Registry No.—1, 66769-63-9; **2**, 13994-57-5; 2-methoxy-3-butyn-2-ol, 115-19-5.

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Electrochemical Reduction of 1-Benzyl-3-carbamoylpyridinium Chloride, a Nicotinamide Adenine Dinucleotide Model Compound

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The electrochemical reduction of pyridine nucleotides, e.g., nicotinamide adenine dinucleotide (NAD^+), and related model compounds has been the subject of active investigation, extensively reviewed.[2-4] It has been consistently found that one- or two-electron reduction products are formed, i.e., respectively tetrahydrobipyridine derivatives and dihydropyridines.

Only in a few cases has the detailed structure of the tetrahydrobipyridines been determined,[5] while generally the structure has been postulated exclusively on the grounds of UV spectroscopic evidence. It appears that further research on the structure of these dimeric compounds is highly desirable, also in view of their possible biological role; for example, a dimer from the NAD^+ has been reported[6] to be involved in the plant phenol oxidase activity.

In this paper we report the results obtained in the electrochemical one-electron reduction of 1-benzyl-3-carbamoylpyridinium chloride (1), a model compound strictly related to the natural coenzyme. The previously reported[7,8] polarographic behavior of 1-benzyl-3-carbamoylpyridinium ion has been confirmed by our experiments. It is essentially characterized by two reduction waves, the first one (wave A) pH independent and the second (wave B) appearing only at alkaline pH values. The first step implies the reversible transfer of one electron to the pyridinium cation to give a radical which irreversibly dimerizes, as shown by fast-scan cyclic voltammetry tests.[9]

Electrolyses of **1** have been performed at different potential values within the wave A plateau, in about 0.1 M solution buffered in the pH range 8 to 10. Under these conditions, a precipitate is invariably formed and adsorption effects, already noted by other workers,[9] were pronounced enough to block the electrode surface and reduce to zero value the current within a short time after the beginning of the electrolysis. This difficulty has been overcome using a 1:1 (v/v) mixture of benzene and aqueous solution under vigorous stirring. In such a way, the precipitate is washed away from the electrode and transferred into the interphase aqueous solution–benzene, ensuring successful completion of the electrolysis. Under these conditions, a faradaic n value of 1 ± 0.1 has been measured.

Table I. ^{1}H NMR Data for Dimers 2 and 3

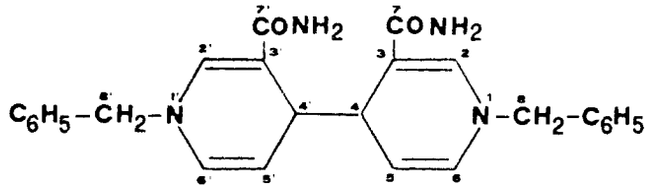
2			3	
δ, ppm	J, Hz	Protons	δ, ppm	J, Hz
7.5–7.1		aromatic	7.5–7.1	
7.24 (d)	1.2	$H_2 + H_{2'}$	7.13 (d)	1.4
6.97		amide	6.33	
6.02 (dd)	1.2	$H_6 + H_{6'}$	5.89 (dd)	1.4
	7.9			7.8
4.36 (dd)	4.7	$H_5 + H_{5'}$	4.47 (dd)	4.6
	7.9			7.8
4.35		benzyl	4.30	
3.24 (d)	4.7	$H_4 + H_{4'}$	3.35 (d)	4.6

Table II. ^{13}C NMR Data for Compounds 2, 3, 4, and 5

2 δ, ppm	carbon atoms	3 δ, pm	4 δ, ppm	carbon atoms	5 δ, ppm
169.3	$C_7 + C_{7'}$	170.3	169.0	C_7	167.5
138.1	$C_2 + C_{2'}$	138.5	137.8	C_2	144.9
130.2	$C_6 + C_{6'}$	129.7	129.5	C_6	47.0
102.2	$C_5 + C_{5'}$	102.2	101.8	C_5	109.1
101.6	$C_3 + C_{3'}$	102.0	100.3	C_3	99.2
56.2	$C_8 + C_{8'}$	56.3	55.9	C_8	58.5
38.9	$C_4 + C_{4'}$	39.2	22.3	C_4	122.5
		benzene rings			
138.2	C_1	138.0			
128.3	$C_3 + C_5$	128.2			
127.1	$C_2 + C_6$	127.2			
127.1	C_4	127.0			

From the crude reduction product the dimers **2** and **3** have been isolated and purified following the procedure described in the Experimental Section. The UV spectra of both **2** and **3** are closely similar and will be discussed in detail below.

