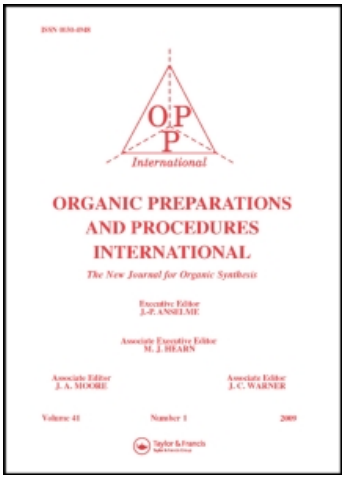


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF CHROMOPHORIC ANALOGS OF ACETYLCHOLINE HALIDES

Leroy H. Klemm[a]; Warner L. Peticolas[a]; Kori L. Clement[a]; K. Jeffry Wilson[a]
[a] Department of Chemistry, University of Oregon, Eugene, OR

To cite this Article Klemm, Leroy H. , Peticolas, Warner L. , Clement, Kori L. and Wilson, K. Jeffry(1989) 'SYNTHESIS OF CHROMOPHORIC ANALOGS OF ACETYLCHOLINE HALIDES', Organic Preparations and Procedures International, 21: 5, 619 — 627
To link to this Article: DOI: 10.1080/00304948909356426
URL: http://dx.doi.org/10.1080/00304948909356426

ORGANIC PREPARATIONS AND PROCEDURES INT. 21(5), 619-627 (1989)

SYNTHESIS OF CHROMOPHORIC ANALOGS OF ACETYLCHOLINE HALIDES

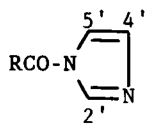
LeRoy H. Klemm,* Warner L. Peticolas,* Kori L. Clement and K. Jeffry Wilson

Department of Chemistry, University of Oregon, Eugene, OR 97403

Acetylcholine (1a) is the common transmitter of the peripheral nervous system, in which it binds to a specific receptor on the postsynaptic membrane. It was the goal of this research to synthesize a number of analogs of 1a which might act either as agonists or antagonists of 1a and be susceptible to study by electronic absorption spectrometry and Raman scattering, both in solution and when bound to the acetylcholine receptor. Specifically, the present paper describes the synthesis and characterization of seven analogs of 1a, i.e. compounds 1b-1e and 5-7, as well as the previously reported intermediate acylimidazoles 3c and 3f.

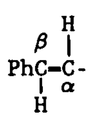
$RCOOCH_2CH_2\overset{+}{N}Me_3\ X^-$
(X^- = I^- in 1b-1e)
(X^- = Cl^- in 1e')
1

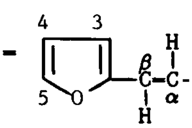
RCO_2H
2


3

$RCOCl$
4

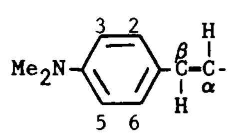
a, R = Me

b, R = 

c, R = 

d, R = Me_3C-

e or e', R = Me_2N-

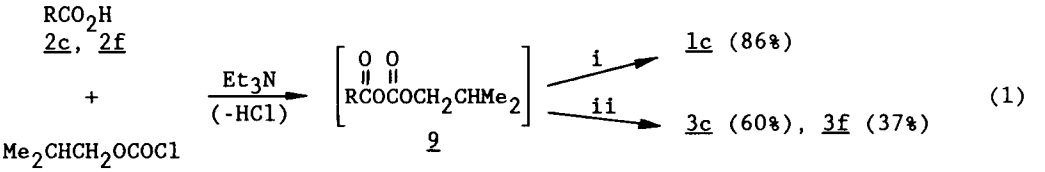
f, R = 

$Me_2N\overset{S}{\overset{\|}{C}}OCH_2CH_2\overset{+}{N}Me_3\ X^-$
5 (X^- = I^-)
5' (X^- = Cl^-)

$CH_3\overset{S}{\overset{\|}{C}}OCH_2CH_2\overset{+}{N}Me_3\ I^-$
6

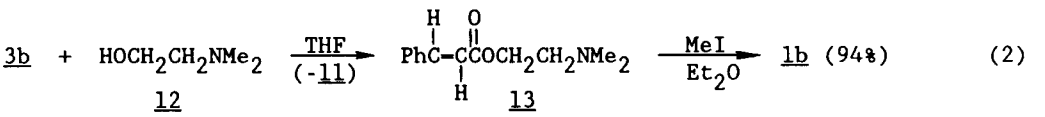
$CH_3\overset{S}{\overset{\|}{C}}SCH_2CH_2\overset{+}{N}Me_3\ I^-$
7

A variety of synthetic routes to these compounds was employed (Eqs. 1-6).



