BIOORGANIC CHEMISTRY 1, 400–408 (1971)

Specificity in Addition of a Halomethyl Group to a Model for a Pyridine Nucleotide Coenzyme[1,2]

ANTHONY LOMBARDO AND DONALD C. DITTMER

Department of Chemistry, Syracuse University, Syracuse, New York 13210

Received August 23, 1971

Reaction of 1-benzyl-3-cyano-1,4-dihydropyridine with 1,1,3-trichloro-1,3,3-trifluoro-2-propanone in acetonitrile gave three dihydropyridines in which a dichlorofluoromethyl group is attached at the 2-, 4-, and 6-positions, respectively. The major products in about identical yield were the 1,2- and the 1,6-dihydropyridine derivatives. Very little of the 1,4-isomer was obtained. These results are interpreted as an indication of a preferred orientation of the haloketone in the transition state for reduction of the carbonyl group. The alkoxide ion produced on reduction undergoes a haloform-like cleavage to generate a dichlorofluoromethyl anion near the 2- or the 6-positions of the pyridinium ring. Addition of the anion to the ring gives the observed products.

INTRODUCTION

The mechanism for hydrogen transfer from reduced pyridine nucleotide coenzymes (e.g., NADH) to substrates (e.g., the carbonyl group) has been considered to be a direct transfer of hydrogen, perhaps as hydride ion (*1*, *2*).[3] The possibility of an indirect transfer via a tryptophane residue in yeast alcohol dehydrogenase or in rabbit muscle lactate dehydrogenase has been raised since tryptophane was found to be tritium labeled when labeled substrate was used (*3*). However, it has been pointed out that such results do not exclude a direct mechanism because the tryptophane labeling may be the result of only a side reaction (*4*, *5*).

Prelog, in a study of the enzymatic reduction of cyclic ketones, proposed that the stereospecificity of a direct hydrogen transfer from coenzyme to carbonyl group could be explained by orientation of the oxygen atom toward the nitrogen atom of the dihydropyridine ring (Fig. 1) (*6*) in a ketone–coenzyme–enzyme complex. Cervinka and Hub obtained results on the enzymatic reduction of acyclic ketones which were at variance with Prelog's hypothesis (*7*), but conformational lability in the acyclic cases may complicate the interpretation of the data.

A charge transfer complex between substrate and models for the dihydropyridine coenzyme have been postulated for the reduction of hexachloroacetone (*8*, *12*)[2] and trifluoroacetophenone (*9*). In this paper, evidence is presented for the orientation of

[1] The authors are grateful to the National Institutes of Health for partial support of this work.

[2] For complete details see A. Lombardo, Ph.D. Thesis, Syracuse University, 1967.

[3] For reviews of hydrogen transfers from the pyridine nucleotide coenzymes or their models see T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. II, Chap. 9, W. A. Benjamin, Inc., New York, 1966; F. H. Westheimer, *Advan. Enzymol.*, **24**, 441 (1962); S. P. Colowick, J. van Eys, and J. H. Park, "Comprehensive Biochemistry" (M. Florkin and E. H. Stotz, Eds.), Vol. 14, Chap. 1, Elsevier Publishing Co., Amsterdam, 1966; H. Sund, H. Diekmann, and K. Wallenfels, *Advan. Enzymol.*, **26**, 115 (1964).

1,1,3-trichloro-1,3,3-trifluoro-2-propanone with respect to 1-benzyl-3-cyano-1,4-dihydropyridine in the attempted reduction of the former.

Reduction of hexachloroacetone by 1,4-dihydropyridine analogs of the coenzyme NADH occurs rapidly to give a good yield of hexachloroisopropanol (*10*, *11*). Other