However, a feature must be immediately emphasized,



2 and 3

namely the absence of any 1,2-dihydropyridine long-wavelength (above 400 nm) absorption, which excludes structures involving dimerization at position 2, and thus restricts the possible structure of these products to 4,4′-, 6,6′- or 4,6′-linked dimers.

In the ^{1}H NMR spectra of both **2** and **3** (Table I) only 13 protons are detectable, namely 5 aromatic, 3 vinyl, 2 methylene, 1 methine, and 2 amide protons, showing the symmetry of the structure and disproving the occurrence of mixed dimers. The following additional ^{1}H NMR data are relevant to the assignment of the structure: (i) the chemical shifts of the methine protons in both **2** and **3** are clearly indicative of 1,4- rather than 1,6-dihydropyridine moieties, by comparison with ^{1}H NMR spectra of the dihydropyridine monomers **4** and **5**;[10] (ii) the value of the coupling constant ($J \approx 8$ Hz) between the two hydrogens on the unsubstituted double bond indicates that its position is α with respect to the ring nitrogen atom, as it is known that this value is greater (about 10 Hz)[5a,10-12] for double bonds in position β with respect to the nitrogen atom. Therefore, these data provide reasonable evidence for a symmetric dimeric 4,4′-linked structure for both **2** and **3**.

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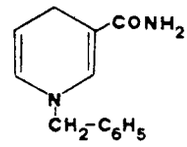
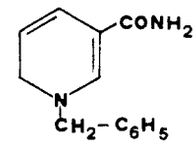
Clear-cut evidence has been attained from a detailed analysis of ^{13}C NMR spectra of compounds **2**, **3**, **4**, and **5** (Table II); comparison of the spectra shows that **2** and **3** are very similar to **4** and different from **5**. In particular the chemical shift values of the methine carbon atom of the dimers



4



5

(δ ~39) must be compared with the chemical shift values of the C-4 in the 1,4-dihydropyridine monomer **4** (δ 22.3) and of the C-6 in the 1,6-dihydropyridine monomer **5** (δ 47.0).

Since it is well known that the introduction of a carbon as a substituent implies a low-field shift of the carbon on which the substitution takes place, and in analogous cases a shift has been found of about 16 ppm,[13] the value observed for the methine carbon in both **2** and **3** fits the value expected for 4,4′-linked dimers. As a whole, ^1H and ^{13}C NMR spectra unambiguously demonstrate a 1,1′-dibenzyl-3,3′-dicarbamoyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine structure for both **2** and **3**, which are therefore a diasteroisomeric pair with respect to the C_4–$C_{4'}$ stereochemistry.

Both compounds **2** and **3** show two UV absorption bands at ca. 270 and 350 nm, respectively; at first sight, such spectral feature is surprising for 1,4-dihydropyridine dimeric structures as **2** and **3**, since it has been claimed[14-16] that the presence of two maxima in the 250–370-nm region is rather typical of 1,6-dihydropyridine dimeric structures. For instance, Wallenfels et al.[14] on treating 1-benzyl-3-carbamoylpyridinium cation with various reducing agents (Cr^{2+}, Mg powder, etc.) have isolated only one dimer, identified as 1,1′-dibenzyl-3,3′-dicarbamoyl-1,1′,6,6′-tetrahydro-6,6′-bipyridine on the grounds of the presence in the UV spectrum of two absorption maxima at 275 and 355 nm and of the ^1H NMR spectrum as well. We have performed the reduction of **1** with Mg powder, following the procedure reported.[14]

In our hands, the reaction has given two dimers, identical in all respects to **2** and **3**. In particular, NMR evidence has shown that the compound identified by Wallenfels as a 6,6′-linked dimer is identical to **2**, and therefore must be regarded as a 4,4′-linked dimer.[17]

From the above considerations, it is clear that 4,4′-linked dimers as well can display UV spectra characterized by two absorption bands in the 250–370-nm region. While, undoubtedly, the intriguing question concerning the spectra–structure correlations for this class of compounds deserves careful reinvestigation, the present data clearly show, contrary to the current literature statements, that the presence of two absorption bands in the 250–370-nm region cannot be used as a diagnostic tool for structures implying dimerization at the 6 position.