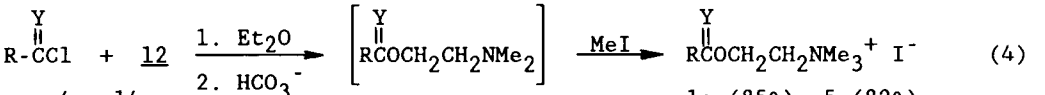
(1)

(i) $Me_3\overset{+}{N}CH_2CH_2OH\ I^-$ (10), THF, MeCN (ii) Imidazole (11)



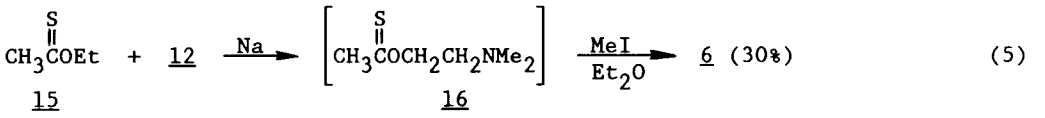
(2)

(3)

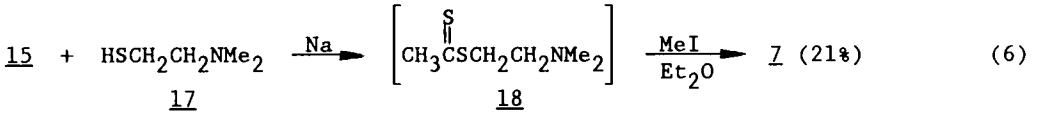


(4)

14: $Me_2\overset{S}{N}CCl$



(5)



(6)

In Eq. 1, furylacrylic acid (2c) reacted with isobutyl chloroformate (8), as reported by Bernhard et al.,[1] to give a solution of mixed anhydride 9. Intermediate 9 in dioxane reacted with imidazole (11) to form acylimidazole 3c[1] or with choline iodide (10) in THF-MeCN to produce 1c. Analogously, 4-dimethylaminocinnamic acid (2f) was converted into the acylimidazole 3f, mp. 147-148°. Our sample of 3f, however, did not show properties consistent with the product (mp. 203-206° dec.) reported by Carey et al.,[2] synthesized in essentially the same way. Commercially available N-trans-cinnamoylimidazole (3b) underwent reaction with

2-dimethylaminoethanol (12) in THF to form liquid aminoester 13, quaternized to 1b by means of methyl iodide (Eq. 2); compound 13 had been synthesized previously from cinnamoyl chloride and 12.[3] Compound 1d was easily obtained by reaction of pivaloyl chloride (4d) with choline salt 10 at 0-25° in THF-MeCN (Eq. 3).

Similarly N,N-dimethylcarbamoyl chloride (4e) and N,N-dimethylthiocarbamoyl chloride (14) were treated first with aminoalcohol 12 and then with iodomethane to form 1e and 5, respectively (Eq. 4). Compound 1e was previously prepared by Haworth et al.[4] in unstated yield as shown in Eq. 7. Compounds 1e and 5 were easily distinguishable at room temperature

$$ClCH_2CH_2O\overset{O}{\overset{\|}{C}}Cl \xrightarrow{Me_2NH} \xrightarrow[\text{ethanol, } \Delta]{NaI} \xrightarrow{Me_3N} \underline{1e} \qquad (7)$$

by their ^1H NMR spectra. The former exhibited one singlet for the six protons of the dimethylamino group, while the latter showed two singlets corresponding to methyl groups syn and anti to the thiono sulfur atom. Additionally the corresponding chloride salts 1e' and 5', obtained by ion exchange, were readily distinguishable by Raman scattering, in which the former absorbed at 1720 cm^{-1} for the carbonyl group, while the latter absorbed at 1290 cm^{-1} for the thiocarbonyl group.

Base-catalyzed ester exchange followed by removal of volatile ethanol (Eqs. 5 and 6) converted commercially available 15 into the intermediates 16 and 18 by the method of Chu and Mautner,[5] who isolated methyl bromide derivatives of these compounds. Bost and Shealy[6] prepared 18 by a four-step process, wherein sodium ethanedithioate reacted with 2-chloro-1-dimethylaminoethane. The Chu and Mautner procedure is much simpler than that of Bost and Shealy, which gave uncertain results in our laboratory.