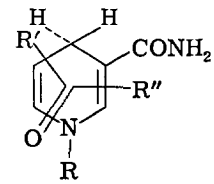
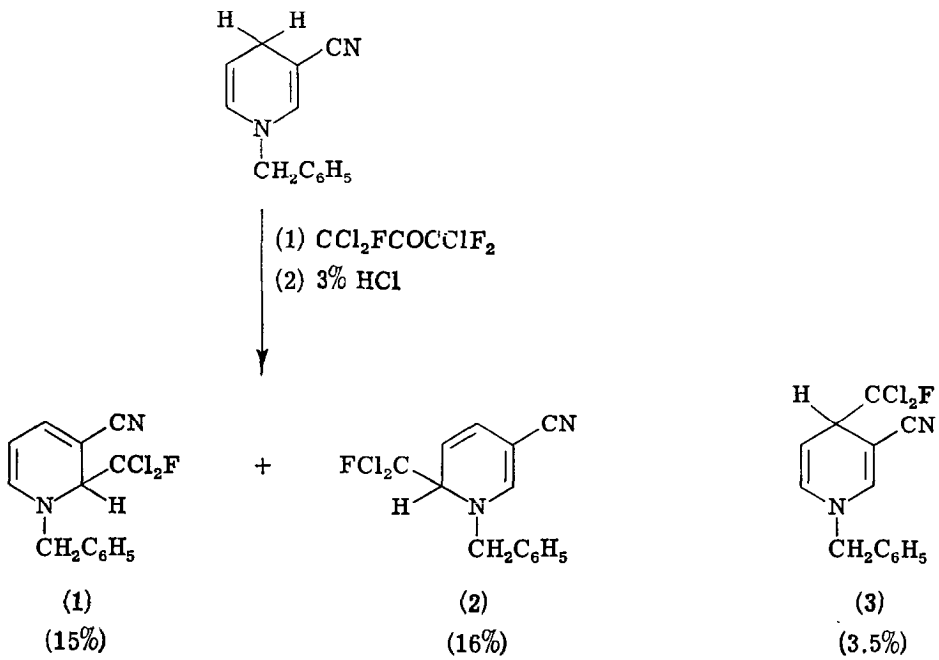


FIG. 1. Orientation of a carbonyl group in a transition state, in which charge separation is minimized, for reduction by a dihydropyridine coenzyme.

haloketones also are reduced (*12*). When the reduction of 1,1,3-trichloro-1,3,3-trifluoro-2-propanone was attempted with 1-benzyl-3-cyano-1,4-dihydropyridine, three products having identical molecular formulas, $C_{14}H_{11}Cl_2FN_2$, were obtained. Only trace amounts of 1,1,3-trichloro-1,3,3-trifluoro-2-propanol were detected. These three compounds, **1** (yellow needles, mp 84–85°), **2** (white flakes, mp 102–104°) and **3** (white crystals, mp 78–79°), are assigned structures of a 1,2-dihydro-, a 1,6-dihydro- and a 1,4-dihydropyridine, respectively, on the basis of elemental analysis and spectroscopic data.

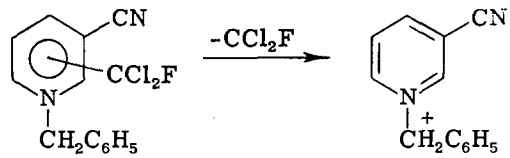


(1) (15%) (2) (16%) (3) (3.5%)

Mass, ultraviolet and infrared spectra. The parent peak in the mass spectra of the two major products (**1** and **2**) is found at *m/e* 296 in agreement with the molecular formula obtained by elemental analysis.[4] The mass spectra of these two isomers are

[4] The peaks at mass 298 and mass 300 caused by the presence of ^{37}Cl are approximately 60 and 10%, respectively, of the parent peak, as expected for a molecule containing two chlorines.

very similar and show abundant ions at *m/e* 195, corresponding to the 1-benzyl-3-cyanopyridinium ion.



m/e 195

The ultraviolet spectra are consistent with the dihydropyridine structures suggested. Isomer **1** in methanol has a single maximum at 383 mμ (ε 7400), as expected for a 1,2-dihydropyridine (*13*, *14*). Compound **2** has two absorption maxima at 247 (ε 7000) and 334 mμ (ε 5200) in agreement with expectation for a 1,6-dihydropyridine (*13*, *14*).