Experimental Section

Compound **1** was prepared according to ref 19. The melting points were taken upon a Kofler apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 177 grating spectrophotometer as Nujol mulls and UV spectra on a Perkin-Elmer 402 spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded in CD_3SOCD_3 on a Varian XL-100-15 spectrometer; the chemical shifts are reported as δ units relative to Me_4Si (δ is 0 ppm) as internal standard. The same apparatus described in a previous paper[20] was used for the electrochemical measurements. Britton–Robinson and NH_3–NH_4Cl buffers were used; the solutions were deoxygenated with 99.99% pure nitrogen or argon, and the temperature was kept at 25.0 ± 0.1 °C. Macroscale electrolysis used a mercury pool electrode (area 63.6 cm^2) in a water-jacketed three-compartment cell; agar salt bridges were inserted on the counter and reference sides of the medium-porosity glass frits separating the compartments. The reference compartment contained a saturated calomel electrode and the counter compartment contained a platinum-gauze cylinder immersed in saturated KCl solution. Buffer solutions were preelectrolyzed at the same potential of the electrolysis. Nitrogen or argon, equilibrated by bubbling through buffer solution, was continuously passed through the cell during the electrolysis.

Electrochemical Reduction of 1-Benzyl-3-carbamoylpyridinium Chloride (1). In a typical run, 6.0 g of **1** was dissolved in 300 mL of 0.1 M NH_3–0.1 M NH_4Cl aqueous solution, an equal volume of benzene was added, and the resulting system was electrolyzed at −1.30 V under vigorous magnetic stirring. Usually the electrolysis took about 10 h to reach completion, as inferred from the complete disappearance of the reduction wave (A) of compound **1** and from the constant value of the current, equal to that obtained at the same potential with a solution containing only the supporting electrolyte. During the electrolysis, the deviation of the voltmeter was ±1 mV with respect to the imposed potential.

After the electrolysis, the benzene–water suspension of the solid reaction product was filtered and small amounts of the mercury pool were removed to give a crude reaction mixture (5.0 g), which was suspended in 2-propanol (40 mL) and stirred at room temperature for 5 min; the solid recovered by filtration, further extracted with boiling 2-propanol (40 mL), recovered by filtration, aand dried under vacuum was essentially pure **2** (2.3 g). An analytical sample of **2** was obtained upon crystallization from MeOH: **2**; mp 180–181 °C dec; UV_{max} (MeOH) 268 (ϵ 6250), 348 nm (ϵ 7250); IR $\bar{\nu}$ 3370, 3170, 1660, 1630, 1595, 1585 cm^{-1}; NMR see Tables I and II. Anal. Calcd for $C_{26}H_{26}N_4O_2$: C, 73.21; H, 6.14; N, 13.14. Found: C, 72.86; H, 5.83; N, 13.23.

The combined mother liquors were evaporated to dryness under reduced pressure and the oily brown residue was treated with cold MeOH (20 mL); the solid formed was recovered by filtration, washed with cold MeOH, and crystallized twice from 2-propanol to give pure **3** (0.6 g): mp 188–189 °C dec; UV_{max} (MeOH) 276 (ϵ 6000), 354 nm (ϵ 8100); IR $\bar{\nu}$ 3470, 3350, 3180, 1680, 1670, 1640, 1600, 1580, 1565, 1555 cm^{-1}; NMR see Tables I and II. Anal. Calcd for $C_{26}H_{26}N_4O_2$: C, 73.21; H, 6.14; N, 13.14. Found: C, 72.98; H, 6.09; N, 12.91.

Chemical Reduction of 1. Mg powder (8.0 g) was added portionwise to a stirred solution of **1** (8.0 g) in H_2O (160 mL) containing NH_4Cl (14.0 g) and 33% aqueous NH_3 (5 mL), kept at 40–45 °C, during 2.5 h. After this time, the reaction mixture was stirred at room temperature for 4 h and the solid was collected by suction and treated with H_2O and CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), and evaporated; the residue was worked up as above, to give **2** and **3**.

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Registry No.—**1**, 5096-13-9; **2–3** isomer 1, 66788-25-8; **2–3** isomer 2, 66788-26-9; **4**, 952-92-1; **5**, 2288-38-2.