EXPERIMENTAL SECTION

Unless otherwise indicated, infrared spectra were obtained on potassium bromide wafers by means of a Beckman IR-10 or a Nicolet 5-DXB FTIR instrument; ultraviolet-visible spectra, by means of a Beckman DU-7

spectrophotometer; ^{1}H NMR spectra, by means of a Varian Associates XL-100A or a General Electric QE-300 instrument; and Raman spectra, at 15° with a Spectra Physics argon ion laser and activation by the 514.5 nm line. Mass spectra were recorded by Dr. Richard E. Wielesek of this laboratory with a CEC model 21-110 apparatus at 70 eV. Elemental analyses were determined by Desert Analytics, Tucson, Arizona or by Galbraith Laboratories, Inc., Knoxville, Tennessee.

β-Dimethylaminoethyl trans-Cinnamate (13).- Three g. (15 mmol) of N-trans-cinnamoylimidazole (3b) (Aldrich), contained in an oven-dried (250°) flask filled with nitrogen gas, was dissolved in 70 ml. of purified (by distillation from lithium aluminum hydride) tetrahydrofuran and treated dropwise, with stirring, at 0° with 1.5 ml. (15 mmol) of 2-dimethylaminoethanol (12) (Aldrich). The mixture was stirred at 60° for 3 days until tlc (silica gel F-254/acetone, UV and iodine detection) showed that all 3b had reacted, R_f values: imidazole, 0; 2-dimethylaminoethanol, 0.48 (yellow); 3b, 0.60; 13, 0.81 (yellow). The THF solution was evaporated to dryness. A solution of the residue in ice-cold ether was washed repeatedly with saturated aqueous sodium chloride solution until tlc showed no spot at R_f 0. Rotary evaporation of the dried (sodium sulfate) ether solution gave 13 as a greenish yellow, viscous liquid, lit.[3] bp. 132-134°/0.1 mm. ^{1}H NMR (acetone-d_6): δ 2.25 (s, NMe_2), 2.59 (t, J = 6 Hz, 2H, CH_2N), 4.29 (t, J = 6 Hz, 2H, OCH_2), 6.56 (d, J_{trans} = 16 Hz, H-α), 7.4-7.6 (m, 3 aromatic H), 7.6-7.8 (m) which overlaps 7.71 (d, 3H total, H-β).

O-trans-Cinnamoylcholine Iodide (1b).- A solution of 1.57 g of preceding, crude 13 in 5 ml. of ether was treated with 1.06 g. (4% excess) of methyl iodide and the solvent was allowed to evaporate in air to give 1.44 g. (94% from 3b) of 1b as prisms, mp. 221-222°. IR: 1725 (C=O), 1640, 1310, 1165, 1155, 970 cm^{-1}. RAMAN (MeOH): 1728 (C=O), 1639 (C=C), 1605 (ring C=C stretch), 1166, 1033, 1005 cm^{-1}. UV (H_2O): λ max. 218 nm (log ε 4.33), 278 (4.32). ^{1}H NMR (DMSO-d_6): δ 3.24 (s, 9H, $\overset{+}{N}Me_3$), 3.7-3.9 and 4.5-4.7 (m and broad s, 4H total, $OCH_2CH_2N^+$), 6.69 (d, J_{trans} = 16 Hz, H-α), 7.4-7.6 (m, 3H), 7.6-7.8 (m) which overlaps 7.75 (d, 3H total, H-β).

Anal. Calcd for $C_{14}H_{20}INO_2$: C, 46.55; H, 5.58; N, 3.88

Found: C, 46.37; H, 5.62; N, 3.73

1-[3-(2-Furyl)acryloyl]imidazole (3c).- Purified furylacrylic acid (2c) (Aldrich), obtained as colorless needles, was dried in vacuo at 78° over phosphorus pentoxide, mp 140-141°, and converted into 3c by a published procedure, mp. 111-112° (60%), lit.[1] mp. 111-114°. IR ($CHCl_3$): 1709 (C=O), 1627, 1619, 1378, 1288, 985 cm^{-1}. RAMAN ($CHCl_3$): 1620 (C=O), 1480, 1390, 1290, 1025, 670 cm^{-1}. ^1H NMR (D_2O): δ 6.57 and 6.85 (2 split s, 1H each, H-3 and H-4), 6.97 (d, J = 12 Hz, H-α), 7.16 (split s, H-4' or H-5'), 7.56 and 7.63 (2 split s, H-5 and H-5' or H-4'), 7.83 (d, H-β), 8.34 (s, H-2').