However, the third isomer also has two maxima in the ultraviolet, 243 mμ (ε 6000) and 322 mμ (ε 6300). If it is a 1,4-dihydropyridine, the long wavelength absorption is displaced from the maximum observed at 340 mμ (ε 5600) for 1-benzyl-3-cyano-1,4-dihydropyridine, **4**, and the intensity is increased. Although the 1,4-dihydropyridines discussed by Wallenfels and coworkers exhibit only a single maximum in the ultraviolet above 220 mμ (aromatic absorption occurs below 220 mμ in the 1-benzyl-dihydro derivatives), in theory at least two absorptions in the ultraviolet are expected (*15*). In fact, a number of 1,4-dihydropyridines with two absorptions are recorded

TABLE 1

INFRARED DOUBLE-BOND STRETCHING FREQUENCIES

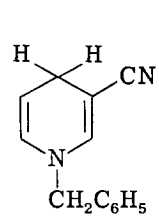
Compound	**1**	**2**	**3**	**4**	**5**[a]
ν, cm^{-1}	1620	1650	1670	1680	1660
	1510	1575	1585	1610	1590

[a] We are indebted to Professor George Büchi for providing us with the spectrum.

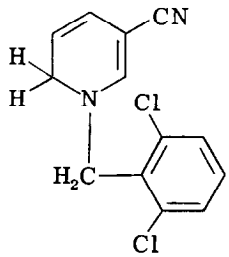
(*16–20*). Displacement of the long wavelength absorption to shorter wavelengths by electronegative 4-substituents also has been documented (*20*). A decrease in wavelength and an increase in intensity of absorption with a 4-methyl substituent has been observed for 1,4-dihydropyridines (*21*). Therefore, the third isomer, and not the second, is favored as being a 1,4-dihydropyridine.

Further support for the assignment of structures is found in the infrared spectra. The absorptions in the double-bond stretching region of the infrared for the three isomers are compared in Table 1 with the corresponding absorptions of the known 1,4-dihydropyridine (**4**) and 1,6-dihydropyridine (**5**). The double-bond stretching frequencies for **1** are lower than those of either **4** or **5** or the two other isomers. This lends support to a 1,2-dihydro structure for **1** since the most extended conjugated system should have the lowest frequency (*22*). With respect to the remaining two isomers, the spectrum of **2** is similar to that of the 1,6-dihydropyridine (**5**), and that of **3**, to the 1,4-dihydropyridine (**4**).[5]

[5] The ratio of the long wavelength absorption, ν_2/ν_3, is 0.988 and is equal to ν_5/ν_4.

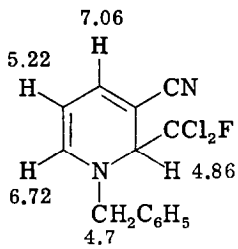


(4)



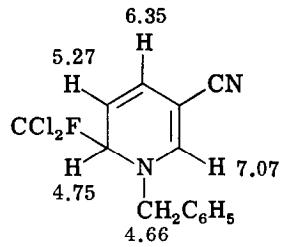
(5)

Nmr Spectra. The ^1H and ^{19}F nmr spectra have been most useful in the assignment of structures of the three isomers. The nmr spectral data are summarized in Fig. 2. (chemical shifts are in δ values). The structural assignments are based on comparisons with the ^1H nmr spectra of the 1,2- 1,4- and 1,6-dihydropyridine



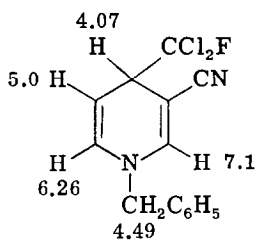
(1)

$J_{5,6}$ 6.5 Hz
$J_{4,5}$ 6.5



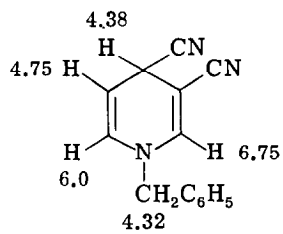
(2)

$J_{5,6}$ 6.5 Hz
$J_{4,5}$ 9.5



(3)

$J_{5,6}$ 7.5 Hz
$J_{4,5}$ 5.0



(6)

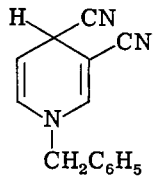
$J_{5,6}$ 8.0 Hz
$J_{4,5}$ 4.0

FIG. 2. ^1H nmr spectral assignments for compounds **1-3**. Numbers are δ values.

derivatives reported by Diekmann, Englert and Wallenfels (*23*) and of the 1,4-dihydropyridine derivative, **6**.

