11] **Tetraethylammonium perchlorate** (TEAP) was prepared by precipitation of the salt from a solution of tetraethylammonium bromide with sodium perchlorate and purified by recrystallization from ethanol and water seven times.

Cyclic Voltammetry. The cyclic voltammetric experiments were performed with a controlled potential operational amplifier polarograph in a conventional three-electron cell consisting of a platinum working electrode, a platinum gauze auxilary electrode, and a saturated calomel reference electrode. All cyclic voltammograms were recorded on a Moseley Model 7030A X-Y recorder.

The platinum electrodes were cleaned before each cyclic voltammogram by immersion in a dilute nitric acid solution rendering each anodic for 10 s then cathodic for 15 s and finally rinsed with distilled water. All cyclic voltammograms were performed in a solution of TEAP (0.1 M) in acetonitrile. The solution was sparged with nitrogen (dried by passing through Drierite) for about 15 min to eliminate any background current due to oxygen. Sufficient sample was dissolved in the acetonitrile to give a solution approximately 2×10^{-3} M in the substrate, and sweeps were made at scan rates of 15 V/min. Sweeps were initiated in both the anodic and cathodic directions to assure the assignments of the current peaks suspected as products of electrode reactions and not species present in the original sample of the substrate undergoing examination.

Coulometric Measurements. Exhaustive coulometric procedures were utilized for determination of the number of faradays required for the anodic and cathodic processes listed in Table I. Solutions containing accurately weighed amounts of the substrate (TEAP used as the carrier) were subjected to the desired reaction at a platinum gauze electrode. A platinum wire inside of a tube fitted with a fritted disk and containing only acetonitrile and TEAP served as the auxiliary electrode. Potentials were adjusted at or slightly beyond the peak potential of the desired reaction. The current flow was monitored and measured with a Wenking Electronischer potentiostat equipped with a digital readout. The solution resulting from the coulometric determinations was concentrated and the products of the electrode reactions identified both by comparisons of their electronic spectra and thin layer chromatographic retention times with those of authentic samples of the compounds.

Sodium Amalgam Reduction of 1. Ten grams of 2,6-dimethyl-3,5-dicarboethoxypyridine was heated for 2 h at 100 °C with 9 ml of freshly distilled methyl sulfate, 0.1 g of copper powder, and 0.25 g of anhydrous potassium carbonate. After cooling, 30 ml of water was added and the mixture extracted three times with 30 ml of ether. The aqueous fraction was cooled in an ice bath and 80 g of 3% sodium amalgam[12] and 3 ml of acetic acid were added with stirring over a 75-min period. The precipitated "primary ester" was filtered out and recrystallized from methanol (mp 162–165 °C). The yield of isolated "primary ester" was 57%.

Electrochemical Reduction of 1. Ten grams of 1,2,6-trimethyl-3,5-dicarboethoxypyridinium perchlorate was dissolved in 100 ml of anhydrous acetonitrile (distilled from phosphorus pentoxide after 2 weeks of storing over calcium hydride). About 2 g of tetraethylammonium perchlorate was dissolved in the solution to serve as the supporting electrolyte. The solution was stirred with a magnetic stirrer, cooled in an ice bath, and sparged with argon gas. The controlled potential electrolysis was performed with a three-electrode potentiostat using a calomel electrode for reference, 8 in.^{2} of platinum gauze as the working electrode, and a carbon rod contained in a glass fritted cell divider as the auxiliary electrode. The pyridinium cation was reduced at −1.1 V (vs. the calomel electrode) until no further current flow was observed (2–3 h). The "primary ester" mixture precipitated from the solution and was obtained in 52% yield (mp 163–166 °C).

1,1′,2,2′,6,6′-Hexamethyl-3,3′,5,5′-tetracarboethoxy-1,1′,-4,4′-tetrahydro-4,4′-bipyridine (4,4′ Dimer 3). Two grams of the "primary ester" mixture was dissolved in 100 ml of toluene and refluxed for 24 h. The toluene was removed under reduced pressure and the residue recrystallized from absolute ethanol, yielding 1.82 g (91% of theory) of the 4,4′ dimer **3**, mp 193 °C (reported 193 °C).[2] The mass

spectrum showed a parent peak at *m/e* 532 (calcd mol wt 532) and a base peak at *m/e* 266, corresponding to the monomeric unit of the dimer. The NMR spectra of this compound in $DCCl_3$ is shown in Figure 3.