O-[3-(2-Furyl)acryloyl]choline Iodide (1c).- A stirred solution of 1.5 g. (10.9 mmol) of preceding 2c in 200 ml. of anhydrous tetrahydrofuran at 0° in a nitrogen atmosphere was treated first with 1.41 ml. (10.8 mmol) of chilled isobutyl chloroformate (8) (Sigma) and then (dropwise) with 1.52 ml. (10.9 mmol) of triethylamine. Stirring was continued for 2 hr. after the mixture had warmed to room temperature. The mixture was filtered to remove $Et_3N{\cdot}HCl$, treated with a solution of 2.52 g. (10.9 mmol) of choline iodide (10) (Aldrich), in 60 ml. of acetonitrile, stirred for 2 days at room temperature, and warmed to reflux temperature. The solvent was removed by rotary evaporation. The residue was dissolved in 25 ml. of ethanol. Product 1c (3.25 g., 86%, mp. 218-219°) precipitated on slow addition of 7 ml. of water to the solution. IR: 1720 (C=O), 1640, 1300, 1210, 1165, 1155 cm^{-1}. RAMAN (H_2O): 1700 (C=O), 1635 (C=C), 1481, 1390, 1286, 1020 cm^{-1}. RAMAN (MeCN): 1713, 1633, 1480, 1392, 1283, 1020 cm^{-1}. UV (H_2O): λ max. 223 nm (log ϵ 4.17), 306 (4.11). ^1H NMR (CD_3CN): δ 3.17 (s, 9H, Me_3N^+), 3.67 and 4.55 (2 m, 4H total, $OCH_2CH_2N^+$), 6.34 (d, J_{trans} = 16 Hz, H-α), 6.62 and 6.87 (2d, J = 3.4 Hz, 1H each, H-3 and H-4), 7.55 (d, H-β), 7.67 (s, H-5). Recrystallization from tetrahydrofuran gave a white

powder, mp. 221-222°.

Anal. Calcd for $C_{12}H_{18}INO_3$: C, 41.04; H, 5.17; N, 3.99

Found: C, 40.70; H, 5.35; N, 3.98

1-(4-Dimethylamino-trans-cinnamoyl)imidazole (3f).- Under very dry conditions, a cold (0°), stirred solution of 2 g. (10.5 mmol) of 4-dimethylamino-trans-cinnamic acid (2f) (Aldrich) in 200 ml. of tetrahydrofuran was treated successively with 1.47 ml. (10.5 mmol) of triethylamine and 1.37 ml. (10.5 mmol) of isobutyl chloroformate (added dropwise). The mixture was stirred 15 minutes longer, filtered, treated with a solution of 1.43 g. (21 mmol) of imidazole in 10 ml. of tetrahydrofuran, stirred 12 hr. at 4°, filtered, and evaporated to remove solvent. Most of the unreacted 2f was removed from the residue by fractional crystallization from chloroform. The mother liquor was then chromatographed by means of silica gel (50 g.)/chloroform to separate 3f (R_f 1.0) from remaining 2f (R_f 0). Recrystallization of 3f from ether/ethyl acetate (1:1) gave 0.93 g. (37%) of yellow crystals, mp. 147-148°, lit.[2] mp. 203-206° dec. IR ($CHCl_3$): 1680 (C=O), 1610, 1535, 1165, 815 cm^{-1}. UV (MeOH): λ max. 385 nm, lit.[2] 420 nm. ^1H NMR ($CDCl_3$): δ 3.07 (s, 6H, Me_2N), 6.69 (d, J = 9 Hz, H-3 and H-5) which overlaps 6.78 (d, J_{trans} = 16 Hz, 3H total, H-α), 7.15 (split s, 1H, H-4′ or H-5′), 7.52 (d, J = 9 Hz, H-2 and H-6) which overlaps 7.63 (split s, 3H total, H-5′ or H-4′), 8.01 (d, H-β), 8.31 (split s, H-2′). MS m/e (relative intensity): 241 (M^+, 16), 175 (14), 174 ($Me_2NC_6H_4CH{=}\overset{+}{C}H{-}O$, 100), 146 ($Me_2C_6H_4CH{=}CH^+$, 16), metastable peaks at 125-126 (241→174) and 122-124 (174→146).

Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.42

Found: C, 69.66; H, 6.30; N, 17.61

O-Pivaloylcholine Iodide (1d).- To a stirred mixture of 11.55 g. (50 mmol) of dried choline iodide, 30 ml. of anhydrous acetonitrile, and 30 ml. of anhydrous tetrahydrofuran was added, dropwise, 6.16 ml. (50 mmol) of

pivaloyl chloride (Aldrich). Thirty minutes later 6.96 ml. (50 mmol) of triethylamine was added dropwise. The mixture was stirred for 12 hr. and the solvent was removed by rotary evaporation. The residue was recrystallized several times from ethanol to give 11.8 g. (78%) of 1d as plates, mp. 183-184°. IR: 1750 (C=O), 1500, 1330, 1160, 970 cm^{-1}. RAMAN (MeCN): 1737 (C=O), 1451, 1046, 953, 805, 789, 716, 596 cm^{-1}. UV (H_2O): λ max. 226 nm. ^1H NMR ($CDCl_3$): δ 1.23 (s, 9H, t-Bu), 3.57 (s, 9H, Me_3N^+), 4.16 and 4.56 (2 m, 2H each, $OCH_2CH_2N^+$).

Anal. Calcd for $C_{10}H_{22}INO_2$: C, 38.11; H, 7.03; N, 4.44

Found: C, 37.92; H, 7.06; N, 4.20

O-(N,N-Dimethylcarbamoyl)choline Iodide (1e) and O-(N-N-Dimethylthiocarbamoyl)choline Iodide (5).- A solution of 2 ml. (20 mmol) of 2-dimethylaminoethanol (12) in anhydrous ether was slowly added to a solution of 22 mmol of acid chloride 4e or 14 (Aldrich) in the same solvent. The resultant slurry, which formed slowly, was extracted with saturated, aqueous sodium bicarbonate. The organic phase was dried (magnesium sulfate) and treated dropwise with 1.3 ml. (20 mmol) of iodomethane. The precipitated salt (crude 1e or 5, respectively) was collected by filtration and recrystallized from acetonitrile-ether to produce prisms, yields 5.1 g. (85%) of 1e, mp. 201° dec.; 5.2 g. (82%) of 5, mp. 185° dec. ^1H NMR (CD_3CN) of 1e: δ 2.87 (s, 6H, Me_2N), 3.14 (s, 9H, Me_3N^+), 3.61 and 4.42 (2m, 2H each, $OCH_2CH_2N^+$).

Anal. Calcd for $C_8H_{19}IN_2O_2$: C, 31.80; H, 6.34; N, 9.27

Found: C, 31.95; H, 6.51; N, 9.01

^1H NMR (CD_3CN) of 5: δ 3.12 and 3.30 (2s, 3H each, syn and anti Me groups in Me_2N), 3.14 (s, 9H, Me_3N^+), 3.73 and 4.85 (2m, 2H each, $OCH_2CH_2N^+$).

Anal. Calcd for $C_8H_{19}IN_2OS$: N, 8.81 Found: N, 8.72

The preceding iodide salts were converted to chloride salts by means of an anion exchange resin (Bio-Rex MSZ 1-X8; Bio-Rad, Richmond, California) and

acetonitrile as solvent to yield 1e', mp. 198° dec., and 5', mp. 204° dec., respectively. RAMAN (H_2O) for 1e': 1720 (C=O), 719 (Me_3-N^+ stretching), 636 cm^{-1} (ester deformation). RAMAN (H_2O) for 5': 1290 (C=S), 721 (Me_3-N^+ stretching), 691 cm^{-1} (ester deformation).

O-Ethyl Ethanethioate (15).- This compound was prepared by a reported procedure,[7] yield 97%, bp. 110-110.5°, lit.[7] yield 71%, bp. 108-110°. IR (neat): 1450, 1240 (C=S),[8] 950, 890 cm^{-1}. RAMAN (neat): 1450, 1362, 1262 (C-O-C antisymmetric stretch), 1223 (C=S), 1103, 725, 691 (C-O-C symmetric stretch), 543, 415 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.39 (t, J_{Et} = 7 Hz, 3H, $CH_2C\underline{H}_3$), 2.57 (s, 3H, CH_3C=S), 4.49 (q, 2H $C\underline{H}_2CH_3$).