In the ^1H nmr spectra reported previously (*23*), seven 1,4-dihydropyridines analogous to **3** had $J_{5,6}$ from 7.9 to 9.0 Hz, and $J_{4,5}$ from 3.4 to 4.3 Hz while two 1,6-dihydropyridines analogous to **2** had $J_{5,6}$ from 3.4 to 3.6 Hz and $J_{4,5}$ from 9.7 to 10 Hz. A single 1,2-dihydropyridine had a $J_{5,6}$ of 6.9 Hz and a $J_{4,5}$ of 4.5 Hz. If one uses these comparisons alone, **3** and **6** are seen to have vicinal coupling constants comparable to those of

1,4-dihydropyridines. These coupling constants for **1** and **2** provide a less clear-cut choice between the 1,2- and the 1,6-dihydropyridine structures although the compound (**2**) with the relatively large $J_{4,5}$ of 9.5 Hz would appear likely to be a 1,6-dihydropyridine.



(6)

In 1,3-disubstituted 1,4- and 1,6-dihydropyridine derivatives the lowest field signal caused by a proton on the dihydropyridine ring is produced by the C-2 proton; the absorption is either a singlet or, with good resolution, a doublet because of weak long-range spin–spin coupling ($J_{2,6} \cong 1.5$ Hz) (*23*, *24*). The absorption at δ 7.06 in the spectrum of **1** is a doublet whose coupling constant (6.5 Hz) is much too large for $J_{2,6}$. Deuterium substitution revealed that this absorption was caused by the C-4 proton: reduction of 1,1,3-trichloro-1,3,3-trifluoro-2-propanone by 1-benzyl-3-cyano-4-deuterio-1,4-dihydropyridine would leave the 4-position of the product partially deuterated. The isomer **1** obtained in this reduction showed a greatly diminished absorption at δ 7.06 relative to the unlabeled product. The absorption of the alphatic proton of the pyridine ring in **1** appears at δ 4.86, a high field component of which is buried under the singlet at δ 4.7 (CH_2). Integration of the benzyl proton signal (2.5 protons) and a scale-expanded 100 MHz nmr spectrum revealed the presence of the high field component. The primary coupling is to fluorine ($J_{H-F} = 11$ Hz) which was confirmed by the ^{19}F nmr spectrum. This observation favors the assignment of a 1,2-dihydropyridine structure to **1** since only in that isomer should the high field proton of the dihydropyridine ring be coupled exclusively to fluorine and not to another proton as well (exclusive of weak, long-range couplings). In the 1,4- and 1,6-dihydropyridines, coupling to the C-5 proton as well as to fluorine is expected.

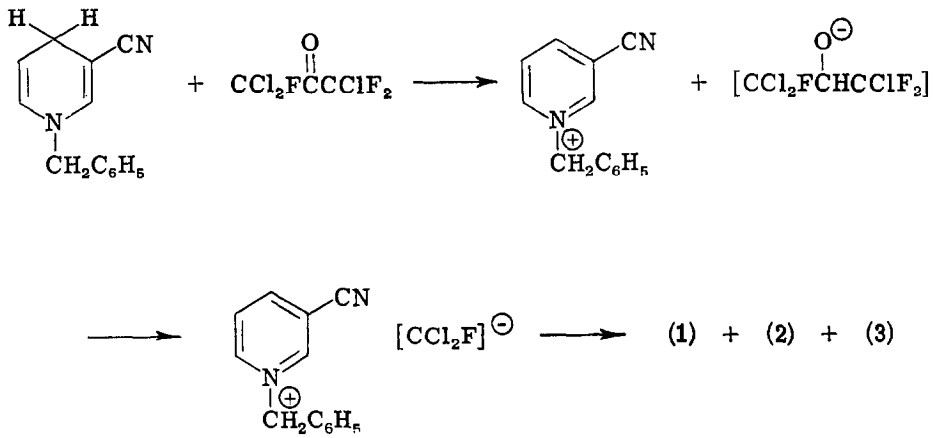
The aliphatic proton (high field) of the dihydropyridine ring in **1**, **2** and **3** should absorb at *lowest* field when it is attached to carbon which bears in addition to the dichlorofluoromethyl group also a nitrogen atom. This situation occurs in the 1,2- and the 1,6-dihydropyridine derivatives. Since the high field ring proton in **3** is at δ 4.07 as compared with δ 4.86 and δ 4.75 for **1** and **2**, respectively, the assignment of the 1,4-dihydropyridine structure to **3** rather than to **2** is reasonable. The small amount of isomer **3** precluded an investigation as extensive as that of the other two isomers. The ^1H nmr spectra of **3** and **6** are similar, the latter compound's being assigned a 1,4-dihydropyridine structure by analogy with 1-benzyl-3-acetyl-4-cyano-1,4-dihydropyridine (*23*, *25*).