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(17) ^1H NMR data reported by Wallenfels:[10] δ 7.33, 6.10, 4.38 (vinyl protons), 3.23 (methine proton), 7.08 (NH_2). It should be pointed out that Kano et al.[18]

by photochemical reduction of 1-benzyl-3-carbamoylpyridinium cation have obtained a dimer, to which they assigned a 6,6′-linked structure by comparison with the product reported by Wallenfels.[14] Consequently, the Kano's photoproduct as well is identical to **2** and therefore must be regarded as a 4,4′-linked dimer.

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Facile Preparation of Optically Active *c*-2,*t*-3-Dimethyl-*r*-1-methoxycyclopropane

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The thermal chemistry of cyclopropane and its derivatives has attained considerable theoretical importance.[3] Elegant experimental studies[4] have complemented and supported the earlier conceptual insights. Mechanistic attention is now shifting to an understanding of substituent and activation effects on reaction stereochemistry as well as the correspondence of observed kinetic parameters with the thermochemical estimates.

For the detailed investigation of the rearrangement chemistry of 2,3-dimethyl-*r*-1-methoxycyclopropane[5,6] and an eventual determination of the dynamic stereochemistry of the stereomutation process, we required each enantiomer of the chiral isomer (**7**). In this note we present a convenient as well as reliable synthesis of optically active *c*-2,*t*-3-dimethyl-*r*-1-methoxycyclopropane (**7**).

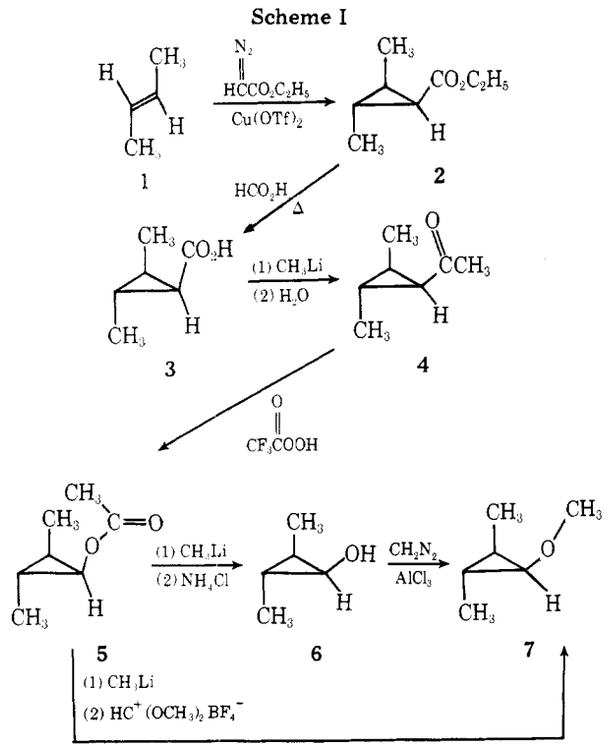
Results and Discussion

Our approach to the preparation of optically active cyclopropane **7** was patterned after the generalized DePuy synthesis[7] of cyclopropanols as illustrated in Scheme I.

The cupric trifluoromethanesulfonate catalyzed cyclopropanation of *trans*-2-butene (**1**) was accomplished in 33% isolated yield.[9,10] Basic saponification of the ethyl *c*-2,*t*-3-dimethyl-*r*-1-cyclopropanecarboxylate (**2**) was found to be unreliable, but transesterification with formic acid[11] afforded *c*-2,*t*-3-dimethylcyclopropane-*r*-1-carboxylic acid (**3**) in 82% yield. The resolution of **3** was achieved through fractional recrystallization of the diastereomeric quinine salts.[12] Optically active carboxylic acid **3** was then transformed into optically active *c*-2,*t*-3-dimethyl-*r*-1-methoxycyclopropane (**7**) through a sequence beginning with a methyllithium treatment and subsequent hydrolysis. Baeyer–Villiger oxidation of the resulting methyl ketone with trifluoroperacetic acid, treatment with methyllithium to produce the cyclopropanol **6**, and immediate methylation with diazomethane catalyzed by boron trifluoride etherate or aluminum trichloride[13] completed the synthesis. An alternate direct conversion of the acetate **5** into the ether **7** employing methyllithium treatment and subsequent reaction with dimethoxycarbonium tetrafluoroborate[14] was less effective.