2-(O-Ethanethioyl)-N,N,N-trimethylethanaminium Iodide (6).- An ether solution of intermediate ester 16[5] [prepared from 4 g. (38 mmol) of 15] was treated with excess methyl iodide and refrigerated. The yellow crystals which precipitated were washed with ether and recrystallized from acetone-ethanol (2:1) to give 3.34 g. (30%) of 6 as tan needles, mp. 146-148°, changed to 147-148° on further recrystallizations. IR: 1490, 1315, 1215 (C=S) cm^{-1}. RAMAN (MeCN): 1446, 1371, 1274 (C-O-C antisymmetric stretch), 1215 (C=S), 730, 720, 696 (C-O-C symmetric stretch), 585 cm^{-1}. UV (MeCN): λ max. 244 nm (log ϵ 4.26), 299 (1.74). ^1H NMR (D_2O): δ 2.62 (s, 3H, CH_3C=S), 3.25 (s, 9H, $\overset{+}{N}Me_3$), 3.89 (t, 2H, OCH_2), 4.92 (t, 2H, $CH_2\overset{+}{N}$). MS m/e (relative intensity): 289 (M^+, 0.6), 147 (16^+, 11), 142 (MeI^+, 44), 103 ([CH_3C(=S)$OCH_2CH_2^+$], 18), 71 (42), 60 (16), 59 (19), 58 (CH_2=C=S^+, 100).

Anal. Calcd for $C_7H_{16}INOS$: C, 29.08; H, 5.58; N, 4.84

Found: C, 29.11; H, 5.74; N, 4.71

2-(Ethanedithioyl)-N,N,N-trimethylethanaminium Iodide (7).- An aqueous solution of 2-dimethylaminoethanethiol hydrochloride (8.6 g., Aldrich) was treated with an equimolar amount of sodium hydroxide. The freed aminothiol 17 was extracted into ether. Evaporation of the dried (sodium sulfate)

extract gave 6 g. (57 mmol, 94%) of crude 17. IR (neat): 2920, 2790, 2740, 2320, 1430 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.27 (s, 6H, NMe_2), 2.30 (s, SH), 2.57 (d of t, 4H, CH_2CH_2).

Treatment of the preceding crude 17 with 0.1 g. of metallic sodium and 8 g. (77 mmol) of 15, by the procedure of Chu and Mautner,[5] gave an ether solution of 18. Addition of 2.3 ml. of methyl iodide caused precipitation of crude 7, triturated with tetrahydrofuran, yield 3.7 g. (21%), mp. 154-156°. Recrystallization from ether-ethanol gave yellow-brown prisms, mp. 164-165°, lit.[6] mp. 172.5-173.5°. IR: 3030, 1485, 1215, 1200, 920, 880 cm^{-1}. RAMAN (MeCN): 1208 (C=S), 867, 750, 580 (C-S) cm^{-1}. UV (H_2O): λ max. 225 nm (log ϵ 4.18), 301 (4.01). ^1H NMR (D_2O): δ 2.88 (s, 3H, CH_3C=S), 3.22 (s, 9H, $\overset{+}{N}Me_3$), 3.49-3.57 and 3.68-3.76 (2m, 2H each, CH_2CH_2).

Anal. Calcd for $C_7H_{16}INS_2$: C, 27.54; H, 5.28; N, 4.59

Found: C, 27.54; H, 5.43; N, 4.85

Acknowledgment.- This study was supported by National Science Foundation grant number 8417199.

REFERENCES

1. S. A. Bernhard, S. J. Lau, and H. Noller, Biochemistry, 4, 1108 (1965).

2. P. R. Carey, R. G. Carriere, D. J. Phelps, and H. Schneider, Biochemistry, 17, 1081 (1978).

3. G. Cerbai and G. F. DiPaco, Boll. Chim. Farm., 105, 45 (1966). [Chem. Abstr., 64, 15833b (1966).]

4. R. D. Haworth, A. H. Lamberton, and D. Woodcock, J. Chem. Soc., 176 (1947).

5. S. H. Chu and H. G. Mautner, J. Med. Chem., 13, 214 (1970).

6. R. W. Bost and O. L. Shealy, J. Am. Chem. Soc., 73, 24 (1951).

7. U. Schmidt, E. Heyman, and K. Kabitzke, Chem. Ber., 96, 1478 (1963).

8. This IR band is reported by P. Reynaud and R. C. Moreau, Bull. Soc. Chim. France, 2999 (1964).

(Received January 26, 1988; in revised form May 22, 1989)