DISCUSSION

Compounds **1**, **2** and **3** are quite stable for dihydropyridines; evidence of decomposition appears after about three-days-exposure to air.

The formation of these isomers may occur by addition of the dichlorofluoromethyl

anion to the 1-benzyl-3-cyanopyridinium cation. The anion could be formed by a haloform-like cleavage of the 1,1,3-trichloro-1,3,3-trifluoro-2-propoxide anion, the initial product of the reduction. The haloform cleavage would be expected to occur to give the dichlorofluoromethyl anion, the most stable of the two possible halomethyl anions (*27*). The cleavage with base of 2,2,2-trichloroethanol to carbon monoxide, formaldehyde and chloride ion (*28*) perhaps proceeds by an analogous haloform-like cleavage.



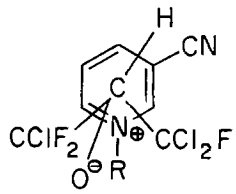
The proposed addition of the dichlorofluoromethyl anion to the pyridinium ring is remarkable in two respects. In most previous additions, usually only one isomer is isolated;[3] in this addition all three possible isomers are isolated. Formation of approximately equal amounts of the 1,2- and the 1,6-dihydropyridines is unusual because one would expect differences in energies of the transition states leading to these two products, since, e.g., there are differences in charge distribution between the 2-, 4- and 6-positions of the pyridinium salt.[6] Although a single product may be favored kinetically, it may be redistributed among the favored thermodynamic products (*26*, *29*, *30*); however, we observe that the three isomers are quite stable in solution and their nmr and ultraviolet spectra do not change with time.

In the transition state for the reduction of the haloketone, the carbonyl oxygen may be oriented towards the nitrogen of the dihydropyridine ring to minimize charge separation (*6*). A representation of the ion pairs, **7a** and **7b**, produced upon hydrogen transfer as hydride from the dihydropyridine ring to the carbonyl group suggests that the halomethyl groups are located closer to the 2- and to the 6-position than to the 4-position of the ring.[7] The haloform-like cleavage will generate the dichlorofluoromethyl anion in the neighborhood of C-2 (**7a**) or C-6 (**7b**) and addition of the anion to these positions will yield **1** and **2**, respectively. The nearly equal amounts of **1** and **2** suggest that orientations **7a** and **7b** are equally probable; the small cyano group in the 3-position apparently exerts no steric effect on the somewhat more bulky dichlorofluoromethyl group. Much the same argument concerning the orientation can be given

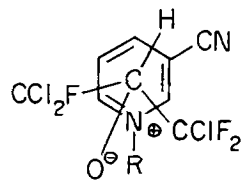
[6] B. Pullman and A. Pullman, "Quantum Biochemistry," p. 525. Interscience Publishers, New York, 1963. The 4-position of nicotinamide salts is predicted to have the greatest electron deficiency, followed by the 2- and the 6-positions in that order.

[7] This also is shown by CPK models of the two reactants.

for a one-electron transfer mechanism in which the dichlorofluoromethyl radical anion and the dihydropyridine radical cation are intermediates.



(7a)



(7b)

ACKNOWLEDGMENT

We wish to thank Dr. W. A. Sheppard for assistance in obtaining the 100 MHz nmr spectra and the ^{19}F spectra.