Heating the "primary ester" for 10 min at 180 °C followed by recrystallization of the resulting material resulted in a 40% yield of 3.

1,1',2,2',6,6'-Hexamethyl-3,3',5,5'-tetracarboethoxy-1,1',-2,4'-tetrahydro-2,4'-bipyridine (2,4' Dimer 8). A Solution of the "primary ester" in methanol was allowed to cool slowly to room temperature. After a few days at room temperature, small amounts of crystalline material were formed. More rapid cooling or at temperatures below room temperature resulted in precipitation of the "primary ester" as a powder. The crystalline material (mp 176.5–177 °C) showed the same parent and base peaks in its mass spectrum as observed for the 4,4 dimer **3**. The NMR spectrum in $DCCl_3$ is shown in Figure 4.

Kinetic Measurements. Solutions (0.01 M) of the "primary ester" mixture in chlorobenzene were placed in a three-neck flask equipped with a large coil condenser. The remaining necks were stoppered and the flask immersed in an oil temperature bath. At appropriate time intervals, a 25-ml portion of the solution was removed and evaporated to dryness on a rotatory evaporator. The resulting residue was dissolved in about 5 ml of 1,1,2,2-tetrachloroethane. Four or five NMR sample tubes from each sample were removed from the reaction mixture.

The NMR analyses were obtained as soon as possible after the tetrachloroethane solutions of the reaction mixtures were prepared to avoid any reaction of the reactants or products of the rearrangement with the solvent. The NMR integrations of the *N*-methyl signals of **3** and **8** in the region of 3.0 ppm were obtained using the field sweep mode with a sweep width of 250 Hz and sweep times of 100 s per sweep. The signals were integrated 14–16 times, and, employing the methodology of Kassler,[13] the best 10–12 integrations used to determine the ratios of the 2,4' dimer **8** and the 4,4' dimer **3**. The extent of reaction of the 2,4' dimer **8** at each time interval was determined from the ratio obtained and from the initial amount of the "primary ester". The first-order rate constants and their standard deviations in Table II were calculated from least-squares treatment of the data obtained in this manner.

Registry No.—**1**, 59348-50-4; 1 perchlorate, 59348-51-5; **3**, 61024-92-8; **4**, 14258-07-2; **6**, 1149-23-1; **8**, 61024-93-9; 2,6-dimethyl-3,5-dicarboethoxypyridine, 1149-24-2; methyl sulfate, 77-78-1.