The overall yield of **7** was 2.7% based on ethyl diazoacetate. The optically active cyclopropyl ether **7**, with $[\alpha]^{22}_{237}$ +13.4°, was found to be chromatographically and spectroscopically identical with an authentic sample obtained from the Schöllkopf reaction between *trans*-2-butene, dichloromethyl methyl ether, and methyllithium.[15]

Scheme I



Experimental Section

^{1}H NMR spectra were obtained on a Varian T-60 instrument. Infrared spectra were recorded on a Beckman IR-20 spectrophotometer. Mass spectra were secured on a Finnigan 1015D quadrupole mass spectrometer with a variable leak inlet, an ion source temperature of 55 °C, and an ionization potential of 70 eV. Analytical and preparative gas chromatographic separations were achieved on Varian Model A90-P and 1400 instruments. Optical rotations were obtained on a Perkin-Elmer Model 241 polarimeter.

Cupric Trifluoromethanesulfonate.[16] In a 750-mL conical flask was placed 12.5 g (101 mmol) of cupric carbonate in 280 mL of acetonitrile. To the stirred suspension, 25.0 g (167 mmol) of trifluoromethanesulfonic acid was cautiously added over 10 min. The reaction mixture was stirred an additional 30 min, filtered into a 1-L round-bottom flask, and concentrated under reduced pressure to give a blue solid which was dried by heating in the same vessel with a Fisher burner at 0.1 Torr to give 28.9 g (96%) of cupric trifluoromethanesulfonate.

(±)-Ethyl *c*-2,*t*-3-Dimethyl-*r*-1-cyclopropanecarboxylate (2).[9,10] *trans*-2-Butene (1.2 L) was condensed in a 5-L round-bottom flask fitted with an addition funnel, a dry ice–acetone cooled condenser,[17] a nitrogen inlet, and a paddle stirrer. Anhydrous ethyl ether (1 L) and finely ground cupric trifluoromethanesulfonate (20.0 g, 55 mmol) were added to the flask before ethyl diazoacetate[8] (82.0 g, 720 mmol) in ethyl ether was added dropwise over 1.5 h. The solution was allowed to reflux as it was stirred for 4.5 h. It was then stirred without the reflux condenser for 2 h as the alkene was boiled off. A solution of 50% ammonium hydroxide was added to the dark residue until two distinct phases were formed. Ammonium hydroxide washes were continued until clear. After washing with water (3 × 75 mL), the ethereal solution was dried ($MgSO_4$), filtered, and concentrated by distillation [bp 34–37 °C (9 Torr)] to give 34.0 g (33%) of **2**, which was identified from its ^{1}H NMR [(60 MHz, $CDCl_3$) δ 4.18 (ester methylene, q, J = 7 Hz, 2 H) and 1.60–0.93 (methyl and cyclopropyl, m, 12 H)], IR [(neat film) $\bar{\nu}_{CH}$ 3010–2885, $\bar{\nu}_{C=O}$ 1755, and $\bar{\nu}_{C-O}$ 1240 cm^{-1}], and electron impact mass spectra [(70 eV) *m/e* 142 (M^+), 127 ($M^+ - CH_3$), 97 ($M^+ - C_2H_5O$), and 69 ($M^+ - C_2H_5CO_2$)].

(±)-*c*-2,*t*-3-Dimethyl-*r*-1-cyclopropanecarboxylic Acid (3). A 500-mL three-neck round-bottom flask was fitted with an addition funnel and a nitrogen inlet, as well as with a distillation head and condenser. The flask was charged with 63.0 g (440 mmol) of (±)-ethyl *c*-2,*t*-3-dimethyl-*r*-1-cyclopropanecarboxylate (**2**), formic acid (5.1 g, 110 mmol), and 2 drops of concentrated sulfuric acid. Ethyl formate was distilled from the mixture at 54 °C while additional formic acid (25.3 g, 550 mmol) was added at a rate equal to the distillation throughput rate. The distillation was continued until only formic acid was being collected. Vacuum distillation [bp 52–54 °C (0.2 Torr)] afforded 41.3 g (82%) of (±)-*c*-2,*t*-3-dimethyl-*r*-1-cyclopropanecarboxylic acid (**3**), whose structure was confirmed from its ^{1}H NMR [(60

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