EXPERIMENTAL SECTION[8]

1-Benzyl-3-cyanopyridinium chloride. 3-Cyanopyridine (30 g, 0.29 mole) and benzyl chloride (36.5 g, 0.288 mole) were refluxed for 22 hr in absolute ethanol (150 ml). Seed crystals were prepared by addition of ether to 2 ml of the reaction solution. Addition of these "seeds" caused rapid precipitation of product (41 g, 62%): mp 207–209° (dec); ir (KBr) 2250, 1640, 1490 cm^{-1}; uv max (CH_3OH) 268 mμ (ϵ 3900); nmr (D_2O) δ 9.4 (s, 1), 9.15 (d, 1), 8.8 (d, 1), 8.26 (quartet, 1), 7.31 (m, 5), 5.8 (s, 2).

Anal. Calcd for $C_{13}H_{11}ClN_2$: C, 67.7; H, 4.77; N, 12.1. Found: C, 67.8; H, 5.05; N, 12.1.

1-Benzyl-3-cyano-1,4-dihydropyridine (4). 1-Benzyl-3-cyanopyridinium chloride (11.5 g, 0.050 mole) in water (50 ml) was added dropwise during 30 min to a vigorously stirred solution of sodium dithionite (34.8 g, 0.200 mole) and sodium carbonate (17.7 g, 0.167 mole) in water (250 ml). After 90 min a yellow precipitate appeared. The solid was recrystallized from ethanol at room temperature by addition of water to the cloud point followed by cooling. Bright yellow needles were obtained (7 g, 71%): mp 52–53° (dec); ir (KBr) 2200, 1680, 1610, 1400, 740, 720, 705 cm^{-1}; uv max (CH_3CN) 340 mμ (ϵ 5600); nmr ($CDCl_3$) δ 7.31 (s, 5), 6.51 (d, 1, $J = 1.5$ Hz), 5.68 (pair of quartets, 1), 4.58 (pair of triplets, 1), 4.18 (s, 2), 3.02 (quartet, 2).

Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.51; H, 6.12; N, 14.28. Found: C, 79.38; H, 6.02; N, 14.45.

1-Benzyl-3-cyano-4-deuterio-1,4-dihydropyridine. Preparation as above except that D_2O replaced water. A yield of 63% was obtained; the nmr spectrum showed diminished absorption at δ 3.02 (1 H).

1-Benzyl-3,4-dicyano-1,4-dihydropyridine (6). The procedure of Anderson and Berkelhammer for the preparation of the 3-acetyl derivative was followed (*25*). Treatment of 1-benzyl-3-cyanopyridinium chloride (1.16 g, 0.005 mole) in water (10 ml)

[8] Melting points are uncorrected. Proton nmr spectra were recorded either on a Varian A-60 spectrometer or on a Varian HR-100 spectrometer. The ^{19}F nmr spectra were recorded on a Varian A56-60 spectrometer. Microanalyses were done by Galbraith Laboratories, Knoxville, Tenn., or by Alfred Bernhardt Mikroanalytisches Laboratorium, Mulheim, West Germany. Mass spectra were obtained on an Hitachi–Perkin Elmer Model RMU-6D spectrometer.

with potassium cyanide (3.25 g, 0.05 mole) in water (10 ml) gave a yellow oil which was extracted with ether. The residue remaining after removal of the ether was dissolved in a small amount of methanol and cooled. Granular, brown crystals (0.5 g, 0.002 mole, 39%) were obtained: mp 62–64° (dec); ir 2200, 1680, 1600, 1410, 1180, 1120, 740, 710 cm^{-1}; uv max (CH_3OH) 333 mμ (ϵ 7,500); nmr ($CDCl_3$) δ 7.31 (m, 5), 6.75 (d, 1, $J = 1.5$ Hz), 6.0 (d, 1, $J = 8.0$ Hz), 4.75 (quartet, 1, $J = 4.0$ Hz), 4.38 (d, 1, overlaps with singlet), 4.32 (s, 2).

Reaction of 1,1,3-trichloro-1,3,3-trifluoro-2-propanone with 1-benzyl-3-cyano-1,4-dihydropyridine. A solution of the haloketone (3.2 g, 0.015 mole) in dry (CaH_2) acetonitrile (10 ml) was added dropwise during 30 min with stirring and under nitrogen to a solution of the dihydropyridine (1.46 g, 0.0074 mole) in dry acetonitrile (40 ml) at room temperature. Hydrochloric acid (20 ml, 3%) was added to the red-orange reaction mixture after 2 hr. Removal of solvents left a dark orange oil which was chromatographed on Florisil. Four fractions were collected on elution with hexane–ether (2:1).