References and Notes

(1) This work was supported by a grant (GM AM 18191) from the Department of Health, Education and Welfare.
(2) (a) O. Mumm and W. Beth, *Ber.*, **54**, 1591 (1921); (b) O. Mumm and H. Ludwig, *ibid.*, **59**, 1605 (1926); (c) O. Mumm and J. Diedricksen, *Justus Liebigs Ann. Chem.*, **538**, 195 (1939).
(3) E. S. Huyser, J. A. K. Harmony, and F. L. McMillian, *J. Am. Chem. Soc.*, **94**, 3176 (1972).
(4) Cf. W. J. Blaedel and R. G. Haas, *Anal. Chem.*, **42**, 918 (1970); W. J. Blaedel and R. A. Jenkins, *ibid.*, **47**, 1337 (1975); R. D. Braun, K. S. V. Santhanam, and P. J. Elring, *J. Am. Chem. Soc.*, **97**, 259 (1975); J. Kuthan, V. Simonek, V. Volkovi, and J. Volke, *Z. Chem.*, **11**, 111 (1971).
(5) For discussion and other examples of nonequivalence of methylene protons arising from chirality introduced by restricted rotation see J. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Vol. 5, 2d ed, Pergamon Press, Oxford, 1969, pp 378–379.
(6) See A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", 2d ed, Wiley, New York, N.Y., 1961, pp 109–115.
(7) A. T. Nielser, D. W. Moore, J. H. Mazur, and K. H. Berry, Jr., *J. Org. Chem.*, **29**, 2898 (1964); P. M. Atlani, J. F. Biellman, and J. Moron, *Tetrahedron*, **29**, 391 (1973); P. Atlani, J. F. Bielman, R. Briere, and A. Rassat, *ibid.*, **28**, 5805 (1972); P. Atlani, J. F. Biellman, R. Briere, H. Lemaire, and A. Rassat, *Ind. Chim. Belg.*, **36**, 1066 (1971); P. Atlani, J. F. Biellman, R. Briere, J. Lemaire, and A. Rassat, *Tetrahedron*, **28**, 2827 (1972).
(8) A. Singer and S. M. McElvain, "Organic Syntheses", Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N.Y., 1943, p 214.
(9) B. Loev and K. M. Snader, *J. Org. Chem.*, **30**, 1914 (1965).
(10) P. R. Brook and P. Karrer, *Justus Liebigs Ann. Chem.*, **605**, 1 (1957).
(11) R. N. Adams, "Electrochemistry at Solid Electrodes", Marcel Dekker, New York, N.Y., 1969, p 30.
(12) R. N. McDonald and C. E. Reineke, *Org. Synth.*, **50**, 50 (1970).
(13) F. Kasler "Quantitative Analysis by NMR Spectroscopy", Academic Press, New York, N.Y., 1973, p 79.

Pyridopyrimidines. 6. Nucleophilic Substitutions in the Pyrido[2,3-*d*]pyrimidine Series[1]

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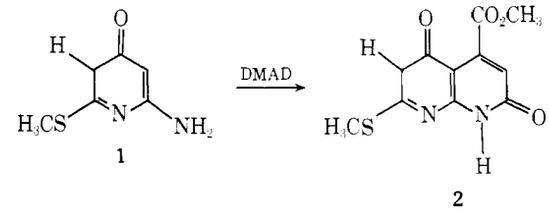
The scope of the reaction between 6-aminopyrimidines and dimethyl acetylenedicarboxylate to give 5-carbomethoxy-7-oxopyrido[2,3-*d*]pyrimidines was found to be limited primarily to 6-aminouracil derivatives. The preparation of a key synthetic intermediate, 2,4,7-trichloropyrido[2,3-*d*]pyrimidine, is reported. A study of nucleophilic displacement on this intermediate revealed that the reactivity was in the order 4 > 7 > 2 except in the case of aqueous sodium hydroxide, which gave 5-carboxy-7-chloro-2,4-dioxopyrido[2,3-*d*]pyrimidine. The observed selectivity enabled the preparation of a number of otherwise inaccessible pyridopyrimidines.

Unsubstituted 6-aminouracil and a variety of its *N*-alkyl derivatives have recently been found to react with dimethyl acetylenedicarboxylate (DMAD) in protic media (water or methanol) to give 5-carboxamido-7-oxopyrido[2,3-*d*]pyrimidines.[2,3] Our interest in pyrido[2,3-*d*]pyrimidines and nucleosides derived from them prompted us to continue the study of the utility of this reaction in providing candidate antitumor pyridopyrimidines. The present paper describes the synthesis of such heterocycles and their characterization; a companion paper[4] will describe the synthesis of ribonucleoside analogues from these bases.

It has been firmly established[2,3] that the reaction of DMAD with 6-aminouracils gave the 7-oxo rather than the 5-oxopyridopyrimidine isomer and the probable mechanism of this reaction has been described.[2] Since the procedure is a very



1 2

simple one, it was of interest to assess the scope of the reaction with a variety of pyrimidines. It was found that 6-amino-2-methylthio-4-oxopyrimidine (**1**) could be converted to 5-carbomethoxy-4,7-dioxo-2-methylthiopyrido[2,3-*d*]pyrimidine (**2**) in low yield. Of a number of other 6-aminopyrimidines studied, including 4,6-diamino-2-methylthio-, 4,6-diamino-2-oxo-, 4-amino-6-methylthio-2-oxo-, and 2,4-diamino-6-