Fraction A. A clear liquid with a pungent odor was obtained. Its infrared spectrum showed the presence of an hydroxyl group and the absence of a carbonyl group ($CClF_2CH_2OH$?). The substance, being isolated only in a small yield, was not characterized further.

Fraction B. A clear yellow solution was obtained. Removal of solvent left a yellow oil which was recrystallized from methanol–water. Bright yellow needles of **1** were obtained (0.335 g, 0.00113 mole, 15%): mp 84–85° (dec); ir (KBr) 3050, 2950, 2200 1620, 1510, 1210, 1140, 928, 915, 840, 735, 720, 690, 675 cm^{-1}; uv max (CH_3OH) 383 mμ (ϵ 7400); ^1H nmr ($CDCl_3$) δ 7.3 (m, 5), 7.06 (d, 1, $J = 6.5$ Hz), 6.72 (two doublets, 1, $J = 6.5$, 1.0 Hz), 5.22 (t, 1), 4.86 (d, 0.5, $J = 1.0$ Hz), 4.7 (s, 2.5); ^{19}F nmr ($CDCl_3$, CCl_3F reference) $\phi^* + 64.6$ (d, 1, $J = 11$ Hz); mass spectrum (70 eV) *m/e* (rel intensity) 296, 195 (82), 104 (57), 91 (100).

Anal. Calcd for $C_{14}H_{11}Cl_2FN_2$: C, 56.67; H, 4.03; Cl, 23.6; F, 6.42; N, 9.43. Found: C, 56.71; H, 3.91; Cl, 23.9; F, 6.23; N, 9.02.

Fraction C. A white solid (**2**) was isolated and recrystallized from methanol–water (0.34 g, 0.0012 mole, 16%); mp 102–104° (dec); ir (KBr) 3020, 2900, 2200, 1650, 1575, 1420, 1210, 1185, 1115, 1080, 840, 756, 748, 695 cm^{-1}; uv max (CH_3OH) 247 mμ (ϵ 7000), 334 (ϵ 5200); ^1H nmr ($CDCl_3$) δ 7.3 (m, 5), 7.07 (s, 1), 6.35 (d, 1, $J = 9.5$ Hz), 5.27 (quartet, 1, $J = 6.5$ Hz), 4.75 (t, 0.67, $J = 6.5$ Hz), 4.66 (s, 2.33); ^{19}F nmr ($CDCl_3$, CCl_3F reference) $\phi^* + 61.6$ (d, $J = 6.5$ Hz); mass spectrum (70 eV), *m/e* 296, 195, 91.

Anal. Calcd for $C_{14}H_{11}Cl_2FN_2$: C, 56.67; H, 4.03; Cl, 23.6; F, 6.42; N, 9.43. Found: C, 56.38; H, 4.19; Cl, 24.01; F, 6.38; N, 9.22.

Fraction D. A small amount of a white solid (**3**) was isolated and recrystallized from methanol–water to give white, granular crystals (0.075 g, 0.00025 mole, 3.5%): mp 78–79°; ir (KBr) 3060, 2950, 2200, 1670, 1585, 1415, 1240, 1190, 930, 840, 796, 750, 730 cm^{-1}; uv max (CH_3OH) 243 mμ (ϵ 6000), 322 (ϵ 6300); nmr ($CDCl_3$) δ 7.3 (m, 5), 7.1 (s, 1), 6.26 (d, 1, $J = 8.0$ Hz), 5.0 (quartet, 1, $J = 8.0$, 5.0 Hz), 4.49 (s, 2), 4.07 (quartet, 1, $J = 5.0$, 7.5 Hz).

Anal. Calcd for $C_{14}H_{11}Cl_2FN_2$: C, 56.67; H, 4.03; N, 9.43. Found: C, 56.34; H, 4.00; N, 9.40.

REFERENCES

1. F. H. Westheimer, H. F. Fisher, E. E. Conn, and B. Vennesland, *J. Amer. Chem. Soc.*, **73**, 2403 (1951).
2. F. Fisher, B. Vennesland, F. H. Westheimer, and E. E. Conn, *J. Biol. Chem.*, **202**, 687 (1953).

3. K. A. SCHELLENBERG, *J. Biol. Chem.*, **240**, 1165 (1965).
4. K. A. SCHELLENBERG, *J. Biol. Chem.*, **242**, 1815 (1967).
5. D. PALM, *Biochem. Biophys. Res. Commun.*, **22**, 151 (1966).
6. V. PRELOG, *Colloq. Ges. Physiol. Chem.*, **14**, 288 (1964).
7. O. CERVINKA AND L. HUB, *Collect. Czech. Chem. Commun.*, **31**, 2615 (1966).
8. A. LOMBARDO, C. S. GREENE, AND D. C. DITTMER, 154th Meeting, Amer. Chem. Soc. Chicago, Ill. Abstr. C-105, Sept., 1967.
9. J. J. STEFFENS AND D. M. CHIPMAN, *J. Amer. Chem. Soc.*, **93**, 6694 (1971).
10. D. C. DITTMER, L. J. STEFFA, J. R. POTOSKI, AND R. A. FOUTY, *Tetrahedron Lett.*, 827 (1961).
11. D. C. DITTMER AND R. A. FOUTY, *J. Amer. Chem. Soc.*, **86**, 91 (1964).
12. C. S. GREENE, Ph.D. Thesis, Syracuse University, 1971.
13. 1,2-Dihydropyridines, λ_{max} 380–420 mμ; 1,6-, 260–270, 330–370 mμ; 1,4-, 330–370 mμ: K. WALLENFELS AND M. GELLRICH, *Chem. Ber.*, **92**, 1406 (1959).
14. K. WALLENFELS, H. SCHULY, AND D. HOFMANN, *Annalen der Chemie*, **621**, 106 (1959).
15. G. CILENTO, E. FILHO, AND A. C. G. ALBANESE, *J. Amer. Chem. Soc.*, **80**, 4472 (1958).
16. E. M. KOSOWER AND T. S. SORENSEN, *J. Org. Chem.*, **27**, 3764 (1962).
17. J. KUTHAN, *Collect. Czech. Chem. Commun.*, **27**, 2175 (1962).
18. E. BULLOCK, B. GREGORY, A. W. JOHNSON, P. J. BRIGNELL, U. EISNER, AND H. WILLIAMS, *Proc. Chem. Soc.*, 122 (1962).
19. T. SEVERIN, H. LERCHE, AND D. BÄTZ, *Chem. Ber.*, **102**, 2163 (1969).
20. J. F. BIELLMANN AND H. J. CALLOT, *Bull. Soc. Chim. Fr.* 1154 (1968).
21. D. HOFMANN, E. M. KOSOWER, AND K. WALLENFELS, *J. Amer. Chem. Soc.*, **83**, 3314 (1961).
22. L. J. BELLAMY, "The Infrared Spectra of Complex Molecules," pp. 35–38, 394. John Wiley and Sons, Inc., New York, 1964.
23. H. DIEKMANN, G. ENGLERT, AND K. WALLENFELS, *Tetrahedron*, **20**, 281 (1964).
24. W. L. MEYER, H. R. MAHLER, AND R. H. BAKER, JR., *Biochem. Biophys. Acta*, **64**, 353 (1962).
25. A. G. ANDERSON, JR. AND G. BERKELHAMMER, *J. Org. Chem.*, **23**, 1109 (1958).
26. R. E. LYLE AND G. J. GAUTHIER, *Tetrahedron Lett.*, 4615 (1965).
27. J. HINE, N. W. BURSKE, M. HINE, AND P. B. LANGFORD, *J. Amer. Chem. Soc.*, **79**, 1406 (1957).
28. E. K. MARSHALL, JR. AND A. H. OWENS, Jr., *Bull. Johns Hopkins Hosp.*, **95**, 2 (1954).
29. R. E. LYLE AND P. S. ANDERSON, *Advan. Heterocycl. Chem.*, **6**, 45 (1966).
30. R. N. LINDQUIST AND E. H. CORDES, *J. Amer. Chem. Soc.*, **90**, 1269 (1968).